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# Ruthenium Complexes of Phosphino-Substituted Ferrocenyloxazolines in the Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones: A Comparison

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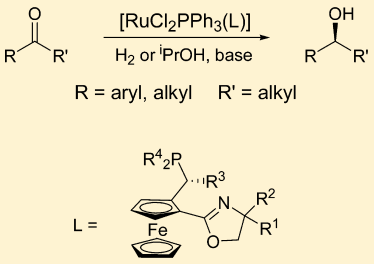
Supporting Information

**ABSTRACT:** Three novel routes have been developed for the synthesis of ferrocenyl-based phosphino-oxazolines in which the phosphino unit is attached to a ferrocenylmethyl or a ferrocenylethyl side chain. In two of the routes the phosphino-substituted ethyl side chain was built up diastereoselectively. Ruthenium complexes of the type $[RuCl_2PPh_3(L)]$ of 12 bidentate phosphine-oxazoline ligands were synthesized, characterized, and tested in the transfer hydrogenation of acetophenone. For the best performing complexes a total of 12 additional ketones were screened in transfer hydrogenations and hydrogenations under transfer hydrogenation conditions. Two catalyst precursors in particular delivered products with an enantiomeric excess of up to 98% in transfer hydrogenations and 99% ee in hydrogenations. The transfer hydrogenation results obtained with all novel ligands were compared to those of two well-established FOXAP ligands. 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 to rationalize some of the observed features by considering a transition-state model. The molecular structures of one synthesis intermediate, two catalyst precursors, and two corresponding acetonitrile complexes were studied by X-ray diffraction.




## INTRODUCTION

Oxazoline derivatives have been employed as ligands in asymmetric catalysts for more than fifteen years.[1] In particular, PHOX-type ligands[2] and their ferrocene-based FOXAP analogues[3] (Chart 1) have been successfully used in a variety of asymmetric transformations. 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 2-propanol was used as the hydrogen source.[4] In addition, the same type of complex gave excellent results in hydrogenations in the presence of hydrogen gas[5] and, under these conditions, upscaling to the large industrial scale became possible.[6]

Very recently, as part of our continuing search for novel asymmetric hydrogenation catalysts,[7] we modified FOXAP-type ligands by extending their ferrocene backbone to a ferrocenylethyl unit.[8] Examples of these ligands, which we called "Raffa-FOX" ligands, are shown in Chart 1 (**3**−**5**). A preliminary high-throughput screening of ruthenium complexes of these ligands ($[RuCl_2(PPh_3)(L)]$, L = **3**−**5**) in the hydrogenation of a small set of three aryl alkyl ketones (acetophenone, 4-methylacetophenone, and phenyl benzyl ketone) gave products with nearly quantitative conversion and with an enantiomeric excess of 97−99%.

Of all the ligands tested, derivatives $(R,R_{Ox},R_{Fc})$-**4** and $(R,R_{Ox},R_{Fc})$-**5** performed best, whereas $(R,R_{Fc})$-**3** always gave slightly lower product ee values. It was also found that the hydrogenation results were strongly dependent on the relative configuration of the ligands applied. For example, when the hydrogenation of acetophenone was carried out with ligand $(R,R_{Ox},R_{Fc})$-**4**, the product 1-phenylethanol with *S* absolute configuration and 98% ee was obtained, while the use of the ligand $(R,S_{Ox},R_{Fc})$-**4**, i.e., on changing the configuration at the oxazoline carbon C4 from $R_{Ox}$ to $S_{Ox}$, gave the product with *R* absolute configuration with 69% ee. In the case of ligands **5** the $(R_{Ox},R_{Fc})$ relative configuration also constitutes the matching and the $(S_{Ox},R_{Fc})$ configuration the mismatching combination of stereogenic units.

Our original synthesis of ligands **3**−**5** 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), but this advantage was limited by the fact that two enantiopure reagents were needed for the synthesis of each ligand. In these ligands the $(R_{Ox},R_{Fc})$ relative configuration was identified as the matching configuration, and we therefore

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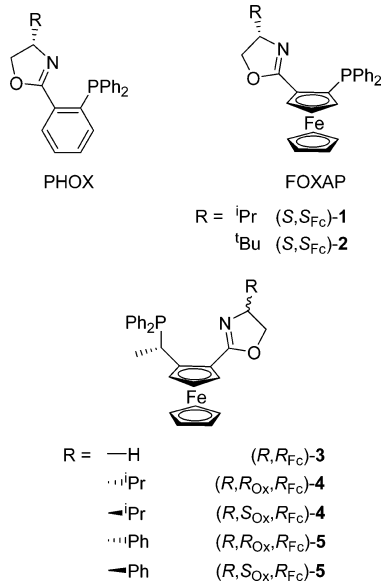
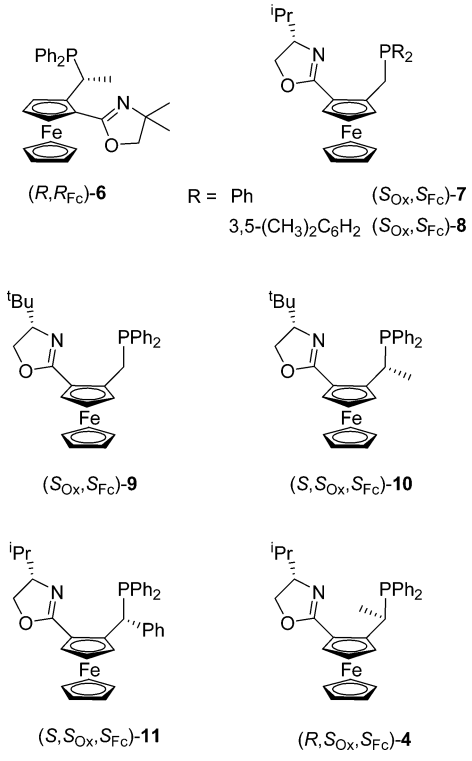
**Chart 1**




reasoned that the synthesis of such derivatives with either $(R_{Ox},R_{Fc})$ or $(S_{Ox},S_{Fc})$ configuration could be simplified. In addition, it seemed interesting to investigate the influence of further substitution patterns in the oxazoline unit, in the side chain, and in the phosphorus aryl groups.

We report here the synthesis of seven additional ligands (Chart 2), all of which feature structural modifications of our

**Chart 2**




previously described ligands **3**–**5**.[8] In a similar way to **3**, ligand **6** lacks a stereogenic center at the oxazoline ring, while ligands **7** and **8** represent analogs of **4**, which lack the stereogenic center in the side chain. Ligands $(S_{Ox},S_{Fc})$-**9** and $(S,S_{Ox},S_{Fc})$-**10** are obtained when the respective isopropyl group of **7** and **4** is replaced by a *tert*-butyl group and in $(S,S_{Ox},S_{Fc})$-**11** the side-chain methyl group of **4** is replaced by a phenyl unit. Finally, $(R,S_{Ox},S_{Fc})$-**4** features the side-chain epimer of ligand $(S,S_{Ox},S_{Fc})$-**4**. In addition to the original synthesis route, three additional approaches for the synthesis of ligands **4**, **5**, and **7**–**11** are reported, and these all start from easily accessible ferrocenyloxazolines and lead to ligands with $(S_{Ox},S_{Fc})$ relative configuration.

We also report on the application of complexes $[RuCl_2(PPh_3)(L)]$ of all ligands (L = **3**–**11**) in the transfer hydrogenations of 13 ketones. As an extension of our previous work, additional hydrogenations under transfer hydrogenation conditions were carried out. The transfer hydrogenation results obtained with **3**–**11** are compared to those obtained with FOXAP ligands **1** and **2**. In addition, a qualitative comparison of the results obtained for transfer hydrogenations and hydrogenations under transfer hydrogenation conditions is given. An attempt is also made to identify the structural features responsible for product enantioselectivity as well as for the experimentally determined product absolute configuration.

## RESULTS AND DISCUSSION

**Synthesis of Ligands and Complexes.** *Synthesis of Ligand (R,RFc)-6.* Phosphino-oxazoline $(R,R_{Fc})$-**6** was prepared following the original synthesis route for ligands **3**–**5** (Scheme 1).[8]

Amino-ester $(R,S_{Fc})$-**12**,[9] which is easily accessible from (*R*)-Ugi's amine, was reacted in the presence of trimethylaluminum[10] with 1,1-dimethyl-2-hydroxyethylamine to give amide $(R,S_{Fc})$-**13**. In the next step this compound was transformed according to the methodology of Appel[11] to oxazoline $(R,S_{Fc})$-**14**. Oxazoline **14** was treated with methyl iodide in acetonitrile, and the crude ammonium salt was subsequently reacted with diphenylphosphinyllithium to give the phosphinyl-substituted derivative $(R,R_{Fc})$-**15**.[12] Reduction of this phosphine oxide with polymethylhydrosiloxane (PMHS) in the presence of titanium isopropoxide[13] gave the desired phosphine-oxazoline $(R,R_{Fc})$-**6**.

*Synthesis of Ligands $(S_{Ox},S_{Fc})$-7–9 and 25.* The synthesis of phosphine-oxazolines **7**–**9** and **25** was achieved in only three steps from easily accessible ferrocenyl oxazolines **16**, **19**, and **22** (Scheme 2). The alcohol intermediates **18**, **21**, and **24** were obtained in analogy with a reported procedure.[14] A subsequent reaction with either diphenylphosphine or bis(3,5-dimethylphenyl)-phosphine in the presence of chlorotrimethylsilane and sodium iodide gave the final products $(S_{Ox},S_{Fc})$-**7**–**9** and **25**, respectively.[15]

*Synthesis of Ligands $(S,S_{Ox},S_{Fc})$-4, 5, 10, and 11.* In order to modify and simplify the original synthesis sequence for ligands **4** and analogues, we explored two novel routes that both start from ferrocenyl oxazolines rather than from Ugi's amine. It was our intention to build up the phosphino-substituted side chain of **4** and analogues in such a way that the use of a second enantiopure reagent could be avoided. Originally, for the synthesis of $(R,R_{Ox},R_{Fc})$-**4**, in addition to Ugi's amine, enantiopure (*R*)-valinol also had to be used in the second step of the reaction sequence (Scheme 1). Furthermore, we aimed to develop synthesis routes that allow for a variation of the configuration at the side-chain $\alpha$-carbon. For this purpose, diastereoselective alkylations of aldehydes **17**, **20**, and **23** (Scheme 3) were employed. As an alternative route, the diastereoselective $\alpha$-deprotonation of phosphine oxides was investigated (Scheme 4).

*Synthesis of Ligands $(S,S_{Ox},S_{Fc})$-4, 5, 10, and 11 and Analogues by Alkyl and Phenyl Transfer from $R_2Zn$ Reagents to Aldehydes.* Several groups have already investigated the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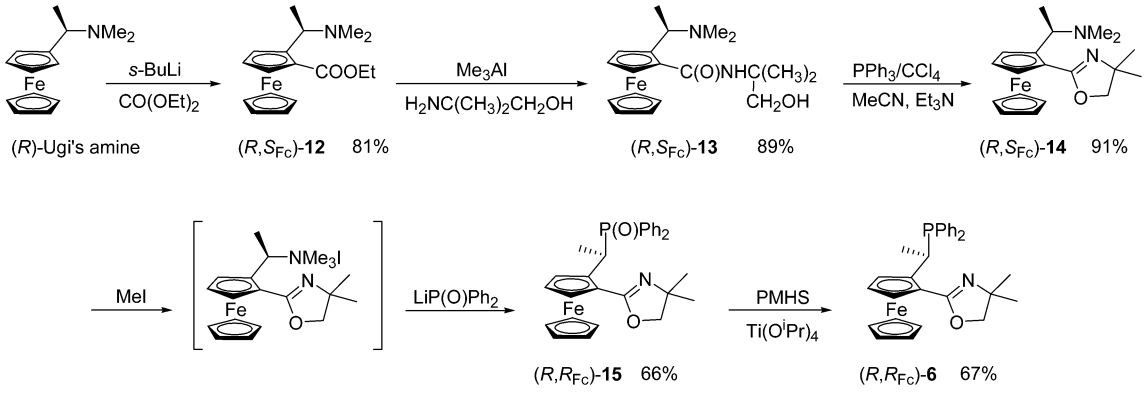
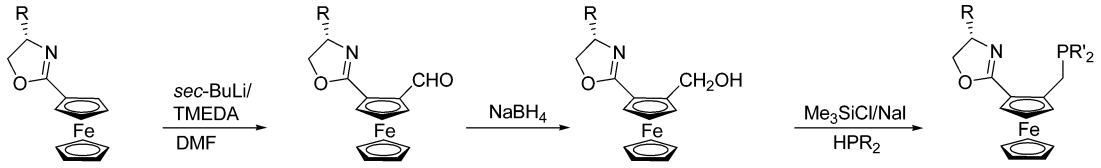
**Scheme 1. Synthesis of Ligand $(S_{Ox},S_{Fc})$-6**

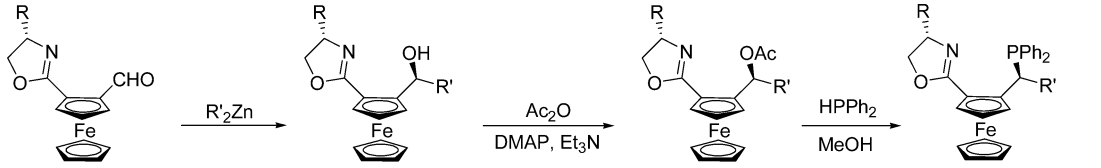



**Scheme 2. Synthesis of Phosphino-oxazolines $(S_{Ox},S_{Fc})$-7−9 and 25**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $(S_{Ox})$-**16** | R = $^{i}$Pr | $(S_{Ox},S_{Fc})$-**17** | 78% | $(S_{Ox},R_{Fc})$-**18** | 97% | R' = Ph | $(S_{Ox},S_{Fc})$-**7** 89% |
| | | | | | | 3,5-$Me_2C_6H_2$ | $(S_{Ox},S_{Fc})$-**8** 88% |
| $(S_{Ox})$-**19** | $^{t}$Bu | $(S_{Ox},S_{Fc})$-**20** | 88% | $(S_{Ox},R_{Fc})$-**21** | 98% | Ph | $(S_{Ox},S_{Fc})$-**9** 91% |
| $(S_{Ox})$-**22** | Ph | $(S_{Ox},S_{Fc})$-**23** | 82% | $(S_{Ox},R_{Fc})$-**24** | 99% | Ph | $(S_{Ox},S_{Fc})$-**25** 87% |

**Scheme 3. Synthesis of Ligands 4, 5, 10, and 11**

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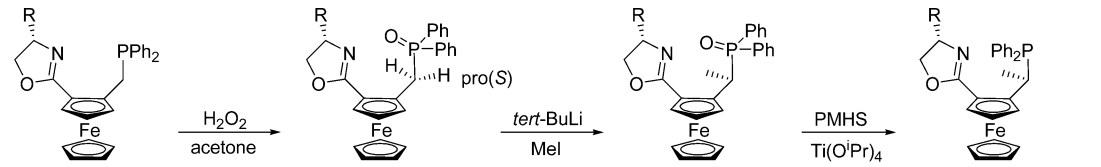
|---|---|---|---|---|---|---|---|
| $(S_{Ox},S_{Fc})$-**17** | R = $^{i}$Pr | $(S,S_{Ox},R_{Fc})$-**26** | 97% | R' = Me | $(S,S_{Ox},S_{Fc})$-**27** | | $(S,S_{Ox},S_{Fc})$-**4** 86% |
| | | $(S,S_{Ox},R_{Fc})$-**28** | 97% | Ph | $(S,S_{Ox},S_{Fc})$-**29** | | $(S,S_{Ox},S_{Fc})$-**11** 84% |
| | | $(S,S_{Ox},R_{Fc})$-**30** | 96% | Et | | | |
| $(S_{Ox},S_{Fc})$-**20** | R = $^{t}$Bu | $(S,S_{Ox},R_{Fc})$-**31** | 73% | R' = Me | $(S,S_{Ox},S_{Fc})$-**32** | | $(S,S_{Ox},S_{Fc})$-**10** 48% |
| $(S_{Ox},S_{Fc})$-**23** | R = Ph | $(S,S_{Ox},R_{Fc})$-**33** | 96% | R' = Me | $(S,S_{Ox},S_{Fc})$-**34** | | $(S,S_{Ox},S_{Fc})$-**5** 80% |

**Scheme 4. Synthesis of Ligands $(R,S_{Ox},S_{Fc})$-4 and $(S,S_{Ox},S_{Fc})$-10**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $(S_{Ox},S_{Fc})$-**7** | R = $^{i}$Pr | $(S_{Ox},S_{Fc})$-**35** | 98% | $(R,S_{Ox},S_{Fc})$-**36** | 93% | R = $^{i}$Pr | $(R,S_{Ox},S_{Fc})$-**4** 90% |
| $(S_{Ox},S_{Fc})$-**9** | $^{t}$Bu | $(S_{Ox},S_{Fc})$-**37** | 97% | $(R,S_{Ox},S_{Fc})$-**38** | 95% | $^{t}$Bu | $(R,S_{Ox},S_{Fc})$-**10** 91% |

diastereoselectivity of alkyl and aryl transfers to 2-substituted ferrocenylaldehydes.[16,17] In this respect, the reactivity of lithium, magnesium, and zinc reagents has mainly been studied. It was found that in many cases the transfer of rather small alkyl groups such as methyl or ethyl substituents worked best with the use of dialkylzinc reagents. Usually, the alkyl transfer from dialkylzinc reagents to aldehydes proceeds rather slowly, but the reaction rate increases significantly when a catalyst such as an amino alcohol is added. However, according to Brocard[16] and Fukuzawa,[17d] the reaction of amino-substituted ferrocenyl carbaldehydes 2-(*N*,*N*-dimethylaminomethyl)ferrocenylcarbaldehyde and 2-(1-*N*,*N*-dimethylaminoethyl)ferrocenylcarbaldehyde with dialkylzinc reagents proceeded smoothly without a catalyst. This finding was rationalized by invoking an autocatalytic or autoactivation mechanism that involves the participation of the dimethylamino nitrogen and the carbonyl oxygen atoms. Since such an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effect had also been reported for a pyrimidyl-substituted ferrocenylaldehyde,[18] we reasoned that oxazoline units may also be able to promote autoactivated alkyl transfers.

Reaction of aldehyde ($S_{Ox}$,$S_{Fc}$)-**17** in toluene with dimethylzinc or diethylzinc (Scheme 3) gave the desired products ($S$,$S_{Ox}$,$R_{Fc}$)-**26** and ($S$,$S_{Ox}$,$R_{Fc}$)-**30** in nearly quantitative yield. Surprisingly, when diphenylzinc was used as the reagent, a phenyl transfer was also possible, resulting in alcohol ($S$,$S_{Ox}$,$R_{Fc}$)-**28**. The reaction of aldehydes ($S_{Ox}$,$S_{Fc}$)-**20** and ($S_{Ox}$,$S_{Fc}$)-**23**—which were easily accessible form ferrocenyloxazolines ($S_{Ox}$)-**19** and ($S_{Ox}$)-**22** (Scheme 2)—and dimethylzinc gave alcohols ($S$,$S_{Ox}$,$R_{Fc}$)-**31** and ($S$,$S_{Ox}$,$R_{Fc}$)-**33** [for details on the synthesis of ($S_{Ox}$)-**22** see Supporting Information]. In all five cases the main product was formed in a diastereomeric ratio of 97:3 and had the desired $S$ side-chain configuration.

Suitable single crystals of alcohol ($S$,$S_{Ox}$,$R_{Fc}$)-**26** could be grown, and the molecular structure of this compound in the solid state was studied by X-ray diffraction, which confirmed both its relative and absolute configuration (Figure 1). Details

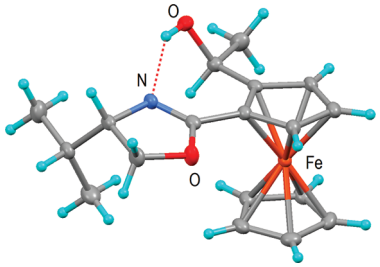



**Figure 1.** Molecular structure of ($S$,$S_{Ox}$,$R_{Fc}$)-**26**.

of this X-ray crystallography study are given in the Supporting Information (Tables S5 and S6, Figure S1).

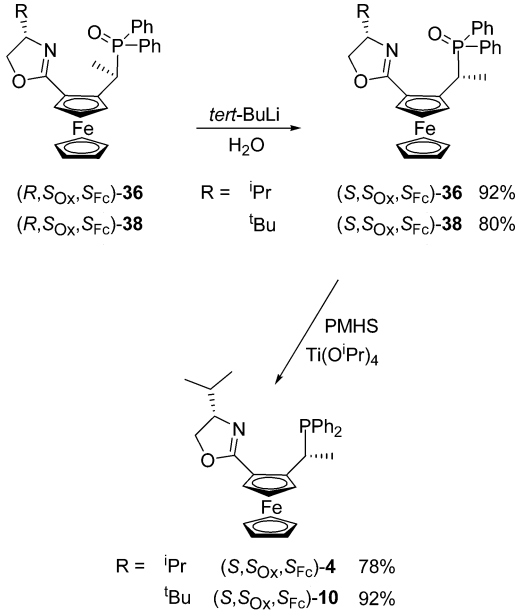
After chromatographic separation of the respective diastereomers, alcohols ($S$,$S_{Ox}$,$R_{Fc}$)-**26**, **28**, **31**, and **33** were transformed into the acetates **27**, **29**, **32**, and **34**. A further reaction with diphenylphosphine led to the desired phosphino-oxazolines ($S$,$S_{Ox}$,$S_{Fc}$)-**4** and ($S$,$S_{Ox}$,$S_{Fc}$)-**5** as well as to the novel ligands ($S$,$S_{Ox}$,$S_{Fc}$)-**10**, with a *tert*-butyl group attached to the oxazoline carbon C4, and ($S$,$S_{Ox}$,$S_{Fc}$)-**11**, which bears a phenyl substituent at the side-chain $\alpha$-carbon. As expected, in all cases the acetate/phosphine exchange proceeded with retention of configuration at the ferrocenyl $\alpha$-carbon.[19,20] It should be mentioned that with this methodology all ligands (**4**, **5**, **10**, and **11**) were obtained with the same ($S$,$S_{Ox}$,$S_{Fc}$) relative configuration, which is identical to the configuration of the ligands that performed best in hydrogenation reactions.

*Synthesis of Ligands **4** and **10** with ($R$,$S_{Ox}$,$S_{Fc}$) Configuration by Diastereoselective $\alpha$-Deprotonation of Phosphine Oxides.* In 1975 Marr reported that—like benzyldiphenylphosphine oxide—ferrocenylmethyl-diphenylphosphine oxide can be deprotonated with butyllithium at the methylene carbon, and the resulting anion can be reacted with electrophiles.[21] Recently this methodology has been used by Stepnicka to derivatize a cyanomethyl-substituted ferrocene diastereoselectively.[22] We envisaged that phosphine oxides **35** and **37** (Scheme 4) could also be deprotonated and alkylated at the side-chain methylene group and considered whether this reaction could be run diastereoselectively. For this purpose phosphine oxides ($S_{Ox}$,$S_{Fc}$)-**35** and ($S_{Ox}$,$S_{Fc}$)-**37** were prepared from phosphines ($S_{Ox}$,$S_{Fc}$)-**7** and ($S_{Ox}$,$S_{Fc}$)-**9** by reaction with $H_2O_2$ in acetone.[19]

In order to optimize the deprotonation reaction conditions, phosphine oxide **35** was treated in THF or $Et_2O$ at different temperatures with bases *n*-BuLi, *t*-BuLi, or Li-TMP, and the intermediate anions were quenched with MeI (see Supporting Information, Table S1). In all cases the product diastereomer ratio was strongly dependent on the reaction temperature and the solvent used. The best diastereoselectivity could be obtained when ($S_{Ox}$,$S_{Fc}$)-**35** was reacted in THF with 1.2 equivalents of *t*-BuLi at −78 °C. Quenching with MeI resulted in a 97:3 mixture of diastereomers ($R$,$S_{Ox}$,$S_{Fc}$)-**36** and ($S$,$S_{Ox}$,$S_{Fc}$)-**36** (93% overall isolated yield). We suspect that this high diastereoselectivity could be caused, at least in part, by a collaborative action of the oxazoline unit and the base. The oxazoline unit is expected to coordinate to lithium, 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 ($R$,$S_{Ox}$,$S_{Fc}$)-**36**. A further reduction of this diastereomer gave ligand ($R$,$S_{Ox}$,$S_{Fc}$)-**4**, which represents the side-chain epimer of ($S$,$S_{Ox}$,$S_{Fc}$)-**4**. When oxide ($S_{Ox}$,$S_{Fc}$)-**37** was reacted with *t*-BuLi and MeI, diastereomerically pure ($R$,$S_{Ox}$,$S_{Fc}$)-**38** was obtained, which on reduction with PMHS/Ti(O$^i$Pr)$_4$ gave ligand **10** with ($R$,$S_{Ox}$,$S_{Fc}$) absolute configuration.

Furthermore, we investigated whether the side-chain epimers of **36** and **38** can be converted into each other. For this purpose ($R$,$S_{Ox}$,$S_{Fc}$)-**36** was reacted with *t*-BuLi, and the lithiated intermediate was quenched with water (Scheme 5). Under optimized

**Scheme 5. Epimerization of ($R$,$S_{Ox}$,$S_{Fc}$)-36 and 38**




conditions (THF, 2 equivalents of base, −78 °C, 30 min) 95% of the epimer ($S$,$S_{Ox}$,$S_{Fc}$)-**36** was formed. In a control experiment ($S$,$S_{Ox}$,$S_{Fc}$)-**36** was subjected to the same reaction conditions, but in this case no epimerization took place. With use of identical reaction conditions ($R$,$S_{Ox}$,$S_{Fc}$)-**38** could also be epimerized but with a diastereomer ratio of only 80:20. In each case, reduction of the main diastereomer of ($S$,$S_{Ox}$,$S_{Fc}$)-**36** and ($S$,$S_{Ox}$,$S_{Fc}$)-**38** gave the final ligands ($S$,$S_{Ox}$,$S_{Fc}$)-**4** and ($S$,$S_{Ox}$,$S_{Fc}$)-**10**.

*Synthesis of Complexes [RuCl$_2$(PPh$_3$)(L)].* Ligands **1**−**11** were reacted with [RuCl$_2$(PPh$_3$)$_3$] in toluene at rt and gave the desired unsaturated orange (**39**) or green (**40**−**49**) complexes. Two of these complexes, ($R$,$R_{Ox}$,$R_{Fc}$)-**42** and ($S_{Ox}$,$S_{Fc}$)-**46**, were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further treated at rt with acetonitrile, and the coordinatively saturated yellow-orange acetonitrile complexes ($R$,$R_{Ox}$,$R_{Fc}$)-**50** and ($S_{Ox}$,$S_{Fc}$)-**51** were isolated (Scheme 6).

**Scheme 6. Synthesis of Complexes 39−51**

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

| L = | complex = |
|---|---|
| ($S_{Ox}$,$S_{Fc}$)-**1** | ($S_{Ox}$,$S_{Fc}$)-**39** |
| ($S_{Ox}$,$S_{Fc}$)-**2** | ($S_{Ox}$,$S_{Fc}$)-**40** |
| ($R$,$R_{Fc}$)-**3** | ($R$,$R_{Fc}$)-**41** |
| ($R$,$R_{Ox}$,$R_{Fc}$)-**4** | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** |
| ($R$,$S_{Ox}$,$R_{Fc}$)-**4** | ($R$,$S_{Ox}$,$R_{Fc}$)-**42** |
| ($R$,$S_{Ox}$,$S_{Fc}$)-**4** | ($R$,$S_{Ox}$,$S_{Fc}$)-**42** |
| ($R$,$R_{Ox}$,$R_{Fc}$)-**5** | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** |
| ($R$,$S_{Ox}$,$R_{Fc}$)-**5** | ($R$,$S_{Ox}$,$R_{Fc}$)-**43** |
| ($R$,$R_{Fc}$)-**6** | ($R$,$R_{Fc}$)-**44** |
| ($S_{Ox}$,$S_{Fc}$)-**7** | ($S_{Ox}$,$S_{Fc}$)-**45** |
| ($S_{Ox}$,$S_{Fc}$)-**8** | ($S_{Ox}$,$S_{Fc}$)-**46** |
| ($S_{Ox}$,$S_{Fc}$)-**9** | ($S_{Ox}$,$S_{Fc}$)-**47** |
| ($S$,$S_{Ox}$,$S_{Fc}$)-**10** | ($S$,$S_{Ox}$,$S_{Fc}$)-**48** |
| ($S$,$S_{Ox}$,$S_{Fc}$)-**11** | ($S$,$S_{Ox}$,$S_{Fc}$)-**49** |

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

| L = | complex = |
|---|---|
| ($R$,$R_{Ox}$,$R_{Fc}$)-**4** | ($R$,$R_{Ox}$,$R_{Fc}$)-**50** |
| ($S_{Ox}$,$S_{Fc}$)-**8** | ($S_{Ox}$,$S_{Fc}$)-**51** |

Single crystals were obtained for two unsaturated, ($R$,$R_{Ox}$,$R_{Fc}$)-**42** and ($R$,$R_{Fc}$)-**44**, and two coordinatively saturated, ($R$,$R_{Ox}$,$R_{Fc}$)-**50** and ($S_{Ox}$,$S_{Fc}$)-**51**, 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 S5). 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 2 and 3 (for selected geometric data see

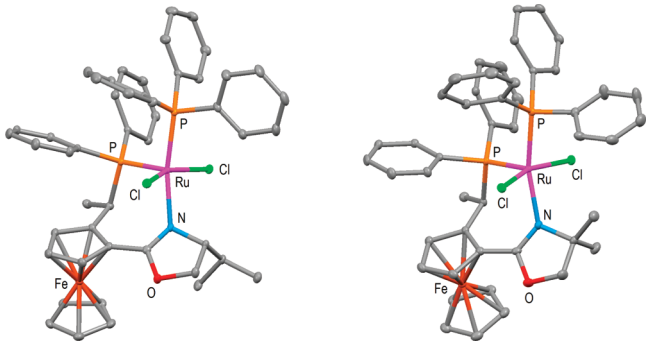


**Figure 2.** Molecular structures of complexes ($R$,$R_{Ox}$,$R_{Fc}$)-**42** (left) and ($R$,$R_{Fc}$)-**44** (right). Hydrogen atoms are omitted for clarity.

Supporting Information, Tables S7−S10). The molecular structure of ($S_{Ox}$,$S_{Fc}$)-**39** had been determined previously,[4c] 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 S6).

As in the case of ($S_{Ox}$,$S_{Fc}$)-**39**, complexes ($R$,$R_{Ox}$,$R_{Fc}$)-**42** and ($R$,$R_{Fc}$)-**44** 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 (**39** and **42**) or an

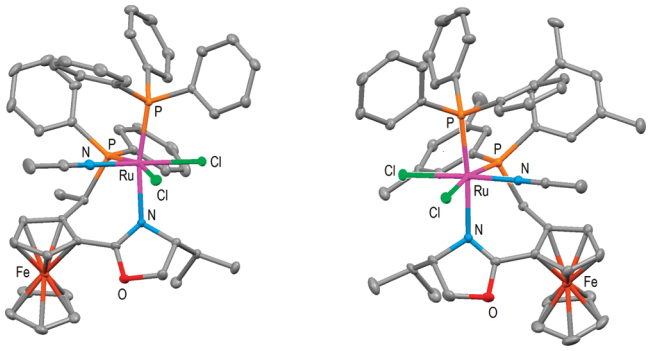


**Figure 3.** Molecular structures of complexes ($R$,$R_{Ox}$,$R_{Fc}$)-**50** (left) and ($S_{Ox}$,$S_{Fc}$)-**51** (right). Hydrogen atoms are omitted for clarity.

oxazoline methyl (**44**) group. However, as compared to **39**, the overall molecular structures and the ligand arrangements differ significantly in **42** and **44**. In **39** the chlorides adopt a *cis* disposition, while in **42** and **44** the chlorides are located *trans* to each other. Furthermore, in **39** the triphenylphosphino phosphorus is *cis* to the oxazoline nitrogen but is *trans* in **42** and **44**. As expected, the acetonitrile complexes ($R_{Ox}$,$R_{Fc}$)-**50** and ($S_{Ox}$,$S_{Fc}$)-**51** adopt an octahedral geometry, but—in contrast to **42** and **44**—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 **39**−**49** were screened in asymmetric transfer hydrogenations (THY) of 13 ketones (Chart 3). In continuation of our previous work, a set of six complexes was screened in asymmetric hydrogenations under transfer hydrogenation conditions against three more aryl alkyl ketones on a customized Symyx high-throughput screening system.[8] All catalysis reactions were carried out with the isolated and fully characterized catalyst precursors.

*Transfer Hydrogenations.* Transfer hydrogenations of acetophenone were carried out with complexes **39**−**49**. Twelve additional ketones were screened against those catalysts that performed best with acetophenone. It was our initial intention to compare the performance of the newly synthesized ligands **3**−**11** (complexes **41**−**49**) with those of the well-established FOXAP ligands **1** and **2** (complexes **39** and **40**). In order to ensure maximum comparability, all complexes (**39**−**49**) were synthesized according to the same protocol.

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, Table S2). On the basis of this optimization procedure, the majority of all screening reactions were carried out at rt 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 **39**−**49** 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 (for details see Scheme 6 and Table 1).

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 ee dropped continuously. Therefore, in all tables the maximum product ee values obtained at the given reaction time are listed together with the corresponding conversion data.


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Chart 3

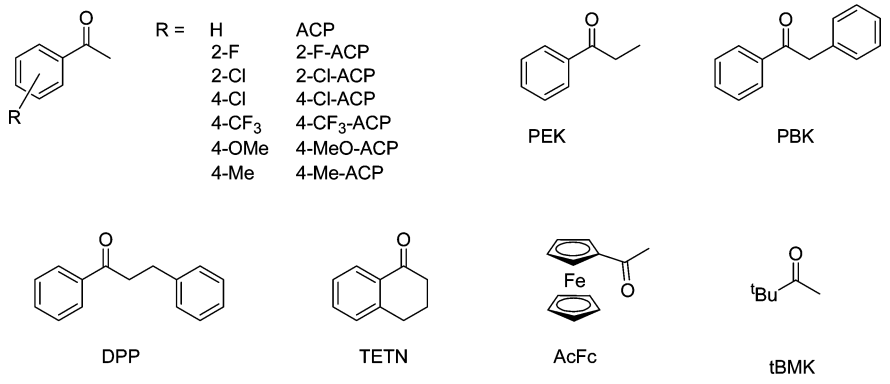


Table 1. THY Results for Acetophenone Obtained with Complexes 39−49

| | | | ligand substitution at | | | | | |
|---|---|---|---|---|---|---|---|---|
| entry | complex | ligand | oxaz. C4 | side chain | time | % conv | % ee | abs conf |
| 1 | ($S_{Ox}$,$S_{Fc}$)-**39** | **1** | $^{i}$Pr/H | | 20 min | 99 | 96 | *R* |
| 2 | ($S_{Ox}$,$S_{Fc}$)-**40** | **2** | $^{t}$Bu/H | | 3 h | 66 | 96 | *R* |
| 3 | ($R$,$R_{Fc}$)-**41** | **3** | H/H | Me/H | 20 min | 98 | 92 | *S* |
| 4 | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | **4** | $^{i}$Pr/H | Me/H | 10 min | 99 | **98** | *S* |
| 5 | ($R$,$S_{Ox}$,$R_{Fc}$)-**42** | **4** | H/$^{i}$Pr | Me/H | 5 h | 18 | 69 | *R* |
| 6 | ($R$,$S_{Ox}$,$S_{Fc}$)-**42** | **4** | $^{i}$Pr/H | H/Me | 1 h | 80 | 41 | *R* |
| 7 | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | **5** | Ph/H | Me/H | 15 min | >99 | **97** | *S* |
| 8 | ($R$,$S_{Ox}$,$R_{Fc}$)-**43** | **5** | H/Ph | Me/H | 6 h | 90 | 73 | *R* |
| 9 | ($R$,$R_{Fc}$)-**44** | **6** | Me/Me | Me/H | 4 h | 78 | 95 | *S* |
| 10 | ($R$,$R_{Fc}$)-**44**[a] | **6** | Me/Me | Me/H | 1 h | 85 | **95** | *S* |
| 11 | ($S_{Ox}$,$S_{Fc}$)-**45** | **7** | $^{i}$Pr/H | H/H | 30 min | 96 | **93** | *R* |
| 12 | ($S_{Ox}$,$S_{Fc}$)-**46** | **8** | $^{i}$Pr/H | H/H | 20 min | 97 | 89 | *R* |
| 13 | ($S_{Ox}$,$S_{Fc}$)-**47** | **9** | $^{t}$Bu/H | H/H | 4 h | 11 | 39 | *R* |
| 14 | ($S$,$S_{Ox}$,$S_{Fc}$)-**48** | **10** | $^{t}$Bu/H | Me/H | 3 h | 26 | 79 | *R* |
| 15 | ($S$,$S_{Ox}$,$S_{Fc}$)-**49** | **11** | $^{i}$Pr/H | Ph/H | 30 min | 97 | 90 | *R* |

[a]Pre-prepared catalyst.

For example, with reference compound ($S_{Ox}$,$S_{Fc}$)-**39** as the catalyst precursor the reaction was essentially finished after 20 min (99% conversion) and the product (*R*)-1-phenylethanol was formed with 96% ee (Table 1, entry 1). In order to estimate the effect of product racemization, enantiopure (*S*)-1-phenylethanol was treated for 24 h in 2-propanol either with base only (KO$^{i}$Pr) or with exposure to the actual catalysis conditions [KO$^{i}$Pr/($S_{Ox}$,$S_{Fc}$)-**39**]. The treatment with base only led to a loss of 5% ee, while under catalysis conditions this process took place much faster, and after 24 h a reduction of 30% ee was observed.

The results obtained for complexes **39**−**49** depended strongly on the substitution pattern and relative configuration of the ligands used (**3**−**11**). The best results were obtained with ligands ($R$,$R_{Ox}$,$R_{Fc}$)-**4** and ($R$,$R_{Ox}$,$R_{Fc}$)-**5** [complexes ($R$,$R_{Ox}$,$R_{Fc}$)-**42** and ($R$,$R_{Ox}$,$R_{Fc}$)-**43**], both of which bear a monosubstituted oxazoline ring and have the ($R_{Ox}$,$R_{Fc}$) relative configuration. As compared to the reference, **39**, both complexes gave rise to slightly higher product ee's within a comparable reaction time (**42**: 98%; **43**: 97%; Table 1, entries 1, 4, and 7). Removal of the oxazoline substituent or the side-chain methyl group [ligands ($R$,$R_{Fc}$)-**3** and ($S_{Ox}$,$S_{Fc}$)-**7**; complexes ($R_{Fc}$)-**41** and ($S_{Ox}$,$S_{Fc}$)-**45**] resulted mainly in a decrease in the product ee (92% and 93%, Table 1, entries 3 and 11). Replacement of the diphenylphosphino group of ($S_{Ox}$,$S_{Fc}$)-**7** by a dixylylphosphino unit [ligand ($S_{Ox}$,$S_{Fc}$)-**8**, complex ($S_{Ox}$,$S_{Fc}$)-**46**] led to a further reduction in the product enantiomeric excess (89%, Table 1, entry 12). Also the exchange of the side-chain methyl group of ($R$,$R_{Ox}$,$R_{Fc}$)-**4** against a phenyl ring (ligand ($S$,$S_{Ox}$,$S_{Fc}$)-**11**, complex ($S$,$S_{Ox}$,$S_{Fc}$)-**49**) led to a comparable drop of the product ee value (Table 1, entries 4 and 15).

Interestingly, the use of ligand ($R$,$R_{Fc}$)-**6** [complex ($R$,$R_{Fc}$)-**44**], which bears two methyl groups at the oxazoline position 4, led to a significant decrease in the rate of the reaction, and after 4 h a conversion of only 78% was achieved. However, this problem could be partly overcome without loss of product ee (95%) when the catalyst precursor ($R$,$R_{Fc}$)-**44** was reacted for 2 h 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 h the product was obtained with 85% conversion and 95% ee (after 2 h: 97% conversion and 94% ee; Table 1, entries 9 and 10). It is clear that with catalyst precursor ($R$,$R_{Fc}$)-**44** the formation of the active catalyst is slowed 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 by steric hindrance caused by one of the oxazoline methyl substituents, which efficiently shields the free coordination site at the metal center [Figure 2 (right) and Supporting Information, Figure S3, C47].

As previously reported by Sammakia,[4f] the ruthenium-based *in situ* transfer hydrogenation of acetophenone became rather slow when the isopropyl-substituted ligand **1** was replaced by


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its *tert*-butyl analogue **2**, but the product ee value did not change significantly. Also with the isolated complex **40** (ligand **2**) a similar trend is seen. Like with reference **39** (ligand **1**), with use of **40** a product with 96% ee was obtained, but at a significantly lower rate (Table 1, entries 1 and 2). However, when the isopropyl group of the best performing ligand, ($R$,$R_{Ox}$,$R_{Fc}$)-**4**, and of ($S_{Ox}$,$S_{Fc}$)-**7** was replaced by a *tert*-butyl group [ligands **10** and **9**, complexes ($S$,$S_{Ox}$,$S_{Fc}$)-**48** and ($S$,$S_{Ox}$,$S_{Fc}$)-**47**], not only did the reactions become very slow but also the product enantiomeric excesses dropped significantly (Table 1, entries 4, 11, 13, and 14).

The strongest influences on the THY reactions were observed when, instead of complexes ($R$,$R_{Ox}$,$R_{Fc}$)-**42** and ($R$,$R_{Ox}$,$R_{Fc}$)-**43**, the diastereomers ($R$,$S_{Ox}$,$R_{Fc}$)-**42** and ($R$,$S_{Ox}$,$R_{Fc}$)-**43** [ligands ($R$,$S_{Ox}$,$R_{Fc}$)-**4** and ($R$,$S_{Ox}$,$R_{Fc}$)-**5**] 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 (ligands **3** and **6**) or when ligands with ($R_{Ox}$,$R_{Fc}$) configuration were applied (**4** and **5**). Consistently, for ligands with ($S_{Ox}$,$S_{Fc}$) configuration (**1**, **2**, **4**, **7**−**11**) a product of *R* configuration was obtained. However, with ligands having the ($S_{Ox}$,$R_{Fc}$) configuration (**4** and **5**) a change of product absolute configuration from *S* to *R* is observed (Table 1, entries 4/5 and 7/8). Interestingly, an identical dependence of the product absolute configuration on the relative configuration of the ligand was reported by Dai and coworkers.[4e] In the transfer hydrogenation of acetophenone with the diastereomeric complexes ($S_{Ox}$,$S_{Fc}$)-**39** and ($S_{Ox}$,$R_{Fc}$)-**39** [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 **42** and **43**, the use of diastereomers ($R_{Ox}$,$R_{Fc}$)-**39** and ($S_{Ox}$,$R_{Fc}$)-**39** leads to products of opposite absolute configuration.

Since the THY of acetophenone was best accomplished with complex ($R$,$R_{Ox}$,$R_{Fc}$)-**42**, the dependence of this process on the substrate concentration and 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 min into the product with 98% ee (99% conversion), a 0.2 molar solution gave the product with 95% ee (90% conversion) within 5 min. 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 ee dropped from 98% to 81%.

In summary, the catalyst precursors ($R$,$R_{Ox}$,$R_{Fc}$)-**42**, ($R$,$R_{Ox}$,$R_{Fc}$)-**43**, ($R$,$R_{Fc}$)-**44**, and ($S_{Ox}$,$S_{Fc}$)-**45** performed best and gave results that are comparable with or slightly better than those of reference ($S_{Ox}$,$S_{Fc}$)-**39** (Table 1, entries 4, 7, 10, and 11).

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 alkyl ketones (phenyl ethyl ketone, PEK; phenyl benzyl ketone, PBK; 1,3-diphenylpropan-1-one, DPP) were tested. Furthermore, a bicyclic system (1-tetralone, TETN), acetylferrocene (AcFc), and one dialkyl ketone (*tert*-butyl methyl ketone, tBMK) were used. For these transfer hydrogenations only those catalyst precursors were used that gave the best results with acetophenone.

In the majority of test reactions (Table 2, Supporting Information Table S3) nearly quantitative conversion could be achieved within 5−30 min. Only with dialkyl ketone tBMK was a prolonged reaction time required. The best results were obtained with complex ($R$,$R_{Ox}$,$R_{Fc}$)-**42** [ligand ($R$,$R_{Ox}$,$R_{Fc}$)-**4**]. 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 ($R$,$R_{Ox}$,$R_{Fc}$)-**43**. In particular, the THY of acetylferrocene gave the product with significantly higher enantiomeric excess, albeit with a very low level of conversion (entry 31).

**Table 2. Best THY Results Obtained for All Substrates Screened**

| entry | substrate | complex | time | % conv | % ee | abs conf |
|---|---|---|---|---|---|---|
| 1 | ACP | ($S_{Ox}$,$S_{Fc}$)-**39** | 20 min | 99 | 96 | *R* |
| 2 | ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 10 min | 99 | **98** | *S* |
| 3 | ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | 15 min | >99 | 97 | *S* |
| 4 | 2-F-ACP | ($S_{Ox}$,$S_{Fc}$)-**39** | 5 min | 99 | **91** | *R* |
| 5 | 2-F-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**41** | 30 min | 99 | 50 | *S* |
| 6 | 2-Cl-ACP | ($S_{Ox}$,$S_{Fc}$)-**39** | 20 min | >99 | **90** | *R* |
| 7 | 2-Cl-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 5 min | >99 | 75 | *S* |
| 8 | 4-Cl-ACP | ($S_{Ox}$,$S_{Fc}$)-**39** | 10 min | >99 | 93 | *R* |
| 9 | 4-Cl-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 5 min | 98 | **94** | *S* |
| 10 | 4-$CF_3$-ACP | ($S_{Ox}$,$S_{Fc}$)-**39** | 5 min | 99 | **90** | *R* |
| 11 | 4-$CF_3$-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 20 min | >99 | 87 | *S* |
| 12 | 4-MeO-ACP | ($S_{Ox}$,$S_{Fc}$)-**39** | 20 min | 80 | 90 | *R* |
| 13 | 4-MeO-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 20 min | 82 | **95** | *S* |
| 14 | 4-MeO-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | 20 min | 75 | **95** | *S* |
| 15 | 4-Me-ACP | ($S_{Ox}$,$S_{Fc}$)-**39** | 10 min | 97 | 96 | *R* |
| 16 | 4-Me-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 10 min | 97 | **98** | *S* |
| 17 | PEK | ($S_{Ox}$,$S_{Fc}$)-**39** | 10 min | 99 | **97** | *R* |
| 18 | PEK | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 20 min | 99 | 96 | *S* |
| 19 | PEK | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | 15 min | 94 | 96 | *S* |
| 20 | PBK | ($S_{Ox}$,$S_{Fc}$)-**39** | 10 min | >99 | 95 | *R* |
| 21 | PBK | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 20 min | >98 | **97** | *S* |
| 22 | PBK | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | 2 h | >99 | 95 | *S* |
| 23 | DPP | ($S_{Ox}$,$S_{Fc}$)-**39** | 10 min | >99 | 94 | *R* |
| 24 | DPP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 15 min | 99 | **96** | *S* |
| 25 | DPP | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | 20 min | >99 | 94 | *S* |
| 26 | TETN | ($S_{Ox}$,$S_{Fc}$)-**39** | 5 min | 71 | **93** | *R* |
| 27 | TETN | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 30 min | 32 | 74 | *S* |
| 28 | TETN | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | 20 min | 21 | 81 | *S* |
| 29 | AcFc | ($S_{Ox}$,$S_{Fc}$)-**39** | 30 min | 24 | 80 | *R* |
| 30 | AcFc | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | 30 min | 10 | 81 | *S* |
| 31 | AcFc | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | 30 min | 16 | **93** | *S* |
| 32 | tBMK | ($S_{Ox}$,$S_{Fc}$)-**39** | 24 h | 85 | **>99** | *S* |
| 33 | tBMK | ($S_{Ox}$,$S_{Fc}$)-**45** | 24 h | 36 | 21 | *R* |

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 4). On employing reference **39** and ACP as the substrate, a product with 96% ee was obtained. Substitution of the ACP phenyl ring with electron-donating or electron-withdrawing substituents led—with the exception of 4-Me-ACP (96% ee)—to a small reduction in the ee values (90−93%), but replacing the methyl group of ACP with other alkyl substituents did not significantly affect the product ee (95−97%; PEK, PBK, DPP). Even the bicyclic compound 1-tetralone was reduced with an enantiomeric excess of 93%.

Similar trends were seen when the best performing complex, ($R$,$R_{Ox}$,$R_{Fc}$)-**42**, was used (Figure 4). As compared to the reference, slightly better product ee values were obtained with


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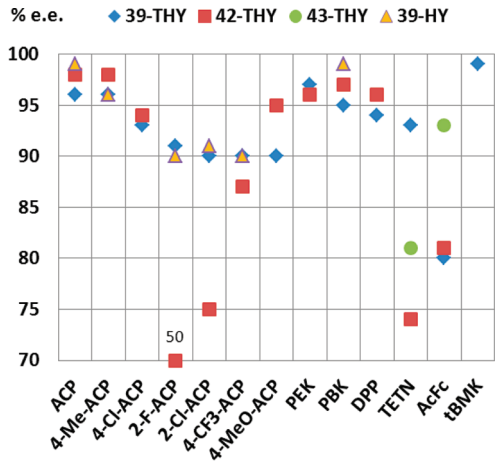


**Figure 4.** Best product enantiomeric excesses (% ee) obtained in THYs and HYs with complexes ($S_{Ox}$,$S_{Fc}$)-**39**, ($R$,$R_{Ox}$,$R_{Fc}$)-**42**, and ($R$,$R_{Ox}$,$R_{Fc}$)-**43**.

seven substrates (ACP, 4-Cl-ACP, 4-MeO-ACP, 4-Me-ACP, PBK, DPP, and AcFc), while slightly lower product ee values 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 ee was found (2-F-ACP: 50%, 2-Cl-ACP: 75%, TETN: 74%).

In summary, in a number of cases complex ($R$,$R_{Ox}$,$R_{Fc}$)-**42** gave slightly better results than the original FOXAP analogue **39**. However, we noticed with surprise that although complexes **39** and **42** adopt totally different molecular structures (**39**: Supporting Information, Figure S6, and **42**: Figure 2, 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 ee values. For complexes **39** and **42** as the catalyst precursors, we consider these findings to be the result of similar asymmetric induction mechanisms.[2,3]

In their original report on THYs of aryl alkyl and dialkyl ketones with FOXAP ruthenium dichloride complexes such as [$RuCl_2(PPh_3)$(($S_{Ox}$,$S_{Fc}$)-**1**)], Uemura and co-workers commented on mechanistic features and presented some NMR evidence for a ruthenium dihydride-based reaction mechanism.[4c] Furthermore, for aryl alkyl ketones a transition-state model was presented (Figure 5, top). On the basis of this report we questioned whether the THY reactions with complex ($R$,$R_{Ox}$,$R_{Fc}$)-**42** 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 ($R$,$R_{Ox}$,$R_{Fc}$)-**50** and ($S_{Ox}$,$S_{Fc}$)-**51** (Figure 3) and is shown in Figure 5 (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.

*Hydrogenations (HY).* As an extension of our previous work, a set of six complexes [$RuCl_2(PPh_3)$(L)] [($R_{Ox}$,$R_{Fc}$)-**41**, ($R$,$R_{Ox}$,$R_{Fc}$)-**42**, ($R$,$S_{Ox}$,$R_{Fc}$)-**42**, ($R$,$R_{Ox}$,$R_{Fc}$)-**43**, ($R$,$S_{Ox}$,$R_{Fc}$)-**43**, ($S_{Ox}$,$S_{Fc}$)-**45**, and ($S_{Ox}$,$S_{Fc}$)-**46**] were screened in asymmetric hydrogenations under transfer hydrogenation conditions against three additional aryl alkyl ketones (2-F-ACP, 2-Cl-ACP, 4-$CF_3$-ACP) on a customized Symyx high-throughput screening system.[8] The best results obtained for all six substrates are listed in Table 3 (for an extended set of data see Supporting Information, Table S4).

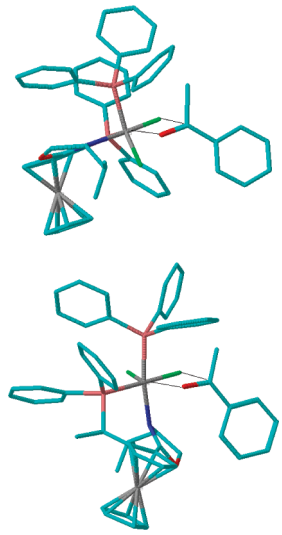

**Figure 5.** Transition-state models for the THYs of aryl alkyl ketones with systems [$RuH_2$(($R_{Ox}$,$R_{Fc}$)-**1**)]/ACP (top; adopted from Cambridge Structural Database, refcode MAPLUK and ref 6c) and [$RuH_2$(($R_{Ox}$,$R_{Fc}$)-**4**)]/ACP (bottom).

**Table 3. Best HY Results Obtained with Complexes 41−46**

| entry | substrate | complex | solvent | base | % conv | % ee | abs conf |
|---|---|---|---|---|---|---|---|
| 1 | ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | Tol/$H_2O$ | $K_2CO_3$ | 99 | **99** | *S* |
| 2 | ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | Tol/$H_2O$ | $K_2CO_3$ | 99 | **98** | *S* |
| 3 | 2-F-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | Tol/$H_2O$ | $K_2CO_3$ | 97 | **90** | *S* |
| 4 | 2-Cl-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | Tol/$H_2O$ | $K_2CO_3$ | 95 | **91** | *S* |
| 5 | 4-$CF_3$-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | Tol/$H_2O$ | $K_2CO_3$ | 97 | **90** | *S* |
| 6 | 4-Me-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | Tol/$H_2O$ | $K_2CO_3$ | 100 | **97** | *S* |
| 7 | 4-Me-ACP | ($R$,$R_{Ox}$,$R_{Fc}$)-**43** | Tol/$H_2O$ | $K_2CO_3$ | 100 | **97** | *S* |
| 8 | PBK | ($R$,$R_{Ox}$,$R_{Fc}$)-**42** | $^i$PrOH | KO$^t$Bu | >99 | **99** | *S* |

As for the THYs, all hydrogenations were carried out with isolated and fully characterized catalyst precursors. Different combinations of solvents and bases were tested. Either 2-propanol in combination with KO$^t$Bu or toluene/water (9:1) with base $K_2CO_3$ or NaOH was applied. The former solvent/base system is typically used in transfer hydrogenation reactions,[2,3] 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.[5,6]

For all substrates screened, reaction conditions were identified that gave products with quantitative or nearly quantitative conversion and with an enantiomeric excess equal to or better than 90%.

As in transfer hydrogenations, catalyst precursor ($R$,$R_{Ox}$,$R_{Fc}$)-**42** gave the best results (Table 3, entries 1, 3−6, and 8), 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, did the $^i$PrOH/KO$^t$Bu system prove to be superior to the toluene/$H_2O$ system,


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resulting in quantitative conversion and a product enantiomeric excess of 99% (entry 8). Once again, in a few cases complex ($R$,$R_{Ox}$,$R_{Fc}$)-**43** gave equally good results to ($R$,$R_{Ox}$,$R_{Fc}$)-**42** [Table 3, entries 1/2 (ACP) and 6/7 (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 ($R$,$R_{Ox}$,$R_{Fc}$)-**42** showed almost identical trends (Figure 4). 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.

*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 ($R$,$R_{Ox}$,$R_{Fc}$)-**42** and, in a few cases, complex ($R$,$R_{Ox}$,$R_{Fc}$)-**43** 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 4).

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 ($R_{Fc}$) or ($R_{Ox}$,$R_{Fc}$) absolute configuration led to the transformation of all tested aryl alkyl ketones into alcohols with the $S$ absolute configuration. Only when the relative configuration of ligands was changed from ($R$,$R_{Ox}$,$R_{Fc}$) to ($R$,$S_{Ox}$,$R_{Fc}$) did the product absolute configuration change from $S$ to $R$ (for the hydrogenation data see Supporting Information, Table S4).

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

**Table 4. Comparison of THY and HY Results Obtained with ($R$,$R_{Ox}$,$R_{Fc}$)-42**

| | THY[a] | | HY | |
|---|---|---|---|---|
| substrate | % conv | % ee | % conv | % ee |
| 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.

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.

## SUMMARY

Ruthenium complexes of the type [$RuCl_2PPh_3$(L)] (**41**−**49**) of 12 bidentate phosphine-oxazoline ligands (L = **3**−**11**), all of which contain a ferrocenylethyl (**41**−**44**, **48**, **49**, L = **3**−**6**, **10**, **11**) or a ferrocenylmethyl (**45**−**47**, L = **7**−**9**) backbone, were synthesized and characterized. For this purpose, in addition to the original synthesis, three synthesis routes were developed that all started from commercially available or easily accessible ferrocenyl-oxazolines. By applying two synthesis strategies, the phosphino-substituted side chain could be built up diastereoselectively. The first route made use of an autoactivated phenyl or alkyl transfer from zinc reagents to 2-oxazolinyl-substituted ferrocene aldehydes, while on the second route 2-phosphinylmethyl-substituted ferrocenyloxazolines were deprotonated and alkylated diastereoselectively at the side-chain methylene group. Especially by applying the zinc-mediated reaction sequence could the original synthesis of the best performing ligands **4** and **5** of ($S$,$S_{Ox}$,$S_{Fc}$) relative configuration be significantly simplified since the use of two enantiopure reagents as well as the final reduction step could be avoided.

All complexes **41**−**49** and, for comparative purposes, also two analogous and well-established FOXAP ruthenium complexes (**39** and **40**) were tested in the transfer hydrogenations of acetophenone. The best performing complexes were also screened in transfer hydrogenations against a total of 12 additional ketones. The molecular structures of one synthesis intermediate, of two catalyst precursors, and of two corresponding acetonitrile complexes were studied by X-ray diffraction. One catalyst precursor in particular, ($R$,$R_{Ox}$,$R_{Fc}$)-**42**, delivered products with an enantiomeric excess of up to 98%. A comparison of the transfer hydrogenation results obtained with the novel complex ($R$,$R_{Ox}$,$R_{Fc}$)-**42** and those of the analogous FOXAP-based catalyst ($S_{Ox}$,$S_{Fc}$)-**39** showed surprising similarities. Although complexes **39** and **42** 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 ee 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 ee values on the substitution patterns of substrates and ligands.

Six complexes were also used as catalyst precursors in high-throughput hydrogenations of six aryl alkyl ketones, and once again complex ($R$,$R_{Ox}$,$R_{Fc}$)-**42** delivered the best results, with product ee 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 products 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.

On the basis of 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. On the basis of the finding that identical catalyst precursors 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.

## 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 rt, 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


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(bottom) using 2-PrOH as the eluent. The filtrate obtained was analyzed by either 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 h at rt 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 $\mu$mol of substrate and 1.67 $\mu$mol of catalyst precursor in a total of 500 $\mu$L of solvent (for analysis data see Supporting Information).

## ■ ASSOCIATED CONTENT

### Supporting Information

Text giving full experimental descriptions and spectroscopic data for all newly synthesized ligands and complexes as well as detailed hydrogenation and transfer hydrogenation data are provided. Crystallographic and geometric data for one synthesis intermediate and 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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### Notes

The authors declare no competing financial interest.

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