Chiral N-heterocyclic carbenes as stereodirecting ligands in asymmetric catalysis

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In recent years, N-heterocyclic carbenes (*NHC*) have proved to be a versatile class of spectator ligands in homogeneous catalysis. Being robust anchoring functions for late transition metals, their ligand donor capacity and their molecular shape is readily modified by variation of the substituents at the N-atoms and the structure of the cyclic backbone. After the first attempts to use chiral *NHC* ligands in asymmetric catalysis in the late 1990's, which initially met with limited success, several novel structural concepts have emerged during the past two years which have led literally to an explosion of the field. With a significant number of highly selective chiral catalysts based on chiral *NHC*s having been reported very recently, several general trends in the design of new *NHC*-containing molecular catalysts for stereoselective transformations in organic synthesis emerge.

1 Introduction

The chemistry of N-heterocyclic carbenes (*NHC*) and, in particular their application as ligands, has developed rapidly since the first synthesis of an isolable carbene species of this type by Arduengo *et al.* in 1991.[1] Generally, complexes of the middle to late transition metals containing *NHC* ligands are kinetically robust, making these ligands potentially excellent spectator ligands in molecular catalysts. A range of very active catalysts has been synthesized in recent years, the most prominent examples being the second and third generation Grubbs olefin metathesis catalysts as well as several novel palladium C–C coupling catalysts for Suzuki–Miyaura and Heck-type reactions.

Vincent César was born in 1977 in Nancy, France. He was educated at the Ecole Normale Supérieure in Lyon and obtained an agrégation *in Physical Sciences (major in chemistry) in 2000. He then joined the group of Professor Gade at the Université Louis Pasteur (Strasbourg) and is currently a third year PhD student in the same group working on chiral oxazolinyl/N-heterocyclic carbene ligands for asymmetric catalysis. He will join the group of Professor Alois Fürstner at the Max Planck Institut für Kohlenforschung in Mülheim (Germany) as a postdoctoral associate later this year.*

Stéphane Bellemin-Laponnaz studied chemistry at Université Joseph Fourier (Grenoble) and Université Louis Pasteur (Strasbourg). In 1994 he joined the group of Professor John A. Osborn at Université Louis Pasteur to obtain his doctorate in 1998 studying the chemistry of rhenium oxo compounds. In 1999, he became a member of the group of Professor Gregory C. Fu (Massachusetts Institute of technology, Cambridge, MA) as a postdoctoral fellow working on kinetic resolution and phosphametallocene chemistry. Since October 2000, he has been a Chargé de recherche CNRS in the group of Professor Lutz H. Gade at the Université Louis Pasteur. His research centres on asymmetric catalysis with highly symmetric ligands and N-heterocyclic carbenes.

Lutz H. Gade is a professor of chemistry at the University of Heidelberg and a director of the Institute of Inorganic Chemistry. His research interests lie in the fields of coordination chemistry, organometallic chemistry and homogeneous catalysis. After completing his undergraduate studies at the University of Bonn and the Technical University of Munich, he went to Cambridge to work for his PhD with Jack Lewis. Having returned to Germany after completing his thesis in 1991, he joined the Chemistry Department at the University of Würzburg where he finished his habilitation in 1996 and where he subsequently worked as a lecturer. In 1998 he moved to Strasbourg to take up a position as a professor of chemistry and Head of the Laboratory of Organometallic Chemistry and Catalysis. In summer 2000 he was elected a member of the Institut Universitaire de France. He accepted a chair of inorganic chemistry at Heidelberg in 2003 while retaining an association with the Strasbourg faculty. Professor Gade is a Fellow of the Royal Society of Chemistry.

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A logical extension of this development is the application of these ligands in stereoselective catalysis. In general, ligand design in asymmetric catalysis is guided by several simple concepts and principles. For instance, the design of chiral catalysts is frequently based on C_2-symmetry in order to reduce the number of diastereomeric intermediates and transition states which play a role in the catalytic cycle.[2] This approach has been vindicated by the successful development of several large families of ("privileged") chiral ligands which nowadays belong to the basic "tool kit" of asymmetric catalysis, such as chiral diphosphines, salen derivatives and bisoxazolines.[3] These privileged families of ligands possess characteristic properties which lead to the induction of high stereoselectivities in their catalytic reactions. The identification of the key structural elements, which induce high enantioselectivities, will thus lie at the root of a successful design of novel stereoselecting ligands based on *NHC* units.

The electronic donor properties of *NHC* ligands are similar to those of phosphines which is why they are frequently regarded as their functional analogues. On the other hand, their stereochemical "topography" is distinctly different from that of diarylphosphine units they aim to replace. N-heterocyclic carbene units will not create an "edge-to-face" arrangement of their aryl substituents, a structural feature common to many chiral diphosphines, such as the derivatives of Diop, Binap, Josiphos, Chiraphos and others. Results obtained in asymmetric catalysis, using chiral phosphine ligands, are therefore not directly transferable to the respective *NHC*-analogues. For the latter we will thus have to determine the characteristic stereodirecting structural elements which distinguish them from the established phosphine based ligand systems.

The quest for novel chiral carbene ligands for asymmetric catalysis began in 1995 with the pioneering work of Enders and Herrmann. However, it was not until 2001 that the first truly efficient chiral catalyst containing an *NHC* unit was published by Burgess *et al.* Currently, the field of stereoselective catalysis based on N-heterocyclic carbenes is in the process of rapid expansion and our understanding of the key factors for successful ligand design is still incomplete. A first overview of the field of chiral *NHC* ligands in catalysis by Burgess *et al.* covered the literature until the end of 2002.[4] Since then the field has grown dramatically, and we are now able to define a number of distinct classes of such ligands which are characterized by the position of the chiral structural motif in relation to the donor unit. Six large families of chiral N-heterocyclic carbine ligands have thus recently emerged:

1. *NHCs* with N-substituents containing centres of chirality;
2. *NHC* ligands containing chiral elements within the N-heterocycle;
3. *NHC* ligands containing an element of axial chirality;
4. Carbenes containing an element of planar chirality;
5. Carbenes joined by a chiral *trans*-cyclohexanediamine ligand backbone;
6. Carbenes incorporating oxazoline units.

2 *NHCs* with N-substituents containing centres of chirality

The first strategy which has been pursued in the design of chiral *NHCs* was based on the introduction of N-substituents containing a chiral centre located on the C-atoms adjacent to the nitrogen atoms in 1 and 3 positions within the ring. Their general formula and structure are as represented in Fig. 1.
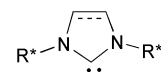
Fig. 1

The first chiral *NHCs* of this type were developed by Herrmann and Enders in 1996. Herrmann's group[5] synthesized a symmetric imidazolium salt **1** (as carbine precursor), starting from an enantiopure chiral amine which was readily converted to the heterocycle using a multi-component reaction previously developed by Arduengo.[6] After coordination to a rhodium (I) complex precursor (Scheme 1), this ligand was tested in the hydrosilylation of acetophenone.

The new catalysts displayed good activity but low stereoselectivity for this transformation (32% ee) (Scheme 2, eqn. 1).

Enders and coworkers developed a nonsymmetrical triazolinylidene ligand containing a single chiral N-substituent, its triazolium precursor being depicted in Fig. 2.[7]

The synthesis of the corresponding rhodium(I) complex led
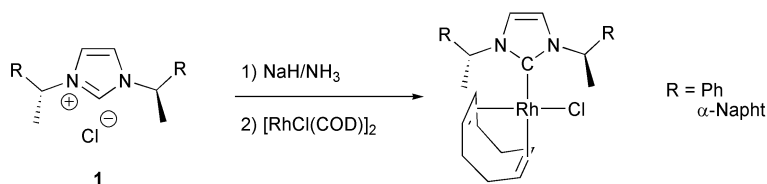
Scheme 1 Synthesis of a rhodium(I) complex from chiral imidazolium **1**.
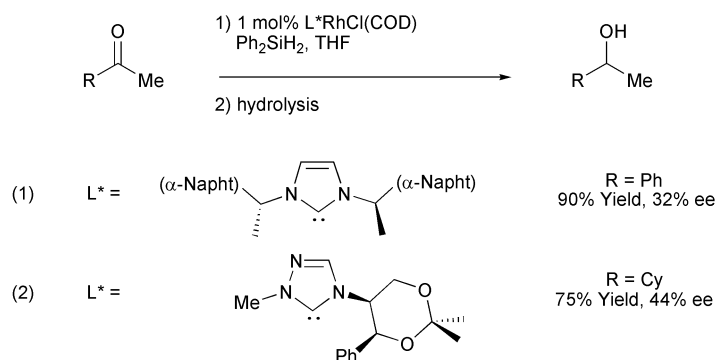
Scheme 2 Asymmetric hydrosilylation using the first chiral *NHCs*.
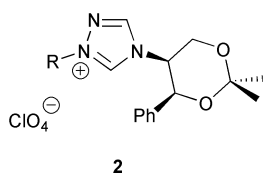
Fig. 2 The chiral triazolium perchlorate salt synthesized in Enders' group.

to the generation of a mixture of diastereomers. This is a consequence of the non-symmetrical carbene ligand which is disposed orthogonally to the square coordination plane of the rhodium complex (Scheme 3). This mixture of complexes has also been tested in the hydrosilylation of methyl ketones giving low to moderate enantioselectivities (ee up to 44%) (Scheme 2, eqn. 2).[8]

In general, the chiral induction of these ligands remained low which is probably due to the rapid internal rotation of the chiral substituents around the C–N axis and the flexibility of the substituents. This leaves the active chiral space at the metal centre relatively ill-defined.

The triazolium salt **2** has also been used as a purely organic catalyst.[9] It is an active catalyst for asymmetric benzoin type condensation reactions yielding the reaction products with enantiomeric excesses of 20 to 82% which at the time marked a major advance with respect to the previously established catalysts (Scheme 4, eqn. 1).[10] It was also found to catalyze the asymmetric intramolecular Stetter reaction with moderate to good enantioselectivity (41–72% ee) (Scheme 4, eqn. 2).[11]

These enantiomeric excesses were improved with a new type of triazolinylidene with a bicyclic molecular structure that was developed in Leeper's group (Fig. 3).[12] The internal rotation around the N–C(substituent) axis is blocked in this bicyclic molecule with a sterically demanding substituent having the same orientation as the ligating atom thus potentially favouring a high asymmetric induction. These carbenes were tested in the benzoin condensation reaction mentioned above (Scheme 4, eqn. 1) pushing the ee's of the products to values of up to 82%. Very recently, related ligand systems have been employed by Rovis et al. (Fig. 3) for the Stetter reaction, giving the coupling products in very high enantioselectivity.[13]

An important contribution to the design of *NHC* ligands with N-substituents containing centres of chirality was made by Hartwig's group in 2001. The imidazolinium salts **3** and **4** were synthesized from (−)-isopinocampheylamine and (+)-bornyl-amine, respectively and were tested as stereodirecting ligands in the palladium-catalyzed asymmetric oxindole reaction.[14] The key step in this reaction is an intramolecular α-arylation of a ketone catalyzed by palladium which the same group had previously reported.[15] These ligands gave superior results to those obtained with the established chiral phosphines, such as Binap, Duphos, Phox and Josiphos, even though there remains potential for improvement of the stereoselectivity of this catalytic reaction (ee's of up to 76% were obtained with **3** and **4**) (Scheme 5).

Finally, Chung et al. reported the enantioselective synthesis of chiral *NHC*s, such as **5**, using a chiral ferrocenyl derivative (Scheme 6).[16] The nucleophilic substitution of the hydroxy function by an imidazole in an acidic medium gives the imidazolium salt with retention of the configuration at the chiral C-atom.

The type **5** carbenes have been used as ligands in the rhodium(I) and iridium(I) catalyzed transfer hydrogenation of
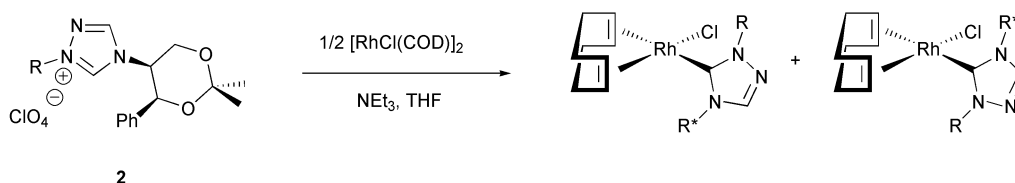
Scheme 3 Complexation of the carbene ligand **2** to a rhodium(I) centre.
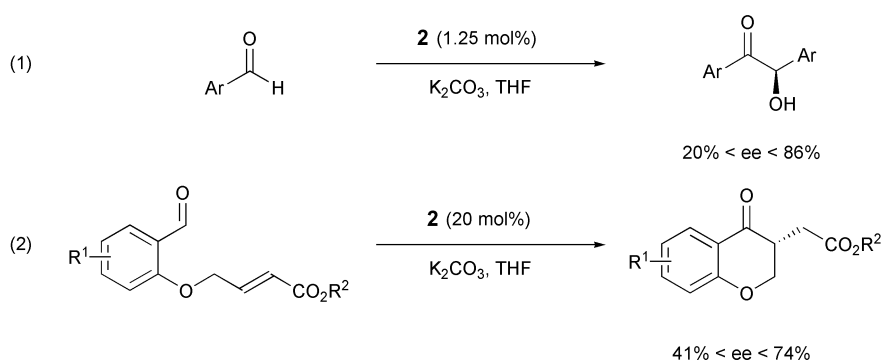
Scheme 4 Application of **2** in the asymmetric organocatalysis.
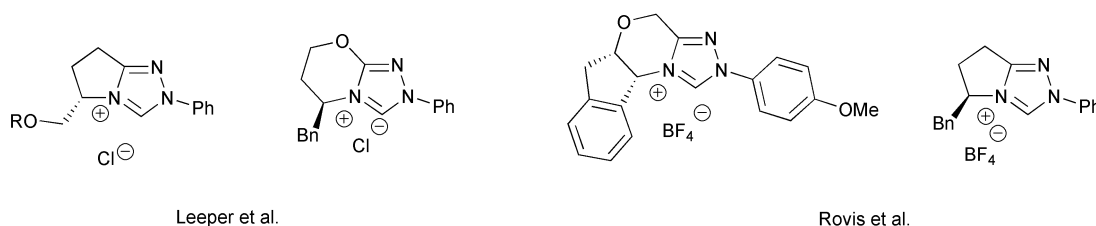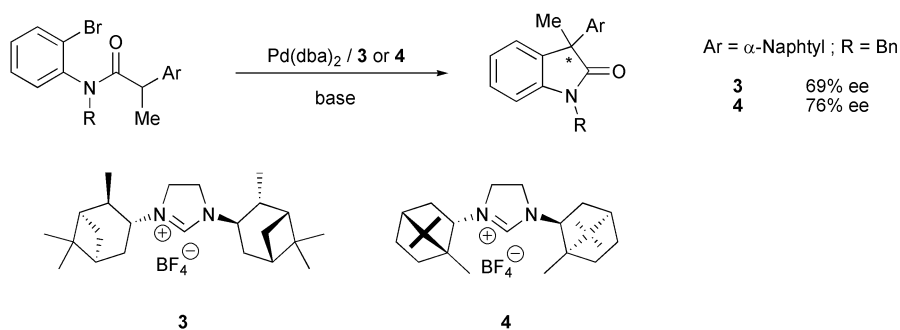

Leeper et al.   Rovis et al.

Fig. 3 Triazolium salts developed by Leeper and Rovis.

Scheme 5 Asymmetric catalytic oxindole synthesis.

ketones displaying low to moderate stereoselectivity in the conversion of most substrates. Somewhat higher enantioselectivities were obtained with complex **7b** containing the chiral C_2-symmetric carbene derived from **6** (Scheme 7).

In conclusion, the *NHC* ligands possessing chiral N-substituents, which have been studied to date, may be efficient as stereodirecting ligands if the N-substituents are either sterically very demanding or locked in fixed conformations. Chiral induction is greater the closer the element of chirality is located with respect to the N-substituent. However, this type of chiral N-heterocyclic carbenes generally gives moderate results in asymmetric catalysis and a truly efficient combination of chiral ligand and catalytic reaction remains to be found.

3 NHC ligands containing chiral elements within the N-heterocycle

Imidazolinylidenes contain sp³-carbon atoms in the 4- and 5-positions of the heterocycle and thus provide the possibility of a second strategy for the generation of chiral *NHC*s. By an appropriate substitution (R) at the 4- and 5-positions two (homo)chiral centres may be obtained and the chiral information then transmitted to the active space at the metal centre of a catalyst by means of the two N-substituents R′ (Fig. 4).

The imidazolinium salts, which are being used as ligand precursors, are generally prepared from C_2-symmetric chiral vicinal diamines[17] as shown in Scheme 8.[18]
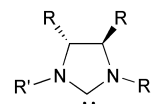

Fig. 4 Schematic representation of an imidazolinylidene ligand.

The coordination of *NHC* ligands greatly enhances the rate of the copper-catalyzed asymmetric addition of diethylzinc to cyclohexenone.[19] Employing imidazolinylidene ligands with chiral centres in the heterocycle, the alkylation of α-enones[20] was systematically studied by the groups of Mangeney and Alexakis.[21,22] A summary of the results obtained is presented in Table 1.

The generation and coordination of the imidazolinylidenes to the Cu[I] centres was preferentially achieved by transmetallation using silver(I) carbene complexes as ligand transfer reagents.[23] This method has the advantage of involving reagents which are air and moisture stable and thus lend themselves to catalyst screening.

Whereas two methyl N-substituents are inefficient in transmitting the chiral information encoded at the rear side of the heterocyclic ligand (Entry 1 in Table 1), the stereoselectivity is improved by the introduction of N-benzyl substituents (Entry 3). The steric repulsion between the *tert*-butyl and benzyl groups leads to a C_2 symmetric arrangement of the latter with respect to the carbene donor function as is apparent in the molecular structure determined by X-ray
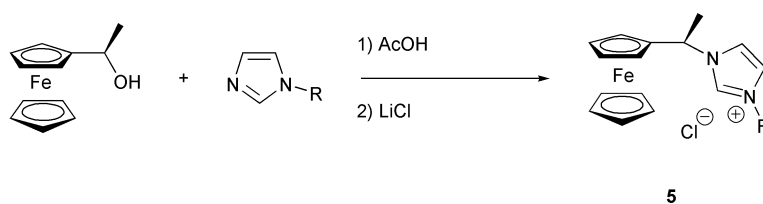
Scheme 6 Synthesis of carbene ligands with 1-(ferrocenyl)ethyl N-substituents.

	yield (%)	ee (%)
[**6**RhCl(COD)] (**7a**)	> 99	6.7 (*R*)
[**6**IrCl(COD)] (**7b**)	> 99	52.6 (*S*)
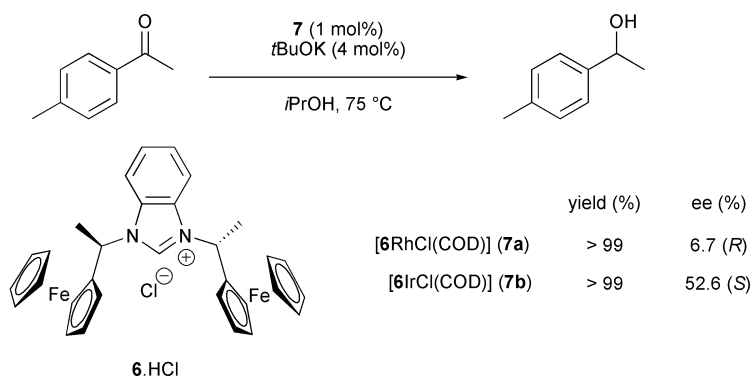
Scheme 7 Transfer hydrogenation of aryl(alkyl)ketones catalyzed by **7**.
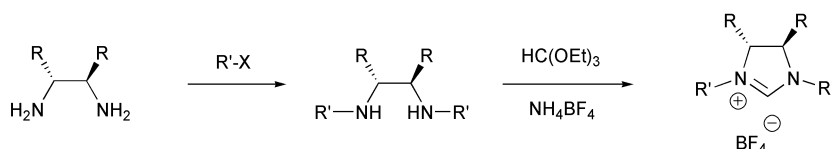
Scheme 8 General synthesis of imidazolinium salts.

diffraction for the silver(ı) complex **10** (Fig. 5).[23] In this way the chirality in the heterocycle is transmitted towards the reaction centre.

Introduction of methoxy groups in the meta-position of the phenyl rings of the benzyl substituents slightly increases the selectivity of the catalyst (Entry 4) and selectivities of up to 93% ee were obtained for some of the cyclic substrates under optimized conditions. However, the selectivity of the 1,4-addition to acyclic α-enones remains modest with these ligands (ee's ranging from 40 to 50%).

The *NHC*s with N-substituents containing centres of chirality of the type discussed in section 1 only induce moderate stereoselectivity in this catalytic process (ee < 62%). The combination of chiral N-substituents with chiral N-heterocycles has also been studied, as is shown in entry 2 of Table 1, however, it is too early to draw general conclusions concerning matching and mismatching effects.[24]

Chiral imidazolinylidenes with N-aryl substituents have been employed by Grubbs and coworkers in the stereoselective ring closing metathesis of olefins.[25] The introduction of the aryl groups as N-substituents was achieved by a palladium catalysed Buchwald–Hartwig coupling (Scheme 9).[26]

Olefin metathesis does not generate stereogenic centres, however, the reaction may be employed in the desymmetrization of prochiral (poly)olefins or the kinetic resolution of
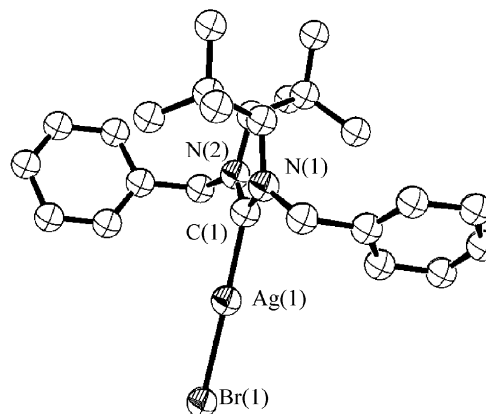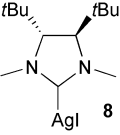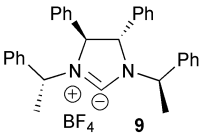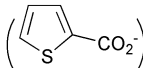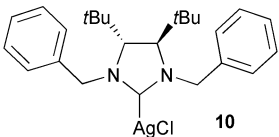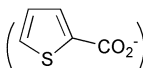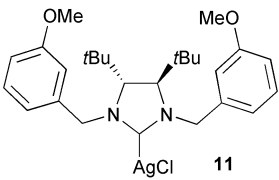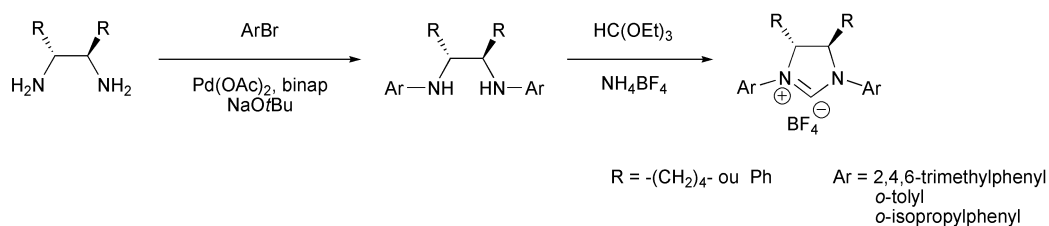

Fig. 5 Molecular structure of **10**.

racemates. In the example depicted in Scheme 10, a trialkene is being desymmetrized, and the preference for the cyclization reaction with one of the two symmetry-equivalent C=C double bonds leads to the enantioselective formation of the reaction product, a chiral dihydrofuran.

The following principal conclusions could be drawn from this study:

Table 1 1,4-addition of diethylzinc to cyclohexenone catalyzed by imidazolinylidene–copper complexes

Entry	Copper source	Ligand	Solvent	Temp.	Ee (%)
1	Cu(OTf)$_2$	**8**	toluene	0 °C	23
2	Cu(OTf)$_2$	**9**	CH$_2$Cl$_2$	−78 °C	50
3	Cu(thiophene-CO$_2^-$)	**10**	Et$_2$O	−78 °C	58
4	Cu(thiophene-CO$_2^-$)	**11**	Et$_2$O	−78 °C	69

Scheme 9 Synthesis of N-arylated chiral imidazolinium salts.

R = -(CH₂)₄- ou Ph Ar = 2,4,6-trimethylphenyl
o-tolyl
o-isopropylphenyl

	Ar	ee
12	Mes	15 %
13	o-Tol	23 %
14	o-iPrPh	23 %
14 (+NaI)	o-iPrPh	39%
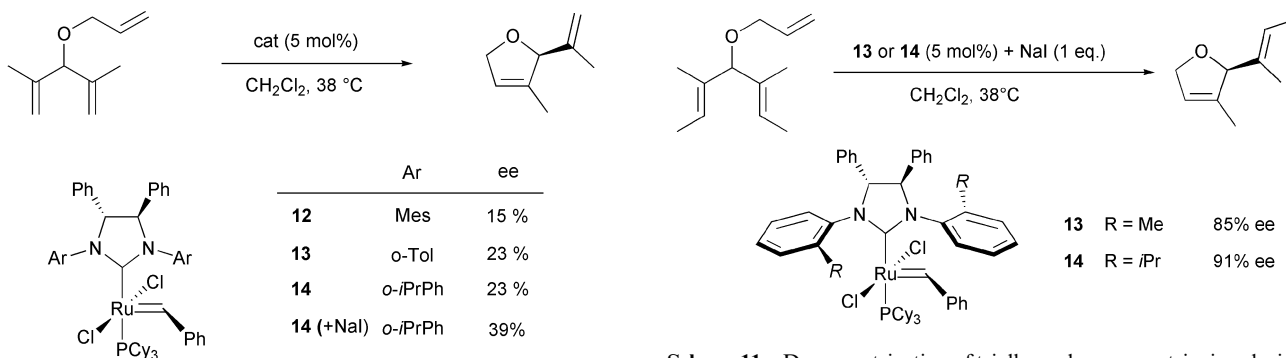
Scheme 10 Stereoselective ring closing olefin metathesis by a desymmetrization strategy.

13	R = Me	85% ee
14	R = iPr	91% ee

Scheme 11 Desymmetrization of trialkenes by asymmetric ring closing metathesis.

1. The stereodirecting ligands containing the 1,2-diphenyl-ethylenediamine backbone gives higher enantioselectivities than the ones with the 1,2-diaminocyclohexane skeleton.

2. *Ortho*-monosubstituted *N*-aryl substituents in the carbene ligands lead to greater selectivity than, for instance, the more symmetrical mesityl-substituted derivative.

The rationale offered for these observations is based on the hypothesis that steric repulsion between the backbone phenyl groups and the *o*-aryl substituents stabilizes their mutual *anti*-conformation which in turn permits a more efficient transmission of the chiral information to the active site of the catalyst.

The application of complexes **13** and **14** in the desymmetrization of triolefins has yielded the ring closing metathesis products in high enantioselectivity, and upon replacement of the *o*-methyl groups by the bulkier isopropyl substituents in **14** the selectivity was even further increased (Scheme 11).
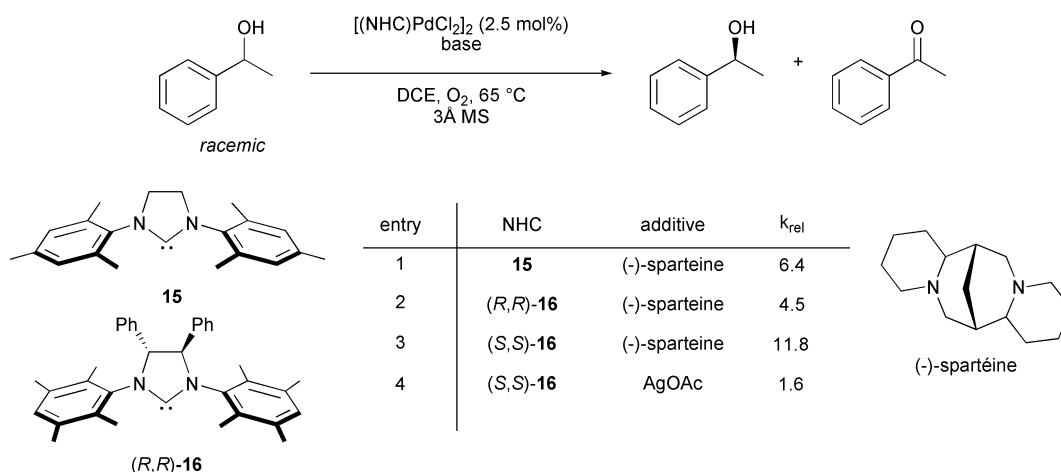
Chiral *N*-arylated imidazolinylidene ligands have been employed in the palladium(II) catalyzed aerobic oxidation of secondary alcohols to the corresponding ketones.[27] The chiral variant of this reaction, which does not generate a new element of chirality, is again based on the kinetic resolution of racemic

mixtures. The active catalyst is formed *in situ* by a combination of two precursors, a dinuclear *NHC*-palladium(II) complex and an achiral (acetate) or chiral base ((−)-sparteine) (Scheme 12).

It had previously been shown that the (−)-sparteine may play a dual role in this catalytic process, that of a chiral ligand and a chiral base.[28] However, in the presence of the *NHC* ligand the ligated (−)-sparteine is being substituted and thus only acts as chiral base. Comparison of the results obtained with ligand **16** with those observed with **15** suggest that the association of the two enantiomers with the chiral base leads to a synergic chiral induction for the (*S*,*S*) enantiomer (Scheme 12, Entry 3) whereas the combination with the (*R*,*R*) enantiomer is unfavourable (Entry 2). This nicely illustrates the concept of match and mismatch for stereodirecting elements in chiral catalysts.[24] The fact that a non-chiral base such as acetate gives rise to a very low selectivity factor in the kinetic resolution indicates the importance of the chiral base (−)-sparteine for the efficiency of the catalytic transformation.

A novel chiral bidentate imidazolinylidene ligand (**17**) has recently been developed in Helmchen's group.[29] It is related to Grubbs' imidazolinylidenes by replacement of one of the two *N*-aryl groups by a 2-diphenylphosphinonaphth-1-yl unit

| entry	NHC	additive	k_{rel}
1	**15**	(-)-sparteine	6.4
2	(*R*,*R*)-**16**	(-)-sparteine	4.5
3	(*S*,*S*)-**16**	(-)-sparteine	11.8
4	(*S*,*S*)-**16**	AgOAc	1.6

Scheme 12 Kinetic resolution of secondary alcohols by aerobic oxidation.
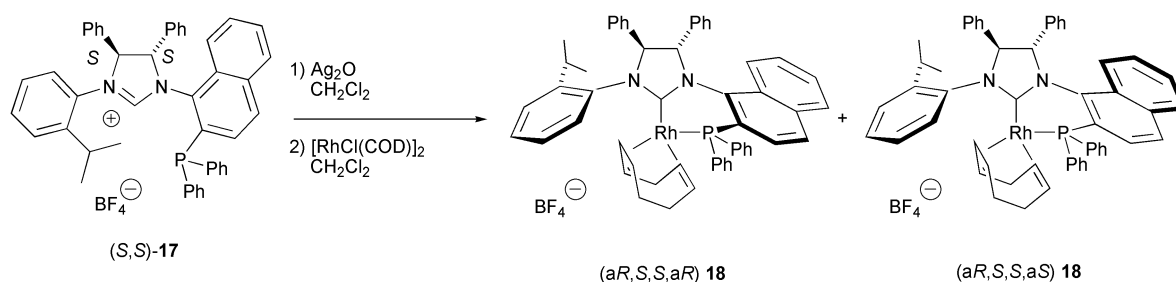
Scheme 13　Formation of diastereomers complexes **18**.

(Scheme 13). The coupling of the naphthylphosphine unit with the N-heterocyclic carbene gives two atropisomers which are configurationally stable at ambient temperature and thus possess a chiral axis. Complexation to rhodium(I) was achieved by transmetallation with the silver(I) complex[30] and yields two diastereomeric atropisomers (**18**) in a ratio of 1 : 2 (Scheme 13).

This mixture of diastereomers of **18** was tested in the catalytic hydrogenation of dimethylitaconate and methyl Z-acetamidoacrylate (Scheme 14). The catalytic activity of
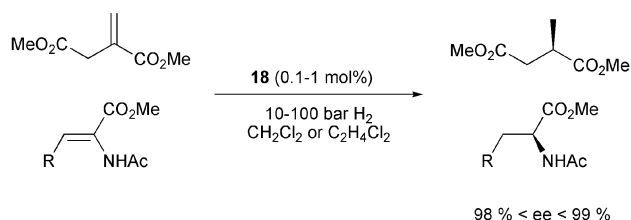
Scheme 14　Asymmetric hydrogenation with the mixture of diastereomers of **18**.

these complexes is relatively high although lower than that of some of the previously studied purely phosphine based systems, while the enantioselectivity proved to be excellent (ee's between 98 and 99% under optimized conditions).

Finally, Fürstner *et al.* published the synthesis of the enantiopure chiral palladium(II) complex **19**, in which the *NHC*, contains a *trans*-1,2-cyclohexanediamine backbone (Scheme 15), although no application of this system in catalysis has been reported to date.[31]

In conclusion, while the first chiral imidazolinylidenes tested in asymmetric catalysis only gave a moderate chiral induction, more recent results have clearly indicated that the encoding of

chiral information in the backbone of the heterocycle may give rise to highly efficient stereodirecting ligands. The potential versatility of this approach is apparent in a recent contribution reporting the synthesis of nonsymmetrical imidazolinylidenes by the reaction sequence displayed in Scheme 16.[32] While the products have only been isolated as racemic mixtures, this concept may lead to novel chiral *NHC* ligands.

## 4　*NHC* ligands containing an element of axial chirality

The 1,1′-binaphthyl unit is one of the most widely used structural motifs in ligand design for asymmetric catalysis. First introduced by Noyori, enantiomerically pure ligands derived from it give rise to some of the most selective catalysts developed to date.[33] The most widely used examples of this family of ligands are BINAP[34] and BINOL[35] which are depicted in Fig. 6. Their chirality is based on the blocked rotation around the C–C axis linking the two naphthyl units giving configurationally stable atropoisomers.[36]

In 2000, Rajanbabu *et al.* published the synthesis and coordination chemistry of the first chiral *NHC* containing a 1,1′-binaphthyl unit as chiral element (Scheme 17).[37] It contains two imidazolium rings linked to the 1,1′-binaphthyl backbone in the 2 and 2′ positions through methylene bridges. This linkage was achieved by nucleophilic substitution and the imidazolium salts subsequently generated in an N-quaternisation step with methyl iodide.

The coordination chemistry of this ligand depends on the metal involved and the method of the *in situ* carbene formation. Whereas **20** is exclusively *trans* coordinating at nickel, regardless of the manner in which the carbene is generated, the same configuration is observed for the corresponding
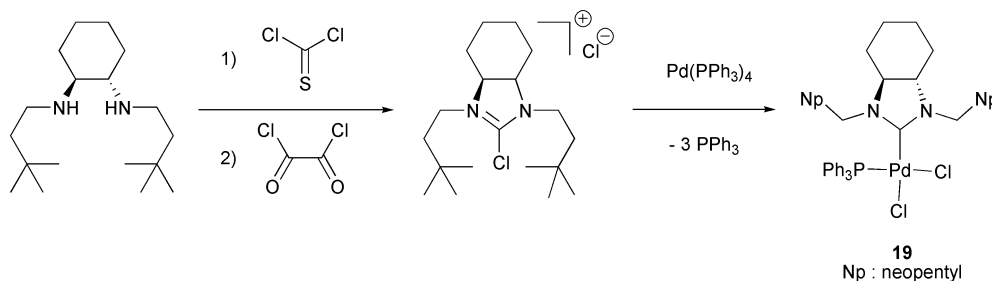
Scheme 15　Synthesis of complex **19** by oxidative addition.
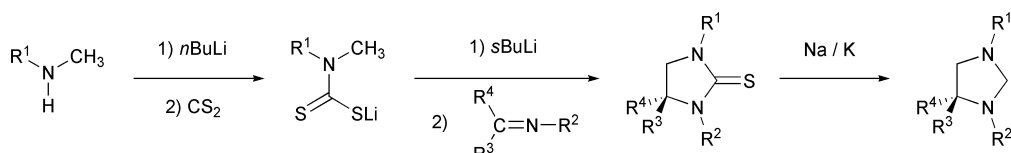
Scheme 16　Synthesis of non-symmetrical imidazolinylidenes reported by Hahn *et al.*
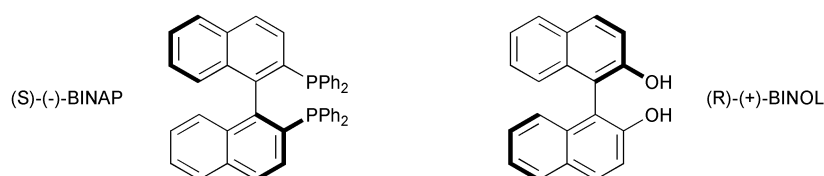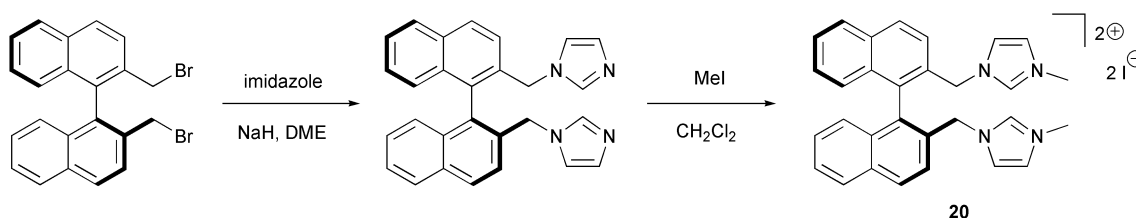
Fig. 6

Scheme 17 Synthesis of the bis(imidazolium) salt **20**.

palladium(II) complex, provided that the free biscarbene has been generated prior to the complexation. Direct metallation of the imidazolium salt by stirring it with a palladium salt in dmso at reflux results in the formation of a *cis/trans* mixture of complexes, the structures of which are shown in Fig. 7.

The formation of *cis–trans* mixtures of the palladium complexes of **20** is due to the flexibility of the ligand and the 11-membered metallacycles. It is not surprising that there are no reports of stereoselective catalysis employing this ligand.

A related bis-carbene ligand **21** (Scheme 18) with greater structural rigidity has been recently reported by the group of Min Shi.[38] In that ligand system the N-heterocycles are directly linked to the 1,1′-binaphthyl backbone in a four-step synthesis starting with enantiomerically pure BINAM. Complexation to rhodium was achieved according to a procedure developed by Crabtree, directly generating the hexacoordinate rhodium(III)

complex in modest yield.[39] The binaphthyl backbone imposes C_2 symmetry upon the biscarbene ligand and a mutual *anti* orientation of the N-methyl substituents with respect to the plane into which chelate ring is inscribed.

Complex **22** has been employed in the asymmetric hydrosilylation of ketones, displaying good activity and excellent enantioselectivity ($92\% <$ ee $< 98\%$) for aryl alkyl ketones, while the selectivity observed in the transformation of the more demanding dialkyl ketones is somewhat lower ($67\% <$ ee $< 96\%$) (Scheme 19).

This is the first example of a chiral bis-carbene ligand acting as an efficient stereodirecting element in an enantioselective catalytic transformation and is encouraging for future developments in the field. The only disadvantage is the divergent synthetic strategy for the ligand, making its systematic variation cumbersome.
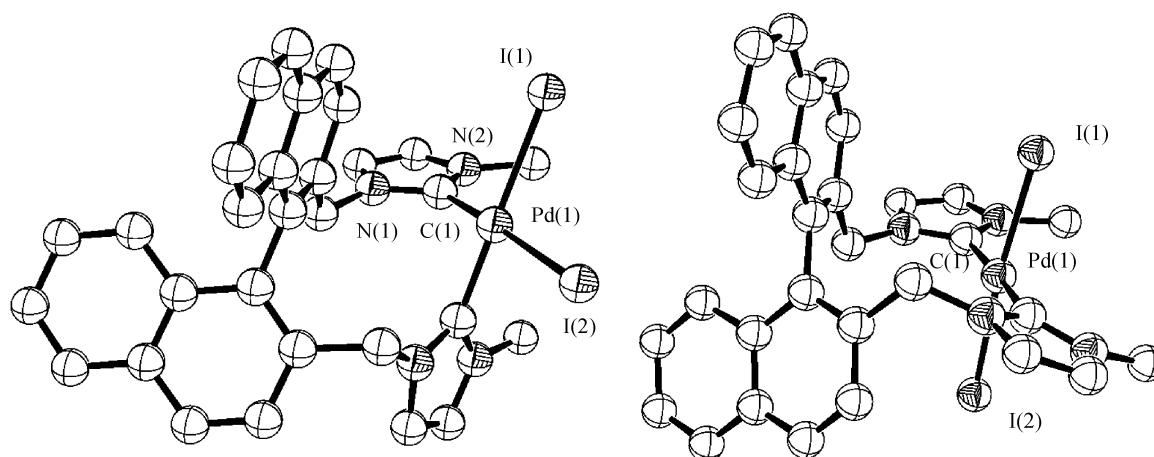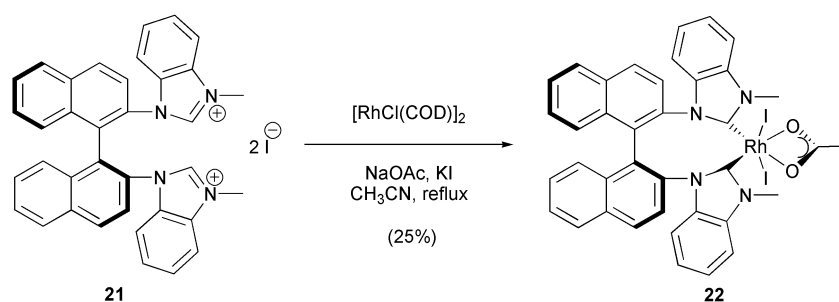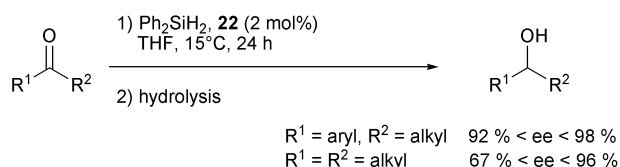

Fig. 7 Molecular structures of *trans*-PdI$_2$(**20**) and *cis*-PdI$_2$(**20**).

Scheme 18 Synthesis of the rhodium(III) complex **22**.

Scheme 19 Asymmetric hydrosilylation of ketones with 22.

In 2002, Hoveyda *et al.* reported the synthesis of a novel chiral anionic bidentate carbene ligand combining an *NHC* unit with a phenolato donor and its use in asymmetric olefin metathesis.[40] The five-step synthesis of the imidazolinium salt 23 requires (*S*)-2-amino-2′-hydroxy-1,1′-binaphthalene (NOBIN) and mesitylamine as starting materials. Its complexation to ruthenium(II) was achieved by reaction of Hoveyda's metathesis catalyst with the *in situ* generated silver(I) carbene complex derived from 23. In this synthesis the silver carbonate acts as a base both for the imidazolium ring and the phenol-OH function (Scheme 20) and plays the role of carbene ligand transfer reagent already mentioned above for various other cases.

Compound 24 was tested both in ring closing reactions and ring opening cross-metatheses. While no stereoselectivity was reported for the ring closures, the asymmetric ring opening

cross-metathesis (AROM/CM) gave interesting results. As displayed in Scheme 21, the latter involve the reaction of a strained bicyclic norbornene-related substrate with a terminal monoalkene.

The newly formed C=C bonds have almost exclusively *trans*-configuration (>98/2), and the excellent enantioselectivity, with which the reaction product is obtained (ee up to 98%), illustrates the considerable potential of complex 24 in asymmetric catalysis. Furthermore, this compound is air stable, may be purified by chromatography on silica, does not require dried solvents and may be reused after catalysis without significant loss in enantioselectivity. Since 24 was found to be slightly less active in olefin metathesis than the previously studied "second generation" Hoveyda catalysts, such as 25 (Fig. 8),[41] several modifications of 24 have been tested.[42] Among these, 26a and 26b displayed in Fig. 8 are, respectively, 130 and 160 times more active than 24 for the reaction shown in Scheme 21.

The introduction of a phenyl substituent in the *ortho* position of the aryl-ether unit in 26a and 26b supports the formation of the catalytically active four-coordinate species derived from 24 leading to the increase in activity by two orders of magnitude, an effect which has previously been observed for derivatives of the achiral catalyst.[43] In the same way, a trifluoromethyl group as substituent in the binaphthyl backbone diminishes the
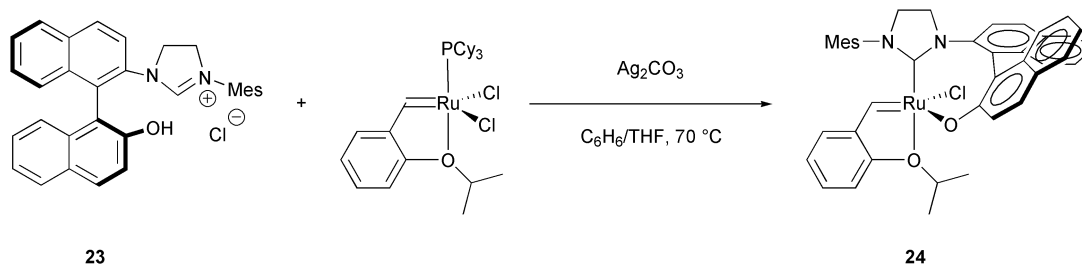
Scheme 20 Synthesis of the olefin metathesis catalyst 24.

E isomer
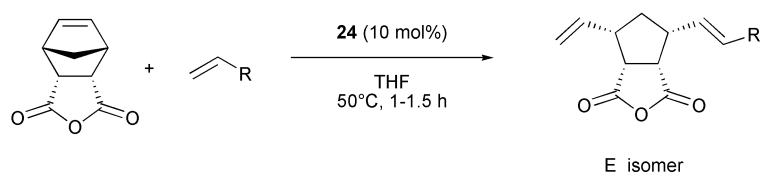
R	E/Z	ee (%)
Ph	> 98/2	80
*n*C₅H₁₁	> 98/2	>98
Cy	> 98/2	> 98

Scheme 21 AROM/CM reaction catalyzed by 24.
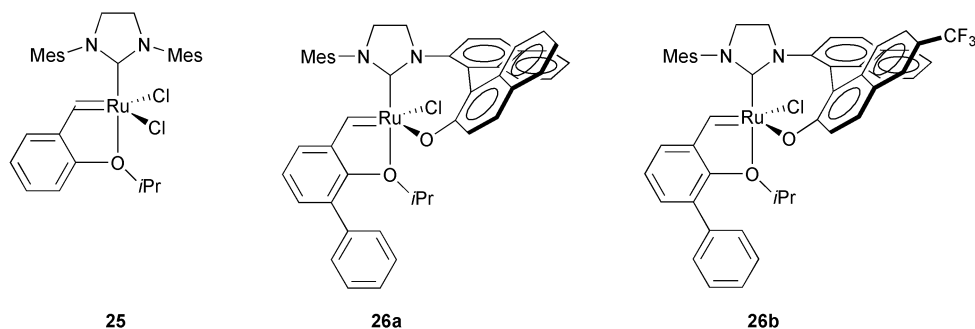
Fig. 8
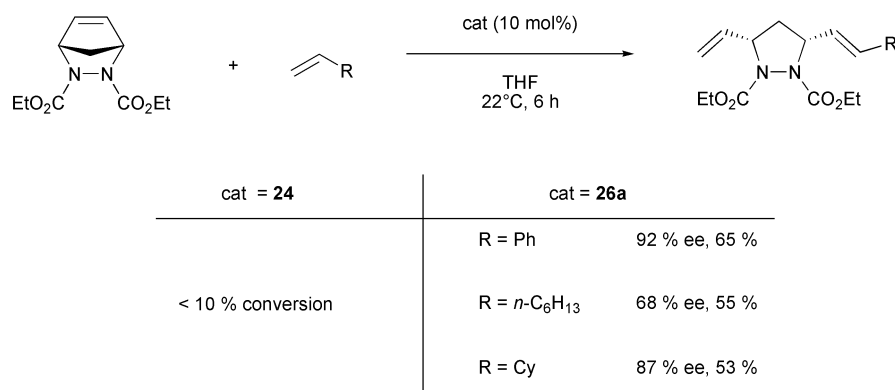
Scheme 22   Ru-catalysed AROM/CM of an N-heterobicyclic alkene.

cat = 24	cat = 26a	
	R = Ph	92 % ee, 65 %
< 10 % conversion	R = n-C$_6$H$_{13}$	68 % ee, 55 %
	R = Cy	87 % ee, 53 %

electron-donating capacity of the naphtholate unit coordinated to the ruthenium, also accelerating the catalytic reaction.[44]

The enhanced AROM/CM activity of catalyst **26a** in comparison to **24** has greatly increased the scope of this reaction as illustrated by the transformation shown in Scheme 22 for which **24** only gave low conversion. In contrast **26a** gives the reaction products in good yield and high enantioselectivity. The N–N-unit in the enantiomerically enriched reaction product in principle allows a multitude of subsequent functionalization steps.

5   Carbenes containing an element of planar chirality

Ligands containing an element of planar chirality, in particular ferrocene derivatives, have proved to be excellent stereodirecting ligands in asymmetric catalysis.[45] Typical examples of this family of ligands are Togni's Josiphos, which is being used industrially,[46] as well as the chiral derivatives of DMAP (4-dimethylaminopyridine) developed by Fu's group which has been successfully used both in organocatalysis and transition metal catalysis (Fig. 9).[47]

Bolm *et al.* reported the first planar chiral *NHC* at the beginning of 2002.[48] The synthetic strategy is based on an oriented *ortho*-metallation starting from a chiral sulfoxide, followed by the conversion of the sulfoxy group to a hydroxymethyl unit. The imidazole ring is then linked to this intermediate with the aid of *N*,*N*-carbonyl diimidazole and subsequently quaternized with methyl iodide to give the imidazolium ligand precursor of the carbene **29** (Scheme 23).

First tests of the ligand in the hydrosilylation of ketones catalyzed by [(**29**)RhI(COD)] only yielded racemic mixtures of

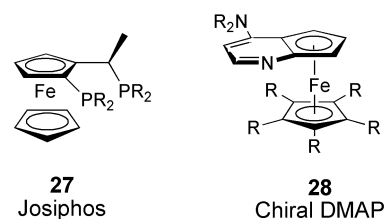**27**
Josiphos

28
Chiral DMAP

Fig. 9   Ligands possessing planar chirality.

the secondary alcohols, and no further application in asymmetric catalysis of **29** has been reported to date.

Following this first publication by Bolm's group, Togni *et al.* reported the synthesis of the C_2-symmetric chiral carbene ligand **30** using Ugi's chiral 1-ferrocenylethylamine as starting material (Scheme 24).[49]

The chiral carbene **30** contains two types of chiral elements, planar chirality in the ferrocenyl units and chiral centres at the carbon atoms linking the ferrocene with the N-heterocycles. This combination is frequently found in ferrocene-derived chiral ligands, however, its interplay determining the selectivity of a stereoselective transformation seems to depend crucially on the type of the reaction and no general conclusions seem to be possible at this stage. So far there are no reports of the use of **30** in asymmetric catalysis.

Ugi's ferrocenylamine has also been used in the synthesis of chiral bidentate *NHC* heterodonor ligands in which the second ligating unit is either a diphenylphosphino or phenylsulfuro group.[50] Several rhodium(I) and iridium(I) have been prepared which are depicted in Scheme 25.
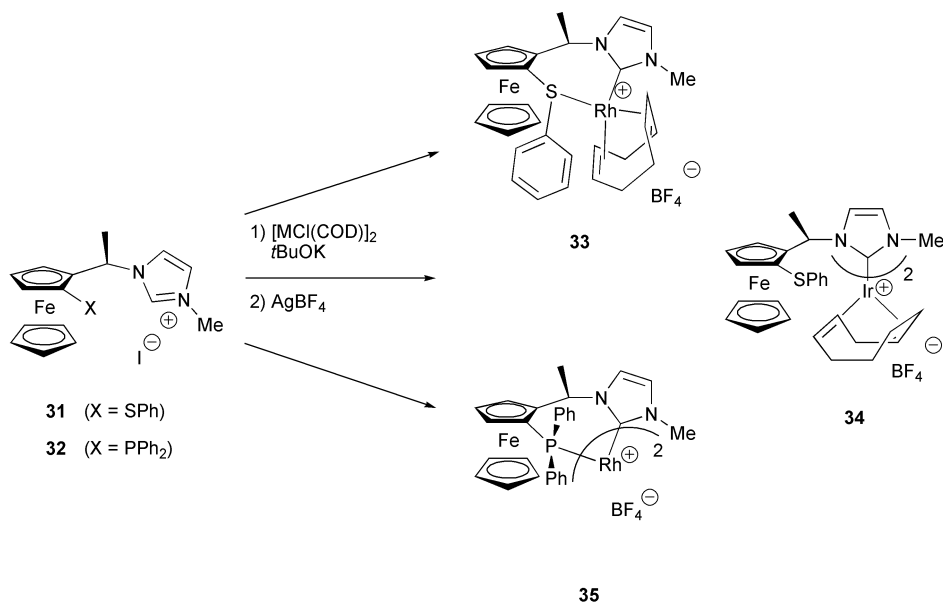
Complexes **34** and **35**, which contain two *NHC* ligands
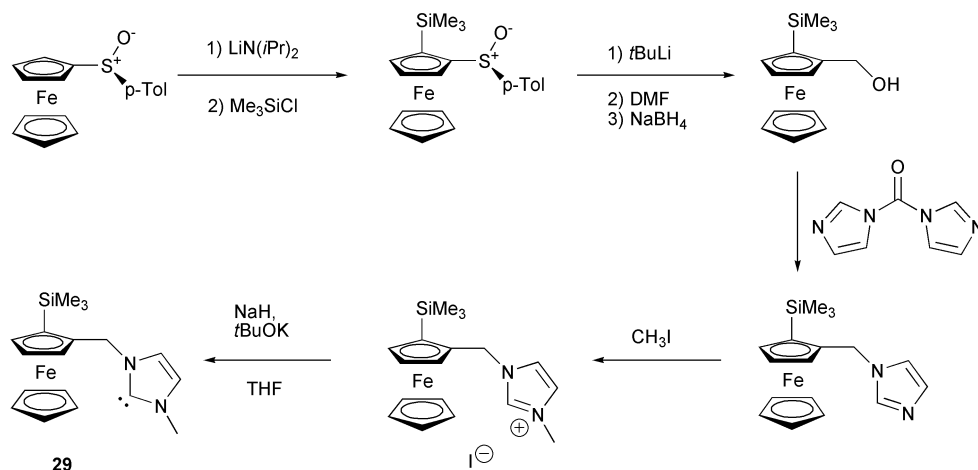
Scheme 23   Synthesis of the planar-chiral *NHC* **29**.

Ugi's amine
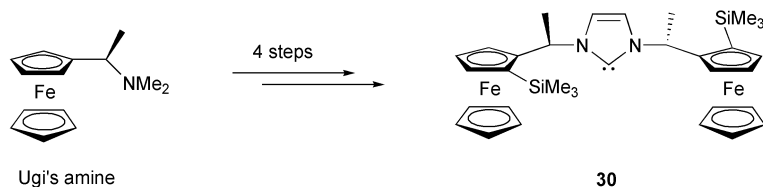
Scheme 24 Chiral imidazolylidene synthesized by Togni *et al.*

30

1) [MCl(COD)]₂
*t*BuOK

2) AgBF₄

31 (X = SPh)
32 (X = PPh₂)

33

34

35

Scheme 25 Complexation of **31** and **32**.

coordinated to the metal centre were found to be inactive in the attempted asymmetric hydrogenation of dimethylitaconate, while **33** catalyzed the reaction with low enantioselectivity (44%, 18% ee) (Scheme 26).

Very recently, Togni reported a chiral C_2-symmetric tridentate PCP ligand (**37**)[51] related to the previously developed triphosphine Pigiphos (**36**) (Fig. 10).[52] This phosphine-carbene ligand has been used in the nickel catalyzed hydroamination of acrylonitrile derivatives.[53]
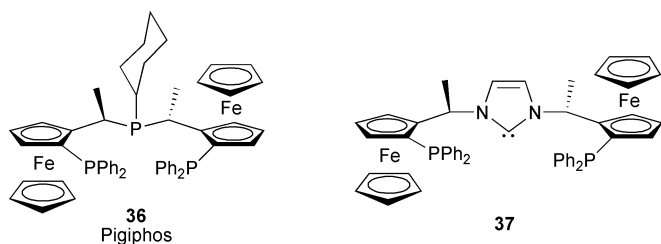
36
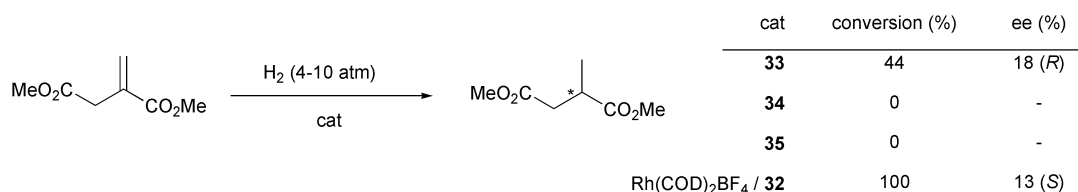Pigiphos

37

Fig. 10

The coordination of **37** to palladium(II) is achieved by direct metallation of the imidazolium salt with Pd(OAc)₂ giving the cationic square planar complex **38** (Scheme 27). The

coordination to ruthenium(II) yielded a mixture of diastereomers of **39** due to the presence of two different halide ligands. Selective abstraction of the chloro ligand gave the complex cation **40** in which the PCP-ligand **37** is meridionally coordinated in contrast to its facial coordination in **39**. The diphosphino-carbene ligand may thus adopt two coordination modes which is due to its skeletal flexibility.
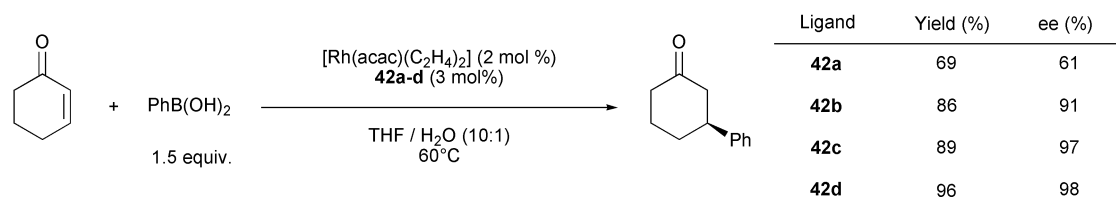
Complex **40** catalyzes, among other reactions, the addition of morpholine to methylacrylonitrile giving the amination product with modest selectivity (37% ee) (Scheme 28).[53] However, due to the modular nature of this ligand system there seems to be ample potential for future improvement.

The synthesis and application in catalysis of a novel monodentate *NHC* ligand, in which the N-substituents are chiral paracyclophanes has been reported at the end of 2003.[54] A Pd-catalysed Suzuki–Miyaura reaction allows the facile coupling of S_p-pseudo-*ortho*-bromoamino[2,2]paracyclophane **41** depicted in Scheme 29 with aryl or cyclohexyl groups,[55] and a subsequent one-pot procedure gives the corresponding imidazolinium dicyclophanes **42a–d**.

These monodentate ligands, containing very bulky chiral N-substituents have been applied in the asymmetric rhodium(I)-catalyzed conjugate addition of arylboronic acids to α-enones (Scheme 30) originally developed by Miyaura, Hayashi and coworkers.[56]

cat	conversion (%)	ee (%)
33	44	18 (*R*)
34	0	-
35	0	-
Rh(COD)₂BF₄ / **32**	100	13 (*S*)

Scheme 26 Catalytic hydrogenation of dimethylitaconate.

Scheme 27 Coordination of the tridentate PCP ligand **37**.

96 % yield
37 % ee

Scheme 28 Hydroamination of methacrylonitrile catalyzed by **40**.

SIPr.HCl =

42a	R = H
42b	R = Ph
42c	R = Cy
42d	R = o-anisyl

Scheme 29 Synthesis of the chiral paracyclophane imidazolinium salts **42a–d**.


Ligand	Yield (%)	ee (%)
42a	69	61
42b	86	91
42c	89	97
42d	96	98
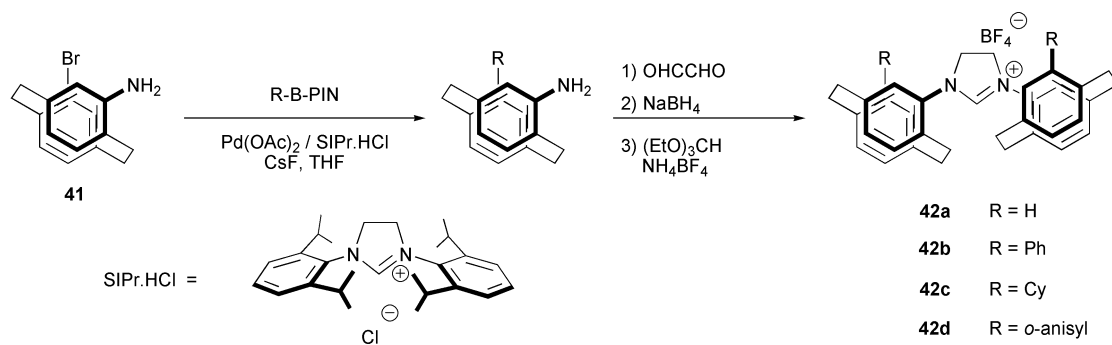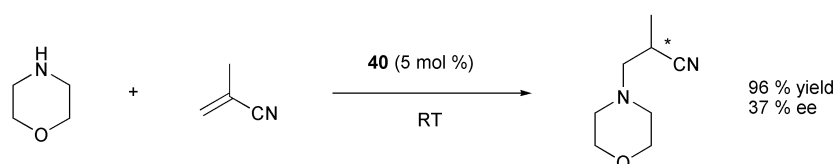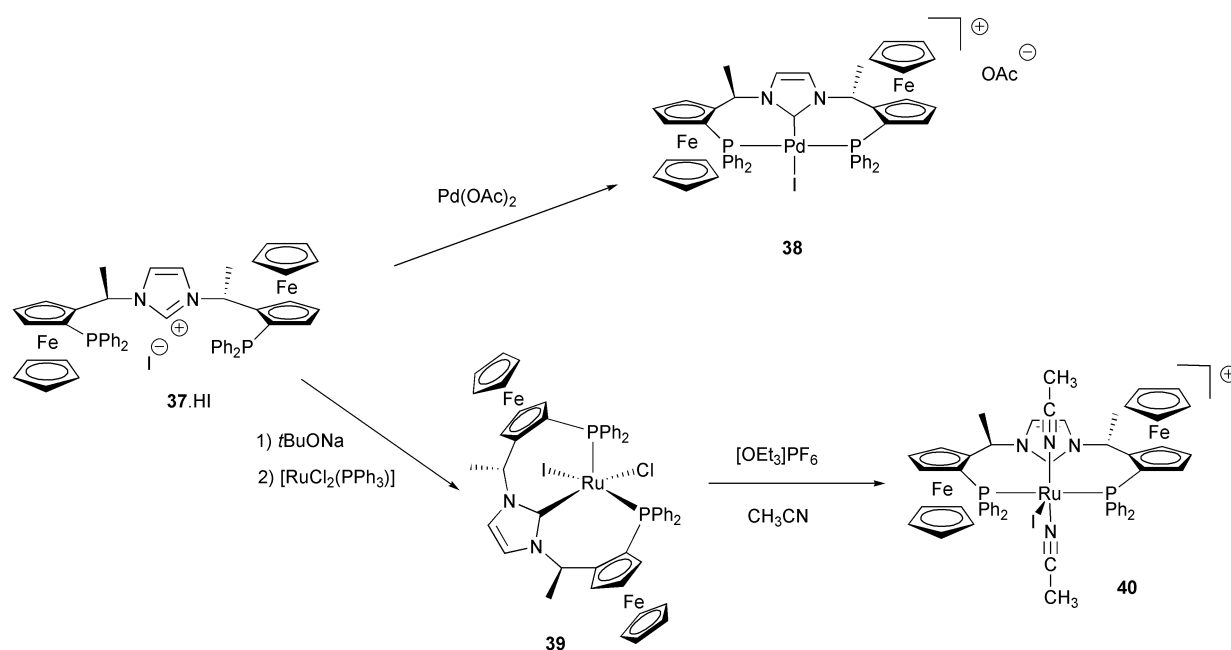
Scheme 30 Rhodium(I)-catalyzed conjugate addition of phenylboronic acid to α-enones.

Using the chiral imidazolinylidenes derived from **42** this reaction could be carried out at lower temperatures as those required with the previously employed catalyst [Rh-(acac)(C₂H₄)₂]/BINAP (100 °C). This increase in activity has to be seen in connection with the same observation made previously for the addition of arylboronic acids to aldehydes[57] and is found, in general, upon going from diphosphines to

monophosphines (such as PtBu₃)[58] and further to bulky *NHC*s (such as IMes and IPr).[59] The enantiomeric excesses of the reaction in Scheme 30, obtained with the optimized catalyst derived from **42**, are good to excellent (ee's ranging from 61 to 98%) and, in particular, with ligand **42d** high selectivities were obtained with a wide range of arylboronic acids and cyclic enones while acyclic enones led to slightly decreased selectivity.
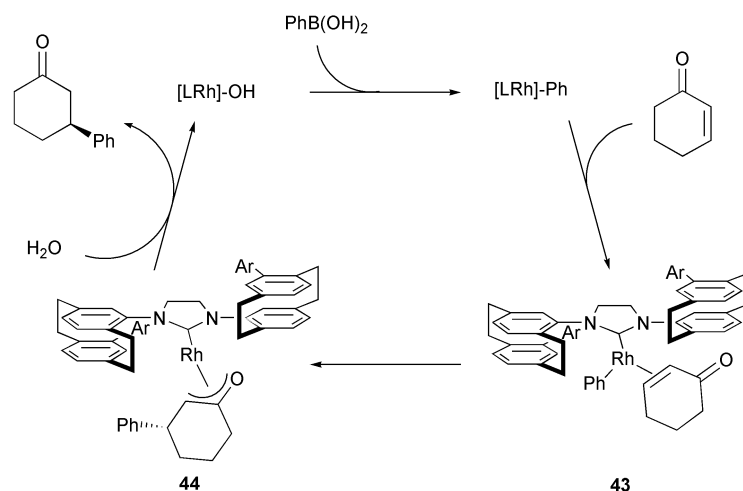
Scheme 31 Proposed catalytic cycle explaining the chiral induction in the rhodium(I)-catalyzed conjugate addition of phenylboronic acid to α-enones.

A mechanistic explanation for the chiral induction in this process has been proposed and is depicted in Scheme 31. It is based on the results obtained in a previous investigation of the BINAP derived catalyst.[60] As discussed for C_2-chiral diphosphines, the active space at the metal centre, the geometry of which is defined by the ancillary ligand, may be viewed as being composed of four quadrants. Two of these quadrants (top-right and bottom-left) are blocked by the cyclophane moieties. Upon phenyl transfer from PhB(OH)$_2$ and coordination of the enone, the intermediate **43** is generated (Scheme 31). The cyclohexenone will preferentially π coordinate, occupying one of the free quadrants to minimize the steric interligand repulsion with ligand **42**. The transfer of the Rh–Ph group to the C=C bond occurs by migratory insertion with attack upon the *Si* face of the olefin to give the oxallylrhodium intermediate **44** which hydrolyzes to re-form the active hydroxy-rhodium complex and (*S*)-3-phenylcyclohexanone. The ligand family **42** has also been tested in the asymmetric hydrosilylation of ketones, however, the results of this study are not yet available.[61]

Finally, Bolm *et al.* tested the iridium(I) complex derivatives **45a–45c** very recently in asymmetric hydrogenations.[62] These complexes contain a bidentate carbene–phosphine ligand with a chiral pseudo-*ortho*-[2,2]paracyclophane unit built into its backbone (Fig. 11).
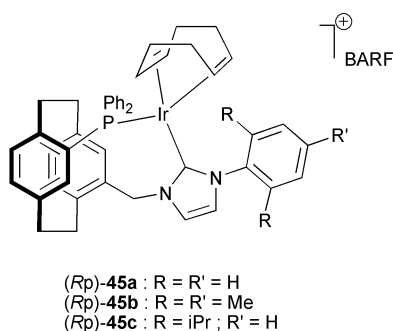

(*R*p)-**45a** : R = R' = H
(*R*p)-**45b** : R = R' = Me
(*R*p)-**45c** : R = iPr ; R' = H

Fig. 11 Iridium complexes containing a chiral phosphine–carbene ligand.

Catalyst **45a** was found to be the most selective for the transformation of non-functionalized alkenes (ee's of up to 82% for *E*-1,2-diphenylpropene) and the increase in the steric bulk on going to **45c** leads to lower enantioselectivities. For functionalized olefines, the hydrogen pressure sensitively influences the selectivity, the best results being obtained with

45c under an H$_2$ pressure of 1 bar (ee's of up to 89% for dimethylitaconate).

In conclusion, even though ferrocenyl-substituted chiral carbenes have so far not given rise to highly efficient enantioselective catalysts, the strategy of using planar chiral structural elements in carbene ligand design is promising in view of the recent results obtained with chiral paracyclophane derivatives. Furthermore, the latter example supports the conclusion at the end of section 1, that increase in the steric bulk of chiral N-substituents leads to greater chiral induction in the enantioselective catalysis with these species.

## 6 Carbenes joined by a chiral *trans*-cyclohexanediamine ligand backbone

Enantiomerically pure *trans*-1,2-diaminocyclohexane has been used as a fundamental building block in the design of chiral ligands, the most prominent example being the chiral salen ligand in Jacobsen's epoxidation catalyst.[63] Such ligands based on chiral diamines have been widely employed in enantioselective catalytic transformations.[64] These results have inspired two research groups in their synthesis of *NHC*s containing a *trans*-cyclohexanediamine backbone.

The first such ligand system (**46**) was developed in Burgess's group and was used in the synthesis of the palladium(II) complex **47**, in which the bis-carbene acts as a *trans*-chelating ligand (Scheme 32).[65] However, there are no reports of the use of **47** in Pd-catalysed reactions.

Douthwaite *et al.* have published two types of chiral bidentate *NHC* ligands.[66] The first of these contains an imidazolylidene and an imine linked by a *trans*-cyclohexanediamine core according to the synthetic strategy outlined in Scheme 33. The facile modular variation of the peripheral substituents in this class of ligands principally allows for the rapid screening of large ligand libraries.

The carbene-imines derived from **48** have been tested in palladium catalyzed allylic alkylations, one example of these being depicted in Scheme 34. As previously observed, *NHC* ligands do not seem to give rise to very active allylic alkylation catalysts[67] and relatively high catalyst loadings (5 mol%) and elevated temperatures (50 °C) are required for this transformation. In general, the increase of the steric demand of the carbene unit in these ligands and its decrease in the imine section lead to the highest enantioselectivities, the best result being that with the ligand shown in Scheme 34.
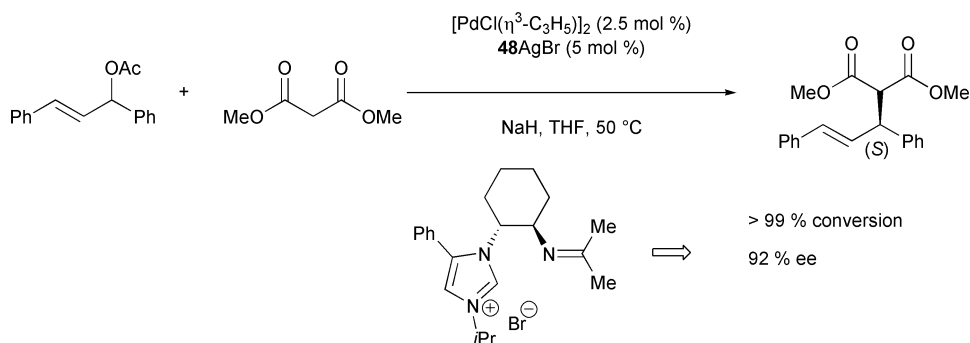
The same group also synthesized the C_2-symmetric di-imidazolium salt **49** shown in Fig. 12.[68] Its palladium(II)
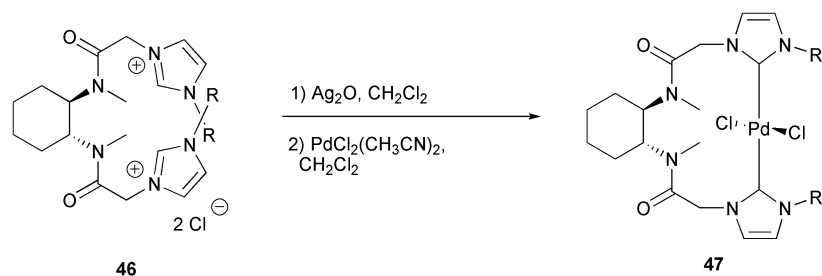
Scheme 32 Coordination of **46** to palladium(II).
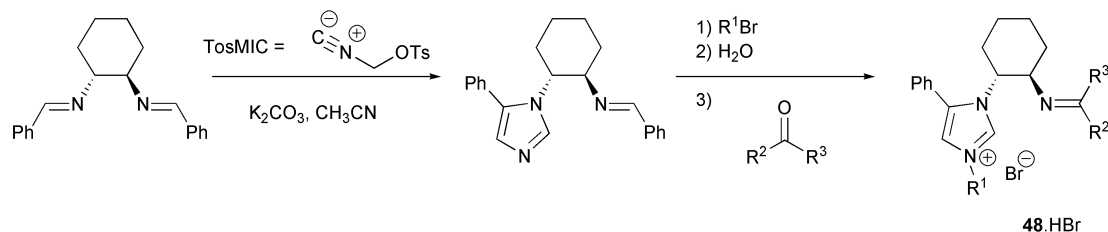
Scheme 33 Synthesis of Douthwaite's imidazolium-imine salts.

Scheme 34 Allylic alkylation catalyzed by a palladium complex bearing the carbene-imine ligand **48**.
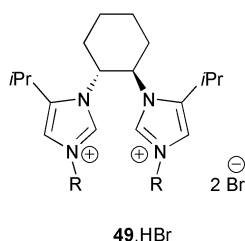

Fig. 12

complex [**49**PdCl₂] has been tested and only showed poor selectivity (11% ee) in the enantioselective α-arylation of amides previously described by Hartwig for the formation of oxindoles (see Scheme 5).

7 Carbenes incorporating oxazoline units

During the past 15 years the oxazoline ring has been established as a "privileged" structural motif in ligand design for asymmetric catalysis.[69] The key features are its rigidity and quasi-planarity as well as its facile accessibility by condensation of an amino-alcohol with a carboxylic acid derivative.[70] In spite of their sensitivity to mineral and Lewis acids, they are remarkably stable towards nucleophiles, bases and radicals. Upon coordination of the oxazoline ring through the N-atom, the stereodirecting substituent will be situated in close proximity to the metal centre and will thus directly control the active space available for the substrate(s). It was therefore of interest to combine this structural element of chiral ligand design with a N-heterocyclic carbene unit. In 1998, Herrmann *et al.* reported the synthesis of the first chiral carbene containing an oxazoline unit. In this bidentate ligand the oxazoline ring is linked in its 2-position to the imidazole ring *via* a methylene bridge.[71] The key step in the synthesis of the imidazolium precursor is the acid-catalyzed cyclization of the oxazoline by reaction of an iminoester, formed *in situ* from a nitrile function, and the amino alcohol (Scheme 35).

Compound **50** was subsequently coordinated as a carbene-oxazoline ligand to rhodium(I) and palladium(II) (Scheme 36). Carbene **50** acts as a bidentate chelating ligand in the rhodium(I) complex and the six-membered metallacycle thus formed adopts a boat conformation. On the other hand, the palladium complex **51** is dinuclear with two oxazoline-carbenes acting as bridging ligands. The rhodium complex **52** was employed in the hydrosilylation of ketones giving the secondary alcohols in moderate enantioselectivity (ee's up to 70%).[72]

A major step forward in the development of asymmetric catalysis with chiral N-heterocyclic carbene complexes has been the work of Burgess *et al.* on the asymmetric hydrogenation of alkenes using iridium(I) catalysts containing *NHC*-oxazolines such as **55**.[73] Their design was inspired by the chiral bidentate phosphine-oxazoline ligands (*Phox*) (Fig. 13) developed by Pfaltz and Helmchen which had proved to be highly selective in
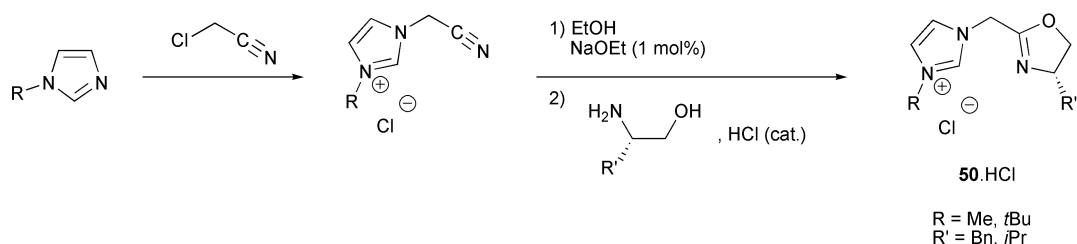
Scheme 35 Synthesis of the imidazolium precursor of Herrmann's oxazolinyl-carbene ligand.
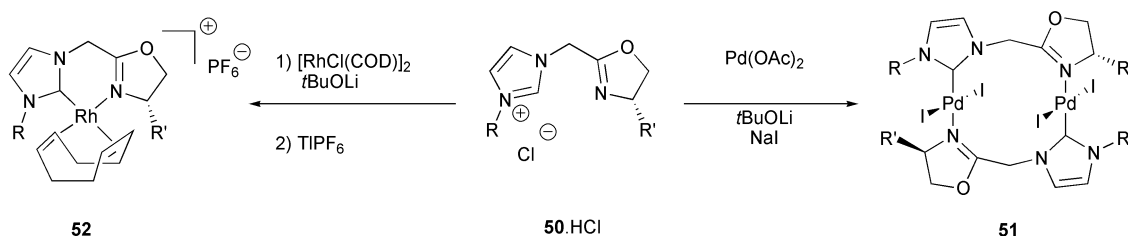
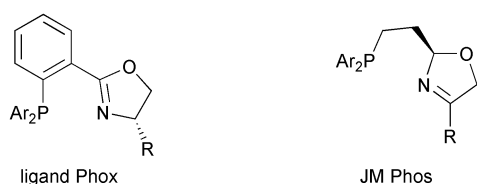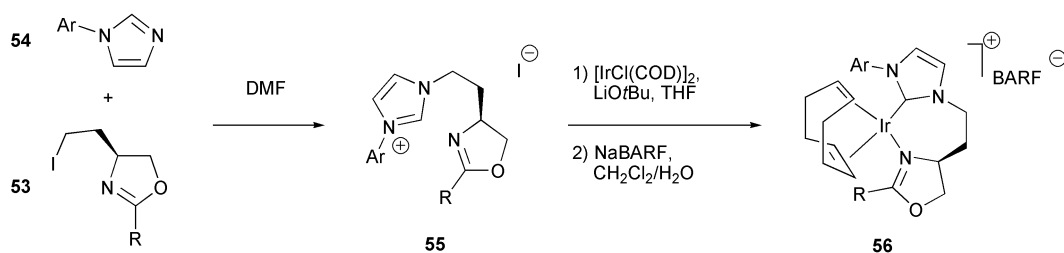**Scheme 36** Coordination of the carbene **50** to rhodium(ı) and palladium(ıı).

Fig. 13 Chiral P,N-ligands employed in asymmetric hydrogenations.

the enantioselective hydrogenation of non-functionalized trisubstituted alkenes.[74] Furthermore, Burgess and coworkers had previously studied a novel family of P,N-ligands, dubbed *JM-Phos*,[75] and were guided by the analogy between phosphanes and *NHC*s in the design of the new class of oxazoline-carbenes represented by **55** (Scheme 37).
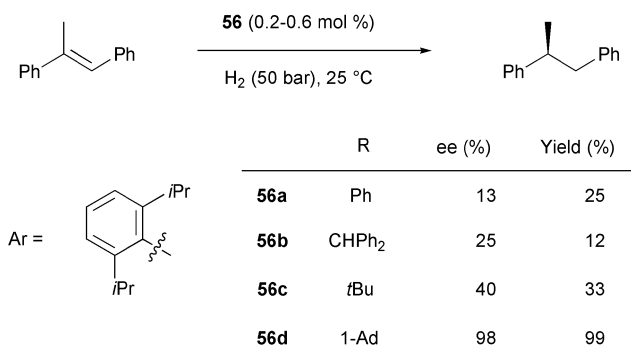
Scheme 37 Catalytic hydrogenation of *E*-1,2-diphenylpropene with complexes **56a–56d**.

In the imidazolium salts **55**, obtained by nucleophilic substitution of the iodo-derivative **53** by an imidazole **54**, the oxazoline is linked by the carbon atom in 4-position. Coordination of the bidentate ligand to the {Ir(COD)}$^+$ complex fragment is then achieved by *in situ* deprotonation (Scheme 37). This modular design allows facile and rapid access to a large ligand library by variation of the substituents in the 2-position of the oxazoline and at the "terminal" N-atom of the heterocyclic carbene.

Complexes **56** have been tested in the asymmetric hydrogenation of *E*-1,2-diphenylpropene, and derivative **56d** proved to be the most active and selective for this reaction. Some results of the catalyst screening are summarized in Scheme 38, illustrating the importance of the modular ligand design.

The authors have put forward an explanation for the high selectivity of catalyst **56d** and point out the key structural features leading to an efficient chiral induction with this class of complexes. The ligand in **56d**, in particular, displays high efficiency since the bulky 2,6-(iPr)$_2$-C$_6$H$_3$ group effectively blocks one of the quadrants of the active space in the catalyst, allowing good control of the geometry of the coordination sphere around the metal.

Gade and co-workers reported the synthesis of an oxazo-linyl-carbene which is obtained by a direct and facile linkage of the two heterocycles. The new ligand was synthesized by reacting the 2-bromooxazoline **57** with an imidazolium precursor in THF (Scheme 39).[76] N-heterocyclic carbene rhodium complexes could then be obtained by reaction of the imidazolium salt **58** with [{Rh(μ-O*t*Bu)(nbd)}$_2$] generated *in situ*.[77]

The direct condensation of an oxazoline to the imidazolium ring provides an easy modular route to the development of a new family of carbene oxazoline ligands. Based on this

Scheme 38 Synthesis of an iridium(ı) complex bearing Burgess's chiral oxazoline-imidazolylidene ligand.
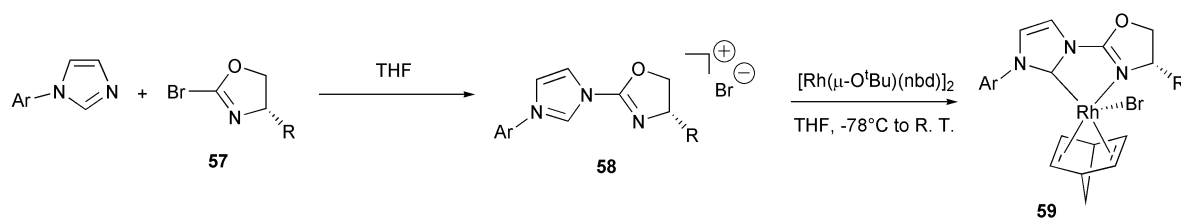
Scheme 39 Synthesis of ligand precursor **58** and complexation with rhodium(I) **59**.

Table 2 Asymmetric hydrosilylation of ketones with catalyst **60**

| Entry	Ketone	ee (%)	Yield (%)
1		90	92
2		79	95
3		88	53
4		95	70

strategy, a highly stereoselective Rh^I catalyst for the asymmetric hydrosilylation of ketones was developed.[78] For example, asymmetric hydrosilylation of acetophenone with complex **60** can be achieved with 92% yield and 90% ee (Table 2, entry 1). However, the enantioselectivities for the aryl alkyl ketones are below those obtained with the most efficient phosphane-based systems. Catalyst **60** was found to be more efficient in the hydrosilylation of unsymmetrical dialkyl ketones which are difficult substrates, some examples being displayed in Table 2 (Entry 2–4).

Another type of bidentate oxazoline–imidazolylidene ligand, in which both units are linked by a chiral paracyclophane has been studied in Bolm's group.[79] In this case, the planar chirality

of the pseudo-*ortho*-paracyclophane is combined with the central chirality of an oxazoline (Scheme 40). Compounds **62** were tested in the asymmetric hydrogenation of olefins displaying but moderate selectivity (ee's of up to 46% for dimethylitaconate in the presence of **62b**). It is another example in which the combination of several elements of chirality does not necessarily lead to improved selectivity.

Finally, two monodentate N-heterocyclic carbenes ligands that contain an oxazoline unit have been reported. Glorius *et al.* reported the synthesis of the imidazolium salts **64** by cyclizing the corresponding bisoxazolines **63** (Scheme 41).[80]

The key step is the introduction of a C$_1$ synthon to link the two oxazoline-N atoms. The combination of chloromethyl

	R^1	R^2	R^3
(*Sp*)-**62a**	Me	Me	Me
(*Sp*)-**62b**	Me	Me	Mes
(*S*,*Sp*)-**62c**	*t*Bu	H	Me
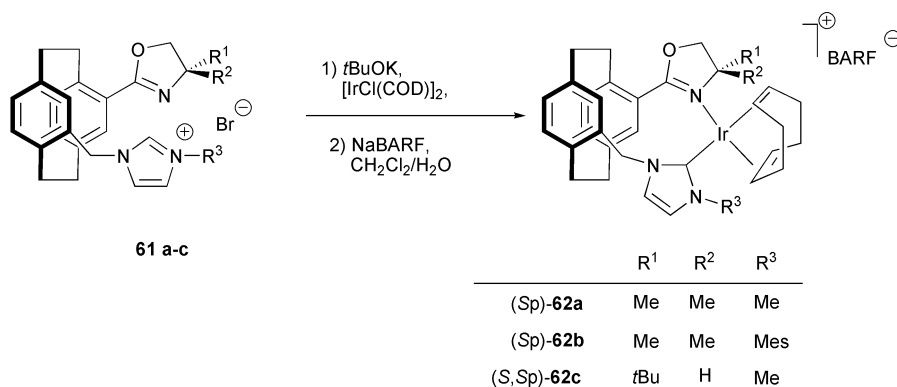
Scheme 40 Oxazoline-*NHC* ligands, bridge by a paracyclophane unit and their iridium complexes.
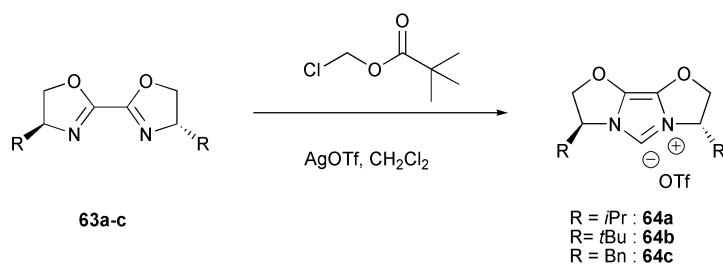
Scheme 41 Synthesis of imidazolium salts from the corresponding bisoxazolines.

Scheme 42 Synthesis of oxazoline-based triazolium salt.

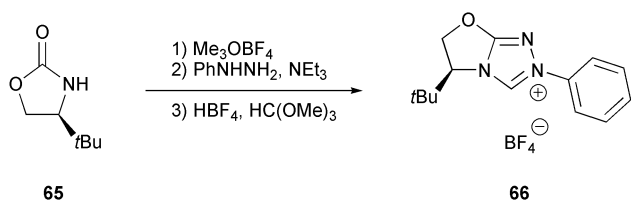pivalate and silver triflate generates a highly electrophilic reagent undergoing double nucleophilic substitution at its central carbon atom and thus giving the desired imidazolium salt. A major advantage of this strategy is the facile accessibility of the bisoxazolines along with the modularity of their synthesis. The imidazolium salts **64** have been employed in Pd-catalyzed asymmetric α-arylations (such as represented in Scheme 5) albeit with only moderate results (ee's <43%).

Enders and Kallfass reported the synthesis of unsymmetrical triazolium salt **66**.[81] This compound is obtained by a 3 step procedure from the corresponding oxazolidinone **65** (Scheme 42).

This ligand, which has a bicyclic structure strongly related to Leeper's and Rovis' ligands (*vide supra*),[12,13] was found to be a very efficient organocatalyst in the asymmetric benzoin condensation (ee's up to 99%, see Scheme 4, eqn. 1).

8 Conclusions

Several basic structural motifs have recently emerged in the design of chiral N-heterocyclic carbene ligands and have been categorized and summarized in this review article. While all of them may be considered in the solution of a particular catalyst design problem, there seems to be a general trend which emerges for the most efficient new ligand systems. For the monodentate carbene ligands a well defined chiral molecular shape – aided by rigid (cross-linked) structural units – appears to be the prerequisite for high stereoselectivity, as has been previously observed for other ligands used in asymmetric catalysis. At this stage it is still too early to draw any conclusions concerning the efficiency of the combination of different chiral elements in a single ligand.

The kinetic robustness of the *NHC* ligand coordinated to a late transition metal makes it an excellent "anchor" function for a stereodirecting ancillary ligand. Such an anchor unit may then readily be combined with the established "privileged" chiral ligating units. In order to facilitate the optimization of a given catalyst, it is of importance that the coupling of the "anchor" (*NHC*) with the stereodirecting element occurs in a simple (preferably the final) reaction step of the ligand synthesis. Much of the expertise gained in the development of functionalized phosphine ligands appears to be applicable to *NHC*-heterodonor ligands while the fundamental stereochemical difference between the tricoordinate phosphorus and the essentially planar direct environment of the carbene function has to be taken into account.

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