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Extending the Substrate Scope in the Hydrogenation of Unfunctionalized Tetrasubstituted Olefins with Ir-P Stereogenic Aminophosphine−Oxazoline Catalysts

Maria Biosca,[†] Ernest Salomó,[‡] Pol de la Cruz-Sánchez,[†] Antoni Riera,[‡,§] Xavier Verdaguer,*[,‡,§] Oscar Pàmies,*[,†] and Montserrat Diéguez*[,†]

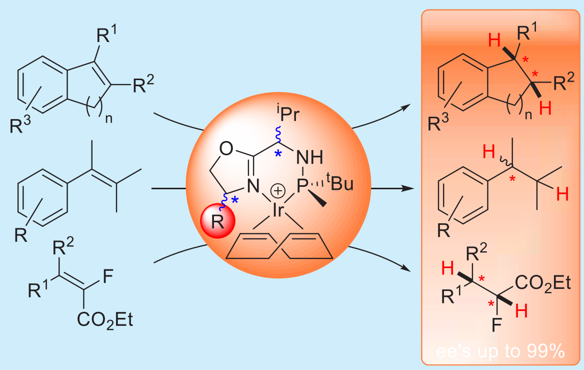
[†]Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo, 1, 43007 Tarragona, Spain

[‡]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology (BIST), C/Baldiri Reixac, 10, 08028 Barcelona, Spain

[§]Departament Química Inorgànica i Orgànica, Secció Orgànica, Universitat de Barcelona, C/Martí i Franquès, 1, 08028 Barcelona, Spain

Supporting Information

ABSTRACT: Air-stable and readily available Ir-catalyst precursors modified with MaxPHOX-type ligands have been successfully applied in the challenging asymmetric hydrogenation of tetrasubstituted olefins under mild reaction conditions. Gratifyingly, these catalyst precursors are able to efficiently hydrogenate not only a range of indene derivatives (ee's up to 96%) but also 1,2-dihydronapthalene derivatives and acyclic olefins (ee's up to 99%), which both constitute the most challenging substrates for this transformation.



Asymmetric hydrogenation (AH) is one of the most common, reliable, and environmentally friendly industrial processes for the preparation of chiral compounds, such as drugs and crop-protecting chemicals.[1] Its strategic relevance has spurred research in both academia and industry over the last decades. Nowadays, an important number of Rh, Ru, and Ir catalysts exist for the AH of a broad range of substrates.[2] However, for some substrates such as tetrasubstituted olefins, attaining high activity and enantioselectivity is still a challenge. Their reduction would open up opportunities to simultaneously generate two vicinal tertiary stereocenters, which are present in many natural and high-valued products.[3] Achieving high enantiocontrol is even more difficult if the olefin lacks a coordinative group that can assist in the transfer of the chiral information from the catalyst to the product.[2] The AH of tetrasubstituted unfunctionalized olefins is therefore underdeveloped compared to the AH of olefins that contain a coordinative functional group.[3] To date, high catalytic performance has been reported in very few publications and with a limited substrate scope. In addition, for each type of olefin a different ligand family was required. In 1999 Buchwald's group reported the first successful AH of tetrasubstituted unfunctionalized olefins.[4] A series of indenes were hydrogenated using the zirconozene catalyst **1** (Figure 1) with moderate-to-high enantioselectivities (ee's in the range 52−99%).[5] They found that enantioselectivity was negatively

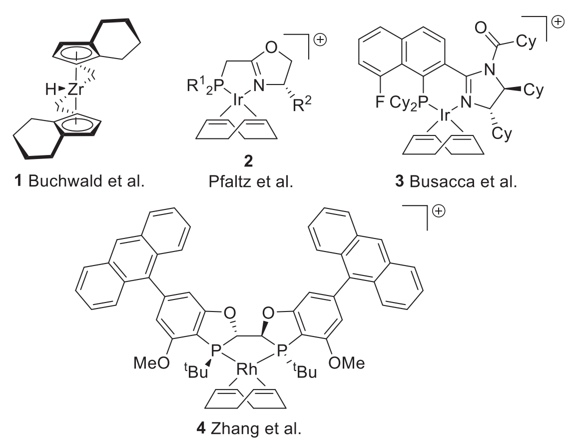


Figure 1. Representative catalysts for the AH of unfunctionalized tetrasubstituted olefins.

affected by substituents other than a methyl in the benzylic position of the substrate. In addition to the low substrate scope, the high catalyst loading (8 mol %), the high H_2 pressure (typically >110 bar) required, and the low stability of

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the catalyst hampered its broad use. Later, Pfaltz and then others demonstrated that the stability and the harsh reaction condition issues of the Zr catalyst can be overcome by using Ir/P-N catalysts. The use of these stable Ir catalysts allowed the AH of tetrasubstituted olefins to be therefore carried out under mild reaction conditions and low catalyst loading (typically 1−2 mol %).[2g] Nevertheless, high enantioselectivities were not achieved until it was found that the optimum ligand structures for tri- and tetrasubstituted olefins differed strongly. This led to specific Ir-catalyst design for the AH of tetrasubstituted olefins (e.g., **2** and **3**, Figure 1 and some of them reported recently).[6] In this context, Pfaltz's group found that Ir-catalysts **2** (Figure 1), which contained ligands that form a 5-membered chelate ring, could hydrogenate a wider range of indenes, with ee's in the range 94−96%, than the Zr-catalyst **1**.[6a] Therefore, catalyst **2** performance proved to be less dependent on the substituents in the benzylic position of the substrate than **1**. Nevertheless, ee's diminished specially for 1,2-dihydronaphthalenes (ee's up to 77%), and for non cyclic olefins high enantioselectivity was only achieved for one substrate (ee's between 89 and 97%). Busacca's group found that the Ir-catalyst **3** could also hydrogenate two cyclic substrates with ee's up to 96% at low catalyst loading. Two inconveniences were that low temperature (0 °C) was required and that the 1,8-disubstituted naphthalene core of the ligand was difficult to prepare.[6b]

In 2017, Zhang's group reported an Rh-catalyst **4** (Figure 1), containing a P-stereogenic diphosphine ligand synthesized in nine steps[7] that provided 85−95% ee's in the AH of indenes.[8] In contrast to Ir catalysts, their Rh catalyst required high catalyst loading (10 mol %), 60 °C, and longer reaction times (4 days).

Despite the relevance of the above-mentioned advances, the substrate scope for the AH of tetrasubstituted olefins still remains limited. Research for a stable, easy to synthesize, catalytic system for the AH of different types of cyclic and acyclic unfunctionalized tetrasubstituted olefins under mild reaction conditions is still needed. In this respect, we thought that the combination in a catalyst system of the advantageous reaction conditions of Pfaltz's Ir/phosphine-N catalysts and Zhang's P-stereogenic concept could be expected to lead to improved stereocontrol in the AH of unfunctionalized tetrasubstituted olefins under mild reaction conditions. This development was however delayed by the difficulty of synthesizing bulky P-sterogenic phosphines in optically pure form. Fortunately, Riera and Verdaguer's group recently presented a novel, straightforward synthetic route that solved this problem and allowed the synthesis of a library of P-stereogenic aminophosphine-oxazoline (MaxPHOX) ligands in which both enantiomeric series are equally available.[9]

We therefore report here the AH of unfunctionalized tetrasubstituted olefins using stable Ir complexes **5−8a−c** (Figure 2), containing MaxPHOX ligands. Compounds **5−8a−c** were easily prepared in four steps from readily available materials,[9b] and their advantageous properties also derive from the bulky P stereogenic center and their high modular approach. Precatalysts **5−8a−c** represent the four diastereomeric possibilities of varying the configuration of substituents at the oxazoline and at the alkyl backbone chain, while maintaining the configuration of the P-stereogenic center (precursors **5−8**). We also studied the effect of increasing the steric bulk of the oxazoline substituent (from **a** to **c**).

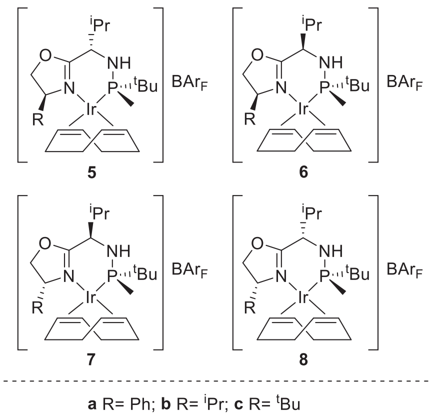
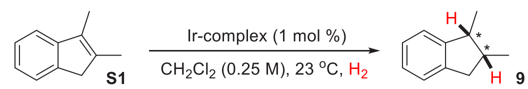


Figure 2. Ir(I)-aminophosphine-oxazoline precatalysts **5−8a−c**.

Initially, we explored the AH of 2,3-dimethyl-1*H*-indene **S1** with Ir-precatalysts **5−8** (Table 1). **S1** was chosen as the model substrate since it could be compared with the results of previous catalysts **1−4**. For the initial reaction conditions, we tested **5−8** in the optimal mild reaction conditions from the previous study with Ir catalysts **2**.[6a] The reactions were therefore carried out at room temperature using 1 mol % of the catalyst under 50 bar of H_2 in dichloromethane. The reactions proceeded smoothly to provide the *cis*-diastereoisomer only. It was observed that both the diastereomeric backbone of the ligand and the oxazoline substituent (entries 1−6) had a remarkable effect on the enantioselectivity. Catalyst precursor **5b** provided the highest enantioselectivity of the series (entry 2, ee up to 93%). Interestingly, lowering the hydrogen pressure, the enantioselectivity increased (see entries 2, 7, and 8).[10] Enantioselectivities up to 95% ee were achieved at only 10 bar of H_2 while maintaining the full conversion (entry 8) under mild reaction conditions. This result is comparable to the best one reported in the literature.

Table 1. Asymmetric Hydrogenation of 2,3-Dimethyl-1*H*-indene S1 Using Ir-Catalyst Precursors 5−8a−c



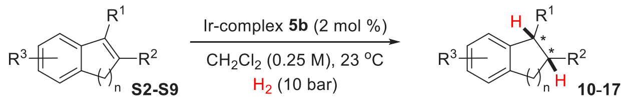
entry	Ir complex	P_{H2} (bar)	% conv (% yield)[a]	% ee[b]
1	**5a**	50	100 (−)[c]	83 (*R*,*R*)
2	**5b**	50	100 (96)	93 (*R*,*R*)
3	**5c**	50	100 (−)[c]	90 (*R*,*R*)
4	**6b**	50	100 (95)	63 (*R*,*R*)
5	**7b**	50	100 (96)	82 (*S*,*S*)
6	**8b**	50	100 (95)	74 (*S*,*S*)
7	**5b**	75	100 (−)[c]	92 (*R*,*R*)
8[d]	**5b**	10	100 (96)	95 (*R*,*R*)

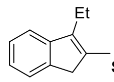
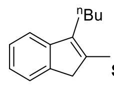
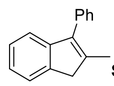
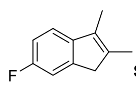
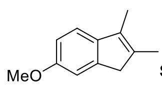
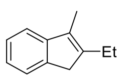
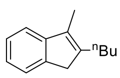
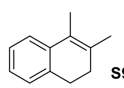
[a]Conversions were measured by ^{1}H NMR spectroscopy after 24 h. [b]Enantiomeric excesses determined by chiral GC. [c]Isolated yield not calculated. [d]Reaction performed using 2 mol % of catalysts.

We further studied the performance of **5b** in the reduction of other indenes (**S2−S8**) and of the demanding 3,4-dimehtyl-1,2-dihydronapthalene **S9** (Table 2).

Substrates **S2−S8** include several substituents at both benzylic (**S2−S4**) and vinylic position (**S7−S8**) and several substituents at the 6-position of the indene (**S5−S6**). We found that precatalyst **5b** tolerated well variations of the alkyl

Table 2. Asymmetric Hydrogenation of Several Indenes S2–S8 and 1,2-Dihydronapthalene S9



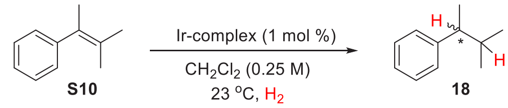
entry	substrate	% conv (% yield)[a]	% ee[b]
1	 S2	100 (98)	95 (*R*,*R*)
2	 S3	100 (96)	96 (*R*,*R*)
3[c]	 S4	45 (-)[d]	82 (*S*,*R*)
4	 S5	100 (94)	85 (*R*,*R*)
5	 S6	100 (96)	91 (*R*,*R*)
6	 S7	100 (91)	92 (*R*,*R*)
7	 S8	100 (92)	91 (*R*,*R*)
8[c]	 S9	100 (93)	89 (*R*,*R*)

[a]Conversions were measured by ^{1}H NMR spectroscopy after 24 h. [b]Enantiomeric excesses determined by chiral GC. [c]Reaction performed using 75 bar of H_2. [d]Isolated yield not calculated.

substituent at both the benzylic (Table 1, entry 8, and Table 2, entries 1–2) and vinylic positions (Table 2, entries 6 and 7). The only exception was substrate **S4** with a phenyl substituent at the benzylic position that led to somewhat lower enantioselectivity (entry 3). The results also indicated that conversion and yields were comparable for substrates **S5** and **S6** (entries 4–5) that contain a different substituent at the 6 position of the indene, although enantioselectivity was slightly better for the methoxy-substituted indene **S6** (entry 5). We should highlight the high enantioselectivity in the hydrogenation of 3,4-dimethyl-1,2-dihydronapthalene **S9** (entry 8), which is one of the most challenging substrates because the catalyst must avoid the dehydrogenation reaction toward the naphthalene derivative. This result improves the previous result by Pfaltz[6a] and is comparable to Busacca's result,[6b] but with our catalyst we do not need to work at low temperature.

Encouraged by the previous results, we then turned our attention to the AH of the most challenging class of tetrasubstituted olefins—the acyclic ones. We first tested Ir precatalysts **5–8a–c** in the AH of (3-methylbut-2-en-2-yl)benzene **S10** as a model substrate (Table 3). The results indicated again that the diastereomeric ligand backbone and the oxazoline substituent had a significant influence (entries 1–6). However, in contrast to what was observed for cyclic olefins, catalyst precursor **6b** provided the highest enantioselectivity of the series (entry 2). This result clearly shows the importance of using a modular scaffold to build a catalyst.

Table 3. Asymmetric Hydrogenation of (3-Methylbut-2-en-2-yl)Benzene S10 Using Ir-Catalyst Precursors 5–8a–c



entry	Ir complex	P_{H2} (bar)	% conv (% yield)[a]	% ee[b]
1	**5b**	75	85 (–)[c]	33 (*S*)
2	**6b**	75	100 (96)	85 (*S*)
3	**7b**	75	100 (94)	44 (*R*)
4	**8b**	75	100 (97)	25 (*R*)
5	**6c**	75	85 (–)[c]	44 (*R*)
6	**6a**	75	100 (–)[c]	75 (*R*)
7	*enant*-**6b**	50	100 (–)[c]	90 (*R*)
8[d]	*enant*-**6b**	10	100 (–)[c]	93 (*R*)
9[d,e]	*enant*-**6b**	2	100 (95)	98 (*R*)

[a]Conversions were measured by ^{1}H NMR spectroscopy after 24 h. [b]Enantiomeric excesses determined by chiral GC. [c]Isolated yield not calculated. [d]Reaction performed using 2 mol % of catalysts. [e]Conversion measured after 36 h.

Again, there is a positive effect on enantioselectivity when the hydrogen pressure is lowered (entries 2 and 7–9). Enantioselectivities increased up to 98% ee when the reduction was done at only 2 bar of H_2 (entry 9).

Under the mild optimal conditions found we further extended our work to the AH of other acyclic tetrasubstituted olefins **S11–S18** (Figure 3). Advantageously, we found that

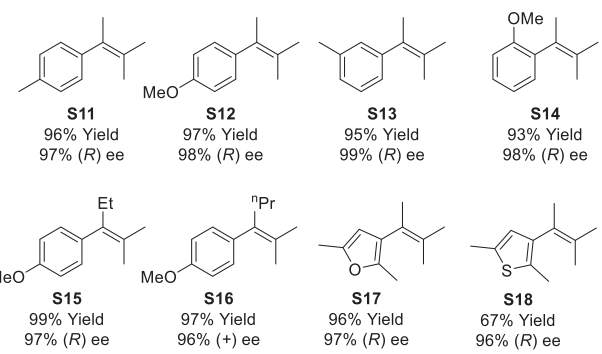


Figure 3. Asymmetric hydrogenation of several acyclic tetrasubstituted olefins **S11–S18** (hydrogenated products **19–26**). Reactions carried out using 2 mol % of *enant*-**6b** at 2 bar of hydrogen at 23 °C for 36 h.

enantioselectivity was neither affected by different electronic and steric decorations of the phenyl group of the substrate (**S10–S14**) nor by the nature of the alkyl chain (**S12**, **S15**, and **S16**), nor by the use of heteroaromatic olefins (**S17** and **S18**). Improving previously reported results,[6a,c] a broad range of substituted acyclic tetrasubstituted olefins were therefore hydrogenated in excellent enantioselectivities (ee's ranging from 96% to 99%; Figure 3).

We finally studied the AH of acyclic tetrasubstituted olefins with relevant poorly coordinative groups. Due to the importance of chiral fluorine molecules, in particular those with two vicinal stereogenic centers,[11] we focused on the AH of acyclic vinyl fluorides as a direct and atom-efficient method for their preparation. We therefore studied the AH of several vinyl fluorides containing an ester group (**S19–S23**, Figure 4; see Supporting Information for reaction condition optimiza-

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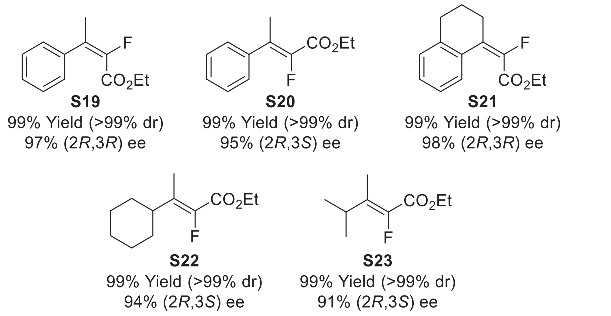

Figure 4. Asymmetric hydrogenation of several acyclic tetrasubstituted vinyl fluorides **S19**–**S23** (hydrogenated products **27**–**30**). Reactions carried out using 2 mol % of **6a** at 2 bar of hydrogen using CH_2Cl_2 as solvent at 23 °C for 24 h.

tion).[6d] The challenge of these substrates is that the catalyst must not only control the face selectivity but also avoid the side defluorination reaction. Advantageously, the reaction proceeded smoothly without defluorination in high diastereo- and enantioselectivities, regardless of the nature of the olefin substituents (aryl or alkyl) and the olefin geometry under mild reaction conditions. Interestingly, the use of olefins with different geometries gives access to both diastereoisomers of the hydrogenated products in high enantioselectivities. Thus, while substrate **S19**, with *E*-geometry, provides the *R*,*R*-diastereoisomer, the *Z*-analogue **S20** gives access to the *R*,*S*-diastereoisomer. These results are comparable to the best ones reported in the literature.[6d]

This paper reports a new approach in catalyst design for the successful hydrogenation of challenging unfunctionalized tetrasubstituted olefins. We therefore present the first application of an Ir/P-stereogenic P–N catalyst library, with a simple, modular architecture, in the AH of a broad range of different types of unfunctionalized tetrasubstituted olefins. These catalysts combine the advantageous reaction conditions of Ir/P,N catalysts with the advantages of having a bulky P-stereogenic center. These air-stable catalysts can also be easily prepared in a few steps from readily available sources. Improving previous results, the same family of catalysts is able to efficiently reduce indenes and the challenging 1,2-dihydronapthalene derivatives (ee's up to 96%) and also a broad range of acyclic olefins with unprecedented enantioselectivities (ee's up to 99%) under mild reaction conditions. Moreover, the excellent catalytic performance is maintained for a range of aryl and alkyl vinyl fluorides (dr's > 99% and ee's up to 98%), where two vicinal stereogenic centers are created. These results pave the way for further development of new generations of modular and readily available Ir/P-stereogenic aminophosphine-oxazoline catalyst libraries for the AH of unfunctionalized tetrasubstituted olefins, including the challenging acyclic ones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04084.

Experimental procedure for the preparation of substrates and for the hydrogenation reactions; copies of NMR spectra of the new substrates and hydrogenation products; and enantiomeric excess determination and characterization details of hydrogenated products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xavier.verdaguer@irbbarcelona.org.
*E-mail: oscar.pamies@urv.cat.
*E-mail: montserrat.dieguez@urv.cat.

ORCID

Antoni Riera: 0000-0001-7142-7675
Xavier Verdaguer: 0000-0002-9229-969X
Montserrat Diéguez: 0000-0002-8450-0656

Notes

The authors declare no competing financial interest.

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(b) Busacca, C. A.; Qu, B.; Grět, N.; Fandrick, K. R.; Saha, A. K.; Marsini, M.; Reeves, D.; Haddad, N.; Eriksson, M.; Wu, J. P.; Grinberg, N.; Lee, H.; Li, Z.; Lu, B.; Chen, D.; Hong, Y.; Ma, S.; Senanayake, C. H. *Adv. Synth. Catal.* **2013**, *355*, 1455−1463. During the writing of this paper two new reports on the use of Ir-P,N catalysts have been published. (c) One of these reports presents the application of Ir/phosphinite-oxazoline catalysts in the AH of some cyclic and acyclic tetrasubstituted olefins. It was also found that the simple substitution of the phosphinite moiety by a phosphite group has an extremely negative effect on enantioselectivity, reinforcing the need of specific ligand design. Biosca, M.; Magre, M.; Pàmies, O.; Diéguez, M. *ACS Catal.* **2018**, *8*, 10316−10320. (d) The second publication reported by Andersson's group showed the successful AH of tetrasubstituted vinyl fluorides using one of their privileged Ir-P,N catalysts for the AH of trisubstituted olefins, with a small modification in the P group. However, this catalyst was not successful for the other classes of cyclic and acyclic tetrasubstituted olefins reported in this paper and also required the use of high H_2 pressure (20−100 bar). Ponra, S.; Rabten, W.; Yang, J.; Wu, H.; Kerdphon, S.; Andersson, P. G. *J. Am. Chem. Soc.* **2018**, *140*, 13878−13883.

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(9) (a) Orgué, S.; Flores, A.; Biosca, M.; Pàmies, O.; Diéguez, M.; Riera, A.; Verdaguer, X. *Chem. Commun.* **2015**, *51*, 17548−17551. The Ir−MaxPHOX complexes have recently been successfully applied in the hydrogenation of functionalized substrates such as cyclic *β*-enamides and imines. See: (b) Salomó, E.; Orgué, S.; Riera, A.; Verdaguer, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 7988−7992. (c) Salomo, E.; Rojo, P.; Hernández-Lladó, P.; Riera, A.; Verdaguer, X. *J. Org. Chem.* **2018**, *83*, 4618−4627.

(10) A similar hydrogen pressure effect on enantioselectivity has been reported by Pfaltz and co-workers. See ref 6a.

(11) During the last decade, the synthesis of chiral fluorinated molecules with two vicinal chiral centers has received a great deal of attention because of their presence in several drugs, such as dexamethasone and fluticasone propionate. Despite this, the number of successful methods for their preparation is very limited, and those methods also require high catalyst loading, drastic reaction conditions, and multiple steps, among other drawbacks. See, for instance: Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1−PR43.

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