FEATURE ARTICLE

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Transition-metal-containing chiral bidentate ligands for enantioselective catalysis: non-metallocene architectural units come of age

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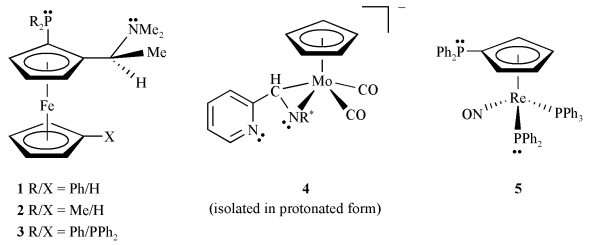
Structural and electronic properties associated with donor ligands that contain 'spectator' transition-metal fragments are analyzed. The current status of such non-ferrocenyl chiral bidentate ligands is reviewed from the standpoint of synthesis, applications in metal-catalyzed enantioselective reactions, and future directions.

1 Introduction

Catalysis represents an exciting, multi-faceted, and never-ending challenge for chemists. In principle, a catalyst can always be improved from the standpoint of rate, lifetime, selectivity, and a host of other criteria. When one considers what would constitute an 'ideal catalyst',[1] it quickly becomes obvious that this is an unattainable limit. This has the happy consequence of guaranteeing ongoing research challenges and continued employment for workers in this field.

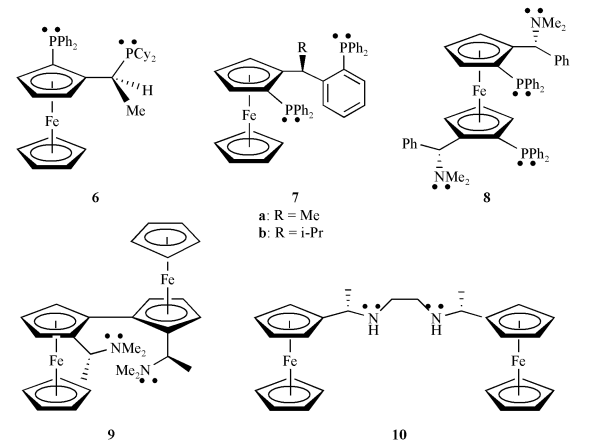
In the quest for improved enantioselective catalysts, chemists have evaluated countless types of chiral building blocks that lead to a multitude of steric environments. Early efforts were biased towards starting materials derived from the naturally occurring 'chiral pool'. However, the many successes with chiral units obtained from non-natural sources, such as substituted binaphthalenes, has unleashed a torrent of activity encompassing nearly every conceivable type of molecular chirality. Many of these studies have involved ligand design for metal-catalyzed reactions. Clearly it was only a matter of time before transition-metal-containing chiral building blocks were evaluated in this context. To distinguish this metal from the catalytically active metal, the adjective 'spectator' can be applied.

Ferrocene-based chiral bidentate chelates are undoubtedly the best-known examples of such ligands.[2,3] Their synthesis and application in metal-catalyzed enantioselective reactions has seen rapidly increasing attention over the last decade. The first representatives, **1**–**3** (Scheme 1), were reported by Kumada in



Scheme 1 First ferrocene-based chiral chelating ligands, and non-ferrocenyl counterparts.

1974, and used in rhodium-catalyzed enantioselective hydrosilylations of ketones.[4] However, the enantioselectivities initially obtained were modest, and the extensive studies of Togni and colleagues such as Spindler, Pugin, and Blaser have played a key role in bringing this field to its present state of maturity.[2a,c,e] These efforts have included the development of commercial applications.[3] In accord with the diverse architectural possibilities inherent in the ferrocene template, all three types of stereogenic elements (centers, planes, axes) have been employed, often in combination. A small sampling of the hundreds of ferrocene-based diphosphines and diamines is given in Scheme 2.



Scheme 2 Representative ferrocene-based chiral diphosphines and diamines.

Implicit in these pioneering studies is an important message. Namely, despite the deserved reputation of transition metals as

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John A. Gladysz observed his 50th birthday on the date that this manuscript was received. Probably most authors who have struggled over a review would agree that the best possible birthday present (other than having it accepted) is getting it off your desk. With this traumatizing chronological milestone, he has sworn to stop counting his publications and other personal numerical statistics. His academic career has included appointments at UCLA (1974–1982), the University of Utah (1982–1998), and the University of Erlangen-Nuremberg (1998–present). His honors include the ACS Award in Organometallic Chemistry (1994), and a von Humboldt Foundation Research Award for Senior Scientists (1995–1996). He has been an Associate Editor of Chemical Reviews *since 1984.*

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reactive centers, their incorporation into donor ligands does not necessarily give less stable or shorter-lived catalyst systems. Ferrocene is of course one of the most robust platforms for synthetic organometallic chemistry, but there are many other types of complexes stable to the various conditions associated with metal-catalyzed organic transformations. As might be expected, extrapolations to ruthenocene-based chiral ligands have been reported.[5] However, the purpose of this review is to highlight the diverse non-metallocene templates for chiral chelating ligands that are now beginning to play major roles in enantioselective catalysis.[6]

This literature will be organized by the type of template. However, to set the stage, some additional themes are briefly treated in this introduction. The first is historical. Which were the first chiral, non-racemic chelating ligands with non-metallocene spectator metals to be described? To the best of the authors′ knowledge, this distinction goes to the molybdenum- and rhenium-containing species **4** and **5** (Scheme 1), which were reported by Brunner and Gladysz in 1986 and 1987, respectively.[7,8] As detailed below, the former gave only modest ee values in enantioselective hydrosilylations, but the latter gave high ee values in enantioselective hydrogenations. For no particular reason, perhaps other than the greater familiarity of most chemists with ferrocene chemistry, the use of such chiral half-metallocene templates then remained dormant for over a decade.

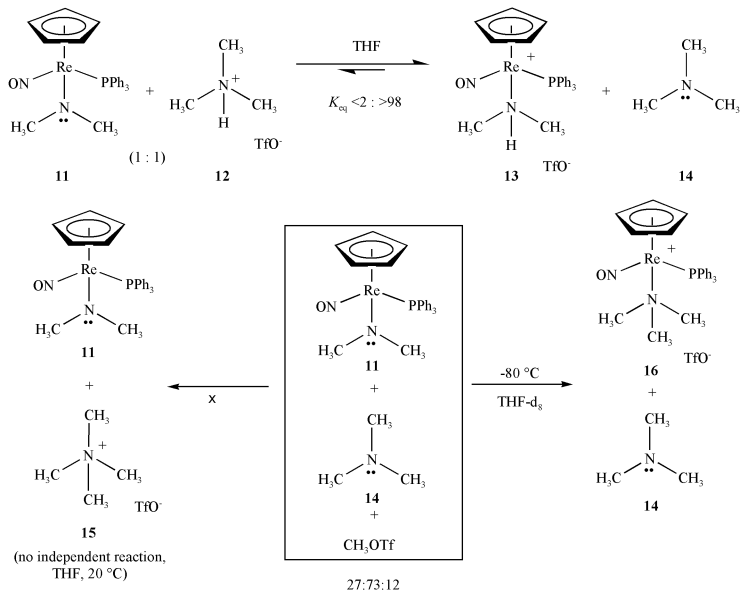
Second, are there any general properties associated with donor heteroatoms in metal coordination spheres? Many metal fragments are bulky in comparison to typical organic substituents, and create a more congested environment for the donor atom. Often this has a beneficial effect on the rate of a metal-catalyzed reaction. There is also the possibility of marked electronic effects. For example, ferrocene has been shown to reduce the Brønsted basicities of amino groups directly bound to the cyclopentadienyl ligand relative to organic model compounds.[9] The same trend is found with an intervening methylene group ($C_5H_4CH_2NR_2$).

The situation appears to be different when the heteroatom is directly bound to, or one or two methylene groups removed from, a coordinately saturated eighteen-valence-electron metal. Some qualitative observations from the authors' group are as follows. Equilibrium and competitive rate experiments of the types shown in Scheme 3 have established that rhenium amido and phosphido complexes (η^5-C_5H_5)Re(NO)(PPh_3)(ER_2) possess much greater basicities and nucleophilicities than the organic analogs ER_3.[10,11] Scheme 4 depicts an equilibrium involving a species with a donor atom not directly bound to rhenium, the 'thioether' (η^5-C_5H_5)Re(NO)(PPh_3)(CH_2SCH_3) (**17**).[12] This lies, within detection limits, completely on the side of the dirhenium complex **19**. Thus, **17** has a much greater Lewis basicity towards the methylidene complex [(η^5-C_5H_5)Re(NO)(PPh_3)(=CH_2)]$^+BF_4^-$ than the organic analog $S(CH_3)_2$.

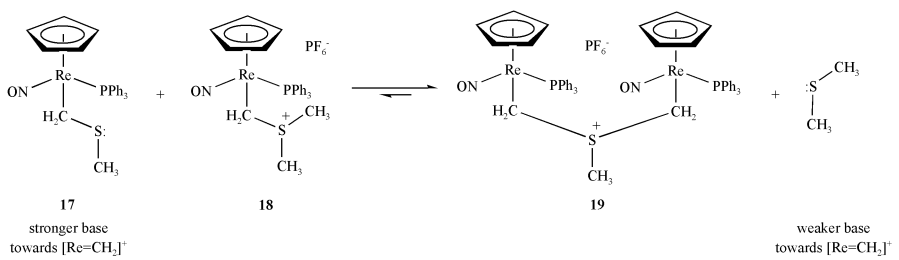
2 Monocyclopentadienyl complexes as templates (I)

2.1

In the seminal Brunner study mentioned above, the diastereomeric cationic molybdenum pyridine/imine complexes **20a**,**b** shown in Scheme 5 were first prepared using several readily available chiral, enantiomerically pure amines R*NH_2.[7,13] The diastereomers could be separated, but the reduction and protonation of either one gave the same mixture of π iminium complexes **21a**–**21d**. These contain four stereocenters, one



Scheme 3 Enhanced basicity and nucleophilicity of a dimethylamido complex.



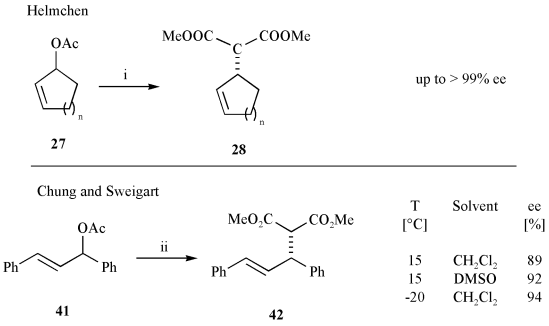
Scheme 4 Enhanced Lewis basicity of a $ReCH_2SR$ complex.

originating from the amine and three (molybdenum, nitrogen, and carbon) formed during the reaction sequence. In most cases, four diastereomers were detected in solution by NMR, which is the maximum number if the non-hydrogen C=N substituents maintain the *trans* relationship required in **20a**,**b**. Silica gel chromatography separated the diastereomers differing in the C=N face bound to molybdenum (**21a**,**b** *vs*. **21c**,**d**), and crystal structures showed hydrogen bonds between the R*NH protons and the pyridine nitrogen atoms.

These complexes were treated with base to generate the anionic π imine complex **4** shown in Scheme 1, which is believed to be in equilibrium with a σ isomer. Reaction with $[Rh(NBD)Cl]_2$ gave the diastereomeric heterobimetallic molybdenum/rhodium complexes **22a**,**b**. The molybdenum-containing ligand can be regarded as a diamine chelate, and a crystal structure showed a semibridging carbonyl ligand. Complexes **22a**,**b** were evaluated as catalyst precursors for the hydrosilylation of acetophenone. However, the results were disappointing. Yields ranged from 7% to 9% and in no case was the ee value of the product greater than 1%. Nevertheless, this study is important as the first application of a non-ferrocenyl metal-containing chiral chelate ligand in a metal-catalyzed reaction. In the authors' opinion, this architecturally novel chelate continues to hold promise for other transformations.

2.2

The next report outside of the authors' efforts with monocyclopentadienyl chelate ligands was by Helmchen in 1998.[14] As shown in Scheme 6, the cyclopentadienyl-manganese phosphine/oxazoline ligands **26a** were synthesized in a three-flask sequence from the cymantrene derivative **23**. In the first step, a commercial enantiomerically pure amino alcohol, tert-leucinol, was used to introduce a carbon stereocenter. The lithiation of oxazoline **25** then generates a planar chirality element. Additions of chlorophosphines $ClPAr_2$ at low temperatures gave the nitrogen/phosphorus chelates **26a** in good yields. When this sequence was carried out at −78 °C with rapid electrophile addition, complete diastereoselectivity was observed. In some cases, racemic chiral chlorophosphines



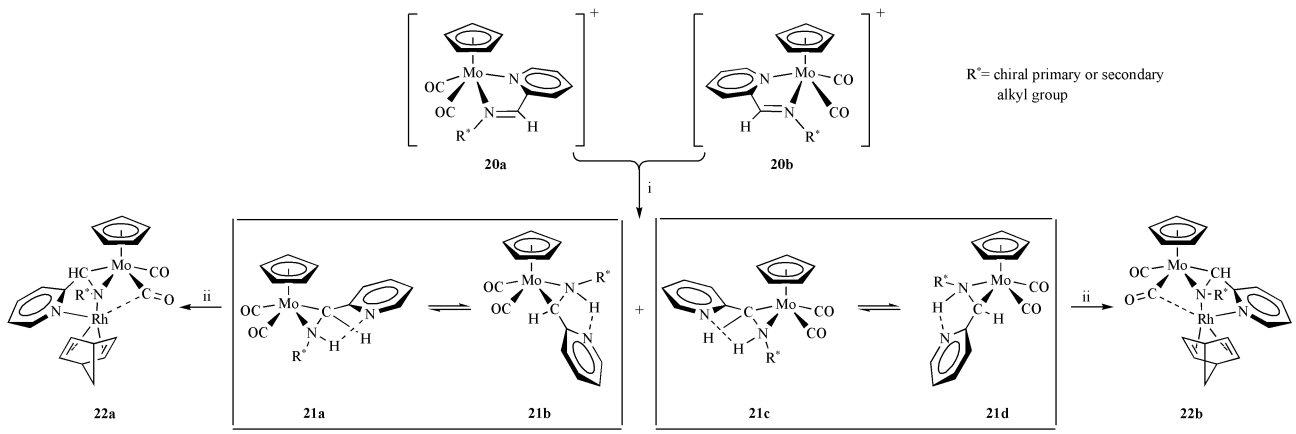
Scheme 7 Palladium-catalyzed allylic substitution reactions. (i) 1.1 mol% **26**, 0.5 mol% $[(\eta\text{-}C_3H_5)PdCl]_2$, $H_2C(CO_2Me)_2$, NaH, DMF; (ii) 1.2 mol% **40**, 0.5 mol% $[(\eta\text{-}C_3H_5)PdCl]_2$, $H_2C(CO_2Me)_2$, *N*,*O*-bis(trimethylsilyl)acetamide, AcOK.

$ClPAr_1Ar_2$ were used, giving **26b**. Both phosphorus diastereomers formed, but could be separated.

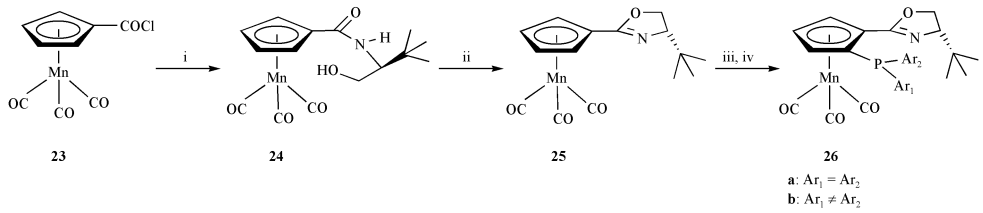
As shown in Scheme 7, these complexes were evaluated in palladium-catalyzed allylic substitution reactions. In contrast to Scheme 5, the heterobimetallic catalysts were generated *in situ*. The results with a ligand of the type **26b** (Ar_1/Ar_2 = Ph/2-biphenylyl) were particularly good. In the case of allylic acetate **27** with $n = 3$ (Scheme 7), the malonate **28** formed with complete enantioselectivity when the reaction was carried out at −20 °C. However, the yield was low (32%). When the reaction was carried out at 0 °C, the yield increased to 86% while the enantioselectivity decreased only slightly to 98% ee. Good results were obtained in a variety of other allylic substitutions.[15]

2.3

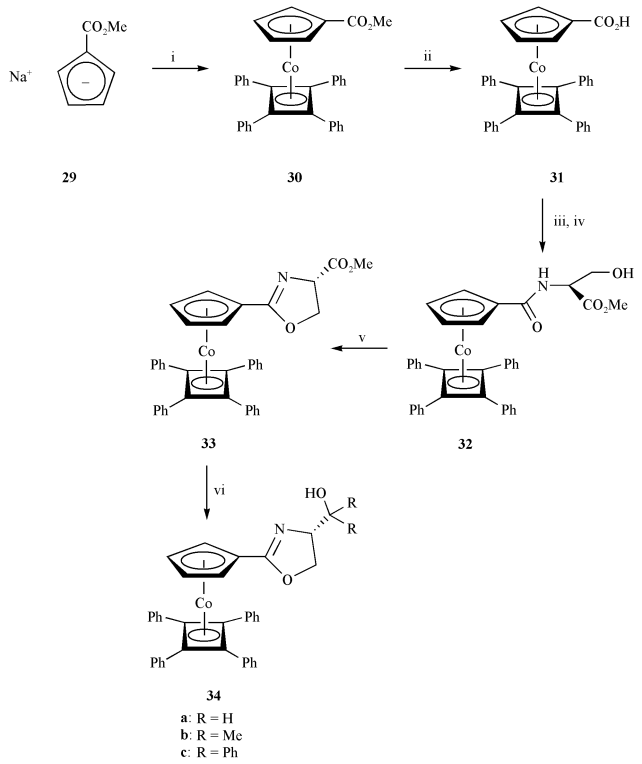
In 2000, Richards reported a cyclopentadienyl cobalt-containing chiral chelate ligand.[16] As shown in Scheme 8, the π tetraphenylcyclobutadiene complex **30** was prepared by a typical procedure. The ester group was then elaborated to the chiral oxazoline **33** *via* a standard sequence involving commer-



Scheme 5 Brunner's molybdenum chelate ligands. (i) Na/Hg, THF, and protonation during workup; (ii) $[Rh(NBD)Cl]_2$, KOH/18-crown-6, toluene.



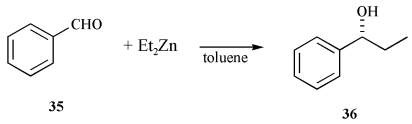
Scheme 6 Helmchen's manganese chelate ligands. (i) (*S*)-tert-leucinol; (ii) TsCl, NEt_3, $CHCl_3$; (iii) s-BuLi, THF; (iv) PAr_1Ar_2Cl, THF.



Scheme 8 Richards' cobalt chelate ligands. (i) PhC≡CPh, $CoCl(PPh_3)_3$, toluene; (ii) t-BuOK, DMSO; (iii) $(COCl)_2$, CH_2Cl_2; (iv) (*S*)-serine methyl ester·HCl, NEt_3, CH_2Cl_2; (v) PPh_3, CCl_4, CH_3CN, NEt_3; (vi) $LiAlH_4$ or RMgX, Et_2O.

cial serine methyl ester. The new ester group in **33** was then transformed to either a primary or tertiary alcohol to give the nitrogen/oxygen donor ligands **34**.

As shown in Scheme 9, these were applied to the ethylation of benzaldehyde (**35**) with Et_2Zn, under which conditions zinc imine/alkoxide chelates are known to be generated. At 5 mol% levels, **34a** and **34b** (R = Me) gave alcohol **36** with enantioselectivities of 68% ee and 54% ee, respectively. To probe the influence of the spatially expansive tetraphenylcyclobutadiene 'floor', an analogous ferrocene-based oxazoline with a pentaphenylcyclopentadienyl ligand was prepared. A slightly higher ee value was obtained (75%). It was proposed that these complexes represent 'planar chirality mimetics' due to restricted rotation about the cyclopentadienyl-oxazolinyl bond (enforced by the bulky 'floor'). This atropisomer-like feature is suggested to control product configuration.



Entry	Ligand	Load [mol%]	T [°C]	Yield [%]	ee [%]
1	**34a**	5	r.t.	>90	68
2	**34b**	5	r.t.	>90	54
3	**70** (R = Et)	5	0 °C	87	93
4	**73a**	5	0 °C	97	96
5	**80** (R = n-Bu)	10	0 °C	99	99
6	**94c**	10	0 °C	67	84

Scheme 9 Enantioselective addition of Et_2Zn to benzaldehyde.

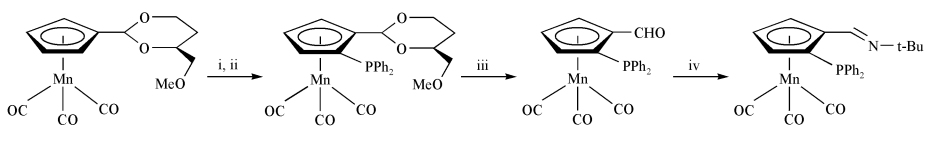
2.4

In 2001, Chung and Sweigart reported a cyclopentadienyl manganese-containing chelate ligand, a nitrogen/phosphorus donor related to **26** in Scheme 6 above. However, as shown in Scheme 10, their system, **40**, features only a planar chirality element.[17] The synthesis utilized an enantiomerically pure ferrocene containing the monosubstituted cyclopentadienyl ligand present in **37**. Heating with naphthalene manganese tricarbonyl effected ligand transfer, giving **37** in 74% yield. Various disubstituted cyclopentadienyl ligands could be similarly transferred (with inversion of the planar chirality element), but were not evaluated in catalysis. Subsequent lithiation and reaction with PPh_2Cl gave **38** with good diastereoselectivity (*ca*. 87 : 13). Recrystallization gave diastereomerically pure **38**, and standard reactions led to the imine/phosphine **40**.

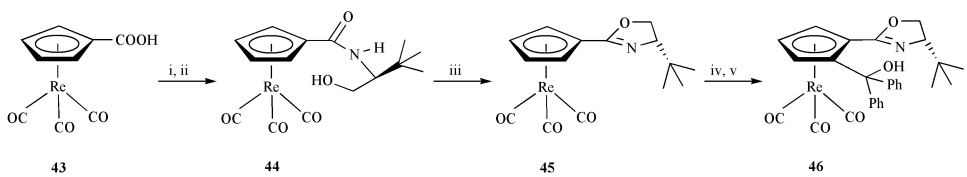
This ligand was evaluated in the palladium-catalyzed allylic substitution reaction shown in Scheme 7. The malonate **42** was obtained in 92% ee and 96% yield in DMSO at 15 °C, or 94% ee and 74% yield in CH_2Cl_2 at −20 °C. With non-metal-containing or ferrocenyl chelate ligands, enantioselectivities of 98–99% ee have been realized.[18] Hence, this first-generation system is already very close to existing benchmarks.

2.5

In 2001, Bolm reported a cyclopentadienyl rhenium-containing chelate ligand, the nitrogen/oxygen donor **46** shown in Scheme 11.[19] The synthesis of the oxazoline **45** was very similar to that reported by Helmchen for the manganese analog **25** in Scheme 6. Subsequent lithiation and reaction with benzophenone gave, after workup, **46** as a 90 : 10 mixture of diastereomers. These were separated by column chromatography, and the major diastereomer was crystallized and structurally characterized. In recently submitted work, these efforts have been extended to similar phosphorus/oxygen donors.[19b]



Scheme 10 Chung and Sweigart's manganese chelate ligand. (i) n-BuLi, Et_2O; (ii) PPh_2Cl, Et_2O; (iii) H^+; (iv) t-$BuNH_2$.



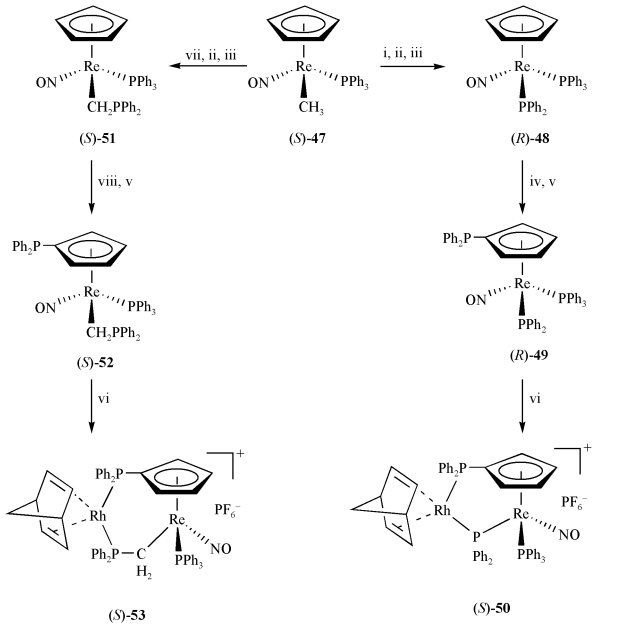
Scheme 11 Bolm's rhenium chelate ligand. (i) $(COCl)_2$, CH_2Cl_2; (ii) (*S*)-tert-leucinol, NEt_3, CH_2Cl_2; (iii) PPh_3, NEt_3, CH_3CN; (iv) n-BuLi, Et_2O; (v) Ph_2CO.

The chelate ligand **46** was then applied in a reaction related to that in Scheme 9, the phenylation of aromatic and aliphatic aldehydes with Ph_2Zn. As described in an earlier paper, Et_2Zn was used as an additive to enhance enantioselectivities. Impressive results were obtained, with ee values reaching as high as 99% with 10 mol% of **46** (*p*-methylbenzaldehyde), or 96% with 2 mol% (*p*-chlorobenzaldehyde). Interestingly, **46** gave equal or better results than the corresponding chiral ferrocene. Thus, it constitutes the current 'record holder' or benchmark ligand for this particular transformation.

3 Monocyclopentadienyl complexes as templates (II): data from the authors' group

The authors' work with chiral chelate ligands derived from monocyclopentadienyl complexes features a distinctive design element, 'chiral-at-metal' rhenium building blocks of the general formula $[(\eta^5\text{-}C_5R_5)Re(NO)(PPh_3)(X)]^{n+}$.[8,20–24] In most cases, only a rhenium stereocenter is present. This is usually incorporated into the chelate backbone, although other architectures are under investigation as exemplified below. Such rhenium complexes are easily obtained in enantiomerically pure form[25] and exhibit exceptional configurational stability. Cationic complexes thermally decompose without racemization (usually > 150 °C). Only neutral amido and alkoxide adducts are configurationally labile at or slightly above room temperature, and the mechanistic basis for this is well understood.[26] The only other 'chiral-at-metal' species above are the molybdenum complexes in Scheme 5, and these always contain additional carbon (and sometimes nitrogen) stereocenters.[27]

The enantiomerically pure rhenium methyl complex (*S*)-**47** shown in Scheme 12 can be prepared by a convenient,



Scheme 12 Syntheses of diphosphines and rhodium complexes with rhenium stereocenters in the backbone. (i) HBF_4, C_6H_5Cl; (ii) PPh_2H; (iii) t-BuOK, THF; (iv) n-BuLi, THF; (v) PPh_2Cl; (vi) $[Rh(NBD)Cl]_2$, $Ag^+PF_6^-$, THF; (vii) $Ph_3C^+BF_4^-$, CH_2Cl_2; (viii) t-BuLi, THF.

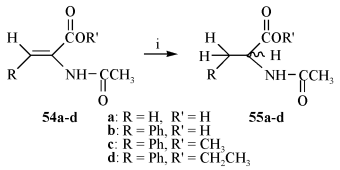
multigram-scale procedure.[25] It can then be converted to the $RePPh_2$ species (*R*)-**48** in a two-flask protocol.[8,20] First HBF_4 is added to give methane and a substitution-labile cationic solvent complex. Addition of PPh_2H gives an air stable $^+RePPh_2H$ species or phosphonium salt. This is isolated and then deprotonated with t-BuOK to give (*R*)-**48**. The authors describe this either as a phosphido complex or a rhenium-substituted monophosphine, depending upon whether inorganic or organic audiences are being addressed. Remarkably, all of these steps occur with complete retention of configuration at rhenium, and the mechanism has been studied in detail.[28]

The lithiation of (*R*)-**48** and subsequent addition of PPh_2Cl gives the diphosphine (*R*)-**49**. Since there is a bond between rhenium and every cyclopentadienyl carbon, this can be viewed as a 1,2-diphosphine, capable of giving a five-membered chelate. Reaction with $[Rh(NBD)Cl]_2$ gives the rhenium/rhodium complex (*S*)-**50**. The crystal structure of the racemate has been carefully analyzed, and shows a chelate conformation analogous to the twist-envelope form of cyclopentane. All steps in this sequence proceed in high yield.

As shown in Scheme 12, the corresponding 1,3-diphosphine, (*S*)-**52**, is also easily prepared from methyl complex (*S*)-**47**. In this sequence, a trityl salt is used to abstract a hydride ion, giving the methylidene complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(=CH_2)]^+BF_4^-$. Addition of PPh_2H gives an air-stable $^+ReCH_2PPh_2H$ species, which is deprotonated to the monophosphine (*S*)-**51**. Reactions analogous to those used with (*R*)-**48** lead to (*S*)-**52** and the rhenium/rhodium six-membered chelate complex (*S*)-**53**. A crystal structure of the racemate shows a chelate conformation analogous to the chair form of cyclohexane, with pseudoaxial and equatorial groups.

The unoptimized overall yields for the ten-step syntheses of rhenium/rhodium complexes (*S*)-**50** and (*S*)-**53** from commercial $Re_2(CO)_{10}$ are 30% and 32%, respectively. As a comparison, the family of diphosphines **7** in Scheme 2 can be prepared from ferrocene in 7 steps and 35% (**7a**) to 15% (**7b**) overall yields.[29] The diphosphine diamine **8** can be synthesized in 7 steps and 40% yield.[5d] However, many ferrocene-based chiral chelating ligands require sequences with similar or greater numbers of steps as (*S*)-**50** and (*S*)-**53**, and similar or lower overall yields. Catalyst expense is another important consideration. Iron starting materials are generally much less costly than rhenium starting materials, but this ratio diminishes when amortized over multistep syntheses involving many other reagents.

The rhenium/rhodium complexes (*S*)-**50** and (*S*)-**53** are highly effective catalyst precursors for the hydrogenation of dehydroamino acids. As summarized in Scheme 13, enantiose-



Entry	Educt	Catalyst	T [°C]	Yield [%]	ee [%]	Config.
1	**54a**	(*S*)-**50**	20-23	82	92	*S*
2	**54b**	(*S*)-**50**	20-23	70	93	*S*
3	**54c**	(*S*)-**50**	20-23	94	88	*S*
4	**54d**	(*S*)-**50**	20-23	86	82	*S*
5	**54a**	(*S*)-**53**	20-23	93	62	*S*
6	**54b**	(*S*)-**53**	20-23	86	72	*S*
7	**54c**	(*S*)-**53**	20-23	98	65	*S*
8	**54d**	(*S*)-**53**	20-23	96	60	*S*
9	**54a**	($S_{Re}S_C$)-**60**	30	85	37	*S*
10	**54b**	($S_{Re}S_C$)-**60**	30	88	62	*S*
11	**54c**	($S_{Re}S_C$)-**60**	30	91	31	*S*
12	**54a**	($S_{Re}R_C$)-**60**	30	90	93	*R*
13	**54b**	($S_{Re}R_C$)-**60**	30	88	94	*R*
14	**54c**	($S_{Re}R_C$)-**60**	30	92	97	*R*

Scheme 13 Catalytic enantioselective hydrogenation of protected dehydroamino acids. (i) 1 atm. H_2, 0.5 mol% catalyst, THF.

lectivities are greater for the five-membered chelate (*S*)-**50**, presumably due to the closer proximity of the reactive rhodium site to the rhenium stereocenter. Turnover numbers of > 1600 could be realized.[20]

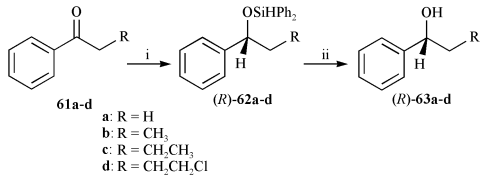
Although the ee values in entries 1–4 of Scheme 13 were competitive at the time of the authors' preliminary communica-

tion in 1987,[8] the bar has been raised considerably higher since. Accordingly, improved results were sought, and one obvious approach would be to replace the methylene group of (*S*)-**53** by a carbon stereocenter. Over the years, methods have been developed for synthesizing either diastereomer of most ReCHRX systems.[30] This plan was put into effect as shown in Scheme 14.[21,22]

The benzyl complex **56** can easily be prepared in enantiomerically pure form. The reaction with $Ph_3C^+BF_4^-$ at low temperature gives the less stable Re=CHPh isomer of benzylidene complex **57**. At room temperature, equilibration to the more stable Re=CHPh isomer occurs ($K_{eq} \geq 99:1$). The mechanistic and stereoelectronic basis for these phenomena have been analyzed in detail.[30a] Importantly, each geometric isomer undergoes highly diastereoselective nucleophilic addition from a direction *anti* to the bulky PPh_3 ligand. Thus, the addition of PPh_2H, followed by deprotonation, gives the diastereomeric monophosphines ($S_{Re}S_C$)-**58** and ($S_{Re}R_C$)-**58**. A series of steps similar to those in Scheme 12 lead to the diphosphines ($S_{Re}S_C$)-**59** and ($S_{Re}R_C$)-**59** and the rhenium/rhodium chelates ($S_{Re}S_C$)-**60** and ($S_{Re}R_C$)-**60**.

It was anticipated that one of the catalyst precursors, ($S_{Re}S_C$)-**60** and ($S_{Re}R_C$)-**60**, would function as a 'matched' diastereomer, giving enantioselectivities higher than (*S*)-**53**, and the other as a 'mismatched' diastereomer, giving lower enantioselectivities. As shown in Scheme 13, ($S_{Re}S_C$)-**60** gives lower ee values, while ($S_{Re}R_C$)-**60** gives the highest values associated with this class of catalysts to date. However, the hydrogenation products exhibit the opposite absolute configuration! This indicates that the carbon stereocenter in ($S_{Re}R_C$)-**60**, which is closer to the rhodium, controls the stereochemistry. Clearly, there is a variety of structural diversity elements in this catalyst family that can be exploited to further enhance enantioselectivities.

All four rhenium/rhodium systems have also been evaluated as catalysts for enantioselective hydrosilylations of aromatic ketones shown in Scheme 15.[22] Surprisingly, the best results are obtained with the six-membered chelate (*S*)-**53**, and only these data are presented. This shows that no firm relationship exists between the chelate ring size—or distance of the reactive



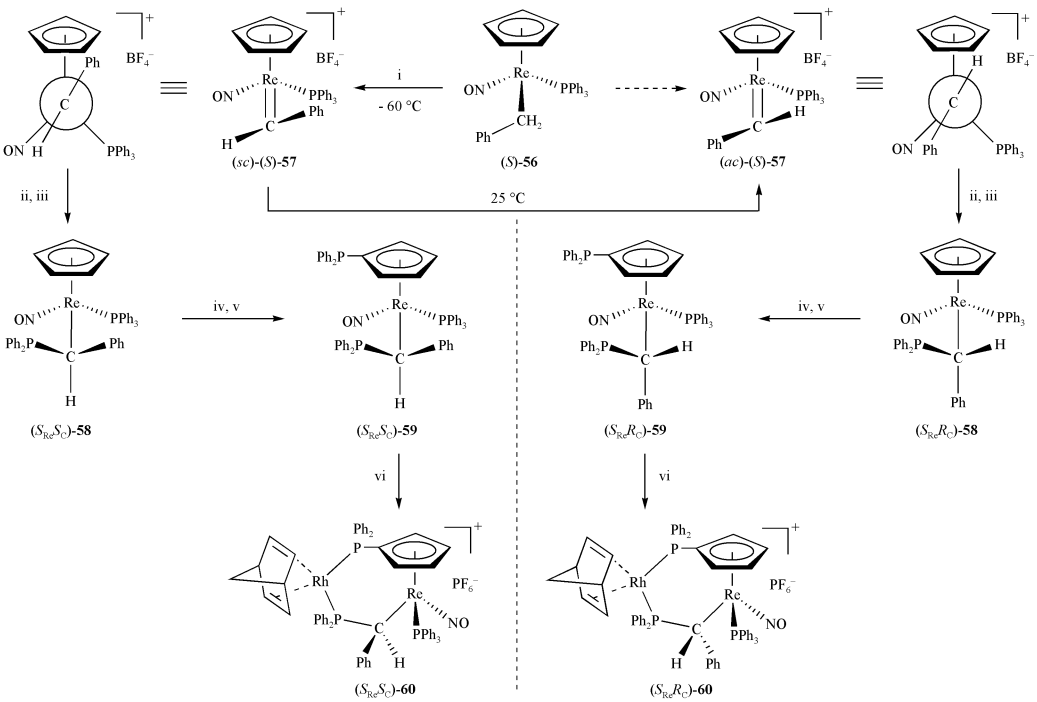
Educt	Catalyst	Conv. (**62**) [%]	Yield (**63**) [%]	ee [%]
61a	(*S*)-**53**	95	75	63
61b	(*S*)-**53**	93	70	62
61c	(*S*)-**53**	92	68	60
61d	(*S*)-**53**	89	72	92

Scheme 15 Catalytic enantioselective hydrosilylation of aromatic ketones. (i) 1.2 equiv. Ph_2SiH_2, 1.0 mol% (*S*)-**50**, (*S*)-**53**, ($S_{Re}S_C$)-**60** or ($S_{Re}R_C$)-**60**, THF, 25 °C; (ii) K_2CO_3, MeOH.

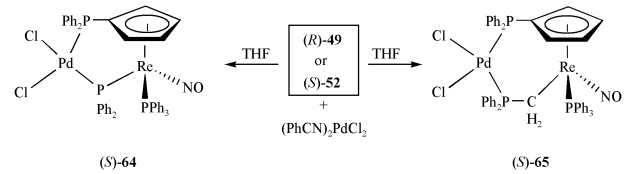
rhodium center from the rhenium stereocenter—and enantioselectivity. Catalysts with identical relative configurations at rhenium give alcohols with identical relative (and coincidentally absolute) configurations at carbon. Thus, in this series of reactions, the rhenium stereocenter always controls the stereochemistry.

Attempts have been made to extend the utility of the above diphosphine ligands beyond rhodium chelate complexes. As shown in Scheme 16, the palladium chelate complexes (*S*)-**64** and (*S*)-**65** are easily prepared, and the latter has been structurally characterized.[23] However, low enantioselectivities were obtained in the asymmetric Heck arylations initially investigated.

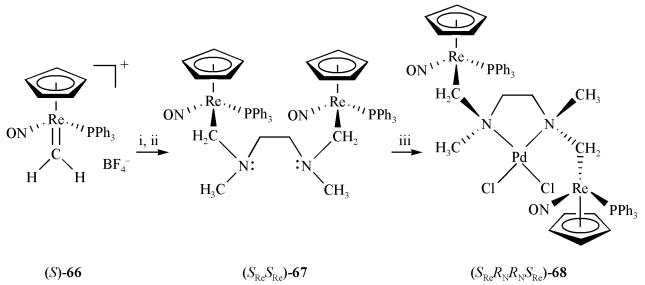
An entirely different type of bidentate ligand and chelate complex is illustrated in Scheme 17. Here, the enantiomerically pure methylidene complex (*S*)-**66** is generated as in reaction vii of (*S*)-**47** in Scheme 12. The addition of 0.5 equivalents of a 1,2-diamine gives a diammonium salt, which is deprotonated to yield the 1,2-diamine ($S_{Re}S_{Re}$)-**67**.[24] In contrast to the diphosphine ligands, the rhenium stereocenters in ($S_{Re}S_{Re}$)-**67** are



Scheme 14 Syntheses of diphosphines and rhodium complexes with rhenium and carbon stereocenters in the backbone. (i) $Ph_3C^+BF_4^-$, CH_2Cl_2; (ii) PPh_2H; (iii) t-BuOK, THF; (iv) t-BuLi, THF; (v) PPh_2Cl; (vi) $[Rh(NBD)_2]^+PF_6^-$, THF.



Scheme 16 Syntheses of palladium chelate complexes.



Scheme 17 Syntheses of a rhenium-containing chiral diamine and palladium complex. (i) *N*,*N*-dimethylethylenediamine (0.5 equiv.), CH_2Cl_2; (ii) t-BuOK, THF; (iii) $(PhCN)_2PdCl_2$, THF.

incorporated into the donor atom substituents as opposed to the chelate backbone. A palladium dichloride chelate is easily formed, and three diastereomers are possible since the labile nitrogen stereocenters of the free ligand become fixed. Only one is detected by NMR, and a crystal structure establishes the structure ($S_{Re}R_NR_NS_{Re}$)-**68**. A detailed rationale for the diastereoselectivity can be made. However, no data for these systems in enantioselective catalysis is yet available.

4 Arene chromium carbonyl and butadiene iron carbonyl templates

4.1

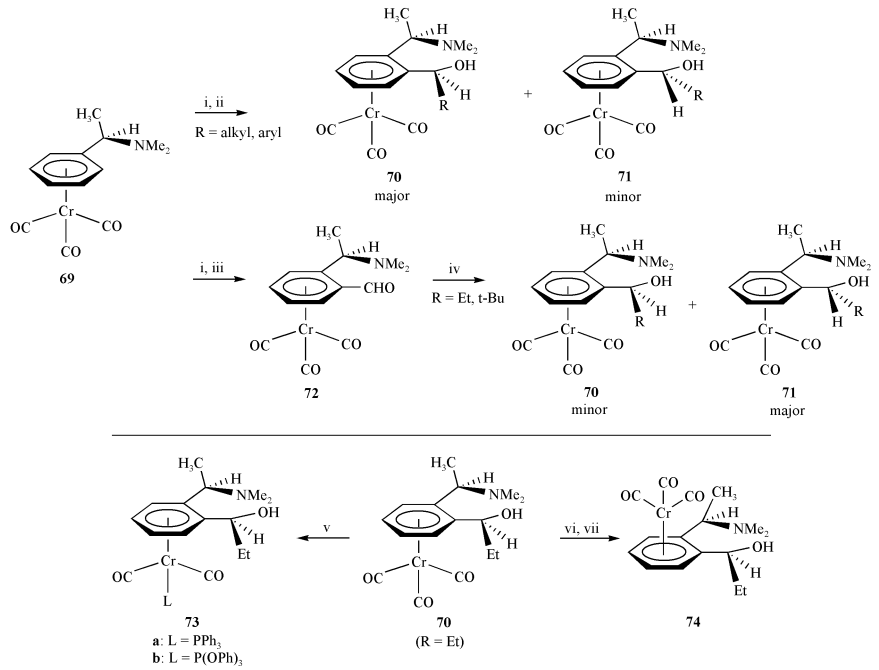
Benzene chromium tricarbonyl ranks second to ferrocene as the most frequently used metal-containing template for chiral chelating ligands. The first report appeared from Uemura's laboratory in 1991.[31] In 1999, Bolm reviewed much of this field, including monodentate ligands.[32] Accordingly, this article is restricted to representative early syntheses of amino alcohols from Uemura, and examples of structurally diverse ligands and catalysts that are complementary to or postdate those in Bolm's review.

Uemura's pioneering studies focused on the amino alcohols in Scheme 18 and 19.[31,33,34] All of these ligands feature a planar chirality element, and those in Scheme 18 contain two carbon stereocenters. Adduct **69** was easily prepared by the complexation of commercial non-racemic *N*,*N*-dimethyl-1-phenylethylamine, and subsequent lithiation was (within detection limits) completely diastereoselective. Additions of appropriate electrophiles gave either the diastereomeric alcohols **70**–**71** or the aldehyde **72**. The diastereomers could be separated chromatographically, and configurations were verified crystallographically. Additions of alkyl lithium reagents to aldehyde **72** also gave **70**–**71**, but with the opposite diastereomer dominating.

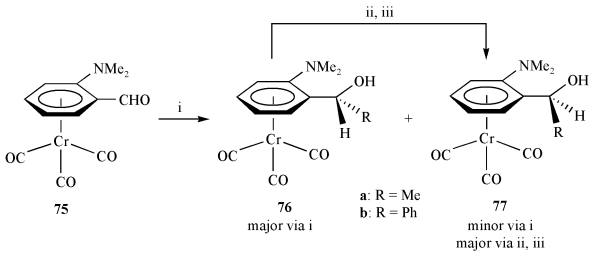
Complex **70** was further elaborated in the case where R = Et. One carbonyl ligand could be substituted by phosphorus donor ligands, giving **73a**,**b** and introducing an additional structural diversity element. The amino alcohol ligand in **70** was also removed and reattached with complete inversion of the ligating diastereoface, giving **74**. In the preferred conformation of the free ligand, both heteroatoms lie on the same side of the arene plane, and these are proposed to direct the incoming chromium.[34]

The amino alcohols shown in Scheme 19, **76** and **77**, feature a single carbon stereocenter, and have the amino group directly bound to the arene. In this case, the planar chirality element was introduced first. The enantiomers of aldehyde **75** could be resolved by first generating the imine derived from L-valinol. The resulting diastereomers were separated chromatographically, and hydrolysis afforded enantiomerically pure **75**. The addition of MeLi gave a 92:8 mixture of **76a** and **77a**. An oxidation/$LiAlH_4$ reduction sequence converted **76a** to a 1:99 mixture of **76a** and **77a**. The addition of PhLi was less diastereoselective, giving a 73:27 mixture of **76b** and **77b**.

The preceding amino alcohols were applied to the ethylation of benzaldehyde by Et_2Zn shown in Scheme 9.[31,34] One of the



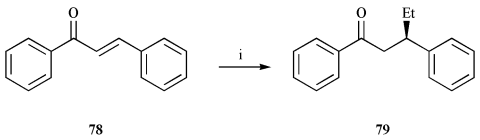
Scheme 18 Uemura's chromium chelate ligands (I). (i) t-BuLi, Et_2O; (ii) RCHO; (iii) DMF; (iv) RLi, Et_2O; (v) *hν*, PPh_3 or $P(OPh)_3$, benzene; (vi) air decomplexation; (vii) (naphthalene)$Cr(CO)_3$, Et_2O, THF.



Scheme 19 Uemura's chromium chelate ligands (II). (i) RLi, Et_2O; (ii) MnO_2, Et_2O; (iii) $LiAlH_4$, THF.

best results was obtained with **70** (R = Et) which at a 5 mol% loading gave alcohol **36** in 87% yield and 93% ee. The uncomplexed ligand gave a lower yield (69%) and a sharply lower enantioselectivity (24% ee). When the CHEtOH stereocenter was inverted (**71**) the enantioselectivity decreased to 50% ee. When the planar chirality element was inverted (**74**), the enantioselectivity decreased to 29% ee and the opposite enantiomer of alcohol **36** dominated. The CHEtOH stereocenter was also eliminated. In the case of the CH_2OH analog, the enantioselectivity decreased to 15% ee, but that of the CEt_2OH analog increased to 95% ee.

Chromium dicarbonyl species such as **73a**,**b** always gave results superior to those of tricarbonyl precursors. In the case of the CEt_2OH analogs (L = PPh_3 or $P(OPh)_3$) enantioselectivities of 97% ee were obtained at 5 mol% loadings. On the other hand, **76a** and **77a** (Scheme 19) gave distinctly poorer results (6% ee and 12% ee). In summary, these data show that very high levels of enantioselection are possible for additions of Et_2Zn to aldehydes with this class of ligands. However, as with non-metallic counterparts, the ligand architecture must be optimized and fine-tuned.

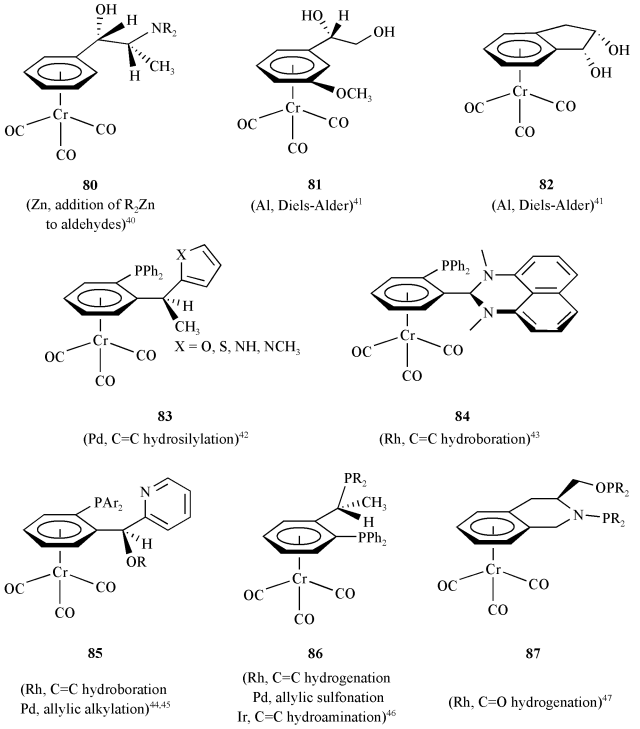


Scheme 20 Enantioselective conjugate addition of Et_2Zn to chalcone. (i) Et_2Zn, 10 mol% **71** (R = Ph), 1 mol% $Ni(acac)_2$, CH_3CN.

As shown in Scheme 20, Uemura extended these studies to the $Ni(acac)_2$-catalyzed conjugate addition of Et_2Zn to chalcone (**78**).[33] When $Ni(acac)_2$ and **70** (R = Ph) were used at 1 mol% and 10 mol% loadings, respectively, the ethylated ketone **79** was obtained in 66% yield and 36% ee. When the proportions of nickel and ligand were increased, yields and ee values increased. When one equivalent of each species was employed, the enantioselectivity reached 78% ee.

Subsequent important contributions by Jones,[35] Brocard,[36] Bolm,[37] Agbossou[38] and Uemura[39] are detailed in Bolm's review.[32] The first three groups have described additional types of amino alcohols. Brocard and Bolm applied these in Et_2Zn additions, whereas Jones elaborated his to oxazaborolidines that catalyzed the reduction of ketones by BH_3·THF (a process not requiring a catalytically active metal center). Agbossou developed an aminophospine/phosphinite chelate that was applied in the rhodium- and ruthenium-catalyzed hydrogenation of α-functionalized ketones. Uemura later developed various amine/phosphines and diphosphines and used them in palladium-catalyzed cross-couplings and allylic alkylations.

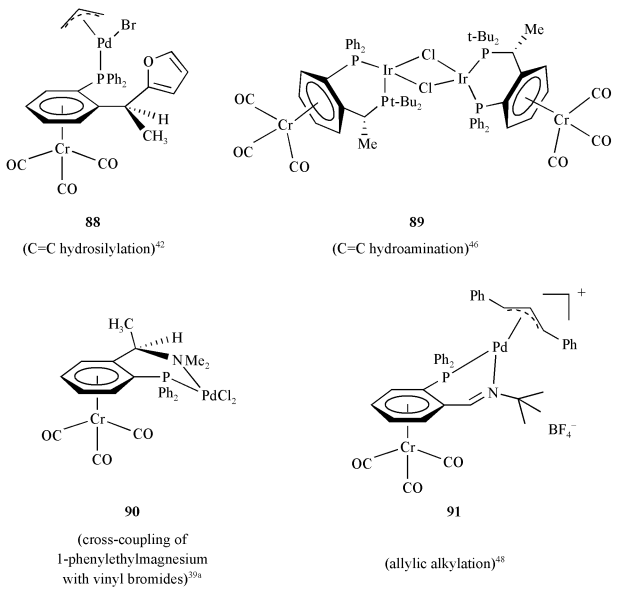
Scheme 21 shows some of the bidentate ligands that have recently been used in conjunction with various metal sources to generate enantioselective catalysts *in situ*.[40–47] All except **80** have a planar chirality element, and all except **84** have a carbon stereocenter. They have been applied in a broad spectrum of



Scheme 21 Other representative arene chromium-based chelate ligands.

reactions, as listed under the compounds. This evidences the robustness of this template under a variety of conditions.

In some cases, metal complexes of arene chromium-containing ligands have been isolated and then used as catalysts.[39a,42,46,48] A list that is believed to be comprehensive is given in Scheme 22, but two cases merit comment. First, **88** is

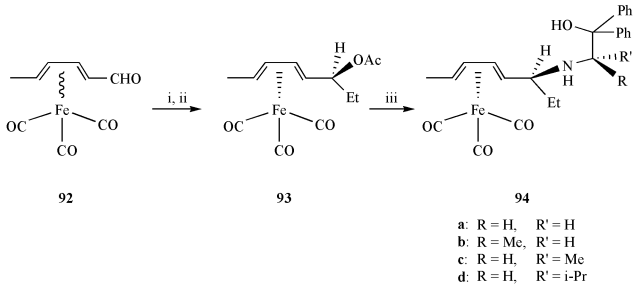


Scheme 22 Metal complexes isolated from the types of ligands in Scheme 19–21.

obviously not a chelate. However, furans can serve as π ligands, and binding interactions may occur at other stages of the catalytic cycle. The same considerations hold for the other types of heterocycles in ligand family **83** (Scheme 21). Second, all allylic alkylations in the study that reported the isolation of **91** were conducted with *in situ* generated palladium catalysts. It is the authors' assumption that **91**, which was independently prepared and crystallographically characterized, would also be a catalyst.

4.2

There are many other types of π ligands upon which metal-containing chiral chelating ligands might be based. However, to the authors' knowledge there is only one additional example that has been applied in enantioselective catalysis. In 2001, Takemoto described a butadiene iron tricarbonyl-based chelate ligand, the amino alcohol **94** shown in Scheme 23.[49a,b] The



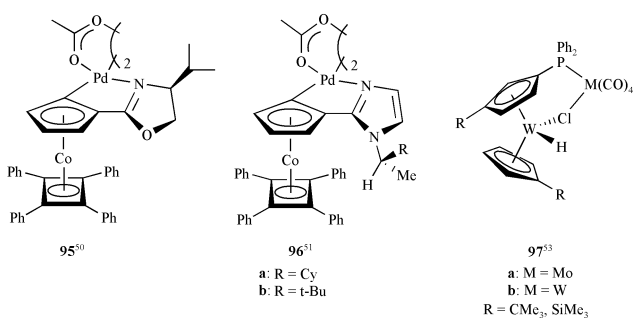
Scheme 23 Takemoto's iron chelate ligands. (i) Et_2Zn, (*S*)-(1-methylpyrrolidin-2-yl)diphenylmethanol, toluene, hexane; (ii) Ac_2O; (iii) $HOCPh_2CRR'NH_2$, CF_3CH_2OH, CH_2Cl_2.

synthesis began with the racemic sorbic aldehyde complex **92**, which contains a planar chirality element. Reaction with an optimized amount of Et_2Zn and a chiral amino alcohol effected a kinetic resolution. A model for the selectivity was proposed, and the resulting mixture of CHEtOH diastereomers could be separated chromatographically.[49a] The major diastereomer was acetylated to give **93** in >95% ee. Under suitable conditions, chiral amino alcohols displaced the acetoxy group with retention of configuration, giving **94a**–**d** in 80–61% yields.

The ligands **94** were then employed at 10 mol% loadings for the ethylation of benzaldehyde by Et_2Zn (Scheme 9). Complex **94c** gave alcohol **36** in the highest yield (67%) and enantioselectivity (84% ee). With 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde, enantioselectivities were 91% and 93% ee. The diene ligand in **94c** could be decomplexed, and the resulting amino alcohol was utilized for the ethylation of 3,4-dimethoxybenzaldehyde. The enantioselectivity decreased to 70% ee, showing the beneficial effect of the iron tricarbonyl moiety. A π–π stacking interaction involving the diene ligand and the arene ring was proposed.

5 Related topics and future direction

Not surprisingly, some metal-containing chelate ligands have been prepared in enantiomerically pure form, and even complexed to metals, but have not yet been applied in catalysis. Two such examples, besides those already given in Scheme 17, are the palladium/cobalt complexes **95** and **96** shown in Scheme 24.[50,51] These are obtained by elaboration of the carboxylic acid

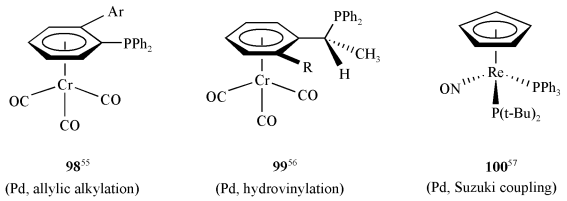


Scheme 24 Selected complexes not yet applied in asymmetric catalysis.

31 in Scheme 8. The final cyclopalladation steps are, within detection limits, completely diastereoselective due to the unfavorable interactions between the oxazoline or imidazole substituents and the η^4-tetraphenylcyclobutadiene ligands. Complexes **95** and **96** are undoubtedly viable catalyst precursors for a variety of carbon–carbon bond-forming reactions.

Metal-containing chiral chelate ligands have also been applied in catalytic reactions in which no new stereocenters are generated.[52] In a related vein, there are a variety of chiral racemic systems in the literature. One interesting family, different in many ways from the above examples, features the tungsten/molybdenum and tungsten/tungsten complexes **97a**,**b** (Scheme 24).[53] These are 'chiral-at-tungsten' and have an additional planar chirality element. Although organic halides are not frequently used as donor groups in chelating ligands, bridging metal halides as in **97** are often quite robust and are probably good choices for 'metal-in-backbone' chelate systems.

In most of the syntheses sketched above, chiral, enantiomerically pure metal-containing monodentate ligands were precursors to the target bidentate ligands. Furthermore, some processes thought to require chiral chelating phosphines for high levels of enantioselection are now known to proceed equally well with appropriate monophosphines.[54] Thus, the rapid development of catalysts based upon metal-containing chiral monodentate ligands can also be anticipated. Some of the few non-metallocene examples studied to date are summarized in Scheme 25.[55–57] The last ligand, **100**, has not yet been applied to a reaction that yields a new stereocenter.



Scheme 25 Selected monodentate ligands applied in catalysis.

Finally, it should also be emphasized that there is no intrinsic requirement that the ligand-based transition metal be 'innocent' with respect to the catalytic chemistry. Given the immense interest in heterobimetallic catalysts where both metals play active roles, it seems only a matter of time before these two themes merge.

6 Summary

The extraordinary structural diversity represented in the various bidentate ligands described above hardly needs to be emphasized. This broad architectural palette is complemented by unique electronic properties. Some of these were noted in the introduction, but additional physical-inorganic studies are needed to better define their full scope. All types of chirality elements can yield effective stereogenesis. Most researchers have emphasized systems with some type of planar chirality, whereas the authors' group has focused on metal-based stereocenters.

It is best appreciated in retrospect how modular many of the syntheses are. For example, in several cases a π ligand is elaborated with a series of chiral components and electrophiles, each of which can be individually varied. Many systems contain carbonyl ligands that can be easily substituted. In the case of the chiral rhenium compounds, phosphines and PR_2 donor groups other than PPh_3 and PPh_2 might be employed. Alternatively, shifting these chiral-at-metal species one group to the right (and two rows up) would give iron complexes of the type $[(\eta^5\text{-}C_5R_5)Fe(L)(L')(X)]^{n+}$, where L/L′ are both two-electron-donor ligands. Here, a very large library could easily be generated.

Transition-metal-containing ligands will often require syntheses that are a few steps longer than those of organic counterparts. There is an admitted trend in metal-catalyzed reactions towards cheap, easily synthesized, and/or commercially available ligands. However, particularly for enantioselective catalysis, it is becoming increasingly apparent that many key problems will not be solved without resorting to 'designer ligands'. Nature has required billions of years to evolve enzymes of sufficient structural intricacy for various enantioselective reactions. Therefore, it is not surprising that somewhat complex catalysts are required abiologically.

Lifetimes and activities are also very important considerations in catalysis. In most of the above studies, the investigators were primarily concerned with optimizing enantioselectivities, and did not define the turnover limit of their systems. The maximum reported value appears to be 6230 (catalyst precursor **60** in C=C hydrogenation),[22] which is not very high by contemporary standards. More importantly, however, none of the catalyst systems appear any less long-lived or active than counterparts without metal-containing ligands.

In conclusion, it can be confidently predicted that this somewhat overlooked area, non-metallocene metal templates for chiral chelating ligands, will see rapidly increasing attention in enantioselective catalysis. This reflects the pioneering efforts of the various research groups mentioned above, and is a natural consequence of the coming of age of organometallic and coordination compounds as synthetic building blocks.[58] Given the immense intrinsic diversity of such compounds, it will not be surprising if some ascend to the status of 'priviliged ligands'.[3b]

Acknowledgment

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