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DISSERTATION

Titel der Dissertation

Chiral Ferrocenyl Ligands:

Synthesis and Application in Asymmetric Catalysis

Verfasserin

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Abstract

This thesis describes the development of novel homogeneous asymmetric hydrogenation catalysts that are all based on chiral non-racemic ferrocene derivatives as the catalyst ligands. For this purpose, phosphino-substituted ferrocenyloxazoline ligands were prepared and tested in ruthenium-catalyzed asymmetric hydrogenations and transfer hydrogenations. Furthermore, two novel and optimized synthesis procedures for such ligands were established. Moreover, a very general and highly modular synthesis procedure for chiral non-racemic 1,2-di- and 1,2,3-trisubstituted ferrocene derivatives has been developed.

All novel phosphino-oxazoline ligands were prepared in good yields by applying two different and highly modular synthesis strategies. One synthesis route started from commercially available Ugi-amine and allowed to build up the desired phosphino-oxazoline ligand in a five step sequence. With use of the second methodology, the desired phosphino-oxazoline ligands could be obtained in only two steps from commercially available ferrocenyloxazoline. Ruthenium complexes $[RuCl_2(PPh_3)(L)]$ of all ligands were prepared. The application of these complexes as catalysts in asymmetric hydrogenations and transfer hydrogenations of ketones delivered excellent results and product with up to 99% e.e. was obtained in hydrogenation and with 98% e.e. in transfer hydrogenation reactions.

In order to further ease the synthesis procedure of such ligands, two additional complementary synthesis routes were worked out and optimized. Both routes started from easily accessible ferrocenyloxazolines and in both cases the phosphino-substituted side chain was build up diastereoselectively. In the first sequence, 2-oxazolinyl substituted ferrocene aldehydes were directly phenylated or alkylated through an auto-activated transfer from diphenyl zinc or dialkyl zinc reagents to the aldehyde functionality and provided alcohols with 94% d.e. and in very high chemical yield. In a further two-step sequence, these alcohols were transformed into the desired phosphino-oxazolines. Alternatively, the ligand side chain could be built up by applying a diastereoselective α-deprotonation reaction to diphenylphosphinylmethyl substituted ferrocene precursors. With this methodology the stereogenic center of the side-chain was introduced with 95% d.e. and 93% chemical yield. Moreover, from a number of additional asymmetric transfer hydrogenations it was concluded that for these ligands the (S,S_{Ox},S_{Fc}) relative configuration constitutes the matching configuration while both a change of the side-chain or of the oxazoline configuration leads to less efficient transfer hydrogenation catalysts.

Furthermore, a number of chiral, non-racemic 1,2-di- and 1,2,3-trisubstituted ferrocene derivatives were synthesized in a highly modular three-step sequence, starting from well-established diastereoselectively *ortho*-directing ferrocenyl amines. *Ortho*-lithiation followed by reaction with electrophiles and subsequent reductive removal of the amino substituents led to enantiopure 1,2-disubstituted ferrocenes. A further *ortho*-lithiation of these products followed by reaction with another electrophile allowed to generate chiral non-racemic 1,2,3-trisubstituted ferrocenes which are inclined to be useful starting materials for the synthesis of chiral, non-racemic ferrocene derivatives such as phosphino- or oxazoline-based catalysts ligands.

Zusammenfassung

Diese Dissertation beschreibt die Weiterentwicklung homogener, asymmetrischer Hydrierkatalysatoren, die alle chirale, nichtrazemische Ferrocenderivate als Katalysatorliganden aufweisen. Zu diesem Zwecke wurden phosphinosubstituierte Ferrocenyloxazoline dargestellt und in Ruthenium-katalysierten asymmetrischen Hydrierungen und Transferhydrierungen getestet. In diesem Rahmen wurden auch zwei neue Wege zur einfacheren Synthese solcher Liganden, sowie eine sehr allgemeine und modulare Synthesesequenz für chirale, nichtrazemische 1,2-di- and 1,2,3-trisubstituierte Ferrocenderivate ausgearbeitet.

Alle neuen Phosphinooxazolin-Liganden wurden auf zwei hochmodularen Synthesewegen hergestellt. Die erste Synthesesequenz beginnt mit kommerziell erhältlichem Ugi-Amin und erlaubt es, die gewünschten Phosphinooxazoline in fünf Schritten darzustellen. Mit Hilfe der zweiten Synthesemethode können solche Liganden – ausgehend von kommerziell erhältlichem Ferrocenyloxazolin – in zwei Stufen hergestellt werden. Von allen dargestellten Liganden konnten Komplexe des Typs $[RuCl_2(PPh_3)(L)]$ erhalten und in asymmetrischen Hydrierungen und Transferhydrierungen von Ketonen getestet werden. Mit beiden Methoden waren Produkte mit einem enantiomeren Überschuss von $\geq 98\%$ zugänglich.

Zur Vereinfachung der Darstellung solcher Oxazolin-Liganden wurden zwei neue komplementäre und optimierte Synthesesequenzen ausgearbeitet. Beide Synthesemethoden begannen mit leicht zugänglichen Ferrocenyloxazolinen und in jedem Fall wurde die benötigte Seitenkette auf einem diastereoselektiven Weg aufgebaut. In der ersten Synthesesequenz wurde von 2-Oxazoliny-substituierten Ferrocenylaldehyden ausgegangen und diese jeweils in einer autoaktivierten Reaktion mittels Diphenylzink oder Dialkylzink-Reagenzien phenyliert beziehungsweise alkyliert. Die dabei entstandenen Alkohole konnten in zwei weiteren Schritten zu den gewünschten Liganden umgesetzt werden. In einer alternativen Synthesesequenz konnten die Seitenkettensubstituenten durch α-Deprotonierung von geeigneten Ferrocenylmethyl-substituierten Phosphinoxiden mit 95% diastereoselektivem Überschuss und 93% chemischer Ausbeute eingeführt werden. Aus den Resultaten weiterer Transferhydrierungen konnte geschlossen werden, dass die besten Ergebnisse dann erhalten werden, wenn Liganden mit (S,S_{Ox},S_{Fc}) Relativkonfiguration eingesetzt werden. Änderungen sowohl der relativen Seitenketten- als auch der Oxazolinkonfiguration führten zu Katalysatorliganden mit geringerer Effizienz.

In einem weiteren Teil dieser Arbeit wird die Synthese von chiralen, nichtrazemischen 1,2-di- und 1,2,3-trisubstitubstituierten Ferrocenderivaten beschrieben, wobei jeweils von etablierten diastereoselektiv *ortho*-dirigierenden Ferrocenylaminen ausgegangen wurde. Durch *ortho*-Lithiierung derartiger Ferrocene, einer nachfolgenden Reaktion mit Elektrophilen und anschließender partieller Entfernung der dirigierenden Gruppe konnten enantiomerenreine 1,2-disubstituierte Ferrocene hergestellt werden. Wurden Elektrophile verwendet, die selber *ortho*-dirigierend wirken, konnten durch nochmalige *ortho*-Lithiierung und Reaktion mit weiteren Elektrophilen 1,2,3-trisubstituierte Ferrocene erhalten werden, die als Ausgangsmaterialien für die Synthese von chiralen, nichtrazemischen Ferrocenderivaten, wie etwa Katalysatorliganden, verwendet werden können.

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To my husband and parents

تقدیم به پدر و مادر و همسر عزیزم

Content

1. Introduction

1.1. General Introduction

The term “catalyst” was raised for the first time by Berzelius in 1836 and in 1894 Ostwald defined a catalyst as a substance that increases the rate of a chemical reaction without itself being substantially consumed. The function of a catalyst usually depends significantly on the type of chemical reaction. A catalyst may either change the rate of a chemical reaction by altering its activation energy or may open up reaction pathways that otherwise are inaccessible. In the case of an equilibrium reaction, a catalyst will accelerate both the forward and the backward reaction without changing the position of equilibrium. In those cases where the reactions can follow simultaneously more than one reaction pathway, a catalyst may accelerate selectively one reaction over the others and this may result in a different product distribution.[1]

A catalytic reaction usually consists of a series of transformations to which a catalyst enters in one step and is regenerated in another step. Such sequences are frequently depicted in a cyclic graph which is called a ‘catalytic cycle’ (Figure 1). The notable difference between a catalytic and a stoichiometric reaction ensues from the fact that – as compared to the reagent – in a catalytic reaction only a substoichiometric amount of the catalyst is required.

Generally, catalysts are categorized either in accordance to their physical state (gas, solid, liquid), their chemical nature (metals, oxides, proteins), the type of catalyzed reaction (oxidation, reduction, cracking, etc.) or according to the number of phases (homogeneous, heterogeneous).[2]

Heterogeneous and homogeneous catalysis constitute two main types of catalysis, which are characterized by significantly different properties and applications.

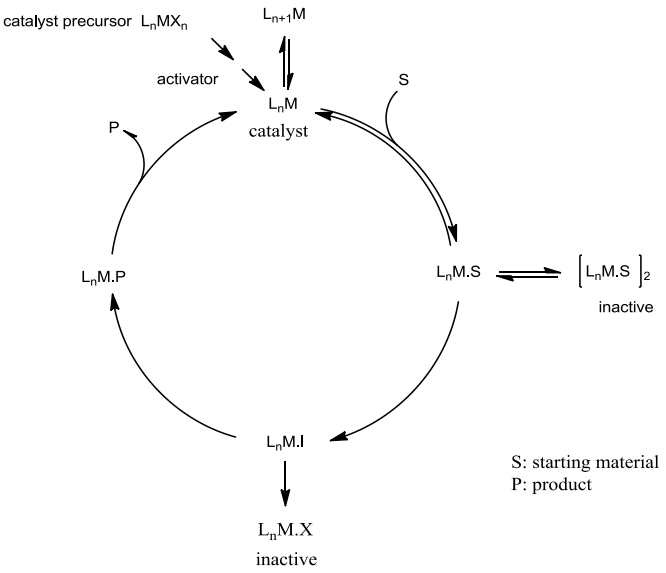


Figure 1. Schematic representation of a catalytic cycle.

In homogeneous catalysis, the catalyst is present in the same phase as the other reaction components and this fact is associated with a number of advantages and disadvantages. Advantages of homogeneous catalysts include (i) high diffusion rates for all reaction components, (ii) the possibility of investigating the progress of reaction by utilizing spectroscopic methods such as NMR spectroscopy (iii) higher reactivity and selectivity. Disadvantages include difficulties in separating catalyst and products as well as the regeneration of catalyst.

In heterogeneous catalysis (surface catalysis), catalyst and reagents are present in different phases. These types of reaction usually occur on the surface of solid catalysts. The advantages of heterogeneous catalysts include low cost, ease of separation, high stability and the possibility of catalyst recycling. Disadvantages include slow rates – and as compared to homogeneous catalysis – lower regio- and stereoselectivity.

Like with stoichiometric reagents also with use of chiral catalysts, chiral non-racemic products can be obtained from prochiral substrates. Such compounds are typically formed in biological systems in which enzymes act as the enantioselective catalysts.[3]

Since usually biological systems constitute a chiral non-racemic environment, enantiomers may act significantly different from each other. For example, one enantiomer could cause a beneficial therapeutic action while the other one could be highly toxic. Hence, the synthesis of enantiomerically pure or highly enriched

biologically active compounds has become an important task in organic chemistry. Several methods have been applied for the synthesis of enantiomerically pure compounds such as resolution of racemates, chromatographic separation of enantiomers, enzymatic resolution, chemical kinetic resolution, asymmetric synthesis and enantioselective catalysis. Amongst these methodologies, frequently, asymmetric catalysis has proved to be superior since a small amount of a chiral non-racemic catalyst can produce a large amount of chiral non-racemic product. Therefore, asymmetric catalysis has become a powerful tool for synthesizing chiral non-racemic compounds.[1,4,5]

Historically, enantioselective catalysis dates back to 1904 when Marckwald reported his pioneering work on the enantioselective decarboxylation of properly substituted malonic acids with use of brucine.[6]

Later on in 1908, Bredig synthesized mandelonitrile from benzaldehyde and HCN in the presence of an alkaloid (quinine or quinidine) as the catalyst.[7] Prelog and Wilhelm continued along this line and in 1954 proposed a mechanistic picture.[8] In the late 1950s in Japan, Izumi and co-workers reported on the impregnation of silk with palladium dichloride and its application in the enantioselective hydrogenation of some dehydroamino acid derivatives.[9] In a further attempt, Izumi modified Raney nickel with tartaric acid derivatives and these modified catalysts were applied in the hydrogenation of methyl acetoacetate.[10] Products were obtained with up to 80% enantiomeric excess.

Since then the development of homogeneous and heterogeneous as well as enantioselective catalysts has progressed enormously and this work has been awarded by several Nobel prizes (Ziegler, Natta 1963; Wilkinson, Fischer, 1973; Knowles, Noyori, Sharpless 2001; Chauvin, Grubbs, Schrock, 2005; Ertl, 2007; Heck, Negishi, Suzuki, 2010).

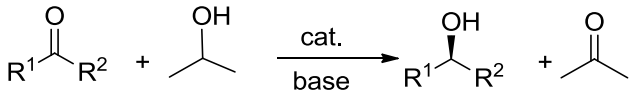
Nowadays, a great variety of highly selective catalysts is available for applications ranging from the small laboratory to the large industrial scale. From an industrial point of view, hydrogenations including enantioselective hydrogenations with use of hydrogen gas belong to the most mature synthesis methodologies available and are used for the large scale production of many achiral as well as chiral products. For enantioselective applications, especially homogenous catalysts[11] are used while for the production of achiral or racemic derivatives heterogeneous catalysts[2] are preferred.

In certain cases, hydrogen gas in hydrogenations can be replaced by other hydrogen sources. These so called transfer hydrogenations are in some respects

complementary to hydrogenations with hydrogen gas and are especially useful for the reduction of polar substrates such as ketones, aldehydes or imines.[2] However, due to some limitations large scale industrial applications are rare. Like hydrogenations, also transfer hydrogenations can be carried out enantioselectively and in many cases products with very high enantiomeric excess can be obtained.

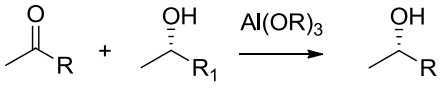
1.2. Asymmetric Transfer Hydrogenation

Asymmetric transfer hydrogenation of ketones and imines with chiral non-racemic catalysts is recognized as an efficient methodology for the preparation of enantiopure or highly enantiomerically enriched alcohols and amines.[12] In catalytic transfer hydrogenation reactions, hydrogen is transferred from a donor to the substrate to yield reduced substrate and oxidized donor (Scheme 1). Common donors include cyclohexadiene, ammonium formate and 2-propanol. Chiral Ru, Rh and Ir catalysts are particularly useful in these reactions and have been intensively studied.[13]



Scheme 1. Schematic representation of transfer hydrogenation reactions.

The first report on asymmetric transfer hydrogenation describes an asymmetric version of the Meerwein-Pondorf-Verley reduction (MPV) (Scheme 2).[9a,14]

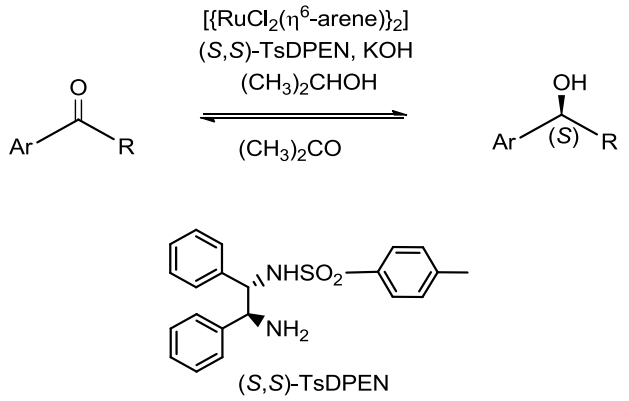


R= $(CH_2)_3CH(CH_3)_2$, *O*-C_6H_{11} 5.9-21.8% e.e.
R_1= C_2H_5, $CH(CH_3)_2$

Scheme 2. Asymmetric Meerwein-Pondorf-Verley (MPV) reduction.

In this case, a chiral non-racemic alcohol was used as the source of chirality. Although the enantioselectivity of this type of MPV reduction was rather low, it is considered a milestone in the development of many chiral catalysts for the asymmetric transfer hydrogenation of ketones and imines. In 1991 Chowdhury and Backvall showed that $RuCl_2(PPh_3)_3$ in the presence of NaOH acts as an effective catalyst for this transformation.[15] A breakthrough came about when Noyori reported the development of

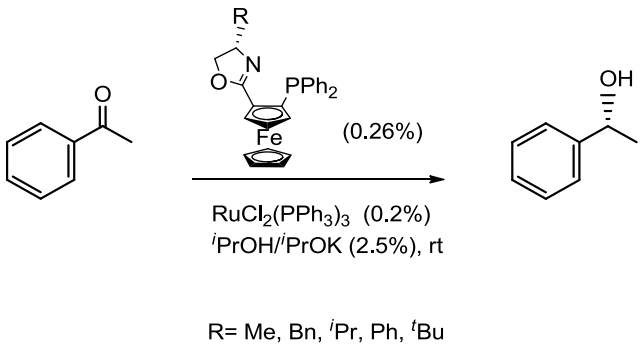
a class of well-designed chiral Ru^{II}-arene complexes that were modified with chiral diamine derivatives (Scheme 3). With applying these catalysts, asymmetric transfer hydrogenation of ketones and imines in the presence of an organic hydrogen donor solvent such as 2-propanol gave products with excellent conversion and enantiomeric excess.[16]



Scheme 3. Asymmetric transfer hydrogenation of aromatic ketones.

Later on in 1997, Sammakia and co-workers applied chiral ferrocenyloxazoline complexes with planar chirality to the asymmetric transfer hydrogenation of aryl ketones. They prepared catalysts in situ from $RuCl_2(PPh_3)_3$ and a variety of ferrocenyloxazolines. In the presence of these catalysts, products with up to 94% e.e. were obtained (Scheme 4).[17]

In 1999 Nishibayashi and co-workers isolated diastereomerically pure ruthenium complexes $[RuCl_2(PPh_3)_3L]$ of oxazolinyl ferrocenylphoshphine ligands. By applying these complexes, extremely high enantionselectivities were obtained in the transfer hydrogenation of alkyl aryl ketones and dialkyl ketones when 2-propanol was used as the hydrogen donor (up to 99% e.e. for acetophenone).[18]



Scheme 4. Asymmetric transfer hydrogenation of aryl ketones catalyzed by $RuCl_2(PPh_3)_3$ and ferrocenyloxazolines.

Some chiral Schiff bases have also been applied as catalyst in asymmetric transfer hydrogenations. In 1999 Kwong and co-workers used *P*,*N*,*O* ligand **1** (Chart 1) for the asymmetric transfer hydrogenation of ketones and reported up to 81% e.e.[19] Later on in 2003, Zheng and co-workers reported on a series of *P*,*N*,*O* ligands (**2**, Chart 1) for ruthenium catalyzed asymmetric transfer hydrogenation of ketones (up to 94% e.e.).[20]

Generally, chiral *PN*, *NN*, *NO* and *P,N,O* ligands have shown to be very successful in asymmetric transfer hydrogenations. Chart 1 summarizes the most effective ligands for the transfer hydrogenation of ketones.[9d,10]

In the last two decades, asymmetric transfer hydrogenation has evolved as a complementary methodology to the well-established asymmetric hydrogenation, especially for producing enantiopure or highly enantiomerically enriched secondary alcohols and amines. Contrary to hydrogenation reactions, the use of transfer hydrogenations does not require hydrogen gas as the reagent and in addition high pressure equipment can be avoided. In most cases isopropanol is used as the hydrogen source.[21]

However, besides some advantages like high stereo- and regioselectivity, there are some disadvantages related to asymmetric transfer hydrogenations that until now have prevented large scale industrial applications: (i) in order to reach reasonable reaction rates, addition of a strong base to the reaction mixture is required and this may result in side reactions of both substrates and products (e.g. aldol reactions of substrate or racemisation of product); (ii) in many cases the reactions have to be carried out at low substrate concentrations, a fact that severely limits up-scaling; and (iii) if isopropanol is used as the hydrogen source, at large scale huge amounts of commercially unusable acetone is produced.

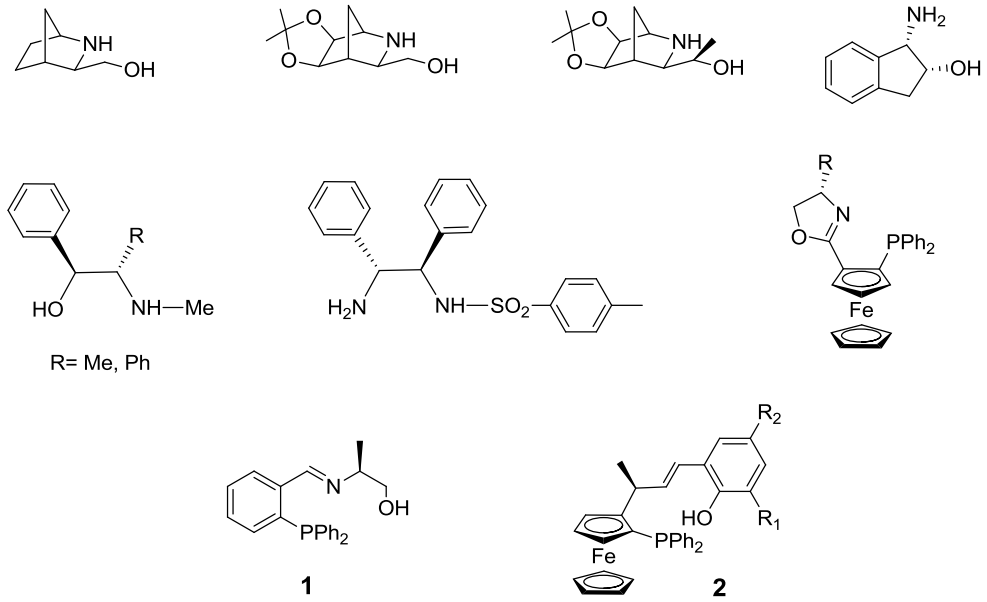


Chart 1. The most effective ligands for transfer hydrogenations of ketones.

1.3 Asymmetric Hydrogenation

Asymmetric hydrogenation of prochiral unsaturated compounds such as alkenes, ketones and imines has been intensively studied and is considered a versatile methodology for the synthesis of chiral compounds ranging from the laboratory to the industrial scale. The discovery of homogenous catalysts for the asymmetric hydrogenation of prochiral olefins, ketones and imines is well recognized as one of the most significant developments in organotransition metal chemistry.[2]

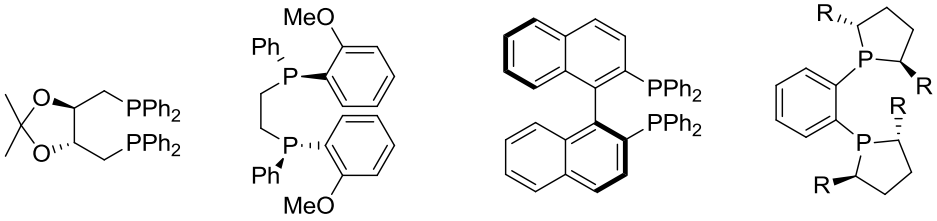
Low valent Ru, Rh or Ir complexes bearing at least one chiral ligand belong to the most effective homogeneous hydrogenation catalyst precursors.[4a,22]

The term “homogeneous hydrogenation” was used for the first time in 1938 by Calvin.[23] He reported on copper based catalysts and used it for the reduction of *p*-benzoquinone. Rhodium amine complexes and later on cyanocobaltate complexes were described by Iguchi.[24] With his discovery of $[RhCl(PPh_3)_3]$ in 1965 Wilkinsons made a very important breakthrough in homogeneous catalysis.[25] Independently, Coffey[26] discovered and also applied this complex in the hydrogenation of a variety of alkenes. The reactions could be carried out under very mild conditions and with high selectivity. In 1968 Horner[27] and Knowles[28] independently published on chiral non-racemic rhodium catalysts all containing *P*-chiral monodentate ligands. In

hydrogenations, these rhodium complexes resulted in measurable but low product enantioselectivities (less than 30%). In 1971 Kagan introduced his rhodium complexes containing the C_2-symmetric diphosphine DIOP [(4*R*,5*R*)-(–)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] as the chiral ligand (**3**, Chart 2).[29,30] His studies resulted in significantly higher product enantioselectivities (up to 88%) for the hydrogenation of alkenes. With Kagan's study about C_2-symmetric chelating diphosphine ligands in view, Knowles synthesized DIPAMP (*R*,*R*)-(-)-1,2-bis[(*o*-methoxy-phenyl)(phenyl)phosphino]ethane; a second generation of *P*-chiral ligands (**4**, Chart 2).[31] Rhodium complexes of this C_2-symmetric ligand catalyzed the hydrogenation of dehydroamino acids and L-DOPA (3,4-dihydroxy-L-phenylalanine), a drug for treating Parkinson's disease, with high enantioselectivity (up to 95% e.e.).[32]

The next outstanding ligand was BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphtyl] which was developed by Noyori in the 1980s (**5**, Chart 2).[33,34] Unlike the previously described ligands, BINAP does not contain carbon stereocenters but belongs to the group of axially chiral compounds. Interestingly, the most active and selective catalysts containing BINAP as the chiral ligand are based on ruthenium rather than on rhodium (e.g. [Ru(BINAP)$(OAc)_2$]). BINAP also belongs to the group of so called privileged ligands, since BINAP based catalysts can be used for a wide range of catalysis reactions as well as for a broad range of substrates.

Ligands containing alkylphosphines such as the DuPhos ligand family (**6**, Chart 2) have been developed by Burk.[35] Catalysts from DuPhos and rhodium precursors show excellent results in enantiosective hydrogenation of many olefins and imines.



3 (*R,R*)-DIOP | **4** (*S,S*)-DIPAMP | **5** (*S*)-BINAP | **6** DuPhos

Chart 2. C_2-symmetric bidentate diphosphine ligands.

During the last 25 years, hundreds of chiral non-racemic ligands have been synthesized and applied in enantioselective catalysis. Among all of these ligands, the group of ferrocene based ligands has been applied most successfully in hydrogenation and transfer hydrogenation reactions.

1.4. Chiral, non-racemic ferrocene ligands

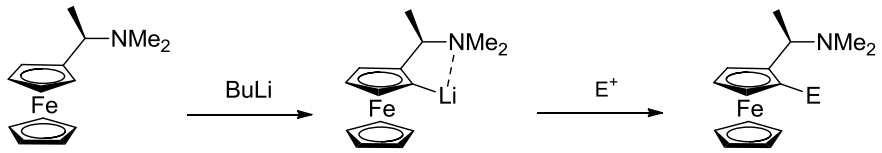
A great number of properly substituted ferrocene derivatives has been synthesized in chiral non-racemic form and such planar chiral derivatives have been applied in a variety of different fields including homogeneous enantioselective catalysis, bioorganometallic chemistry, polymers and dendrimers, electrooptical materials as well as thermotropic liquid crystals.[36]

In 1959 the first optically active planar chiral ferrocene was prepared by Thomson via chemical resolution (**7**, Chart 3).[37]

7 (*R*)-**8**

Chart 3. First optically active planar chiral ferrocene, **7**, and Ugi's amine, **8**.

In 1970 Nozaki and Ugi independently used a diastereoselective *ortho*-directing group (2-methylpyrrolidine) in the synthesis of chiral non-racemic 1,2-disubstituted ferrocenes. In the same year, Ugi and co-workers also reported on *N,N*-dimethylferrocenylethylamine (Ugi's amine) (**8**, Chart 3), a ferrocene derivative that bears a highly diastereoselective *ortho*-directing group.[38] Ugi's amine marks a turning point in the synthesis of chiral 1,2-disubstituted ferrocenes since by reaction with butyl lithium and subsequent trapping with electrophiles a variety of substituents can be introduced in the *ortho*-position (Scheme 5).

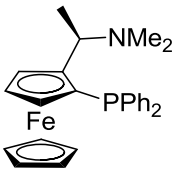


(*R*)-**8** (*R*,R_{Fc})-**9** (*R*,S_{Fc})-**10**

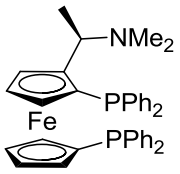
Scheme 5. Synthesis of chiral ferrocenyl derivatives with planar chirality.

Chiral ferrocenylphosphines were prepared for the first time in 1974 by Hayashi and Kumada with use of Ugi's methodology.[39] Diastereoselective *ortho*-lithiation of (*R*)-**8** yielded (*R*,R_{Fc})-**9** with high diastereoselectivity (92% d.e.) and subsequent quenching with chlordiphenylphosphine resulted in PPFA (**11**, Chart 4). In addition to

aminophosphine PPFA, diphosphine BPPFA (**12**, Chart 4) was synthesized. It turned out that these derivatives are very valuable ligands in a variety of catalytic asymmetric transformations such as cross-coupling reactions and asymmetric hydrosilylations of olefins.[40]



(R,S_{Fc})-**11** PPFA



(R,S_{Fc})-**12** BPPFA

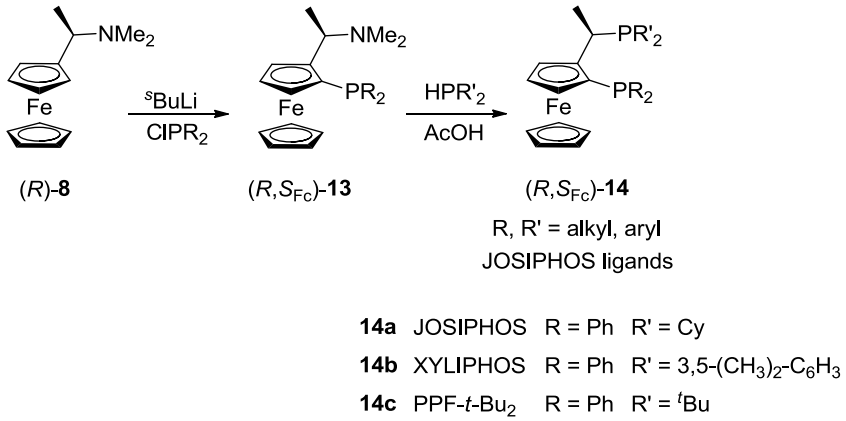
Chart 4. First ferrocenyl-based chiral ligands.

Further stereospecific S_N1-type reactions of the dimethylamino moiety with different nucleophiles such as acetate, R_2PH, pyrazoles and others, which take place with retention of configuration, have led to a wide variety of chiral non-racemic ferrocene ligands. Among the huge number of ferrocene based catalyst ligands the so called Josiphos ligand family (**14**, Scheme 6) – developed by Togni, Spindler and co-workers – holds a dominant role amongst C_1-symmetric ferrocene-based ligands. In Scheme 6 the synthesis approach of Joshiphos ligands is depicted. This method starts from readily available Ugi's amine and follows Ugi's original diastereoselective *ortho*-lithiation procedure. Then by quenching with chlorodiphenylphosphine the first phosphino substituent is added. In a second step, by replacing the *ortho*-directing *N*,*N*-dimethyl-amino group by another phosphine the second substituent is introduced. This short and highly modular approach has allowed the synthesis of a huge number of Josiphos type ligands.[12d,41]

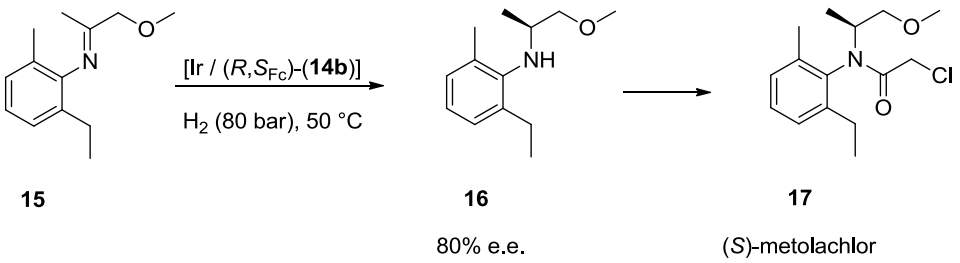
Josiphos ligands proved to be excellent ligands in the asymmetric hydrogenation of alkenes, ketones, imines and enamines.[2,42] Especially Xyliphos[43] (**14b**) represents an outstanding example of the Josiphos family and is intensively applied in an industrial process. The iridium catalyzed large scale hydrogenation of imine **15** yields amine **16** which is an intermediate in the synthesis of herbicide (*S*)-metolachlor (**17**, Scheme 7). This herbicide is produced on a 10.000 ton scale per year. To date this is considered to be the most successful asymmetric hydrogenation process on industrial scale with exceptional turnover numbers (2.000.000) and turnover frequencies (400.000 h^{-1}) as well as acceptable product enantioselectivity (80% e.e.).[44]

Josiphos-type ligands are also applied by industry for the preparation of β-amino acid derivatives, which are important intermediates in the synthesis of biologically active

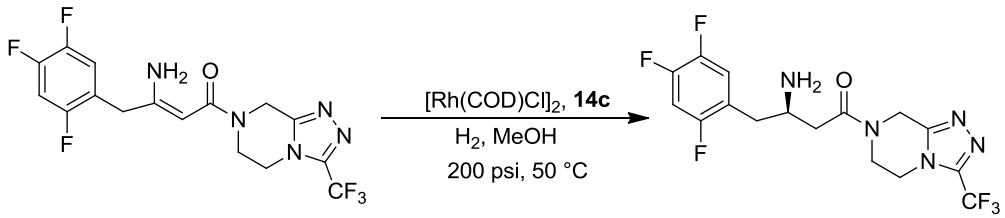
molecules. For this purpose, unprotected prochiral enamines are enantioselectively hydrogenated with use of a diphosphine-modified rhodium catalyst. PPF-*t*-Bu_2 (**14c**) proved to act as the most effective diphosphine ligand in this process (Scheme 8).[45,46]



Scheme 6. Synthesis of Josiphos ligands.



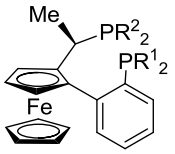
Scheme 7. Synthesis of (*S*)-metolachlor.



Scheme 8. Synthesis of β-amino acid derivatives.

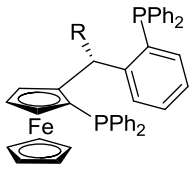
Like Josiphos, Walphos-type ligands, (**18**, Chart 5) were prepared in a highly modular approach from Ugi's amine.[47] Walphos derivatives were found to be promising catalyst precursors for the enantioselective hydrogenation of olefins and ketones, as well as for C–C bond forming reactions.[48] As an industrial application of one Walphos ligand, the preparation of Synthon A, an intermediate in the synthesis of the rennin inhibitor Aliskiren, should be mentioned. On a large scale, it was prepared quantitatively

and with high enantioselectivity from the appropriately substituted 2-isopropyl cinnamic acid (Scheme 9).[12d,49]



Walphos Ligands 18

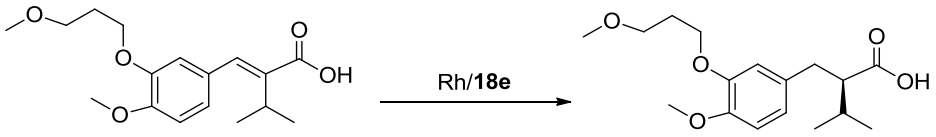
a R^1 = Ph R^2 = Cy
b R^1 = Ph R^2 = ^{t}Bu
c R^1 = Ph R^2 = Ph
d R^1 = Ph R^2 = 3,5-$(CH_3)_2$-4-$(CH_3O)C_6H_2$
e R^1 = Ph R^2 = 3,5-$(CF_3)_2C_6H_3$
f R^1 = 3,5-$(CH_3)_2$-4-$(CH_3O)C_6H_2$
R^2 = 3,5-$(CF_3)_2C_6H_3$



Taniaphos Ligands 19

a R = H
b R = Me
c R = ^{i}Pr
d R = NMe_2
e R = OH

Chart 5. Structure of C_1-symmetric ferrocenyl-based Walphos and Taniaphos ligands.



Synthon A

95% e.e.
TON 5,000
TOF ca. 800 h^{-1}

Scheme 9. Application of a Walphos ligand (**18e**) on large scale.

Taniaphos-type ligands[50] (**19**, Chart 5) constitute another class of C_1-symmetric ferrocene-based diphosphines that proved superior in the rhodium and ruthenium catalyzed hydrogenation.[51] Within this class of ligands the product enantioselectivity strongly depends on the nature of the backbone substituent R attached to the benzylic methylene position. For example, in the hydrogenation of β-dicarbonyl compounds, ligand **19b** (R = Me) and **19d** (R = NMe_2) resulted in product of opposite absolute configuration.

Furthermore, ferrocenyl diphosphine ligands with planar chirality as the sole source of chirality (**20** and **21**, Chart 6)[52] – originally developed by Kagan's group – have been screened in hydrogenations of a variety of alkenes, however, only in the

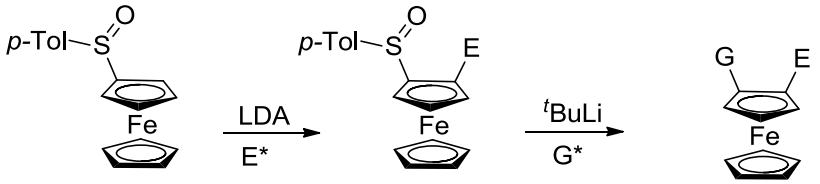
hydrogenation of dimethyl itaconate high enantioselectivities could be obtained (98 and 92% e.e. for ligand **20**, R = Cy and cyclopentyl).[16]

20 **21**

Chart 6. Exclusively planar chiral diphosphine ligands.

As mentioned above, for the synthesis of 1,2-disubstituted ferrocene derivatives different *ortho*-directing groups can be applied. Besides amines also sulfoxides, acetals, oxazolines and miscellaneous chiral auxiliaries are in use.

Amongst all stereogenic *ortho*-directing groups, Kagan's *p*-tolylsulfinyl group[53] is a unique directing group since it can be fully replaced by reaction of ^{t}BuLi and subsequent quenching with an electrophile (Scheme 10). Although this exchange reaction is very efficient on the laboratory scale, up-scaling to the large industrial scale was not possible.



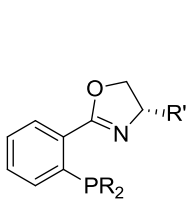
Scheme 10. Synthesis of planar chiral 1,2-disubstituted ferrocenes by sulfoxide/lithium exchange.

1.5. Phosphino-substituted ferrocenyloxazolines

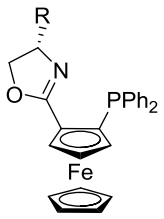
In 1993, aryl based phosphinooxazolines – the so called PHOX ligands[54] – ((*S*)-**22,** Chart 7) were independently synthesized by Pfaltz, Helmchen and Williams and have been applied in a variety of catalysis reactions.[55] Their outstanding results raised the idea of extending this concept to ferrocene derivatives ((*S*,S_{Fc})-**23**, Chart 7).

These FOXAP ((*S*,S_{Fc})-**23**) type derivatives were synthesized independently by Sammakia,[56] Richards[57] and Ahn[58] almost at the same time and are now recognized to

be versatile ligands in a wide variety of enantioselectively catalyzed reactions, including enantioselective hydrogenations,[59] transfer hydrogenations,[40k,60] hydrosilylations,[40k,61] cross-coupling reactions,[62] Heck-reactions,[63] alkylations of aldehydes,[64] allylic substitutions,[40k,43c,65] and many other transformations.[49d,66]



(*S*)-**22**
PHOX

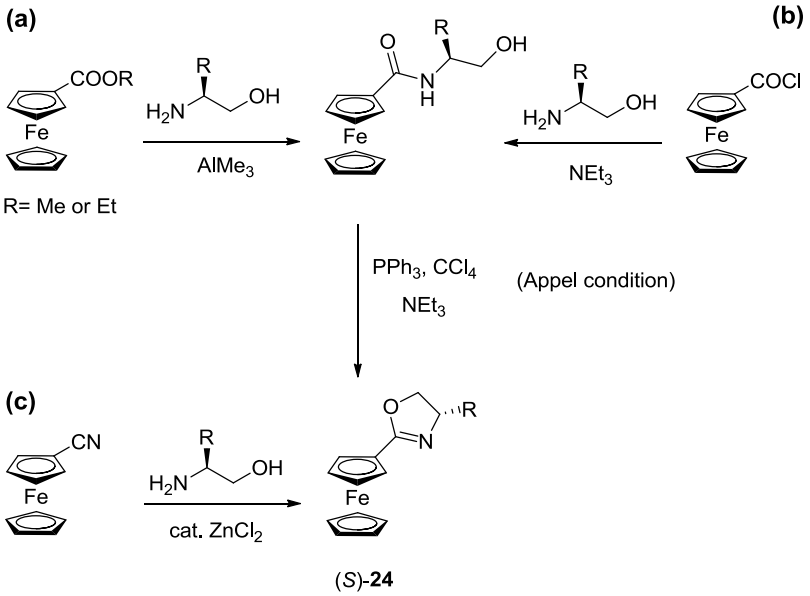


(*S*,S_{Fc})-**23**
R = alkyl, aryl
FOXAP

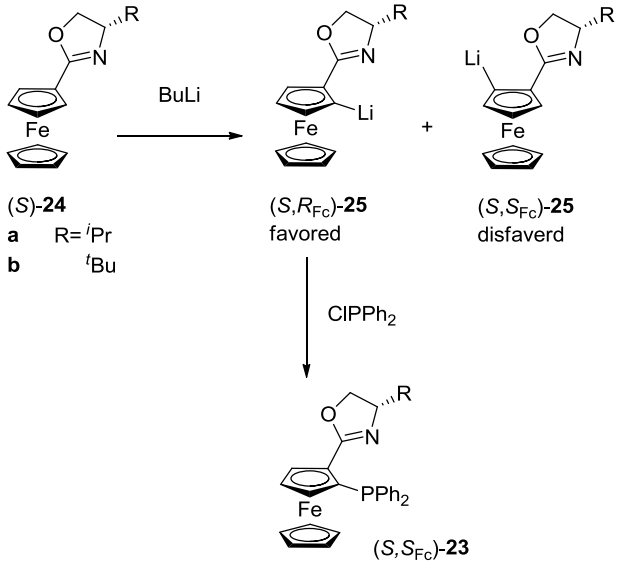
Chart 7. Aryl and ferrocene-based phosphine-oxazoline ligands.

Several routes for the synthesis of these FOXAP ligands have been reported which differ only in the preparation procedure of ferrocenyl oxazolines (*S*)-**24** (Scheme 11). These intermediates are accessible either from esters of ferrocenecarbonic acid (route 11a)[56], from the acid chloride of ferrocenecarbonic acid (route 11b),[67] or from cyanoferrocene (route 11c).[68] In the latter cases reaction of cyanoferrocene with a suitable amino alcohol in the presence of $ZnCl_2$ leads directly to the oxazolines (*S*)-**24**. In the former cases an amide is formed as the intermediate which can be cyclised with use of different methodologies to the desired ferrocenyl oxazolines.

As already reported by Richards[55,65], Sammakia[54a] and Uemura[69] ferrocenyloxazolines (*S*)-**24** can be diastereoselectively *ortho*-deprotonated with butyl lithium (Scheme 13). In the presence of ^{n}BuLi or ^{s}BuLi and diethyether as the solvent diastereomeric ratios of up to 39:1 of (*S*,S_{Fc})-**25** were obtained (Scheme 12). Later on, Sammakia and co-workers increased this ratio to >500:1 by adding tetramethylethylendiamine and by changing the solvent to hexane.[54b] Finally, trapping of the lithiated species ((*S*,S_{Fc})-**25**) with chlorodiphenylphosphine as the electrophile results in the planar chiral FOXAP ligands (*S*,S_{Fc})-**23**.



Scheme 11. Synthesis of optically active ferrocenyloxazoline.

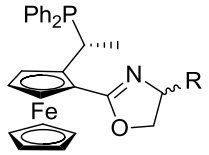


Scheme 12. Diastereoselective *ortho*-lithiation of ferrocenyloxazolines and synthesis of the FOXAP ligand family.

Generally, FOXAP ligands show a good performance in both hydrogenation and transfer hydrogenation catalysis. In 1997 Sammakia[13] and later on Uemura[70] (1999) reported that ruthenium complexes of FOXAP ligands ([$RuCl_2(PPh_3)(L)$], L = FOXAP ligands) perform very efficiently as catalysts for transfer hydrogenations of ketones in the presence of isopropanol as the hydrogen source and a sodium or potassium alkoxide as the base. Especially aryl-alkyl ketones and in some cases also dialkyl ketones could be transformed at room temperature into secondary alcohols with almost

quantitative conversion and with excellent enantioselectivity. In 2006 Naud[63c] and co-workers found that [$RuCl_2(PPh_3)$(FOXAP)] complexes are not only able to catalyze transfer hydrogenations but also hydrogenations in the presence of hydrogen gas even when transfer hydrogenation conditions such as isopropanol as the solvent and KO^tBu as the base are applied. With these conditions the limitation of transfer hydrogenations (high dilution and product racemisation) could be overcome without losing product enantiomeric excess. Hence, up-scaling even to the large industrial scale became possible and as a result a few industrial pilot projects have been carried out.[65b]

Very recently, the backbone of FOXAP type ligands was further modified in our group by replacing the ferrocene unit by a ferrocenylethyl unit (Chart 8). A preliminary high throughput screening of ruthenium complexes of these ligands ([$RuCl_2(PPh_3)$(L)] L = **26**–**28**) in the hydrogenation of a small set of three aryl-alkyl ketones provided products in nearly quantitative conversion and with an enantiomeric excess of 97–99%. Because of their excellent performance, these ligands were called with reference to one inventor Raffa-FOX ligands.[71]



R =	—H	(R,R_{Fc})-**26**
	◄CHMe$_2$	(R,S_{Ox},R_{Fc})-**27**
	····CHMe$_2$	(R,R_{Ox},R_{Fc})-**27**
	◄Ph	(R,S_{Ox},R_{Fc})-**28**
	····Ph	(R,R_{Ox},R_{Fc})-**28**

Chart 8. Ferrocenylethyl based phosphinooxazolines.

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2 Aim and scope of this thesis

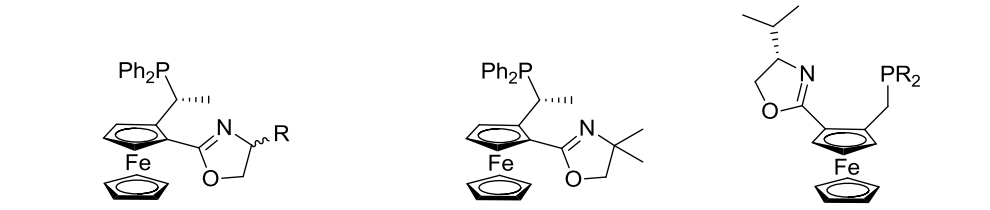
The main intention of this thesis was (i) to develop further phosphino-substituted ferrocenyloxazolines based catalysts, (ii) to test and to compare their performance in asymmetric hydrogenations and transfer hydrogenations, (iii) to develop additional straightforward and easy to handle synthesis routes for Raffa-FOX ligands and (iv) to explore methodologies for the synthesis of enantiopure 1,2-di- and 1,2,3-trisubstituted ferrocenes that could serve as starting material for the synthesis of ferrocene based ligands including oxazoline derivatives.

These topics are summarized in Chapter 3 of this thesis. In the first part (Chapter 3.1), the synthesis of additional Raffa-FOX ligands and their performance in the asymmetric transfer hydrogenation of ketones is described. Moreover, a quantitative comparison between asymmetric transfer hydrogenation and asymmetric hydrogenation reactions is reported. The second part (Chapter 3.2) reports on a novel and optimised synthesis procedure for Raffa-FOX ligands that starts from well-known and easily accessible ferrocenyloxazolines. The third part (Chapter 3.3) describes a simplified methodology for removing *ortho*-directing amines in the presence of various substituents. With use of this methodology a number of enantiopure 1,2-di- and 1,2,3-trisubstituted ferrocenes could be synthesized.

2.1 Phosphino-substituted ferrocenyloxazolines: asymmetric hydrogenation and asymmetric transfer hydrogenation of ketones

As described in the introduction, preliminary test reactions of our newly developed Raffa-FOX ligands (**26**–**28**, Chart 9) provided excellent results in the asymmetric hydrogenation of a small set of ketones. Nearly quantitative conversion and product e.e.s of 97–99% were observed when ruthenium complexes $[RuCl_2(PPh_3)(L)]$ of ligands L = **26**–**28** were used as the catalyst precursors. It was therefore obvious to

extend this concept towards several directions. First of all, we questioned whether structural changes of these ligands could improve the catalysts performance or could ease and shorten the original preparation procedures. For this purpose novel synthesis routes for ligands **29**–**31** were developed. Like ligand **26**, ligand **29** lacks the stereogenic center of the oxazoline unit while ligands **30** and **31** lack the stereogenic center of the side-chain carbon. Secondly, it was of interest to explore the scope of substrates with respect to asymmetric hydrogenations and transfer hydrogenations. In addition we questioned whether ruthenium complexes of type $[RuCl_2(PPh_3)(L)]$ could be used for both hydrogenations and transfer hydrogenations and how these results would compare to each other. Results related to this topic are presented in Chapter 3.1.



R = —H (R,R_{Fc})-**26**
CHMe$_2$ (R,S_{Ox},R_{Fc})-**27**
CHMe$_2$ (R,R_{Ox},R_{Fc})-**27**
Ph (R,S_{Ox},R_{Fc})-**28**
Ph (R,R_{Ox},R_{Fc})-**28**

(R,R_{Fc})-**29**

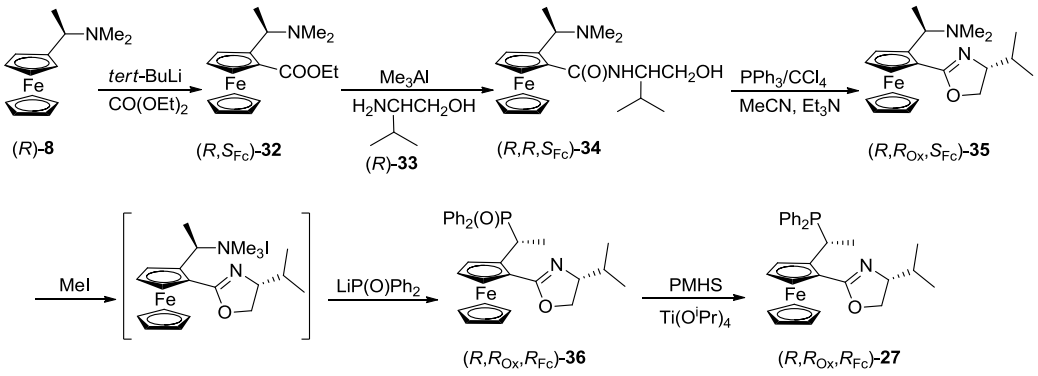
R = Ph (S_{Ox},S_{Fc})-**30**
3,5-(CH$_3$)$_2$C$_6$H$_2$ (S_{Ox},S_{Fc})-**31**

Chart 9. Raffa-FOX ligands **26**–**28** and newly proposed analogs **29**–**31**.

2.2 Diastereoselective synthesis of phosphino-substituted ferrocenyloxazolines

Amongst all ligands tested in the ruthenium catalysed hydrogenation and transfer hydrogenation of alkyl-aryl ketones ($[RuCl_2(PPh_3)(L)]$, L= **26**–**31**) ligand (R,R_{Ox},R_{Fc})-**27** performed best. Additionally, in certain cases ligand (R,R_{Ox},R_{Fc})-**28** provided comparable results while (S_{Ox},S_{Fc})-**23** always led to slightly lower product e.e. values.

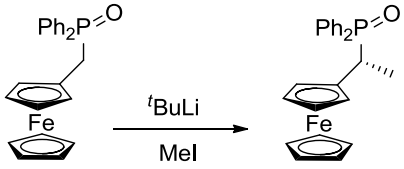
The original synthesis route for ligands of type **27** not only requires several steps but also two enantiopure reagents are needed (Scheme 13).



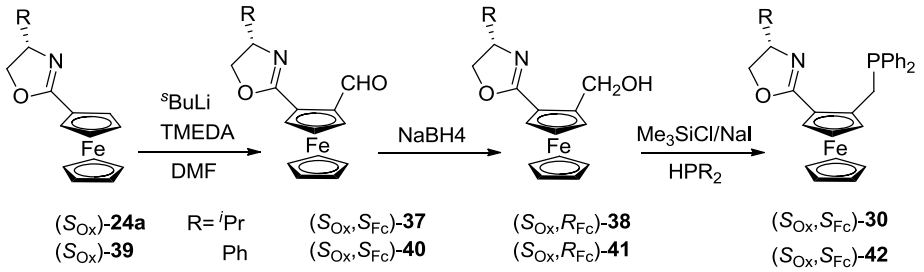
Scheme 13. Original synthesis route for ligand **27** and analogs.

For example, for the synthesis of the (R,R_{Ox},R_{Fc})-**27** enantiopure starting materials (R)-**8** and (R)-valinol, (R)-**33**, are required. Therefore, we questioned whether this synthesis route for ligands with either (R_{Ox},R_{Fc}) or (S_{Ox},S_{Fc}) configuration could be significantly simplified and shortened. For this purpose two different methodologies were considered.

The first methodology is based on a report of Marr who showed that ferrocenyl phosphine oxides can be α-deprotonated and reacted with electrophiles such as methyl iodide (Scheme 14). Recently, a diastereoselective version of this reaction has been published by Stepnicka. It was therefore our intention to investigate whether this methodology could be applied for the synthesis of ligands **27** and **28** when the easily accessible derivatives **24a** and **39** (Scheme 15) are used as the precursors (Scheme 16).

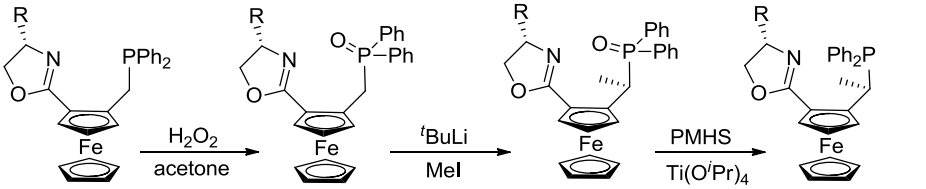


Scheme 14. α-Deprotonation of a ferrocenyl phosphine oxide.



(S_{Ox})-**24a** R= ^{i}Pr (S_{Ox},S_{Fc})-**37** (S_{Ox},R_{Fc})-**38** (S_{Ox},S_{Fc})-**30**
(S_{Ox})-**39** Ph (S_{Ox},S_{Fc})-**40** (S_{Ox},R_{Fc})-**41** (S_{Ox},S_{Fc})-**42**

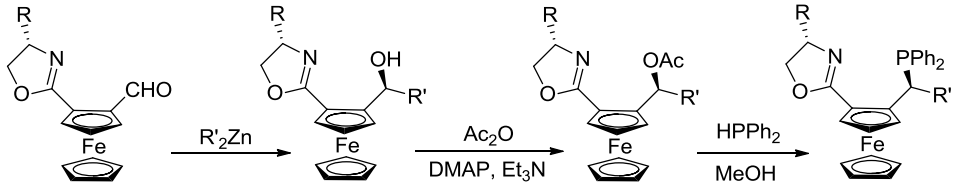
Scheme 15. Synthesis of ligands (S_{Ox},S_{Fc})-**30** and (S_{Ox},S_{Fc})-**42**.



(S_{Ox},S_{Fc})-**30** R = ^{i}Pr (S_{Ox},S_{Fc})-**43** (R,S_{Ox},S_{Fc})-**44** (R,S_{Ox},S_{Fc})-**27**
(S_{Ox},S_{Fc})-**42** Ph (S_{Ox},S_{Fc})-**45** (R,S_{Ox},S_{Fc})-**46** (R,S_{Ox},S_{Fc})-**28**

Scheme 16. Diastereoselective side-chain alkylation.

The second methodology relates to work of Brocard who has shown that alkyl groups from dialkyl zinc reagents can be transferred autocatalytically to aldehydes. Based on this report, we considered to autocatalytically alkylate amino-aldehydes (S,S_{Fc})-**37** and **40** with dialkylzinc reagents and to transform the alcohol intermediates into the desired phosphino-oxazolines (Scheme 17).



(S_{Ox},S_{Fc})-**37** R = ^{i}Pr (S,S_{Ox},R_{Fc})-**47** R' = Me (S,S_{Ox},S_{Fc})-**48** (S,S_{Ox},S_{Fc})-**27**
(S,S_{Ox},R_{Fc})-**49** Ph (S,S_{Ox},S_{Fc})-**50** (S,S_{Ox},S_{Fc})-**51**
(S,S_{Ox},R_{Fc})-**52** Et (S,S_{Ox},S_{Fc})-**53** (S,S_{Ox},S_{Fc})-**54**

(S_{Ox},S_{Fc})-**40** R = Ph (S,S_{Ox},R_{Fc})-**55** R' = Me (S,S_{Ox},S_{Fc})-**56** (S,S_{Ox},S_{Fc})-**28**

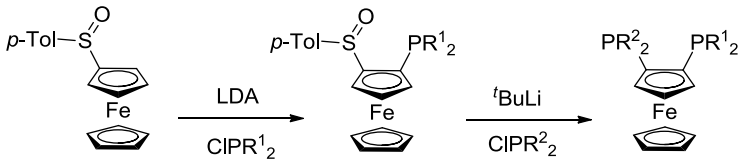
Scheme 17. Autocatalytic alkylation of oxazolinyl-aldehydes with dialkylzinc reagents.

Results related to this topic are presented in Chapter 3.2.

2.3. Synthesis of chiral, non-racemic ferrocene derivatives via *ortho*-metallation and partial reductive removal of *ortho*-directing amino groups.

As mentioned in the introduction, chiral non-racemic 1,2-disubstituted ferrocene derivatives have found widespread application in homogeneous catalysis. Among the prevalent methodologies for the preparation of 1,2-disubstituted ferrocene derivatives, the *p*-tolylsulfinyl group (**57**) holds a unique position since it is the only diastereosective *ortho*-directing ferrocene substituent that undergoes full sulphur/lithium exchange with ^{t}BuLi. However, replacement of the sulfinyl group by other electrophiles works well only on the laboratory scale but up-scaling to the larger industrial scale has proved to be very difficult (Scheme 18).

In order to circumvent this problem, other strategies have been reported by industrial researchers. One approach was to use an *ortho*-directing group and to only partially remove it. For example, 2-bromo-(*N*,*N*-dimethylaminoethyl)-ferrocene, (R,S_{FC})-**58**, was prepared from Ugi's amine and subsequently, in a two-step sequence, the *ortho*-directing group was transformed into a non-coordinating ethyl group, (S_{Fc})-**60**. Since the *ortho*-position next to the bromide can also be deprotonated, various phosphino units could be introduced, (R_{Fc})-**61**. A further exchange of bromide by a second set of phosphino groups allowed the synthesis of a variety of ferrocenyl diphosphines (**62**, Scheme 19).



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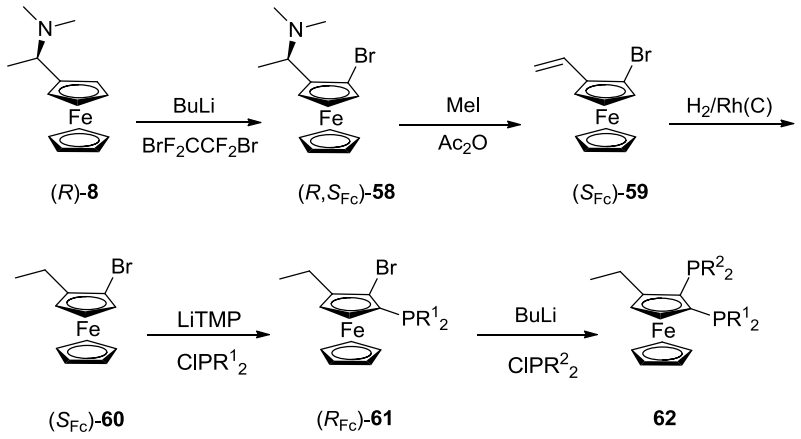
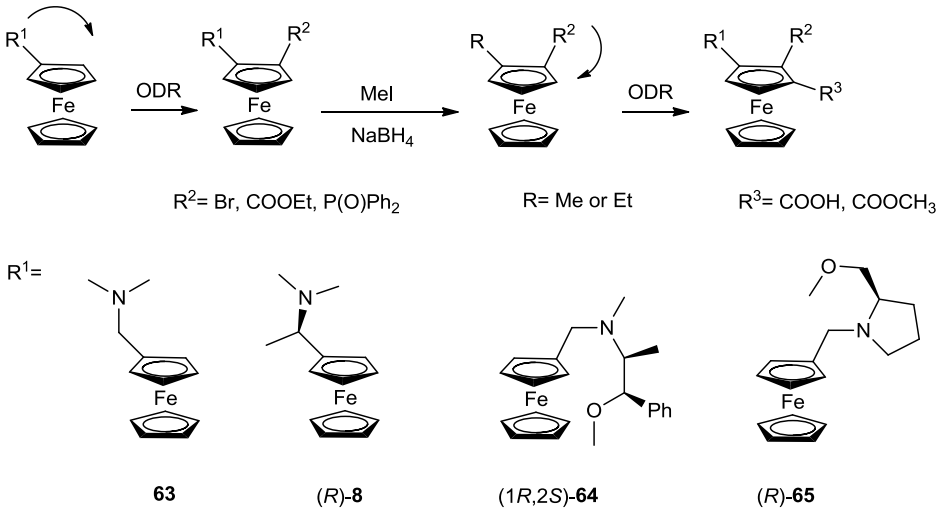
Scheme 18. Preparation of 1,2-disubstituted ferrocene derivatives via the *p*-tolylsulfinyl directing group.



Scheme 19. Preparation of 1,2-disubstituted ferrocene derivatives from Ugi's amine.

Due to the importance of these types of ligands, we anticipated that simplifying this procedure and by using additional *ortho*-directing groups and substituents others than bromide a much broader applicability of this methodology could be achieved.

Therefore this project is aiming for an extention of this methodology with respect to the type of *ortho*-directing groups, (*R*)-**8** and **63-65**, as well as with focus on the synthesis of 1,2-di- and 1,2,3-trisubstiuted ferrocenes (Scheme 20).



Scheme 20. Synthesis of non-racemic 1,2-di- and 1,2,3-trisubstituted ferrocenes.

Details of this work are reported in Chapter 3.3.

3. Results

This thesis is based on the following papers and manuscripts.

Ruthenium complexes of phosphino-substituted ferrocenyloxazolines in the asymmetric hydrogenation and transfer hydrogenation of ketones: a comparison.

Afrooz Zirakzadeh, Raffael Schuecker, Kurt Mereiter, Felix Spindler, and Walter Weissensteiner

Organometallics, submitted

The use of α-deprotonation- and autoactivated alkylation-reactions in the diastereoselective synthesis of phosphino-substituted ferrocenyloxazolines.

Afrooz Zirakzadeh, Kurt Mereiter, and Walter Weissensteiner

Manuscript prepared

Synthesis of chiral, nonracemic ferrocene derivatives via *ortho*-metallation and partial reductive removal of *ortho*-directing amino groups.

Afrooz Zirakzadeh, Raffael Schuecker, Walter Weissensteiner

Tetrahedron: Asymmetry **2010**, *21*, 1494–1502

3.1. Ruthenium complexes of phosphino-substituted ferrocenyloxazolines in the asymmetric hydrogenation and transfer hydrogenation of ketones: a comparison.

Afrooz Zirakzadeh, Raffael Schuecker, Kurt Mereiter, Felix Spindler, and Walter Weissensteiner

Organometallics, submitted

Ruthenium complexes of phosphino-substituted ferrocenyloxazolines in the asymmetric hydrogenation and transfer hydrogenation of ketones: a comparison.

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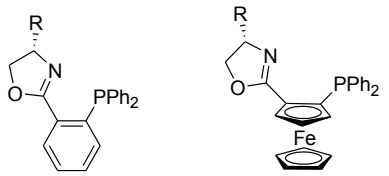
Abstract

Ruthenium complexes of the type $[RuCl_2PPh_3(L)]$ with eight novel bidentate ferrocene-based phosphine-oxazoline ligands were prepared and tested as catalysts in the asymmetric hydrogenation and transfer hydrogenation of fourteen ketones. The molecular structures of two catalyst precursors and of two corresponding acetonitrile complexes were studied by X-ray diffraction. Two catalysts delivered products in high yield and with enantiomeric excesses of up to 99%. The transfer hydrogenation results obtained with all novel ligands were compared to those of one well-established and commercially available FOXAP ligand. Furthermore, a qualitative comparison with the hydrogenation data was carried out. In both cases surprising similarities in product enantiomeric excess and product absolute configuration were found. Attempts were made with use of a transition state model to rationalize these features.

Introduction

For more than two decades phosphino-oxazolines such as the so called PHOX-type ligands[1] (Chart 1) have been successfully used in a huge number of asymmetric transformations as hetero-bidentate ligands of transition metal-based catalysts.[2] In 1995 several groups independently extended the concept of PHOX-type ligands by replacing the ligand aryl backbone by a ferrocene unit.[3] The resulting FOXAP ligands (Chart 1) were found to perform excellently in a wide variety of enantioselectively catalyzed reactions,[4] including hydrogenations,[5] transfer hydrogenations,[5i,6] hydrosilylations,[3d,7] cross-coupling reactions,[3b,8] Heck reactions,[9] alkylations of aldehydes,[10] allylic substitutions,[5i,8c,11] and many other transformations.[12]



PHOX FOXAP

Chart 1.

Sammakia[6e] (1997), Dai[6d] (1998) and Uemura[6b] (1999) reported that ruthenium complexes of FOXAP ligands ($[RuCl_2(PPh_3)(L)]$, L = FOXAP ligands) performed very efficiently as catalyst precursors in the transfer hydrogenation of ketones when 2-propanol was used as the hydrogen source and sodium hydroxide or a sodium (potassium) alkoxide was used as the base. In particular, aryl-alkyl ketones – and in some cases also dialkyl ketones – could be transformed at room temperature into secondary alcohols with almost quantitative conversion and with excellent enantioselectivity. In 2006 Naud and co-workers found that $[RuCl_2(PPh_3)(FOXAP)]$ complexes are not only able to catalyze transfer hydrogenations but also hydrogenations in the presence of hydrogen gas, even when transfer hydrogenation conditions such as the use of 2-propanol as the solvent and KO^tBu as the base were applied.[13] On using these conditions some limitations of transfer hydrogenations (high dilution, product racemization) could be overcome without losing product enantiomeric excess and scale-up even to the large industrial scale became possible.[13a]

Within this framework, and as a continuation of our search for novel chiral non-racemic catalysts and catalyst ligands,[14] we very recently made further modifications to the ligand backbone of FOXAP ligands by replacing the ferrocene unit by a ferrocenylethyl unit (derivatives **2**–**4**, Chart 2). This structural modification led to the addition of a further stereogenic unit to the ligand system and for the corresponding

ruthenium complexes to an increase in chelate ring size from six to seven.[15] A preliminary high throughput screening of ruthenium complexes of these 'Raffa-FOX' ligands ([$RuCl_2(PPh_3)(L)$] L = **2**–**4**) in the hydrogenation of a small set of three aryl-alkyl ketones gave products with nearly quantitative conversion and with an enantiomeric excess of 97–99%.

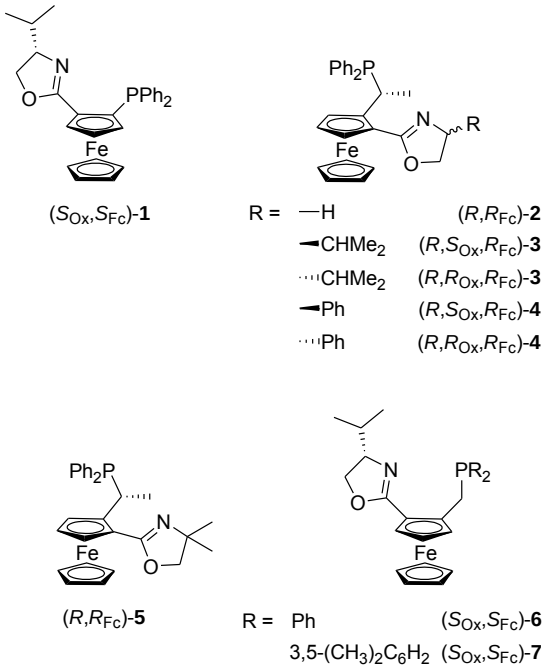


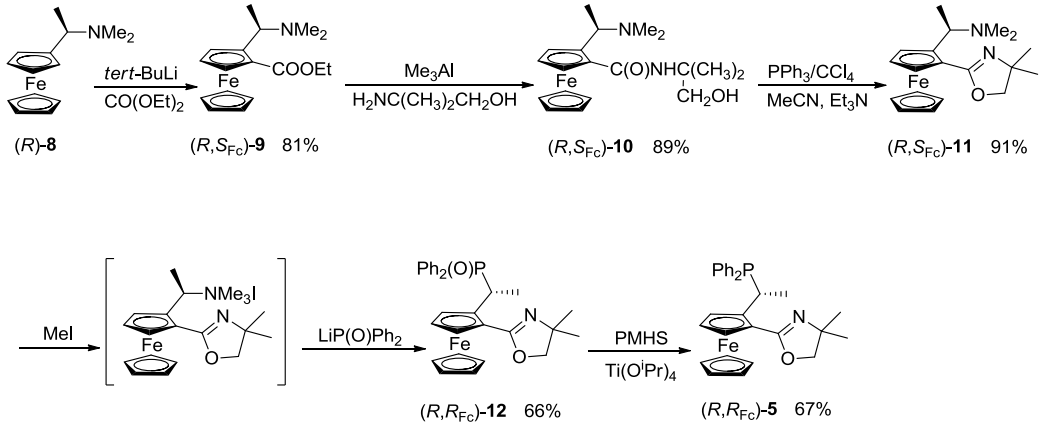
Chart 2.

In this contribution we report the synthesis of three additional ligands (**5**, **6**, and **7**), all of which feature structural modifications of our previously described ligands **2**–**4**[15]. Like **2**, ligand **5** lacks a stereogenic center at the oxazoline ring while ligands **6** and **7** represent analogs of **3** lacking the stereogenic center of the side chain. Complexes [$RuCl_2(PPh_3)(L)$] of all ligands (L = **2**–**7**) have been extensively tested in transfer hydrogenations and hydrogenations of fourteen ketones. The transfer hydrogenation results obtained with **2**–**7** are compared to those of FOXAP ligand **1**. In addition, a qualitative comparison of the results obtained for transfer hydrogenations and hydrogenations under transfer hydrogenation conditions is given. Attempts are also made to identify structural features responsible for product enantioselectivity as well as for the experimentally determined product absolute configuration.

Results and Discussion

Synthesis of Ligands 5–7 and Complexes 19–23

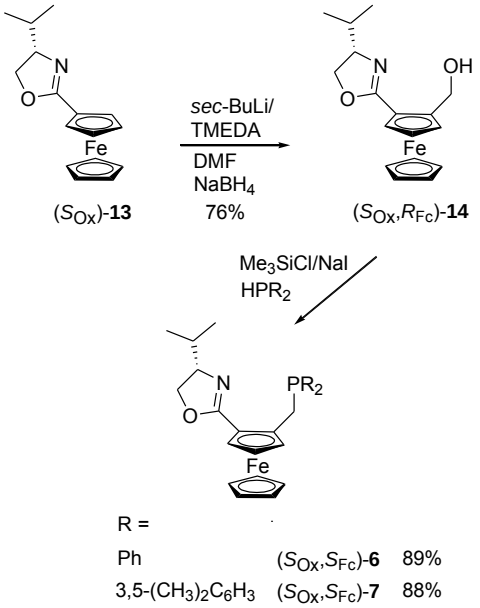
Ligand **5** was prepared by the same synthesis route as ligands **2**–**4** (Scheme 1). Amino-ester (R,S_{Fc})-**9**,[16] which is easily accessible from Ugi's amine, (R)-**8**, was reacted in the presence of trimethylaluminium[8g] with 1,1-dimethyl-2-hydroxyethylamine to give amide (R,S_{Fc})-**10**. In the next step this compound was transformed according to the methodology of Appel[17] to oxazoline (R,S_{Fc})-**11**. Oxazoline **11** was treated with methyl iodide in acetonitrile and the crude ammonium salt was subsequently reacted with diphenylphosphinyl lithium to give the phosphinyl-substituted derivative (R,R_{Fc})-**12**.[18] Reduction of this phosphine oxide with polymethylhydrosiloxane (PMHS) in the presence of titanium isopropoxide[19] gave the desired phosphine-oxazoline (R,R_{Fc})-**5**.



Scheme 1.

The synthesis of ligands **6** and **7** was achieved in only two steps from commercially available ferrocenyl oxazoline (S_{Ox})-**13** (Scheme 2). Alcohol (S_{Ox},R_{Fc})-**14** was obtained from (S_{Ox})-**13** in analogy to a reported procedure.[20] Subsequent reactions with diphenylphosphine or bis(3,5-dimethylphenyl)phosphine in the presence of chlorotrimethylsilane and sodium iodide gave ligands (S_{Ox},S_{Fc})-**6** and (S_{Ox},S_{Fc})-**7**, respectively.[21]

Complexes [$RuCl_2(PPh_3)(L)$] of ligands **5**–**7** (**19**–**21**) were prepared in exactly the manner as the complexes of ligands **1**–**4** (Scheme 3, **16**–**18**). Reaction of phosphino-oxazoline ligands **5**–**7** with [$RuCl_2(PPh_3)_3$] in toluene at r.t. gave the desired unsaturated green complexes **19**–**21**. Two of these complexes, (R_{Ox},R_{Fc})-**17** and (S_{Ox},S_{Fc})-**21**, were further treated at r.t. with acetonitrile and the coordinatively saturated yellow-orange acetonitrile complexes (R_{Ox},R_{Fc})-**22** and (S_{Ox},S_{Fc})-**23** were obtained (Scheme 3, bottom).



Scheme 2.

$[RuCl_2(PPh_3)_3]$ + L $\xrightarrow[\text{toluene}]{}$ $[RuCl_2(PPh_3)(L)]$

L =	complex =
(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**
(R,R_{Fc})-**2**	(R_{Fc})-**16**
(R,S_{Ox},R_{Fc})-**3**	(S_{Ox},R_{Fc})-**17**
(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**
(R,S_{Ox},R_{Fc})-**4**	(S_{Ox},R_{Fc})-**18**
(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**
(R,R_{Fc})-**5**	(R_{Fc})-**19**
(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**
(S_{Ox},S_{Fc})-**7**	(S_{Ox},S_{Fc})-**21**

$[RuCl_2(PPh_3)(L)] \xrightarrow{CH_3CN} [RuCl_2(CH_3CN)(PPh_3)(L)]$

L =	complex =
(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**22**
(S_{Ox},S_{Fc})-**7**	(S_{Ox},S_{Fc})-**23**

Scheme 3.

Single crystals were obtained for two unsaturated, (R_{Ox},R_{Fc})-**17** and (R_{Fc})-**19**, and two coordinatively saturated, (R_{Ox},R_{Fc})-**22** and (S_{Ox},S_{Fc})-**23**, complexes and their molecular structures in the solid state were studied by X-ray diffraction. Details of these X-ray crystallography studies are given in the Experimental section and in the Supporting Information (Table S4). The absolute configuration of each compound was determined from the X-ray anomalous dispersion effects and was consistent with the

chemical evidence. Views of the molecular structures of these compounds are shown in Figures 1 and 2 (for selected geometric data see Supporting Information, Tables S5–S8). The molecular structure of (S_{Ox},S_{Fc})-**15** had been determined previously[6c] and the data for this compound were used for comparative purposes (retrieved from Cambridge Structural Database, refcode MAPLUK; for a view of the molecular structure see Supporting Information, Figure S5).

As in the case of (S_{Ox},S_{Fc})-**15**, complexes (R_{Ox},R_{Fc})-**17** and (R_{Fc})-**19** adopt a square pyramidal rather than a trigonal bipyramidal molecular structure. In all cases the free coordination site is well shielded by either a PPh_3 phenyl (**15** and **17**) or an oxazoline methyl (**19**) group. However, as compared to **15** the overall molecular structures and the ligand arrangements differ significantly in **17** and **19**. In **15** the chlorides adopt a *cis* disposition while in **17** and **19** the chlorides are located *trans* to each other. Furthermore, in **15** the triphenylphosphino phosphorus is *cis* to the oxazoline nitrogen but is *trans* in **17** and **19**.

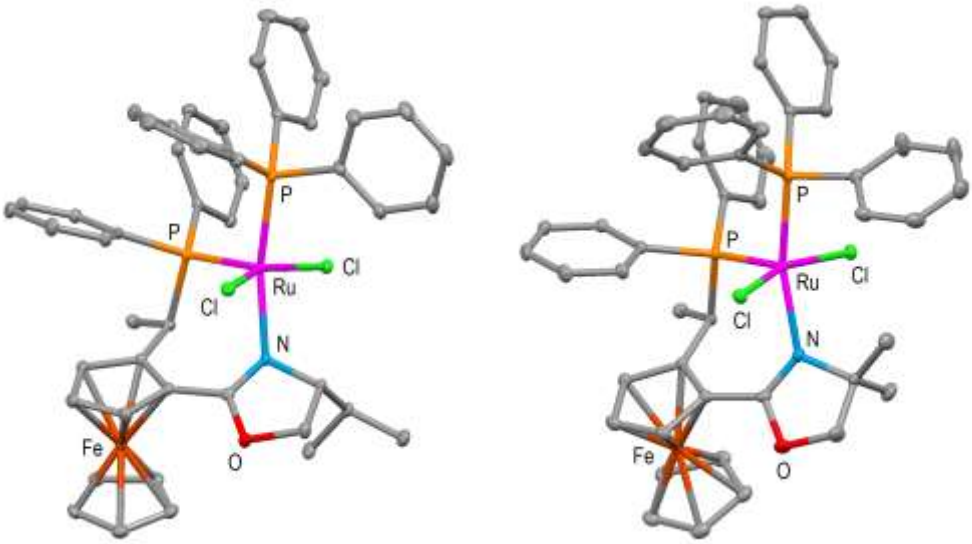


Figure 1. Molecular structures of complexes (R_{Ox},R_{Fc})-**17** (left) and (R_{Fc})-**19** (right). Hydrogen atoms omitted for clarity.

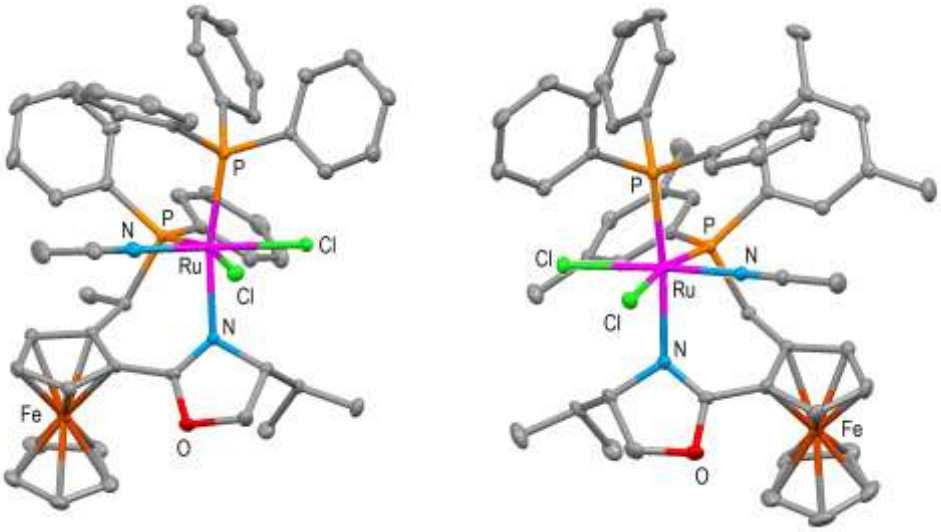


Figure 2. Molecular structures of complexes (R_{Ox},R_{Fc})-**22** (left) and (S_{Ox},S_{Fc})-**23** (right). Hydrogen atoms omitted for clarity.

As expected, the acetonitrile complexes (R_{Ox},R_{Fc})-**22** and (S_{Ox},S_{Fc})-**23** adopt an octahedral geometry, but – in contrast to **17** and **19** – the chlorides are positioned in a *cis* rather than in a *trans* arrangement and the acetonitrile nitrogen is *trans* to one of the chlorides.

Catalysis

Complexes **16**–**21** were screened in asymmetric hydrogenations (HY) and transfer hydrogenations (THY) of a total of fourteen ketones (Chart 3). All catalysis reactions were carried out with the isolated and fully characterized catalyst precursors **16**–**21**. Complex **15** was used as the reference.

Transfer Hydrogenations (THY)

Transfer hydrogenations of thirteen ketones were carried out with complexes **15**–**21**. It was our initial intention to compare the performance of the newly synthesized complexes **16**–**21** with that of the well-established FOXAP ligand **15**. In order to ensure maximum comparability, all complexes (**15**–**21**) were synthesized according to the same protocol.

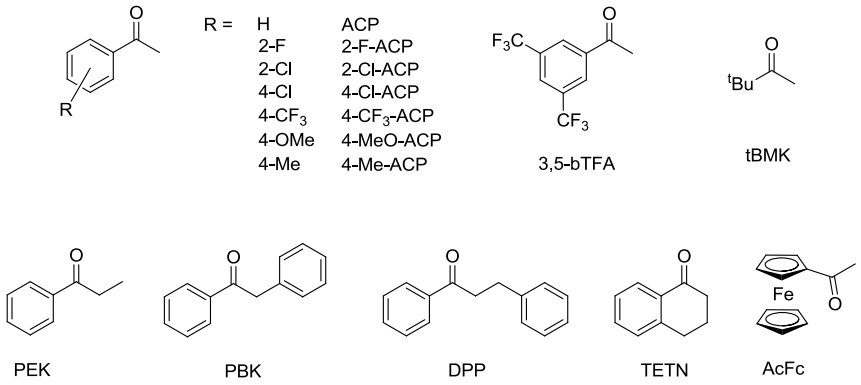


Chart 3.

The THY conditions were first optimized with respect to the type and amount of base, the substrate concentration, the substrate-to-catalyst ratio (S/C), and the reaction temperature (for details see Supporting Information). Based on this optimization procedure, the majority of all screening reactions were carried out at r.t. using 1 mmol of substrate in 51 mL of 2-propanol (19.6 mM), 0.5% catalyst and 2% base (S/C/base = 200/1/4). In an effort to ensure consistency and reproducibility, all transfer hydrogenations were carried out at least twice.

The THY results obtained with acetophenone (ACP) as the substrate and complexes **15**–**21** as the catalyst precursors are summarized in Table 1. It is important to note that as a result of the availability of ligands for these THY reactions, complexes with a different absolute configuration at the ferrocene unit were applied. Complexes **15**, **20** and **21** had the (S_{Fc}) absolute configuration and derivatives **16**–**19** had the (R_{Fc}) configuration.

In all THYs carried out, we observed that the product enantiomeric excess was significantly dependent on the reaction time due to product racemization. After reaching a maximum value, the product e.e. dropped continuously. Therefore, in all Tables the maximum product e.e. values obtained at the given reaction time are listed together with the corresponding conversion data.

Table 1. THY results for acetophenone obtained with complexes **15**–**21**.

entry	substrate	complex	time	% conv.	% e.e.	abs. conf.
1	ACP	(S_{Ox},S_{Fc})-**15**	20 min	99	96	*R*
2	ACP	(R_{Fc})-**16**	20 min	98	92	*S*
3	ACP	(R_{Ox},R_{Fc})-**17**	10 min	99	**98**	*S*
4	ACP	(S_{Ox},R_{Fc})-**17**	5 h	18	69	*R*
5	ACP	(R_{Ox},R_{Fc})-**18**	15 min	>99	**97**	*S*
6	ACP	(S_{Ox},R_{Fc})-**18**	6 h	90	73	*R*
7	ACP	(R_{Fc})-**19**	4 h	78	95	*S*
8	ACP	(R_{Fc})-**19**[a]	1 h	85	95	*S*
9	ACP	(S_{Ox},S_{Fc})-**20**	30 min	96	93	*R*
10	ACP	(S_{Ox},S_{Fc})-**21**	20 min	97	89	*R*

[a] pre-prepared catalyst

For example, with reference (S_{Ox},S_{Fc})-**15** as the catalyst precursor the reaction was essentially finished after 20 min (99% conversion) and the product (*R*)-1-phenylethanol was formed with 96% e.e. (Table 1, entry 1). In order to estimate the effect of product racemization, enantiopure (*S*)-1-phenylethanol was treated for 24 hours in 2-propanol either with base only (KO^iPr) or it was exposed to the actual catalysis conditions [KO^iPr/(S_{Ox},S_{Fc})-**15**]. The treatment with base only led to a loss of 5% e.e. while under catalysis conditions this process took place much faster and after 24 hours a reduction of 30% e.e. was observed.

The results obtained for complexes **16**–**21** to some extent depended on the substitution pattern and relative configuration of the ligands used (**2**–**7**). The best results were obtained with ligands (*R*,R_{Ox},R_{Fc})-**3** and (*R*,R_{Ox},R_{Fc})-**4** [complexes (R_{Ox},R_{Fc})-**17** and (R_{Ox},R_{Fc})-**18**], both of which bear a mono-substituted oxazoline ring and have the (R_{Ox},R_{Fc}) relative configuration. As compared to the reference, both complexes gave rise to slightly higher product e.e.s in a shorter reaction time (**17**: 98%; **18**: 97%; Table 1, entries 3 and 5). Removal of the oxazoline substituent or the side chain methyl group [ligands (*R*,R_{Fc})-**2** and (S_{Ox},S_{Fc})-**6**; complexes (R_{Fc})-**16** and (S_{Ox},S_{Fc})-**20**] resulted mainly in a decrease in the product e.e. (92% and 93%, Table 1, entries 2 and 9). Replacement of the diphenylphosphino group of (S_{Ox},S_{Fc})-**6** by a dixylylphosphino unit [ligand (S_{Ox},S_{Fc})-**7**, complex (S_{Ox},S_{Fc})-**21**] led to a further reduction in the product enantiomeric excess (89%, Table 1, entry 10).

Interestingly, the use of ligand (R,R_{Fc})-**5** [complex (R_{Fc})-**19**], which bears two methyl groups at the oxazoline position 4, led to a significant decrease in the rate of the reaction and after 4 hours a conversion of only 78% was achieved. However, this problem could be partly overcome without loss of product e.e. (95%) when the catalyst precursor (R_{Fc})-**19** was reacted for 2 hours with base in 2-propanol before the substrate was added. The use of such a pre-prepared catalyst led to a markedly faster THY process and after 1 hour the product was obtained with 85% conversion and 95% e.e. (after 2 h: 97% conversion and 94% e.e.; Table 1, entries 7 and 8). It is clear that with catalyst precursor (R_{Fc})-**19** the formation of the active catalyst is slowed down significantly. From the chemical and structural evidence it is plausible to assume that the transformation of the ruthenium dichloride complex into the active ruthenium hydride catalyst is slowed down by steric hindrance caused by one of the oxazoline methyl substituents, which efficiently shields the free coordination site at the metal center [Figure 1 (right) and Supporting Information, Figure S2, C47].

The strongest influences on the THY reactions were observed when, instead of complexes (R_{Ox},R_{Fc})-**17** and (R_{Ox},R_{Fc})-**18**, the diastereomers (S_{Ox},R_{Fc})-**17** and (S_{Ox},R_{Fc})-**18** [ligands (R,S_{Ox},R_{Fc})-**3** and (R,S_{Ox},R_{Fc})-**4**] were applied – both of which have the (S) configuration at the oxazoline carbon C4. In these cases, not only did the reaction become very slow but the product absolute configuration also changed from (S) to (R).

Generally, the product of (S) absolute configuration was obtained either when ligands were used that adopted an (R_{Fc}) absolute configuration at the ferrocene unit but lacked a further stereogenic unit at the oxazoline ring (**16** and **19**) or when ligands with (R_{Ox},R_{Fc}) relative and absolute configuration were applied (**15**, **17**, **18**, **20** and **21**). However, with phenyl or 2-propyl substituents a change in the configuration at the oxazoline carbon C4 led to ligands having the (S_{Ox},R_{Fc}) relative configuration and this resulted in a change of product absolute configuration from (S) to (R) (Table 1, entries 4 and 6). Interestingly, an identical dependence of the product absolute configuration on the relative configuration of the ligand was reported by Dai and co-workers.[6d] In the transfer hydrogenation of acetophenone with the diastereomeric complexes (S_{Ox},S_{Fc})-**15** and (S_{Ox},R_{Fc})-**15** [ligands (S_{Ox},S_{Fc})-**1** and (S_{Ox},R_{Fc})-**1**] the product with the same (R) absolute configuration was formed. This means that – as with **17** and **18** – the use of diastereomers (R_{Ox},R_{Fc})-**15** and (S_{Ox},R_{Fc})-**15** leads to products of opposite absolute configuration.

Since the THY of acetophenone was best accomplished with complex (R_{Ox},R_{Fc})-**17**, the dependence of this process on the substrate concentration as well as on the

substrate-to-catalyst ratio was investigated. The dependence on the substrate concentration was found to be rather small. While a 0.02 molar solution was transformed within 10 minutes into the product with 98% e.e. (99% conversion), a 0.2 molar solution gave the product with 95% e.e. (90% conversion) within 5 minutes. Only when a 0.02 molar solution was used and the S/C ratio was increased from 200/1 to 1000/1 did the conversion become slow and the maximum product e.e. dropped from 98% to 81%.

In summary, with the exception of complexes (S_{Ox},R_{Fc})-**17** and (S_{Ox},R_{Fc})-**18**, all catalyst precursors gave results that are comparable to those of the reference. Surprisingly, for these complexes the type of oxazoline substituent as well as the oxazoline substitution pattern [non- (**16**), mono- (**17**, **18**) or di-substitution (**19**)] hardly had any influence on the product enantiomeric excess (**16**: 92%; **17**: 98%; **18**: 97%; **19**: 95% e.e.).

In order to study the influence of steric and electronic effects, 2- and 4-substituted acetophenones (2-F-ACP, 2-Cl-ACP, 4-CF_3-ACP, 4-MeO-ACP, and 4-Me-ACP) together with additional phenyl-alkylketones (phenyl-ethylketone, PEK; phenyl-benzylketone, PBK; 1,3-diphenylpropan-1-one, DPP) were tested. Furthermore, a bicyclic system (1-tetralone, TETN), acetylferrocene (AcFc), and one dialkylketone (*tert*-butylmethylketone, tBMK) were used. For these transfer hydrogenations only those catalyst precursors were used that gave the best results with acetophenone as the substrate [reference (S_{Ox},S_{Fc})-**15**, (R_{Ox},R_{Fc})-**17**, (R_{Ox},R_{Fc})-**18**, (R_{Fc})-**19**, and (S_{Ox},S_{Fc})-**20**].

In the majority of test reactions (Table 2) nearly quantitative conversion could be achieved within 5–30 minutes. Only with the electron-rich substrates 4-MeO-ACP and AcFc, with the sterically more demanding bicyclic 1-tetralone (TETN) and, especially, with dialkyl ketone tBMK was a prolonged reaction time required. The best results were obtained with complex (R_{Ox},R_{Fc})-**17** [ligand (R,R_{Ox},R_{Fc})-**3**]. In a few cases comparable (Table 2, entries 2/3, 13/14, 18/19, 21/22, and 24/25) or even better (entries 27/28 and 30/31) results could be obtained on using complex (R_{Ox},R_{Fc})-**18**. In particular, the THY of acetylferrocene gave the product with significantly higher enantiomeric excess, albeit with a very low level of conversion (entry 31).

As for acetophenone, when the THY reactions were carried out with catalyst precursors of (R_{Fc}) or (R_{Ox},R_{Fc}) configuration and with aryl-alkyl ketones as the substrates, products with the (*S*) absolute configuration were obtained consistently. As one might expect, the product enantiomeric excess was also dependent on the substrate substitution pattern (Figure 3). On employing reference **15** and ACP as the

substrates, products with 96% e.e. were obtained. Substitution of the ACP phenyl ring with electron-donating or electron-withdrawing substituents led – with the exception of 4-Me-ACP (96% e.e.) – to a small reduction in the e.e. values (90–93%) but replacing the methyl group of ACP with other alkyl substituents did not significantly affect the product e.e. (95–97%; PEK, PBK, DPP). Even the bicyclic compound 1-tetralone (TETN) was reduced with an enantiomeric excess of 93%.

Similar trends were seen when the best performing complex (R_{Ox},R_{Fc})-**17** was used (Figure 3). As compared to the reference, slightly better product e.e.s were obtained with seven substrates (ACP, 4-Cl-ACP, 4-MeO-ACP, 4-Me-ACP, PBK, DPP, and AcFc) while slightly lower product e.e.s were found in the THY reactions of substrates 4-CF_3-ACP and PEK. Interestingly, with both 2-substituted acetophenones (2-F-ACP and 2-Cl-ACP) and with tetralone a sharp drop in product e.e. was found (2-F-ACP: 50%, 2-Cl-ACP: 75%, TETN: 74%).

In summary, in a number of cases complex (R_{Ox},R_{Fc})-**17** gave slightly better results than the original FOXAP analog **15**. However, we noticed with surprise that although complexes **15** and **17** adopt totally different molecular structures (**15**: Supporting Information, Figure S5 and **17**: Figure 1, left) their performance in THY reactions was found to be remarkably similar. Except for the 2-substituted acetophenones and 1-tetralone, structural changes in the substrates were comparably reflected in changes of product e.e. values. For complexes **15** and **17** as the catalyst precursors, we consider these findings to be the result of similar asymmetric induction mechanisms.[22]

In their original report on THYs of aryl-alkyl and dialkyl ketones with FOXAP ruthenium dichloride complexes such as [$RuCl_2$((S_{Ox},S_{Fc})-**1**)], Uemura and co-workers commented on mechanistic features and presented some NMR evidence for a ruthenium dihydride-based reaction mechanism.[6b] Furthermore, for aryl-alkyl ketones a transition state model was presented (Figure 4, top). Based on this report we questioned whether the THY reactions with complex (R_{Ox},R_{Fc})-**17** or similar complexes could be explained in terms of a related transition state model. Like Uemura's proposal, our suggestion is based on structural and chemical evidence. Our model was mainly derived from the molecular structures of complexes (R_{Ox},R_{Fc})-**22** and (S_{Ox},S_{Fc})-**23** (Figure 2) and is shown in Figure 4 (bottom).

Table 2. Best THY results obtained for all substrates screened.

entry	substrate	complex	time	% conv.	% e.e.	abs. conf.
1	ACP	(S_{Ox},S_{Fc})-**15**	20 min	99	96	*R*
2	ACP	(R_{Ox},R_{Fc})-**17**	10 min	99	**98**	*S*
3	ACP	(R_{Ox},R_{Fc})-**18**	15 min	>99	97	*S*
4	2-F-ACP	(S_{Ox},S_{Fc})-**15**	5 min	99	**91**	*R*
5	2-F-ACP	(R_{Ox},R_{Fc})-**17**	30 min	99	50	*S*
6	2-Cl-ACP	(S_{Ox},S_{Fc})-**15**	20 min	>99	**90**	*R*
7	2-Cl-ACP	(R_{Ox},R_{Fc})-**17**	5 min	>99	75	*S*
8	4-Cl-ACP	(S_{Ox},S_{Fc})-**15**	10 min	>99	93	*R*
9	4-Cl-ACP	(R_{Ox},R_{Fc})-**17**	5 min	98	**94**	*S*
10	4-CF_3-ACP	(S_{Ox},S_{Fc})-**15**	5 min	99	**90**	*R*
11	4-CF_3-ACP	(R_{Ox},R_{Fc})-**17**	20 min	>99	87	*S*
12	4-MeO-ACP	(S_{Ox},S_{Fc})-**15**	20 min	80	90	*R*
13	4-MeO-ACP	(R_{Ox},R_{Fc})-**17**	20 min	82	**95**	*S*
14	4-MeO-ACP	(R_{Ox},R_{Fc})-**18**	20 min	75	**95**	*S*
15	4-Me-ACP	(S_{Ox},S_{Fc})-**15**	10 min	97	96	*R*
16	4-Me-ACP	(R_{Ox},R_{Fc})-**17**	10 min	97	**98**	*S*
17	PEK	(S_{Ox},S_{Fc})-**15**	10 min	99	**97**	*R*
18	PEK	(R_{Ox},R_{Fc})-**17**	20 min	99	96	*S*
19	PEK	(R_{Ox},R_{Fc})-**18**	15 min	94	96	*S*
20	PBK	(S_{Ox},S_{Fc})-**15**	10 min	>99	95	*R*
21	PBK	(R_{Ox},R_{Fc})-**17**	20 min	>98	**97**	*S*
22	PBK	(R_{Ox},R_{Fc})-**18**	2 h	>99	95	*S*
23	DPP	(S_{Ox},S_{Fc})-**15**	10 min	>99	94	*R*
24	DPP	(R_{Ox},R_{Fc})-**17**	15 min	99	**96**	*S*
25	DPP	(R_{Ox},R_{Fc})-**18**	20 min	>99	94	*S*
26	TETN	(S_{Ox},S_{Fc})-**15**	5 min	71	**93**	*R*
27	TETN	(R_{Ox},R_{Fc})-**17**	30 min	32	74	*S*
28	TETN	(R_{Ox},R_{Fc})-**18**	20 min	21	81	*S*
29	AcFc	(S_{Ox},S_{Fc})-**15**	30 min	24	80	*R*
30	AcFc	(R_{Ox},R_{Fc})-**17**	30 min	10	81	*S*
31	AcFc	(R_{Ox},R_{Fc})-**18**	30 min	16	**93**	*S*
32	tBMK	(S_{Ox},S_{Fc})-**15**	24 h	85	**>99**	*S*
33	tBMK	(S_{Ox},S_{Fc})-**20**	24 h	36	21	*R*

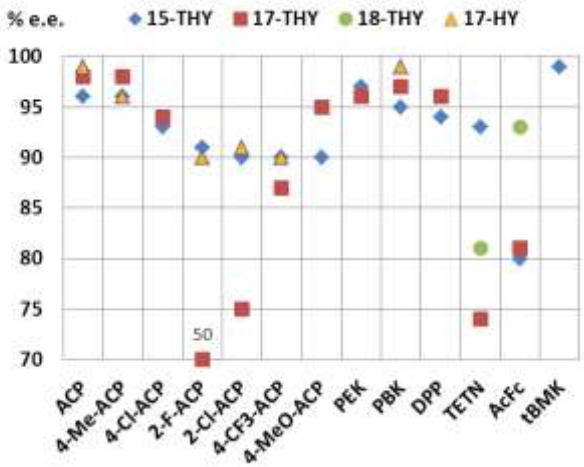


Figure 3. Best product enantiomeric excesses (% e.e.) obtained in THYs and HYs.

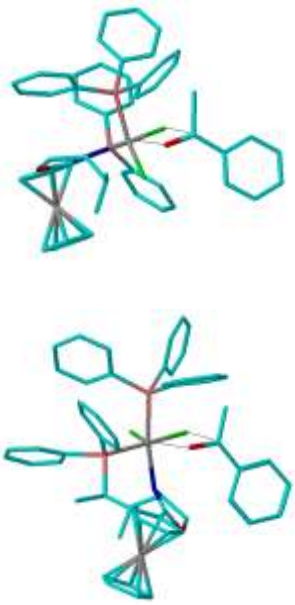


Figure 4. Transition state models for the THYs of aryl-alkyl ketones with systems [RuH_2((R_{Ox},R_{Fc})-**1**)]/ACP (top; adopted from Cambridge Structural Database, refcode MAPLUK and reference [6c]), and [RuH_2((R_{Ox},R_{Fc})-**3**)]/ACP (bottom).

This model is able to explain why acetophenone or similar ketones coordinate to the (R_{Ox},R_{Fc})-configured metal hydride with their (*Si*) side and therefore the product of (*S*) absolute configuration is obtained. Furthermore, unlike with the FOXAP-type ligands, phenyl *ortho*- and *meta*-substituents are more prone to interfere with the oxazoline-substituted ferrocenyl Cp-ring and this view correlates well with the observed drop in product enantiomeric excess when substrates 2-F-ACP, 2-Cl-ACP and TETN

were used. On the other hand, the steric influence of phenyl *para*-substituents or of different side chain alkyl groups is expected to be much smaller.

It is also clear from this model that, unlike with FOXAP-type catalysts, the oxazoline substituents at carbon C4 and the substrate are located far from each other and therefore in most cases a change in this substituent only leads to a rather small change of the product enantiomeric excess. However, when the phenyl groups of the diphenylphosphino unit are replaced by xylyl groups a greater steric interaction between one xylyl group and the substrate is expected and this is again consistent with the experimentally observed drop in enantioselectivity when catalyst precursor **20** was replaced by **21** (Table 1, entries 9 and 10).

Hydrogenations (HY)

Since complexes of the type [$RuCl_2$(FOXAP)] are known to be very efficient catalyst precursors for asymmetric hydrogenation reactions,[13] the full set of novel complexes **16**–**21** was screened against seven aryl-alkyl ketones on a customized Symyx high throughput screening system.[23] Typical results are listed in Table 3.

As for the THYs, all hydrogenations were carried out with isolated and fully characterized catalyst precursors. Reactions were run for 16 hours at a temperature of 25 °C under hydrogen gas at a pressure of 25 bar, a substrate concentration of 41.67 µmol/500 µL (83 mM), and a substrate-to-catalyst ratio of 25:1. Different combinations of solvents and bases were tested. Either 2-propanol in combination with KO^tBu or toluene/water (9:1) with bases K_2CO_3 or NaOH were applied. The former solvent/base system is typically used in transfer hydrogenation reactions[22] while the latter conditions were found to give excellent results in the hydrogenation of ketones using ruthenium-FOXAP-based catalysts, even on a large industrial scale.[13]

For all substrates screened, reaction conditions were identified that gave products with quantitative or nearly quantitative conversion and – with the exception of bis(3,5-trifluoromethyl)acetophenone – with an enantiomeric excess equal to or better than 90%.

As in transfer hydrogenations, catalyst precursor (R_{Ox},R_{Fc})-**17** gave the best results (Table 3, entries 2, 9, 12, 15, and 17), especially when it was used in combination with the solvent/base system toluene/H_2O/K_2CO_3.

Only in the case of phenyl benzyl ketone, PBK, did the ^{i}PrOH/KO^tBu system prove to be superior to the toluene/H_2O system, resulting in quantitative conversion and

a product enantiomeric excess of 99% (entry 20). Once again, in a few cases complex (R_{Ox},R_{Fc})-**18** gave equally good results to (R_{Ox},R_{Fc})-**17** [Table 3, entries 2/6 (ACP), and 17/19 (4-Me-ACP)].

With respect to the substrate substitution pattern and to the relative configuration of ligands and complexes, the hydrogenation and transfer hydrogenation results obtained with (R_{Ox},R_{Fc})-**17** showed almost identical trends (Figure 3). Only in the hydrogenation of the 2-substituted acetophenones 2-F-ACP and 2-Cl-ACP were significantly better results obtained in comparison to transfer hydrogenations. Interestingly, the hydrogenation reactions of substrates 2-F-ACP and 2-Cl-ACP showed a very strong dependence on the solvent/base system used. When the reactions were carried out in the 2-PrOH/KO^{t}Bu system instead of the toluene/H_2O/K_2CO_3 system – as in transfer hydrogenations – a very significant drop in product enantiomeric excess was seen [Table 3, entries 10/11 (2-F-ACP) and 13/14 (2-Cl-ACP)].

Comparison of Transfer Hydrogenation and Hydrogenation Results

Despite the fact that significantly different reaction conditions were used for the transfer hydrogenation and hydrogenation reactions, a number of surprising similarities were observed. Of all the novel catalyst precursors tested, complex (R_{Ox},R_{Fc})-**17** and, in a few cases, complex (R_{Ox},R_{Fc})-**18** gave the best results. A similar dependence of the product enantiomeric excesses on the catalyst precursors and on the substrate substitution pattern was found (Tables 2 and 3, Figure 2).

Table 3. Typical HY results obtained with complexes **16**–**21**.

entry	substrate	complex	solvent	base	% conv.	% e.e.	abs. conf.
1	ACP	(R_{Fc})-**16**	Tol/H_2O	K_2CO_3	99	95	*S*
2	ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	K_2CO_3	99	**99**	*S*
3	ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	NaOH	99	97	*S*
4	ACP	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	95	94	*S*
5	ACP	(S_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	95	58	*R*
6	ACP	(R_{Ox},R_{Fc})-**18**	Tol/H_2O	K_2CO_3	99	**98**	*S*
7	ACP	(R_{Ox},R_{Fc})-**18**	Tol/H_2O	NaOH	99	96	*S*
8	ACP	(S_{Ox},R_{Fc})-**18**	^{i}PrOH	KO^{t}Bu	95	62	*R*
9	2-F-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	K_2CO_3	97	**90**	*S*
10	2-F-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	NaOH	96	87	*S*
11	2-F-ACP	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	99	70	*S*
12	2-Cl-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	K_2CO_3	95	**91**	*S*
13	2-Cl-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	NaOH	98	90	*S*
14	2-Cl-ACP	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	80	82	*S*
15	4-CF_3-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	K_2CO_3	97	**90**	*S*
16	4-CF_3-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	NaOH	97	89	*S*
17	4-Me-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	K_2CO_3	100	**97**	*S*
18	4-Me-ACP	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	NaOH	99	95	*S*
19	4-Me-ACP	(R_{Ox},R_{Fc})-**18**	Tol/H_2O	K_2CO_3	100	**97**	*S*
20	PBK	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	>99	**99**	*S*
21	PBK	(R_{Ox},R_{Fc})-**18**	^{i}PrOH	KO^{t}Bu	>99	93	*S*
22	3,5-bTFA	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	K_2CO_3	95	40	*S*
23	3,5-bTFA	(R_{Ox},R_{Fc})-**18**	Tol/H_2O	NaOH	95	41	*S*

For both transfer hydrogenations and hydrogenations an identical correlation between catalyst and product absolute configuration was found. All of the ligands and complexes with an (R_{Fc}) (**2** and **5**) or (R_{Ox},R_{Fc}) absolute configuration (**3**, **4**, **6**, and **7**) led to the transformation of all tested aryl-alkyl ketones into alcohols with the (*S*) absolute configuration. Only when the relative configuration of ligands **3** and **4** (complexes **17** and **18**) was changed from (R_{Ox},R_{Fc}) to (S_{Ox},R_{Fc}) did the product absolute configuration change from (*S*) to (*R*) (Table 3, entries 2/5 and 6/8).

Table 4. Comparison of THY and HY results obtained with (R_{Ox},R_{Fc})-**17**.

	THY[a]		HY	
substrate	% conv.	% e.e.	% conv.	% e.e.
ACP	99	98 (*S*)[d]	99	99[b] (*S*)[d]
2-F-ACP	99	50 (*S*)	97	90[b] (*S*)
2-Cl-ACP	>99	75 (*S*)	95	91[b] (*S*)
4-CF_3-ACP	>99	87 (*S*)	97	90[b] (*S*)
4-Me-ACP	97	98 (*S*)	>99	97[b] (*S*)
PBK	>99	97 (*S*)	>99	99[c] (*S*)

[a] Solvent/base: 2-PrOH/KO^{i}Pr; [b] solvent/base: Tol/H_2O/K_2CO_3; [c] solvent/base: 2-PrOH/KO^{t}Bu; [d] product absolute configuration

Furthermore, for all substrates tested, hydrogenation conditions could be identified that gave the desired product with comparable or higher enantiomeric excess than in transfer hydrogenations (Table 4). This was especially the case when the hydrogenations were carried out in the toluene/H_2O/K_2CO_3 solvent/base system. Clearly these reaction conditions lead to much slower product racemization than in the 2-PrOH/KO^{t}Bu system.

Conclusion

Ruthenium complexes of the type [$RuCl_2PPh_3$(L)] (**16**–**21**) of eight bidentate phosphine-oxazoline ligands (L = **2**–**7**), all of which contain a ferrocenylethyl (**16**–**19**, L = **2**–**5**) or a ferrocenylmethyl (**20** and **21**, L = **6** and **7**) backbone, were synthesized, characterized and screened in transfer hydrogenations and hydrogenations against a total of one dialkyl and thirteen aryl-alkyl ketones. In addition, for comparative purposes, the transfer hydrogenations of all substrates were carried out with one analogous and well-established FOXAP ruthenium complex (**15**). The molecular structures of two catalyst precursors and of two corresponding acetonitrile complexes were studied by X-ray diffraction. One catalyst precursor in particular (**17**) delivered products with an enantiomeric excess of up to 98%. A comparison of the transfer hydrogenation results obtained with the novel complex **17** and those of the analogous FOXAP-based catalyst **15** showed surprising similarities. Although complexes **15** and **17** adopt totally different molecular structures, most substrates were transformed into products with nearly identical enantioselectivity. Except for the 2-substituted acetophenones and 1-tetralone, structural changes in the substrates were comparably reflected in changes in the

product e.e. values. Based on structural and chemical evidence, a transition state model was proposed that allows qualitative rationalization of the absolute configuration of the product as well as the dependence of e.e. values on the substitution patterns of substrates and ligands.

Complexes **16**–**21** were also used as catalyst precursors in hydrogenations of seven aryl-alkyl ketones and once again complex **17** delivered the best results, with product e.e. values of up to 99%. A comparison with the transfer hydrogenation results revealed that, for all substrates tested, hydrogenation conditions could be identified that gave product with comparable or higher enantiomeric excess. Furthermore, a similar dependence of the product enantiomeric excesses on the catalyst precursors and on the substrate substitution patterns was found. Also, for both transfer hydrogenations and hydrogenations an identical dependence of catalyst and product absolute configuration was seen.

Based on these results, we expect that in most cases the use of catalyst precursors [$RuCl_2PPh_3$(P-oxazolines)] in the transfer hydrogenation and hydrogenation of aryl-alkyl ketones will deliver products of comparable enantiomeric excess. In these particular cases, the transfer hydrogenation results may be used to estimate achievable hydrogenation results. Based on the finding that complexes **15**–**21** gave highly comparable results in the hydrogenations as well as in the transfer hydrogenations of ketones, one might speculate whether this could be the result of comparable mechanistic features. Work is currently underway to clarify this possibility.

Experimental Section

General procedure for the asymmetric transfer hydrogenation of ketones

To a solution of ruthenium complex (0.005 mmol, 0.5%) in anhydrous 2-PrOH (50 mL) were added a solution of ketone (1 mmol) in 2-PrOH (1 mL) and a solution of 2-PrOK (0.02 mmol) in 2-PrOH (5% w/v). The reaction mixture was stirred at r.t. and the progress of the reaction was monitored by periodically analyzing 1 mL samples of the reaction mixture. The samples were quenched with aqueous H_3PO_4 (0.5 M, 0.5 mL), diethyl ether (1 mL) was added and the product was extracted. The organic phase was washed with brine and filtered through a short plug of $MgSO_4$ (top) and aluminum oxide 90 (bottom) using 2-PrOH as the eluent. The filtrate obtained was analyzed either by GC or HPLC (for details see Supporting Information).

General procedure for the asymmetric hydrogenation of ketones

For hydrogenations a customized Symyx high throughput screening system was used. All hydrogenations were carried out for 16 hours at r.t. under hydrogen gas at a pressure of 25 bar and a substrate to catalyst ratio of 25:1. Typically the following amounts of substrate, catalyst, and solvent were used: 41.67 µmol substrate and 1.67 µmol catalyst precursor in a total of 500 µL solvent (for analysis data see Supporting Information).

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Supporting Information Available Text giving full experimental descriptions and spectroscopic data for all newly synthesized ligands and complexes as well as detailed hydrogenation and transfer hydrogenation data. Crystallographic and geometric data for four ruthenium complexes of the type [$RuCl_2(PPh_3)(L)$] and [$RuCl_2(MeCN)(PPh_3)(L)$] are given in the Supporting text and in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Supporting Information

Ruthenium complexes of phosphino-substituted ferrocenyloxazolines in the asymmetric hydrogenation and transfer hydrogenation of ketones: a comparison.

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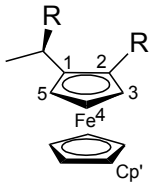
Contents

General considerations

All reactions required inert conditions and were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried by standard procedures and distilled before use. Preparative chromatographic separations were performed under gravity on standardised aluminium oxide 90 (MERCK). Petroleum ether with a boiling range of 55–65 °C was used for chromatography. Abbreviations: PE: petroleum ether; DEE: diethyl ether; EA: ethyl acetate; DCM: dichloromethane; THF: tetrahydrofurane. The following substrates were purchased and were used without further purification: (*S*)-(4-isopropyloxazolin-2-yl)ferrocene (TCI), acetophenone (FLUKA), propiophenone (FLUKA), pinacolone (ABCR). All other substrates were purified by chromatography before use: 2'-fluoroacetophenone (FLUKA), 2'-chloro-acetophenone (ALDRICH), 4'-chloroacetophenone (ALDRICH), 4'-(trifluoromethyl)-acetophenone (ALDRICH), 1-(4-methoxyphenyl)ethanone (ALDRICH), 4'-methyl-acetophenone (ALDRICH), 3′,5′-Bis(trifluoromethyl)acetophenone (ALDRICH), 1,2-diphenylethanone (ALDRICH), 1,3-diphenyl-1-propanone (ABCR), acetylferrocene (ABCR) and 1-tetralone (ABCR).

NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ or CD_2Cl_2. Chemical shifts (δ) are given relative to $CHCl_3$ (^{1}H: 7.26 ppm), $CDCl_3$ (^{13}C: 77.0 ppm), CH_2Cl_2 (^{1}H: 5.32 ppm), CD_2Cl_2 (^{13}C: 54.0 ppm) and 85% H_3PO_4 (^{31}P: 0 ppm). The coupling constants in $^{13}C\{^1H\}$ spectra are due to ^{13}C-^{31}P coupling. For signal assignment the following terms were used: s, bs, d, dd, t, q and m refer to singlet, broad singlet, doublet, doublet of doublets, triplet, quartet and multiplet, respectively. The terms Ph^A and Ph^B were used to distinguish phenyl groups of diphenylphosphino units. A general atom numbering scheme used for proton and carbon assignment is given below. Melting points were determined on a Kofler melting point apparatus and are uncorrected. Mass spectra were recorded on instruments Finnigan MAT 900 S, MAT 95 S and Bruker ESI-Qq aoTOF. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Conversion and e.e. values were measured with use of an Agilent 7890 A GC or an Agilent 1200 HPLC. Elemental analysis was carried out at the Mikroanalytisches Labor at the Faculty of Chemistry (University of Vienna).



Atom numbering scheme for NMR assignment of ferrocenes.

(*R*,*R*$_{Fc}$)-2-(4,5-Dihydro-4,4-dimethyloxazol-2-yl)-1-[1-(diphenylphosphino)ethyl]-ferrocene, (*R*,*R*$_{Fc}$)-5

To a solution of (*R*,*R*$_{Fc}$)-**12** (1.029 g, 2.01 mmol) in THF (5 mL) were added polymethylhydrosiloxane (1.3 g) and titanium(IV) isopropoxide (2.29 g, 8.04 mmol) and the resulting mixture was reacted for 30 minutes at 80 °C. After cooling to r.t. and without further workup was the resulting dark solution chromatographed twice on aluminium oxide 90 under inert conditions and with use of deoxygenated solvents (eluent: PE/EA/TEA = 5/5/1). A third chromatography with use of PE/EA/TEA = 8/2/1 as the eluent gave the desired product as a yellow semisolid (669 mg, 1.35 mmol, 67 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.17 (s, 3H, C(C*H*$_3$)(CH$_3$)), 1.18 (s, 3H, C(CH$_3$)(C*H*$_3$)), 1.51 (dd, *J* = 7.2 Hz, *J* = 15.1 Hz, 3H, CHC*H*$_3$), 3.58, 3.78 (AB, *J* = 7.6 Hz, 2H, CH$_2$), 4.14 (s, 5H, Cp'), 4.26–4.32 (m, 3H, H3/5 + H4 + C*H*CH$_3$), 4.63 (dd, *J* = 2.6 Hz, *J* = 1.6 Hz, 1H, H3/5), 6.84–6.88 (m, 2H, Ph^{A}-*ortho*), 7.05–7.09 (m, 2H, Ph^{A}-*meta*), 7.11–7.15 (m, 1H, Ph^{A}-*para*), 7.40–7.44 (m, 3H, Ph^{B}-*meta* + Ph^{B}-*para*), 7.62–7.66 (m, 2H, Ph^{B}-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): *δ* 18.8 (d, *J* = 20.9 Hz, CH*C*H$_3$), 27.9 (C(*C*H$_3$)(CH$_3$)), 28.3 (C(CH$_3$)(*C*H$_3$)), 29.3 (d, *J* = 14.3 Hz, *C*HCH$_3$), 66.5 (*C*(CH$_3$)$_2$), 68.4 (C3/5), 68.7 (C4), 68.8 (C3/5), 69.8 (Cp'), 77.8 (CH$_2$O), 93.8 (C1), 127.4 (d, *J* = 6.1 Hz, 2C, Ph^{A}-*meta*), 127.7 (Ph^{A}-*para*), 128.3 (d, *J* = 7.8 Hz, 2C, Ph^{B}-*meta*), 129.2 (Ph^{B}-*para*), 132.9 (d, *J* = 17.6 Hz, 2C, Ph^{A}-*ortho*), 134.7 (d, *J* = 19.7 Hz, 2C, Ph^{B}-*ortho*), 135.9 (d, *J* = 16.4 Hz, Ph^{B}-*ipso*), 137.1 (d, *J* = 17.6 Hz, Ph^{A}-*ipso*), 164.1 (C=N), C2 not observed. ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 11.4 (PPh$_2$). HR-MS (ESI, MeOH/MeCN): *m/z* = [M+Na]$^{+}$ calcd. 518.1312 for $C_{29}H_{30}FeNOPNa$; found: 518.1319. $[\alpha]^{20}_{\lambda}$ (nm): –273 (589), –307 (578), –468 (546) (*c* 0.275, $CHCl_3$).

(*S*$_{Ox}$,*S*$_{Fc}$)-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-diphenylphosphino-methyl]-ferrocene, (*S*$_{Ox}$,*S*$_{Fc}$)-6

To a stirred solution of (*S*$_{Ox}$,*R*$_{Fc}$)-**14** (1.5 g, 4.58 mmol) and sodium iodide (1.37 g, 9.14 mmol) in acetonitrile (40 mL) was added chlorotrimethylsilane (1.08 g, 11.45 mmol) which led to a change of color from orange to red. After additional stirring for 10 min at r.t. diphenylphosphine (938 mg, 5.04 mmol) was added and this resulted in a change of

color from red to orange. The reaction mixture was stirred for 24 h at r.t.; subsequently without previous workup the crude product was purified by chromatography under inert conditions with deoxygenated solvents on aluminium oxide 90. The solvent mixture PE/DEE = 20/1 removed excess of diphenylphosphine and PE/EA/TEA = 2/1/1 + 10% DCM eluted the title compound as a red oil (2.02 g, 4.08 mmol, 89 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, J = 6.7 Hz, 3H, CH(CH_3)(CH_3)), 1.04 (d, J = 6.7 Hz, 3H, CH(CH_3)(CH_3)), 1.74–1.84 (m, 1H, CH(CH_3)$_2$), 3.38 (dd, J = 2.5 Hz, J = 13.8 Hz, 1H, CHHP), 3.89–3.92 (m, 1H, H5), 3.92–4.00 (m, 3H, CHHO + CHHP + CHN), 4.07–4.10 (m, 1H, H4), 4.09 (s, 5H, Cp'), 4.21–4.28 (m, 1H, CHHO), 4.61 (dd, J = 1.5 Hz, J = 2.5 Hz, 1H, H3), 7.27–7.37 (m, 6H, Ph-*meta* + Ph-*para*), 7.39–7.45 (m, 2H, Ph-*ortho*), 7.45–7.51 (m, 2H, Ph-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 18.5 (CH(CH_3)(CH_3)), 18.9 (CH(CH_3)(CH_3)), 29.2 (d, J = 14.9 Hz, CH_2P), 32.8 (CH(CH_3)$_2$), 68.3 (C4), 69.2 (2C, CH_2O + C3), 69.5 (C2), 70.3 (Cp'), 71.6 (d, J = 5.3 Hz, C5), 72.6 (CHN), 86.1 (d, J = 16.9 Hz, C1), 127.9 (Ph-*para*), 128.2 (d, J = 6.2 Hz, 2C, Ph-*meta*), 128.3 (d, J = 7.2 Hz, 2C, Ph-*meta*), 128.8 (Ph-*para*), 132.2 (d, J = 17.5 Hz, 2C, Ph-*ortho*), 133.8 (d, J = 19.7 Hz, 2C, Ph-*ortho*), 139.0 (d, J = 124.7 Hz, Ph-*ipso*), 141.6 (d, J = 115.8 Hz, Ph-*ipso*), 165.6 (C=N). ^{31}P NMR (162 MHz, $CDCl_3$): δ –10.0 (PPh_2). HR-MS (EI, 30 °C): m/z = $[M + H]^+$ calcd. 496.1492 for $C_{29}H_{31}FeNOP$; found: 496.1491. $[\alpha]^{20}_{\lambda}$ (nm): –50.5 (589), –59.9 (578), –112 (546) (c 0.192, $CHCl_3$).

(S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[bis(3,5-dimethylphenyl)-phosphinomethyl]-ferrocene, (S_{Ox},S_{Fc})-7

To a solution of (S_{Ox},R_{Fc})-**14** (1.5 g, 4.58 mmol) and sodium iodide (1.37 g, 9.14 mmol) in acetonitrile (40 mL) was added chlorotrimethylsilane (1.08 g, 11.45 mmol) which resulted in a change of color from orange to red. After further stirring the solution at r.t. for 10 min bis(3,5-dimethylphenyl)phosphine (1.39 g, 5.04 mmol) was added and this led to a slow change of color from red to orange. The reaction mixture was stirred for 24 h at r.t. and subsequently without previous workup the crude product was chromatographed under inert conditions with deoxygenated solvents on aluminium oxide 90. A mixture of PE/DEE = 20/1 removed excess of diphenylphosphine while with use of PE/EA/TEA = 2/1/1 + 10% DCM the title compound was obtained as a red oil (2.23 g, 4.04 mmol, 88 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.08 (d, J = 6.7 Hz, 3H, CH(CH_3)(CH_3)), 1.74–1.85 (m, 1H, CH(CH_3)$_2$), 2.29 (s, 6H, CH_3^A), 2.31 (s, 6H, CH_3^B), 3.39 (dd, J = 2.4 Hz, J = 14.0 Hz, 1H, CHHP), 3.89 (d, J = 14.0 Hz, 1H, CHHP), 3.94–3.97 (m, 1H, H5), 3.98–4.02 (m, 2H, CHHO + CHN), 4.11 (t, J = 2.6 Hz, 1H, H4), 4.12 (s, 5H, Cp'), 4.22–4.30 (m, 1H, CHHO), 4.62 (dd, J = 1.6 Hz, J = 2.6 Hz, 1H, H3), 6.92 (s, 1H, Ph^A-*para*), 6.98 (s, 1H, Ph^B-*para*), 7.07

(d, *J* = 7.3 Hz, 2H, Ph^A-*ortho*), 7.11 (d, *J* = 7.6 Hz, 2H, Ph^B-*ortho*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 18.6 ($CH(CH_3)(CH_3)$), 19.0 ($CH(CH_3)(CH_3)$), 21.2 (2C, CH_3^A), 21.3 (2C, CH_3^B), 28.9 (d, *J* = 14.6 Hz, CH_2P), 32.9 ($CH(CH_3)_2$), 68.1 (C4), 69.0 (C3), 69.2 (CH_2O), 69.4 (d, *J* = 3.4 Hz, C2), 70.2 (Cp'), 71.7 (d, *J* = 6.2 Hz, C5), 72.6 (CHN), 86.5 (d, *J* = 17.1 Hz, C1), 129.8 (Ph^A-*para*), 129.9 (d, *J* = 17.8 Hz, 2C, Ph^A-*ortho*), 130.5 (Ph^B-*para*), 131.3 (d, *J* = 20.0 Hz, 2C, Ph^B-*ortho*), 137.4 (d, *J* = 6.1 Hz, 2C, Ph-*meta*), 137.5 (d, *J* = 6.8 Hz, 2C, Ph-*meta*), 138.2 (d, *J* = 14.8 Hz, Ph-*ipso*), 139.3 (d, *J* = 15.5 Hz, Ph-*ipso*), 165.5 (C=N). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* –10.6 (PPh_2). HR-MS (EI, 30 °C): *m/z* = $[M + H]^+$ calcd. 552.2119 for $C_{33}H_{39}FeNOP$; found: 552.2116. $[\alpha]^{20}_{\lambda}$ (nm): –56.8 (589), –64.0 (578), –117.4 (546) (*c* 0.236, $CHCl_3$).

(*R*,S_{Fc})-1-[1-(*N*,*N*-Dimethylamino)ethyl]-2-[(2-hydroxy-1,1-dimethylethyl)amino-carbonyl]-ferrocene, (*R*,S_{Fc})-10

A solution of 2-amino-2-methyl-1-propanol (600 mg, 6.73 mmol) in toluene (10 mL) was cooled to 0 °C and treated with a solution of trimethylaluminium in toluene (2.0 M, 6.68 mL, 13.36 mmol). After stirring for 5 min the solution was warmed to r.t. and stirring was continued for additional 45 min. Subsequently, a solution of (*R,S*$_{Fc}$)-**9** (2.00 g, 6.07 mmol) in toluene (10 mL) was added and the resulting mixture was stirred for 16 h at 126 °C. After cooling to r.t., the reaction mixture was quenched carefully by addition of water and the phases were separated. The aqueous phase was extracted with EA (3 x 50 mL), the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by chromatography on aluminium oxide 90 (eluent PE/EA/TEA = 1/1/1) to give the title compound as an orange solid (2.01 g, 5.40 mmol, 89 % yield). Mp: 117 °C. ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.27 (s, 3H, $C(CH_3)(CH_3)$), 1.34 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 1.36 (s, 3H, $C(CH_3)(CH_3)$), 2.11 (s, 6H, $N(CH_3)_2$), 3.63 (bs, 2H, CH_2O), 4.11 (q, *J* = 6.9 Hz, 1H, $CHCH_3$), 4.13 (s, 5H, Cp'), 4.22–4.28 (m, 2H, H4 + H5), 4.90 (dd, *J* = 2.5 Hz, *J* = 1.7 Hz, 1H, H3), 6.20 (bs, 1H, OH), 10.19 (bs, 1H, NH). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 7.4 ($CHCH_3$), 25.1 (2C, $C(CH_3)_2$), 38.7 (2C, $N(CH_3)_2$), 55.6 ($C(CH_3)_2$), 57.9 ($CHCH_3$), 68.0 (C4), 69.9 (C5), 70.6 (Cp'), 71.9 (CH_2O), 73.8 (C3), 79.1 (C2), 86.0 (C1), 171.5 (C=O). HR-MS (EI, 30 °C): *m/z* = $[M]^+$ calcd. 372.1500 for $C_{19}H_{28}FeN_2O_2$; found: 372.1465. $[\alpha]^{20}_{\lambda}$ (nm): –8.8 (589), –4.8 (578), 28.0 (546) (*c* 0.25, $CHCl_3$).

(*R*,S_{Fc})-2-(4,5-Dihydro-4,4-dimethyloxazol-2-yl)-1-[1-(*N*,*N*-dimethylamino)ethyl]-ferrocene, (*R*,S_{Fc})-11

To a solution of (*R*,S_{Fc})-**10** (3 g, 8.06 mmol) in acetonitrile (50 mL) were added triphenylphosphine (3.17 g, 12.09 mmol), triethylamine (3.67 g, 36.27 mmol) and

carbon tetrachloride (11.16 g, 72.54mmol) and the resulting mixture was stirred for 16 h at r.t. The reaction was quenched by addition of water (10 mL) and the resulting mixture was acidified with an aqueous solution of citric acid. The aqueous phase was extracted with DCM (3 x 50 mL) and the organic phases were discarded. The aqueous phase was made basic by addition of an aqueous sodium hydroxide solution, followed by extraction with DCM (2 x 50 mL). The combined organics were washed with water and brine, dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by chromatography on aluminium oxide 90 with use of PE/EA/TEA = 5/5/1 as the eluent to give the title compound as an orange-red solid (2.60 g, 7.34 mmol, 91 % yield). Mp: 105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 6H, $C(CH_3)_2$), 1.52 (d, J = 7.0 Hz, 3H, $CHCH_3$), 2.02 (s, 6H, $N(CH_3)_2$), 3.92, 4.04 (AB, J = 7.9 Hz, 2H, CH_2O), 4.13 (s, 5H, Cp'), 4.25–4.28 (m, 1H, H5), 4.30 (t, J = 2.5 Hz, 1H, H4), 4.38 (q, J = 7.0 Hz, 1H, $CHCH_3$), 4.3 (dd, J = 2.5 Hz, J = 1.5 Hz, 1H, H3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 17.6 ($CHCH_3$), 28.2 ($C(CH_3)(CH_3)$), 28.4 ($C(CH_3)(CH_3)$), 40.5 (2C, $N(CH_3)_2$), 54.7 ($CHCH_3$), 66.9 ($C(CH_3)_2$), 68.5 (C4), 69.2 (C3), 69.5 (C5), 69.9 (C2), 70.2 (Cp'), 78.4 (CH_2O), 88.4 (C1), 164.9 (C=N). HR-MS (EI, 30 °C): m/z = $[M]^+$ calcd. 354.1394 for $C_{19}H_{26}FeN_2O$; found: 354.1365. $[\alpha]^{20}_{\lambda}$ (nm): –336.2 (589), –373.0 (578), –581.0 (546) (c 0.315, $CHCl_3$).

(R,R_{Fc})-2-(4,5-Dihydro-4,4-dimethyloxazol-2-yl)-1-[1-(diphenylphosphinyl)ethyl]-ferrocene, (R,R_{Fc})-12

To a stirred solution of (R,S_{Fc})-**11** (1.66 g, 4.69 mmol) in acetonitrile (10 mL) was added iodomethane (2.0 g, 14.07 mmol) at 0 °C and stirring was continued for 1 h at r.t. The solvent was removed under reduced pressure and the crude salt was dried in vacuo. In a separate flask, diphenylphosphine oxide (1.043 g, 5.16 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of n-BuLi in hexane (1.6 M, 3.52 mL, 5.63 mmol) was added dropwise and the resulting mixture was stirred at r.t. for 1 h. The solvent was removed under reduced pressure and the crude diphenylphosphinyl lithium was dried in vacuo. The methiodide salt was then redissolved in THF (20 mL) and was transferred to the dried diphenylphosphinyl lithium. The resulting mixture was heated to 85 °C for 1 h, cooled to r.t. and subsequently quenched by addition of water. The product was extracted with EA (3 x 50 mL), the combined organics were washed with water and brine and dried over $MgSO_4$. After removing the solvent on a rotary evaporator, the crude product was chromatographed on aluminium oxide using EA/TEA/methanol = 100/10/1 as the eluent. The title compound was obtained as a yellow solid (1.59 g, 3.11 mmol, 66 % yield). Mp: 178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 6H, $C(CH_3)_2$), 1.66 (dd, J = 7.4 Hz, J = 15.5 Hz, 3H, $CHCH_3$), 3.68, 3.70 (AB, J = 7.8 Hz, 2H, CH_2O), 4.14 (s, 5H, Cp'), 4.33 (t, J = 2.6 Hz, 1H, H4), 4.50 (dd, J = 2.6

Hz, *J* = 1.6 Hz, 1H, H3), 4.48–456 (m, *J* = 7.4 Hz, 1H, C*H*CH_3), 4.59–4.62 (m, 1H, H5), 7.07–7.13 (m, 2H, Ph^A-*meta*), 7.14–7.22 (m, 2H, Ph^A-*ortho*), 7.23–7.29 (m, 1H, Ph^A-*para*), 7.51–7.59 (m, 3H, Ph^B-*meta* + Ph^B-*para*), 7.96–8.04 (m, 2H, Ph^B-*ortho*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 15.0 (d, *J* = 2.2 Hz, CH*C*H_3), 28.2 (C(*C*H_3)(CH_3)), 28.4 (C(CH_3)(*C*H_3)), 32.4 (d, *J* = 65.2 Hz, *C*HCH_3), 67.0 (*C*(CH_3)$_2$), 68.5 (C3), 69.1 (C4), 69.2 (C2), 69.9 (Cp'), 70.2 (d, *J* = 2.3 Hz, C5), 77.7 (CH_2O), 88.8 (d, *J* = 1.5 Hz, C1), 127.3 (d, *J* = 11.7 Hz, 2C, Ph^A-*meta*), 128.5 (d, *J* = 10.8 Hz, 2C, Ph^B-*meta*), 130.9 (d, *J* = 3.2 Hz, Ph^A-*para*), 131.5 (d, *J* = 9.2 Hz, Ph^A-*ortho*), 131.6 (d, *J* = 3.1 Hz, Ph^B-*para*), 131.7 (d, *J* = 8.4 Hz, 2C, Ph^B-*ortho*), 132.2 (d, *J* = 62.0 Hz, Ph^A-*ipso*), 163.8 (C=N), Ph^B-*ipso* not observed. ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 36.3 (P(O)PPh_2). HR-MS (EI, 30 °C): m/z = $[M]^+$ calcd. 511.1363 for $C_{29}H_{30}FeNO_2P$; found: 511.1368. $[\alpha]^{20}_{\lambda}$ (nm): –100 (589),–112 (578), –172 (546) (*c* 0.240, $CHCl_3$).

(S_{Ox},R_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-hydroxymethyl-ferrocene, (S_{Ox},R_{Fc})-14

To a solution of (*S*)-**13** (1.0 g, 3.37 mmol) and tetramethylethylenediamine (431 mg, 3.71 mmol) in anhydrous DEE (30 mL) cooled to –78 °C was added dropwise a solution of *sec*-BuLi in cyclohexane (1.4 M, 2.9 mL, 4.04 mmol). Stirring was continued for 2 h at –78 °C. Subsequently, dimethylformamide (259 mg, 3.54 mmol) was added to the reaction mixture. Stirring was continued for 30 min at –78 °C and for additional 45 min at r.t. The reaction mixture was quenched by addition of water, the phases were separated and the aqueous phase was extracted with DEE (3 x 50 mL). The combined organics were washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. In the next step the crude product (1.02 g, 3.14 mmol) was dissolved in MeOH (20 mL), cooled to 0 °C and $NaBH_4$ (356.4 mg, 9.42 mmol) was added in portions. The reaction mixture was stirred for 2 h at r.t. Subsequently, the reaction mixture was quenched by addition of water at 0 °C, the phases were separated and the aqueous phase was extracted with DEE (3 x 50 mL). The combined organics were washed with water and brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was chromatographed on aluminum oxide 90 using PE/EA = 5/1 as the eluent. The desired compound was obtained as an orange solid (0.84 g, 2.57 mmol, 76 % yield). The spectroscopic data are in accordance with those reported in reference 20.

Synthesis of neutral ruthenium complexes – General procedure

A mixture of oxazoline ligand (1.00 mmol) and $[RuCl_2(PPh_3)_3]$ (0.95 mmol) dissolved in freshly distilled and degassed toluene (3 mL) was stirred for 16 h at r.t. Degassed

hexane was added to precipitate the product. The green solid was filtered off under inert conditions and was washed with freshly distilled and degassed hexane (2 × 2 mL). The crude product was redissolved in toluene, precipitated by addition of hexane and dried *in vacuo* to yield a green powder.

Dichloro[(*R*,R_{Fc})-2-[4,5-Dihydro-4,4-dimethyloxazol-*κ*N)-1-[1-(diphenylphosphino)-ethyl-*κ*P]-ferrocene]triphenylphosphine ruthenium, [$RuCl_2(PPh_3)$((*R*,R_{Fc})-5)], (R_{Fc})-19

Starting from (*R*,R_{Fc})-**5** (250 mg, 0.505 mmol) and following the general procedure given above the desired product was obtained as a green powder (369.8 mg, 397.8 mmol, 79 % yield). Single crystals suitable for X-ray crystallography were obtained from a solution of the product in Tol/PE by slow evaporation of the solvents. Mp: > 230 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.24 (s, 3H, C(C*H*$_3$)(CH_3)), 1.51 (dd, *J* = 7.1 Hz, *J* = 13.9 Hz, 3H, CHC*H*$_3$), 1.69 (s, 3H, C(CH_3)(C*H*$_3$)), 3.87–3.89 (m, 1H, H5), 3.88 (t, *J* = 2.7 Hz, 1H, H4), 4.01, 4.23 (AB, *J* = 7.7 Hz, 2H, CH_2), 4.14 (s, 5H, Cp'), 4.29–4.39 (m, 1H, C*H*CH_3), 4.85 (dd, *J* = 2.5 Hz, *J* = 1.5 Hz, 1H, H3), 6.86–7.56 (m, 25H, Ph). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): *δ* 18.8 (d, *J* = 6.3 Hz, CH*C*H_3), 23.5 (C(*C*H_3)(CH_3)), 28.6 (C(CH_3)(*C*H_3)), 39.7 (d, *J* = 21.3 Hz, *C*HCH_3), 69.0 (C4), 69.6 (bs, C5), 68.8 (*C*(CH_3)$_2$), 70.2 (Cp'), 72.4 (C3), 79.8 (CH_2), 125–138 (aromatic C, unresolved), C1, C2 and C=N not observed. ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 48.3 (d, *J* = 43.6 Hz, PPh_3), 95.1 (d, *J* = 43.6 Hz, PN). HR-MS (ESI in MeOH/MeCN): *m/z* [M-Cl+ACN]$^+$ calcd for $C_{49}H_{48}FeN_2OP_2RuCl$: 935.1323, found: 935.1344. $[\alpha]^{20}_{\lambda}$ (nm): +1159 (589), +1154 (578), +1072 (546) (*c* 0.022, $CHCl_3$).

Dichloro[(S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl-*κ*N)-1-[1-diphenyl-phosphinomethyl-*κ*P]-ferrocene]triphenylphosphine ruthenium, [$RuCl_2(PPh_3)$((S_{Ox},S_{Fc})-6)], (S_{Ox},S_{Fc})-20

Starting from (S_{Ox},S_{Fc})-**6** (0.80 g, 1.62 mmol) and following the general procedure given above the desired product was obtained as a green powder (1.03 g, 1.11 mmol, 69 % yield). Mp: > 230 °C (dec.). ^{1}H NMR (400 MHz, CD_2Cl_2): *δ* 0.88 (d, *J* = 7.1 Hz, 3H, CH(C*H*$_3$)(CH_3)), 1.06 (d, *J* = 6.7 Hz, 3H, CH(CH_3)(C*H*$_3$)), 2.99–3.11 (m, 1H, C*H*(CH_3)$_2$), 3.37–3.48 (m, 1H, C*H*HP), 3.48–3.52 (m, 1H, H5), 3.89 (t, *J* = 2.6 Hz, 1H, H4), 4.15–4.21 (m, 1H, CHN), 4.18 (s, 5H, Cp'), 4.22–4.29 (m, 1H, C*H*HO), 4.52 (dd, *J* = 3.9 Hz, *J* = 8.3 Hz, 1H, CH*H*O), 4.66 (dd, *J* = 10.1 Hz, *J* = 12.8 Hz, 1H, CH*H*P), 4.71 (dd, *J* = 2.6 Hz, *J* = 1.6 Hz, 1H, H3), 6.93–7.60 (m, 25H, Ph). ^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): *δ* 15.2 (CH(*C*H_3)(CH_3)), 19.5 (CH(CH_3)(*C*H_3)), 28.1 (*C*H(CH_3)$_2$), 39.6 (d, *J* = 26.1 Hz, CH_2P), 67.6 (CH_2O), 69.3 (C4), 70.8 (Cp'), 72.6 (C3), 72.9 (CHN), 73.6 (bs, C5), 82.3

(d, *J* = 1.9 Hz, C1), 125.5 (Ph-*para*), 127.0 (d, *J* = 10.4 Hz, 2C, Ph-*meta*), 127.5 (d, *J* = 10.0 Hz, 2C, Ph-*meta*), 128.5 (Ph-*para*), 133.5 (d, *J* = 7.8 Hz, 2C, Ph-*ortho*), 135.3 (d, *J* = 10.4 Hz, 2C, Ph-*ortho*), 173.7 (C=N), C_2 and Ph-*ipso* not observed, signals of PPh_3 are very broad and unresolved. ^{31}P NMR (162 MHz, CD_2Cl_2): *δ* 48.3 (d, *J* = 43.7 Hz, PPh_3), 84.6 (*J* = 43.8 Hz, PN). Anal. Calcd for $C_{47}H_{45}Cl_2FeNOP_2Ru$ x toluene: C, 63.47; H, 5.23; N, 1.37. Found: C, 63.92; H, 5.14; N, 1.38. HR-MS (ESI in MeOH/MeCN): *m/z* $[M\text{-}Cl]^+$ calcd for $C_{47}H_{45}ClFeNOP_2Ru$: 894.1058, found: 894.1062. $[\alpha]^{20}_{\lambda}$ (nm): –766 (589), –860 (578), –996 (546) (*c* 0.022, CH_2Cl_2).

Dichloro[(S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl-*κ*N)-1-[bis(3,5-dimethylphenyl)phosphinomethyl-*κ*P]-ferrocene]triphenylphosphine ruthenium, [$RuCl_2(PPh_3)$((S_{Ox},S_{Fc})-7)], (S_{Ox},S_{Fc})-21

Starting from (S_{Ox},S_{Fc})-**7** (950 mg, 1.72 mmol) and following the general procedure given above the desired product was obtained as a green powder (1.05 g, 1.07 mmol, 62 % yield). Mp: > 230 °C (dec.). ^{1}H NMR (400 MHz, CD_2Cl_2): *δ* 0.88 (d, *J* = 7.2 Hz, 3H, CH(C*H*$_3$)(CH$_3$)), 1.06 (d, *J* = 6.7 Hz, 3H, CH(CH$_3$)(C*H*$_3$)), 2.01 (s, 6H, CH$_3$), 2.08 (s, 6H, CH$_3$), 3.03–3.14 (m, 1H, C*H*(CH$_3$)$_2$), 3.35–3.45 (m, 1H, C*H*HP), 3.51–3.54 (m, 1H, H5), 3.89 (t, *J* = 2.6 Hz, 1H, H4), 4.12–4.19 (m, 1H, CHN), 4.18 (s, 5H, Cp'), 4.21–4.27 (m, 1H, C*H*HO), 4.50 (dd, *J* = 4.0 Hz, *J* = 8.3 Hz, 1H, CH*H*O), 4.60 (dd, *J* = 9.8 Hz, *J* = 12.8 Hz, 1H, CH*H*P), 4.7 (dd, *J* = 2.6 Hz, *J* = 1.6 Hz, 1H, H3), 6.35–7.74 (m, 21H, Ph). ^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): *δ* 15.3 (CH(*C*H$_3$)(CH$_3$)), 19.5 (CH(CH$_3$)(*C*H$_3$)), 21.2 (2C, CH$_3$), 21.3 (2C, CH$_3$), 28.1 (*C*H(CH$_3$)$_2$), 39.4 (d, *J* = 26.5 Hz, CH$_2$P), 67.4 (C2), 67.5 (d, *J* = 1.6 Hz, CH$_2$O), 69.1 (C4), 70.7 (Cp'), 72.4 (C3), 72.9 (CHN), 73.7 (d, *J* = 1.5 Hz, C5), 82.7 (d, *J* = 1.5 Hz, C1), 131.2 (d, *J* = 7.7 Hz, 2C, Ph-*ortho*), 131.3 (d, *J* = 3.0 Hz, Ph-*para*), 131.4 (d, *J* = 2.4 Hz, Ph-*para*), 133.0 (d, *J* = 10.5 Hz, 2C, Ph-*ortho*), 136.4 (d, *J* = 11.5 Hz, 2C, Ph-*meta*), 137.0 (d, *J* = 10.8 Hz, 2C, Ph-*meta*), 140.4, 140.45, 140.9, 150.0 (2C, Ph-*ipso*), 173.8 (C=N), signals of PPh_3: very broad and unresolved. ^{31}P NMR (162 MHz, CD_2Cl_2): *δ* 48.9 (d, *J* = 44.2 Hz, PPh_3), 83.4 (d, *J* = 43.5 Hz, PN). Anal. Calcd for $C_{51}H_{53}Cl_2FeNOP_2Ru$ x 0.25 toluene: C, 62.81; H, 5.49; N, 1.39. Found: C, 62.38; H, 5.25; N, 1.38. HR-MS (ESI in MeOH/MeCN): *m/z* $[M\text{-}Cl]^+$ calcd for $C_{51}H_{53}ClFeNOP_2Ru$: 950.1684, found: 950.1692. $[\alpha]^{20}_{\lambda}$ (nm): –805 (589), –880 (578), –1005 (546) (*c* 0.020, CH_2Cl_2).

Synthesis of the saturated acetonitrile complexes – General procedure

The ruthenium complex (0.05 mmol) was dissolved at r.t. in freshly distilled and degassed acetonitrile (2 mL) which resulted in an immediate change of color from green

to yellow. After 15 minutes stirring, the solvent was removed under reduced pressure. The complexes were characterized without further purification.

Dichloro(acetonitrile)[(*R*,R_{Ox},R_{Fc}))-2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl-*κ*N)-1-[1-(diphenylphosphino)ethyl-*κ*P]-ferrocene]triphenylphosphine ruthenium, [$RuCl_2(CH_3CN)(PPh_3)$((*R*,R_{Ox},R_{Fc})-3)], (R_{Ox},R_{Fc})-22

Starting from complex (R_{OX})**-17** (50 mg, 0.053 mmol) and following the general procedure given above the desired product was obtained. Single crystals suitable for X-ray crystallography were obtained from a DCM solution by slow evaporation of the solvent. Mp: > 230 °C (dec.). ^{1}H NMR (400 MHz, CD_2Cl_2): *δ* 1.07 (d, *J* = 7.2 Hz, 3H, CH(C*H*$_3$)(CH_3)), 1.09 (d, *J* = 6.8 Hz, 3H, CH(CH_3)(C*H*$_3$)), 1.11 (s, 3H, CH_3CN), 1.16 (dd, *J* = 7.1 Hz, *J* = 10.8 Hz, 3H, CHC*H*$_3$), 2.97–3.07 (m, 1H, C*H*(CH_3)$_2$), 3.29–3.39 (m, 1H, C*H*CH_3), 4.15 (s, 5H, Cp'), 4.26–4.29 (m, 1H, H4), 4.31–4.35 (m, 1H, H5), 4.43 (t, *J* = 8.4 Hz, 1H, C*H*HO), 4.67 (dd, *J* = 2.2 Hz, *J* = 8.4 Hz, 1H, CH*H*O), 4.75–4.79 (m, 1H, H3), 5.48–5.53 (m, 1H, NCH), 6.63 (t, *J* = 8.1 Hz, 2H, Ph^A-*ortho*), 6.86 –7.59 (m, 21H), 7.81–7.95 (m, 2H, Ph^B-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): *δ* 4.6 (*C*H_3CN), 15.6 (CH(*C*H_3)(CH_3)), 17.0 (d, *J* = 5.0 Hz, CH*C*H_3), 19.1 (CH(CH_3)(*C*H_3)), 31.1 (*C*H(CH_3)$_2$), 41.1 (d, *J* = 19.2 Hz, C*H*CH_3), 68.9 (C4), 69.9 (CH_2O), 70.3 (C3), 71.0 (C5), 71.2 (Cp'), 73.1 (CHN), 126.8–136 (Ph), Signals from C1, C2, C=N, CN not observed. ^{31}P NMR (162 MHz, CD_2Cl_2): *δ* 44.4 (d, *J* = 29.8 Hz, *P*Ph_3), 68.4 (d, *J* = 29.8 Hz, *P*N). HR-MS (ESI in MeOH/MeCN): *m/z* [M-Cl]$^+$ calcd for $C_{50}H_{50}ClFeN_2OP_2Ru$: 949.1480, found: 949.11486.

Dichloro(acetonitrile)[(S_{Ox},S_{Fc})-2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl-*κ*N)-1-[bis(3,5-dimethylphenyl)phosphinomethyl-*κ*P]-ferrocene]triphenylphosphine ruthenium, [$RuCl_2$ (CH_3CN)(PPh_3)((S_{Ox},S_{Fc})-7)], (S_{Ox},S_{Fc})-23

Starting from Complex (S_{Ox},S_{Fc})**-7** (50 mg, 0.051 mmol) and following the general procedure given above the desired product was obtained. Single crystals suitable for X-ray crystallography were obtained from a Tol/PE solution by slow evaporation of the solvents. Mp: > 230 °C (dec.). ^{1}H NMR (400MHz, CD_2Cl_2): *δ* 0.99 (d, *J* = 7.1 Hz, 3H, CH(C*H*$_3$)(CH_3)), 1.1 (d, *J* = 7.0 Hz, 3H, CH(CH_3)(C*H*$_3$)), 1.13 (s, 3H, CH_3CN), 1.99 (s, 6H, CH_3^A), 2.35 (s, 6H, CH_3^B), 2.96–3.07 (m, 1H, C*H*(CH_3)$_2$), 3.21–3.39 (m, 2H, CH_2P), 4.12 (s, 5H, Cp'), 4.21–4.24 (m, 1H, H4), 4.38–4.40 (m, 1H, H3/5), 4.41 (t, *J* = 8.5 Hz, 1H, C*H*HO), 4.62–4.67 (m, 1H, CH*H*O), 4.70–4.74 (m, 1H, H3/5), 5.45–5.51(m, 1H, CHN), 6.29 (d, *J* = 9.1 Hz, 2H, Ph^A-*ortho*), 6.91–7.01 (m, 7H, Ph^A-*para* + PPh_3-*meta*), 7.07–7.17 (m, 7H, Ph^B-*para* + PPh_3-*para*), 7.18 –7.91 (PPh_3-*ortho*), 8.0 (d, *J* = 10.4 Hz, 2H, Ph^B-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): *δ* 5.2 (*C*H_3CN), 16.3

(CH(CH_3)(CH_3)), 19.5 (CH(CH_3)(CH_3)), 21.8 (2C, CH_3), 21.9 (2C, CH_3), 31.5 ($CH(CH_3)_2$), 43.4 (d, *J* = 22.5 Hz, CH_2P), 69.2 (C4), 70.3 (C3/5), 70.8 (CH_2O), 71.7 (Cp'), 73.0 (CHN), 73.4 (C3/5), 127.6 (d, *J* = 9.3 Hz, 6C, PPh_3-*meta*), 129.1 (6C, PPh_3-*para*), 130.9 (Ph^A-*para*), 131.7 (m, 3C, Ph^A-*ortho*+ Ph^B-*para*), 132.9 (d, *J* = 9.3 Hz, 2C, Ph^B-*ortho*), 135.0 –135.8 (bm, PPh_3-*ortho*), 137.1 (d, *J* = 8.6 Hz, 2C, Ph^A-*meta*), 137.7 (d, *J* = 9.9 Hz, 2C, Ph^B-*meta*). Signals of C1, C2, C=N, CN, all Ph-*ipso* not observed. ^{31}P {^1H} NMR (100.6 MHz, CD_2Cl_2): *δ* 46.5 (d, *J* = 31.7 Hz, *P*Ph_3), 50.8 (*J* = 31.7 Hz, *P*N). HR-MS (ESI in MeOH/MeCN): *m/z* $[M\text{-}Cl]^+$ calcd for $C_{53}H_{56}ClFeN_2OP_2Ru$: 991.1949, found: 991.1945.

Catalysis

Asymmetric transfer hydrogenations

Optimization of transfer hydrogenation reactions

Test reactions were carried out with acetophenone in 2-propanol (19.6 mM), complex **15** (0.5 %) as the catalyst precursor and the three different bases ^{i}PrONa, ^{i}PrOK, and ^{t}BuOK (2%). In all three cases product with nearly identical e.e. values (95–96%) was obtained, however the reaction rates differed significantly for the sodium and the potassium alkoxides. In order to reach 95% conversion 1 h was needed with ^{i}PrONa, 30 min with ^{t}BuOK and 20 min with ^{i}PrOK (Table S1). Based on these results potassium isopropoxide was used as the base for all further reactions. When in the reaction with ACP and 15 the amount of base was increased from 2 to 6% the reaction rate was hardly influenced but a very small decrease in product e.e. was seen (95 versus 96%). Reducing the reaction temperature from 25 °C to 0 °C reduced only the reaction rate but did not significantly alter the enantioselectivity. An increase in substrate concentration from 19.6 mM to 0.1 M did neither result in a significant change of conversion nor in a change of enantiomeric excess. Only when a 0.2 M solution was used the product e.e. dropped to 89%.

Table S1. THY optimization results obtained with complexes **15** and **17**

entry	complex		time	% conv.	% e.e.
effect of type of base		**base**			
1	(S_{Ox},S_{Fc})-**15**	iPrONa	1 h	98	95
2	(S_{Ox},S_{Fc})-**15**	tBuOK	30 m	97	95
3	(S_{Ox},S_{Fc})-**15**	iPrOK	20 m	99	96
effect of amount of base		**% base**			
4	(S_{Ox},S_{Fc})-**15**	2	20 m	99	96
5	(S_{Ox},S_{Fc})-**15**	6	30 m	99	95
effect of temperature		**temp.**			
6	(S_{Ox},S_{Fc})-**15**	25 °C	20 m	99	96
7	(S_{Ox},S_{Fc})-**15**	10 °C	2 h	94	95
8	(S_{Ox},S_{Fc})-**15**	0 °C	3 h	46	96
effect of concentration		**molarity**			
9	(S_{Ox},S_{Fc})-**15**	19.6 mM	20 m	99	96
10	(S_{Ox},S_{Fc})-**15**	0.1 M	5 m	94	95
11	(S_{Ox},S_{Fc})-**15**	0.2 M	5 m	92	89
12	(R_{Ox},R_{Fc})-**17**	19.6 mM	10 m	99	98
13	(R_{Ox},R_{Fc})-**17**	0.1 M	10 m	90	96
14	(R_{Ox},R_{Fc})-**17**	0.2 M	5 m	90	95
effect of S/C ratio		**S/C ratio**			
15	(S_{Ox},S_{Fc})-**17**	200/1	10 m	99	98
16	(S_{Ox},S_{Fc})-**17**	1000/1	1 h	13	81

Table S2. Typical THY results obtained with complexes **15**–**21**.

entry	substrate	ligand	complex	time	% conv.	% e.e.	abs. conf.
1	ACP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	20 m	99	96	*R*
2	ACP	(*R*,R_{Fc})-**2**	(R_{Fc})-**16**	20 m	98	92	*S*
3	ACP	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	10 m	99	98	*S*
4	ACP	(*R*,S_{Ox},R_{Fc})-**3**	(S_{Ox},R_{Fc})-**17**	5 h	18	69	*R*
5	ACP	(*R*,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	15 m	>99	97	*S*
6	ACP	(*R*,S_{Ox},R_{Fc})-**4**	(S_{Ox},R_{Fc})-**18**	6 h	90	73	*R*
7	ACP	(*R*,R_{Fc})-**5**	(R_{Fc})-**19**	4 h	78	95	*S*
8	ACP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	30 m	96	93	*R*
9	ACP	(S_{Ox},S_{Fc})-**7**	(S_{Ox},S_{Fc})-**21**	20 m	97	89	*R*
10	2-F-ACP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	5 m	99	91	*R*

11	2-F-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	30 m	99	50	*S*
12	2-Cl-ACP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	20 m	>99	90	*R*
13	2-Cl-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	5 m	>99	75	*S*
14	2-Cl-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	30 m	>99	67	*S*
15	2-Cl-ACP	(R,R_{Fc})-**5**	(R_{Fc})-**19**	6 h	89	10	*S*
16	2-Cl-ACP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	30 m	64	27	*R*
17	4-Cl-ACP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	10 m	>99	93	*R*
18	4-Cl-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	5 m	98	94	*S*
19	4-Cl-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	10 m	>99	90	*S*
20	4-Cl-ACP	(R,R_{Fc})-**5**	(R_{Fc})-**19**	2 h	91	85	*S*
21	4-Cl-ACP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	20 m	99	83	*R*
22	4-CF_3-ACP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	5 m	99	90	*R*
23	4-CF_3-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	20 m	>99	87	*S*
24	4-MeO-ACP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	20 m	80	90	*R*
25	4-MeO-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	20 m	82	95	*S*
26	4-MeO-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	20 m	75	95	*S*
27	4-MeO-ACP	(R,R_{Fc})-**5**	(R_{Fc})-**19**	4 h	32	88	*S*
28	4-MeO-ACP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	1 h	72	87	*R*
29	4-Me-ACP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	10 m	97	96	*R*
30	4-Me-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	10 m	97	98	*S*
31	PEK	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	10 m	99	97	*R*
32	PEK	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	20 m	99	96	*S*
33	PEK	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	15 m	94	96	*S*
34	PEK	(R,R_{Fc})-**5**	(R_{Fc})-**19**	3 h	89	91	*S*
35	PEK	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	1 h	97	88	*R*
36	PBK	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	10 m	>99	95	*R*
37	PBK	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	20 m	>98	97	*S*
38	PBK	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	2 h	>99	95	*S*
39	PBK	(R,R_{Fc})-**5**	(R_{Fc})-**19**	3 h	77	93	*S*
40	PBK	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	4 h	>99	91	*R*
41	DPP	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	10 m	>99	94	*R*
42	DPP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	15 m	99	96	*S*
43	DPP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	20 m	>99	94	*S*
44	DPP	(R,R_{Fc})-**5**	(R_{Fc})-**19**	3 h	77	93	*S*

45	DPP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	30 m	98	90	*R*
46	TETN	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	5 m	71	93	*R*
47	TETN	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	30 m	32	74	*S*
48	TETN	(*R*,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	20 m	21	81	*S*
49	TETN	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	2 h	50	72	*R*
50	AcFc	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	30 m	24	80	*R*
51	AcFc	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	30 m	10	81	*S*
52	AcFc	(*R*,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	30 m	16	93	*S*
53	AcFc	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	30 m	16	62	*R*
54	^{t}BMK	(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**15**	24 h	85	>99	*S*
55	^{t}BMK	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	24 h	42	9	*R*
56	^{t}BMK	(*R*,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	24 h	11	3	*R*
57	^{t}BMK	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	24 h	36	21	*R*

Asymmetric hydrogenations

Table S3. Selected HY results obtained with complexes **15**–**21**.

entry	substrate	ligand	complex	Solvent	Base	% conv.	% e.e.	abs. conf.
1	ACP	(*R*,R_{Fc})-**2**	(R_{Fc})-**16**	Tol, H_2O	K_2CO_3	99	95	*S*
2	ACP	(*R*,R_{Fc})-**2**	(R_{Fc})-**16**	Tol, H_2O	NaOH	99	94	*S*
3	ACP	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	K_2CO_3	99	99	*S*
4	ACP	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	NaOH	99	97	*S*
5	ACP	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	95	94	*S*
6	ACP	(*R*,S_{Ox},R_{Fc})-**3**	(S_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	95	58	*R*
7	ACP	(*R*,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	Tol, H_2O	K_2CO_3	99	98	*S*
8	ACP	(*R*,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	Tol, H_2O	NaOH	99	96	*S*
9	ACP	(*R*,S_{Ox},R_{Fc})-**4**	(S_{Ox},R_{Fc})-**18**	^{i}PrOH	KO^{t}Bu	95	62	*R*
10	2-F-ACP	(R_{Ox},R_{Fc})-**1**	(R_{Ox},R_{Fc})-**15**	Tol, H_2O	K_2CO_3	94	93	*S*
11	2-F-ACP	(R_{Ox},R_{Fc})-**1**	(R_{Ox},R_{Fc})-**15**	Tol, H_2O	NaOH	96	91	*S*
12	2-F-ACP	(*R*,R_{Fc})-**2**	(R_{Fc})-**16**	Tol, H_2O	K_2CO_3	98	74	*S*
13	2-F-ACP	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	K_2CO_3	97	90	*S*
14	2-F-ACP	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	NaOH	96	87	*S*
15	2-F-ACP	(*R*,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	99	70	*S*

14	2-F-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	Tol, H_2O	K_2CO_3	97	83	*S*
16	2-F-ACP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	Tol, H_2O	NaOH	93	85	*R*
17	2-F-ACP	(S_{Ox},S_{Fc})-**7**	(S_{Ox},S_{Fc})-**21**	Tol, H_2O	NaOH	95	70	*R*
18	2-Cl-ACP	(R,R_{Fc})-**2**	(R_{Fc})-**16**	Tol, H_2O	K_2CO_3	97	71	*S*
19	2-Cl-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	K_2CO_3	95	91	*S*
20	2-Cl-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	NaOH	98	90	*S*
21	2-Cl-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	80	82	*S*
22	2-Cl-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	80	82	*S*
23	2-Cl-ACP	(R,S_{Ox},R_{Fc})-**3**	(S_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	73	59	*R*
24	2-Cl-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	Tol, H_2O	K_2CO_3	96	87	*S*
25	2-Cl-ACP	(R,S_{Ox},R_{Fc})-**4**	(S_{Ox},R_{Fc})-**18**	^{i}PrOH	KO^{t}Bu	76	75	*R*
26	4-CF_3-ACP	(R_{Ox},R_{Fc})-**1**	(R_{Ox},R_{Fc})-**15**	Tol, H_2O	K_2CO_3	97	91	*S*
27	4-CF_3-ACP	(R,R_{Fc})-**2**	(R_{Fc})-**16**	Tol, H_2O	K_2CO_3	98	64	*S*
28	4-CF_3-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	K_2CO_3	97	90	*S*
29	4-CF_3-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol/H_2O	NaOH	97	89	*S*
30	4-CF_3-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	Tol, H_2O	K_2CO_3	98	80	*S*
31	4-CF_3-ACP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	Tol, H_2O	K_2CO_3	95	80	*R*
32	4-CF_3-ACP	(S_{Ox},S_{Fc})-**7**	(S_{Ox},S_{Fc})-**21**	Tol, H_2O	NaOH	94	69	*R*
33	4-Me-ACP	(R_{Ox},R_{Fc})-**1**	(R_{Ox},R_{Fc})-**15**	Tol, H_2O	K_2CO_3	100	91	*S*
34	4-Me-ACP	(R,R_{Fc})-**2**	(R_{Fc})-**16**	Tol, H_2O	K_2CO_3	100	88	*S*
35	4-Me-ACP	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	K_2CO_3	100	97	*S*
36	4-Me-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	^{i}PrOH	KO^{t}Bu	>99	93	*S*
37	4-Me-ACP	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	Tol, H_2O	K_2CO_3	100	97	*S*
38	4-Me-ACP	(S_{Ox},S_{Fc})-**6**	(S_{Ox},S_{Fc})-**20**	Tol, H_2O	K_2CO_3	99	92	*R*
39	4-Me-ACP	(S_{Ox},S_{Fc})-**7**	(S_{Ox},S_{Fc})-**21**	Tol, H_2O	K_2CO_3	98	86	*R*
41	PBK	(R,R_{Fc})-**2**	(R_{Fc})-**16**	^{i}PrOH	KO^{t}Bu	>99	74	*S*
42	PBK	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	^{i}PrOH	KO^{t}Bu	>99	99	*S*
43	PBK	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	^{i}PrOH	KO^{t}Bu	>99	93	*S*
44	3,5-bTFA	(R_{Ox},R_{Fc})-**1**	(R_{Ox},R_{Fc})-**15**	Tol, H_2O	K_2CO_3	99	94	*S*
45	3,5-bTFA	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	K_2CO_3	95	40	*S*
46	3,5-bTFA	(R,R_{Ox},R_{Fc})-**3**	(R_{Ox},R_{Fc})-**17**	Tol, H_2O	K_2CO_3	95	40	*S*
47	3,5-bTFA	(R,R_{Ox},R_{Fc})-**4**	(R_{Ox},R_{Fc})-**18**	Tol, H_2O	NaOH	95	41	*S*

Analysis data:

Conversions and e.e. values of substrates **ACP**, **2-F-ACP**, **2-Cl-ACP**, **4-Cl-ACP**, **4-CF_3-ACP**, **4-MeO-ACP**, **4-Me-ACP**, **3,5-bTFA**, **^{t}BMK**, **PEK** and **TETN** were determined by GC. Retention times are given for the reactants and both product enantiomers.

Substrate **^{t}BMK**: Column: Supelco, Beta Dex™ 110 (30m); 62 °C isothermal, carrier gas He, 15.3 psi, split 100:1.

^{t}BMK = 4.6 min, (*R*) = 9.3 min, (*S*) = 9.7 min.

Substrates **ACP**, **PEK** and **3,5-bTFA**: column: Supelco, Beta Dex™ 110 (30m); 110 °C isothermal, carrier gas He, 15.3 psi, split 30:1.

ACP = 10.4 min, (*R*) = 15.6 min, (*S*) = 16.4 min.

PEK = 16.5 min, (*R*) = 25.7 min, (*S*) = 26.9 min.

3,5-bTFA = 3.8 min, (*R*) = 7.5 min, (*S*) = 8.0 min.

Substrates **2-F-ACP**, **4-Me-ACP**: column: Supelco, Beta Dex™ 110 (30m); 120 °C isothermal, carrier gas He, 15.3 psi, split 30:1.

2-F-ACP = 4.2 min, (*R*) = 6.7 min, (*S*) = 6.9 min.

4-Me-ACP = 9.4 min, (*R*) = 10.4 min, (*S*) = 11.0 min.

Substrates **4-MeO-ACP**, **TETN**: Column: Supelco, Beta Dex™ 110 (30m); 125 °C isothermal, carrier gas He,17 psi, split 30:1.

4-MeO-ACP = 28.3 min, (*R*) = 30.0 min, (*S*) = 31.2 min.

TETN = 30.9 min, (*S*) =37.1 min, (*R*) = 37.7 min.

Substrates **2-Cl-ACP**, **4-Cl-ACP** and **4-CF_3-ACP**: column: Supelco, Beta Dex™ 110 (30m); 130 °C isothermal, carrier gas He, 15.3 psi, split 30:1.

2-Cl-ACP = 10.4 min, (*R*) = 19.2 min, (*S*) = 22.7 min.

4-Cl-ACP = 13.5 min, (*R*) = 22.2 min, (*S*) = 23.8 min.

4-CF_3-ACP = 4.5 min, (*R*) = 7.7 min, (*S*) = 8.2 min.

Conversions and e.e. values of substrates **PBK**, **DPP** and **AcFc** were determined by HPLC. Retention times are given for the reactants and both product enantiomers.

Substrate **PBK**: column: Daicel, Chiraldex OD-H, temperature: 25 ºC, eluent: hexane/iPrOH 96:4, flow rate: 0.6 mL/min, detector: DAD, Sig = 230 nm, 8, ref = 360 nm, 100.

PBK = 17.6 min, (*R*) = 20.4 min, (*S*) = 25.8 min.

Substrate **DPP**: column: Daicel, Chiraldex OD-H, temperature: 25 ºC, solvent: hexane/iPrOH 9:1, Flow rate: 0.8 mL/min, detector: DAD, Sig = 215 nm, 8, ref = 360nm, 100.

DPP = 8.2 min, (*R*) = 12.4 min, (*S*) = 14.8 min.

Substrate **AcFc**: column: Daicel, Chiraldex OJ, temperature: 25 ºC, solvent: hexane/iPrOH 97:3, flow rate: 0.8 mL/min, detector: DAD, Sig = 210 nm, 8, Ref = 650 nm, 100.

AcFc = 16.2 min, (*R*) = 19.0 min, (*S*) = 26.7 min.

X-ray structure determination of the complexes (R_{Ox},R_{Fc})-17, (R_{Fc})-19, (R_{Ox},R_{Fc})-22, and (S_{Ox},S_{Fc})-23.

Single crystals of the four complexes were obtained by layering toluene solutions ((R_{Ox},R_{Fc})-**17**, (R_{Fc})-**19,** (S_{Ox},S_{Fc})-**23**) or dichloromethane solutions ((R_{Ox},R_{Fc})-**22**) with diethyl ether or pentane as antisolvent. Except for (R_{Ox},R_{Fc})-**17**, which was unsolvated, all crystals represented either toluene ((R_{Fc})-**19**, (S_{Ox},S_{Fc})-**23**) or dichloromethane solvates ((R_{Ox},R_{Fc})-**22**). The crystals of (R_{Ox},R_{Fc})-**17** and (R_{Fc})-**19** were emerald-green, those of ((R_{Ox},R_{Fc})-**22**) and (S_{Ox},S_{Fc})-**23**) were orange. X-ray data were collected on a Bruker Kappa APEX-2 CCD diffractometer with a cryostream cooler (Oxford Cryosystems) using graphite-monochromatised Mo-Kα radiation (λ = 0.71073 Å) and 0.5° φ- and ω-scan frames covering complete Ewald spheres with θ_{max} = 30° or 25° ((S_{Ox},S_{Fc})-**23**). The frames were integrated with program SAINT and corrections for absorption and λ/2 effects were applied with program SADABS. After structure solution with program SHELXS97 and direct methods, refinement on F^2 was carried out with the program SHELXL97 (Sheldrick, 2008). Non-hydrogen atoms were refined anisotropically. All H atoms were placed in calculated positions and thereafter refined as riding. The absolute structures of all compounds could be unambiguously determined by anomalous dispersion effects and the Flack absolute structure parameter. Variata: The toluene solvent in (R_{Fc})-**19** resided in channels parallel to the *a*-axis of the orthorhombic unit cell (one toluene molecule per formula unit) and showed very large anisotropic displacement ellipsoids. Therefore its contribution to the structure factors was removed with procedure SQUEEZE of program PLATON (Spek, 2003) prior to the final refinement. Crystallographic data are compiled in Table S4 and atomic parameters are provided in CIF-format in the Supporting. Structural diagrams of the complexes (Fig. S1 – S4) and Tables (Tab. S5 – S8) with selected geometric parameters are given below. For molecular graphics the programs XP (Bruker) and MERCURY (Macrae et al., 2006) were used.

Bruker programs: APEX2; SAINT, version 7.68A; SADABS, version 2008/1; SHELXTL, version 2008/4; XP, version 5 (Bruker AXS Inc., Madison, WI, 2009).

SHELXS97 and SHELXL97: G. M. Sheldrick, Acta Cryst. **2008**, *A64*, 112-122.

PLATON: Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

MERCURY: Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E., Shields, G. P., Taylor, R., Towler, M. & van de Streek, J. (2006). *J. Appl. Cryst.* **39**, 453–457.

Table S4. Crystal data and structure refinement for the four investigated complexes (R_{Ox},R_{Fc})-**17**, (R_{Fc})-**19**, (R_{Ox},R_{Fc})-**22**, and (S_{Ox},S_{Fc})-**23**.

	(R_{Ox},R_{Fc})-**17**	(R_{Fc})-**19**·C_7H_8 [a)]	(R_{Ox},R_{Fc})-**22**·CH_2Cl_2	(S_{Ox},S_{Fc})-**23**·C_7H_8
formula	$C_{48}H_{47}Cl_2FeNOP_2Ru$	$C_{47}H_{45}Cl_2FeNOP_2Ru \cdot C_7H_8$	$C_{50}H_{50}Cl_2FeN_2OP_2Ru \cdot CH_2Cl_2$	$C_{53}H_{56}Cl_2FeN_2OP_2Ru \cdot C_7H_8$
fw	943.63	1021.73	1069.61	1118.89
cryst.size, mm	0.38 × 0.15 × 0.13	0.41 × 0.29 × 0.25	0.55 × 0.29 × 0.10	0.22 × 0.15 × 0.03
crystal system	monoclinic	orthorhombic	triclinic	orthorhombic
space group	$P2_1$ (no. 4)	$P2_12_12_1$ (no. 19)	$P1$ (no. 1)	$P2_12_12_1$ (no. 19)
a, Å	13.4450(4)	10.3672(4)	10.0952(6)	11.531(2)
b, Å	11.3616(3)	15.3829(6)	11.0657(6)	21.358(4)
c, Å	13.8849(4)	29.4389(12)	12.6518(12)	22.000(4)
α, deg	90	90	105.215(4)	90
β, deg	104.865(2)	90	96.050(4)	90
γ, deg	90	90	115.719(2)	90
V, Å^3	2050.03(10)	4694.8(3)	1188.96(15)	5418.4(17)
T, K	100	100	100	299
Z	2	4	1	4
ρ_{calc}, g cm^{-3}	1.529	1.446	1.494	1.372
μ, mm^{-1} (MoKα)	0.970	0.853	0.955	0.746
F(000)	968	2104	548	2320
absorption corrections	multi-scan, 0.88-0.73	multi-scan, 0.82-0.66	multi-scan, 0.92-0.74	multi-scan, 0.98-0.83
θ range, deg	2.3 - 30.0	1.9 - 30.0	2.2 - 30.0	1.9 - 25.0
no. of rflns measd / R_{int}	44495 / 0.042	129187 / 0.038	36346 / 0.051	59588 / 0.11
no. of rflns unique	11827	13664	13554	9550
no. of rflns $I>2\sigma(I)$	10932	13211	13243	7038
no. of params / restraints	508 / 1	499 / 0	563 / 3	617 / 271
R_1 ($I > 2\sigma(I)$)	0.0280	0.0226	0.0414	0.0476
R_1 (all data)	0.0338	0.0242	0.0424	0.0815
wR_2 ($I > 2\sigma(I)$)	0.0640	0.0535	0.1064	0.0805
wR_2 (all data)	0.0672	0.0541	0.1075	0.0910
Flack abs.str. param.	-0.023(10)	-0.005(8)	-0.016(8)	0.00(2)
Diff.Four.peaks min/max, eÅ^{-3}	-0.45 / 1.13	-0.64 / 0.47	-1.41 / 2.45	-0.39 / 0.56

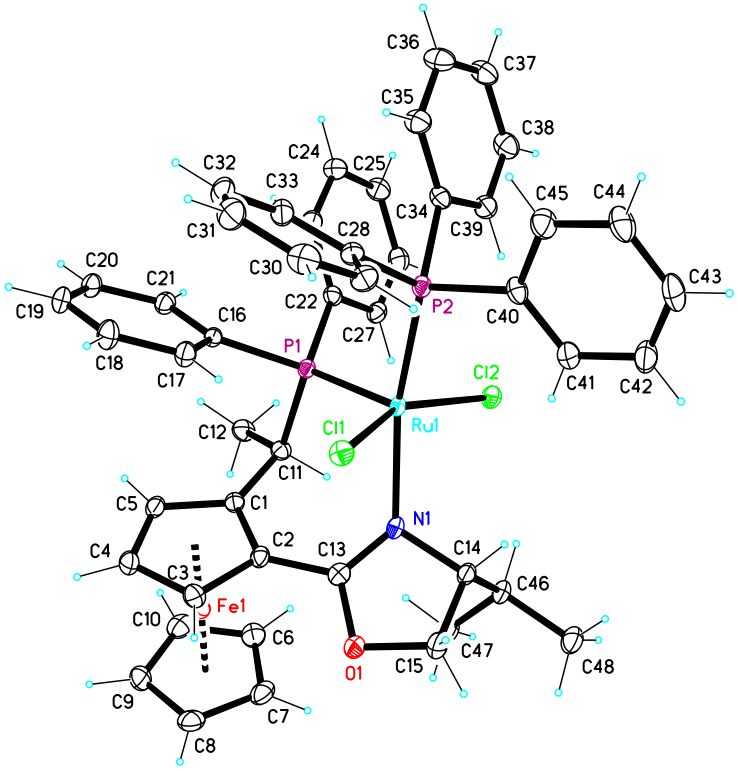


Figure S1. Structural diagram of the asymmetric unit of (R_{Ox},R_{Fc})-**17** showing 50% ellipsoids and the atom numbering.

Table S5. Selected geometric data (Å, deg) of (R_{Ox},R_{Fc})-**17**.

Ru(1)-N(1)	2.1588(18)	P(1)-C(11)	1.888(2)
Ru(1)-P(1)	2.1979(6)	P(1)-C(16)	1.836(2)
Ru(1)-P(2)	2.2834(6)	P(1)-C(22)	1.829(2)
Ru(1)-Cl(1)	2.3704(6)		
Ru(1)-Cl(2)	2.3943(6)	P(2)-C(28)	1.831(2)
		P(2)-C(34)	1.843(2)
Fe(1)-C(1)	2.061(2)	P(2)-C(40)	1.833(2)
Fe(1)-C(2)	2.049(2)		
Fe(1)-C(3)	2.047(2)	N(1)-C(13)	1.284(3)
Fe(1)-C(4)	2.066(2)	N(1)-C(14)	1.494(3)
Fe(1)-C(5)	2.054(2)	O(1)-C(13)	1.346(3)
Fe(1)-C(6)	2.045(2)	O(1)-C(15)	1.468(3)
Fe(1)-C(7)	2.049(2)	C(14)-C(15)	1.528(3)
Fe(1)-C(8)	2.067(2)	C(14)-C(46)	1.541(3)
Fe(1)-C(9)	2.062(2)	C(46)-C(47)	1.519(3)
Fe(1)-C(10)	2.051(2)	C(46)-C(48)	1.524(3)

C(1)-C(2)	1.440(3)	C(37)-C(38)	1.388(4)
C(1)-C(5)	1.429(3)	C(38)-C(39)	1.385(3)
C(1)-C(11)	1.504(3)		
C(2)-C(3)	1.431(3)	C(40)-C(41)	1.391(4)
C(2)-C(13)	1.455(3)	C(40)-C(45)	1.397(3)
C(3)-C(4)	1.420(3)	C(41)-C(42)	1.393(4)
C(4)-C(5)	1.420(3)	C(42)-C(43)	1.377(4)
C(6)-C(7)	1.420(4)	C(43)-C(44)	1.389(4)
C(6)-C(10)	1.418(4)	C(44)-C(45)	1.391(4)
C(7)-C(8)	1.428(4)	N(1)-Ru(1)-P(1)	99.20(5)
C(8)-C(9)	1.418(4)	N(1)-Ru(1)-P(2)	163.61(5)
C(9)-C(10)	1.428(4)	P(1)-Ru(1)-P(2)	96.74(2)
		N(1)-Ru(1)-Cl(1)	81.80(5)
C(11)-C(12)	1.541(3)	P(1)-Ru(1)-Cl(1)	108.79(2)
		P(2)-Ru(1)-Cl(1)	89.48(2)
C(16)-C(17)	1.396(3)	N(1)-Ru(1)-Cl(2)	86.22(5)
C(16)-C(21)	1.405(3)	P(1)-Ru(1)-Cl(2)	94.82(2)
C(17)-C(18)	1.396(3)	P(2)-Ru(1)-Cl(2)	96.26(2)
C(18)-C(19)	1.382(4)	Cl(1)-Ru(1)-Cl(2)	154.89(2)
C(19)-C(20)	1.389(3)		
C(20)-C(21)	1.385(4)	C(22)-P(1)-C(16)	102.57(10)
		C(22)-P(1)-C(11)	106.08(10)
C(22)-C(27)	1.394(3)	C(16)-P(1)-C(11)	100.76(10)
C(22)-C(23)	1.405(3)	C(22)-P(1)-Ru(1)	115.08(7)
C(23)-C(24)	1.388(3)	C(16)-P(1)-Ru(1)	122.95(7)
C(24)-C(25)	1.394(4)	C(11)-P(1)-Ru(1)	107.49(7)
C(25)-C(26)	1.389(3)		
C(26)-C(27)	1.385(3)	C(28)-P(2)-C(40)	101.63(10)
		C(28)-P(2)-C(34)	104.41(10)
C(28)-C(33)	1.392(3)	C(40)-P(2)-C(34)	97.85(10)
C(28)-C(29)	1.406(3)	C(28)-P(2)-Ru(1)	115.24(8)
C(29)-C(30)	1.386(3)	C(40)-P(2)-Ru(1)	108.34(8)
C(30)-C(31)	1.394(4)	C(34)-P(2)-Ru(1)	125.59(7)
C(31)-C(32)	1.377(4)		
C(32)-C(33)	1.393(3)	C(13)-N(1)-C(14)	106.53(18)
		C(13)-N(1)-Ru(1)	125.83(16)
C(34)-C(35)	1.397(3)	C(14)-N(1)-Ru(1)	117.94(14)
C(34)-C(39)	1.399(3)	C(13)-O(1)-C(15)	104.70(17)
C(35)-C(36)	1.390(3)		
C(36)-C(37)	1.390(4)		

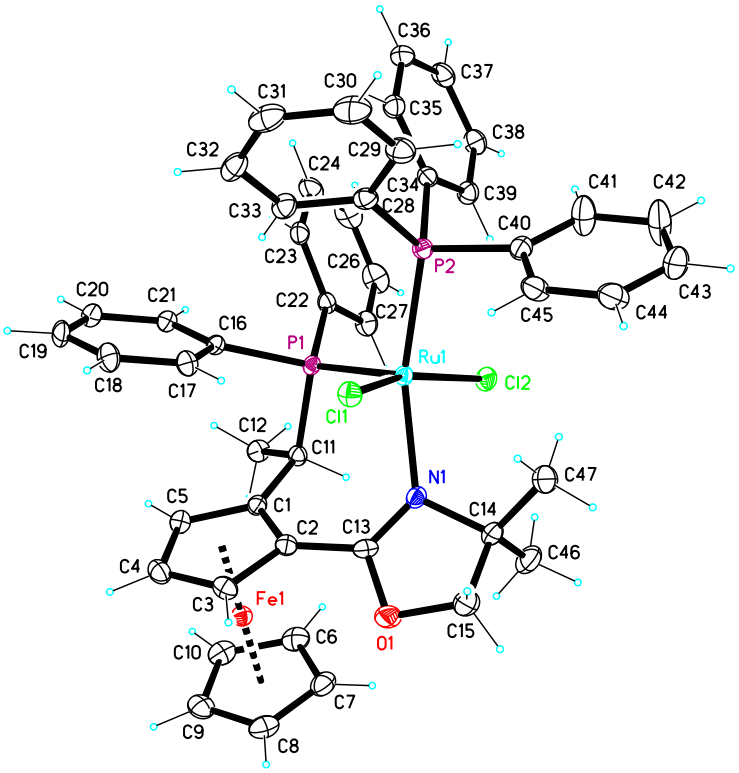


Figure S2. Structural diagram of the asymmetric unit of (R_{Fc})-**19**·C_7H_8 showing 50% ellipsoids and the atom numbering. The toluene solvent molecule was squeezed with program PLATON and is not shown therefore.

Table S6. Selected geometric data (Å, deg) of (R_{Fc})-**19**·C_7H_8.

Ru(1)-N(1)	2.1623(13)	Fe(1)-C(10)	2.0405(17)
Ru(1)-P(2)	2.2858(4)		
Ru(1)-P(1)	2.1993(4)	P(1)-C(11)	1.8876(17)
Ru(1)-Cl(1)	2.3987(4)	P(1)-C(16)	1.8325(17)
Ru(1)-Cl(2)	2.3767(4)	P(1)-C(22)	1.8292(16)
		P(2)-C(28)	1.8270(18)
Fe(1)-C(1)	2.0446(16)	P(2)-C(34)	1.8368(17)
Fe(1)-C(2)	2.0378(16)	P(2)-C(40)	1.8326(17)
Fe(1)-C(3)	2.0485(17)		
Fe(1)-C(4)	2.0626(18)	O(1)-C(13)	1.3586(19)
Fe(1)-C(5)	2.0503(17)	O(1)-C(15)	1.452(2)
Fe(1)-C(6)	2.0443(18)	N(1)-C(13)	1.281(2)
Fe(1)-C(7)	2.0563(19)	N(1)-C(14)	1.518(2)
Fe(1)-C(8)	2.0629(18)	C(14)-C(15)	1.531(3)
Fe(1)-C(9)	2.0488(17)	C(14)-C(46)	1.526(3)

C(14)-C(47)	1.514(2)
C(1)-C(2)	1.437(2)
C(1)-C(5)	1.425(2)
C(1)-C(11)	1.507(2)
C(2)-C(3)	1.432(2)
C(2)-C(13)	1.454(2)
C(3)-C(4)	1.415(2)
C(4)-C(5)	1.419(2)
C(6)-C(7)	1.425(3)
C(6)-C(10)	1.420(3)
C(7)-C(8)	1.418(3)
C(8)-C(9)	1.417(3)
C(9)-C(10)	1.416(3)
C(11)-C(12)	1.540(2)
C(16)-C(17)	1.397(2)
C(16)-C(21)	1.403(2)
C(17)-C(18)	1.389(2)
C(18)-C(19)	1.394(2)
C(19)-C(20)	1.384(2)
C(20)-C(21)	1.397(2)
C(22)-C(23)	1.400(2)
C(22)-C(27)	1.403(2)
C(23)-C(24)	1.391(2)
C(24)-C(25)	1.388(3)
C(25)-C(26)	1.376(3)
C(26)-C(27)	1.392(2)
C(28)-C(33)	1.390(3)
C(28)-C(29)	1.398(2)
C(29)-C(30)	1.386(3)
C(30)-C(31)	1.390(3)
C(31)-C(32)	1.387(3)
C(32)-C(33)	1.394(2)
C(34)-C(35)	1.396(2)
C(34)-C(39)	1.401(2)
C(35)-C(36)	1.394(2)
C(36)-C(37)	1.388(3)
C(37)-C(38)	1.393(3)
C(38)-C(39)	1.391(2)
C(40)-C(41)	1.392(3)
C(40)-C(45)	1.393(2)
C(41)-C(42)	1.395(3)
C(42)-C(43)	1.378(3)
C(43)-C(44)	1.374(3)
C(44)-C(45)	1.381(3)
N(1)-Ru(1)-P(1)	100.61(4)
N(1)-Ru(1)-P(2)	161.15(4)
P(1)-Ru(1)-P(2)	98.234(16)
N(1)-Ru(1)-Cl(2)	86.31(4)
P(1)-Ru(1)-Cl(2)	89.641(16)
P(2)-Ru(1)-Cl(2)	94.279(15)
N(1)-Ru(1)-Cl(1)	82.88(4)
P(1)-Ru(1)-Cl(1)	108.069(16)
P(2)-Ru(1)-Cl(1)	90.897(15)
Cl(2)-Ru(1)-Cl(1)	160.650(15)
C(22)-P(1)-C(16)	102.41(7)
C(22)-P(1)-C(11)	105.23(7)
C(16)-P(1)-C(11)	99.31(7)
C(22)-P(1)-Ru(1)	116.10(6)
C(16)-P(1)-Ru(1)	122.68(5)
C(11)-P(1)-Ru(1)	108.73(5)
C(28)-P(2)-C(40)	102.65(8)
C(28)-P(2)-C(34)	101.51(7)
C(40)-P(2)-C(34)	102.80(8)
C(28)-P(2)-Ru(1)	118.24(6)
C(40)-P(2)-Ru(1)	100.90(5)
C(34)-P(2)-Ru(1)	127.14(5)
C(13)-O(1)-C(15)	105.13(13)
C(13)-N(1)-C(14)	106.33(13)
C(13)-N(1)-Ru(1)	129.00(12)
C(14)-N(1)-Ru(1)	120.14(10)

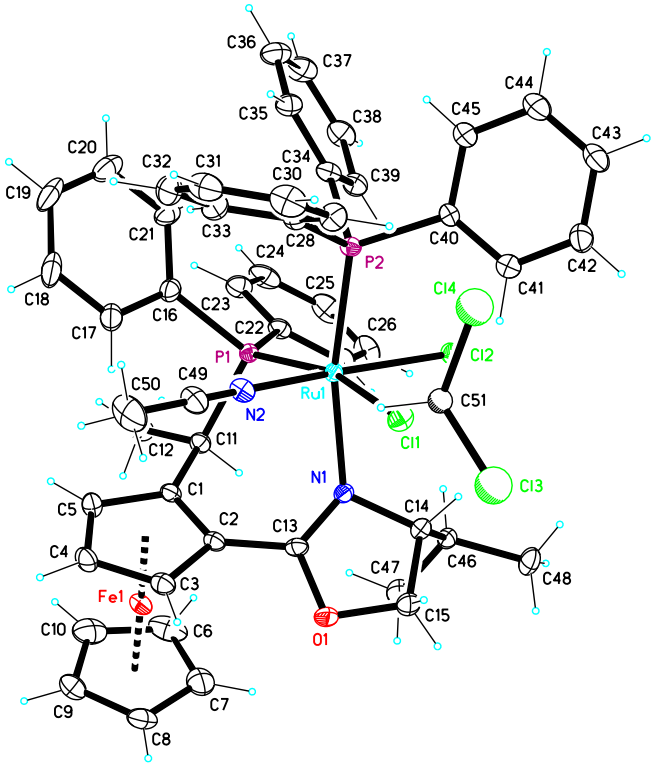


Figure S3. Structural diagram of the asymmetric unit of (R_{Ox},R_{Fc})-**22**·CH_2Cl_2 showing 50% ellipsoids (except for the CH_2Cl_2 solvent molecule) and the atom numbering.

Table S7. Selected geometric data (Å, deg) of (R_{Ox},R_{Fc})-**22**·CH_2Cl_2

Ru(1)-N(1)	2.190(2)	O(1)-C(15)	1.452(4)
Ru(1)-N(2)	2.007(3)	N(1)-C(13)	1.288(4)
Ru(1)-P(1)	2.2908(7)	N(1)-C(14)	1.495(4)
Ru(1)-P(2)	2.3076(7)	C(14)-C(15)	1.533(4)
Ru(1)-Cl(1)	2.4793(7)	C(14)-C(46)	1.544(4)
Ru(1)-Cl(2)	2.4191(7)	C(46)-C(48)	1.531(4)
		C(46)-C(47)	1.532(4)
Fe(1)-C(1)	2.062(3)		
Fe(1)-C(2)	2.046(3)	N(2)-C(49)	1.134(4)
Fe(1)-C(3)	2.041(3)	C(49)-C(50)	1.471(5)
Fe(1)-C(4)	2.058(3)	C(1)-C(2)	1.431(4)
Fe(1)-C(5)	2.044(3)	C(1)-C(5)	1.438(4)
Fe(1)-C(6)	2.040(3)	C(1)-C(11)	1.517(4)
Fe(1)-C(7)	2.051(4)	C(2)-C(3)	1.438(4)
Fe(1)-C(8)	2.065(3)	C(2)-C(13)	1.444(4)
Fe(1)-C(9)	2.060(3)	C(3)-C(4)	1.431(4)
Fe(1)-C(10)	2.038(3)	C(4)-C(5)	1.426(4)
P(1)-C(11)	1.900(3)	C(6)-C(7)	1.414(6)
P(1)-C(16)	1.834(3)	C(6)-C(10)	1.432(7)
P(1)-C(22)	1.845(3)	C(7)-C(8)	1.423(5)
P(2)-C(28)	1.828(3)	C(8)-C(9)	1.425(5)
P(2)-C(34)	1.839(3)	C(9)-C(10)	1.424(6)
P(2)-C(40)	1.851(3)		
		C(11)-C(12)	1.531(4)
O(1)-C(13)	1.352(3)		

C(16)-C(17)	1.398(5)
C(16)-C(21)	1.406(4)
C(17)-C(18)	1.392(5)
C(18)-C(19)	1.389(6)
C(19)-C(20)	1.367(7)
C(20)-C(21)	1.393(5)
C(22)-C(27)	1.392(4)
C(22)-C(23)	1.405(4)
C(23)-C(24)	1.391(5)
C(24)-C(25)	1.381(6)
C(25)-C(26)	1.389(5)
C(26)-C(27)	1.399(4)
C(28)-C(33)	1.389(5)
C(28)-C(29)	1.404(4)
C(29)-C(30)	1.404(5)
C(30)-C(31)	1.384(6)
C(31)-C(32)	1.400(6)
C(32)-C(33)	1.396(5)
C(34)-C(35)	1.393(4)
C(34)-C(39)	1.402(4)
C(35)-C(36)	1.390(4)
C(36)-C(37)	1.393(5)
C(37)-C(38)	1.393(5)
C(38)-C(39)	1.383(4)
C(40)-C(41)	1.399(4)
C(40)-C(45)	1.404(4)
C(41)-C(42)	1.398(4)
C(42)-C(43)	1.386(5)
C(43)-C(44)	1.392(5)
C(44)-C(45)	1.381(5)
C(51)-Cl(3)	1.730(8)
C(51)-Cl(4)	1.759(7)
N(2)-Ru(1)-N(1)	92.94(10)
N(2)-Ru(1)-P(1)	86.99(8)
N(1)-Ru(1)-P(1)	92.02(7)
N(2)-Ru(1)-P(2)	93.67(8)
N(1)-Ru(1)-P(2)	167.30(6)
P(1)-Ru(1)-P(2)	99.14(3)
N(2)-Ru(1)-Cl(2)	171.99(7)
N(1)-Ru(1)-Cl(2)	87.43(7)
P(1)-Ru(1)-Cl(2)	101.00(2)
P(2)-Ru(1)-Cl(2)	84.52(2)
N(2)-Ru(1)-Cl(1)	79.16(8)
N(1)-Ru(1)-Cl(1)	80.89(6)
P(1)-Ru(1)-Cl(1)	164.03(2)
P(2)-Ru(1)-Cl(1)	89.72(3)
Cl(2)-Ru(1)-Cl(1)	93.01(2)
C(16)-P(1)-C(22)	106.56(14)
C(16)-P(1)-C(11)	102.89(13)
C(22)-P(1)-C(11)	96.17(12)
C(16)-P(1)-Ru(1)	114.85(10)
C(22)-P(1)-Ru(1)	121.97(10)
C(11)-P(1)-Ru(1)	111.34(9)
C(28)-P(2)-C(34)	104.80(14)
C(28)-P(2)-C(40)	100.38(13)
C(34)-P(2)-C(40)	99.09(13)
C(28)-P(2)-Ru(1)	113.60(10)
C(34)-P(2)-Ru(1)	118.31(9)
C(40)-P(2)-Ru(1)	118.06(10)
C(13)-O(1)-C(15)	105.2(2)
C(13)-N(1)-C(14)	106.1(2)
C(13)-N(1)-Ru(1)	127.0(2)
C(14)-N(1)-Ru(1)	118.98(17)
C(49)-N(2)-Ru(1)	173.0(3)
N(2)-C(49)-C(50)	178.6(4)
Cl(3)-C(51)-Cl(4)	112.4(4)

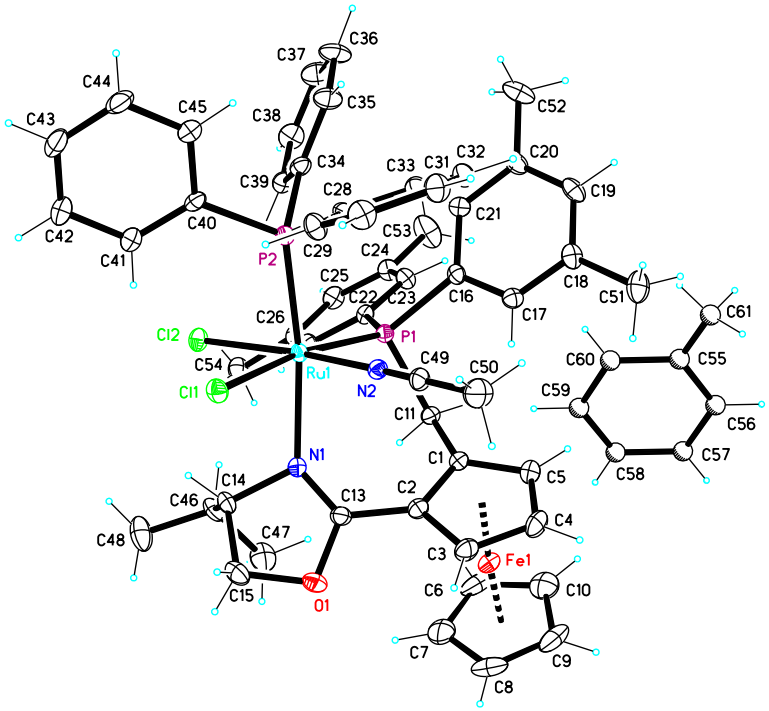


Figure S4. Structural diagram of the asymmetric unit of (S_{Ox},S_{Fc})-**23**·C_7H_8 showing 20% ellipsoids (except for the toluene solvent molecule) and the atom numbering.

Table S8. Selected geometric data (Å, deg) of (S_{Ox},S_{Fc})-**23**·C_7H_8.

Ru(1)-N(1)	2.215(4)	N(1)-C(14)	1.511(6)
Ru(1)-N(2)	1.988(4)	C(14)-C(15)	1.525(8)
Ru(1)-P(1)	2.3014(15)	C(14)-C(46)	1.551(8)
Ru(1)-P(2)	2.2968(15)	C(46)-C(47)	1.528(8)
Ru(1)-Cl(1)	2.4773(14)	C(46)-C(48)	1.513(8)
Ru(1)-Cl(2)	2.4162(14)		
		N(2)-C(49)	1.118(6)
Fe(1)-C(1)	2.062(6)	C(49)-C(50)	1.462(8)
Fe(1)-C(2)	2.045(6)		
Fe(1)-C(3)	2.016(6)	C(1)-C(2)	1.437(7)
Fe(1)-C(4)	2.034(6)	C(1)-C(5)	1.415(8)
Fe(1)-C(5)	2.023(6)	C(1)-C(11)	1.483(7)
Fe(1)-C(6)	2.023(8)	C(2)-C(3)	1.436(7)
Fe(1)-C(7)	2.041(8)	C(2)-C(13)	1.460(8)
Fe(1)-C(8)	2.043(7)	C(3)-C(4)	1.409(8)
Fe(1)-C(9)	2.031(7)	C(4)-C(5)	1.398(8)
Fe(1)-C(10)	2.026(7)	C(6)-C(7)	1.389(11)
		C(6)-C(10)	1.374(10)
P(1)-C(16)	1.839(5)	C(7)-C(8)	1.413(11)
P(1)-C(22)	1.849(5)	C(8)-C(9)	1.386(11)
P(1)-C(11)	1.877(5)	C(9)-C(10)	1.425(11)
P(2)-C(28)	1.826(5)		
P(2)-C(40)	1.837(5)	C(16)-C(21)	1.391(7)
P(2)-C(34)	1.843(6)	C(16)-C(17)	1.393(7)
		C(17)-C(18)	1.384(7)
O(1)-C(13)	1.357(6)	C(18)-C(19)	1.358(8)
O(1)-C(15)	1.452(7)	C(18)-C(51)	1.539(8)
N(1)-C(13)	1.276(7)	C(19)-C(20)	1.407(8)

C(20)-C(21)	1.397(7)	N(2)-C(49)-C(50)	178.5(7)
C(20)-C(52)	1.496(8)		
C(22)-C(27)	1.396(7)		
C(22)-C(23)	1.398(7)		
C(23)-C(24)	1.392(7)		
C(24)-C(25)	1.381(8)		
C(24)-C(53)	1.489(8)		
C(25)-C(26)	1.385(8)		
C(26)-C(27)	1.383(8)		
C(26)-C(54)	1.491(8)		
C(28)-C(33)	1.381(7)		
C(28)-C(29)	1.399(7)		
C(29)-C(30)	1.390(8)		
C(30)-C(31)	1.373(8)		
C(31)-C(32)	1.374(9)		
C(32)-C(33)	1.394(8)		
C(34)-C(39)	1.366(7)		
C(34)-C(35)	1.407(8)		
C(35)-C(36)	1.388(8)		
C(36)-C(37)	1.366(9)		
C(37)-C(38)	1.353(9)		
C(38)-C(39)	1.386(7)		
C(40)-C(41)	1.375(7)		
C(40)-C(45)	1.394(7)		
C(41)-C(42)	1.400(8)		
C(42)-C(43)	1.351(8)		
C(43)-C(44)	1.352(9)		
C(44)-C(45)	1.388(8)		
N(2)-Ru(1)-N(1)	89.88(17)		
N(2)-Ru(1)-P(2)	91.28(13)		
N(1)-Ru(1)-P(2)	170.36(12)		
N(2)-Ru(1)-P(1)	87.70(13)		
N(1)-Ru(1)-P(1)	92.09(12)		
P(2)-Ru(1)-P(1)	97.52(5)		
N(2)-Ru(1)-Cl(2)	172.29(13)		
N(1)-Ru(1)-Cl(2)	88.32(12)		
P(2)-Ru(1)-Cl(2)	89.26(5)		
P(1)-Ru(1)-Cl(2)	99.85(5)		
N(2)-Ru(1)-Cl(1)	82.78(13)		
N(1)-Ru(1)-Cl(1)	82.58(12)		
P(2)-Ru(1)-Cl(1)	88.08(5)		
P(1)-Ru(1)-Cl(1)	169.07(5)		
Cl(2)-Ru(1)-Cl(1)	89.56(5)		
C(16)-P(1)-C(22)	104.4(2)		
C(16)-P(1)-C(11)	102.5(2)		
C(22)-P(1)-C(11)	95.1(2)		
C(16)-P(1)-Ru(1)	117.71(17)		
C(22)-P(1)-Ru(1)	123.35(17)		
C(11)-P(1)-Ru(1)	109.71(18)		
C(28)-P(2)-C(40)	100.3(2)		
C(28)-P(2)-C(34)	106.4(3)		
C(40)-P(2)-C(34)	97.0(2)		
C(28)-P(2)-Ru(1)	111.11(17)		
C(40)-P(2)-Ru(1)	120.31(19)		
C(34)-P(2)-Ru(1)	119.11(18)		
C(13)-O(1)-C(15)	104.4(4)		
C(13)-N(1)-C(14)	106.3(4)		
C(13)-N(1)-Ru(1)	129.0(4)		
C(14)-N(1)-Ru(1)	118.7(3)		
C(49)-N(2)-Ru(1)	174.5(5)		

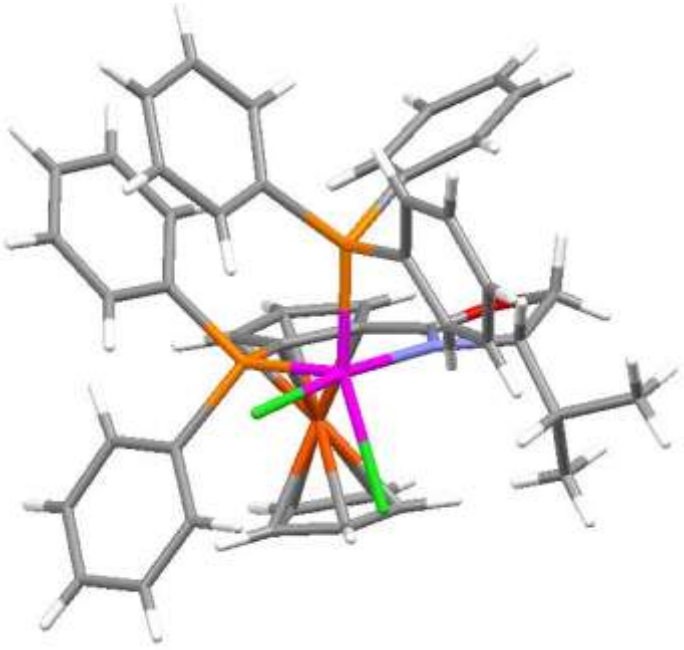


Figure S5. Molecular structure of (S_{Ox},S_{Fc})-**15** (retrieved from the Cambridge Structural Database, refcode MAPLUK)[6c]

3.2. The use of α-deprotonation- and autoactivated alkylation-reactions in the diastereoselective synthesis of phosphino-substituted ferrocenyloxazolines.

Afrooz Zirakzadeh, Kurt Mereiter, and Walter Weissensteiner

Manuscript prepared

The use of α-deprotonation- and autoactivated alkylation-reactions in the diastereoselective synthesis of phosphino-substituted ferrocenyloxazolines.

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Abstract

Two complementary and highly modular routes were developed for the synthesis of ferrocenyl-based phosphino-oxazolines all having the phosphino unit attached to a ferrocenylmethyl or a ferrocenylethyl side-chain. Both routes started from (*S*)-4-*iso*-propyl- (**5**) or (*S*)-4-phenyl-2-ferrocenyloxazoline (**8**) and in both cases was the phosphino-substituted side chain built up diastereoselectively. In the first synthesis sequence, 2-oxazolinyl substituted ferrocene aldehydes were prepared from **5** and **8** and subsequently arylated or alkylated through an auto-activated phenyl or alkyl transfer either from diphenyl zinc or from dialkyl zinc reagents and provided the product alcohols in form of single diastereomers. Furthermore, these alcohols were transformed into the desired phosphino-oxazolines all having the matching (S,S_{Ox},S_{Fc}) relative and absolute configuration. In the second sequence, starting from **5** and **8**, 2-phosphinylmethyl substituted ferrocenyl-oxazolines were prepared. These phosphine oxides were subjected to a diastereoselective α-deprotonation with *tert*-BuLi in THF at –78 °C. Quenching with MeI and subsequent reduction resulted in phosphino-oxazoline ligands with (R,S_{Ox},S_{Fc}) absolute configuration. These side chain epimers could be isomerized

with *tert*-butyl lithium and water to the desired (S,S_{Ox},S_{Fc}) configured ligands. All newly synthesized ligands were transformed into [$RuCl_2(PPh_3)(L)$] complexes and were used as catalyst precursors for transfer hydrogenations of ketones. From a comparison of these catalysis results with our previously reported data it is concluded that for this type of ligand the (S,S_{Ox},S_{Fc}) relative configuration constitutes the matching configuration while a change of either the side-chain or the oxazoline configuration leads to less efficient transfer hydrogenation catalysts. With the matching ligands and complexes products were obtained with quantitative conversion and in up to 98% enantiomeric excess.

Introduction

Since more than fifteen years have oxazoline based ferrocene derivatives been employed as ligands of asymmetric catalysts.[1] Especially FOXAP type ligands such as derivative (S_{Ox},S_{Fc})-**1** (Chart 1) were successfully used in asymmetric transformations.[2] For example, ruthenium complexes of FOXAP ligands ([$RuCl_2(PPh_3)$(FOXAP)]) performed very efficiently as catalyst precursors in the transfer hydrogenation of ketones when isopropanol was used as the hydrogen source.[3] In addition, the same type of complexes gave excellent results in hydrogenations in the presence of hydrogen gas[4] and with these conditions up-scaling even to the large industrial scale became possible.[5]

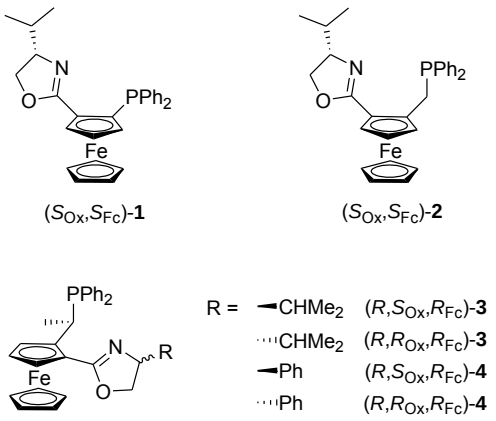


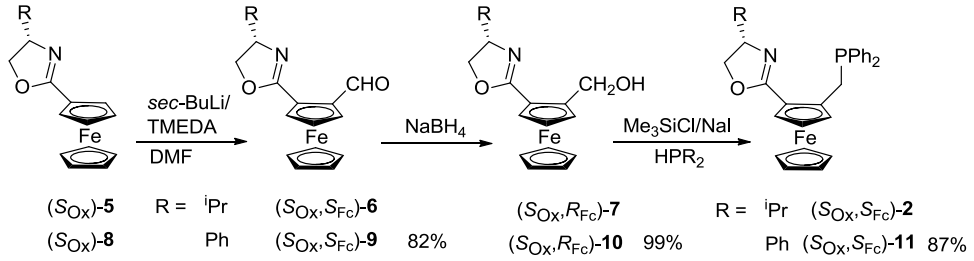
Chart 1.

Very recently, in a search for novel asymmetric hydrogenation catalysts, we have modified FOXAP type ligands by extending their ferrocene backbone to a ferrocenylmethyl or a ferrocenylethyl unit.[6] Examples of these ligands, that we called 'Raffa-FOX' ligands, are shown in Chart 1 (**2**–**4**). Ruthenium complexes

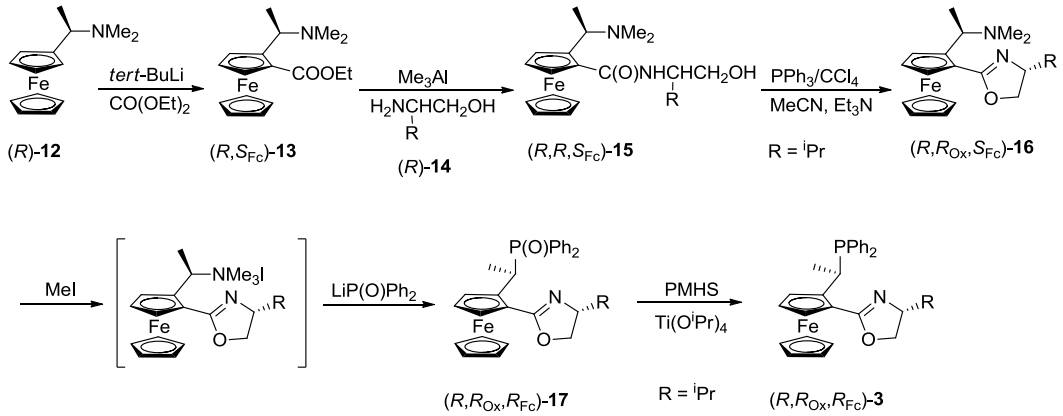
$[RuCl_2(PPh_3)(L)]$ of a number of such ligands were extensively tested as catalysts in transfer hydrogenations and hydrogenations of alkyl-aryl ketones (see Chapter 3.1). In both types of reaction several substrates were transformed into product with quantitative conversion and with an enantiomeric excess of up to 99%. From all ligands tested, derivative (R,R_{Ox},R_{Fc})-**3** performed best. In certain cases also ligand (R,R_{Ox},R_{Fc})-**4** gave comparable results while with (S_{Ox},S_{Fc})-**2** always slightly lower product e.e. values were obtained. It was also found that the results of both hydrogenation and transfer hydrogenation reactions were strongly depending on the relative configuration of the ligands applied. For example, when the transfer hydrogenation of acetophenone was carried out with use of ligand (R,R_{Ox},R_{Fc})-**3**, product 1-phenylethanol with (S) absolute configuration and 98% e.e. was obtained while when the configuration at the oxazoline carbon C4 was changed from (R_{Ox}) to (S_{Ox}) and the resulting ligand (R,S_{Ox},R_{Fc})-**3** was used, product with (R) absolute configuration and 69% e.e. was formed. Also for ligands **4** the (R_{Ox},R_{Fc}) relative configuration constitutes the matching and the (S_{Ox},R_{Fc}) configuration the mismatching combination of stereogenic units.

Our reported synthesis of ligands of type (S_{Ox},S_{Fc})-**2** required only three straightforward steps from easily accessible and commercially available ferrocenyl oxazoline (S_{Ox})-**5** (see Chapter 3.1). In the first step a diastereoselective *ortho*-deprotonation followed by reaction with dimethylformamide resulted in aldehyde (S_{Ox},S_{Fc})-**6** which after reduction to alcohol (S_{Ox},S_{Fc})-**7** was transformed into the final product. It is obvious that the *ortho*-deprotonation step already determined the relative configuration of the final product.

The original synthesis of diastereomeric ligands **3** and their analogs was designed to allow for a variation of the oxazoline substituent and the relative configuration at the oxazoline carbon to which this substituent is bound (C4). These variations could be achieved by choosing a proper aminoalcohol in the second step of the reaction sequence (Scheme 2) but this advantage was limited by the fact that for the synthesis of each ligand two enantiopure reagents were needed. For example, for the synthesis of (R,R_{Ox},R_{Fc})-**3** enantiopure starting material (R)-**12** as well as (R)-valinol, (R)-**14**, were required.



Scheme 1. Synthesis of ligands (S_{Ox},S_{Fc})-**2** and (S_{Ox},S_{Fc})-**11**.



Scheme 2. Synthesis route for ligand **3** (R = ^{i}Pr) and analogs.

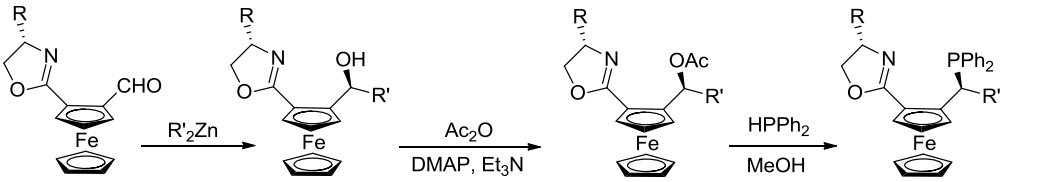
Since for **3** and analogs the (R_{Ox},R_{Fc}) relative configuration was identified as the matching configuration, we questioned whether the synthesis of such ligands with either (R_{Ox},R_{Fc}) or (S_{Ox},S_{Fc}) configuration could be simplified. As mentioned above, the *ortho* deprotonation of (*S*)-**5** and further transformations led to ligand **2** having the desired (S_{Ox},S_{Fc}) relative configuration. It seemed therefore promising to start an alternative synthesis route for **3** and related derivatives from ferrocenyl oxazolines such as **5** and **8** (Scheme 1) and to build up the side chain diastereoselectively instead of starting from enantiopure **12** that has the side chain already in place (Scheme 2).

For introducing the side chains and side chain substituents diastereoselectively, two different methodologies were taken into account. The first one is related to work of Brocard who has shown that ferrocenyl amino-aldehydes can be directly alkylated with dialkylzinc reagents.[7] The second methodology makes use of an α-deprotonation reaction. As originally reported by Marr, ferrocenylmethyl substituted phosphineoxides can be deprotonated and alkylated at the ferrocene α-position.[8] Later on Stepnicka applied this methodology to cyanomethyl substituted ferrocenes.[9]

In this contribution we describe two complementary approaches for the synthesis of ligands **3** and analogs all having (S_{Ox},S_{Fc}) configuration and either (*R*) or (*S*) configuration at the side chain α-carbon. In addition, we report on a few transfer hydrogenations that show the influence of different side chain substituents as well as of different side chain configurations on the product enantiomeric excess.

Results

*Synthesis of ligands (S_{Ox},S_{Fc})-**3** and analogs.* In order to modify and simplify the original synthesis sequence we explored two novel routes that both start from ferrocenyl oxazolines (S_{Ox})-**5** and (S_{Ox})-**8**. It was our intention to build up the phosphino-substituted side chain of **3** and analogs in such a way that the use of a second enantiopure reagent could be avoided. Furthermore, we aimed for synthesis routes that allow for a variation of the configuration at the side chain α-carbon. For this purpose, diastereoselective alkylations of aldehydes **6** and **9** (Scheme 3) were employed. As an alternative route, the diastereoselective α-deprotonation of phosphine oxides **26** and **27** was investigated (Scheme 4).



(S_{Ox},S_{Fc})-**6** R = ^{i}Pr (S,S_{Ox},R_{Fc})-**18** 97% R' = Me (S,S_{Ox},S_{Fc})-**19** (S,S_{Ox},S_{Fc})-**3** 86%
(S,S_{Ox},R_{Fc})-**20** 97% Ph (S,S_{Ox},S_{Fc})-**21** (S,S_{Ox},S_{Fc})-**22** 84%
(S,S_{Ox},R_{Fc})-**23** 96% Et
(S_{Ox},S_{Fc})-**9** R = Ph (S,S_{Ox},R_{Fc})-**24** 96% R' = Me (S,S_{Ox},S_{Fc})-**25** (S,S_{Ox},S_{Fc})-**4** 80%

Scheme 3.

Alkyl and phenyl transfer with use of R_2Zn reagents. Several groups have already investigated the diastereoselectivity of alkyl and aryl transfers to 2-substituted ferrocenylaldehydes.[7,10] Mainly the reactivity of lithium, magnesium and zinc reagents was studied. It was found that in many cases the transfer of rather small alkyl groups such as methyl or ethyl substituents work best with use of dialkyl zinc reagents. Usually, the alkyl transfer from dialkyl zinc reagents to aldehydes proceeds rather slowly, but its reaction rate increases significantly when a catalyst such as an amino alcohol is added. However, according to Brocard[7] and Fukuzawa,[10d] the reaction of amino substituted ferrocenyl carbaldehydes 2-(*N*,*N*-dimethylaminomethyl)-ferrocenylcarbaldehyde and 2-

(1-*N*,*N*-dimethylaminoethyl)-ferrocenylcarbaldehyde with dialkyl zinc reagents went on smoothly without a catalyst and this fact was rationalized by invoking an autocatalytic or auto-activation mechanism that involves the participation of the dimethylamino nitrogen and the carbonyl oxygen. Since such an effect has also been reported for a pyrimidyl substituted ferrocenylaldehyde[11] we reasoned whether oxazoline units could also promote autocatalytic alkyl transfers.

When aldehyde (S_{Ox},S_{Fc})-**6** was reacted in toluene with dimethyl zinc or diethyl zinc (Scheme 3), indeed, the desired product alcohols (S,S_{Ox},R_{Fc})-**18** and (S,S_{Ox},R_{Fc})-**23** were obtained in nearly quantitative yield and in each case with a diastereomer ratio of 97:3. Surprisingly, when diphenyl zinc was used as the reagent also a phenyl transfer was possible resulting in alcohol (S,S_{Ox},R_{Fc})-**20**. With oxazoline (S_{Ox},S_{Fc})-**9**, which was easily accessible form (S_{Ox})-**8**, and dimethyl zinc alcohol (S,S_{Ox},R_{Fc})-**24** was formed again with a diastereomer ratio of 97:3 (for details on the synthesis of (S_{Ox})-**8** see Supporting). In all cases had the main product the desired (S) side chain configuration.

From alcohol (S,S_{Ox},R_{Fc})-**18** suitable single crystals could be grown and its molecular structure in the solid state was studied by X-ray diffraction confirming both its relative and absolute configuration (Figure 1). Details of this X-ray crystallography study are given in Table 1 of the Supporting Information.

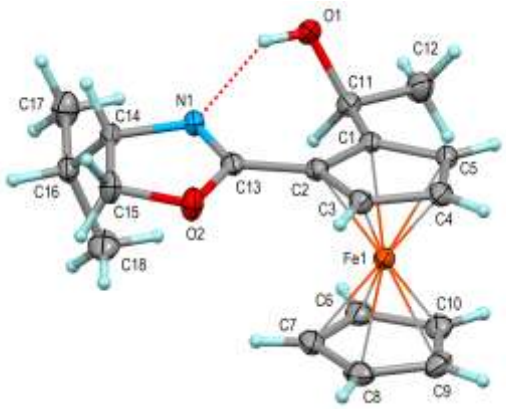


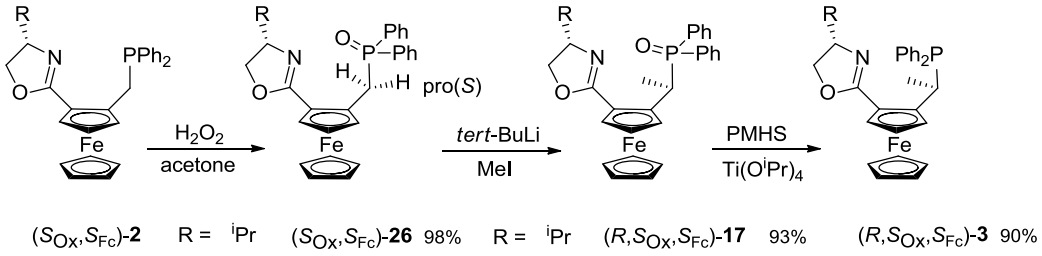
Figure 1. Molecular structure of (S,S_{Ox},R_{Fc})-**18**.

After chromatographic separation of the respective diastereomers, alcohols (S,S_{Ox},R_{Fc})-**18**, **20**, and **24** were transformed into the acetates **19**, **21**, and **25**. A further reaction with diphenylphosphine led to the desired phosphino-oxazolines (S,S_{Ox},S_{Fc})-**3** and (S,S_{Ox},S_{Fc})-**4** as well as to the novel ligand (S,S_{Ox},S_{Fc})-**22** having a phenyl substituent attached to the side chain α-carbon. As expected, the acetate/phosphine exchange proceeded with retention of configuration at the ferrocenyl α-carbon.[12] It

should be mentioned that ligands **3** and **4** were obtained with the same relative configuration, (S,S_{Ox},S_{Fc}), than those that preformed best in transfer hydrogenation and hydrogenation reactions.

Diastereoselective α-deprotonation of phosphine oxides

In 1975 Marr reported that – like benzyldiphenylphosphine oxide – also ferrocenylmethyldiphenylphosphine oxide can be deprotonated with butyl lithium at the α-position and the resulting anion can be reacted with electrophiles.[8] Recently this methodology has been used by Stepnicka to derivatize a cyanomethyl substituted ferrocene diastereoselectively.[9] Therefore we questioned whether phosphine oxide **26** (Scheme 4) could also be deprotonated and alkylated at the side chain methylene group and whether this reaction could be run diastereoselectively.



(S_{Ox},S_{Fc})-**2** R = ^{i}Pr (S_{Ox},S_{Fc})-**26** 98% R = ^{i}Pr (R,S_{Ox},S_{Fc})-**17** 93% (R,S_{Ox},S_{Fc})-**3** 90%

Scheme 4.

For this purpose phosphine oxide (S_{Ox},S_{Fc})-**26** was prepared from phosphine (S_{Ox},S_{Fc})-**2** (98%) by reaction with H_2O_2 in acetone.[12] As mentioned above, this precursor, (S_{Ox},S_{Fc})-**2**, is accessible in three steps from oxazoline (S_{Ox})-**5** (Scheme 1). In order to optimize the reaction conditions, phosphine oxide **26** was treated in THF or Et_2O at different temperatures with bases *n*-BuLi, *tert*-BuLi or Li-TMP and the intermediate anions were quenched with MeI (Table 1). In all cases was the product diastereomer ratio strongly depending on the reaction temperature and the solvent used.

The best diastereoselectivity could be obtained when (S_{Ox},S_{Fc})-**26** was reacted in THF with 1.2 equivalents of *tert*-BuLi at –78 °C (Table 1, entry 6). Quenching with MeI resulted in a 97/3 mixture of diastereomers (R,S_{Ox},S_{Fc})-**17** and (S,S_{Ox},S_{Fc})-**17** (93% overall isolated yield). We suspect that this high diastereoselectivity could at least in part be caused by a corroborative action of the oxazoline unit and the base. The oxazoline unit is expected to co-ordinate to lithium and thereby directing the base to the pro-(R) methylene hydrogen of the side chain. Quenching with MeI under retention of configuration would result in the observed main diastereomer (R,S_{Ox},S_{Fc})-**17**. A further

reduction of this diastereomer gave ligand (R,S_{Ox},S_{Fc})-**3** which represents the side chain epimer of (S,S_{Ox},S_{Fc})-**3.** As already mentioned, its enantiomer (R,R_{Ox},R_{Fc})-**3** had performed the best in the hydrogenation and transfer hydrogenation of ketones.

Table 1. α-Alkylation of (S_{Ox},S_{Fc})-**26** with different bases and MeI.

entry	base/solvent	equiv. base	T, °C	(R)-**17**[a]/(S)-**17**[b]/**30**[c]
1	*n*-BuLi / THF	1.1	r.t.	65/15/20[d]
2	*tert*-BuLi / THF	1.1	r.t.	80/17/3
3	*tert*-BuLi / Et_2O	1.1	r.t.	57/43/0
4	Li-TMP / THF	1.1	0	79/16/5
5	*tert*-BuLi / THF	1.1	–78	94/6/0
6	*tert*-BuLi / THF	1.2	–78	**97/3/0**
7	*n*-BuLi / THF	1.2	–78	91/4/5
8	Li-TMP / THF	1.2	–78	92/3/5

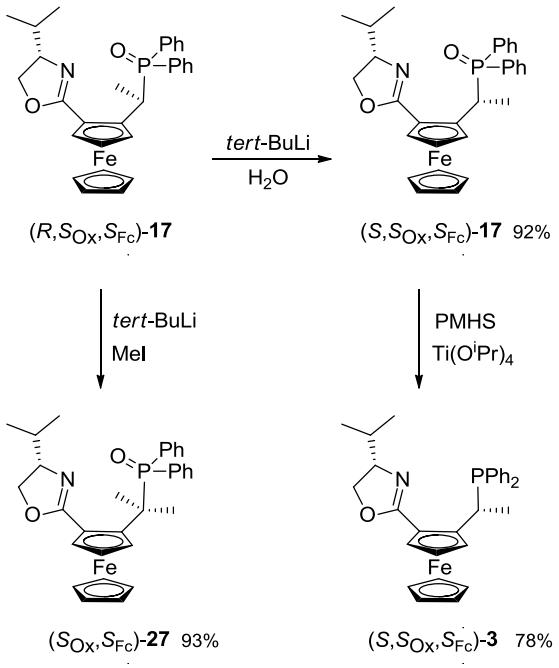
[a] (R,S_{Ox},S_{Fc})-**17**, [b] (S,S_{Ox},S_{Fc})-**17**, [c] unreacted starting material, [d] ratios determined by ^{1}H-NMR

Since the alkylation of (S_{Ox},S_{Fc})-**26** to (R,S_{Ox},S_{Fc})-**17** could be carried out with full conversion of substrate and with high diastereoselectivity, we questioned whether **17** could be alkylated a second time at the ferrocenyl α-position. Indeed, when (R,S_{Ox},S_{Fc})-**17** was reacted in THF with 1.2 equivalents of *tert*-BuLi at –78 °C, after quenching with MeI, the doubly α-substituted ferrocene derivative (S_{Ox},S_{Fc})-**27** was obtained 93% isolated yield.

Furthermore, we investigated whether the epimers (R,S_{Ox},S_{Fc})-**17** and (S,S_{Ox},S_{Fc})-**17** can be converted into each other. For this purpose (R,S_{Ox},S_{Fc})-**17** was reacted with *tert*-BuLi and the lithiated intermediate was quenched with water (Scheme 5). Under optimized conditions (THF, 2 equivalents of base, –78 °C) 95% of the epimer (S,S_{Ox},S_{Fc})-**17** was formed. In a control experiment (S,S_{Ox},S_{Fc})-**17** was subjected to the same reaction conditions, but in this case no epimerization took place. This result indicates that phosphine oxide (S,S_{Ox},S_{Fc})-**17** is thermodynamically more stable than its epimer (R,S_{Ox},S_{Fc})-**17** and consequently, in the alkylation of (S_{Ox},S_{Fc})-**26** with *tert*-BuLi and MeI the thermodynamically less stable diastereomer (R,S_{Ox},S_{Fc})-**17** was formed.

In summary, the reaction of the oxazoline substituted ferrocenyl aldehydes (S_{Ox},S_{Fc})-**6** and (S_{Ox},S_{Fc})-**9** with dimethyl- and diphenyl zinc gave alcohols **18**, **20**, and

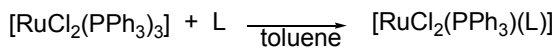
24 with very high diastereoselectivity (94% d.e.) which could be further transformed into the desired ligands **3**, **4**, and **22**. In this case, all ligands were obtained with (S,S_{Ox},S_{Fc}) absolute configuration. Complementary, α-deprotonation and alkylation of phosphine oxide (S_{Ox},S_{Fc})-**26** gave intermediate **17** which after reduction of the phosphine oxide resulted in the side chain epimer (R,S_{Ox},S_{Fc})-**3**.



Scheme 5. α-Alkylation and isomerization of (R,S_{Ox},S_{Fc})-**17**.

Transfer hydrogenation of ketones

Since with use of ruthenium complex [$RuCl_2(PPh_3)$((R,R_{Ox},R_{Fc})-**3**)] excellent results had been obtained in the transfer hydrogenation and hydrogenation of a variety of aryl-alkyl ketones,[6] it was of interest to compare the performance of this ligand with that of its side-chain epimer (S,R_{Ox},R_{Fc})-**3** and its side-chain substituted analog (R,R_{Ox},R_{Fc})-**22** that bears a phenyl instead of a methyl group at the ferrocenyl α-position. Because of synthetic availability, for the transfer hydrogenations of ketones the enantiomers (R,S_{Ox},S_{Fc})-**3** and (S,S_{Ox},S_{Fc})-**22** were used. For this purpose complexes (R,S_{Ox},S_{Fc})-**29** and (S,S_{Ox},S_{Fc})-**30** were prepared by reaction of ligands (R,S_{Ox},S_{Fc})-**3** and (S,S_{Ox},S_{Fc})-**22** with [$RuCl_2(PPh_3)_3$] (Scheme 6).



L =	complex =
(S_{Ox},S_{Fc})-**1**	(S_{Ox},S_{Fc})-**28**
(R,R_{Ox},R_{Fc})-**3**	(R,R_{Ox},R_{Fc})-**29**
(R,S_{Ox},S_{Fc})-**3**	(R,S_{Ox},S_{Fc})-**29**
(S,S_{Ox},S_{Fc})-**22**	(S,S_{Ox},S_{Fc})-**30**

Scheme 6.

All transfer hydrogenations were carried out at r.t. with 2-propanol as the hydrogen source and potassium isopropoxide as the base (for reaction details see Experimental). The transfer hydrogenation results obtained with ketones acetophenone (ACP), 4-methyl-acetophenone (4-Me-ACP) and phenyl-benzylketone (PBK) and complexes (R,R_{Ox},R_{Fc})-**29**, (R,S_{Ox},S_{Fc})-**29** and (S,S_{Ox},S_{Fc})-**30** are summarized in Table 2. In all cases only isolated ruthenium complexes were used as the catalyst precursors. For assuring comparable reaction conditions, FOXAP complex (S_{Ox},S_{Fc})-**28** (Scheme 6) of ligand **1** (Chart 1) was used as the reference.

A comparison of all data of Table 2 shows that complex (R,R_{Ox},R_{Fc})-**29** [ligand (R,R_{Ox},R_{Fc})-**3**] performed best with all three substrates (entries 2,6,10). When complex (S,S_{Ox},S_{Fc})-**30** with the side-chain phenyl substituted ligand (S,S_{Ox},S_{Fc})-**22** was used all product e.e.s dropped by about 10% and also the reaction rate decreased (entries 4,8,12). With complex (R,S_{Ox},S_{Fc})-**29** [ligand (R,S_{Ox},S_{Fc})-**3**] the most significant changes were observed. Not only decreased the reaction rates further, but also the product e.e.s became very low (entries 3, 7 and11).

With respect to product absolute configuration a consistent picture is seen. With all complexes of (R_{Ox},R_{Fc}) absolute configuration always products of (S) configuration were obtained. From these and our previously reported transfer hydrogenation results some conclusions can be drawn. When the performance of the diastereomeric complexes and ligands (R,R_{Ox},R_{Fc})-**29** [ligand (R,R_{Ox},R_{Fc})-**3**], (R,S_{Ox},R_{Fc})-**29** [ligand (R,S_{Ox},R_{Fc})-**3**], and (S,R_{Ox},R_{Fc})-**29** [ligand (S,R_{Ox},R_{Fc})-**3**] – all normalized to the same (R_{Fc}) ferrocene configuration – are compared to each other some general features are seen. With all investigated substrates ligand (R,R_{Ox},R_{Fc})-**3** performed best with respect to product e.e. and therefore we consider the (R,R_{Ox},R_{Fc}) relative configuration to be the matching configuration. Changes either of the side-chain [ligand (S,R_{Ox},R_{Fc})-**3**] or the oxazoline configuration [ligand (R,S_{Ox},R_{Fc})-**3**] led to lower product e.e.s. Furthermore, a change of the side-chain substituent of ligand (R,R_{Ox},R_{Fc})-**3** from methyl to phenyl [ligand (R,R_{Ox},R_{Fc})-**22**] resulted in a drop of product enantiomeric excess.

Table 2. Transfer hydrogenation results obtained for three ketones.[a]

entry	substrate	complex	time[e]	% conv.	% e.e.	abs. conf.
1	ACP[b]	(S_{Ox},S_{Fc})-**28**	20 min	99	96	*R*
2	ACP	(R,R_{Ox},R_{Fc})-**29**	10 min	99	**98**	*S*
3	ACP	(R,S_{Ox},S_{Fc})-**29**	1 h	80	41	*R*
4	ACP	(S,S_{Ox},S_{Fc})-**30**	30 min	97	90	*R*
5	4-Me-ACP[c]	(S_{Ox},S_{Fc})-**28**	10 min	97	96	*R*
6	4-Me-ACP	(R,R_{Ox},R_{Fc})-**29**	10 min	97	**98**	*S*
7	4-Me-ACP	(R,S_{Ox},S_{Fc})-**29**	2 h	95	28	*R*
8	4-Me-ACP	(S,S_{Ox},S_{Fc})-**30**	30 min	95	88	*R*
9	PBK[d]	(S_{Ox},S_{Fc})-**28**	10 min	>99	95	*R*
10	PBK	(R,R_{Ox},R_{Fc})-**29**	20 min	>98	**97**	*S*
11	PBK	(R,S_{Ox},S_{Fc})-**29**	4 h	35	57	*R*
12	PBK	(S,S_{Ox},S_{Fc})-**30**	4 h	57	87	*R*

[a] Reaction conditions: 1 mmol of substrate in 51 mL of 2-propanol (19.6 mM), 0.5% catalyst and 2% base (S/C/base = 200/1/4), [b] ACP: acetophenone, [c] 4-Me-ACP: 4-methyl-acetophenone, [d] PBK: phenylbenzyl ketone, [e] reaction time optimised with respect to conversion and product e.e.

Conclusions

In order to simplify the synthesis of ferrocenyl-based phosphino-oxazolines that have the phosphino unit attached to a ferrocenylmethyl or a ferrocenylethyl side-chain two complementary synthesis routes were explored. Both routes started from easily accessible ferrocenyl-oxazolines and in both cases the phosphino-substituted side chain was build up diastereoselectively. The first route made use of an auto-activated alkyl transfer either from diphenyl zinc or from dialkyl zinc reagents to 2-oxazolinyl substituted ferrocene aldehydes. The resulting alcohols were obtained in form of single diastereomers and could be further transformed into the desired phosphino-oxazolines. Via this route differently substituted ligands all suitable for use in transfer hydrogenations of ketones and all having the matching (S,S_{Ox},S_{Fc}) relative configuration could be obtained in enantiomerically pure form.

The second route made use of the fact that phosphine oxides can be deprotonated and alkylated at their α-positions. In this case 2-phosphinylmethyl substituted ferrocenyloxazolines were deprotonated and alkylated at the side-chain

methylene group. However in this case product with (R,S_{Ox},S_{Fc}) configuration was obtained in very high diastereoselectivity. Furthermore, it was shown that with use of this methodology not only one but two alkyl (methyl) groups can be attached consecutively to the ferrocene side-chain α-position. In addition, the epimerization of phosphine oxazoline (R,S_{Ox},S_{Fc})-3 into (S,S_{Ox},S_{Fc})-3 was studied. It was found that (R,S_{Ox},S_{Fc})-3 can be transformed almost quantitatively into its thermodynamically more stable epimer (S,S_{Ox},S_{Fc})-3. Therefore both epimers of 3 are accessible via this route.

Transfer hydrogenations with 2-propanol as the hydrogen source and potassium alkoxide as the base were carried out with use of [$RuCl_2(PPh_3)(L)$] complexes of two ligands and three aryl-alkyl ketones. The results obtained were compared with our previously reported data. It was concluded that for this type of ligand the (S,S_{Ox},S_{Fc}) relative configuration constitutes the matching configuration while both changes of the side-chain or of the oxazoline configuration leads to less efficient transfer hydrogenation catalysts.

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Supporting Information Available Text giving full experimental descriptions and spectroscopic data for all newly synthesized ligands and complexes as well as detailed hydrogenation and transfer hydrogenation data is provided. Crystallographic and geometric data for (S,S_{Ox},R_{Fc})-**18** is given in the Supporting text and in CIF format. This material is available free of charge via the Internet.

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Supporting Information

The use of α-deprotonation- and autoactivated alkylation-reactions in the diastereoselective synthesis of phosphino-substituted ferrocenyloxazolines.

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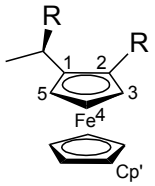
Contents

General considerations

All reactions required inert conditions and were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried by standard procedures and distilled before use. Preparative chromatographic separations were performed under gravity on standardised aluminium oxide 90 (MERCK). Petroleum ether with a boiling range of 55–65 °C was used for chromatography. Abbreviations: PE: petroleum ether; DEE: diethyl ether; EA: ethyl acetate; DCM: dichloromethane; THF: tetrahydrofurane, DMAP: 4-N,N-dimethylaminopyridine. The following substrates were purchased and were used without further purification: (*S*)-(4-isopropyloxazolin-2-yl)ferrocene (TCI), diethylzinc solution in toluene (Aldrich). NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ or CD_2Cl_2. Chemical shifts (δ) are given relative to $CHCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.0 ppm), CH_2Cl_2 (^{1}H: 5.32 ppm, ^{13}C: 54.0 ppm) and 85% H_3PO_4 (^{31}P: 0 ppm). The coupling constants in $^{13}C\{^1H\}$ spectra are due to ^{13}C-^{31}P coupling. For signal assignment the following terms were used: s, bs, d, dd, t, q and m refer to singlet, broad singlet, doublet, doublet of doublets, triplet, quartet and multiplet, respectively. The terms Ph^A and Ph^B were used to distinguish phenyl groups of diphenylphosphino units and Ph^{Ox} and Ph^P were used to distinguish phenyl groups of oxazoline and diphenylphosphino units. A general atom numbering scheme used for proton and carbon assignment is given below. Melting points were determined on a Kofler melting point apparatus and are uncorrected. Mass spectra were recorded on instruments Finnigan MAT 900 S, MAT 95 S and Bruker ESI-Qq aoTOF. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Conversion and e.e. values were measured with use of an Agilent 7890 A GC or an Agilent 1200 HPLC.



Atom numbering scheme for NMR assignment of ferrocenes.

(R,S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-(diphenylphosphino)-ethyl]-ferrocene, (R,S_{Ox},S_{Fc})-3

To a solution of (R,S_{Ox},S_{Fc})**-17** (1.0 g, 1.90 mmol) in THF (5 mL) were added polymethylhydrosiloxane (1.23 g) and titanium(IV) isopropoxide (2.16 g, 7.6 mmol) and the resulting mixture was heated at 80 °C for 30 minutes. After cooling to r.t, the dark solution was chromatographed on aluminium oxide 90 without previous workup under inert conditions with deoxygenated solvents. The crude product was chromatographed twice using PE/EA/TEA = 5/5/1 as the eluent. A third chromatography using PE/EA/TEA = 8/2/1 provided the pure product as an orange semisolid (873 mg, 1.71 mmol, 90% yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.03 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.06 (dd, J = 7.4 Hz, J = 8.3 Hz, 3H, CHCH_3), 1.01 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.83–1.94 (m, 1H, CH(CH_3)$_2$), 3.99–4.8 (m, 7H, Cp' + CHHO + CHN), 4.23 (t, J = 2.5 Hz, 1H, H4), 4.24–4.28 (m, 1H, CHHO), 4.64 (m, 1H, H5), 4.41–4.497 (m, 1H, C$H$$CH_3$), 4.62–4.67 (dd, J = 1.5 Hz, J = 2.5 Hz, 1H, H3), 7.29–7.40 (m, 6H, Ph-*meta* + Ph-*para*), 7.55–7.62 (m, 2H, Ph-*ortho*), 7.66–7.73 (m, 2H, Ph-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 18.4 (CH($C$$H_3$)($CH_3$)), 19.0 (CH($CH_3$)($C$$H_3$)), 21.3 (d, J = 4.8 Hz, CH$C$$H_3$), 28.7 (d, J = 13.6 Hz, CHCH$_3$), 32.8 (CH(CH_3)$_2$), 68.4 (C4), 68.8 (CH_2O), 69.0 (d, J = 2.2 Hz, C3), 70.3 (Cp'), 70.7 (d, J = 10.8 Hz, C5), 72.7 (CHN), 95.1 (C1), 128.0, 128.1, 128.2 (3C, Ph-*meta* + Ph-*para*), 128.4 (d, J = 6.1 Hz, 2C, Ph-*meta*), 128.9 (Ph-*para*), 132.9 (d, J = 17.6 Hz, 2C, Ph-*ortho*), 135.3 (d, J = 21.6 Hz, 2C, Ph-*ortho*), 165.7 (C=N). C2 and Ph-*ipso* not observed. ^{31}P{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 0.6 (PPh_2), HR-MS (ESI in MeOH/MeCN): *m/z* [M+H]$^+$ calcd. for $C_{30}H_{33}FeNOP$: 510.1649, found: 510.1652. $[\alpha]^{20}_{\lambda}$ (nm): –80 (589), –90 (578), –131 (546) (*c* 0.740, $CHCl_3$).

(S_{Ox},R_{Fc})-2-[4,5-Dihydro-4-(phenyl)oxazol-2-yl)-1-hydroxymethyl-ferrocene, (S_{Ox},R_{Fc})-10

To a solution of (S_{Ox},S_{Fc})**-9** (1.5 g, 4.18 mmol) in methanol (50 mL) was added $NaBH_4$ (474 mg, 12.53 mmol) in portions at 0 °C. The mixture was warmed to r.t. and stirred for 90 minutes. After cooling again to 0 °C, the reaction mixture was quenched by dropwise addition of water, and then the phases were separated. The aqueous phase was extracted with DEE (3 × 25 mL), and the organic phase was washed with water and dried over $MgSO_4$ and then the solvents were removed under reduced pressure. The crude product was chromatographed on aluminium oxide 90 using PE/EA = 5/1 as eluent giving the pure compound as an orange oil (1.49 g, 4.12 mmol, 99% yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 4.26 (s, 5H, Cp'), 4.27–4.31 (m, 2H, CHHO + H5), 4.38–4.47 (m,

2H, C*H*HOH + H3/4), 4.65–4.75 (m, 3H, CH*H*O + CH*H*OH + H3/4), 5.21–5.31 (m, 1H, CHN), 6.11 (bs, 1H, OH), 7.29–7.36 (m, 3H, Ph-*ortho* + Ph-*para*), 7.38–7.44 (m, 2H, Ph-*meta*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 59.6 (CH_2OH), 68.4 (C5), 68.4 (C2), 69.1 (CHN), 70.1 (Cp'), 70.5 (C3/4), 72.3 (C3/4), 74.8 (CH_2O), 89.8 (C1), 126.2 (2C, Ph-*ortho*), 127.7 (Ph-*para*), 128.3 (2C, Ph-*meta*), 142.4 (Ph-*ipso*), 169.1 (C=N). HR-MS (ESI in MeOH/MeCN): *m/z* $[M+H]^+$ calcd. for $C_{20}H_{20}FeNO_2$: 362.0843, found: 362.0836. $[\alpha]^{20}_{\lambda}$ (nm): –410 (589), –468 (578), –750 (546) (*c* 0.285, $CHCl_3$).

(S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(phenyl)oxazol-2-yl)-1-(diphenylphosphino)methyl-ferrocene, (S_{Ox},S_{Fc})-11

To a stirred solution of (S_{Ox},R_{Fc})**-10** (1.3 g, 3.60 mmol) and sodium iodide (1.08 g, 7.21 mmol) in acetonitrile (35 mL) was added chlorotrimethylsilane (978 mg, 9.0 mmol). which led to a change of color from orange to red. After additional stirring for 10 minutes at r.t. diphenylphosphine (804 mg, 4.32 mmol) was added. The reaction mixture was stirred for 24 h at r.t.; subsequently without previous workup the crude product was purified by chromatography under inert conditions with deoxygenated solvents on aluminium oxide 90. The solvent mixture PE/DEE = 20/1 removed excess of diphenylphosphine and PE/EA/TEA = 2/1/1 + 10% DCM eluted the title compound as an orange semisolid (1.65 g, 3.12 mmol, 86% yield). ^1H NMR (400MHz, $CDCl_3$): δ 3.39 (dd, *J* = 1.9 Hz, *J* = 13.8 Hz, 1H, C*H*HP), 3.96–4.01 (m, 2H, CH*H*P + H5), 4.09 (t, *J* = 8.2 Hz, 1H, C*H*HO), 4.14 (s, 5H, Cp'), 4.14–4.17(m, 1H, H4), 4.63 (dd, *J* = 8.2 Hz, *J* = 9.9 Hz, 1H, CH*H*O), 4.68–4.72 (m, 1H, H3), 5.24 (dd, *J* = 8.2 Hz, *J* = 9.9 Hz, 1H, CHN), 7.20–7.52 (18H, Ph). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 29.4 (d, *J* = 15.3 Hz, CH_2P), 68.6 (C4), 68.9 (C2), 69.3 (C3), 69.9 (CHN), 70.3 (Cp'), 71.9 (d, *J* = 5.4 Hz, C5), 79.9 (CH_2O), 86.4 (d, *J* = 17.3 Hz, C1), 126.7 (2C, Ph^{Ox}-*ortho*), 127.3 (Ph-*para*), 128.0 (Ph-*para*), 128.1 (d, *J* = 6.9 Hz, 2C, Ph^{P}-*meta*), 128.3 (d, *J* = 6.9 Hz, 2C, Ph^{P}-*meta*), 128.6 (Ph^{Ox}-*meta*), 128.8 (Ph-*para*), 132.2 (d, *J* = 17.6 Hz, 2C, Ph^{P}-*ortho*), 133.7 (d, *J* = 19.9 Hz, 2C, Ph^{P}-*ortho*), 138.3 (d, *J* = 15.7 Hz, Ph^{P}-*ipso*), 139.4 (d, *J* = 16.5 Hz, Ph^{P}-*ipso*), 143.2 (Ph^{Ox}-*ipso*), 167.3 (C=N). $^{31}P\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ –9.1 (PPh_2). HR-MS (ESI in MeOH/MeCN): *m/z* $[M+CH_3OH+H]^+$ calcd. for $C_{33}H_{33}FeNO_2P$: 562.1598, found: 562.1050. $[\alpha]^{20}_{\lambda}$ (nm): +2 (589), +0.4 (578), –12 (546) (*c* 0.280, $CHCl_3$).

(R,S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-(diphenylphosphinyl)-ethyl]-ferrocene, (R,S_{Ox},S_{Fc})-17

To a solution of (S_{Ox},S_{Fc})-**26** (1.5 g, 2.93 mmol) in THF (20 mL) was added ^{t}BuLi (2.2 mL, 1.6 M, 3.52 mmol) at –78 °C which immediately led to a change of color from orange to dark red. After stirring at –78 °C for 30 minutes, methyl iodide (1.32 g, 8.79 mmol) was added. The reaction mixture was stirred for 30 minutes at –78 ºC, and for additional 3 h at r.t. Subsequently, the reaction mixture was quenched by addition of water and the phases were separated. The aqueous phase was extracted with DEE (3 x 25 mL). The organics were combined, washed with water and brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by chromatography on aluminium oxide 90 (eluent PE/EA/TEA = 1/1/1) to provide the title compound as an orange semisolid (1.43 g, 2.72 mmol, 93% yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.06 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.13 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.15 (dd, J = 7.3 Hz, J = 16.2 Hz, 3H, CHCH_3), 1.89–1.99 (m, 1H, CH(CH_3)$_2$), 3.67 (s, 5H, Cp'), 3.99–4.08 (m, 2H, CHHO + CHN), 4.18–4.29 (m, 1H, CHHO), 4.31 (t, J = 2.5 Hz, 1H, H4), 4.64–4.68 (m, 1H, H3), 4.74–4.82 (m, 1H, C$H$$CH_3$), 4.82–4.86 (m, 1H, H5), 7.42–7.48 (m, 3H, Ph^{A}-*meta* + Ph^{A}-*para*), 7.49–7.57 (m, 3H, Ph^{B}-*meta* + Ph^{B}-*para*), 7.79–7.89 (m, 2H, Ph^{A}-*ortho*), 8.17–8.26 (m, 2H, Ph^{B}-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 18.3 (CH(*C*H_3)(CH_3)), 18.9 (CH(CH_3)(*C*H_3)), 20.8 (bs, CH*C*H_3), 29.9 (d, J = 73.6 Hz, *C*HCH_3), 32.7 (*C*H(CH_3)$_2$), 68.52 (C3), 68.54 (CH_2O), 69.0 (C4), 70.3 (Cp'), 71.6 (C2), 71.8 (bs, C5), 72.6 (CHN), 89.4 (bs, C1), 128.5 (d, J = 11.0 Hz, 2C, Ph^{A}-*meta*), 128.7 (d, J = 11.1 Hz, 2C, Ph^{B}-*meta*), 130.7 (d, J = 8.4 Hz, 2C, Ph^{A}-*ortho*), 130.9 (d, J = 2.3 Hz, Ph^{A}-*para*), 131.4 (d, J = 8.7 Hz, 2C, Ph^{B}-*ortho*), 131.5 (d, J = 2.4 Hz, Ph^{B}-*para*), 165.8 (C=N), Ph-*ipso* not observed. ^{31}P{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 34.9 (P(O)Ph_2), HR-MS (ESI in MeOH/MeCN): *m/z* $[M+H]^+$ calcd. for $C_{30}H_{32}FeNO_2P$: 526.1598, found: 526.1593. $[\alpha]^{20}_{\lambda}$ (nm): –168 (589), –189 (578), –272 (546) (*c* 0.263, $CHCl_3$).

(S,S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-(hydroxy)ethyl]-ferrocene, (S,S_{Ox},S_{Fc})-18

To a solution of (S_{Ox},S_{Fc})-**6** (1.0 g, 3.08 mmol) in THF (30 mL) was added a solution of dimethylzinc in toluene (5.64 mL, 1.2 M, 6.77 mmol) at 0 °C. After warming up to r.t and stirring overnight, the reaction mixture was quenched by addition of water and the phases were separated. The aqueous phase was extracted with DEE (3 x 25 mL); the organics were combined, washed with water and brine and dried over $MgSO_4$. The

solvent was removed under reduced pressure and the crude product was purified by chromatography on aluminium oxide 90 (eluent PE/EA = 5/1) to give the title compound as an orange solid (1.02 g, 2.99 mmol, 97% yield). Single crystals suitable for X-ray crystallography were obtained from EA solution by slow evaporation of the solvent. M.p.: 112 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.01 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.04 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.53 (d, J = 6.7 Hz, 3H, CHCH_3), 1.77–1.87 (m, 1H, CH(CH_3)$_2$), 3.96–4.05 (m, 1H, CHN), 4.12–4.19 (m, 1H, CHHO), 4.15 (s, 5H, Cp'), 4.24 (t, J = 2.5 Hz, 1H, H4), 4.28–4.35 (m, 1H, CHHO), 4.40 (dd, J = 1.5 Hz, J = 2.5 Hz, 1H, H5), 4.60 (dd, J = 1.5 Hz, J = 2.5 Hz, 1H, H3), 4.99 (q, J = 6.7 Hz, 1H, CHCH3), 6.82 (bs, 1H, OH). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 18.4 (CH(*C*H_3)(CH_3)), 18.5 (CH(CH_3)(*C*H_3)), 20.9 (CH*C*H_3), 32.6 (*C*H(CH_3)$_2$), 64.8 (*C*HCH$_3$), 68.1 (C4), 69.1 (C2), 69.4 (C5), 70.1 (Cp'), 70.2 (CH_2O), 70.6 (C3), 71.6 (CHN), 93.3 (C1), 167.6 (C=N). HR-MS (ESI in MeOH/MeCN): *m/z* [M+Na]$^{+}$ calcd. for $C_{18}H_{23}FeNO_2Na$: 364.0976, found: 364.0968. $[\alpha]^{20}_{\lambda}$ (nm): –322 (589), –372 (578), –629 (546) (*c* 0.260, $CHCl_3$).

(*S*,*S*$_{Ox}$,*S*$_{Fc}$)-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-(acetoxy)ethyl]--ferrocene, (*S*,*S*$_{Ox}$,*S*$_{Fc}$)-19

A solution of a catalytic amount of DMAP in Ac_2O (1.17 mL, 12.35 mmol) was added to a stirred solution of (*S*,*S*$_{Ox}$,*S*$_{Fc}$)-**18** (836 mg, 2.45 mmol) in freshly distilled triethylamine (4.5 mL). After stirring for 17 h at r.t, the reaction mixture was quenched by addition of water and the phases were separated. The aqueous phase was extracted with EA (3 x 25 mL); the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was used without any further purification (854 mg, 2.23 mmol). ^{1}H NMR (400MHz, $CDCl_3$): δ 0.89 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 0.96 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.67 (d, J = 6.5 Hz, 3H, CHCH_3), 1.72–1.84 (m, 1H, CH(CH_3)$_2$), 1.92 (s, 3H, COCH_3), 3.90–4.03 (m, 2H, CHN + CHHO), 4.16 (s, 5H, Cp'), 4.24–4.31 (m, 1H, CHHO), 4.34 (t, J = 2.5 Hz, 1H, H4), 4.44–4.48 (m, 1H, H5), 4.79 (dd, J = 1.5 Hz, J = 2.5 Hz, 1H, H3), 6.29 (q, J = 6.5 Hz, 1H, CHCH$_3$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 17.9 (CH(*C*H_3)(CH_3)), 18.5 (CH(CH_3)(*C*H_3)), 18.6 (CH*C*H_3), 21.2 (CO*C*H_3), 32.4 (*C*H(CH_3)$_2$), 68.5 (*C*HCH$_3$), 68.9 (C5), 69.1 (C4), 69.5 (CH_2O), 70.3 (Cp'), 70.9 (C3), 72.0 (CHN), 87.4 (C1), 165.2 (C=N), 170.5 (C=O). C2 not observed. HR-MS (ESI in MeOH/MeCN): *m/z* [M–CH_3COO]$^{+}$ calcd. for $C_{18}H_{22}FeNO$: 324.1051, found: 324.1046.

(S,S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-hydroxy-1-(phenyl)-methyl]-ferrocene, (S,S_{Ox},S_{Fc})-20

A solution of diphenylzinc (446 mg, 2.03 mmol) in THF (5 mL) was added to a stirred solution of (S_{Ox},S_{Fc})-**6** (300 mg, 0.923 mmol) in THF (10 mL) at 0 °C. After warming up to r.t and stirring for 24 h, the reaction mixture was quenched by addition of water and the phases were separated. The aqueous phase was extracted with DEE (3 x 25 mL); the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography on aluminium oxide 90 (eluent PE/EA = 5/1) to give the title compound as an orange oil (361 mg, 0.895 mmol, 97% yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.04 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.09 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.79–1.91 (m, 1H, CH(CH_3)$_2$), 3.95–4.04 (m, 2H, H5 + CHN), 4.14–4.19 (m, 1H, CHHO), 4.21 (t, J = 2.6 Hz, 1H, H4), 4.24 (s, 5H, Cp'), 4.29–4.37 (m, 1H, CHHO), 4.65 (dd, J = 1.5 Hz, J = 2.6 Hz, 1H, H3), 5.84 (bs, 1H, CHPh), 7.23–7.28 (m, 1H, Ph-*para*), 7.29–7.37 (m, 2H, Ph-*meta*), 7.45–7.51 (m, 2H, Ph-*ortho*), 7.91 (bs, 1H, OH). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 18.5 (CH(CH_3)(CH_3)), 18.6 (CH(CH_3)(CH_3)), 32.6 (CH(CH_3)$_2$), 67.8 (C2), 68.4 (C4), 70.4 (6C, Cp' + CH_2O), 70.7 (C3), 71.5 (CHN), 71.9 (CHPh/C5), 72.0 (CHPh/C5), 93.5 (C1), 126.8 (2C, Ph-*ortho*), 127.0 (Ph-*para*), 128.0 (2C, Ph-*meta*), 143.5 (Ph-*ipso*), 167.4 (C=N). HR-MS (ESI in MeOH/MeCN): *m/z* [M-OH]$^+$ calcd. for $C_{23}H_{24}FeNO$: 386.1207, found: 386.1213. $[\alpha]^{20}_{\lambda}$ (nm): –297 (589), –339 (578), –554 (546) (*c* 0.300, $CHCl_3$).

(S,S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-(acetoxy)-1-(phenyl)-methyl]-ferrocene, (S,S_{Ox},S_{Fc})-21

A solution of a catalytic amount of DMAP in Ac_2O (0.805 mL, 8.57 mmol) was added to a stirred solution of (S,S_{Ox},S_{Fc})-**20** (685 mg, 1.70 mmol) in freshly distilled triethylamine (3.2 mL). After stirring for 17 h at r.t, the reaction mixture was quenched by addition of water and the phases were separated. The aqueous phase was extracted with EA (3 x 25 mL); the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was used without any further purification (695 mg, 1.56 mmol). ^{1}H NMR (400MHz, $CDCl_3$): δ 0.96 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.03 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.77–1.89 (m, 1H, CH(CH_3)$_2$), 1.94 (s, 3H, $COCH_3$), 3.92–4.07 (m, 8H, CHN + CHHO + Cp' + H5), 4.26 (t, J = 2.5 Hz, 1H, H4), 4.30–4.37 (m, 1H, CHHO), 4.79–4.82 (m, 1H, H3), 7.18 (s, 1H, CHPh), 7.31–7.39 (m, 1H,Ph-*para*), 7.39–7.48 (m, 2H, Ph-*meta*), 7.55–7.63 (m, 2H, Ph-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 18.1 (CH(CH_3)(CH_3)), 18.7

(CH(CH_3)(*C*H_3)), 21.1 (CO*C*H_3), 32.4 (*C*H(CH_3)$_2$), 69.2 (C4), 69.5 (CH_2O), 70.2 (C2), 70.4 (Cp'), 70.8 (C3), 71.3 (C5), 72.4 (CHN), 74.1 (CHPh), 87.4 (C1), 127.6 (2C, Ph-*ortho*), 127.9 (Ph-*para*), 128.1 (2C, Ph-*meta*), 140.0 (Ph-*ipso*), 164.5 (C=N), 169.2 (C=O). HR-MS (ESI in MeOH/MeCN): *m/z* [M-CH_3COO]$^+$ calcd. for $C_{23}H_{24}$FeNO: 386.1207, found: 386.1214. [α]$^{20}_{\lambda}$ (nm): +53 (589), +62 (578), +120 (546) (*c* 0.320, $CHCl_3$).

(*S*,*S*$_{Ox}$,*S*$_{Fc}$)-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)]-1-[1-phenyl-1-(diphenylphosphino)methyl]-ferrocene, (*S*,*S*$_{Ox}$,*S*$_{Fc}$)-22

To a stirred solution of (*S*,*S*$_{Ox}$,*S*$_{Fc}$)**-21** (830 mg, 1.86 mmol) in methanol (50 mL) was added diphenylphosphine (3.46 g, 18.6 mmol). The reaction mixture was refluxed for 7 h. After cooling to r.t, subsequently was the crude product chromatographed without previous workup under inert conditions with deoxygenated solvents on aluminium oxide 90. A mixture of PE/DEE = 20/1 removed excess of diphenylphosphine while with use of PE/EA/TEA = 9/1/ the title compound was obtained as a yellow solid (895 mg, 1.57 mmol, 84% yield). M.p.: 149 °C. ^{1}H NMR (400MHz, $CDCl_3$): *δ* 1.02 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)(CH$_3$)), 1.12 (d, *J* = 6.8 Hz, 3H, CH(CH$_3$)(C*H*$_3$)), 1.71–1.83 (m, 1H, C*H*(CH$_3$)$_2$), 3.62 (s, 5H, Cp'), 3.76–3.87 (m, 2H, C*H*HO + CHN), 4.03–4.10 (m, 1H, CH*H*O), 4.23 (t, *J* = 2.6 Hz, 1H, H4), 4.39 (dd, *J* = 1.5 Hz, *J* = 2.6 Hz, 1H, H3), 4.59 (dd, *J* = 1.5 Hz, *J* = 2.6 Hz, 1H, H5), 6.02 (d, *J* = 7.5 Hz, 1H, CHPh), 6.99–7.06 (m, 2H, Ph^A-*meta*), 7.07–7.15 (m, 3H, Ph^A-*ortho* + Ph^A-*para*), 7.16–7.27 (m, 4H, Ph^B-*meta* + Ph^B-*para* + Ph^C-*para*), 7.28–7.35 (m, 2H, Ph^C-*meta*), 7.46–7.54 (m, 2H, Ph^B-*ortho*), 7.61–7.68 (m, 2H, Ph^C-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): *δ* 18.9 (CH(*C*H$_3$)(CH$_3$)), 18.98 (CH(CH$_3$)(*C*H$_3$)), 32.9 (*C*H(CH$_3$)$_2$), 41.3 (d, *J* = 11.9 Hz, *C*HPh), 67.8 (C3), 67.7 (CH_2O), 67.8 (C4), 69.2 (C2), 69.9 (Cp'), 41.3 (d, *J* = 11.9 Hz, C5), 72.6 (CHN), 93.0 (d, *J* = 17.6 Hz, C1), 126.2 (d, *J* = 1.5 Hz, Ph^C-*para*), 127.0 (d, *J* = 6.9 Hz, 2C, Ph^A-*meta*), 127.8–128.0 (4C, Ph^C-*meta* + Ph^B-*meta*), 128.1 (Ph^A-*para*), 128.5 (Ph^B-*para*), 130 (d, *J* = 9.9 Hz, 2C, Ph^C-*ortho*), 133.8 (d, *J* =19.6 Hz, 2C, Ph^B-*ortho*), 134.1 (d, *J* = 19.5 Hz, 2C, Ph^A-*ortho*), 136.8 (d, *J* = 16.0 Hz, Ph^A-*ipso*), 137.2 (d, *J* = 15.3 Hz, Ph^B-*ipso*), 144.3 (d, *J* = 14.2 Hz, Ph^C-*ipso*), 165.1 (C=N). ^{31}P{^{1}H} NMR (100.6 MHz, $CDCl_3$): *δ* 10.3 (PPh_2), HRMS (ESI in MeOH/MeCN): *m/z* [M+H]$^+$ calcd. for $C_{35}H_{35}$FeNOP: 572.1806, found: 572.1810. [α]$^{20}_{\lambda}$ (nm): –15 (589), –17 (578), –27 (546) (*c* 0.230, $CHCl_3$).

(S,S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-(hydroxy)propyl]-ferrocene, (S,S_{Ox},S_{Fc})-23

To a solution of (S_{Ox},S_{Fc})**-6** (500 mg, 1.54 mmol) in THF (15 mL) was added a solution of diethylzinc in toluene (3.38 mL, 1.0 M, 3.38 mmol) at 0 °C. After warming up to r.t. and stirring overnight, the reaction mixture was quenched by addition of water and the phases were separated. The aqueous phase was extracted with DEE (3 x 25 mL); the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography on aluminium oxide 90 (eluent PE/EA = 5/1) to provide the title compound as an orange solid (525 mg, 1.48 mmol, 96% yield). M.p.: 81 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 1.00 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.03 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.04 (d, J = 6.8 Hz, 3H, CH(CH_3)(CH_3)), 1.73–1.89 (m, 3H, CH_2CH_3 + CH(CH_3)$_2$), 3.93–4.01 (m, 1H, CHN), 4.13 (dd, J = 7.5 Hz, J = 8.3 Hz, 1H, CHHO), 4.19 (s, 5H, Cp'), 4.23 (t, J = 2.5 Hz, 1H, H4), 4.31 (dd, J = 8.3 Hz, J =9.6 Hz, 1H, CHHO), 4.34 (dd, J = 1.5 Hz, J = 2.5 Hz, 1H, H5), 4.5 (q, J = 6.6 Hz, 1H, CHEt), 4.60 (dd, J = 1.5 Hz, J = 2.5 Hz, 1H, H3), 6.98 (d, J = 6.5 Hz, 1H, OH). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 11.1 (CH_2CH_3), 18.6 (2C, CH(CH_3)$_2$), 29.7 (CH_2CH_3), 32.6 (CH(CH_3)$_2$), 66.7 (C2), 68.21 (C4), 70.18 (CH_2O), 70.21 (Cp'), 70.3 (C3), 70.6 (C5), 70.9 (CHEt), 71.7 (CHN), 93.8 (C1), 167.8 (C=N). HR-MS (ESI in MeOH/MeCN): m/z $[M+H]^+$ calcd. for $C_{19}H_{26}FeNO_2$: 356.1313, found: 356.1317. $[\alpha]^{20}_{\lambda}$ (nm): –301(589), –347 (578), –575 (546) (c 0.365, $CHCl_3$).

(S,S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(phenyl)oxazol-2-yl)-1-[1-(hydroxy)ethyl]-ferrocene, (S,S_{Ox},S_{Fc})-24

To a solution of (S_{Ox},S_{Fc})**-9** (1.0 g, 2.78 mmol) in THF (30 mL) was added dimethylzinc (5.1 mL, 1.2 M, 6.12 mmol) at 0 ºC. After warming up to r.t and stirring for 24 h, the reaction mixture was quenched by addition of water and the phases were separated. The aqueous phase was extracted with DEE (3 x 25 mL); the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by chromatography on aluminium oxide 90 (eluent PE/EA = 5/1) to provide the title compound as an orange oil (1.0 g, 2.66 mmol, 96% yield). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.54 (d, J = 6.7 Hz, 3H, CHCH_3), 4.22 (s, 5H, Cp'), 4.69 (dd, J = 7.2 Hz, J = 9.9 Hz, 1H, CHHO), 4.70 (t, J = 2.6 Hz, 1H, H4), 4.48 (dd, J = 1.5 Hz, J = 2.6 Hz, 1H, H5), 4.64–4.74 (m, 2H, H3 + CHHO), 5.01–5.11 (q, J = 6.7 Hz, 1H, CHCH$_3$), 5.28 (dd, J = 7.2 Hz, J = 9.9 Hz, 1H, CHN), 6.55 (bs, 1H, OH), 7.29–7.36 (m, 3H, Ph-*para* + Ph-*ortho*), 7.38–7.45 (m, 2H, Ph-*meta*). ^{13}C{^{1}H} NMR

(100.6 MHz, $CDCl_3$): δ 21.1 (CH*C*H_3), 64.8 (*C*HCH$_3$), 68.3 (C2), 68.5 (C4), 69.1 (CHN), 69.8 (C5), 70.2 (Cp'), 70.9 (C3), 74.8 (CH_2O), 93.3 (C1), 126.3 (2C, Ph-*ortho*), 127.7 (Ph-*para*), 128.6 (2C, Ph-*meta*), 142.5 (Ph-*ipso*), 169.1 (C=N). HR-MS (ESI in MeOH/MeCN): *m/z* $[M\text{-}OH]^+$ calcd. for $C_{21}H_{20}FeNO$: 358.0894, found: 358.0888; *m/z* $[M+H]^+$ calcd. for $C_{21}H_{22}FeNO_2$: 376.1000, found: 376.0994. $[\alpha]^{20}_{\lambda}$ (nm): –460 (589), –524 (578), –833 (546) (*c* 0.220, $CHCl_3$).

(*S*,*S*$_{Ox}$,*S*$_{Fc}$)-2-[4,5-Dihydro-4-(phenyl)oxazol-2-yl)-1-[1-(acetoxy)ethyl]-ferrocene, (*S*,*S*$_{Ox}$,*S*$_{Fc}$)-25

A solution of a catalytic amount of DMAP in Ac_2O (0.620 mL, 6.60 mmol) was added to a stirred solution of (*S*,*S*$_{Ox}$,*S*$_{Fc}$)**-24** (492 mg, 1.31 mmol) in freshly distilled triethylamine (2.4 mL). After stirring for 17 h at r.t, the reaction mixture was quenched by addition of water and the aqueous phase was extracted with EA (3 x 25 mL); the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product (red oil) was used without any further purification (498 mg, 1.19 mmol). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.71 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.93 (s, 3H, COCH$_3$), 4.10 (t, *J* = 8.3 Hz, 1H, C*H*HO), 4.21 (s, 5H, Cp'), 4.40 (t, *J* = 2.6 Hz, 1H, H4), 4.52 (dd, *J* = 1.5 Hz, *J* = 2.6 Hz, 1H, H5), 4.70 (dd, *J* = 8.3 Hz, *J* = 9.9 Hz, 1H, CH*H*O), 4.89 (dd, *J* = 1.5 Hz, *J* = 2.6 Hz, 1H, H3), 5.23 (dd, *J* = 8.3 Hz, *J* = 9.9 Hz, 1H, CHN), 6.40 (d, *J* = 6.5 Hz, 1H, C*H*CH$_3$), 7.23–7.29 (m, 3H, Ph-*para* + Ph-*ortho*), 7.31–7.37 (m, 2H, Ph-*meta*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 18.8 (CH*C*H$_3$), 21.2 (CO*C*H$_3$), 68.6 (*C*HCH$_3$), 69.1 (C5), 69.4 (C4), 69.7 (CHN), 69.9 (C2), 70.4 (Cp'), 71.0 (C3), 74.4 (CH_2O), 87.5 (C1), 126.5 (2C, Ph-*ortho*), 127.4 (Ph-*para*), 128.6 (2C, Ph-*meta*), 142.6 (Ph-*ipso*), 166.8 (C=N), 170.1 (C=O). HR-MS (ESI in MeOH/MeCN): *m/z* $[M\text{-}CH_3COO]^+$ calcd. for $C_{21}H_{20}FeNO$: 358.0894, found: 358.0887; *m/z* $[M+H]^+$ calcd. for $C_{23}H_{24}FeNO_3$: 418.1105, found: 418.1090.

(*S*$_{Ox}$,*S*$_{Fc}$)-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-(diphenylphosphinyl)-methyl]-ferrocene, (*S*$_{Ox}$,*S*$_{Fc}$)-26

To a solution of (*S*$_{Ox}$,*S*$_{Fc}$)**-2** (2 g, 4.04 mmol) in acetone (80 mL) was added an aqueous solution of hydrogen peroxide (5 mL, 30%). After stirring for 1 h at r.t., the reaction mixture was quenched with $Na_2S_2O_3$, and acetone was removed under reduced pressure. The residue was dissolved in DCM and washed with water and brine and dried over $MgSO_4$. The solvents were removed under reduced pressure. The title compound was obtained as a yellow powder (2.02 g, 3.95 mmol, 98% yield). M.p.: 151 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 0.96 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)(CH$_3$)), 1.06 (d, *J* = 6.8 Hz, 3H,

$CH(CH_3)(CH_3)$), 1.63–1.79 (m, 1H, $CH(CH_3)_2$), 3.49 (dd, *J* = 15.0 Hz, *J* = 18.4 Hz, 1H, CHHP), 3.78–3.88 (m, 2H, CHHO + CHN), 4.08 (s, 5H, Cp'), 4.11–4.18 (m, 1H, CHHO), 4.23 (t, *J* = 2.5 Hz, 1H, H4), 4.48–4.52 (m, 1H, H3), 4.62–4.67 (m, 1H, H5), 4.79 (dd, *J* = 8.2 Hz, *J* = 15.0 Hz, 1H, CHHP), 7.20–7.27 (m, 2H, Ph^A-*meta*), 7.31–7.38 (m, 1H, Ph^A-*para*), 7.44–7.62 (m, 5H, Ph^A-*ortho* + Ph^B-*meta* + Ph^B-*para*), 7.84–7.93 (m, 2H, Ph^B-*ortho*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 18.7 ($CH(CH_3)(CH_3)$), 19.0 ($CH(CH_3)(CH_3)$), 31.4 (d, *J* = 66.6 Hz, CH_2P), 32.8 ($CH(CH_3)_2$), 69.0 (C3), 69.1 (CH_2O), 69.2 (C4), 70.5 (Cp'), 72.3 (d, *J* = 1.8 Hz, C5), 72.6 (CHN), 79.9 (d, *J* = 3.2 Hz, C1), 127.7 (d, *J* = 12.1 Hz, 2C, Ph^A-*meta*), 128.4 (d, *J* = 11.3 Hz, 2C, Ph^B-*meta*), 131.1–131.6 (m, 6C, Ph-*ortho* + Ph-*para*), 131.7 (d, *J* = 17.5 Hz, Ph^A-*ipso*). C2, Ph^B-*ipso* and C=N not observed. $^{31}P\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 30.9 ($P(O)Ph_2$), HR-MS (ESI in MeOH/MeCN): *m/z* $[M+H]^+$ calcd. for $C_{29}H_{31}FeNO_2P$: 512.1442, found: 512.1462. $[\alpha]^{20}_{\lambda}$ (nm): –35 (589), –41 (578), –82 (546) (*c* 0.230, $CHCl_3$).

(S_{Ox},S_{Fc})-2-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl)-1-[1-methyl-1-(diphenyl-phosphinyl)ethyl]-ferrocene, (S_{Ox},S_{Fc})-27

To a solution of (R,S_{Ox},S_{Fc})-**17** (1.5 g, 2.85 mmol) in THF (20 mL) was added ^{t}BuLi (2.2 mL, 1.6 M, 3.52 mmol) at –78 °C. which immediately led to a change of color from orange to dark red. After stirring at -78 °C for 30 minutes, methyl iodide (1.28 g, 8.55 mmol) was added. The reaction mixture was stirred for 30 minutes at –78 ºC, and for additional 3 h at r.t. Subsequently, the reaction mixture was quenched by addition of water. After phase separation, the aqueous phase was extracted with DEE (2 x 25 mL). The organics were combined, washed with water and brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by chromatography on aluminium oxide 90 (eluent PE/EA/TEA = 1/1/1) to provide the title compound as an orange semisolid (1.43 g, 2.65 mmol, 93% yield). Mp: 110 °C. ^1H NMR (400MHz, $CDCl_3$): *δ* 0.78 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)(CH_3)$), 0.88 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)(CH_3)$), 1.48–1.58 (m, 1H, $CH(CH_3)_2$), 1.66 (d, *J* = 14.4 Hz, 3H, $C(CH_3)(CH_3)$), 1.96 (d, *J* = 15.4 Hz, 3H, $C(CH_3)(CH_3)$), 3.44–3.53 (m, 1H, CHN), 3.62 (t, *J* = 8.3 Hz, 1H, CHHO), 3.97 (dd, *J* = 8.3 Hz, *J* = 9.7 Hz, 1H, CHHO), 4.00–4.04 (m, 1H, H5), 4.20 (s, 5H, Cp'), 4.26 (t, *J* = 2.6 Hz, 1H, H4), 4.63 (dd, *J* = 1.6 Hz, *J* = 2.6 Hz, 1H, H3), 7.27–7.37 (m, 4H, Ph-*meta*), 7.38–7.44 (m, 2H, Ph-*para*), 7.57–7.65 (m, 2H, Ph-*ortho*), 7.65–7.72 (m, 2H, Ph-*ortho*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 18.5 ($CH(CH_3)(CH_3)$), 19.0 ($CH(CH_3)(CH_3)$), 23.9 ($C(CH_3)(CH_3)$), 26.8 ($C(CH_3)(CH_3)$), 32.6 ($CH(CH_3)_2$), 39.8 (*J* = 64.8 Hz, $C(CH_3)(CH_3)$), 67.8 (C4), 69.1 (CH_2O), 70.1 (Cp'), 72.0 (C3), 72.6 (d, *J* = 1.9 Hz, C5), 72.7 (d, *J* = 1.7 Hz, C2), 73.2 (CHN), 92.4 (d, *J* = 4.6 Hz, C1), 127.5 (d, *J* = 10.7

Hz, 2C, Ph-*meta*), 127.7 (d, *J* = 11.4 Hz, 2C, Ph-*meta*), 130.39, 130.4, 131.29, 131.3 (Ph-*ipso*), 130.9 (d, *J* = 2.7 Hz, 2C, Ph-*para*), 131.1 (d, *J* = 2.6 Hz, Ph-*para*), 132.8 (d, *J* = 4.6 Hz, Ph-*ortho*), 132.9 (d, *J* = 4.7 Hz, 2C, Ph-*ortho*), 164.0 (C=N). $^{31}P\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 36.9 ($P(O)Ph_2$), HR-MS (ESI in MeOH/MeCN): *m/z* $[M+H]^+$ calcd. for $C_{31}H_{35}FeNO_2P$: 540.1755, found: 540.1761. $[\alpha]^{20}_{\lambda}$ (nm): +129 (589), +162 (578), +229 (546) (*c* 0.337, $CHCl_3$).

(S_{Ox})-{*N*-[2-hydroxy-1-(phenyl)eth-1-yl]aminocarbonyl}-ferrocene,

A solution of (+)-(*S*)-2-amino-2-phenylethanol (2.30 g, 16.8 mmol) in toluene (50 mL) was cooled to 0 °C and treated with a solution of trimethylaluminium in toluene (16.7 mL, 2.0 M, 33.4 mmol). After stirring for 5 minutes the solution was warmed to r.t. and stirring was continued for additional 45 minutes. Subsequently, a solution of (methoxycarbonyl)-Ferrocene (3.70 g, 15.2 mmol) in toluene (20 mL) was added and the resulting mixture was stirred for 16 h at 126 °C. After cooling to r.t, the reaction mixture was quenched carefully by addition of water and the phases were separated. The aqueous phase was extracted with EA (3 x 25 mL), the organics were combined, washed with water and brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by crysallisation (DCM and PE) and afforded the title compound as yellow crystals (5.12 g, 14.66 mmol, 97% yield). M.p.: 158 °C. ^{1}HNMR (400 MHz, $CDCl_3$): *δ* 2.82 (bs, 1H, OH), 3.91–3.04 (m, 2H, CH_2), 4.10 (s, 5H, Cp'), 4.33–4.39 (m, 2H, H3 + H4), 4.67–4.70 (m, 1H, H2/H5), 4.70–4.75 (m, 1H, H2/H5), 5.18–5.26 (m, 1H, CHPh), 6.37 (d, *J* = 6.9 Hz, 1H, NH), 7.29–7.45 (m, 5H, Ph). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): *δ* 55.9 (CHPh), 66.8 (CH_2O), 68.0 (C2/C5), 68.5 (C2/C5), 69.8 (Cp'), 70.6 (C3/C4), 70.7 (C3/C4), 75.5 (C1), 126.7 (2C, Ph), 127.9 (Ph-*para*), 128.9 (2C, Ph), 139.4 (Ph-*ipso*), 171.0 (C=O). HR-MS (ESI in MeOH/MeCN): *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{19}FeNNaO_2$: 372.0663, found: 372.0664. $[\alpha]^{20}_{\lambda}$ (nm): +29 (589), +31 (578), +42 (546) (*c* 0.344, $CHCl_3$).

Synthesis of neutral ruthenium complexes – General procedure

A mixture of oxazoline ligand (1.0 mmol) and $[RuCl_2(PPh_3)_3]$ (0.95 mmol) dissolved in freshly distilled and degassed toluene (3 mL) was stirred for 16 h at r.t. Degassed hexane was added to precipitate the product. The green solid was filtered off under inert conditions and was washed with freshly distilled and degassed hexane (2 × 2 mL). The crude product was redissolved in toluene, precipitated by addition of hexane and dried *in vacuo* to yield a green powder.

Dichloro[(*R*,S_{Ox},S_{Fc})-2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl-*κ*N)-1-[1-(diphenylphosphino)ethyl-*κ*P]-ferrocene]triphenylphosphine ruthenium, [$RuCl_2(PPh_3)$((*R*,S_{Ox},S_{Fc})-3)], (*R*,S_{Ox},S_{Fc})-29

Starting from (*R*,S_{Ox},S_{Fc})-**3** (195 mg, 0.383 mmol) and following the general procedure stated above the desired product was obtained as a green powder (292 mg, 0.310 mmol, 81% yield). Mp: > 230 °C (dec.). ^{1}H NMR (400 MHz, CD_2Cl_2): *δ* 0.90 (d, *J* = 7.2 Hz, 3H, CH(C*H*$_3$)(CH$_3$)), 1.08 (d, *J* = 6.8 Hz, 3H, CH(CH$_3$)(C*H*$_3$)), 2.16 (dd, *J* = 7.0 Hz, *J* = 15.2 Hz, 3H, CHC*H*$_3$), 2.15–3.29 (m, 2H, C*H*(CH$_3$)$_2$ + C*H*CH$_3$), 3.51–3.54 (m, 1H, H5), 3.97 (d, *J* = 2.6 Hz, 1H, H4), 3.99–4.05 (m, 1H, CHN), 4.22–4.28 (m, 6H, Cp' + C*H*HO), 4.55 (dd, *J* = 3.3 Hz, *J* = 8.5 Hz, 1H, CH*H*O), 4.79 (dd, *J* = 1.5 Hz, *J* = 2.6 Hz, 1H, H3), 6.90 –7.31 (m, 25H, Ph). ^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): *δ* 15.1 (CH(*C*H$_3$)(CH$_3$)), 20.0 (CH(CH$_3$)(*C*H$_3$)), 22.3 (d, *J* = 4.1 Hz, CH*C*H$_3$), 28.5 (*C*H(CH$_3$)$_2$), 42.0 (d, *J* = 25.1 Hz, C*H*CH$_3$), 67.7 (d, *J* = 3.8 Hz, C2), 68.27 (C4), 68.28 (CH$_2$O), 70.2 (Cp'), 73.1 (2C, C3 + CHN), 74.4 (d, *J* = 3.0 Hz, C5), 93.1 (d, *J* = 4.6 Hz, C1), 126.2–139.5 (Ph), 176.1 (C=N). ^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): *δ* 45.6 (d, *J* = 39.8 Hz, *P*Ph$_3$), 103.9 (d, *J* = 39.8 Hz, *P*N). HR-MS (ESI in MeOH/MeCN): *m/z* [M-Cl]$^+$ calcd. for $C_{48}H_{47}ClFeNOP_2Ru$: 908.1214, found: 908.1192. $[\alpha]^{20}_{\lambda}$ (nm): –908 (589), –950 (578), –1013 (546) (*c* 0.0240, CH_2Cl_2).

Dichloro[(*S*,S_{Ox},S_{Fc})-2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl-*κ*N)-1-[1-phenyl-1-(diphenylphosphino)methyl-*κ*P]-ferrocene]triphenylphosphine ruthenium, [$RuCl_2(PPh_3)$((*S*,S_{Ox},S_{Fc})-22], (*S*,S_{Ox},S_{Fc})-30

Starting from (*S*,S_{Ox},S_{Fc})-**22** (300 mg, 0.525 mmol) and following the general procedure stated above the desired product was obtained as a green powder (456 mg, 0.453 mmol, 86% yield). Mp: > 230 °C (dec.). ^{1}H NMR (400MHz, $CDCl_3$): *δ* 0.97 (d, *J* = 7.1 Hz, 3H, CH(C*H*$_3$)(CH$_3$)), 1.19 (d, *J* = 6.8 Hz, 3H, CH(CH$_3$)(C*H*$_3$)), 3.21–3.33 (m, 1H, C*H*(CH$_3$)$_2$), 3.50–3.56(m, 1H, H5), 3.86 (s, 5H, Cp'), 3.97 (t, *J* = 2.6 Hz, 1H, H4), 4.13–4.22 (m, 1H, CHN), 4.34 (t, *J* = 8.7 Hz, 1H, C*H*HO), 4.61 (dd, *J* = 4.1 Hz, *J* = 8.7 Hz, 1H, CH*H*O), 4.86–4.89 (m, 1H, H3), 6.17 (d, *J* = 13.5 Hz, 1H, C*H*Ph), 6.46–7.88 (Ph). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): *δ* 15.3 (CH(*C*H$_3$)(CH$_3$)), 19.5 (CH(CH$_3$)(*C*H$_3$)), 28.2 (*C*H(CH$_3$)$_2$), 53.3 (d, *J* = 16.1 Hz, CHPh), 67.9 (d, *J* = 1.7 Hz, CH$_2$O), 70.5 (C4), 70.6 (Cp'), 71.2 (bs, C5), 72.6 (C3), 73.0 (CHN), 88.2 (d, *J* = 4.6 Hz, C1), 125.4–141.0 (Ph), 175.4 (C=N). C2 not obsereved. ^{31}P{^{1}H} NMR (100.6 MHz, CD_2Cl_2): *δ* 48.6 (d, *J* = 39.5 Hz, *P*Ph$_3$), 95.1 (*J* = 39.6 Hz, *P*N). HR-MS (ESI in MeOH/MeCN): *m/z* [M-Cl]$^+$ calcd. for $C_{53}H_{49}ClFeNOP_2Ru$: 970.1371, found: 970.1381. $[\alpha]^{20}_{\lambda}$ (nm): –688 (589), –722 (578), –803 (546) (*c* 0.025, CH_2Cl_2).

Asymmetric transfer hydrogenations

To a solution of ruthenium complex (0.005 mmol, 0.5%) in anhydrous 2-PrOH (50 mL) were added a solution of ketone (1 mmol) in 2-PrOH (1 mL) and a solution of 2-PrOK (0.02 mmol) in 2-PrOH (5% w/v). The reaction mixture was stirred at r.t. and the progress of the reaction was monitored by periodically analyzing 1 mL samples of the reaction mixture. The samples were quenched with aqueous H_3PO_4 (0.5 M, 0.5 mL), diethyl ether (1 mL) was added and the product was extracted. The organic phase was washed with brine and filtered through a short plug of $MgSO_4$ (top) and aluminum oxide 90 (bottom) using 2-PrOH as the eluent. The filtrate obtained was analyzed either by GC or HPLC.

Analysis data:

Conversions and e.e. values of substrates **ACP** and **4-Me-ACP** were determined by GC. Retention times are given for the reactants and both product enantiomers.

Substrate **ACP**: column: Supelco, Beta Dex^{TM} 110 (30m); 110 °C isothermal, carrier gas He, 15.3 psi, split 30:1.
ACP = 10.4 min, (*R*) = 15.6 min, (*S*) = 16.4 min.
Substrate **4-Me-ACP**: column: Supelco, Beta Dex^{TM} 110 (30m); 120 °C isothermal, carrier gas He, 15.3 psi, split 30:1.
4-Me-ACP = 9.4 min, (*R*) = 10.4 min, (*S*) = 11.0 min.

Conversions and e.e. values of substrate **PBK** as determined by HPLC. Retention times are given for the reactant and both product enantiomers.
Substrate **PBK**: column: Daicel, Chiraldex OD-H, temperature: 25 ºC, eluent: hexane/iPrOH 96:4, flow rate: 0.6 mL/min, detector: DAD, Sig = 230 nm, 8, ref = 360 nm, 100.
PBK = 17.6 min, (*R*) = 20.4 min, (*S*) = 25.8 min.

X-ray structure determination of (S,S_{Ox},S_{Fc})-18

Orange single crystals of the (S,S_{Ox},S_{Fc})-**18** were obtained from EA solution by slow evaporation of the solvent. X-ray data were collected on a Bruker Kappa APEX-2 CCD diffractometer with a cryostream cooler (Oxford Cryosystems) using graphite-monochromatised Mo-Kα radiation (λ = 0.71073 Å) and 0.5° φ- and ω-scan frames covering complete Ewald spheres with θ_{max} = 30° or 25° ((S_{Ox},S_{Fc})-**23**). The frames were integrated with program SAINT and corrections for absorption and λ/2 effects were applied with program SADABS. After structure solution with program SHELXS97 and direct methods, refinement on F^2 was carried out with the program SHELXL97 (Sheldrick, 2008). Non-hydrogen atoms were refined anisotropically. All H atoms were placed in calculated positions and thereafter refined as riding. The absolute structures of all compounds could be unambiguously determined by anomalous dispersion effects and the Flack absolute structure parameter. Crystallographic data are compiled in Table S1. A structural diagram of complex **18** is shown in Figure S1. Atomic coordinates and anisotropic displacement parameters are given in Tables S2–S4. For molecular graphics the programs XP (Bruker) and MERCURY (Macrae et al., 2006) were used.

Bruker programs: APEX2; SAINT, version 7.68A; SADABS, version 2008/1; SHELXTL, version 2008/4; XP, version 5 (Bruker AXS Inc., Madison, WI, 2009).
SHELXS97 and SHELXL97: G. M. Sheldrick, Acta Cryst. **2008**, *A64*, 112-122.
PLATON: Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
MERCURY: Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E., Shields, G. P., Taylor, R., Towler, M. & van de Streek, J. (2006). *J. Appl. Cryst.* **39**, 453–457.

Table S1. Crystal data and structure refinement for (S,S_{Ox},S_{Fc})-**18**.

	(S,S_{Ox},S_{Fc})-**18**
formula	$C_{18}H_{23}FeNO_2$
fw	341.22
cryst.size, mm	0.45 x 0.25 x 0.04
crystal system	Orthorhombic
space group	$P2_1$…(no. 3)
a, Å	9.8793(3)
b, Å	12.7041(4)
c, Å	12.8138(4)
α, deg	90
β, deg	90
γ, deg	90
V, Å^3	1608.23(9)
T, K	100
Z	4
ρ_{calc}, g cm^{-3}	1.409
μ, mm^{-1} (MoKα)	0.944
F(000)	720
absorption corrections	multi-scan, 0.96–0.60
θ range, deg	2.2–30.0
no. of rflns measd / R_{int}	55009 / 0.069
no. of rflns unique	4490
no. of rflns $I>2\sigma(I)$	4490
no. of params / restraints	203
R_1 ($I > 2\sigma(I)$)	0.0266
R_1 (all data)	0.0311
wR_2 ($I > 2\sigma(I)$)	0.0655
wR_2 (all data)	0.0675
Flack abs.str. param.	-0.012(11)
Diff.Four.peaks, min/max, eÅ^{-3}	-0.43 / 0.59

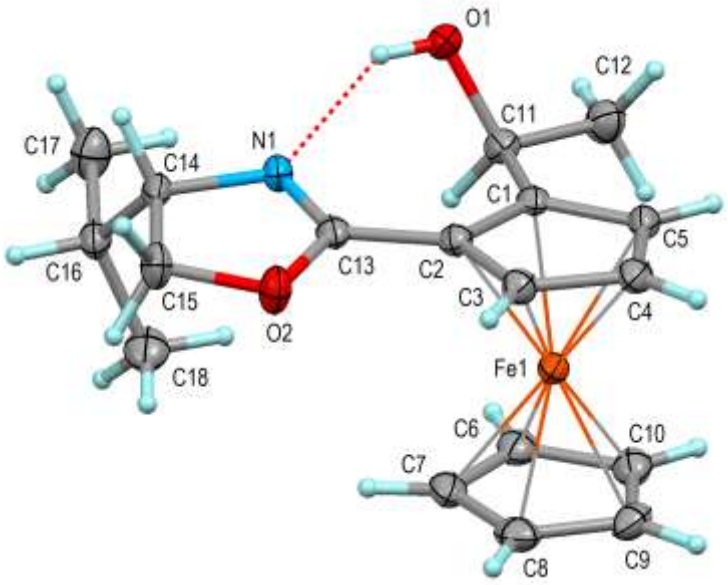


Figure S1. Structural diagram of the asymmetric unit of (S,S_{Ox},S_{Fc})-**18** showing 50% ellipsoids and the atom numbering.

Table 2. Bond lengths [Å] and angles [deg] for (S,S_{Ox},S_{Fc})-**18**.

Bond	distances
Fe(1)-C(2)	2.0339(14)
Fe(1)-C(1)	2.0438(16)
Fe(1)-C(7)	2.0456(16)
Fe(1)-C(8)	2.0458(17)
Fe(1)-C(3)	2.0464(15)
Fe(1)-C(9)	2.0509(16)
Fe(1)-C(6)	2.0512(16)
Fe(1)-C(10)	2.0517(16)
Fe(1)-C(5)	2.0564(16)
Fe(1)-C(4)	2.0571(16)
O(1)-C(11)	1.4377(18)
O(1)-H(1)	0.84
O(2)-C(13)	1.3611(16)
O(2)-C(15)	1.4581(16)
N(1)-C(13)	1.2711(18)
N(1)-C(14)	1.4802(17)
C(1)-C(5)	1.4315(19)
C(1)-C(2)	1.4395(19)
C(1)-C(11)	1.517(2)
C(2)-C(3)	1.4325(19)
C(2)-C(13)	1.4590(17)
C(3)-C(4)	1.424(2)
C(3)-H(3)	0.95
C(4)-C(5)	1.417(2)
C(4)-H(4)	0.95
C(5)-H(5)	0.95
C(6)-C(7)	1.422(2)
C(6)-C(10)	1.430(2)
C(6)-H(6)	0.95
C(7)-C(8)	1.416(2)
C(7)-H(7)	0.95
C(8)-C(9)	1.423(2)
C(8)-H(8)	0.95
C(9)-C(10)	1.423(2)
C(9)-H(9)	0.95
C(10)-H(10)	0.95
C(11)-C(12)	1.511(2)
C(11)-H(11)	1.00
C(12)-H(12A)	0.98
C(12)-H(12B)	0.98
C(12)-H(12C)	0.98
C(14)-C(16)	1.532(2)
C(14)-C(15)	1.538(2)
C(14)-H(14)	1.00
C(15)-H(15A)	0.99
C(15)-H(15B)	0.99
C(16)-C(18)	1.526(2)
C(16)-C(17)	1.527(2)
C(16)-H(16)	1.00
C(17)-H(17A)	0.98
C(17)-H(17B)	0.98
C(17)-H(17C)	0.98
C(18)-H(18A)	0.98
C(18)-H(18B)	0.98
C(18)-H(18C)	0.98

Bond	angles
C(1)-Fe(1)-C(5)	40.87(5)
C(2)-Fe(1)-C(1)	41.34(6)
C(2)-Fe(1)-C(3)	41.10(5)

C(3)-Fe(1)-C(4)	40.60(6)
C(5)-Fe(1)-C(4)	40.30(7)
C(7)-Fe(1)-C(8)	40.50(6)
C(8)-Fe(1)-C(9)	40.66(6)
C(7)-Fe(1)-C(6)	40.61(6)
C(9)-Fe(1)-C(10)	40.60(7)
C(6)-Fe(1)-C(10)	40.80(6)
C(11)-O(1)-H(1)	109.5
C(13)-O(2)-C(15)	105.46(11)
C(13)-N(1)-C(14)	107.33(11)
C(5)-C(1)-C(2)	106.50(12)
C(5)-C(1)-C(11)	127.33(12)
C(2)-C(1)-C(11)	126.17(12)
C(5)-C(1)-Fe(1)	70.04(9)
C(2)-C(1)-Fe(1)	68.96(8)
C(11)-C(1)-Fe(1)	126.05(11)
C(3)-C(2)-C(1)	108.51(12)
C(3)-C(2)-C(13)	125.87(12)
C(1)-C(2)-C(13)	125.62(12)
C(3)-C(2)-Fe(1)	69.92(8)
C(1)-C(2)-Fe(1)	69.70(8)
C(13)-C(2)-Fe(1)	127.01(11)
C(4)-C(3)-C(2)	107.66(13)
C(4)-C(3)-Fe(1)	70.10(9)
C(2)-C(3)-Fe(1)	68.98(8)
C(4)-C(3)-H(3)	126.2
C(2)-C(3)-H(3)	126.2
Fe(1)-C(3)-H(3)	126.3
C(5)-C(4)-C(3)	108.18(13)
C(5)-C(4)-Fe(1)	69.82(9)
C(3)-C(4)-Fe(1)	69.30(9)
C(5)-C(4)-H(4)	125.9
C(3)-C(4)-H(4)	125.9
Fe(1)-C(4)-H(4)	126.5
C(4)-C(5)-C(1)	109.15(13)
C(4)-C(5)-Fe(1)	69.88(10)
C(1)-C(5)-Fe(1)	69.10(9)
C(4)-C(5)-H(5)	125.4
C(1)-C(5)-H(5)	125.4
Fe(1)-C(5)-H(5)	127.2
C(7)-C(6)-C(10)	107.58(14)
C(7)-C(6)-Fe(1)	69.48(9)
C(10)-C(6)-Fe(1)	69.62(9)
C(7)-C(6)-H(6)	126.2
C(10)-C(6)-H(6)	126.2
Fe(1)-C(6)-H(6)	126.3
C(8)-C(7)-C(6)	108.61(13)
C(8)-C(7)-Fe(1)	69.76(9)
C(6)-C(7)-Fe(1)	69.90(9)
C(8)-C(7)-H(7)	125.7
C(6)-C(7)-H(7)	125.7
Fe(1)-C(7)-H(7)	126.2
C(7)-C(8)-C(9)	107.82(14)
C(7)-C(8)-Fe(1)	69.74(9)
C(9)-C(8)-Fe(1)	69.86(9)
C(7)-C(8)-H(8)	126.1
C(9)-C(8)-H(8)	126.1
Fe(1)-C(8)-H(8)	125.9
C(8)-C(9)-C(10)	108.19(13)
C(8)-C(9)-Fe(1)	69.48(9)
C(10)-C(9)-Fe(1)	69.73(9)
C(8)-C(9)-H(9)	125.9
C(10)-C(9)-H(9)	125.9
Fe(1)-C(9)-H(9)	126.5
C(9)-C(10)-C(6)	107.80(14)
C(9)-C(10)-Fe(1)	69.67(9)
C(6)-C(10)-Fe(1)	69.58(9)
C(9)-C(10)-H(10)	126.1
C(6)-C(10)-H(10)	126.1
Fe(1)-C(10)-H(10)	126.2
O(1)-C(11)-C(12)	107.71(13)
O(1)-C(11)-C(1)	110.51(12)
C(12)-C(11)-C(1)	111.82(11)
O(1)-C(11)-H(11)	108.9
C(12)-C(11)-H(11)	108.9
C(1)-C(11)-H(11)	108.9
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
N(1)-C(13)-O(2)	118.54(12)
N(1)-C(13)-C(2)	125.55(13)
O(2)-C(13)-C(2)	115.87(12)
N(1)-C(14)-C(16)	111.28(11)
N(1)-C(14)-C(15)	103.77(11)
C(16)-C(14)-C(15)	114.82(13)
N(1)-C(14)-H(14)	108.9
C(16)-C(14)-H(14)	108.9
C(15)-C(14)-H(14)	108.9
O(2)-C(15)-C(14)	104.75(11)
O(2)-C(15)-H(15A)	110.8
C(14)-C(15)-H(15A)	110.8
O(2)-C(15)-H(15B)	110.8
C(14)-C(15)-H(15B)	110.8
H(15A)-C(15)-H(15B)	108.9
C(18)-C(16)-C(17)	110.77(13)
C(18)-C(16)-C(14)	112.71(12)
C(17)-C(16)-C(14)	110.20(14)
C(18)-C(16)-H(16)	107.7
C(17)-C(16)-H(16)	107.7
C(14)-C(16)-H(16)	107.7
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(16)-C(18)-H(18A)	109.5
C(16)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(16)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

Torsion	angles
C5-C1-C2-C3	-0.96(17)
C11-C1-C2-C3	179.33(14)
Fe1-C1-C2-C3	59.34(11)
C5-C1-C2-C13	178.06(14)
C11-C1-C2-C13	-1.6(2)
Fe1-C1-C2-C13	-121.64(15)
C5-C1-C2-Fe1	-60.30(11)
C11-C1-C2-Fe1	119.99(15)
C1-C2-C3-C4	0.47(18)
C13-C2-C3-C4	-178.55(15)
Fe1-C2-C3-C4	59.67(11)
C1-C2-C3-Fe1	-59.20(10)
C13-C2-C3-Fe1	121.78(15)
C2-C3-C4-C5	0.23(18)
Fe1-C3-C4-C5	59.19(12)
C2-C3-C4-Fe1	-58.96(11)
C3-C4-C5-C1	-0.84(19)
Fe1-C4-C5-C1	58.03(11)
C3-C4-C5-Fe1	-58.87(12)

C2-C1-C5-C4	1.11(18)	C5-C1-C11-C12	4.0(2)
C11-C1-C5-C4	-179.19(15)	C2-C1-C11-C12	-176.39(15)
Fe1-C1-C5-C4	-58.50(12)	Fe1-C1-C11-C12	-87.42(15)
C2-C1-C5-Fe1	59.61(10)	C14-N1-C13-O2	-2.75(19)
C11-C1-C5-Fe1	-120.69(16)	C14-N1-C13-C2	179.58(14)
C10-C6-C7-C8	0.23(19)	C15-O2-C13-N1	0.34(18)
Fe1-C6-C7-C8	-59.20(11)	C15-O2-C13-C2	178.23(13)
C10-C6-C7-Fe1	59.43(11)	C3-C2-C13-N1	166.58(16)
C6-C7-C8-C9	-0.43(19)	C1-C2-C13-N1	-12.3(2)
Fe1-C7-C8-C9	-59.73(12)	Fe1-C2-C13-N1	-102.59(17)
C6-C7-C8-Fe1	59.29(11)	C3-C2-C13-O2	-11.1(2)
C7-C8-C9-C10	0.47(19)	C1-C2-C13-O2	170.00(14)
Fe1-C8-C9-C10	-59.18(12)	Fe1-C2-C13-O2	79.68(15)
C7-C8-C9-Fe1	59.65(12)	C13-N1-C14-C16	-120.25(14)
C8-C9-C10-C6	-0.33(19)	C13-N1-C14-C15	3.75(17)
Fe1-C9-C10-C6	-59.35(11)	C13-O2-C15-C14	2.11(16)
C8-C9-C10-Fe1	59.02(11)	N1-C14-C15-O2	-3.49(16)
C7-C6-C10-C9	0.07(19)	C16-C14-C15-O2	118.18(13)
Fe1-C6-C10-C9	59.41(12)	N1-C14-C16-C18	56.67(17)
C7-C6-C10-Fe1	-59.34(11)	C15-C14-C16-C18	-60.82(16)
C5-C1-C11-O1	-116.02(16)	N1-C14-C16-C17	-67.64(16)
C2-C1-C11-O1	63.63(19)	C15-C14-C16-C17	174.88(12)
Fe1-C1-C11-O1	152.60(10)		

Hydrogen-bond

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...N(1)	0.84	2.06	2.7912(16)	145.1

3.3. Synthesis of chiral, non-racemic ferrocene derivatives by ortho-metallation and partial reductive removal of ortho-directing amino groups

Afrooz Zirakzadeh, Raffael Schuecker, Walter Weissensteiner

Tetrahedron: Asymmetry **2010**, *21*, 1494–1502

Synthesis of chiral, nonracemic ferrocene derivatives by *ortho*-metallation and partial reductive removal of *ortho*-directing amino groups.

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Dedicated to Professor Henri B. Kagan on the occasion of his 80th birthday.

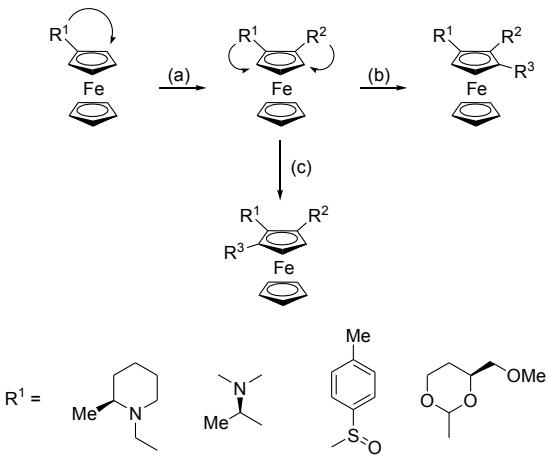
Abstract: Chiral, nonracemic 1,2-disubstituted ferrocenes have been prepared from monosubstituted ferrocene derivatives by amine-mediated *ortho*-directed reactions and subsequent partial reductive removal of the stereogenic *ortho*-directing group. It was found that the *ortho*-directing amino group of 2-substituted derivatives of *N*,*N*-dimethylaminoethyl-ferrocene and similar compounds can – after quaternisation with methyl iodide – be reductively removed with sodium borohydride to give 2-substituted methyl- or ethylferrocenes. In most cases the substituents I, Br, COOEt, $P(O)Ph_2$ and CN tolerate the reaction conditions used. In addition, a few examples are reported that show how the use of LiTMP allows 2-bromo- and especially 2-cyano-substituted derivatives to be further *ortho*-lithiated and reacted to give 1,2,3-trisubstituted ferrocenes.

Keywords: ferrocenes, stereoselective synthesis, *ortho*-metallation, reduction, sodium borohydride

1. Introduction

Chiral, nonracemic ferrocene derivatives have found widespread applications in a variety of different fields, including homogeneous enantioselective catalysis, bioorganometallic chemistry, polymers and dendrimers, electrooptical materials and thermotropic liquid crystals.[1] In catalytic applications 1,2-disubstituted ferrocenes, as well as more highly substituted analogues, were found to give excellent results as catalyst ligands in enantioselectively catalysed reactions.[1–4] Almost all synthetic approaches to ferrocene derivatives with such substitution patterns involve directed metallation, mainly directed *ortho*-lithiation steps.[5] For example, 1,2-disubstituted enantiopure or highly enantiomerically enriched ferrocenes have been prepared by *ortho*-lithiation of a monosubstituted ferrocene Fc-R^1, where R^1 is either a stereogenic or, less frequently, a nonstereogenic *ortho*-directing substituent.[6] In the latter case, chiral lithiation reagents such as an alkyllithium in the presence of (–)-sparteine have been used.[7–9]

The *ortho*-metallation strategy has been extended further to the synthesis of chiral, nonracemic 1,2,3-trisubstituted ferrocene derivatives. Depending on the *ortho*-directing properties of substituents R^1 and R^2 of the 1,2-disubstituted ferrocenes, a third substituent R^3 can be introduced either next to R^2 or next to R^1 [Scheme 1, reactions (b) and (c)].[10–15]



Scheme 1. Synthesis routes to 1,2-di- and 1,2,3-trisubstituted ferrocenes.

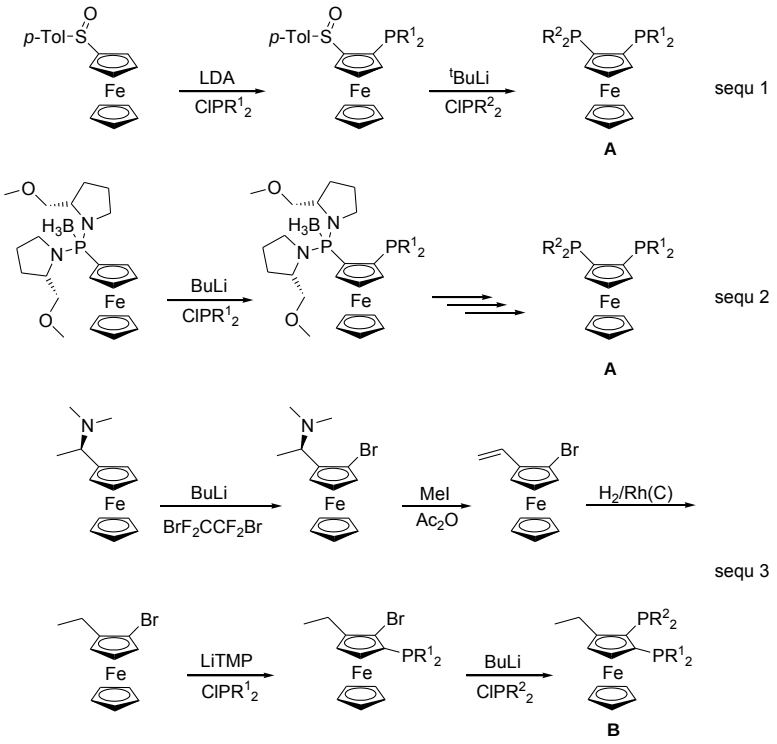
In 1970 Nozaki,[16] as well as Ugi[17] and co-workers, reported the first diastereoselective *ortho*-lithiation of a monosubstituted ferrocene derivative [lithiation of (*S*)-*N*-ferrocenylmethyl-2-methylpiperidine (Scheme 1) with butyllithium] and since that time a variety of stereogenic *ortho*-directing groups have been developed. The *N*,*N*-dimethylaminoethyl group (Scheme 1), again introduced by Ugi,[18] and the *p*-tolylsulfinyl-

and 4-methoxymethyl-1,3-dioxan-2-yl groups developed by Kagan[19–23] have been the most frequently applied.

Within the group of stereogenic *ortho*-directing substituents the *p*-tolylsulfinyl group holds a unique position since, to the best of our knowledge, it is the only *ortho*-directing stereogenic ferrocene substituent that can be fully replaced by other electrophiles. This feature has been extensively used for the preparation of 1,2-disubstituted ferrocene derivatives.[24] For example, starting from *p*-tolylsulfinylferrocene, Kagan and co-workers synthesised purely ferrocene-stereogenic 1,2-disubstituted diphosphino-ferrocenes[25] (Scheme 2, sequence 1, **A**), compounds that are difficult to prepare otherwise. These and other derivatives prepared from *p*-tolylsulfinyl-ferrocene have been very successfully applied as catalyst ligands in enantioselectively catalysed reactions.[1,5,24]

Interestingly, replacement of the sulfinyl group by other electrophiles (Scheme 2, sequence 1, second step) works nicely on the small to medium laboratory scale, but unfortunately the process on the larger industrial scale proved to be difficult. In order to circumvent this problem, workaround strategies have been developed. For example, the synthesis of purely ferrocene-stereogenic diphosphines could be achieved by using a novel directing group that allows the introduction of different phosphino groups into the *ortho*-position and in a subsequent step the directing group can be transformed into a second set of phosphino units (Scheme 2, sequence 2).[26,27]

An alternative approach has been used to achieve the same aim (Scheme 2, sequence 3). In a first *ortho*-directed reaction 2-bromo-*N*,*N*-dimethylaminoethyl-ferrocene was prepared from *N*,*N*-dimethylaminoethylferrocene and in a subsequent two-step sequence the dimethylamino group was removed, thus transforming the *ortho*-directing group into a noncoordinating ethyl group. Further *ortho*-lithiation adjacent to the bromide allowed the introduction of various phosphino units and subsequent bromide/lithium exchange enabled a second set of phosphino groups to be attached.[28,29] Both approaches allowed the synthesis of a variety of diphosphines of types **A** and **B** (Scheme 2) in a very flexible way.



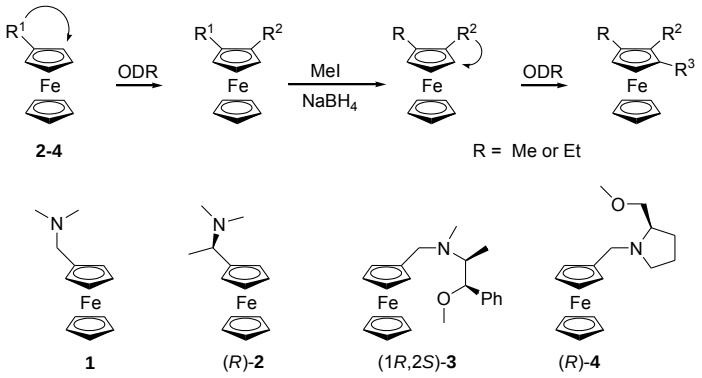
Scheme 2.

In this context we envisaged that simplifying and extending the latter strategy to additional *ortho*-directing groups and substituents other than bromide could lead to a much broader applicability of this methodology.

In this contribution we report a simple method for the partial removal of *ortho*-directing amines in the presence of various substituents, which themselves are able to *ortho*-direct further metallation reactions. Several examples of such *ortho*-metallation reactions that led to chiral, nonracemic 1,2,3-trisubstituted ferrocenes as the final products are given.

2. Results and discussion

A three-step sequence for the preparation of chiral, nonracemic ferrocene derivatives was explored (Scheme 3). In the first step 1,2-disubstituted derivatives were synthesised by diastereoselective *ortho*-directed reactions (ODR). For this purpose the well-established ferrocenyl amines (*R*)-2,[18] (1*R*,2*S*)-3,[30,31] and (*R*)-4[32] were used as the starting materials. In the second step, suitable reaction conditions for the reductive removal of the amino substituents were investigated and in a few cases possibilities for the synthesis of 1,2,3-trisubstituted ferrocenes through further *ortho*-directed reactions were explored.



Scheme 3.

2.1. Reductive removal of quaternised amino substituents

The reduction of ferrocenylmethyl ammonium iodides to methylferrocenes with the use of sodium amalgam,[33] sodium in liquid ammonia[34] or sodium borohydride[35] has been reported previously. Since a number of functional groups tolerate sodium borohydride as the reducing agent, its use for the removal of the amino substituents from derivatives of **2**–**4** seemed to be the most promising approach.

In order to identify suitable reaction conditions, amines **1**–**4** were reacted with methyl iodide and the resulting ammonium salts were subjected to the reduction with sodium borohydride in different solvents (acetonitrile, dimethylsulfoxide, dimethylformamide) and at different reaction temperatures (80 °C, 100 °C). As shown in Table 1, the ammonium salts of all amines tested could be reduced in good (**1**) to excellent (**2**–**4**) yields to either methylferrocene (**5**) or ethylferrocene (**6**).

Based on these promising results, the selective reduction of 2-substituted derivatives of **2**–**4** bearing various substituents [I, Br, COOEt, $P(O)Ph_2$, CN] was investigated. Starting from enantiomerically pure amines (*R*)-**2**, (1*R*,2*S*)-**3** and (*R*)-**4** (e.e. >99%), the 2-substituted derivatives (R,S_p)-**7a**–**7e**, (1*R*,2*S*,R_p)-**8a**–**8e** and (R,R_p)-**9a**, **9c**, **9e** [**a**: I, **b**: Br, **c**: COOEt, **d**: $P(O)Ph_2$, **e**: CN] were prepared by *ortho*-lithiation with tBuLi (**2**[36] and **3**[30]) or sBuLi (**4**[32]) and an appropriate electrophile [Scheme 4; E: I_2, $BrCl_2CCCl_2Br$, $CO(OEt)_2$, $ClPPh_2$ followed by H_2O_2, 4-$CH_3C_6H_4SO_2CN$]. It should be mentioned that the use of tosylcyanide as the electrophile gave the 2-cyano-substituted derivatives **7e**, **8e** and **9e** in good to excellent yields (**7e**: 88%; **8e**: 77%; **9e**: 90%).[37]

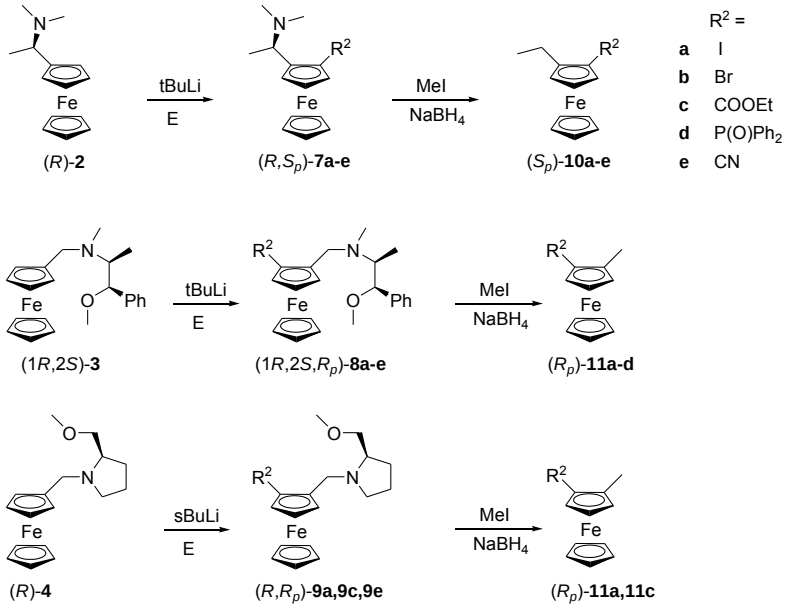
Table 1: Isolated yields obtained in the reduction of the ammonium iodide salts of **1**–**4** with $NaBH_4$ [a]

amine	product[b]	CH_3CN 80 °C	DMSO 100 °C	DMF 100 °C
1	**5**	38	89	87
2	**6**	98	89	94
3	**5**	97	98	96
4	**5**	99	94	96

[a] reaction time: 4 h; [b] **5**: methylferrocene, **6**: ethylferrocene

All amines **7a**–**7e**, **8a**–**8e** and **9a**, **9c**, **9e** were transformed with methyl iodide into their corresponding ammonium iodide salts, which were subjected to reductions with sodium borohydride. In most cases suitable reaction conditions could be found. The reaction conditions, products and yields are summarised in Table 2. All derivatives of amine **2** [(*R*,S_p)-**7a**–**7e**] were nicely reduced in acetonitrile at 80 °C to give products (S_p)-**10a**–**10e** in 79–96% isolated yield. The *O*-methylephedrine derivatives (1*R*,2*S*,R_p)-**8a**–**8d** could be reduced in dimethylsulfoxide at 100 °C to give products (R_p)-**11a**–**11d** in 72–93% yield. Interestingly, in the reduction of the iodo- and bromo-derivatives **8a** and **8b** a rather small amount (<5%) of dehalogenated product (methylferrocene, **5**) was obtained in addition to the expected products **11a** and **11b**. However, in the case of iodide **9a** not only did the overall yield drop significantly but the dehalogenation side reaction became very pronounced. In this particular case, both facts severely restrict the synthetic applicability of this transformation. In addition, in contrast to the cyano derivative **7e**, which could be reduced without difficulties to **10e**, synthetically suitable reaction conditions have not yet been identified for the reduction of the analogous derivatives **8e** and **9e**.

When the ammonium salt of ester **9c** was reacted with $NaBH_4$ in DMSO at 100 °C the overall conversion was low and **11c** was isolated in only 42% yield. However, an increase in the reaction temperature to 120 °C led to full conversion and the product was isolated in 80% yield. Interestingly, although the ammonium iodide salt of pyrrolidine derivative **4** can be reduced at 80 °C (Table 1), the reduction of its 2-substituted derivatives requires significantly higher reaction temperatures. This effect is likely to be steric in nature but is much less pronounced for the corresponding *O*-methylephedrine derivatives **8a**–**8d**.



Scheme 4. Preparation of derivatives **7–11**.

2.2. Synthesis of 1,2,3-trisubstituted derivatives by *ortho*-directed reactions

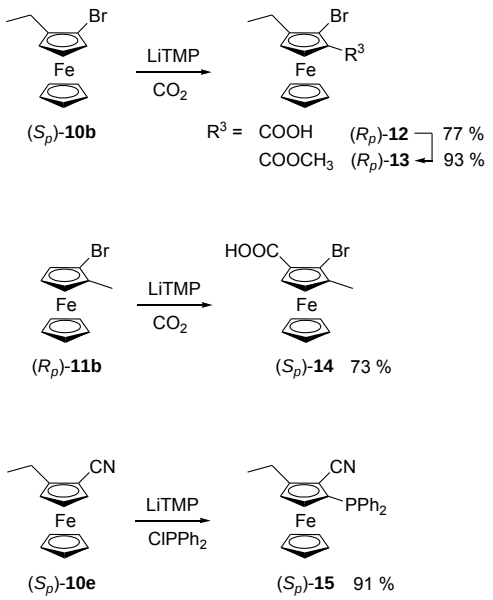
The substituents Br,[11,38–40] COOEt,[6,41–43] $P(O)Ph_2$[41,44–46] and CN[41] are well recognised *ortho*-directing groups. Therefore, the derivatives **10b**–**10e** and **11b**–**11d** should all be suitable starting materials for the preparation of chiral, nonracemic 1,2,3-trisubstituted ferrocenes – including exclusively ferrocene-stereogenic (planar chiral) derivatives. In order to prove and extend this concept, a few examples of further *ortho*-directed reactions have been explored without extensive optimisation of reaction conditions.

According to our previously reported protocol,[39] bromo derivatives (S_p)-**10b** and (R_p)-**11b** were *ortho*-deprotonated with 2 equivalents of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and quenched with CO_2 as the electrophile. These reactions gave the ferrocenecarbonic acids (R_p)-**12** and (S_p)-**14** in 77% and 73% yield, respectively (Scheme 5). Since acid **12** was accompanied by a small amount of by-product (about 5%), it was transformed with diazomethane into the corresponding methyl ester (R_p)-**13**, which could be purified easily. Whereas *ortho*-lithiation of ferrocenylbromides has been applied several times for the synthesis of catalyst ligands[28,29,38] – as well as for the preparation of pincer-type 1,3-disubstituted ferrocenes[39,47] – to the best of our knowledge the *ortho*-metallation of ferrocenyl cyanides has been reported only once.[41]

Table 2: Reduction of the ammonium iodide salts of **7**–**9** with $NaBH_4$[a]

amine	solvent	reaction temp. (°C)	product	Isolated yield (%)
7a	CH_3CN	80	**10a**	86
7b	CH_3CN	80	**10b**	96
7c	CH_3CN	80	**10c**	90
7d	CH_3CN	80	**10d**	79
7e	CH_3CN	80	**10e**	91
8a	DMSO	100	**11a**	93
8b	DMSO	100	**11b**	92
8c	DMSO	100	**11c**	72
8d	DMSO	100	**11d**	78
9a	CH_3CN	80	**11a/5**	36[b] (64/36)[c]
9a	DMSO	100	**11a/5**	68[b] (61/39)[c]
9a	DMF	100	**11a/5**	50[b] (0/100)[c]
9c	DMSO	100	**11c**	42
9c	DMSO	120	**11c**	80

[a] reaction time: 4 h; [b] conversion; [c] ratio of **11a**/**5** as determined by ^{1}H-NMR



Scheme 5. Synthesis of 1,2,3-substituted ferrocenes **12**–**15**.

It has been shown that ferrocenyl cyanides can be *ortho*-magnesiated with TMP-MgCl.LiCl and further reacted with electrophiles to give 2-substituted cyanoferrocenes.[41] Interestingly, the application of our *ortho*-lithiation protocol for bromides to cyanide derivative (S_p)-**10e**, followed by quenching with $ClPPh_2$ as the

electrophile, gave product (S_p)-**15** in 91% yield, thus providing an alternative route to *ortho*-substituted cyanoferrocenes.

It is worth mentioning that not only the disubstituted ferrocenes **10a**–**10e** and **11a**–**11d** but also all derivatives **12**–**15** can serve as precursors for the preparation of catalyst ligands, e.g. for the synthesis of ferrocenyl phosphinooxazolines.[48–52]

3. Conclusion

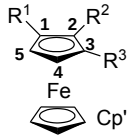
A number of 1,2-disubstituted ferrocene derivatives have been prepared starting from the monosubstituted and *ortho*-directing ferrocenyl amines (*R*)-**2**, (1*R*,2*S*)-**3** and (*R*)-**4**. Quaternisation of their amino-nitrogen with methyl iodide and subsequent reduction with sodium borohydride led to the removal of the *ortho*-directing amino-substituents to give to 2-substituted chiral, nonracemic methyl- or ethylferrocenes. In most cases, *ortho*-substituents I, Br, COOEt, $P(O)Ph_2$ and CN were found to tolerate the reaction conditions used. Furthermore, it was shown in a few examples that 2-bromo- and, most interestingly, 2-cyano-methyl (or ethyl)ferrocene can be further *ortho*-deprotonated next to the bromo and the cyano group by treatment with LiTMP. The subsequent reaction of these intermediates with an appropriate electrophile gave chiral, nonracemic 1,2,3-substituted ferrocene derivatives. In particular, we consider the deaminated 1,2-disubstituted ferrocenes **10a**–**10e**, **11a**–**11d** and similar derivatives to be useful starting materials for the synthesis of chiral, nonracemic ferrocenes for use as, for example, phosphino- or oxazoline-based catalysts ligands.

4. Experimental

4.1. General methods

NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are given relative to $CHCl_3$ (^{1}H: 7.26 ppm), $CDCl_3$ (^{13}C: 77.0 ppm), DMSO (^{1}H: 2.50 ppm), $CDCl_3$ (^{13}C: 39.5 ppm) or 85% H_3PO_4 (^{31}P: 0 ppm). The coupling constants in $^{13}C\{^1H\}$ spectra are due to ^{13}C-^{31}P coupling. For signal assignment the following terms were used: s, bs, d, dd, t, q and m refer to singlet, broad singlet, doublet, doublet of doublets, triplet, quartet and multiplet, respectively. The terms $Ph^{A\text{-}C}$ were used for phenyl units. In this respect, superscripts A and B were used to distinguish between rings attached to phosphorus atoms. A general atom numbering scheme used for proton and carbon assignment only is given in Figure 1. Melting points

were determined on a Kofler melting point apparatus and are uncorrected. Mass spectra were recorded on Finnigan MAT 900 and MAT 95 spectrometers. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. All reactions required inert conditions and were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried according to standard procedures and distilled before use. Chromatographic separations were performed under gravity either on silica (MERCK, 40–63 µm) or on standardized aluminium oxide 90 (MERCK). Petroleum ether with a boiling range of 55–65 °C was used for chromatography. Abbreviations: PE: petroleum ether, DEE: diethyl ether, EA: ethyl acetate; TEA: triethylamine.



R^1 = amine, Me or Et

Figure 1: Numbering scheme (for NMR signal assignment only)

4.2. Synthesis of ferrocenes (*R*,S_p)-7a–7e, (1*R*,2*S*,R_p)-8a–8e and (*R*,R_p)-9a, 9c, 9e

Compounds (*R*,S_p)-**7a**,[53] **7b**,[54] **7c**,[55] **7d**[15] were synthesised from (*R*)-**2**, (1*R*,2*S*,R_p)-**8a**,[31] **8b**[31] from (1*R*,2*S*)-**3**, and (*R*,R_p)-**9a**,[56] **9c**[57] from (*R*)-**4** according to reported procedures.

4.2.1. (*R*,S_p)-*N*-1-(2-Cyano-ferrocenyleth-1-yl)-*N*,*N*-dimethylamine (*R*,S_p)-7e

To a solution of (*R*)-**2** (500 mg, 1.94 mmol) in diethyl ether (15 mL) was added dropwise a solution of tBuLi in pentane (1.7 M, 1.26 mL, 2.14 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then at r.t. for a further 3 h. The mixture was added to a solution of tosyl cyanide (703 mg, 3.88 mmol) in THF (10 mL) at –78 °C. After 20 min at –78 °C, the solution was allowed to warm up to r.t. and an aqueous solution of NaOH (0.5 M, 5 mL) was added. After stirring for an additional 15 min, the mixture was poured into a solution of NaOH (1 M, 150 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by chromatography on silica with PE/EA/TEA = 30/10/1 as eluent to give the title compound as orange crystals (483 mg, 88% yield). mp 85 °C. $[\alpha]^{20}_{\lambda}$ (nm) = –33.9 (589), –30.4 (578), –6.8 (546) (*c* 0.280, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.54 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 2.10 [s, 6H, N(CH_3)$_2$], 3.75 (q, *J* = 6.8 Hz, 1H, *CH*CH_3), 4.27 (s, 5H, Cp'), 4.33 (dd, *J* = 2.5 Hz, *J*

= 1.3 Hz, 1H, H5), 4.37 (t, *J* = 2.5 Hz, 1H, H4), 4.64 (dd, *J* = 2.5 Hz, *J* = 1.3 Hz, 1H, H3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) *δ*: 17.4 ($CHCH_3$), 41.2 [$N(CH_3)_2$], 53.1 (C2), 57.6 ($CHCH_3$), 69.2 (C5), 69.5 (C4), 70.9 (C3), 71.1 (Cp'), 90.4 (C1), 120.4 (CN). HR-MS (EI, 30 °C): *m*/*z* $[M]^+$ calcd 282.0819 for $C_{15}H_{18}FeN_2$; found 282.0811.

4.2.2. (1*R*,2*S*,*R*$_p$)-*N*-(2-Ethoxycarbonyl-ferrocenylmethyl)-*N*-methyl-1-methoxy-1-phenylprop-2-ylamine (1*R*,2*S*,*R*$_p$)-8c

A solution of (1*R*,2*S*)-**3** (5.00 g, 13.25 mmol) in pentane (100 mL) was cooled to –78 °C and the resulting suspension was treated with a solution of tBuLi in pentane (1.7 M, 9.35 mL, 15.90 mmol). Stirring was continued at this temperature for 1.5 h followed by warming to –30 °C and stirring for an additional 2.5 h. The mixture was again cooled to –78 °C and diethyl carbonate (35 mL) was added in one portion with vigorous stirring. The reaction was kept at –78 °C for 30 min and at r.t. for 1 h. Addition of water led to phase separation and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvents were evaporated. The crude product was chromatographed on aluminium oxide 90 using PE/DE/TEA = 80/20/1 as the eluent to give the title compound as a red oil (4.26 g, 72% yield). $[\alpha]^{20}_{\lambda}$ (nm) = –22.9 (589), –23.5 (578), –27.0 (546) (*c* 0.808, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 1.08 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.32 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.26 (s, 3H, NCH_3), 2.88–2.97 (m, 1H, $CHCH_3$), 3.23 (s, 3H, OCH_3), 3.57 (d, *J* = 13.9 Hz, 1H, CH^AH^B), 3.99 (d, *J* = 13.9 Hz, 1H, CH^AH^B), 4.06 (s, 5H, Cp'), 4.17–4.28 (m, 5H, H5 + H4 + CH_2CH_3 + $CHOCH_3$), 4.68–4.72 (m, 1H, H3), 7.17–7.32 (m, 5H, Ph). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) *δ*: 9.5 (s, $CHCH_3$), 11.6 (s, CH_2CH_3), 37.0 (s, NCH_3), 53.0 (s, CH^AH^B), 56.7 (OCH_3), 59.8 (CH_2CH_3), 63.3 ($CHCH_3$), 69.3 (C4), 69.4 (C1/C2), 70.2 (Cp'), 70.7 (C3), 73.9 (C5), 85.1 ($CHOCH_3$), 88.8 (C1/C2), 126.9 (Ph-*para*), 127.0 (Ph-*ortho*), 127.9 (Ph-*meta*), 141.7 (Ph-*ipso*), 171.9 (C=O). HR-MS (ESI): *m*/*z* $[M + H]^+$ calcd 450.1732 for $C_{25}H_{32}FeNO_3$; found 450.1713.

4.2.3. (1*R*,2*S*,*R*$_p$)-*N*-(2-Diphenylphosphinyl-ferrocenylmethyl)-*N*-methyl-1-methoxy-1-phenylprop-2-ylamine (1*R*,2*S*,*R*$_p$)-8d

To a stirred solution of (1*R*,2*S*,*R*$_p$)-*N*-(2-diphenylphosphino-ferrocenylmethyl)-*N*-methyl-1-methoxy-1-phenylprop-2-ylamine[31] (7.44 g, 13.25 mmol) in acetone (100 mL) was added a 30% solution of hydrogen peroxide in water (12 mL). Stirring was continued for 1 h at r.t. and excess peroxide was decomposed by dropwise addition of saturated aqueous $Na_2S_2O_3$ (20 mL). Acetone was then removed under reduced pressure and the residue was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvents were

removed on a rotary evaporator. The crude phosphine oxide was purified by chromatography on aluminium oxide 90 using EA as the eluent to give the title compound as an orange-yellow semisolid (5.98 g, 78% yield). $[\alpha]^{20}_{\lambda}$ (nm) = +45.0 (589), +45.7 (578), +41.5 (546) (*c* 1.230, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.73 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.98 (s, 3H, NCH_3), 2.70–2.78 (m, 1H, C*H*CH_3), 3.17 (s, 3H, OCH_3), 3.49 (d, *J* = 13.9 Hz, 1H, C*H*^{A}H^B), 3.80 (d, *J* = 13.9 Hz, 1H, CH^A*H*^{B}), 3.79–3.82 (m, 1H, H3), 4.06–4.10 (m, 1H, C*H*OCH_3), 4.16 (s, 5H, Cp'), 4.19–4.23 (m, 1H, H4), 4.31–4.34 (m, 1H, H5), 7.16–7.20 (m, 2H, Ph^C-*ortho*), 7.20–7.25 (m, 1H, Ph^C-*para*), 7.27–7.36 (m, 4H, Ph^B-*meta* + Ph^C-*meta*), 7.37–7.42 (m, 1H, Ph^B-*para*), 7.42–7.53 (m, 3H, Ph^A-*meta* + Ph^A-*para*), 7.57–7.64 (m, 2H, Ph^B-*ortho*), 7.74–7.81 (m, 2H, Ph^A-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) *δ*: 8.8 (CH*C*H_3), 35.9 (NCH_3), 53.7 (CH^{A}H^B), 56.4 (OCH_3), 64.1 (*C*HCH_3), 69.3 (d, *J* = 11.3 Hz, C4), 70.2 (Cp'), 71.3 (d, *J* = 115.0 Hz, C2), 73.6 (d, *J* = 15.2 Hz, C3), 73.8 (d, *J* = 10.0 Hz, C5), 84.8 (*C*$HOCH_3$), 91.3 (d, *J* = 10.7 Hz, C1), 126.69 (Ph^C-*para*), 126.74 (Ph^C-*ortho*), 127.8 (d, *J* = 6.1 Hz, Ph$^{A/B}$-*meta*), 127.88 (Ph^C-*meta*), 127.9 (d, *J* = 5.6 Hz, Ph$^{A/B}$-*meta*), 131.0 (d, *J* = 2.5 Hz, Ph$^{A/B}$-*para*), 131.1 (d, *J* = 2.5 Hz, Ph$^{A/B}$-*para*), 131.48 (d, *J* = 9.5 Hz, Ph$^{A/B}$-*ortho*), 131.51 (d, *J* = 9.9 Hz, Ph$^{A/B}$-*ortho*), 134.1 (d, *J* = 99.4 Hz, Ph^A-*ipso*), 135.2 (d, *J* = 101.0 Hz, Ph^B-*ipso*), 141.9 (s, Ph^C-*ipso*). ^{31}P NMR (162 MHz, $CDCl_3$) *δ*: 29.6 (P(O)Ph_2). HR-MS (ESI): *m*/*z* $[M + H]^+$ calcd 578.1912 for $C_{34}H_{37}FeNO_2P$; found 578.1916.

4.2.4. (1*R*,2*S*,*R*$_p$)-*N*-(2-Cyano-ferrocenyl)-*N*-methyl-1-methoxy-1-phenylprop-2-ylamine (1*R*,2*S*,*R*$_p$)-8e

A solution of (1*R*,2*S*)-**3** (5.00 g, 13.25 mmol) in pentane (100 mL) was cooled to –78 °C and the resulting suspension was treated with a solution of tBuLi in pentane (1.7 M, 9.35 mL, 15.90 mmol). Stirring was continued at this temperature for 1.5 h followed by warming to 0 °C and stirring was continued for a further 2.5 h. The mixture was again cooled to –78 °C and a solution of tosylcyanide (3.60 g, 19.87 mmol) in THF (10 mL) was added dropwise with stirring. The reaction was warmed to r.t. and stirred for a further 1 h. Addition of water led to phase separation and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvents were evaporated. The crude product was chromatographed on silica using DEE as eluent to give the title compound as a dark red oil (4.12 g, 77% yield). $[\alpha]^{20}_{\lambda}$ (nm) = –32.6 (589), –37.9 (578), –57.1 (546) (*c* 0.298, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.07 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 2.25 (s, 3H, NCH_3), 2.78–2.88 (m, 1H, C*H*CH_3), 3.27 (s, 3H, OCH_3), 3.56–3.67 (m, 2H, CH^{A}H^B), 4.23 (s, 5H, Cp'), 4.24–4.30 (m, 3H, H4 + H5 + C*H*OCH_3), 4.54–4.57 (m, 1H, H3), 7.20–7.27 (m, 3H, Ph-*ortho* + Ph-*para*), 7.28–7.34 (m, 2H, Ph-*meta*). ^{13}C{^{1}H} NMR (100.6 MHz,

$CDCl_3$) δ: 8.9 ($CHCH_3$), 37.6 (NCH_3), 52.1 (CH^AH^B), 53.3 (C2), 56.7 (OCH_3), 63.7 ($CHCH_3$), 69.7 (C4), 71.0 (Cp'), 71.3 (C3), 72.1 (C5), 85.3 ($CHOCH_3$), 89.5 (C1), 119.8 (C≡N), 126.9 (Ph-*ortho*), 127.0 (Ph-*para*), 128.0 (Ph-*meta*), 141.4 (Ph-*ipso*). HR-MS (ESI): *m*/*z* $[M + H]^+$ calcd 403.1473 for $C_{23}H_{27}FeN_2O$; found 403.1478.

4.2.5. (*R*,*R*$_p$)-*N*-(2-Cyano-ferrocenylmethyl)-2-methoxymethyl-pyrrolidine (*R*,*R*$_p$)-9e

To a stirred solution of (*R*)-**4**[32] (5.00 g, 15.96 mmol) in diethyl ether (80 mL) was added dropwise at –78 °C a solution of sBuLi in cyclohexane (1.4 M, 13.7 mL, 19.15 mmol). The resulting mixture was stirred for 1.5 h at –78 °C and for an additional 1.5 h at –30 °C. During this time an orange suspension evolved and this was again cooled to –78 °C followed by addition of a solution of tosyl cyanide (4.34 g, 23.94 mmol) in diethyl ether (60 mL). Stirring was continued for an additional 30 min at –78 °C. The mixture was warmed to r.t. and quenched by the addition of water. The aqueous phase was made basic with an aqueous sodium hydroxide solution and the product was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvents were evaporated. The crude product was subjected to chromatography on silica using PE/EA/TEA = 10/1/1 → 2/1/1 as the eluent to give the title compound as a red oil (4.88 g, 90% yield). $[\alpha]^{20}_{\lambda}$ (nm) = +79.6 (589), +79.3 (578), +63.5 (546) (*c* 0.690, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50–1.75 (m, 3H, NCH_2CH_2CHH), 1.75–1.90 (m, 1H, NCH_2CH_2CHH), 2.18–2.30 (m, 1H, $NCHH$), 2.62–2.75 (m, 1H, NCH), 2.95–3.03 (m, 1H, $NCHH$), 3.29 (dd, *J* = 9.4 Hz, *J* = 5.4 Hz, 1H, CH_3OCHH), 3.37 (s, 3H, CH_3), 3.42 (dd, *J* = 9.4 Hz, *J* = 5.4 Hz, 1H, CH_3OCHH), 3.59 (d, *J* = 13.5 Hz, 1H, $FcCHH$), 3.99 (d, *J* = 13.5 Hz, 1H, $FcCHH$), 4.28 (s, 5H, Cp'), 4.30–4.34 (m, 1H, H4), 4.41–4.47 (m, 1H, H5), 4.59–4.64 (m, 1H, H3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ: 22.7 (NCH_2CH_2), 28.4 ($NCH_2CH_2CH_2$), 51.8 ($FcCH_2$), 53.7 (C2), 54.2 (NCH_2), 59.1 (CH_3), 61.7 (NCH), 70.0 (C4), 71.0 (Cp'), 71.6 (C3), 72.3 (C5), 76.4 (CH_3OCH_2), 87.8 (C1), 119.7 (s, C≡N). HR-MS (ESI): *m*/*z* $[M + H]^+$ calcd 339.1160 for $C_{18}H_{23}FeN_2O$; found 339.1158.

4.3. General procedure for the preparation of the ammonium iodide salts of (*R*,*S*$_p$)-7a–7e, (1*R*,2*S*,*R*$_p$)-8a–8d and (*R*,*R*$_p$)-9a, 9c

To a solution of amines (*R*,*S*$_p$)-**7a**–**7e**, (1*R*,2*S*,*R*$_p$)-**8a**–**8d** or (*R*,*R*$_p$)-**9a,9c** (10 mmol) in anhydrous acetonitrile (50 mL) was added dropwise methyl iodide (30 mmol) and the mixture was stirred at r.t. for 1 h. In the cases of **7a**, **7b**, **8a**, **8b** and **9a** diethyl ether (100 mL) was added and a yellow precipitate was formed. After stirring for an additional 30 min the precipitate was filtered off, washed with diethyl ether and dried under vacuum to give a crystalline solid. In the cases of **7c**–**7e**, **8c**, **8d** and **9c** all volatiles

were removed, the residues were dried under vacuum and the remaining yellow salts were used without further purification.

4.4. General procedure for the preparation of (S_p)-10a–10e

The ammonium iodide salts (10 mmol) of (R,S_p)-**7a**–**7e** (prepared according to the general procedure 4.3.) were suspended in anhydrous acetonitrile (50 mL) and $NaBH_4$ (30 mmol) was added in portions. The resulting mixture was stirred for 4 h at 80 °C. The reaction mixture was cooled to r.t. and was quenched with water (30 mL). Diethyl ether was added, the phases were separated and the organic phase was washed with water (3×) and brine. After drying with $MgSO_4$ the solvent was removed under reduced pressure and the crude product was purified by chromatography on aluminium oxide 90.

4.4.1. (S_p)-2-Ethyl-1-iodo-ferrocene (S_p)-10a

The crude product prepared from the ammonium iodide salt of (R,S_p)-**7a** (676 mg, 1.29 mmol) and $NaBH_4$ (146 mg, 3.86 mmol) was purified by chromatography on aluminium oxide 90 with eluent PE/EA = 9/1 to give the title compound as a red oil (375 mg, 86% yield). $[\alpha]^{20}_{\lambda}$ (nm) = –5.2 (589), –3.3 (578), +16.6 (546) (*c* 0.484, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.32–2.45 (m, 2H, CH_2CH_3), 4.10 (s, 5H, Cp'), 4.11–4.14 (m, 2H, H4 + H5), 4.37 (dd, J = 2.3 Hz, J = 1.5 Hz, 1H, H3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ: 14.5 (CH_2CH_3), 23.1 (CH_2CH_3), 45.3 (C2), 66.2 (C5), 67.6 (C4), 71.4 (Cp'), 73.8 (C3), 91.8 (C1). HR-MS (EI, 30 °C): m/z $[M]^+$ calcd 339.9411 for $C_{12}H_{13}FeI$; found 339.9410.

4.4.2. (S_p)-1-Bromo-2-ethyl-ferrocene (S_p)-10b[29]

The crude product prepared from the ammonium iodide salt of (R,S_p)-**7b** (2.74 g, 5.74 mmol) and $NaBH_4$ (651 mg, 17.20 mmol) was purified by chromatography on aluminium oxide 90 with eluent PE/EA = 9/1 to give the title compound as a yellow oil (1.62 g, 96% yield). $[\alpha]^{20}_{\lambda}$ (nm) = –2.5 (589), –1.7 (578), +8.3 (546) (*c* 0.485, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.44 (q, J = 7.5 Hz, 2H, CH_2CH_3), 4.01 (t, J = 2.5 Hz, 1H, H4), 4.05–4.08 (m, 1H, H5), 4.14 (s, 5H, Cp'), 4.35–4.39 (dd, J = 2.5 Hz, J = 1.4 Hz, 1H, H3). ^{13}C{^{1}H} NMR (100.6 MHz) δ: 14.4 (CH_2CH_3), 21.4 (CH_2CH_3), 65.1 (C4), 65.6 (C5), 69.4 (C3), 71.0 (Cp'), 79.8 (C2), 89.3 (C1). HR-MS (EI, 30 °C): m/z $[M]^+$ calcd 291.9552 for $C_{12}H_{13}FeBr$; found 291.9553.

4.4.3. (S_p)-1-Ethoxycarbonyl-2-ethyl-ferrocene (S_p)-10c

The crude product prepared from amine (R,S_p)-**7c** (2 g, 6.075 mmol) and $NaBH_4$ (689 mg, 18.22 mmol) was purified by chromatography on aluminium oxide 90 with eluent PE/EA = 15/1 to give the title compound as a red oil (1.56 g, 90% yield). $[\alpha]^{20}_{\lambda}$ (nm) = –15.5 (589), +12.3 (578), +17.8 (546) (*c* 0.252, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.36 (t, J = 7.3 Hz, 3H, OCH_2CH_3), 2.61–2.72 (m, 1H, $CH^AH^BCH_3$), 2.74–2.85 (m, 1H, $CH^AH^BCH_3$), 4.12 (s, 5H, Cp'), 4.19–4.35 (m, 2H, OCH_2CH_3), 4.24 (t, J = 2.5 Hz, 1H, H4), 4.31–4.33 (m, 1H, H5), 4.75 (dd, J = 2.5 Hz, J = 1.6 Hz, 1H, H3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ: 14.5 (OCH_2CH_3), 15.0 (CH_2CH_3), 21.9 (CH_2CH_3), 59.7 (OCH_2CH_3), 68.7 (C4), 69.1 (C2), 70.0 (Cp'), 70.5 (C3), 71.4 (C5), 93.5 (C1), 172.4 (C=O). HR-MS (ESI): m/z $[M]^+$ calcd 286.0656 for $C_{15}H_{18}FeO_2$; found 286.0659.

4.4.4. (S_p)-1-Diphenylphosphinyl-2-ethyl-ferrocene (S_p)-10d[15]

The crude product prepared from amine (R,S_p)-**7d** (2.285 g, 4.996 mmol) and $NaBH_4$ (0.582 g, 1.54 mmol) was purified by chromatography on aluminium oxide 90 with EA as the eluent to provide the title compound as a yellow solid (1.64 g, 79% yield); mp 150 °C. $[\alpha]^{20}_{\lambda}$ (nm) = –115.7 (589), –117.1 (578), –128.8 (546) (*c* 0.281, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.32–2.43 (m, 1H, $CH^AH^BCH_3$), 2.59–2.70 (m, 1H, $CH^AH^BCH_3$), 3.73–3.77 (m, 1H, H3), 4.22–4.25 (m, 1H, H4), 4.27 (s, 5H, Cp'), 4.39–4.43 (m, 1H, H5), 7.44–7.42 (m, 2H, Ph^B-*meta*), 7.43–7.55 (m, 4H, Ph^A-*meta* + Ph^A-*para* + Ph^B-*para*), 7.57–7.65 (m, 2H, Ph^B-*ortho*), 7.71–7.79 (m, 2H, Ph^A-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ: 15.2 (CH_2CH_3), 22.2 (CH_2CH_3), 69.1 (d, J = 11.5 Hz, C5), 70.0 (Cp'), 71.2 (d, J = 10.4 Hz, C4), 71.7 (d, J = 114.5 Hz, C2), 73.5 (d, J = 15.7 Hz, C3), 95.2 (d, J = 11.5 Hz, C1), 128.0 (d, J = 12.3 Hz, Ph^A-*meta*), 128.2 (d, J = 12.3 Hz, Ph^A-*meta*), 131.2–131.4 (m, Ph^A-*para* + Ph^B-*para*), 131.5 (d, J = 10.0 Hz, 2C-*ortho*), 131.6 (d, J = 10.0 Hz, 2C-*ortho*), 133.9 (d, J = 88.8 Hz, Ph^A-*ipso*), 134.9 (d, J = 88.8 Hz, Ph^B - *ipso*). ^{31}P NMR (162.6 MHz, $CDCl_3$) δ: 31.3 [$P(O)PPh_2$]. HR-MS (EI, 30 °C): m/z $[M]^+$ calcd 414.0836 for $C_{24}H_{23}FePO$; found 414.0823.

4.4.5. (S_p)-1-Cyano-2-ethyl-ferrocene (S_p)-10e

The crude product prepared from amine (R,S_p)-7e (2.485 g, 8.81 mmol) and $NaBH_4$ (999 mg, 26.4 mmol) was purified by chromatography on aluminium oxide 90 with eluent PE/EA = 9/1 to give the title compound as a red oil (1.91 g, 91% yield). $[\alpha]^{20}_{\lambda}$ (nm) = +24.3 (589), +34.8 (578), +103.7 (546) (*c* 0.485, $CHCl_3$). ^{1}H NMR (400 MHz,

$CDCl_3$) δ: 1.23 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.46–2.60 (m, 2H, CH_2CH_3), 4.25–4.27 (m, 1H, H4), 4.27 (s, 5H, Cp'), 4.29–4.33 (m, 1H, H5), 4.57 (dd, J = 2.5 Hz, J = 1.3 Hz, 1H, H3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ: 14.9 (CH_2CH_3), 21.4 ($CHCH_3$), 52.2 (C2), 69.2 (C5), 69.6 (C3), 70.7 (C4), 70.8 (Cp'), 94.6 (C1), 120.0 (C≡N). HR-MS (ESI): m/z $[M]^+$ calcd 239.0397 for $C_{13}H_{13}FeN$; found 239.0398.

4.5. General procedure for the preparation of (R_p)-11a–11d

To a stirred suspension of the ammonium iodide salts of (1R,2S,R_p)-8a–8d and (R,R_p)-9c (5 mmol, prepared according to the general procedure 4.3., in dimethyl sulfoxide (10 mL) was added sodium borohydride (15 mmol) in portions. The resulting mixture was heated to 100 °C (8a–8d) or 120 °C (9c) for 4 h and was subsequently cooled to r.t., diluted with water (200 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was purified by column chromatography on silica or aluminium oxide 90.

4.5.1. (R_p)-1-Iodo-2-methyl-ferrocene (R_p)-11a

The crude product obtained from the ammonium iodide salt of (1R,2S,R_p)-8a (1.00 g, 1.550 mmol) and sodium borohydride (176 mg, 4.650 mmol) in dimethyl sulfoxide (4 mL) was purified by filtration through a short plug of aluminium oxide 90 using PE as the eluent. The product was obtained as an orange solid (470 mg, 93% yield). mp 44–47 °C. $[\alpha]^{20}_{\lambda}$ (nm) = +29.9 (589), +30.1 (578), +22.9 (546) (c 0.708, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.02 (s, 3H, CH_3), 4.09 (s, 5H, Cp'), 4.08–4.11 (m, 1H, H4), 4.14–4.17 (m, 1H, H5), 4.34–4.37 (m, 1H, H3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ: 15.7 (CH_3), 46.5 (C2), 67.7 (C4/C5), 67.9 (C4/C5), 71.6 (Cp'), 73.7 (C3), 85.9 (C1). HR-MS (ESI): m/z $[M]^+$ calcd 325.9255 for $C_{11}H_{11}FeI$; found 325.9248.

4.5.2. (R_p)-1-Bromo-2-methyl-ferrocene (R_p)-11b[58]

The crude product obtained from the ammonium iodide salt of (1R,2S,R_p)-8b (5.03 g, 8.409 mmol) and sodium borohydride (1.00 g, 26.43 mmol) in dimethyl sulfoxide (20 mL) was purified by filtration through a short plug of aluminium oxide 90 using PE as eluent. Traces of methylferrocene were removed by heating the mixture in a bulb to bulb distillation apparatus under vacuum at 50 °C for 1 h. The remaining pure product was obtained as an orange solid (2.16 g, 92% yield). mp 70–74 °C. $[\alpha]^{20}_{\lambda}$ (nm) = +26.6 (589), +27.0 (578), +24.9 (546) (c 0.957, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.05 (s, 3H, CH_3), 3.97–4.00 (m, 1H, H4), 4.07–4.10 (m, 1H, H5), 4.13 (s, 5H, Cp'), 4.33–4.36 (m, 1H, H3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$) δ: 13.7 (CH_3), 65.1 (C4), 67.4 (C5), 69.2 (C3),

71.1 (Cp'), 80.6 (C1/C2), 83.1 (C1/C2). HR-MS (ESI): *m*/*z* $[M]^+$ calcd 277.9395 for $C_{11}H_{11}BrFe$; found 277.9393.

4.5.3. (R_p)-1-Ethoxycarbonyl-2-methyl-ferrocene (R_p)-11c

The crude product obtained from amine (1*R*,2*S*,R_p)-8c (4.172 g, 9.284 mmol) and $NaBH_4$ (1.054 g, 27.85 mmol) was purified by column chromatography on silica using PE/EA = 10/1 as the eluent to give the title compound as an orange oil (2.155 g, 85% yield). $[\alpha]^{20}_{\lambda}$ (nm) = +22.1 (589), +18.8 (578), –6.3 (546) (*c* 0.521, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.37 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.27 (s, 3H, CH_3), 4.12 (s, 5H, Cp'), 4.21–4.23 (m, 1H, H4), 4.23–4.34 (m, 3H, H5 + CH_2CH_3), 4.70–4.73 (m, 1H, H3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) *δ*: 14.59, 14.63 (CH_2CH_3 + CH_3), 59.8 (CH_2CH_3), 68.8 (C4), 69.7 (C2), 70.3 (C3), 70.4 (Cp'), 73.6 (C5), 87.0 (C1), 172.4 (C=O). HR-MS (ESI): *m*/*z* $[M]^+$ calcd 272.0500 for $C_{14}H_{16}FeO_2$; found 272.0502.

4.5.4. (R_p)-1-Diphenylphosphinyl-2-methyl-ferrocene (R_p)-11d

The crude product obtained from amine (1*R*,2*S*,R_p)-8d (5.071 g, 8.781 mmol) and $NaBH_4$ (996 mg, 26.34 mmol) was purified by column chromatography on aluminium oxide 90 using EA as the eluent to give the title compound as an orange solid (2.495 g, 71% yield). mp 130–134 °C. $[\alpha]^{20}_{\lambda}$ (nm) = +118.9 (589), +120.7 (578), +113.7 (546) (*c* 0.996, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.04 (s, 3H, CH_3), 3.70–3.74 (m, 1H, H3), 4.17–4.21 (m, 1H, H4), 4.24 (s, 5H, Cp'), 4.35–4.39 (m, 1H, H5), 7.34–7.41 (m, 2H, Ph^B-*meta*), 7.41–7.48 (m, 3H, Ph^A-*meta* + Ph^B-*para*), 7.48–7.54 (m, 1H, Ph^A-*para*), 7.54–7.61 (m, 2H, Ph^B-*ortho*), 7.69–7.78 (m, 2H, Ph^A-*ortho*). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) *δ*: 14.1 (CH_3), 69.1 (d, *J* = 11.4 Hz, C4), 70.1 (Cp'), 72.1 (d, *J* = 115.1 Hz, C2), 73.5 (d, *J* = 15.4 Hz, C3), 73.6 (d, *J* = 10.1 Hz, C5), 88.3 (d, *J* = 10.9 Hz, C1), 127.9 (d, *J* = 12.1 Hz, Ph^A-*meta*), 128.2 (d, *J* = 11.9 Hz, Ph^B-*meta*), 131.2–131.3 (m, Ph^A-*para* + Ph^B-*para*), 131.4 (d, *J* = 6.7 Hz, $Ph^{A/B}$-*ortho*), 131.5 (d, *J* = 6.8 Hz, $Ph^{A/B}$-*ortho*), 133.5, 134.2, 134.3, 135.2 (Ph^A-*ipso* + Ph^B-*ipso*). ^{31}P NMR (162 MHz, $CDCl_3$) *δ*: 30.6 ($P(O)Ph_2$). HR-MS (ESI): *m*/*z* $[M + H]^+$ calcd 401.0758 for $C_{23}H_{22}FeOP$; found 401.0760.

4.6. Synthesis of 1,2,3-trisubstituted ferrocenes

4.6.1. (R_p)-1-Bromo-5-ethyl-2-hydroxycarbonyl-ferrocene (R_p)-12

To a solution of (S_p)-10b (437 mg, 1.491 mmol) in dry THF (5 mL) was added a solution of LiTMP in THF/hexane (0.73 M, 4.08 mL, 2.98 mmol) at –78 °C. After stirring for 30 min at –78 °C, the temperature was raised to –30 °C and the mixture was stirred for an additional 4 h. The reaction mixture was transferred onto crushed dry ice. After 1 h at r.t.

the reaction mixture was dissolved in diethyl ether and extracted with a 10% aqueous NaOH solution (50 mL). The basic aqueous phase was extracted with diethyl ether (3 × 50 mL, organic phases discarded) and the aqueous phase was made acidic with 10% phosphoric acid. After extraction with diethyl ether (3 × 50 mL) the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The title compound was obtained as a yellow solid (0.386 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.35–2.56 (m, 2H, CH_2CH_3), 4.18 (s, 5H, Cp'), 4.47–4.53 (m, 1H, H5), 4.64–4.72 (m, 1H, H4), 12.38 (s, 1H, COOH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6) δ: 14.2 (CH_2CH_3), 21.5 (CH_2CH_3), 68.0 (Cq), 68.5 (C5), 68.9 (C2), 72.4 (Cp'), 80.5 (Cq), 92.8 (C1), 170.9 (COOH). HR-MS (EI, 30 °C): m/z [M – H]$^+$ calcd 334.9372 for $C_{13}H_{12}FeBrO_2$; found 334.9368.

4.6.2. (R_p)-1-Bromo-2-ethoxycarbonyl-5-ethyl-ferrocene (R_p)-13

To a solution of (R_p)-12 (290 mg, 861 mmol) in dichloromethane (23 mL) and methanol (2.3 mL) at r.t. was added a solution of diazomethane in diethyl ether (1M, 18 mL, 18 mmol). The mixture was stirred for 30 min and the solvents were evaporated. The crude product was purified by chromatography on aluminium oxide 90 with PE/EA = 5/1 as the eluent to give the title compound as an orange solid (2.81 mg, 93% yield). mp 83 °C. $[\alpha]^{20}_{\lambda}$ (nm) = +0.61 (589),+3.1 (578), +26.7 (546) (c 0.330, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.40–2.57 (m, 2H, CH_2CH_3), 3.84 (s, 3H, CH_3), 4.17 (s, 5H, Cp'), 4.36 (d, J = 2.8 Hz, 1H, H5), 4.73 (d, J = 2.8 Hz, 1H, H4). ^{13}C {^{1}H}NMR (100.6 MHz, $CDCl_3$) δ: 14.0 (CH_2CH_3), 21.9 (CH_2CH_3), 51.7 (CH_3), 67.8 (C4), 68.6 (C5), 72.7 (Cp'), 80.1 (Cq), 94.0 (C1), 1 Cq was not observed. HR-MS (EI, 30 °C): m/z [M]$^+$ calcd 349.9605 for $C_{14}H_{15}BrFeO_2$; found 349.9606.

4.6.3. (S_p)-1-Bromo-2-hydroxycarbonyl-5-methyl-ferrocene (S_p)-14

To a solution of (R_p)-11b (200 mg, 0.7170 mmol) in THF (6 mL) was added dropwise a solution of LiTMP in THF/hexane (0.73 M, 1.96 mL, 1.434 mmol) at –78 °C. The resulting mixture was stirred at –78 °C for a further 30 min and at –30 °C for 3 h. The solution was poured onto crushed dry ice and the heterogeneous mixture was left to warm up to r.t. The residue was dissolved in diethyl ether and extracted with 10% aqueous sodium hydroxide (50 mL). The basic aqueous phase was extracted twice with diethyl ether (organic phases discarded), the aqueous phase was made acidic with 10% phosphoric acid and extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was obtained as an orange-yellow solid (169 mg, 73% yield). mp 145–168 °C (dec.). $[\alpha]^{20}_{\lambda}$ (nm): +9.8 (589), +5.1 (578), –26.2 (546) (c 0.654,

$CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.04 (s, 3H, CH_3), 4.16 (s, 5H, Cp'), 4.53 (d, J = 2.7 Hz, 1H, H5), 4.66 (d, J = 2.7 Hz, 1H, H4), 12.39 (bs, 1H, COOH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6) δ: 13.9 (CH_3), 68.0 (C4), 68.6 (Cq), 70.1 (C5), 72.6 (Cp'), 80.6 (Cq), 86.9 (Cq), 170.9 (COOH). HR-MS (ESI): m/z $[M]^+$ calcd 321.9293 for $C_{12}H_{11}BrFeO_2$; found 321.9296.

4.6.4. (S_p)-2-Cyano-1-diphenylphosphino-3-ethyl-ferrocene (S_p)-15

To a solution of (S_p)-10e (269 mg, 1.125 mmol) in dry THF/hexane (5 mL) was added LiTMP (0.73 M, 3.08 mL, 2.250 mmol) at –78 °C. After stirring for 30 min at –78 °C, the temperature was raised to –30 °C and the mixture was stirred for additional 4 h. The mixture was cooled to –78 °C and chlorodiphenylphosphine (0.437 mL, 2.363 mmol) was added. After 30 min stirring at –78 °C, the reaction mixture was allowed to warm up to r.t. Stirring was continued for an additional 16 h and the reaction was quenched by the dropwise addition of water (5 mL). Diethyl ether was added and the phases were separated. The organic phase was washed with water and brine (3×), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by chromatography on aluminium oxide 90 with PE/EA = 9/1 as the eluent to give the title compound as a yellow solid (433 mg, 91% yield). mp 162 °C. $[\alpha]^{20}_{\lambda}$ (nm) = –108.1 (589), –111.4 (578), –131.9 (546) (c 0.298, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.8 Hz, 3H, CH_2CH_3), 2.59 (q, J = 7.8 Hz, 2H, CH_2CH_3), 3.95 (dd, J = 2.5 Hz, J = 1.0 Hz, 1H, H4), 4.45(d, J = 2.5 Hz, 1H, H5), 7.16–7.23 (m, 2H, Ph^A-*ortho*), 7.25–7.30 (m, 3H, Ph^A-*meta* + Ph^A-*para*), 7.37–7.43 (m, 3H, Ph^B-*meta* + Ph^B-*para*), 7.52–7.60 (m, 2H, Ph^B-*ortho*). ^{13}C{^{1}H}NMR (100.6 MHz, $CDCl_3$) δ: 14.5 (CH_2CH_3), 21.8 (CH_2CH_3), 58.5 (d, J = 28.9, 2C Hz, C2), 71.3 (C4), 72.1 (Cp'), 73.6 (d, J = 2.4 Hz, C5), 80.1 (d, J = 14.5 Hz, C3), 97.8 (d, J = 2.7 Hz, C1), 119.0 (CN), 128.3 (d, J = 6.2 Hz, Ph^A-*meta*), 125.35 (Ph^A-*para*), 128.4 (d, J = 6.9 Hz, Ph^B-*meta*), 129. 5 (Ph^B-*para*), 132.3 (d, J = 18.3 Hz, Ph^A-*ortho*), 134.8 (d, J = 21.4 Hz, Ph^B-*ortho*), 136.5 (d, J = 9.5 Hz, Ph^B-*ipso*), 138.4 (d, J = 10.7Hz, Ph^A-*ipso*). HR-MS (EI, 30 °C): m/z $[M + H]^+$ calcd 424.0918 for $C_{25}H_{23}FeNP$; found 424.0923.

Acknowledgments

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4. Summary

4.1 Ruthenium complexes of phosphino-substituted ferrocenyl-oxazolines in the asymmetric hydrogenation and transfer hydrogenation of ketones: a comparison.

As described in Chapter 3.1*, a number of phosphino-substituted ferrocenyloxazolines with altered structural features were prepared and tested in the ruthenium-catalyzed transfer hydrogenation and hydrogenation of ketones. It was one intention of this work to investigate correlations in between ligand structure and catalyst performance. Furthermore, it was of interest to compare the results of transfer hydrogenations and hydrogenations when these reactions were carried out with identical catalyst precursors. For this purpose five ligands, **2–4**, recently developed in our group plus three newly prepared ligands, **5–7**, with varied structural features were used (Chart 10).

Ligand (R,R_{Fc})-**5** which lacks the stereogenic center of the oxazoline unit, was prepared by the synthesis procedure depicted in Scheme 21. Amino-ester (R,S_{Fc})-**9** which was easily accessible from Ugi's amine, (R)-**8**, underwent with the appropriate amino alcohol an aluminium mediated transamidation that afforded the corresponding amide (R,S_{Fc})-**10**. In the next step, (R,S_{Fc})-**10** was transformed according to Appel's methodology to oxazoline (R,S_{Fc})-**11**. Subsequently, treatment with methyl iodide in acetonitrile and reaction of the crude ammonium salt with diphenylphosphinyl lithium generated the phosphinyl-substituted derivative (R,R_{Fc})-**12**. Reduction of this phosphine oxide with polymethylhydrosiloxane (PMHS) in the presence of titanium isopropoxide provided the desired phosphine-oxazoline (R,R_{Fc})-**5**.

Ligands (S_{Ox},S_{Fc})-**6** and (S_{Ox},S_{Fc})-**7** which both lack the stereogenic center of the side-chain carbon were achieved in only two steps from commercially available ferrocenyl oxazoline (S_{Ox})-**13**. Alcohol (S_{Ox},R_{Fc})-**14**, easily obtainable from (S_{Ox})-**13**, was transformed with either diphenylphosphine or bis(3,5-dimethylphenyl)phosphine in the presence of chlorotrimethylsilane and sodium iodide into ligands (S_{Ox},S_{Fc})-**6** and (S_{Ox},S_{Fc})-**7** (Scheme 22).

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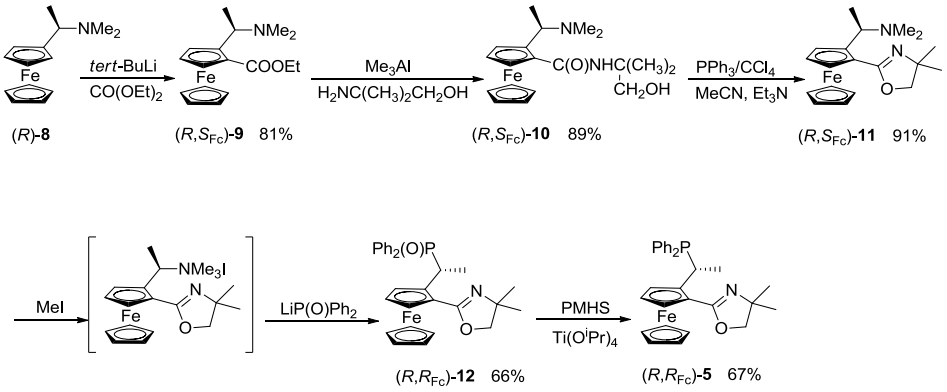
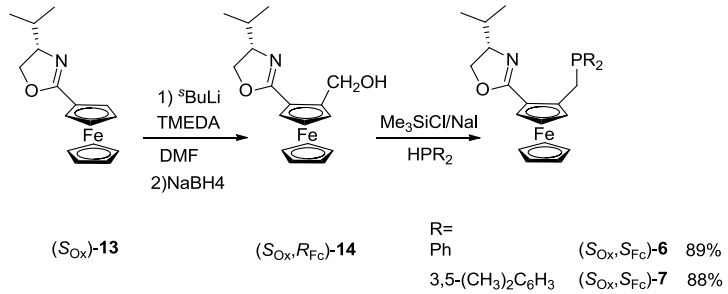
* The substance numbering is adapted from chapter 3.



Scheme 21. Synthesis route for ligand (R,R_{Fc})-**5**.



Scheme 22. Synthesis route for ligands (S_{Ox},S_{Fc})-**6** and (S_{Ox},S_{Fc})-**7**.

Ruthenium complexes of the type [$RuCl_2PPh_3$(L)] were prepared from all eight bidentate phosphine-oxazoline ligands L = **2**–**7** plus one reference ligand L = **1** (Chart 10) and were tested as catalyst precursors in the asymmetric hydrogenation and transfer hydrogenation of fourteen ketones.

In summary, ruthenium complexes [$RuCl_2PPh_3$(L)] of eight novel bidentate phosphine-oxazoline ligands were synthesized, characterized and screened in transfer hydrogenations and hydrogenations of a series of dialkyl and aryl-alkyl ketones. In addition, for comparative purposes, the transfer hydrogenations of all substrates were carried out with one analogous and well-established FOXAP ruthenium complex (L = **1**). Two catalysts delivered products with enantiomeric excesses of up to 99% in hydrogenation and 98% in transfer hydrogenation. A structural comparison of all ligands allowed to deduce that the (S,S_{Ox},S_{Fc}) relative configuration constitutes the matching configuration while a change of the oxazoline configuration leads to a decrease in product enantiomeric excess. Furthermore, a comparison of transfer hydrogenation and hydrogenation data showed surprising similarities. In both types of reaction nearly identical product e.e.s were obtained when identical catalyst precursors were used and

this fact is likely to be the result of comparable reaction mechanisms. The molecular structures of two catalyst precursors and of two corresponding acetonitrile complexes were studied by X-ray diffraction. From these structures a transition state model for the transfer hydrogenations reactions was deduced that allowed a correlation of ligand and product absolute configurations.

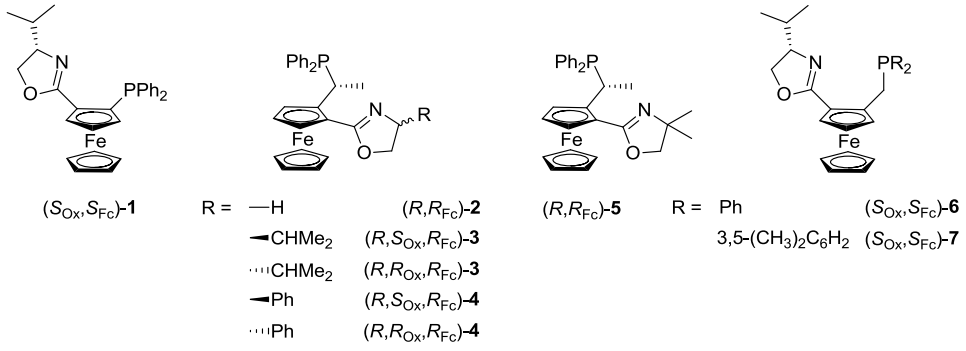
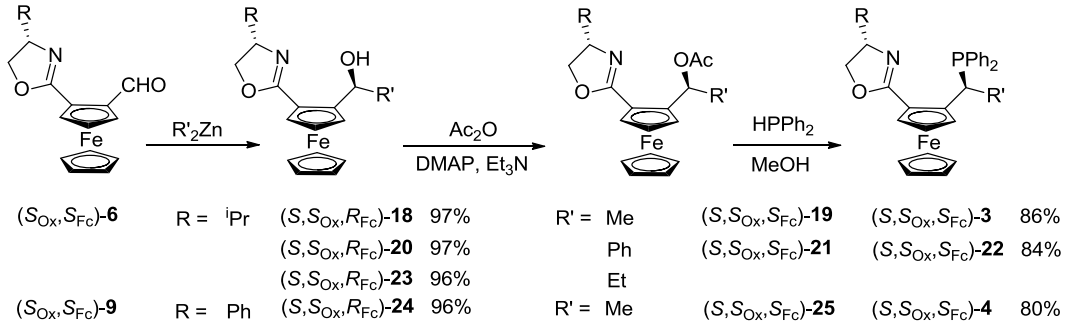


Chart 10. Ligands **1–7**.

4.2 Diastereoselective α-deprotonations and autocatalytic alkylations: synthesis of phosphino-substituted ferrocenyl-oxazolines

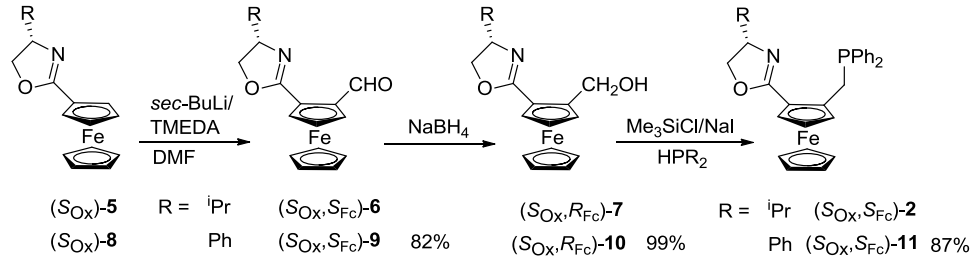
As reported in chapter 3.2, two novel routes were developed for the synthesis of the most efficient phosphino-substituted ferrocenyloxazoline ligands (Raffa-FOX ligands) (S_{Ox},S_{Fc})-**3** and analogs. As compared to the original synthesis, these novel routes avoid the use of two enantiopure starting materials and in addition allow the synthesis of previously inaccessible diastereomers.

Both routes started from easily accessible ferrocenyl-oxazolines and in both cases the phosphino-substituted side chain was built up diastereoselectively. In the first synthesis sequence, 2-oxazolinyl substituted ferrocene aldehydes were directly arylated or alkylated through an auto-activated phenyl or alkyl transfer either from diphenyl zinc or from dialkyl zinc reagents and provided alcohols (S,S_{Ox},R_{Fc})-**18, 20, 23** and **24** in form of single diastereomers. Furthermore, these alcohols were transformed into the desired phosphino-oxazolines (S,S_{Ox},S_{Fc})-**3, 4** and **22** in enantiomerically pure form all having the desired (S,S_{Ox},S_{Fc}) relative configuration (Scheme 23).

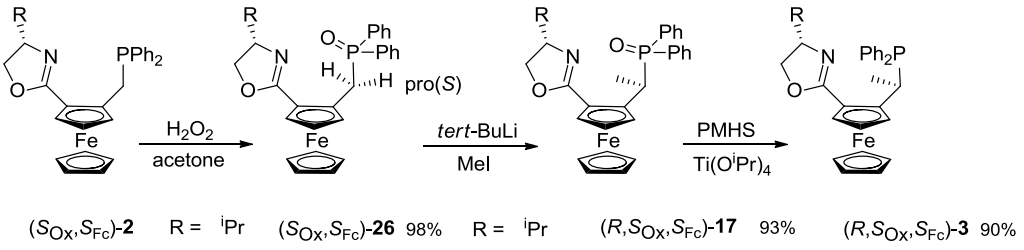


Scheme 23. Synthesis of different phosphino-oxazolines via auto-activated phenyl or alkyl transfers.

In the second sequence, ligands of type (S_{Ox},S_{Fc})-**2** were synthesized in three straightforward steps from easily accessible and commercially available ferrocenyl oxazoline (S_{Ox})-**5** (Scheme 24). Subsequently, (S_{Ox},S_{Fc})-**2** was oxidized to phosphine oxide (S_{Ox},S_{Fc})-**26**. Diastereoselective α-deprotonation of (S_{Ox},S_{Fc})-**26** with ^{t}BuLi in THF at –78 °C and quenching with MeI formed (R,S_{Ox},S_{Fc})-**17** as the main diastereomer. In the next step, reduction of (R,S_{Ox},S_{Fc})-**17** resulted in (R,S_{Ox},S_{Fc})-**3** which represents the side chain epimer of (S,S_{Ox},S_{Fc})-**3** (Scheme 25).



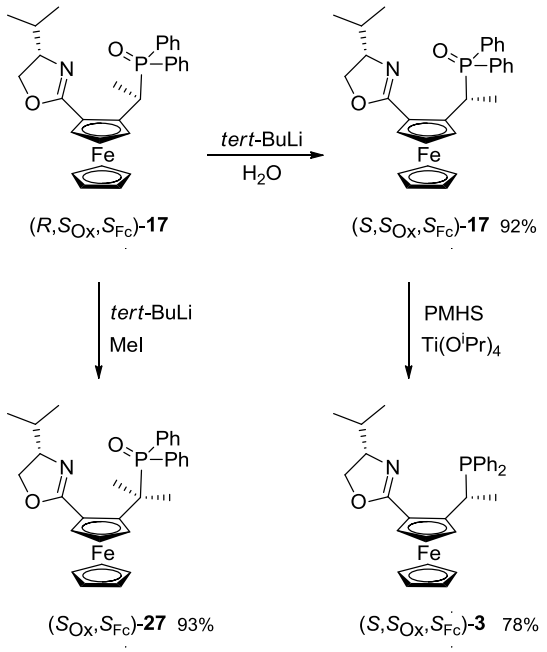
Scheme 24. Synthesis of ligands (S_{Ox},S_{Fc})-**2** and (S_{Ox},S_{Fc})-**11**.



Scheme 25. Diastereoselective α-deprotonation of (S_{Ox},S_{Fc})-**26**.

Surprisingly, when (R,S_{Ox},S_{Fc})-**17** was reacted with ^{t}BuLi and when the lithiated intermediate was quenched with water, it cleanly epimerized to (S,S_{Ox},S_{Fc})-**17**.

Subsequently, reduction of (S,S_{Ox},S_{Fc})-**17** resulted in (S,S_{Ox},S_{Fc})-**3** which in form of its enantiomer (R,R_{Ox},R_{Fc})-**3** had performed best in the hydrogenation and transfer hydrogenation of ketones (Scheme 26). Furthermore, the α-dimethylsubstituted ferrocene derivative (S_{Ox},S_{Fc})-**27** was obtained by treating (R,S_{Ox},S_{Fc})-**17** with ^{t}BuLi and quenching with MeI (Scheme 26).



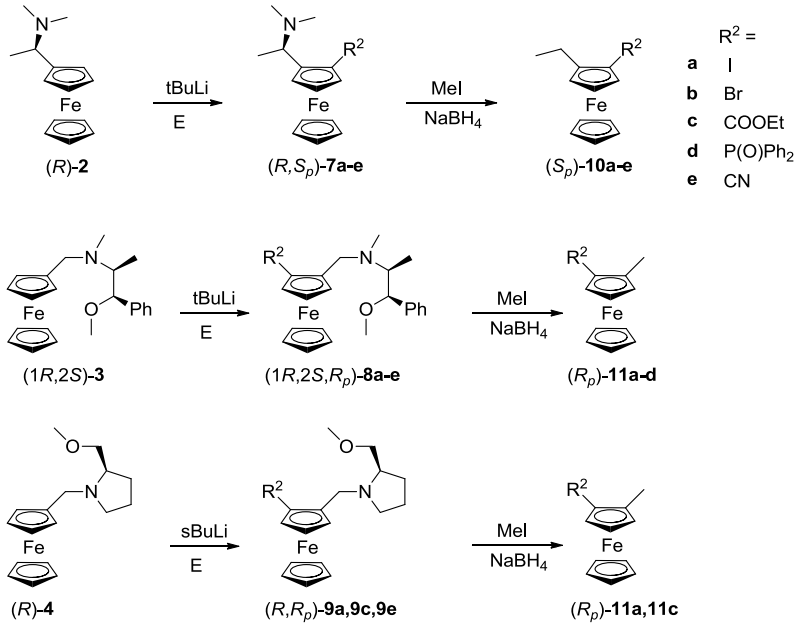
Scheme 26. Synthesis of (S,S_{Ox},S_{Fc})-**3** and (S_{Ox},S_{Fc})-**27**.

In summary, two complementary and highly modular synthesis routes for ferrocenyl-based phosphino-oxazolines were explored that have the phosphino unit attached to a ferrocenylmethyl or a ferrocenylethyl side-chain. Furthermore, a number of transfer hydrogenations of ketones were carried out. From a comparison of these catalysis results with our previously reported data it is concluded that for this type of ligand the (S,S_{Ox},S_{Fc}) relative configuration constitutes the matching configuration while a change of either the side-chain or the oxazoline configuration leads to less efficient transfer hydrogenation catalysts.

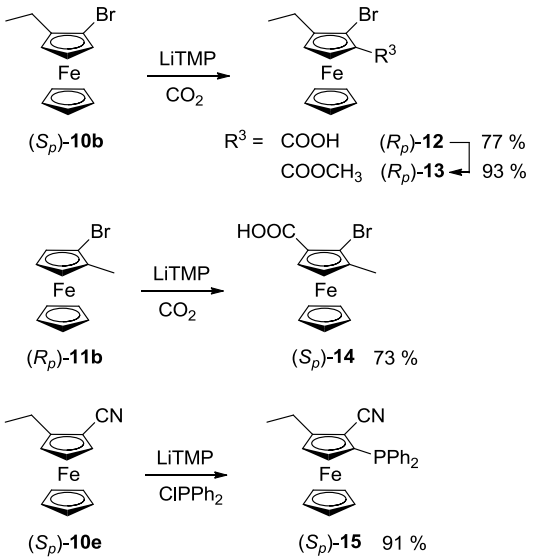
4.3 Synthesis of chiral, non-racemic ferrocene derivatives via *ortho*-metallation and partial reductive removal of *ortho*-directing amino groups

As described in chapter 3.3, a three step sequence for the preparation of chiral, nonracemic ferrocene derivatives was explored. In the first step 1,2-disubstituted derivatives were synthesized from the well-established ferrocenyl amines (*R*)-**2**, (1*R*,2*S*)-**3**, and (*R*)-**4** via diastereoselective *ortho*-directed reactions. In the second step, suitable reaction conditions for the reductive removal of the amino substituents were developed (Scheme 27). A further *ortho*-lithiation of derivatives **10b**–**10e** and **11b**–**11d** which contain well recognised *ortho*-directing substituents (Br, COOEt, $P(O)Ph_2$ and CN) resulted in chiral non-racemic 1,2,3-trisubstituted ferrocenes (Scheme 28).

In summary, a very general and highly modular procedure has been developed for the synthesis of chiral non-racemic 1,2-di- and 1,2,3-trisubstituted ferrocene derivatives which all are inclined to be useful starting materials for the preparation of chiral, non-racemic ferrocenes such as phosphino or oxazoline based catalysts ligands.



Scheme 27. Preparation of derivatives **7**–**11**.



Scheme 28. Synthesis of 1,2,3-trisubstituted ferrocenes **12**–**15**.

5. Curriculum vitae

Personal Data

Name: Afrooz Zirakzadeh

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Education

Since 05/2009 **PhD thesis:** '*Chiral Ferrocenyl Ligands: Synthesis and Application in Asymmetric Catalysis*', Institute of Organic Chemistry, University of Vienna (Supervisor: Prof. Dr. Walter Weissensteiner)

2003 – 2005 **M.Sc:** Chemistry, Institute of Organic Chemistry Tehran University

Master Thesis: '*Synthesis and Characterization of New Modified Polyacrylamide Supported Palladium Catalysts and their Application in Heck Reactions*',

1999 – 2003 **B.Sc:** Chemistry, Isfahan University, IRAN

1994 – 1998 **High School:** Tohid, Isfahan, IRAN

Professional Experiences

Since 04/2011 Research associate at the Institute of Organic Chemistry, University of Vienna

2005 – 2009 Lecturer of Hormozgan University and Azad Bandarabbas University, Iran

Grants

Forschungsstipendium 2010, University of Vienna

Publications

1) *'{(R,S_{Fc},S_{Fc})-2''-Bromo-2-[1-(dimethylamino)ethyl-κN]-1,1''-biferrocene}trihydridoboron.'*

   Yaping Wang, Afrooz Zirakzadeh, Walter Weissensteiner and Kurt Mereiter, *Acta Cryst.* **2011**. *E67*, m1806–m1807.

2) '*Synthesis, Coordination Behavior, and Structural Features of Chiral Amino-, Pyrazolyl-, and Phosphino-Substituted Ferrocenyloxazolines and Their Application in Asymmetric Hydrogenations.*'

   Raffael Schuecker, Afrooz Zirakzadeh, Kurt Mereiter, Felix Spindler, and Walter Weissensteiner, *Organometallics* **2011**, *30 (17)*, p 4711–4719.

3) *'Ruthenium arene derivatives of chiral ferrocene-based P, N or P, O ligands. Transformation of chloro-alcohol into hydrido-carbonyl complexes.'*

   Torres, Javier; Sepulveda, Francisco; Carrion, M. Carmen; Jalon, Felix A.; Manzano, Blanca R.; Rodriguez, Ana M.; Zirakzadeh, Afrooz; Weissensteiner, Walter; Mucientes, Antonio E.; Angeles de la Pena, M., *Organometallics* **2011**, *30(13)*, 3490–3503.

4) *'Synthesis of chiral, non-racemic ferrocene derivatives by ortho-metallation and partial reductive removal of ortho-directing amino groups.'*

   Afrooz Zirakzadeh, Raffael Schuecker, Walter Weissensteiner, *Tetrahedron: Asymmetry*, **2010**, *21*, 1494–1502.

5) *'Modified Cross-linked Polyacrylamide Supported Palladium Salts as a New Heterogeneous Catalyst for Heck Reaction.'*

Mahdavi, H.; Zirakzadeh, A.; Amani, J., *Reactive and Functional Polymers* **2007**, *67*, 716–722.

6) *'Ruthenium complexes of phosphino-substituted ferrocenyloxazolines in the asymmetric hydrogenation and transfer hydrogenation of ketones: a comparison.'*

Afrooz Zirakzadeh, Raffael Schuecker, Kurt Mereiter, Felix Spindler, and Walter Weissensteiner. *Organometallics*, submitted.

7) *'The use of* α*-deprotonation- and autoactivated alkylation-reactions in the diastereoselective synthesis of phosphino-substituted ferrocenyloxazolines.'*

Afrooz Zirakzadeh, Kurt Mereiter, and Walter Weissensteiner. Manuscript prepared.

Poster presentation

Mahdavi, H.; Zirakzadeh, A.; Amani, J., '*Modified Cross-linked Polyacrylamide Supported Palladium Salts as a New Heterogeneous Catalyst for Heck Reaction.*' 4th International Seminar on Polymer Science and Technology, Tehran, IRAN, September 27–29, 2005.