<http://www.diva-portal.org>

Postprint

This is the accepted version of a paper published in *Journal of Organometallic Chemistry*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Cadu, A., Andersson, P. (2012)

Development of iridium-catalyzed asymmetric hydrogenation: New catalysts, new substrate scope..

Journal of Organometallic Chemistry, 714: 3-11

<http://dx.doi.org/10.1016/j.jorganchem.2012.04.002>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-187584>

Review

Development of Iridium -Catalyzed Asymmetric Hydrogenation: New Catalysts, New Substrate Scope

Alban Cadu^a, Pher G. Andersson^{a,b*}

^a:Department of Biochemistry and Organic Chemistry, Uppsala University, Husargatan, Box 576, SE-75123, Uppsala, Sweden

Fax: +46 18-471-3818; Tel: +46 18-471-3816

^b: School of Chemistry, University of KwaZulu-Natal, Durban, South Africa

Email: pher.andersson@biorg.uu.se

Received: tbd

Content

1. Introduction: Origins of Asymmetric Hydrogenation
2. Early Development: the Need for New Catalysts
3. Substrate Classes
4. One Step Further: Asymmetric Hydrogenation as a Key-Step in the Synthesis of Chiral Building Blocks
5. Conclusion

Abstract:

The asymmetric hydrogenation of olefins is a tremendously powerful tool used to synthesize chiral molecules. The field was pioneered using rhodium- and ruthenium- based catalysts; however, catalysts based on both of these metals suffer from limitations, such as the need for directing substituents near or even adjacent to the olefin. Iridium-based catalysts do not suffer from this flaw and can thus hydrogenate a wide variety of olefins, including some tetra substituted ones. It is also possible for iridium-based catalysts to hydrogenate hetero- π bonds such as those found in hetero-aromatic rings. This review summarizes the contributions made to this field by our research group over the past few years.

Keywords: Asymmetric catalysis, Iridium, Hydrogenation, Alkenes

Graphical Abstract:

1. Introduction

In 2001, Prof. R. Noyori and Dr. W.S. Knowles¹ were jointly awarded the Nobel Prize in Chemistry for their key contributions to the field of asymmetric catalysis. More specifically, they developed the field of asymmetric hydrogenation, in which H₂ is reductively added to an unsaturated bond. Early catalysts were based on rhodium and ruthenium centers ligated with chiral diphosphines such as DIPAMP, DIOP and BINAP (see Figure 1), all of which are still commonly used.²

Rhodium- and ruthenium-based catalysts, usually require a coordinating group to orient the olefin at the metal center. The need for a coordinating group, often in the allylic position, to direct the stereoselection of hydrogenation is a common limitation of these catalysts. The most common coordinating groups are esters, carboxylic acids as well as amides.³ The mechanism of stereoselection that directs hydrogenation by iridium catalysts does not rely upon coordinating groups in the substrate, but mainly on steric bulk. Therefore the iridium-based catalysts can directly hydrogenate olefins without coordinating substituents.⁴

Schemes 1 and 2 show the different catalytic cycles for olefin hydrogenation by catalysts based on iridium⁵ and rhodium.⁶

Scheme 1, Proposed catalytic cycle for the hydrogenation of an olefin by an N,P-ligated iridium catalyst. DCM = dichloromethane, the solvent.

Scheme 2, Mechanism of the rhodium-catalyzed asymmetric hydrogenation of an alkene.⁷

The field of iridium-catalyzed hydrogenation can be traced back to the discovery of Crabtree's catalyst,⁸ $[\text{Ir}(\text{pyridine})(\text{Cy}_3\text{P})(\text{COD})]\text{PF}_6$ (COD: 1,4-cyclooctadiene, Figure 1). The field turned to stereogenesis in 1998 thanks to the Pfaltz group⁹ who introduced PHOX type N,P ligand complexes that transcended the limitations of the competing ruthenium and rhodium compounds because they could hydrogenate non-functionalized alkenes, imines and heterocycles. The now-commercialized PHOX ligand has inspired numerous other N,P ligands with its basic skeletal structure.¹⁰ In the past 13 years the field has progressed considerably, with very high *enantiomeric excesses* and conversions now routinely obtained in the hydrogenation of a wide variety of olefins even at very low catalyst loading¹¹.

In this mini-review, we provide an overview of our recent contributions to this field, from the development of new catalysts to the introduction of novel

substrate classes, and the combination with named reactions in order to produce valuable synthetic intermediates.

Figure 1, Top: Crabtree and Pfaltz' iridium-based catalysts for olefin hydrogenation. Center: Chiral N,P ligands that were developed in the Andersson group and that are mentioned in this review. Bottom: common chiral diphosphine ligands for ruthenium- and rhodium-based catalysis.

2. Early developments

A variety of chiral ligands for iridium-based hydrogenation catalysts have been developed over the years, with the most successful class being the bidentate N,P ligands. (C,N ligands have also been developed by the Burgess et al.¹² among others, but will not be discussed in this review).

The versatility of the N,P ligand class comes from the ease with which the electronegativity of the nitrogen atom can be tuned by employing different azapentacycles in the ligands (Figure 2). The π -electron excess and basicity in the ligand can be varied, as shown in Figure 2. The identity of the non-coordinating heteroatom in the ring is a key determinant of the ligand basicity, which increases with the electron donating character of the non-coordinating heteroatom. Imidazole, the strongest base used, donates more electron density to the catalytic iridium center; whereas the oxazole, a poor base, leads to lower electron density at the iridium center. This opens the possibility of fine-tuning the catalyst to match the substrate to be hydrogenated.

Figure 2, Basicity of different N,P chiral ligands for iridium.

3. Substrate classes

This section uses examples to illustrate the generality and wide scope of asymmetric iridium-catalyzed hydrogenation. The four examples show vastly different substrates: electron-rich enol phosphonates, electron poor fluorinated olefins, bulky di- and tri-aryl substituted olefins and finally strongly coordinating phosphonates.

3-a. Enol Phosphonates

The asymmetric hydrogenation of enol ethers and enol phosphonate ethers can be difficult at best, as Kumada and coworkers discovered, in their synthesis of chiral alcohols using the asymmetric hydrogenation of olefins (*ee* values ranged from 25 to 80%).¹³ Further research was conducted by Takaya and co-workers, using a ruthenium-BINAP complex: $\text{Ru}_2\text{Cl}_4[(S)\text{-BINAP}]_2(\text{NEt}_3)$, (see Figure 1 for structure of BINAP) to generate a selection of cyclic enol ethers (up to 95% *ee*).¹⁴ Enol phosphonates can, however be hydrogenated in excellent *ee* using properly chosen iridium catalysts (Table 1). A variety of ligands were tested but the highest conversion and *ee* were produced using ligand **F2**.¹⁵

Scheme 3, hydrogenation of enol ethers and phosphorylated compound

Entry	Substituents on Substrate		Conversion (%)	ee(%)
	R' =	R''		
1	Ph	H	>99	95 (<i>R</i>)
2	4-Me-C ₆ H ₄	H	97	96 (<i>R</i>)
3	4-MeO-C ₆ H ₄	H	48	98 (<i>R</i>)
4	4- ^t Bu-C ₆ H ₄	H	93	94 (<i>R</i>)
5	4-F ₃ C-C ₆ H ₄	H	>99	99 (<i>R</i>)
6	4-Br-C ₆ H ₄	H	>99	>99 (<i>R</i>)
7	4-O ₂ N-C ₆ H ₄	H	>99	92 (<i>R</i>)
8	Naphthyl	H	>99	85
9	Cy	H	>99	99 (<i>R</i>)
10	^t Bu	H	>99	>99 (<i>R</i>)
11	Hexyl	H	>99	92 (<i>R</i>)
12	ⁱ Pr	H	>99	92 (<i>R</i>)
13	^s Bu	H	>99	98 (+)
14	^t Bu	Et	>99	90 (+)
15	ⁱ Pr	Me	>99	91 (+)
16	Ph	COOEt	>99	>99
17	4-Me-C ₆ H ₄	COOEt	>99	99
18	4-F ₃ C-C ₆ H ₄	COOEt	>99	98
19	4-Br-C ₆ H ₄	COOEt	>99	98
20	Me	COOEt	>99	>99
21	Et	COOEt	>99	99
22	ⁱ Pr	COOEt	>99	>99
23	^t Bu	COOEt	98	93
24	Cl-CH ₂ -	COOEt	58	92
25	Ph	Me	>99	96
26	Ph	Et	90	92
27	^t Bu	Et	>99	90

Reaction conditions: 0.5mol% catalyst at room temperature, overnight, 30 to 50 bar H₂ in freshly distilled dichloromethane.

Table 1, Hydrogenation of enol phosphonate ethers.¹⁵

3-b. Trifluoromethyl-substituted olefins

Chiral fluorinated compounds have a wide range of applications in agrochemicals, pharmaceuticals and even in LCD screens.¹⁶ Historically most chiral F₃C- bearing compounds were generated either by the chemo- or bio-catalytic resolution of racemates, which requires half of the product to be discarded, or by asymmetric fluorination, which is difficult.¹⁷ The trifluoromethyl group is much more electron-withdrawing than carboxylic acids

or esters.¹⁸ Iseki *et al.*¹⁹ attempted the asymmetric hydrogenation of trifluoromethyl olefins using Ru-(R)-BINAP, and Koenig and co-workers tried using (R,R) DiPAMP and (S,S)-Chiraphos with rhodium.²⁰ The ruthenium catalyst converted most unsaturated F₃C- substituted esters into near-racemic products mixtures for most compounds, though *ee* values of up to 83% were obtained in a few cases, and the rhodium catalysts failed to obtain enantiomeric excesses above 77%. However an iridium catalyst [E-IrCOD]⁺BARF⁻ hydrogenated F₃C-substituents in up to 96% *ee* (Table 2).

Scheme 4, hydrogenation of F₃C- substituted olefin by [E-IrCOD]⁺BARF⁻.

Entry	Substituents on Substrate			Conversion (%)	ee (%)
	R	R'	R''		
1	Ph	Me	H	94	94 (-)
2	Ph	Pr	H	87	92 (-)
3	Ph	Pentyl	H	88	96 (-)
4	Ph	Octyl	H	85	95 (-)
5	Ph	(CH ₂) ₂ Ph	H	21	90 (-)
6	5-F-C ₆ H ₄	Pentyl	H	84	81 (-)
7	5-Me-C ₆ H ₄	Octyl	H	92	84 (-)
8	Cy	H	Ph	96	74 (-)
9 ^a	Ph ₂ P(O)O	H	Ph	99	96 (+)

Reaction conditions: 0.5-1 mol% catalyst, 72h, room temperature, in freshly distilled dichloromethane, 100 bar H₂. ^a: P(H₂) = 50 bar.

Table 2, Hydrogenation of CF₃-substituted olefins by [E-IrCOD]⁺BARF⁻.

Table 2 summarizes the hydrogenations of F₃C-substituted olefins by Engman *et al.*²¹ and Cheruku *et al.*²². In both these reports, the authors noted that the *E* and *Z* isomers reacted at different rates; this phenomenon was also seen for the hydrogenation of these substrates by ruthenium catalysts.²³ Interestingly, the *E* and *Z* isomers of a F₃C- substituted olefin are hydrogenated to identical products, whereas configurational isomers of non-fluorinated olefins are hydrogenated to alkanes of opposite configuration.²⁴ Due to the strong polarization of the double bond by the -CF₃ moiety, these olefins could be of great use in studies on the influence of electron density on asymmetric hydrogenation. Another set of olefins with highly polarized double bonds, the vinyl fluorides, have also been hydrogenated by chiral N,P-ligated iridium complexes, with variable success.²⁵ As mentioned in Section 2, the electron density at the iridium (i.e. the electron donating nature of the nitrogen substituent of the N,P ligand) has an influence on the chemoselectivity of asymmetric hydrogenation;²⁶ thus several different ligands are used: electron-enriching ligands employed with electron-poor

substrates and conversely electron-withdrawing ligands used for electron-rich substrates.

3-c. 1,1-Diaryls and 1,1,2-Triaryls

Zoloft (sertraline hydrochloride), one of the most well known anti depressants, is a chiral 1,1-diaryl compound that can be synthesized using the asymmetric hydrogenation of an alkene. Aryl substituted olefins are difficult compounds to hydrogenate stereoselectively due to the large steric bulk of the substituents.

Table 3 shows that an iridium catalyst bearing used with ligand A hydrogenated a series of 1,1 diaryls and 1,1,2 triaryls in excellent conversions and enantiomeric excesses. This is achieved by harnessing the bulkiness of the substituents in relation to those of the aryl groups on the catalyst to impose a specific conformation on the substrate, as per the selectivity model.²⁷

Figure 2. Selectivity model for the asymmetric hydrogenation of alkenes.

Scheme 5, hydrogenation of a di- or tri- aryl

Entry	Substituents on Substrate			Yield (%)	ee (%)
	R'	R''	R'''		
1	4-Me-C ₆ H ₄	H	Ph	>99	>99 (-)
2	4-MeO-C ₆ H ₄	H	Ph	>99	95 (-)
3	3,5-Me,Me-C ₆ H ₃	H	Ph	>99	>99 (+)
4	4-Me-C ₆ H ₄	H	pentyl	>99	97 (-)
5	4-Br-C ₆ H ₄	Me	H	>99	99 (-)
6	4-Ph-C ₆ H ₄	H	pentyl	99	99 (+)
7	4-Ph-C ₆ H ₄	pentyl	H	99	99 (-)

Reaction conditions: 0.25 mol% catalyst, overnight, room temperature, in freshly distilled dichloromethane, 50 bar H₂.

Table 3, Hydrogenation of 1,1-diaryl compounds by [A-IrCOD]⁺BARF.^{28,29}

As can be seen in Table 3, the bulk of the tri-substitution of the olefin does not hamper the yield of the reaction or the ee of the product. 1,2 diaryl olefins have also been used as substrates in asymmetric hydrogenation. The simpler α-

methyl stilbene is hydrogenated to give full conversion and in very high ee for a wide variety of iridium catalysts, including biaryl-phosphite and phosphinite oxazoline N,P ligands.³⁰

3-d. Phosphonates

Chiral phosphites are often produced by the resolution of racemic mixtures;³¹ however iridium offers a reliable catalytic method to produce them with excellent stereoselectivities.³² Chiral phosphites and phosphonic acid derivatives are primarily used by the pharmaceutical industry: as drugs for metabolic diseases or neurological disorders amongst others.³³ Also, the potential of phosphorus as a metal chelator allows these phosphites to be used in the field of carboxyalkylphosphonates as precursors.³⁴ [A-IrCOD]⁺BARF⁻ hydrogenated many trisubstituted vinyl phosphonates in full conversion and near-perfect enantioselectivity (Table 4).

Scheme 6, asymmetric hydrogenation of phosphonates

Entry	Substituents on Substrate			Conversion (%)	ee (%)
	R	R'	R''		
1	Ph	Ph	H	>99	>99 (R)
2	4-Me-C ₆ H ₄	Ph	H	>99	>99 (+)
3	4-MeO-C ₆ H ₄	Ph	H	>99	>99 (+)
4	4-F-C ₆ H ₄	Ph	H	>99	>99 (+)
5	4-F ₃ C-C ₆ H ₄	Ph	H	>99	93 (+)
6	2-Me-C ₆ H ₄	Ph	H	>99	>99 (+)
7	Cyclohexyl	Ph	H	>99	99 (+)
8	^t Bu	Ph	H	98	90 (+)
9	CH ₂ OH	Ph	H	>99	>99 (-)
10	CH ₂ OAc	Ph	H	>99	>99 (-)
11	CH ₂ Ph	Ph	H	>99	>99 (+)
12	Ph	OEt	H	>99	>99
13	CH ₂ Ph	OEt	COOEt	>99	>99
14	Ph	OEt	COOEt	>99	>99

Reaction conditions: 0.5 mol% catalyst, 6-12 hours (O.N.), room temperature (R.T.), in freshly distilled dichloromethane, 30-50 bar H₂.

Table 4, The asymmetric hydrogenation of vinyl phosphates by [A-IrCOD]⁺BARF⁻.

Phosphonates are coordinating groups that are often used as ligands for ruthenium³⁵ and rhodium.³⁶ The synthesis of chiral phosphate groups by this asymmetric hydrogenation could therefore be used to generate such ligands. The asymmetric hydrogenation of phosphonates by rhodium catalysts has been undertaken, though in only one instance for the reduction of

carboxyethylvinylphosphonates.³⁷ In all cases where phosphonates were hydrogenated by Ru or Rh, the olefin was terminal with an aryl substituent.

4. One Step Further: Asymmetric Hydrogenation as a Key-Step in the Synthesis of Chiral Building Blocks

As discussed in the previous section, iridium-based catalysts have been used to hydrogenate a variety of test substrates in high enantioselectivity. However the true test of the use of a chemical process is its concrete applications. In the following section, we explore the combination of iridium asymmetric hydrogenation in conjunction with well-known reactions, to produce novel, practical processes.

4-a. The Birch Reaction Followed by Asymmetric Hydrogenation.

The Birch reduction is an old, well-known and well-understood reaction that allows the conversion of aromatic compounds into cyclic 1,4-dienes.³⁸ The reaction is regioselective, as the positions of the double bonds are determined by the substituents, as shown in Scheme 8. Although the Birch reduction is often used to produce prochiral intermediates in the syntheses of natural products³⁹, it had not been combined with asymmetric catalysis until recently.⁴⁰ Excellent regioselectivity and enantiomeric excesses were obtained in the sequential Birch reduction and asymmetric hydrogenation of a wide selection of 1,3-, 1,4- and 1,2,4- di- and tri-substituted benzene rings (see Table 5). The catalysts used were the **[D1-IrCOD]⁺BARF⁻** and **[I-IrCOD]⁺BARF⁻** the catalysts based on ligands **D1** and **I**. A follow up article was written, detailing the more precisely procedure followed.⁴¹

Scheme 7, Birch reduction followed by asymmetric hydrogenation of the substituents

Entry	1: First step			Yields ^a			ee (%) ^c		Ligand ^d
	R'	R''	R'''		trans	cis ^b	trans	cis	
1	MeO	Me	H	63	76	24	97	48	D1
2	H	Me	MeO	76	40	60	-	-	I
3	MeO	iPr	H	60	86	14	94	21	D1
4	iPrO	Me	H	48	75	25	94	77	D1
5	MeO	CH(OH)Bu	H	70	83	17	98	62	I
6	Me	Me	H	40	91	9	97	-	I
7	CH(OH)Me	CH(OH)Me	H	41	54	46 ^e	75	-	I
8	Me ₂ (OH)C	Et	H	61	56	44 ^e	96	61	D1

9	iPr	iPr	H	45	76	75	25	>99	-	D1
10	MeO	iBu	H	52	68	82	18	98	66	I
11	MeO	CH(OH)Ph	H	82	84	78	22	>99	60	I
12	MeO	MeO	H	65	56	>99	1	>99	-	D1
13	MeO	Me	Me	77	-	-	-	97	-	I
14	MeO	Me	iPr	51	-	-	-	89	-	I
15	MeO	iPr	Me	69	60 ^f	-	-	97	-	I

Reaction conditions: 0.5-1 mol% catalyst, 18 hours, room temperature, in freshly distilled dichloromethane, 20 bar H₂.

^a: isolated yields, ^b: determined by NMR, ^c: determined by NMR, ^d: Ligand used as an Ir complex of the type: [L-IrCOD]⁺BARF⁻ at 0.5-1% cat. loading, with L= **I** or **D1**
^e: yield determined by chiral GC-MS, ^f: Isolated yield of the corresponding ketone.

Table 5, Results of the sequential Birch reduction and asymmetric hydrogenation.⁴¹

As can be seen in scheme 7, catalyst **D1** and **I** were used to asymmetrically hydrogenate the Birch reduction products with high stereo- and enantio-selection. It should be noted that one can predict whether the double bonds will be placed in ipso-ortho & meta-para or doubly ortho-meta positions of the resulting cyclohexadiene (scheme 8).

Scheme 8, The position of the double bonds of the cyclohexadiene in relation with the properties of the substituent.

When the Birch reduction-asymmetric hydrogenation protocol was applied to substituted naphthalene rings, the products were chiral octahydronaphthalenes that could be oxidized to form compounds with large rings (scheme 9).⁴¹ The new chiral centers were maintained through the oxidation.

Scheme 9, The formation of a chiral substituted cyclodecane via the sequential Birch reduction-asymmetric hydrogenation-oxidation.

4-b. Asymmetric Hydrogenation of a Cyclic Sulfone followed by Ramberg-Bäcklund Rearrangement.

The Ramberg-Bäcklund rearrangement, developed at Uppsala University, is another old reaction,⁴² and is used in the synthesis and extension of chiral olefin chains. Thus the reliable production of chiral sulfones is doubly rewarding; not only are they useful in their own right, as they are present in several HIV-1 and hepatitis-C protease inhibitors,⁴³ but they can also be transformed into interesting alkenes using the Ramberg-Bäcklund. Zhou *et al.*⁴⁴ synthesized allylic sulfones and asymmetrically hydrogenated them using catalyst $[G-IrCOD]^+BARF^-$. Acyclic sulfones were generated using the well-explored oxidation of thioether by meta-chloroperoxybenzoic acid (m-CPBA).⁴⁵ Initial hydrogenation results were very good, the example below has a 90% yield for the final step (Ramberg-Bäcklund reaction) and it maintains the 96% enantiomeric excess generated by the asymmetric hydrogenation, while producing exclusively the E configurational isomer.

a: CH_3MgBr , $CeCl_3$. b: m-CPBA. c: $[G-IrCOD]^+BARF^-$, DMAP, Et_3N , TFAA, H_2 (50 bars), 17h. S- (+) product was obtained
d: KOH (Al_2O_3), CBr_2F_2 , $tBuOH$, $0^\circ C$, R (+) product.

Scheme 10, The conversion of an alkene sulfone into a chiral olefin.⁴⁴

Cyclic sulfones were also synthesized, asymmetrically hydrogenated and then subjected to the Ramberg-Bäcklund reaction. In this case, the rearrangement reduced the ring size by one atom, as can be seen in Scheme 10. In all cases, the configuration of the chiral center generated in the hydrogenation step was maintained; no racemization occurred in the final, Ramberg-Bäcklund, step.

a: $PhMgBr$, $CeCl_3$. b: TFA, $-78^\circ C$. c: m-CPBA. d: $[G-IrCOD]^+BARF^-$, DMAP, Et_3N , TFAA, H_2 (50bar), 17h R- (-) product. e: KOH (Al_2O_3), CBr_2F_2 , $tBuOH$, $60^\circ C$ (microwave), S- (-) product.

Scheme 11, Synthesis of a chiral cyclohexene via asymmetric hydrogenation followed by the Ramberg-Bäcklund rearrangement.

4-c. Chiral Hetero- and Carbocycles

Just as cyclic sulfones can be hydrogenated asymmetrically, so can a variety of hetero- and carbocycles, which find many uses including those in medical applications.⁴⁶ Generally, the enantioselective synthesis of chiral heterocycles with a stereocenter two or even three atoms away from the heteroatom is very difficult by other methods.

Verendel *et al.*⁴⁷ synthesized and asymmetrically hydrogenated a range of cyclic substrates (Scheme 11). High yields were obtained for some compounds, and high enantiomeric excesses were achieved for a wide series of substrates. Substrates of note included conjugated cyclohexenone and dihydrofuran rings, which were both hydrogenated in quantitative conversion and >90% *ee*.

Overall six membered rings were hydrogenated more selectively than the five membered rings, whose hydrogenation was more dependent on the hetero-functionality. Most selectively hydrogenated were the six-membered rings that bore electron-withdrawing groups, which accelerated the reaction because the catalyst had electron-rich ligands. It should be noted that poor results were encountered with 2-phenyl-substituted dihydropyranes and with tetrahydropyridine. This is due to the preference of the iridium-bound hydride to attack the α -position, which is sterically disfavored in those cases.

Scheme 12, Hydrogenation of hetero- and carbocycles, as reported by Verendel *et al.*^{47b}

5. Conclusion

The field of iridium catalyzed asymmetric hydrogenation has advanced greatly in the past 15 years. The new PHOX-type N,P ligands as well as the discovery of a better counter ion (supplanting the previously dominant PF₆⁻)⁴⁸ have enabled the expansion of the scope of Crabtree-like catalysts into powerful and well-rounded tools. Excellent enantioselectivities are now routinely obtained in the reduction of wide ranges of alkene substrates. In the past decade, the focus has lain on the tailoring of ligands and catalysts to specific substrate types, but recent works have begun to show the versatility of the reaction and to explore the possibilities regarding integration of iridium-catalyzed asymmetric

hydrogenation into modern, efficient syntheses of organic molecules with defined applications.

Acknowledgements

Our thanks go to all the members of the Andersson group past and present, who conducted the research presented here. We would also like to extend our gratitude to the Knut & Alice Wallenberg foundation, NordForsk, the Swedish science and research council (VR), VR/SIDA, Nordic Energy Research (N-INNER II) and the Swedish foundation for strategic research that funded and allowed us to carry out our research.

Vitae

Pher G. Andersson was born 1963 in Växjö, Sweden. He was educated at Uppsala University where he received his BSc in 1988 and his PhD in 1991. After postdoctoral research at Scripps Research Institute with Prof. K. B. Sharpless, he returned to Uppsala where he became Docent in 1994 and full Professor in 1999. Since 2010 he also holds the position of Honorary Professor in Durban, South Africa. His main research interests involve organometallic chemistry, stereoselective synthesis, and asymmetric catalysis.

Alban Cadu was born in 1987 in Rouen, France. He received a BSc from Imperial College London with Joint Honours in Chemistry with Management in 2010, his research focused on thiirane synthesis and comparative European and South East Asian politico-economic integration. He received an M1 Masters in Organic and Analytical Chemistry at the University of Rouen in 2011 before joining

Professor Andersson at Uppsala University, where he works towards a PhD, focusing on organometallic substitutions of small organic molecules.

-
- ¹ (a) W. S. Knowles, *Angew. Chem., Int. Ed.* **2002**, 41, 1998–2007, R. Noyori, *Angew. Chem., Int. Ed.* **2002**, 41, 2008–2022, (b) W. S. Knowles and R. Noyori, *Acc. Chem. Res.* **2007**, 40, 1238–123
- ² Halterman *Comprehensive Asymmetric Catalysis* Springer **1999**, vol.1, 183-195.
- ³ (a) M.T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, 39, 21, -3889-3890 (b) J. Louie, C.W. Bielawski, R.H. Grubbs, *J. Am. Chem. Soc.*, **2001**, 123, 11312–11313
- ⁴ X. Cui, K. Burgess, *Chem. Rev.*, **2005**, 105, 3272–3296
- ⁵ (a) P. Brandt, C. Hedberg, P.G. Andersson, *Chem. Eur. J.* **2003**, 9, 339, (b) T.L. Church, T. Rasmussen, P.G. Andersson, *Organometallics*, **2010**, 29, 6769
- ⁶ C.R. Landis; J. Halpern *J. Am. Chem. Soc.* **1987**, 109, 1746.
- ⁷ J. Halpern, *Science*, **1982**, 217, 4558
- ⁸ (a) R.H. Crabtree, H. Felkin, G.E. Morris, *J. Organomet. Chem.* **1977**, 141, 205 (b) R. Crabtree, *Acc. Chem. Res.*, **1979**, 12 (9), 331–337
- ⁹ A. Lightfoot, P. Schnider and A. Pfaltz, *Angew. Chem., Int. Ed.* **1998**, 37, 2897–2899.
- ¹⁰ G.Helmchen; A. Pfaltz, *Acc. Chem. Res.* **2000**, 33, 336-345.
- ¹¹ (a) J. J. Verendel; P. G Andersson, *Dalton. Trans.* **2007**, 47, 5603 (b) T.L. Church; P.G. Andersson, *Coord. Chem. Rev.* **2008**, 252, 513-531
- ¹² X. Cui; J.W. Ogle; K. Burgess, *Chem. Comm.* **2005**, 5, 672-67
- ¹³ T. Hayashi, K. Kanehira, M. Kumada, *Tetrahedron Lett.* **1981**, 22, 4417.
- ¹⁴ T. Ohta, T. Miyake, N. Seido, H. Kumobayashi, H. Takaya, *J. Org. Chem.* **1995**, 60, 357
- ¹⁵ P. Cheruku, J. Diesen, P.G. Andersson, *J. Am. Chem. Soc.* **2008**, 130, 5595–5599
- ¹⁶ (a) M. Schlosser, *Angew. Chem.* **1998**, 110, 1538–1556; (b) Y. Suzuki, T. Hagiwara, I. Kawamura, N. Okamura, T. Kitazume, M. Kakimoto, Y. Imai, Y. Ouchi, H. Takezoe, A. Fukuda, *Liq. Cryst.* **2006**, 33, 1344–1349.
- ¹⁷ (a) P. Bravo, G. Resnati, *Tetrahedron: Asymmetry*, **1990**, 1, 661–692; (b) K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Soc. Rev.* 2004, 104, 1–16; (c) J.-A. Ma, D. Cahard, *Chem. Soc. Rev.* **2004**, 104, 6119 – 6146; (d) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, 117, 218 – 234; *Angew.Chem. Int. Ed.* **2005**, 44, 214 – 231.
- ¹⁸ C. Hansch, A. Leo, R.W. Taft, *Chem. Soc. Rev.* **1991**, 91, 165.
- ¹⁹ K. Iseki, Y. Kuroki, T. Nagai, Y. Kobayashi, *J. Fluorine Chem.* **1994**, 69, 5-6
- ²⁰ K.E. Koenig, G.L. Bachman, B.D. Vineyard, *J. Org. Chem.* **1980**, 45, 2362.
- ²¹ M. Engman, P. Cheruku, P. Tolstoy, J. Bergquist, S.F. Völker, P.G.Andersson, *Adv. Synth. Catal.* **2009**, 351, 375-378
- ²² P. Cheruku, S. Gohil, P.G. Andersson, *Org.Lett.* **2007**, 9, 1659-1661
- ²³ K. Iseki, Y. Kuroki, T. Nagai, Y. Kobayashi, *Chem. Pharm. Bull.* **1996**, 44, 477-480.
- ²⁴ T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, 52, 3174.
- ²⁵ P. Kaukoranta, M. Engman, C. Hedberg, J. Bergquist, P.G. Andersson, *Adv. Synth. Catal.* **2008**, 350, 1168-1176
- ²⁶ M. Engman, J.S. Diesen, A. Paptchikhine, P.G. Andersson, *J. Am. Chem. Soc.* **2007**, 129, 4536-4537
- ²⁷ J.-Q. Li, X. Quan, P.G. Andersson, submitted to *Chem. Eur. J.*, Marsh 2012.

- ²⁸ J.-Q. Li, A. Paptchikhine, T. Govender, P.G. Andersson, *Tetrahedron: Asymmetry*, **2010**, *21*, 1328-1333
- ²⁹ P. Tolstoy, M. Engman, . Paptchikhine, J. Bergquist, T.L. Church, A. W.-M.-Leung, P.G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8855-8860.
- ³⁰ M. Dieguez, J. Mazuela, O. Pamies, J.J. Verendel, P.G. Andersson, *Chem. Commun.* **2008**, *33*, 3888.
- ³¹ Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, **2003**
- ³² P. Cheruku, A. Paptchikhine, T.L. Church, P.G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8285-8289.
- ³³ (a) C. Bellucci, F. Gualtieri, S. Scapecchi, E. Teodori, R. Budriesi, A. Chiarini, *Farmaco*, **1989**, *44*, 1167-1191. (b) N.A. Bondarenko, I.N. Lermontova, G.N. Bondarenko, N.S. Gulyukina, T.M. Dolgina, S.O. Bachurin, I.P. Beletskaya, *Pharm. Chem. J.* **2003**, *37*, 226-228. (c) N.S. Gulyukina, T.M. Dolgina, G.N. Bondarenko, I.P. Beletskaya, N.A. Bondarenko, J.-C. Henry, D. Lavergne, V. Ratovelomanana-Vidal, J.-P. Genet, *Russ. J. Org. Chem.* **2002**, *38*, 573-587. (d) K.W. Jung, K.D. Janda, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2281-2282.
- ³⁴ (a) S.T. Frey, W.D. Horrocks, Jr. *Inorg. Chem.* **1991**, *30*, 1073-1079. (b) T. Schnepf, S. Finkler, A. Czap, R. van Eldik, M. Heus, P. Nieuwenhuizen, C. Wreesmann, W. Abma, *Eur. J. Inorg. Chem.* **2001**, 491-501. (c) S. Gardner, M. Motevalli, K. Shastri, A.C. Sullivan, P.B. Wyatt, *New J. Chem.* **2002**, *26*, 433-439.
- ³⁵ H.L. Ngo, A. Hu, W. Lin, *Tet. Lett.* **2005**, *46*, 595-597
- ³⁶ C. Maillet, P. Janvier, M. Pipelier, T. Praveen, Y. Andre, B. Bujoli, *Chem. Mater.*, **2001**, *13*, 2879-2884.
- ³⁷ R. Kadyrov, R. Selke, R. Giernoth, J. Bargon, *Synthesis*, **1999**, 1056-1062.
- ³⁸ A. Birch, *J. Chem. Soc.* **1944**, 430.
- ³⁹ P.W. Rabideau, J. Maricynow *J. Org. React.* **1992**, *42*, 1.
- ⁴⁰ A. Paptchikhine, K. Itto, P.G. Andersson, *Chem. Commun.* **2011**, *47*, 3989.
- ⁴¹ A. Cadu, A. Paptchikhine, P.G. Andersson, *Synthesis*, **2011**, *23*, 3796-3800
- ⁴² L. Ramberg, B. Bäcklund, *Arkiv. Kemi. Mineral. Geol.* **1940**, *13A*, No. 27; *Chem. Abstr.* **1940**, *34*, 4725
- ⁴³ (a) Ghosh, A.K.; et al. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 83. (b) E. N. Prilezhaeva, *Russ. Chem. Rev.* **2000**, *69*, 367-408; (c) Kim, C. U.; et al. *J. Med. Chem.* **1996**, *39*, 3431. (d) Buynak, J. D.; Vogeti, L.; Chen, H. *Org. Lett.* **2001**, *3*, 2953. (e) Velazquez, F.; et al. *J. Med. Chem.* **2010**, *53*, 3075.
- ⁴⁴ T. Zhou, B. Peters, M. F. Maldonado, T. Govender, P. G. Andersson, under submission
- ⁴⁵ (a) E. Lukevics, P. Arsenyan, S. Belyakov, J. Popelis, O. Pudova, *Organometallics*, **1999**, *18*, 3187-3193 (b) Q. Yao, Y. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 74-75
- ⁴⁶ Y.K. Agrawal, H.G. Bhatt, H.G. Raval, P.M. Oza, P.J. Gogoi, *Mini-Rev. Med. Chem.* **2007**, *7*, 451
- ⁴⁷ (a) J. J. Verendel, T. Zhou, J.-Q. Li, A. Paptchikhine, O. Lebedev, P.G. Andersson, *J. Am. Chem. Soc.* **2010**, *132*, 8880. (b) J.J. Verendel, J.-Q. Li, X. Quan, B. Peters, T. Zhou, O.R. Gautun, T. Govender and P.G. Andersson, *Chem. Eur. J.*
- Accepted 2nd Feb 2012, DOI: 10.1002/chem.201104073
- ⁴⁸ S.P. Smidt, N. Zimmermann, M. Studer, A. Pfaltz, *Chem. Eur. J.*, **2004**, *10*, 4685