Leibniz–Institut für Katalyse e.V. an der Universität Rostock

New Aspects in Homogeneous Hydrogenation – Development of Practical Rhodium Phosphine Catalysts and Environmentally Benign Iron Catalysts

Dissertation
zur Erlangung des akademischen Grades eines
Doktor rerum naturalium (Dr. rer. nat.)

vorgelegt der

Mathematisch–Naturwissenschaftlichen Fakultät der Universität Rostock

von

Stephan Enthaler
geb. am 27.02.1980

Rostock, Mai 2007

Die vorliegende Arbeit entstand in der Zeit von September 2004 bis April 2007 am Leibniz–Institut für Katalyse e.V. an der Universität Rostock.

Vollständiger Abdruck der von der Mathematisch–Naturwissenschaftlichen Fakultät der Universität Rostock zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaft genehmigten Dissertation.

Gutachter der Dissertation:	Prof. Dr. Matthias Beller, Leibniz–Institut für Katalyse e.V. an der Universität Rostock (Erstgutachten)
	Prof. Dr. Serafino Gladiali, Dipartimento di Chimica, Universita` di Sassari, Sassari, Italien (Zweitgutachten)
	Prof. Dr. Uwe Rosenthal, Leibniz–Institut für Katalyse e.V. an der Universität Rostock (Drittgutachten)
Termin des Rigorosums:	05. November 2007
Prüfungsvorsitzender:	Prof. Dr. Eckhard Vogel, Universität Rostock
Prüfer Hauptfach (Organische Chemie):	Prof. Dr. Matthias Beller, Leibniz–Institut für Katalyse e. V. an der Universität Rostock
Prüferin Nebenfach (Toxikologie):	PD Dr. Birgit Tiefenbach, Universität Rostock
Wissenschaftliches Kolloquium:	15. Januar 2008

Ändere die Welt; sie braucht es.

Bertolt Brecht (1898-1956)

Ich danke herzlich meinem hochgeschätzten Lehrer

Prof. Dr. Matthias Beller

für die Aufnahme in seine Arbeitsgruppe, die ausgezeichneten Arbeitsbedingungen, seinen unerschöpflichen Ideenreichtum und sein großes Interesse am Gelingen dieser Arbeit, sowie die gewährte wissenschaftliche Freiheit und sein Vertrauen.

Weiterhin gilt mein besonderer Dank den Mitgliedern der explorativen Projektgruppe „Synthese von neuen chiralen Liganden“ die einen maßgeblichen Anteil am Gelingen dieser Arbeit hatte: Meiner Themenleiterin *Frau Dr. Kathrin Junge* für die ausgezeichnete und freundschaftliche Zusammenarbeit und die gewährten Freiheiten während der letzten Jahre, *Dipl.–Chem. Giulia Erre* für ihre Freundschaft, Zusammenarbeit, den unzähligen Korrekturen und der kritischen Durchsicht dieser Arbeit (molte grazie!), ferner *Dr. Bernhard Hagemann* für seine Freundschaft und die vielen „wissenschaftlichen“ Diskussionen.

Ferner gilt mein Dank *Monika Heyken, Caroline Voss* und *Christine Mewes* für die Durchführung ungezählter Experimente.

Allen Freunden und Kollegen danke ich für ihre Unterstützung, Diskussionen, Chemikalien und die hervorragende Arbeitsatmosphäre: *Dr. Sandra Hübner, Dipl. Chem. Kristin Schröder, Dipl.–Chem. Björn „Hartmut“ Loges, Dipl.–Chem. Hanns Martin Kaiser, Dipl.–Chem. Bianca Bitterlich, Dr. Kristin Mertins, Dipl.–Chem. Jan Schumacher, Dr. Jette Kischel, Dipl.–Chem. Cathleen Buch, Dr. Andrea „Lingelchen“ Christiansen, , Dr. Dirk Strübing, Dipl.–Chem. Anne Grotevendt, Dipl.–Chem. Anne Brennführer, Dipl.–Chem. Nicolle Schwarz, Dipl.–Chem. Karolin Alex, Karin Buchholz, Sandra Giertz, Dipl.–Chem. Benjamin Schäffner, Dipl.–Chem. Christian Torborg, Dipl.–Chem. Stefan Schulz, Dr.. Stefan Klaus, Dipl.–Chem. Thomas „Bob“ Schmidt, Dr. Marko Hapke, Dr. Ralf Jackstell, Dr. Henrik Junge, Dr. Helfried Neumann, Dr. Alexander Zapf, Dr. Hajun Jiao, Dr. Irina Jovel, Dr. Thomas Schareina, Dr. Holger Klein, Dr. Alexey Sergeev, Dr. Nicolas Clement, Chem. Ing. Christa Fuhrmann, Dr. Jens Holz, Dr. Annegret Tillack* und vielen mehr.

Herrn Dr. Man–Kin Tse danke ich für unzählige Diskussionen und den unerschöpflichen Vorrat an neuen Liganden.

Prof. Dr. Serafino Gladiali für die vielen Diskussionen und die Zusammenarbeit.

Dr. Torsten Dwars für die unzähligen Diskussionen und die unkomplizierte Chemikalienbeschaffung.

Dem Analytik Team des Leibniz–Instituts für Katalyse: *Dr. Dirk Michalik, Dr. Christine Fischer, Dr. Anke Spanneberg*, *Dr. Wolgang Baumann, Susanne Schareina, Karin Buchholz*,

Kathleen Mevius, Astrid Lehmann, Kathrin Reincke, Christine Domke und im Besonderen *Susann Buchholz* für die Messung unzähliger GC–Proben.

Der *Degussa Homogeneous Catalysis* (DHC) für die freundliche Bereitstellung verschiedenster Liganden.

Mein ganz besonderer Dank gebührt meinen Eltern für ihre Unterstützung.

Table of Contents

Abbreviations

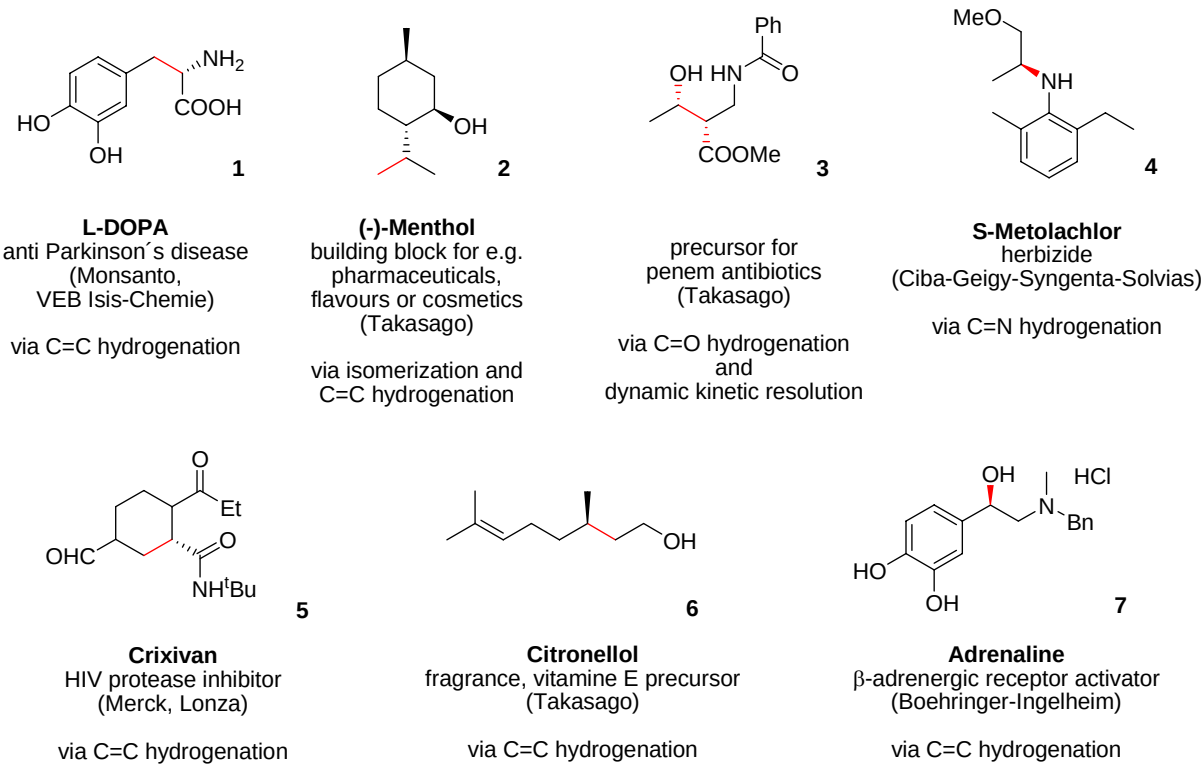
Ac	Acetyl
Acac	Acetylacetonate
Anisyl	Methoxylphenyl group
Ar	Aryl
BICHEP	2,2′–bis(diphenylphosphino)–6,6′–dimethoxy–1,1′–biphenyl
BINAP	2,2′–Bis(diphenylphosphino)–1,1′–binaphthyl
Binaphane	1,2–Bis[4,5–dihydro–3*H*–binaphtho[1,2–c:2′,1′–e]phosphepino]benzene
f-Binaphane	1,1′–Bis{4,5–dihydro–3*H*-dinaphtho[1,2–c: 2′,1′–e]phosphepino}ferrocene
Binapine	4,4′–Di–*tert*–butyl–4,4′,5,5′–tetrahydro–3,3′–bis-3*H*–dinaphtho[2,1–c:1′,2′–e]phosphepine
BINEPINE	4,5–Dihydro–3*H*–dinaphtho[2,1–c;1′,2′–e]phosphepine
BINOL	2,2′–Binaphthol
Bipy-*tb*	Bis–*tert*–butyl–bipyridine
Bn	Benzyl
BMPP	Benzyl methyl phenyl phosphine
Bopa-*ip*	Bis(2–((*S*)–4–*iso*–propyl–4,5–dihydrooxazol–2–yl)phenyl)amine
Bopa-*tb*	Bis(2–((*S*)–4–*tert*–butyl–4,5–dihydrooxazol–2–yl)phenyl)amine
BPE	1,2-Bis(2,5–diethylphospholano)ethane
BPPM	Butoxycarbonyl–4–diphenylphosphino–2–diphenylphosphinomethyl–pyrrolidine
t–Bu	*tert*–Butyl
i–Bu	*iso*–Butyl
Bz	Benzoyl
CAMP	Cyclohexyl *o*–anisylmethylphosphine
Cat.	Catalyst
ChiraPhos	Bis(diphenylphosphino)butane
cod	1,5–Cyclooctadiene
coe	Cyclooctene
Conv.	Conversion
Cp	Cyclopentadienyl
Cp′	Substituted cyclopentadienyl
Cy	Cyclohexyl
DABCO	1,4–Diazabicyclo[2.2.2]octane
DeguPhos	Bis(diphenyl-phosphino)–1–benzyl–pyrrolidine
DIOP	O-Isopropyliden–2,3–dihydroxy–1,4–bis(diphenylphosphino)butane
L–DOPA	3,4–Dihydroxyphenylalanine
DIPAMP	1,2–Bis[(2–methoxyphenyl)(phenyl)phosphino]ethane
DMSO	Dimethylsulfoxide
DPPE	1,2-Bis(diphenylphosphino)ethane
DuPhos	Bis(2,5–dimethylphospholano)benzene
ee	Enantiomeric excess
e.g.	Exempli gratia
equiv.	Equivalent
Et	Ethyl
et al.	et alii, et aliae or et alia
gem	Geminal
h	Hour
JosiPhos	1–[2–(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine

L	Ligand
MandyPhos	2,2′-Bis[(*N*,*N*-dimethylamino)(phenyl)methyl]–1,1′–bisdicyclohexylphosphino)ferrocene
Me	Methyl
Ment	Menthyl
MeOH	Methanol
MonoPhos	3,5–Dioxa–4–phosphacyclohepta[2,1–a;3,4–a′]dinapthalen–4–yl)dimethylamine
MPPP	Methyl phenyl *n*–propyl phosphine
nbd	Norbornadiene
NMDPP	Neomenthyldiphenylphosphine
NorPhos	2,3–Bis(diphenylphosphino)–bicyclo[2.2.1]hept–5–ene
OAc	Acetate
OMe	Methoxy
o	Ortho
PAMP	Phenyl *o*–anisylmethylphosphine
Ph	Phenyl
i–Pr	*i*–Propyl
n–Pr	*n*–Propyl
2-PrOH	2–Propanol
Pybox	2,6–Bisoxazolin–2–yl pyridine
R	Organic rest
r.t.	Room temperature
SDS	Sodium dodecylsulfonate
SiPhos	10,11,12,13–Tetrahydrodiindeno[7,1–de:1′,7′–fg][1,3,2]dioxaphosphocin–5–dimethylaniline
Terpy	2,2′:6′,2′′–Terpyridine
THF	Tetrahydrofuran
tmeda	*N*,*N*,*N*′,*N*′–Tetramethylethylendiamine
TMS	Trimethylsilyl
TOF	Turnover frequency
TON	Turnover number
X	Halide

1. Introduction

The importance of chiral compounds is demonstrated by their auspicious widespread applications as building blocks or intermediates for the synthesis of pharmaceuticals, agrochemicals, polymers, natural compounds, auxiliaries, ligands and synthons in organic syntheses.[1] To serve the growing demand of enantiomerically pure products various synthetic approaches were developed. Within the diverse consumers of chiral compounds the pharmaceutical industry provides one of the main impulses for new products, since nowadays only drugs containing single enantiomers are allowed to sign up for market.[2] This requirement was initiated as a consequence of different pharmacological studies, which affirmed different behaviour of both enantiomers, and proven by accidents with racemic drugs.[3] Hence, the development of new and improved methods for the preparation of enantiomerically pure compounds is an important target of industrial and academic research. Several synthetic approaches to optically active compounds have been realized in the past. Still one of the most practical approach is the separation of enantiomers via resolution, e.g. in the presence of chiral acids or enzymatic processes. The main drawback of this concept is the poor atom efficiency and the negative environmental impact, albeit nowadays promising efforts on dynamic kinetic resolutions have been established.[4] A more attractive access is represented by applying enantiopure materials from the "chiral pool". Another powerful strategy is the application of stereoselective syntheses in particular reactions catalyzed by transition metal complexes, biocatalysts, and in recent years by organocatalysts.[1e-g,5] Within the different molecular transformations to chiral compounds transition metal catalyzed reactions offer an efficient and versatile strategy and presents a key technology for the advancement of "green chemistry", specifically for waste prevention, reducing energy consumption, achieving high atom efficiency and generating advantageous economics.[6] Since the mid of the last century manifold catalytic reactions have been reported, e.g. polymerization, metathesis, cross couplings, hydroformylations, aminations or epoxidations.[1g] One of the most popular and extensive studied catalytic reaction with respect to industrial applications is the asymmetric hydrogenation of unsaturated compounds containing C=C, C=O and C=N bonds since addition of molecular hydrogen provides high atom efficiency and the starting material are often readily available.[7] In this regard, for activation of the molecular hydrogen or hydrogen donors and transfer of chiral information the use of transition metal catalysts containing chiral ligands is essential. Commonly, chiral phosphorous ligands were used as source of chirality since catalysts including phosphorous systems proved to be highly

active as well as enantioselective. Furthermore diverse representatives are available on large scale.[8] The relevance of hydrogenation processes are impressively confirmed by several integrations in industrial applications (Scheme 1).



Scheme 1. Selection of industrial important compounds synthesized via hydrogenation protocols in the presence of chiral catalysts containing chiral phosphines.[9]

However, the generality of asymmetric hydrogenation is deeply limited by the substrate-structure and transferability of method since no universal catalyst is on hand, which shows extraordinary behaviour for most classes of substrates. Hence the discovery of new effective ligands is an important challenge for industrial and academic research.[7,10] Furthermore the final breakthrough in industry is hampered by catalysts containing expensive and toxic late transition metals (Ir, Rh or Ru). Therefore, substitution by ubiquitous available, inexpensive and less toxic metals is one of the challenging objectives for future research. In this regard the use of iron catalysts is especially desirable.[11]

2. Phosphorous containing ligands in the field of asymmetric hydrogenation

"The inherent generality of this method offers almost unlimited opportunities for matching substrates with catalysts in a rational manner and we are hopeful that our current effort will result in real progress towards complete stereospecificity." W. S. Knowles and M. J. Sabacky[12]

Since the pioneering investigations on asymmetric hydrogenation by Knowles, Kagan, and others in the late 1960s of the last century extensive efforts were undertaken to develop this powerful method. In the early stage of investigations phosphorous ligands have been proven to be beneficial by supporting the catalyst activity and transferring the chiral information. A huge number of successful ligand concepts have been developed during the last decades. Nowadays they are most frequently used in the field of asymmetric C=C bond hydrogenations. However, even if several industrial applications on small to medium scale are established the final breakthrough is so far not reached, due to the low transferability of technique to novel demands. Therefore, tailor–made catalysts designed for well–defined tasks are important tools for achieving high activity and enantioselectivity. Based on this fact the discovery of new effective ligands is a key challenge for industrial and academic research. Innovative catalysts must fulfil several requirements for successful industrial applications. On the one hand an easy to adopt synthetic approach on large scale and straightforward structural variation of the ligand key structure must be available (ligand library). Furthermore, the catalyst must attain reasonable activity and enantioselectivity in the investigated reaction. On the other hand intellectual property should be accessible.[13]

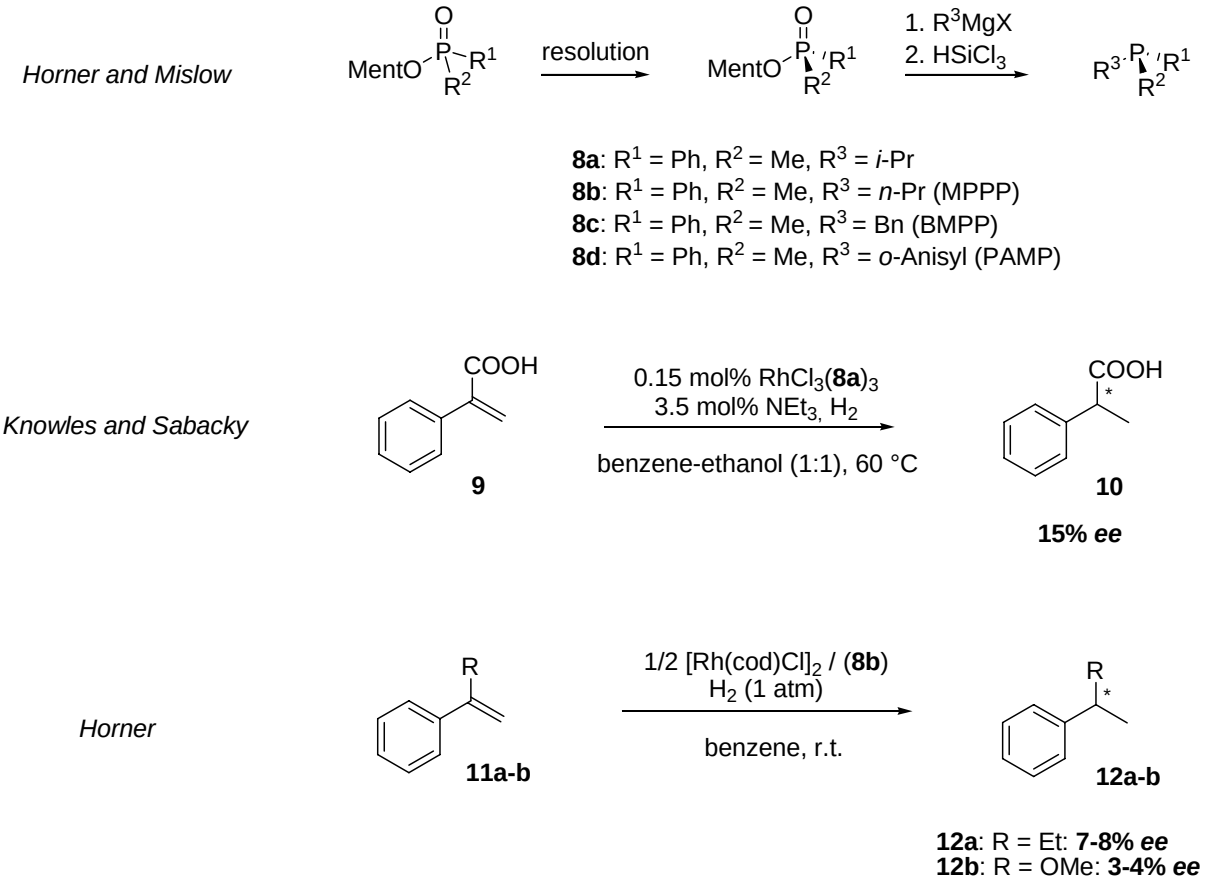
In this regard, the development of new ligands for asymmetric hydrogenation has focused on the synthesis of bidentate ligands for nearly 30 years. However, at the end of the 20th century the predominant role of bidentate ligands changed and monodentate ligands received more attention.[14,15] The advantages of monodentate phosphorous ligands are their easier synthesis and tunability compared to bidentate counterparts. The capabilities of monodentate ligands were successful demonstrated in several reactions.[16] Nowadays monodentate ligands are accepted as additional tool in asymmetric hydrogenations.

This review will focus on the application of monodentate phosphine ligands in asymmetric hydrogenations of C–C double bonds.

2.1. Monodentate phosphine ligands in rhodium–catalyzed asymmetric hydrogenation reactions of C–C double bonds

"The considerable variation of yields with phosphine structure clearly shows the need for a match of catalyst and substrate." W. S. Knowles, M. J. Sabacky, and B. D. Vineyard[17]

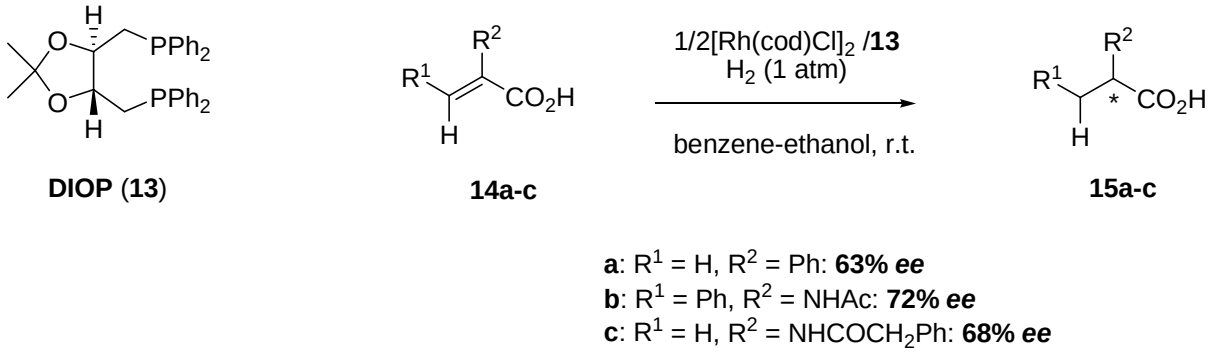
The beginning of homogenous hydrogenation started in the mid of the sixties of the last century and is connected with the groups of Wilkinson and Vaska. Thereby the group of Wilkinson reported the first successful application of a well–defined complex $[RhCl(PPh_3)_3]$ (Wilkinson´s catalyst)[18] in homogeneous hydrogenation of simple olefins with molecular hydrogen, while shortly after Vaska obtained similar results with $Ir(CO)(PPh_3)_3$ as catalyst (Vaska´s complex).[19] Based on this seminal work a first chiral version was independently presented by the groups of Knowles and Horner[20] in 1968 right after Mislow *et al.*[21] and Horner *et al.*[22] established an approach to P–chiral ligands via resolution of diastereomeric menthyl phosphinates and subsequent reaction with Grignard reagents and phosphine oxide reduction (Scheme 2).



Scheme 2. Synthetic approach to chiral monodentate phosphines and first asymmetric hydrogenations carried out with homogeneous catalyst.

In the reduction of *α*–phenylacrylic acid **9** a promising enantiomeric excess of 15% was attained when using rhodium–complexes with ligands of type **8**. Hereafter, various attempts, specially focused on modification of the ligand structure were carried out to improve the enantioselectivity but unfortunately no decisively enhancement was gained.[23] Parallel to this work Horner *et al.* applied an *in situ* catalyst composed of $[Rh(cod)Cl]_2$ and 4 equiv. of optical active methylphenyl–*n*–propylphosphine **8b** in the asymmetric hydrogenation of *α*–ethylstyrene **11a** and *α*–methoxystyrene **11b**, only low enantioselectivities (<8% *ee*) were observed. Later on, the group of Morison showed enantioselectivities up to 61% *ee* in the hydrogenation of (*E*)–*β*–methylcinnamic acid, when shifting the chiral information from phosphorous atom to the carbon–skeleton by synthesis of neomenthyldiphenylphosphine (NMDPP).[24]

However, the breakthrough in homogeneous asymmetric hydrogenation was reached in the early 1970s by Kagan *et al.* when bridging two monodentate phosphines to yield chelating bidentate phosphines. Extraordinary enantioselectivities up to 72% *ee* were obtained in the presence of a rhodium–DIOP–complex (Scheme 3).[25]



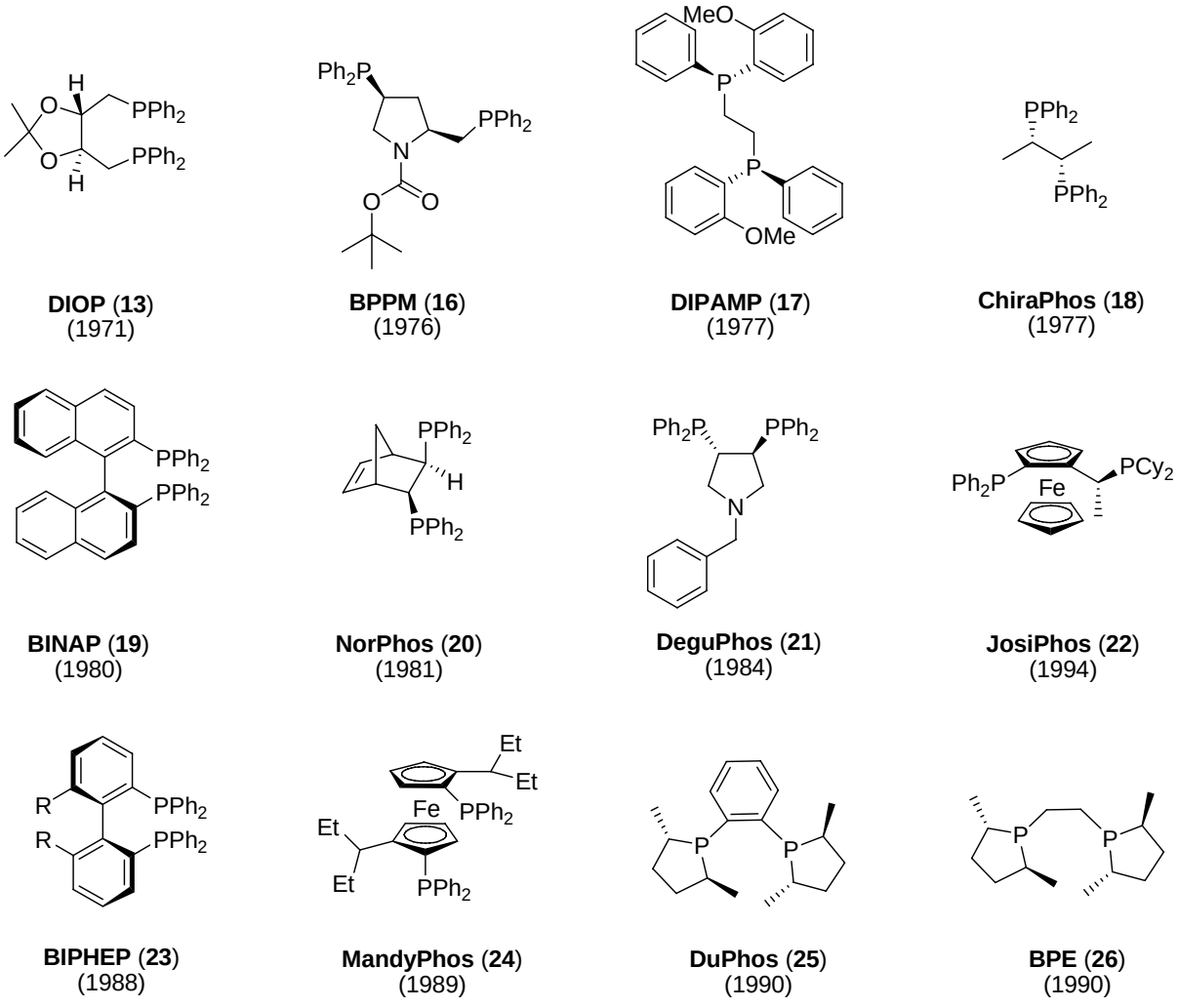
DIOP (**13**) **14a-c** **15a-c**

a: R^1 = H, R^2 = Ph: **63% *ee***
b: R^1 = Ph, R^2 = NHAc: **72% *ee***
c: R^1 = H, R^2 = $NHCOCH_2Ph$: **68% *ee***

Scheme 3. First asymmetric hydrogenation catalyzed by rhodium–diphosphine complexes.[26]

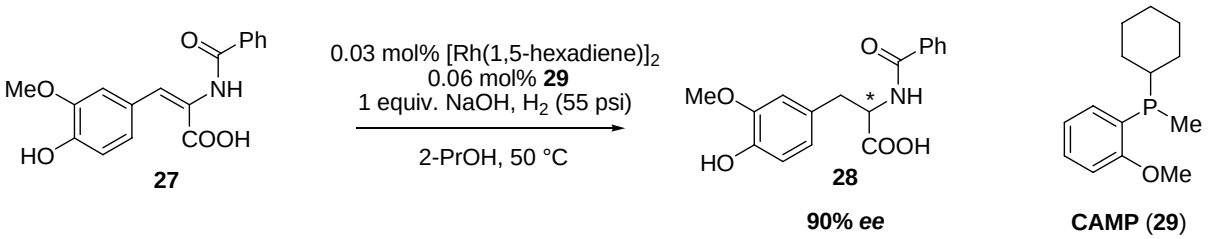
The improvement of this ligand concept was accompanied by two additional strategies. Since the ligand preparation based on chiral phosphorous atoms and further on the resolution of the P–chiral–enantiomers via diastereomers, which gave moderate optical purities, therefore great synthetic efforts were necessary to break-trough. The group of Kagan used as carrier for the chiral information tartaric acid which is accessible from the "chiral pool". Thus the chiral information was moved from the phosphorous atom to the backbone of the ligand as previously discussed by Morison *et al.* Furthermore the complicated separation of ligand enantiomers was avoided. In the following period the concept of bidentate ligands was refined

to further improve the enantioselectivity in asymmetric hydrogenations. During the years various strategies for inducing the chirality were successfully demonstrated, for instance transfer of chirality by different sources, e.g. axial chirality or P–chirality. Furthermore, the bite angle model (phosphorous–metal–phosphorous angle) and the formed ring sizes of phosphorous–metal–phosphorous system displayed to be crucial. In Scheme 4 a selection of outstanding bidentate ligand systems is presented. Enantioselectivities greater then >99% *ee* for a tremendous number of substrates were reported.



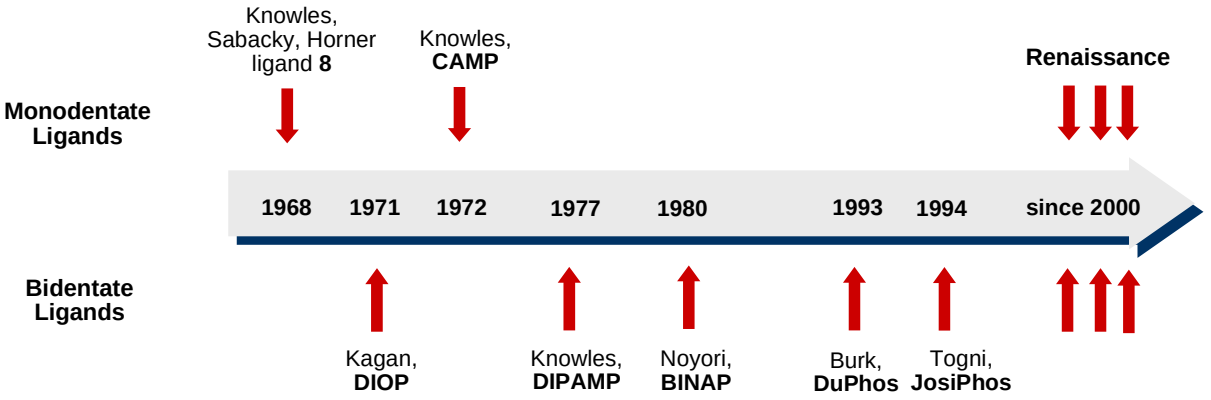
Scheme 4. Selection of outstanding bidentate ligands.[25,27]

At the early stage of bidentate ligands, enantioselectivities up to 90% *ee* were obtained in the hydrogenation of phenyl alanine derivatives with monodentate CAMP ligand **29** by Knowles *et al.* by increasing the optical purity[28] of P–chiral ligands and the introduction of *o*–anisyl group, which probably affords a hemilabile second coordination via methoxy–group.[17,23,29]



Scheme 5. Asymmetric hydrogenation of *α*–dehydroamino acid derivatives to yield a L–DOPA precursor.

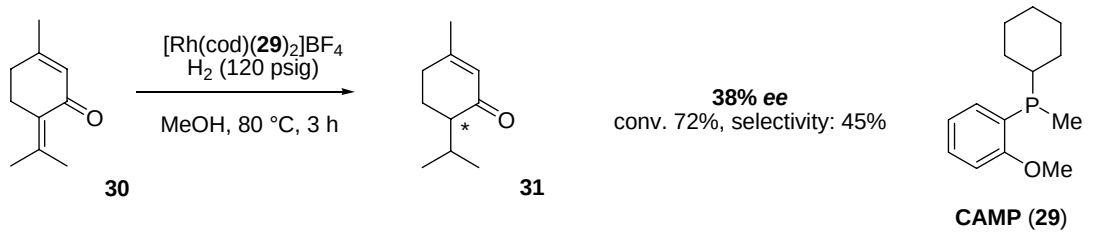
Although this excellent enantioselectivities were gained, the displacement of monodentate ligands by bidentate systems could not be impeded and led to a resting state for approximately 30 years (Scheme 6). Also the pioneers of this research area directed their efforts to bidentate ligands, e.g. Knowles and co–workers synthesized a dimeric version of the PAMP ligand (Scheme 2, **8d**), so called DIPAMP **17** (Scheme 4) and achieved enantioselectivities up to 96% *ee*.[30]



Scheme 6. Historical classification of developments in ligand synthesis.

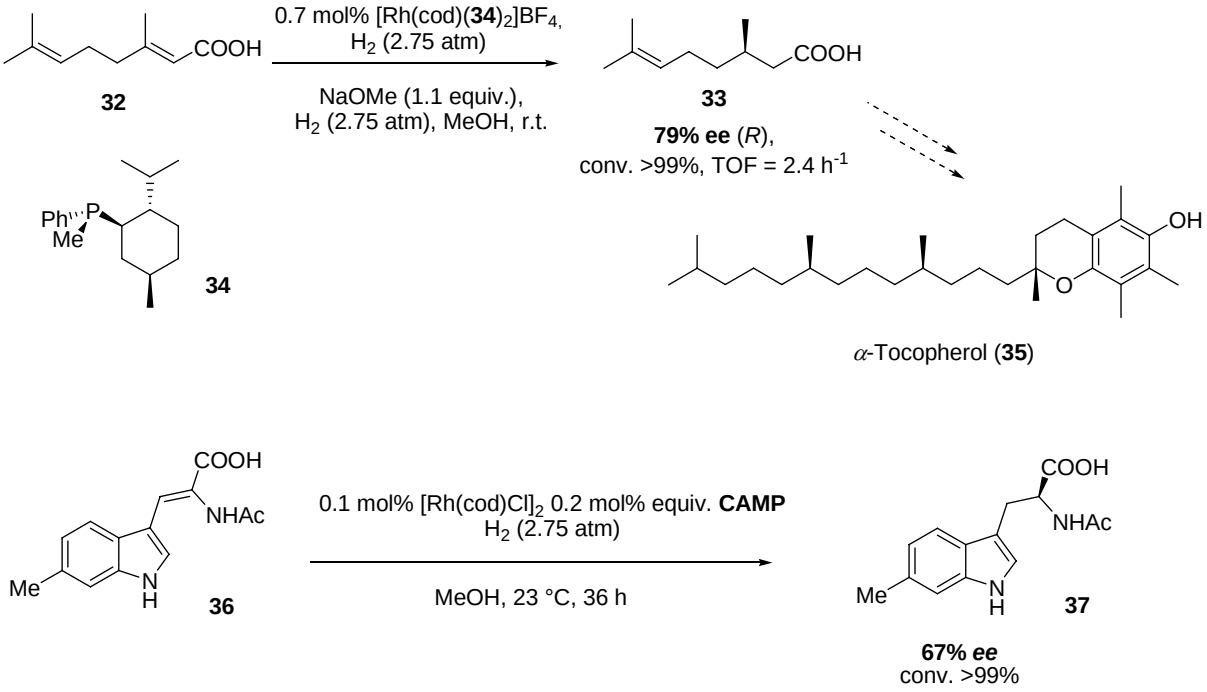
Albeit from time to time attempts were undertaken to refocus on monodentate systems the situation did not change significantly. For instance at the end of the 70th the ligand concept presented in Scheme 2 was taken up again by Solodar for the asymmetric hydrogenation of challenging piperitenone **30**, thereby monodentate ligands induced higher enantioselectivity than bidentate systems, even if the obtained enantiomeric excesses were comparatively low (up to 38% *ee*) (Scheme 7).[31] The influence of reaction conditions on enantioselectivity and chemoselectivity were studied in detail but no considerable improvements were attained. Noteworthy, the chemoselectivity is crucial for this type of substrate, because as side products pulegone (hydrogenation of the endocyclic double bond), menthones (hydrogenation of both

double bonds) and menthols (hydrogenation of both double bonds and the ketone functionality) were observed.



Scheme 7. Synthesis of piperitone **31** via asymmetric hydrogenation.

Valentine *et al.* used a similar ligand concept as described by Morison and co–workers[24] for the reduction of ambitious compound **32** (Scheme 8), which resembles a precursor of α–tocopherol (vitamin E) or phylloquinone (vitamin K_1).[32] As additional chiral carrier to the chiral menthyl–group a P–chirality was embedded and enantioselectivities up to 79% *ee* were attained with rhodium catalyst [Rh(cod)(**34**)$_2$]BF_4. Unfortunately, no information on the outcome of the reaction was given regarding the influence of ligand stereochemistry since matched and mismatched combinations are feasible.

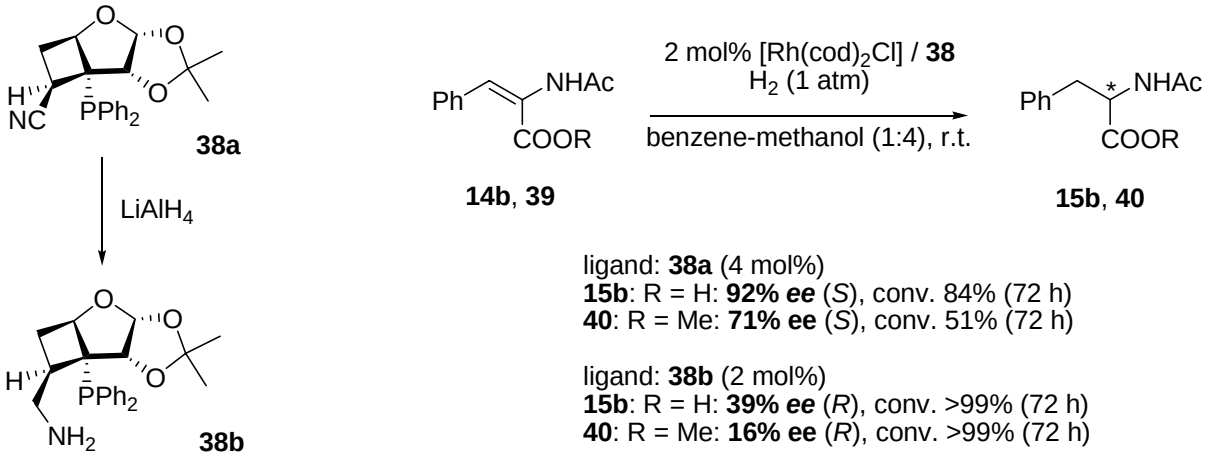


Scheme 8. Asymmetric hydrogenations carried out by Valentine *et al.*

Furthermore, α–dehydroamino acids precursors were hydrogenated in the presence of monodentate ligands, e.g. CAMP **29**, in a comparative study with DIOP **13**. The obtained

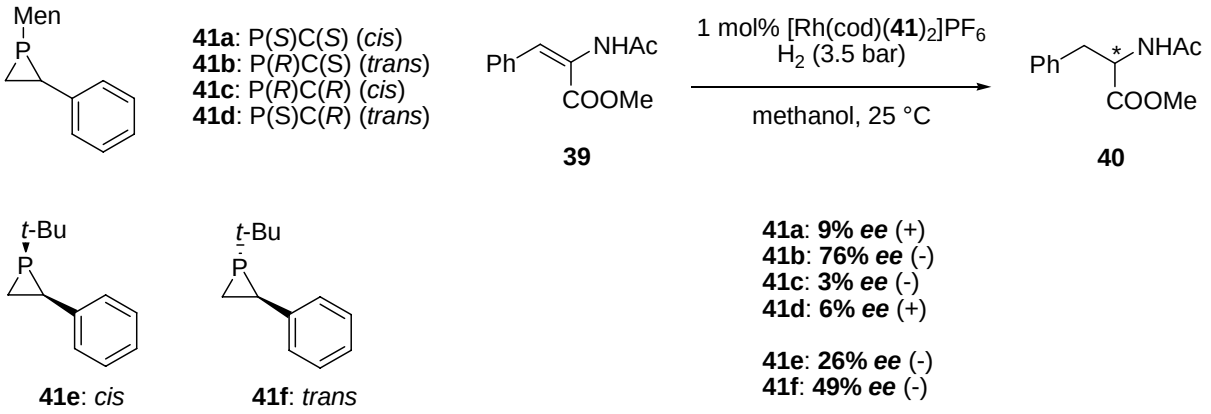
results led to a marginal higher enantioselectivity for DIOP (72% *ee*) compared to CAMP (67% *ee*).

In the mid of the 1980s Morita *et al.* developed an approach to sugar–based monodentate phosphines.[33] Initially started from readily available D–glucose a series of chemical transformations were carried out to attain ligand **38a**. The catalytic potential was tested in the rhodium–catalyzed asymmetric hydrogenation of *N*–acetyl dehydrophenylalanine and the corresponding methyl ester (Scheme 9). Excellent enantioselectivity of 92% *ee* was obtained, albeit long reaction times were necessary. A competitive experiment performed with DIOP as ligand lead to somewhat lower enantioselectivity of 75% *ee* and demonstrated the extraordinary behaviour of monodentate ligand **38a** under described conditions. The unfavourable long reaction times were overcome by increasing the initial hydrogen pressure, unfortunately accompanied by degradation of enantioselectivity. Furthermore, the influence of metal–ligand–ratio was studied. A significant effect on enantioselectivity as well as conversion was found when a ratio of 1:1 was used. The enantioselectivity decreased to 31% *ee* and a prolonged reaction time of one week was necessary to reach full conversion. Indeed, this result was approved by previous works by Knowles *et al.* concerning the necessity of 2 equiv. ligands with respect to the metal, when a monodentate coordination mode is present. However, the catalytic behaviour of ligand **38b**, synthesized by reduction of **38a**, displayed a converse performance, since utilizing a metal–ligand–ratio of 1:1 a slight increase of enantioselectivity and a comparable conversion were observed. Interestingly, also the antipode enantiomer was detected. The authors assumed a bidentate coordination of the ligand, due to the attendance of the NH_2–functionality and the construction of a six–membered ring. In addition, both systems were tested in the hydrogenation of itaconic acid derivatives; thereby ligand **38a** exhibited once more an extraordinary enantioselectivity up to 90% *ee*.



Scheme 9. Sugar–based monodentate ligands by Morita *et al.*

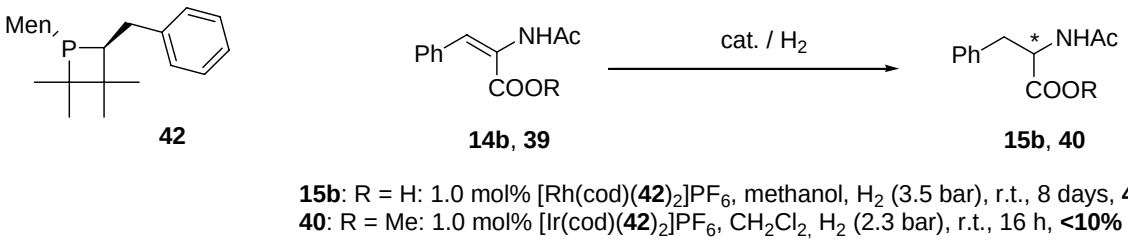
Marinetti and co–workers focused on the synthesis of chiral phosphiranes, which are interesting ligands, because of their high s–character of the phosphorous lone pair, but unfortunately accompanied by high cyclic strain, which causes easy ring opening.[34] However, insertion of optical active phosphorous compounds into enantiopure styrene oxide yields molybdenum phosphirane complexes and subsequent transmetallation with rhodium complexes attained suitable precursors for asymmetric hydrogenation. The authors carried out a matched and mismatched study of all diasteriomeric combinations of ligand **41** in the hydrogenation of *N*–acetyl dehydrophenylalanine methyl ester **39** (Scheme 10). The best performance was shown by ligand **41b** with an enantioselectivity of 76% *ee*, while all other combinations gained almost racemic mixtures. Marinetti *et al.* assume a better transfer of chirality, due to the *cis*–position of the phenyl group with respect to the metal, which causes steric interactions and in consequence a formation of a more stereospecific pocket. Changing the L–menthyl by *t*–butyl group (**41e** and **41f**) confirmed the assumption, because *trans*–system led to higher enantioselectivity.



Scheme 10. Phosphiranes as ligand in asymmetric hydrogenation.

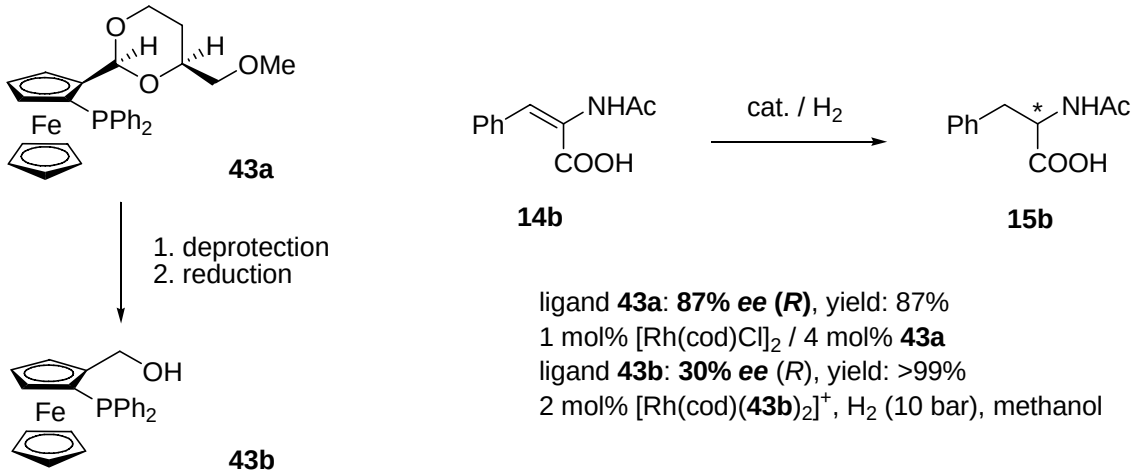
Later the same group reported about an expansion of the ring size of the ligand.[35] The synthesis of chiral phosphetanes of type **42** (Scheme 11) was carried out according to the McBride approach, by reaction of branched olefins with chlorophosphine–$AlCl_3$ complexes. The stereochemistry was regulated by chiral induction of L–menthyl as auxiliary. The acidic protons adjacent to the phosphorous atom enable further functionalization, for instance deprotonation with *n*–butyl lithium and subsequent quenching with benzyl bromide yields ligand **42**. Ligand **42** was subjected to hydrogenation benchmark tests, but unfortunately the standard protocol, e.g. hydrogenation of *N*–acetyl dehydrophenylalanine with rhodium

catalyst attained only low catalytic activity (8 days reaction time) and moderate enantiomeric excess of 40% *ee*. After switching to iridium as metal source, improved activity after 16 h was observed, but accompanied by lower enantioselectivity (<10% *ee*).



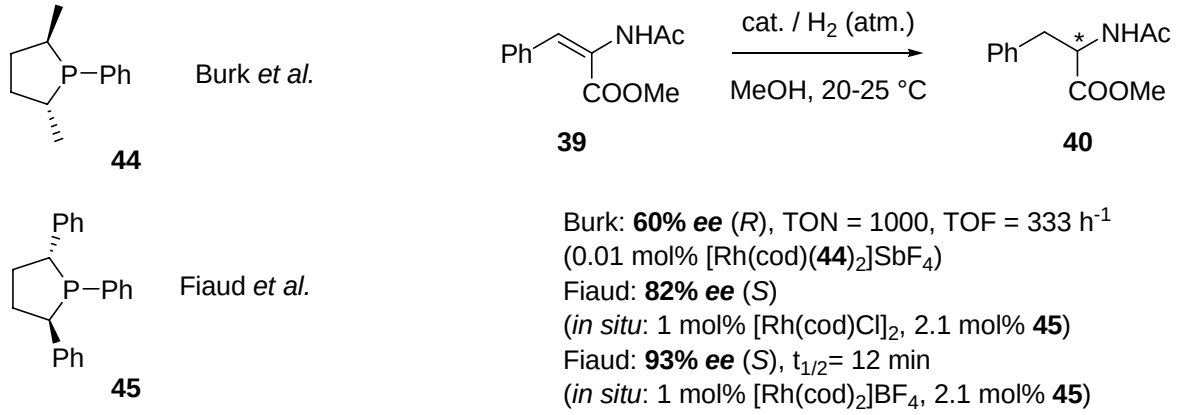
Scheme 11. Monodentate phosphetane ligands for asymmetric hydrogenation.

In 1997 the group of Kagan reported efforts on the synthesis of chiral ferrocene–based ligands (Scheme 12).[36] Starting from ferrocenecarboxaldehyde a three step synthesis was affiliated to establish chiral acetal as chiral auxiliary, which was necessary to control the stereochemistry of *ortho*–substitution with Ph_2PCl via lithiation protocol. The abilities of obtained ferrocene ligand **43a** were investigated in the reduction of *N*–acetyl dehydrophenylalanine with cationic rhodium complexes under standard conditions. Good enantioselectivity of 87% *ee* and yield (87%) were achieved. Furthermore, Kagan *et al.* presented an access to hydroxy–ligand **43b** by removal of the chiral auxiliary of ligand **43a** and subsequent reduction with sodium borohydride. Obviously the free hydroxyl–functionality had a disordered effect on enantioselectivity (30% *ee*), while full conversion was reached in applied time frame.



Scheme 12. Ferrocene–based monodentate ligands.

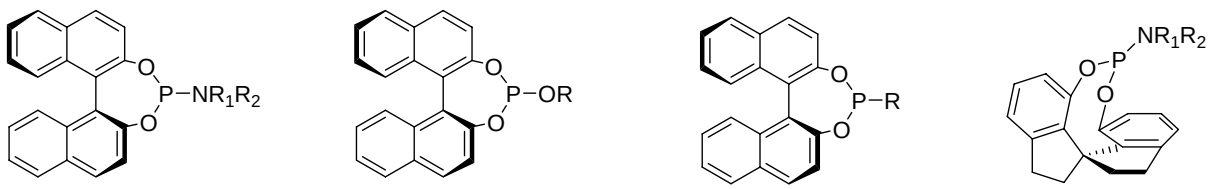
Pioneering work in the second age of monodentate ligands was presented in the late 90th of the last century by the group of Fiaud applying a monodentate phospholane ligand (*R*,*R*)–**45** (Scheme 13), which resembles the structural motif of DuPhos **25**.[37] Albeit the group of Burk demonstrated in one of their early articles the potential of ligand substituted with methyl groups (*R*,*R*)–**44** in the hydrogenation of **39** (60% *ee* (*R*)) and dimethyl itaconate (65% *ee* (*R*)) with catalyst activities up to 500 h^{-1}, their research interest focused on the development of new chiral bisphosphines and **44** was mainly used as intermediate or building block.[38] However, Fiaud obtained an enantioselectivity of 82% *ee* in the rhodium–catalyzed hydrogenation of *N*–acetyl dehydrophenylalanine methyl ester using an *in situ* catalyst composed of 1 mol% $[RhCl(cod)]_2$ and 2.1 mol% corresponding ligand.



Scheme 13. Asymmetric hydrogenation of *N*–acetyl dehydrophenylalanine methyl ester with monodentate phospholanes.

Later on the same group reported efforts on improving the enantioselectivity, by switching from $[RhCl(cod)]_2$ as metal source to $[Rh(cod)_2]BF_4$ which resulted in a significant increase of enantiomeric excess to 93% *ee*.[39] Furthermore, the scope and limitation of ligand **45** was displayed by substrate variation, once dimethyl itaconate was hydrogenated in 55% optical yield, while for the corresponding acid a selectivity of 73% *ee* was attained. On the other hand *N*–acetyl enamides, for instance (*Z*)–*N*–(1–phenylprop–1–enyl)acetamide, were hydrogenated with good enantioselectivities up to 73% *ee*. In their ongoing research they became interested in stabilizing the air–sensitive phosphine by the phospholanium tetrafluoroborate counterpart and liberate the phosphine during the formation of the catalyst precursor. A slight decrease of enantioselectivity (86% *ee* (*R*)), accompanied by higher catalyst activities, was shown when applying this precursor in the hydrogenation of *N*–acetyl dehydrophenylalanine methyl ester with comparable reaction conditions as previous reported by them.[40]

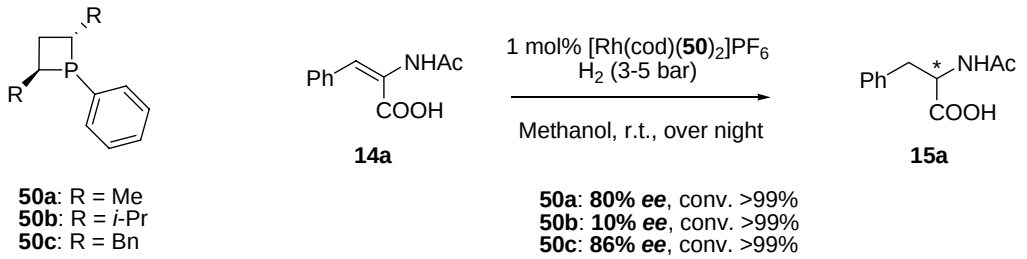
At the end of the 20th century the predominant role of bidentate ligands changed and monodentate ligands received more attention since first attempts by different groups have proven extraordinary transfer of chirality by applying monodentate phosphorous ligands based on binaphthol in asymmetric hydrogenation.[41,42,43] The advantages of this type of monodentate phosphorous ligands are their easier synthesis and high tunability compared to bidentate phosphines, because designated target is accomplished in commonly 1–2 step synthesis starting from low cost chiral binaphthol. Scheme 14 illustrates some examples of monodentate phosphorous ligands for asymmetric hydrogenation based on the chiral 1,1´–binaphthol skeleton. Important contributions in this area came independently from Feringa and de Vries *et al.*[41] (phosphoramidites **46**), Reetz *et al.*[42] (phosphites **47**), and Pringle and Claver *et al.*[43] (phosphonites **48**). Furthermore, excellent enantioselectivity was shown by Zhou and co–workers applying monodentate spiro phosphoramidites (SIPHOS, **49**)[44] and many others.[45] The rediscovery of monodentate ligands was furthermore driven by conceptual review articles by Kagan and Börner, who assumed a better transfer of the chiral information due to the catalyst structure. Until now various systems based on the preliminary structure motif (**46**–**48**) have been proven to be highly active in diverse classes of asymmetric hydrogenations with enantioselectivities up to >99% *ee* and a few numbers of representatives have been commercialized.



46 **47** **48** **49**

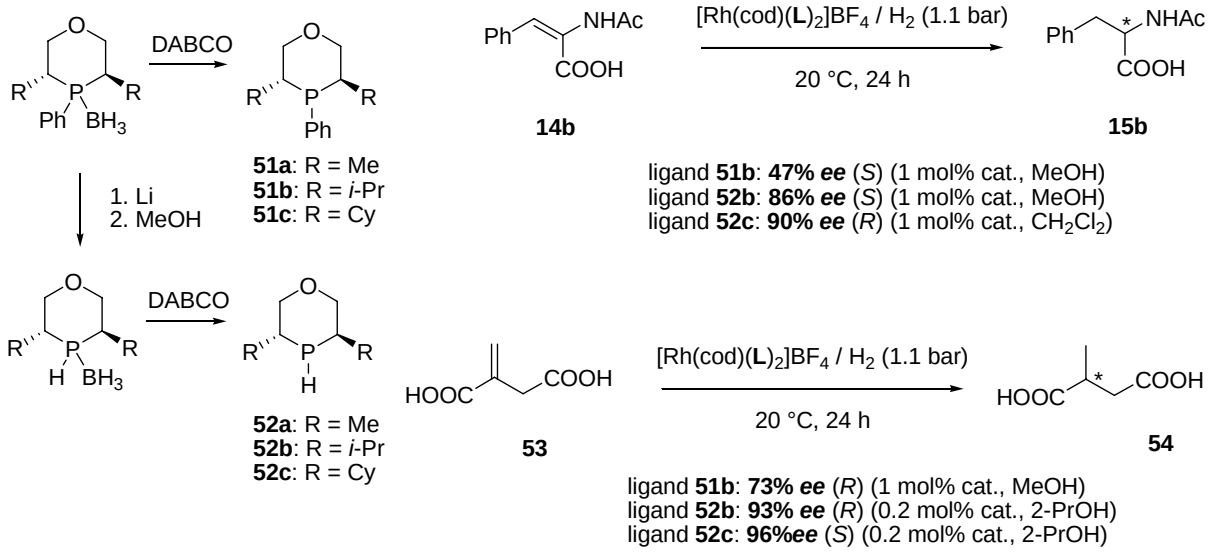
Scheme 14. Selection of successful chiral monodentate ligands in asymmetric hydrogenations.

However, during this time also some efforts on monodentate phosphines were reported. Marinetti and co–workers adopted the synthetic strategy of DuPhos–ligands, via formation of cyclic sulfates, for the synthesis of monodentate phosphetanes **50** (Scheme 15).[46] A huge number of potential ligands were accessible. Three ligands were chosen for testing their abilities in asymmetric hydrogenation of *N*–acetyl dehydrophenylalanine. In comparison to former achievements with phosphetanes an improved enantioselectivity up to 86% *ee* was monitored, albeit the *i*–propyl–derivative gave only low selectivity.



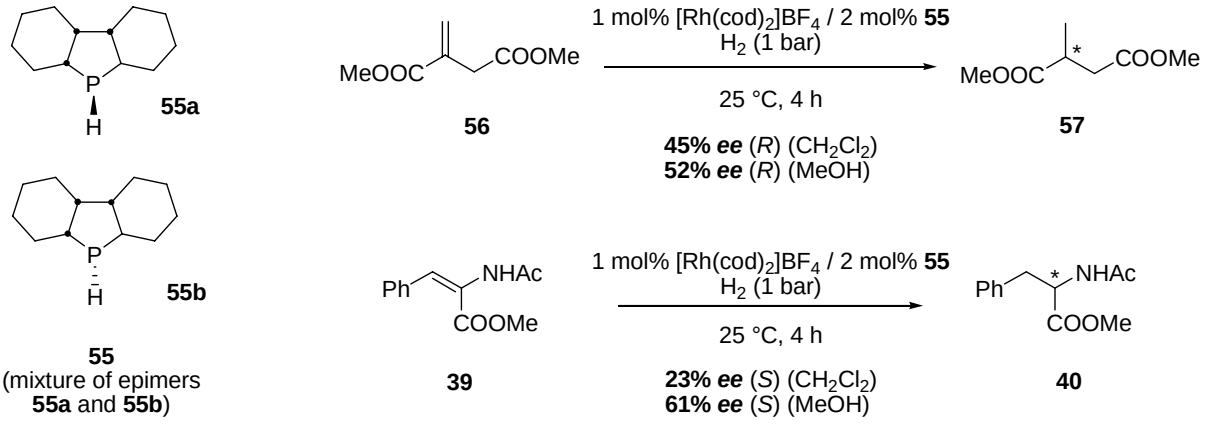
Scheme 15. Phosphetane ligands established by Marinetti *et al.*

Afterwards Helmchen *et al.* exposed the extraordinary catalytic behaviour of oxaphosphinanes in asymmetric hydrogenation reactions (Scheme 16).[47] The ligands were synthesized by mesylation of enantiopure diolethers and subsequent reaction with dilithiophenylphosphine. Because of oxygen–sensitivity a stabilization with BH_3 was appropriated. The oxaphosphinanes boranes were deprotected with DABCO (1,4–diazabicyclo[2.2.2]octane) before pre–catalyst formation was carried out. Preliminary experiments with ligand **51b** pointed out moderate enantioselectivity of 47% *ee* for hydrogenation of *N*–acetyl dehydrophenylalanine. However, the authors assumed an unfavoured sterical shielding of the rhodium therefore the phenyl group was removed and substituted by hydrogen. Indeed, significant higher enantioselectivity (86% *ee*) and reaction rates were attained after re–starting the catalytic investigations with secondary phosphine **52b**. This fact was further approved in the hydrogenation of itaconic acid **53**, because 73% *ee* for **51b** and 93% *ee* for **52b**, respectively, were achieved. Moreover, excellent enantioselectivity up to 96% *ee* was induced by variation of the α–position adjacent to the phosphorous atom.



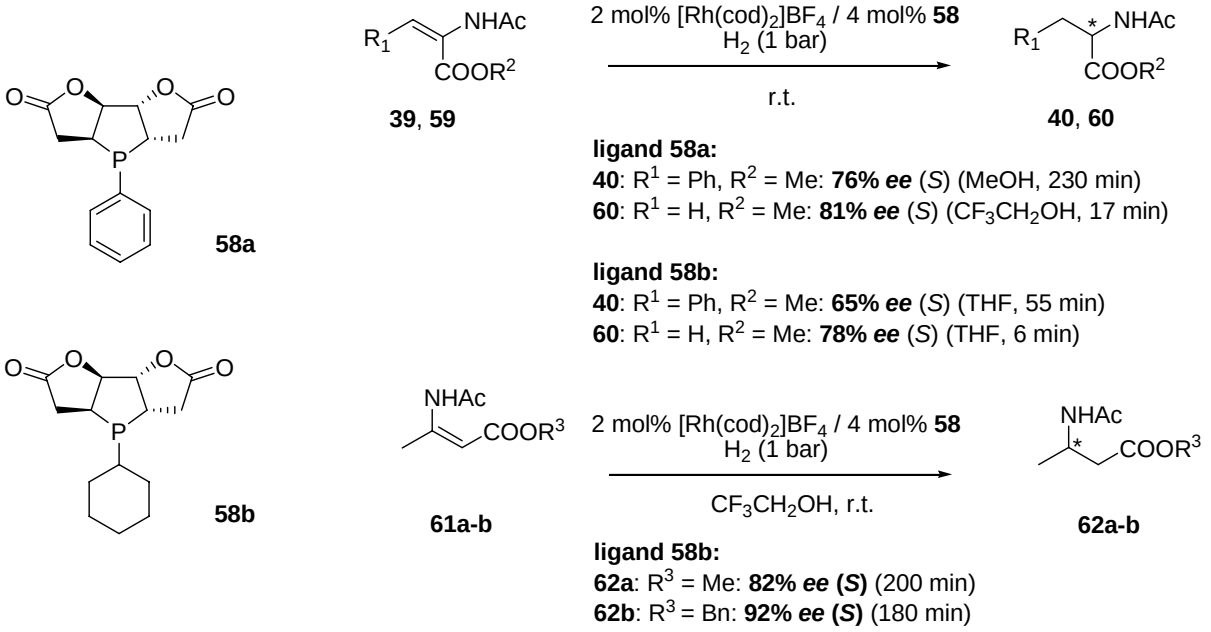
Scheme 16. Oxaphosphinanes approached by Helmchen *et al.*

The group of Börner reported the synthesis and catalytic application of monodentate chiral phospholanes **55** (Scheme 17).[48] Two general synthetic sequences were envisaged. On the one hand, as key step a heterogeneous arene hydrogenation of dibenzophosphole acid was carried out, but unfortunately only a single product was isolated, while in total five diastereomers could be formed. The X–ray structure analysis indicated a *cis*–selective hydrogenation. Secondly, an improved McCormack reaction was performed to build up the basic ligand structure, and follow up chemistry yields ligand **55**. Further on epimerization was investigated theoretically as well as practically to broaden the access to other diastereomers. As predicted by calculations the stereocenter adjacent to the phosphorous atom allows epimerization in the presence of base and subsequent acidification. Transformation of received acids to the corresponding secondary phosphines yields two diastereomers, which were separated via borane adduct. Unfortunately, deprotection of the single diastereomers led to epimerization of the P–chiral phosphorous atom. However, the mixture of diastereomers was tested in the hydrogenation of dimethyl itaconate and *N*–acetyl dehydrophenylalanine methyl ester, thereby moderate enantioselectivities were attained.



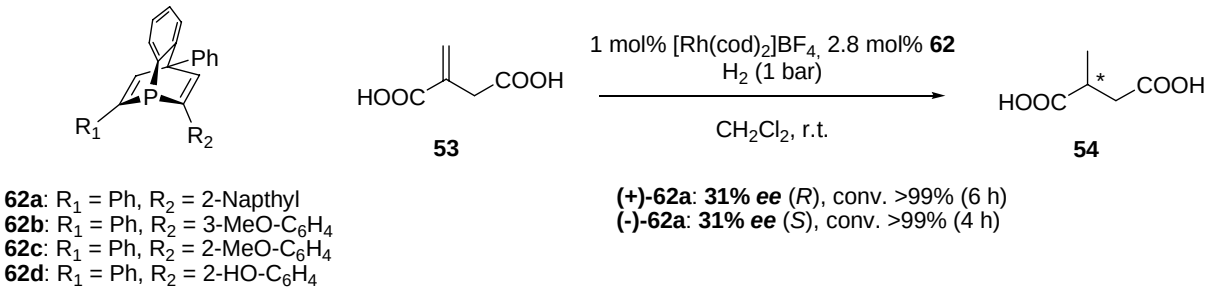
Scheme 17. Secondary phosphine based on phospholane in asymmetric hydrogenation.

More recently, Börner *et al.* reported a second type of monodentate phospholes, based on tartaric acid, which allows easy integration of chiral informations.[49] The key step was a double hydrophosphination. The obtained ligands were subjected to asymmetric hydrogenation of α– and β–dehydroamino acid derivates. Excellent enantioselectivity of 92% *ee* was attained for the hydrogenation of β–dehydroamino acid derivatives.



Scheme 18. Monodentate phospholane ligands based on tartaric acid.

Breit *et al.* reported the synthesis of chiral phosphabarrelenes **62**, which contain highly pyramidalized phosphorous atoms.[50] The ligands were accessible by Diels Alder reaction of substituted phosphabenzene and benzyne and subsequent separation of isomers. Unfortunately, testing these monodentate ligands in asymmetric hydrogenation protocols only moderate enantioselectivities were obtained in the hydrogenation of itaconic acids. However, improvement of enantioselectivity up to 90% *ee* was attained when the phosphabarrelene **62d** was reacted with compound **48** (Scheme 14, R = Cl) to yield a bidentate ligand system.

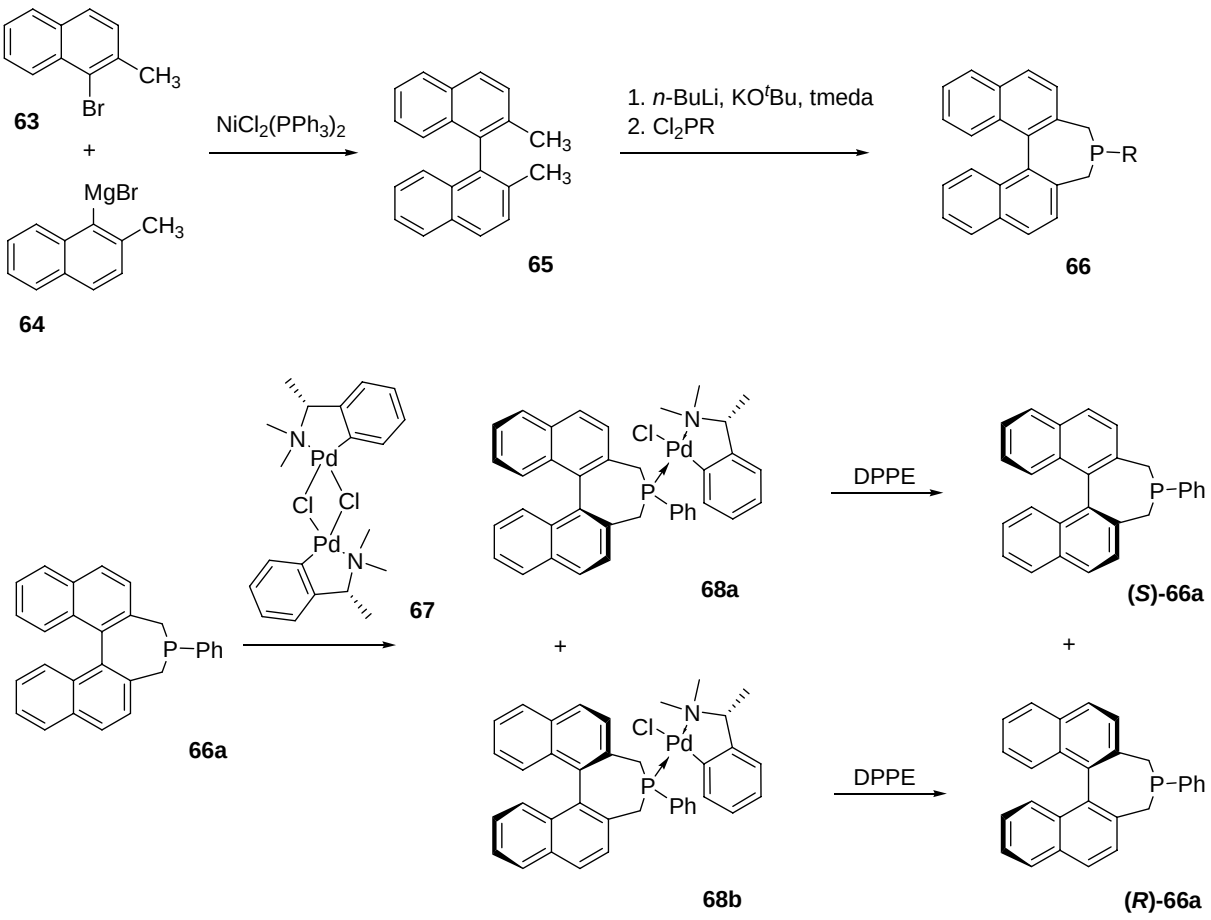


Scheme 19. Chiral phophabarrelene in asymmetric hydrogenation.

2.2. Monodentate ligands based on 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine motif in asymmetric hydrogenations of C–C double bonds

"We can expect that they (monophosphines) will play a role of increasing importance in many aspects of organometallic catalysis." F. Lagasse and H. B. Kagan

Ligands based on the 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine scaffold **66** are known since the early 90´s (Scheme 20) when Gladiali and co–workers reported the first successful synthesis of this ligand class.[51] The synthetic route is presented in Scheme 20. As initial step 2,2´–dimethylbinapthyl was synthesized via nickel–catalyzed Kumada coupling reaction of 1–bromo–1–methylnapthaline **63** and the corresponding Grignard reagent **64**.

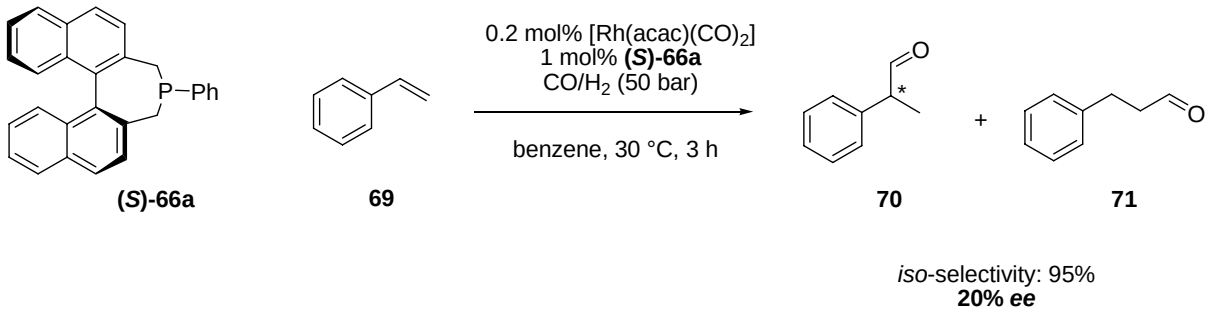


Scheme 20. Approach to chiral phosphepines according to Gladiali *et al.*

The racemic 2,2´–dimethylbinapthyl **65** was selectively double–lithiated on the methyl groups and subsequent quenched with dichlorophosphines to yield the racemic 4,5–dihydro–3*H*–

dinaphtho[2,1–c;1′,2′–e]phosphepines **66**. Resolution of the enantiomers was undertaken on racemic **66a** and carried out by reacting the racemic mixture with (+)–di–μ–chloro-bis[(*S*)–*N*,*N*–dimethyl–α–phenylethylamine–2C,–*N*]-dipalladium **67**[52] to form diastereomeric complexes **68a** and **68b**. The complexes were separated via crystallization. Finally, the enantiopure monodentate phosphine **66a** (Ph–BINEPINE) was liberated by reacting the single diastereomeric complex with bidentate phosphines (e.g. DPPE).

The potential of obtained enantiopure ligand (*S*)–**66a** was tested in asymmetric rhodium–catalyzed hydroformylation of styrene **69** under standard conditions (Scheme 21). Good *iso*/*n*–ratio of aldehyde (**70**:**71**) was found (95:5) and even if low enantioselectivity up to 20% *ee* was reached until this point it was the highest enantiomeric excess induced by monodentate ligands for this type of reaction.[51,53]

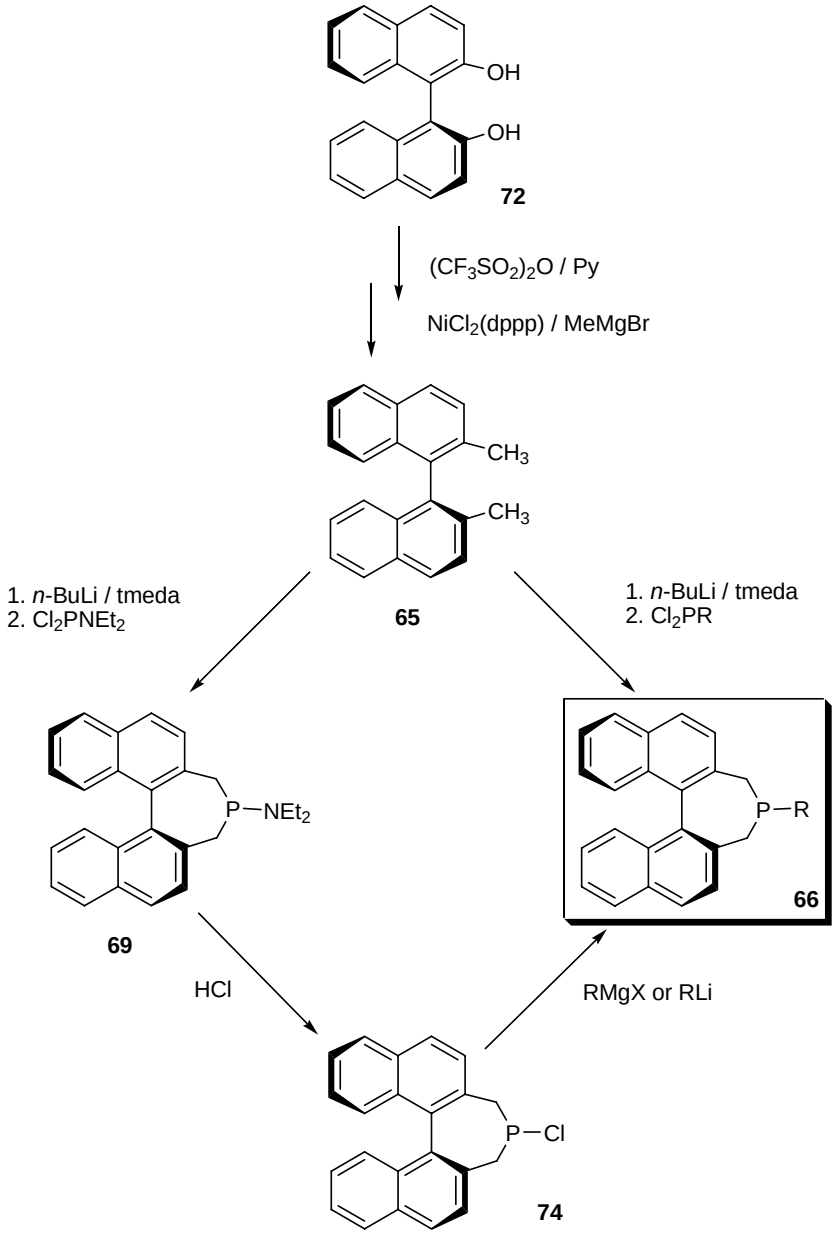


Scheme 21. Enantioselective hydroformylation in the presence of catalyst containing ligand **66a**.

Some years later the group of Stelzer reported the synthesis of secondary phosphine based on phosphepine scaffold **66** (R = H) in good yields.[54] The described achiral secondary phosphine was used as building block or precursor for various ligand systems. However, from practical point of view the approaches invented by Gladiali *et al.* and Stelzer *et al.* causes some difficulties with respect to up–scaling and industrial demands since expensive auxiliaries were used and a low overall yield of final ligand was achieved.

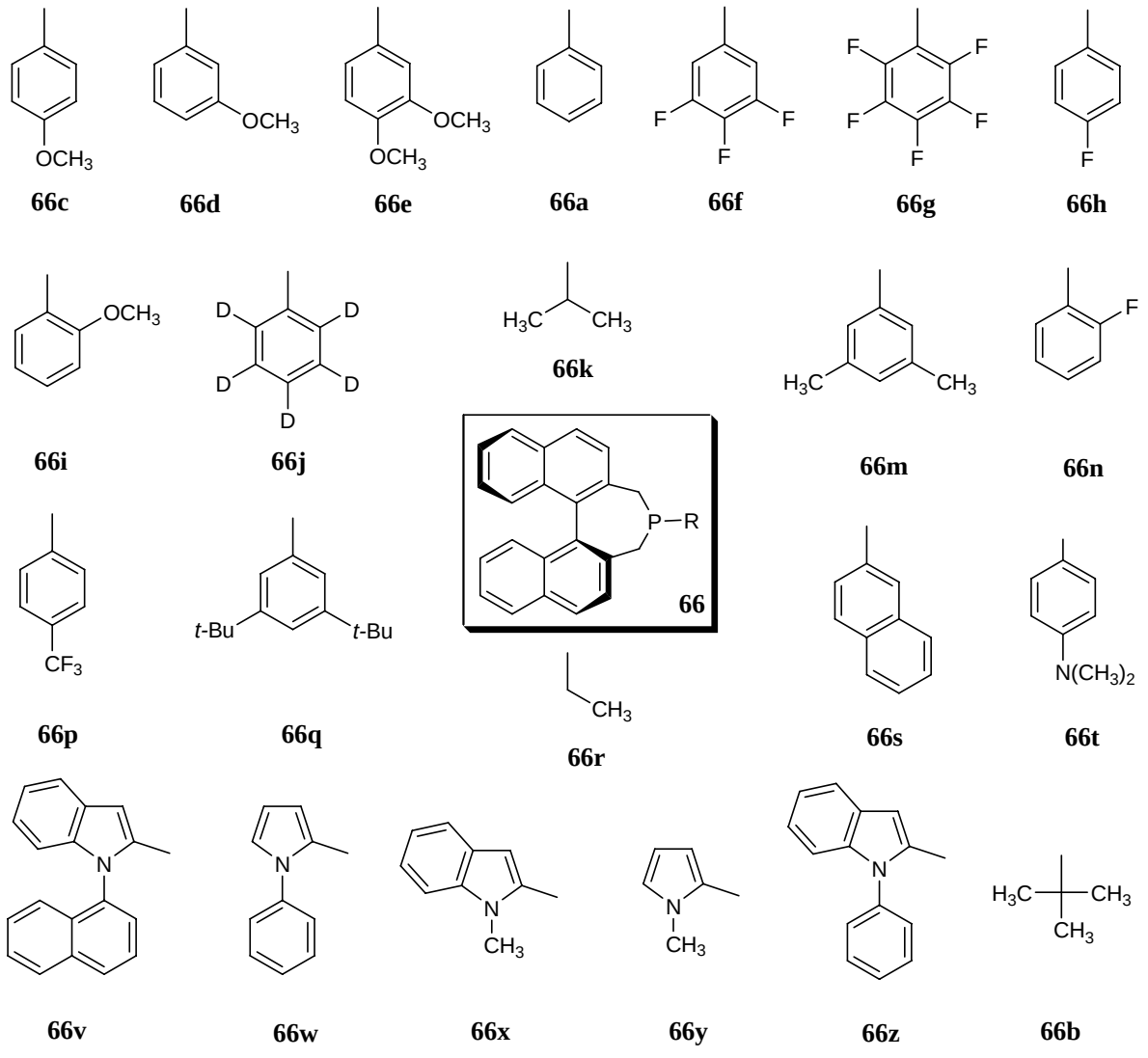
Different attempts were reported on the synthesis of 2,2′–dimethylbinaphthyl **65** in an enantiomeric pure form.[55] On the one hand various chiral versions were described for C–C bond formation via Kumada coupling by exchange of triphenylphosphine by chiral ligands, but so far best enantioselectivity of 95% *ee* was reported by Ito *et al.*[56] Furthermore, few Suzuki coupling reactions were published with comparable low enantioselectivities (85% *ee*).[57] Although some excellent enantioselectivities were demonstrated by C–C coupling methods, the up–scaling of these methods is limited by the availability of applied ligands. On the other hand a more convenient two step pathway starting from enantiomeric pure 2,2′–binaphthol (98% *ee*) was lately established since nowadays the available of 2,2′–binaphthol is

feasible on large scale.[58,59] The updated synthesis of binaphthophosphepines starts with diesterification of enantiomerically pure 2,2′–binaphthol **72** with trifluoromethanesulfonic acid anhydride in the presence of pyridine (Scheme 22).[60] The corresponding diester was obtained in quantitative yield and subsequent nickel–catalyzed Kumada coupling with methyl magnesium bromide leads to 2,2′–dimethylbinaphthyl **65** in 95% yield.[61] Two different synthetic strategies were established to obtain 4,5–dihydro–3*H*–dinaphtho[2,1–*c*;1′,2′–*e*]phosphepine ligands **66**. On the one hand, double metallation of 2,2′–dimethylbinaphthyl **65** with *n*–butyl lithium in the presence of tmeda (*N*,*N*,*N*′,*N*′–tetramethylethylenediamine) followed by quenching with commercially available dichlorophosphines gives ligands such as **66a** (P–phenyl) and **66b** (P–*t*–butyl) in 60–83% yield.



Scheme 22. Synthetic approach to 4,5–dihydro–3*H*–dinaphtho[2,1–c;1′,2′–e]phosphepine developed by Beller *et al.*

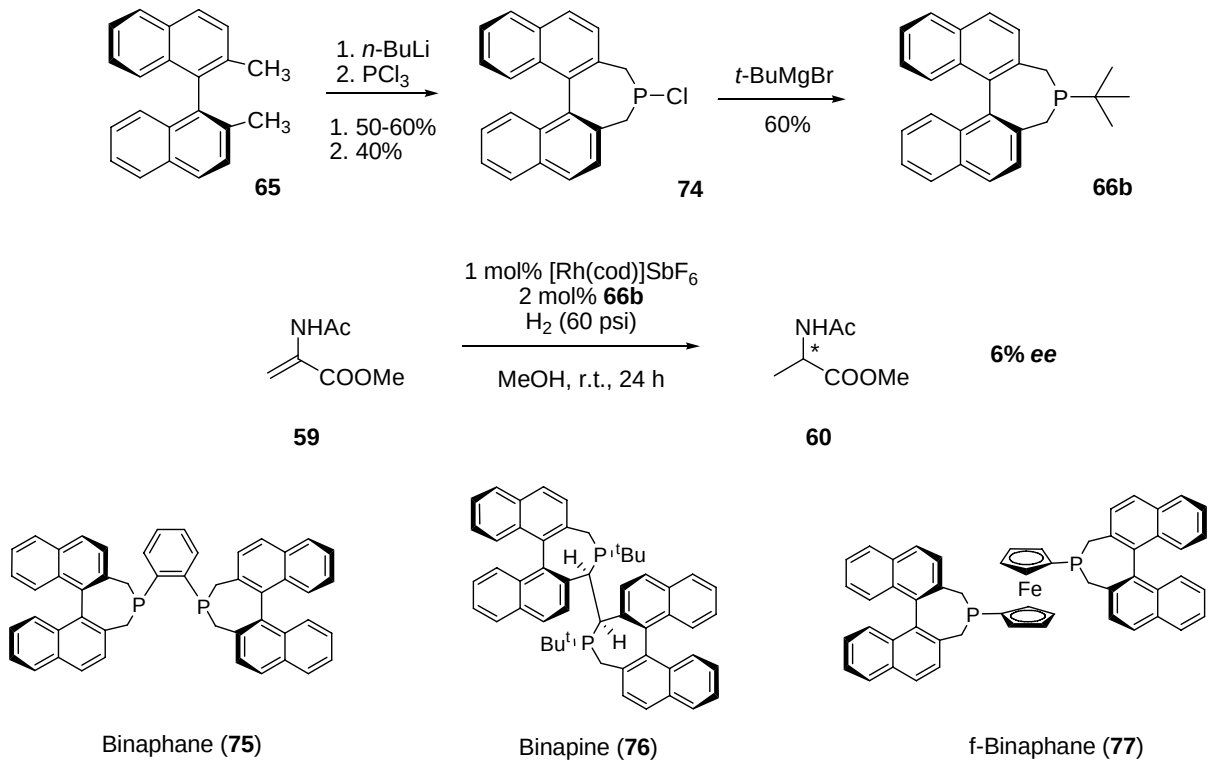
Both ligands have been synthesized on >10g–scale. In the second procedure the dilithiated 2,2´–dimethylbinaphthyl **65** is quenched with diethylaminodichlorophosphine to produce the phosphepine **73**[62] which, upon treatment with gaseous HCl is converted into 4–chloro–4,5–dihydro–3*H*–dinaphtho[2,1–*c*;1´,2´–*e*]phosphepine **74** in 80% yield. This enantiomerically pure chlorophosphine is easily coupled with various Grignard or lithium reagents to render a broad selection of ligand **66**. The limited number of commercially available dichlorophosphines and the large diversity of Grignard compounds make the access through 4–chloro–4,5–dihydro–3*H*–dinaphtho[2,1–*c*;1´,2´–*e*]phosphepine **74** the route of choice to a library of ligands **66** (Scheme 23).[59]



Schema 23. Ligand library based on 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine motif.

Noteworthy, parallel to the work of Beller *et al.* the group of Zhang described a similar synthetic approach, but using monodentate system as intermediate since their research mainly

focused on bidentate ligands and preliminary unpromising results with ligand **66b** in asymmetric hydrogenations were obtained (Scheme 24).[63] Extraordinary enantioselectivity was obtained for bidentate ligands containing the phosphepine moiety (Scheme 24, **75–77**).[64]

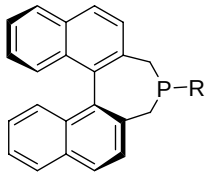


Scheme 24. Synthesis of 4,5–dihydro–3*H*–dinaphtho[2,1–c;1′,2′–e]phosphepine by a protocol established by Zhang *et al.*

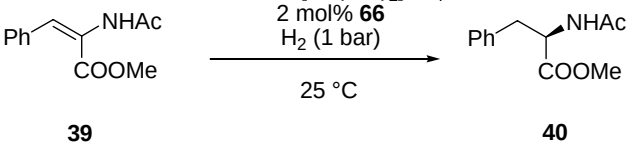
Nevertheless, the group of Beller applied tool box **66** in various catalytic reactions. First set of catalytic experiments with ligand library **66** were dedicated to the rhodium–catalyzed asymmetric hydrogenation of α–amino acid precursors.[59c] Here, methyl (*Z*)–α–acetamidocinnamate **39** and methyl α–acetamidoacrylate **59** were chosen as model systems. Representative results are summarized in Table 1 and Table 2. Surprisingly, initial experiment with different solvents pointed out a benefit for toluene even if toluene is an unusual solvent for hydrogenation purpose, due to catalyst inhibition.[65] However, best enantioselectivities up to 95% *ee* were achieved in toluene with high catalyst activities (TOF 1000–6000 h^{-1}). In some cases a slight improvement of enantioselectivity and reactivity was found when catalytic amount of tenside sodium dodecylsulfonate (SDS) were placed in the reaction (Table 1, entries 2 and 3). Analysis of presented results indicates a crucial influence of substitution pattern at the phosphorous atom. Best enantioselectivities were obtained with aryl systems, while alkyl derivatives lead to low enantiomeric excess (Table 1, entry 1). In the case of asymmetric hydrogenation of substrate **39** a detailed study of various ligands with

substituted–aryl groups connected to the phosphorous demonstrated no significant change in enantioselectivity, when electron–donating or electron–withdrawing functionalities were sited in the *para*–position. Analogous substitution in *ortho*–position decreased the enantioselectivity (Table 1). For the reduction of **59** a converse behaviour was attained since substitution on the aromatic unit improved the enantioselectivity (Table 2).

Table 1. Asymmetric hydrogenation of **39** in the presence of catalysts containing ligand class **66**.



66a: R = Ph
66b: R = *t*-Bu
66c: R = 4-CH_3O-C_6H_4
66e: R = 3,4-$(CH_3O)_2C_6H_3$
66i: R = 2-CH_3O-C_6H_4
66n: R = 2-F-C_6H_4
66q: R = 3,5-$(t\text{-Bu})_2C_6H_3$
66s: R = 2-Naphthyl

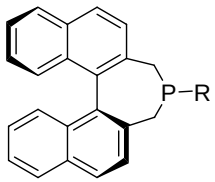


39 **40**

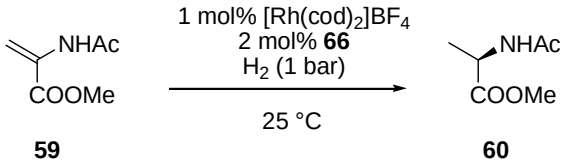
Entry	Ligand	Solvent	*t/2* [min]	Conversion [%]	*ee* [%] (*R*)
1	**66b**	Toluene	31	> 99	20
2	**66a**	Toluene	50	> 99	90
3[a]	**66a**	Toluene + SDS	33	> 99	**95**
4	**66c**	Ethyl acetate	4	> 99	88
5[a]	**66q**	Toluene + SDS	2	> 99	**95**
6	**66i**	Toluene	59	> 99	64
7[a]	**66n**	Toluene + SDS	53	> 99	91
8[a]	**66s**	Toluene + SDS	50	> 99	94
9	**66e**	Toluene	-	> 99	93

[a] 20 mol% SDS (sodium dodecylsulfonate).

Table 2. Asymmetric hydrogenation of **59** in the presence of catalysts containing ligand class **66**.



66a: R = Ph
66c: R = 4-CH_3O-C_6H_4
66i: R = 3-CH_3O-C_6H_4
66n: R = 2-F-C_6H_4
66q: R = 3,5-$(t\text{-Bu})_2C_6H_3$



59 **60**

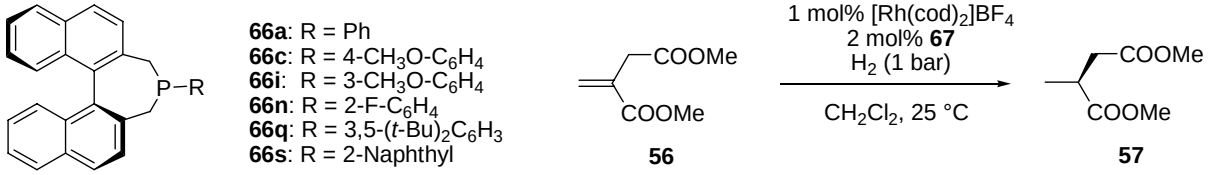
Entry	Ligand	Solvent	*t/2* [min]	Conversion [%]	*ee* [%] (*R*)
1	**66a**	Toluene	18	> 99	67
2	**66c**	Ethyl acetate	2	> 99	51
3	**66q**	Toluene	1	> 99	**94**
4[a]	**66n**	Toluene + SDS	20	> 99	84
5[a]	**66i**	Toluene + SDS	17	> 99	86

[a] 20 mol% SDS (sodium dodecylsulfonate).

Next the potential of ligand library **66** was tested in the asymmetric hydrogenation of dimethyl itaconate **56** (Table 3). Here, best reaction outcome was obtained in

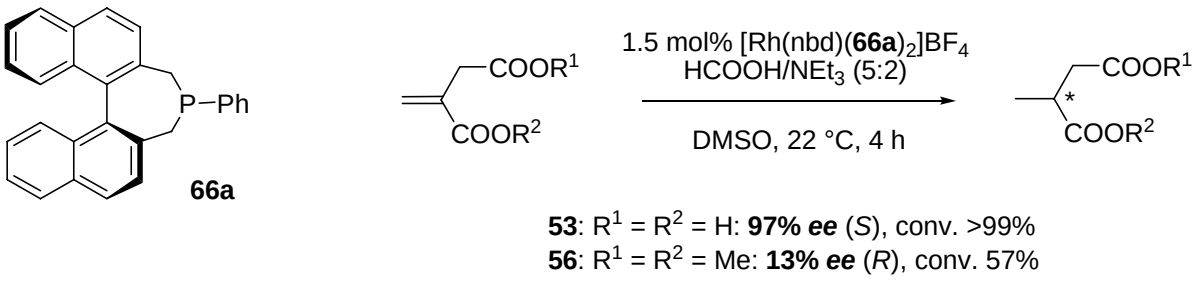
dichloromethane as solvent, even if to some extend lower enantioselectivities up to 88% *ee* were observed.

Table 3. Asymmetric hydrogenation of dimethyl itaconate **56**.



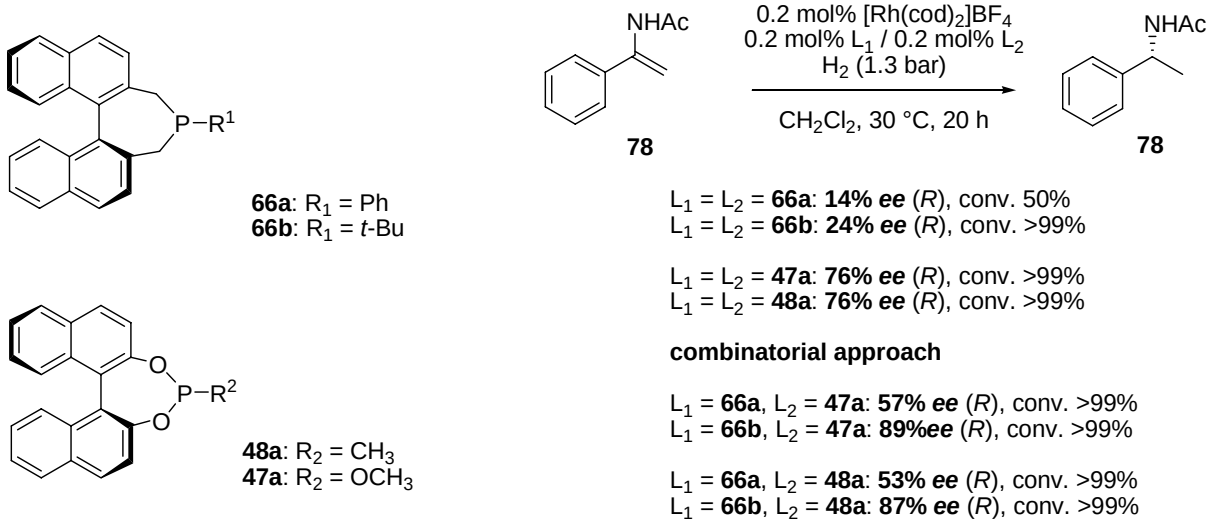
Entry	Ligand	Conversion [%]	*t/2* [min]	*ee* [%] (*S*)
1	**66a**	> 99	56	**86**
2	**66c**	> 99	-	**86**
3	**66q**	> 99	16	83
4	**66n**	86	16	77
5	**66s**	29	34	70
6	**66i**	> 99	-	**88**

A more convincing approach to enantiopure itaconic acid was quite recently reported by Gladiali and co–workers (Scheme 25).[66] Excellent enantioselectivities up to 97% *ee* were attained when subjecting itaconic acid to a rhodium–catalyzed transfer hydrogenation under mild reaction conditions in the presence of well–defined cationic $[Rh(nbd)(\mathbf{66a})_2]^+$ complexes. As suitable source of hydrogen formic acid was chosen since carbon dioxide arises as only side product. Notably, by utilizing the corresponding dimethyl ester or the two possible monomethyl esters under same conditions a decrease of enantioselectivity was noticed, accompanied by a switch of product configuration. Furthermore, a comparative study was carried out by testing several monodentate as well as bidentate ligands. The presented results pointed out the potential of this ligand since only a BINAP complex achieved similar enantioselectivity.



Scheme 25. Transfer hydrogenation of itaconic acid derivatives.

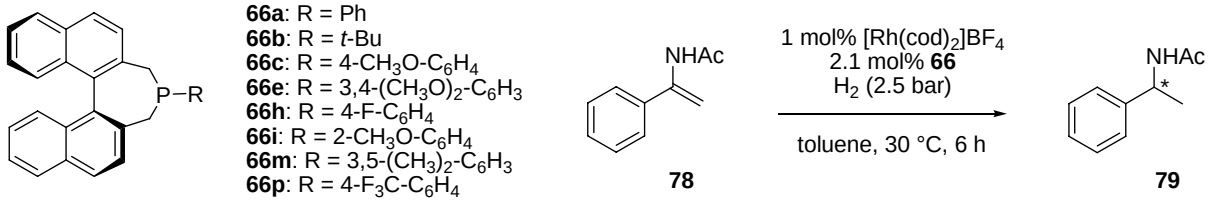
The application of ligand class **66** was furthermore demonstrated in the hydrogenation of *N*–acyl enamide **78** by the group of Reetz (Scheme 26).[67] The obtained enantioselectivities are comparable low, but surprisingly the *tert*–butyl–substituted ligand **66b** (conversion: 94%; enantiomeric excess: 24% (*R*)) showed better selectivity and conversion than the phenyl–substituted ligand **66a** (conversion: 50%; enantiomeric excess: 14% (*R*)), while in other benchmark tests such as the asymmetric hydrogenation of α–amino acid precursors, dimethyl itaconate and β–ketoesters always the opposite behaviour was observed. However, in combination with BINOL–derived phosphites or phosphonites a significant enhancement of enantioselectivity up to 89% *ee* was found. This combinatorial approach displayed impressively one advantage of monodentate phosphorous ligands, as the reaction outcome can easily be tuned by different combination of ligands.[42m,68]



Scheme 26. Asymmetric hydrogenation of *N*–acyl enamides.

Following the original work of Reetz *et al.* the group of Beller investigated the reaction in presence of chiral monodentate 4,5–dihydro–3*H*–dinaphtho[2,1–c;1′,2′–e]phosphepine **66** in more detail (Table 4).[59f] After optimization of different reaction parameters enantioselectivities up to 93% *ee* were achieved with rhodium catalyst containing 2 equiv. of ligand **66a**. As shown in Table 4 the enantioselectivity is largely dependent on the nature of the substituent at the phosphorous atom. Further improvement up to 95% *ee*, which is up to now the highest enantiomeric excess obtained with monodentate phosphine ligands for this purpose, was attained when the substrate structure was modified by introduction of electron–donating groups at the aromatic part of the substrate, while substrates containing electron–withdrawing groups were hydrogenated with somewhat lower enantioselectivities.

Table 4. Extension of asymmetric hydrogenation of *N*–acyl enamides.

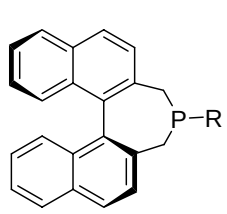


Entry	Ligand	Conversion [%]	*ee* [%]
1	**66a**	>99	**93** (*R*)
2	**66p**	>99	72 (*R*)
3	**66h**	>99	88 (*R*)
4	**66m**	>99	87 (*R*)
5	**66c**	>99	**93** (*R*)
6	**66i**	>99	63 (*R*)
7	**66e**	>99	90 (*R*)
8	**66b**	>99	16 (*S*)

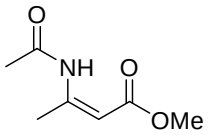
Apart from *α*–amino acids *β*–amino acids received significant attention since they are useful building blocks for pharmaceuticals. Hence the groups of Beller and Gladiali reported on the successful application of ligand class **66** in the rhodium–catalyzed asymmetric hydrogenation of *β*–dehydroamino acids derivatives to give optical active *β*–amino acids derivatives.[69] First experiments emphasized a necessity of different reaction conditions for the *E*– and *Z*–isomer (Table 5). Good enantioselectivity (79% *ee* (*R*)) for the *E*–isomer was obtained by using 2–propanol at 2.5 bar hydrogen pressure, while higher pressure (50 bar) in ethanol was worthwhile for the *Z*–isomer (92% *ee* (*R*)). Noteworthy, a switch of product configuration was observed depending on the nature of the double bond, which has been scarcely reported.[70] Furthermore, a higher reaction rate was monitored for the *Z*–isomer, while converse behaviour was demonstrated for most other catalysts.[71] After separate optimization of reaction parameters for both isomers the ligand library **66** was subjected to catalytic reaction. Surprisingly, in the case of hydrogenation of *E*–**61a** good enantioselectivity was achieved with alkyl ligand **66b**, while for other catalytic reactions (*vide supra*) poor to moderate enantioselectivities were reported (Table 5, entry 6). However, in the hydrogenation of the corresponding *Z*–isomer the catalyst containing ligand **66b** was completely inactive. Here best enantiomeric excess was reached by ligand **66a** (Table 5, entry 1). The usefulness of this concept was confirmed on the hydrogenation of several *β*–dehydroamino acids derivatives. An improved enantioselectivity of 94% *ee* was attained by replacement of methyl ester by ethyl ester. Some mechanistical attempts showed the necessity of 2 equiv. ligands per

metal, which is in agreement with previous findings by Knowles *et al.* This circumstance offers the possibility for a combinatorial ligand approach. Beller and Gladiali *et al.* adopted this concept and combined ligand **66a** with achiral phosphorous ligands. Unfortunately, no significant positive effect was attained.

Table 5. Hydrogenation of *E*–**61a** and *Z*–**61a** with different 4,5–dihydro–3*H*–dinaphtho[2,1–*c*;1′,2′–*e*]phosphepines **66**.



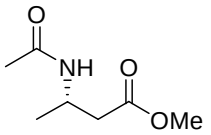
66a: R = Ph
66b: R = *t*-Bu
66c: R = 4-CH_3O-C_6H_4
66d: R = 3-CH_3O-C_6H_4
66e: R = 3,4-$(CH_3O)_2$-C_6H_3
66m: R = 3,5-$(CH_3)_2$-C_6H_3



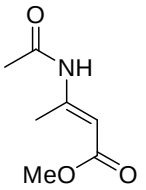
***Z*-61a**

$[Rh(cod)_2]BF_4$ + 2.1 (**66**)

H_2 (50 bar), EtOH, 10 °C, 24 h



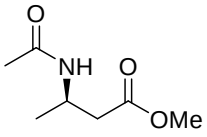
(*S*)-62a



***E*-61a**

$[Rh(cod)_2]BF_4$ + 2.1 (**66**)

H_2 (2.5 bar), 2-PrOH, 10 °C, 24 h

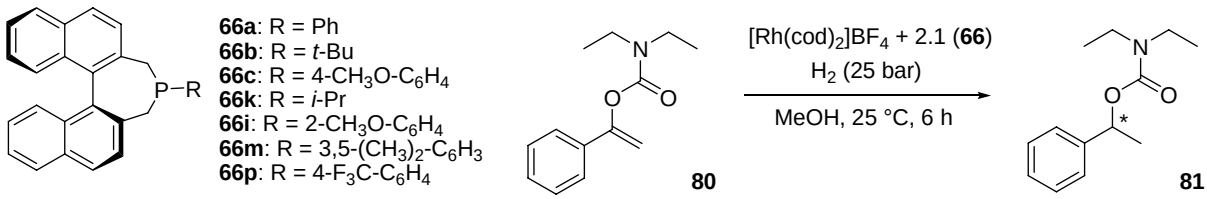


(*R*)-62a

Entry	Ligand	Isomer[a]	Conv. [%]	*ee* [%]	Isomer[b]	Conv. [%]	*ee* [%]
1	**66a**	*E*–**61a**	>99	79 (*R*)	*Z*–**61a**	>99	**92 (*S*)**
2	**66m**	*E*–**61a**	80	69 (*R*)	*Z*–**61a**	>99	80 (*S*)
3	**66c**	*E*–**61a**	>99	**88 (*R*)**	*Z*–**61a**	>99	86 (*S*)
4	**66d**	*E*–**61a**	91	81 (*R*)	*Z*–**61a**	90	40 (*S*)
5	**66e**	*E*–**61a**	>99	**90 (*R*)**	*Z*–**61a**	>99	**89 (*S*)**
6	**66b**	*E*–**61a**	>99	**87 (*R*)**	*Z*–**61a**	3	60 (*S*)

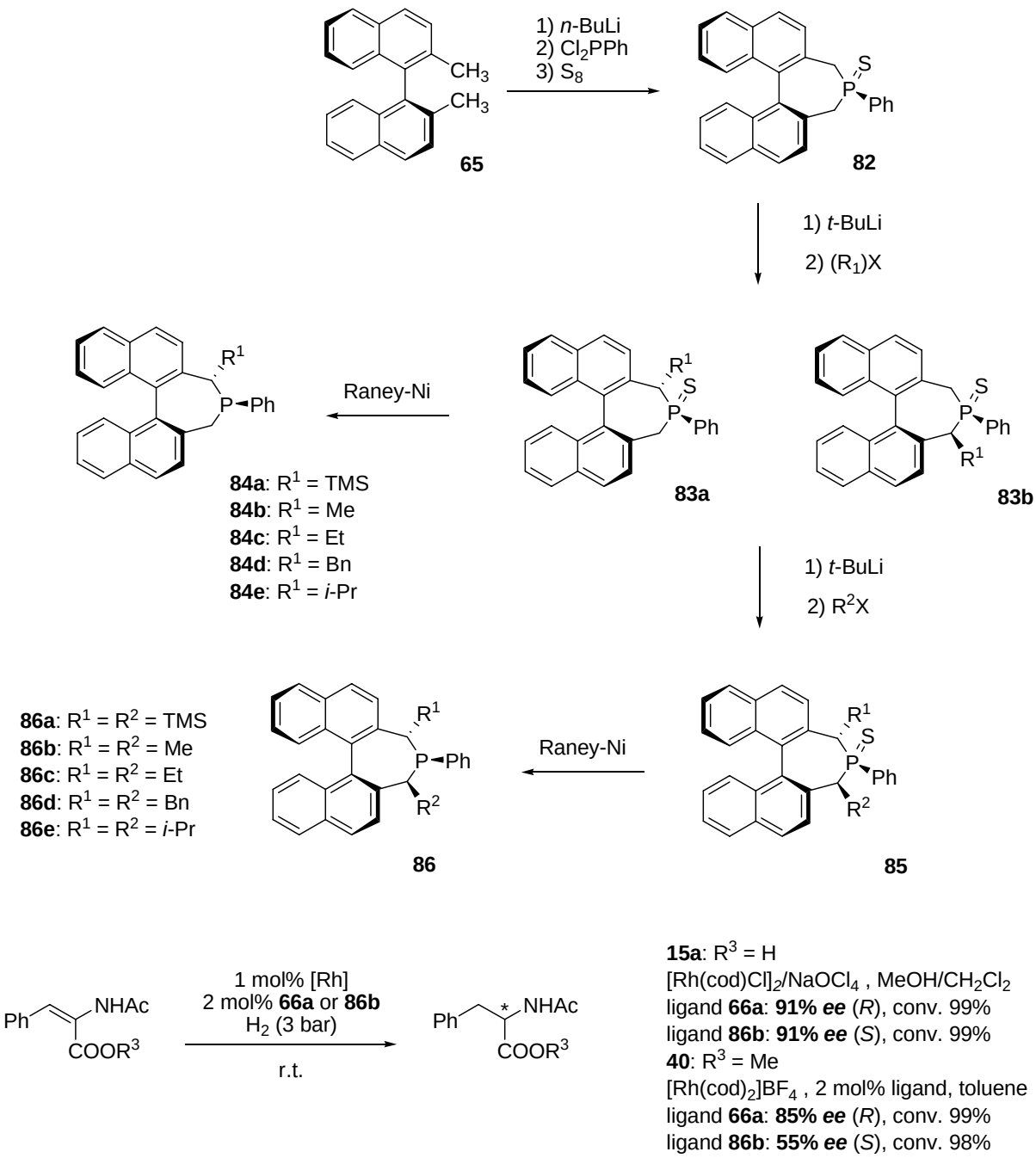
In addition, the group of Beller carried out an enantioselective reduction of enol carbamates, which allows an alternative approach to chiral alcohols.[72] Pioneering work in the field of asymmetric hydrogenation of enol carbamates has been reported by Feringa, de Vries, Minnaard and co–workers who have scored enantioselectivities up to 98% *ee* with rhodium-catalysts containing monodentate phosphoramidites (MonoPhos–family).[41l,73] Utilizing compound **80** as model substrate various reaction parameters were investigated in detail and enantioselectivities up to 96% *ee* were achieved with an *in situ* catalyst composed of $[Rh(cod)_2]BF_4$ and ligand **66a**. Noteworthy, high thermal stability of the catalyst in the range of 10–90 °C was noticed with respect to enantioselectivity (94–96% *ee*). With these suitable conditions ligand library **66** was subjected to a series of enol carbamates. Despite all attempts only **66a** displayed extraordinary selectivity.

Table 6. Hydrogenation of compound **80** with different 4,5–dihydro–3*H*–dinaphtho[2,1–*c*;1′,2′–*e*]phosphepines **66**.



Entry	Ligand	Conv. [%]	Yield [%]	*ee* [%]
1	**66a**	>99	>99	**96 (*S*)**
2	**66p**	40	40	28 (*S*)
3	**66m**	>99	>99	66 (*S*)
4	**66c**	>99	>99	72 (*S*)
5	**66i**	>99	>99	51 (*S*)
6	**66k**	40	40	12 (*S*)
7	**66c**	41	41	50 (*R*)

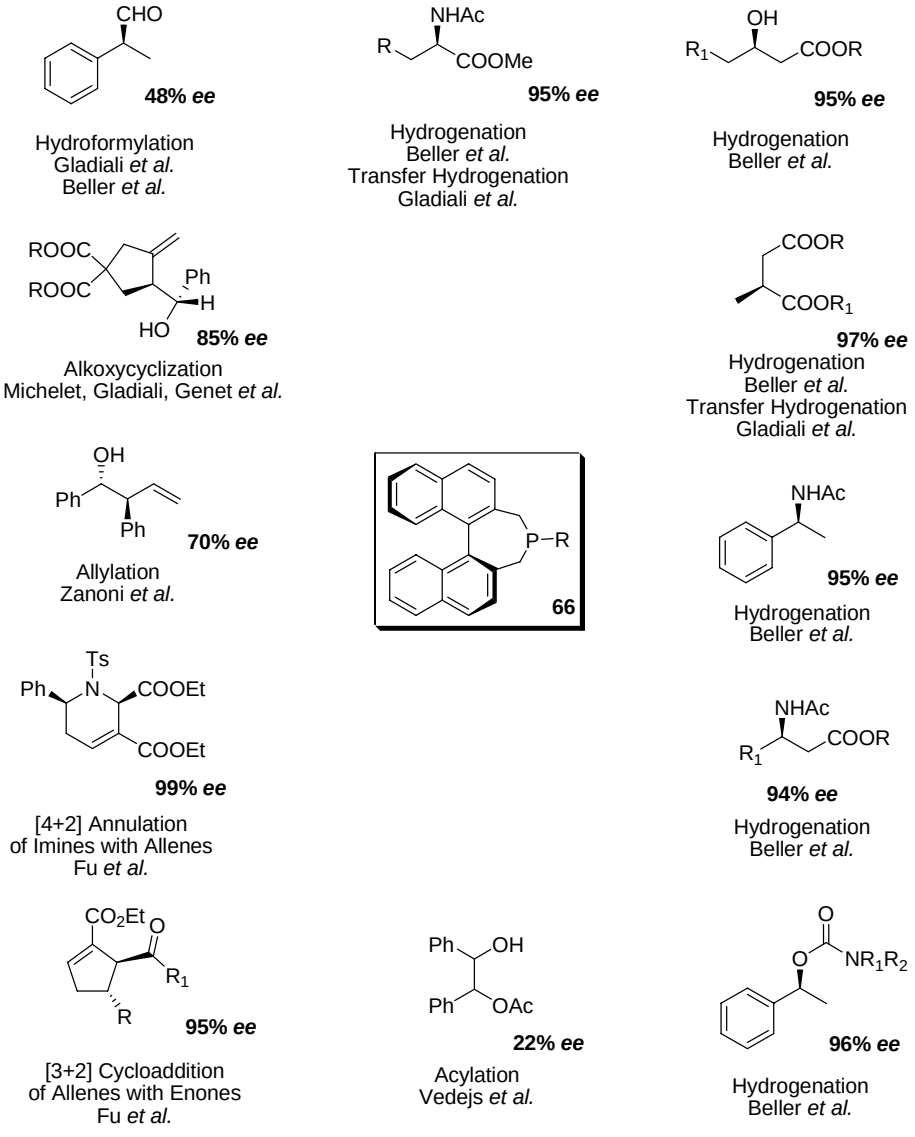
While the group of Beller mainly focused on the variation of substituent at the phosphorous in 4,5–dihydro–3*H*–dinaphtho[2,1–*c*;1′,2′–*e*]phosphepines Widhalm *et al.* reported efforts on the α–substitution adjacent to the phosphorous atom (Scheme 27).[74] Due to the rise of new stereocenters which are closer to the metal a better transfer of chiral information was assumed. Starting from **66a**, which was synthesized according to literature procedures, the corresponding sulfide **82** was prepared. In addition, a deprotonation protocol was established which offers a huge variety of mono– as well as disubstituted ligands after reduction since simple quenching with electrophils are displayed. The substitution was highly stereoselective, because only single diastereomers were obtained. With these ligands in hand a comparative study was carried out to explore the influence of α– and α,α'–substitution. In the rhodium–catalyzed hydrogenation of **14a** and **39** only with the α,α'–dimethyl ligand **86b** comparable enantioselectivities to unsubstituted system were reported, while monosubstituted and other disubstituted representatives lead to moderate selectivity. Interestingly, similar enantioselectivity and activity was attained by utilization of only 1 equiv. of ligand with respect to rhodium. Noteworthy, substitution gained a switch of product configuration.



Scheme 27. Synthesis of α–substituted and α,α'–substituted phosphepine ligands.

2.2.1. Monodentate ligands based on 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine scaffold in asymmetric synthesis

Apart from numerous attempts on asymmetric hydrogenation of C–C double bonds further asymmetric catalytic applications have been demonstrated the usefulness of monodentate phosphines based on 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine motif e.g. the ruthenium-catalyzed asymmetric hydrogenation of *β*–ketoesters,[75] asymmetric borylation, asymmetric Suzuki coupling reactions catalyzed by palladium complexes, the Pd–catalyzed umpoled–allylation of aldehydes[76] and the Pt–catalyzed alkoxycyclization of 1,5–enynes.[77] The ligand itself without any metal has been proven as efficient organocatalyst for the enantioselective acylation of diols, [3+2] cycloadditions and [4+2] annulations (Scheme 27).[78]



Scheme 27. Applications of ligand class **66** in asymmetric synthesis.

2.3. Concluding remarks

The rediscovery of monodentate phosphorous ligands displayed a milestone in asymmetric hydrogenation since high activities, enantioselectivities and ligand combinations for tuning the outcome of the reaction are feasible. In the case of chiral monodentate phosphines until now only a few number of ligands have been proven to entrance enantioselectivities above 90% *ee*. Here ligands with 4,5–dihydro–3*H*–dinaphtho[2,1–c;1′,2′–e]phosphepine structure motif demonstrated excellent enantioselectivities up to 96% *ee* in several catalytic applications. However, the discovery of new effective phosphines will be an important challenge for future research due to there superior stability in comparison to monodentate phosphoramidites, phosphites and phosphonites.

2.4. References

1 a) I. C. Lennon, J. A. Ramsden, *Org. Process Res. Dev.* **2005**, *9*, 110–112; b) J. M. Hawkins, T. J. N. Watson, *Angew. Chem.* **2004**, *116*, 3286–3290; c) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; d) M. Miyagi, J. Takehara, S. Collet, K. Okano, *Org. Process Res. Dev.* **2000**, *4*, 346–348; e) E. N. Jacobsen, A. Pfaltz, Yamamoto, H. (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, 1999; f) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; g) M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis*, Wiley–VCH, Weinheim, 2nd Ed. 2004.

2 a) W. H. De Camp, *Chirality* **1989**, *1*, 2–6; b) M. N. Cayen, *Chirality* **1991**, *3*, 94–98; c) FDA, *Chirality* **1992**, *4*, 338–340.

3 a) J. M. Brown, S. G. Davies, *Nature* **1989**, *342*, 631–636; b) A. P. de Silva, *Nature* **1995**, *374*, 310–311; see also: K. Roth, *Chem. Unserer Zeit* **2005,** *39*, 212–217.

4 a) U. T. Strauss, U. Felfer, K. Faber, *Tetrahedron: Asymmetry* **1999**, *10*, 107–117; b) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; c) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; d) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.* **2003**, *103*, 3247–3261; e) V. Ratovelomanana-Vidal, J. P. Genêt, *Can. J. Chem.* **2000**, *78*, 846–851.

5 P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286.

6 a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; b) P. T. Anastas, M. M. Kirchhoff, T. C. Williamson, *Appl. Catal. A: Gen.* **2001**, *221*, 3–13.

7 a) H.-U. Blaser, B. Pugin, F. Spindler, *J. Mol. Catal.* **2005**, *231*, 1–20; b) H.-U. Blaser, *Chem. Commun.* **2003**, 293–296; c) H.-U. Blaser in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 4–5.

8 a) D. Geffroy, F. Handcock, W. P. Hems, A. Zanotti-Gerosa in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 38–41; b) M. Thommen, H.-U. Blaser in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 6–8; c) Z. Zhang in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 10–17; d) M. van den Berg, D. Peña, A. J. Minnaard, B. L. Feringa, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 18–21; e) C. Le Ret, O. Briel in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 29–32; f) I. C. Lennon, P. H. Moran in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 34–37.

9 a) W.S. Knowles, *Angew. Chem.* **2002**, *114*, 2097–2107; b) R. Selke, H. Pracejus, *J. Mol. Catal.* **1986**, *37*, 213–225; c) R. Selke, *J. Organomet. Chem.* **1989**, *370*, 241–248; d) S. Akutagawa, *Appl. Catal.* **1995**, *128*, 171–207; e) H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 17–31; f) WO 1996-EP2729, WO 2000-US22976; g) J. F. McGarrity, W. Brieden, R. Fuchs, H.-P. Mettler, B. Schmidt, O. Werbitzky in H.-U. Blaser, E. Schmidt (Eds), *Large Scale Asymmetric Catalysis*, Wiley-VCH, Weinheim, 2003; h) S. Akutagawa, *Topics in Catal.* **1997**, *4*, 271–274; i) H.-U. Blaser, F. Spindler, M. Thommen, in J. G. de Vries, C. J. Elsevier (Eds.), *Handbook of homogeneous hydrogenation*, Wiley–VCH, Weinheim, 2007, 1279–1324.

10 X. Zhang, *Tetrahedron: Asymmetry* **2004**, *15*, 2099–2100.

11 The price for iron is relatively low (current price for 1 t of iron ~300 US-dollar) in comparison to rhodium (5975 US-dollar per troy ounce), ruthenium (870 US-dollar per troy ounce) or iridium (460 US-dollar per troy ounce), due to the widespread abundance of iron in earth´s crust and the easy accessibility. Furthermore, iron is an essential trace element (daily dose for humans 5–28 mg) and plays an important role in an extensive number of biological processes.

12 W. S. Knowles, M. J. Sabacky, *Chem. Commun.* **1968**, 1445–1446.

13 H.-U. Blaser, M. Studer, *Chirality* **1999**, *11*, 459–464.

14 F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315–324.

15 I. V. Komarov, A. Börner, *Angew. Chem.* **2001**, *113*, 1237–1240.

16 T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101–2111.

17 W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc. Chem. Commun.* **1972**, 10–11.

18 a) J. F. Young, J. A. Osbourne, F. A. Wilkinson, *Chem. Commun.* **1965**, 131–132; b) J. A. Osbourne, F. H. Jardine, J. F. Young, F. A. Wilkinson, *J. Chem. Soc. (A)* **1966**, 1711–1732; c) P. S. Hallman, D. Evans, J. A. Osborn, G. Wilkinson, *Chem. Commun.* **1967**, 305–306; d) L. Horner, H. Büthe, H. Siegel, *Tetrahedron Lett.* **1968**, 4023–4026; e) C. K. Brown, G. Wilkinson, *Tetrahedron Lett.* **1969**, *22*, 1725–1726; f) R. R. Schrock, J. A. Osborn, *Chem. Commun.* **1970**, 567–568.

19 L. Vaska, R. E. Rhodes, *J. Am. Chem. Soc.* **1965**, *87*, 4970–4971.

20 L. Horner, H. Siegel, H. Büthe, *Angew. Chem.* **1968**, *80*, 1034–1035.

21 a) O. Korpiun, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 4784–4786; b) O. Korpiun, R. A. Lewis, J. Chickos, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4842–4846.

22 L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffman, P. Beck, *Tetrahedron Lett.* **1961**, *5*, 161–166.

23 W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *Chem. Technol.* **1972**, *2*, 590–593.

24 J. D. Morison, R. E. Burnett, A. M. Aguiar, C. J. Morrow, C. Phillips, *J. Am. Chem. Soc.* **1971**, *93*, 1301–1303.

25 T. P. Dang, H. B. Kagan, *Chem. Commun.* **1971**, 481–482.

26 Enantioselectivity based on (*R*)-alanine, after hydrolysis.

27 a) K. Achiwa, *J. Am. Chem. Soc.* **1976**, *98*, 8265–8266; b) M. B. Fryzuk, B. Bosnich, *J. Am. Chem. Soc.* **1977**, *99*, 6262–6267; c) M. B. Fryzuk, B. Bosnich, *J. Am. Chem. Soc.* **1979**, *101*, 3043–3049; d) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934; e) H. Brunner, W. Pieronczyk, B. Schönhammer, K. Streng, I. Bernal, J. Korp, *Chem. Ber.* **1981**, *114*, 1137–1149; f) U. Nagel, *Angew. Chem. Int. Ed.* **1984**, *23*, 435–436; g) R. Schmid, M. Ceregetti, B. Heiser, P. Schönholzer, H.-J. Hansen, *Helv. Chim. Acta* **1988**, *71*, 897–929; h) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125–12138; i) T. Hayashi, A. Yamamoto, M. Hojo, Y. Ito, *J. Chem. Soc. Chem. Commun.* **1989**, 495–496; j) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066.

28 Up to 95% optical purity was attained, compared to former 69%.

29 B. Bogdanović, *Angew. Chem. Int. Ed.* **1973**, *12*, 954–964.

30 W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, *97*, 2567–2568.

31 J. Solodar, *J. Org. Chem.* **1978**, *43*, 1787–1789.

32 D. Valentine Jr., K. K. Johnson, W. Priester, R. C. Sun, K. Toth, G. Saucy, *J. Org. Chem.* **1980**, *45*, 3698–3703.

33 a) S. Saito, Y. Nakamura, Y. Morita, *Chem. Pharm. Bull.* **1985**, *33*, 5284–5293; b) S. Saito, T. Kato, Y. Morita, H. Miyamae, *Chem. Pharm. Bull.* **1985**, *33*, 3092–3095.

34 A. Marinetti, F. Mathey, L. Ricard, *Organometallics* **1993**, *12*, 1207–1212.

35 a) A. Marinetti, L. Ricard, *Tetrahedron* **1993**, *45*, 10291–10304; b) A. Marinetti, L. Ricard, *Organometallics* **1994**, *13*, 3956–3962.

36 O. Riant, O. Samuel, T. Flessner, S. Taudien, H. B. Kagan, *J. Org. Chem.* **1997**, *62*, 6733–6745.

37 F. Guillen, J.-C. Fiaud, *Tetrahedron Lett.* **1999**, *40*, 2939–2942.

38 M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron: Asymmetry* **1991**, *2*, 569–592.

39 F. Guillen, M. Rivard, M. Toffano, J.-Y. Legros, J. C. Daran, J.-C. Fiaud, *Tetrahedron* **2002**, *58*, 5895–5904.

40 C. Dobrota, M. Toffano, J.-C. Fiaud, *Tetrahedron Lett.* **2004**, *45*, 8153–8156.

41 a) L. A. Arnold, R. Imobos, A. Manoli, A. H. M. de Vries, R. Naasz, B. Feringa, *Tetrahedron* **2000**, *56*, 2865–2878; b) M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc*. **2000**, *122*, 11539–11540; c) A. J. Minnaard, M. van den Berg, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. Feringa, *Chim. Oggi* **2001**, *19*, 12–13; d) D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc*. **2002**, *124*, 14552–14553; e) M. van den Berg, R. M. Haak, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Adv. Synth. Catal*. **2002**, *344*, 1003–1007; f) M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv. Synth. Catal*. **2003**, *345*, 308–323; g) D. Peña, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Lett.* **2003**, *5*, 475–478; h) R. Eelkema, R. A. van Delden, B. L. Feringa, *Angew. Chem. Int. Ed*. **2004**, *43*, 5013–5016; i) A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045–8052; j) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943–951 ; k) L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, *Org. Lett.* **2004**, *6*, 1733–1735; l) L. Panella, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 4177–4180; m) R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4209–4212; n) L. Panella, A. M. Aleixandre, G. J. Kruidhof, J. Robertus, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *J. Org. Chem.* **2006**, *71*, 2026–2036; o) F. Giacomina, A. Meetsma, L. Panella, L. Lefort, A. H. M. de Vries, J. G. de Vries, *Angew. Chem.* **2007**, *119*, 1519–1522.

42 a) M. T. Reetz, T. Sell, *Tetrahedron Lett*. **2000**, *41*, 6333–6336; b) M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, *39*, 3889–3891; c) M. T. Reetz, G. Mehler, A. Meiswinkel, T. Sell, *Tetrahedron Lett.* **2002**, *43*, 7941–7493; d) M. T. Reetz, G. Mehler, A. Meiswinkel, T. Sell, *Angew. Chem. Int. Ed*. **2003**, *42*, 790–793; e) M. T. Reetz, G. Mehler, *Tetrahedron Lett*. **2003**, *44*, 4593–4596; f) M. T. Reetz, G. Mehler, A. Meiswinkel, *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167; g) M. T. Reetz, X. G. Li, *Tetrahedron* **2004**, *60*, 9709–9714; h) M. T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem. Int. Ed*. **2005**, *44*, 412–414; i) M. T. Reetz, Y. Fu, A. Meiswinkel, *Angew. Chem.* **2006**, *118*, 1440–1443; j) M. T. Reetz, X. Li, *Synthesis* **2005**, 3183–3185; k) M. T. Reetz, O. G. Bondarev, H.-J. Gais, C. Bolm, *Tetrahedron Lett.* **2005**, *46*, 5643–5646; l) M. T. Reetz, A. Meiswinkel, G. Mehler, K. Angermund, M. Graf, W. Thiel, R. Mynott, D. G. Blackmond, *J. Am. Chem. Soc*. **2005**, *127*, 10305–10313; m) M. T.

Reetz, X. Li, *Angew Chem. Int. Ed.* **2005**, *44*, 2959–2962; n) M. T. Reetz, M. Surowiec, *Heterocycles* **2006**, *67*, 567–574.

43 a) C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Comm.* **2000**, 961–962; b) A. Martorell, R. Naasz, B. L. Feringa, P. G. Pringle, *Tetrahedron: Asymmetry* **2001**, *12*, 2497–2499.

44 a) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2002**, *114*, 2454–2456; b) Y. Fu, X.-X. Guo, S.-F. Zhu, A.-G. Hu, J.-H. Xie, Q.-L. Zhou, *J. Org. Chem.* **2004**, *69*, 4648–4655; c) Y. Fu, G.-H. Hou, J.-H. Xie, L. Xing, L.-X. Wang, Q.-L. Zhou, *J. Org. Chem.* **2004**, *69*, 8157–8160.

45 M. van den Berg, B. L. Feringa, A. J. Minnaard in J. G. de Vries, C. J. Elsevier (Eds.), *Handbook of homogeneous hydrogenation*, Wiley–VCH, Weinheim, 2007, 995–1027.

46 a) A. Martinetti, V. Kruger, F.-X. Buzin, *Tetrahedron Lett.* **1997**, *38*, 2947–2950; b) A. Marinetti, S. Jus, F. Labrue, A. Lemarchand, J.-P. Genêt, L. Ricard, *Synthesis* **2001**, 2095–2104.

47 M. Ostermeier, J. Prieß, G. Helmchen, *Angew. Chem.* **2002**, *114*, 625–628.

48 N. V. Dubrovina, H. Jiao, V. I. Tararov, A. Spannenberg, R. Kadyrov, A. Monsees, A. Christiansen, A. Börner, *Eur. J. Org. Chem.* **2006**, 3412–3420.

49 V. Bilenko, A. Spannenberg, W. Baumann, I. Komarov, A. Börner, *Tetrahedron: Asymmetry* **2006**, *17*, 2082–2087.

50 B. Breit, E. Fuchs, *Synthesis* **2006**, 2121–2128.

51 a) S. Gladiali, A. Dore, D. Fabbri, O. De Lucchi, M. Manassero, *Tetrahedron: Asymmmetry* **1994**, *5*, 511–514; b) S. Gladiali, A. Dore, D. Fabbri, O. De Lucchi, G. Valle, *J. Org. Chem.* **1994**, *59*, 6363–6371; c) S. Gladiali, D. Fabbri, *Chem. Ber./ Rec. Trav. Chim. Pays Bas.* **1997**, *130*, 543–554; d) J. Durand, S. Gladiali, G. Erre, E. Zangrando, B. Milani, *Organometallics* **2007**, *26*, 810–818.

52 a) K. Tani, L. D. Brown, J. Ahmed, J. A. Ibers, M. Yokota, A. Nakamura, S. Otsuka, *J. Am. Chem Soc.* **1977**, *99*, 7876–7886; b) A. Cope, E. C. Friedrich, *J. Am. Chem. Soc.* **1968**, *90*, 909–913.

53 More recently the reaction was extended by Beller and co–workers applying representatives of ligand library **66**. G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *J. Mol. Catal. A*, **2008**, 280, 148–155.

54 F. Bitterer, O. Herd, M. Kühnel, O. Stelzer, N. Weferling, W. S. Sheldrick, J. Hahn, S. Nagel, N. Rösch, *Inorg. Chem.* **1998**, *37*, 6408–6417.

55 G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563.

56 T. Hayashi, K. Hayashizaki, T. Kiyoi, Y. Ito, *J. Am. Chem. Soc.* **1988**, 110, 8153–8156; see also: L. Dahlenburg, V. Kurth, *Inorg. Chim. Acta* **2001**, *319*, 176–182; A. Terfort, H. Brunner, *J. Chem. Soc. Perkin Trans. 1*, **1996**, 1467–1479.

57 a) F. J. Jensen, M. Johannsen, *Org. Lett.* **2003**, *5*, 3025–3028; b) A. N. Cammidge, K. V. L. Crepy, *Chem. Commun.* **2000**, 1723–1724; c) A. N. Cammidge, K. V. L. Crepy, *Tetrahedron* **2004**, *60*, 4377–4386; d) A. N. Cammidge, K. V. L. Crepy, *Chem. Comm.* **2000**, 1723–1724.

58 Optically pure 2,2´–binaphthol is available on large scale from RCA (Reuter Chemische Apparatebau KG), Engesserstr. 4, 79108 Freiburg, Germany. (current price: 1 kg ~ 500 €)

59 a) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Tetrahedron Lett*. **2002**, *43*, 4977–4980; b) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *J. Organomet. Chem.* **2003**, *675*, 91–96; c) K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; d) S. Enthaler, B. Hagemann, K. Junge, G. Erre, M. Beller, *Eur. J. Org. Chem.* **2006**, 2912–2917.

60 a) Y. Uozumi, M. Kawatsura, T. Hayashi, *Org. Synth.* **2002**, *78*, 1–13; b) D. Cai, J. F. Payack, D. R. Bender, D. L. Hughes, T. R. Verhoeven, P. J. Reider, *Org. Synth.*, **1999**, *76*, 6–11.

61 The synthesis of 2,2´–bistriflate-1,1´–binaphthyl (1.2 mol, 615 g, 92%) and 2,2´–dimethyl–1,1`–binaphthyl (0.74 mol, 201 g, 96%) was carried out in large scale by the group of Zhang (See reference 62).

62 Aminophosphinite **70** was also used as ligand in the asymmetric hydrogenation of α–dehydro amino acid derivatives. The corresponding saturated compound was obtained with enantioselectivities up to 90% *ee*. By variation of the substituents on the amino functionality the enantioselectivity was improved to 96% *ee* (See reference: 56b).

63 Y. Chi, X. Zhang, *Tetrahedron Lett*. **2002**, *43*, 4849–4852.

64 a) W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem. Int. Ed*. **2003**, *42*, 3506–3509; b) Y. Chi, Y.-G. Zhou, X. Zhang, *J. Org. Chem.* **2003**, *68*, 4120–4122; c) D. Xiao, X. Zhang, *Angew. Chem. Int. Ed*. **2001**, *40*, 3425–3428; d) D. Xiao, Z. Zhang, X. Zhang, *Org. Lett.* **1999**, *1*, 1679–1681; Q. Dai, W. Yang, X. Zhang, *Org. Lett*. **2005**, *7*, 5343–5345; e) A. Lei, M. Chen, M. He, X. Zhang, *Eur. J. Org. Chem.* **2006**, 4343–4347.

65 H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, *103*, 480–518.

66 E. Alberico, I. Nieddu, R. Taras, S. Gladiali, *Helv. Chim. Acta* **2006**, *89*, 1716–1729.

67 M. T. Reetz, G. Mehler, A. Meiswinkel, *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167.

68 a) M. T. Reetz, X. Li, *Angew. Chem. Int. Ed.* **2005**, *44*, 2962–2964; b) A. Duursma, R. Hoen, J. Schuppan, R. Hulst, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 3111–3113; c) A. Duursma, D. Peña, A. J. Minnaard, B. L. Feringa, *Tetrahedron: Asymmetry* **2005**, *16*, 1901–1904; d) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087–1089; e) C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries, L. Lefort, *Chem. Eur. J.* **2005**, *11*, 6701–6717; f) K. Ding, H. Du, Y. Yuan, J. Long, *Chem. Eur. J.* **2004**, *10*, 2872–2884; g) J. G. de Vries, L. Lefort, *Chem. Eur. J.* **2006**, *12*, 4722–4734.

69 S. Enthaler, G. Erre, K. Junge, J. Holz, A. Börner, E. Alberico, I. Nieddu, S. Gladiali, M. Beller, *Org. Process Res. Dev.* **2007**, *11*, 568–577.

70 a) W. D. Lubell, M. Kitamura, R. Noyori, *Tetrahedron: Asymmetry* **1991**, *2*, 543–554; b) X.-P. Hu, Z. Zheng, *Org. Lett.* **2005**, *7*, 419–422.

71 a) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5947–5952; b) K. Achiwa, T. Soga, *Tetrahedron Lett.* **1978**, *13*, 1119–1120; c) W. D. Lubell, M. Kitamura, R. Noyori, *Tetrahedron: Asymmetry* **1991**, *2*, 543–554; d) G. Zhu, Z. Chen, X. Zhang, *J. Org. Chem.* **1999**, *64*, 6907–6910; e) D. Heller, J. Holz, H.-J. Drexler, J. Lang, K. Drauz, H.-P. Krimmer, A. Börner, *J. Org. Chem.* **2001**, *66*, 6816–6817; f) M. Yasutake, I. D. Gridnev, N. Higashi, T. Imamoto, *Org. Lett.* **2001**, *3*, 1701–1704; g) D. Heller, H.-J. Drexler, J. You, W. Baumann, K. Drauz, H.-P. Krimmer, A. Börner, *Chem. Eur. J.* **2002**, *8*, 5196–5203; h) Y.-G. Zhou, W. Tang, W.-B. Wang, W. Li, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 4952–4953; i) W. Yang, S. Wu, X. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571; j) I. V. Komarov, A. Monsees, A. Spannenberg, W. Baumann, U. Schmidt, C. Fischer, A. Börner, *Eur. J. Org. Chem.* **2003**, 138–150; k) J. You, H.-J. Drexler, S. Zhang, C. Fischer, D. Heller, *Angew. Chem.* **2003**, *115*, 942–945; m) J. Holz, A. Monsees, H. Jiao, J. You, I. V. Komarov, C. Fischer, K. Drauz, A. Börner, *J. Org. Chem.* **2003**, *68*, 1701–1707; n) J. Wu, X. Chen, R. Guo, C.-h. Yeung, A. S. C. Chan, *J. Org. Chem.* **2003**, *68*, 2490–2493; o) H.-P. Wu, G. Hoge, *Org. Lett.* **2004**, *6*, 3645–3647; p) Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong III, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919.

72 S. Enthaler, G. Erre, K. Junge, D. Michalik, A. Spannenberg, S. Gladiali, M. Beller, *Tetrahedron: Asymmetry*, **2007**, *18*, 1288–1298.

73 X. Jiang, M. van den Berg, A. J. Minnaard, B. Feringa, J. G. de Vries, *Tetrahedron: Asymmetry* **2004**, *15*, 2223–2229.

74 P. Kasák, K. Mereiter, M. Widhalm, *Tetrahedron: Asymmetry* **2005**, *16*, 3416–3426.

75 a) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066–5069; b) B. Hagemann, K. Junge, S. Enthaler, M. Michalik, T. Riermeier, A. Monsees, M. Beller, *Adv. Synth. Catal.* **2005**, *347*, 1978–1986.

76 G. Zanoni, S. Gladiali, A. Marchetti, P. Piccinini, I. Tredici, G. Vidari, *Angew. Chem. Int. Ed*. **2004**, *43*, 846–849.

77 L. Charruault, V. Michelet, R. Taras, S. Gladiali, J.-P. Genêt, *Chem. Commun.* **2004**, 850–851.

78 a) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235; b) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430–431; c) J. E. Wilson, G. C. Fu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1426–1429.

3. Reduction of unsaturated compounds with homogeneous iron catalysts

Stephan Enthaler, Kathrin Junge, and Matthias Beller*, in B. Plietker (Ed.) “Iron catalysis in organic chemistry“ Wiley VCH, Weinheim, 2008.

Contributions

The subchapter “Hydrosilylation” was written by Dr. K. Junge.

3. Reduction of unsaturated compounds with homogeneous iron catalysts

Stephan Enthaler, Kathrin Junge, and Matthias Beller

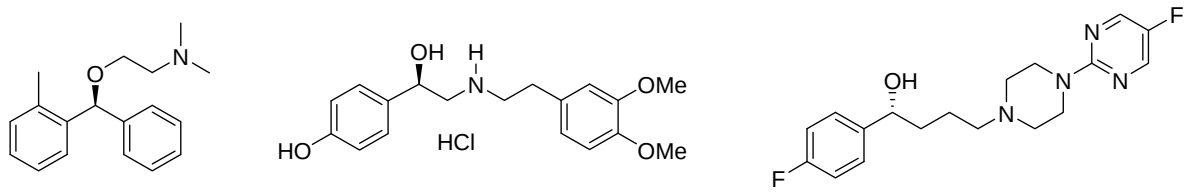
Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany. Fax: 49-381-1281-5000; Tel: 49-381-1281-113; E-mail: matthias.beller@catalysis.de

3.1. Introduction

Within the different molecular transformations reduction processes plays one of the major roles in organic chemistry. Apart from stoichiometric reactions, transition metal catalyzed reactions offer an efficient and versatile strategy and present a key technology for the advancement of “green chemistry”, specifically for waste prevention, reducing energy consumption, achieving high atom efficiency and creating advantageous economics.[1] Among the most popular and extensive studied catalytic reactions with respect to industrial applications is the hydrogenation of unsaturated compounds containing C=C, C=O and C=N bonds since addition of molecular hydrogen provides high atom efficiency.[2] In this regard, for activation of the molecular hydrogen or hydrogen donors, transition metal catalysts are essential. Commonly expensive and rare late transition metals (Ir, Rh or Ru) are applied as catalyst core. Therefore, substitution by ubiquitous available, inexpensive and less toxic metals is one of the major challenges for future research. Consequently, the use of iron catalysts is especially desirable.[3] This chapter will summarize the impact of iron catalysts on hydrogenation and hydrosilylation chemistry and mainly directed to the reduction of C=C, C=O and C=N bonds. Further catalytic applications were summarized elsewhere e.g. reduction of nitro compounds or dehalogenations.[4]

3.2. Hydrogenation of carbonyl compounds

The relevance of carbonyl hydrogenation processes is impressively emphasized by the broad scope of applications for example as building blocks and synthons for pharmaceuticals, agrochemicals, polymers, synthesis of natural compounds, auxiliaries, ligands and key intermediates in organic syntheses (Scheme 1).[5]



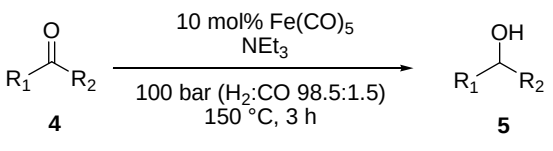
Orphenadrin (1)
anticholinergic drug

(*R*)-Denopamine-Hydrochloride (2)
β_1-receptor antagonist

BMS 181100 (3)
antipsychotica

Scheme 1. Selected pharmaceuticals based on chiral alcohols.[6]

In the past this field has been dominated by ruthenium, rhodium and iridium catalysts with extraordinary activities and furthermore superior enantioselectivities, however some investigations were carried out with iron catalysts. Early efforts were reported on the successful use of hydridocarbonyliron complexes ($HFe_m(CO)_n^-$) as reducing reagent for α,β-unsaturated carbonyl compounds, dienes and C=N double bonds, albeit complexes were used in stoichiometric amounts.[7] The first catalytic approach was presented by Markó and co-workers on the reduction of acetone in the presence of $Fe_3(CO)_{12}$ or $Fe(CO)_5$.[8] In this reaction the hydrogen is delivered by water under more drastic reaction conditions (100 bar, 100 °C). Addition of NEt_3 as co-catalyst was necessary to obtain reasonable yields. The authors assumed a reaction of $Fe(CO)_5$ with hydroxide ions to yield $HFe(CO)_4^-$ under liberation of carbon dioxide since basic conditions are present, and excluded formation of molecular hydrogen via water gas shift reaction. $HFe(CO)_4^-$ is believed to be the active catalyst, which transferred the hydride to the acceptor. The presented catalyst displayed activity in the reduction of several ketones and aldehydes (Scheme 2).[9]

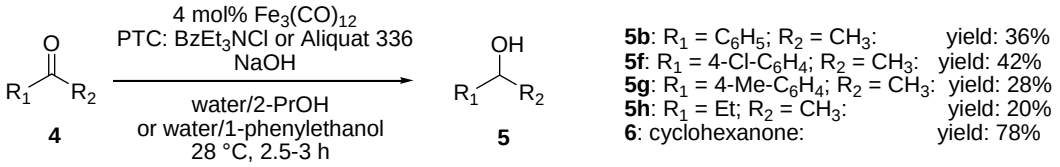


4 → **5**

5a: $R_1 = CH_3$; $R_2 = CH_3$: conv.: >99%
5b: $R_1 = C_6H_5$; $R_2 = CH_3$: conv.: 62%
5c: R_1 = *i*-Bu; $R_2 = CH_3$: conv.: 30%
5d: $R_1 = C_6H_5$; R_2 = H: conv.: 95%
5e: R_1 = *n*-Pr; R_2 = H: conv.: 98%
6: cyclohexanone: conv.: >99%

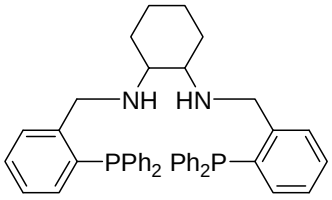
Scheme 2. Reduction of ketones and aldehydes by using the $Fe(CO)_5/NEt_3$ system according to Markó *et al*.

Later on, the group of Vancheesan referred on transfer hydrogenation of ketones utilizing 2-propanol or 1-phenylethanol as hydrogen source (Scheme 3).[10] A phase transfer catalyst was essential to support the hydrogenation catalyst $Fe_3(CO)_{12}$ or $Fe(CO)_5$ since a liquid-liquid biphasic system was used as solvent. Under mild reaction conditions several ketones were hydrogenated to the corresponding alcohols with turnover frequencies up to 13 h^{-1}. Mechanistic investigations indicated a similar process as reported by Markó *et al.*[8]

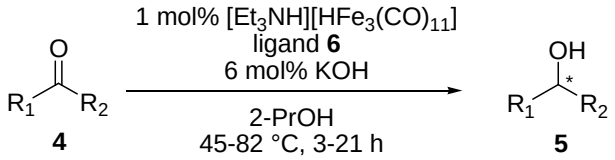


Schema 3. Phase transfer catalyzed transfer hydrogenation of ketones by Vancheesan *et al.*

More recently, Gao *et al.* reported in a special chinese journal an asymmetric transfer hydrogenation (Scheme 4) based on $[Et_3NH][HFe_3(CO)_{11}]$ and chelating chiral ligands.[11] In the presence of enantiopure diaminodiphosphine iron catalysts they claim good conversion and enantioselectivity up to 98% *ee* (substrate **5j**).



(*S*,*S*)-**6**
(*R*,*R*)-**6**



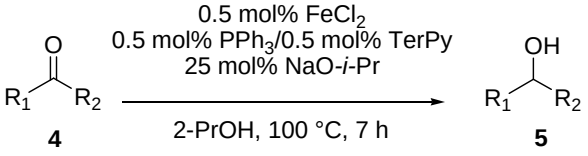
ligand: (*S*,*S*)-**6**
5b: $R_1 = C_6H_5$; $R_2 = CH_3$: **56% *ee*** (*R*), yield: 92% (82 °C, 7 h)
5i: $R_1 = C_6H_5$; $R_2 = C(CH_3)_3$: **93% *ee*** (*S*), yield: 19% (82 °C, 7 h)
5j: $R_1 = CH(C_6H_5)_2$; $R_2 = CH_3$: **98% *ee*** (*S*), yield: 18% (65 °C, 21 h)
5k: $R_1 = C_6H_5$; R_2 =Cy: **78% *ee*** (*S*), yield: 73% (82 °C, 17 h)

ligand: (*R*,*R*)-**6**
5m: $R_1 = C_6H_5$; $R_2 = C_2H_5$: **72% *ee*** (*S*), yield: 87% (45 °C, 4.5 h)
5n: $R_1 = C_6H_5$; $R_2 = CH(CH_3)_2$: **78% *ee*** (*S*), yield: 98% (45 °C, 3 h)

Schema 4. Enantioselective transfer hydrogenation catalyzed by iron complexes by Gao *et al*.

In 2006 we reported the application of an easy to adopt *in situ* concept composed of an iron source e.g. $FeCl_2$ or $Fe_3(CO)_{12}$, monodentate phosphines and tridentate nitrogen ligands in the transfer hydrogenation of aliphatic and aromatic ketones using 2-propanol as hydrogen source (Scheme 5).[12] The influence of different reaction parameters on the reduction of model substrate acetophenone **5b** were studied in detail. A crucial influence of base and base concentration was displayed since only sodium isopropoxide gave reasonable amount of product. In comparison to ruthenium-based transfer hydrogenations a higher temperature is necessary. Notably, the advantage of this *in situ* concept is underlined by easy tuneability of the iron catalyst, due to the broad availability of simple phosphines and amines. Plenty of phosphorous and amine ligands were subjected to the model reaction. However, best results were found with a catalyst composed of $Fe_3(CO)_{12}$, triphenylphosphine and 2,2´:6´,2´´-terpyridine or, surprisingly, 3 equiv. of pyridine with respect to iron. The later one resembles

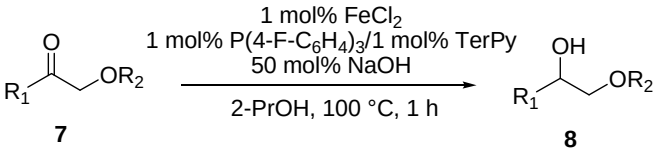
a straightforward catalyst regarding to industrial applications. After several optimization steps an active catalyst was developed which exhibit comparable activity to $Ru_3(CO)_{12}$ based catalysts and was successfull for the reduction of several ketones with good to excellent conversions.[13]



5b: $R_1 = C_6H_5$; $R_2 = CH_3$: yield: 95%
5f: R_1 = 4-Cl-C_6H_4; $R_2 = CH_3$: yield: 97%
5g: R_1 = 4-Me-C_6H_4; $R_2 = CH_3$: yield: 83%
5m: $R_1 = C_6H_5$; $R_2 = C_2H_5$: yield: 92%
5o: R_1 = 4-MeO-C_6H_4; $R_2 = CH_3$: yield: 75%
5p: R_1 = 2-MeO-C_6H_4; $R_2 = CH_3$: yield: >99%
5q: $R_1 = C_6H_5$; $R_2 = CH_2Cl$: yield: 8%
5r: R_1 = Cy; $R_2 = CH_3$: yield: 93%
5s: R_1 = *t*-Bu; $R_2 = CH_3$: yield: >99%

Scheme 5. *In situ* catalyst based on $FeCl_2$/terpy/PPh_3 in the transfer hydrogenation of ketones.

Very recently the effectiveness of $FeCl_2$/terpy/PAr_3 catalysts is proven in the hydrogenation of α-substituted ketones, which are interesting 1,2-diol precursors (Scheme 6).[14] Excellent yields, chemoselectivities and activities (TOF: up to 2000 h^{-1}) were achieved under optimized conditions.

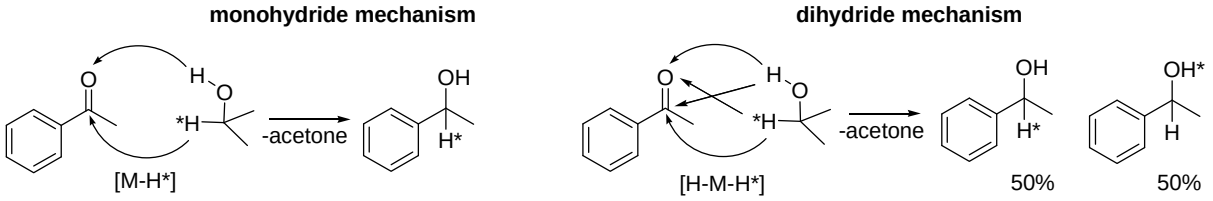


8a: $R_1 = C_6H_5$; $R_2 = CH_3$: yield: 92%
8b: $R_1 = C_6H_5$; $R_2 = C_6H_5$: yield: 94%
8c: $R_1 = C_6H_5$; R_2 = 4-Cl-C_6H_4: yield: >99%
8d: $R_1 = C_6H_5$; R_2 = 2,6-(*i*-Pr)$_2C_6H_4$: yield: 45%
8e: R_1 = 4-Me-C_6H_5; $R_2 = C_6H_5$: yield: 99%
8f: R_1 = 4-MeO-C_6H_5; $R_2 = C_6H_5$: yield: 85%
8g: R_1 = *t*-Bu; $R_2 = C_6H_5$: yield: 22%

Scheme 6. Reduction of α-substituted ketones in the presence of iron catalyst.

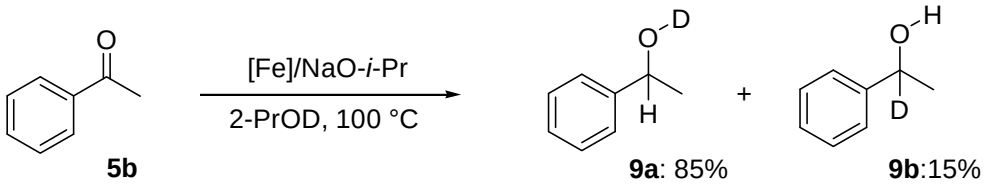
Apart from synthetic aspects we attained some useful informations concerning the mechanism, even if the "real" catalyst structure is so far unclear. Various experiments proved the presence of a homogeneous catalyst. Following the original works on Ru-, Rh- or Ir-catalyst, deuterated hydrogen donors were applied since for transfer hydrogenation two common mechanisms are established, nominated as direct hydrogen transfer via formation of a six-membered cyclic transition state constituted of metal, hydrogen-donor and -acceptor, and secondly the hydridic route, which is subdivided into two pathways, the monohydride and dihydride mechanism (Scheme 7). More specifically, the formation of monohydride-metal-complexes promote an exclusive hydride transfer from carbon (donor) to carbonyl carbon (acceptor), whereas a hydride transfer via dihydride-metal-complexes leads to no accurate

prediction of hydride resting state, for the reason that the former hydride was transferred to carbonyl carbon (acceptor) as well as to the carbonyl oxygen (acceptor).[15]



Scheme 7. Hydridic route established for transfer hydrogenation with Rh-, Ru- and Ir-catalysts.

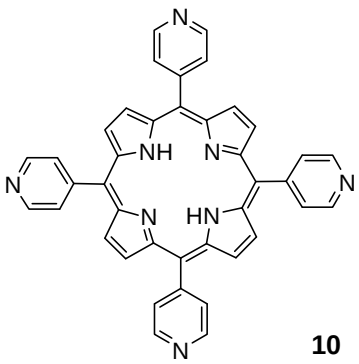
To specify the position and the nature of the transferred hydride, the reaction was performed with 2-propanol-d_1 as solvent/donor, sodium 2-propylate as base and $Fe_3(CO)_{12}/PPh_3$/TerPy as catalyst under optimized conditions. In the transfer hydrogenation of acetophenone a mixture of two deuterated 1-phenylethanols was obtained (Scheme 8, **9a** and **9b**). The ratio between **9a** and **9b** (85:15) indicated a specific migration of the hydride, albeit some scrambling was detected. However, the incorporation is in agreement with the monohydride mechanism, implying a formation of metal monohydride species in the catalytic cycle.



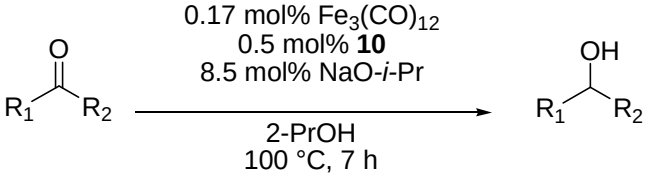
Scheme 8. Deuterium incorporation catalyzed by $Fe_3(CO)_{12}$/terpy/PPh_3 system under transfer hydrogenation conditions.

Parallel to the work on *in situ* three component catalysts we developed a nature inspired *in situ* catalyst based on iron porphyrin complexes since a high stability of the complexes are known and inertness against oxygen and moisture is feasible.[16] The porphyrin catalysts achieved even higher activities than three component system in the transfer hydrogenation of ketones (Scheme 9). After optimization of reaction parameters turnover frequencies up to 642 h^{-1} at low catalyst loadings (0.01 mol%) were attained. A ligand screening emphasized porphyrin **10** as module of a highly active catalyst and makes it suitable for further investigations on substrate variation. Various ketones were reduced in good to excellent yields. Notably, also naturally occurring hemin has been used in this study. Even if lower

activity was gained it is a worthwhile system, due to the abundance and easy handling. Advantageously, no pre-catalyst formation is necessary.



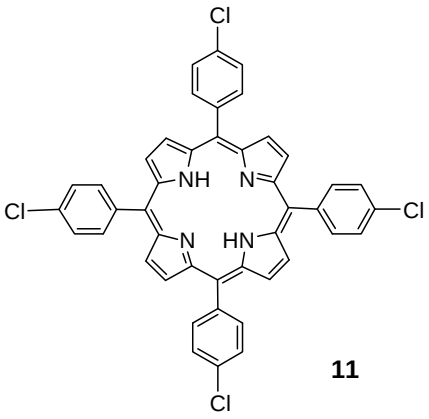
10



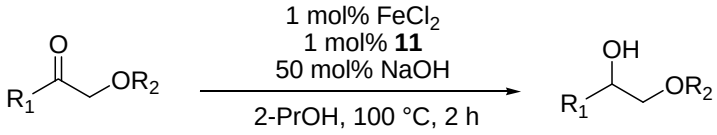
5f: R_1 = 4-Cl-C_6H_4; R_2 = CH_3: yield: 95%
5b: R_1 = C_6H_5; R_2 = CH_3: yield: 94%
5g: R_1 = 4-Me-C_6H_4; R_2 = CH_3: yield: 68%
5o: R_1 = 4-MeO-C_6H_4; R_2 = CH_3: yield: 72%
5p: R_1 = 2-MeO-C_6H_4; R_2 = CH_3: yield: >99%
5m: R_1 = C_6H_5; R_2 = C_2H_5: yield: 87%
5r: R_1 = Cy; R_2 = CH_3: yield: 89%
5s: R_1 = *t*-Bu; R_2 = CH_3: yield: 90%

Scheme 9. Biomimetic transfer hydrogenation of ketones with iron porphyrin catalysts.

Applying Fe porphyrin catalysts and 2-propanol as hydrogen donor various α-hydroxyl-protected ketones are reduced to the corresponding mono protected 1,2-diols in good to excellent yield after optimization (Scheme 10).[17] Remarkable, addition of small amounts of water (5–10 mol%) boosted the catalysts activity up to 2500 h^{-1} at low catalyst loadings (0.01 mol%).



11



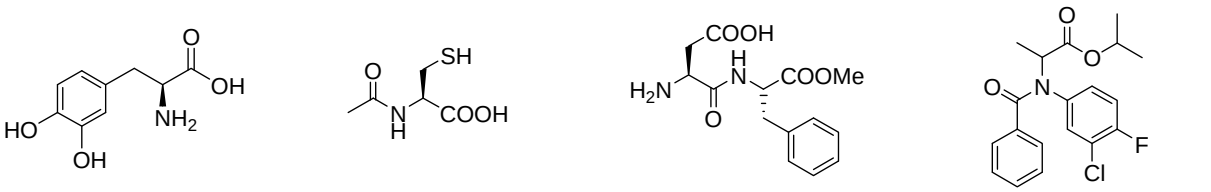
8a: R_1 = C_6H_5; R_2 = CH_3: yield: >99%
8b: R_1 = C_6H_5; R_2 = C_6H_5: yield: 92%
8c: R_1 = C_6H_5; R_2 = 4-Cl-C_6H_4: yield: >99%
8d: R_1 = C_6H_5; R_2 = 2,6-(*i*-Pr)$_2$$C_6H_4$: yield: 74%
8e: R_1 = 4-Me-C_6H_5; R_2 = C_6H_5: yield: >99%
8f: R_1 = 4-MeO-C_6H_5; R_2 = C_6H_5: yield: 83%
8g: R_1 = *t*-Bu; R_2 = C_6H_5: yield: 48%

Scheme 10. Reduction of α-substituted ketones in the presence of iron porphyrin catalysts.

3.3. Hydrogenation of Carbon-Carbon Double Bounds

Since the 60th of the last century tremendous efforts were undertaken in the field of homogeneous hydrogenation of C-C double bonds emphasized by innumerable reports and later on rewarded by integrations in several industrial processes (Scheme 11). However, an

even broader use in industry is expected by the availability of similar active and selective hydrogenation catalysts containing inexpensive metals (e.g. Fe and Cu).



L-DOPA (12)
anti Parkinson´s disease

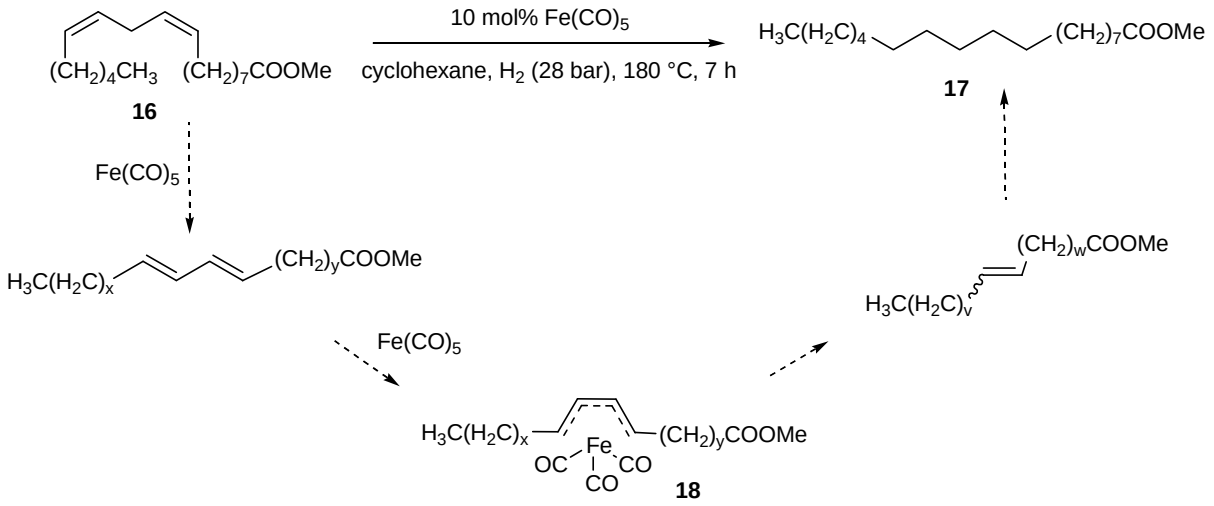
N-Acetylcystein (13)
mucolytic therapy

Aspartam (14)
artificial sweetener

Flamprop-isopropyl (15)
herbizide

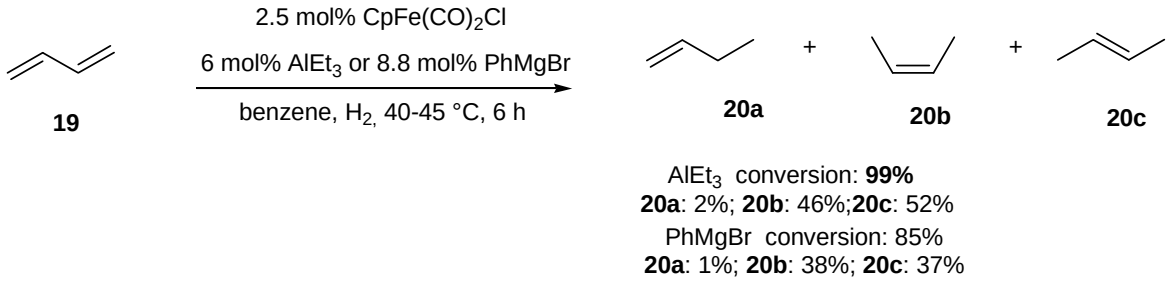
Scheme 11. Selected pharmaceuticals, which are accessible by asymmetric C-C double bond hydrogenation.[5,18]

Indeed iron catalysts are known to transfer hydrogen to C-C double bonds. Early examples were carried out with metal salts activated by aluminium compounds in the hydrogenation of non-funtionalized olefins at comparable mild reaction conditions (0–35 °C and low hydrogen pressure).[19] Some research groups focused on the application of iron carbonyls due to the easier removal of the carbonyl ligands, for generating an active site, compared to halogens and avoidance of activating reagents.[20] Unsaturated carboxylic acid derivatives, for instance methyl linoleate and methyl linolenate, which contain two or three non-conjugated double bonds, respectively, were described in the mid of the 1960s (Scheme 12).[21,22] As catalyst precursor $Fe(CO)_5$ was utilized at high temperature. The authors proposed as first step an isomerization of the double bonds catalyzed by $Fe(CO)_5$ to obtain various dienes or trienes. Hydrogenation process was observed in case of conjugated dienes to yield monoenes via an iron-carbonyl-diene complex **18**, while dienes were formed for the hydrogenation of methyl linolenate **16**. The activity of the system was improved, when the iron-carbonyl-diene-complex **18** is used as precursor instead of $Fe(CO)_5$. Analysis of the reaction mixture displayed mononenes as major products with unselective double bond distribution accompanied by small amounts of fully saturated compounds. Later on, Cais and co-worker studied the reaction of methyl hexa-2,4-dienoate as a model for fatty acids in more detail and reported several mechanistic considerations.[23]



Scheme 12. Fe-catalyzed hydrogenation of methyl linoleate.

Tajima and Kunioka described the hydrogenation of conjugated diolefins, in particular 1,3-butadiene in the presence of activated [$CpFe(CO)_2Cl$].[24] $AlEt_3$ and PhMgBr were tested as activation reagents, thereby the $AlEt_3$-activated complex showed the best performance. The authors proposed the formation of iron-alkyl species which undergoes hydrogenolysis to create an active metal-hydride. The composition of the final mixture is dominated by *cis*-but-2-ene and *trans*-but-2-ene (ratio ~1:1). Furthermore traces of 1-butene were observed, whereas the catalyst was completely inactive for the hydrogenation of the mono-olefin to yield *n*-butane.



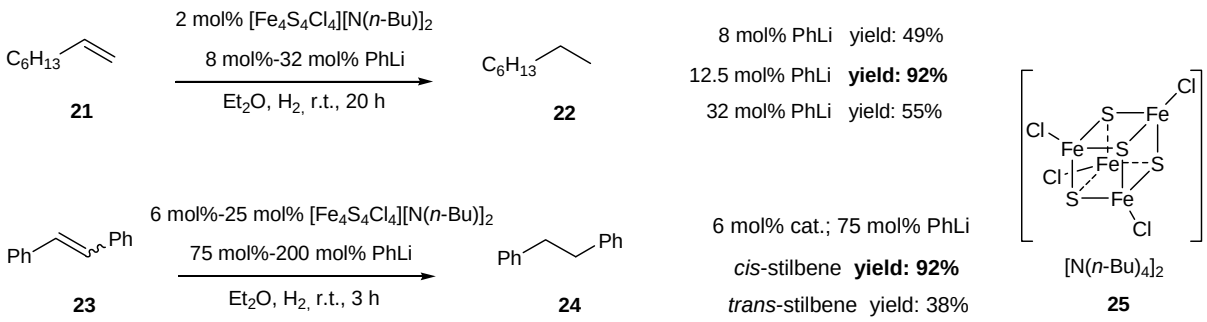
Scheme 13. Hydrogenation of butadiene with $CpFe(CO)_2Cl$ (Cp = cyclopentadienyl).

Nishiguchi and Fukuzumi reported on the transfer hydrogenation of 1,5-cyclooctadiene (cod) in the presence of catalytic amounts of $FeCl_2(PPh_3)_2$ (10 mol%) at high temperature (up to 240 °C).[25] As hydrogen source polyhydroxybenzenes, for instance pyrogallol, pyrocatechol or hydrochinone, have been proven to be superior for this reaction, while primary and secondary alcohols led to lower conversion. The hydrogenation of 1,5-cyclooctadiene led to cyclooctane

as main-product, but the unsaturated cyclooctene and isomerization products were also observed.

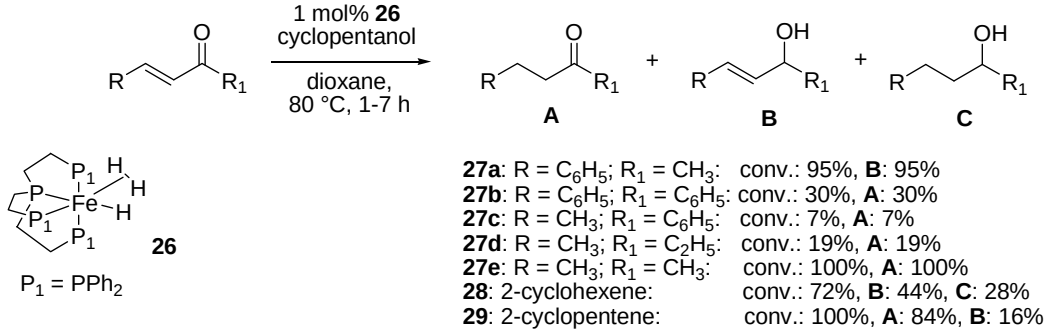
Later on Wrighton and co-workers recognized a reactivity increase with respect to hydrogenation rate when $Fe(CO)_5$ was treated with light.[26,27] The authors assumed an expulsion of one carbonyl ligand to form an unsaturated species induced by near-ultraviolet irradiation. After complexation of the olefin again activation by light removed another carbonyl ligand to allow hydrogen coordination/activation. A number of unsubstituted olefins (e.g. ethylene, propylene, *cis*-3-hexene, cyclopentene, cyclooctene), were hydrogenated to give alkanes in moderate yield (up to 50%), while the catalyst is inactive for sterical demanding olefins (e.g. 1,2-dimethylcyclohexene) or aldehydes and nitriles. Furthermore, acetylenes were subjected to this photo-catalyzed reduction. However, only low yield (<5%) of the corresponding olefin was obtained.

Inspired by the properties of metalloproteins and metalloenzymes in biological processes the group of Inoue established a hydrogenation protocol based on active sites of enzyme hydrogenases, which contain an iron-sulfur cluster (Scheme 14).[28,29] For their biomimetic approach the Fe_4S_4-cluster **24** was used as an active-site model and tested in the hydrogenation of octene **21** and stilbene **23** with molecular hydrogen. A necessity for activation of the cluster with phenyl-lithium was reported. The amount of activation-reagent played a crucial role for the catalytic activity and selectivity; thereby an optimum in the hydrogenation of octene was attained when 12.5 mol% phenyl-lithium and 75 mol% for stilbene hydrogenation, respectively, were applied. Noteworthy, in the case of defined internal octenes an isomerization of the double bond takes place to obtain different internal octenes, due to β-hydride elimination. 1-Octene is extracted to some extend faster out of this melange by hydrogenation.[28] The final composition of *cis*-stilbene hydrogenation indicated also an isomerization, because significant amounts of *trans*-stilbene are observed, while the hydrogenation of *trans*-stilbene is unaffected by isomerization.[29]



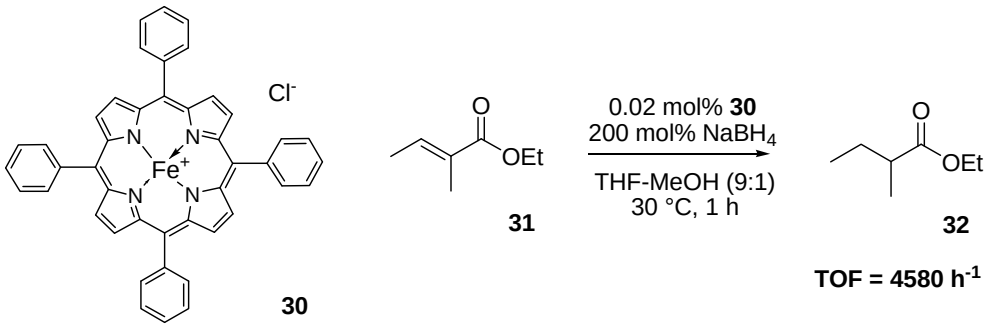
Scheme 14. Bio-inspired iron catalyst in the hydrogenation of C-C double bonds.

At the beginning of the 90th of the last century a switch to iron catalysts stabilized by either phosphines or nitrogen ligands took place. Here, Bianchini and co-workers carried out a detailed comparative study on the transfer hydrogenation of α,β-unsaturated ketones by nonclassical trihydride iron, ruthenium and osmium complexes containing tetradentate phosphines (Scheme 15).[30,31] In the presence of cyclopentanol as hydrogen donor several α,β-unsaturated ketones were hydrogenated to the corresponding saturated ketones with good to excellent selectivity under mild reaction conditions (Scheme 15). In some cases, e.g. benzylideneacetone or 2,3-cyclohexenone, the unsaturated or saturated alcohols were formed by the catalyst **26**, thereby also good selectivity was noticed. Noteworthy, no co-catalyst, e.g. base, was necessary to activate the catalyst or the hydrogen donor, which is needed for other catalyst systems. However, for carbonyl hydrogenation, e.g. acetophenone and cyclohexanone, the iron catalyst displayed only low activity. No activity was found for aldehydes and C=C systems without additional carbonyl functionality.



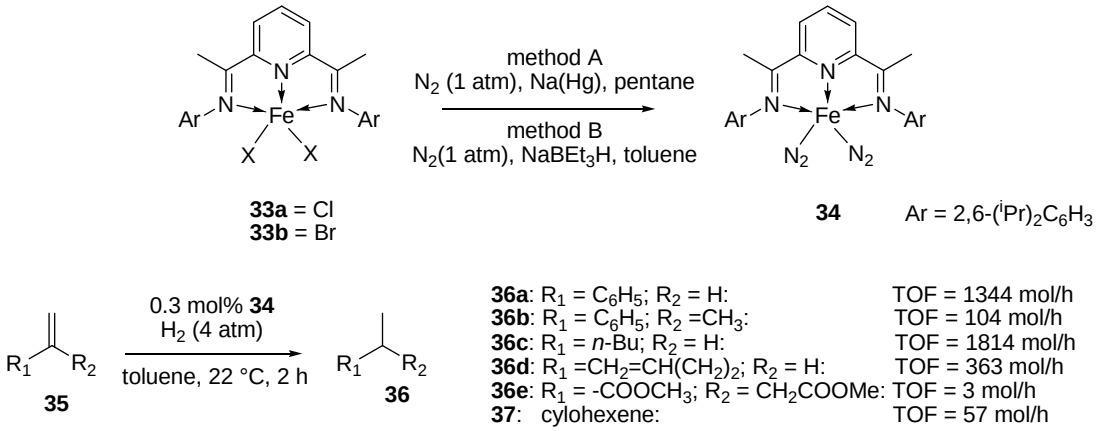
Scheme 15. Application of nonclassical iron trihydride complex in transfer hydrogenation according to Bianchini and co-workers.

Reduction of styrene was reported by Kano *et al.* using $NaBH_4$ as hydrogen source in the presence of iron porphyrin complex **30** (Scheme 16).[32] Good turnover frequencies up to 81 h^{-1} and good chemoselectvities are obtained in protic solvents with catalyst loading of 1 mol% at room temperature. The reaction has been proven to be a radical process since to some extent 2,3-diphenylbutane was detected. A similar approach was carried out by Sakaki and co-workers on the hydrogenation of α,β-unsaturated esters, who reported improvement of the catalyst activity (turnover frequency, tof = 4580 h^{-1}).[33] A detailed study of the reaction mechanism displayed a crucial influence of the protic solvent because the hydride is assigned by $NaBH_4$ and the proton by methanol.



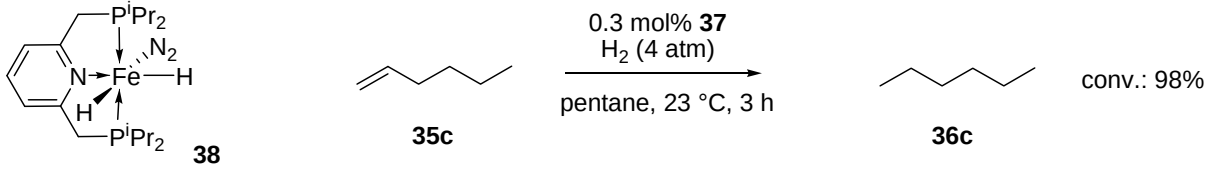
Scheme 16. Reduction of α,β-unsaturated ester catalyzed by iron porphyrin **30**.

More recently, the group of Chirik have shown elegantly the application of low valent iron complexes in the hydrogenation of various C-C double and C-C triple bounds.[34] Based on the mentioned work of Wrighton *et al.* an approach to stabilized 14 electron $L_3Fe(0)$ fragments was presented. The catalyst precursors were synthesized by reduction of dihalogen complexes **33** containing a tridentate pyridinediimine ligand with sodium amalgam or with sodium triethylborohydride under an atmosphere of nitrogen (Scheme 17). The obtained bis-dinitrogen complexes **34** are relative labile compounds and a loss of one equivalent of dinitrogen in solution at room temperature or an easy exchange against hydrogen or alkynes occurred. The catalyst activity was studied in the field of C-C double and C-C triple bond hydrogenation. Applying 0.3 mol% of the iron catalyst simple olefins such as 1-hexene or cyclohexene were hydrogenated with high turnover frequencies up to 1814 mol/h under comparatively mild reaction conditions (4 atm of hydrogen pressure and room temperature). The reaction was also carried out under preferred solvent-free conditions in neat substrates and leading to comparable activity. The scope and limitation of the catalyst system was demonstrated in the hydrogenation of various olefin units enclosing geminal, internal and trisubstituted olefins and furthermore diolefins. In the course of this it was ascertained that best activity was attained for terminal olefins > internal olefins = geminal olefins > trisubstituted olefins. In addition, one example of a functionalized olefin was mentioned. However, only a diminished activity was observed for dimethyl itaconate, albeit using higher catalyst loadings. In the case of cyclohexene some detailed investigations emphasized a deactivation of the catalyst by arene complexation either from the solvent or the aryl groups in the ligand.[35] Noteworthy, when comparing activity of catalyst **34** (1814 mol/h) with common catalysts e.g. Pd/C (TOF = 366 mol/h), $RhCl(PPh_3)_3$ (10 mol/h) or $[Ir(cod)(PCy_3)(py)]PF_6$ (75 mol/h) in the hydrogenation of 1-hexene under optimized conditions a significant higher value was reached with the iron catalyst.



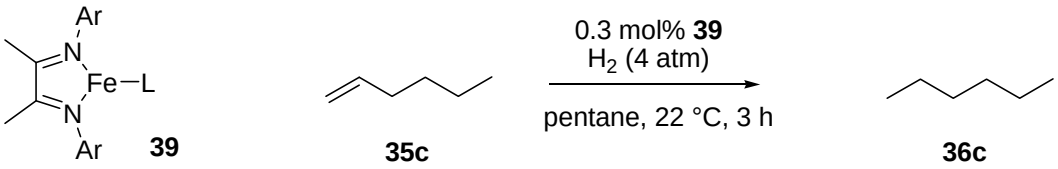
Scheme 17. Preparation of catalyst precursors containing tridentate nitrogen ligands and abilities in catalytic reaction according to Chirik and co-workers.

Further on the group of Chirik studied the influence of replacing the imino functionalities in ligand system **34** by phosphino groups (Scheme 18).[36] A different coordination mode was found since only one nitrogen ligand was replaced by hydrogen. The unstable complex **38** was also tested in the hydrogenation of 1-hexene, but no improvement of activity was observed.



Scheme 18. Application of iron aminodiphosphine complexes in hydrogenation reaction.

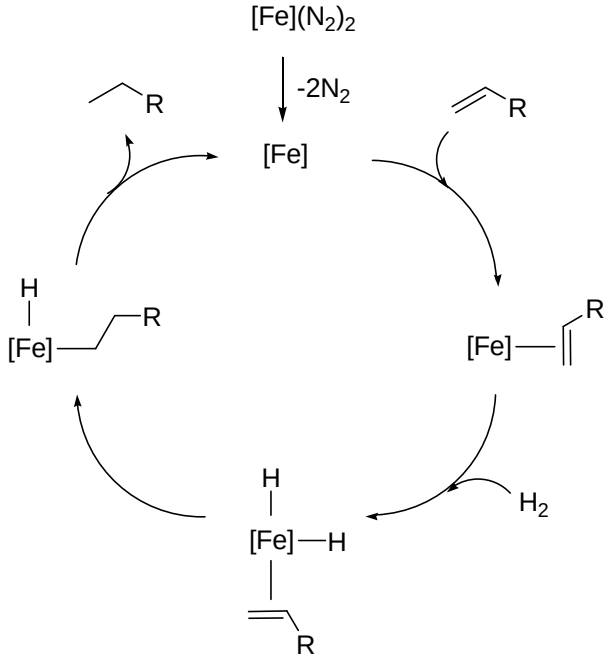
Using the same synthetic method as described for catalyst **34** also diime complexes **39** were attainable (Scheme 19).[37] Due to the instability of dinitrogen complexes stabilization was carried out by introducing more suitable ligands e.g. alkynes, olefins or diolefins. However, in the hydrogenation of 1-hexene under comparable conditions only low activities were observed. Apart from synthesis and application of low valent iron complexes Chirik *et al.* carried out some mechanistic investigations. The suggestion of the catalytic cycle is presented in Scheme 20. Initially, an unsaturated iron complex is formed by expulsion of both dinitrogen molecules.



39a: Ar = 2,6-(^{i}Pr)$_2$C$_6$H$_3$; L = (Me$_3$Si)$_2$C$_2$ TOF = 4 mol/h
39b: Ar = 2,6-(^{i}Pr)$_2$C$_6$H$_3$; L = cod TOF = 90 mol/h
39c: Ar = 2,6-(^{i}Pr)$_2$C$_6$H$_3$; L = coe TOF = 90 mol/h

Scheme 19. Hydrogenation with low valent iron complexes. (cod = 1,5-cyclooctadiene, coe = cyclooctene).

Next coordination of olefin takes place, which is preferred since also activation of hydrogen is feasible. After olefin coordination oxidative addition of hydrogen yields a formally 18 electron complex. Insertion of the olefin obtained an alkyl complex, which recreate the starting complex via reductive elimination. Notably, the olefin complex also supports an isomerization of the double bond; hence an extension of possible intermediates is conceivable.

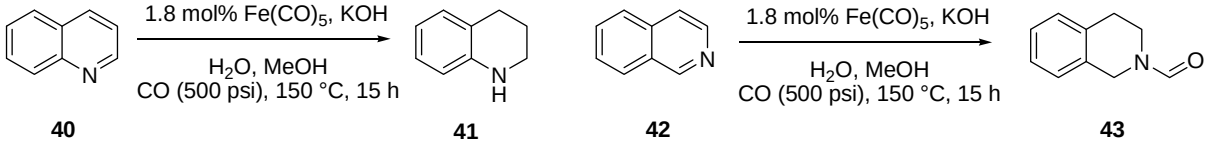


Scheme 20. Mechanism for the hydrogenation process proposed by Chirik *et al.*

3.4. Hydrogenation of imines and similar compounds

Until today only a scarce number of hydrogenations of unsaturated CN functionalities have been described utilizing iron catalysts. On the one hand hydrogenation of *N*-

benzylideneaniline to yield *N*-benzylaniline was carried out by Markó *et al.* in presence of catalytic amounts of $[NEt_3H][HFe(CO)_4]$, which was also applied for ketones/aldehydes reduction (*vide supra*).[38] Even if good to excellent activities were obtained in various solvents, for proceeding the reaction harsh conditions are required (150 °C, 100 bar). On the other hand Kaesz and co-workers reported the reduction of nitrogen heterocycles under water-gas shift conditions.[39] As catalyst $Fe(CO)_5$ was used under high temperature and pressure. Moderate turnover numbers in the range of 18–37 were obtained. In the case of isoquinoline **42** as main product the formylated compound **43** is observed.



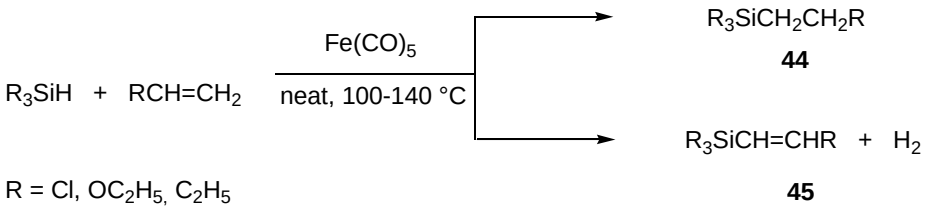
40 **41** **42** **43**

Scheme 21. Hydrogenation of aromatic nitrogen heterocycles.

3.5. Catalytic hydrosilylations

In addition to catalytic reductions with molecular hydrogen or hydrogen donors also silanes represent useful reducing agents.[40]

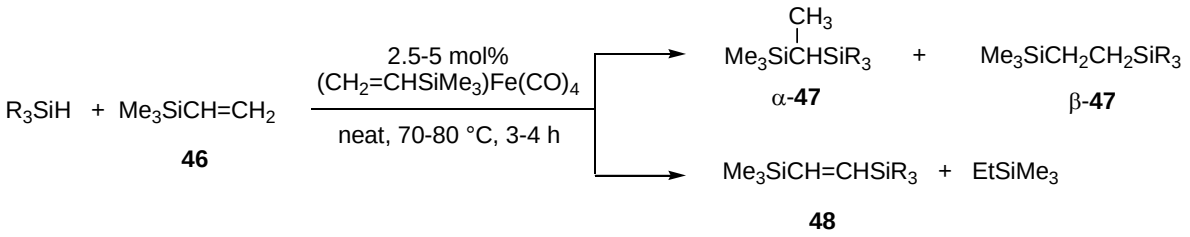
Most examples in literature for hydrosilylation with iron complexes as catalyst are known for $Fe(CO)_5$ or related iron carbonyl compounds.[41] The first use of iron pentacarbonyl was reported for the reaction of silicon hydrides with olefins at 100–140 °C to form saturated and unsaturated silanes according to Scheme 22.[42,43]



Scheme 22. Fe-catalyzed hydrosilylation of C-C double bonds.

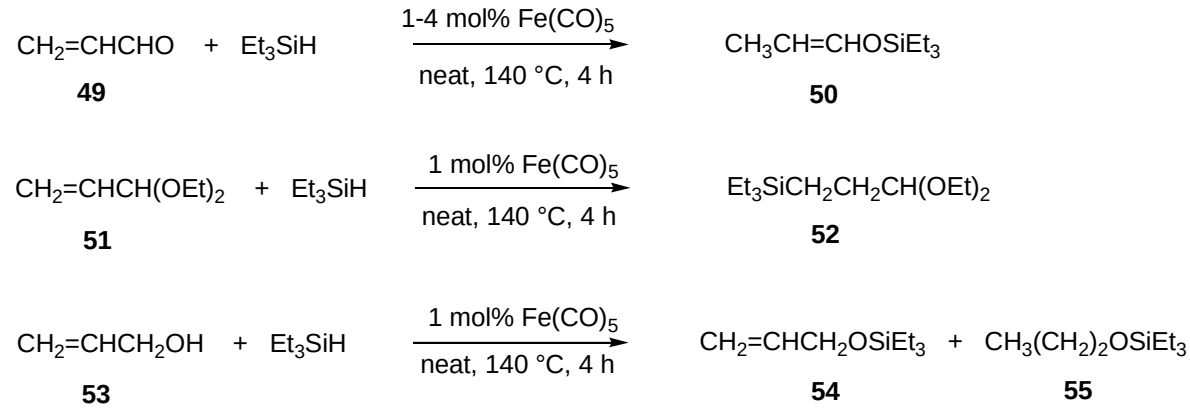
An excess of olefin favours the formation of the unsaturated product **44** while the silylated compound **45** dominated at higher ratio of silane to alkene. The described reaction was also carried out in the presence of colloidal iron and lead to results similar to those obtained with $Fe(CO)_5$. Hydrosilylation of vinyltrimethylsilane **46** with chlorosilanes R_3SiH using the modified iron carbonyl complex $(CH_2{=}CHSiMe_3)Fe(CO)_4$[44,45] gave a mixture of α- and β-

isomers of the silylated product **47** and the unsaturated product **48** attained by dehydrogenative silylation (Scheme 23).



Scheme 23. Hydrosilylation of vinyltrimethylsilane **46**.

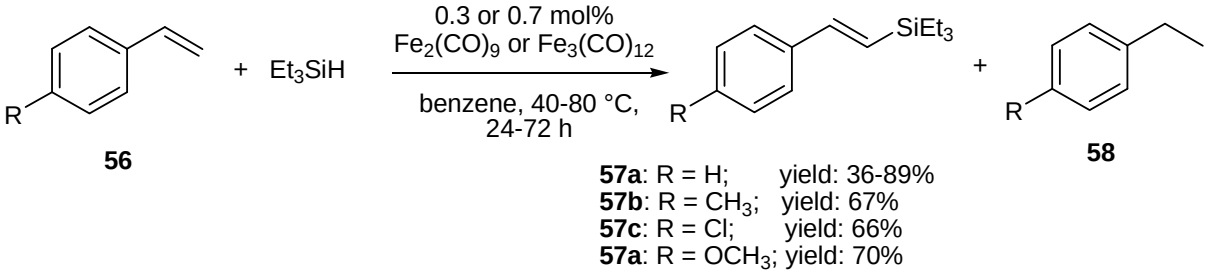
The ratio of formed compounds α-**47**, β-**47** and **48** depends on the nature of the used hydrosilane R_3SiH. There exists an indirect relationship between the yield of the unsaturated silane **48** and the catalytic activity of R_3SiH (Cl_3SiH > Cl_2MeSiH > $ClMe_2SiH$ > Me_3SiH). With exception of Me_3SiH the α-isomer is mainly formed in all studied reactions. Iron pentacarbonyl is known to hydrosilylate functionalized olefins (Scheme 24).[46] For instance hydrosilylation of acrolein **49** with Et_3SiH gave up to 95% of a mixture of *cis*- and *trans*-$MeCH=CHOSiEt_3$ **50** while acrolein diethyl acetal **51** forms the Markovnikov product $Et_3SiCH_2CH_2CH(OEt)_2$ **52** and Et_3SiOEt via C-O bond cleavage. Allylic alcohol reacts in the presence of $Fe(CO)_5$ to give $CH_2=CHCH_2OSiEt_3$ **54** and propyl$OSiEt_3$ **55**.



Scheme 24. Hydrosilylation of functionalized olefins.

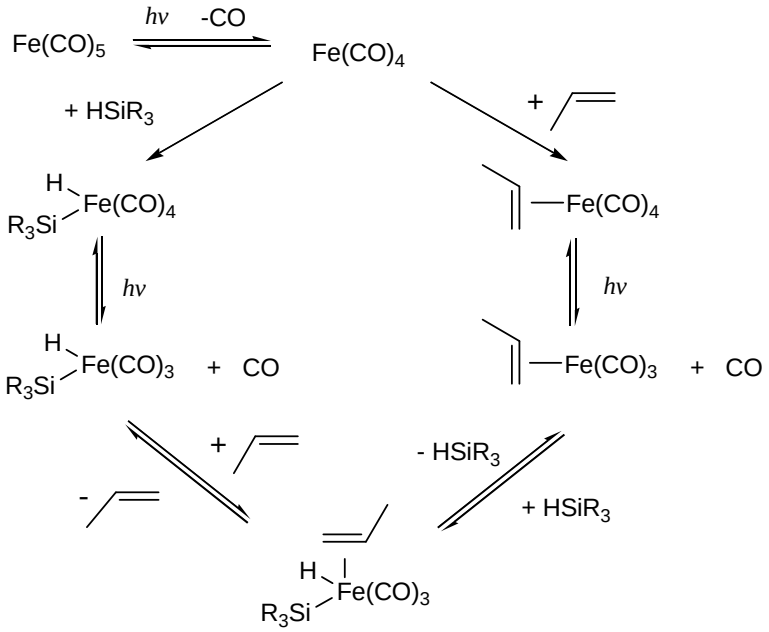
In 1993 the group of Murai has examined the effectiveness of the iron-triad carbonyl complexes, $Fe(CO)_5$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$, as catalysts for the reaction of styrene with triethylsilane.[47] While $Fe(CO)_5$ showed no catalytic activity $Fe_2(CO)_9$, and $Fe_3(CO)_{12}$ form selectively β-silylstyrene and ethylbenzene. Interestingly, $Fe_3(CO)_{12}$ is the catalyst that exhibited the highest selectivity. This trinuclear iron carbonyl catalyst was also successful

applied for the reaction of different *p*-substituted styrenes with Et_3SiH giving only the (*E*)-β-triethylstyrenes in 66–70% yield.



Scheme 25. Hydrosilylation of styrene derivatives.

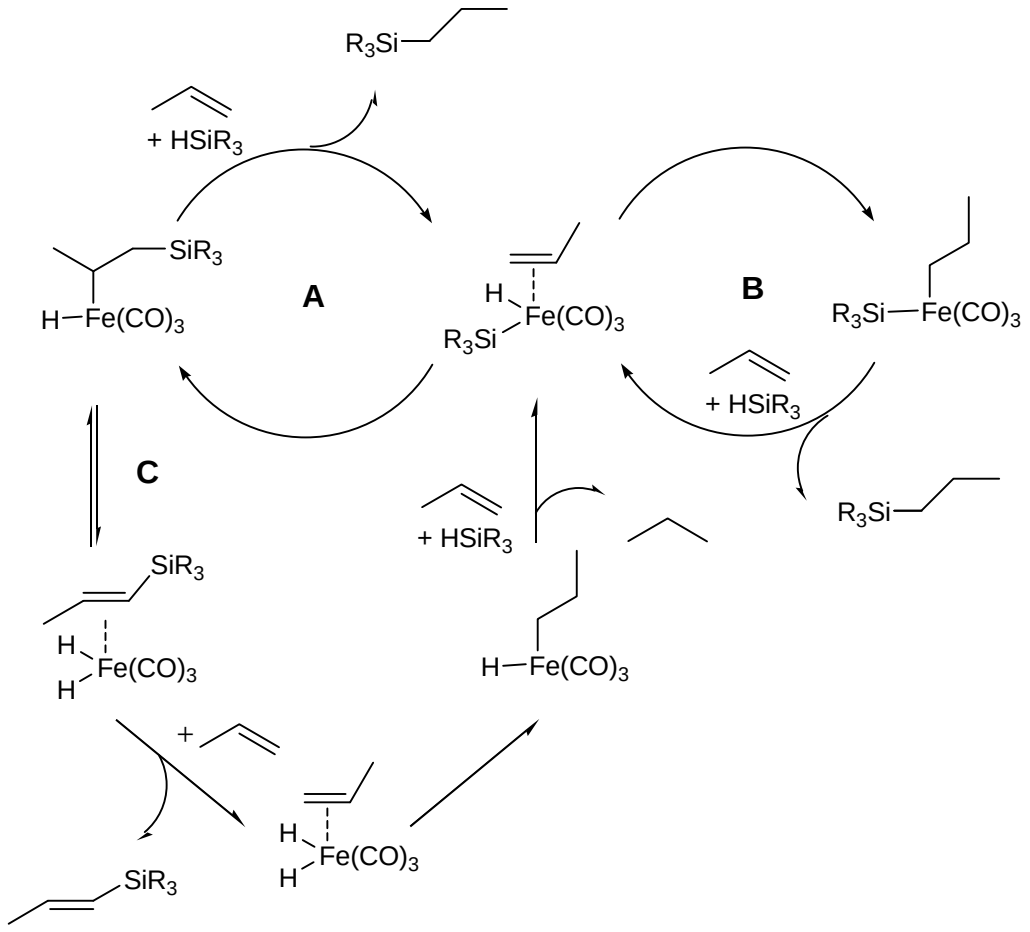
Hydrosilylation reactions catalyzed by iron carbonyl compounds often occur under drastic thermal conditions. Wrighton *et al.* have reported a photocatalyzed reaction of trialkylsilanes with alkenes in the presence of $Fe(CO)_5$ at low temperature (0–50 °C).[48] It is well known that irradiation of mononuclear metal carbonyls leads to efficient dissociative loss of CO to yield coordinative unsaturated, 16-electron, intermediates (Scheme 26).[26]



Scheme 26. Formation of the catalytic active species by irradiation.

Irradiation of $Fe(CO)_5$ in the presence of trialkylsilane R_3SiH and alkene initially yields a mixture of $Fe(CO)_4$(alkene) and $(H)(SiR_3)Fe(CO)_4$ which were determined by infrared spectroscopy. $(H)(SiR_3)Fe(CO)_3$(alkene) is postulated to be the catalytic active species

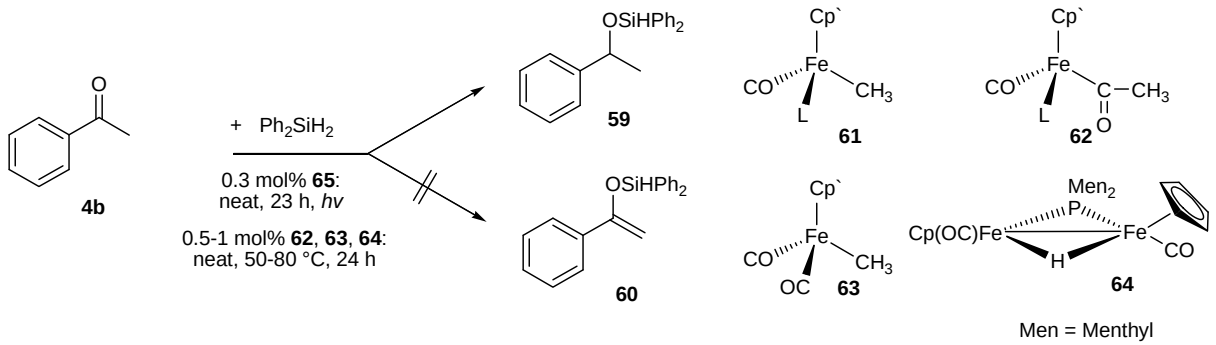
photogenerated from these intermediates according to Scheme 26. Continuous irradiation is needed to maintain a steady-state concentration of the repeating unit "$Fe(CO)_3$". Such an iron tricarbonyl complex was also detected by infrared spectroscopy in the photoinduced addition of R_3SiH to 1,3-butadiene with $Fe(CO)_5$.[49] Polymer-anchored ironcarbonyl species were described to catalyze the hydrosilylation of 1-pentene with $HSiEt_3$ to give a mixture of pentyl- and pentenylsilanes.[50] The different pathways of the mechanism of transition metal-catalyzed hydrosilylation are summarized in Scheme 27. A commonly proposed mechanism involves the insertion of the olefin into the Fe-H bond of complex $(H)(SiR_3)Fe(CO)_3$(alkene) followed by reductive elimination of the alkyl and the silyl group to form an alkylsilane (pathway **B**). In an alternative mechanism insertion of the olefin into the Fe-Si bond of complex $(H)(SiR_3)Fe(CO)_3$(alkene) is discussed (pathway **A**). This route which is also suggested for the use of $Fe_3(CO)_{12}$ explains the formation of vinylsilanes as by-product in hydrosilylations.[51]



Scheme 27. Proposed catalytic cycle for the hydrosilylation of olefins in the presence of $Fe(CO)_5$.

The photoinduced alkene insertion into the Fe-Si bond of (η^5-C_5Me_5)Fe(CO)R was shown to be reversible (reaction **C**).[52] A reactivity study of complex (H)Fe(CO)$_4$SiPh$_3$ with nucleophiles allowed a better understanding of the underlying reaction processes.[53] Under photochemical conditions the activation or the substitution of the carbonyl ligands supports the classical mechanism involving insertion of the coordinated olefin in the Fe-Si (**A**) or the Fe-H (**B**) bonds. Under thermal conditions, however, a direct addition of the Fe-H group by a radical or ionic process can occur as observed in the reaction of (H)Fe(CO)$_4$SiPh$_3$ with isoprene. These mechanistic investigations for photo-generated hydrosilylation have been transmitted to the reaction of the iron carbonyl complex (CH_2=CHSiMe$_3$)Fe(CO)$_4$ with vinylsilane and R_3SiH.[45] Tetrahedral heterometallic clusters containing iron have proven to be suitable catalysts in the photoinitiated hydrosilylation of acetophenone with triethylsilane.[54] Although a chiral FeCoMoS tetrahedron was used only racemic product and racemic cluster have been isolated. This fact can be explained by photo-racemization of the chiral catalyst which proceeds faster than hydrosilylation reaction. Instead of irradiation metal vapour generation at -196 °C was described as activation method for transition metal catalysts.[55] Iron vapour co-condensed with isoprene catalyzed the hydrosilylation with triethoxysilane. Not surprisingly exclusive 1,4-addition is observed.

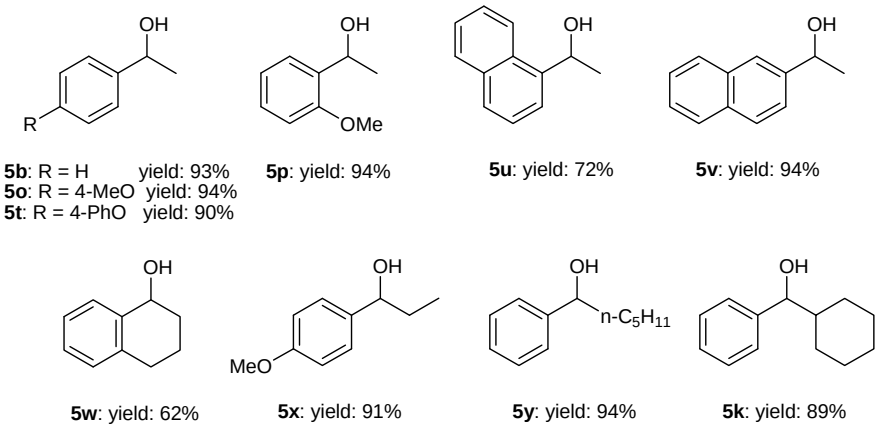
The group of Brunner investigated the influence of thermal or photoinduced activation of Fe(Cp)(CO) complexes in the hydrosilylation of acetophenone **4b** with diphenylsilane forming quantitatively the silylated 1-phenylethanol **59** (Scheme 28).[56,57]



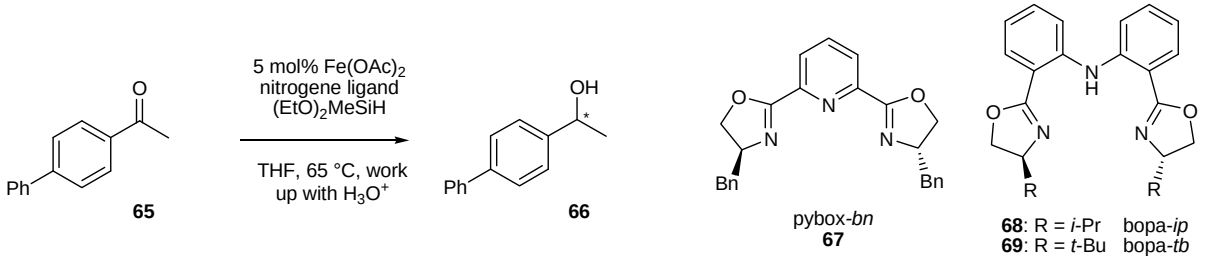
Scheme 28. Asymmetric hydrosilylation with chiral iron complexes.

The absence of silyl enol ether **60** can be explained by a hydrosilylation mechanism involving a Fe-Si-H three-centre bond rather than a Fe-H species. Although optically active ligands of type **61**, **62** and **63** containing chiral iron atoms were used, only poor enantioselectivities below 10% *ee* have been achieved (L = DIOP [O-isopropyliden-2,3-dihydroxy-1,4-

bis(diphenylphosphino)butane]).[58] The rate determining step in this reaction is the thermal loss of the phosphine ligand L in **61** and **62** and methyl migration in **63**, followed by addition of phenylsilane and subsequent reaction with acetophenone. Under photo-irradiation conditions hydrosilylation occured very fast with complex **64** as catalyst producing the silylated (*S*)-1-phenylethanol **59** in 33% *ee*. This was the first appreciable example for an enantioselective iron-catalyzed hydrosilylation of ketones. Very recently, Nishiyama *et al.* pursued a different elegant strategy to find an efficient catalytic system based on iron.[59] They combined $Fe(OAc)_2$ and multi-nitrogen-based ligand such as *N,N,N´,N´*-tetramethylethylendiamine (tmeda), bis-*tert*-butyl-bipyridine (bipy-*tb*), or bis(oxazolinyl)pyridine (pybox) to catalyze the hydrosilylation of ketones to give the corresponding alcohol after acidic cleavage of the silyl ether (Scheme 29). The reaction was carried out under mild condition (THF at 65 °C, 24 hours) producing yields up to 95%. Using tmeda as nitrogen ligand hydrosilylation works also with other aromatic ketones.



Scheme 29. Substrate cope of the Fe-catalyzed hydrosilylation of ketones in the presence of tmeda.



Scheme 30. Asymmetric hydrosilylation of ketone **65** with iron catalysts according to Nishiyama and co-workers.

The application of chiral tridentate nitrogen ligands leads to the enantioselective reduction of methyl 4-phenylphenylketone **65**. While pybox-*bn* **67** gives 37% *ee* of **66**, bopa-*ip* **68** and *tb* **69** increased the enantioselectivity up to 57% *ee* and 79% *ee*, respectively. Recent results from our group revealed that it is possible to perform Fe-catalyzed hydrosilylations of acetophenone also in the presence of chiral phosphine ligands. Here enantioselectivities up to 80% *ee* have been achieved.[60]

Iron-catalyzed hydrosilylations of olefins in the presence of nitrogen ligands were first realized by Chirik *et al.*[34,35] They investigated the reaction of 1-hexene with $PhSiH_3$ or Ph_3SiH in the presence of iron catalyst **34** containing a tridentate pyridinediimine ligand (Scheme 17) which produce hydrosilylation over a course of minutes at ambient temperature. In both cases, the anti-Markovnikov product was formed exclusively. On the basis of these results a series of olefins (see Scheme 17) was examined. Terminal alkenes such as 1-hexene and styrene react most rapidly followed by *gem*-disubstituted olefins and internal olefins. The silylation of alkynes was also examined and proceeds efficiently under mild conditions to the corresponding silylalkene.

3.6. Concluding Remarks

Since the beginning of transition metal catalyzed hydrogenations and hydrosilylations more than 40 years ago a tremendous number of studies were directed to develop powerful methods for organic synthesis. In the past Rh, Ir and Ru clearly constitute the metals of choice for such transformations. Several hundreds of catalysts are nowadays commercially available for chemists around the world. However, the accelerated costs and the stronger requirements for pharmaceuticals cast a shadow on these commonly used transition metals.

For the mid-term future we expect an increased use of more available and “biomimetic” metals. Clearly, iron is an ideal example for this. Unfortunately simple method transfer from Rh, Ir and Ru to Fe is not readily possible. So far iron based hydrogenations and hydrosilylations are far off to be general methods for organic chemistry. Typically comparably high catalyst loadings and harsh reaction conditions are required. In order to allow for more synthetic applications especially more functional group tolerance and also efficient control of stereoselectivity is needed. There are some promising developments like the recent work of Chirik and Nishiyama who demonstrates that these goals can be achieved. It will be interesting to take part in this renaissance of iron chemistry.

3.7. References

1 a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; b) P. T. Anastas, M. M. Kirchhoff, T. C. Williamson, *Appl. Catal. A: Gen.* **2001**, *221*, 3–13.

2 a) H.-U. Blaser, B. Pugin, F. Spindler, *J. Mol. Catal.* **2005**, *231*, 1–20; b) H.-U. Blaser, *Chem. Commun.* **2003**, 293–296; c) H.-U. Blaser in "Chiral Catalysis – Asymmetric Hydrogenations" supplement to *chimica oggi* **2004**, 4–5.

3 The price for iron is relatively low (current price for 1 t of iron ~300 US-dollar) in comparison to rhodium (5975 US-dollar per troy ounce), ruthenium (870 US-dollar per troy ounce) or iridium (460 US-dollar per troy ounce), due to the widespread abundance of iron in earth's crust and the easy accessibility. Furthermore, iron is an essential trace element (daily dose for humans 5–28 mg) and plays an important role in an extensive number of biological processes.

4 For an excellent review see: C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254.

5 a) I. C. Lennon, J. A. Ramsden, *Org. Process Res. Dev.* **2005**, *9*, 110–112; b) J. M. Hawkins, T. J. N. Watson, *Angew. Chem.* **2004**, *116*, 3286–3290; c) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; d) M. Miyagi, J. Takehara, S. Collet, K. Okano, *Org. Process Res. Dev.* **2000**, *4*, 346–348; e) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, 1999; f) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994.

6 a) T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *J. Am. Chem. Soc.* **2007**, in press; b) S. Sakuraba, K. Achiwa, *Synlett* **1991**, 689–690; c) S. Sakuraba, N. Nakajima, K. Achiwa, *Synlett* **1992**, 829–830; d) T. Kawaguchi, K. Saito, K. Matsuki, T. Iwakuma, M.Takeda, *Chem. Pharm. Bull.* **1993**, *41*, 639–642; e) T. Ohkuma, M. Koizuma, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530; f) T. Ohkuma, H. Ooka, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 10417–10418; g) T. Ohkuma, H. Ikehira, T. Ikariya, R. Noyori, *Synlett* **1997**, 467–468.

7 a) Y. Takegami, Y. Watanabe, I. Kanaya, T. Mitsudo, T. Okajima, Y. Morishita, H. Masada, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2990–2994; b) R. Noyori, I. Umeda, T. Istigami, *J. Org. Chem.* **1972**, *37*, 1542–1545; c) Y. Watanabe, M. Yashita, T.-a. Mitsudo, M. Tanaka, Y. Takegami, *Tetrahedron Lett.* **1974**, *22*, 1879–1880; d) J. P. Collmann, R. G. Finke, P. L. Matlock, R. Wahren, J. I. Brauman, *J. Am. Chem. Soc.* **1976**, *98*, 4685–4687; e) M. Yamashita, K. Miyoshi, Y. Okada, R. Suemitsu, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1329–

1330; f) more recently: Y. Moglie, F. Alonso, C. Vitale, M. Yus, G. Radivoy, *Tetrahedron* **2006**, *62*, 2812–2819.

8 L. Markó, M. A. Radhi, I. Ötvös, *J. Organomet. Chem.* **1981**, *218*, 369–376.

9 L. Markó, J. Palágyi, *Transition Met. Chem.* **1983**, *8*, 207–209.

10 a) K. Jothimony, S. Vancheesan, *J. Mol. Catal.* **1989**, *52*, 301–304; b) K. Jothimony, S. Vancheesan, J. C. Kuriacose, *J. Mol. Catal.* **1985**, *32*, 11–16.

11 J.-S. Chen, L.-L. Chen, Y. Xing, G. Chen, W.-Y. Shen, Z.-R. Dong, Y.-Y. Li, J.-X. Gao, *Huaxue Xuebao* **2004**, *62*, 1745–1750.

12 S. Enthaler, B. Hagemann, G. Erre, K. Junge, M. Beller, *Chem. Asian. J.* **2006**, *1*, 598–604.

13 H. Zhang, C.-B. Yang, Y.-Y. Li, Z.-R. Donga, J.-X. Gao, H. Nakamura, K. Murata, T. Ikariya, *Chem. Commun.* **2003**, 142–143.

14 S. Enthaler, G. Erre, K. Junge, M. Beller, manuscript submitted.

15 a) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237–248; b) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406 and references therein; c) H. Guan, M. Iimura, M. P. Magee, J. R. Norton, G. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 7805–7814; d) M. Gómez, S. Janset, G. Muller, G. Aullón, M. A. Maestro, *Eur. J. Inorg. Chem.* **2005**, 4341–4351; e) K. Muñiz, *Angew. Chem.* **2005**, *117*, 6780–6785; *Angew. Chem. Int. Ed.* **2005**, *44*, 6622–6627; f) C. Hedberg, K. Källström, P. I. Arvidsson, P. Brandt, P. G. Andersson, *J. Am. Chem. Soc.* **2005**, *127*, 15083–15090; g) A. S. Y. Yim, M. Wills, *Tetrahedron* **2005**, *61*, 7994–8004; h) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201–2237; i) T. Koike, T. Ikariya, *Adv. Synth. Catal.* **2004**, *346*, 37–41; j) P. Brandt, P. Roth, P. G. Andersson, *J. Org. Chem.* **2004**, *69*, 4885–4890; k) J.-W. Handgraaf, J. N. H. Reek, E. J. Meijer, *Organometallics* **2003**, *22*, 3150–3157; l) C. P. Casey, J. B. Johnson, *J. Org. Chem.* **2003**, *68*, 1998–2001; m) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; n) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; o) C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, M. Kavana, *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100; p) O. Pàmies, J. E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058; q) C. S. Yi, Z. He, *Organometallics* **2001**, *20*, 3641–3643; r) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931–7944; s) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478; t) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588; u) D. G. I. Petra, J. N. H. Reek, J.-W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2000**, *6*, 2818–2829; v) A. Aranyos, G. Csjernyik, K. J. Szabó, J.

E. Bäckvall, *Chem. Commun.* **1999**, 351–352; w) M. L. S. Almeida, M. Beller, G. Z. Wang, J. E. Bäckvall, *Chem. Eur. J.* **1996**, *2*, 1533–1536.

16 S. Enthaler, G. Erre, M. K. Tse, K. Junge, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8095–8099.

17 S. Enthaler, B. Spilker, G. Erre, M. K. Tse, K. Junge, M. Beller, manuscript submitted.

18 a) W. S. Knowles, M. J. Sabacky, *J. Chem. Soc. Chem. Commun.* **1968**, 1445–1446; b) W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2097–2107; c) R. Selke, H. Pracejus, *J. Mol. Catal.* **1986**, *37*, 213–225; d) R. Selke, *J. Organomet. Chem.* **1989**, *370*, 241–248.

19 a) H. Pracejus, *Koordinationschemische Katalyse organischer Reaktionen*, Verlag Theodor Steinkopf, Dresden, 1977; b) Y. Takegami, T. Ueno, T. Fujii, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1663–1667; c) J. W. Kalecic, F. K. Schmidt, *Cinetica i Kataliz Moskva* **1966**, *7*, 614–618; d) W. G. Lipovic, F. K. Schmidt, J. W. Kalecic, *Cinetica i Kataliz Moskva* **1967**, *8*, 1300–1306.

20 Y. Takegami, Y. Watanabe, I. Kanaya, T. Mitsudo, T. Okajima, Y. Morishita, H. Masada, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2990–2994 and references therein.

21 E. N. Frankel, E. A. Emken, H. M. Peters, V. L. Davison, R. O. Butterfield, *J. Org. Chem.* **1964**, *29*, 3292–3297.

22 E. N. Frankel, E. A. Emken, V. L. Davison, *J. Org. Chem.* **1965**, *30*, 2739–2745.

23 M. Cais, N. Maoz, *J. Chem. Soc. (A)* **1971**, 1811–1820.

24 Y. Tajima, E. Kunioka, *J. Org. Chem.* **1968**, *33*, 1689–1690.

25 T. Nishiguchi, K. Fukuzumi, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1656–1660.

26 M. A. Schroeder, M. S. Wrighton, *J. Am. Chem. Soc.* **1976**, *98*, 551–558.

27 a) R. L. Whetten, K.-J. Fu, E. R. Grant, *J. Am. Chem. Soc.* **1982**, *104*, 4270–4272; b) M. E. Miller, E. R. Grant, *J. Am. Chem. Soc.* **1984**, *106*, 4635–4636; c) H. Nagorski, M. J. Mirbach, *J. Organomet. Chem.* **1985**, *291*, 199–204.

28 H. Inoue, M. Sato, *J. Chem. Soc. Chem. Commun.* **1983**, 983–984.

29 H. Inoue, M. Suzuki, *J. Chem. Soc. Chem. Commun.* **1980**, 817–818.

30 Complex **26** furthermore exhibited activity in the hydrogenation of alkynes to yield alkenes. C. Bianchini, A. Mell, M. Peruzzini, P. Frediani, C. Bohanna, M. A. Esteruelas, L. A. Oro, *Organometallics* **1992**, *11*, 138–145.

31 C. Bianchini, E. Farnetti, M. Graziani, M. Peruzzini, A. Polo, *Organometallics* **1993**, *12*, 3753–3761.

32 K. Kano, M. Takeuchi, S. Hashimoto, Z.-i. Yoshida, *J. Chem. Soc. Chem. Commun.* **1991**, 1728–1729.

33 a) S. Sakaki, T. Sagara, T. Arai, T. Kojima, T. Ogata, K. Obkubo, *J. Mol. Catal.* **1992**, *75*, L33–L37; b) S. Sakaki, T.-i. Kojima, T. Arai, *J. Chem. Soc. Dalton Trans.* **1994**, 7–11.

34 S. C. Bart, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2004**, *126*, 13794–13807.

35 A. M. Archer, M. W. Bouwkamp, M.-P. Cortez, E. Lobkovsky, P. J. Chirik, *Organometallics* **2006**, *25*, 4269–4278.

36 R. J. Trovitch, E. Lobkovsky, P. J. Chirik, *Inorg. Chem.* **2006**, *45*, 7252–7260.

37 S. C. Bart, E. J. Hawrelak, E. Lobkovsky, *Organometallics* **2005**, *24*, 5518–5527.

38 M. A. Radhi, L. Markó, *J. Organomet. Chem.* **1984**, *262*, 359–364.

39 T. J. Lynch, M. Banah, H. D. Kaesz, C. R. Porter, *J. Org. Chem.* **1984**, *49*, 1266–1270.

40 K. Yamamoto, T. Hayashi in M. Beller, C. Bolm, (Eds.), *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, 2nd Ed. 2004.

41 B. Marciniec, *Comprehensive Handbook on Hydrosilylation*, Pergamon Press, Oxford, 1992.

42 R. K. Freidlina, E. C. Chukovskaya, J. Tsao, A. N. Nesmeyanov, *Dokl. Akad. Nauk. SSSR*, **1960**, *132*, 374–377.

43 A. N. Nesmeyanov, R. Kh. Freidlina, E. C. Chukovskaya, R. G. Petrova, A. B. Belyavsky, *Tetrahedron* **1962**, *17*, 61–68.

44 G. V. Nurtdinova, G. Gailiunas, V. P. Yur`ev, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, *11*, 2652.

45 G. Gailiunas, G. V. Nurtdinova, V. P. Yur`ev, G. A. Tolstikov, S. R. Rafikov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, *4*, 914–920.

46 I. V. Savos`kina, N. A. Kuz`min, G. G. Galust`yan, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, *2*, 483–485.

47 F. Kakiuchi, Y. Tanaka, N. Chatani, S. Murai, *J. Orgmet. Chem.* **1993**, *456*, 45–47.

48 M. A. Schroeder, M. S. Wrighton, *J. Organomet. Chem.* **1977**, *128*, 345–358.

49 I. Fischler, F.-W. Grevels, *J. Organomet. Chem.* **1980**, *204*, 181–190.

50 C. U. Pittman Jr., W. D. Honnick, M. S. Wrighton, R. D. Sanner, R. G. Austin, *Fundamental Research Homogeneous Catalysis* **1979**, *3*, 603–619.

51 R. G. Austin, R. S. Paonessa, P. J. Giordano, M. S. Wrighton, *Adv. Chem. Ser.* **1978**, *168*, 189–214.

52 C. L. Randolph, M. S. Wrighton, *J. Am. Chem. Soc.* **1986**, *108*, 3366-3374.

53 G. Bellachioma, G. Cardaci, E. Colomer, R. J. P. Corriu, A. Vioux, *Inorg. Chem.* **1989**, *28*, 519–525.

54 C. U. Pittman Jr., M. G. Richmond, M. Absi-Halabi, H. Beurich, F. Richter, H. Vahrenkamp, *Angew. Chem.* **1982**, *94*, 805-806; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 786-787.

55 A. J. Cornish, M. F. Lappert, J. J. MacQuitty, R. K. Maskell, *J. Organomet. Chem.* **1979**, *177*, 153–161.

56 H. Brunner, K. Fisch, *Angew. Chem.* **1990**, *102*, 1189–1191; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1131–1132. Brunner et al. reported the successful application of [(indenyl)Fe(CO)2(CH3)] complexes in hydrosilylation of ketones, but extension to hydrogenation of styrenes with molecular hydrogen was impossible since catalyst deactivation was observed.

57 H. Brunner, K. Fisch, *J. Organomet. Chem.* **1991**, *412*, C11–C13.

58 H. Brunner, R. Eder, B. Hammer, U. Klement, *J. Organomet. Chem.* **1990**, *394*, 555–567.

59 H. Nishiyama, A. Furuta, *Chem. Commun.* **2007**, *7*, 760–762.

60 N. Shaik, S. Enthaler, K. Junge, M. Beller, unpublished results.

4. Objectives of the work

4.1. Application of monodentate phosphine ligands in asymmetric hydrogenations

Since earlier works have proven an excellent behaviour of ligands containing 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine scaffold in the asymmetric hydrogenation of *α*–amino acid precursors, itaconic acid derivatives and *β*–ketoesters, we focused our attention on extension of scope and limitation of this ligand tool box. Several challenging substrate classes, based on unsaturated C-C bonds, were synthesized and subjected to catalytic reduction.

4.1.1. Asymmetric hydrogenation of *N*–acyl enamides

Until the end of 2004 only two reports were published dealing with the rhodium–catalyzed hydrogenation of *N*–acyl enamides in the presence of monodentate phosphines. On the one hand the utilization of chiral phospholanes by Fiaud and co–workers, which attained good enantioselectivities up to 73% *ee*, when (*Z*)–*N*–(1–phenylprop–1–enyl)acetamide was hydrogenated.[1] On the other hand, Reetz *et al.* described the rhodium–catalyzed hydrogenation of *N*–(1–phenylvinyl)–acetamide with ligands based on 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine (*vide supra*).[2] Surprisingly, the *tert*–butyl–substituted ligand showed better selectivity and yield than the phenyl–substituted ligand, which is in contrast to other benchmark tests such as the asymmetric hydrogenation of *α*–amino acid precursors, dimethyl itaconate and *β*–ketoesters where always the opposite behaviour was observed. The interesting results of Reetz and co–workers stimulated us to study the potential of our ligand library in the field of asymmetric hydrogenation of *N*–acyl enamides in more detail.

4.1.2. Asymmetric hydrogenation of *β*–dehydroamino acid derivatives

Since, *β*–amino acids are interesting building blocks for the synthesis of biologically active compounds the synthesis via asymmetric hydrogenation of unsaturated precursors offers a versatile and powerful approach. Currently bidentate phosphorous ligands have been proven to be effective in the asymmetric hydrogenation of *β*–dehydroamino acid derivatives with enantioselectivities up >99% *ee*, while a monodentate version is so far scarcely reported. Here only the group of Börner accounted enantioselectivities up to 93% *ee* with monodentate

phospholane ligand.[3] We became interested in studying the behaviour of chiral monodentate 44,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine in the rhodium–catalyzed asymmetric hydrogenation of various *β*–dehydroamino acid derivatives to give optically active *β*–amino acids.

4.1.3. Asymmetric hydrogenation of enol carbamates

Pioneering work in the field of enantioselective hydrogenation of enol carbamates, which are suitable precursors for chiral alcohols, has been reported by Feringa, de Vries, Minnaard and co–workers applying rhodium–catalysts containing monodentate phosphoramidites (MonoPhos–family) and obtaining enantioselectivities up to 98% *ee*.[4] However, until today no additional studies on the reduction of enol carbamates were reported. Hence, we became interested in testing our ligand library in this purpose.

4.2. Transfer hydrogenation

4.2.1. Homogeneous iron catalyst in reduction chemistry

With regard to future catalyst developments a fundamental challenge will be the substitution of expensive and rare transition metals by inexpensive and abundantly available metals such as iron. So far, homogeneous iron catalysts have been most frequently applied for carbon–carbon coupling reactions, such as olefin polymerizations, cross couplings, and cycloadditions. However, much less attention was directed towards iron–catalyzed (transfer) hydrogenations, albeit the relevance of such reductions is evident even with respect to industrial applications. Until today only a few number of research groups reported the application of iron salts and iron complexes in the reduction of *α*,*β*–unsaturated carbonyl compounds and ketones using a transfer hydrogenation protocol.[5] For tuning the activity and selectivity of these catalysts oxygen and moisture sensitive tetradentate phosphines or aminophosphines have been predominantly applied as ligands. Our goal was to develop a practical iron hydrogenation catalyst system, which should be easily prepared and highly tuneable. Thus, the use of commercially available iron complexes in combination with two different ligands (phosphines and amines) instead of tetradentate ligands seemed to be a useful approach. Furthermore inspired by nature we thought that multidentate nitrogen ligands should be also suitable ligands for stabilizing iron as metal center in transfer hydrogenations. The influence of different reaction parameters on the catalytic activity will be investigated in

the transfer hydrogenation of aliphatic and aromatic ketones utilizing 2–propanol as hydrogen donor in the presence of base.

4.2.2. Transfer hydrogenation of ketones with ruthenium catalysts

4.2.2.1. Transfer hydrogenation with ruthenium carbene catalysts

With regard to transfer hydrogenations different carbene or carbene-phosphine–systems containing Rh, Ir, Ru or Ni have been reported. Excellent turnover frequencies up to 120000 h^{-1} were reported by the groups of Baratta and Herrmann applying a ruthenium–carbene–phosphine–catalyst.[6] However, for reduction of a typical substrate, e.g. acetophenone, with phosphine–free ruthenium–carbene catalysts lower turnover frequencies (TOF 333 h^{-1})[7] were achieved in comparison to iridium (500 h^{-1})[8] and rhodium systems (583 h^{-1}).[9] Due to the economical benefit of ruthenium metal compared to rhodium or iridium and the advantages of phosphine–free systems, it will be an important goal to search for more active ruthenium carbene catalysts.

4.2.2.2. Asymmetric transfer hydrogenation with ruthenium catalysts

Significantly less is known of the transfer of chiral information for tridentate ligands, while transfer hydrogenation is dominated by highly active bidentate systems.[10] Up to now only a limited number of auspicious tridentate nitrogen-containing *N,N,N*–ligands were established. For example (*R*)–phenyl–ambox and different pyridinebisoxazoline (pybox) ligands have been applied for the reduction of acetophenone. More recently, a new class of chiral tridentate amines so called pybim (parent structure: 2,6-bis–([*4R,5R*]–4,5–diphenyl–4,5–dihydro–1*H*–imidazol–2-yl)–pyridine) for the ruthenium–catalyzed epoxidations was introduced by Beller *et al.*[11] The resemblance between pybim and pybox stimulated our research to study the potential of this class of ligands in the transfer hydrogenation of aromatic and aliphatic ketones.

4.3. References

1 C. Dobrota, M. Toffano, J.-C. Fiaud, *Tetrahedron Lett.* **2004**, *45*, 8153–8156.

2 M. T. Reetz, G. Mehler, A. Meiswinkel, *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167.

3 V. Bilenko, A. Spannenberg, W. Baumann, I. Komarov, A. Börner, *Tetrahedron: Asymmetry* **2006**, *17*, 2082–2087.

4 a) X. Jiang, M. van den Berg, A. J. Minnaard, B. Feringa, J. G. de Vries, *Tetrahedron: Asymmetry* **2004**, *15*, 2223–2229; b) L. Panella, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 4177–4180.

5 a) K. Jothimony, S. Vancheesan, *J. Mol. Catal.* **1989**, *52*, 301–304; b) K. Jothimony, S. Vancheesan, J. C. Kuriacose, *J. Mol. Catal.* **1985**, *32*, 11–16; c) J.-S. Chen, L.-L. Chen, Y. Xing, G. Chen, W.-Y. Shen, Z.-R. Dong, Y.-Y. Li, J.-X. Gao, *Huaxue Xuebao* **2004**, *62*, 1745–1750; d) C. Bianchini, E. Farnetti, M. Graziani, M. Peruzzini, A. Polo, *Organometallics* **1993**, *12*, 3753–3761.

6 W. Baratta, J. Schütz, E. Herdtweck, W. A. Herrmann, P. Rigo, *J. Organomet. Chem.* **2005**, *690*, 5570–5575.

7 A. A. Danopoulos, S. Winston, W. B. Motherwell, *Chem. Commun.* **2002**, 1376–1377.

8 M. Albrecht, J. R. Miecznikowski, A. Samuel, J. W. Faller, R. H. Crabtree, *Organometallics* **2002**, *21*, 3596–3604.

9 M. Poyatos, E. Mas-Marzá, J. A. Mata, M. Sanaú, E. Peris, *Eur. J. Inorg. Chem.* **2003**, 1215–1221.

10 a) Y. Jiang, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 3817–3818; b) D. Cuervo, M. P. Gamasa, J. Gimeno, *Chem. Eur. J.* **2004**, *10*, 425–432.

11 a) S. Bhor, G. Anilkumar, M. K. Tse, M. Klawonn, C. Döbler, B. Bitterlich, A. Grotevendt, M. Beller, *Org. Lett.* **2005**, *7*, 3393–3396; b) G. Anilkumar, S. Bhor, M. K. Tse, M. Klawonn, B. Bitterlich, M. Beller, *Tetrahedron: Asymmetry* **2005**, *16*, 3536–3561.

5.1. Enantioselective rhodium–catalyzed hydrogenation of enamides in the presence of chiral monodentate phosphines

Stephan Enthaler, Bernhard Hagemann, Kathrin Junge, Giulia Erre, and Matthias Beller*, *Eur. J. Org. Chem.* **2006**, 2912–2917.

Contributions

Ligands **5c** and **5f** were synthesized by Dr. B. Hagemann. Furthermore, the asymmetric hydrogenation of substrate **6f** and the combinatorial ligand approach (Table 3) were carried by Dr. B. Hagemann.

DOI: 10.1002/ejoc.200600024

Enantioselective Rhodium-Catalyzed Hydrogenation of Enamides in the Presence of Chiral Monodentate Phosphanes

Stephan Enthaler,[a] Bernhard Hagemann,[a] Kathrin Junge,[a] Giulia Erre,[a] and Matthias Beller*[a]

Keywords: Asymmetric catalysis / Homogeneous catalysis / Hydrogenation / Monodentate phosphane ligands / Enamides

The rhodium-catalyzed asymmetric hydrogenation of different acyclic and cyclic *N*-acyl enamides to give *N*-acyl-protected optically active amines has been examined for the first time in detail in the presence of chiral monodentate 4,5-dihydro-3*H*-dinaphthophosphepines **5a**–**i**. The enantioselectivity is largely dependent on the nature of the substituent at the phosphorus atom and the enamide substrate. Applying optimized conditions up to 95% *ee* and catalyst activity up to 2000 h^{-1} (TOF) have been achieved.

Introduction

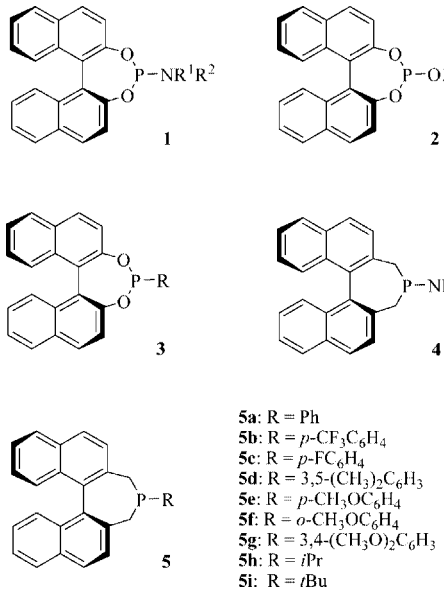
The importance of chiral amines is demonstrated by their broad scope of applications as building blocks and synthons for pharmaceuticals and agrochemicals. In addition, they are of significant use for the synthesis of natural compounds, chiral auxiliaries, and optically active ligands.[1] Hence, the development of new and improved methods for the preparation of enantiomerically pure amines is an important target of industrial and academic research. Several synthetic approaches to optically active amines have been established in the past. Still one of the most practical approaches is the separation of enantiomers through resolution, e.g. in the presence of chiral acids. The main drawback of this concept is the poor atom efficiency and the negative environmental impact. A more attractive access is represented by applying enantiomerically pure starting materials from the "chiral pool". Another powerful strategy is the application of stereoselective syntheses in particular reactions catalyzed by transition-metal complexes.[2] Examples of such transition-metal-catalyzed reactions, which offer a versatile and elegant approach to enantiomerically pure amines, are the alkylation or arylation of imines, hydrocyanation of carbon–carbon double bonds and aziridination.[2c] However, the most popular catalytic reaction with respect to industrial applications is the asymmetric hydrogenation of imines or *N*-protected enamines and enamides.[3]

Pioneering work in the field of enantioselective hydrogenation of enamides has been reported by Kagan and co-workers. Applying diphosphane rhodium catalysts enantioselectivity up to 90% has been obtained.[4] Over a period of nearly 30 years the development of new ligands for asymmetric hydrogenation has focused on the synthesis of bidentate ligands. During this time several effective bidentate phosphanes such as Me-DuPhos, Me-BPE, DIOP, BINAP and others were developed for the hydrogenation of enamides.[4,5] At the end of the 20th century the predominant role of bidentate ligands changed and monodentate ligands received more attention.[6,7] The advantages of monodentate phosphorus ligands are their easier synthesis and tunability compared to bidentate phosphanes. Scheme 1 illustrates some examples of monodentate phosphorus ligands for asymmetric hydrogenation on the basis of the chiral 1,1′-binaphthol skeleton. Important contributions in this area came independently from Feringa and de Vries et al.[8] (phosphoramidites **1**), Reetz et al.[9] (phosphites **2**), and Pringle and Claver et al.[10] (phosphonites **3**). Furthermore, excellent enantioselectivity was shown by Zhou and co-workers applying monodentate spiro phosphoramidites (SIPHOS).[11]

Following the original work of Gladiali[12] and parallel to Zhang,[13] we have established the synthesis of various monodentate phosphanes based on a 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine framework (**4** and **5a**–**i**), which resembles the 1,1′-binaphthol core.[14] Recently, we have shown that asymmetric hydrogenation of amino acid precursors, dimethyl itaconate and β-keto esters proceeds with enantioselectivities up to 95% *ee* in the presence of ligand **5a**.[13] Moreover, other groups demonstrated the usefulness of these ligands in several catalytic asymmetric reactions.[15]

To the best of our knowledge there exists only one publication dealing with the hydrogenation of enamides in the

[a] Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert-Einstein-Str. 29A, 18059 Rostock, Germany
Fax: +49-381-12815000
E-mail: matthias.beller@ifok-rostock.de



Scheme 1. Chiral monodentate ligands with 2,2′-binaphthyl framework.

presence of monodentate phosphepines. Here, Reetz et al.[16] described the rhodium-catalyzed hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**) with ligands **5a** [conversion: 50%; enantiomeric excess: 14% (*R*)] and **5i** [conversion: 94%; enantiomeric excess: 24% (*R*)] in dichloromethane. To our surprise the *tert*-butyl-substituted ligand **5i** showed better selectivity and yield than the phenyl-substituted ligand **5a**. In our benchmark tests, for instance, in the asymmetric hydrogenation of amino acid precursors, dimethyl itaconate and β-keto esters, we always observed the opposite behaviour.

Discussion

The interesting results of Reetz and co-workers[15] stimulated us to study the potential of our ligand library **5a**–**i** in the field of asymmetric hydrogenation of enamides in more detail. In general, the ligands are prepared by metallation of 2,2′-dimethylbinaphthyl with two equiv. of *n*-butyllithium, followed by quenching with diethylamino(dichloro)phosphane. Deprotection with gaseous HCl produced 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine in a yield of 80%. This enantiomerically pure chlorophosphane is easily coupled with various Grignard reagents to give a broad selection of ligands of type **5**.

Unsubstituted and substituted *N*-(1-phenylvinyl)acetamides **6a**–**6e** were obtained by reacting the corresponding benzonitrile with a methyl Grignard followed by addition of acetic anhydride.[8e] The cyclic *N*-acyl enamide **6f** was synthesized by a standard protocol implying transformation of the ketone to the corresponding oxime and subsequent reductive acylation with iron in the presence of acetic acid anhydride.[17]

Initial studies on the influence of reaction conditions were carried out with *N*-(1-phenylvinyl)acetamide (**6a**) as substrate and 4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (**5a**) as our standard ligand. Typically, we used an in situ pre-catalytic mixture of 1 mol-% $[Rh(cod)_2]BF_4$ and 2.1 mol-% of the corresponding ligand. All hydrogenation reactions were carried out in an 8fold parallel reactor array with 3.0 mL reactor volume.[18]

At first, we focused our attention on the influence of different solvents, such as dichloromethane, methanol, ethyl acetate, toluene, and also variation of the initial pressure (1.0 bar, 5.0 bar and 10 bar). Selected results are presented in Figure 1.

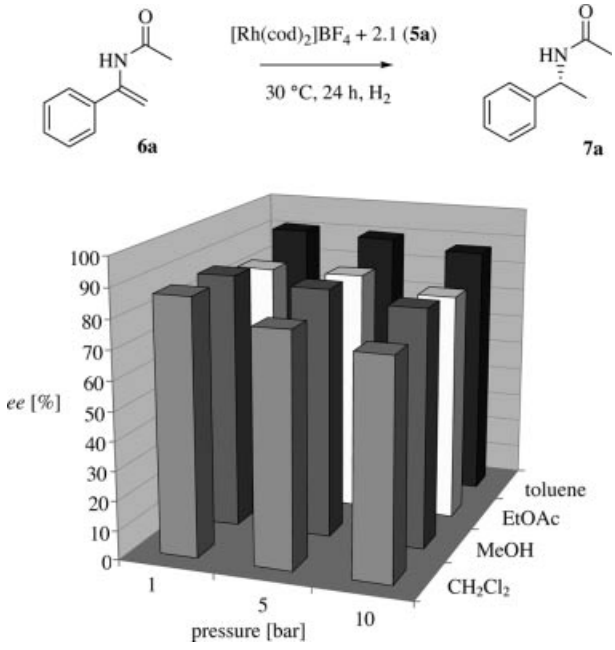


Figure 1. Solvent and pressure variation. Reactions were carried out at 30 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand **5a** and 0.24 mmol substrate in 2.0 mL solvent. Conversion and *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min]. The absolute configuration was determined by comparing the sign of specific rotation with reported data and the original sample (Aldrich).[5i]

For all solvents best enantioselectivity (80–90% *ee*) is achieved at 1.0 bar, but without complete conversion within reasonable time (24 h). Increasing the pressure of hydrogen to 5.0 bar or 10.0 bar accelerated the reaction and full conversion is reached, but at somewhat lower selectivity. The results also indicated toluene as the solvent of choice for our model reaction (conversion: 96%; enantioselectivity: 91%).

To find the optimum of the enantioselectivity−pressure dependency we performed a fine tuning of the hydrogen pressure in toluene. At 2.5 bar hydrogen pressure both good enantioselectivity (93% *ee*) and acceptable reaction time (6 h) have been achieved.

Next, we investigated the influence of the temperature on the selectivity and yield as described in Figure 2. Applying our model ligand **5a** there is no pronounced effect on the selectivity between 10 and 30 °C.[19] At higher temperatures a decrease of the *ee* is observed (87% *ee* at 50 °C and 83% *ee* at 70 °C).

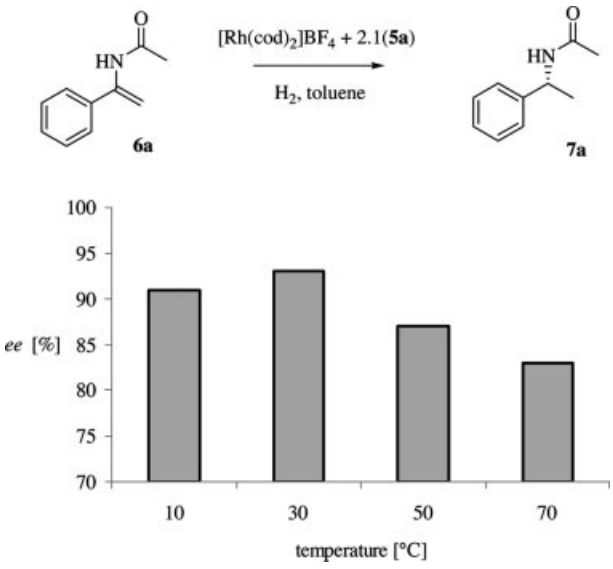
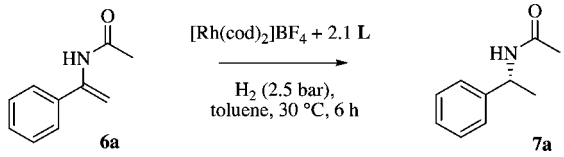


Figure 2. Dependency of enantioselectivity vs. temperature. Reactions were carried out at the corresponding temperature for 1–24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand **5a** and 0.24 mmol substrate in 2.0 mL toluene. Conversion and *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min].[5i]

Table 1. Hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**).[a]



Entry	Ligand	Conversion [%][b]	*ee* [%][b,c]
1	**5a**	>99	**93** (*R*)
2	**5b**	>99	72 (*R*)
3	**5c**	>99	88 (*R*)
4	**5d**	>99	87 (*R*)
5	**5e**	>99	**93** (*R*)
6	**5f**	>99	63 (*R*)
7	**5g**	>99	90 (*R*)
8	**5h**	>99	30 (*R*)
9	**5i**	>99	16 (*S*)
10	**1**	4	19 (*S*)

[a] All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in toluene (2.0 mL). [b] Conversion and *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min]. [c] The absolute configuration was determined by comparing the sign of specific rotation with reported data and the original sample (Aldrich).[5i]

To estimate the activity of the catalyst in more detail the ratio between metal and substrate was varied starting from initially 1:100 to 1:2000. At 50 °C and 2.5 bar of hydrogen complete conversion was observed within one hour, which corresponds to a turnover frequency (TOF) of 2000 h^{-1}.

In order to evaluate the substituent effect at the phosphorus atom of the ligand, we studied the asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**) in the presence of nine different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines (**5a**–**5i**) using the optimized reaction conditions (2.5 bar hydrogen pressure, toluene, 30 °C, 6 h). These results are presented in Table 1.

In agreement with our previous studies, it appeared that for obtaining good enantioselectivity aryl-substituted phosphepine ligands are necessary, while alkyl-substituted ligands showed significantly lower selectivity. Substitution on the phenyl ring at the phosphorus atom with electron-withdrawing (**5b**, **5c**) as well as electron-donating groups (**5d**–**5g**) resulted in decreased selectivity in comparison to the phenyl ligand **5a**. Here, only ligand **5e** represented an exception (Table 1, Entry 5), which led to 93% *ee*.

Interestingly, the behaviour of the *tert*-butyl ligand **5i** is quite different in the hydrogenation of **6a**. In contrast to the results obtained by Reetz et al., under our reaction conditions compound **5i** induced a change in the absolute configuration of the product to the opposite (*S*)-enantiomer, albeit with significantly lower *ee*.

In addition to the ligands **5**, we also tested the commercially available (*S*)-MonoPhos ligand (**1**, $R^1 = R^2 = Me$), which gives excellent enantioselectivity in various hydrogenations of prochiral double bonds.[8,20] However, in the present test reaction we obtained only poor yield and enantioselectivity (Table 1, Entry 10).

To demonstrate the scope and limitations of our ligand toolbox we performed the asymmetric hydrogenation of four different *N*-(1-phenylvinyl)acetamides (Table 2). Regarding the substrates both electron-donating substituents at the phenyl group, in particularly a methoxy group in *para*- as well as in *meta*-position and electron-withdrawing substituents such as *para*-fluoro or *para*-trifluoromethyl have been tested. Enantioselectivity up to 95% *ee* is obtained with ligands **5a** (Table 2, Entry 1) and **5e** (Table 2, Entry 5) for electron-rich substrates. In general, aryl phosphepines with electron-donating substituents showed better selectivity than phosphepines having electron-withdrawing groups.

The introduction of electron-withdrawing substituents in *N*-(1-phenylvinyl)acetamide **6d** and **6e** decreased the enantioselectivity compared to the non-substituted *N*-(1-phenylvinyl)acetamide (**6a**). Here, the best selectivities of 83–86% *ee* are obtained with ligands **5a**, **5e** and **5g**.

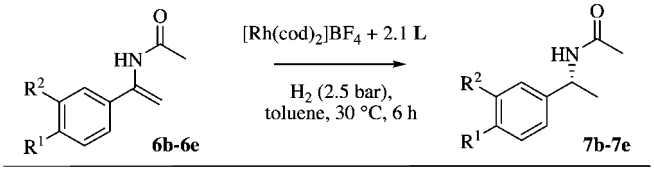
Again for all substrates **6a**–**6e** the alkyl-substituted 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines gave significantly lower selectivity.

Next, the hydrogenation of the sterically more hindered *N*-(3,4-dihydro-1-naphthyl)acetamide (**6f**) was tested (Scheme 2). The use of different pre-catalysts including $[Rh(\mathbf{5a})_2(cod)]BF_4$, $[Rh(\mathbf{5e})_2(cod)]BF_4$ and $[Rh(\mathbf{5i})_2(cod)]BF_4$ gave an excellent yield (>99%) of **7f**.

However, the observed enantioselectivity is significantly lower [**5a**: 15% (*S*); **5e**: 11% (*S*); **5i**: 35% (*R*)] when compared to 1,1-disubstituted enamides. These results indicate a crucial influence of the substitution pattern on the enamide group.

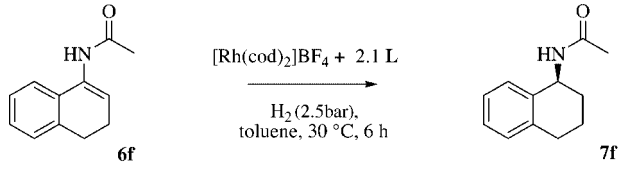
It is important to note that in comparison to bidentate ligands the application of monodentate ligands offers an

Table 2. Asymmetric hydrogenation of substituted *N*-(1-phenylvinyl)acetamides **6b**–**6e**.[a]



Entry	Ligand	**7b** (R^1 = CH_3O; R^2 = H) *ee* [%][b,c]	**7c** (R^1 = H; R^2 = CH_3O) *ee* [%][b,d]
1	**5a**	**91** (*R*)	**95** (*R*)
2	**5b**	63 (*R*)	72 (*R*)
3	**5c**	79 (*R*)	84 (*R*)
4	**5d**	87 (*R*)	87 (*R*)
5	**5e**	**92** (*R*)	89 (*R*)
6	**5f**	33 (*R*)	53 (*R*)
7	**5g**	89 (*R*)	89 (*R*)
8	**5h**	*rac*	26 (*R*)
9	**5i**	21 (*S*)	23 (*S*)
Entry	Ligand	**7d** (R^1 = F) *ee* [%][b,c]	**7e** (R^1 = CF_3) *ee* [%][b,c]
10	**5a**	86 (*R*)	78 (*R*)
11	**5b**	51 (*R*)	62 (*R*)
12	**5c**	71 (*R*)	73 (*R*)
13	**5d**	71 (*R*)	65 (*R*)
14	**5e**	86 (*R*)	78 (*R*)
15	**5f**	34 (*R*)	68 (*R*)
16	**5g**	83 (*R*)	85 (*R*)
17	**5h**	4 (*R*)	44 (*R*)
18	**5i**	*rac*	25 (*S*)

[a] All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2.0 mL toluene. [b] Conversion (>99%) was determined by GC (Agilent Technologies, 30 m, 50–300 °C), *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 100–180 °C, (*R*)-**7b** 36.1 min, (*S*)-**7b** 36.4 min, (*R*)-**7c** 34.8 min, (*S*)-**7c** 35.0 min, (*R*)-**7d** 31.0 min, (*S*)-**7d** 31.2 min, (*R*)-**7e** 32.4 min, (*S*)-**7e** 32.7 min]. [c] The absolute configurations were determined by comparing the sign of specific rotation with reported data.[5i] [d] Absolute configuration of product was assigned by analogy.

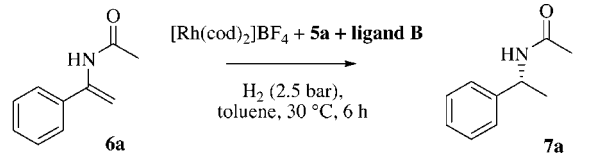


Scheme 2. Asymmetric hydrogenation of *N*-(3,4-dihydro-1-naphthyl)acetamide (**6f**). All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2.0 mL toluene. Conversion was determined by GC (Agilent Technologies, 30 m, 50–300 °C) and *ee* values were determined by HPLC [AD-H Chiralpak (Agilent Technologies), *n*-hexane/ethanol, 95:5, rate 1.0 mL/min, (*S*)-**7f** 6.2 min, (*R*)-**7f** 7.2 min]. The absolute configuration was determined by comparing the sign of specific rotation with reported data.

opportunity to replace one equiv. of the ligand by other chiral or achiral monodentate ligands. This remarkable combinatorial approach was introduced by Reetz et al.,[9d–9f,15,21] and Feringa et al.[22] for different transition-metal-catalyzed reactions.[23]

We followed this concept and used 4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (**5a**) with different achiral phosphanes in a ratio of 1.05 to 1.05 equiv. in the presence of 1.0 equiv. of $[Rh(cod)_2]BF_4$. The results obtained for the hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**) under optimized reaction conditions are presented in Table 3.

Table 3. Application of ligand mixtures in the asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**).[a]



Entry	Ligand B	Conversion [%][b]	*ee* [%][b,c]
1	**5a**	>99	93 (*R*)
2	PPh_3	>99	85 (*R*)
3	$P(p\text{-MeO-}C_6H_4)_3$	>99	88 (*R*)
4	$P(p\text{-Me-}C_6H_4)_3$	>99	81 (*R*)
5	PCy_3	>99	74 (*R*)

[a] All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.0025 mmol ligand **5a**, 0.0025 mmol achiral ligand and 0.24 mmol substrate in 2.0 mL toluene. [b] Conversion and *ee* values determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min]. [c] The absolute configuration was determined by comparing the sign of specific rotation with reported data and the original sample (Aldrich).[5i]

In general, we observed a slight decrease in enantioselectivity from that observed when using 2.1 equiv. of ligand **5a**. On the assumption that probably three different metal complexes could be formed, in particular, two homocombination products, the chiral $[Rh(\mathbf{5a})(\mathbf{5a})(cod)]BF_4$ and the achiral $[Rh(L)(L)(cod)]BF_4$, and the hetero-combination product $[Rh(L)(\mathbf{5a})(cod)]BF_4$, we deduce a significantly lower reaction rate or inactivity for the achiral complex $[Rh(L)(L)(cod)]BF_4$ relative to complex $[Rh(\mathbf{5a})(\mathbf{5a})(cod)]BF_4$ or $[Rh(L)(\mathbf{5a})(cod)]BF_4$. Tricyclohexylphosphane (Table 3, Entry 5) was found to be the only exception, as we noticed a more pronounced decrease of the enantiomeric excess.

Conclusions

We demonstrated the application of monodentate 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines **5** in the rhodium-catalyzed asymmetric hydrogenation of various enamides. The influences of different reaction parameters are presented. For the first time high enantioselectivity (up to 95% *ee*) for such reactions is obtained in the presence of

monodentate phosphanes. Best results were observed with aryl-substituted phosphepine ligands for reduction of *N*-(1-phenylvinyl)acetamide, while alkyl-substituted phosphepine ligands yielded only low selectivity.

Experimental Section

All manipulations were performed under argon using standard Schlenk techniques. Diethyl ether and toluene were distilled from sodium benzophenone ketyl under argon. Methanol was distilled from Mg under argon. Dichloromethane was distilled from CaH_2 under argon. The ligands **5** were synthesized according to our previously published protocols.[13] $[Rh(cod)_2]BF_4$ (purchased from Fluka) was used without further purification.

General Procedure for the Synthesis of Substituted *N*-(1-Phenylvinyl)-acetamides 6a–6e: To a stirred solution of methylmagnesium bromide (17.0 mmol, 3.0 mol/L diethyl ether, 6.0 mL) in diethyl ether (50 mL) at 0 °C a solution of the corresponding benzonitrile (17.0 mmol) in diethyl ether (20 mL) was added dropwise during a period of 30 minutes. After complete addition the solution was refluxed for eight hours. Within a few hours a yellow precipitate was formed. After refluxing the reaction mixture was cooled to 0 °C, and a solution of acetic anhydride (17.0 mmol) in diethyl ether (20 mL) was added carefully over 30 minutes. The reaction mixture was refluxed for eight hours. To the resulting suspension methanol was added at room temperature whilst stirring until all precipitates were dissolved (approximately 50 mL). The homogeneous solution was mixed with water/ethyl acetate (1:1, 100 mL). After phase separation the aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic layers were dried with $MgSO_4$. After removing of the solvents the semi crystalline crude oil was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1). Removal of the solvent yielded the crystalline products. [yields: (**6a**) 1.51 g (55%), (**6b**) 1.66 g (51%), (**6c**) 1.50 g (46%), (**6d**) 1.52 g (50%), (**6e**) 1.91 g (49%)]

General Procedure for the Synthesis of the Cyclic *N*-Acyl Enamide 6f: A stirred solution of the corresponding ketone (30.3 mmol), hydroxylamine–hydrochloride (73 mmol) and pyridine (62.2 mmol) in ethanol (40 mL) was heated to 85 °C for a period of 16 hours. The solvent was removed, and the residue was dissolved in ethyl acetate/water. The organic phase was washed two times with water (20 mL) and dried with $MgSO_4$. After removal of the solvents the product was recrystallized from toluene. The corresponding ketoximine (18.6 mmol) was solved in toluene (30 mL) under argon. To the stirred solution acetic acid anhydride (55.9 mmol), acetic acid (55.9 mmol), and Fe powder (37.3 mmol, Aldrich 325 mesh) were added and then heated to 70 °C for 4 hours. The mixture was filtered through a plug of celite after cooling to room temperature. Dichloromethane was added to the filtrate, followed by washing with 2.0 M NaOH (2×25 mL) at 0 °C. The separated organic phase was concentrated to half volume. The crystalline product was obtained after 12 hours at 0 °C. The crystals were filtered and dried in vacuo. [overall yield: 2.05 g (59%)]

General Procedure for the Catalytic Hydrogenation of Enamides: A solution of enamide (0.24 mmol) and 1.0 mL solvent was transferred via syringe into the secured autoclave. Because of the poor solubility in toluene at room temperature the solution was heated to 50 °C before it was transferred. The catalyst was generated in situ by mixing $[Rh(cod)_2]BF_4$ (0.0024 mmol) and the corresponding 4,5-dihydro-3*H*-dinaphthophosphepine ligands (0.005 mmol) in 1.0 mL solvent for a period of 10 min, and afterwards, it was transferred via syringe into the autoclave. Then, the autoclave was charged with hydrogen and the mixture was stirred at the required temperature. After the predetermined time the hydrogen was released and the reaction mixture passed through a short plug of silica gel. The enantioselectivity and conversion were measured by GC or HPLC without further modifications.

Acknowledgments

We thank M. Heyken, S. Buchholz and Dr. C. Fischer (all Leibniz-Institut für Katalyse e. V. an der Universität Rostock) for excellent technical assistance and Prof. Dr. S. Gladiali for general discussions. Generous financial support from the state of Mecklenburg-Western Pomerania and the BMBF is gratefully acknowledged.

[1] a) Y.-G. Zhou, P.-Y. Yang, X. W. Han, *J. Org. Chem.* **2005**, *70*, 1679–1683; b) P. Harrison, G. Meek, *Tetrahedron Lett.* **2004**, *45*, 9277–9280; c) S. A. Lawrence, *Amines*, Cambridge University Press, Cambridge, **2004**; d) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2231; e) H.-P. Jacqueline, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, John Wiley & Sons, New York, **1995**; f) M. Nógradi, *Stereoselective Synthesis*, Wiley-VCH, Weinheim, 2nd ed., **1995**; g) D. M. Tschaen, L. Abramson, D. Cai, R. Desmond, U.-H. Dolling, L. Frey, S. Karady, Y.-J. Shi, T. R. Verhoeven, *J. Org. Chem.* **1995**, *60*, 4324–4330; h) P. A. Chaloner, M. A. Esteruelas, F. Joó, L. A. Oro, *Homogeneous Hydrogenation*, Kluwer, Dordrecht, **1994**; i) M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, R. Noyori, *J. Org. Chem.* **1994**, *59*, 297–310; j) H. P. Buser, B. Pugin, F. Spindler, M. Sutter, *Tetrahedron* **1991**, *47*, 5709–5716; k) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, H. Takaya, *J. Am. Chem. Soc.* **1986**, *108*, 7117–7119.

[2] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, 2nd ed., **2004**; c) E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, **1999**.

[3] H.-U. Blaser, B. Pugin, F. Spindler, *J. Mol. Catal. A* **2005**, *231*, 1–20.

[4] a) H. B. Kagan, N. Langlois, T. P. Dang, *J. Organomet. Chem.* **1975**, *90*, 353–365; b) D. Sinou, H. B. Kagan, *J. Organomet. Chem.* **1976**, *114*, 325–337.

[5] a) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125–12138; b) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934; c) W. Li, X. Zhang, *J. Org. Chem.* **2000**, *65*, 5871–5874; d) W. Hu, M. Yan, C.-P. Lau, S. M. Yang, A. S. C. Chan, *Tetrahedron Lett.* **1999**, *40*, 973–976; e) Z. Zhang, G. Zhu, Q. Jiang, D. Xiao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 1774–1775; f) P. Dupau, P. Le Gendre, C. Bruneau, P. H. Dixneuf, *Synlett* **1999**, *11*, 1832–1834; g) G. Zhu, X. Zhang, *J. Org. Chem.* **1998**, *63*, 9590–9593; h) T. Morimoto, M. Chiba, K. Achiwa, *Chem. Pharm. Bull.* **1992**, *40*, 2894–2896; i) M. J. Burk, Y. M. Wang, J. R. Lee, *J. Am. Chem. Soc.* **1996**, *118*, 5142–5143; j) F.-Y. Zhang, C.-C. Pai, A. S. C. Chan, *J. Am. Chem. Soc.* **1998**, *120*, 5808–5809; k) M. Hayashi, Y. Hashimoto, H. Takezaki, Y. Watanabe, K. Saigo, *Tetrahedron: Asymmetry* **1998**, *9*, 1863–1866.

[6] F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315–324.

[7] I. V. Komarov, A. Börner, *Angew. Chem.* **2001**, *113*, 1237–1240.

[8] a) L. A. Arnold, R. Imobos, A. Manoli, A. H. M. de Vries, R. Naasz, B. Feringa, *Tetrahedron* **2000**, *56*, 2865–2878; b) M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540; c) A. J. Minnaard, M.

van den Berg, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. Feringa, *Chim. Oggi* **2001**, *19*, 12–13; d) D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553; e) M. van den Berg, R. M. Haak, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Adv. Synth. Catal.* **2002**, *344*, 1003–1007; f) M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv. Synth. Catal.* **2003**, *345*, 308–323; g) D. Peña, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Lett.* **2003**, *5*, 475–478; h) X. Jiang, M. van den Berg, A. J. Minnaard, B. Feringa, J. G. de Vries, *Tetrahedron: Asymmetry* **2004**, *15*, 2223–2229; i) R. Eelkema, R. A. van Delden, B. L. Feringa, *Angew. Chem. Int. Ed.* **2004**, *43*, 5013–5016; j) A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045–8052; k) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943–951.

[9] a) M. T. Reetz, T. Sell, *Tetrahedron Lett.* **2000**, *41*, 6333–6336; b) M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, *39*, 3889–3891; c) M. T. Reetz, G. Mehler, G. Meiswinkel, T. Sell, *Tetrahedron Lett.* **2002**, *43*, 7941–7943; d) M. T. Reetz, G. Mehler, G. Meiswinkel, T. Sell, *Angew. Chem. Int. Ed.* **2003**, *42*, 790–793; e) M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593–4596; f) M. T. Reetz, G. Mehler, A. Meiswinkel, *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167; g) M. T. Reetz, X. G. Li, *Tetrahedron* **2004**, *60*, 9709–9714; h) M. T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem. Int. Ed.* **2005**, *44*, 412–414.

[10] a) C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Commun.* **2000**, 961–962; b) A. Martorell, R. Naasz, B. L. Feringa, P. G. Pringle, *Tetrahedron: Asymmetry* **2001**, *12*, 2497–2499.

[11] A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2002**, *114*, 2454–2456.

[12] a) S. Gladiali, A. Dore, D. Fabbri, O. De Lucchi, M. Manassero, *Tetrahedron: Asymmetry* **1994**, *5*, 511–514; b) L. Charruault, V. Michelet, R. Taras, S. Gladiali, J.-P. Genet, *Chem. Commun.* **2004**, 850–851; c) G. Zanoni, S. Gladiali, A. Marchetti, P. Piccinini, I. Tredici, G. Vidari, *Angew. Chem. Int. Ed.* **2004**, *43*, 846–849.

[13] a) Y. Chi, X. Zhang, *Tetrahedron Lett.* **2002**, *43*, 4849–4852; b) W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem. Int. Ed.* **2003**, *42*, 3506–3509; c) Y. Chi, Y.-G. Zhou, X. Zhang, *J. Org. Chem.* **2003**, *68*, 4120–4122; d) D. Xiao, X. Zhang, *Angew. Chem. Int. Ed.* **2001**, *40*, 3425–3428; e) D. Xiao, Z. Zhang, X. Zhang, *Org. Lett.* **1999**, *1*, 1679–1681.

[14] a) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Tetrahedron Lett.* **2002**, *43*, 4977–4980; b) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *J. Organomet. Chem.* **2003**, *675*, 91–96; c) K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; d) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066–5069.

[15] a) G. Zanoni, S. Gladiali, A. Marchetti, P. Piccinini, I. Tredici, G. Vidari, *Angew. Chem.* **2004**, *116*, 864–867; b) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235; c) L. Charruault, V. Michelet, R. Tarras, S. Gladiali, J.-P. Genêt, *Chem. Commun.* **2004**, 850–851; d) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430–431.

[16] M. T. Reetz, G. Mehler, A. Meiswinkel, *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167.

[17] M. J. Burk, G. Casy, N. B. Johnson, *J. Org. Chem.* **1998**, *63*, 6084–6085.

[18] Institute of Automation (IAT), Richard Wagner Str. 31/ H. 8, 18119 Rostock-Warnemünde, Germany.

[19] X. Jia, X. Li, L. Xu, Q. Shi, X. Yao, A. S. C. Chan, *J. Org. Chem.* **2003**, *68*, 4539–4541.

[20] MonoPhos is commercially available by Strem.

[21] a) M. T. Reetz, X. Li, *Angew. Chem. Int. Ed.* **2005**, *44*, 2959–2962; b) M. T. Reetz, X. Li, *Angew. Chem. Int. Ed.* **2005**, *44*, 2962–2964.

[22] a) A. Duursma, R. Hoen, J. Schuppan, R. Hulst, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 3111–3113; b) A. Duursma, D. Peña, A. J. Minnaard, B. L. Feringa, *Tetrahedron: Asymmetry* **2005**, *16*, 1901–1904; c) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087–1089.

[23] a) C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries, L. Lefort, *Chem. Eur. J.* **2005**, *11*, 6701–6717; b) K. Ding, H. Du, Y. Yuan, J. Long, *Chem. Eur. J.* **2004**, *10*, 2872–2884.

Received: January 13, 2006
Published Online: April 26, 2006

5.2. Development of Practical Rhodium Phosphine Catalysts for the Hydrogenation of β–Dehydroamino Acid Derivates

Stephan Enthaler, Giulia Erre, Kathrin Junge, Jens Holz, Armin Börner, Elisabetta Alberico, Ilenia Nieddu, Serafino Gladiali*, and Matthias Beller*, *Org. Process Res. Dev.* **2007**, *11*, 568–577.

Contributions

Dr. Jens Holz carried out preliminary experiments with BINEPINE–ligands which are not stated in the article. Investigations with different metal precursors and defined complexes for instance catalysis with $[Rh(6a)_2(nbd)]SO_3CF_3$ and $[Rh(nbd)_2]BF_4$ were realized by the group of Prof. Gladiali. Furthermore, ligands (*R*)–**6a** and **6e** were synthesized by Dr. B. Hagemann.

Organic Process Research & Development **2007**, *11*, 568–577

Development of Practical Rhodium Phosphine Catalysts for the Hydrogenation of β-Dehydroamino Acid Derivatives

Stephan Enthaler,[†] Giulia Erre,[†] Kathrin Junge,[†] Jens Holz,[†] Armin Börner,[†,‡] Elisabetta Alberico,[§] Ilenia Nieddu,[∥] Serafino Gladiali,*[,∥] and Matthias Beller*[,†]

Leibniz Institut für Katalyse an der Universität Rostock e.V., Albert-Einstein Strasse 29a, 18059 Rostock, Germany, Institut für Chemie der Universität Rostock, Albert-Einstein Strasse 3a, 18059 Rostock, Germany, Istituto di Chimica Biomolecolare - CNR, trav. La Crucca 3, 07040 Sassari, Italy, and Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy

Abstract:

The rhodium-catalyzed asymmetric hydrogenation of various β-dehydroamino acid derivatives to give optically active β-amino acids has been examined. Chiral monodentate 4,5-dihydro-3*H*-dinaphthophosphepines, which are easily tuned and accessible in a multi-10-g scale, have been used as ligands. The enantioselectivity is largely dependent on the nature of the substituent at the phosphorous atom and on the structure of the substrate. Applying optimized conditions up to 94% ee was achieved.

Introduction

The discovery of new effective drugs is an important challenge for industrial and academic research. During the last decades an intense area of research in medicinal chemistry was the development of peptide-based therapeutics, mainly constructed by α-amino acids. More recently, significant attention was also directed to non-natural β-amino acids, which are interesting building blocks for the synthesis of biologically active compounds such as β-lactam antibiotics, the taxol derivatives, and β-peptides (Scheme 1).[1] In view of the growing demand of chiral β-amino acids, an increasing number of synthetic methods have been established for their preparation such as homologation of α-amino acids, conjugate addition of amines to carbonyl compounds, Mannich reaction, hydrogenation etc.[1c,2] Within these methodologies, asymmetric catalytic hydrogenation constitutes the most attractive and versatile technology as to industrial applications due to the remarkable improvements achieved in the past few years in the asymmetric hydrogenation of β-dehydroamino acid derivatives. Good-to-excellent enantioselectivities have been obtained in this reaction by applying rhodium- or ruthenium-catalysts with chiral diphosphines such as MeDuPhos, cat*AS*ium M, BINAP, BINAPO, BICP, TunaPhos, FerroTane, JosiPhos, DIOP, BPPM, P-Phos and others.[3]

A current trend in asymmetric catalysis is to switch from chiral bidentate to chiral monodentate phosphines because the latter are more easily accessible and tuneable than the bidentate counterparts.[4,5] Seminal contributions in this field have come from Feringa and de Vries et al.[6] (phosphoramidites), Reetz et al.[7] (phosphites), and Pringle and Claver et al.[8] (phosphonites). Furthermore, excellent enantioselectivities were reported by Zhou and co-workers applying monodentate spiro phosphoramidites (SIPHOS).[9,10]

Following the first report by Gladiali[11] and parallel to the work of Zhang,[12] we have focused in recent years on different monodentate phosphines based on a 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine framework (**5** and **6a**−**j**)

* To whom correspondence should be addressed. E-mail: matthias.beller@catalysis.de. Fax: 49 381 12815000. Telephone: 49 381 1281113.

[†] Leibniz Institut für Katalyse e.V an der Universität Rostock.

[‡] Institut für Chemie der Universität Rostock.

[§] Istituto di Chimica Biomolecolare - CNR.

[∥] Dipartimento di Chimica, Università di Sassari.

(1) (a) Guénard, D.; Guritte-Voegelein, R.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160−167. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (c) Juaristi, E.; Soloshonok, V. *Enantioselective Synthesis of β-amino acids*, 2nd ed.; Wiley-Interscience: New Jersey, 2005. (d) Lui, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (e) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355−361. (f) Ma, J. *Angew. Chem.* **2003**, *115*, 4426−4435. (g) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (h) Kubota, D.; Ishikawa, M.; Yamamoto, M.; Murakami, S.; Hachisu, M.; Katano, K.; Ajito, K., *Bioorg. Med. Chem.* **2006**, *7*, 2089−2108.

(2) (a) Gellman, S. H., *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022.

(3) (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5947−5952. (b) Achiwa, K.; Soga, T. *Tetrahedron Lett.* **1978**, *13*, 1119−1120. (c) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543−554. (d) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907−6910. (e) Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* **2001**, *66*, 6816−6817. (f) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701−1704. (g) Heller, D.; Drexler, H.-J.; You, J.; Baumann, W.; Drauz, K.; Krimmer, H.-P.; Börner, A. *Chem. Eur. J.* **2002**, *8*, 5196−5203. (h) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952−4953. (i) Yang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570−9571. (j) Komarov, I. V.; Monsees, A.; Spannenberg, A.; Baumann, W.; Schmidt, U.; Fischer, C.; Börner, A. *Eur. J. Org. Chem.* **2003**, 138−150. (k) You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem.* **2003**, *115*, 942−945. (l) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701−1707. (m) Wu, J.; Chen, X.; Guo, R.; Yeung, C.-h.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 2490−2493. (n) Henschke, J. P.; Burk, M. J.; Malan, C. G.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300−307. (o) Robinson, A. J.; Lim, C. Y.; He, L.; Ma, P.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4141−4147. (p) Robinson, A. J.; Stanislawski, P.; Mulholland, D.; He, L.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4148−4152. (q) Wu, H.-P.; Hoge, G. *Org. Lett.* **2004**, *6*, 3645−3647. (r) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D., III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918−9919. (s) Dai. Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343−5345. (t) Hansen, K. B.; Rosner, T.; Kubryk, M.; Dormer, P. G.; Armstrong, J. D., III. *Org. Lett.* **2005**, *7*, 4935−4938. (u) Drexler, H.-J.; Baumann, W.; Schmidt, T.; Zhang, S.; Sun, A.; Spannenberg, A.; Fischer, C.; Buschmann, H.; Heller, D. *Angew. Chem.* **2005**, *117*, 1208−1212. (v) Holz, J.; Zayas, O.; Jiao, H.; Baumann, W.; Spannenberg, A.; Monsees, A.; Riermeier, T. H.; Almena, J.; Kadyrov, R.; Börner, A. *Chem. Eur. J.* **2006**, *12*, 5001−5013.

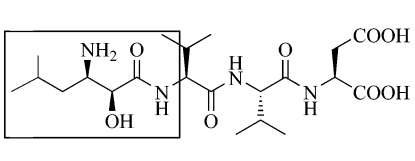
(4) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315−324.

(5) Komarov, I. V.; Börner, A. *Angew. Chem.* **2001**, *113*, 1237−1240.

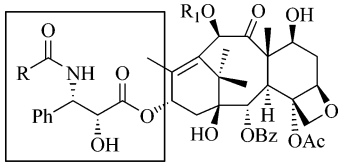
Published on Web 12/30/2006

10.1021/op0602270 CCC: $37.00

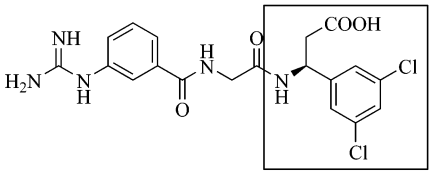
Scheme 1. **Selection of biologically active compounds containing β-amino acid units**



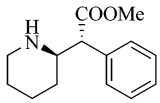
Amastatin (1)
Aminopeptidase A inhibitor



Taxol (2)
anti cancer drug



(3)
integrin antagonist



Methylphenidate (4)
anti attention-deficit disorder drug

(Scheme 3).[13] The first catalytic application of such a ligand (Ph-BINEPINE; **6a**) in the Rh-catalyzed asymmetric hydroformylation of styrene was reported by one of us (S.G.) in the early 1990s.[11a] In the following years, the Rostock group has expanded the structural diversity of the BINEPINE ligand family **6** into a library of ligands which has been screened with remarkable success (ee up to 95%) in the asymmetric hydrogenation with Rh- and Ru-catalysts of α-amino acid precursors, dimethyl itaconate, enamides and β-ketoesters.[13] In the meantime, the utility of Ph-BINEPINE **6a** has been demonstrated in a range of asymmetric reactions catalyzed by different transition metals such as the Pd-catalyzed umpoled-allylation of aldehydes and the Pt-catalyzed alkoxycyclization of 1,5-enynes. The ligand itself without any metal is an efficient chiral catalyst for the enantioselective acylation of diols, and for [3 + 2] cycloadditions and [4 + 2] annulations (Scheme 2).[11d,e,14] Quite recently excellent enantioselectivities have been scored in the Rh-catalyzed transfer hydrogenation of α-amino acid precursors and itaconic acid derivatives using formic acid as H-donor. Under these conditions β-dehydroamino acids derivatives have also been successfully hydrogenated, albeit in modest stereoselectivity.[11f]

Pursuing our ongoing research in hydrogenation chemistry, we report herein on the Rh-catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives. A multi-10-g scale synthesis of binaphthophosphepines is described, which allowed these ligands to be commercialized last year.[15]

(6) (a) Arnold, L. A.; Imobos, R.; Manoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. *Tetrahedron* **2000**, *56*, 2865−2878. (b) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc*. **2000**, *122*, 11539−11540. (c) Minnaard, A. J.; van den Berg, M.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. *Chim. Oggi* **2001**, *19*, 12−13. (d) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc*. **2002**, *124*, 14552−14553. (e) van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L.; *Adv. Synth. Catal*. **2002**, *344*, 1003−1007. (f) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal*. **2003**, *345*, 308−323. (g) Peña, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L.; *Org. Lett*. **2003**, *5*, 475−478. (h) Jiang, X.; van den Berg, M.; Minnaard, A. J.; Feringa, B.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223−2229. (i) Eelkema, R.; van Delden, R. A.; Feringa, B. L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5013−5016. (j) Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045−8052. (k) Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Org. Lett.* **2004**, *6*, 1733−1735. (l) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem*. **2005**, *70*, 943−951.

(7) (a) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333−6336. (b) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889−3891. (c) Reetz, M. T.; Mehler, G.; Meiswinkel, G.; Sell, T. *Tetrahedron Lett*. **2002**, *43*, 7941−7493. (d) Reetz, M. T.; Mehler, G.; Meiswinkel, G.; Sell, T. *Angew. Chem., Int. Ed*. **2003**, *42*, 790−793. (e) Reetz, M. T.; Mehler, G. *Tetrahedron Lett*. **2003**, *44*, 4593−4596. (f) Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2165−2167. (g) Reetz, M. T.; Li, X. G. *Tetrahedron* **2004**, *60*, 9709−9714. (h) Reetz, M. T.; Ma, J.-A.; Goddard, R. *Angew. Chem., Int. Ed*. **2005**, *44*, 412−414. (i) Reetz, M. T.; Fu, Y.; Meiswinkel, A. *Angew. Chem.* **2006**, *118*, 1440−1443.

(8) (a) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961−962. (b) Martorell, A.; Naasz, R.; Feringa, B. L.; Pringle, P. G. *Tetrahedron: Asymmetry* **2001**, *12*, 2497−2499.

(9) (a) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem.* **2002**, *114*, 2454−2456. (b) Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. *J. Org. Chem.* **2004**, *69*, 4648−4655. (c) Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2004**, *69*, 8157−8160.

(10) For other monodentate system see also: (a) Jerphagnon, T.; Renaud, L.-L.; Demonchauc, P.; Ferreira, A.; Bruneau, C. *Adv. Synth. Catal.* **2004**, *346*, 33−36. (b) Bilenko, V.; Spannenberg, A.; Baumann, W.; Komarov, I.; Börner, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2082−2087.

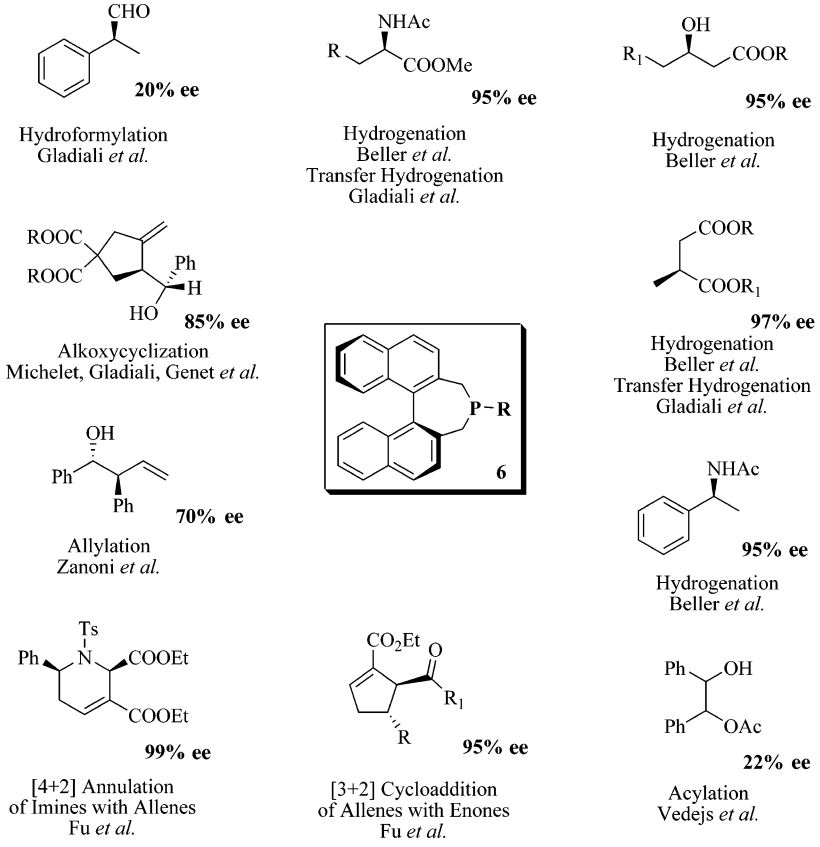
(11) (a) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Manassero, M. *Tetrahedron: Asymmmetry* **1994**, *5*, 511−514. (b) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Valle, G. *J. Org. Chem.* **1994**, *59*, 6363−6371. (c) Gladiali, S.; Frabbi, D. *Chem. Ber./ Rec. Trav. Chim. Pays Bas.* **1997**, *130*, 543−554. (d) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850−851. (e) Zanoni, G.; Gladiali, S.; Marchetti, A.; Piccinini, P.; Tredici, I.; Vidari, G. *Angew. Chem., Int. Ed*. **2004**, *43*, 846−849. (f) Alberico, E.; Nieddu, I.; Taras, R.; Gladiali, S. *Helv. Chim. Acta* **2006**, *89*, 1716−1729.

(12) (a) Chi, Y.; Zhang, X. *Tetrahedron Lett*. **2002**, *43*, 4849−4852. (b) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed*. **2003**, *42*, 3506−3509. (c) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120−4122. (d) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed*. **2001**, *40*, 3425−3428. (e) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679−1681.

(13) (a) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett*. **2002**, *43*, 4977−4980. (b) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *J. Organomet. Chem.* **2003**, *675*, 91−96. (c) Junge, K.; Hagemann, B.; Enthaler, S.; Spannenberg, A.; Michalik, M.; Oehme, G.; Monsees, A.; Riermeier, T.; Beller, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2621−2631. (d) Junge, K.; Hagemann, B.; Enthaler, S.; Oehme, G.; Michalik, M.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Angew. Chem.* **2004**, *116*, 5176−5179; *Angew. Chem., Int. Ed.* **2004**, *43*, 5066−5069. (e) Hagemann, B.; Junge, K.; Enthaler, S.; Michalik, M.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal*. **2005**, *347*, 1978−1986. (f) Enthaler, S.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *Eur. J. Org. Chem.* **2006**, 2912−2917.

(14) (a) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234−12235. (b) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431. (c) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426−1429.

Scheme 2. **Applications of ligand class 6 in asymmetric synthesis**



Results and Discussion

The synthesis of binaphthophosphepines starts with diesterification of enantiomerically pure 2,2′-binaphthol[16] (98% ee) with trifluoromethanesulfonic acid anhydride in the presence of pyridine (Scheme 3). The corresponding diester was obtained in 99% yield, and subsequent nickel-catalyzed Kumada coupling with methyl magnesium bromide led to 2,2′-dimethylbinaphthyl in 95% yield.[13,17] Two different synthetic strategies were established to obtain 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands **6**. On the one hand, double metalation of 2,2′-dimethylbinaphthyl with *n*-butyl lithium in the presence of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) followed by quenching with commercially available dichlorophosphines gives ligands **6a** (P-phenyl) and **6i** (P-*tert*-butyl) in 60−83% yield. Both ligands have been synthesized on >10-g scale. In the second procedure the dilithiated dimethyl binaphthalene is quenched with diethylaminodichlorophosphine, giving the phosphepine **5** which, upon treatment with gaseous HCl, is converted into 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine in 80% yield. This enantiomerically pure chlorophosphine is easily coupled with various Grignard or lithium reagents to give a broad selection of ligand **6**. The limited number of commercially available dichlorophosphines and the large diversity of Grignard compounds make the access through 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]-phosphepine the route of choice to a library of ligands **6**.

The syntheses of β-acetamido acrylates **7**−**11** and **14** were carried out according to literature protocols by reaction of the corresponding β-ketoester with NH_4OAc followed by acylation of the β-amino acrylate intermediate.[3c,d] *E*/*Z*-Isomers were separated by crystallization and column chromatography. Ethyl 3-acetamido-3-phenyl-2-propenoate (**12**) and methyl 3-benzamido butenoate (**13**) were synthesized by reaction of the corresponding β-amino acrylate with acyl chloride or benzoyl chloride.[3l]

To compare the behaviour of the *Z*- and *E*-isomers, initial catalytic runs were carried out separately on the (*Z*)- and (*E*)-methyl 3-acetamido butenoates (*Z*-**7** and *E*-**7,** respectively) as substrates and 4-phenyl-4,5-dihydro-3*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]phosphepine (**6a**) as our standard ligand.[13] Typically, we used an in situ precatalytic mixture of 1 mol % $[Rh(cod)_2]BF_4$ and 2.1 mol % of the corresponding ligand. All hydrogenation reactions were carried out in an 8-fold parallel reactor array with a reactor volume of 3.0 mL.[18]

We first focused our attention on the influence of the solvent and the hydrogen pressure. The first set of reactions was run at constant concentration in toluene, dichloromethane, methanol, ethanol,[19] and 2-propanol at three

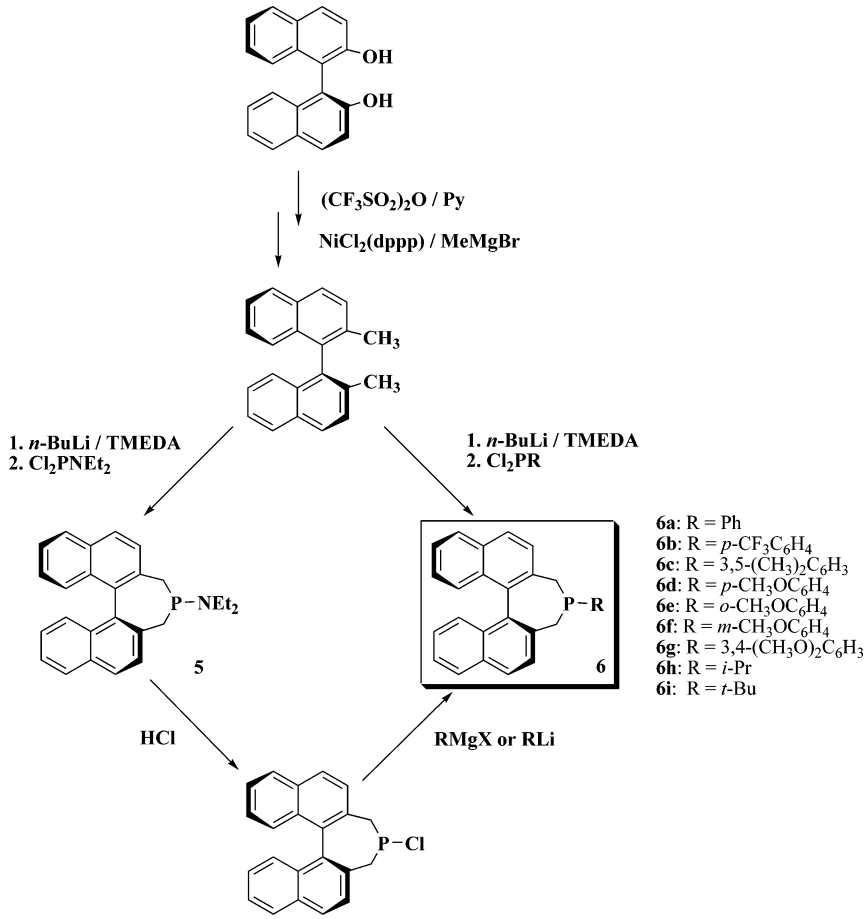
(15) The ligands Ph-BINEPINE (**6a**) and *t*-Bu-BINEPINE (**6i**) are commercially available by Degussa DHC (Degussa Homogeneous Catalysis, Rodenbacher Chaussee 4, building 097, 63457 Haunau (Wolfgang), Germany, (www.creavis.com/site_dhc/de/default.cfm)) with the product names cat*A*Sium KPh (**6a**) and cat*A*Sium KtB (**6i**).

(16) Optically pure 2,2′-binaphthol is available on large scale from RCA (Reuter Chemische Apparatebau KG), Engesserstr. 4, 79108 Freiburg, Germany.

(17) The synthesis of 2,2′-bistriflate-1,1′-binaphthyl (1.2 mol, 615 g, 92%) and 2,2′-dimethyl-1,1′-binaphthyl (0.74 mol, 201 g, 96%) was carried out in large scale by the group of Zhang (See ref 11b).

(18) Institute of Automation (IAT), Richard Wagner Str. 31/ H. 8, 18119 Rostock-Warnemünde, Germany.

Scheme 3. **Synthetic approach to 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands 6**



different pressures (2.5, 10.0, and 50.0 bar). Selected results are presented in Figure 1.

In the case of hydrogenation of *E*-**7** the best enantioselectivity was consistently achieved at the lowest pressure (2.5 bar) and ranged between 42−79% ee, depending on the solvent. After 24 h the reaction was complete only in 2-propanol, whereas lower conversions were observed in ethanol, methanol, and toluene.[20] No reaction at all took place in dichloromethane. The stereoselectivity decreased upon increasing the pressure of hydrogen to 10.0 bar or 50.0 bar. From these results 2-propanol and 2.5 bar were selected as solvent and pressure of choice, respectively, for the hydrogenation of the *E*-isomer (conversion: >99%; enantioselectivity: 79%). The hydrogenation of *Z*-**7** resulted in higher enantioselectivities in all the solvents (up to 92% ee). Notably, compared to *E*-**7** the configuration of the prevailing enantiomer was always opposite. Furthermore, in ethanol and in methanol the enantioselectivity/pressure trend was reversed, the top value (92% ee) having been reached at the highest pressure (50.0 bar) compared to 86% ee at 2.5 bar. Full conversions were obtained in all the experiments, except in toluene (37%) and in dichloromethane (45%). These results indicated ethanol and methanol as the best solvents and 50.0 bar as the pressure of choice for the hydrogenation of the *Z*-isomer (conversion: >99%; enantioselectivity: 92%).

No incorporation of deuterium in the product was noticed upon running the reaction in methanol-d_4. This is in line with the absence in the reduction process of any interference of transfer hydrogenation as well as of protonolysis of the Rh−C bond of an alkyl rhodium intermediate.[21] Two facets deserving mention are (1) the *Z*-isomer gives higher ee's than the *E*-isomer, whereas in most cases the opposite behaviour has been reported[3] and (2) the configuration switches depending on the different geometry of the double bond, which has been scarcely reported.[3c,22]

Next, we investigated the influence of temperature on enantioselectivity and conversion as shown in Figure 2.[23] Applying our model ligand **6a** we found a pronounced negative effect on the enantioselectivity at higher temperatures for both isomers. Interestingly, the loss of enantioselectivity for the hydrogenation of *E*-**7** is higher than for *Z*-**7** (10 °C: *E*-**7** 79% ee (*R*) and *Z*-**7** 88% ee (*S*); 90 °C: *E*-**7** *rac* and *Z*-**7** 60% ee (*S*)).

(19) The hydrogenation performed in ethanol and 2-propanol led exclusively to product **7**. No transesterification was observed.

(20) In the case of toluene we assume an inhibition of the catalyst by the solvent, due to the formation of catalytical inactive rhodium−arene complexes. Heller, D.; Drexler, H.-J.; Spannenberg, A.; Heller, B.; You, J.; Baumann, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 777−780.

(21) Tsukamoto, M.; Yoshimura, M.; Tsuda, K.; Kitamura, M. *Tetrahedron* **2006**, *62*, 5448−5453.

(22) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419−422.

(23) Jerphagnon, T.; Renaud, J.-L.; Demonchaux, P.; Ferreira, A.; Bruneau, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1973−1977.

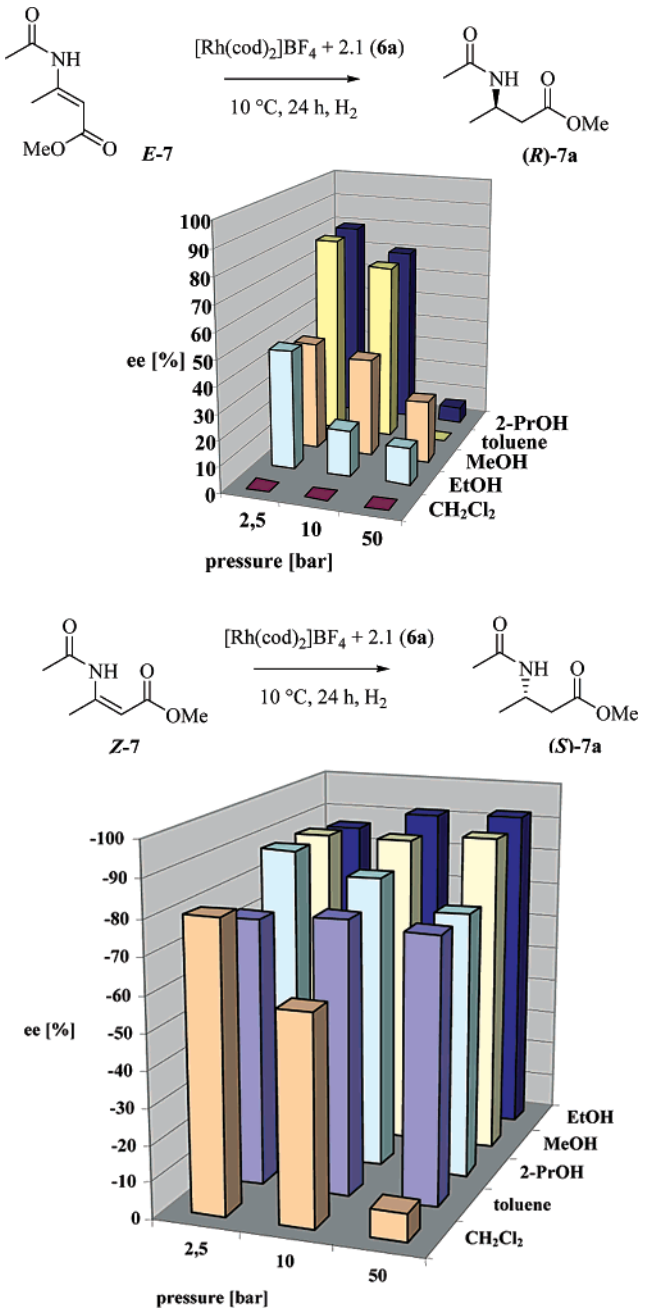


Figure 1. **Solvent and pressure variation. Reactions were carried out at 10 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of solvent. Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min). The absolute configuration was determined by comparison with reported data.[3l]**

For estimating the feasible enantioselectivity at lower temperature we analysed the corresponding Eyring plot[24] for both isomers. As a consequence we considered 10 °C as temperature of choice, because of good enantioselectivity and also acceptable reaction times.

The original protocol used for the synthesis of methyl 3-acetamido butenoate (**7**) gives a mixture of *E*- and *Z*-isomers whose composition depends on the reaction conditions.[1f] Although separation of the isomers by fractional

(24) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem.* **1991**, *103*, 480−518.

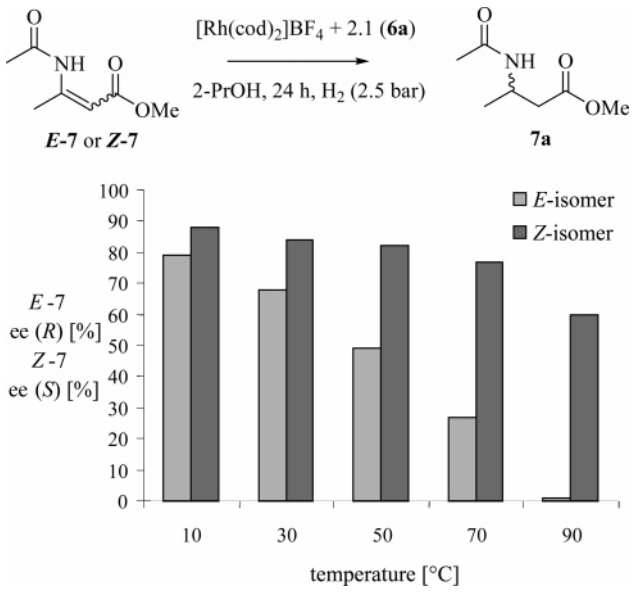


Figure 2. **Dependency of enantioselectivity versus temperature. Reactions were carried out at corresponding temperature for 1−24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of 2-propanol. Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

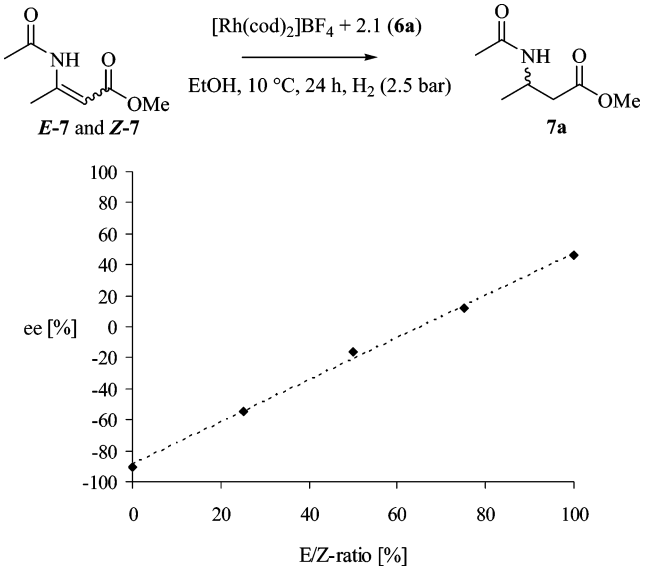


Figure 3. **Dependency of enantioselectivity versus *E*/*Z* ratio. Reactions were carried out at 10 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of ethanol. Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

crystallization is feasible, the selective hydrogenation of the mixture is clearly advantageous. This prompted us to explore the hydrogenation of different *E*/*Z* ratios including the mixture obtained from the synthesis (Figure 3). The results showed a linear decrease of enantioselectivity for all mixtures and demostrated that the hydrogenation of the single isomers led to highest enantioselectivity.

Recently, Heller and Börner have reported kinetics and mechanistic investigations for the hydrogenation of *E*-**7** and *Z*-**7** through the use of bidentate phosphine ligands. The mentioned results modified the existent declaration that the

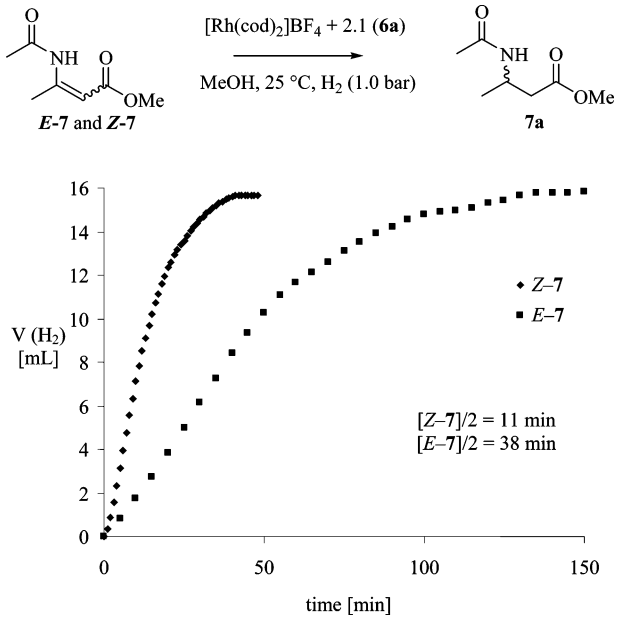


Figure 4. **Dependency of hydrogen consumption versus reaction time. Reactions were carried out under isobaric conditions (1.0 bar) at 25 °C. [Rh(cod)$_2$]BF$_4$ (0.0072 mmol) and 0.015 mmol ligand 6a were stirred for 10 min under hydrogen atmosphere in 10.0 mL of methanol. Afterwards the substrate (0.72 mmol) was added in 1.0 mL of methanol. The conversions and ee's were determined by GC (50 m Chiraldex *β*-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

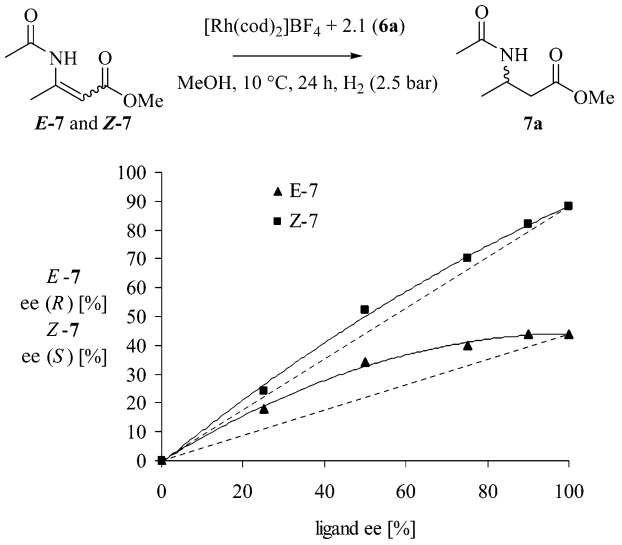


Figure 5. **Dependency of the optical purity of ligand 6a on product selectivity. Reactions were carried out at 10 °C for 24 h with 0.0024 mmol [Rh(cod)$_2$]BF$_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of methanol. Conversions and ee's were determined by GC (50 m Chiraldex *β*-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

reaction rate for hydrogenation of *E*-isomers is higher than that for the *Z*-isomers, because in some cases the opposite behaviour was observed.[3g]

To classify ligand **6a** we recorded the hydrogen uptake in relation to the reaction time for the asymmetric hydrogenation of *E*-**7** and *Z*-**7** with our catalyst in isobaric conditions and under normal pressure of hydrogen (Figure 4).

To minimize the interfering effect of cyclooctadiene (cod), the precatalyst was stirred for 10 min under hydrogen atmosphere before adding the substrate *E*-**7** or *Z*-**7**. We were surprised to see that, unlike the case of most bidentate ligands, in our case at 50% conversion it was the *Z*-isomer which was hydrogenated faster (about 3.5 times the *E*-isomer).

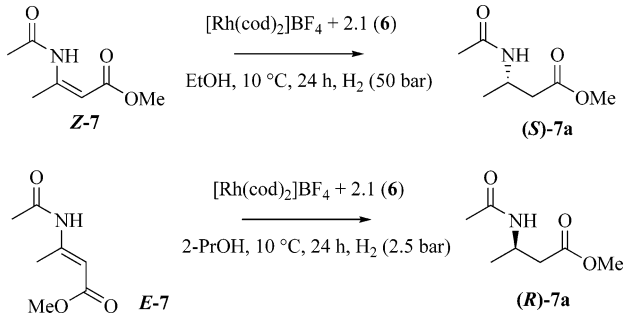
For gaining an insight into the structure of the catalyst, the hydrogenation of *Z*-**7** was perfomed using the preformed complex [Rh(**6a**)$_2$(nbd)]$^+$CF$_3$SO$_3^-$ as the catalyst. This cationic complex was prepared as previously reported by us,[11f] and the reaction was run in MeOH at 5 bar at 25 °C. Under these conditions, *Z*-**7** was completely hydrogenated in 12 h to give the (*S*)-enantiomer in 92% ee. This result is quite close to the one obtained with the catalysts prepared in situ by adding 2 equiv of the ligand **6a** either to [Rh(nbd)$_2$]$^+$BF$_4^-$ (89% ee) or to [Rh(cod)$_2$]$^+$BF$_4^-$ (88% ee). From this it follows that the catalytically active species most likely contain two monodentate P-ligands per Rh center and that the ancillary diolefin ligand has a negligible effect, if any, on the stereoselectivity, while the anion may exert some influence. Further support to the presence of two ligands around the metal comes from the search of nonlinear effect (NLE) in the model reaction.[25] A set of hydrogenations was performed on both the isomers using various samples of ligand **6a** of different enantiomeric purity, and the ee's observed have been plotted against the enantiomeric purity of the ligand (Figure 5). For both *Z*-**7** and *E*-**7** a positive nonlinear effect, which implies the bonding of at least two ligands to the rhodium, is clearly apparent. Similar results were reported by Reetz,[7i] Zhou,[9b] and Feringa[6f] for the asymmetric hydrogenation of itaconic esters or α-amino acid derivatives by the use of different monodentate P-donor ligands. To verify the positive nonlinear effect we decreased the amount of ligand to 1 equiv with respect to rhodium. Here, we observed a diminished reaction rate compared to the rate of hydrogenation with 2 equiv of ligand. In addition, the amount of ligand was increased to 4 equiv with respect to rhodium, but also in this case a reduced reaction rate was monitored.

In previous studies we have shown the pronounced effect that the substitution pattern at the P-centre of BINEPINE ligands has on the stereoselectivity of the asymmetric process.[13] In order to evaluate this substituent effect the asymmetric hydrogenation of *E*-**7** and *Z*-**7** was performed in the optimized conditions previously devised with nine different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines (**6a**−**6i**) (*E*−**7**: 2.5 bar hydrogen pressure, 2-propanol, 10 °C, 24 h; *Z*-**7**: 50.0 bar, ethanol, 10 °C, 24 h) (Table 1).

In the hydrogenation of *E*-**7** the best enantioselectivities up to 90, 88, and 87% ee, respectively, were achieved with ligands **6g**, **6d**, and much to our surprise, with **6i** (Table 1, entries 7, 4, and 9). The last one has always given quite poor results in the other benchmark tests where it has been screened. The presence of electron-donating groups on the P-aryl substituent has a positive effect on the stereoselectivity (Table 1, entries 4, 6, and 7), whereas the opposite occurs for electron-withdrawing groups (Table 1, entry 2). This trend

(25) (a) Girard, C.; Kagan, H. B.; *Angew. Chem.* **1998**, *110*, 3088−3127. (b) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804−805.

Table 1. **Hydrogenation of *E*-7 and *Z*-7 with different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines (6a−6i)**



entry	ligand	isomer[a]	conv. [%][b]	ee [%][b]	isomer[c]	conv. [%][b]	ee [%][b]
1	**6a**	*E*	>99	79 (*R*)	*Z*	>99	**92 (*S*)**
2	**6b**	*E*	91	40 (*R*)	*Z*	>99	32 (*S*)
3	**6c**	*E*	80	69 (*R*)	*Z*	>99	80 (*S*)
4	**6d**	*E*	>99	**88 (*R*)**	*Z*	>99	86 (*S*)
5	**6e**	*E*	>99	20 (*R*)	*Z*	>99	*rac*
6	**6f**	*E*	91	81 (*R*)	*Z*	90	40 (*S*)
7	**6g**	*E*	>99	**90 (*R*)**	*Z*	>99	**89 (*S*)**
8	**6h**	*E*	>99	76 (*R*)	*Z*	5	38 (*S*)
9	**6i**	*E*	>99	**87 (*R*)**	*Z*	3	60 (*S*)

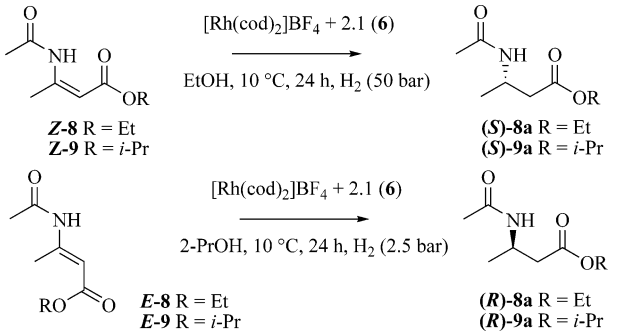
[a] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [b] Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-**7a** 15.1 min, (*R*)-**7a** 16.4 min). The absolute configuration was determined by comparing with reported data.[3l] [c] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL).

is similar to the one observed in the hydrogenation of *Z*-**7** although in that case the best ee was scored with the plain phenyl ligand **6a**. Alkyl-substituted phosphepines **6h** and **6i** produced catalysts of negligible activity in hydrogenation of this substrate (Table 1, entries 8 and 9).

To explore scope and limitation of our ligand toolbox, the asymmetric hydrogenation of a range of β-dehydroamino acids derivatives was performed under optimized conditions (Table 2). First the influence of the ester-group on the hydrogenation of both *Z*- and *E*-isomers was investigated in detail. For *E*-**7** changing from methyl to isopropyl ester resulted consistently in a slight decrease of stereoselectivity, whereas in the case of the *Z*-isomer no reliable correlation between ester functionality and enantioselectivity was detected. Notably, a diminished yield for all hydrogenations of *Z*-**9** was attained (Table 2).

Finally, the influence of β^3- and β^2-substitution was investigated on a set of seven different substrates (Scheme 4 and Table 3). While substitution of a methyl with an ethyl group has negligible effects, an increase in the branching of the alkyl group resulted in an improved selectivity with ligands **6g** and **6i**. Furthermore, we also carried out a substitution in the β^3-position by an aromatic group (compound *Z*-**12**). As a tendency, depletion of conversion and enantioselectivity was observed in comparison to *Z*-**8** (Table 1, entries 1−7 and Table 2, entries 15−21). A similar negative effect was found after substitution of the acyl protecting group by benzoyl and subjecting *Z*-**13** in the hydrogenation reaction (Table 3, entries 15−21).

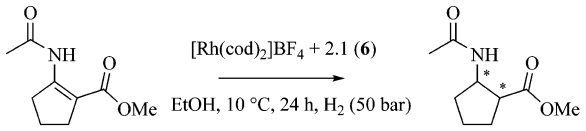
Table 2. **Influence of ester group on conversion and enantioselectivity**



entry	ligand	isomer[a]	conv. [%][b]	ee [%][b]	isomer[c]	conv. [%][b]	ee [%][b]
1	**6a**	*E*-**8**	98	83 (*R*)	*Z*-**8**	>99	**94 (*S*)**
2	**6b**	*E*-**8**	79	46 (*R*)	*Z*-**8**	>99	*rac*
3	**6c**	*E*-**8**	65	20 (*R*)	*Z*-**8**	>99	36 (*S*)
4	**6d**	*E*-**8**	98	84 (*R*)	*Z*-**8**	>99	83 (*S*)
5	**6g**	*E*-**8**	97	**84 (*R*)**	*Z*-**8**	>99	85 (*S*)
6	**6h**	*E*-**8**	>99	66 (*R*)	*Z*-**8**	>99	*rac*
7	**6i**	*E*-**8**	>99	80 (*R*)	*Z*-**8**	>99	*rac*
8	**6a**	*E*-**9**	>99	70 (*R*)	*Z*-**9**	52	78 (*S*)
9	**6b**	*E*-**9**	63	40 (*R*)	*Z*-**9**	23	46 (*S*)
10	**6c**	*E*-**9**	73	20 (*R*)	*Z*-**9**	61	24 (*S*)
11	**6d**	*E*-**9**	>99	**76 (*R*)**	*Z*-**9**	69	**91 (*S*)**
12	**6g**	*E*-**9**	92	72 (*R*)	*Z*-**9**	55	73 (*S*)
13	**6h**	*E*-**9**	>99	66 (*R*)	*Z*-**9**	34	*rac*
14	**6i**	*E*-**9**	>99	**76 (*R*)**	*Z*-**9**	32	6 (*S*)

[a] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [b] Conversions and ee's were determined by GC (**8** (25 m Lipodex E, 70/40-8-180, (*R*)-**8a** 33.2 min, (*S*)-**8a** 33.4 min), **9** (25 m Lipodex E, 70/25-10-180, (*R*)-**9a** 33.2 min, (*S*)-**9a** 33.4 min). The absolute configurations were determined by comparing the sign of specific rotation with reported data.[3d] [c] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL).

Scheme 4. **Asymmetric hydrogenation of methyl 2-acetamidocylopent-1-enecarboxylate (14)[a]**



6a: conv. 96%; >99% de; 76% ee
6b: conv. 52%; >99% de; 66% ee

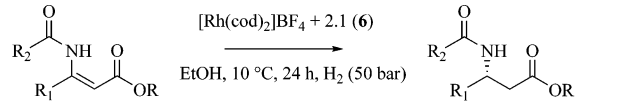
[a] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL). Conversion, de's and ee's were determined by GC (25 m Chirasil Val, 120 °C, **14a1** 26.8 min, **14a2** 27.6 min, **14a3** 52.1 min, **14a4** 53.0 min).

As an example for tetra-substituted β-dehydroamino acid precursor (β^3- and β^2-substitution) we tested methyl2-acetamidocyclopent-1-enecarboxylate (**14**)[26] under optimized conditions for *Z*-isomers (Scheme 4). In the majority of cases excellent diastereoselectivities up to >99% de were achieved, accompanied by good to moderate conversions. Best enantioselectivities up to 76% ee were obtained by utilizing ligands **6a** and **6b** (Scheme 4).

An additional possibility offered by monodentate ligands from which one can profit in asymmetric catalysis is the possibility to introduce in the coordination sphere of the

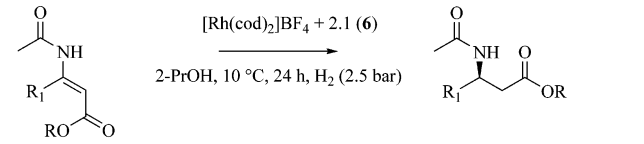
(26) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570−9571.

Table 3. **Influence of β^3-substitution on conversion and enantioselectivity**



***Z*-10** R = Me; R_1 = Et; R_2 = Me
***Z*-11** R = Me; R_1 = *i*-Pr; R_2 = Me
***Z*-12** R = Et; R_1 = Ph; R_2 = Me
***Z*-13** R = Me; R_1 = Me; R_2 = Ph

(*S*)-10a R = Me; R_1 = Et; R_2 = Me
(*S*)-11a R = Me; R_1 = *i*-Pr; R_2 = Me
(*S*)-12a R = Et; R_1 = Ph; R_2 = Me
(+/-)-13a R = Me; R_1 = Me; R_2 = Ph



***E*-10** R = Me; R_1 = Et
***E*-11** R = Me; R_1 = *i*-Pr

(*R*)-10a R = Me; R_1 = Et
(*R*)-11a R = Me; R_1 = *i*-Pr

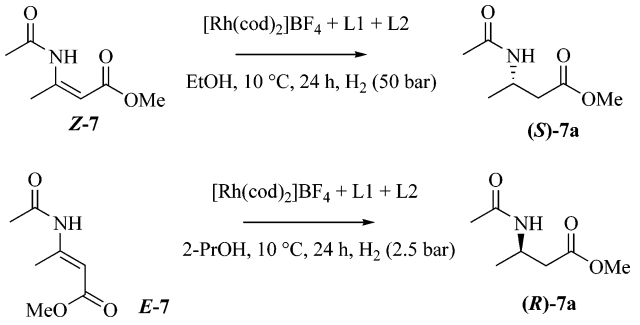
entry	ligand	isomer[a]	conv. [%][b]	ee [%][b]	isomer[c]	conv. [%][b]	ee [%][b]
1	**6a**	*E*-**10**	>99	78 (*R*)	*Z*-**10**	98	86 (*S*)
2	**6b**	*E*-**10**	91	44 (*R*)	*Z*-**10**	96	58 (*S*)
3	**6c**	*E*-**10**	95	60 (*R*)	*Z*-**10**	>99	20 (*S*)
4	**6d**	*E*-**10**	>99	78 (*R*)	*Z*-**10**	97	50 (*S*)
5	**6g**	*E*-**10**	>99	75 (*R*)	*Z*-**10**	93	48 (*S*)
6	**6h**	*E*-**10**	>99	72 (*R*)	*Z*-**10**	97	rac
7	**6i**	*E*-**10**	>99	**84 (*R*)**	*Z*-**10**	47	24 (*R*)
8	**6a**	*E*-**11**	>99	26 (*R*)	*Z*-**11**	>99	78 (*S*)
9	**6b**	*E*-**11**	39	42 (*R*)	*Z*-**11**	99	68 (*S*)
10	**6c**	*E*-**11**	88	70 (*R*)	*Z*-**11**	99	28 (*S*)
11	**6d**	*E*-**11**	50	60 (*R*)	*Z*-**11**	94	26 (*S*)
12	**6g**	*E*-**11**	>99	88 (*R*)	*Z*-**11**	94	68 (*S*)
13	**6h**	*E*-**11**	98	34 (*R*)	*Z*-**11**	67	rac
14	**6i**	*E*-**11**	>99	**90 (*R*)**	*Z*-**11**	10	58 (*R*)
15	**6a**	*Z*-**12**	99	**70 (*R*)**	*Z*-**13**	19	70 (−)
16	**6b**	*Z*-**12**	46	26 (*R*)	*Z*-**13**	9	4 (−)
17	**6c**	*Z*-**12**	90	47 (*R*)	*Z*-**13**	7	46 (+)
18	**6d**	*Z*-**12**	95	52 (*R*)	*Z*-**13**	<1	n.d.
19	**6g**	*Z*-**12**	91	38 (*R*)	*Z*-**13**	11	48 (−)
20	**6h**	*Z*-**12**	25	54 (*R*)	*Z*-**13**	<1	n.d.
21	**6i**	*Z*-**12**	33	36 (*R*)	*Z*-**13**	10	40 (−)

[a] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [b] Conversion was determined by GC or ^{1}H NMR. The enantiomeric excess was determined by GC or HPLC (**10** (25 m Lipodex E, 120/30, (*R*)-**10a** 31.8 min, (*S*)-**10a** 32.2 min), **11** (25 m Lipodex E, 130/20, (*R*)-**11a** 33.2 min, (*S*)-**11a** 33.4 min), **12** (OD−H, *n*-hexane/ethanol 98:2, 1.3 mL/min, (*S*)-**12a** 27.8 min, (*R*)-**12a** 36.8 min), **13** (Chiralcel OB−H, *n*-hexane/2-propanol 90:10, 1.0 mL/min, (+)-**13a** 15.9 min, (−)-**13a** 18.8 min)). The absolute configuration was determined by comparing with reported data or by reported sign of specific rotation.[3d,l] [c] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL).

metal two different ligands and to play the game of matching−mismatching combinations of chiral elements. This opens the way to a combinatorial approach as developed by Reetz et al.[7d−f,27] and Feringa et al.[28] for different transition metal-catalyzed reactions.[29]

To foster this possibility, we have selected **6a** and **6i** as the pivotal ligands for the hydrogenation of *Z*-**7** and *E*-**7**, respectively, in combination with achiral phosphines and phosphites. The catalysts were prepared in situ using a ratio

Table 4. **Application of ligand mixtures in the asymmetric hydrogenation of *Z*-7 and *E*-7**



entry	L1	L2	isomer	conv. [%][c]	ee [%][c]
1	**6a**	**6a**	*Z*[a]	>99	92 (*S*)
2	**6a**	PPh_3	*Z*[a]	>99	76 (*S*)
3	**6a**	PCy_3	*Z*[a]	>99	78 (*S*)
4	**6i**	**6i**	*E*[b]	>99	87 (*R*)
5	**6i**	PPh_3	*E*[b]	>99	34 (*R*)
6	**6i**	PCy_3	*E*[b]	>99	88 (*R*)
7	**6i**	**15**[d]	*E*[b]	21	12 (*R*)

[a] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL). [b] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [c] Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-**7a** 15.1 min, (*R*)-**7a** 16.4 min). The absolute configuration was determined by comparing with reported data.[3l] [d] **15** = tris(2,4-di-*tert*-butylphenyl)phosphite.

of 1.05 to 1.05 equiv of the two ligands with respect to 1.0 equiv of $[Rh(cod)_2]BF_4$, and the reactions were carried out under the optimized conditions defined above. As a general trend, the heterocombination of monodentate ligands was always less stereoselective compared to the homocombination of the pivotal ligands (Table 4). There was just one notable exception for the system **6i**/tricyclohexylphosphine (Table 4, entry 6) which gave the same ee as obtained when **6i** was used alone. Even if these results do not permit to draw any substantial conclusion, we may infer that in these conditions the catalytic activity of the different complexes which are formed in solution lies in the same range and that they compete for the substrate.

Summary

In conclusion, we have shown that monodentate chiral 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands can be synthesized on multi-10-g scale from 2,2′-binaphthol. They can be tuned easily by variation of the substituent at the P-atom. This class of ligands can be used for various rhodium- and ruthenium-catalyzed hydrogenations. For the first time their application towards the synthesis of β-amino acid derivatives is shown, and enantioselectivities up to 94% ee were achieved.

Experimental Section

All manipulations were performed under argon atmosphere using standard Schlenk techniques. Toluene, *n*-hexane, and diethyl ether were distilled from sodium benzophenone ketyl under argon. Methanol was distilled from magnesium under argon. Ethanol and 2-propanol were

(27) (a) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959−2962. (b) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2962−2964.
(28) (a) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111−3113. (b) Duursma, A.; Peña, D.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **2005**, *16*, 1901−1904. (c) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087−1089.
(29) (a) Monti, C.; Gennari, C.; Piarulli, U.; de Vries, J. G.; de Vries, A. H. M.; Lefort, L. *Chem. Eur. J.* **2005**, *11*, 6701−6717. (b) Ding, K.; Du, H.; Yuan, Y.; Long, J. *Chem. Eur. J.* **2004**, *10*, 2872−2884.

distilled from sodium under argon. Methylene chloride was distilled from CaH_2 under argon. Ligands **6** were synthesized according to our previously published protocols.[13] $[Rh(cod)_2]$-BF_4 (purchased from Fluka) was used without further purification. The synthesis of (*S*)-2,2′-dimethyl-1,1′-binaphthyl in a 200-g scale has been described in the literature.[12b]

Synthesis of 4-Phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (6a) and 4-*tert*-Butyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (6i) on 10-g Scale. *Synthesis of the Dilithio Species.* A solution of *n*-BuLi (0.19 mol, 120 mL, 1.6 M in *n*-hexane) was concentrated under vacuum and the residual oil dissolved in diethyl ether (60 mL). After cooling the mixture to 0 °C a solution of (*S*)-2,2′-dimethyl-1,1′-binaphthyl (74.5 mmol, 21 g) in diethyl ether (140 mL) was added over a dropping funnel during 20 min to give a red solution. Afterwards TMEDA (192 mmol, 28.6 mL, distilled over CaH_2) was added slowly, and the resulting solution was kept for 24 h at room temperature, yielding deep red crystals. The supernatant solution was decanted via a tube. The crystals were washed two times with dry *n*-hexane (30 mL, removed by a tube) and dried under vacuum to give 60−80% yield (24.6−37.8 g).

*Synthesis of the 4-Phenyl-4,5-dihydro-3H-dinaphtho[2,1-c;1′,2′-e]phosphepine (**6a**).* Starting with the dilithium salt of (*S*)-2,2′-dimethyl-1,1′-binaphthyl (24.5 g, 44.4 mmol) in *n*-hexane (130 mL) a solution of phenyl dichlorophosphine (6.8 mL, 50.3 mmol) in *n*-hexane (55 mL) was added at 0 °C. After 2 h refluxing, the reaction mixture was quenched with water/toluene. The organic layer was separated and dried over $MgSO_4$. The ligand **6a** was purified by column chromatography in dry toluene and gave light-yellow foam (12.9 g; 75%).

*Synthesis of the 4-tert-Butyl-4,5-dihydro-3H-dinaphtho-[2,1-c;1′,2′-e]phosphepine (**6i**).* Starting with the dilithium salt of (*S*)-2,2′-dimethyl-1,1′-binaphthyl (24.5 g, 44.4 mmol) in *n*-hexane (130 mL) a solution of *tert*-butyl dichlorophosphine (8 g, 50.3 mmol) in *n*-hexane (55 mL) was added at 0 °C. After 3 h refluxing, the reaction mixture was quenched with water/toluene. The organic layer was separated and dried over $MgSO_4$. The ligand **6i** was purified by crystallization from toluene (13.2 g; 81%).

General Synthesis of β-Dehydroamino Acid Derivatives 7−11 and 14.[3c] To a solution of NH_4OAc (0.36 mol) in methanol, ethanol, or 2-propanol (depending on the ester-functionality (100 mL)) was added the corresponding β-ketoester (0.07 mol). After stirring for 60 h at room temperature the solvent was removed, and a mixture of $CHCl_3$ and water was added. The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, yielding the corresponding 3-amino-2-alkenoate. The 3-amino-2-alkenoate (0.07 mol), pyridine (0.13 mol), and acetic anhydride (0.32 mol) were dissolved in THF (50 mL) and stirred for 12 h at 70 °C (procedure A) or 95 °C (procedure B). The solution was reduced to half of the volume and ethylacetate was added. After washing with water, HCl, $NaHCO_3$, brine and drying over Na_2SO_4, the solvent was removed.

Procedure A (E-Isomer Enriched Residue). Dissolving the residue in ethylacetate/*n*-hexane (1:1) and storing the solution overnight at −20 °C yielded the *E*-isomers of β-dehydroamino acid derivatives **7**−**11**, which were recrystallized three times from ethylacetate/*n*-hexane (1:1) to give colorless crystals [yield of the main fraction referred to β-ketoester: *E*-**7**: 1.4 g (11%), *E*-**8**: 1.2 g (10%), *E*-**9**: 1.5 g (11%), *E*-**10**: 1.4 g (12%), *E*-**11**: 1.8 g (14%)].

Procedure B (Z-isomer Enriched Residue). The pure *Z*-isomer was obtained by column chromatography (eluent: ethylacetate/*n*-hexane, 1:1 or 1:2) [yield referred to β-ketoester: *Z*-**7**: 4.3 g (39%), *Z*-**8**: 1.2 g (35%) (0.035 mmol β-ketoester), *Z*-**9**: 6.0 g (46%), *Z*-**10**: 1.6 g (26%) (0.035 mmol β-ketoester), *Z*-**11**: 4.0 g (31%)]. In the case of methyl 2-acetamidocyclopent-1-enecarboxylate (**14**) purification was carried out by crystallization (3×) from ethylacetate/*n*-hexane (1:1), yielding brown crystals [yield of the main fraction: 4.1 g (32%)].

Synthesis of Ethyl 3-Acetamido-3-phenyl-2-propenoate (*Z*-12).[3l] To a solution of NH_4OAc (0.65 mol) in ethanol (100 mL) was added the corresponding β-ketoester (0.13 mol). After stirring for 60 h at room temperature the solvent was removed, and a mixture of $CHCl_3$ and water was added. The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, yielding the corresponding 3-amino-2-alkenoate. To a stirred solution of the corresponding 3-amino-2-alkenoate (0.026 mmol) and pyridine (0.046 mol) in toluene (50 mL) was added dropwise a solution of acetyl chloride (0.027 mol) in toluene (10 mL) at 0 °C. The mixture was stirred for 48 h at 25 °C. A further amount of acetylchloride (0.027 mol) in toluene (10 mL) was added at 0 °C, and the resulting mixture was stirred for 48 h. After quenching with aqueous $NH_4H_2PO_4$ solution the mixture was extracted with ethylacetate (3 × 50 mL). The organic layer was washed with water (2 × 50 mL) and dried over Na_2SO_4. The solvents were removed in vacuo, and the obtained yellow oil was purified by column chromatography (eluent: ethylacetate/*n*-hexane, 1:1), yielding yellow crystals [yield: *Z*-**12**: 0.59 g (10%)].

Synthesis of Methyl 3-Benzamido-2-butenoate (*Z*-13).[3l] To a solution of NH_4OAc (0.65 mol) in ethanol (100 mL) was added the corresponding β-ketoester (0.13 mol). After stirring for 60 h at room temperature the solvent was removed, and a mixture of $CHCl_3$ and water was added. The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and was dried over Na_2SO_4. The solvent was evaporated under reduced pressure, yielding the corresponding 3-amino-2-alkenoate. To a stirred solution of the corresponding 3-amino-2-alkenoate (0.026 mmol) and pyridine (0.046 mol) in diethylether (70 mL) was added dropwise a solution of benzoyl chloride (0.027 mol) in toluene (10 mL) at −30 °C. The mixture was stirred for 12 h at −30 °C and for 24 h at room temperature. After quenching with aqueous water the mixture was extracted with ethylacetate (3 × 50 mL). The organic layer was washed with HCl (1 mol/L) and brine and dried over Na_2SO_4. The solvents were removed in vacuo, and the obtained yellow oil was purified by column chromatography (eluent: ethylacetate/*n*-hexane, 1:1), yielding crystals [yield: *Z*-**13**: 2.9 g (9%)].

General Procedure for the Catalytic Hydrogenation of β-Dehydroamino Acid Derivatives. A solution of the β-dehydroamino acid derivative (0.24 mmol) and 1.0 mL of solvent was transferred via syringe into an autoclave charged with argon. The catalyst was generated in situ by stirring $[Rh(cod)_2]BF_4$ (0.0024 mmol) and the corresponding 4,5-dihydro-3*H*-dinaphthophosphepine ligand (0.005 mmol) in 1.0 mL of solvent for a period of 10 min and afterwards transferring via syringe into the autoclave. The autoclave was then charged with hydrogen and stirred at the required temperature. After the predetermined time the hydrogen was released, and the reaction mixture passed through a short plug of silica gel. The conversion was measured by GC or ^{1}H NMR and the enantioselectivity by GC or HPLC.

Acknowledgment

We thank Mrs. M. Heyken, Mrs. C. Voss, Mrs. G. Wenzel, Mrs. K. Schröder, Mrs. S. Buchholz, and Dr. C. Fischer (all Leibniz Institut für Katalyse e.V. an der Universität Rostock) for excellent technical and analytical assistance. Dr. B. Hagemann is gratefully thanked for the syntheses of ligands **6e** and (*R*)-**6a**. Generous financial support from the state of Mecklenburg-Western Pomerania and the BMBF as well as the Deutsche Forschungsgemeinschaft (Leibniz-Price) is gratefully acknowledged.

Received for review October 30, 2006.

OP0602270

5.3. Enantioselective rhodium–catalyzed hydrogenation of enol carbamates in the presence of monodentate phosphines

Stephan Enthaler, Giulia Erre, Kathrin Junge, Dirk Michalik, Anke Spannenberg, Serafino Gladiali, and Matthias Beller*, *Tetrahedron: Asymmetry*, **2007,** *18*, 1288–1298.

Contributions

The synthetic route to ligand **7** was carried by G. Erre via compound **5a** and **6**. Suitable x–ray crystals of compound **5b** were grown by Dr. K. Junge, while crystals for oxide **6** were obtained by G. Erre. The synthesis of substrates **9**, **10**, **11**, **14** and the corresponding hydrogenation experiments stated in table 2 and table 3 were performed by G. Erre.

Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1288–1298

Enantioselective rhodium-catalyzed hydrogenation of enol carbamates in the presence of monodentate phosphines

Stephan Enthaler,[a] Giulia Erre,[a] Kathrin Junge,[a] Dirk Michalik,[a] Anke Spannenberg,[a] Fabrizio Marras,[b] Serafino Gladiali[b] and Matthias Beller[a,*]

[a]*Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany*
[b]*Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy*

Received 27 March 2007; accepted 1 June 2007

Abstract—The rhodium-catalyzed asymmetric hydrogenation of different acyclic and cyclic enol carbamates to give optically active carbamates has been examined in the presence of chiral monodentate ligands based on a 4,5-dihydro-3*H*-dinaphthophosphepine motif **4**. The enantioselectivity is largely dependent upon the reaction conditions, the nature of substituents on the phosphorus ligand and structure of the enol carbamate. By applying the optimized reaction conditions, enantioselectivities of up to 96% ee have been achieved.

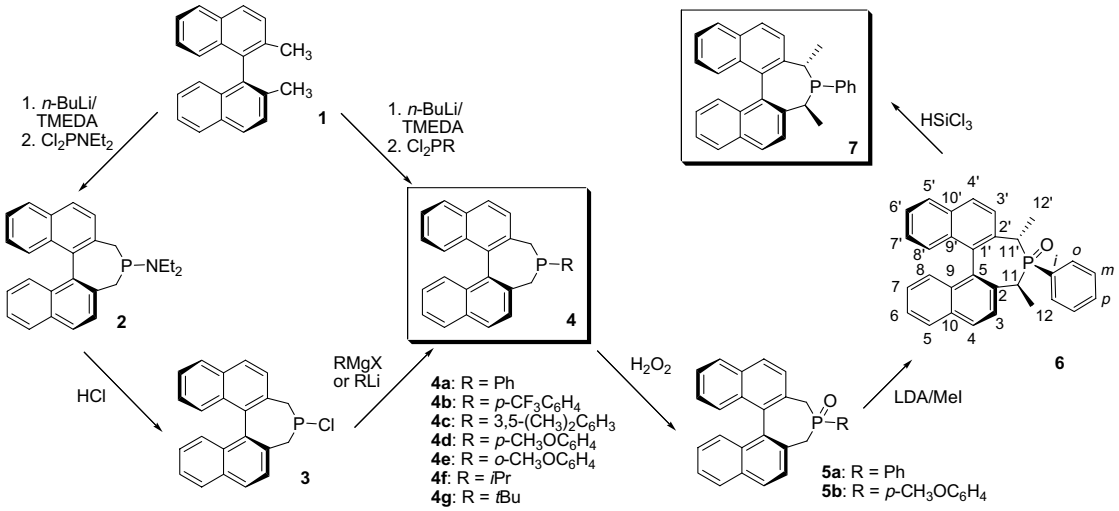
1. Introduction

The importance of enantiomerically pure compounds is demonstrated by their widespread application as either building blocks or intermediates for the synthesis of pharmaceuticals, agrochemicals, polymers, natural compounds, auxiliaries, ligands and synthons in organic syntheses.[1] To serve the growing demand for enantiomerically pure compounds, various synthetic approaches have been developed. Within the different molecular transformations to chiral compounds, catalytic reactions offer an efficient and versatile strategy and present a key technology for the advancement of 'green chemistry', specifically for waste prevention, reducing energy consumption, achieving high atom efficiency and generating advantageous economics.[2] In this regard, the use of molecular hydrogen in reductions of C=C, C=O and C=N bonds is one of the most extensively studied fields. For activation of the hydrogen and transfer of chirality, the use of transition metal catalysts containing chiral ligands are essential. Over a period of nearly 30 years, the synthesis of new ligands focused mainly on bidentate phosphorus systems, because of the promising results in the first few years of homogeneous asymmetric hydrogenation. However, at the end of the 20th century, the situation changed and monodentate ligands received more attention.[3,4] The advantages of monodentate phosphorus ligands compared to bidentate ligands are their easier synthesis, high tunability and even a higher efficiency in the transfer of chiral information as observed in several cases. Important contributions in this field with excellent enantioselectivities for various classes of substrates were reported by Feringa and de Vries et al.[5] (phosphoramidites), Reetz et al.[6] (phosphites), Pringle and Claver et al.[7] (phosphonites) and Zhou et al. (spiro phosphoramidites).[8]

Following the effort of one of us (S.G.)[9] and parallel to the work of Zhang,[10] we constructed a ligand library of approximately 25 different monodentate phosphines based on a 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine framework **4** (Scheme 1), which is reminiscent of the 1,1′-binaphthol core, which is present in the ligands mentioned above (Scheme 1).[11] The potential of this ligand class **4** in asymmetric hydrogenation with molecular hydrogen, such as the reduction of α-amino acid precursors, dimethyl itaconate, enamides and β-ketoesters achieving enantioselectivities up to 95% ee was previously reported by us.[11] Moreover, other groups demonstrated the usefulness of these ligands in several catalytic asymmetric reactions.[12] The promising results obtained in the asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamides with enantioselectivities of up to 95% ee and catalyst activities up to 2000 h^{-1} (TOF) motivated us to explore our ligand library **4** in the hydrogenation of structurally similar enol carbamates, which offer an alternative approach to chiral

* Corresponding author. Tel.: +49 381 1281 113; fax: +49 381 1281 5000; e-mail: Matthias.Beller@catalysis.de

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.06.001



Scheme 1. General synthesis of ligands with 2,2′-binaphthyl framework.

alcohols. Pioneering work in the field of enantioselective hydrogenation of enol carbamates has been reported by Feringa, de Vries and Minnaard et al. who have scored enantioselectivities of up to 98% ee with rhodium-catalysts containing monodentate phosphoramidites (MonoPhos-family).

2. Results and discussion

2.1. Ligand synthesis

In general, the ligands were prepared by double metallation of 2,2′-dimethylbinaphthyl **1** with 2 equiv of *n*-butyl lithium, followed by quenching with diethylaminodichlorophosphine or with aryl and alkyl dichlorophosphines. Deprotection of the diethylamino phosphine **2** with gaseous HCl produced 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **3** in 80% yield. This enantiomerically pure chlorophosphine is easily coupled with various Grignard reagents or organo-lithium compounds to give a broad selection of ligands **4**. In order to expand the application of this class of ligands, we prepared derivatives of **1**, bearing substituents on the aliphatic carbon at the α-position to the phosphorus. The desired bis-methylated product **7** has been obtained via a deprotonation–alkylation protocol. After the preliminary step of oxidation of 4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **4a** with H_2O_2, lithiation and alkylation were performed by the addition of LDA (3 equiv) and CH_3I (2 equiv) at room temperature. The reaction is completely stereoselective, and only one of the possible dialkylated products is obtained (Scheme 1).

Recently, Widhalm et al. reported a similar approach to the synthesis of compound **7**, via the phosphepine sulfide instead of the oxide.[13] To compare the two procedures, the stereochemistry of the new stereogenic centres in the phosphepine oxide **6** was studied in detail.

The stereochemistry of compound **6** was confirmed by NMR spectroscopy. The initial ^{31}P NMR measurements displayed the occurrence of exclusively one enantiomer for **6** and **7** in each case, since only one single signal was found and racemization of the binaphthyl backbone over the course of reactions was excluded. In a two-dimensional

Table 1. Selected bond lengths [Å] and angles [°] of the phosphepine oxides **5a**, **5b** and **6**

5a		**6**		**5b**[a]	
P1–C1	1.812(5)	P1–C25	1.799(3)	P1–C1	1.824(4)
				[P2–C30]	[1.825(4)]
P1–C7	1.813(4)	P1–C22	1.832(2)	P1–C29	1.833(4)
				[P2–C58]	[1.846(4)]
P1–C28	1.814(5)	P1–C1	1.834(2)	P1–C8	1.837(4)
				[P2–C37]	[1.819(4)]
P1–O1	1.481(3)	P1–O1	1.483(2)	P1–O1	1.444(3)
				[P2–O3]	[1.407(5)]
C7–P1–C1	109.6(2)	C25–P1–C22	108.6(1)	C1–P1–C29	107.9 (2)
				[C30–P2–C37]	[107.2 (2)]
C28–P1–C1	104.0(2)	C25–P1–C1	104.2(1)	C1–P1–C8	105.4(2)
				[C30–P2–C58]	[103.0(2)]
C7–P1–C28	103.1(2)	C22–P1–C1	108.8 (1)	C29–P1–C8	102.3(2)
				[C58–P2–C37]	[100.8(2)]

[a] Values of the second molecule in the asymmetric unit are in brackets.

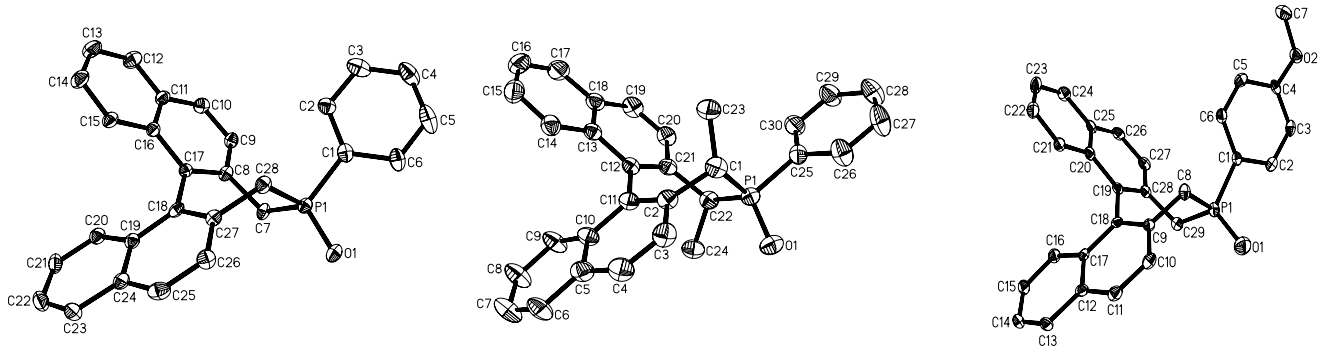


Figure 1. ORTEP plot of compounds **5a**, **6** and **5b**. Hydrogen atoms are omitted for clarity. The thermal ellipsoids correspond to 30% probability. With respect to compound **5b**, only one of the two symmetry-independent molecules of the asymmetric unit is depicted.

NOESY spectrum, correlations between the following protons were observed: *o*-Ph with H-3′, H-11′ and Me(12); H-3 with H-11 and H-3′ with H-11′, respectively, indicating the bis-axial orientation of both methyl groups. The spatial proximity of the methyl group Me(12) and of the phenyl group is also reflected by the difference in ^{1}H chemical shift values of both methyl groups (δMe(12) = 0.61 and Me(12′) = 0.95). The high-field shift of the signal for the methyl group Me(12) can be explained by the anisotropic effect of the phenyl substituent on the phosphorus.

In addition, useful structural data were gained by X-ray crystallography of oxide **6**. For comparison, X-ray structure analyses of the corresponding unsubstituted systems **5a** and **5b** were determined. Selected bond lengths and angles are shown in Table 1. The molecular structures of the three oxides are given in Figure 1. In the case of **5b**, two molecules have been found in the asymmetric unit with similar structural features. As expected in all compounds the substituents show an approximately tetrahedral arrangement at the phosphorus atom. The α,α-disubstituted phosphepine oxide **6** features shorter exocyclic (P1–C25 1.799(3) Å) than the endocyclic P–C bonds (P1–C22 1.832(2) Å and P1–C1 1.834(2) Å) in comparison with the unsubstituted system **5a** where all P–C bonds are equally long (Table 1). Furthermore, the α,α-substitution promotes a pronounced expansion of the endocyclic C–P–C angle up to 108.8(1)° (**6**) from 103.1(2)° (**5a**).

In accordance with the NMR studies and the X-ray structure analysis, the configuration of compound **6** was assigned to be (S,S,S_a). The stereochemistry of ligand **7** was allotted in analogy to the one of the corresponding oxide.

2.2. Catalytic experiments

The synthesis of enol carbamates **8**–**14** was carried out in analogy to literature protocols, by reacting the corresponding ketone with NaH and subsequent addition of the corresponding carbamoyl chloride.[5m,14]

Initial studies on the influence of reaction conditions were performed with 1-phenylvinyl *N*,*N*-diethylcarbamate **8** as substrate and 4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **4a** as our standard ligand. Typically, we used an in situ pre-catalytic mixture of 1.0 mol % [Rh(cod)$_2$]BF$_4$ and 2.1 mol % of the ligand. All hydrogenation reactions were carried out in an eightfold parallel reactor array with a 3.0 ml reactor volume.[15]

First we investigated the influence of different solvents, such as methylene chloride, methanol, ethanol and 2-propanol in combination with a variation of the initial hydrogen pressure (1.0, 5.0, 10.0, 25.0 and 50.0 bar). Selected results are presented in Figure 2.

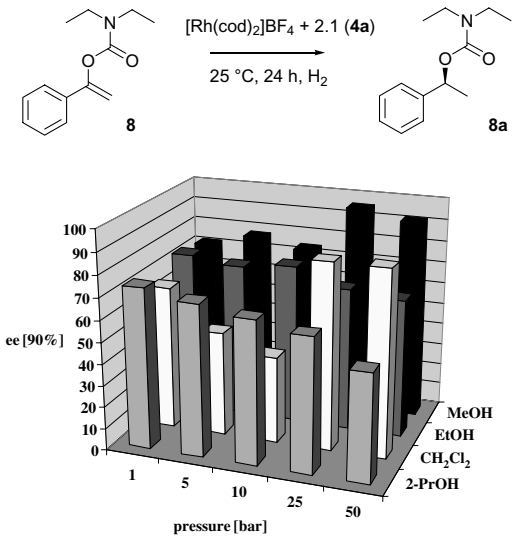


Figure 2. Solvent and pressure variation. Reactions were carried out at 25 °C for 24 h with 0.0024 mmol [Rh(cod)$_2$]BF$_4$, 0.005 mmol ligand **4a** and 0.24 mmol **8** in 2.0 ml solvent.

Surprisingly, by applying toluene as solvent in the hydrogenation of enol carbamate **8** no reaction occurred, while in previous studies toluene was found to be the solvent of choice for the hydrogenation of enamides and α-amino acids.[11c,e] The best enantioselectivities of up to 96% ee were obtained with methanol as solvent with a hydrogen pressure of 25 bar.

Two different pressure-enantioselectivity-dependencies have been noticed. In ethanol and 2-propanol, the enantioselectivity decreased when increasing the hydrogen pressure (1 bar: ethanol: 74% ee, 2-propanol: 74% ee, 50 bar: ethanol:

64% ee, 2-propanol: 50% ee) whereas in methylene chloride and methanol, the reverse behaviour was observed (1 bar: methanol: 72% ee, methylene chloride: 66% ee, 50 bar: methanol: 92% ee, methylene chloride: 86% ee). With the exception of 2-propanol (>99%), moderate to good conversions (60–90%) were observed at lower pressures within a reasonable time (24 h), while at higher pressure a complete conversion was achieved. The results indicated methanol as the solvent of choice (conversion: >99%; enantioselectivity: 96% ee). In addition, in order to estimate the effect of the protic solvent on the product structure the reaction was performed in methanol-d_4. Analysis of the ^{1}H NMR spectra showed that no incorporation of deuterium in the product had occurred. Therefore, one can rule out any interference of the solvent in the catalytic cycle due to transfer hydrogenation and/or protonolysis of Rh-C-species.[16]

In order to assess the optimum reaction conditions, a detailed pressure investigation was performed (Fig. 3). The results illustrated a constant range of enantioselectivity (~74% ee) between initial pressures of 1–18 bar, followed by an increase of up to a maximum of 96% ee at 25 bar. A further increase in the hydrogen pressure did not result in any improvement while enantioselectivities ranged between 92% and 94% ee in the region of 30–50 bar.

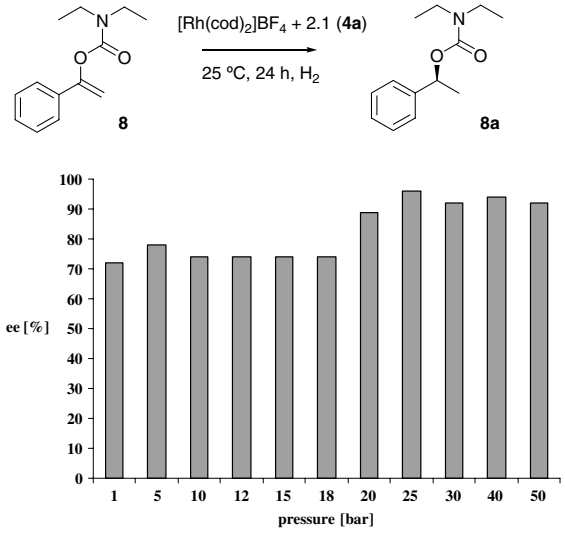


Figure 3. Study of pressure-enantioselectivity-dependency. Reactions were carried out at 25 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand **4a** and 0.24 mmol **8** in 2.0 ml methanol.

The optimal reaction conditions devised in the solvent-pressure investigation (methanol as solvent and 25 bar as initial hydrogen pressure) were applied in a temperature study (Fig. 4). With the model ligand **4a** in the hydrogenation of compound **8**, we observed a high stability of the enantioselectivity (94–96% ee) in the range of 10–90 °C albeit with a reduction of conversion at 90 °C. A further increase to 110 °C produced a racemic mixture of **8a**, probably as a result of ligand degradation.[17]

In order to evaluate the substituent effect at the phosphorus atom of the ligand, we studied the model reaction of 1-phenylvinyl *N*,*N*-diethylcarbamate **8** in the presence of eight different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines **4a**–**4g** and **7** using the optimized reaction conditions (2.5 bar hydrogen pressure, methanol, 30 °C, 6 h). The results are presented in Table 2. In the hydrogenation of **8**, the best enantioselectivities of up to 90% and 72% ee, respectively, were achieved with ligand **4a** and **4d** (Table 2, entries 1 and 4). The presence of electron-donating groups, as well as electron-withdrawing groups onto the P-aryl substituent, led to a significant decrease of the stereoselectivity (Table 1, entries 2–5).

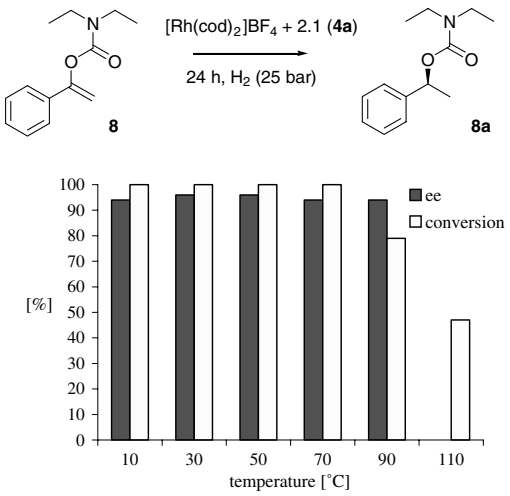
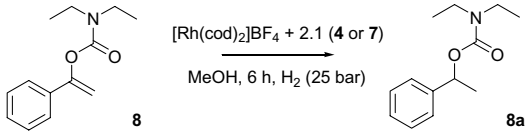


Figure 4. Dependency of enantioselectivity versus temperature. Reactions were carried out at corresponding temperature for 1–24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand **4a** and 0.24 mmol **8** in 2.0 ml methanol.

Table 2. Hydrogenation of compound **8** with different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines **4a**–**4g** and ligand **7**[a]



Entry	Ligand	Conv. (%)	Yield (%)	ee (%)
1	**4a**	>99	>99	**96 (*S*)**
2	**4b**	40	40	28 (*S*)
3	**4c**	>99	>99	66 (*S*)
4	**4d**	>99	>99	72 (*S*)
5	**4e**	>99	>99	51 (*S*)
6	**4f**	40	40	12 (*S*)
7	**4g**	41	41	50 (*R*)
8[b]	**7**	>99	>99	42 (*R*)

[a] All reactions were carried out at 25 °C under 25 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol **8** in methanol (2.0 ml).

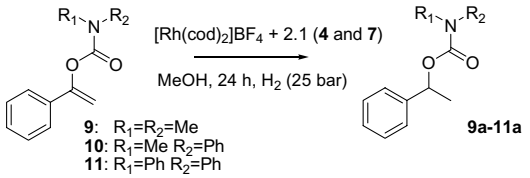
[b] 24 h.

Catalysts containing alkyl-substituted phosphepines **4f** or **4g** gave a significant lower activity and enantioselectivity compared to aryl-substituted phosphepines. Interestingly, in the case of ligand **4g** and **7**, the opposite enantiomer is formed during the reaction. A similar behaviour of the

tert-butyl ligand **4g** was previously reported for other asymmetric hydrogenations.[11c,f]

To explore the scope and limitation of our ligand toolbox, the asymmetric hydrogenation of a range of enol carbamates was performed under optimized conditions (Tables 3 and 4). First the influence of the substitution at the carbamoyl-nitrogen was investigated (Table 3).

Table 3. Variation of the protecting group in the substrate moiety[a]



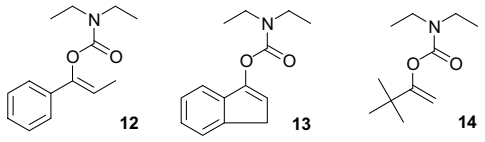
Entry	Ligand	R_1	R_2	Conv. (%)	Yield (%)	ee (%)
1	**4a**	Me	Me	>99	>99	68 (*S*)
2	**4b**	Me	Me	33	33	26 (*S*)
3	**4c**	Me	Me	87	87	65 (*S*)
4	**4d**	Me	Me	>99	>99	**75 (*S*)**
5	**4e**	Me	Me	99	99	40 (*S*)
6	**4f**	Me	Me	26	26	17 (*S*)
7	**4g**	Me	Me	44	44	33 (*R*)
8	**7**	Me	Me	80	80	27 (*R*)
9	**4a**	Me	Ph	>99	>99	58 (*S*)
10	**4b**	Me	Ph	98	98	37 (*S*)
11	**4c**	Me	Ph	>99	>99	61 (*S*)
12	**4d**	Me	Ph	>99	>99	**65 (*S*)**
13	**4e**	Me	Ph	>99	>99	42 (*S*)
14	**4f**	Me	Ph	53	53	4 (*S*)
15	**4g**	Me	Ph	>99	>99	45 (*R*)
16	**7**	Me	Ph	>99	>99	53 (*R*)
17	**4a**	Ph	Ph	>99	88	10 (*S*)
18	**4b**	Ph	Ph	98	77	Rac
19[b]	**4c**	Ph	Ph	89	75	41 (*S*)
20	**4d**	Ph	Ph	>99	87	11 (*S*)
21	**4e**	Ph	Ph	>99	87	55 (*S*)
22	**4f**	Ph	Ph	98	62	4 (*S*)
23	**4g**	Ph	Ph	>99	98	70 (*R*)
24	**7**	Ph	Ph	>99	98	**76 (*R*)**

[a] All reactions were carried out at 25 °C under 25 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in methanol (2.0 ml).
[b] Reaction was carried out for 6 h.

All substrates were hydrogenated under the optimized conditions with eight different ligands **4a**–**4g** and **7**. The enol carbamates **9**–**11** undergo the reaction with good conversion in most cases (Table 3). The negative influence on the activity was again observed by the electron-withdrawing substituent on the phenyl (entries 2, 10 and 18) and by the alkyl group on the phosphorus, mainly *i*-Pr (Table 3, entries 6, 7, 14 and 22). On the other hand in some cases a positive effect on the selectivity by substitution with electron donating groups was observed (Table 3, entries 4 and 12). Again the stereoselectivity was reversed in the case of ligand **7** and **4g**, with **7** being the higher inducer of chirality for system **11**. The overall results for the three substrates **9**–**11** are comparable, showing little influence of the different substituents on the carbamoyl nitrogen on the reaction path.

Finally, the sensitivity on the variations in the double bond was investigated. Table 4 summarizes the results for three substrates with different substitutions: substitution of the phenyl-group by an alkyl-group **14**, substitution in the 2-position of the 1,1-olefin **12** and a cyclic substrate **13**. Substrate *Z*-**12** was hydrogenated with excellent conversion and good enantioselectivity by ligand **4d**, while **13**, which is structurally related to the *E*-isomer of substrate **12**, fails to be hydrogenated with all the ligands but exceptionally ligand **7** (Table 4, entry 8). The alkyl enol carbamate **14** is best hydrogenated by ligands **4a** and **7**, again leading to an inversion of enantioselectivity with ligand **7**. In general the behaviour of substrates **12** and **14** is comparable to that of the previous enol carbamates.

Table 4. Variations of the substituent in the olefin[a]



Entry	Lig.	**12a**		**13a**		**14a**	
		Conv. (%)	ee[b] (%)	Conv. (%)	ee (%)	Conv. (%)	ee (%)
1	**4a**	94	50 (*S*)	<1	n.d.	>99	48
2	**4b**	10	12 (*R*)	<1	n.d.	24	1
3	**4c**	7	8 (*S*)	<1	n.d.	90	39
4	**4d**	93	**72** (*S*)	<1	n.d.	89	48
5	**4e**	29	14 (*S*)	<1	n.d.	81	Rac
6	**4f**	1	n.d.	<1	n.d.	39	11
7	**4g**	2	n.d.	<1	n.d.	44	42
8	**7**	37	6 (*R*)	30	n.d.	98	**−67**

[a] All reactions were carried out at 25 °C under 25 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in methanol (2.0 ml).
[b] The absolute configuration was assigned by analogy.

3. Conclusions

Monodentate phosphine ligands based on a 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines structure **4** and **7** have been successfully exploited in the rhodium-catalyzed asymmetric hydrogenation of various enol carbamates. The influences of different reaction parameters have been investigated. For the first time in this reaction a high enantioselectivity (up to 96% ee) was obtained in the presence of monodentate phosphines.

4. Experimental

4.1. General

^1H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker Spectrometer AVANCE 500, 400 and 300 (^1H: 500.13 MHz, 400.13 MHz and 300.13 MHz; ^{13}C: 125.8 MHz, 100.6 MHz and 75.5 MHz; ^{31}P: 162.0 MHz). The calibration

of ^{1}H and ^{13}C spectra was carried out on solvent signals ($\delta(CDCl_3) = 7.25$ and 77.0). The ^{31}P chemical shifts are referenced to 85% H_3PO_4. Mass spectra were recorded on an AMD 402 spectrometer. Optical rotations were measured on a Gyromat-HP polarimeter. IR spectra were recorded as KBr pellets or Nujol mulls on a Nicolet Magna 550. All manipulations with air sensitive compounds were performed under argon atmosphere using standard Schlenk techniques. Toluene was distilled from sodium benzophenone ketyl under argon. Methanol was distilled from Mg under argon. Ethanol and 2-propanol were distilled from Na under argon. Methylene chloride was distilled from CaH_2 under argon. Dimethyl sulfoxide (on molecular sieves) and $[Rh(cod)_2]BF_4$ were purchased from Fluka and used without further purifications. Ligands **4** were synthesized according to our previously published protocols.[11]

4.2. Synthesis of ligands

4.2.1. (*S*)-4-Phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]-phosphepine oxide 5a. Ligand **4a** (1.5 g, 3.86 mmol) were dissolved in acetone (10 ml) and 7.7 ml of 10% sol. H_2O_2 (23 mmol) were added carefully, cooling with ice-bath. After few minutes stirring at room temperature, the solution was refluxed at 100 °C for 1 h. The solvent was evaporated and the resulting yellow oil taken up with CH_2Cl_2 and dried over $MgSO_4$. Purification by column chromatography (eluent: ethyl acetate/petroleum ether 4:1) yielded 1.17 g (75%) of white solid. Mp: 167–168 °C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 8.02$ (d, 1H, $^{3}J_{3,4} = 8.5$ Hz, H-4); 7.96, 7.95 (2d, 2H, $^{3}J_{5,6} = 8.2$ Hz, $^{3}J_{5',6'} = 8.2$ Hz, H-5, H-5′); 7.90 (d, 1H, $^{3}J_{3',4'} = 8.5$ Hz, H-4′); 7.70 (d, 1H, $^{3}J_{3,4} = 8.5$ Hz, H-3); 7.53–7.35 (m, 7H, H-6, H-6′, Ph); 7.29–7.21 (m, 3H), 7.16 (d, 1H, $^{3}J = 8.5$ Hz, H-7, H-7′, H-8, H-8′); 7.21 (d, 1H, $^{3}J_{3',4'} = 8.5$ Hz, H-3′); 3.36 (dd, 1H, $^{2}J_{H,H} = 14.2$ Hz, $^{2}J_{P,H} = 8.2$ Hz, H-11a); 3.32 (dd, 1H, $^{2}J_{P,H} = 22.5$ Hz, $^{2}J_{H,H} = 14.2$ Hz, H-11′a); 3.22 (dd, 1H, $^{2}J_{H,H} = 14.2$ Hz, $^{2}J_{P,H} = 13.0$ Hz, H-11b); 3.21 (dd, 1H, $^{2}J_{P,H} = 16.0$ Hz, $^{2}J_{H,H} = 14.2$ Hz, H-11′b). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 134.0$ (d, $J = 4.0$ Hz), 133.4 (d, $J = 4.0$ Hz), 133.0 (d, $J = 1.8$ Hz), 132.9 (d, $J = 1.8$ Hz), 132.4 (d, $J = 2.5$ Hz), 132.2 (d, $J = 1.8$ Hz), 130.4 (d, $J = 8.2$ Hz), 129.6 (d, $J = 10.0$ Hz, C-1, C-1′, C-2, C-2′, C-9, C-9′, C-10, C-10′); 132.1 (d, $J = 2.5$ Hz, *p*-Ph); 132.0 (d, $J = 88.0$ Hz, *i*-Ph); 130.9 (d, $J = 8.5$ Hz, *o*-Ph); 129.4 (d, $J = 1.8$ Hz, C-4); 128.6 (d, $J = 1.8$ Hz, C-4′); 128.5 (d, $J = 11.0$ Hz, *m*-Ph); 128.5 (d, $J = 3.5$ Hz, C-3); 128.4, 128.2 (C-5, C-5′); 128.3 (d, $J = 4.5$ Hz, C-3′); 127.1, 126.7, 126.5, 126.3 (C-7, C-7′, C-8, C-8′); 125.9 (C-6); 125.6 (C-6′); 37.4 (d, $J = 65.0$ Hz, C-11′); 36.0 (d, $J = 64.0$ Hz, C-11). ^{31}P NMR (121.5 MHz, $CDCl_3$) $\delta = 54.0$. IR (KBr, cm^{-1}): 3052 m; 3008 w; 2951 w; 1618 w; 1592 w; 1508 m; 1435 m; 1405 m; 1359 w; 1328 w; 1251 m; 1221 s; 1199 m; 1159 m; 1114 m; 1102 m; 1061 w; 1026 w; 998 w; 973 w; 960 w; 931 w; 884 w; 866 w; 836 s; 833 m; 820 s; 802 w; 770 m; 752m; 742 s; 726 w; 713 w; 703 m; 694 m; 672 w; 661 m; 622 m; 586 w; 568 w; 544 m; 523 m; 496 w; 470 m; 436 w; 424 w. MS (ESI): *m*/*z* (%) = 404 ([M^+], 100); 365 (6); 266 (34); 202 (4); 139 (4); 73 (7). HRMS calcd for $C_{28}H_{21}O_1P$: 404.13245, found: 404.132628. $[\alpha]_D^{22} = +79.0$ (*c* 0.46, $CHCl_3$). Retention time: 64.6 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.2.2. (*S*)-4-(4-Methoxy)phenyl-4,5-dihydro-3*H*-dinaphtho-[2,1-*c*:1′,2′-*e*]phosphepine oxide 5b. (*S*)-4-(4-Methoxy)-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphepine **4d** (4.2 mmol) was dissolved in acetone (15 ml) and a mixture of water (1.1 ml) and 35% sol. H_2O_2 (5.0 mmol) was added carefully. After stirring for 4 h at room temperature, the solvent was evaporated and the residue dissolved in dichloromethane. The organic phase was washed with water, brine and dried over $MgSO_4$. The solvent was removed to obtain an off-white foam. Yield: 99%. Mp: 112–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.03$–7.89 (m, 4H); 7.69 (dd, 1H, $J = 8.5$ Hz, $J = 1.2$ Hz); 7.51–7.41 (m, 2H); 7.40–7.31 (m, 2H, C_6H_4); 7.29–7.15 (m, 5H); 6.89 (m, 2H, C_6H_4); 3.83 (s, 3H, OMe); 3.37–3.12 (m, 4H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 162.5$ (d, $J = 3.0$ Hz, C_6H_4); 133.9 (d, $J = 3.8$ Hz); 133.5 (d, $J = 3.8$ Hz); 132.9 (d, $J = 2.0$ Hz); 132.7 (d, $J = 2.0$ Hz); 132.7 (d, $J = 10.2$ Hz, C_6H_4); 132.4 (d, $J = 2.5$ Hz); 132.1 (d, $J = 2.0$ Hz); 130.6 (d, $J = 8.2$ Hz); 129.8 (d, $J = 9.5$ Hz); 129.3 (d, $J = 1.8$ Hz); 128.6 (d, $J = 1.8$ Hz); 128.4 (d, $J = 3.8$ Hz); 128.4; 128.3 (d, $J = 4.5$ Hz); 128.2; 127.1; 126.7; 126.5; 126.3; 125.8; 125.6; 123.0 (d, $J = 93.5$ Hz, C_6H_4); 114.0 (d, $J = 12.0$ Hz, C_6H_4); 55.3 (OMe); 37.7 (d, $J = 66.0$ Hz, CH_2); 36.3 (d, $J = 64.2$ Hz, CH_2). ^{31}P NMR (121.5 MHz, $CDCl_3$) $\delta = 54.1$. IR (KBr, cm^{-1}): 3053 m; 2957 w; 2836 w; 1596 s; 1569 w; 1503 s; 1460 m; 1441 m; 1407 m; 1294 m; 1255 s; 1217 m; 1178 s; 1117 s; 1027 m; 931 w; 871 w; 816 s; 744 m; 684 w; 660 w; 623 w; 567 w; 544 m; 527 m; 496 w; 457 w; 419 w. MS (EI): *m*/*z* (%) = 434 ([M^+], 100); 282 (20); 279 (37); 266 (32); 121 (27). HRMS calcd for $C_{29}H_{23}O_2P$: 434.14302, found: 434.142805. $[\alpha]_D^{22} = -293$ (*c* 0.25, $CHCl_3$).

4.2.3. (*S*,*S*,*S*$_a$)-3,5-Dimethyl-4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphepine oxide 6. Phosphepine oxide **5** (1.37 g, 3.4 mmol) is dissolved in 14 ml of THF, followed by the addition of 0.42 ml (6.8 mmol) of methyl iodide. To the well stirred solution, 22 ml of LDA (11 mmol, 0.5 M) are added slowly at room temperature. The dark red solution was stirred for 1 h and afterwards quenched with few drops of water. The solvents were evaporated under reduced pressure. The product was taken up with 50 ml of CH_2Cl_2, washed with 50 ml of H_2O and the water phase extracted with CH_2Cl_2 (2 × 50 ml). The organic phases are dried over $MgSO_4$ and the solvents evaporated, yielding 1.45 g of light yellow foam. Purification by column chromatography on SiO_2, eluting with acetone/petroleum ether 1:1 yielded 0.56 g (38%) of a white solid. Mp: 292–305 °C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 8.02$ (d, 1H, $^{3}J_{3',4'} = 8.5$ Hz, H-4′); 7.97 (d, 1H, $^{3}J_{3,4} = 8.5$ Hz, H-4); 7.95 (d, 1H, $^{3}J_{5,6} = 8.2$ Hz, H-5); 7.92 (d, 1H, $^{3}J_{5',6'} = 8.2$ Hz, H-5′); 7.72–7.68 (m, 2H, *o*-Ph); 7.65 (d, 1H, $^{3}J_{3,4} = 8.5$ Hz, H-3); 7.55 (d, 1H, $^{3}J_{3',4'} = 8.5$ Hz, H-3′); 7.50–7.39 (m, 5H, H-6, H-6′, *m*-, *p*-Ph); 7.24–7.18 (m, 3H), 7.05 (d, 1H, $^{3}J = 8.5$ Hz, H-7, H-7′, H-8, H-8′); 3.62 (m, 1H, $^{2}J_{P,H} = 15.0$ Hz, $^{3}J_{11',12'} = 7.7$ Hz, H-11′); 3.43 (dq, 1H, $^{2}J_{P,H} = 22.0$ Hz, $^{3}J_{11,12} = 7.7$ Hz, H-11); 0.95 (dd, 1H, $^{3}J_{P,H} = 14.0$ Hz, $^{3}J_{11',12'} = 7.7$ Hz, H-12′); 0.61

(dd, 1H, $^3J_{P,H} = 16.1$ Hz, $^3J_{11,12} = 7.7$ Hz, H-12). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 135.2$ (d, $J = 3.2$ Hz, C-1′); 134.5 (d, $J = 5.0$ Hz, C-2′); 134.0 (d, $J = 7.0$ Hz, C-2); 133.9 (d, $J = 3.0$ Hz), 133.8 (d, $J = 1.8$ Hz), 133.4 (d, $J = 1.8$ Hz), 133.0 (d, $J = 1.5$ Hz), 132.8 (d, $J = 1.5$ Hz, C-1, C-9, C-9′, C-10, C-10′); 133.2 (d, $J = 83.0$ Hz, *i*-Ph); 131.7 (d, $J = 2.5$ Hz, *p*-Ph); 131.1 (d, $J = 8.2$ Hz, *o*-Ph); 130.1 (d, $J = 5.0$ Hz, C-3); 129.3 (d, $J = 6.8$ Hz, C-3′); 129.2 (C-4); 129.1 (C-4′); 128.2, 128.0 (C-5, C-5′); 128.2 (d, $J = 10.0$ Hz, *m*-Ph); 127.0, 126.6, 126.5, 126.3 (C-7, C-7′, C-8, C-8′); 126.1 (C-6); 125.7 (C-6′); 46.4 (d, $J = 59.5$ Hz, C-11); 43.2 (d, $J = 63.0$ Hz, C-11′); 17.0 (C-12); 14.6 (d, $J = 4.5$ Hz, C-12′). ^{31}P NMR (121.5 MHz, $CDCl_3$) $\delta = 51.3$. IR (KBr, cm^{-1}): 3039 m; 2990 m; 2931 m; 2874 w; 1618 w; 1594 m; 1568 w; 1504 m; 1455 w; 1436 m; 1375 w; 1341 w; 1325 w; 1292 w; 1253 m; 1225 w; 1184 m; 1166 s; 1112 m; 1092 m; 1057 m; 1028 w; 999 w; 957 w; 915 w; 896 m; 871 w; 838 m; 820 s; 796 w; 768 w; 756 m; 739 s; 711 m; 704 m; 689 m; 667 s; 632 w; 583 w; 564 s; 534 m; 520 w; 509 w; 482 m; 459 m; 418 w; 403 w. MS (ESI): *m*/*z* (%) = 432 ([M$^+$], 44); 417 (2); 388 (2); 360 (1); 328 (2); 293 (15); 278 (100); 265 (15); 231 (4); 208 (12); 179 (2); 145 (16); 132 (33); 77 (7); 47 (4). HRMS calcd for $C_{30}H_{25}OP$: 432.16375, found: 432.163562. $[\alpha]_D^{22} = +93.5$ (*c* 0.25, $CHCl_3$). Retention time: 58.6 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.2.4. (*S*,*S*,*S*$_a$)-3,5-Dimethyl-4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphepine 7. Phosphepine oxide **6** (0.08 g, 0.2 mmol) was dissolved in dry toluene (6 ml) and triethylamine (0.2 ml, 1.4 mmol) was added to the solution. The mixture was cooled to 0 °C with an ice-bath and $HSiCl_3$ (0.1 ml, 1 mmol) was added. After the addition was complete, the solution was refluxed for 4 h. The reaction was quenched by 5 ml basic aqueous solution, and the aqueous phase washed with toluene (2×5 ml). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Yield 70 mg (91%). Mp: 212 °C. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 8.04$–7.90 (m, 4H); 7.73–7.63 (m, 3H); 7.55 (d, 1H, $J = 8.5$ Hz); 7.51–7.38 (m, 5H); 7.26–7.16 (m, 3H); 7.06 (d, 1H, $J = 8.5$ Hz); 3.62 (m, 1H, $^2J_{P,H} = 15.5$ Hz, $^3J_{H,Me} = 7.5$ Hz, C*H*Me); 3.43 (dq, 1H, $^2J_{P,H} = 22.0$ Hz, $^3J_{H,Me} = 7.5$ Hz, C*H*Me); 0.95 (dd, 3H, $^3J_{P,H} = 13.9$ Hz, $^3J_{H,Me} = 7.5$ Hz, Me); 0.61 (dd, 3H, $^3J_{P,H} = 16.0$ Hz, $^3J_{H,Me} = .5$ Hz, Me). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 141.2$ (d, $J = 2.5$ Hz); 138.5 (d, $J = 1.0$ Hz); 138.5 (d, $J = 25.8$ Hz); 134.7 (d, $J = 5.8$ Hz); 134.3; 133.9; 133.86 (d, $J = 2.8$ Hz); 132.8 (d, $J = 19.5$ Hz); 132.7; 132.2; 128.9 (d, $J = 3.0$ Hz); 128.8; 128.6 (d, $J = 1.0$ Hz); 128.4; 128.3 (d, $J = 3.2$ Hz); 128.2; 128.1; 127.9; 126.6; 126.5; 126.0; 126.0; 125.2; 125.1; 39.3 (d, $J = 20.0$ Hz, *C*HMe); 36.6 (d, $J = 20.0$ Hz, *C*HMe); 22.3 (d, $J = 35.5$ Hz, Me); 14.0 (d, $J = 3.5$ Hz, Me). ^{31}P NMR $\delta = 31.46$ (s). MS (ESI): *m*/*z* (%): 416 ([M$^+$], 100), 360 (10), 265 (38), 149 (9). HRMS: calcd for $C_{30}H_{25}P$ 416.16884, found: 416.167881. $[\alpha]_D^{25} = +87.5$ (*c* 0.2, $CHCl_3$).

4.3. General synthesis of enol carbamate derivates 8–14[14,5m]

A solution of sodium hydride (0.11 mol) in dry dimethyl sulfoxide (200 ml) was stirred for 2 h at 50 °C under an atmosphere of argon. The grey suspension was added dropwise to the corresponding ketone (0.1 mol) in 25 ml of dimethyl sulfoxide at room temperature. The orange solution was stirred for 15 min at room temperature and then cooled to 10 °C. The addition of the corresponding carbamoyl chloride (0.11 mol) in dimethyl sulfoxide (0.11 mol) was carried out in 30 min while maintaining the temperature at 10 °C. After stirring overnight at room temperature, the solution was carefully quenched with water (250 ml), extracted with *n*-hexane or heptane (3×250 ml), washed with brine (250 ml) and dried over $MgSO_4$ or Na_2SO_4. The solvents were removed in vacuo and the obtained yellow oil purified by column chromatography or crystallization.

4.3.1. 1-Phenylvinyl *N*,*N*-diethylcarbamate 8. Purification by column chromatography (eluent: ethylacetate/*n*-hexane 1:10) yielded a yellow oil. Yield: 18%. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.44$–7.39 (m, 2H, Ph); 7.30–7.19 (m, 3H, Ph); 5.35 (d, 1H, $J = 2.0$ Hz, =CH_2); 4.96 (d, 1H, $J = 2.0$ Hz, =CH_2); 3.35 (q, 2H, $J = 7.0$ Hz, CH_2); 3.25 (q, 2H, $J = 7.0$ Hz, CH_2); 1.20 (t, 3H, $J = 7.0$ Hz, CH_3); 1.10 (t, 3H, $J = 7.0$ Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 153.8$; 153.4; 135.2; 128.6; 128.4; 124.8; 101.3; 42.0; 41.7; 14.3; 13.3. IR (KBr, cm^{-1}): 3059 w; 3027 w; 2975 m; 2934 m; 2876 w; 1719 s; 1641 m; 1600 w; 1577 w; 1495 m; 1474 m; 1457 m; 1420 s; 1380 m; 1351 w; 1314 w; 1255 s; 1225 m; 1158 s; 1097 m; 1076 m; 1050 m; 1027 w; 981 w; 902 w; 869 m; 787 m; 771 m; 759 m; 703 m; w; 638 w; 578 w. MS (ESI): *m*/*z* (%) = 219 ([M$^+$], 9); 103 (12); 100 (100); 77 (16); 72 (72); 44 (16). HRMS calcd for $C_{13}H_{17}O_2N$: 219.1254, found: 219.1253. Retention time: 17.8 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.3.2. 1-Phenylvinyl *N*,*N*-dimethylcarbamate 9. Purification by column chromatography on silica gel eluting with hexane/ethyl acetate 4:1 yielded 6.4 g of an orange oil. Yield: 34%. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.48$–7.28 (m, 5H, Ph); 5.41 (1H, d, $J = 2.0$ Hz, =CH_2); 5.02 (d, 1H, $J = 2.0$ Hz, =CH_2); 3.10 (s, 3H, CH_3); 2.96 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 154.5$; 153.4; 135.1; 128.7; 128.5; 124.9; 101.6; 36.7; 36.4. IR (KBr, cm^{-1}): 3084 w, 3058 w, 3023 w, 2934 m, 1958 w, 1724 s, 1643 m, 1601 w, 1577 m, 1494 s, 1445 s, 1391 s, 1313 m, 1295 m, 1262 s, 1168 s, 1098 m, 1076 m, 1030 m, 928 m, 875 m, 858 m, 772 s, 759 m, 708 m, 692 m, 641 w, 581 w. MS (ESI): *m*/*z* (%) = 191 ([M$^+$], 12); 103 (4); 91 (4); 77 (7); 72 (100); 51 (5). HRMS calcd for $C_{11}H_{13}O_2N$: 191.09408, found: 191.09370. Retention time: 16.8 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.3.3. 1-Phenylvinyl *N*-methyl *N*-phenylcarbamate 10. Purification by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate 1:1 followed by crystallization with acetone/diethylether/*n*-hexane 1:2:4. Yield: 25%. Mp: 56–59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.42$–7.26 (m, 10H, Ph); 5.39 (1H, d, $J = 1.7$ Hz, =CH_2); 5.06 (d, 1H, $J = 1.7$ Hz, =CH_2); 3.38 (br s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 153.6$; 153.4; 143.0; 134.9; 129.2; 128.8; 128.4; 126.7 (br); 126.0 (br); 125.0; 101.6;

38.3. IR (KBr, cm^{-1}): 3762 w; 3407 w; 3119 w; 3085w; 3067 w; 3037 w; 2975 w; 2937 w; 2557 w; 1966w; 1891 w; 1813 w; 1717 s; 1643 m; 1592 m; 1578 w; 1493 s; 1446 m; 1420 m; 1370 s; 1294 m; 1257 s; 1180 w; 1146 s; 1088 m; 1072 m; 1050 w; 1025 m; 1004 w; 981 m; 916 w; 875 m; 840 w; 827 w; 771 m; 754 m; 705 s; 687 m; 602 w; 588 m; 563 w; 529 w; 429 w; 408 m. MS (ESI): m/z (%) = 253 ([M^+], 4); 134 (100); 119 (4); 106 (37); 91 (6); 77 (38); 65 (4); 51 (10); 39 (3). HRMS calcd for $C_{16}H_{15}O_2N$: 253.10973, found: 253.10977. Retention time: 23.1 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.3.4. 1-Phenylvinyl *N,N*-diphenylcarbamate 11. Crystallization from acetone/diethylether/*n*-hexane 1:2:5 yielded white-greenish crystals. Yield: 38%. Mp: 72–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26–7.21 (m, 15H, Ph); 5.40 (1H, d, J = 2.2 Hz, =CH_2); 5.14 (1H, d, J = 2.2 Hz, =CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 153.2; 152.5; 142.2; 134.7; 129.1; 128.8; 128.4; 126.8; 126.5; 125.0; 101.6. IR (KBr, cm^{-1}): 3088 w; 3057 m; 1952 w; 1879 w; 1801 w; 1721 s; 1646 m; 1590 m; 1492 s; 1451 m; 1384 w; 1347 s; 1328 m; 1307 m; 1293 m; 1256 s; 1201 s; 1184 m; 1172 m; 1097 m; 1078 m; 1044 m; 1032 m; 1024 m; 913 w; 870 m; 836 w; 770 s; 761 s; 694 s; 638 m; 620 w; 597 m; 566 w; 530 m; 512 m; 443 w; 412 w. MS (ESI): m/z (%) = 315 ([M^+], 13); 196 (100); 168 (46); 103 (17); 91 (4); 77 (22); 51 (7). HRMS calcd for $C_{21}H_{17}O_2N$: 315.12538, found: 315.12538. Retention time: 28.2 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.3.5. (*Z*)-1-Phenylprop-1-enyl *N,N*-diethylcarbamate 12.[18] Colourless oil was obtained after column chromatography (eluent: ethyl acetate/*n*-hexane 1:10). Yield: 38%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40 (m, 2H, *o*-Ph); 7.30 (m, 2H, *m*-Ph); 7.23 (m, 2H, *p*-Ph); 5.85 (q, 1H, $^3J_{1,2}$ = 7.0 Hz, H-2); 3.49, 3.36 (2q, 4H, H-5, H-5′); 1.74 (d, 3H, $^3J_{1,2}$=7.0 Hz, H-1); 1.29, 1.17 (2t, 6H, $^3J_{5,6}$ = 7.0 Hz, $^3J_{5',6'}$ = 7.0 Hz, H-6, H-6′). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 153.4 (C=O); 147.3 (C–O); 136.0 (*i*-Ph); 128.3 (*m*-Ph); 127.6 (*p*-Ph); 124.3 (*o*-Ph); 112.4 (C-2); 42.1, 41.7 (C-5, C-5′); 14.4, 13.4 (C-6, C-6′); 11.4 (C-1). IR (KBr, cm^{-1}): 3058 w; 2975 m; 2934 m; 2875 w; 1717 s; 1673 m; 1600 w; 1577 w; 1495 m; 1474 m; 1458 m; 1420 s; 1380 m; 1351 w; 1313 m; 1258 s; 1225 m; 1158 s; 1116 m; 1097 m; 1061 m; 1033 w; 1006 m; 972 w; 951 w; 926 w; 851 w; 793 w; 753 s; 692 m; 652 w; 637 w; 574 w. MS (ESI): m/z (%) = 233 ([M^+], 6); 115 (9); 105 (8); 100 (100); 77 (12); 72 (52); 44 (12). HRMS calcd for $C_{14}H_{19}O_2N$: 233.14103, found: 233.14101. Retention time: 19.3 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5). Retention time (HPLC): 8.72 min (eluent: *n*-hexane/ethanol 98:2; flow: 1.0 ml/min).

4.3.6. 1*H*-Inden-3-yl *N,N*-diethyl carbamate 13. An orange oil was obtained after column chromatography (eluent: ethyl acetate/*n*-hexane 1:10). Yield: 58%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34–7.10 (m, 4H); 6.19 (t, 1H, J = 2.3 Hz, CH); 3.41–3.27 (m, 4H, CH_2CH_3); 3.29 (d, 2H, J = 2.3 Hz, CH_2CH); 1.22–1.08 (m, 6H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 153.0; 149.4; 141.9; 139.7; 126.1; 125.4; 124.0; 117.8; 113.6; 42.3; 42.1; 34.8; 14.3; 13.4. IR (KBr, cm^{-1}): 3074 w; 3024 w; 2975 m; 2934 m; 2890 m; 1726 s; 1653 w; 1616 m; 1605 m; 1577 m; 1474 m; 1459 m; 1420 s; 1380 m; 1361 m; 1316 m; 1267 s; 1235 m; 1223 m; 1204 m; 1172 s; 1156 s; 1118 m; 1098 m; 1076 m; 1017 w; 973 m; 953 m; 932 m; 915 w; 844 w; 761 s; 717 m; 635 w; 593 w; 553 w; 511 w; 467 w; 412 w. MS (ESI): m/z (%) = 231 ([M^+], 6); 131 (10); 115 (6); 103 (11); 100 (100); 77 (14); 72 (62); 44 (17). HRMS calcd for $C_{14}H_{17}O_2N$: 231.12538; Found: 231.124840. Retention time: 21.3 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.3.7. 3,3-Dimethylbut-1-en-2-yl *N,N*-diethyl carbamate 14. A colourless oil was obtained after column chromatography (eluent: ethyl acetate/*n*-hexane 1:3). Yield: 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.76 (d, 1H, J = 1.9 Hz, =CH_2); 4.64 (d, 1H, J = 1.9 Hz, =CH_2); 3.31 (q, 4H, J = 7.0 Hz, CH_2CH_3); 1.16–1.12 (br, 6H, CH_2CH_3); 1.10 (s, 9H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 163.0; 154.1; 96.2; 42.0; 41.6; 36.2; 27.9; 14.2; 13.4. IR (KBr, cm^{-1}): 3125 w; 2973 s; 2936 m; 2876 m; 1720 s; 1653 m; 1555 w; 1506 w; 1474 m; 1461 m; 1419 s; 1380 m; 1362 m; 1317 m; 1264 s; 1225 m; 1148 s; 1097 m; 1054 m; 979 m; 938 w; 859 m; 786 m; 756 m; 703 w; 655 w; 593 w; 488 w. MS (ESI): m/z (%) = 199 ([M^+], 1); 118 (1); 100 (100); 85 (2); 72 (50); 67 (3); 55 (5); 44 (15). HRMS calcd for $C_{11}H_{21}O_2N$: 199.15668, found: 199.155983. Retention time: 11.5 min (30 m HP Agilent Technologies 50-8-260/5-8-280/5-8-300/5).

4.4. General procedure for the catalytic hydrogenation of enol carbamates

The catalyst was generated in situ by stirring [Rh(cod)$_2$]-BF_4 (0.0024 mmol) and the corresponding 4,5-dihydro-3*H*-dinaphthophosphepines ligand (0.005 mmol) in 1.0 ml of solvent for a period of 10 min and afterwards transferring via syringe into the autoclave. A solution of the enol carbamate (0.24 mmol) and 1.0 ml solvent was transferred via syringe into the autoclave. Then, the autoclave was charged with hydrogen and stirred at the required temperature. After a predetermined time the hydrogen was released and the reaction mixture passed through a short plug of silica gel. The conversion and enantioselectivity were measured by GC and HPLC without further modifications.

4.4.1. 1-Phenylethyl *N,N*-diethylcarbamate 8a. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31–7.11 (m, 5H, Ph); 5.73 (d, 1H, J = 6.5 Hz, CH); 3.20 (q, 4H, J = 7.0 Hz, CH_2); 1.44 (d, 3H, J = 6.5 Hz, CH_3); 1.02 (t, 6H, J = 7.0 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 155.1; 142.6; 128.2; 127.3; 125.7; 72.6; 41.5; 41.1; 22.7; 14.0; 13.4. IR (KBr, cm^{-1}): 3087 w; 3064 w; 3033 w; 2977 s; 2933 m; 2875 w; 1700 s; 1630 m; 1586 w; 1539 w; 1495 m; 1476 s; 1457 s; 1425 s; 1379 m; 1316 m; 2174 s; 1227 m; 1210 m; 1172 s; 1069 s; 1030 m; 1010 m; 998 m; 973 m; 940 w; 911 w; 877 w; 787 m; 766 m; 700 s; 630 w; 576 w; 535 m. MS (ESI): m/z (%) = 221 ([M^+], 2); 105 (100); 100 (5); 77 (16); 72 (5); 58 (7); 51 (6); 44 (8). HRMS calcd for $C_{13}H_{19}O_2N$: 221.14103, found: 221.140593. $[\alpha]_D^{23}$ = −146.1 (*c* 0.5, CH_2Cl_2/MeOH, 96% ee (*S*)). Conversions were determined by GC (Agilent Technologies, 30 m,

50–300 °C, (50-8-260/5-8-280/5-8-300/5)) and ees by HPLC (Whelk (*R*,*R*), (*S*)-**8a** 8.29 min and (*R*)-**8a** 28.7 min (eluent: *n*-hexane/ethanol 99:1; flow: 1.0 ml/min)).

4.4.2. (*S*)-1-Phenylethyl *N*,*N*-diethylcarbamate 8a. To a solution of (*S*)-1-phenylethanol (3.3 mmol) in THF (10 ml) was added NaH (3.4 mmol). The solution was stirred for 30 min at room temperature under an argon atmosphere. The solution was cooled to 0 °C and *N*,*N*-diethyl carbamoyl chloride (3.4 mmol) in THF (5 ml) was added. After stirring for 2 h at room temperature the reaction was quenched with water. The mixture was extracted with ethylacetate/*n*-hexane (1:1), washed with brine and dried over Na_2SO_4. The solvents were removed in vacuum and the crude oil was purified by flash column chromatography (ethylacetate/*n*-hexane 1:1) to yield a colourless oil (yield: 56%). The analytical data are in agreement with **8a** obtained by the hydrogenation protocol.

4.4.3. 1-Phenylethyl *N*,*N*-dimethylcarbamate 9a. Oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.34$–7.22 (m, 5H, Ph); 5.78 (q, 1H, $J = 6.6$ Hz, CH); 2.93 (br s, 3H, CH_3); 2.88 (br s, 3H, CH_3); 1.51 (d, 3H, $J = 6.6$ Hz, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 156.0$; 142.7; 128.5; 127.6; 125.9; 73.1; 36.4; 35.9; 22.9. IR (KBr, cm^{-1}): 3033 w; 2980 w; 2932 w; 1704 s; 1495 m; 1450 m; 1393 m; 1273 w; 1191 s; 1069 m; 1030 w; 1007 w; 995 w; 894 w; 844 w; 766 m; 700 m; 638 w; 569 w; 532 w. MS (ESI): *m*/*z* (%) = 193 ([M$^+$], 6); 134 (13); 121 (1); 105 (100); 90 (1); 77 (13); 63 (1); 51 (4). HRMS calcd for $C_{11}H_{15}O_2N$: 193.10973, found: 193.109345. $[\alpha]_D^{22} = -2.9$ (*c* 0.3, $CHCl_3$, 75% ee (*S*)). Conversions were determined by NMR and ees by HPLC (Chiralpak AD-H, (*R*)-**9a** 23.6 min and (*S*)-**9a** 31.3 min, eluent: *n*-hexane/ethanol 99:1; flow: 1.0 ml/min). The absolute configuration was assigned by analogy.

4.4.4. 1-Phenylethyl *N*-methyl *N*-phenylcarbamate 10a. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.35$–7.16 (m, 10H, Ph); 5.83 (q, 1H, $J = 6.5$ Hz, CH); 3.28 (s, 3H, CH_3); 1.47 (d, 3H, $J = 6.5$ Hz, $CHCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 155.0$; 143.4; 142.3; 128.8; 128.4; 127.6; 125.9 (br); 125.8; 125.7 (br); 73.8; 37.7; 23.0. IR (KBr, cm^{-1}): 3064 w; 3033 w; 3980 m; 2932 w; 1706 s; 1598 m; 1496 s; 1453 m; 1437 m; 1422 m; 1374 s; 1327 m; 1299 s; 1277 s; 1210 m; 1159 s; 1113 m; 1063 s; 1029 m; 1010 m; 997 m; 974 m; 912 w; 885 w; 819 w; 762 s; 698 s; 665 w; 625 w; 599 w; 544 m. MS (ESI): *m*/*z* (%) = 255 ([M$^+$], 1); 211 (2); 196 (7); 151 (1); 134 (2); 105 (100); 91 (1); 77 (20); 65 (2); 51 (7). HRMS calcd for $C_{16}H_{17}NO_2$: 255.12538, found: 255.125229. $[\alpha]_D^{22} = +19.9$ (*c* 0.26, $CHCl_3$, 65% ee (*S*)). Conversions were determined by NMR and ees by HPLC (Chiralcel OD-H, (*R*)-**10a** 25.4 min and (*S*)-**10a** 47.2 min, eluent: *n*-hexane/ethanol 99:1; flow: 1.0 ml/min). The absolute configuration was assigned by analogy.

4.4.5. 1-Phenylethyl *N*,*N*-diphenylcarbamate 11a. Crystals. Mp: 76–78 °C. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.32$–7.14 (m, 15H, Ph), 5.88 (q, 1H, $J = 6.5$ Hz, CH), 1.47 (d, 3H, $J = 6.5$ Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 154.1$; 142.6; 141.9; 128.9; 128.4; 127.7; 127.0; 126.1; 125.9; 74.3; 22.9. IR (KBr, cm^{-1}): 3064 w; 3033 m; 2984 m; 2934 w; 1702 s; 1591 s; 1491 s; 1450 m; 1369 s; 1343 s; 1325 s; 1299 s; 1281 s; 1220 s; 1208 s; 1178 m; 1159 w; 1128 w; 1058 s; 1048 s; 1023 s; 1008 m; 993 m; 951 w; 913 w; 901 w; 860 m; 837 w; 814 w; 781 m; 764 s; 758 s; 693 s; 672 m; 642 w; 622 w; 603 w; 548 s; 516 m; 492 w. MS (ESI): *m*/*z* (%) = 317 ([M$^+$], 2); 273 (2); 258 (2); 196 (1); 169 (41); 139 (1); 105 (100); 77 (12); 51 (5). HRMS calcd for $C_{21}H_{19}O_2N$: 317.14103, found: 317.141098. $[\alpha]_D^{21} = -16.8$ (*c* 0.33, $CHCl_3$, 76% ee (*R*)). Conversions were determined by NMR and ees by HPLC (Chiralcel OD-H, (*R*)-**11a** 6.8 min and (*S*)-**11a** 9.6 min, eluent: *n*-hexane/ethanol 99.5:0.5; flow: 1.0 ml/min). The absolute configuration was assigned by analogy.

4.4.6. 1-Phenylpropyl *N*,*N*-diethylcarbamate 12a. Colourless oil. Yield: 98%. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.28$–7.16 (m, 5H, Ph); 5.54 (1H, dd, $J = 6.4$ Hz, $J = 7.2$ Hz, $CHCH_2$); 3.23 (br, 4H, NCH_2); 1.83 (m, 2H, $CHCH_2CH_3$); 1.06 (br, 6H, NCH_2CH_3); 0.83 (t, 3H, $J = 7.4$ Hz, $CHCH_2CH_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 155.5$; 141.6; 128.3; 127.5; 126.4; 77.8; 41.8; 41.3; 29.9; 14.3; 13.6; 9.9. IR (KBr, cm^{-1}): 2972 m; 2934 m; 2877 w; 1700 s; 1475 m; 1457 m; 1424 m; 1380 w; 1273 s; 1226 w; 1171 s; 1063 m; 987 m; 903 w; 763 w; 700 m; 528 w. MS (ESI): *m*/*z* (%) = 235 ([M$^+$], 9); 162 (15); 119 (54); 100 (12); 91 (100); 77 (7). HRMS calcd for $C_{14}H_{19}O_2N$: 235.15668, found: 235.157242. $[\alpha]_D^{23} = -143.7$ (*c* 0.5, CH_2Cl_2/MeOH, 50% ee). Conversions and ees were determined by GC (Retention time: 17.9 min, 30 m HP Agilent Technologies 50–300 °C: 50-8-260/5-8-280/5-8-300/5) and HPLC (Whelk (*R*,*R*), *n*-hexane/ethanol 98:2, flow 1.0 ml/min, (*S*)-**12a** 4.84 min and (*R*)-**12a** 10.10 min).

4.4.7. 3,3-Dimethylbutan-2-yl *N*,*N*-diethylcarbamate 14a. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 4.56$ (q, 1H, $J = 6.4$ Hz, CH); 3.25 (br d, 4H, CH_2); 1.12 (d, 3H, $J = 6.4$ Hz, CH_3); 1.10 (t, 6H, CH_2CH_3); 0.90 (s, 9H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) $\delta = 155.9$; 78.1; 41.6; 34.4; 25.9; 15.3; 14.2. IR (KBr, cm^{-1}): 2971 s; 2935 m; 2874 w; 1696 s; 1653 w; 1559 w; 1540 w; 1506 w; 1475 m; 1457 m; 1423 s; 1395 w; 1378 m; 1365 w; 1316 w; 1275 m; 1227 w; 1210 w; 1174 m; 1076 m; 1007 w; 972 w; 893 w; 824 w; 783 w; 768 w; 744 w; 697 w; 617 w; 537 w. MS (ESI): *m*/*z* (%) = 201 ([M$^+$], 7); 186 (3); 144 (2); 116 (16); 100 (100); 85 (44); 72 (25); 58 (21); 43 (46). HRMS calcd for $C_{11}H_{23}O_2N$: 201.17233, found: 201.172292. $[\alpha]_D^{22} = +135$ (*c* 0.04, $CHCl_3$/MeOH, 67% ee). Conversions and ees were determined by GC (50m Chiraldex β-PH, 50.0 m × 250 μm × 0.25 μm, 100/25-4-180/5, (−)-**14a** 25.6 min and (+)-**14a** 26.0 min).

4.5. X-ray crystallographic studies of 5a, 5b and 6

Data were collected with a STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structures were solved by direct methods[19] and refined by full-matrix least-squares techniques against F^2.[20] XP (BRUKER AXS) was used for graphical representations. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 641493–641495. Copies of the data can be obtained free of charge on application to http://www.ccdc.cam.ac.uk/data_request/cif.

4.5.1. Compound 5a. Space group $P3_121$, trigonal, $a = 11.174(2)$, $c = 32.520(7)$ Å, $V = 3516(1)$ Å^3, $Z = 6$, $\rho_{calcd} = 1.230$ g cm^{-3}, 18,941 reflections measured, 3621 were independent of symmetry, of which 2550 were observed ($I > 2\sigma(I)$), $R1 = 0.055$, wR^2 (all data) $= 0.145$, 281 parameters, Flack parameter $x = 0.05(18)$.

4.5.2. Compound 5b. Space group $P2_1$, monoclinic, $a = 7.985(2)$, $b = 11.407(2)$, $c = 12.625(3)$ Å, $\beta = 98.27(3)°$, $V = 1138.0(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.262$ g cm^{-3}, 15,617 reflections measured, 4452 were independent of symmetry, of which 2645 were observed ($I > 2\sigma(I)$), $R1 = 0.034$, wR^2 (all data) $= 0.059$, 289 parameters, Flack parameter $x = 0.02(8)$.

4.5.3. Compound 6. Space group $P2_1$, monoclinic, $a = 9.445(2)$, $b = 16.801(3)$, $c = 14.081(3)$ Å, $\beta = 91.75(3)°$, $V = 2233.4(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.292$ g cm^{-3}, 13,676 reflections measured, 7244 were independent of symmetry, of which 5881 were observed ($I > 2\sigma(I)$), $R1 = 0.047$, wR^2 (all data) $= 0.118$, 577 parameters, Flack parameter $x = -0.07(10)$.

Acknowledgements

We thank Mrs. M. Heyken, Mrs. S. Buchholz and Dr. C. Fischer (all Leibniz-Institut für Katalyse e.V. an der Universität Rostock) for excellent technical and analytical assistance. Dr. B. Hagemann is gratefully thanked for the synthesis of ligand **4e**. Generous financial support from the state of Mecklenburg-Western Pomerania and the BMBF as well as the Deutsche Forschungsgemeinschaft (Leibniz-price) are gratefully acknowledged.

References

1. (a) Lennon, I. C.; Ramsden, J. A. *Org. Process Res. Dev.* **2005**, *9*, 110–112; (b) Hawkins, J. M.; Watson, T. J. N. *Angew. Chem.* **2004**, *116*, 3286–3290; (c) Noyori, R.; Ohkuma, T. *Angew. Chem.* **2001**, *113*, 40–75; Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process Res. Dev.* **2000**, *4*, 346–348; (d) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
2. (a) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686–694; (b) Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C. *Appl. Catal. A: Gen.* **2001**, *221*, 3–13.
3. Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315–324.
4. Komarov, I. V.; Börner, A. *Angew. Chem.* **2001**, *113*, 1237–1240.
5. (a) Arnold, L. A.; Imobos, R.; Manoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. *Tetrahedron* **2000**, *56*, 2865–2878; (b) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540; (c) Minnaard, A. J.; van den Berg, M.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Chim. Oggi* **2001**, *19*, 12–13; (d) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553; (e) van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003–1007; (f) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308–323; (g) Peña, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 475–478; (h) Jiang, X.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223–2229; (i) Eelkema, R.; van Delden, R. A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5013–5016; (j) Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045–8052; (k) Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Org. Lett.* **2004**, *6*, 1733–1735; (l) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943–951; (m) Panella, L.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 4177–4180; (n) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4209–4212; (o) Panella, L.; Aleixandre, A. M.; Kruidhof, G. J.; Robertus, J.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *J. Org. Chem.* **2006**, *71*, 2026–2036.
6. (a) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333–6336; (b) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3891; (c) Reetz, M. T.; Mehler, G.; Meiswinkel, G.; Sell, T. *Tetrahedron Lett.* **2002**, *43*, 7941–7943; (d) Reetz, M. T.; Mehler, G.; Meiswinkel, G.; Sell, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 790–793; (e) Reetz, M. T.; Mehler, G. *Tetrahedron Lett.* **2003**, *44*, 4593–4596; (f) Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167; (g) Reetz, M. T.; Li, X. G. *Tetrahedron* **2004**, *60*, 9709–9714; (h) Reetz, M. T.; Ma, J.-A.; Goddard, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 412–414; (i) Reetz, M. T.; Fu, Y.; Meiswinkel, A. *Angew. Chem.* **2006**, *118*, 1440–1443; (j) Reetz, M. T.; Li, X. *Synthesis* **2005**, 3183–3185; (k) Reetz, M. T.; Bondarev, O. G.; Gais, H.-J.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 5643–5646; (l) Reetz, M. T.; Meiswinkel, A.; Mehler, G.; Angermund, K.; Graf, M.; Thiel, W.; Mynott, R.; Blackmond, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 10305–10313; (m) Reetz, M. T.; Li, X. *Angew Chem., Int. Ed.* **2005**, *44*, 2959–2962; (n) Reetz, M. T.; Surowiec, M. *Heterocycles* **2006**, *67*, 567–574.
7. (a) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961–962; (b) Martorell, A.; Naasz, R.; Feringa, B. L.; Pringle, P. G. *Tetrahedron: Asymmetry* **2001**, *12*, 2497–2499.
8. (a) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem.* **2002**, *114*, 2454–2456; (b) Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. *J. Org. Chem.* **2004**, *69*, 4648–4655; (c) Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2004**, *69*, 8157–8160.
9. (a) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Manassero, M. *Tetrahedron: Asymmetry* **1994**, *5*, 511–514; (b) Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Valle, G. *J. Org. Chem.* **1994**, *59*, 6363–6371; (c) Gladiali, S.; Fabbri, D. *Chem. Ber./Recl. Trav. Chim. Pays-Bas* **1997**, *130*, 543–554; (d) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genet, J.-P. *Chem. Commun.* **2004**, 850–851; (e) Zanoni, G.; Gladiali, S.; Marchetti, A.; Piccinini, P.; Tredici, I.; Vidari, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 846–849; (f)

Alberico, E.; Nieddu, I.; Taras, R.; Gladiali, S.. *Helv. Chim. Acta* **2006**, *89*, 1716–1729.
10. (a) Chi, Y.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 4849–4852; (b) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3506–3509; (c) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120–4122; (d) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425–3428; (e) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679–1681.
11. (a) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett.* **2002**, *43*, 4977–4980; (b) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *J. Organomet. Chem.* **2003**, *675*, 91–96; (c) Junge, K.; Hagemann, B.; Enthaler, S.; Spannenberg, A.; Michalik, M.; Oehme, G.; Monsees, A.; Riermeier, T.; Beller, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; (d) Junge, K.; Hagemann, B.; Enthaler, S.; Oehme, G.; Michalik, M.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem., Int. Ed.* **2004**, *43*, 5066–5069; (e) Hagemann, B.; Junge, K.; Enthaler, S.; Michalik, M.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2005**, *347*, 1978–1986; (f) Enthaler, S.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *Eur. J. Org. Chem.* **2006**, 2912–2917.
12. (a) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426–1429; (b) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235; (c) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430–431.
13. Kasák, P.; Mereiter, K.; Widhalm, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3416–3426.
14. (a) Olofson, R. A.; Cuomo, J.; Bauman, B. A. *J. Org. Chem.* **1978**, *43*, 2073–2075; (b) Jiang, X.-b.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223–2229.
15. Institute of Automation (IAT), Richard Wagner Str. 31/H. 8, 18119 Rostock-Warnemünde, Germany.
16. Tsukamoto, M.; Yoshimura, M.; Tsuda, K.; Kitamura, M. *Tetrahedron* **2006**, *62*, 5448–5453.
17. The reaction is stopped after 1 h and a black precipitate (rhodium-black) is formed.
18. During the synthesis the *Z*-isomer is formed exclusively, which was characterized by NMR. In a NOESY spectrum a correlation was observed between the *ortho*-hydrogen of the phenyl group and the olefinic hydrogen.
19. Sheldrick, G. M. SHELXS-97, Program of Crystal Structure Solution; University of Göttingen: Germany, 1997.
20. Sheldrick, G. M. SHELXL-97, Program of Crystal Structure Refinement; University of Göttingen: Germany, 1997.

6.1.1. An environmentally benign process for the hydrogenation of ketones with homogeneous iron catalysts

Stephan Enthaler, Bernhard Hagemann, Giulia Erre, Kathrin Junge, and Matthias Beller*, *Chem. Asian. J.* **2006**, *1*, 598–604.

Contributions

The $BuP(Ad)_2$ ligand was synthesized by Dr. R. Jackstell.

DOI: 10.1002/asia.200600105

An Environmentally Benign Process for the Hydrogenation of Ketones with Homogeneous Iron Catalysts

Stephan Enthaler, Bernhard Hagemann, Giulia Erre, Kathrin Junge, and Matthias Beller*[a]

Abstract: Iron complexes generated in situ catalyze homogeneously the transfer hydrogenation of aliphatic and aromatic ketones by utilizing 2-propanol as a hydrogen donor in the presence of base. The influence of different reaction parameters on the catalytic activity is investigated in detail by applying a three-component catalyst system composed of an iron salt, 2,2′:6′,2″-terpyridine, and PPh_3. The scope and limitations of the described catalyst is shown in the reduction of 11 different ketones. In most cases, high conversion and excellent chemoselectivity are obtained. Mechanistic studies indicate a monohydride reaction pathway for the homogeneous iron catalyst.

Keywords: homogeneous catalysis · iron · ketones · ligand effects · transfer hydrogenation

Introduction

Catalysis is a key technology for the advancement of green chemistry, specifically for waste prevention, decreasing energy consumption, achieving high atom efficiency and generating advantageous economics.[1] There is an increasing interest in substituting toxic and expensive late transition metals by readily available and less-toxic metals. In this regard, the use of iron catalysts is especially desirable.[2] So far, homogeneous iron catalysts have been successfully applied for various C–C coupling reactions such as Friedel–Crafts-type reactions, olefin polymerizations, cross-couplings, cycloadditions, and substitution reactions.[3] However, much less is known in the area of industrially important catalytic reductions. Here, comparatively few Fe-catalyzed hydrogenations have been established, mainly for the reduction of olefins[4] and nitro compounds.[5] Clearly, the quest for practical hydrogenation catalysts based on Fe complexes constitutes a major challenge for the development of more sustainable reductions.

Recently, we became interested in applying homogeneous Fe catalysts with respect to C–H functionalization reactions of arenes.[6] Based on that work and our ongoing research in hydrogenation chemistry,[7] we started to explore Fe catalysts for transfer hydrogenations[8] of carbonyl compounds. To the best of our knowledge, only iron carbonyls[9,10] or complexes that contain tetradentate aminophosphines[11] or phosphines[12] have been described for the transfer hydrogenations of ketones and α,β-unsaturated carbonyl compounds. In the latter case, mainly hydrogenation of the olefin occurred.[9,12]

Our goal is to develop a practical Fe hydrogenation catalyst system, which should be easy to prepare and tunable. Thus, the use of commercially available Fe complexes in combination with two different ligands (phosphines and amines) instead of tetradentate ligands seems to be a useful approach. Based on this idea, we report herein the application of new three-component iron catalysts prepared in situ based on iron salts, 2,2′:6′,2″-terpyridine (terpy), and PPh_3. These catalysts give excellent yield and selectivity in the reduction of aromatic and aliphatic ketones to alcohols.

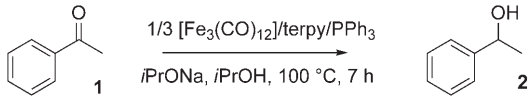
Results and Discussion

As a starting point, 2-propanol-based transfer hydrogenation of acetophenone (**1**) was examined with Fe catalysts in the presence of combinations of nitrogen and phosphorus ligands. In exploratory experiments, terpy and PPh_3 were used as ligands. Typically, the precatalyst was prepared in situ by stirring a solution of $[Fe_3(CO)_{12}]$ (0.3 mol%), terpy (1 mol%), and PPh_3 (1 mol%) in 2-propanol (1.0 mL)

[a] S. Enthaler, B. Hagemann, G. Erre, Dr. K. Junge, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Str. 29a
18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: matthias.beller@ifok-rostock.de

for 16 h at 65 °C. Initially, we investigated the influence of terpy and PPh_3 in the presence of $[Fe_3(CO)_{12}]$, which can be easily handled without special precautions (Table 1). To our

Table 1. Transfer hydrogenation of acetophenone (**1**) with $[Fe_3(CO)_{12}]$/terpy/PPh_3 catalyst.[a]



Entry	Terpy[b]	PPh_3[b]	Yield [%][c]	Selectivity [%][d]
1	–	–	23	>99
2	1	1	78	>99
3	1	–	18	>99
4	–	1	6	>99
5	–	2	21	>99
6	–	10	29	>99
7	5	1	27	>99
8	1	5	24	>99

[a] Reaction conditions: in situ catalyst (0.0038 mmol) ($[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), PPh_3 (0.0038 mmol), 2-propanol (2.0 mL) for 16 h at 65 °C), *i*PrONa (0.019 mmol), 5 min at 100 °C, then addition of **1** (0.38 mmol), 7 h at 100 °C. [b] Ligand to Fe ratio. [c] Yield was determined by GC (50 m Lipodex E, 95–200 °C) with diglyme as internal standard (yield is equivalent to conversion). [d] Selectivity refers to chemoselectivity.

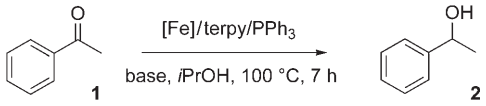
delight, a 1:1 mixture of terpy and PPh_3 gave an active catalyst for the test reaction that was superior to all other combinations (Table 1, entry 2). Notably, low catalytic activity was observed without the use of any ligands (Table 1, entry 1). Increasing the ligand concentration resulted in a significant decrease in activity (Table 1, entries 7 and 8). Importantly, the catalyst systems differ mainly with respect to reactivity, as the chemoselectivity was excellent in all cases.

Next, the influence of base and the iron precatalyst was investigated in more detail (Table 2). The best results were obtained with $[Fe_2(CO)_9]$ and $[Fe_3(CO)_{12}]$ in the presence of catalytic amounts of sodium 2-propylate or sodium *tert*-butylate (Table 2, entries 1, 6, 16). Surprisingly, the most commonly used bases for transfer hydrogenation, such as NaOH, KOH, and *t*BuOK, showed only low activity in this model reaction (Table 2, entries 3–5). Furthermore, different inorganic bases such as K_2CO_3, Cs_2CO_3, and K_3PO_4 (Table 2, entries 7–9) as well as nitrogen-containing organic bases, for instance, pyridine, NEt_3, $N(iPr)_2Et$, DBU, and DABCO (Table 2, entries 10–14), did not prove to be effective. As expected, no transfer of hydrogen was observed in the absence of base (Table 2, entry 15).

To improve the catalytic system, various iron sources with different oxidation states (0, +2, and +3) were tested. Besides $[Fe_2(CO)_9]$ and $[Fe_3(CO)_{12}]$, $FeCl_2$ (Table 2, entry 20) also produced reasonable conversion. To facilitate the formation of active iron hydride complexes, we tested $[Et_3NH][HFe(CO)_4]$[13] as precatalyst, but only limited conversion was detected (Table 2, entry 19).

Following these results, we focused on the nature of the ligands. The results in Table 3 indicate no improvement of

Table 2. Influence of different bases and iron sources in the Fe-catalyzed transfer hydrogenation of **1**.[a]

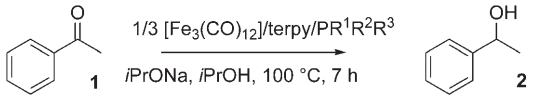


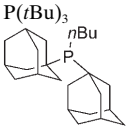
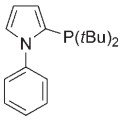
Entry	Iron source	Base	Yield [%][b]
1	$[Fe_3(CO)_{12}]$	*i*PrONa	78
2	$[Fe_3(CO)_{12}]$	LiOH	2
3	$[Fe_3(CO)_{12}]$	NaOH	<1
4	$[Fe_3(CO)_{12}]$	KOH	<1
5	$[Fe_3(CO)_{12}]$	*t*BuOK	12
6	$[Fe_3(CO)_{12}]$	*t*BuONa	76
7	$[Fe_3(CO)_{12}]$	K_2CO_3	3
8	$[Fe_3(CO)_{12}]$	Cs_2CO_3	3
9	$[Fe_3(CO)_{12}]$	K_3PO_4	<1
10	$[Fe_3(CO)_{12}]$	pyridine	1
11	$[Fe_3(CO)_{12}]$	NEt_3	2
12	$[Fe_3(CO)_{12}]$	$N(iPr)_2Et$	<1
13	$[Fe_3(CO)_{12}]$	DBU	<1
14	$[Fe_3(CO)_{12}]$	DABCO	<1
15	$[Fe_3(CO)_{12}]$	–	0
16	$[Fe_2(CO)_9]$	*i*PrONa	84
17	$[Fe(CO)_5]$	*i*PrONa	2
18	$[CpFe(CO)_2I]$	*i*PrONa	3
19	$[Et_3NH][HFe(CO)_4]$	*i*PrONa	11
20	$FeCl_2$	*i*PrONa	45
21	$FeCl_3 \cdot xH_2O$	*i*PrONa	<1
22	$FeBr_2$	*i*PrONa	9
23	$FeSO_4 \cdot 7H_2O$	*i*PrONa	9
24	$Fe(acac)_2$	*i*PrONa	17
25	$Fe(acac)_3$	*i*PrONa	3

[a] Reaction conditions: in situ catalyst (0.0038 mmol) ($[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), PPh_3 (0.0038 mmol), 2-propanol (2.0 mL) for 16 h at 65 °C), base (0.019 mmol), 5 min at 100 °C, then addition of **1** (0.38 mmol), 7 h at 100 °C. [b] Yield was determined by GC (50 m Lipodex E, 95–200 °C) with diglyme as internal standard (yield is equivalent to conversion). acac = Acetylacetonate, Cp = cyclopentadienyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene.

conversion when PPh_3 was substituted by other phosphorus ligands. Variation in the substitution pattern of PPh_3 with electron-donating (Table 3, entry 2) or electron-withdrawing groups (Table 3, entries 3–5) as well as more-basic and sterically hindered phosphines (Table 3, entries 6–9) decreased the yield of 1-phenylethanol (**2**). We also applied diphosphine ligands in the model reaction. Good activity was obtained with 1,1-bis-(diphenylphosphanyl)methane (dppm) and 1,2-bis(diphenylphosphanyl)ethane (dppe) (Table 3, entries 12–13). Next, we explored the nature of the nitrogen-containing ligand. To our surprise, substituted terpyridines such as 4′-chloro-2,2′:6′,2″-terpyridine (**3**), 6,6′-dibromo-2,2′:6,6′-terpyridine (**4**), and 4,4′,4″-tri-*tert*-butyl-2,2′:6,2″-terpyridine (**5**) led to a significant decrease in alcohol formation (Table 4, entries 1–4). Similarly, the application of structurally related *N*,*N*′,*N*″-ligands **6** and **7** showed no pronounced activity (Table 4, entries 5 and 6). However, in the presence of pyridine (3 mol %) and triphenylphosphine, a reasonable yield of **2** (54 %) was obtained. Clearly, Fe/pyridine/PPh_3 represents one of the least demanding homogenous transfer-hydrogenation catalysts around. Furthermore,

Table 3. Influence of phosphorus ligands in the Fe-catalyzed transfer hydrogenation of **1**.[a]



Entry	Phosphine	Conversion [%][b]
1	PPh_3	78
2	$P(p\text{-MeO-}C_6H_4)_3$	13
3	$P(p\text{-Me-}C_6H_4)_3$	22
4	$P(p\text{-F-}C_6H_4)_3$	23
5	$P(3,4\text{-}CF_3\text{-}C_6H_3)_3$	5
6	PCy_3	11
7	$P(t\text{Bu})_3$	32
8		34
9		31
10	$P(OPh)_3$	8
11	$P(O\text{i}Pr)_3$	7
12	$Ph_2PCH_2PPh_2$	64
13	$Ph_2P(CH_2)_2PPh_2$	50
14	$Ph_2P(CH_2)_4PPh_2$	3
15	$Ph_2P(CH_2)_6PPh_2$	3

[a] Reaction conditions: in situ catalyst (0.0038 mmol) ($[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), phosphorus ligand (0.0038 mmol), 2-propanol (2.0 mL) for 16 h at 65 °C), *i*PrONa (0.019 mmol), 5 min at 100 °C, then addition of **1** (0.38 mmol), 7 h at 100 °C. [b] Yield was determined by GC (50 m Lipodex E, 95–200 °C) with diglyme as internal standard (yield is equivalent to conversion). Cy = cyclohexyl.

the combination of (−)-sparteine and triphenylphosphine provided an active catalyst system (Table 4, entries 11–12).

Next, the optimized general protocol for transfer hydrogenations was applied to aromatic and aliphatic ketones. Here, both $[Fe_3(CO)_{12}]$/terpy/PPh_3 and $FeCl_2$/terpy/PPh_3 were tested for the reduction of 10 different ketones (Table 5). Acetophenone, 4-chloroacetophenone, 2-methoxyacetophenone, and propiophenone were hydrogenated in excellent yield and selectivity (92–99%) (Table 5, entries 1, 2, 5, 6). Acetophenones with electron-donating substituents in the *para* position gave good but somewhat lower yields (75–83%). A chloro substituent in the α position to the carbonyl group proved to be problematic and deactivated both catalysts (Table 5, entry 7). Aliphatic ketones are more challenging substrates than aromatic ketones, but they also react in excellent yield (95–99%).

Notably, similar activities for the reduction of ketones with regard to our $[Fe_3(CO)_{12}]$-based system were reported when other transition-metal carbonyl complexes, for instance, $[Ru_3(CO)_{12}]$-based catalysts, were applied.[14] The $[Fe_3(CO)_{12}]$- and $FeCl_2$-based catalysts showed no significant difference in productivity. Hence, we assume the formation of a similar active species. Indeed, the two catalyst systems produced similar conversion curves (Figure 1). At the start of the reaction, we observe in both cases an induction

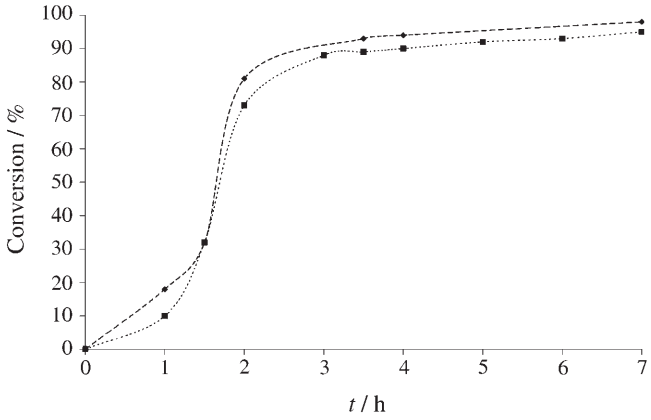


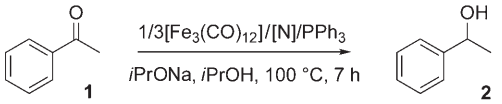
Figure 1. Conversion–time behavior of the different precatalysts containing $[Fe_3(CO)_{12}]$ and $FeCl_2$. Reaction conditions: in situ catalyst (0.0038 mmol) ($[Fe_3(CO)_{12}]$ (0.0013 mmol) or $FeCl_2$ (0.0038 mmol), terpy (0.0038 mmol), and PPh_3 (0.0038 mmol) in 2-propanol (2.0 mL), 16 h at 65 °C), *i*PrONa (0.38 mmol), 5 min at 100 °C, then addition of **1** (0.76 mmol), reaction at 100 °C. Conversion was determined by GC (50 m Lipodex E, 95-200 °C) with diglyme as internal standard (conversion is equivalent to yield). ◆ = $[Fe_3(CO)_{12}]$/terpy/PPh_3, ■ = $FeCl_2$/terpy/PPh_3.

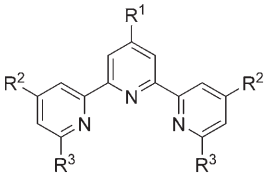
period of nearly one hour, whereby the $FeCl_2$ system showed a slightly lower reaction rate, probably due to the slower elimination of chlorides and the change of oxidation state. The induction period can be shortened by increasing the catalyst preformation time. Thus, when the precatalyst ($[Fe_3(CO)_{12}]$/terpy/PPh_3) was treated with a base for one hour instead of 5 min at the reaction temperature, an increase in conversion into 1-phenylethanol from 18% to 32% in the first hour was recorded.

Next, we focused our attention on the reaction mechanism. To exclude the formation of heterogeneous Fe catalysts,[15] a large excess of Hg(0) was added to the well-stirred reaction mixture after the reaction had proceeded for one hour, so that the "real" catalyst should be formed.[16,17] No significant suppression of the reaction rate in the reduction of **1** was observed (73% yield after 7 h), whereas a positive poisoning of the catalyst should have led to approximately 18% of **2** (see also Figure 1). In another experiment, the reaction was carried out under standard conditions and filtered through celite after one hour.[18] The filtrate was allowed to react for a further six hours. Thereafter, the applied celite was stirred with fresh 2-propanol, sodium 2-propylate, and **1** under reaction conditions for another six hours. The results obtained showed no suppression of reaction rate for the filtrate (92%), whereas no conversion was detected (< 1%) with the celite system. Consequently, both experiments indicate a definite homogeneous catalyst.

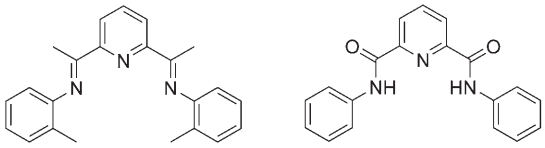
Various methods (^1H, ^{31}P, and ^{13}C NMR and IR spectroscopy and MS) were used for the characterization of the active catalyst species. Unfortunately, the structural composition of the catalyst is still unclear. No evidence for an Fe–H species was detected by ^1H NMR spectroscopy after reaction of the precatalyst with base (5 equiv).[19] The ^{31}P NMR spectrum of the precatalyst in $[D_4]$MeOH or $[D_8]$*i*PrOH showed three singlets with a ratio of 20:1:10 at −5.3 ppm

Table 4. Variation of nitrogen ligands in the Fe-catalyzed transfer hydrogenation of **1**.[a]





3 R^1 = Cl; R^2 = H; R^3 = H
4 R^1 = H; R^2 =Br; R^3 = Br
5 R^1 = *t*Bu; R^2 = *t*Bu; R^3 = *t*Bu



6 **7**

Entry	Ligand	Ligand/metal	Conversion [%][b]
1	terpy	1	78
2	**3**	1	23
3	**4**	1	28
4	**5**	1	14
5	**6**	1	13
6	**7**	1	7
7	2,2′-bipyridine	1	8
8	2,2′-bipyridine	2	6
9	tmeda[c]	1	18
10	tmeda[c]	2	13
11	(−)-sparteine	1	43[d]
12	(−)-sparteine	2	38[d]
13	pyridine	3	54
14	pyridine	6	5

[a] Reaction conditions: in situ catalyst (0.0038 mmol) ([$Fe_3(CO)_{12}$] (0.0013 mmol), nitrogen ligand (0.0038 mmol), PPh_3 (0.0038 mmol), 2-propanol (2.0 mL) for 16 h at 65 °C), *i*PrONa (0.019 mmol), 5 min at 100 °C, then addition of **1** (0.38 mmol), 7 h at 100 °C. [b] Yield was determined by GC (50 m Lipodex E, 95–200 °C) with diglyme as internal standard (yield is equivalent to conversion). [c] tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylendiamine. [d] A racemic mixture of **2** was detected.

(free PPh_3) and two unknown signals at 32.9 and 71.3 ppm.[20] The addition of 5 equivalents of base (sodium 2-propylate) with respect to iron and stirring of the mixture for 5 min at 100 °C did not affect the chemical shift and ratio of the observed ^{31}P NMR signals.[19] Mass spectrometric investigations also gave no clear information about the composition of the precatalyst, because indications for a number of possible candidates or fragments of labile complexes were detected, such as compounds containing terpy, PPh_3, CO, and Fe in a ratio of 1:1:1(2):1 or terpy, CO, and Fe in a ratio of 1:3:1. The utilization of [$Fe_3(CO)_{12}$] represents a potential option for IR spectroscopy. Hence, we recorded the IR spectra of our precatalyst in a solution of 2-propanol. The activation of the precatalyst by sodium 2-propylate (10 equiv) for 5 min at 100 °C resulted in the http://www.dict.cc/?s = disappearance of absorption signals at 1889 and 1718 cm^{-1}. Addition of **1** to the activated precatalyst led to the http://www.dict.cc/?s = disappearance of the signal at 1654 cm^{-1} and emergence of a signal at 1679 cm^{-1}. Interestingly, a similar behavior was described by Gao and co-workers when they followed the formation of the transfer-hydrogenation catalyst composed of [$Fe_3(CO)_{12}$] and tetradentate aminophosphines in 2-propanol in the presence of base.[11]

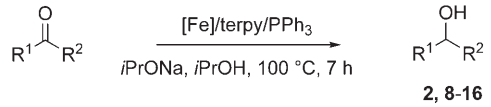
Although the nature of the active Fe–H species remains unclear, we turned our attention to the mechanism of the hydride transfer. To exclude a radical-type reduction, the reaction of cyclopropyl phenyl ketone was examined in more detail ("radical clock" substrate) (Table 5, entry 8). In the presence of [$Fe_3(CO)_{12}$]/terpy/PPh_3 catalyst, the corresponding cyclopropyl phenyl alcohol **14** was detected by ^1H NMR spectroscopy in > 99 % purity. There was apparently no radical-induced reduction, because no opening of the cyclopropyl ring occurred.[21] Consequently, a radical-reduction mechanism promoted by sodium alkoxides, whereby the transition metal plays a marginal role, can also be excluded.[22]

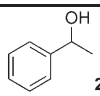
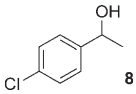
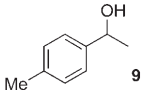
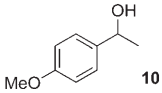
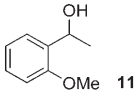
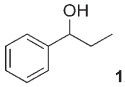
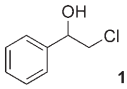
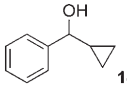
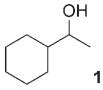
In general, for transition-metal-catalyzed transfer hydrogenation, two mechanisms are accepted: direct hydrogen transfer via formation of a six-membered cyclic transition state composed of metal and hydrogen donor and acceptor, and the hydridic route, which is subdivided into two pathways, the monohydride and the dihydride mechanism (Scheme 1). More specifically, the formation of monohydride metal complexes promote an exclusive hydride transfer from carbon (donor) to carbonyl carbon (acceptor) (Scheme 1, pathway A), whereas a hydride transfer from carbon (donor) to carbonyl carbon (acceptor) as well as carbonyl oxygen (acceptor) was proposed for the formation of dihydride metal complexes (Scheme 1, pathway B).[8a,c,e] Evidence for both pathways (hydridic route) were determined by various researchers when investigating the hydride transfer catalyzed by metal complexes of, for example, Ru, Rh, or Ir.[23] So far nothing is known with respect to iron catalysts in transfer hydrogenations.

To rule out an exchange of hydrogen atoms, for example, by C–H activation, we investigated the transfer hydrogenation with a completely deuterated donor molecule.[24] The [$Fe_3(CO)_{12}$]/terpy/PPh_3 precatalytic system was dissolved in [D_8]*i*PrOH and treated with [D_7]*i*PrONa for 5 min at 100 °C. After addition of **1**, the solution was stirred for 5 h at 100 °C. Only alcohol **17** was detected as product by ^1H NMR spectroscopy (Scheme 2; > 99 %).[25] This result indicates an exclusive transfer of the deuterium into the carbonyl group. Apparently no C–H activation processes and enol formation occurred under the described conditions.[26]

To clarify the pathway of hydrogen transfer from the hydrogen donor to the substrate molecule, we used [D]*i*PrOH (the hydroxy group was deuterated) as solvent/donor and sodium 2-propylate as base in the transfer hydrogenation of **1** (Scheme 2). We obtained a mixture of two different deuterated 1-phenylethanols **18** and **19** in the ratio 85:15.[27]

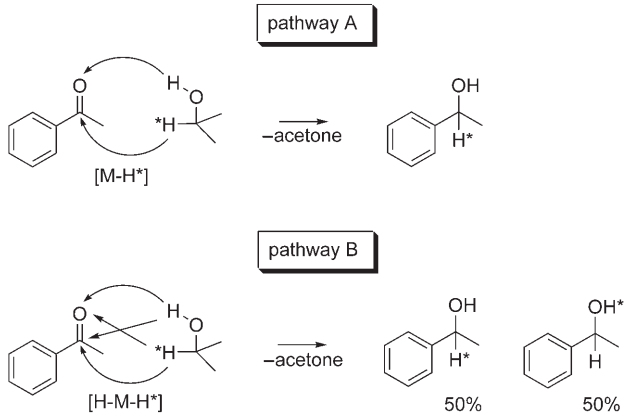
Table 5. $[Fe_3(CO)_{12}]$/terpy/PPh_3- and $FeCl_2$/terpy/PPh_3-catalyzed hydrogenation of ketones.[a]



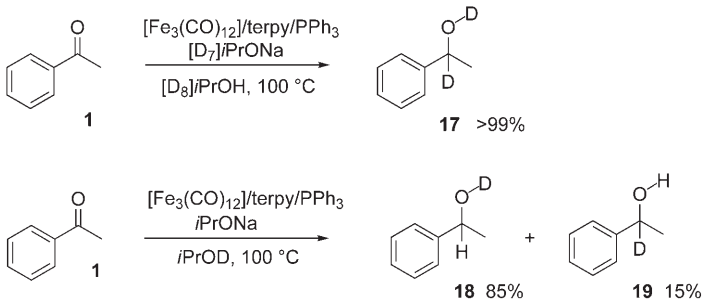
Entry	Alcohol	Yield [%][b] $[Fe_3(CO)_{12}]$	Yield [%][b] $FeCl_2$
1	 **2**	95	91
2	 **8**	>99	97
3	 **9**	84	83
4	 **10**	63	75
5	 **11**	>99	>99
6	 **12**	81	92
7	 **13**	5	8
8	 **14**	48	57
9	 **15**	95	93
10	 **16**	>99	>99

[a] Reaction conditions: in situ catalyst (0.0038 mmol) ($[Fe_3(CO)_{12}]$ (0.0013 mmol) or $FeCl_2$ (0.0038 mmol), terpy (0.0038 mmol), PPh_3 (0.0038 mmol) in 2-propanol (2.0 mL), 16 h at 65 °C), *i*PrONa (0.38 mmol), 5 min at 100 °C, then addition of ketone (0.76 mmol), reaction for 7 h at 100 °C. [b] Yield was determined by GC (**2**: 50 m Lipodex E, 95–200 °C, **8**: 25 m Lipodex E, 100 °C, **9**: 50 m Lipodex E, 90–105 °C, **10**: 25 m Lipodex E, 80–180 °C, **11**, **14**, **15**, and **16**: 30 m, HP Agilent Technologies, 50–300 °C, **12**: 25 m Lipodex E, 90–180 °C, **13**: 50 m Lipodex E, 90–180 °C) with diglyme as internal standard (yield is equivalent to conversion).

This specific migration is in agreement with the described monohydride mechanism, which implies that a major formation of the metal monohydride in the catalytic cycle occurred, albeit with a small amount of **19**.[8c] This H/D scrambling is explained by the reversibility of the hydrogen-transfer process due to the hydrogen-donating ability of 1-phenylethanol (low oxidation potential).[8c]



Scheme 1. Monohydride (pathway A) and dihydride (pathway B) mechanisms of transition-metal-catalyzed transfer hydrogenation of acetophenone.



Scheme 2. Deuterium incorporation into acetophenone (**1**) catalyzed by $[Fe_3(CO)_{12}]$/terpy/PPh_3 in the presence of base.

Conclusions

We have developed the first general homogeneous Fe catalyst system for the transfer hydrogenation of aliphatic and aromatic ketones. In the presence of 1 mol% of $[Fe_3(CO)_{12}]$/terpy/PPh_3 or $FeCl_2$/terpy/PPh_3, the corresponding alcohols are obtained in good to excellent yield and chemoselectivity. The active catalyst systems are easily generated in the presence of cheap available nitrogen and phosphorus ligands. Mechanistic experiments indicate a transfer of hydrogen from the donor molecule to the substrate by a monohydride mechanism. Further work in the direction of stereoselective Fe-based hydrogenation catalysts is under way in our laboratories.

Experimental Section

General

All manipulations were performed under argon atmosphere with standard Schlenk techniques. Unless otherwise specified, all chemicals are commercially available and used as received. 2-Propanol, pyridine, and triethylamine were used without further purification (purchased from Fluka, dried over molecular sieves). Sodium 2-propylate and sodium *tert*-butylate were prepared by treating sodium with 2-propanol or *tert*-butanol under argon atmosphere (stock solution). Ketones **1**, **8**, **9**, **11**, **12**, **14**,

15, and **16** were dried over CaH_2, distilled under vacuum, and stored under argon. Ketones **10** and **13** were treated with vacuum/argon cycles and stored under argon. Tmeda was distilled under Argon. $[Et_3NH][HFeCO_4]$,[13] BuP(adamantyl)$_2$,[28] and *N*-phenyl-2-(di-*tert*-butylphosphanyl)pyrrole[29] were synthesized according to literature protocols. $[D_8]$- and [D]*i*PrOH were dried over CaH_2 and distilled under argon atmosphere.

General Procedure for Transfer Hydrogenation of Ketones

In a Schlenk tube (10 mL), the catalyst (0.0038 mmol) was generated in situ by stirring a solution of $[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), and PPh_3 (0.0038 mmol) in 2-propanol (1.0 mL) for 16 h at 65 °C. The precatalytic system was treated with sodium 2-propylate (0.38 mmol) at 100 °C for 5 min. After addition of the corresponding ketone (0.38 or 0.76 mmol), the reaction mixture was stirred for 7 h at 100 °C. The solution was cooled to room temperature and filtered over a plug of silica. The conversion was measured by GC without further purification.

Procedures for Distinguishing Homogeneous and Heterogeneous Catalysts

Mercury poisoning: In a Schlenk tube (10 mL), a solution of $[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), and PPh_3 (0.0038 mmol) in 2-propanol (1.0 mL) was stirred for 16 h at 65 °C. The precatalyst was treated at 100 °C with sodium 2-propylate (0.38 mmol) in 2-propanol (0.5 mL) for 5 min, followed by **1** (0.76 mmol) in 2-propanol (0.5 mL). The reaction mixture was kept for 1 h at 100 °C. After that, a drop of mercury, which was degassed and stored under argon, was added, and the reaction was continued for 7 h. The reaction mixture was cooled to room temperature and filtered over a plug of silica gel. The conversion was determined by GC without further purification.

Maitlis test: In a Schlenk tube (10 mL), a solution of $[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), and PPh_3 (0.0038 mmol) in 2-propanol (1.0 mL) was stirred for 16 h at 65 °C. The precatalyst was treated at 100 °C with sodium 2-propylate (0.38 mmol) in 2-propanol (0.5 mL) for 5 min, followed by **1** (0.76 mmol) in 2-propanol (0.5 mL). The reaction mixture was kept for 1 h at 100 °C. After that, the solution was filtered under an atmosphere of argon through a filter supported by a plug of celite (heated in vacuum and stored under argon). The filtrate was heated again to 100 °C and the reaction allowed to proceed for another 6 h. The celite phase was transferred into a Schlenk tube (10 mL) and mixed with 2-propanol (1.0 mL), sodium 2-propylate (0.38 mmol) in 2-propanol (0.5 mL), and **1** (0.76 mmol) in 2-propanol (0.5 mL). After the reaction was complete, both mixtures were cooled to room temperature and filtered over a plug of silica gel. The conversion was determined by GC without further purification.

*Transfer Hydrogenation with $[D_8]$i*PrOH as Hydride Source

In a Schlenk tube (10 mL), $[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), and PPh_3 (0.0038 mmol) in $[D_8]$*i*PrOH (1.0 mL) were stirred for 16 h at 65 °C. After mixing the precatalytic solution with $[D_7]$*i*PrONa (0.38 mmol, prepared by reacting sodium (0.38 mmol) with $[D_8]$*i*PrOH (0.5 mL)) at 100 °C for 5 min, a solution of **1** (0.76 mmol) in $[D_8]$*i*PrOH (0.5 mL) was added. The reaction mixture was kept for 5 h at 100 °C, then cooled to room temperature and filtered over a plug of silica. The conversion was determined by ^{1}H NMR spectroscopy.

*Transfer Hydrogenation with [D]i*PrOH as Hydride Source

In a Schlenk tube (10 mL), $[Fe_3(CO)_{12}]$ (0.0013 mmol), terpy (0.0038 mmol), and PPh_3 (0.0038 mmol) in [D]*i*PrOH (1.0 mL) were stirred for 16 h at 65 °C. After mixing the precatalytic solution with sodium 2-propylate (0.38 mmol, prepared by treating sodium (0.38 mmol) with [D]*i*PrOH (0.5 mL)) at 100 °C for 5 min, a solution of **1** (0.76 mmol) in [D]*i*PrOH (0.5 mL) was added. The reaction mixture was kept for 5 h at 100 °C. (To avoid side effects, for instance, scrambling, the reaction was stopped before full conversion.) The solution was cooled to room temperature and filtered over a plug of silica. The solvent was removed under vacuum, and the residue was dissolved in $CDCl_3$. The conversion was determined by ^{1}H NMR spectroscopy. The ratio of **18** to **19** was based on the integrals of the ^{1}H NMR signals of the CH_3 groups.

Acknowledgements

This work was financed by the State of Mecklenburg-Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF). We thank Mrs. C. Voss, Mrs. C. Mewes, Mrs. M. Heyken, Mrs. S. Buchholz, and Dr. C. Fischer (all Leibniz-Institut für Katalyse e.V. an der Universität Rostock) for their excellent technical and analytical support.

[1] a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; b) P. T. Anastas, M. M. Kirchhoff, T. C. Williamson, *Appl. Catal. A* **2001**, *221*, 3–13.

[2] The cost of iron is low relative to that of rhodium, ruthenium, or iridium (current price for 1 ton of iron ≈ US$300), due to the widespread abundance of iron in the earth's crust and its easy accessibility. Furthermore, iron is an essential mineral for life (daily dose for humans 5–28 mg) and plays an important role in a large number of biological processes.

[3] For an excellent review, see: C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254.

[4] a) S. C. Bart, E. J. Hawrelak, E. Lobkovsky, P. J. Chirik, *Organometallics* **2005**, *24*, 5518–5527; b) S. C. Bart, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2004**, *126*, 13794–13807; c) Q. Knijnenburg, A. D. Horton, H. van der Heijden, W. A. Gal, P. Budzelaar, M. Henricus, PCT Int. Appl. WO 2003042131, **2003**; d) H. Nagorski, M. J. Mirbach, *J. Organomet. Chem.* **1985**, *291*, 199–204; e) M. E. Miller, E. R. Grant, *J. Am. Chem. Soc.* **1984**, *106*, 4635–4636; f) T. J. Lynch, M. Banah, H. D. Kaesz, C. R. Porter, *J. Org. Chem.* **1984**, *49*, 1266–1270; g) M. A. Rafhi, L. Markó, *J. Organomet. Chem.* **1984**, *262*, 359–364; h) H. Inoue, M. Sato, *J. Chem. Soc. Chem. Commun.* **1983**, 983–984; i) L. Markó, M. A. Radhi, I. Ötvös, *J. Organomet. Chem.* **1981**, *218*, 369–376.

[5] a) S. R. Boothroyd, M. A. Kerr, *Tetrahedron Lett.* **1995**, *36*, 2411–2414; b) H. Alper, K. E. Hashem, *J. Am. Chem. Soc.* **1981**, *103*, 6514–6515; c) J. F. Knifton, *J. Org. Chem.* **1976**, *41*, 1200–1206.

[6] I. Iovel, K. Mertins, J. Kischel, A. Zapf, M. Beller, *Angew. Chem.* **2005**, *117*, 3981–3985; *Angew. Chem. Int. Ed.* **2005**, *44*, 3913–3916.

[7] a) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Tetrahedron Lett.* **2002**, *43*, 4977–4980; b) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *J. Organomet. Chem.* **2003**, *675*, 91–96; c) K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; d) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066–5069; e) B. Hagemann, K. Junge, S. Enthaler, M. Michalik, T. Riermeier, A. Monsees, M. Beller, *Adv. Synth. Catal.* **2005**, *347*, 1978–1986; f) S. Enthaler, B. Hagemann, K. Junge, G. Erre, M. Beller, *Eur. J. Org. Chem.* **2006**, 2912–2917.

[8] a) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051–1069; b) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; c) S. Gladiali, G. Mestroni in *Transition Metals for Organic Synthesis, 2nd ed.* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 145–166; d) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; e) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236.

[9] R. Noyori, I. Umeda, T. Ishigami, *J. Org. Chem.* **1972**, *37*, 1542–1545.

[10] a) K. Jothimony, S. Vancheesan, *J. Mol. Catal.* **1989**, *52*, 301–304; b) K. Jothimony, S. Vancheesan, J. C. Kuriacose, *J. Mol. Catal.* **1985**, *32*, 11–16.

[11] J.-S. Chen, L.-L. Chen, Y. Xing, G. Chen, W.-Y. Shen, Z.-R. Dong, Y.-Y. Li, J.-X. Gao, *Acta Chimica Sinica*, **2004**, *62*, 1745–1750.

[12] C. Bianchini, E. Farnetti, M. Graziani, M. Peruzzini, A. Polo, *Organometallics* **1993**, *12*, 3753–3761.
[13] L. F. Dahl, J. F. Blount, *Inorg. Chem.* **1965**, *4*, 1373–1375.
[14] H. Zhang, C.-B. Yang, Y.-Y. Li, Z.-R. Donga, J.-X. Gao, H. Nakamura, K. Murata, T. Ikariya, *Chem. Commun.* **2003**, 142–143.
[15] a) C. Milone, R. Ingoglia, L. Schipilliti, C. Crisafulli, G. Neri, S. Galvagno, *J. Catal.* **2005**, *236*, 80–90; b) C. Milone, R. Ingoglia, M. L. Tropeano, G. Neri, S. Galvagno, *Chem. Commun.* **2003**, 868–869; c) S. Narayanan, R. Unnikrishnan, *J. Chem. Soc. Faraday Trans.* **1998**, *94*, 1123–1128; d) H. Itoh, H. Hosaka, T. Ono, E. Kikuchi, *Appl. Catal.* **1988**, *40*, 53–66; <lit e> L. S. Glebov, A. I. Mikaya, V. I. Smetanin, V. G. Zaikin, G. A. Kliger, S. M. Loktev, *J. Catal.* **1985**, *93*, 75–82.
[16] G. M. Whitesides, M. Hackett, R. L. Brainard, J. P. P. M. Lavalleye, A. F. Sowinski, A. N. Izumi, S. S. Moore, D. W. Brown, E. M. Staudt, *Organometallics* **1985**, *4*, 1819–1830.
[17] a) C. M. Hagen, L. Vieille-Petit, G. Laurenczy, G. Süss-Fink, R. G. Finke, *Organometallics* **2005**, *24*, 1819–1831; b) J. A. Widegren, R. G. Finke, *J. Mol. Catal. A: Chem.* **2003**, *198*, 317–341.
[18] J. E. Hamlin, K. Hirai, A. Millan, P. M. Maitlis, *J. Mol. Catal.* **1980**, *7*, 543–544.
[19] The preparation of the precatalyst was carried out in a similar manner to the described procedure, with $[Fe_3(CO)_{12}]$, terpy, and PPh_3, stirring for 16 h at 65 °C in $[D_8]$*i*PrOH, addition of sodium 2-propylate (5 equiv), and transfer into an NMR tube. The suspension was heated to 100 °C, and after 5 min the reaction mixture was quickly cooled to room temperature and immediately subjected to ^1H or ^{31}P NMR spectroscopy.
[20] The preparation of the precatalyst was carried out in a manner similar to the described procedure, with $[Fe_3(CO)_{12}]$, terpy, and PPh_3, stirring for 16 h at 65 °C in $[D_8]$*i*PrOH or 2-propanol, followed by transfer of the suspension into an NMR tube or removal of 2-propanol and dissolution of the residue in $[D_4]$MeOH, $CDCl_3$, $[D_6]$acetone, or $[D_6]$benzene.
[21] a) D. D. Tanner, G. E. Diaz, A. Potter, *J. Org. Chem.* **1985**, *50*, 2149–2154; b) M. Degueil-Castaing, A. Rahm, *J. Org. Chem.* **1986**, *51*, 1672–1676;c) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530; d) J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung, A. S. C. Chan, *Chem. Eur. J.* **2003**, *9*, 2963–2968.
[22] E. C. Ashby, J. N. Argyropoulos, *J. Org. Chem.* **1986**, *51*, 3593–3597.
[23] a) For recent reviews, see: J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237–248; b) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406 and references therein; c) H. Guan, M. Iimura, M. P. Magee, J. R. Norton, G. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 7805–7814; d) M. Gómez, S. Janset, G. Muller, G. Aullón, M. A. Maestro, *Eur. J. Inorg. Chem.* **2005**, 4341–4351; e) K. Muñiz, *Angew. Chem.* **2005**, *117*, 6780–6785; *Angew. Chem. Int. Ed.* **2005**, *44*, 6622–6627; f) C. Hedberg, K. Källström, P. I. Arvidsson, P. Brandt, P. G. Andersson, *J. Am. Chem. Soc.* **2005**, *127*, 15083–15090; g) A. S. Y. Yim, M. Wills, *Tetrahedron* **2005**, *61*, 7994–8004; h) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201–2237; i) T. Koike, T. Ikariya, *Adv. Synth. Catal.* **2004**, *346*, 37–41; j) P. Brandt, P. Roth, P. G. Andersson, *J. Org. Chem.* **2004**, *69*, 4885–4890; k) J.-W. Handgraaf, J. N. H. Reek, E. J. Meijer, *Organometallics* **2003**, *22*, 3150–3157; l) C. P. Casey, J. B. Johnson, *J. Org. Chem.* **2003**, *68*, 1998–2001; m) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; n) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; o) C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, M. Kavana, *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100; p) O. Pàmies, J. E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058; q) C. S. Yi, Z. He, *Organometallics* **2001**, *20*, 3641–3643; r) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931–7944; s) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478; t) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588; u) D. G. I. Petra, J. N. H. Reek, J.-W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2000**, *6*, 2818–2829; v) A. Aranyos, G. Csjernyik, K. J. Szabó, J. E. Bäckvall, *Chem. Commun.* **1999**, 351–352; w) M. L. S. Almeida, M. Beller, G. Z. Wang, J. E. Bäckvall, *Chem. Eur. J.* **1996**, *2*, 1533–1536.
[24] a) L. Dahlenburg, R. Götz, *Eur. J. Inorg. Chem.* **2004**, 88–905; b) P. W. C. Cross, G. J. Ellames, J. S. Gibson, J. M. Herbert, W. J. Kerr, A. H. McNeill, T. W. Mathers, *Tetrahedron* **2003**, *59*, 3349–3358.
[25] a) L. Y. Kuo, D. M. Finigan, N. N. Tadros, *Organometallics* **2003**, *22*, 2422–2425; b) R. L. Elsenbaumer, H. S. Mosher, *J. Org. Chem.* **1979**, *44*, 600–604.
[26] D. Klomp, T. Maschmeyer, U. Hanefeld, J. A. Peters, *Chem. Eur. J.* **2004**, *10*, 2088–2093.
[27] The ratio of **18** to **19** was determined by ^1H NMR spectroscopy based on the integrals of the signals for the CH_3 groups.
[28] A. Ehrentraut, A. Zapf, M. Beller, *Synlett* **2000**, 1589–1592.
[29] A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen, M. Beller, *Chem. Commun.* **2004**, 38–39.

Received: April 4, 2006
Revised: July 5, 2006

6.1.2. Biomimetic transfer hydrogenation of ketones with iron porphyrin catalysts

Stephan Enthaler, Giulia Erre, Man Kin Tse, Kathrin Junge, and Matthias Beller*, *Tetrahedron Lett.* **2006**, *47*, 8095–8099.

Contributions

Ligands **1a** and **1d** were synthesized by Dr. M. K. Tse.

Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8095–8099

Biomimetic transfer hydrogenation of ketones with iron porphyrin catalysts

Stephan Enthaler, Giulia Erre, Man Kin Tse, Kathrin Junge and Matthias Beller*

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, D-18059 Rostock, Germany

Received 17 July 2006; revised 11 September 2006; accepted 12 September 2006
Available online 4 October 2006

Abstract—For the first time in situ generated iron porphyrins have been applied as homogeneous catalysts for the transfer hydrogenation of ketones. Using 2-propanol as hydrogen source various ketones are reduced to the corresponding alcohols in good to excellent yield and selectivity. Under optimized reaction conditions high catalyst turnover frequencies up to 642 h^{-1} are achieved.

Alcohols are key intermediates for the synthesis of pharmaceuticals, agrochemicals, polymers and new materials.[1,2] Starting from carbonyl compounds various catalytic approaches toward the synthesis of alcohols have been developed. Typical examples are the addition of organometallic compounds to aldehydes, hydrosilylation, and hydrogenation of aldehydes or ketones.[2] Among these transformations hydrogenations represent the most atom-efficient and environmentally benign methodology. In particular, transfer hydrogenation is a powerful strategy because of the ease of performance and general applicability.[3] More specifically, a broad scope of alcohols is available by transfer hydrogenation using non-toxic hydrogen donors, for example, 2-propanol or $HCOOH/NEt_3$, under mild reaction conditions in the presence of precious metal catalysts based on Ir, Rh, Ru, or Ni.[4]

With regard to the upcoming catalyst developments a fundamental challenge is the substitution of these expensive and rare transition metals by less toxic, inexpensive and abundantly available metals such as iron.[5] Until now, homogeneous iron catalysts have been most frequently applied for carbon–carbon coupling reactions, such as olefin polymerizations, cross-couplings and cycloadditions as well as reductions of nitro compounds.[6] However, much less attention was directed toward iron-catalyzed (transfer) hydrogenations, although the relevance of such reductions is evident even with respect to industrial applications. To the best of our knowledge only the groups of Noyori,[7] Vancheesan,[8] Bianchini[9] and Gao[10] reported the utilization of iron salts and iron complexes in the reduction of α,β-unsaturated carbonyl compounds and ketones. For tuning the activity and selectivity of these catalysts, oxygen and moisture sensitive tetradentate phosphines[9] or aminophosphines[10] have been predominantly applied as ligands.

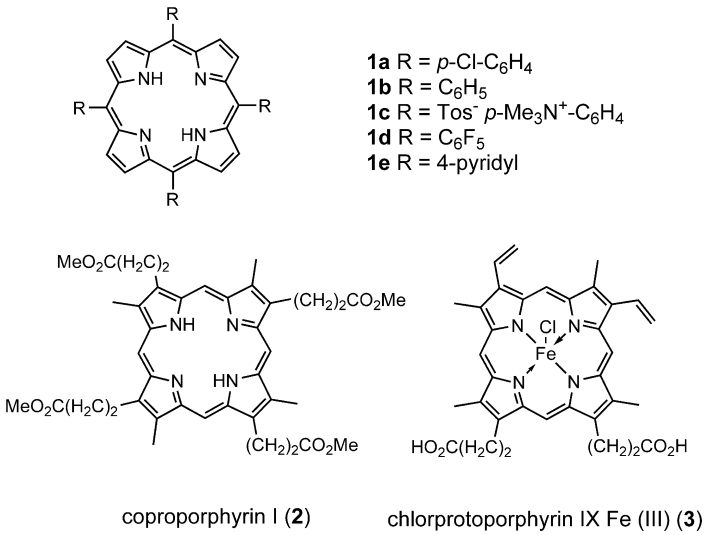
Inspired by nature we thought that multidentate nitrogen ligands should be also suitable ligands for stabilizing iron as metal centre in transfer hydrogenations. In the past biomimetic ligand toolboxes were invented, which are based on natural sources or similar structural motifs, for example, amino alcohols, quinidines, bisoxazolines and porphyrins.[11] Within these potential ligands, porphyrins, which are involved in manifold biological redox processes, seemed of special interest to us due to their strong ability to stabilize the iron centre.[12,13]

Stimulated by our ongoing research in catalytic hydrogenations[15] we became interested in developing new hydrogenation catalysts based on iron. Thus, we report herein for the first time a combination of iron and porphyrins as catalysts for the efficient reduction of various ketones (Scheme 1).

In exploratory experiments, 2-propanol-based transfer hydrogenation of acetophenone was examined using an easy to adopt in situ catalyst system comprising $Fe_3(CO)_{12}$ and porphyrin **1a**. Typically, the active catalyst is prepared by stirring a solution of 1 mol % iron source and 1 mol % **1a** in 2-propanol (1.0 mL) for 16 h

* Corresponding author. Tel.: +49 381 1281 113; fax: +49 381 1281 5000; e-mail: matthias.beller@catalysis.de

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.09.058



Scheme 1. Selection of applied porphyrins.[14]

at 65 °C. After the addition of 50 mol % base the mixture is heated for 5 min at 100 °C and the standard substrate acetophenone **4** is added.[16]

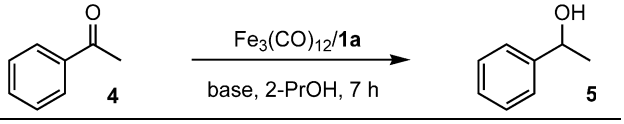
Initially, the influence of temperature and various bases on the reaction rate was investigated. An optimal catalyst activity is obtained at 100 °C (Table 1, entries 1–3). In general, sodium and potassium alkoxides gave an excellent yield of 1-phenylethanol (96–99%, Table 1, entries 4–8). Noteworthy from a practical point of view is that NaOH and K_2CO_3 also led to a high product yield. However, in the presence of organic bases such as NEt_3 and pyridine (Table 1, entries 10 and 11) no significant amount of product is formed in reasonable time. Diminishing the base concentration resulted in a decrease of 1-phenylethanol. In the absence of a base, no transfer of hydrogen was observed.

Interestingly, the transfer hydrogenation proceeds highly chemoselectively (>99%). In no case significant amounts (>1%) of by-products (e.g., aldol condensation products) are obtained.

Next, attempts were made concerning the iron source (Table 2).[17] The best activity was obtained for $Fe_3(CO)_{12}$, $FeBr_2$, $Fe(acac)_3$ and $[Et_3NH][HFe(CO)_4]$.[18]

Surprisingly, no reliable correlation between the oxidation state and reaction rate was observed as high activity was detected for Fe(0)-, Fe(II)- and Fe(III)-salts. Hence, the formation of the active catalyst species is complete for the various pre-catalysts under the applied conditions. However, studying the dependency of conversion versus reaction time in the presence of $Fe_3(CO)_{12}$ revealed an induction period of nearly 2 h.

Table 1. Catalytic transfer hydrogenation of acetophenone **4**

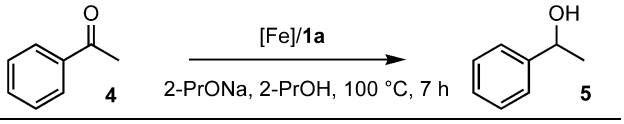


Entry	Iron source	Base	Temperature (°C)	Yield (%)[a]
1	$Fe_3(CO)_{12}$	2-PrONa	80	56
2	$Fe_3(CO)_{12}$	2-PrONa	90	68
3	$Fe_3(CO)_{12}$	2-PrONa	100	96
4	$Fe_3(CO)_{12}$	NaOH	100	98
5	$Fe_3(CO)_{12}$	KOH	100	42
6	$Fe_3(CO)_{12}$	LiOH	100	5
7	$Fe_3(CO)_{12}$	K-*t*-OBu	100	**99**
8	$Fe_3(CO)_{12}$	Na-*t*-OBu	100	97
9	$Fe_3(CO)_{12}$	K_2CO_3	100	89
10	$Fe_3(CO)_{12}$	NEt_3	100	<1
11	$Fe_3(CO)_{12}$	Pyridine	100	<1

Standard reaction conditions: 0.0038 mmol in situ catalyst (0.0013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol **1a** in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol base, 5 min at described temperature, then the addition of 0.38 mmol acetophenone **4**, 7 h at described temperature.

[a] Yield and conversion were determined by GC analysis (50 m Lipodex E, 95–150 °C) with diglyme as an internal standard.

Table 2. Influence of iron sources in the transfer hydrogenation of acetophenone **4**



Entry	Iron source	Yield (%)[a]
1	$Fe_3(CO)_{12}$	96
2	$FeBr_2$	**98**
3	$FeCl_2$	90
4	$FeCl_3$	86
5	$Fe(acac)_2$	74
6	$Fe(acac)_3$	97
7	$CpFe(CO)_2I$	44
8	$FeSO_4$	46
9	$[Et_3NH][HFe(CO)_4]$	97

Standard reaction conditions: 0.0038 mmol in situ catalyst (0.0038 mmol Fe-source or 0.0013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol **1a** in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol base, 5 min at 100 °C, then the addition of 0.38 mmol acetophenone **4**, 7 h at 100 °C.

[a] Yield and conversion were determined by GC analysis (50 m Lipodex E, 95–150 °C) with diglyme as an internal standard.

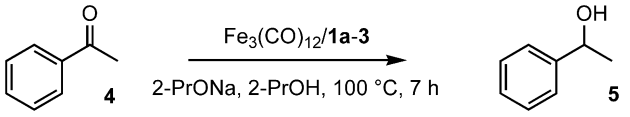
In the case of $Fe(acac)_2$ and $Fe(acac)_3$ a favourable conversion was observed for the Fe(III)-salt. Comparing the results of $FeCl_2$ and $FeBr_2$, a small influence of the corresponding halide was also detected.

Next, we focused our attention on the influence of the metal–ligand ratio. Even without any ligand some catalytic activity is obtained (54% of **5**). The addition of 0.5 or 0.2 equiv of **1a** (with respect to Fe) increased the yield of 1-phenylethanol to 74% and 86%, respectively. The highest yield is obtained at a metal–ligand ratio of 1:1. A further increase of the number of ligand with respect to iron (2:1) resulted in a slight decrease of activity (89% of **5**).

In order to further improve the catalyst system, we applied different porphyrin ligands (**1a**–**3**) in the model reaction in the presence of 0.5 mol % Fe catalyst ($Fe_3(CO)_{12}$, sodium 2-propylate, 100 °C). As shown in Table 3, best yields were achieved with *meso*-substituted porphyrins **1b** and **1e** (Table 3, entries 3 and 6). Substitution in the *meso*-phenylic system of porphyrin **1b** with electron withdrawing groups (**1a**, **1c**, and **1d**) displayed a decrease in activity (Table 3, entries 1, 3 and 4).

In addition, porphyrins substituted in the β-pyrrolenic positions were employed in the reduction of acetophenone. The activity of the symmetric coproporphyrin I **2** was to some extend lower when compared with *meso*-substituted porphyrins. The natural complex chloroprotoporphyrin IX Fe(III) **3** was utilized without catalysts pre-formation as described for all other ligands, and a moderate yield of 1-phenylethanol was detected (Table 3, entry 8). Nevertheless, complex **3** is an interesting catalyst for such reactions due to easier handling and availability.

Table 3. Testing of different porphyrins in the transfer hydrogenation of acetophenone **4**



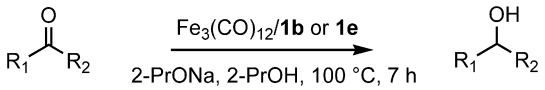
Entry	Porphyrin	Catalyst loading (mol %)	Yield (%)[a]	TOF (h^{-1})[b]
1	**1a**	0.5	90	26
2	**1a**	0.01	45	**642**
3	**1b**	0.5	93	27
4	**1c**	0.5	68	19
5	**1d**	0.5	56	16
6	**1e**	0.5	**94**	27
7	**2**	0.5	45	13
8	**3**	0.5	51	15

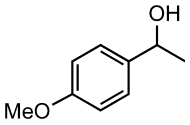
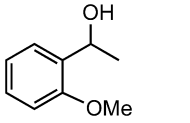
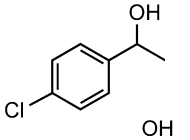
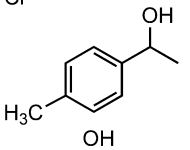
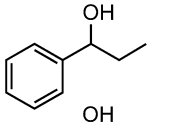
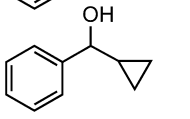
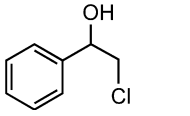
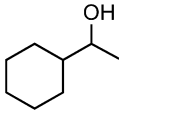
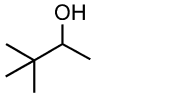
Standard reaction conditions: 0.0038 mmol or 0.000038 mmol in situ catalyst (0.0013 mmol or 0.000013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol or 0.000038 mmol porphyrin in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol or 0.0019 mmol sodium 2-propylate, 5 min at 100 °C, then the addition of 0.76 mmol acetophenone **4**, 7 h at 100 °C.

[a] Conversion was determined by GC analysis (50 m Lipodex E, 95–150 °C) with diglyme as an internal standard.

[b] Turnover frequencies were determined after 7 h.

Table 4. Fe-catalyzed reduction of various ketones in the presence of porphyrins **1b** and **1e**



Entry	Product	**1b** Yield (%)[a]	**1e** Yield (%)[a]
1		46	72
2		>99	>99
3		93	95
4		50	68
5		92	87
6		21	22
7		<1	<1
8		26 [71][b]	89
9		11 [55][b]	90

Standard reaction conditions: 0.0038 mmol in situ catalyst (0.0013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol porphyrin in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol sodium 2-propylate, 5 min at 100 °C, then addition of the corresponding ketone (0.76 mmol), 7 h at 100 °C.

[a] Conversion was determined by GC analysis (entry 1 (25 m Lipodex E, 80–180 °C), entries 2, 6, 8 and 9 (30 m, HP Agilent Technologies, 50–300 °C), entry 3 (25 m Lipodex E, 100 °C), entry 4 (50 m Lipodex E, 90–105 °C), entry 5 (25 m Lipodex E, 90–180 °C), entry 7 (50 m Lipodex E, 90–180 °C)) with diglyme as internal standard.

[b] In brackets the results after 24 h reaction time.

In order to demonstrate the utility of our concept, we selected ligand **1b** and **1e** and used the corresponding Fe pre-catalysts in the reduction of nine aliphatic and aromatic ketones (Table 4). When using 0.5 mol % pre-catalyst in the presence of 50 mol % sodium 2-propylate, most substrates were hydrogenated in a good yield. Only disappointing activities were obtained for ketones substituted adjacent to the carbonyl group by a chloromethyl or a cyclopropyl group (Table 4, entries

6 and 7). Comparing different substitutions on the phenyl ring no reliable relationship between electron donating and electron withdrawing substituents and activity was observed (Table 4, entries 1–4). Similar to the model reaction, in all cases conversion and yield were nearly identical.

In agreement with previous findings the highest yield is obtained with 2-methoxyacetophenone due to the presence of a second coordination site.[19]

In addition to aryl alkyl ketones, we also examined more challenging dialkyl ketones in this iron-catalyzed transfer hydrogenation. Good conversion and yield (89–90%) were observed for both substrates applying an iron catalyst containing **1e** as ligand. In general, ligand **1e** gave better results compared to **1b**. This effect is especially pronounced for the dialkyl substrates (Table 4, entries 8 and 9).

In conclusion, we have demonstrated for the first time the successful application of in situ prepared iron porphyrin catalysts in the transfer hydrogenation of ketones. The catalyst system is easily prepared and mimics biologically occurring Fe complexes. Under optimized conditions turnover frequencies up to 642 h^{-1} were achieved. The scope and limitation of the catalyst were demonstrated on the reduction of nine different ketones with good to excellent yields.

Acknowledgements

This work has been financed by the State of Mecklenburg-Western Pomerania, the Bundesministerium für Bildung und Forschung (BMBF) and the Deutsche Forschungsgemeinschaft (Leibniz-award). We thank Mr. B. Hagemann, Mrs. C. Mewes, Mrs. M. Heyken, Mrs. S. Buchholz, and Dr. C. Fischer (all Leibniz-Institut für Katalyse e.V. an der Universität Rostock) for their excellent technical and analytical support.

References and notes

1. (a) Lennon, I. C.; Ramsden, J. A. *Org. Process Res. Dev.* **2005**, *9*, 110–112; (b) Hawkins, J. M.; Watson, T. J. N. *Angew. Chem.* **2004**, *116*, 3286–3290; (c) Noyori, R.; Ohkuma, T. *Angew. Chem.* **2001**, *113*, 40–75; (d) Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process Res. Dev.* **2000**, *4*, 346–348.
2. (a) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; (b) Cornils, B.; Herrmann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; Wiley-VCH: Weinheim, 1996; (c) Kitamura, M.; Noyori, R. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; (d) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
3. (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *51*, 1051–1069; (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102; (c) Gladiali, S.; Mestroni, G. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; pp 145–166; (d) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151; (e) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236; (f) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248.
4. Selected recent examples of transfer hydrogenations: (a) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6731–6734; (b) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584–3591; (c) Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3407–3411; (d) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319; (e) Baratta, W.; Chelucci, G.; Gladiali, S.; Siega, K.; Toniutti, M.; Zanette, M.; Zangrando, E.; Rigo, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 6214–6219.
5. Due to the widespread abundance of iron in earth's crust and the easy accessibility the current price of iron is relatively low (approximately 300 US-dollar/t) compared to rhodium, iridium or ruthenium. Furthermore, iron is an essential trace element (daily dose for humans 5–28 mg) and is involved in an extensive number of biological processes.
6. Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254.
7. Noyori, R.; Umeda, I.; Ishigami, T. *J. Org. Chem.* **1972**, *37*, 1542–1545.
8. (a) Jothimony, K.; Vancheesan, S. *J. Mol. Catal.* **1989**, *52*, 301–304; (b) Jothimony, K.; Vancheesan, S.; Kuriacose, J. C. *J. Mol. Catal.* **1985**, *32*, 11–16.
9. Bianchini, C.; Farnetti, E.; Graziani, M.; Peruzzini, M.; Polo, A. *Organometallics* **1993**, *12*, 3753–3761.
10. Chen, J.-S.; Chen, L.-L.; Xing, Y.; Chen, G.; Shen, W.-Y.; Dong, Z.-R.; Li, Y.-Y.; Gao, J.-X. *Huaxue Xuebao* **2004**, *62*, 1745–1750.
11. (a) Jacqueline, H.-P. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1995; (b) Larrow, J. F.; Jacobsen, E. N. *Topics Organomet. Chem.* **2004**, *6*, 123–152.
12. (a) *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Netherlands, 1975; (b) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; (c) Che, C.-M.; Huang, J.-S. *Coord. Chem. Rev.* **2002**, *231*, 151–164; (d) Simonneaux, G.; Le Maux, P. *Coord. Chem. Rev.* **2002**, *228*, 43–60; (e) Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu-Etheve, M. *Chem. Soc. Rev.* **2005**, *34*, 573–583.
13. (a) Munire, B. *Chem. Rev.* **1992**, *92*, 1411–1456; (b) Mansuy, D. *Coor. Chem. Rev.* **1993**, *125*, 129–141; (c) *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; M. Dekker Inc.: New York, 1994; (d) Che, C.-M.; Yu, W.-Y. *Pure Appl. Chem.* **1999**, *71*, 281–288; (e) Vinhado, F. S.; Martins, P. R.; Iamamoto, Y. *Curr. Topics. Catal.* **2002**, *3*, 199–213; (f) Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu-Etheve, M. *Chem. Soc. Rev.* **2005**, *34*, 573–583; (g) Shitama, H.; Katsuki, T. *Tetrahedron Lett.* **2006**, *47*, 3203–3207; (h) Zhou, C. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 325–328; (i) Berkessel, A. *Pure Appl. Chem.* **2005**, *77*, 1277–1284.
14. All porphyrins are commercial available by Strem or Aldrich except porphyrin **1d**, which was synthesized according to a literature protocol: (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969–4970; (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
15. (a) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett.* **2002**, *43*,

4977–4980; (b) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *J. Organomet. Chem.* **2003**, *675*, 91–96; (c) Junge, K.; Hagemann, B.; Enthaler, S.; Spannenberg, A.; Michalik, M.; Oehme, G.; Monsees, A.; Riermeier, T.; Beller, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; (d) Junge, K.; Hagemann, B.; Enthaler, S.; Oehme, G.; Michalik, M.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem., Int. Ed.* **2004**, *43*, 5066–5069; (e) Hagemann, B.; Junge, K.; Enthaler, S.; Michalik, M.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2005**, *347*, 1978–1986; (f) Enthaler, S.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *Eur. J. Org. Chem.* **2006**, 2912–2917.

16. All experiments were carried out under an inert gas atmosphere (argon) with exclusion of air. For the standard reaction procedure $Fe_3(CO)_{12}$ (0.0013 mmol) and porphyrin **1a** (0.0038 mmol) is dissolved in 1.0 mL 2-propanol and stirred for 16 h at 65 °C. Then a solution of sodium 2-propylate (0.19 mmol) in 0.5 mL 2-propanol is added. The solution is stirred for 5 min at 100 °C followed by the addition of 0.38 mmol acetophenone **4**. After 7 h at 100 °C, the mixture is cooled to rt and filtered over a plug of silica gel. The conversion and yield were determined by GC without further purification. All synthesized alcohols are known compounds. Their characterization is done by a comparison with authentic samples.
17. Sodium 2-propylate was chosen due to easier handling.
18. Dahl, L. F.; Blount, J. F. *Inorg. Chem.* **1965**, *4*, 1373–1375.
19. Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chem. Asian J.* **2006**, *1*, in press.

6.1.3. Biomimetic Transfer Hydrogenation of 2–Alkoxy– and 2–Aryloxyketones with Iron Porphyrin Catalysts

Stephan Enthaler, Björn Spilker, Giulia Erre, Man Kin Tse, Kathrin Junge, and Matthias Beller*, *Tetrahedron* **2007**, *submitted.*

Contributions

Ligands **1a** and **1d** were synthesized by Dr. M. K. Tse. Electrochemical experiments were carried out by Dr. B. Spilker.

Pergamon

TETRAHEDRON

Biomimetic Transfer Hydrogenation of 2-Alkoxy- and 2-Aryloxyketones with Iron Porphyrin Catalysts

Stephan Enthaler, Björn Spilker, Giulia Erre, Kathrin Junge, Man Kin Tse, and Matthias Beller*

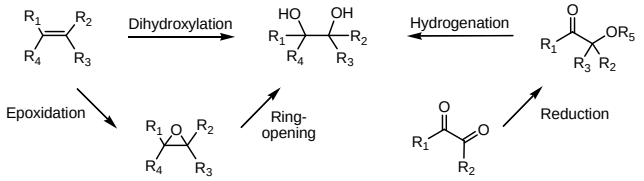
Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, D-18059 Rostock, Germany

Abstract— *In situ* generated iron porphyrins are applied as homogeneous catalysts in the transfer hydrogenation of α-substituted ketones. Using 2-propanol as hydrogen donor various hydroxyl-protected 1,2-hydroxyketones are reduced to the corresponding mono-substituted 1,2-diols in good to excellent yield. Under optimized reaction conditions catalyst turnover frequencies up to 2500 h^{-1} have been achieved.

1. Introduction

The relevance of 1,2-diols is impressively shown by the production of ethylene and propylene glycol on multi-million-ton scale for the synthesis of polymers and anti-freeze compounds. In addition, more complex 1,2-diols and their derivatives constitute interesting building blocks for a variety of biologically active compounds.

In general, synthetic approaches to 1,2-diols are based on oxidative processes of olefins. Typical processes include the epoxidation of C=C double bonds with peracids or hydroperoxides and subsequent hydrolysis, and secondly the dihydroxylation of olefins in the presence of osmium catalysts (Scheme 1).[1]



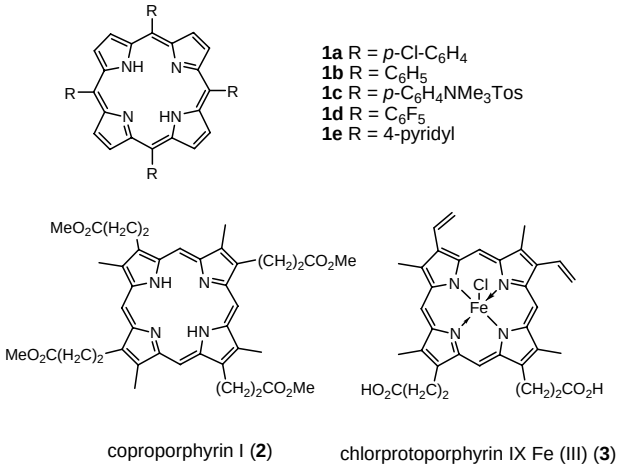
Scheme 1. Possible approaches to 1,2-diols.

A much less explored reaction is the transition metal-catalyzed reduction of 1,2-hydroxyketones. Among the different reductions, the transfer hydrogenation with 2-propanol as non-toxic hydrogen donor is practical and easy to perform.[2,3] Until now only a few number of applications were reported using Rh or Ru based metal catalysts in the reduction of hydroxy-protected 1,2-hydroxyketones, which is in contrast to the well-studied reduction of acetophenone.[4]

A major challenge for catalytic hydrogenations is the substitution of expensive and rare transition metals (Ir, Rh, Ru) by ubiquitous available, inexpensive and less toxic metals. Consequently, the use of iron catalysts is especially desirable.[5] Up to now, homogeneous iron catalysts have been mostly used for carbon-carbon bond formation, such as olefin polymerizations, cross couplings, and cycloadditions as well as reduction of nitro compounds.[6] However, much less attention was directed towards iron-catalyzed transfer hydrogenation. Only the groups of Noyori,[7] Vancheesan,[8] Bianchini,[9] and Gao[10] reported the utilization of iron salts and iron complexes, containing tetradentate phosphines[9] or aminophosphines[10], in the reduction of ketones to obtain alcohols and α,β-unsaturated carbonyl compounds to yield α,β-saturated carbonyl compounds.

More recently, we established two iron-based methods for the effective transfer hydrogenation of aryl alkyl as well as alkyl alkyl ketones utilizing 2-propanol as the hydrogen source.[11] On the one hand we applied a combination of iron salts, tridentate amines and phosphines as catalysts.[11a] On the other hand an *in situ* catalyst composed of an iron salt and porphyrins has been used (Scheme 2).[11b] Unfortunately, both catalyst systems faced some difficulties with α-substituted alkyl aryl ketones. Herein we report for the first time the successful hydrogenation of α-alkoxy- and α-aryloxy-substituted acetophenones in the presence of iron-porphyrin-complexes.

* Tel: +49-381-1281-113; Fax: +49-381-1281-5000; e-mail: matthias.beller@catalysis.de.



Scheme 2. Selection of applied porphyrin ligands.[11b]

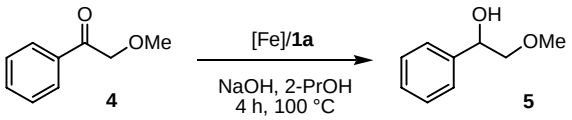
2. Results and Discussion

For exploratory experiments the hydrogenation of 2-methoxyacetophenone was used as a model reaction. Typically, the pre-catalyst is prepared by stirring a solution of 1 mol% iron salt and 1 mol% **1a** in 2-propanol (1.0 mL) for 16 h at 65 °C. After addition of 50 mol% base the mixture is heated for 5 minutes at 100 °C and the substrate 2-methoxyacetophenone **4** is added. At first, the influence of different iron precursors on the reaction rate was studied (Table 1). To our delight full conversion is obtained in all cases within 4 h. Obviously, the formation of the active catalyst is independent from the Fe-salt and is complete for all stated pre-catalysts under the standard conditions. Without any Fe present no conversion took place, also using $FeCl_2$ without ligand gave only 37% yield. From a practical point of view we chose $FeCl_2$ as iron source for further investigations.

It is well known, that the kind and also the amount of base are important parameters for obtaining reasonable quantities of product in transfer hydrogenations. Thus, we investigated frequently used bases, such as NaOH, KOH and KO^{t}Bu. In all cases excellent yields are achieved, except for LiOH and Cs_2CO_3 (Table 2, entries 1–9). Diminishing the base concentration to 5–10 mol% resulted in a decrease of yield of 2-methoxy-1-phenylethanol **5**, while 25 mol% base still gave excellent yield within two hours. Noteworthy, in the absence of base no transfer of hydrogen occurred (Table 2, entry 15). In addition, nitrogen-containing bases (e.g. pyridine, NEt_3, DBU) were tested, but only unsatisfactory results were attained (conversion: <1%).

Next, we focused our attention on the influence of the reaction temperature (Table 2, entries 1 and 11–14). An optimal catalyst activity was obtained in the range of 60–100 °C. However, even at lower temperature a moderate yield was attained (40 °C, conversion: 18%). To support the formation of the active catalyst at low temperature two different activation methods were carried out.

Table 1: Influence of iron salts in the transfer hydrogenation of 2-methoxyacetophenone **4**.



Entry	Iron source	Yield [%][a)]
1	-	<1
2	FeF_2	>99
3	$FeCl_2$	>99
4[b)]	$FeCl_2$	37
5	$FeCl_3$	>99
6	$FeBr_2$	>99
7	FeI_2	>99
8	$Fe(acac)_2$	>99
9	$Fe(acac)_3$	>99
10	$FeSO_4\ 7H_2O$	>99
11	$CpFe(CO)_2I$	>99
12[c)]	Fe(III)citrate H_2O	>99
13	$Fe_3(CO)_{12}$	>99

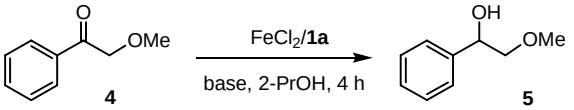
Reaction conditions: 0.0038 mmol *in situ* catalyst (0.0038 mmol Fe-source or 0.0013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol **1a** in 1.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol NaOH in 0.5 mL 2-propanol, 0.38 mmol 2-methoxyacetophenone **4** in 0.5 mL 2-propanol, 4 h at 100 °C. [a)] Yield was determined by GC analysis (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard. [b)] No ligands are added. [c)] Fe(III)citrate was recrystallized before use.[12]

On the one hand, substitution of strong coordinating chloride ligands by weaker BF_4^- ligands via addition of $AgBF_4$ was done. On the other hand activation of the catalyst by light irradiation (Perkin–Elmer PE300BF lamp with hot mirror, ~380–770 nm) has been tried. Surprisingly, both procedures led to complete deactivation of the catalysts with respect to hydrogenation reaction.

In order to further improve the catalyst system we applied different porphyrin ligands (**1a**–**3**) under the optimized conditions, namely 0.5 mol% Fe catalyst or 0.01 mol%, respectively, ($FeCl_2$ and the corresponding porphyrin in a ratio of 1:1), sodium hydroxide (25 mol% or 0.5 mol%) at 100 °C (Table 3). In case of 0.5 mol% catalyst loading for all iron-porphyrin catalysts excellent conversion was attained. For 0.01 mol% catalyst loading best performance was achieved with the *meso*-substituted porphyrin **1a** (Table 3, entry 2). Substitution at the *meso*-phenylic system of porphyrin with electron withdrawing groups (**1c** and **1d**) lowered the catalyst activity. Furthermore, an excellent turnover frequency of 1850 h^{-1} was observed with a

porphyrin **s**ubstituted at the β–pyrrolenic positions (Table 3, entry 12). The complex chloroprotoporphyrin IX Fe(III) **3** was utilized without catalysts pre-formation as described for all other representatives, and good turnover numbers were determined (Table 3, entries 13–14). Reducing the catalyst loading to 0.01 mol% turnover frequencies up to 2100 h^{-1} were realized (Table 3, entries 1–3).

Table 2: Influence of temperature and base in the Fe-catalyzed transfer hydrogenation of 2-methoxyacetophenone **4**.



4 **5**

Entry	Base	Base [mol%]	Temp. [°C]	Yield [%][a)]
1	NaOH	50	100	>99
2	KOH	50	100	>99
3	LiOH	50	100	49
4	NaO^iPr	50	100	>99
5	KO^tBu	50	100	>99
6[b)]	NaO^tBu	50	100	>99
7	K_2CO_3	50	100	>99
8	Na_2CO_3	50	100	97
9	Cs_2CO_3	50	100	37
10[c)]	NaOH	50	25	<1
11	NaOH	50	40	18
12[d)]	NaOH	50	40	<1
13	NaOH	50	60	>99
14	NaOH	50	80	>99
15[e)]	-	-	100	<1
16[e)]	NaOH	5	100	17
17[e)]	NaOH	10	100	55
18[e)]	NaOH	25	100	>99
19[e)]	NaOH	50	100	>99

Reaction conditions: 0.0038 mmol *in situ* catalyst (0.0038 mmol $FeCl_2$ and 0.0038 mmol **1a** in 1.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol base in 0.5 mL 2-propanol, 0.38 mmol 2-methoxyacetophenone **4** in 0.5 mL 2-propanol, 4 h at described temperature. [a)] Yield was determined by GC analysis (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard. [b)] A mixture of solvents was used *t*-BuOH and 2-propanol 1:4. [c)] Light assisted reaction, thereby only the visible range was applied since the ultraviolet range was shielded. [d)] Addition of 2 equiv. $AgBF_4$ with respect to $FeCl_2$. [e)] Reaction time: 2 h.

Notably, the addition of small amounts of water (5 mol% to 10 mol%) accelerated the transfer hydrogenation compared to the water-free conditions and turnover frequencies up to 2500 h^{-1} were achieved. Higher amounts of water (up to 500 mol%) hampered the reaction.

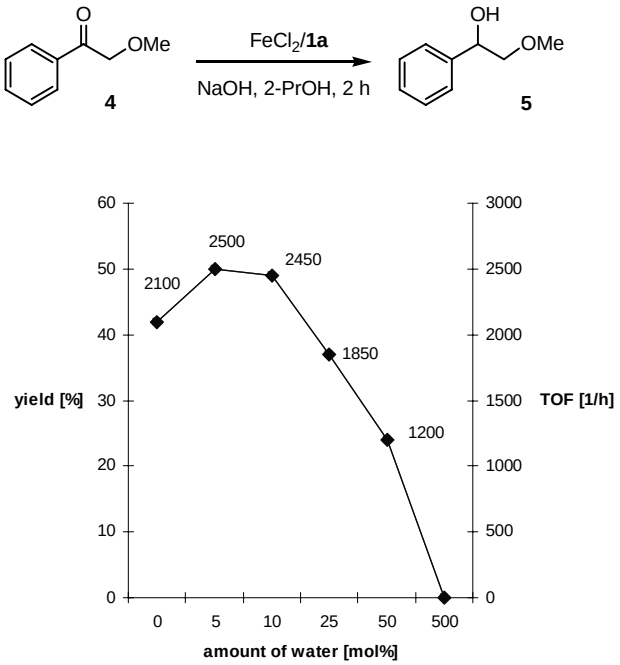


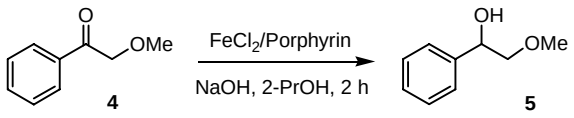
Figure 1. The influence of water addition on hydrogenation of 2-methoxyacetophenone **4**. Reaction conditions: 0.038 μmol *in situ* catalyst (0.038 μmol $FeCl_2$ and 0.08 μmol **1a** in 1.0 mL 2-propanol for 16 h at 65 °C), 1.9 μmol NaOH in 0.5 mL 2-propanol, the corresponding amount of water, 0.38 mmol substrate in 0.5 mL 2-propanol, temperature: 100 °C , reaction time: 2 h. [a)] Yield was determined by GC analysis (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard.

Under optimized conditions (*vide supra*), $FeCl_2$, **1a**, NaOH, 100 °C, we compared the activity of the catalytic system for the reduction of acetophenone **6**, *ortho*-methoxyacetophenone **8** and 2-methoxyacetophenone **4**. Here, the yield of 1-phenylethanol **7**, *ortho*-methoxy-1-phenylethanol **9** and 2-methoxy-1-phenylethanol **5** was monitored during the reaction.

The attained curves are shown in Figure 2. The reduction of 2-methoxyacetophenone proceeded without any induction period or deactivation process. Similar behaviour was observed for *ortho*-methoxyacetophenone, albeit a slight deceleration occurred after nearly 100 min. Nevertheless, full conversion was reached after 7 hours. In case of acetophenone the reduction process was significantly slower. After 8 hours a deactivation took place. Notably, the activities are in agreement with the oxidation potentials of the applied ketones (2-methoxyacetophenone, E_0 = 213 mV; *ortho*-methoxyacetophenone, E_0 = 141 mV[13]; acetophenone, E_0 = 118 mV).

In order to demonstrate the usefulness of our concept the catalyst containing ligand **1a** was tested in the hydrogenation of several hydroxy-protected 1,2-hydroxyketones (Table 4).

Table 3: Screening of different porphyrins in the Fe-catalyzed transfer hydrogenation of 2-methoxyacetophenone **4**.



4 **5**

Entry	Ligand	Catalyst loading [mol%]	Yield [%][a)]	TOF [h^{-1}][b)]
1	**1a**	0.5	>99	>99
2	**1a**	0.01	42	**2100**
3	**1b**	0.5	>99	>99
4	**1b**	0.01	30	1500
5	**1c**	0.5	>99	>99
6	**1c**	0.01	18	900
7	**1d**	0.5	>99	>99
8	**1d**	0.01	23	1150
9	**1e**	0.5	>99	>99
10	**1e**	0.01	24	1200
11	**2**	0.5	>99	>99
12	**2**	0.01	37	1850
13	**3**	0.5	>99	>99
14	**3**	0.01	26	1300

Reaction conditions: 0.0019 mmol or 0.038 mmol *in situ* catalyst (0.0019 mmol or 0.038 µmol $FeCl_2$ and 0.0019 mmol or 0.038 µmol porphyrin in 1.0 mL 2-propanol for 16 h at 65 °C), 0.095 mmol or 0.0019 mmol sodium hydroxide in 0.5 mL 2-propanol, 0.38 mmol 2-methoxyacetophenone **4** in 0.5 mL 2-propanol, 2 h at 100 °C. [a)] Yield was determined by GC analysis (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard. [b)] Turnover frequencies were determined after 2 h.

In general, the substrates were synthesized by reacting 2-bromo ketones with different alcohols in the presence of base.[14] A first set of experiments was dedicated to the variation of the protecting group. Good to excellent yield was obtained by changing the methoxy-group by phenoxy substituents. Best results were achieved with the *p*-chlorophenoxy substituent (Table 4, entry 2). Increasing the bulkiness at 2- and 6-position the conversion decreased significantly (Table 4, entry 4), while substitution only at 2-position led to excellent conversion of the desired product. Substitution on the acetophenone skeleton by a *p*-methyl or *p*-methoxy group gave good to full conversion. In addition, indanone and pinacolin based substrates were synthesized and tested in this transfer hydrogenation, thereby moderate conversions were obtained (Table 4, entries 7 and 8). Unfortunately, variation of the hydroxyl protecting group to common acetyl and *tert*-butyldimethylsilyl groups displayed an inactivity of presented catalyst (Table 4, entries 11 and 12). The hydrogenation of 2-hydroxy-acetophenone **20** and 2-hydroxy-2-methyl-1-phenylpropan-1-one **21** were not successful since decomposition was observed. In addition, 2-morpholino-acetophenone **22**, which is a promising precursor for 1,2-amino alcohols, was subjected to the transfer hydrogenation protocol. Unfortunately, no conversion was observed even if the reaction time was extended to 24 hours (Table 4, entry 15).

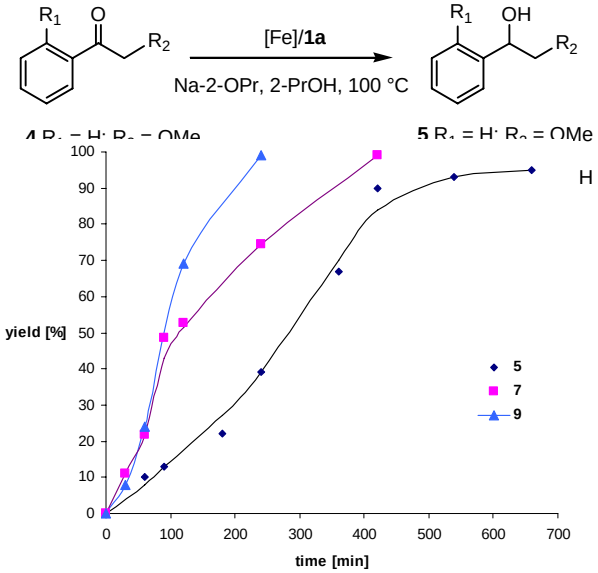


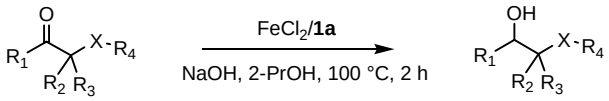
Figure 2. Comparative study between acetophenone **6**, *ortho*-methoxyacetophenone **8** and 2-methoxyacetophenone **4**. Reaction conditions: 0.0038 mmol *in situ* catalyst (0.0038 mmol $FeCl_2$ and 0.0038 mmol **1a** in 1.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol base in 0.5 mL 2-propanol, 0.76 mmol substrate in 0.5 mL 2-propanol, temperature: 100 °C. [a)] Yield was determined by GC analysis (**7**: 50 m Lipodex E, 95–150 °C, **7**: 50 m Lipodex E, 90–180 °C, **9**: 30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard.

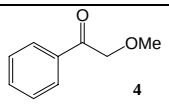
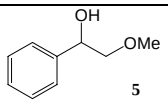
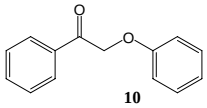
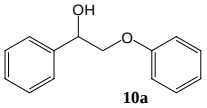
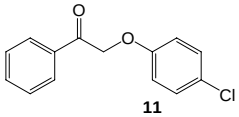
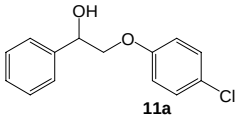
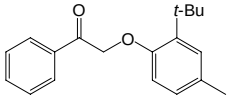
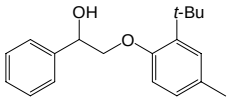
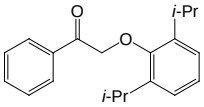
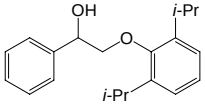
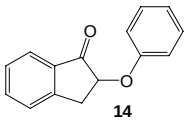
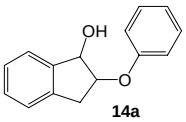
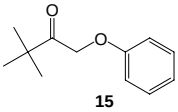
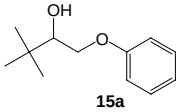
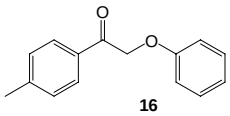
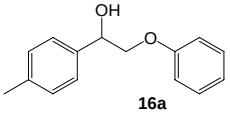
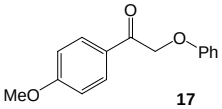
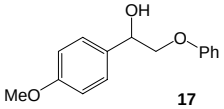
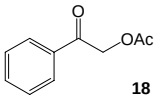
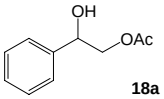
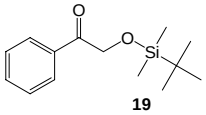
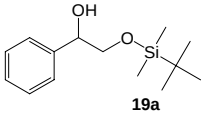
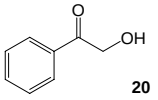
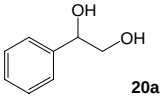
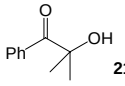
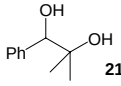
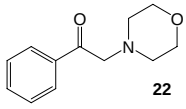
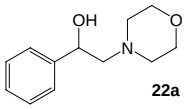
In order to get further informations about the presented catalytic system we carried out electrochemical investigations of the *in situ* catalysts containing ligands **1a-e**. Cyclic voltammetry has been established as a useful tool for studying the electrochemical properties of porphyrins and metalloporphyrins.[15] The measurement conditions were as close to the reaction conditions as possible. However, under strong basic conditions, no reliable measurements were possible, due to low catalyst solubility at room temperature. Therefore measurements were performed in the absence of base. The temperature dependence of the potentials according to the Nernst equation have to be similar for all Fe-porphyrins and should be in the range of 20 to 30 mV between room temperature and the reaction temperature of 100 °C. The electrochemical analysis is presented in Figure 3.

All cyclic voltammograms illustrate clearly the oxidation of Fe(II) to Fe(III) in the potential range above ca. 0.2 V vs. SCE. The small (negative) reduction currents result probably from Fe(III) contamination of the $FeCl_2$ or from oxidation of $FeCl_2$ from other impurities (e.g. O_2). From the

colour of the solutions (light brown to red-brown) and the height of oxidation current (compared to 5 mmol/L $FeCl_2$) the curves result from free $FeCl_2$ (light yellow coloured solution) or incomplete Fe(II)-porphyrin formation can be excluded.[16]

Table 4: Reduction of α-substituted ketones in the presence of iron catalyst containing porphyrin **1a**.



Run	Substrate	Product	conv. [%]
1	 **4**	 **5**	>99
2	 **10**	 **10a**	92
3	 **11**	 **11a**	>99[a]
4	 **12**	 **12a**	97
6	 **13**	 **13a**	74[a]
7	 **14**	 **14a**	43
8	 **15**	 **15a**	48
9	 **16**	 **16a**	>99[a]
10	 **17**	 **17**	83[a]
11	 **18**	 **18a**	<1[a]
12	 **19**	 **19a**	<1[a]
13	 **20**	 **20a**	<1[b]
14	 **21**	 **21a**	<1[b]
15	 **22**	 **22a**	3 (<1)[c]

Reaction conditions: 0.0019 mmol *in situ* catalyst (0.0019 mmol $FeCl_2$ and 0.0019 mmol porphyrin in 1.0 mL 2-propanol for 16 h at 65 °C), 0.095 mmol sodium hydroxide in 0.5 mL 2-propanol, 0.34 mmol substrate in 0.5 mL 2-propanol, 2 h at 100 °C. Yield was determined by GC analysis (30 m HP Agilent Technologies 50–300 °C) [a] ^{1}H NMR [b] Decomposition. [c] Reaction time: 24 h.

Most likely the difference in oxidation currents results from different solubilities of the Fe-porphyrins, since the diffusion coefficients should be similar. The porphyrins without $FeCl_2$ (violet coloured solution) generate only a small oxidation current in the region above ca. 0.6 V which is shown by the cyclic voltammogram of the porphyrin **1a** without $FeCl_2$ (Figure 3). This oxidation current was also observable in the curves of the Fe(II)-porphyrins in the same potential range.

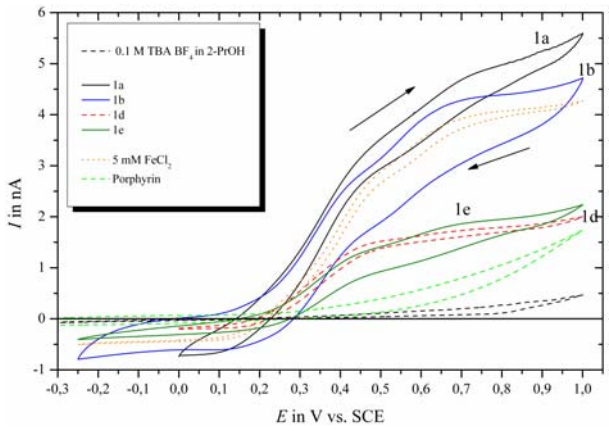


Figure 3. Cyclic voltammograms of porphyrins with $FeCl_2$ in 0.1 mol/L TBA BF_4 in 2-PrOH. Start at 0 V in positive direction with 10 mV/s at platinum microelectrode.

The second oxidation steps visible in all curves (0.5 to 0.6 V) cannot clearly be interpreted under the applied conditions. Most likely the second oxidation step is caused

by formation of other complexes, since 2-propanol and chloride ions are present in the solution, which are possible ligands for the axial position. During oxidation of Fe(II)- to Fe(III)-porphyrin one anion has to fulfil the unsaturated situation at the Fe(III) center analogue to compound **3** in Scheme 2. At the same time it has to be considered that Fe(II)-porphyrins can also be coordinated with two axial ligands (six-coordinate Fe(II)).[15,17] The small amount of dissolved chlorid results maybe in slower kinetics of the Fe(III)-porphyrin formation, seen by the reversible potential values (Table 5).

Table 5: Half-wave potentials and values for reversibility.

Compound	TOF	$E_{1/2}$ vs. SCE / mV	slope / mV
1d	1150	326	146
1e	1200	339	141
1b	1500	338	152
1a	2100	330	204
$FeCl_2$	-	380	205
Ferrocene	-	525	61

Due to the influence of the axial ligand a change or different coordination of the porphyrins at the axial positions results in a shift of potential (with an excess of chlorid the potentials shift to lower values with higher reversibility).[15] The half-wave potentials for the first oxidation step resulting from the measurements under these conditions are presented in Table 5. Under conditions identical with those for the porphyrins the ferrocenium/ferrocene couple has a half-wave potential of 525 mV and a slope of 61 mV ($E_{1/2}$ = 480 mV in 0.1 mol/L TBA PF_6 / CH_2Cl_2).[18] With the half-wave potentials of the Fe-porphyrins no correlation with the TOF can be found. In addition following our standard protocol the formation of the pre-catalyst was studied by *in situ* mass spectroscopy. After stirring $FeCl_2$ and ligand **1a** for 16 hours at 65 °C the corresponding iron complex[19] formed by elimination of 2 equiv. of HCl was detected, which is in agreement with previous reports.[20] Unfortunately, no other catalyst intermediate could be unambiguously identified. Thus, the detailed mechanism of the Fe-based hydrogenation catalysts is still unclear.

In conclusion, we have demonstrated the successful extension of the Fe-catalyzed transferhydrogenation to α-hydroxy-protected hydroxyketones. Under optimized conditions turnover frequencies up to 2500 h^{-1} were achieved. The scope and limitation of the catalyst were demonstrated on reduction of ten different ketones with good to excellent yields.

3. Experimental Section

3.1. General

^1H and ^{13}C NMR spectra were recorded on Bruker Spectrometer 400 and 300 (^1H: 400.13 MHz, and 300.13 MHz; ^{13}C: 100.6 MHz, and 75.5 MHz). The calibration of ^1H and ^{13}C spectra was carried out either on solvent signals (δ $CDCl_3$) = 7.25 and 77.0) or TMS. Mass spectra were recorded on an AMD 402 spectrometer. IR spectra were recorded as KBr pellets or Nujol mulls on a Nicolet Magna 550. All manipulations were performed under argon atmosphere using standard Schlenk techniques. Unless specified, all chemicals are commercially available and used as received. 2-Propanol was used without further purification (purchased from Fluka, dried over molecular sieves). Sodium 2-propylate and sodium *t*-butylate were prepared by reacting sodium with 2-propanol or *t*-butanol, respectively, under an argon atmosphere (stock solution). Ketone **8** was dried over CaH_2, distilled in vacuum and stored under argon. Substrates **18** and **19** were used without further purifications. Porphyrins **1a** and **1d** were synthesized according to literature protocols.[21] Fe(III)citrate was recrystallized from water/ethanol before use since it was purchased in technical grade.

3.2. General procedure for the synthesis of substrates:

A solution of 2-bromo ketone (10.1 mmol), phenol (10.1 mmol), K_2CO_3 (15 mmol) in acetone (15 mL) was refluxed for 3 hours. The solvent was removed in vacuum and the residue dissolved in ethyl acetate / diethyl ether and washed with water and brine. After drying over Na_2SO_4 the solvent was removed and the crude product was purified by crystallization.

2-Phenoxy-acetophenone (**10**): 10.1 mmol scale, flash column chromatography (eluent: ethyl acetate/n-hexane 4:1), recrystallized from 2-propanol. Yield: 39% (white crystals). Mp = 60–61 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.02–7.98 (m, 2H); 7.64–7.58 (m, 1H); 7.53–7.46 (m, 2H); 7.31–7.22 (m, 2H); 7.01–6.90 (m, 3H); 5.28 (s, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.5; 157.9; 134.5; 133.8; 129.5; 128.8; 128.1; 121.6; 114.7; 70.7. IR (KBr): 3387 w; 3060 w; 2897 w; 2843 w; 2749 w; 1928 w; 1708 s; 1599 s; 1499 s; 1480 m; 1449 m; 1433 m; 1386 w; 1341 w; 1303 m; 1292 m; 1250 s; 1228 s; 1189 m; 1175 m; 1094 m; 1076 m; 1028 w; 1001 m; 975 m; 921 w; 886 w; 872 m; 751 s; 688 s; 665 m; 614 w; 584 w; 555 w; 511 m; 414 w. MS (EI): *m/z* (%) = 212 ([M^+], 26); 105 (100); 77 (43); 51 (12). HRMS calculated for $C_{14}H_{14}O_2$: 214.09883; Found: 214.098506.

2-(4-Chlorophenoxy)-acetophenone (**11**): 7.8 mmol scale, refluxing time: 12 h, crystallized from 2-propanol. Yield: 73% (white plates). Mp = 87–88 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.01–7.96 (m, 2H); 7.66–7.56 (m, 1H); 7.54–7.47 (m, 2H); 7.26–7.20 (m, 2H); 6.90–6.83 (m, 2H); 5.26

(s, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.0; 156.6; 134.3; 134.0; 129.4; 128.9; 128.0; 126.5; 116.1; 70.9. IR (KBr): 3375 w; 3060 w; 2901 w; 2851 w; 2737 w; 1699 s; 1596 s; 1581 m; 1490 s; 1448 m; 1437 s; 1409 w; 1385 w; 1338 w; 1317 w; 1289 s; 1231 s; 1172 m; 1106 m; 1096 m; 1089 m; 1075 m; 1001 m; 983 s; 921 w; 870 w; 830 s; 813 m; 786 w; 756 s; 701 w; 686 s; 634 w; 587 m; 508 m; 476 w; 457 w; 441 w; 422 w; 406 w. MS (EI): *m/z* (%) = 246 ([M^+], 15); 105 (100); 77 (30). HRMS calculated for $C_{14}H_{11}ClO_2$: 246.04421; Found: 246.044678.

2-(2-*tert*-Butyl-4-methylphenoxy)-acetophenone (**12**): 6.0 mmol scale, refluxing time: 12 h, crystallized from 2-propanol. Yield: 44% (white needles). Mp = 94–95 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.05–8.00 (m, 2H); 7.66–7.59 (m, 1H); 7.55–7.48 (m, 2H); 7.13 (d, 1H, *J* = 2.26 Hz); 6.96 (ddd, 1H, *J* = 8.10 Hz, *J* = 2.26 Hz, *J* = 0.75 Hz); 6.76 (d, 1H, *J* = 8.22 Hz); 5.29 (s, 2H, CH_2); 2.30 (s, 3H, CH_3); 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.5; 154.8; 138.4; 134.7; 133.7; 130.3; 128.8; 128.1; 127.8; 127.1; 112.3; 71.0; 34.7; 29.9; 20.8. IR (KBr): 3399 w; 3051 w; 2958 s; 2901 m; 2856 m; 2733 w; 1709 s; 1598 m; 1581 w; 1499 s; 1448 m; 1439 m; 1404 w; 1386 m; 1357 w; 1287 m; 1266 m; 1244 m; 1226 s; 1181 w; 1156 w; 1107 m; 1074 w; 1020 w; 1001 m; 980 s; 930 w; 919 w; 876 w; 861 m; 802 s; 751 s; 687 s; 655 m; 584 m; 491 m. MS (EI): *m/z* (%) = 282 ([M^+], 64); 267 (21); 249 (21); 161 (11); 121 (13); 119 (16); 117 (14); 105 (100); 91 (33); 77 (29). HRMS calculated for $C_{19}H_{22}O_2$: 28216143; Found: 282.162186.

2-(2,6-Di-*iso*-propylphenoxy)-acetophenone (**13**): 5.6 mmol scale, refluxing time: 12 h, crystallized from 2-propanol. Yield: 34% (yellow crystals). Mp = 60–65 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.01–7.95 (m, 2H); 7.66–7.59 (m, 1H); 7.55–7.47 (m, 2H); 7.16 (s, 3H); 5.12 (s, 2H, CH_2); 3.34 (sept, 2H, *J* = 6.91 Hz, CH); 1.25 (d, 12H, *J* = 6.87 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 193.9; 153.0; 141.6; 133.7; 128.8; 127.8; 125.2; 124.3; 76.7; 26.5; 24.1. IR (KBr): 3442 br; 3063 w; 3028 w; 2967 s; 2868 m; 1706 s; 1597 m; 1580 w; 1451 m; 1429 m; 1381 w; 1371 w; 1360 m; 1334 m; 1255 m; 1227 m; 1185 s; 1163 m; 1100 m; 1085 m; 1075 w; 1058 w; 1042 w; 1001 w; 992 w; 972 m; 934 w; 854 w; 801 m; 763 m; 755 s; 692 m; 648 w; 617 w; 586 w; 556 w; 521 w; 472 w; 434 w. MS (EI): *m/z* (%) = 296 ([M^+], 10); 176 (83); 161 (100); 147 (20); 133 (16); 105 (59); 91 (44); 77 (28); 43 (11). HRMS calculated for $C_{20}H_{24}O_2$: 296.17708; Found: 296.176483.

2-Phenoxy-2,3-dihydro-1*H*-inden-1-one (**14**): 9.5 mmol scale, refluxing time: 16 h, Yield: 56% (off-white crystals). Mp = 75–78 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.85 (d, 1H, *J* = 7.72 Hz); 7.67 (dt, 1H, *J* = 7.44 Hz, *J* = 1.13 Hz); 7.50–7.41 (m, 2H); 7.37–6.99 (m, 2H); 7.10–6.99 (m, 3H); 5.09 (dd, 1H, *J* = 7.54 Hz, *J* = 4.52 Hz, CH); 3.73 (dd, 1H, *J* = 7.54 Hz, *J* = 16.95 Hz, CH_2); 3.19 (dd, 1H, *J* = 16.95 Hz, *J* = 4.33 Hz, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 201.7; 157.9; 150.6; 135.9; 134.6; 129.5; 128.2; 126.7; 124.6; 121.7; 115.7; 77.8; 34.1. IR (KBr): 3413 br; 3063 w; 3039 w; 3028 w; 2916 w; 2906 w; 1716 s; 1608 m; 1597 m; 1587 m; 1493 m; 1474 m; 1464 m; 1431 w; 1325 w; 1299 m; 1276 m; 1250 m; 1233 s; 1208 w; 1174 w; 1156 w; 1080 m; 1070 m; 1038 w; 1020 w; 1005 m; 956 w; 913 m; 889 w; 753 s; 725 m; 691 m; 618 w; 607 w; 502 w; 455 w. MS (EI): *m/z* (%) = 224 ([M^+], 53); 131 (100); 103 (32); 94 (11); 77 (25). HRMS calculated for $C_{15}H_{12}O_2$: 224.08318; Found: 224.083160.

3,3-Dimethyl-1-phenoxybutan-2-one (**15**): 11.2 mmol scale, refluxing time: 16 h. Yield: 92% (off-white crystals). Mp = 33–36 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.32–7.24 (m, 2H); 7.00–6.93 (m, 1H); 6.91–6.84 (m, 2H); 4.87 (s, 2H, CH_2); 1.25 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 209.4; 158.0; 129.5; 121.4; 114.6; 68.8; 43.1; 26.3. IR (KBr): 3420 br; 3105 w; 3065 w; 3043 w; 2973 m; 2931 m; 2872 w; 2846 w; 2747 w; 1721 s; 1678 w; 1599 m; 1587 m; 1494 s; 1461 m; 1446 m; 1431 m; 1386 w; 1365 m; 1329 w; 1291 m; 1234 s; 1179 m; 1152 w; 1113 m; 1078 w; 1052 s; 1026 w; 1000 m; 990 s; 962 m; 935 w; 880 m; 825 m; 766 s; 759 s; 693 m; 587 w; 545 w; 522 m. MS (EI): *m/z* (%) = 192 ([M^+], 33); 108 (13); 77 (26); 57 (100); 41 (16). HRMS calculated for $C_{12}H_{16}O_2$: 192.11448; Found: 192.114302.

2-Phenoxy-4´-methylacetophenone (**16**): 9.4 mmol scale, refluxing time: 16 h, crystallized from 2-propanol. Yield: 51% (colourless crystals). Mp = 62–63 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.94–7.88 (m, 2H); 7.33–7.24 (m, 4H); 7.02–6.91 (m, 3H); 5.25 (s, 2H, CH_2); 2.43 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.1; 158.0; 144.8; 132.1; 129.54; 129.48; 128.2; 121.6; 114.6; 70.7; 21.8. IR (KBr): 3441 br, 3063 w; 3036 w; 2919 w; 2902 w; 2847 w; 1695 s; 1606 s; 1587 m; 1576 m; 1498 s; 1455 w; 1433 m; 1411 m; 1385 w; 1292 m; 1254 m; 1236 s; 1208 m; 1192 m; 1174 m; 1149 w; 1124 w; 1113 w; 1092 m; 1075 w; 1044 w; 1027 w; 1001 m; 979 m; 885 m; 871 m; 816m; 749 s; 711 w; 690 m; 609 w; 584 m; 551 w; 517 w; 498 w; 461 w. MS (EI): *m/z* (%) = 226 ([M^+], 15); 119 (100); 91 (24); 77 (10). HRMS calculated for $C_{15}H_{14}O_2$: 226.09883; Found: 226.099202.

2-Phenoxy-4´-methoxyacetophenone (**17**): 8.7 mmol scale, refluxing time: 16 h, crystallized from 2-propanol. Yield: 74% (off-white needles). Mp = 54–55 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.96–7.89 (m, 2H); 7.24–7.16 (m, 2H); 6.93–6.84 (m, 5H); 5.13 (s, 2H, CH_2); 3.80 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 193.1; 164.0; 158.0; 130.5; 129.0; 127.6; 121.5; 114.7; 114.0; 70.7; 55.5. IR (KBr): 3442 br; 3056 w; 3006 w; 2955 w; 2934 w; 2840 w; 1960 m; 1687 s; 1653 w; 1601 s; 1511 m; 1497 s; 1459 m; 1419 w; 1368 m; 1314 m; 1265 s; 1245 m; 1226 s; 1171 s; 1154 w; 1116 m; 1075 m; 1032 m; 976 s; 884 m; 835 m; 789 m; 769 m; 751 s; 691 m; 631 w; 608 m; 582 m; 543 w; 511 w; 492 w. MS (EI): *m/z* (%) = 242 ([M^+], 10); 135 (100); 77 (18). HRMS calculated for $C_{15}H_{14}O_3$: 242.09375; Found: 242.093706.

2-Oxo-2-phenylethyl acetate (**18**): 2–Hydroxy–1–phenylethanone (8.0 mmol) was dissolved in dichloromethane (10 mL) and acetic anhydride (8.0 mmol), pyridine (8.5 mmol) and 4–dimethylaminopyridine (0.08 mmol) were added. The solution was stirred for 2 hours under refluxing conditions. The mixture was washed with water and brine. After drying over Na_2SO_4 the solvent was removed and yellow crystals were obtained. Yield: 83%. Mp = 48–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93–7.88 (m, 2H); 7.63–7.56 (m, 1H); 7.51–7.44 (m, 2H); 5.34 (s, 2H, CH_2); 2.22 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.0; 170.3; 134.1; 133.8; 128.7; 127.6; 65.9; 20.4. IR (KBr): 3460 w; 3375 w; 3064 m; 2982 w; 2937 m; 1741 s; 1699 s; 1599 m; 1581 w; 1493 w; 1452 m; 1423 m; 1374 m; 1321 w; 1280 m; 1244 s; 1228 s; 1185 m; 1087 m; 1077 m; 1047 m; 1020 m; 996 m; 970 m; 849 m; 812 m; 757 m; 688 m; 634 m; 597 m; 566 m; 483 m; 443 w; 414 w. MS (EI): *m/z* (%) = 178 ([M^+], 1); 105 (100); 77 (34); 51 (10); 43 (14). HRMS calculated for $C_{15}H_{14}O_3$: 178.06245; Found: 178.063004.

2-(*tert*-Butyldimethylsilyloxy)-1-phenylethanone (**19**): 2–Hydroxy–1–phenylethanone (8.0 mmol) was dissolved in dichloromethane (10 mL) and imidazole (8.5 mmol) was added. After stirring for 10 minutes at room temperature *tert*–butyldimethylchlorosilane (8.5 mmol) was added dropwise, while rapidly a white precipitate was formed. The mixture was stirred for 5 hours at room temperature. Water was added and the organic layer was washed with water and brine. After removal of the solvent a yellow oil was obtained. Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.95–7.89 (m, 2H); 7.61–7.42 (m, 3H); 4.93 (s, 2H, CH_2); 0.94 (s, 9H, $C(CH_3)_3$); 0.13 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 197.4; 134.9; 132.2; 128.6; 127.9; 67.4; 25.8; 18.5; -5.4. IR (KBr): 2953 w; 2929 m; 2885 w; 2856 m;1705 s; 1599 m; 1581 w; 1472 m; 1449 m; 1390 w; 1362 w; 1288 m; 1254 m; 1229 m; 1151 s; 1025 w; 1002 m; 974 s; 939 w; 834 s; 777 s; 753 s; 712 m; 688 s; 670 s. MS (EI): *m/z* (%) = 251 ([M^++H], 16); 193 (66); 181 (10); 149 (12); 135 (13); 105 (100); 75 (73).

2-Morpholino-acetophenone (**22**): Morpholine (62 mmol) was added dropwise to a solution of 2–bromoacetophenone (7.5 mmol) in THF (15 mL). A white precipitate was formed while the mixture was refluxed for one day. An aqueous solution of $NaHCO_3$ was added. After extraction with diethyl ether the organic layer was washed with aqueous solution of NaOH and dried over Na_2SO_4. The crude product was purified by flash column chromatography (eluent: ethyl acetate/*n*–hexane 1:1) to yield a brownish oil. Yield: 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02–7.97 (m, 2H); 7.60–7.55 (m, 1H); 7.50–7.43 (m, 2H); 3.83 (s, 2H, $C(O)CH_2$); 3.79 (m, 4H, CH_2); 2.62 (m, 4H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.0; 160.9; 131.9; 129.6; 128.1; 67.1; 66.4; 64.4; 41.7; 40.6. IR (KBr): 3415 w; 3060 m; 2970 m; 2852 m; 2762 w; 1924 w; 1674 s; 1598 s; 1558 m; 1493 w; 1449 s; 1384 s; 1314 m; 1300 m; 1271 s; 1230 m; 1176 m; 1113 s; 1069 m; 1047 w; 1022 m; 1006 m; 981 w; 931 w; 876 w; 840 w; 812 w; 788 w; 757 w; 722 m; 693 w; 674 w; 593 w; 547 w; 449 w. MS (EI): *m/z* (%) = 205 ([M^+], 2); 100 (100); 77 (18); 56 (21). HRMS calculated for $C_{12}H_{15}O_2N$: 205.10973; Found: 205.109149. R_f (ethyl acetate/*n*-hexane 1:1) = 0.14.

General procedure for the catalytic transfer hydrogenation: In a 10 mL Schlenk tube, the *in situ* catalyst (0.0038 mmol) is prepared stirring a solution of $FeCl_2$ (0.0038 mmol) and porphyrin (0.0038 mmol) in 1.0 mL 2-propanol for 16 h at 65 °C. The pre-catalyst system is reacted with sodium hydroxide (0.38 mmol in 0.5 mL 2-propanol) and 2-methoxyacetophenone (0.38 mmol in 0.5 mL 2-propanol) for 2 h at 100 °C. The solution is cooled to r.t. and filtered over a plug of silica. The conversion was measured by GC without further manipulations and the products were isolated by column chromatography or crystallization.

2-Phenoxy-1-phenylethanol (**10a**): Mp = 48–50 °C (white crystals). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40–7.15 (m, 7H, Ph); 6.92–6.80 (m, 3H, Ph); 5.03 (dd, 1H, *J* = 8.67 Hz, *J* = 3.20 Hz, CH); 4.03–3.88 (m, 2H, CH_2); 2.55 (br, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.3; 139.6; 129.5; 128.5; 128.2; 126.3; 121.3; 114.6; 73.2; 72.5. IR (KBr): 3302 br; 3060 w; 3028 w; 2932 w; 2877 w; 1598 s; 1585 M; 1498 s; 1453 M; 1389 w; 1346 w; 1303 m; 1292 m; 1249 s; 1196 m; 1172 m; 1152 w; 1098 m; 1078 m; 1067 m; 1046 m; 1028 m; 995 w; 917 m; 884 w; 863 m; 792 w; 754 s; 701 s; 692 s; 637 m; 615 m; 594 m; 541 m; 512 m. MS (EI): *m/z* (%) = 214 ([M^+], 12); 108 (100); 94 (46); 79 (60); 51 (18). HRMS calculated for $C_{14}H_{14}O_2$: 214.09883; Found: 214.098407.

2-(4-Chlorophenoxy)-1-phenylethanol (**11a**): Mp = 46–48 °C (white crystals). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48–7.19 (m, 7H); 6.87–6.80 (m, 2H); 5.11 (dd, 1H, *J* = 8.48 Hz, *J* = 3.38 Hz, CH); 4.08–3.95 (m, 2H, CH_2); 2.70 (br, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.0; 139.4; 129.4; 128.6; 128.3; 126.2; 126.1; 115.8; 72.6; 72.5. IR (KBr): 3313 br; 3059 w; 3032 w; 2933 w; 2875 w; 1596 m; 1581 m; 1491 s; 1453 m; 1388 w; 1345 w; 1290 m; 1242 s; 1196 w; 1169 m; 1093 m; 1066 m; 1039 m; 1006 m; 914 m; 864 w; 825 m; 801 m; 749 m; 700 m; 671 m; 633 w; 616 m; 559 w; 507 m. MS (EI): *m/z* (%) = 248 ([M^+], 21); 142 (34); 128 (70); 107 (100); 91 (12); 79 (31). HRMS calculated for $C_{14}H_{13}ClO_2$: 248.05986; Found: 248.059204.

2-(2-*tert*-Butyl-4-methylphenoxy)-1-phenylethanol (**12a**): Mp = 61–64 °C (colourless crystals). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53–7.32 (m, 5H, Ph); 7.13 (d, 1H, *J* = 2.13 Hz, Ph); 6.98 (ddd, 1H, *J* = 8.29 Hz, *J* = 2.26 Hz, *J* = 0.75 Hz, Ph); 6.78 (d, 1H, *J* = 8.09 Hz, Ph); 5.21 (dd, 1H, *J* = 7.35 Hz, *J* = 4.71 Hz, CH); 4.18–4.08 (m, 2H, CH_2); 2.67 (br, 1H, OH); 2.31 (s, 3H, CH_3); 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.0; 139.9; 137.7; 129.9; 128.5; 128.1; 127.7; 127.1; 126.3; 112.2; 73.5; 72.9; 34.7;

30.0; 20.8. IR (KBr): 3570 m; 3030 w; 2994 w; 2856 m; 2917 m; 2867 m; 1605 w; 1581 w; 1497 s; 1451 s; 1406 m; 1389 m; 1359 m; 1327 w; 1294 m; 1264 m; 1228 s; 1198 m; 1151 m; 1095 m; 1060 m; 1033 s; 1001 w; 934 w; 911 m; 881 w; 854 m; 809 m; 764 m; 702 s; 624 w; 602 w; 592 w; 553 w; 516 w; 493 w. MS (EI): *m/z* (%) = 284 ([M^+], 27); 164 (31); 149 (100); 121 (18); 107 (17); 91 (21); 77 (16). HRMS calculated for $C_{19}H_{24}O_2$: 284.17708; Found: 284.176978.

2-(2,6-Di-*iso*-propylphenoxy)-1-phenylethanol (**13a**): Mp = 67–69 °C (colourless crystals). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46–7.26 (m, 5H); 7.09 (s, 3H); 5.16 (dd, 1H, *J* = 7.53 Hz, *J* = 4.40 Hz, CH); 3.92–3.82 (m, 2H, CH_2); 3.29 (sept, 2H, *J* = 6.91 Hz, C*H*(CH_3)$_2$); 3.10 (br, 1H); 1.22 (dd, 12H, *J* = 6.90 Hz, *J* = 1.29 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.4; 141.6; 139.8; 128.4; 128.0; 126.1; 125.8; 124.9; 79.3; 73.3; 26.4; 24.04; 24.00. IR (KBr): 3064 m; 3030 m; 2963 s; 2927 s; 2868 m; 1604 w; 1589 w; 1454 s; 1384 m; 1362 m; 1327 m; 1255 m; 1182 s; 1100 m; 1047 s; 1020 s; 936 w; 913 m; 861 w; 834 w; 802 m; 755 m; 700 s; 682 w; 623 w; 590 w; 527 w. MS (EI): *m/z* (%) = 298 ([M^+], 8); 178 (51); 163 (100); 107 (15); 91 (16); 77 (11). HRMS calculated for $C_{20}H_{26}O_2$: 298.19273; Found: 298.192353.

2-Phenoxy-2,3-dihydro-1*H*-inden-1-ol (**14a**): colourless crystals. During the reaction a mixture of diastereomers were formed in a ratio of 1:3 (D1:D2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–6.93 (m); 5.34 (d, 1H, *J* = 4.12 Hz, D1); 5.28 (d, *J* = 5.22 Hz, D2); 5.08–5.02 (m, 1H, D2); 4.98–4.89 (m, 1H, D1); 3.53 (dd, 1H, *J* = 16.37 Hz, *J* = 6.92 Hz, D1); 3.20 (d, 2H, *J* = 4.40 Hz, D2); 2.98 (dd, 1H, *J* = 16.37 Hz, *J* = 5.32 Hz, D1); 2.81 (br, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 157.7; 142.4; 139.5; 139.2; 129.6; 129.5; 128.9; 128.6; 127.3; 125.1; 125.0; 124.8; 124.5; 121.7; 121.6; 121.0; 115.8; 115.5; 85.4; 80.3; 75.6; 36.4; 35.9. IR (Nujol): 3182 w; 2723 w; 1598 m; 1585 m; 1496 m; 1459 s; 1377 s; 1291 m; 1250 s; 1207 w; 1170 w; 1155 w; 1118 m; 1073 w; 1050 w; 1020 w; 1001 w; 879 w; 849 w; 779 w; 746 s; 723 m; 693 m; 639 w; 511 w; 413 w. MS (EI): *m/z* (%) = 226 ([M^+], 19); 133 (100); 115 (21); 103 (21); 94 (61); 77 (29); 65 (11). HRMS calculated for $C_{15}H_{14}O_2$: 226.09883; Found: 226.099031.

3,3-Dimethyl-1-phenoxybutan-2-ol (**15a**): Mp = 31–33 °C (colourless crystals). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33–7.24 (m, 2H); 7.00–6.88 (m, 3H); 4.14 (dd, 1H, *J* = 9.23 Hz, *J* = 2.45 Hz, CH); 3.86 (m, 2H, CH_2); 2.35 (br, 1H, OH); 1.01 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.6; 129.5; 121.1; 114.6; 77.2; 69.3; 33.5; 26.0. IR (KBr): 3272 br; 3035 w; 2954 s; 2876 m; 1601 m; 1586 m; 1499 s; 1459 m; 1393 w; 1366 m; 1338 m; 1296 m; 1245 s; 1190 w; 1174 m; 1152 w; 1095 m; 1079 m; 1044 m; 1020 m; 1020 m; 1005 m; 992 w; 942 w; 926 m; 902 m; 895 m; 821 w; 754 s; 692 m; 598 w; 572 w; 513 m; 402 w. MS (EI): *m/z* (%) = 194 ([M^+], 26); 119 (10); 108 (63); 94 (100); 87 (19); 77 (22); 69 (14); 57 (24); 41 (17). HRMS calculated for $C_{12}H_{18}O_2$: 194.13013; Found: 194. 129870.

2-Phenoxy-1-(4´-methylphenyl)ethanol (**16a**): Mp = 50–51 °C (colourless crystals). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34–7.14 (m, 6H); 6.98–6.85 (m, 3H); 5.05 (dd, 1H, *J* = 8.64 Hz, *J* = 3.36 Hz, CH); 4.04 –3.97 (m, 2H, CH_2); 2.87 (br, 1H, OH); 2.34 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.3; 137.8; 136.7; 129.5; 129.2; 126.2; 121.1; 114.5; 73.2; 72.3; 21.1. IR (KBr): 3297 br; 3027 w; 2912 w; 2880 w; 1932 w; 1599 m; 1586 m; 1514 m; 1498 s; 1460 m; 1388 m; 1340 m; 1293 m; 1250 s; 1195 m; 1180 m; 1172 m; 1151 w; 1090 s; 1045 m; 1021 m; 995 w; 975 w; 943 w; 916 m; 886 w; 868 m; 838 w; 815 m; 756 s; 716 w; 693 m; 616 w; 597 m; 575 w; 537 m; 513 m; 487 w; 464 w; 403 w. MS (EI): *m/z* (%) = 228 ([M^+], 6); 121 (100); 108 (68); 105 (15); 65 (11). HRMS calculated for $C_{15}H_{16}O_2$: 228.11448; Found: 228.114429.

2-Phenoxy-1-(4´-methoxyphenyl)ethanol (**17a**): yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32–7.15 (m, 4H); 6.92–6.77 (m, 5H); 4.98 (dd, 1H, *J* = 8.67 Hz, *J* = 3.39 Hz, CH); 4.00–3.87 (m, 2H, CH_2); 3.73 (s, 3H, CH_3); 2.77 (br, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.4; 158.3; 131.7; 129.5; 127.5; 121.2; 114.6; 113.9; 73.2; 72.1; 55.3. IR (KBr): 3440 br; 3072 w; 3044 w; 2999 w; 2929 m; 2831 w; 1728 w; 1612 m; 1600 m; 1587 m; 1514 s; 1497 s; 1456 m; 1303 m; 1245 s; 1174 m; 1154 w; 1114 w; 1080 m; 1036 m; 912 w; 867 w; 832 m; 755 m; 692 m; 639 w; 596 w; 552 w; 511 w. MS (EI): *m/z* (%) = 244 ([M^+], 2); 137 (100); 121 (10); 108 (23); 94 (12); 77 (21). HRMS calculated for $C_{15}H_{16}O_3$: 244.10940; Found: 244.109218.

3.3. Electrochemical measurements

The electrochemical workstation is composed of an Autolab PGSTAT 10 potentiostat from ECO Chemie and a P-450 PC with GPES 4.9 software. A three-electrode arrangement with a platinum microelectrode (25 µm diameter) as the working electrode, a saturated calomel electrode (SCE) as reference electrode and a platinum counter electrode (16 mm^2 area) was used. All potentials in the following are cited against SCE. All measurements were carried out in 2-PrOH at room temperature. As supporting electrolyte we used 0.1 mol/L tetra-*n*-butylammonium tetrafluoraborate. Due to the low solubility at r.t. all solutions of porphyrins with $FeCl_2$ were saturated solutions. For some porphyrins (e.g. compound **3**) solubility was too low to see any currents. Reversibility was determined by plotting E vs. log[(I_a-I)/I-I_c] for the nearly linear range of the forward scan and determining the slope for the quasi-reversible electrode reactions. Anodic diffusion current (I_a) and cathodic diffusion current (I_c) are determined from the results of a sigmoidal fit with Microcal Origin 7.5.

Acknowledgments

We thank Mrs. S. Buchholz, and Dr. C. Fischer (both Leibniz–Institut für Katalyse e.V. an der Universität Rostock) for excellent analytical assistance and Prof. Jeroschewski for general discussions. Generous financial support from the state of Mecklenburg–Western Pomerania and the BMBF as well as the Deutsche Forschungsgemeinschaft (Leibniz–price) are gratefully acknowledged.

Note and References

1. (a) Noyori, R. (Ed.) *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; (b) Cornils B.; Herrmann, W. A. (Eds.) *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, 1996; (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, 1999; (d) Kitamura, M.; Noyori, R. in Murahashi, S.-I. (Ed.) *Ruthenium in Organic Synthesis*, Wiley-VCH, Weinheim, 2004; (e) Beller, M.; Bolm, C. (Eds.), *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, 2nd Ed. 2004; (f) J.-E. Bäckvall (Ed.), *Modern Oxidation Methods*, Wiley-VCH, Weinheim, 2004.
2. (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *51*, 1051-1069; (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102; (c) Gladiali, S.; Mestroni, G. in Beller, M.; Bolm, C. (Eds.), *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, 2nd Ed. **2004**, 145-166; (d) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103-151; (e) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236; (f) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248.
3. Selected recent examples of transfer hydrogenations: (a) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2004**, *43*, 6731–6734; (b) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584–3591; (c) Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3407–3411; (d) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319; (e) Baratta, W.; Chelucci, G.; Gladiali, S.; Siega, K.; Toniutti, M.; Zanette, M.; Zangrando, E.; Rigo, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 6214–6219; (f) Enthaler, S.; Jackstell, R.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *J. Organomet. Chem.* **2006**, *691*, 4652–4659; (g) Enthaler, S.; Hagemann, B.; Bhor, S.; Anilkumar, G.; Tse, M. K.; Bitterlich, B.; Junge, K.; Erre, G.; Beller, M. *Adv. Synth. Catal.* **2007**, *accepted*.
4. (a) Cheung, F. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. *J. Org. Chem.* **2005**, *70*, 3188-3197; (b) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489–5491; (c) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron*, **2006,** *62*, 1864-1876; (c) Hamada, T.; Torii, T.; Izawa, K.; Ikariya, T. *Tetrahedron* **2004,** *60*, 7411-7417.
5. The price for iron is relatively low (current price for 1 t of iron ~300 US-dollar) in comparison to rhodium (~5975 US-dollar per troy ounce), ruthenium (~870 US-dollar per troy ounce) or iridium (~460 US-dollar per troy ounce) due to the widespread abundance of iron in earth´s crust and the easy accessibility. Furthermore, iron is an essential trace element (daily dose for humans 5–28 mg) and plays an important role in an extensive number of biological processes.
6. Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254.
7. Noyori, R.; Umeda, I.; Ishigami, T. *J. Org. Chem.* **1972**, *37*, 1542–1545.
8. (a) Jothimony, K.; Vancheesan, S. *J. Mol. Catal.* **1989**, *52*, 301–304; (b) Jothimony, K.; Vancheesan, S.; Kuriacose, J. C. *J. Mol. Catal.* **1985**, *32*, 11–16.
9. Bianchini, C.; Farnetti, E.; Graziani, M.; Peruzzini, M.; Polo, A. *Organometallics* **1993**, *12*, 3753–3761.
10. Chen, J.-S.; Chen, L.-L.; Xing, Y.; Chen, G.; Shen, W.-Y.; Dong, Z.-R.; Li, Y.-Y.; Gao, J.-X. *Huaxue Xuebao* **2004**, *62*, 1745–1750.
11. (a) Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller M. *Chem. Asian. J.* **2006**, *1*, 598–604; (b) Enthaler, S.; Erre, G.; Tse, M. K.; Junge, K.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8095–8099.
12. After crystallization step Fe(III)citrate was subjected to ICP-AAS to ensure the non-existence of impurifications e.g. Rh, Ru or Ir.
13. Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71*, 3622–3629.
14. (a) Sun, C.-L.; Pang, R.-F.; Zhang, H.; Yang, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3257–3262; (b) Fabbri, C.; Bietti, M.; Lanzalunga, O. *J. Org. Chem.* **2005**, *70*, 2720–2728; (c) Kandanarachchi, P. H.; Autrey, T.; Franz, J. A. *J. Org. Chem.* **2002**, *67*, 7937–7945.
15. Kadish, K. M.; Finikova, O. S.; Espinosa, E.; Gros, C. P.; De Stefano, G.; Cheprakov, A. V.; Beletskaya, I. P.; Guilard, R. *Journal Porphyrins and Phthalocyanines* **2004**, *8*, 1062–1066.
16. In case of catalyst containing ligand **1a** the formation of iron-porphyrin complex was confirmed by MS.
17. Alexiou, C.; Lever, A. B. P. *Coord. Chem. Rev.* **2001**, *216–217*, 45–54.
18. Hodge, J. A.; Hill, M. G.; Gray, H. B. *Inorg. Chem.* **1995**, *34*, 809–812.
19. After stirring $FeCl_2$ and ligand **1a** for 16 hours at 65 °C a sample was taken and immediately submitted to MS investigations. Iron porphyrin complex: calculated: m/z = 806 found: MS (EI): m/z = 806.
20. (a) Hu, C.; Noll, B. C.; Schulz, C. E.; Scheidt, W. R. *Inorg. Chem.* **2007**, *46*, 619–621; (b) Melin, F.; Choua, S.; Bernard, M.; Turek, P.; Weiss, J. *Inorg. Chem.* **2006**, *45*, 10750–10757; (c) Liu, C.; Shen, D.-M.; Chen, Q.-Y. *Eur. J. Org. Chem.* **2006**, *12*, 2703–2706; (d) Ruzie, C.; Even, P.; Ricard, D.; Roisnel, T.; Boitrel, B. *Inorg. Chem.* **2006**, *45*, 1338–1348; (e) Even, P.; Ruzie, C.; Ricard, D.; Boitrel, B. *Org. Lett.* **2005**, *7*, 4325–4328.
21. (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C.; *Tetrahedron Lett.* **1986**, *27*, 4969–4970; (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.

6.2.1. Efficient transfer hydrogenation of ketones in the presence of ruthenium *N*–heterocyclic carbene catalysts

Stephan Enthaler, Ralf Jackstell, Bernhard Hagemann, Kathrin Junge, Giulia Erre and Matthias Beller*, *J. Organomet. Chem.* **2006**, *691*, 4652–4659.

Contributions

Imidazolium salts **1**, **2**, **5**, **6**, **8** and **9** were synthesized by Dr. R. Jackstell and Imidazolium salts **11** and **12** were a chemical gift by solvent innovation.

Available online at www.sciencedirect.com
ScienceDirect
Journal of Organometallic Chemistry 691 (2006) 4652–4659
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Efficient transfer hydrogenation of ketones in the presence of ruthenium *N*-heterocyclic carbene catalysts

Stephan Enthaler, Ralf Jackstell, Bernhard Hagemann, Kathrin Junge, Giulia Erre, Matthias Beller *

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

Received 27 April 2006; received in revised form 7 July 2006; accepted 13 July 2006
Available online 27 July 2006

Abstract

Novel ruthenium carbene complexes have been *in situ* generated and tested for the transfer hydrogenation of ketones. Applying $Ru(cod)(methylallyl)_2$ in the presence of imidazolium salts in 2-propanol and sodium-2-propanolate as base, turnover frequencies up to 346 h^{-1} have been obtained for reduction of acetophenone. A comparative study involving ruthenium carbene and ruthenium phosphine complexes demonstrated the higher activity of ruthenium carbene complexes.

Keywords: Ruthenium; Homogeneous catalysis; Transfer hydrogenation; *N*-heterocyclic carbenes; Ketones

1. Introduction

The preparation of alcohols has become an important field of activity for transition metal catalyzed reactions [1]. Within the different catalytic approaches developed, for instance addition of organometallic reagents to carbonyl compounds, hydroxylation of olefins, functionalization reactions of epoxides, the hydrogenation of ketones or aldehydes is the most powerful tool with respect to industrial applications. In particular, transfer hydrogenations represent a potent strategy, because of high atom efficiency, no need of pressure, and economic as well as environmental advantages [2]. In more detail, a broad scope of alcohols is accessible by transfer hydrogenation using non-toxic hydrogen donors under mild reaction conditions in the presence of various metal catalysts, such as Ir, Rh or Ru [2d]. Noteworthy, a prerequisite for achieving high activity and selectivity is the fine tuning of the metal catalyst by introduction of ligands. So far the development of new ligands for catalytic reductions focused predominantly on phosphines and amines.

More recently carbene ligands found increasing interest for exploiting new catalytic reactions [3]. Stable *N*-heterocyclic carbenes (NHC) were first introduced in the early 1990's by Arduengo et al. [4]. Since the mid 1990's Herrmann et al. [5] and then the groups of Bertrand [6], Blechert [7], Cavell [8], Fürstner [9]. Glorius [10], Grubbs [11], Nolan [12] and others [13] demonstrated the catalytic potential of NHC metal complexes. In this context we reported that palladium carbene complexes are excellent catalysts for different coupling reactions of aryl halides and telomerizations [14].

With regard to transfer hydrogenations different carbene or carbene-phosphine-systems containing Rh [15], Ir [15,16], Ru [17] and Ni [18] have been reported. Excellent turnover frequencies up to 120,000 h^{-1} were reported by the groups of Baratta and Herrmann applying a ruthenium-carbene-phosphine-catalysts [19]. However, for reduction of a typical substrate, e.g. acetophenone, with phosphine-free ruthenium-carbene catalysts lower turnover frequencies (TOF 333 h^{-1}) [17e] were achieved in comparison to iridium (500 h^{-1}) [16c] and rhodium systems (583 h^{-1}) [15b]. Due to the economical benefit of ruthenium metal compared to rhodium or iridium and the advantages of phosphine-free systems, it is an important

* Corresponding author. Tel.: +49 381 1281 0; fax: +49 381 1281 5000.
E-mail address: matthias.beller@ifok-rostock.de (M. Beller).

0022-328X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2006.07.013

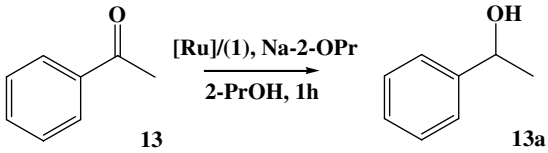
goal to search for more active ruthenium carbene catalysts. Herein, we report the application of novel *in situ* prepared ruthenium carbene catalysts in the reduction of different ketones.

2. Results and discussion

Based on our experience in the synthesis of carbene ligands and their application in homogeneous catalysis, we became interested in demonstrating the usefulness of carbene-complexes in ruthenium-catalyzed transfer hydrogenations [20]. From a practical point of view the application of *in situ* prepared catalysts has significant advantages. Thus, we used a small library of various imidazolium salts (Scheme 1, **1**–**12**) as carbene precursors. In exploratory experiments, 2-propanol-based transfer hydrogenation of acetophenone was examined. In order to ensure complete formation of the active catalyst a 2-propanol solution of 1 mol% ruthenium-source and 1 mol% 1,3-bis(2,6-di-*i*-propylphenyl)-imidazolium chloride (**1**) is stirred in the presence of 5 mol% sodium 2-propylate for 16 h at 65 °C.

Initial investigations showed a crucial effect on reactivity by using different ruthenium sources such as $[RuCl_2(C_6H_6)]_2$, $Ru_3(CO)_{12}$, and $Ru(cod)(methylallyl)_2$ in combination with imidazolium salt **1** (Table 1). Best conversion and yield are obtained for $Ru(cod)(methylallyl)_2$/**1** at 100 °C (Table 1, entry 8). Noteworthy, there is a significant temperature effect on the reaction rate (Table 1, entries 5–8).

Table 1
Screening of various ruthenium sources and yield-temperature dependency for the transfer hydrogenation of acetophenone (**13**)[a]



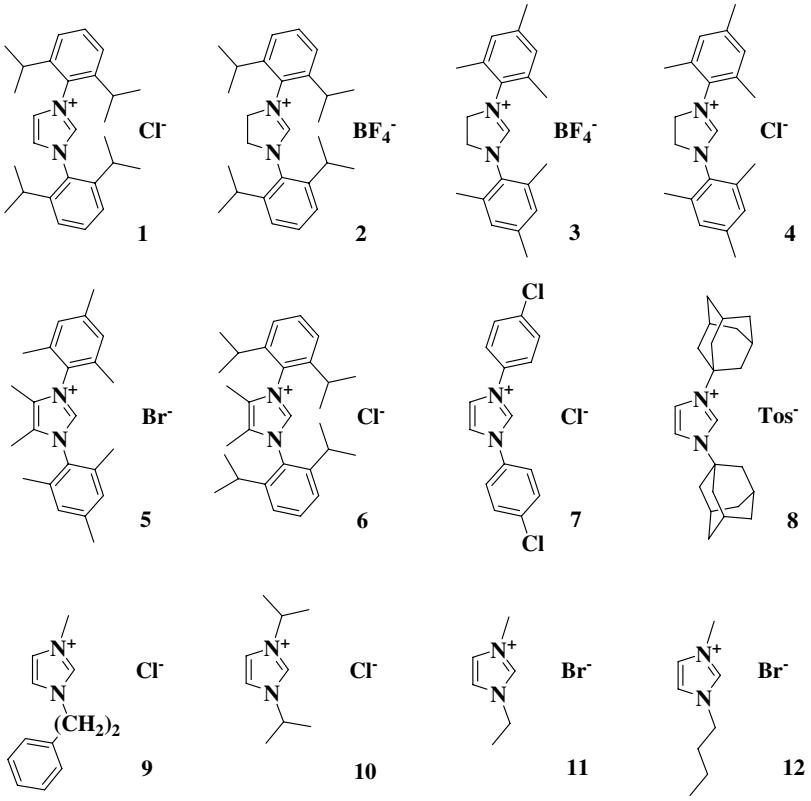
13 **13a**

Entry	Source	Temperature (°C)	Yield (%)[b]
1	$[RuCl_2(C_6H_6)]_2$	90	9
2	$[RuCl_2(C_6H_6)]_2$	100	80
3	$Ru_3(CO)_{12}$	90	40
4	$Ru_3(CO)_{12}$	100	16
5	$Ru(cod)(methylallyl)_2$	70	2
6	$Ru(cod)(methylallyl)_2$	80	43
7	$Ru(cod)(methylallyl)_2$	90	55
8	$Ru(cod)(methylallyl)_2$	100	>99

[a] *Reaction conditions*: *in situ* catalyst: 1.3×10^{-6} mol $Ru_3(CO)_{12}$, 1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$ or 3.8×10^{-6} mol $Ru(cod)(methylallyl)_2$, 3.8×10^{-6} mol imidazolium salt **1** and 1.9×10^{-5} mol Na–2-OPr in 2.0 mL 2-propanol for 16 h at 65 °C, addition of 3.8×10^{-4} mol acetophenone (**13**), reaction 1 h at described temperature.

[b] Conversion is determined by GC analysis (50 m Lipodex E, 95–200 °C) with diglyme as internal standard.

It is well-known that transfer hydrogenations are sensitive to the nature of the base. Thus, the influence of sodium 2-propylate, potassium *tert*-butylate, potassium carbonate and sodium hydroxide on selectivity and conversion was investigated. In all cases excellent selectivity (>99%) is



Scheme 1. Selection of imidazolium salts.

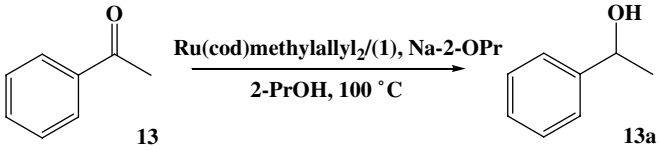
observed. Best conversion after 1 h at 100 °C are obtained in the presence of sodium 2-propylate (>99%) and potassium *tert*-butylate (95%). However, poor yields of 1-phenylethanol are achieved with potassium carbonate (53%). Interestingly, sodium hydroxide, one of the most common bases for transfer hydrogenation, induced only low conversion (62%). By increasing the amount of base a further acceleration of reaction rate is recorded, while no reaction occurred in the absence of base.

Next, the influence of the ligand concentration was investigated by variation of the metal to ligand-ratio. When increasing the equivalents of ligand per metal a negative effect on the reaction rate is observed (Table 2). We assume a catalyst deactivation by more than one carbene ligand, due to suppressing the metal hydride formation or blocking the active binding site for the substrate. However, 1 equiv. of ligand is necessary for achieving good conversion. Hence, transfer hydrogenations in absence of the carbene gave only moderate yield (Table 2, entry 1).

The stability of metal carbene complexes against moisture and oxygen has been documented [13]. Thus, the addition of water (10 mol%) to the reaction mixture decreased only slightly the conversion to 73% (TOF: 73 h^{-1}). Even in the presence of 100 mol% of water the catalyst showed significant activity (TOF: 54 h^{-1}).

To classify the potential of our catalytic system we compared Ru(cod)(methylallyl)$_2$/**1** with Ru(cod)(methylallyl)$_2$/PPh_3 and Ru(cod)(methylallyl)$_2$/PCy_3 (Fig. 1). More specifically, we studied the behaviour of Ru(cod)(methylallyl)$_2$/**1** and Ru(cod)(methylallyl)$_2$/PPh_3 by monitoring the conversion at different reaction times. The results showed similar catalytic behaviour at the beginning of the reaction.

Table 2
Influence of metal-ligand-ratio on the reduction of acetophenone (**13**)



Entry	Carbene:metal	Substrate:metal	Base:metal	Time (h)	Yield (%)[c]	TOF (h^{-1})[d]
1[a]	0	100	5	1	41	41
2[a]	1	100	5	1	>99	99
3[a]	2	100	5	1	61	61
4[a]	10	100	5	1	57	57
5[b]	1	5000	100	12	83	346
6[b]	2	5000	100	12	81	338
7[b]	10	5000	100	12	67	279

[a] *Reaction conditions*: *in situ* catalyst: 3.8×10^{-6} mol Ru(cod)(methylallyl)$_2$, 3.8×10^{-6} mol imidazolium salt **1** and 1.9×10^{-5} mol Na–2-OPr in 2.0 mL 2-propanol for 16 h at 65 °C, addition of 3.8×10^{-4} mol acetophenone (**13**), reaction temperature 100 °C.
[b] *Reaction conditions*: *in situ* catalyst: 9.7×10^{-7} mol Ru(cod)(methylallyl)$_2$, 9.7×10^{-7} mol imidazolium salt **1** and 9.7×10^{-5} mol Na–2-OPr in 5.0 mL 2-propanol for 16 h at 65 °C, addition of 4.85×10^{-3} mol acetophenone (**13**), reaction temperature 100 °C.
[c] Conversion is determined by GC analysis (50 m Lipodex E, 95–200 °C) with diglyme as internal standard.
[d] Turnover frequency = mol product/(mol catalyst × time), determined after 12 h.

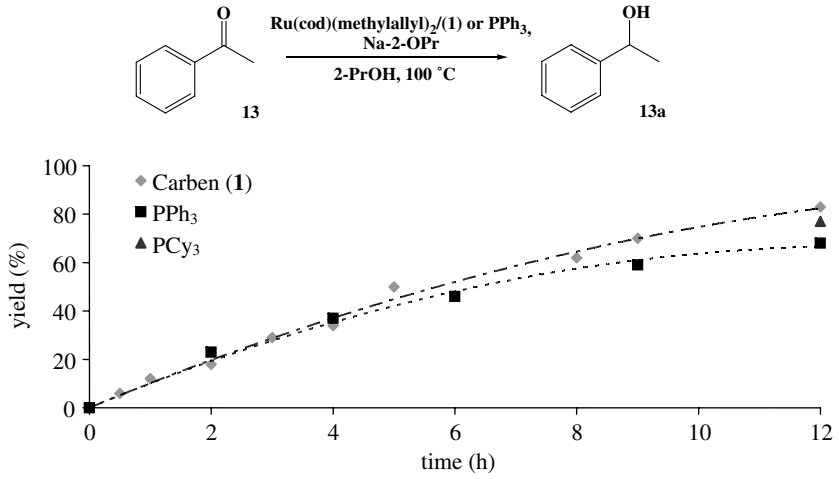


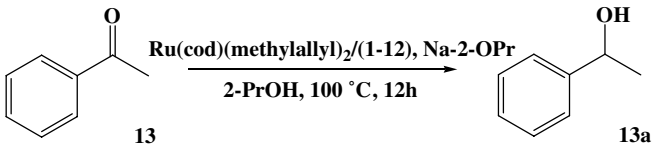
Fig. 1. Comparative study using imidazolium salt **1** and PPh_3 as ligands. *Note*: *Reaction conditions*: *in situ* catalyst: 9.7×10^{-7} mol Ru(cod)(methylallyl)$_2$, 9.7×10^{-7} mol imidazolium salt **1** or PPh_3 and 9.7×10^{-5} mol Na-2-OPr in 5.0 mL 2-propanol for 16 h at 65 °C, addition of 4.85×10^{-3} mol acetophenone (**13**), reaction at 100 °C. Conversion is determined by GC analysis (50 m Lipodex E, 95–200 °C) with diglyme as internal standard.

However, during the reaction a higher deactivation rate of the PPh_3-system is detected, which resulted in a lower yield of 1-phenylethanol after 12 h (68% vs 83%). The Ru(cod)(methylallyl)$_2$/PCy_3 yielded comparable amounts of 1-phenylethanol to Ru(cod)(methylallyl)$_2$/**1**.

As shown in Table 3 we examined 12 examples out of the growing number of carbene precursors (**1**–**12**) under the previously optimized conditions for the transfer hydrogenation of acetophenone (**13**). In order to estimate differences between the various carbene precursors we applied low catalyst loadings (0.02 mol%) at 100 °C. After 12 h average turnover frequencies up to 346 h^{-1} are achieved for the preparation of 1-phenylethanol applying ligand **1**. Summarizing the activities of 4,5-dihydroimidazolium salts, no pronounced influence is observed by variation of substitutents at the nitrogen atoms (2,6-di-*iso*-propylphenyl or mesitylene groups) or by changing the anion of the imidazolium salt (Table 3, entries 2–4). On the other hand by introduction of methyl groups in the 4,5-position of the imidazolium unit a depletion of activity is monitored (Table 3, entries 5 and 6).

In general, application of *N*-alkyl carbenes led to a lower activity compared to *N*-aryl carbenes (Scheme 1, **8**–**12**). In the presence of 1-ethyl-3-methylimidazolium bromide ([EMIM]Br, **11**) and 1-butyl-3-methylimidazolium bromide ([BMIM]Br, **12**), which are usually used as ionic liquids [21], the recorded yields were lower (Table 3, entries 11 and 12).

Table 3
Variation of imidazolium salts in the transfer hydrogenation of acetophenone (**13**)[a]



13 **13a**

Entry	Imidazolium salt	Yield (%)[b]	TOF (h^{-1})[c]	TON[d]
1	1	83	346	4150
2	2	75	313	3750
3	3	68	283	3400
4	4	73	304	3650
5	5	53	221	2650
6	6	61	254	3050
7	7	62	258	3100
8	8	67	279	3350
9	9	77	320	3850
10	10	69	288	3450
11	11	54	225	2700
12	12	38	158	1900

[a] *Reaction conditions*: *in situ* catalyst: 9.7×10^{-7} mol Ru(cod)(methylallyl)$_2$, 9.7×10^{-7} mol imidazolium salt and 9.7×10^{-5} mol Na-2-OPr in 5.0 mL 2-propanol for 16 h at 65 °C, addition of 4.85×10^{-3} mol acetophenone (**13**), reaction for 12 h at 100 °C.

[b] Conversion is determined by GC analysis (50 m Lipodex E, 95–200 °C) with diglyme as internal standard.

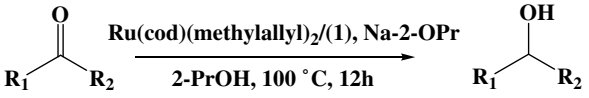
[c] Turnover frequency = mol product/(mol catalyst × time), determined after 12 h.

[d] Turnover number = mol product/mol catalyst, determined after 12 h.

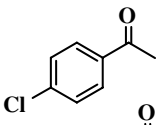
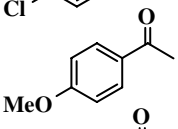
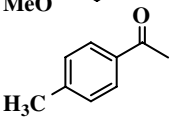
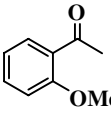
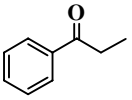
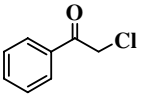
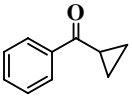
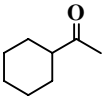
In order to demonstrate the usefulness of the catalysts in a more general manner we employed the catalyst system Ru(cod)(methylallyl)$_2$/**1** in the transfer hydrogenation of nine aromatic and aliphatic ketones (Table 4).

In general, all substrates were hydrogenated with excellent chemoselectivity (>99%). Best activity (TOF up to 338 h^{-1}) is achieved with dialkyl ketones (Table 4, entries

Table 4
Scope and limitations of Ru(cod)(methylallyl)$_2$/**1**-system-catalyzed ketone reduction[a]



14-22 **14a-22a**

Entry	Compound	Ketone	Conversion (%)[b]	TOF (h^{-1})[c]
1	**14**		68 [96]	285
2	**15**		41	171
3	**16**		62 [92]	258
4	**17**		68 [97]	283
5	**18**		67 [93]	281
6	**19**		2	6
7	**20**		40	166
8	**21**		77	321
9	**22**		81	338

[a] *Reaction conditions*: *in situ* catalyst: 9.7×10^{-7} mol Ru(cod)(methylallyl)$_2$, 9.7×10^{-7} mol imidazolium salt **1** and 9.7×10^{-5} mol Na-2-OPr in 5.0 mL 2-propanol for 16 h at 65 °C, addition of 4.85×10^{-3} mol ketone, reaction for 12 h at 100 °C.

[b] Conversion is determined by GC analysis (**14** (25 m Lipodex E, 100 °C), **15** (50 m Lipodex E, 90–105 °C), **16** (25 m Lipodex E, 80–180 °C), **17** (30 m HP Agilent Technologies 50–300 °C), **18** (25 m Lipodex E, 90–180 °C), **19** (50 m Lipodex E, 90–180 °C), **20**–**22** (30 m HP Agilent Technologies 50–300 °C)) with diglyme as internal standard. In brackets the conversion after 24 h is given.

[c] Turnover frequency = mol product/(mol catalyst × time), determined after 12 h.

8 and 9). In comparison, *para*-substituted acetophenones containing an electron-withdrawing group (Table 4, entry 1) showed better conversion than *para*-substituted substrates with an electron-donating group (Table 4, entry 2). Noteworthy, by changing the electron-donating group from *para*- to *ortho*-position a significant increase of the yield is detected (Table 4, entries 2 and 4). We assume for **17** a possible second coordination site at the metal center. No major change in activity is observed for substitution adjacent to the carbonyl group by an ethyl group, whereas introduction of a chloromethyl deactivated the catalyst (Table 4, entries 5 and 6). Moderate activity is monitored when increasing the bulkiness next to the active center by a cyclopropyl group (Table 4, entry 7).

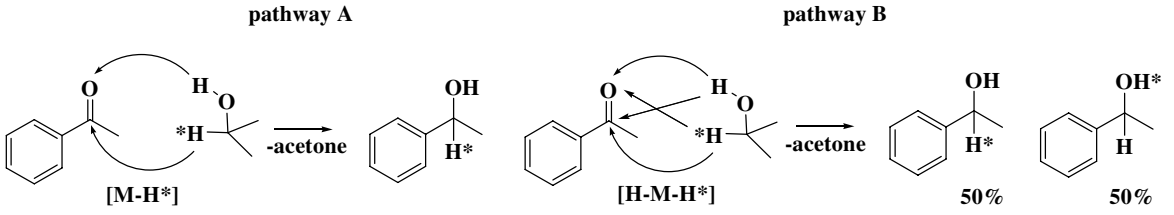
Finally, we were interested in mechanistic aspects. In general, for transition metal catalyzed transfer hydrogenation two mechanisms are accepted, designated as direct hydrogen transfer, via formation of a six-membered cyclic transition state composed of donor, metal and acceptor, and the hydridic route which shows two possible pathways, the monohydride or dihydride mechanism. In more detail, formation of a monohydride-metal-complex promoted an exclusive hydride transfer from carbon (donor) to carbonyl carbon (acceptor) (Scheme 2, pathway A), whereas a hydride transfer from carbon (donor) to carbonyl carbon (acceptor) as well as to the carbonyl oxygen (acceptor) was proposed for a dihydride-metal-complex formation (Scheme 2, pathway B). Indications for both pathways were published by Bäckvall et al. and other groups, when following the hydride transfer catalyzed by various metal complexes [22].

Mechanistic studies have been mostly published for catalysts containing phosphines, amines or cyclopentadienyls as ligands [22a]. For transition metal complexes containing carbene ligands Faller and Crabtree described investigations on an iridium dicarbene system [16c]. They assumed a monohydride mechanism, because the hydride is mainly transferred in the 1-position of acetophenone. So far there is no mechanistic investigation known in transfer hydrogenations applying Ru carbene catalysts.

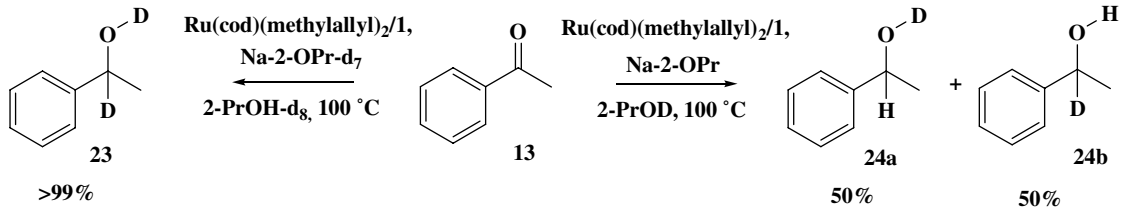
Reaction of ketone **20** (''radical clock''-substrate) with 2-propanol in the presence of 1 mol% Ru(cod)(methylallyl)$_2$/**1** gave only the corresponding cyclopropyl phenyl alcohol (>99% by ^{1}H NMR). Apparently, there is no radical induced reduction [23]. Owing to this a radical reduction mechanism promoted by sodium alkoxides can be also excluded, whereby the transition metal plays only a marginal role [24]. This assumption is also confirmed by performing the reduction of acetophenone (**13**) in the presence of base and in the absence of ruthenium catalyst. Here, no reduction product was detected.

Next, we followed the transfer of hydrogen from the donor molecule into the product by applying a deuterated donor [25]. The catalytic precursor is generated by stirring a solution of 2-propanol-d$_8$, Ru(cod)(methylallyl)$_2$ and imidazolium salt **1** in the presence of sodium 2-propanolate-d_7 for 16 h at 65 °C. Then, acetophenone (**13**) was added and the solution was stirred for 30 min at 100 °C. As main product (>99%) **23** was observed by ^{1}H NMR (Scheme 3) [26]. The result showed an exclusive transfer of the deuterium into the carbonyl group, so that no C–H activation on the substrate occurred under the described conditions. Furthermore, this result rules out enol formation in the catalytic cycle [27].

To clarify the transfer of hydrogen from the hydrogen donor into the substrate the reaction was run with 2-propanol-d_1 (hydroxy-group deuterated) as solvent/donor and sodium 2-propylate as base. In the transfer hydrogenation of acetophenone (**13**) we obtained a mixture of two different deuterated 1-phenylethanols (Scheme 2, **24a** and **24b**). Here, a scrambling of the transferred proton and deuteride is found (**24a** and **24b** = 1:1). In conclusion the non-specific



Scheme 2. Comparison of monohydride and dihydride mechanism for transfer hydrogenations.



Scheme 3. Deuterium incorporation into acetophenone catalyzed by Ru(cod)(methylallyl)$_2$/**1**-system in the presence of base.

migration is in agreement with the dihydride mechanism, implying a formation of metal dihydride species in the catalytic cycle [2d].

3. Summary

We demonstrated the successful application of *in situ* prepared ruthenium catalysts containing carbene ligands in the transfer hydrogenation of various ketones. In the reduction of acetophenone (**13**) turnover frequencies up to 346 h^{-1} were found for a catalyst system containing Ru(cod)(methylallyl)$_2$/1,3-bis(2,6-di-*i*-propylphenyl)-imidazolium chloride (**1**). Mechanistic experiments indicated the transfer of hydrogen from the donor molecule into the substrate via a dihydride mechanism.

4. Experimental section

4.1. General

All manipulations were performed under argon atmosphere using standard Schlenk techniques. Unless specified, all chemicals are commercially available and used as received. Sodium 2-propylate was prepared by reacting sodium with 2-propanol under an argon atmosphere. 2-Propanol was used without further purification (purchased from Fluka, dried over molecular sieves). Imidazolium salts **1**, **2**, **5**, **6**, **8** and **9** were synthesized according to the published protocols [4,28]. Imidazolium salts **11** and **12** were a gift by Solvent Innovation. Imidazolium salts **3**, **4**, **7** and **10** are commercially available by Strem. All ketones were dried over CaH_2, distilled in vacuum and stored under argon, except ketones **17** and **19**, which were cycled with vacuum-argon and stored under argon.

4.2. General procedure for catalytic transfer hydrogenation of ketones

In a 10 mL Schlenk tube, the *in situ* catalyst (9.7×10^{-7} mol) was prepared by stirring a solution of Ru(cod)(methylallyl)$_2$ (9.7×10^{-7} mol), imidazolium salt (9.7×10^{-7} mol) and sodium 2-propylate (4.85×10^{-6} mol) in 1.0 mL 2-propanol for 16 h at 65 °C. After addition of the corresponding ketone (4.85×10^{-3} mol) and the internal standard diglyme in 4.0 mL 2-propanol the Schlenk tube was sealed and the reaction mixture was heated to 100 °C. After 12 h the conversion was measured by GC without further purification. In the case of ^{1}H NMR determination of the yield, the solvent was removed in vacuum and the residue was dissolved in $CDCl_3$ and submitted to ^{1}H NMR.

4.3. Procedure for transfer hydrogenation of acetophenone with 2-propanol-d_8 as hydride source

In a 10 mL Schlenk tube, Ru(cod)(methylallyl)$_2$ (3.8×10^{-6} mol), imidazolium salt **1** (3.8×10^{-6} mol) and sodium 2-propylate-d_7 (1.9×10^{-5} mol, prepared by reacting sodium with 2-propanol-d_8) was solved in 1.0 mL 2-propanol-d_8 and stirred for 16 h at 65 °C. After addition of the acetophenone (**13**) (3.8×10^{-4} mol) in 2.0 mL 2-propanol-d_8 the reaction mixture was heated to 100 °C for 30 min. The solution was cooled to r.t. and filtrated over a plug of silica. The conversion was determined by ^{1}H NMR.

4.4. Procedure for transfer hydrogenation of acetophenone with 2-propanol-d_1 as hydride source

In a 10 mL Schlenk tube, Ru(cod)(methylallyl)$_2$ (3.8×10^{-6} mol), imidazolium salt **1** (3.8×10^{-6} mol) and sodium 2-propylate (1.9×10^{-5} mol, prepared by reacting sodium with 2-propanol) was solved in 1.0 mL 2-propanol-d_1 (deuterium fixed as hydroxyl proton) and stirred for 16 h at 65 °C. The reaction mixture was heated to 100 °C for 10 min after addition of the acetophenone (**13**) (3.8×10^{-4} mol) in 2.0 mL 2-propanol-d_1. (To avoid side effects reaction was not run to full conversion.) The solution was cooled to r.t. and filtrated over a plug of silica. The solvent was removed in vacuum and the residue was solved in $CDCl_3$. The conversion was determined by ^{1}H NMR.

4.5. Product characterization

The obtained alcohols are known compounds. They were characterized by comparison with authentic samples and mass spectroscopy (Agilent Technologies 6890N, MSD 5973) or ^{1}H NMR (Bruker ARX-400). Product **13a:** *m*/*z* (%) = 122 (M^+, 21); 107 (72); 79 (100); 51 (34); 43 (36); 39 (13); 32 (15). Product **14a**: *m*/*z* (%) = 156 (M^+, 26); 141 (100); 121 (14); 113 (33); 103 (9); 77 (85); 51 (12); 43 (22). Product **15a**: *m*/*z* (%) = 152 (M^+, 24); 137 (100); 134 (32); 119 (20); 109 (48); 94 (38); 91 (34); 77 (46); 65 (31); 51 (16); 43 (37); 39 (21). Product **16a**: *m*/*z* (%) = 136 (M^+, 32); 121 (100); 117 (14); 91 (94); 77 (53); 65 (29); 51 (16); 43 (57); 39 (23). Product **17a**: *m*/*z* (%) = 152 (M^+, 31); 137 (100); 134 (20); 119 (10); 109 (46); 94 (29); 91 (16); 77 (28); 65 (12); 43 (13). Product **18a**: *m*/*z* (%) = 152 (M^+, 11); 107 (100); 79 (79); 51 (13). Product **19a**: *m*/*z* (%) = 156 (M^+, 3); 107 (100); 91 (7); 79 (67); 77 (50); 51 (19). Product **20a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 0.34 (1H, m); 0.44 (1H, m); 0.51 (1H, m); 0.58 (1H, m); 1.00 (1H, m); 2.31 (1H, s); 3.98 (1H, d, J = 8.16 Hz); 7.24 (3H, m); 7.99 (1H, d, J = 7.52 Hz). Product **21a**: *m*/*z* (%) = 128 (M^+, 17); 110 (34); 95 (18); 81 (100); 67 (71); 55 (78); 41 (46). Product **22a**: *m*/*z* (%) = 102 (M^+, 3); 87 (26); 57 (100); 45 (83); 41 (53).

Acknowledgements

This work has been financed by the State of Mecklenburg-Pomerania and the Bundesministerium für Bildung und Forschung (BMBF). We thank Mrs. C. Voss, Mrs. C. Mewes, Mrs. M. Heyken, Mrs. S. Buchholz and Dr. C. Fischer (all Leibniz-Institut für Katalyse e.V.) for their

excellent technical and analytical support. Solvent Innovation is gratefully thanked for a chemical gift.

References

[1] (a) M. Beller, C. Bolm (Eds.), Transition Metals for Organic Synthesis, second ed., Wiley–VCH, Weinheim, 2004;
(b) B. Cornils, W.A. Herrmann, Applied Homogeneous Catalysis with Organometallic Compounds, second ed., Wiley–VCH, Weinheim, 2002;
(c) M. Kitamura, R. Noyori, in: S.-I. Murahashi (Ed.), Ruthenium in Organic Synthesis, Wiley–VCH, Weinheim, 2004;
(d) E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis, Springer, Berlin, 1999;
(e) R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley, New York, 1994.

[2] (a) S. Gladiali, E. Alberico, Chem. Soc. Rev. 35 (2006) 226–236;
(b) G. Zassinovich, G. Mestroni, S. Gladiali, Chem. Rev. 51 (1992) 1051–1069;
(c) R. Noyori, S. Hashiguchi, Acc. Chem. Res. 30 (1997) 97–102;
(d) S. Gladiali, G. Mestroni, in: M. Beller, C. Bolm (Eds.), Transition Metals for Organic Synthesis, second ed., Wiley–VCH, Weinheim, 2004, pp. 145–166;
(e) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, M. Studer, Adv. Synth. Catal. 345 (2003) 103–151.

[3] (a) For reviews see: E. Peris, R.H. Crabtree, Coordin. Chem. Rev. 248 (2004) 2239–2246;
(b) M.C. Perry, K. Burgess, Tetrahedron: Asymmetr. 14 (2003) 951–961;
(c) W.A. Herrmann, Angew. Chem. 114 (2002) 1342–1363;
(d) T.M. Trnka, R.H. Grubbs, Acc. Chem. Res. 34 (2001) 18–29;
(e) D. Bourisou, O. Guerret, F.P. Gabbai, G. Bertrand, Chem. Rev. 100 (2000) 39–91;
(f) W.A. Herrmann, C. Köcher, Angew. Chem. 109 (1997) 2256–2282.

[4] (a) A.J. Arduengo III, R.L. Harlow, M. Kline, J. Am. Chem. Soc. 113 (1991) 361–363;
(b) A.J. Arduengo III, Acc. Chem. Res. 32 (1999) 913–921;
(c) A.J. Arduengo III, R. Krafczyk, R. Schmutzler, H.A. Craig, J.R. Goerlich, W.J. Marshall, M. Unverzagt, Tetrahedron 55 (1999) 14523–14534.

[5] (a) C.W.K. Gstöttmayr, V.P.W. Böhm, E. Herdtweck, M. Grosche, W.A. Herrmann, Angew. Chem., Int. Ed. 41 (2002) 1363–1365;
(b) W.A. Herrmann, L.J. Gooßen, C. Köcher, G.R.J.. Artus, Angew. Chem., Int. Ed. 35 (1996) 2805–2807;
(c) W.A. Herrmann, M. Elison, J. Fischer, C. Köcher, G.R.J. Artus, Angew. Chem., Int. Ed. 34 (1995) 2371–2374.

[6] (a) V. Lavallo, Y. Canac, A. DeHope, B. Donnadieu, G. Bertrand, Angew. Chem., Int. Ed. 44 (2005) 7236–7239;
(b) G. Bertrand, E. Diez-Barra, J. Fernandez-Baeza, H. Gornitzka, A. Moreno, A. Otero, R.I. Rodriguez-Curiel, J. Tejeda, Eur. J. Inorg. Chem. 11 (1999) 1965–1971.

[7] (a) K. Vehlow, S. Maechling, S. Blechert, Organometallics 25 (2006) 25–28;
(b) R. Stragies, U. Voigtmann, S. Blechert, Tetrahedron Lett. 41 (2000) 5465–5468;
(c) S. Gessler, S. Randl, S. Blechert, Tetrahedron Lett. 41 (2000) 9973–9976.

[8] (a) J.W. Sprengers, J. Wassenaar, N.D. Clement, K.J. Cavell, Angew. Chem., Int. Ed. 44 (2005) 2026–2029;
(b) N.D. Clement, K.J. Cavell, Angew. Chem., Int. Ed. 43 (2004) 3845–3847;
(c) D.S. McGuinness, K.J. Cavell, Organometallics 19 (2000) 741–748;
(d) D.S. McGuinness, M.J. Green, K.J. Cavell, B.W. Skelton, A.H. White, J. Organomet. Chem. 565 (1998) 165–178.

[9] (a) A. Fürstner, O.R. Thiel, C.W. Lehmann, Organometallics 21 (2002) 331–335;
(b) A. Fürstner, L. Ackermann, K. Beck, H. Hori, D. Koch, K. Langemann, M. Liebl, C. Six, W. Leitner, J. Am. Chem. Soc. 123 (2001) 9000–9006;
(c) A. Fürstner, O.R. Thiel, L. Ackermann, H.-J. Schanz, S.P. Nolan, J. Org. Chem. 65 (2000);
(d) A. Fürstner, O.R. Thiel, N. Kindler, B. Bartkowska, J. Org. Chem. 65 (2000) 7990–7995.

[10] (a) G. Altenhoff, R. Goddard, C.W. Lehmann, F. Glorius, J. Am. Chem. Soc. 126 (2004) 15195–15201;
(b) G. Altenhoff, R. Goddard, C.W. Lehmann, F. Glorius, Angew. Chem., Int. Ed. 42 (2003) 3690–3693.

[11] (a) T.W. Funk, J.M. Berlin, R.H. Grubbs, J. Am. Chem. Soc. 128 (2006) 1840–1846;
(b) J.P. Morgan, R.H. Grubbs, Org. Lett. 2 (2000) 3153–3155;
(c) C.W. Bielawski, R.H. Grubbs, Angew. Chem., Int. Ed. 39 (2000) 2903–2906.

[12] (a) N. Marion, O. Navarro, J. Mei, E.D. Stevens, N.M. Scott, S.P. Nolan, J. Am. Chem. Soc. 128 (2006) 4101–4111;
(b) S. Díez-González, H. Kaur, F.K. Zinn, E.D. Stevens, S.P. Nolan, J. Org. Chem. 70 (2005) 4784–4796;
(c) H.M. Lee, T. Jiang, E.D. Stevens, S.P. Nolan, Organometallics 20 (2001) 1255–1258;
(d) J. Huang, E.D. Stevens, S.P. Nolan, J.L. Petersen, J. Am. Chem. Soc. 121 (1999) 2674–2678;
(e) J. Huang, S.P. Nolan, J. Am. Chem. Soc. 121 (1999) 9889–9890;
(f) J. Huang, G. Grasa, S.P. Nolan, Org. Lett. 1 (1999) 1307–1309.

[13] (a) M.J. Schultz, S.S. Hamilton, D.R. Jensen, M.S. Sigman, J. Org. Chem. 70 (2005) 3343–3352;
(b) C.M. Crudden, D.P. Allen, Coordin. Chem. Rev. 248 (2004) 2247–2273;
(c) M.K. Denk, J.M. Rodezno, S. Gupta, A.J. Lough, J. Organomet. Chem. 617–618 (2001) 242–253;
(d) M. Regitz, Angew. Chem. 108 (1996) 791–794.

[14] (a) S. Harkal, R. Jackstell, F. Nierlich, D. Ortmann, M. Beller, Org. Lett. 7 (2005) 541–544;
(b) A. Zapf, M. Beller, Chem. Commun. (2005) 431–440;
(c) C.-F. Huo, T. Zeng, Y.-W. Li, M. Beller, H. Jiao, Organometallics 24 (2005) 6037–6042;
(d) R. Jackstell, S. Harkal, H. Jiao, A. Spannenberg, C. Borgmann, D. Röttger, F. Nierlich, M. Elliot, S. Niven, K. Cavell, O. Navarro, M.S. Viciu, S.P. Nolan, M. Beller, Chem. Eur. J. 10 (2004) 3891–3900;
(e) A.C. Frisch, F. Rataboul, A. Zapf, M. Beller, J. Organomet. Chem. 687 (2003) 403–409;
(f) R. Jackstell, M.G. Andreu, A. Frisch, K. Selvakumar, A. Zapf, H. Klein, A. Spannenberg, D. Röttger, O. Briel, R. Karch, M. Beller, Angew. Chem., Int. Ed. 41 (2002) 986–989.

[15] (a) E. Mas-Marzá, M. Poyatos, M. Sanaú, E. Peris, Organometallics 23 (2004) 323–325;
(b) M. Poyatos, E. Mas-Marzá, J.A. Mata, M. Sanaú, E. Peris, Eur. J. Inorg. Chem. (2003) 1215–1221;
(c) M. Albrecht, R.H. Crabtree, J. Mata, E. Peris, Chem. Commun. (2002) 32–33.

[16] (a) F.E. Hahn, C. Holtgrewe, T. Pape, M. Martin, E. Sola, L.A. Oro, Organometallics 24 (2005) 2203–2209;
(b) J.R. Miecznikowski, R.H. Crabtree, Organometallics 23 (2004) 629–631;
(c) M. Albrecht, J.R. Miecznikowski, A. Samuel, J.W. Faller, R.H. Crabtree, Organometallics 21 (2002) 3596–3604;
(d) A.C. Hillier, H.M. Lee, E.D. Stevens, S.P. Nolan, Organometallics 20 (2001) 4246–4252.

[17] (a) S. Burling, M.K. Whittlesey, J.M.J. Williams, Adv. Synth. Catal. 347 (2005) 591–594;
(b) P.L. Chiu, H.M. Lee, Organometallics 24 (2005) 1692–1702;

(c) M.G. Edwards, R.F.R. Jazzar, B.M. Paine, D.J. Shermer, M.K. Whittlesey, J.M.J. Williams, D.D. Edney, Chem. Commun. (2004) 90–91;
(d) M. Poyatos, J.A. Mata, E. Falomir, R.H. Crabtree, E. Peris, Organometallics 22 (2003) 1110–1114;
(e) A.A. Danopoulos, S. Winston, W.B. Motherwell, Chem. Commun. (2002) 1376–1377.

[18] S. Kuhl, R. Schneider, Y. Fort, Organometallics 22 (2003) 4184–4186.

[19] W. Baratta, J. Schütz, E. Herdtweck, W.A. Herrmann, P. Rigo, J. Organomet. Chem. 690 (2005) 5570–5575.

[20] (a) F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, Chem. Eur. J. 10 (2004) 2983–2990;
(b) A.C. Frisch, A. Zapf, O. Briel, B. Kayser, N. Shaikh, M. Beller, J. Mol. Catal. 214 (2004) 231–239;
(c) A.M. Seayad, K. Selvakumar, A. Moballigh, M. Beller, Tetrahedron Lett. 44 (2003) 1679–1683;
(d) A.C. Frisch, N. Shaikh, A. Zapf, M. Beller, Angew. Chem., Int. Ed. 41 (2002) 4056–4059;
(e) K. Selvakumar, A. Zapf, A. Spannenberg, M. Beller, Chem. Eur. J. 8 (2002) 3901–3906;
(f) K. Selvakumar, A. Zapf, M. Beller, Org. Lett. 4 (2002) 3031–3033;
(g) R. Jackstell, A. Frisch, M. Beller, D. Röttger, M. Malaun, B. Bildstein, J. Mol. Catal. 185 (2002) 105–112.

[21] P. Wasserscheid, W. Keim, Angew. Chem., Int. Ed. 39 (2000) 3773–3789.

[22] (a) O. Pàmies, J.E. Bäckvall, Chem. Eur. J. 7 (2001) 5052–5058;
(b) A. Aranyos, G. Csjernyik, K.J. Szabó, J.E. Bäckvall, Chem. Commun. (1999) 351–352;
(c) M.L.S. Almeida, M. Beller, G.Z. Wang, J.E. Bäckvall, Chem. Eur. J. 2 (1996) 1533–1536;
(d) G.Z. Wang, J.E. Bäckvall, J. Chem. Soc. Chem. Commun. (1992) 337–339;
(e) G.Z. Wang, J.E. Bäckvall, J. Chem. Soc. Chem. Commun. (1992) 980–982;
(f) R.L. Chowdhury, J.E. Bäckvall, J. Chem. Soc. Chem. Commun. (1991) 1063–1064;
(g) B.N. Chaudret, D.J. Cole-Hamilton, R.S. Nohr, G. Wilkinson, J. Chem. Soc. Dalton Trans. (1977) 1546–1557;
(h) J. Chatt, B.L. Shaw, A.E. Field, J. Chem. Soc. (1964) 3466–3475;
(i) J.S.M. Samec, J.-E. Bäckvall, P.G. Andersson, P. Brandt, Chem. Soc. Rev. 35 (2006) 237–248.

[23] (a) D.D. Tanner, G.E. Diaz, A. Potter, J. Org. Chem. 50 (1985) 2149–2154;
(b) M. Degueil-Castaing, A. Rahm, J. Org. Chem. 51 (1986) 1672–1676;
(c) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 120 (1998) 13529–13530;
(d) J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung, A.S.C. Chan, Chem. Eur. J. 9 (2003) 2963–2968.

[24] E.C. Ashby, J.N. Argyropoulos, J. Org. Chem. 51 (1986) 3593–3597.

[25] (a) L. Dahlenburg, R. Götz, Eur. J. Inorg. Chem. (2004) 888–905;
(b) P.W.C. Cross, G.J. Ellames, J.S. Gibson, J.M. Herbert, W.J. Kerr, A.H. McNeill, T.W. Mathers, Tetrahedron 59 (2003) 3349–3358.

[26] (a) L.Y. Kuo, D.M. Finigan, N.N. Tadros, Organometallics 22 (2003) 2422–2425;
(b) R.L. Elsenbaumer, H.S. Mosher, J. Org. Chem. 44 (1979) 600–604.

[27] D. Klomp, T. Maschmeyer, U. Hanefeld, J.A. Peters, Chem. Eur. J. 10 (2004) 2088–2093.

[28] (a) L. Jafarpour, E.D. Stevens, S.P. Nolan, J. Organomet. Chem. 606 (2000) 49–54;
(b) S.V. Dzyuba, R.A. Bartsch, J. Heterocylic Chem. 38 (2001) 265–268.

6.2.2. New Ruthenium Catalysts for Asymmetric Transfer Hydrogenation of prochiral Ketones

Stephan Enthaler, Bernhard Hagemann, Santosh Bhor, Gopinathan Anilkumar, Man Kin Tse, Bianca Bitterlich, Kathrin Junge, Giulia Erre, and Matthias Beller*, *Adv. Synth. Catal.* **2007**, *349*, 853–860.

Contributions

Ligands **3a**–**3e** were synthesized by Dr. S. Bhor, Dr. G. Anilkumar, Dr. M. K. Tse and B. Bitterlich. The experiments stated in table 4 entries 2 (cat. A), 3 (cat. B) and 6 (cat. A and cat. B) were carried out by Dr. B. Hagemann.

DOI: 10.1002/adsc.200600475

New Ruthenium Catalysts for Asymmetric Transfer Hydrogenation of Prochiral Ketones

Stephan Enthaler,[a] Bernhard Hagemann,[a] Santosh Bhor,[a] Gopinathan Anilkumar,[a] Man Kin Tse,[a] Bianca Bitterlich,[a] Kathrin Junge,[a] Giulia Erre,[a] and Matthias Beller[a,*]

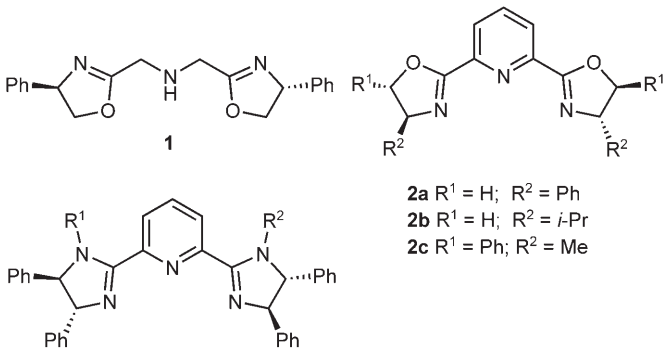
[a] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
Fax: (+49)-381-1281-5000; e-mail: matthias.beller@catalysis.de

Received: September 15, 2006; Revised: February 5, 2007

Abstract: Tridentate *N,N,N*-pyridinebisimidazolines have been studied as new ligands for the enantioselective transfer hydrogenation of prochiral ketones. High yields and excellent enantioselectivity up to >99% *ee* have been achieved with an *in situ* generated catalytic system containing dichlorotris(triphenylphosphine)ruthenium and 2,6-bis-([*4R,5R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine (**3a**) in the presence of sodium isopropoxide.

Keywords: asymmetric transfer hydrogenation; ketones; phosphines; ruthenium; tridentate nitrogen ligands

Enantiomerically pure alcohols have a wide range of applications, for example, building blocks and synthons for pharmaceuticals, agrochemicals, polymers, syntheses of natural compounds, auxiliaries, ligands and key intermediates in organic syntheses.[1] Within the different molecular transformations to chiral alcohols, transition metal-catalyzed reactions offer efficient and versatile strategies, such as addition of organometallic compounds to aldehydes, hydrosilylation, and hydrogenation of prochiral ketones.[2] From an economic and environmental point of view the asymmetric hydrogenation, in particular the transfer hydrogenation, represents a powerful tool for their synthesis because of its high atom economy and safety advantages.[3] Here, Noyori's ruthenium-based catalysts comprising chiral tosylated diamines constitute state-of-the-art transfer hydrogenation systems.[3d,4] Based on this seminal work an increasing number of ruthenium catalysts with chiral bidentate *N,N*-ligands were developed in the last decade.[3] Significantly fewer systems are known in which transfer of chiral information is promoted by tridentate ligands.[5,6] Up to now only a limited number of auspicious tridentate nitrogen-containing *N,N,N* ligands were established in the field of transfer hydrogenation. For example (*R*)-phenyl-ambox (**1**)[5] and different pyridinebisoxazoline (pybox) ligands (**2**)[6] have been applied for the reduction of acetophenone (Scheme 1).



Scheme 1. *N,N,N*-Tridentate ligands.

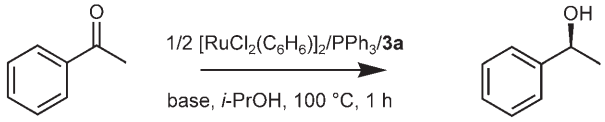
Recently, we reported the synthesis of a new class of chiral tridentate amines.[7] The preparation and tunability of these pyridinebisimidazolines (**3**) (so-called pybim ligands, Scheme 1) are easier and more flexible compared to the popular pyboxes, making the former a suitable ligand tool box for various asymmetric transformations. To date there is no report on the performance of these ligands in hydrogenation reactions. The resemblance between pybim (**3**) and pybox (**2**) stimulated our research to study the potential of this class of ligands in the transfer hydrogenation of aromatic and aliphatic ketones.

In exploratory experiments, isopropyl alcohol-based transfer hydrogenation of acetophenone was examined using a simple *in situ* catalyst system composed of $[RuCl_2(C_6H_6)]_2$, 2,6-bis-([*4R,5R*]-4,5-diphenyl-4,5-

dihydro-1*H*-imidazol-2-yl)-pyridine (**3**) and triphenylphosphine. To ensure complete formation of the active catalyst and avoid an induction period the reaction mixture was heated for 10 min at 100 °C in the presence of base followed by addition of acetophenone. First, studies for optimizing the reaction conditions were carried out with 1 mol% of pre-catalyst and 5 mol% of base. It is well-known that transfer hydrogenations are sensitive to the nature of the base. Thus, the influence of different bases on selectivity and conversion was investigated initially (Table 1). Best results were obtained for sodium isopropoxide and K_2CO_3 with conversions up to 95% and enantiomeric excesses up to 94% (Table 1, entries 1 and 8). Interestingly, NaOH and KOH the most commonly used bases for transfer hydrogenations gave only moderate enantioselectivity (78% and 80%, Table 1, entries 3 and 4). In addition, we tested some organic nitrogen-containing systems such as DBU, DABCO, NEt_3, $N(i\text{-}Pr)_2Et$ and pyridine, but only with $N(i\text{-}Pr)_2Et$ did we obtain significant amounts of product in a reasonable time (Table 1, entry 10). Next, the concentration of sodium isopropoxide was varied at different temperatures. As expected, the increase of the amount of base led to an acceleration of reaction rate; however, this was accompanied by an unacceptable decrease of enantioselectivity (Table 1, entries 13–15). In contrast, improved *ee* is obtained by reducing the amount of base to a ruthenium-to-base ratio of 1 to 0.5 (Table 1, entries 16 and 17). Notably, in the absence of base the transfer of hydrogen did not occur. Based on these results we investigated the behavior of the metal precursor.

Applying different ruthenium sources such as $[RuCl_2(PPh_3)_3]$, $[RuHCl(PPh_3)_3]$,[8] $RuCl_3 \cdot x\,H_2O$, $Ru_3(CO)_{12}$ and Ru(cod)(methylallyl)$_2$, lower conversion and/or poor selectivity were achieved. Nevertheless, $[RuCl_2(PPh_3)_3]$ showed an enantiomeric excess of >99%, which is to our knowledge the highest enantioselectivity in this model reaction for a chiral tridentate ligand (Table 1, entry 17). However, a slight excess of pybim **3a**, 3 equivs. with respect to 1 equiv.

Table 1. Transfer hydrogenation of acetophenone in the presence of pybim ligand **3a** and different bases.[a]



Entry	Base	Base:Metal	Temp. [°C]	Conv. [%][b]	*ee* [%][b]
1	NaO-*i*-Pr	5	100	80	**94 (*S*)**
2	KO-*t*-Bu	5	100	99	9 (*S*)
3	NaOH	5	100	79	78 (*S*)
4	KOH	5	100	85	80 (*S*)
5	LiOH	5	100	72	80 (*S*)
6	K_3PO_4	5	100	65	70 (*S*)
7	K_2HPO_4	5	100	19	96 (*S*)
8	K_2CO_3	5	100	95	93 (*S*)
9	Cs_2CO_3	5	100	45	67 (*S*)
10	$N(i\text{-}Pr)_2Et$	5	100	18	90 (*S*)
11	NaO-*i*-Pr	5	60	93	84 (*S*)[c]
12	NaO-*i*-Pr	5	80	91	83 (*S*)[d]
13	NaO-*i*-Pr	5	90	91	88 (*S*)
14	NaO-*i*-Pr	50	90	98	87 (*S*)
15	NaO-*i*-Pr	250	90	99	44 (*S*)
16	NaO-*i*-Pr	0.5	100	88	95 (*S*)
17	NaO-*i*-Pr	0.5	100	96	**>99 (*S*)**[e]
18	NaO-*i*-Pr	0.5	110	58	84 (*S*)

[a] *Reaction conditions: in situ* catalyst **A** {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol ligand **3a**, 3.8×10^{-6} mol PPh_3}; addition of the corresponding base: entries 1–13: 1.9×10^{-5} mol, entry 14: 1.9×10^{-4} mol, entry 15: 9.5×10^{-4} mol and for entries 16–18: 1.9×10^{-6} mol in 2.0 mL isopropyl alcohol, 10 min at corresponding temperature then addition of 3.8×10^{-4} mol acetophenone, 1 h at corresponding temperature.

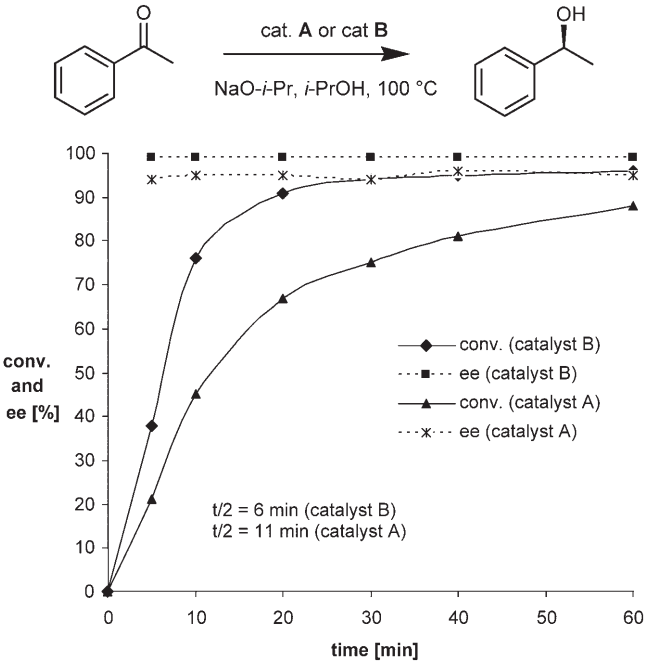
[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95–200 °C) analysis with diglyme as internal standard.

[c] Reaction time 14 h.

[d] Reaction time 4 h.

[e] *In situ* catalyst **B** {3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**}. Conversion was determined by GC (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard and *ee* was determined by chiral HPLC (Chiralcel OB-H, eluent: *n*-hexane/ethanol, 99:1, flow rate: 2 mL min^{-1}) analysis.

of ruthenium, was necessary to achieve high enantioselectivity. To compare the difference of catalyst system **A** and catalyst system **B**, we investigated the conversion-time and the enantioselectivity-time dependency (Scheme 2). No significant change of enan-



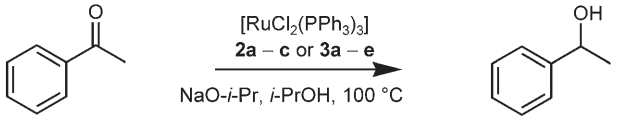
Scheme 2. Conversion-time and enantioselectivity-time behavior of catalyst **A** and catalyst **B**. *Reaction conditions: in situ* catalyst **A** (1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol ligand **3a**, 3.8×10^{-6} mol PPh_3) or *in situ* catalyst **B** (3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**); addition of sodium isopropoxide (1.9×10^{-6} mol) in 2.0 mL 2-propanol, 10 min at 100 °C then addition of 3.8×10^{-4} mol acetophenone, reaction temperature: 100 °C. Conversion was determined by GC (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard and *ee* was determined by chiral HPLC (Chiralcel OB-H, eluent: *n*-hexane/ethanol, 99:1, flow rate: 2 mL min^{-1}) analysis.

tioselectivity was observed in the shown time frame, while after 24 h full racemization occurred with catalyst **A**. Noteworthy, the analysis of the conversion-time behavior proved a higher catalyst activity for catalyst **B**, while for catalyst **A** a slight deceleration was monitored. We assume a better stabilization of the active species by an excess of **3a** and PPh_3.

As shown in Table 2 we also examined different pybox ligands (**2a–c**), but only unsatisfying results were obtained demonstrating the advantage of **3a** (Table 2, entries 1–3).

Noyori et al. proposed a metal-ligand bifunctional mechanism for the hydride transfer process ("NH effect").[4,13b] Hence, the NH group of the imidazoline rings could be involved in the selectivity transfer and increase the coordination affinity between substrate

Table 2. Transfer hydrogenation of acetophenone in the presence of different pybox and pybim ligands.[a]



Entry	Ligand	Time [h]	Conv. [%][b]	*ee* [%][b]
1	**2a**	1	6	11 (*R*)
2	**2b**	1	10	18 (*S*)
3	**2c**	1	22	8 (*R*)
4	**3a**	1	83	**98 (*S*)**
5	**3b**	2	95	26 (*R*)
6	**3c**	2	74	29 (*S*)
7	**3d**	1	4	7 (*R*)
8	**3e**	1	77	7 (*S*)

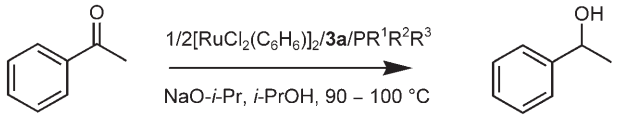
[a] Reaction conditions: 3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol ligand, 3.8×10^{-6} mol PPh_3, 1.9×10^{-6} mol NaO-*i*-Pr, 2.0 mL isopropyl alcohol, 10 min at 100 °C then addition of 3.8×10^{-4} mol acetophenone.

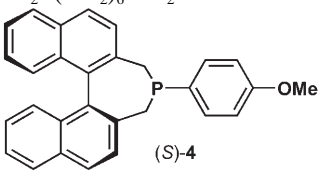
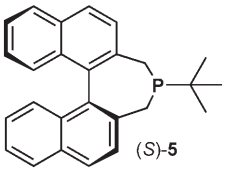
[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95–200 °C) analysis with diglyme as internal standard.

and catalyst. Due to the formation of a second binding site, a more favorable position for transferring the chiral information is attained.[5,9,13]

In order to understand the role of the free NH functionality for our pybim ligand **3a**, different substitutions at the imidazoline units were carried out. The corresponding monoprotected ligands **3b**, **c** were synthesized by reaction of **3a** with one equivalent of 3,5-di-*tert*-butylbenzoic acid chloride or $Ph_2P(O)Cl$. We presumed that the resulting unsymmetrical complexes would direct the substrate to occupy a specific orientation in the transition state and thereby induce increased selectivity during catalysis. However, 3,5-(*t*-Bu)$_2$C$_6$H$_3$)CO (**3b**) or Ph_2PO substitution (**3c**) decreased the enantioselectivity in the model reaction significantly (Table 2, entries 5 and 6). To confirm the results of the monosubstituted ligands an exchange of both hydrogens with Boc (**3d**) or Bz (**3e**) protecting groups was carried out. A further decrease of enantioselectivity was observed (Table 2, entries 7 and 8). Thus, there is a crucial necessity of both NH functionalities for obtaining high enantioselectivity in the transfer hydrogenation of acetophenone. Interestingly, the NH group is not necessary to achieve significant conversions (Table 2, entry 8), which is in contrast to previous reports by Noyori et al., for example catalysts containing *N*-dimethylamino alcohols are completely inactive compared to their *N*-monomethyl counterparts.[3d,13b] To estimate the influence of the ligands in more detail we varied also the phosphorus ligand part (Table 3). Among the different achiral ligands best results were obtained with PPh_3, (*p*-MeO-C$_6$H$_4$)$_3$P and (*p*-Me-C$_6$H$_4$)$_3$P (Table 3, entries 1, 3 and

Table 3. Influence of different phosphorus ligands on the transfer hydrogenation of acetophenone.[a]



Entry	P Ligand	Temp. [°C]	Conv. [%][b]	*ee* [%][b]
1	Ph_3P	100	80	**94 (*S*)**
2	without	100	61	7 (*S*)
3	$(p\text{-MeO-}C_6H_4)_3P$	90	91	**87 (*S*)**[c]
4	$(o\text{-Me-}C_6H_4)_3P$	100	20	*rac*
5	$(p\text{-Me-}C_6H_4)_3P$	100	41	**97 (*S*)**
6	$[3,4\text{-}(CF_3)_2\text{-}C_6H_3]_3P$	90	24	66 (S)[c]
7	$(p\text{-F-}C_6H_4)_3P$	100	53	76 (*S*)
8	Cy_3P	90	2	15 (*S*)[c]
9	$t\text{-}Bu_3P$	100	1	12 (*S*)
10	$n\text{-BuPAd}_2$	100	4	5 (*S*)
11	$(i\text{-PrO})_3P$	100	28	75 (*S*)
12	$Ph_2P(CH_2)PPh_2$	100	37	*rac*
13	$Ph_2P(CH_2)_2PPh_2$	100	43	*rac*
14	$Ph_2P(CH_2)_5PPh_2$	100	43	6 (*S*)
15	$Ph_2P(CH_2)_6PPh_2$	100	15	37 (*S*)
16	 (*S*)-**4**	90	90	95 (*S*)[c]
17	 (*S*)-**5**	90	8	24 (*S*)

[a] *Reaction conditions: in situ* catalyst {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol **3a**, 3.8×10^{-6} mol of the corresponding P ligand}, 1.9×10^{-5} mol NaO-*i*-Pr, 2.0 mL isopropyl alcohol, 10 min at described temperature then addition of 3.8×10^{-4} mol acetophenone, 1 h at described temperature.

[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95–200 °C) analysis with diglyme as internal standard.

[c] Experiments also performed at 100 °C, but only low enantioselectivities or conversions were obtained.

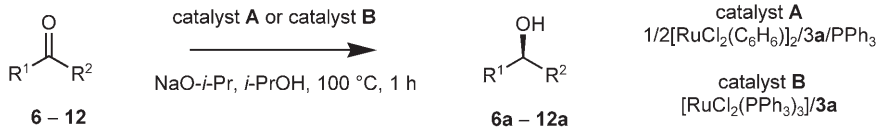
5). Methyl substitution in the *o*-position of arylphosphines decreased the enantioselectivity dramatically compared to that at the *p*-position (from 97% *ee* to *rac*, entries 4 and 5). Moderate conversion and selectivity were obtained for electron-poor substituted arylphosphines (Table 3, entries 6 and 7). Interestingly, also more basic and sterically hindered alkylphosphines such as PCy_3, $P(t\text{-Bu})_3$, and $n\text{-BuPAd}_2$ showed only low activity (Table 3, entries 8–10).

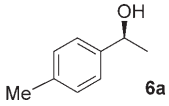
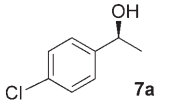
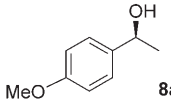
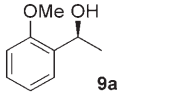
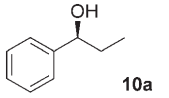
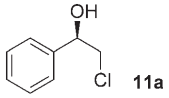
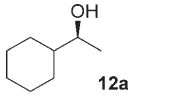
Furthermore, we applied chelating arylphosphine ligands. For bis(diphenylphosphino)methane (DPPM) only disappointing conversion and selectivity were obtained (Table 3, entry 12). By increasing the number of CH_2 groups in the bridge an increase of the enantiomeric excess was detected (Table 3, entries 13–15), probably due to a weaker coordination of the second phosphine group to the ruthenium. In addition, to improve the enantioselectivity and to increase the enantiomeric differentiation in the shape of the catalysts, we investigated the influence of chiral phosphines. Therefore, we tested chiral monodentate ligands (*S*)-**4** and (*S*)-**5** in the transfer hydrogenation of acetophenone in combination with pybim ligand **3a**. Recently, we have demonstrated the successful application of such chiral monodentate 4,5-dihydro-3*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]phosphepines in various asymmetric hydrogenations using molecular hydrogen.[10] Furthermore, Gladiali and co-workers reported previously the application of this ligand class in the rhodium-catalyzed asymmetric hydrogenation of C=C bonds.[21] However, only ligand (*S*)-**4** showed comparable enantioselectivity to PPh_3 of 95% *ee*, while (*S*)-**5** gave poor selectivity and conversion, due to a similar basicity to achiral alkylphosphines (Table 3, entry 16 and 17).

Next, we explored the influence of the concentration of PPh_3. The results indicated a necessity of 1 equiv. of PPh_3 relating to 1 equiv. of ruthenium, while the reaction with more than 1 equiv. of PPh_3 or in the absence of PPh_3 resulted in a decrease of enantioselectivity (Table 3, entries 1 and 2). Noteworthy, the use of an excess of PPh_3 has no disordered effect on selectivity while a negative influence was reported for other catalytic systems when PPh_3 was not removed.[5,6] In analogy to Gimeno et al.[6,11] and Yu et al.[12] we assume a *cis*-coordination of the phosphine with respect to the *N*-*N*-*N* plane, which forms after removal of the *cis*-coordinated chlorides (with respect to each other) a highly selective vacancy for substrate coordination and chirality transfer.

To demonstrate the usefulness of the novel catalysts we employed system **A** ($[RuCl_2(C_6H_6)]_2$/pybim/PPh_3) and **B** ($[RuCl_2(PPh_3)_3]$/pybim) in the asymmetric transfer hydrogenation of six aromatic and one aliphatic ketones (Table 4). In general, catalyst system **A** gave some higher enantioselectivities compared to catalyst **B**. Substituted acetophenones and propiophenone gave enantioselectivities up to 98% *ee* (Table 4, entries 1–5). In the case of methoxy-substitution the position of the substituent plays an important role, because *ortho*-substitution was favored (Table 4, entries 3 and 4). A chloro substituent in the α-position to the carbonyl group proved to be problematic and deactivated both catalysts (Table 4, entry 6). Compared to aromatic ketones, aliphatic ketones are more challenging substrates. Nevertheless, 1-cyclohexylethanone was reduced by catalyst **A** in good yield and enantioselectivity (Table 4, entry 7).

Table 4. Transfer hydrogenation of prochiral ketones.[a]



Entry	Alcohol	Catalyst **A**[b,c,d]		Catalyst **B**[b,c,d]	
		Conv. [%]	*ee* [%]	Conv. [%]	*ee* [%]
1	 **6a**	89	89 (*S*)	>99	85 (*S*)
2	 **7a**	84	94 (*S*)	>99	89 (*S*)
3	 **8a**	86[e]	72 (*S*)	68[f]	74 (*S*)
4	 **9a**	>99	98 (−)	99 [g]	70 (−)
5	 **10a**	>99	97 (*S*)	98[e]	87 (*S*)
6	 **11a**	12[g]	70 (*R*)	<2[f]	12 (*R*)
7	 **12a**	91	82 (*S*)	96[f]	72 (*S*)

[a] *Reaction conditions: in situ* catalyst **A** {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol **3a**, 3.8×10^{-6} mol PPh_3), 1.9×10^{-5} mol NaO-*i*-Pr, 2.0 mL isopropyl alcohol, 10 min at 100 °C then addition of 3.8×10^{-4} mol substrate, 1 h at 100 °C.

[b] Conversion and *ee* were determined by chiral GC (entry 1: 25 m Lipodex E, 80–180 °C; entry 2: 25 m Lipodex E, 100 °C; entry 3: 50 m Lipodex E, 90–105 °C; entry 4: 50 m Lipodex E, 90–180 °C; entry 5: 25 m Lipodex E, 90–180 °C; entry 6: 50 m Lipodex E, 95–180 °C; entry 7: 25 m Lipodex E, 100 °C) analysis with diglyme as internal standard.

[c] *In situ* catalyst **B** {3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**}.

[d] The absolute configurations were determined by comparing the sign of specific rotation with reported data.

[e] 4 h.

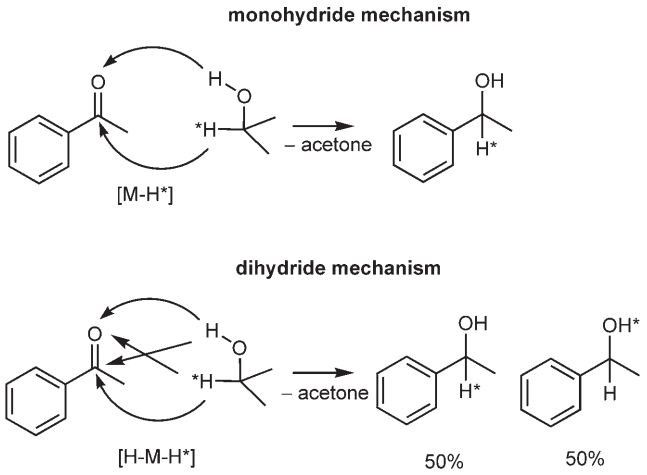
[f] 8 h.

[g] 24 h.

Various methods (^{1}H, ^{13}C, ^{31}P and ^{15}N NMR, COSY NMR, HMQC NMR and MS) were used for characterization of the pre-catalyst, but unfortunately no precise structure has been proven. The ^{31}P NMR spectrum of the pre-catalyst in $CDCl_3$ indicated a single compound, because a singlet appeared at 30 ppm (free PPh_3: −6 ppm and O=PPh_3: 27 ppm). Furthermore, the composition of the pre-catalyst was confirmed by HR-MS as $[RuCl_2(PPh_3)$(**3a**)] (calculated mass: 953.17549, detected mass: 953.17572). However, the coordination abilities of ligand **3a** are so far unclear, because a rapid exchange of NH protons was detected, which causes a broad signal in the ^{1}H NMR spectrum for the four protons adjacent to the nitrogen atoms and furthermore one signal for the corresponding carbons in the ^{13}C NMR spectrum.

Next, we focused our attention on a deeper comprehension of the reaction mechanism. For metal-catalyzed transfer hydrogenation two general mechanisms are accepted, designated as direct hydrogen transfer *via* formation of a six-membered cyclic transition state composed of metal, hydrogen donor and acceptor, and the hydridic route, which is subdivided into two pathways, the monohydride and dihydride mechanism (Scheme 3). More specifically, the formation of monohydride-metal complexes promotes an

exclusive hydride transfer from carbon (donor) to carbonyl carbon (acceptor) (Scheme 3), whereas a hydride transfer *via* dihydride-metal complexes leads to



Scheme 3. Monohydride and dihydride mechanisms for transfer hydrogenations.

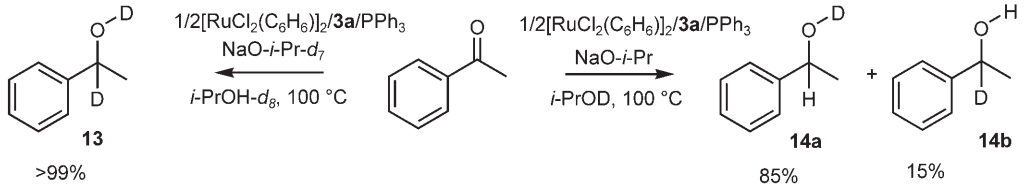
no accurate prediction of hydride resting state, because the former hydride was transferred to the carbonyl carbon (acceptor) as well as to the carbonyl oxygen (acceptor) (Scheme 3). Indications for both pathways (hydridic route) have been established by various research groups, when following the hydride transfer catalyzed by metal complexes, e.g., Ru, Rh or Ir.[13]

Reaction of cyclopropyl phenyl ketone ("radical clock"-substrate) with isopropyl alcohol in the presence of 1 mol% catalyst **A** gave exclusively the corresponding cyclopropylphenyl alcohol (>99% by ^{1}H NMR). Apparently there is no radical reduction induced by the transition metal or by sodium alkoxides.[14] The second assumption is also confirmed by performing the reduction of acetophenone in the presence of base and in the absence of the ruthenium catalyst. Here, no product at all was detected.

Next, we followed the incorporation of hydrogen from the donor molecule (isopropyl alcohol) into the product by applying a deuterated donor.[15] The precatalyst (1 mol%) is generated by stirring a solution of isopropyl alcohol-d_8, 0.5 equivs. of $[RuCl_2(C_6H_6)]_2$, ligand **3a** and PPh_3 for 16 h at 65 °C. Then, sodium isopropoxide-d_7 was added and the solution was stirred for 10 min at 100 °C. The reaction mixture was charged with acetophenone and after 1 h compound **13** was observed as main product (>99%) by ^{1}H NMR (Scheme 4).[16] The result proved an exclusive transfer of the deuterium into the carbonyl group, therefore a C–H activation of the substrate/product under the described conditions did not occur. Furthermore, this result rules out an enol formation in the catalytic cycle.[17]

To specify the position and the nature of the transferred hydride, the reaction was performed with isopropyl alcohol-d_1 (hydroxy group deuterated) as solvent/donor and sodium isopropoxide as base under identical reaction conditions. In the transfer hydrogenation of acetophenone we obtained a mixture of two deuterated 1-phenylethanols (Scheme 4, **14a** and **14b**).The ratio between **14a** and **14b** (85:15) indicated a specific migration of the hydride, albeit some scrambling was detected.[18] This was probably caused by rearrangement of the hydride complex, starting from HN–Ru–D *via* N=Ru(HD) to DN–Ru–H and subsequent transfer process into acetophenone yielding **14b**. In conclusion the incorporation is in agreement with the monohydride mechanism, implying the formation of a metal hydride species in the catalytic cycle (Scheme 3). Furthermore, this indication is confirmed by the above-mentioned influence of the NH groups. In conclusion, the transfer of hydrogen, in the case of catalyst **A**, is subdivided into the hydride transfer by the metal and the proton transfer by the NH group in analogy to the metal-ligand bifunctional catalysis.[13r]

We demonstrated for the first time the successful application of chiral tridentate pyridinebisimidazoline ligands in the asymmetric ruthenium-catalyzed transfer hydrogenation of aliphatic and aromatic ketones. Enantioselectivities up to >99% *ee* were obtained under optimized reaction conditions. Comparison experiments of **3a** with monoprotected pybims and pybox ligands displayed the crucial influence of the free NH functionality. Mechanistic experiments indicated the transfer of hydrogen from the donor molecule into the substrate *via* a metal-ligand bifunctional mechanism.



Scheme 4. Deuterium incorporation into acetophenone catalyzed by catalyst system **A**.

Experimental Section

General Remarks

All manipulations were performed under an argon atmosphere using standard Schlenk techniques. Isopropyl alcohol was used without further purification (purchased from Fluka, dried over molecular sieves). Sodium isopropoxide was prepared by reacting sodium with isopropyl alcohol under an argon atmosphere (stock solution). All ketones were dried over CaH_2, distilled in vacuum and stored under argon, except 4′-methoxyacetophenone and phenacyl chloride, which were used without further purification. $BuP(Ad)_2$[19] and *N*-phenyl-2-(di-*tert*-butylphosphino)-pyrrole[20] were synthesized according to literature protocols.

General Procedure for the Transfer Hydrogenation of Ketones

In a 10-mL Schlenk tube, the *in situ* catalyst was prepared by stirring a solution of $[RuCl_2(C_6H_5)]_2$ (1.9×10^{-6} mmol), ligand **3a** (3.8×10^{-6} mmol) and PPh_3 (3.8×10^{-6} mmol) in 1.0 mL isopropyl alcohol for 16 h at 65 °C. To this mixture sodium isopropoxide (1.9×10^{-5} mmol in 0.5 mL isopropyl alcohol (stock solution)) was added and the solution stirred at 100 °C for 10 min. After addition of the corresponding ketone (0.38 mmol in 0.5 mL isopropyl alcohol (stock solution)) the reaction mixture was stirred for 1 h at 100 °C. The solution was cooled to room temperature and filtered over a plug of silica. The conversion and *ee* were measured by GC without further manipulations.

Acknowledgements

This work has been supported by the State of Mecklenburg-Western Pomerania and the "Bundesministerium für Bildung und Forschung (BMBF)". Additional support came from the BMBF excellence center "CELISCA" and the "Graduiertenkolleg 1213 - Neue Methoden für Nachhaltigkeit in Katalyse und Technik" and Leibniz price of the DFG. We thank Mrs. M. Heyken, Mrs. C. Voss, Dr. C. Fischer, Mrs. S. Buchholz (all Leibniz-Institut für Katalyse e.V. an der Universität Rostock) and J. Schumacher (Universität Rostock) for their excellent technical and analytical support.

References

[1] a) I. C. Lennon, J. A. Ramsden, *Org. Process Res. Dev.* **2005**, *9*, 110–112; b) J. M. Hawkins, T. J. N. Watson, *Angew. Chem.* **2004**, *116*, 3286–3290; c) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; d) M. Miyagi, J. Takehara, S. Collet, K. Okano, *Org. Process Res. Dev.* **2000**, *4*, 346–348; e) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, **1999**; f) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.

[2] a) M. Beller, C. Bolm, (Eds.), *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, 2nd edn, **2004**; b) B. Cornils, W. A. Herrmann, *Applied homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, **1996**.

[3] a) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236; b) S. Gladiali, G. Mestroni, in: *Transition Metals for Organic Synthesis*, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd edn, **2004**, pp 145–166; c) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; d) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; e) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *51*, 1051–1069.

[4] a) T. Ikariya, S. Hashiguchi, K. Murata, R. Noyori, *Org. Synth.* **2005**, *82*, 10–17; b) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739; c) S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1997**, *36*, 288–290; d) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1997**, *36*, 285–288; e) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917; f) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522; g) J.-X. Gao, T. Ikariya, R. Noyori, *Organometallics* **1996**, *15*, 1087–1089; h) J. Takehara, S. Hashiguchi, A. Fujii, S. Inoue, T. Ikariya, R. Noyori, *Chem. Commun.* **1996**, 233–234; i) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563.

[5] Y. Jiang, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 3817–3818.

[6] D. Cuervo, M. P. Gamasa, J. Gimeno, *Chem. Eur. J.* **2004**, *10*, 425–432.

[7] a) S. Bhor, G. Anilkumar, M. K. Tse, M. Klawonn, C. Döbler, B. Bitterlich, A. Grotevendt, M. Beller, *Org. Lett.* **2005**, *7*, 3393–3396; b) G. Anilkumar, S. Bhor, M. K. Tse, M. Klawonn, B. Bitterlich, M. Beller, *Tetrahedron: Asymmetry* **2005**, *16*, 3536–3561.

[8] No product was obtained when $[RuHCl(PPh_3)_3]$/**3a** was performed without addition of base.

[9] Y. Shvo, D. Czarkie, Y. Rahamim, *J. Am. Chem. Soc.* **1986**, *108*, 7400–7402.

[10] a) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Tetrahedron Lett.* **2002**, *43*, 4977–4980; b) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *J. Organomet. Chem.* **2003**, *675*, 91–96; c) K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; d) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem. Int. Ed.* **2004**, 43, 5066–5069; e) B. Hagemann, K. Junge, S. Enthaler, M. Michalik, T. Riermeier, A. Monsees, M. Beller, *Adv. Synth. Catal.* **2005**, *347*, 1978–1986; f) S. Enthaler, B. Hagemann, K. Junge, G. Erre, M. Beller, *Eur. J. Org. Chem.* **2006**, 2912–2917.

[11] V. Cadierno, M. P. Gamasa, J. Gimeno, L. Iglesias, *Inorg. Chem.* **1999**, *38*, 2874–2879.

[12] H. Deng, Z. Yu, J. Dong, S. Wu, *Organometallics* **2005**, *24*, 4110–4112.

[13] For recent review see: a) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*,

237–248; b) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406, and cited references therein; c) H. Guan, M. Iimura, M. P. Magee, J. R. Norton, G. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 7805–7814; d) M. Gómez, S. Janset, G. Muller, G. Aullón, M. A. Maestro, *Eur. J. Inorg. Chem.* **2005**, 4341–4351; e) K. Muñiz, *Angew. Chem.* **2005**, *117*, 6780–6785; *Angew. Chem. Int. Ed.* **2005**, *44*, 6622–6627; f) C. Hedberg, K. Källström, P. I. Arvidsson, P. Brandt, P. G. Andersson, *J. Am. Chem. Soc.* **2005**, *127*, 15083–15090; g) A. S. Y. Yim, M. Wills, *Tetrahedron* **2005**, *61*, 7994–8004; h) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201–2237; i) T. Koike, T. Ikariya, *Adv. Synth. Catal.* **2004**, *346*, 37–41; j) P. Brandt, P. Roth, P. G. Andersson, *J. Org. Chem.* **2004**, *69*, 4885–4890; k) J.-W. Handgraaf, J. N. H. Reek, E. J. Meijer, *Organometallics* **2003**, *22*, 3150–3157; l) C. P. Casey, J. B. Johnson, *J. Org. Chem.* **2003**, *68*, 1998–2001; m) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; n) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; o) C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, M. Kavana, *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100; p) O. Pàmies, J. E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058; q) C. S. Yi, Z. He, *Organometallics* **2001**, *20*, 3641–3643; r) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931–7944; s) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478; t) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588; u) D. G. I. Petra, J. N. H. Reek, J.-W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2000**, *6*, 2818–2829; v) A. Aranyos, G. Csjernyik, K. J. Szabó, J. E. Bäckvall, *Chem. Commun.* **1999**, 351–352; w) M. L. S. Almeida, M. Beller, G. Z. Wang, J. E. Bäckvall, *Chem. Eur. J.* **1996**, *2*, 1533–1536.

[14] a) D. D. Tanner, G. E. Diaz, A. Potter, *J. Org. Chem.* **1985**, *50*, 2149–2154; b) M. Degueil-Castaing, A. Rahm, *J. Org. Chem.* **1986**, *51*, 1672–1676; c) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530; d) J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung, A. S. C. Chan, *Chem. Eur. J.* **2003**, *9*, 2963–2968; e) E. C. Ashby, J. N. Argyropoulos, *J. Org. Chem.* **1986**, *51*, 3593–3597.

[15] a) L. Dahlenburg, R. Götz, *Eur. J. Inorg. Chem.* **2004**, 888–905; b) P. W. C. Cross, G. J. Ellames, J. M. Gibson, J. M. Herbert, W. J. Kerr, A. H. McNeill, T. W. Mathers, *Tetrahedron* **2003**, *59*, 3349–3358.

[16] a) L. Y. Kuo, D. M. Finigan, N. N. Tadros, *Organometallics* **2003**, *22*, 2422–2425; b) R. L. Elsenbaumer, H. S. Mosher, *J. Org. Chem.* **1979**, *44*, 600–604.

[17] D. Klomp, T. Maschmeyer, U. Hanefeld, J. A. Peters, *Chem. Eur. J.* **2004**, *10*, 2088–2093.

[18] The ratio between **14a** and **14b** was determined by ^{1}H NMR based on the integrals of the signals for the CH_3 groups.

[19] A. Ehrentraut, A. Zapf, M. Beller, *Synlett* **2000**, 1589–1592.

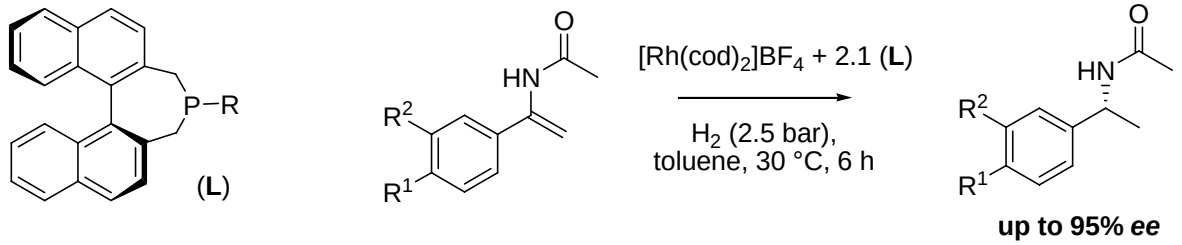
[20] A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen, M. Beller, *Chem. Commun.* **2004**, 38–39.

[21] E. Alberico, I. Nieddu, R. Taras, S. Gladiali, *Helv. Chim. Acta* **2006**, *89*, 1716–1729.

7. Summary

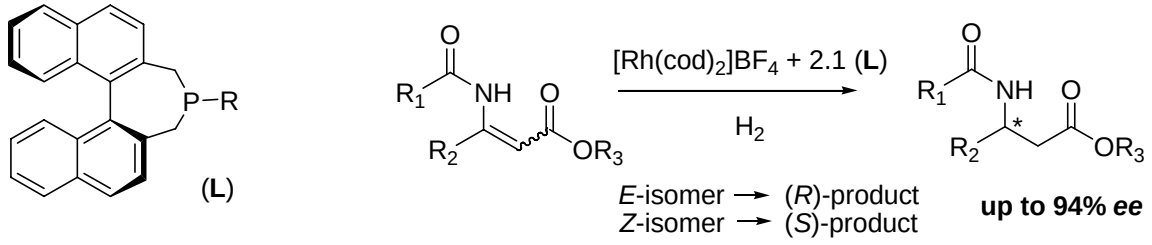
7.1. Application of monodentate phosphines in asymmetric hydrogenations

Since previous works have proven an excellent behaviour of ligands containing 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine motif in asymmetric hydrogenation of *α*–amino acid precursors, itaconic acid derivatives and *β*–ketoesters, we extended the scope and limitation in the reduction of unsaturated C–C bonds. The rhodium–catalyzed asymmetric hydrogenation of different *N*–acyl enamides to give *N*–acyl protected optically active amines has been examined for the first time in detail in the presence of chiral monodentate 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine (Scheme 1). The enantioselectivity is largely dependent on the nature of the substituent at the phosphorous atom and the enamide structure. Under optimized conditions up to 95% *ee* and catalyst activity up to 2000 h^{-1} have been achieved.



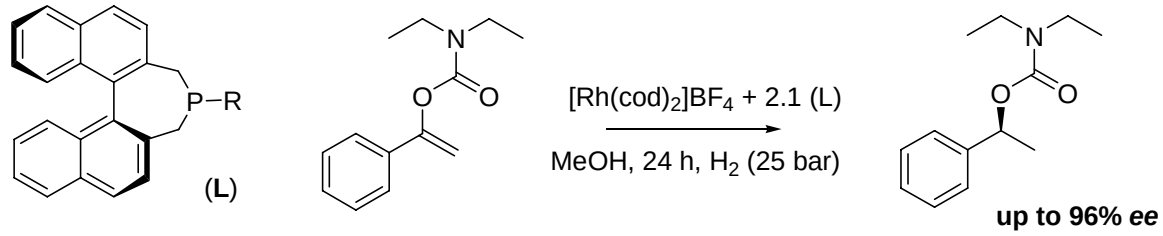
Scheme 1. Asymmetric hydrogenation of *N*–acyl enamides.

Furthermore the potential of presented monophosphine ligands were shown in the rhodium–catalyzed asymmetric hydrogenation of various *β*–dehydroamino acid derivatives to give optically active *β*–amino acids (Scheme 2). Here enantioselectivities up to 94% *ee* were obtained after optimization of reaction conditions. Noteworthy, contradictory performance was observed for the *E*– and *Z*–isomer and different reaction conditions were necessary to achieve best enantioselectivity. In addition a switch of product configuration was observed depending on the nature of the double bond, which has been scarcely reported.



Scheme 2. Asymmetric hydrogenation of *β*–dehydroamino acid derivates.

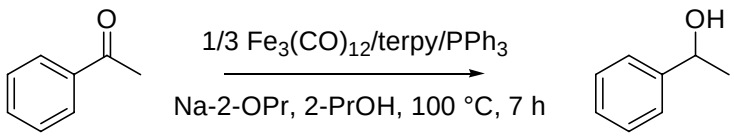
Based on the pioneering work of Feringa, de Vries, Minnaard and co–workers the rhodium–catalyzed asymmetric hydrogenation of different acyclic and cyclic enol carbamates to yield optically active carbamates has been studied in the presence of chiral monodentate ligands based on a 4,5–dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine scaffold (Scheme 3). Various reaction parameters have been investigated in detail and enantioselectivities up to 96% *ee* have been achieved with an *in situ* catalyst. Noteworthy, high thermal stability of the catalyst in the range of 10–90 °C was noticed with respect to enantioselectivity (94–96% *ee*).



Scheme 3. Asymmetric hydrogenation of enol carbamates.

7.2. Transfer hydrogenation

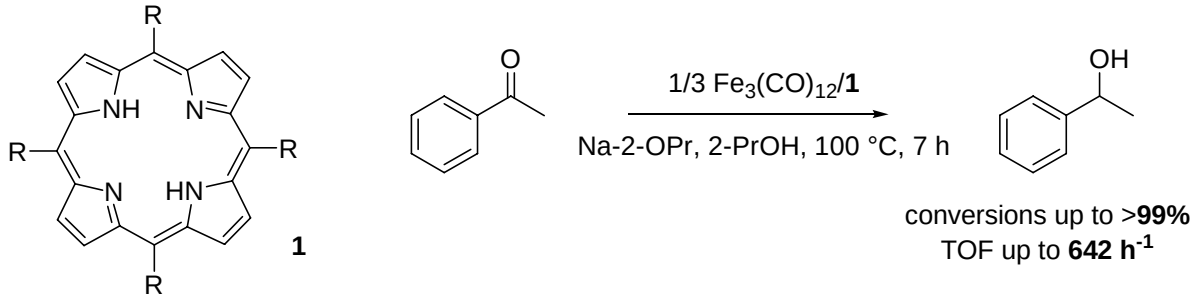
In situ generated homogeneous iron complexes catalyze the transfer hydrogenation of aliphatic and aromatic ketones utilizing 2–propanol as hydrogen donor in the presence of base. The influence of different reaction parameters on the catalytic activity was investigated in detail applying a three component catalyst system, composed of an iron salt, 2,2´:6´,2´´–terpyridine and PPh_3 (Scheme 4). The scope and limitations of the described catalyst have been shown in the reduction of eleven different ketones. In most cases high conversion and excellent chemoselectivity are achieved. Mechanistic studies indicate a monohydride reaction pathway for the homogeneous iron catalyst.



Scheme 4. Homogeneous iron catalyst for reduction of ketones.

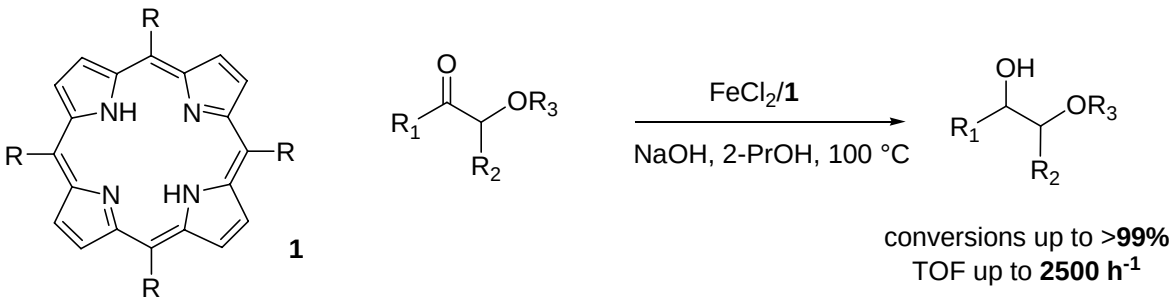
Furthermore, for the first time *in situ* generated iron porphyrins have been applied as homogeneous catalysts for the transfer hydrogenation of ketones. Using 2–propanol as hydrogen source various ketones are reduced to the corresponding alcohols in good to

excellent yield and selectivity. Under optimized reaction conditions high catalyst turnover frequencies up to 642 h^{-1} were achieved (Scheme 5).



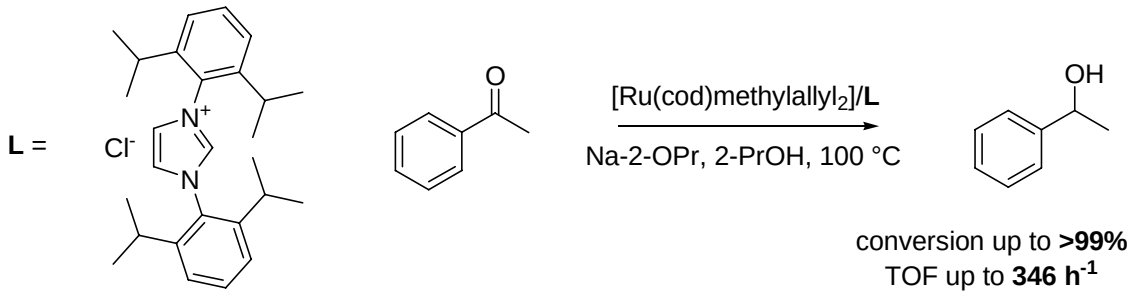
Scheme 5. Transfer hydrogenation of ketones in the presence of biomimetic iron porphyrin catalysts.

In situ generated iron porphyrins have been furthermore applied as homogeneous catalysts for the transfer hydrogenation of α–substituted ketones. Using 2–propanol as hydrogen donor various hydroxyl-protected 1,2–hydroxyketones are reduced to the corresponding mono protected 1,2–diols in good to excellent yield. Under optimized reaction conditions catalyst turnover frequencies up to 2500 h^{-1} have been achieved (Scheme 6).



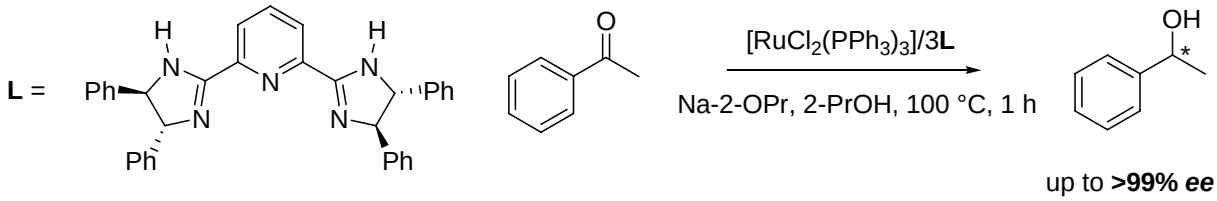
Scheme 6. Transfer hydrogenation of α–substituted ketones in the presence of biomimetic iron porphyrin catalysts.

Novel ruthenium carbene complexes have been *in situ* generated and tested for the transfer hydrogenation of ketones. Applying Ru(cod)(methylallyl)$_2$ in the presence of imidazolium salts in 2–propanol and sodium–2–propanolate as base, turnover frequencies up to 346 h^{-1} have been obtained for the reduction of acetophenone (Scheme 7). A comparative study involving ruthenium carbene and ruthenium phosphine complexes demonstrated higher activity of ruthenium carbene complexes.



Scheme 7. Transfer hydrogenation of ketones in the presence of ruthenium carbene catalysts.

Tridentate *N,N,N*–pyridinebisimidazolines have been studied as new ligands for the enantioselective transfer hydrogenation of prochiral ketones. High yield and excellent enantioselectivity up to >99% *ee* have been achieved with an *in situ* generated catalytic system containing dichlorotris(triphenylphosphine)ruthenium and 2,6–bis–([*4R,5R*]–4,5–diphenyl–4,5–dihydro–1*H*–imidazol–2–yl)–pyridine in the presence of sodium 2–propanolate (Scheme 8).



Scheme 8. New ruthenium catalysts for asymmetric transfer hydrogenation of prochiral ketones.

Abstract

Die vorliegende Dissertation beschäftigte sich mit der Anwendung von monodentaten Phosphinliganden in der asymmetrischen Hydrierung von C–C Doppelbindungen. Dabei konnte die Wirksamkeit von Rhodiumkatalysatoren, die Phosphinliganden mit der 4,5–Dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepin–Struktureinheit enthielten, gezeigt werden. Verschiedenste prochirale Substratklassen, wurden mit exzellenten Enantioselektivitäten von bis zu 96% *ee* zu den entsprechenden ungesättigten Derivaten reduziert. Ein zweiter Schwerpunkt der Arbeit lag in der Entwicklung neuartiger eisenbasierter Hydrierkatalysatoren und deren Anwendung in der Transferhydrierung von Ketonen, wobei Katalysatoraktivitäten von bis zu 2500 h^{-1} (TOF) erzielt werden konnten.

This dissertation deals with the application of monodentate phosphine ligands in asymmetric hydrogenation of C–C double bonds. The usefulness of rhodium catalysts containing phosphines based on the 4,5–Dihydro–3*H*–dinaphtho[2,1–c;1´,2´–e]phosphepine scaffold was demonstrated in the reduction of various prochiral substrates, since excellent enantioselectivities up to 96% *ee* were achieved. Furthermore, the properties of iron–based catalysts were studied in the field of transfer hydrogenation. Here high catalyst activities up to 2500 h^{-1} were obtained in the reduction of ketones.

Curriculum Vitae

PERSONAL INFORMATION

Surname:	Enthaler
First name:	Stephan
Current adress:	Thomas-Müntzer-Platz 21
	18057 Rostock (Germany)
Nationality:	German
Birthday:	27.02.1980
Birthplace:	Hagenow (Germany)

EDUCATION

1986 – 1990	Elementary school “Ludwig-Reinhard-Schule“ in Boizenburg/Elbe
1990 – 1992	August-Bebel-Schule in Boizenburg/Elbe
1992 – 1998	Gymnasium Boizenburg
1998	Abitur (degree: General qualification for university entrance)
1999 – 2004	Course of studies: Chemistry at the University of Rostock (Diplom-Chemie)
2003 – 2004	Master thesis (Diplomarbeit): “Synthesis and application of novel monodentate phosphine ligands in asymmetric hydrogenations“ under the supervision of Prof. M. Beller
2004	Degree: Diplom-Chemiker (Master of Science)
since 2004	PhD thesis at the University of Rostock under the supervision of Prof. M. Beller

RESEARCH EXPERIENCE

2001	Student assistant in the group of Prof. R. Mietchen at the University of Rostock: “Phase transfer catalysis assisted by ultrasound“

TEACHING EXPERIENCE

2002 Student assistant at the University of Rostock: “Practical course for medical students“

RELATED PROFESSIONAL EXPERIENCE

2002 Student assistant at the University of Rostock: “IUPAC Conference on Chemical Thermodynamics (ICCT-2002)”

DEPARTMENTAL ACTIVITIES

2000 – 2003 Representative of the chemistry student council at the University of Rostock

PROFESSIONAL ASSOCIATIONS

GDCh (Gesellschaft Deutscher Chemiker)

MILITARY SERVICE

1998 – 1999 Basic military service: 3./183 and 1./183 armoured battalion in Boostedt

PUBLICATIONS

JOURNAL CONTRIBUTIONS

1. "Synthesis of chiral monodentate binaphthophosphepine ligands and their application in asymmetric hydrogenation" K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631.

2. "Enantioselective hydrogenation of β–ketoesters with monodentate ligands" K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem. Int. Ed.* **2004**, *43*, 6150; *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066–5069.

3. "A general method fort the enantioselective hydrogenation of β–ketoesters using monodentate binaphthophosphepine ligands" B. Hagemann, K. Junge, S. Enthaler, M. Michalik, T. Riermeier, A. Monsees, M. Beller, *Adv. Synth. Catal.* **2005**, 1978–1986.

4. "Enantioselective rhodium–catalyzed hydrogenation of enamides in the presence of chiral monodentate phosphanes" S. Enthaler, B. Hagemann, G. Erre, K. Junge, M. Beller, *Eur. J. Org. Chem.* **2006**, 2912–2917.

5. "An environmentally benign process for the hydrogenation of ketones with homogeneous iron catalysts" S. Enthaler, B. Hagemann, G. Erre, K. Junge, M. Beller *Chem. Asian. J.* **2006**, *1*, 598–604.

6. "Biomimetic transfer hydrogenation of ketones with iron porphyrin catalysts" S. Enthaler, G. Erre, M. K. Tse, K. Junge, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8095–8099.

7. "Efficient transfer hydrogenation of ketones in the presence of ruthenium *N*-heterocyclic carbene catalysts" S. Enthaler, R. Jackstell, B. Hagemann, K. Junge, G. Erre, M. Beller, *J. Organomet. Chem.* **2006**, *691*, 4652–4659.

8. "Synthesis and catalytic application of novel binaphthyl–derived phosphorous ligands" K. Junge, B. Hagemann, S. Enthaler, G. Erre, M. Beller, *ARKIVOC*, **2007**, *5*, 50–66.

9. "Development of practical rhodium phosphine catalysts for the hydrogenation of *β*–dehydroamino acid derivates" S. Enthaler, G. Erre, K. Junge, J. Holz, A. Börner, E. Alberico, I. Nieddu, S. Gladiali, M. Beller, *Org. Process Res. Dev.* **2007**, *11*, 568–577.

10. "New ruthenium catalysts for asymmetric transfer hydrogenation of ketones" S. Enthaler, B. Hagemann, S. Bhor, G. Anilkumar, M. K. Tse, B. Bitterlich, K. Junge, G. Erre, M. Beller *Adv. Synth. Catal.* **2007**, *349*, 853–860.

11. "Enantioselective rhodium-catalyzed hydrogenation of enol carbamates in the presence of monodentate phosphines" S. Enthaler, G. Erre, K. Junge, D. Michalik, A. Spannenberg, S. Gladiali, M. Beller, *Tetrahedron: Asymmetry*, **2007**, *18*, 1288–1298.

12. "Novel rhodium catalyst for asymmetric hydroformylation of styrene: Study of electronic and steric effects of phosphorus seven–membered ring ligands" G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *J. Mol. Catal. A*, **2008**, 280, 148–155.

13. "Synthesis and application of chiral monodentate phosphines in asymmetric hydrogenation" G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *Coord. Chem. Rev.* **2008**, *in print.*

14. "2–Hydroxy– and 2–amino–functional arylphosphines – syntheses, reactivity and use in catalysis" J. Heinicke, W. Wawrzyniak, N. Peulecke, B. R. Aluri, M. K. Kindermann, P. G. Jones, S. Enthaler, M. Beller, *Phosphorus, Sulfur, Silicon and Rel. Elements*, **2008**, *in print*.

15. "Synthesis of 1,2-diols via biomimetic transfer hydrogenation with iron porphyrin catalysts" S. Enthaler, B. Spilker, G. Erre, M. K. Tse, K. Junge, M. Beller, *Tetrahedron*, *in print*.

16. "Iron–catalyzed Enantioselective Hydrosilylation of Ketoneș" N. S. Shaikh, S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *accepted*.

17. "Sustainable metal catalysis with iron – from rust to a rising star?" S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *accepted*.

18. "Synthesis of new monodentate phosphoramidites and their application in iridium-catalyzed asymmetric hydrogenations" G. Erre, K. Junge, S. Enthaler, D. Addis, D. Michalik, A. Spannenberg, M. Beller, *Chem. Asian J.* **2008**, *submitted*.

POSTER CONTRIBUTIONS

1. "First enantioselective hydrogenation of β–ketoesters using monodentate ligands" K. Junge, B. Hagemann, S. Enthaler, M. Beller, A. Monsees, T. Riermeier, *ORCHEM*, Bad Nauheim (Germany), 9–11 September **2004**.

2. "Enantioselective hydrogenation of β–ketoesters using monodentate ligands" S. Enthaler, K. Junge, B. Hagemann, A. Monsees, T. Riermeier, M. Beller, *COST-D24 STEREOCAT2004*, Venedig (Italy), 16–19 September **2004**.

3. "Enantioselective hydrogenation of β–ketoesters using monodentate phosphepine ligands" B. Hagemann, K. Junge, S. Enthaler, A. Monsees, T. Riermeier, M. Beller, 8. *SFB Symposium FB 380*, FZ-Jülich (Germany), 7–8 Oktober **2004**.

4. "Application of monodentate binaphthophosphepine ligands in asymmetric hydrogenations" S. Enthaler, K. Junge, B. Hagemann, A. Monsees, T. Riermeier, M.

Beller, *XXXVIII. Jahrestreffen Deutscher Katalytiker*, Weimar (Germany), 16–18 March **2005**.

5. "Application of monodentate binaphthophosphepine ligands in asymmetric hydrogenations" S. Enthaler, K. Junge, B. Hagemann, A. Monsees, T. Riermeier, M. Beller, *Green Chemistry: Development of Sustainable Processes,* Rostock (Germany), 30 March – 1 April **2005**.

6. "First enantioselective hydrogenation of β–ketoesters using monodentate ligands" K. Junge, S. Enthaler, B. Hagemann, A. Monsees, T. Riermeier, M. Beller, *Green Chemistry: Development of Sustainable Processes,* Rostock (Germany), 30 March – 1 April **2005**.

7. "Synthesis of monodentate binaphthophosphepine ligands and their application in asymmetric hydrogenation" B. Hagemann, K. Junge, S. Enthaler, G. Erre, A. Monsees, T. Riermeier, M. Beller, *The 2005 European Younger Chemists´ Conference*, Brno (Czech Republic), 31 August – 3 September **2005**.

8. "Novel axially–chiral monodentate P–donor ligands for asymmetric catalysis" G. Erre, K. Junge, S. Enthaler, B. Hagemann, F. Marras, S. Gladiali, M. Beller, *XXXIX. Jahrestreffen Deutscher Katalytiker*, Weimar (Germany), 15–17 March **2006**.

9. "Novel axially–chiral monodentate P–donor ligands for asymmetric catalysis" G. Erre, K. Junge, S. Enthaler, B. Hagemann, F. Marras, S. Gladiali, M. Beller, *XXII International Conference on Organometallic Chemistry* (ICOMC 2006), Zaragoza (Spain), 23–28 July **2006**.

10. "Enantioselective rhodium–catalyzed hydrogenation of enamides in the presence of chiral monodentate phosphines" S. Enthaler, B. Hagemann, K. Junge, G. Erre, M. Beller, *Bayer–Doktorandenkurs*, Leverkusen–Monheim–Wuppertal (Germany), 20–25 August **2006**.

11. "Enantioselective hydrogenation of enamides and enol carbamates with monodentate binaphthophosphepines" S. Enthaler, G. Erre, K. Junge, M. Beller, *1st European Chemistry Congress (1st ECC)*, Budapest (Hungary), 26 August – 01 September **2006**.

12. "Synthesis of chiral binaphthophosphepine ligands and their application in asymmetric catalysis" G. Erre, K. Junge, B. Hagemann, S. Enthaler, M. Beller, *4th International Forum Life Science Automation*, Rostock (Germany), 14–15 September **2006**.

13. "Synthesis and catalytic applications of novel binaphthyl–derived phosphorous ligands" K. Junge, G. Erre, S. Enthaler, M. Beller, *40. Jahrestreffen Deutscher Katalytiker*, Weimar (Germany), 14–16 March **2007**.

14. "Rhodium phosphine catalysts for the hydrogenation of *β*–dehydroamino acid derivates" S. Enthaler, G. Erre, K. Junge, J. Holz, A. Börner, E. Alberico, I. Nieddu, S. Gladiali, M. Beller, *Heidelberg Forum of Molecular Catalysis*, Heidelberg (Germany), 22 June **2007**.

15. "Asymmetric hydrogenation of enamides – from benchmark substrates to indol alkaloids" S. Enthaler, G. Erre, K. Junge, M. Beller, *15th European Symposium on Organic Chemistry*, Dublin (Ireland), 8–13 July, **2007**.

16. "Rhodium phosphine catalysts for the hydrogenation of *β*–dehydroamino acid derivates" S. Enthaler, G. Erre, K. Junge, J. Holz, A. Börner, E. Alberico, I. Nieddu, S. Gladiali, M. Beller, *10th JCF–Frühjahrssymposium*, Rostock (Germany), 27–29 March **2008**.

17. "New phosphine–Ligands for palladium–catalyzed coupling reactions" T. Schulz, S. Enthaler, C. Torborg, T. Schareina, A. Zapf, M. Beller, *10th JCF–Frühjahrssymposium*, Rostock (Germany), 27–29 March **2008**.

PATENTS

1. "Chirale Eisen–Phosphan–Katalysatoren und deren Verwendung in selektiven Hydrierungsreaktionen" S. Enthaler, K. Junge, M. Beller, *DE, submitted*.

2. „Chirale Eisen–Katalysatoren mit stickstoffhaltigen Liganden und deren Verwendung in selektiven Hydrierungsreaktionen" S. Enthaler, K. Junge, M. Beller, *DE, submitted*.

BOOK CONTRIBUTIONS

"Applications of iron catalysts in reduction chemistry" S. Enthaler, K. Junge, M. Beller in B. Plietker (Ed.) "Iron catalysis in organic chemistry" Wiley–VCH, Weinheim, **2008**.

TALKS

1. "Development of new monodentate phosphine ligands for asymmetric hydrogenation" S. Enthaler, *COST–D24 STEREOCAT2005*, Barcelona (Spain), 15–18 September **2005**.

2. "Development of new monodentate phosphine ligands for asymmetric hydrogenation" S. Enthaler, *BASF–IfOK–Symposium*, Ludwigshafen (Germany), 14–16 November **2005**.

Eidesstattliche Erklärung

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, den 04.05.2007