29
P,N and Non-Phosphorus Ligands

Andreas Pfaltz and Sharon Bell

29.1
Introduction

The first homogeneous enantioselective hydrogenation catalysts were developed during the 1960s [1, 2]. Since then the range and scope of chiral hydrogenation catalysts has expanded to the point where many functionalized substrates can be hydrogenated in good enantiomeric excess. This breakthrough is largely due to the C_2-symmetric diphosphine catalysts such as DIOP [3], the first such diphosphine, and DIPAMP [4], used in the first industrial-scale enantioselective homogeneous hydrogenation to produce L-DOPA. Since that time, numerous other phosphorus ligands have been introduced, which have considerably expanded the scope of enantioselective hydrogenation.

More recently, there has been increasing interest in the synthesis of hydrogenation catalysts with ligands other than the diphosphines. The initial success of titanocene catalysts in the hydrogenation of unfunctionalized alkenes (see Section 29.5) led to a great deal of research into metallocene catalysts. Iridium complexes with ligands bearing a coordinating phosphorus (P) and nitrogen (N) atoms have shown considerable success in recent years.

P,N and non-phosphorus ligands have been most successful in the enantiomeric iridium-catalyzed hydrogenation of unfunctionalized alkenes [5], and for this reason this chapter necessarily overlaps with Chapter 30. Here, the emphasis is on ligand synthesis and structure, whereas Chapter 30 expands on substrates, reaction conditions and reaction optimization. However, a number of specific substrates are mentioned in the comparison of catalysts, and their structures are illustrated in Figure 29.1.

The Handbook of Homogeneous Hydrogenation.
Edited by J. G. de Vries and C. J. Elsevier

ISBN: 978-3-527-31161-3

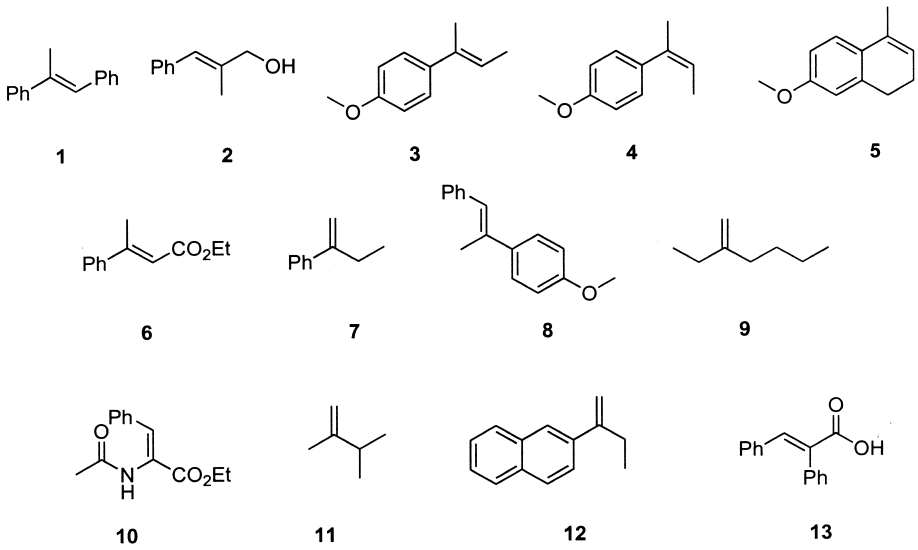


Fig. 29.1 Substrates discussed in this chapter.

29.2
Oxazoline-Derived P,N Ligands

The Crabtree catalyst ($[Ir(PCy_3)(py)(COD)]PF_6$) [6] shows remarkable activity in the hydrogenation of alkenes, particularly sterically hindered tri- and even tetra-substituted alkenes. Its structure has inspired a great deal of research into chiral P,N ligands for enantioselective hydrogenation, producing a variety of useful catalysts. The largest and most successful group of chiral analogues of the Crabtree catalyst are iridium complexes with oxazoline-derived P,N ligands.

The oxazoline-derived P,N ligands can be classified into four groups according to structure: phosphino-oxazolines; phosphite- and phosphinite-oxazolines; catalysts containing a P–N bond; and structurally related non-oxazoline catalysts.

29.2.1
Phosphino-oxazolines

The most extensively studied of these systems are the phosphino-oxazoline (PHOX) catalysts **14** (Fig. 29.2). Good enantioselectivity has been achieved with these catalysts over a broad range of substrates [7].

The highest enantioselectivity in the hydrogenation of unfunctionalized trisubstituted alkenes has been achieved with catalyst **14a**. The same catalyst was also used to hydrogenate *α,β*-unsaturated phosphonates with enantiomeric excesses (ee) of 70 to 94% [8].

The PHOX ligands have a modular structure (Scheme 29.1). They are synthesized from chiral amino alcohols and benzonitrile or bromobenzonitrile: the

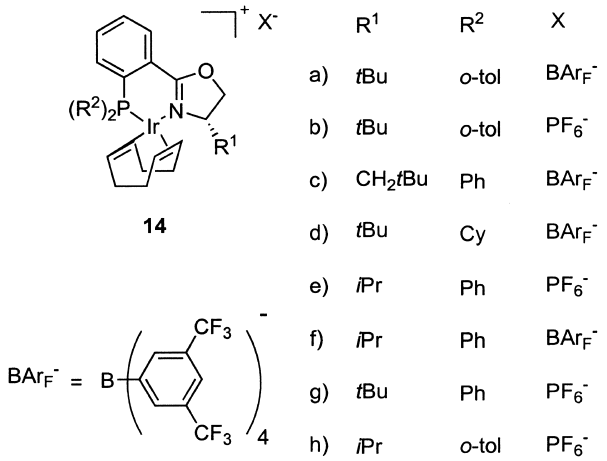
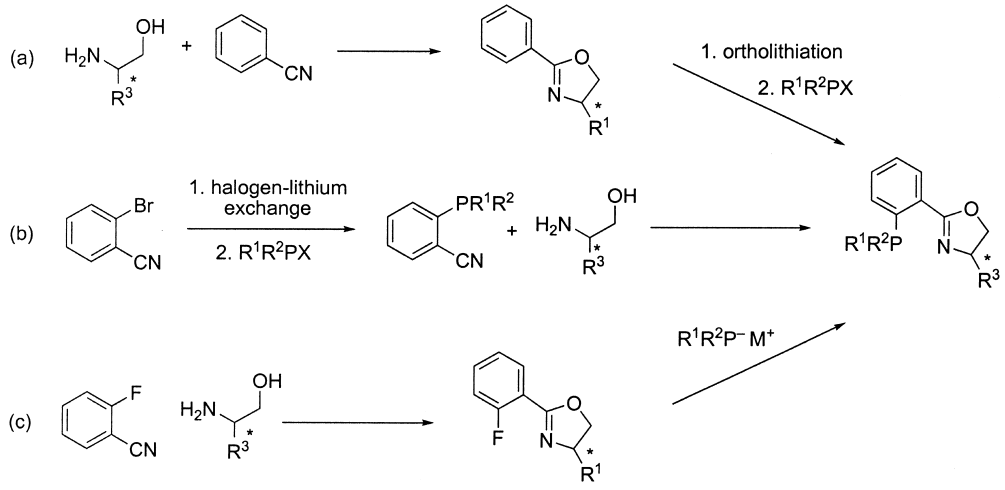


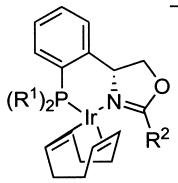
Fig. 29.2 PHOX catalyst **14**.



Scheme 29.1 Synthesis routes to the PHOX ligand.

phosphine is introduced *via* ortholithiation [9, 10] or lithium–halogen exchange as the first step [10–12] in ligand synthesis. Alternatively, the phosphine moiety can be introduced by nucleophilic substitution using an *ortho*-fluorophenyloxazoline as precursor (Scheme 29.1, route c) [13].

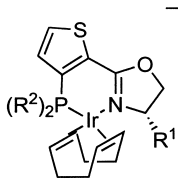
The stability of the PHOX catalysts containing the BAr_F counterion was found to be higher than that of those containing a PF_6^- counterion. The catalysts were more stable to air and moisture and, during hydrogenation, were deactivated more slowly than the corresponding PF_6^- catalysts, giving full conversion at >0.02 mol% catalyst loading [10].



15

	R^1	R^2
a)	Ph	*t*Bu
b)	Ph	$CHPh_2$
c)	Ph	3,5-*t*Bu$_2$C$_6$H$_3$
d)	Ph	adamantyl
e)	Cy	*t*Bu

Fig. 29.3 PHOX catalysts **15**.



16

26a-d

	R^1	R^2
a)	*i*Pr	Ph
b)	*t*Bu	Ph
c)	*t*Bu	*o*-tol
d)	*t*Bu	Cy

Fig. 29.4 HetPHOX catalyst **6**.

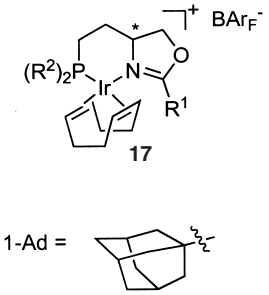
A series of analogues of the original PHOX catalyst, in which the phenyl bridge is attached to C(4) instead of C(2) of the oxazoline ring (**15**, Fig. 29.3), were recently synthesized [14]. These catalysts were used to hydrogenate a number of substrates, including a range of 1-phenylbutenoic acids, with >90% ee.

Another PHOX analogue has the aryl ring of the PHOX catalyst replaced by a thiophene unit **16** (Fig. 29.4) [15]. The synthesis is similar to that of the PHOX catalysts, starting with *ortho*-metallation of the thiophene. The catalysts showed similar selectivity to PHOX, and were used to hydrogenate substrates **1** and **2** with maximum enantioselectivities of 99% and 94%, respectively.

JM-Phos, a PHOX analogue with an alkyl backbone (**17**, Fig. 29.5) has been used to hydrogenate a number of substrates with moderate to good enantioselectivity [16].

Another alkyl-bridged PHOX (**18**, Fig. 29.6) was recently synthesized [17], and used to hydrogenate a series of substituted methylstilbenes in 75–95% ee, and β-methylcinnamic esters in 80–99% ee. The hydrogenation results suggest that the selectivity of these catalysts is mainly derived from the substitution at the stereogenic center on the oxazoline ring, with the other stereocenter having a relatively minor effect on the ee-value.

The ligand synthesis is straightforward, using amino alcohols as the source of chirality in the oxazoline ring, whereas the stereochemistry in the phospholane ring is controlled by an enantioselective deprotonation using sparteine (Scheme 29.2).



	R^1	R^2		R^1	R^2
a)	Me	Ph	f)	$CH(Ph)_2$	Ph
b)	*t*Bu	Ph	g)	$CH(Ph)_2$	*o*-tol
c)	*t*Bu	*o*-tol	h)	$C(Ph)_2Me$	*o*-tol
d)	1-Ad	Ph	i)	Ph	Ph
e)	$C(Ph)_3$	Ph	j)	3,5-*t*Bu$_2$C$_6$H$_3$	Ph

Fig. 29.5 JM-PHOS catalyst **17**.

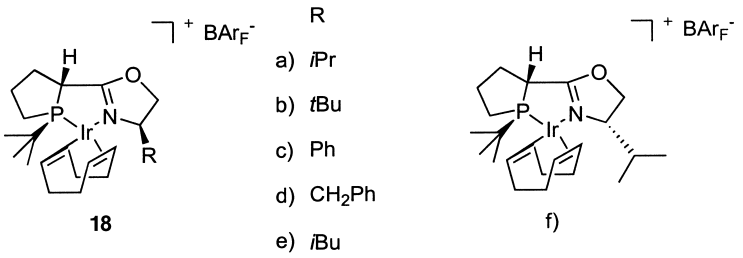
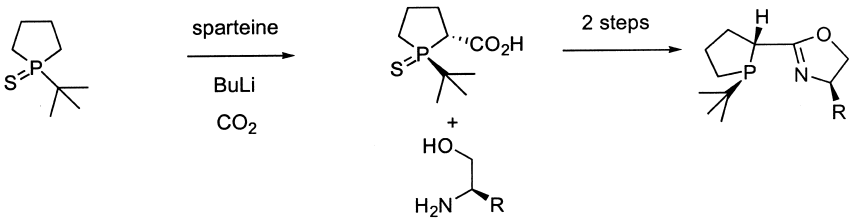


Fig. 29.6 Phospholane-oxazoline catalyst **18**.

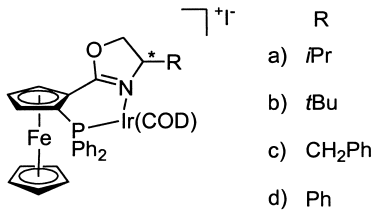


Scheme 29.2 Synthesis of ligands for catalyst **18**.

The ferrocene-oxazoline catalyst **19** (Fig. 29.7) has recently been used to hydrogenate substituted quinolines [18]. The ligand synthesis is again similar to that of the original PHOX ligand, with introduction of phosphorus *via* orthometallation.

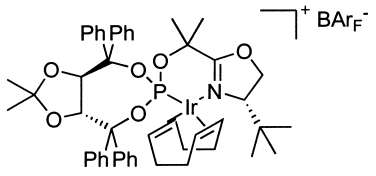
29.2.2
Phosphite and Phosphinite Oxazolines

A PHOX analogue containing a P–O bond, the TADDOL-derived phosphite oxazoline catalyst **20a** (Fig. 29.8) has been used in the hydrogenation of a number of substituted styrenes, as well as in asymmetric allylic alkylation [19]. However,



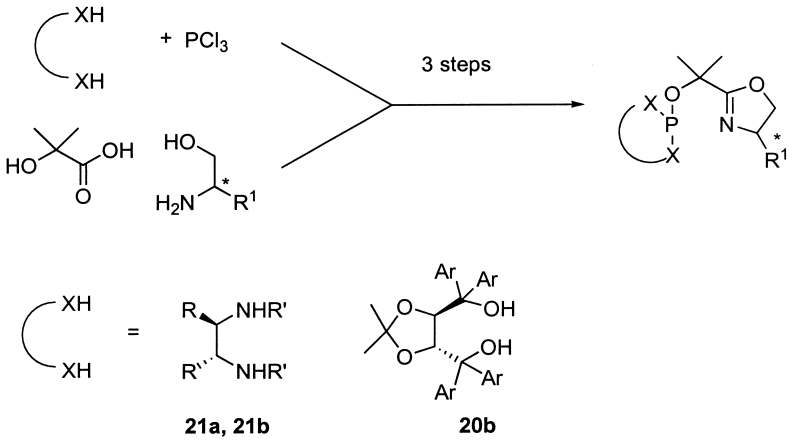
19

Fig. 29.7 Ferrocene-oxazoline catalyst **19**.



20

Fig. 29.8 Catalyst **20**.



21a, 21b 20b

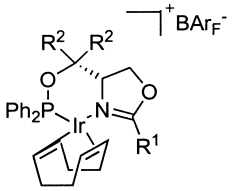
Scheme 29.3 Synthesis of aminophosphine and phosphinite catalysts **20b**, **21a** and **21b**.

the enantioselectivities were only moderate and catalytic activity was low, requiring 4 mol% catalyst.

The synthesis strategy is shown in Scheme 29.3. The incorporation of a diol or diamine gives ligand **20b** or ligands **21a** and **21b**, respectively.

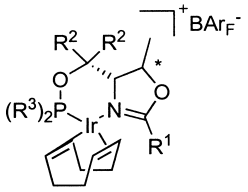
More recent developments are the SerPHOX catalyst **22** [20] and the ThrePHOX catalyst **23** [21] (Fig. 29.9), derived from serine or threonine, respectively (Scheme 29.4).

In many cases, these catalysts proved to be superior to the PHOX complexes **14**. Complexes **23a** and **23g** are among the most efficient catalysts (and are



22

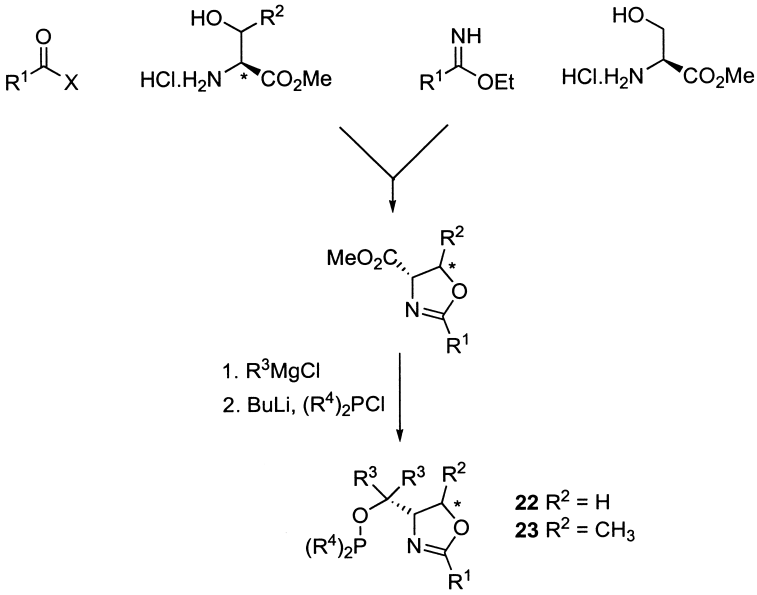
R^1	R^2
a) ferrocenyl	*i*Pr
b) ferrocenyl	*i*Bu
c) ferrocenyl	CH_2Ph
d) 3,5-*t*$Bu_2C_6H_3$	CH_2Ph



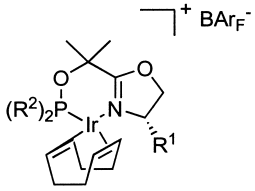
23

	R^1	R^2	R^3	
a)	Ph	CH_2Ph	Ph	(4*S*, 5*S*)
b)	Ph	CH_2Ph	Ph	(4*S*, 5*R*)
c)	Ph	CH_2Ph	*o*-tol	
d)	Ph	Me	Ph	
e)	3,5-$Me_2C_6H_3$	CH_2Ph	Ph	
f)	3,5-*t*$Bu_2C_6H_3$	CH_2Ph	Ph	
g)	Ph	CH_2Ph	Cy	

Fig. 29.9 SerPHOX and ThrePHOX catalysts **22** and **23**.



Scheme 29.4 Synthesis of SerPHOX (**22**) and ThrePHOX (**23**) catalysts.



24

	R^1	R^2
a)	*t*Bu	Ph
b)	*t*Bu	*o*-tol
c)	*i*Pr	Ph
d)	*i*Pr	*o*-tol

Fig. 29.10 SimplePHOX catalyst **24**.

Scheme 29.5 Synthesis of SimplePHOX catalysts.

now commercially available [22]), giving high enantioselectivities and turnover numbers (TONs) for a range of trisubstituted and 1,1-disubstituted alkenes. The additional methyl group on the oxazoline ring of ThrePHOX ligands led to greater selectivity in the hydrogenation of substrates **1**, **3**, and **4** [21]. The synthesis is again modular (Scheme 29.4).

Another efficient, readily available catalyst is the SimplePHOX complex (**24**, Fig. 29.10) [23].

The ligand synthesis requires only two steps from simple starting materials. As with the PHOX type catalysts, chirality is built in through the use of a chiral amino alcohol (Scheme 29.5).

Complex **24a** proved to be a particularly efficient catalyst for the hydrogenation of the cyclic substrate **5**, affording 95% ee, which currently is the highest ee-value obtained with any catalyst for this substrate. High enantioselectivities were also obtained with α,β-unsaturated substrate **6**. Catalyst **24a** also gave higher selectivity than the ThrePHOX catalysts **23** in the hydrogenation of substrates **2** and **4**.

29.2.3
Oxazoline-Derived Ligands Containing a P–N Bond

The first oxazoline-derived catalysts containing P–N bonds to be synthesized were the diaminophosphines **21** (Fig. 29.11) (details of the synthesis are shown in Scheme 29.3). This class of catalysts gave good enantiomeric excesses in the hydrogenations of some unfunctionalized olefins, albeit with low conversions and high catalyst loading (4 mol%) [19, 24]. Analogous complexes with N-aryl-

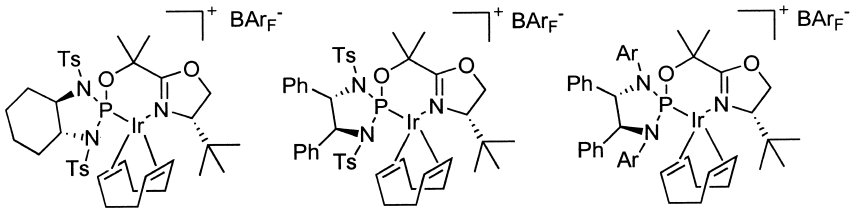


Fig. 29.11 Diaminophosphine catalysts **21**.

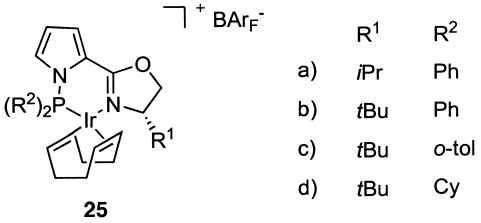


Fig. 29.12 PyrPHOX catalyst **25**.

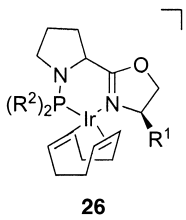
Scheme 29.6 Synthesis of PyrPHOX catalysts.

substituted ligands **21c** demonstrate much higher reactivity, and have been shown to be particularly efficient catalysts for the hydrogenation of α,β-unsaturated carboxylic esters [5].

PyrPHOX catalysts **25** (Fig. 29.12) [25], with a pyrrole instead of a phenyl bridge, showed selectivity which was comparable to – and in some cases better than – that of the PHOX catalysts **14**.

The synthesis is similar to that of the PHOX catalysts (Scheme 29.6), starting with oxazoline formation from the pyrrole nitrile and an amino alcohol, followed by introduction of the phosphine group.

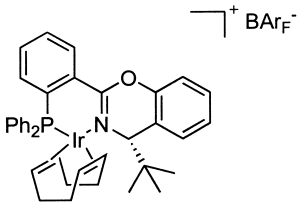
The pyrrolidine-oxazoline catalysts **26** (Fig. 29.13) can be conveniently synthesized from proline in five steps, and have been used to hydrogenate the methylstilbenes **1** and **8** in 92% ee and 94% ee, respectively [26].



26

	R^1	R^2	X^-
a)	*i*Pr	Ph	PF_6^-
b)	*i*Pr	Ph	BAr_F^-
c)	*t*Bu	Ph	BAr_F^-
d)	*t*Bu	*o*-tol	PF_6^-
e)	*t*Bu	*o*-tol	BAr_F^-
f)	*t*Bu	2-Ethylphenyl	BAr_F^-
g)	*t*Bu	2,3-$Me_2C_6H_3$	BAr_F^-
h)	*t*Bu	2,4-$Me_2C_6H_3$	BAr_F^-

Fig. 29.13 Pyrrolidine-oxazoline catalyst **26**.



27

Fig. 29.14 Phosphino-benzoxazine catalyst **27**.

29.2.4 Structurally Related Ligands

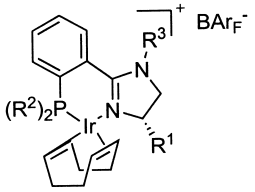
A number of ligands have been synthesized which have structural similarities to the oxazoline-derived ligands.

The first of these was the phosphino-benzoxazine catalyst **27** (Fig. 29.14) [27]. This catalyst contains a six-membered benzoxazine ring in place of the five-membered oxazoline ring in the PHOX catalysts. It was hoped that this change would bring the chiral center on the ring into closer contact with the metal, resulting in higher enantioselectivities. However, enantiomeric excesses were only modest with the substrates chosen.

The phosphino-imidazoline catalyst **28** (Fig. 29.15) is a close analogue of the original PHOX ligand.

Phosphino-imidazoline ligands of this type were originally synthesized by Busacca and coworkers and used in an enantioselective Heck reaction [28].

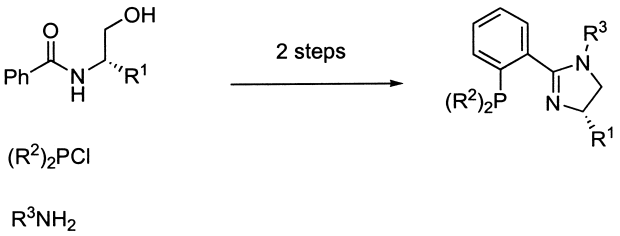
The additional nitrogen atom in the ring gives another site for substitution (Scheme 29.7), and thus for steric and electronic tuning of the ligand structure. A range of catalysts were prepared and used in the hydrogenation of unfunctionalized alkenes. These outperformed the original PHOX catalyst in the hydrogenation of substrates **3**, **4**, and **5** [29]. They have also been successfully applied to the hydrogenation of terpenoid dienes and trienes [30].



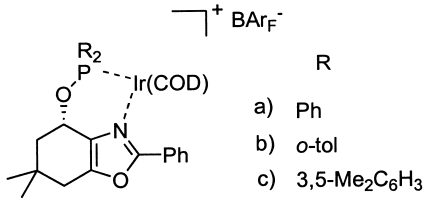
28

	R^1	R^2	R^3
a)	*i*Pr	Ph	*i*Pr
b)	*i*Pr	Ph	Cy
c)	*i*Pr	Ph	CH_2Ph
d)	*i*Pr	Ph	Ph
e)	*t*Bu	Ph	Ph
f)	*t*Bu	Ph	*p*-$MeOC_6H_4$
g)	*t*Bu	Ph	*p*-$CF_3C_6H_4$
h)	*t*Bu	Ph	*p*-tol
i)	*t*Bu	*o*-tol	Ph
j)	*t*Bu	*o*-tol	CH_2Ph

Fig. 29.15 Phosphino-imidazoline catalysts **28**.



Scheme 29.7 Synthesis of phosphino-imidazoline ligands.



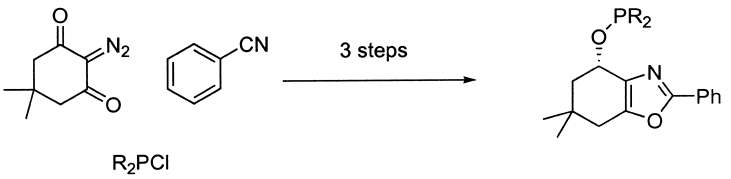
29

R

a) Ph
b) *o*-tol
c) 3,5-$Me_2C_6H_3$

Fig. 29.16 Phosphinite-oxazole catalyst **29**.

Finally, the phosphinite-oxazole catalyst **29** (Fig. 29.16) was recently reported and used to hydrogenate a series of functionalized and unfunctionalized alkenes [31]. It was anticipated that the planar oxazole unit and the fused ring system would improve the enantioselectivity compared to the PHOX catalyst by increasing rigidity in the six-membered chelating ring [32]. Indeed, these catalysts



Scheme 29.8 Synthesis of phosphinite-oxazole catalysts.

proved to be highly selective, rivaling the most selective oxazoline-based catalysts in the hydrogenation of a range of substrates.

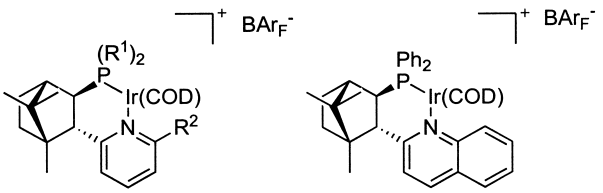
The ligands are synthesized from achiral starting materials using a ketocarbene-nitrile cycloaddition as the key step (Scheme 29.8). The stereogenic center is introduced by enantioselective reduction of the carbonyl group in the cycloaddition product.

29.3
Pyridine and Quinoline-Derived P,N Ligands

Knochel and coworkers synthesized a series of camphor-derived pyridine and quinoline P,N ligands. The catalysts **30** (Fig. 29.17) were used to hydrogenate substrates **1** and **2** in up to 95% and 96% ee, respectively [33]. The selectivities were moderate for other unfunctionalized alkenes; however, a high enantioselectivity was reported for the hydrogenation of ethyl acetamidocinnamate **10** [34].

The ligands derive their chirality from the ring bearing the phosphorus atom, synthesized from (+)-camphor (R = H) or (+)-nopinone ($R = CH_3$) (Scheme 29.9).

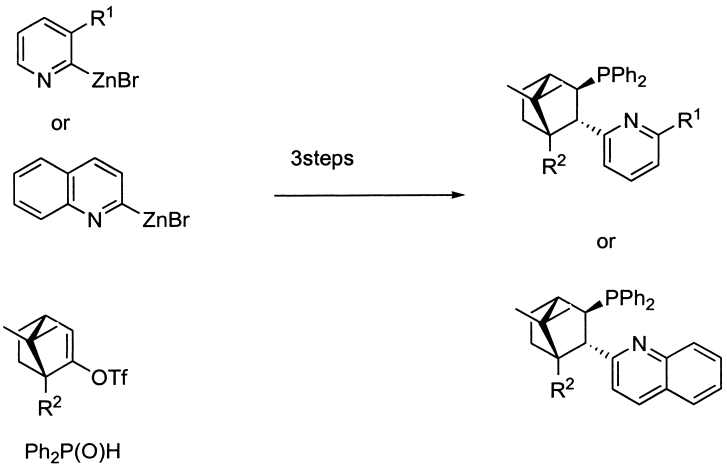
Recently, a series of pyridine- and quinoline-derived catalysts **31** (Fig. 29.18) have been developed. Ligands **31 a–k** were obtained by reduction of pyridyl ke-



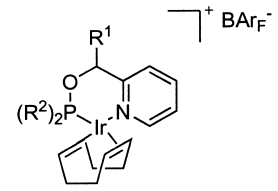
30a-c **30d**

	R^1	R^2
a)	Ph	H
b)	Ph	Ph
c)	Cy	H

Fig. 29.17 Catalyst **30**.

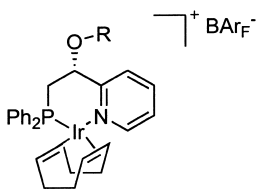


Scheme 29.9 Synthesis of pyridine-derived ligands for catalysts **30**.



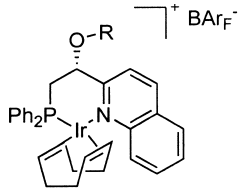
31 a-k

	R^1	R^2
a)	Me	Ph
b)	Me	*o*-tol
c)	Ph	Ph
d)	Ph	*o*-tol
e)	Ph	Cy
f)	Ph	*t*Bu
g)	*t*Bu	Ph
h)	*t*Bu	*o*-tol
i)	*t*Bu	Cy
j)	*t*Bu	*t*Bu
k)	trityl	Ph



31 l-n

	R
l)	Si(*t*Bu)Me_2
m)	Si(*i*Pr)$_3$
n)	Si(*t*Bu)Ph_2



31 o-r

	R
o)	Si(*t*Bu)Me_2
p)	Si(*i*Pr)$_3$
q)	Si(*t*Bu)Ph_2

Fig. 29.18 Pyridine-based catalysts **31**.

tones and resolution of the resulting alcohols. Ligands **31l–n** were synthesized *via* enantioselective reduction of pyridyl ketones and protection as silyl ethers, and ligands **31o–q** were accessed through Sharpless dihydroxylation of a quinolyl alkene, followed by tosylation and introduction of the phosphine group.

In the hydrogenation of **1**, catalysts **31a–j** gave 87–97% ee, whereas catalyst **31k**, with the very bulky trityl substituent on the alkyl backbone, only gave 38% ee. The silyl substituent was found to have a significant effect on selectivity: catalyst **31l** gave 88% ee, while catalyst **31n** gave only 4% ee with substrate **1** [35]. This remarkable effect was rationalized based on X-ray structural data.

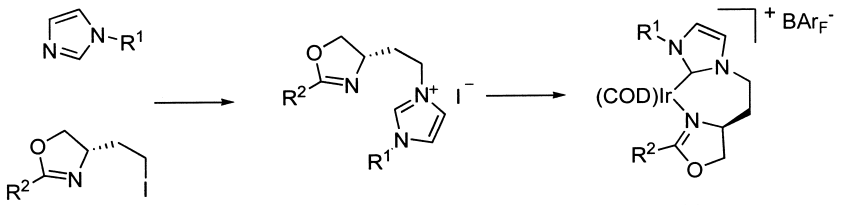
29.4
Carbenoid Imidazolylidene Ligands

The first application of a heterocyclic carbenoid achiral ligand for hydrogenation of alkenes was reported in 2001 by Nolan and coworkers. Both ruthenium [36] and iridium [37] complexes proved to be active catalysts. Turnover frequency (TOF) values of up to 24 000 h^{-1} (at 373 K) were measured for a ruthenium catalyst in the hydrogenation of 1-hexene.

Another series of achiral iridium catalysts containing phosphine and heterocyclic carbenes have also been tested in the hydrogenation of unfunctionalized alkenes [38]. These showed similar activity to the Crabtree catalyst, with one analogue giving improved conversion in the hydrogenation of **11**.

Subsequently, Burgess and coworkers developed the chiral carbenoid ligands **32** (Scheme 29.10), which were structurally related to the JM-PHOS ligand [39, 40].

The most selective catalyst in this series, complex **32c**, with very bulky substituents at the oxazoline and the imidazolylidene moiety, was used to hydrogenate a range of trisubstituted alkenes with enantiomeric excesses of greater than



32

	R^1	R^2
a)	Ph	2,6-(*i*Pr)$_2$C$_6$H$_3$
b)	*t*Bu	2,6-(*i*Pr)$_2$C$_6$H$_3$
c)	1-Ad	2,6-(*i*Pr)$_2$C$_6$H$_3$
d)	$CHPh_2$	2,6-(*i*Pr)$_2$C$_6$H$_3$
e)	1-Ad	2,5-(Et)$_2$C$_6$H$_3$

Scheme 29.10 Carbenoid imidazolylidene ligands based on the JM-PHOS ligand (**32**).

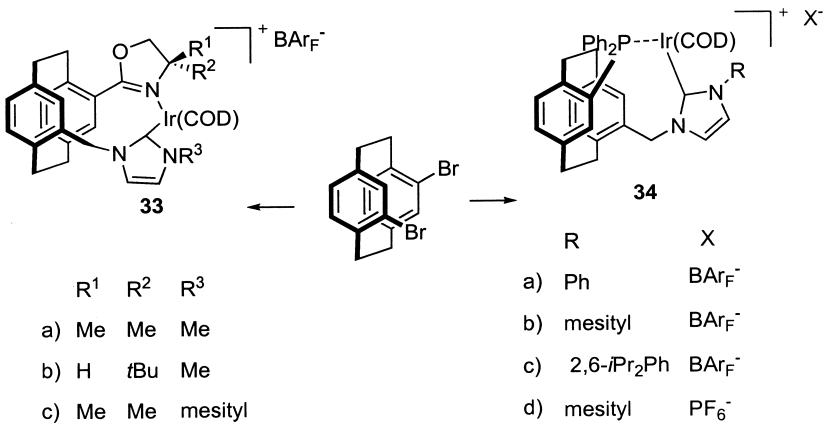


Fig. 29.19 Paracyclophane catalysts.

90%. It was found that the R^1 substituent on the carbenoid ring had a greater effect on selectivity than the R^2 substituent on the oxazoline. All the other catalysts **32a**, **32b**, **32d** and **32e** gave distinctly lower enantioselectivities.

Recently, carbene-oxazoline catalysts **33** and carbene-phosphine catalysts **34** (Fig. 29.19) with a chiral paracyclophane backbone have been synthesized and used to hydrogenate a variety of alkenes, with modest selectivity [41].

29.5 Metallocenes

The metallocenes are described in greater detail in Chapter 30.

Catalyst **35b** was used by Buchwald and coworkers with $[PhMe_2NH]^+$-$[(BC_6F_5)_4]^-$ to hydrogenate tetrasubstituted unfunctionalized cyclic olefins with up to 97% ee [42].

The enantiopure catalyst **35b** was synthesized from **35c** [43] *via* the binaphtholate **35a** [44, 45].

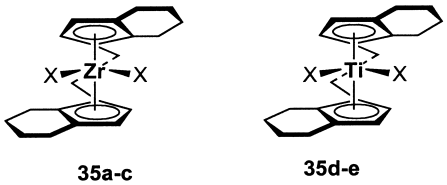


Fig. 29.20 EBTHI catalysts **35**.

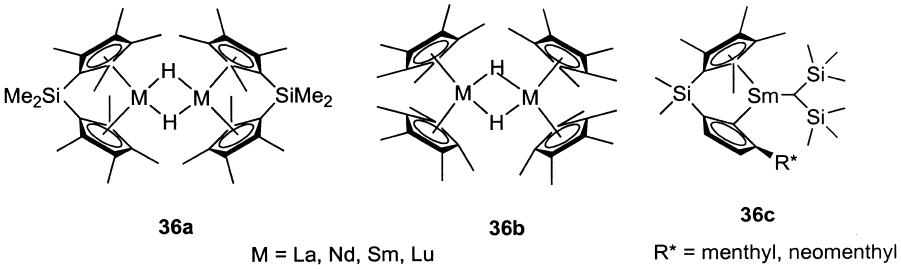


Fig. 29.21 Cyclopentadienyl lanthanide catalysts **36**.

The most selective – and also most general – titanocene catalyst is complex **35 d**, also studied by Buchwald and coworkers. This catalyst was used to hydrogenate a variety of functionalized and unfunctionalized cyclic and acyclic alkenes with excellent ee-values in most cases [46]. Enamines could also be hydrogenated with enantiomeric excesses of 80–90% [47]. However, high catalyst loadings (5–8 mol%) and long reaction times were required to drive the reactions to completion.

Marks and coworkers developed a series of cyclopentadienyl-lanthanide complexes. In the initial investigations on achiral catalysts **36 a** and **36 b** (Fig. 29.21), TOFs greater than 100 000 h^{-1} were observed in the hydrogenation of 1,2-disubstituted unfunctionalized alkenes [48].

Chiral analogue **36 c** was then synthesized [49]. Catalyst **36 c** (R = menthyl) hydrogenated 2-phenyl-1-butene **7** with 96% ee at 195 K, with enantioselectivity being found to be highly temperature-dependent.

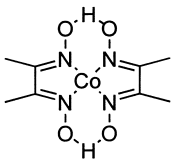
29.6 Other Ligands

The cobalt complex **37** was used in combination with quinine as a chiral coordinating base to hydrogenate 1,2-diphenyl-2-propene-1-one in 49% ee (Fig. 29.22) [50]. However, no further studies of this type of catalyst were reported.

Corma and coworkers tested a number of rhodium and other transition metal complexes with ligands based on proline (Fig. 29.23). These authors reported ee-values of 54–90% for the hydrogenation of dehydroamino acid derivatives with a catalyst prepared from ligand **38** [51]. With ligand **39**, an ee-value of 34% was recorded for the hydrogenation of ethyl acetamidocinnamate **10** [52].

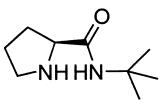
Brauer and coworkers also prepared a rhodium catalyst, using an amino-phospholane ligand, catalyst **40** (Fig. 29.24). This was used to hydrogenate ethyl acetamidocinnamate **10** in 60% ee [53].

Catalyst **41** (Fig. 29.29) is based on a sulfinyl imine, with the stereogenic center at the sulfinamide group. The best catalyst in this series, **41 a**, gave 94% ee in the hydrogenation of substrate **1** [54]. The catalyst has low activity, with 5 mol% catalyst being required.

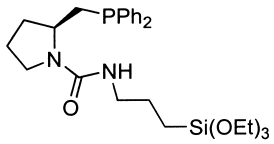


37

Fig. 29.22 Cobalt catalyst **37**.

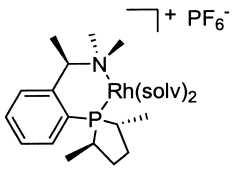


38



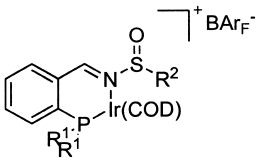
39

Fig. 29.23 Ligands **38** and **39**.



40

Fig. 29.24 Catalyst **40**.

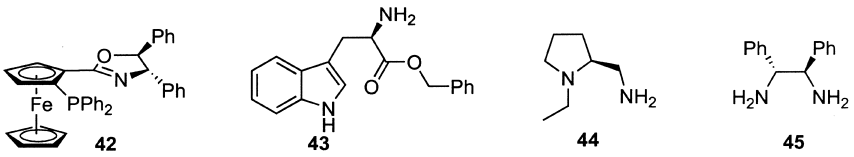


41

	R^1	R^2
a)	*o*-tol	*t*Bu
b)	*o*-tol	1-Ad
c)	*o*-tol	3-ethylpentyl
d)	*o*-tol	*p*-tol
e)	*o*-tol	mesityl
f)	3,5-$Me_2C_6H_3$	*t*Bu
g)	Ph	*t*Bu

Fig. 29.25 Sulfinyl imine catalyst **41**.

Finally, another group of rhodium catalysts based on ligands **42** to **45** (Fig. 29.26) has recently been synthesized and tested on the enantiomeric hydrogenation of *α*-phenylcinnamic acid **13**, giving 59 to 84% ee [55, 56]. The same complexes, when immobilized on mesoporous silica, were found to be even more enantioselective. The results obtained with rhodium complexes based on ligands such as **38**, **43**, **44**, or **45** are in contrast to the general experience that catalysts containing only nitrogen ligands are catalytically inactive and show a tendency to decompose under hydrogen pressure to give metallic rhodium.



42-45 $[Rh(COD)L]^+CF_3SO_3^-$

Fig. 29.26 Catalysts **42** to **45**.

Further studies will be necessary to confirm these results and to establish the potential of catalysts of this type.

29.7 Conclusions

The development of chiral P,N and non-phosphorus ligands for the asymmetric hydrogenation of C=C bonds remains a young and rapidly developing field of research. The application range of these ligands is largely complementary to chiral phosphines. While chiral phosphines form efficient catalysts in combination with Rh and Ru, the primary domain of P,N ligands is Ir-catalyzed hydrogenation (see Chapter 30). Iridium complexes with chiral P,N ligands have considerably expanded the application range of asymmetric hydrogenation to unfunctionalized alkenes as well as various functionalized olefins, which give poor results with Rh or Ru catalysts. The most efficient P,N ligands developed to date have been oxazoline derivatives such as ThrePHOX 23 or SimplePHOX 24, and the bicyclic oxazole derivative **29**. Promising results have also been obtained with the carbenoid P,C ligand **32**. Metallocene catalysts have also been successfully applied for asymmetric hydrogenation of unfunctionalized alkenes, though as yet this class of catalysts has found only limited use.

Abbreviations

ee	enantiomeric excess
PHOX	phosphino-oxazoline
TOF	turnover frequency
TON	turnover number

References

1 L. Horner, H. Siegel, H. Büthe, *Angew. Chem.* **1968**, 1034.
2 W. S. Knowles, M. J. Sabacky, *J. Chem. Soc. Chem. Commun.* **1968**, 1445.
3 T. P. Dang, H. B. Kagan, *J. Chem. Soc. Chem. Commun.* **1971**, 481.
4 B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946.
5 A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33.
6 R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331.
7 A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897.
8 N. S. Goulioukina, M. Dolgina, G. N. Bondarenko, I. P. Beletskaya, M. M. Ilyin, V. A. Davankov, A. Pfaltz, *Tetrahedron Asymm.* **2003**, *14*, 1397.
9 D. G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider, N. Zimmermann, *Chirality* **2000**, *12*, 442.
10 G. Koch, G. C. Lloyd-Jones, O. Loiseleur, A. Pfaltz, R. Pretot, S. Schaffner, P. Schnider, P. von Matt, *Rec. Trav. Chim. Pays-Bas* **1995**, *114*, 206.
11 P. Von Matt, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 556.
12 J. V. Allen, G. J. Dawson, C. G. Frost, J. M. J. Williams, *Tetrahedron* **1994**, *50*, 799.
13 M. Peer, J. C. de Jong, M. Kiefer, T. Langer, H. Rieck, H. Schell, P. Sennhenn, J. Sprinz, H. Steinhagen, B. Wiese, G. Helmchen, *Tetrahedron* **1996**, *52*, 7547.
14 D. Liu, W. Tang, X. Zhang, *Org. Lett.* **2004**, *6*, 513.
15 P. G. Cozzi, F. Menges, S. Kaiser, *Synlett* **2003**, *6*, 829.
16 D. R. Hou, J. H. Reibenspies, T. J. Colacot, K. Burgess, *Chem. Eur. J.* **2001**, *7*, 5391.
17 W. Tang, W. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2003**, *42*, 943.
18 S. Lu, X. Han, Y. Zhou, *Adv. Synth. Catal.* **2004**, *346*, 909.
19 R. Hilgraf, A. Pfaltz, *Synlett* **1999**, *11*, 1814.
20 J. Blankenstein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445.
21 F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40.
22 Available from STREM: complex **23a** catalog number 77-5020, complex **23g** catalog number 77-5010.
23 S. P. Smidt, F. Menges, A. Pfaltz, *Org. Lett.* **2004**, *6*, 2023.
24 R. Hilgraf, A. Pfaltz, *Adv. Synth. Catal.* **2005**, *347*, 61.
25 P. G. Cozzi, N. Zimmermann, R. Hilgraf, S. Schaffner, A. Pfaltz, *Adv. Synth. Catal.* **2001**, *343*, 450.
26 G. Xu, S. R. Gilbertson, *Tetrahedron Lett.* **2003**, *44*, 953.
27 G. H. Bernardinelli, E. P. Kündig, P. Meier, A. Pfaltz, K. Radkowski, N. Zimmermann, M. Neuburger-Zehnder, *Helv. Chim. Acta* **2001**, *84*, 3233.
28 C. Busacca, WO2001018012, **2001**.
29 F. Menges, M. Neuburger, A. Pfaltz, *Org. Lett.* **2002**, *4*, 4173.
30 Patent application: B. Wüstenberg, F. Menges, T. Netscher, A. Pfaltz, (DSM), 22. 12. 2004.
31 K. Källstrom, C. Hedberg, P. Brandt, A. Bayer, P. G. Andersson, *J. Am. Chem. Soc.* **2004**, *126*, 14308.
32 P. Brandt, C. Hedberg, P. G. Andersson, *Chem. Eur. J.* **2003**, *9*, 339.
33 T. Bunlaksananusorn, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *42*, 3941.
34 T. Bunlaksananusorn, P. Knochel, *J. Org. Chem.* **2004**, *69*, 4595.
35 W. J. Drury, N. Zimmermann, M. Keenan, M. Hayashi, S, Kaiser, R. Goddard, A. Pfaltz, *Angew. Chem. Int. Ed.* **2004**, *43*, 70.
36 H. M. Lee, D. C. Smith, Z. He, E. D. Stevens, C. S. Yi, S. P. Nolan, *Organometallics* **2001**, *20*, 794.
37 H. M. Lee, T. Jiang, E. D. Stevens, S. P. Nolan, *Organometallics* **2001**, *20*, 1255.
38 L. D. Vázquez-Serrano, B. T. Owens, J. M. Buriak, *J. Chem. Soc. Chem. Commun.* **2002**, 2518.
39 M. T. Powell, D. R. Hou, M. C. Perry, X. Cui, K. Burgess, *J. Am. Chem. Soc.* **2001**, *123*, 8878.

40 M. C. Perry, X. Cui, M. T. Powell, D. R. Hou, J. H. Riebenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113.

41 C. Bolm, T. Focken, G. Raabe, *Tetrahedron Asymm.* **2003**, *14*, 1733.

42 M. V. Troutman, D. H. Appella, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4916.

43 F. R. W. P. Wild, L. Zsolnai, G. Huttner, H. H. Brintzinger, *J. Organomet. Chem.* **1985**, *232*, 233.

44 R. B. Grossman, W. M. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **1991**, *113*, 2321.

45 R. M. Waymouth, F. Bangerter, P. Pino, *Inorg. Chem.* **1988**, *27*, 758.

46 R. D. Broene, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 12569.

47 N. E. Lee, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 5985.

48 G. Jeske, H. Lauke, H. Mauermann, H. Schumann, T. J. Marks, *J. Am. Chem. Soc.* **1985**, *107*, 8111.

49 V. P. Conticello, L. Brard, M. A. Giardello, Y. Tsuji, M. Sabat, C. L Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 2761.

50 Y. Ohgo, S. Takeuchi, Y. Natori, J. Yoshimura, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2124.

51 A. Corma, M. Iglesias, C. Del Pino, F. Sánchez, *J. Chem. Soc. Chem. Commun.* **1991**, *1252*, 1253.

52 A. Carmona, A. Corma, M. Iglesias, A. San José, F. Sánchez, *J. Organomet. Chem.* **1995**, *492*, 11.

53 D. J. Brauer, K. W. Kottsieper, S. Rossenbach, O. Stelzer, *Eur. J. Inorg. Chem.* **2003**, 1748.

54 L. B. Schenkel, J. A. Ellman, *J. Org. Chem.* **2003**, *69*, 1800.

55 J. Rouzaud, M. D. Jones, R. Raja, B. F. G. Johnson, J. M. Thomas, M. J. Duer, *Helv. Chim. Acta* **2003**, *86*, 1753.

56 M. D. Jones, R. Raja, J. M. Thomas, B. F. G. Johnson, D. W. Lewis, J. Rouzaud, K. D. M. Harris, *Angew. Chem. Int. Ed.* **2003**, *42*, 4326.