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Asymmetric Hydrogenation of Minimally Functionalised Terminal Olefins: An Alternative Sustainable and Direct Strategy for Preparing Enantioenriched Hydrocarbons

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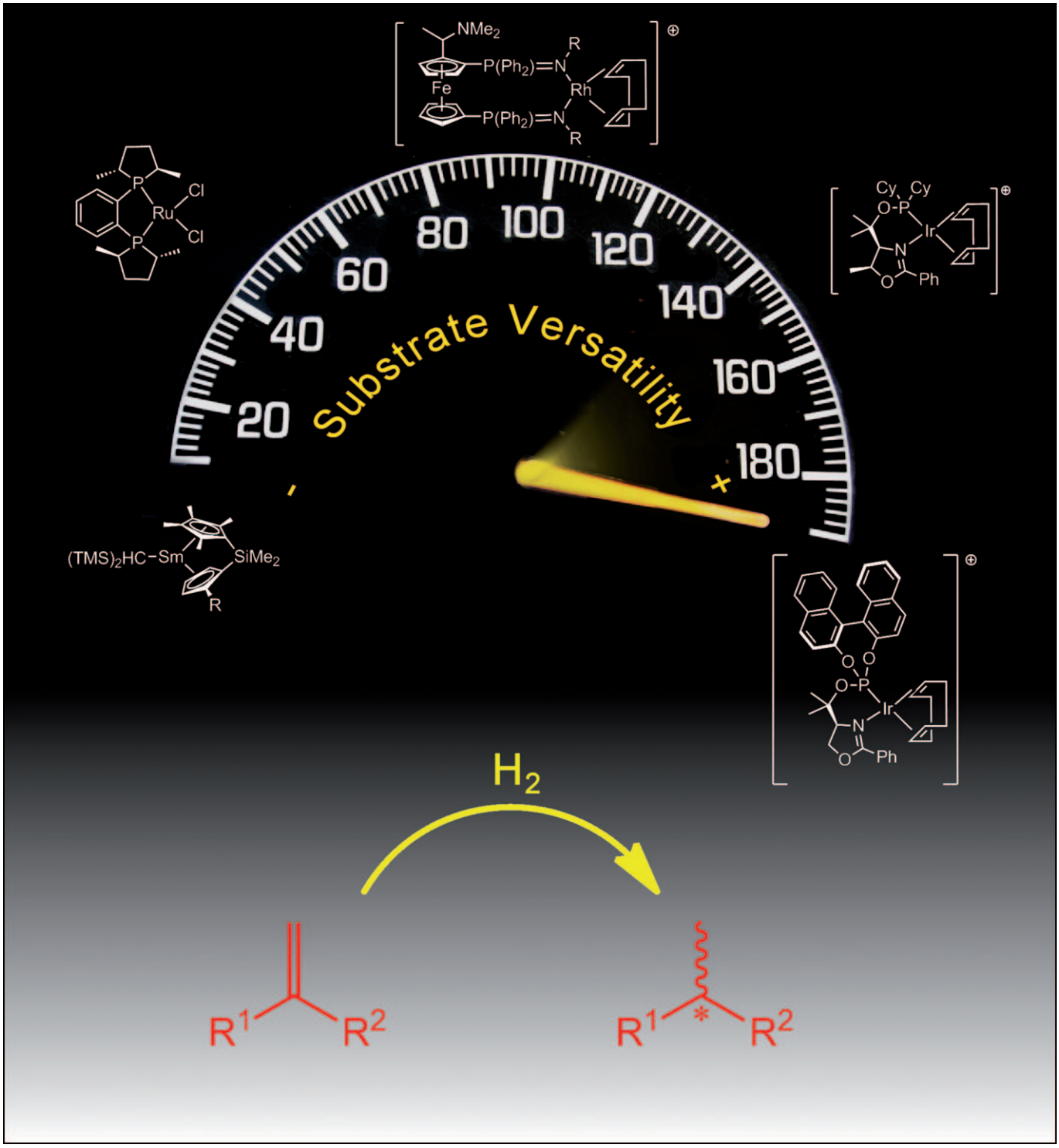
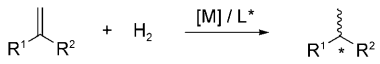


Abstract: This account discusses the progress made in the asymmetric hydrogenation of minimally functionalised terminal olefins as a new, alternative, sustainable and direct strategy for preparing enantioenriched hydrocarbons. It discusses the latest development in catalyst design, from the initial discovery of lanthanide catalytic precursors, through the use of transition-metal/diphosphine–iminophosphorane precursors, to the successful iridium/P,N catalytic systems.

Keywords: carbene ligands · hydrogenation · iridium · olefins · P ligands

Introduction

Enantiopure hydrocarbons are important intermediates for the preparation of drugs and research materials. The quest for an efficient methodology that is compatible with the goals of sustainable and "green" chemistry and which can convert minimally functionalised terminal alkenes into enantiopure hydrocarbons is still one of the main challenges in asymmetric catalysis. Despite the many approaches that have been used to find such a methodology,[1] only limited success has been achieved. Because of its atom economy and operational simplicity, the asymmetric hydrogenation of terminal alkenes could be an alternative sustainable and direct synthetic tool for preparing these compounds (Scheme 1).



Scheme 1. Preparation of chiral hydrocarbons through asymmetric hydrogenation of minimally functionalised 1,1-disubstituted terminal alkenes.

The reduction of olefins containing an adjacent polar group (i.e., dehydroaminoacids) by Rh- and Ru- catalyst precursors modified with phosphorus ligands has a long history.[2] However, efficient catalysts for the hydrogenation of minimally functionalised olefins were not developed until recently.[3] Chiral Ir/P,N complexes have become extremely useful catalytic precursors for the hydrogenation of minimally functionalised tri- and tetra-substituted olefins.[3] The most successful ligands contain a phosphine, phosphinite or phosphite moiety as P-donor group and either an oxazoline,[4a,b,f,g] oxazole,[4c,h] thiazole[4d] or pyridine[4e] as N-donor group (Figure 1).

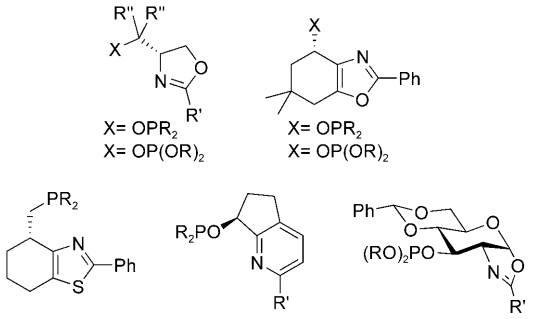
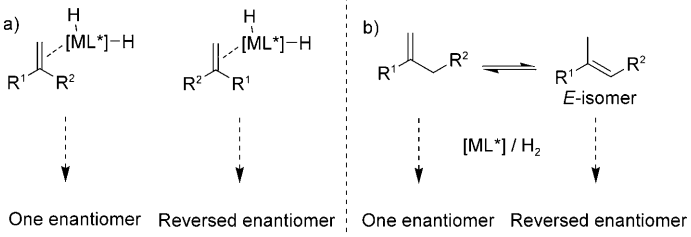


Figure 1. Privileged P,N-ligands for Ir-catalysed hydrogenation of alkenes.

However, less attention has been given to the reduction of minimally functionalised 1,1-disubstituted terminal alkenes to give chiral hydrocarbons, which has remained a significant challenge in the field of asymmetric hydrogenation. This is largely for two reasons.[3d] The first is that the two substituents of the substrate R^1 and R^2 can easily exchange positions in the chiral environment formed by the catalysts, thus reversing the face selectivity (Scheme 2a). The second reason is that the terminal double bond can isomerise to form the more stable internal (*E*)-alkene, which usually leads to the predominant formation of the other enantiomer of the hydrogenated product (Scheme 2b).



Scheme 2.

This account discusses the progress made in the asymmetric hydrogenation of minimally functionalised terminal olefins as an alternative sustainable and direct strategy for preparing enantioenriched hydrocarbons. It pays special attention to the latest developments and provides useful future research directions.

Early Success: Lanthanide Catalytic Systems

The first efficient enantioselective hydrogenation of terminal olefins used chiral metallocene samarium biscyclopentadienyl complexes **1**, developed in 1992 by Marks' group

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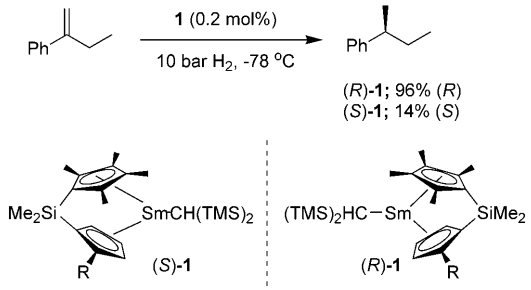
(Scheme 3).[5a] Subsequently the same group extended the range of metallocene biscyclopentadienyl catalysts by using other lanthanide metals (Ln = Y, La, Nd and Lu). They

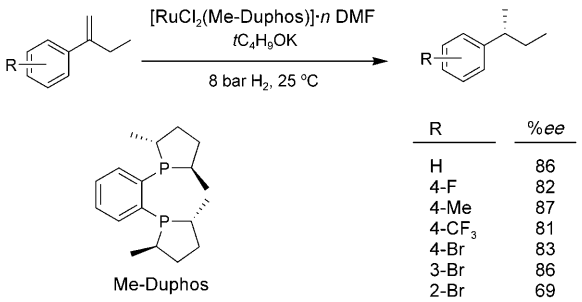


Scheme 3. Sm-catalysed asymmetric hydrogenation. R = (−)-Menthyl.

found that enantioselectivity was very sensitive to the identity/size of the Ln. The enantioselectivities, therefore, decreased markedly as the Ln ionic radius decreased.[5b] Their work provided high enantioselectivities (up to 96%) in the reduction of 2-phenylbut-1-ene and demonstrated that chiral hydrocarbons could be formed using asymmetric hydrogenation. However, the low temperatures needed to achieve high enantioselectivities (−78 °C) and the low modularity of the catalytic system hampers their potential efficiency.

Use of Ru/Diphosphine and Rh/- and Ir/ Iminophosphorane Catalytic Systems

In 2000, Noyori et al. used [$RuCl_2$(Me-Duphos)]·*n* DMF (**2**) in the asymmetric hydrogenation of a limited range of 2-phenylbut-1-enes under basic conditions to provide *ee*'s up to 89% (Scheme 4).[6] They found that enantioselectivity



R	%*ee*
H	86
4-F	82
4-Me	87
4-CF_3	81
4-Br	83
3-Br	86
2-Br	69

Scheme 4. Asymmetric Ru-catalysed hydrogenation of terminal alkenes.

was relatively insensitive to the *para*- and *meta*-substituents of the substrate. However, the *ortho*-analogues provided moderate yields and enantioselectivitites. A mechanistic study suggests that the reduction of 2-phenylbut-1-enes with [$RuCl_2$(Me-Duphos)]·*n* DMF occurs directly without isomerisation to the internal olefins. Using bulkier Et-Duphos or BINAP (2,2′–bis(diphenylphosphino)–1,1′–binaphthyl), which is a fully aromatic phosphine, was not effective. This study opened up the asymmetric hydrogenation of terminal alkenes to more frequently used transition-metal/phosphine catalytic systems. However, basic conditions can hamper the substrate scope, limiting the asymmetric hydrogenation of terminal olefins only to those lacking a base-sensitive group.

Recently, M/chiral (iminophosphoranyl)ferrocene catalyst precursors (M = Rh and Ir; **3–6**) have been developed for this process. The catalyst system (*S*,*R*)-**3** has been successfully used in the hydrogenation of 6-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (*ee*'s up to 94% using M = Rh) and 2-(4-methoxyphenyl)-1-butene (*ee*'s up to 97% using M = Rh) (Scheme 5).[7] Despite this success, no other

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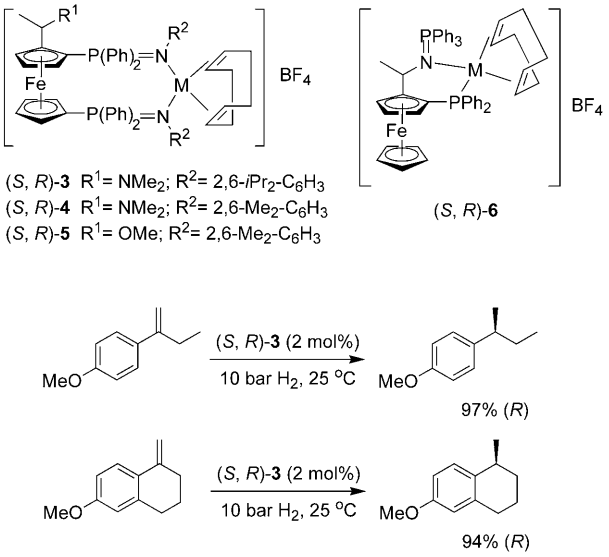
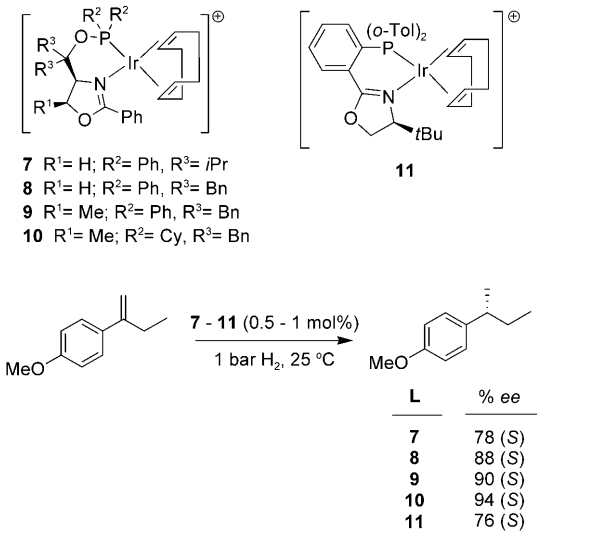
Montserrat Diéguez studied chemistry at the Rovira i Virgili University in Tarragona (Spain), where she received her Ph.D. in 1997 working in the group of Prof. C. Claver. After a year as postdoctoral fellow with Prof. R.H. Crabtree at Yale University in New Haven (USA), she returned to Tarragona in 1999. She is currently working as an associate professor at the Rovira i Virgili University. She obtained the Distinction from the Generalitat de Catalunya for the promotion of University Research in 2004 and the Grant for Research Intensification from URV in 2008. Recently she has been awarded the ICREA Academia Prize 2009 from the Catalan Institution for Research and Advanced Studies. Her present research is focused on organometallic chemistry, mainly the synthesis of chiral ligands and asymmetric catalysis using a combinatorial approach.

Pher G Andersson was educated at Uppsala University where he received his BSc in 1988 and his PhD in 1991 under the supervision of Prof. Jan-E Bäckvall. After postdoctoral research at the Scripps Research Institute with Prof. K. B. Sharpless, he returned to Uppsala University where he became docent 1994 and full professor 1999. He obtained the Bjurzon's Price for an excellent thesis in 1992, a Fulbright Fellowship in 1993, the Oscar's Prize in 1995, a Junior Individual Grant For Outstanding Researchers in 1996 and recently the Astra&Zeneca's prize for Creativity in Organic Chemistry in 2005. His main research interests involve organometallic chemistry, stereoselective synthesis, and asymmetric catalysis.



Scheme 5. Metal/chiral (iminophosphoranyl)ferrocene catalyst precursors **3**–**6**. The enantioselectivities obtained by using Rh-complex **3** in the hydrogenation of terminal alkenes are also shown.



Scheme 6. Representative Ir/phosphinite–oxazoline and Ir/phosphine–oxazoline catalyst precursors developed by Pfaltz and co-workers. $BArF^-$ as counterion. A summary of the enantioselectivities obtained in the hydrogenation of 2-(4-methoxyphenyl)-1-butene using **7**–**11** is also given.

systems or substrates have been applied and the potential of these types of catalyst system needs to be verified.

Use of Ir/P,N and Ir/C,N Catalytic Systems

An important breakthrough in this area of research was made by Pfaltz et al. They successfully applied the protocols that use Ir/P,N catalytic systems for the hydrogenation of minimally functionalised tri- and tetrasubstituted olefins to terminal olefins.[3] They evaluated a series of iridium complexes containing highly modular phosphinite–oxazoline, derived from serine (**7** and **8**) and threonine (**9** and **10**), and phosphine–oxazoline PHOX (**11**) ligands (Scheme 6).[4a,8] Results indicated that the ligand parameters have an important effect on enantioselectivity. The enantioselectivities (*ee*'s up to 94%) were best with the Ir catalytic system **10** containing the basic cyclohexyl phosphinite-oxazoline derived from threonine (Scheme 6).

Catalytic system **10** was also successfully applied to a range of differently substituted 2-arylbut-1-enes and the allylic alcohol 2-(4-chlorophenyl)prop-2-en-1-ol (Figure 2).[4a,8] As observed by Noyori et al., when the Ru/(Me-Duphos) catalytic system (**2**) is used, the enantioselectivity is relatively insensitive to the electronic effects in the phenyl ring. In addition, lowering the reaction temperature to 0°C noticeably decreases enantioselectivity (i.e., from 94 to 90% for 2-(4-methoxyphenyl)-1-butene). A plausible explanation for this can be that the isomerisation of the substrate is more favoured at low temperature than at room temperature. They also found that selectivity is highly pressure dependent in the Ir-catalysed reduction of these terminal alkenes. Hydrogenation at atmospheric pressure of H_2 gave significantly higher *ee*'s than at higher pressures (*ee* decreases from 94 to 58% when pressure is increased to 50 bar).

More recently, Pfaltz and co-workers extended the scope of catalysts **10** and **11** to the asymmetric hydrogenation of terminal enamines with enantioselectivities up to 93% (Figure 2).[9] In general, results were best with (1-phenylvinyl)-amines bearing a phenyl or benzyl substitutent on the nitrogen atom, which were hydrogenated with an enantiomeric excess of >90%. Enantioselectivities in the hydrogenation of cyclic and acyclic 1,2-disubstituted enamines were lower. In addition, the results suggest that the choice of the right Ir-catalyst precursor depends on the type of substituent present on the nitrogen atom of the substrate. Thus, when a benzyl substituent is present, enantioselectivities are best

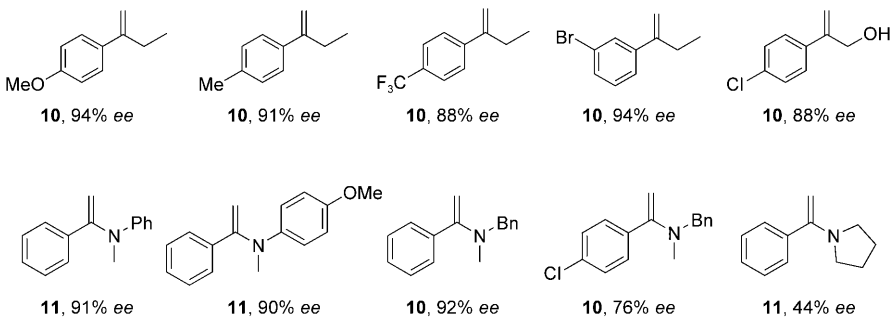


Figure 2. Summary of the best results obtained in the asymmetric Ir-catalysed hydrogenation of minimally functionalised terminal olefins using catalyst precursors **7**–**11** developed by Pfaltz.

with an Ir catalyst precursor **10**. When a phenyl substitutent is present, however, the best catalyst is **11**.

In 2003, Burgess and co-workers replaced the P-donor moiety with a carbene group by using Ir complexes containing N-heterocyclic carbene/oxazoline ligands.[10] These catalyst precursors were applied to the reduction of 2-(4-methoxyphenyl)-1-butene (Figure 3). Enantioselectivities up to

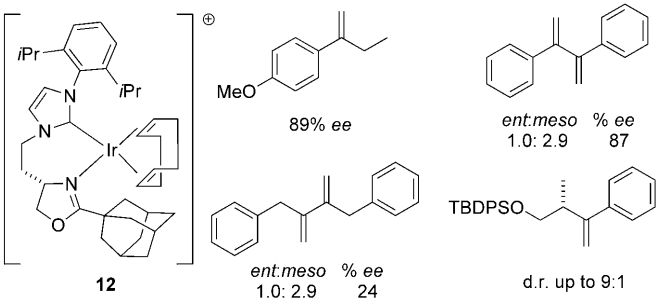


Figure 3. Ir/carbene–oxazoline complex **12** developed by Burgess and co-workers. $BArF^-$ as counterion. A summary of the enantioselectivities obtained in the hydrogenation of 2-(4-methoxyphenyl)-1-butene and several 1,1-disubstituted dienes is also given.

89% were obtained using precursor **12** (Figure 3).[10] This catalytic system was also used in the asymmetric reduction of unfunctionalised 1,1-disubstituted dienes with enantioselectivities up to 87% and moderate diastereoselectivities (Figure 3).[11] As expected, the reduction of trisubstituted dienes provided the hydrogenated products in higher diastereo- (up to 20:1) and enantioselectivities (up to 99%). More recently, the same authors extended their work to the diastereoselective reduction of 1,1-disubstituted olefins containing polar groups with moderate success.[12]

Subsequently, Andersson and co-workers applied Ir/phosphinite–oxazole catalytic system **13** to hydrogenate 2-(4-methoxyphenyl)-1-butene with enantioselectivities up to 97%.[4c] However, enantioselectivities were only moderate for other terminal 2-arylbut-1-enes (Scheme 7).[13] Interestingly, the same authors developed Ir/aminophosphine–oxazoline catalytic systems **14**[14] and **15**[15] and Ir/aminophosphine–thiazole catalytic system **16**[16] which provide high enantioselectivities in the reduction of terminal enolphosphinates,[17] vinylboronates and diphenylvinylphosphine oxides, respectively (ee's up to >99%, Scheme 7).

Despite all these important contributions, the asymmetric hydrogenation of terminal alkenes using Ir/P,N catalyst systems still suffered from a limited substrate scope. In 2008, Andersson, Diéguez and their respective groups discovered that the presence of biaryl-phosphite moieties in ligand design is highly advantageous for the Ir-catalysed reduction of unfunctionalised olefins.[4f,g] Ir/phosphite–oxazoline catalytic systems **17**, derived from inexpensive D-glucosamine, and **18**, related to ligands **7** and **8**, provided greater substrate versatility than previous Ir/phosphinite–oxazoline systems, as well as high activities and enantioselectivities in the reduction of di- and trisubstituted olefins (Figure 4). Interestingly, catalyst precursors **17** and **18** also provided the highest enantioselectivities in the reduction of some α-alkylstyrenes (Table 1, entries 1, 2, 4, 5, 7 and 8).

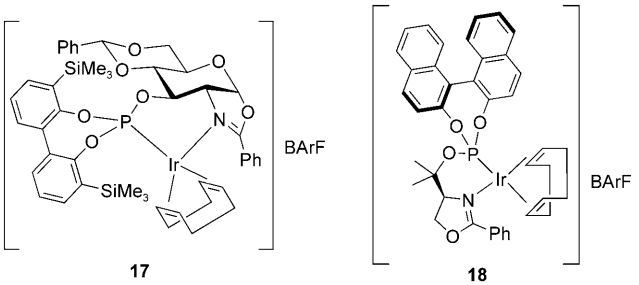
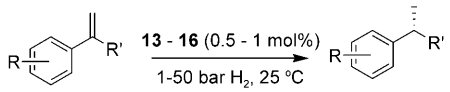
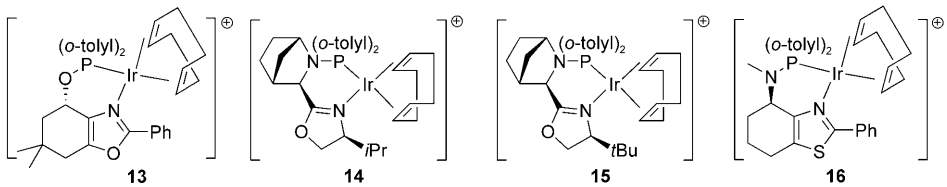


Figure 4. Privileged Ir/phosphite–oxazoline catalytic systems **17** and **18**.

On the basis of these results, in 2009, the same authors together with Börner's group extended their previous work to include other phosphite–oxazoline ligands (**L1**–**L16a**–**f**, Figure 5) and other terminal substrates.[18] This resulted in the discovery that [Ir(cod)(**L15f**)]BArF (**19**; BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) is a privileged catalytic system for the hydrogenation of several types of minimally functionalised terminal olefins. This catalytic system was successfully applied in the hydrogenation of several 1,1,-disubstituted aryl-alkyl substrates (Table 1, entries 3, 6, 9–16). Several *para*-substituted 2-phenylbut-2-enes and several α-alkylstyrenes bearing increasingly sterically demanding alkyl substituents were hydrogenated with excellent enantioselectivi-





R	R'	% ee
4-OMe	Et	97
H	Et	41

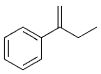
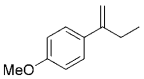
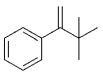
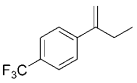
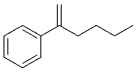
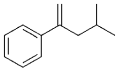
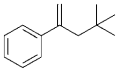
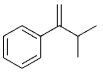
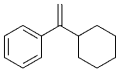
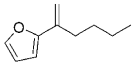
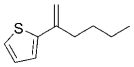
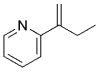
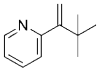
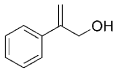
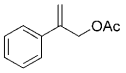
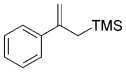
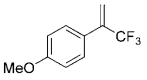
R	R'	% ee
4-OMe	$OP(O)Ph_2$	95
H	$OP(O)Ph_2$	98
*t*Bu	$OP(O)Ph_2$	>99

R	R'	% ee
H	Bpin	89
4-OMe	Bpin	76

R	R'	% ee
4-OMe	$P(O)Ph_2$	>99
H	$P(O)Ph_2$	>99
Cy	$P(O)Ph_2$	99

Scheme 7. Summary of the best results obtained in the asymmetric Ir-catalysed hydrogenation of minimally functionalised terminal olefins using catalyst precursors **13**–**16**. $BArF^-$ as counterion.

Table 1. Asymmetric hydrogenation of minimally functionalised terminal alkenes using Ir/phosphite–oxazoline catalysts **17**–**19**.[a]

Entry	Substrate	Ligand	*ee* [%][b]
1		**17**	99 (*S*)
2		**18**	95 (*S*)
3		**19**	99 (*S*)
4		**17**	>99 (*S*)
5		**18**	97 (*S*)
6		**19**	>99 (*S*)
7		**17**	97 (*S*)
8		**18**	>99 (*S*)
9		**19**	>99 (*S*)
10		**19**	96 (*S*)
11		**19**	94 (*S*)
12		**19**	93 (*S*)
13		**19**	90 (*S*)
14		**19**	97 (*S*)
15		**19**	97 (*S*)
16[c]		**19**	87 (*S*)
17		**19**	99 (−)
18		**19**	96 (−)
19		**19**	99 (+)
20		**19**	>99 (+)
21		**19**	95 (*R*)
22		**19**	91 (*R*)
23		**19**	96 (*S*)
24		**19**	75 (−)

[a] Reactions carried out at 0.2–0.5 mol% using CH_2Cl_2 as solvent. All reactions were run at 1 bar of H_2 except for entries 21–23 for which 50 bar of H_2 was used. Yields >99% after 2 h. [b] Enantiomeric excess. [c] Reaction carried out at 100 bar of H_2 and 1 mol% of catalyst precursor using PC as solvent at 40 °C for 10 h.

ties (90–99% *ee*). This Ir-phosphite/oxazoline catalytic system was also able to reduce a wide range of 1,1-heteroaromatic alkenes, such as thiophene, pyridyl and furan derivatives (96–99% *ee*) with high enantioselectivities (Table 1, entries 17–20). This is interesting because heterocycles are used in industry and because the heterocyclic part can be modified post-hydrogenation. This was also the first attempt to hydrogenate this type of substrate.

It should be noted that catalytic system **19** is also highly tolerant of the presence of a neighbouring polar group. Therefore, 1,1-disubstituted allylic alcohols, acetates and silanes can be hydrogenated in high enantioselectivities (*ee*'s up to 96%) (Table 1, entries 21–23). This was the first successful asymmetric hydrogenation of allylic acetates and silanes. It also considerably improves the preparation of enantioenriched 2-phenylpropanol, because it provides higher enantioselectivities and activities than those obtained in the asymmetric Zr-catalysed methylalumination of α-olefins[1f] and the lipase-mediated kinetic resolution of racemic 2-phenyl propanol.[19]

In addition, catalytic system **19** provided promising enantioselectivities in the asymmetric hydrogenation of trifluoromethyl olefins (Table 1, entry 24). This meant that, for the first time, the asymmetric hydrogenation of these substrates could be used to prepare chiral organofluorine compounds, which are of great importance in the pharmaceutical and agrochemical industries, among others.[20]

Enantiopure diarylalkanes are important intermediates for the preparation of drugs and research materials.[1a–c] To date, the approaches used to prepare optically active diarylalkanes have been rather laborious,[1a–d] but asymmetric hydrogenation may be more efficient. In this context, the Ir/phosphite–oxazoline catalytic system **18**, related to **19**, hydrogenated 1,1-diaryl terminal olefins containing sterically different aryl substituents with excellent enantioselectivities (>99%) (Figure 6).[18] Also, a 1,1-diaryl olefin in which the enantiodiscrimination process is mainly electronic was hydrogenated with enantioselectivities as high as 65%.

More recently, we decided to go one step further in the design of ligands for this process and study whether the biaryl phosphite moiety is still as effective when combined with N-donor groups other than oxazolines. For this purpose, we took two of the most successful ligand families (phosphinite–oxazole[4c] and phosphine–thiazole[4d]) used in the asymmetric reduction of unfunctionalised trisubstituted olefins and replaced their phosphinite or phosphine moieties with biarylphosphite groups to give ligands **L17**–**L23a**–**h** (Figure 7).[4h] These ligands combine the advantages of the oxazole/thiazole moieties with those of the phosphite moiety. So they are more stable than their oxazoline counterparts,[21] less sensitive to air and other oxidising agents than phosphines and phosphinites, and easy to synthesise from readily available alcohols.[22] The results indicated that the Ir catalyst precursor containing phosphite–thiazole **L21a** ligand provides high enantioselectivities in the reduction of a large series of α-alkylstyrenes, 1,1-heteroaromatic alkenes and silanes (Figure 8). For allylic alcohols and acetates, the enantioselectivities are best with catalyst precursor Ir/**L22a** (*ee*'s up to 90%). In addition the Ir catalyst precursor containing phosphite–oxazole ligand **L17a** provides better con-

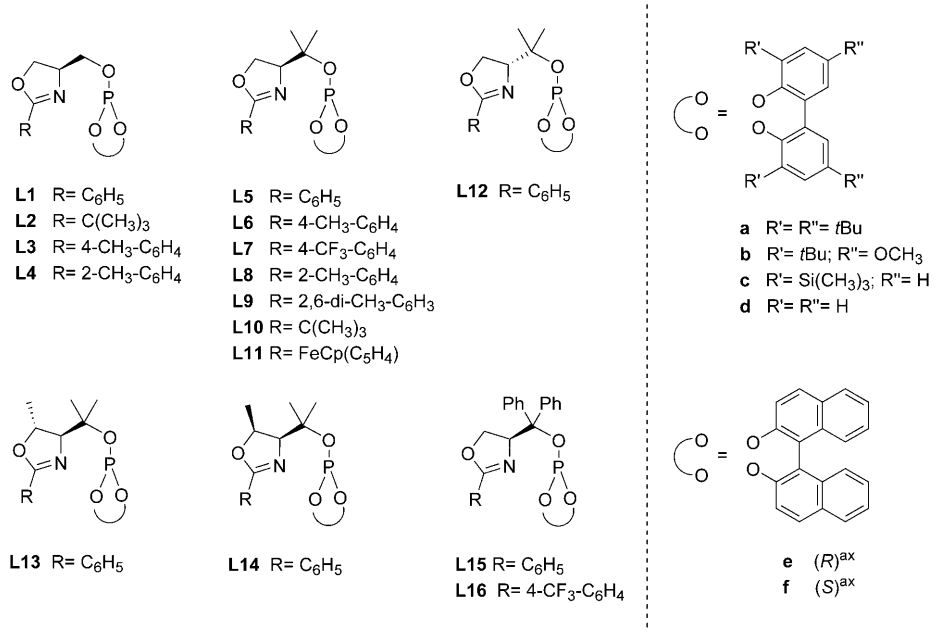


Figure 5. Phosphite-oxazoline ligand library (**L1**–**L16a**–**f**) applied to the asymmetric Ir-catalysed reduction of minimally functionalised olefins.

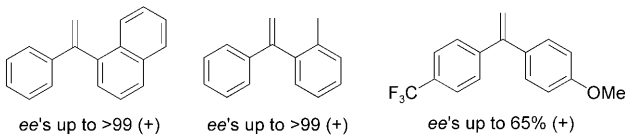


Figure 6. Asymmetric hydrogenation of 1,1-diaryl terminal olefins by using the Ir catalytic system **18**.

versions and enantioselectivities than those obtained with related phosphinite–oxazole ligands in the hydrogenation of enol phosphinate.[14a]

The latest innovation in this field is that propylene carbonate (PC) has been used as an environmentally friendly alternative to standard organic solvents.[23] Their use has shown two main advantages. The first one is that isomerisation of the terminal double bond to the more stable internal alkene is slower in PC than in dichloromethane. For example, the isomerisation of 1-methylene-1,2,3,4-tetrahydronaphthalene to 1-methyl-3,4-dihydronaphthalene is around three times slower in PC than in dichloromethane. The suppression of the undesired isomerisation has a positive effect on enantioselectivity (Figure 9).

The second advantage of using PC as solvent is that it allows catalysts to be repeatedly recycled by a simple two-phase extraction with an apolar solvent. In this context, several aryl–alkyl, heteroaryl–alkyl and diaryl substrates were hydrogenated in PC with catalyst precursors **10**,[23] **18**[18] and **19**[18] and the products were removed by extraction with hexane. Catalysts were used up to five times with no significant losses in enantioselectivity (Figure 10), although the reaction time increased. This is probably due to the iridium catalyst partially passing into the hexane phase[23] and/or the formation of inactive triiridium hydride clusters.[24]

Summary and Outlook

In conclusion, iridium complexes modified with heterodonor P,N-ligands are the state-of-the-art in the asymmetric hydrogenation of minimally functionalised terminal olefins. In this respect, the recent introduction of biaryl phosphite moieties into the ligand design has led to a major improvement in substrate versatility. For the first time, highly versatile catalysts have been developed. This paper, then, demonstrates the asymmetric hydrogenation of a wide range of 1,1-disubstituted terminal alkenes, including 1,1-heteroaryl-alkyl and 1,1-diaryl substrates for which no asym-

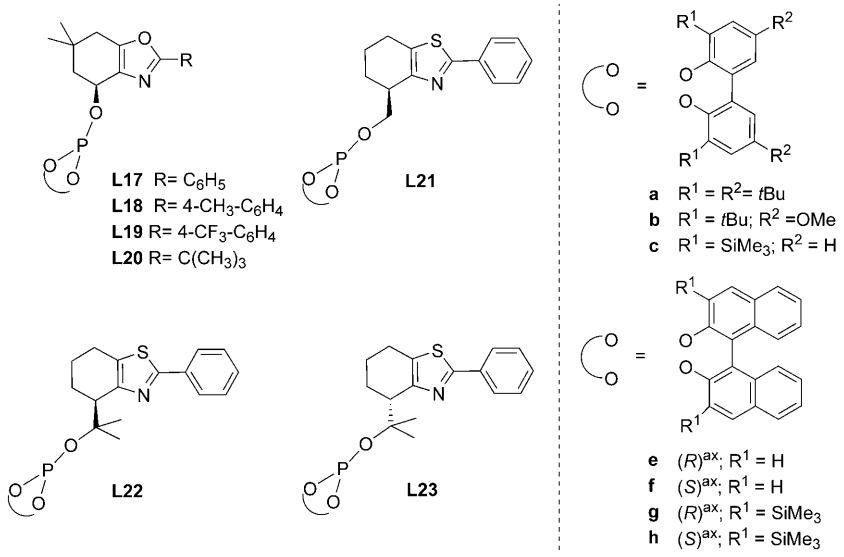


Figure 7. Phosphite–oxazole and phosphite–thiazole ligand library **L17**–**L23a**–**h**.

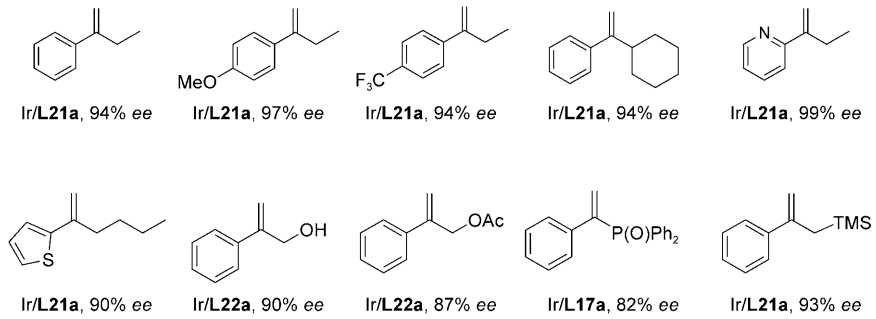
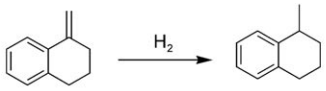


Figure 8. Summary of the best results obtained in the asymmetric Ir-catalysed hydrogenation of minimally functionalised terminal olefins using catalyst precursors [Ir(cod)(**L**)]BArF (**L** = **L17**–**L23a**–**h**).



Catalyst	Solvent	% Conv	% ee
10	CH_2Cl_2	100	17 (*R*)
10	PC	100	82 (*R*)
19	CH_2Cl_2	100	25 (*R*)
19	PC	99	87 (*R*)

Figure 9. Hydrogenation of 1-methylene-1,2,3,4-tetrahydronaphthalene using iridium catalysts **10** and **19**.

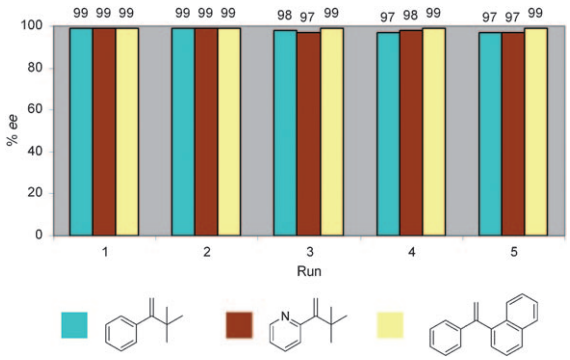


Figure 10. Recycling experiments with the catalysts **18** and **19** in PC.

metric hydrogenation has been reported. These results open up a new sustainable strategy for the preparation of chiral hydrocarbons. The basis in this field has been established and we therefore hope to see further research activity centred on elucidating the mechanism and creating more and more challenging substrates.

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