FEATURE ARTICLE

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Asymmetric catalysis using planar chiral arene chromium complexes

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Planar chiral (arene)$Cr(CO)_3$ complexes are emerging as a valuable and versatile class of ligand for asymmetric catalysis. Development of new approaches to their synthesis, including some which are modular and versatile, and some which provide access to highly attractive complexes such as systems containing elements of tetrahedral, planar and axial chirality, has opened up many new possibilities in this area in the last two or three years. Emerging applications are promising and early results in areas as diverse as asymmetric allylic alkylation, hydrovinylation and hydroamination point to the rich potential of these ligands in asymmetric catalysis.

Introduction

The reactivity changes that arise upon the complexation of an arene to the tricarbonylchromium fragment allow a variety of transformations to be carried out that are otherwise inaccessible.[1] The ease in which this fragment can be removed to release the modified arene or a reduced form makes (arene)$Cr(CO)_3$ complexes unique among stoichiometric organometallic reagents in synthesis. This versatility has been widely recognized and, as a result, they have been used as key building blocks in the synthesis of several natural products, especially targets with a highly substituted benzene or cyclohexane backbone.[2]

In contrast, applications of (arene)$Cr(CO)_3$ complexes in asymmetric catalysis have been rare. This is particularly the case if compared with ferrocene based systems which have already found several applications on an industrial scale.[3] This is somewhat intriguing considering the rich chemistry of (arene)$Cr(CO)_3$ complexes and the accessibility of many enantiomerically pure arene compounds. These complexes have, however, started to receive much more attention and, as a result, a marked increase in the number of papers reporting on the use of these complexes in asymmetric transformations has been observed in the last few years.

This Article provides an update on recent developments and advances in the synthesis and applications in asymmetric catalysis of planar chiral (arene)$Cr(CO)_3$ complexes, an expanding area of research that was first reviewed by Bolm and Muñiz.[4] It aims to stimulate further research into the design and synthesis of planar chiral ligands for asymmetric catalysis.

Definition and nomenclature

The only symmetry element present in a non-symmetrically 1,2- or 1,3-disubstituted arene ring is a mirror plane. Transformations that lead to a differentiation of the top and bottom half of this plane would result in a molecule without symmetry elements. This can be achieved, for instance, by complexation to a $Cr(CO)_3$ fragment (Fig. 1).

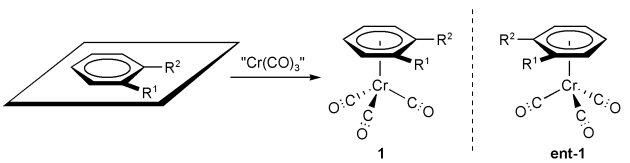

Fig. 1

As a consequence complex **1** cannot be superimposed on its mirror image ***ent*-1**; complexes such as **1** and ***ent*-1** are planar chiral. Two different approaches to the stereochemical assignment of such complexes have been described in the literature, namely the rules introduced by Schlögl[5] and the extended Cahn–Ingold–Prelog rules.[6] The latter will be applied throughout this Article and will be explained by means of complex **2**.

As shown in Fig. 2, all carbons of the coordinated arene ring are considered to be pseudo-tetrahedral with the chromium atom occupying the fourth corner of the tetrahedron. The priorities are assigned according to the CIP rules and as illustrated the tetrahedron is rotated so that the position with the

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Hasim Ibrahim graduated from Philipps-University of Marburg in 1999 with a Diploma in Chemistry. His studies included research under the supervision of Professor Thorsten Bach on model studies directed towards the synthesis of Wailupemycin A, and a semester as an ERASMUS exchange student at Imperial College, London where he worked with Dr G. Brent Young on mechanistic aspects of silicon-containing platinum complexes. In 1999, he joined Professor Gibson's group at King's College London to study for his Ph.D. His doctoral studies have included work on the development of a new and flexible route to planar chiral arene chromium complexes and the application of the complexes in asymmetric catalysis. In 2002 he will join the group of Professor Antonio Togni at ETH Zürich as a post-doctoral co-worker.

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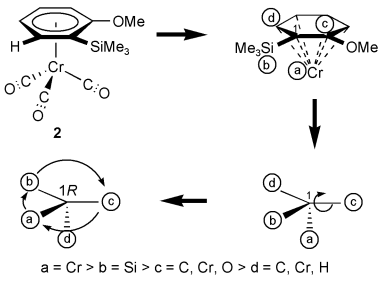


Fig. 2

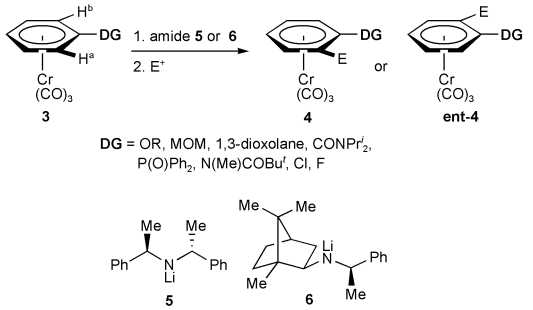
lowest priority is furthest from the observer; in the case illustrated this results in a clockwise screw and therefore a (1*R*) centre. Applying the same procedure for the carbon atom with the methoxy substituent results in a (2*S*) centre. All the carbon centres around the ring may be assigned in this manner and the full stereochemical assignment for complex **2** would therefore be (1*R*,2*S*,3*S*,4*S*,5*R*,6*S*)-**2**. It is, however, in most cases sufficient to classify only the stereogenic centre with the highest priority substituent. To further specify the element of chirality, or if other elements of chirality are present, a (*p*) for planar is put in front, or after, the assignment attributed to the planar chirality leaving complex **2** described as (1*pR*)-**2**. It should, however, be mentioned that the assignment according to Schlögl gives the opposite sign and would be written as (1*Sp*)-**2**.

Synthesis of planar chiral (arene)Cr(CO)$_3$ complexes

Non-racemic chiral base mediated synthesis

The desymmetrisation of prochiral (arene)Cr(CO)$_3$ complexes by directed enantioselective *ortho*-metalation[7] and subsequent quench with an electrophile (E^+) remains one of the most efficient methods for the generation of planar chiral chromium complexes.[8] This concept, which was originally developed independently by the groups of Kündig,[9] Schmalz,[10] Simpkins[11] and Uemura,[12] relies on the increased acidity of aromatic hydrogens of complexed arenes, which are about seven pK_a units more acidic then their uncomplexed counterparts. Provided that intermolecular equilibrium processes are absent,[13] complexes carrying heteroatom-containing substituents are readily deprotonated by chiral lithium amides to give stabilized non-racemic lithiated arenes that may be quenched with appropriate electrophiles to give enantiomerically enriched planar chiral (arene)Cr(CO)$_3$ complexes.

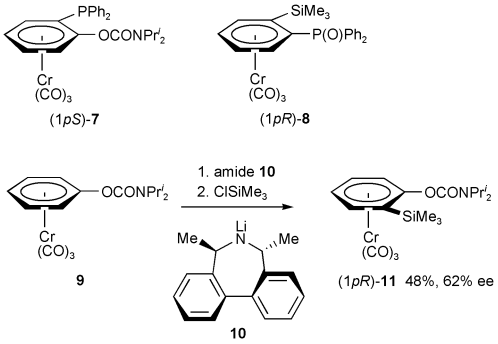
Application of this strategy has been so far dominated by amides **5** and **6**. They have been used to deprotonate the prochiral mono-substituted complexes **3**, executing a directing group (DG) assisted, kinetically controlled asymmetric lithiation to give after electrophilic quench a wide range of *ortho*-substituted complexes **4** or ***ent*-4** in moderate to high yields and enantioselectivities (Scheme 1).[8–13] In many cases, such as



Scheme 1

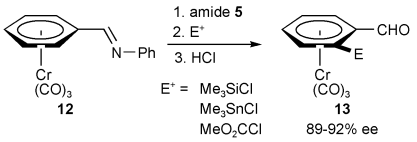
those that generate complexes (1*pS*)-**7**[14] and (1*pR*)-**8**,[15] a single recrystallisation of the product allowed the isolation of enantiomerically pure material.

Recent studies in this area include the application of several new amides and substrates. Kündig and co-workers reported the application of a cyclic analogue of **5** in the enantioselective lithiation/silylation of phenyl carbamate complex **9** (Scheme 2).



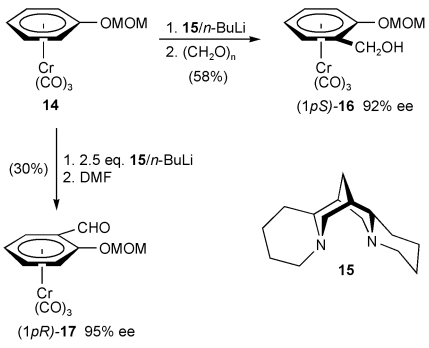
Scheme 2

Compared with **5**, which gave an enantiomeric excess of 39%, the axially chiral lithium-azepine **10** showed better stereocontrol and gave the corresponding silylated complex (1*pR*)-**11** in 62% ee.[16] In a subsequent study, this group examined the reactivity of constrained cyclic derivatives of amide **5** with five different chromium complexes. No increase in asymmetric induction was observed and amide **5** proved to be superior to all other amides tested, giving particularly high enantioselectivities with benzaldimine complex **12**. *Ortho*-substituted arylaldehyde complexes **13** (E = $SiMe_3$, $SnMe_3$, CO_2Me) were obtained after mild hydrolysis in good yields and up to 92% ee (Scheme 3).[17]



Scheme 3

A survey of enantioselective *ortho*-lithiation of some directing group substituted chromium complexes of type **3** with BuLi/(−)-sparteine was disclosed by Widdowson and co-workers. Unlike related studies by Snieckus on ferrocenecarboxamides,[18] the directing group of choice in this system turned out to be the OCH_2OMe (OMOM) group so that complex **14** could be selectively deprotonated using diamine **15** and *n*-BuLi to give after electrophilic quench with $(CH_2O)_n$ the planar chiral complex (1*pS*)-**16** in 58% yield and 92% ee (Scheme 4).[19] In a



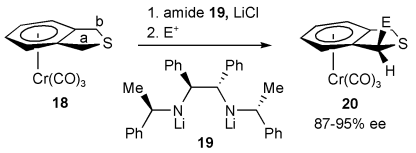
Scheme 4

subsequent study the same group showed that the opposite stereochemistry was also accessible *via* a dilithiation approach using 2.5 equivalents of diamine **15**/*n*-BuLi, thus avoiding the use of non-commercially available (+)-sparteine. Using this strategy, complex (1*pR*)-**17** was obtained in 95% ee and in 30%

yield (Scheme 4).[20] This *n*-BuLi/(−)-sparteine based desymmetrisation approach was successfully applied in the preparation of a key intermediate of an *ent*-actinoidinic acid synthesis.[21]

The concept of differentiating enantiotopic *ortho*-hydrogens by chiral non-racemic amides has been recently successfully extended to prochiral complexes bearing enantiotopic benzylic methylene and methyl groups.

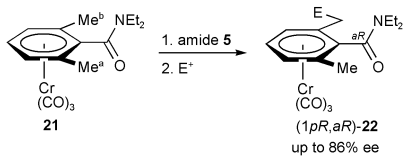
(1,3-Dihydroisobenzofuran)$Cr(CO)_3$ complex has been shown by Simpkins and co-workers to undergo highly enantioselective benzylic functionalisation facilitated by bis-amide **19**.[13] This group disclosed also the application of this methodology to the sulfur analogue, complex **18** (Scheme 5).



Scheme 5

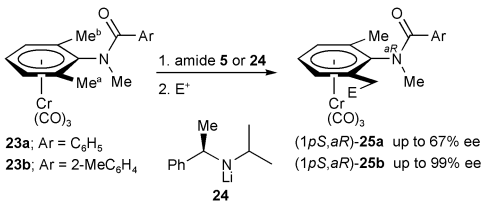
Here, the bis-amide **19** proved to be highly efficient in discriminating between the benzylic methylene groups and complexes **20** (E = $SiMe_3$, Me, Et, $PhCH_2$, C_3H_5 (allyl), CPh_2OH, 2-naphthylmethyl) could be obtained in high chemical yields and in up to 95% ee.[15,22] The enantiomeric excess of some complexes (E = $SiMe_3$, Me, CPh_2OH, 2-naphthylmethyl) could be further improved to >99% by recrystallisation. It is noteworthy that using amide **5** under identical conditions gave products in only about 5% ee. The methodology described above is particularly attractive because it allows the stereocontrolled introduction of two different elements of chirality in a single synthetic step.

Axially chiral benzamides and naphthamides, a relatively new class of non-biaryl atropisomers, are gaining importance as ligands in asymmetric catalysis.[23] Uemura recently introduced an elegant concept for the first direct synthesis of atropisomeric benzamides and anilides from prochiral precursors, involving a chiral amide mediated desymmetrisation of prochiral 2,6-dimethylsubstituted benzamide and anilide chromium complexes **21**, **23** and **26**.[24–26] In this study several amides were screened in order to assess their performance in the selection of one of the two benzylic methyl groups. Amide **5** performed best with prochiral benzamide complex **21** giving, after reaction with an electrophile (E^+ = MeI, $PhCH_2Br$, C_3H_5Br), the planar and axial chiral complexes (1*pR*,*aR*)-**22** in an enantiomeric excess of up to 86% and yields of up to 85% (Scheme 6). The *N*-

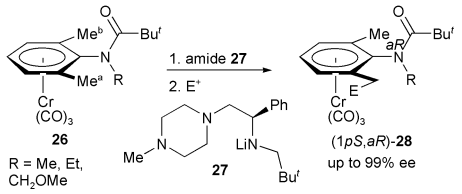


Scheme 6

benzoylaniline complexes **23** were also desymmetrised by chiral amides to give complexes **25**. In the case of complex **23a**, amide **24** performed better then amide **5** giving substituted complex **25a** in up to 67% ee (for E^+ = MeI). The moderate enantioselectivity achieved was attributed to the equilibrium between the *cis*- and *trans*-rotamers of the amide bond [MeN–C(O)Ar] in solution. Switching to the *ortho*-methyl-substituted system **23b** resulted in a shift to one predominant rotamer and as a consequence complex (1*pS*,*aR*)-**25b** was obtained in excellent enantioselectivity of up to 99% ee using amide **5** (Scheme 7).[24,26] The enantioselective lithiation was further examined with the *N*-pivaloyl-2,6-dimethylaniline complexes **26** (Scheme 8). Here, the piperazinyl substituted amide **27**



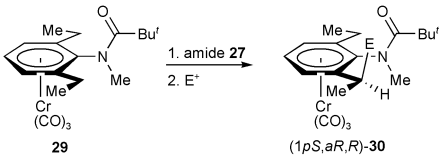
Scheme 7



Scheme 8

turned out to be the amide of choice leading to the axial chiral complex (1*pS*,*aR*)-**28** in excellent selectivity of up to 99% ee and in good yield.[25,26] Interestingly, amide **5** lithiated the Me^a group in preference to the Me^b group in complexes **23** and **26** whereas the benzamide complex **21** led to the opposite scenario. It is argued that the positioning of the carbonyl group towards or away from the $Cr(CO)_3$ rotor is influencing the outcome of the lithiation. In the case of complexes **23** and **26** the amide equilibrium (see above) forces the carbonyl group above the arene plane.[26]

As an extension to the work with complex **26**, the desymmetrisation of 2,6-diethylaniline complex **29** was investigated (Scheme 9). In a rather remarkable reaction it was shown



Scheme 9

that amide **27** could not only differentiate between the two benzylic ethyl groups but also between the pro-(*R*) and the pro-(*S*) hydrogens of the favoured benzylic methylene group resulting after electrophilic quench (E^+ = $PhCH_2Br$, C_3H_5Br) in the isolation of a single diastereoisomer (1*pS*,*aR*,*R*)-**30** with three different elements of chirality. The stereochemical outcome is explained by the deprotonation of the *pro*-(*R*) hydrogen in a sterically favoured conformation **29a** (Fig. 3).[26] It

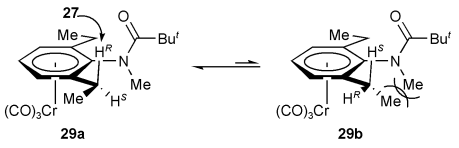


Fig. 3

is expected that the methodology described above will lead to many exciting applications in asymmetric catalysis and synthesis.

Synthesis based on chiral acetal and aminal auxiliaries

In recent years, non-racemic planar chiral chromium complexes of arylaldehydes have become valuable intermediates in a wide range of applications, including natural product synthesis,[27] reaction methodology[28] and asymmetric catalysis.[29]

Accordingly, several strategies have been described in the literature aiming at the efficient and stereocontrolled synthesis

of such complexes. In addition to the methods described above, three approaches, all relying on chiral auxiliaries as the source of chiral information, have been found to be particularly useful. The diastereoselective complexation of arenes bearing chiral acetals or aminals and the classical resolution of racemic planar chiral arylaldehyde chromium complexes are already established routes to planar chiral arylaldehyde complexes. A recent example in which both of these methods where employed is the synthesis of the planar chiral complex **36**, an intermediate in Ratni and Kündig's stereoselective synthesis of (−)-lasubine(l) **37** (Scheme 10).[30] Starting from the benzaldehyde **31**, both diastereoselective complexation of aminal **32**[31] and resolution of aldehyde complex **34** *via* the imine formation with L-valinol[32] led after hydrolysis of complexes **33** and **35** to the enantiomerically pure complex **36**.

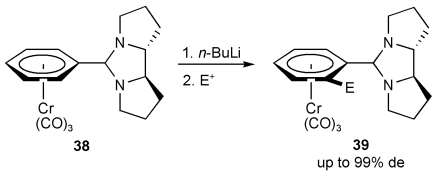
The third strategy, which has found widespread applications in recent years, provides direct access to planar chiral arylaldehyde complexes through the diastereoselective *ortho*-lithiation of chiral acetal and aminal complexes.

Recently, Alexakis and co-workers demonstrated that the benzaminal complex **38** derived from enantiopure (*R,R*)-2,2′-bipyrrolidine and $(PhCHO)Cr(CO)_3$ could undergo highly diastereoselective lithiation, so that after electrophilic quench [E^+ = MeI, PPh_2Cl, $(PhS)_2$] complex **39** was obtained in high yield and diastereoselectivity (Scheme 11). Employing Me_3SnCl and Me_3SiCl as electrophiles resulted in an *in situ* deaminalisation and the corresponding aldehyde complexes were isolated in an enantiomeric excess of 91%.[33]

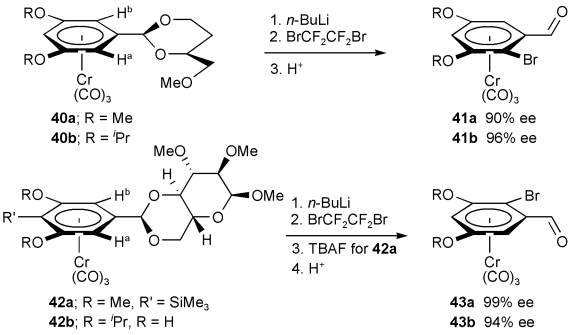
Chiral acetal complexes of benzaldehyde elaborated with D-glucose[34] or tartrate derivatives[35] have been reported to undergo highly selective *ortho*-lithiation; the former was reported to give rise to perfect selectivity in the deprotonation step.

Uemura and co-workers recently disclosed an extension of this strategy to 3,5-dialkoxy substituted benzaldehyde complexes **40** and **42** as part of a study aimed at the elaboration of planar chiral arene chromium complexes for use in the synthesis of axially chiral natural products.[36] In this study, which was directed towards the bromination of such substrates, (*S*)-1,2,4-butanetriol (an established auxiliary in ferrocene chemistry[37]) was introduced as an additional auxiliary capable of directing the lithiation to the H^a hydrogen of complex **40**, *i.e.* opposite to the lithiation observed in the D-glucose derived acetal complex **42** (Scheme 12). Thus, both enantiomers of the *ortho*-brominated 3,5-dialkoxybenzaldehyde complexes **41** and **43** could be obtained in high enantiomeric purity and in moderate to good overall chemical yield.[28c] In the case of complex **42a**, the absence of a TMS group at the *para*-position led exclusively to the *para*-brominated product as a result of chelation of the lithium by the two methoxy groups.

In a similar manner, an acetal complex derived from (*S*)-1,2,4-butanetriol and $(3,4,5\text{-}Me_3C_6H_2CHO)Cr(CO)_3$ was brominated to give benzaldehyde complex **44** in 90% ee which



Scheme 11



Scheme 12

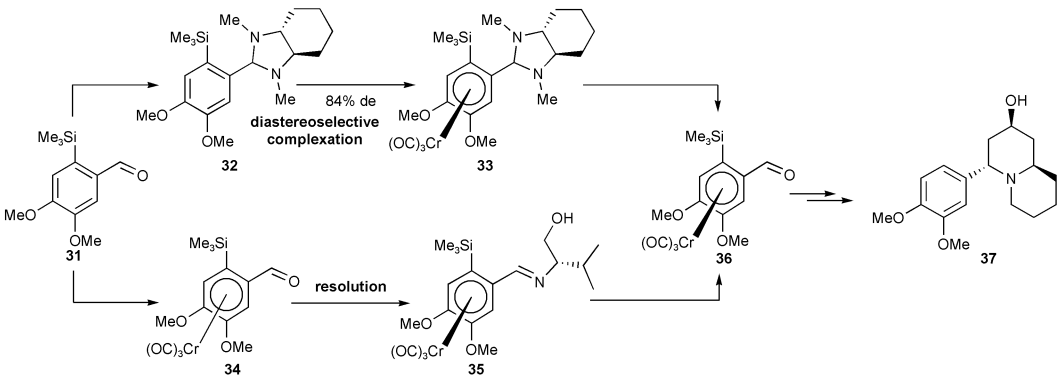
could be increased to >99% ee by one fractional recrystallisation.[36]

The brominated planar chiral benzaldehyde complexes described above were used in the stereoselective synthesis of axially chiral natural products such as (−)-steganone **45**,[36,38] korupensamine A[39] and the A–B ring system of vancomycin,[40] where they proved to be excellent coupling partners in diastereoselective Suzuki–Miyaura cross-couplings with arylboronic acids.

Intramolecular transfer of central chirality

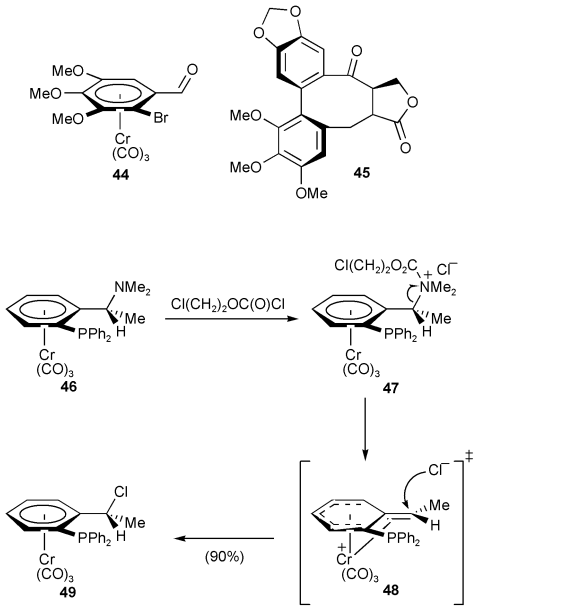
Creating planar chirality in $(arene)Cr(CO)_3$ complexes by utilizing existing tetrahedral chirality to direct *ortho*-lithiation remains one of the most efficient and versatile routes to planar chiral arene chromium complexes. As for ferrocene based systems, this strategy is particularly important in the design of $(arene)Cr(CO)_3$ based ligands for asymmetric catalysis. So far, much of the work in this area has focused on the elaboration of complexes derived from enantiopure α-methylbenzylamine by directed *ortho*-lithiation/electrophilic quench procedures.[41] This method, however, has its limitations when faced with the task of synthesizing complexes with heteroatom donors other than nitrogen or benzylic substituents other than methyl. A more flexible synthetic route avoiding such limitations would immensely enhance the scope of this strategy.

Progress towards varying the heteroatom at the benzylic position has been made by Salzer and co-workers.[42,43] Here, treating the planar chiral complex **46**, for example, with chloroethyl chloroformate allowed the stereocontrolled ex-



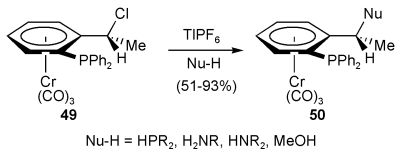
Scheme 10

change of the NMe_2 group with a chloro substituent. This reaction proceeds *via* a configurationally locked carbocation **48**, which is trapped by the generated chloride ion with overall retention of configuration (Scheme 13). The chloro substituent



Scheme 13

in complex **49** is more prone towards nucleophilic displacement than the amine of complex **46** and is readily replaced in the presence of $TlPF_6$ by P-, N- and O-nucleophiles to give the planar chiral complex **50** (Scheme 14).[44] All transformations

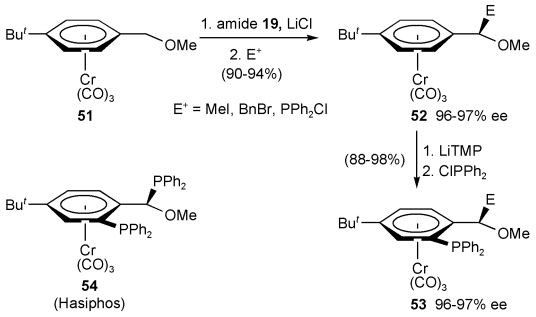


Scheme 14

shown are high yielding and proceed without loss of enantiomeric purity to give a variety of C_1-symmetrical bidentate ligands that are closely related in structure to the widely used ferrocenes containing planar and central chirality.[3]

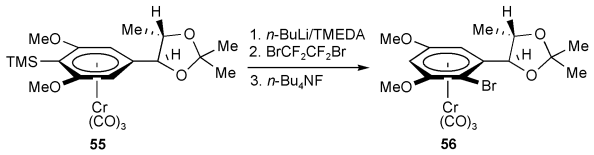
An approach towards varying the substituent at the benzylic position was reported recently by this laboratory, the basis of which is a sequence of two highly selective transformations starting from complex **51**. An enantioselective lithiation mediated by chiral bis-amide **19** followed by an electrophilic quench gave complex **52** in high enantiomeric purity. Reaction of **52** with LiTMP followed by electrophilic quench with PPh_2Cl resulted in a highly chemo- and diastereoselective OMe group directed *ortho*-lithation/electrophilic quench sequence to give complex **53** (Scheme 15).[45] Blocking the *para*-position with a *tert*-butyl group was crucial, in order to avoid substitution at the *meta*- and *para*-positions. In the course of this study, it was further demonstrated that the stabilized benzylic anion generated by amide **19** could be trapped not only by carbon electrophiles but also by phosphorus electrophiles. The phosphinated complex **52** was found to be configurationally stable and capable of undergoing a second phosphination at the *ortho*-position to give complex **54**.[46] This broadened the scope of this strategy still further, rendering it particularly attractive for the efficient and versatile synthesis of arene chromium based planar chiral ligands.

Uemura and co-workers presented another system in which an *ortho*-lithiation is directed by a chiral ether functionality. In



Scheme 15

this case complex **56** was required as an advanced intermediate in a stereoselective synthesis of *O*,*O*′-dimethylkorupensamine A.[36] As seen in Scheme 16 complex **55** was subjected to



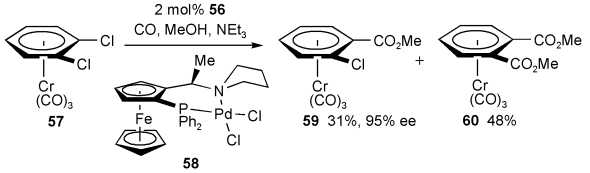
Scheme 16

lithiation with *n*-BuLi/TMEDA followed by the addition of $BrCF_2CF_2Br$ which gave the brominated product in 98% yield with perfect stereocontrol. Subsequent desilylation gave the desired complex **56**.

Desymmetrisation of $(1,2\text{-}Cl_2C_6H_4)Cr(CO)_3$

The desymmetrisation of prochiral (arene)$Cr(CO)_3$ complexes by a reaction that discriminates between two equivalent groups other than hydrogen provides a particularly attractive entry to planar chiral bifunctional chromium complexes. The dihalide $(1,2\text{-}Cl_2C_6H_4)Cr(CO)_3$ **57** has been at the centre of such efforts. Uemura *et al.* reported in 1994 that this complex underwent enantioselective Pd-catalysed cross coupling reactions, and that the best results were obtained with the Suzuki coupling using phenylboronic acid, which gave the coupling product in moderate yield and 69% ee.[47] The moderate yield was due to the formation of the bis-phenylated complex.

In a recent study Gotov and Schmalz disclosed an investigation into the enantioselective methoxycarbonylation of complex **57**.[48] Several chiral Pd-catalysts were allowed to react with **57** in a 2:1 mixture of MeOH and NEt_3 under 1 atm of CO pressure. Complex **58**, derived from the ferrocene (*pR*,*R*)-PPF-pyrrolidine, performed best and gave the desired product in 95% ee, albeit in a low yield of 31% (Scheme 17). The reaction



Scheme 17

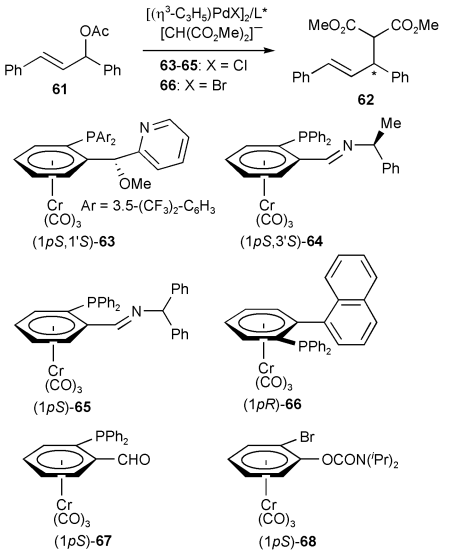
generated substantial amounts of the bis-methoxycarbonylated product **60**, the formation of which had a beneficial effect on the enantioselectivities obtained: the initial reaction is followed by a kinetic resolution so that the formation of **60** results in a higher enantiomeric excess for **59**. In spite of the low yield obtained here, this method is the only catalytic entry to potentially valuable bifunctional planar chiral chromium complexes such as **59** and it can be expected that further developments of this method will appear in the near future.

Applications in asymmetric catalysis

Asymmetric carbon–carbon bond forming reactions

In view of the importance of asymmetric versions of C–C bond forming reactions in organic synthesis and the successful application of planar chiral ferrocenes in such reactions, it was to be expected that the pioneering studies by Uemura and co-workers using planar chiral (arene)$Cr(CO)_3$ complexes as ligands[49] would give rise to further investigations in this area.

The allylic alkylation of racemic 1,3-diphenyl-1-acetoxyprop-2-ene **61** with malonate nucleophiles has played a central role in assessing the performance of a new ligand class. Several structurally diverse planar chiral arene chromium complexes have been employed successfully in this reaction (Scheme 18).



Scheme 18

The ligands employed vary from P,N-based bidentate ligands **63**–**65**, with and without central chirality, to the simple monodentate P-ligand **66**. Complexes **63**–**65** have the benzaldehyde complex **67** as a common precursor, and this can be obtained by methods described above. The synthesis of complex **66** was achieved by a Suzuki coupling of **68** with naphthylboronic acid followed by a S_NAr2 displacement of the carbamate group with lithium diphenylphosphide.[50]

The results obtained from these studies are summarized in Table 1. Evaluation of these results in terms of their performance/structure relationship reveals some interesting trends.

Table 1 Planar chiral arene chromium complexes in Pd-catalyzed allylic alkylation

Entry	Ligand	Conditions	Yield (%)	Ee (%)	Config.
1	(1*pS*,1′*S*)-**63**	A	95	89	*R*
2	(1*pS*,1′*R*)-**63**	A	98	89	*S*
3	(1*pS*,1′*R*)-**63**	B	83	93	*S*
4	(1*pS*,3′*S*)-**64**	C	68	82	*S*
5	(1*pS*,3′*R*)-**64**	C	74	85	*S*
6	(1*pS*)-**65**	C	93	> 98	*S*
7	(1*pR*)-**65**	C	85	95	*R*
8	(1*pR*)-**66**	A	89	92	*R*

A: $CH_2(CO_2Me)_2$, *N*,*O*-bis(trimethylsilyll)acetamide (BSA) , KOAc (cat), DCM; B: $CH_2(CO_2Me)_2$, NaH, DMF; C: $NaCH(CO_2Me)_2$, DMSO.

Ligand **63** was one of six structurally related P,N-ligands examined in a detailed study.[51] The effect of varying the absolute configuration as well as the substituent at the benzylic centre (OH *vs.* OMe) were investigated. Furthermore, the electronic nature of the phosphine donor was tuned by introducing aryl groups with one or two CF_3 groups. Using Trost's alkylation conditions (condition A in Table 1) in the presence of 1 mol% of an *in situ* prepared Pd-catalyst, the enantioselectivities obtained increased with the number of the CF_3 groups on the aryl phosphine and reached values of around 90% ee.

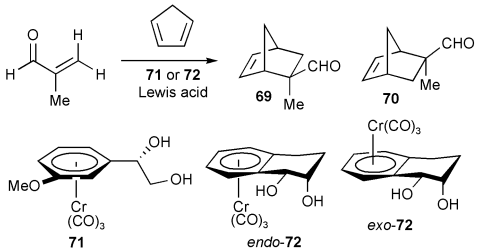
Perhaps more significant is the fact that the sense of the chiral induction seemed to depend only on the absolute configuration of the benzylic centre (Table 1, entries 1 and 2). Unfortunately, efforts to obtain the metal-free ligand failed so that no evaluation could be made about the steric and electronic effects that arose from the complexation, as well as the role of the additional element of planar chirality. The highest enantiomeric excess obtained in this study (93%) was with the ligand (1*pS*,1′*R*)-**63** employing a modified procedure B.

Somewhat surprising were the results obtained with complexes **64** and **65** (Table 1, entries 4–7).[29] In the case of ligand **64**, and in contrast to **63**, the absolute configuration of the tetrahedral centre attached to the imine moiety appeared to have virtually no influence on the stereochemistry of the alkylated product **62**. Epimers (1*pS*,3′*S*)-**64** and (1*pS*,3′*R*)-**64** gave the (*S*)-configuration with almost identical enantiomeric excesses so that it can be concluded that only the element of planar chirality is responsible for the chiral induction. This suggestion was supported by the observation that both planar chiral P,N-ligands (1*pS*)-**65** and (1*pR*)-**65** induced high enantioselectivities of opposite configurations (Table 1, entries 6 and 7). Ligand (1*pS*)-**65** produced the alkylated product **62** in an enantiomeric excess of > 98% ee, which is the highest value reported to date using a planar chiral arene complex ligand for this reaction.

The structurally simple planar chiral triphenylphosphine derivative ligand (1*pR*)-**66** proved also to be efficient in the Pd-catalysed allylic alkylation of **61**. The (*R*) configuration of the product was obtained in 92% ee employing 5 mol% of a precatalyst derived from [(η^3-C_3H_5)PdBr] and (1*pR*)-**66**.[50] Ligands **65** and **66** clearly demonstrate that planar chirality alone is a powerful tool in asymmetric allylic alkylation reactions.

Jones *et al.* have presented the first example of the use of a planar chiral arene chromium complex as a ligand for the asymmetric Diels–Alder reaction.[52] In a detailed study of 1,2-diol complexes, the Lewis acid catalysed cycloaddition reaction of 2-methacrolein and cyclopentadiene was investigated. The diol complexes were readily prepared by the diastereoselective complexation of the free diols with $Cr(CO)_6$ and the catalyst was generated *in situ* by the addition of conventional aluminum, boron or titanium Lewis acids to form the active metallacycles. In all cases, a catalyst loading of 20 mol% was required in order to achieve the highest enantiomeric excesses.

The catalyst derived from **71** and $EtAlCl_2$ (Scheme 19) gave the (*S*)-configured cycloadduct **70** in 99% yield and 61% ee (with an *exo*:*endo* ratio of 95:5). The corresponding *exo*-complex of **71** gave **70** in 53% ee, whereas the uncomplexed analogue of **71** resulted in an ee of 29%. An indication that the doubling in product ee is due to the added element of planar

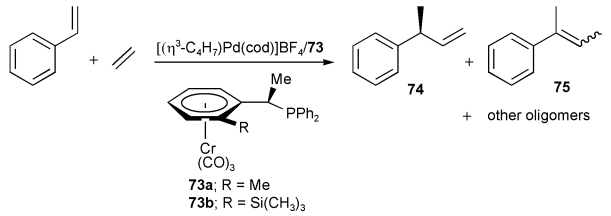


Scheme 19

chirality in **71** was obtained by examining an analogue of **71** lacking the OMe group, which gave an ee of 17%. A more rigid framework was obtained by the complexation of commercially available (1*R*,2*S*)-1,2,3,4-tetrahydro-1,2-naphthalenediol. The catalyst derived from complex *endo*-**72** and Et_2AlCl proved to be very selective in promoting the cycloaddition to the (*R*)-cycloadduct **69**. At −78 °C an enantiomeric excess of 90% was obtained which could be improved to >95% ee (with *exo* to *endo* ratio of 98:2) upon performing the reaction at −95 °C. The corresponding *exo*-complex, *exo*-**72**, resulted in an ee of 25% and the free diol produced **69** in 54% ee. These results suggest that additional interactions of the aluminum species with the metal carbonyl tripod could be responsible for the high levels of asymmetric induction obtained using *endo*-**72**. Interestingly, examining the five-membered ring analogue of **72**, which could be obtained in only 47% ee, together with $BH_2Br.Me_2S$ as Lewis acid, gave the product in a promising 62% ee. Mixed-ligand derivatives of complexes **71** and **72** were also investigated, but no increase in enantioselectivity was obtained.

Asymmetric hydrovinylation is a very useful C–C bond forming reaction. Of special interest is the reaction between vinyl arenes and ethene, as this provides a route to the widely used anti-inflammatory 2-arylpropanoic acids.

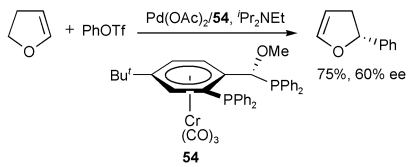
An enantioselective approach to the reaction of styrene with ethene was published recently using planar chiral chromium complex **73** as ligand (Scheme 20).[43] The catalyst used was



Scheme 20

generated *in situ* by ligand exchange with $[(\eta^3\text{-}C_4H_7)Pd(cod)]BF_4$. Ligand **73b** was superior to ligand **73a** in respect of activity, stability, chemo- and enantioselectivity. The catalyst derived from phosphine **73b** showed high conversions to the products **74** and **75** (~98%). The desired product **74** could be isolated within 0.5 h in 49% yield and in 92% ee. These results indicate that the planar chiral arene chromium ligand **73b** forms one of the best Pd-catalysts described so far for asymmetric hydrovinylation.

The first application of a planar chiral arene chromium complex in the asymmetric Heck reaction was conducted recently in our laboratory using the bench-mark system of 2,3-dihydrofuran and phenyl triflate. The palladium-catalyst generated *in situ* from (−)-Hasiphos **54** and $Pd(OAc)_2$ catalyzed at room temperature the formation of (*R*)-2-phenyl-2,3-dihydrofuran in 75% yield and 60% ee (Scheme 21).[53] The formation of the phenylated 2,5-isomer was not observed.

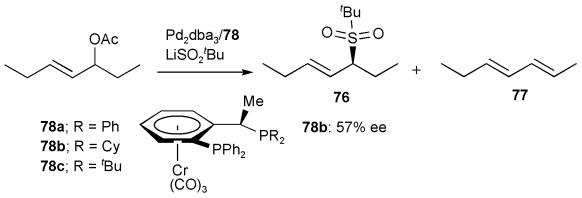


Scheme 21

Asymmetric carbon-heteroatom bond forming reactions

Planar chiral chromium complexes have been employed as ligands in the asymmetric Pd-catalyzed allylic sulfonation, Rh-catalyzed hydroboration and Ir-catalyzed hydroamination.

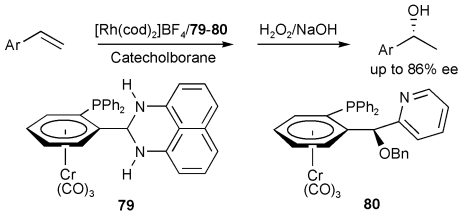
Complexes **78a–c** were used in the Pd-catalyzed substitution of racemic 3-acetoxyhept-4-ene with lithium *tert*-butylsulfonate.[44] The reaction proceeds to complete conversion in the presence of an *in situ* prepared catalyst but with differences in product selectivity (Scheme 22). Using ligand **78c**, complete



Scheme 22

chemoselectivity was observed and the sulfone **76** was obtained in quantitative yield and in 11% ee. The highest enantiomeric excess, however, was delivered by ligand **78b**, Daniphos, which gave a mixture of **76** and **77** in a 73:27 ratio with **76** having an enantiomeric excess of 57%. These results suggest that there is scope for improvement by tuning the electronic and steric nature of these ligands.

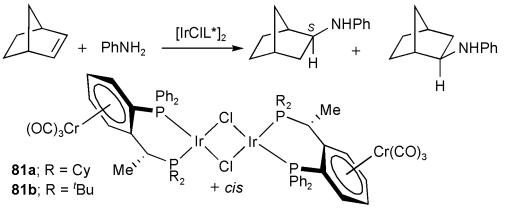
In the Rh-catalyzed asymmetric hydroboration of vinylarenes, two structurally different P,N-ligands were investigated (Scheme 23). Thus, reaction of catecholborane in the presence



Scheme 23

of 2 mol% of an *in situ* prepared Rh-catalyst, derived from **79** and $[Rh(cod)_2]BF_4$, with a series of vinylarenes at −15 °C resulted in the formation of the (*R*)-enantiomer of the corresponding *sec*-alcohols in good yields and in enantiomeric excesses ranging from 19% for 4-bromostyrene to 81% for 2,4-dimethylstyrene.[54] Complex **80** was also examined in the asymmetric hydroboration of vinylarenes, employing the same reagents and conditions but at 0 °C. Enantioselectivities of up to 86% in favour of the (*R*)-enantiomer were observed. In contrast with **79**, the ee values obtained were not sensitive to electronic effects exerted by the substituents on the styrene ring.[55]

Another reaction where planar chiral arene chromium complexes have been used is the intermolecular enantioselective hydroamination of norbornene, a process recently pioneered by Togni and co-workers.[56] This study compared the ferrocene ligands Josiphos and its *tert*-butyl derivative and the corresponding chromium complexes **78b** and **78c**. Reactions were performed in aniline at 60 °C for 96 h using 0.1 mol% of an inseparable *cis*/*trans* mixture of the dimeric iridium complexes **81a** and **81b** and their Josiphos analogues as catalysts (Scheme 24). Although, only small amounts of the



Scheme 24

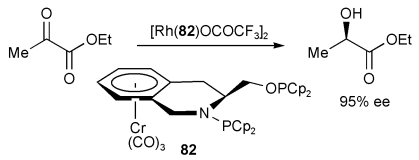
hydroamination product were isolated when **81** was employed, higher enantiomeric excess was obtained in comparison to the

Josiphos analogues. Complex **81a** gave the (*S*)-product in 70% ee, which represents the highest enantiomeric excess achieved in this study.[44]

Asymmetric hydrogenation

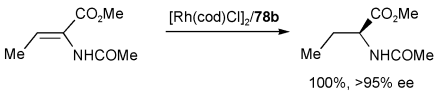
The application of planar chiral arene chromium complexes as ligands in asymmetric reductions with molecular hydrogen is becoming increasingly popular.

In particular, complexed aminophosphine-phosphinite (AMPP) ligands derived from 2-hydroxymethylindoline have proved to be very selective in the asymmetric hydrogenation of α-functionalised ketones.[57] In a related study, asymmetric hydrogenations using $Cr(CO)_3$ complexed AMPP ligands, derived from (*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, were investigated.[58] Here, the aminophosphine-phosphinite ligand **82** and its corresponding *endo*-complex, as well as the uncomplexed arene, were examined in the hydrogenation of five α-functionalised ketones. Catalysts were generated from the rhodium salts $[Rh(cod)Cl]_2$ and $[Rh(cod)(OCOCF_3)]_2$. Apart from ethyl phenylglyoxylate, enantioselectivities were between 95 and > 99% ee with no significant difference in the selectivity between **82** and its free arene. In the case of ethyl pyruvate, however, complexation resulted in an increase of 13% ee indicating that an additional steric effect might be operating (Scheme 25).



Scheme 25

In another application of diphosphine ligand **78**, the asymmetric hydrogenation of methyl acetamidoacrylate was investigated. Applying 0.2 mol% of an *in situ* prepared rhodium catalyst derived from Daniphos **78b** and $[(cod)RhCl]_2$, the (*S*)-enantiomer of the hydrogenated product was obtained quantitatively and in > 95% ee (Scheme 26). The hydrogenation of



Scheme 26

acetamidocinnamic acid with the same catalyst gave the hydrogenated product with a significantly lower enantioselectivity of 78%.[44] Selectivities obtained in this study were comparable to those obtained using a rhodium catalyst derived from the structurally related ferrocene Josiphos.

Conclusion

The recent developments in the synthesis and applications in asymmetric catalysis of planar chiral $(arene)Cr(CO)_3$ complexes described in this Article clearly demonstrate that these complexes are starting to emerge as a valuable and versatile class of compounds. Several efficient and versatile synthetic strategies are now available and provide access to a great variety of structures in optically pure form. These methods lead not only to complexes with planar chirality alone, but also to complexes with a combination of different elements of chirality. Moreover, the ease in which backbone modifications and electronic tuning can be carried out makes them particularly suited for applications in asymmetric catalysis. As a consequence of their ready availability, the past five years have seen many new and structurally diverse planar chiral arene chromium based ligands being tested successfully in various catalytic asymmetric transformations. Their potential in this area of research, however, is far from exhausted and it is expected that many new applications will appear in the near future.

Acknowledgement

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