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

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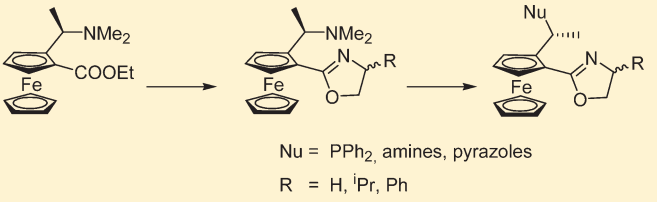
Supporting Information

ABSTRACT: A highly flexible and modular synthesis of 15 chiral nonracemic ferrocenyloxazolines—all based on a ferrocenylethyl backbone—is described. Starting from *N*,*N*-dimethylaminoethyl ferrocene a range of oxazoline derivatives with various oxazoline substituents were prepared in a three-step sequence. After reaction with methyl iodide, the quaternized dimethylamino group was replaced by different amino, pyrazolyl, and phosphinyl groups. Subsequent reduction of the phosphinyl groups gave phosphinooxazoline derivatives. The molecular structures of three palladium $[PdCl_2(L)]$ and three ruthenium $[RuCl(p\text{-cymene})(L)]PF_6$ complexes of representative ferrocenyloxazoline ligands were studied by X-ray diffraction. In addition, five ruthenium complexes $[RuCl_2(PPh_3)(L)]$ were prepared. These complexes were tested, using a high-throughput screening system, in the asymmetric hydrogenation of three ketones. Enantioselectivities of up to 99% ee were obtained.

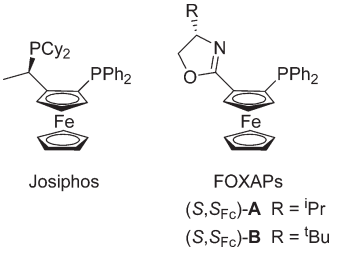


INTRODUCTION

For more than three decades chiral ferrocene derivatives have been employed as ligands for asymmetric catalysts,[1] and at present they are even used in large-scale industrial processes.[2] Ferrocenyldiphosphines such as Josiphos-type ligands are certainly the most prominent examples (Chart 1).[3] In addition to a variety of diphosphines, oxazoline-based ferrocene derivatives have also been successfully used in a huge number of asymmetric transformations.[4] In 1995 several groups reported independently on the synthesis of 1-phosphino-2-oxazolinyl-substituted ferrocenes[5] (Chart 1) and their 1,2,1′,2′-tetrasubstituted analogues.[6] Since that time these so-called FOXAP ligands have found applications in enantioselective hydrogenations,[7] transfer hydrogenations,[7k,8] hydrosilylations,[5d,7k,9] cross-coupling reactions,[5b,10] Heck reactions,[11] alkylations of aldehydes,[12] allylic substitutions,[7k,10c,13] and many other transformations.[14] The success of this class of ligand has initiated additional attempts to develop ferrocenyloxazolines with alternative substitution patterns, with alternative combinations of functional groups, or with ligands that have more extended backbones such as biferrocene,[15] ferrocenylmethyl,[16] ferrocenylethyl,[17] or related units.[18]

Both classes of compound, i.e., Josiphos-type[19] and FOXAP-type ligands,[4e] can be prepared in a very straightforward and modular manner. In both cases the phosphino and the oxazoline substituents can be varied easily and independently (Scheme 1), and this feature has given rise to a large number of representatives of both ligand groups. In this context we considered combining the structural features of both classes of ligands and, by making use of the ease and high modularity of both synthesis routes, attempting to prepare a new class of oxazoline ligand.

Chart 1



In continuation of our previous research in this field,[20] in this contribution we report on a very general and modular synthesis of a novel class of oxazoline ligand, all of which are based on a ferrocenylethyl backbone with differently substituted oxazoline units attached directly to the ferrocene core and additional amino, pyrazolyl, or phosphino groups connected to the ethyl side chain. Furthermore, the synthesis of a number of palladium and ruthenium complexes is described along with some of their structural features and applications of selected ruthenium complexes in the asymmetric hydrogenation of ketones.

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RESULTS AND DISCUSSION

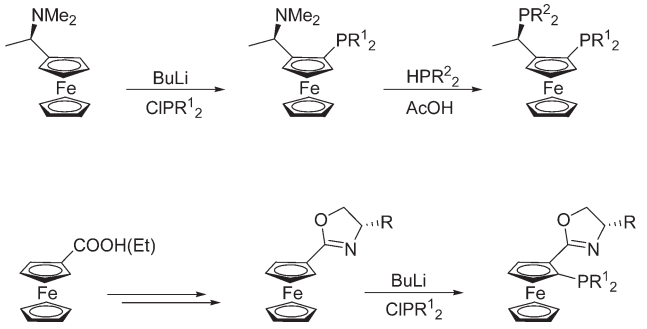
Ligand Synthesis. Starting from Ugi's amine, (*R*)-**1**,[21] five oxazoline derivatives with different substituents R were prepared in a three-step sequence (Scheme 2). In the first step the ethyl ester (R,S_{Fc})-**2** was obtained from (*R*)-**1** by a diastereoselective *ortho*-lithiation with *t*-BuLi and subsequent reaction with diethyl carbonate.[22] In the second step ester **2** was reacted in the presence of trimethylaluminum[10f] with five differently substituted amino alcohols to give amides (R,S_{Fc})-**3**, ($1S,1'R,S_{Fc}$)-**4**, ($1R,1'R,S_{Fc}$)-**4**, ($1S,1'R,S_{Fc}$)-**5**, and ($1R,1'R,S_{Fc}$)-**5**, which in the third step could be transformed according to the methodology of Appel[23] to oxazolines (R,S_{Fc})-**6**, ($4S,1'R,S_{Fc}$)-**7**, ($4R,1'R,S_{Fc}$)-**7**, ($4S,1'R,S_{Fc}$)-**8**, and ($4R,1'R,S_{Fc}$)-**8**. It is clear that the substitution pattern of the oxazoline unit can be determined by choosing the appropriate amino alcohol in step 2.

Methods for the replacement of the dimethylamino group by other nucleophiles were subsequently explored by studying oxazoline **6**. It was found that the most widely used methodology—quaternization of the amino nitrogen with methyl iodide followed by nucleophilic substitution—worked best.[21b] Therefore, **6** was treated with methyl iodide in acetonitrile, and the crude ammonium salt was subsequently reacted with either diisopropylamine, pyrrolidine, piperidine, pyrazole, or 3,5-dimethylpyrazole to give the amino- and pyrazolyl-substituted ferrocenyloxazoline derivatives (R,S_{Fc})-**9**−**13**.

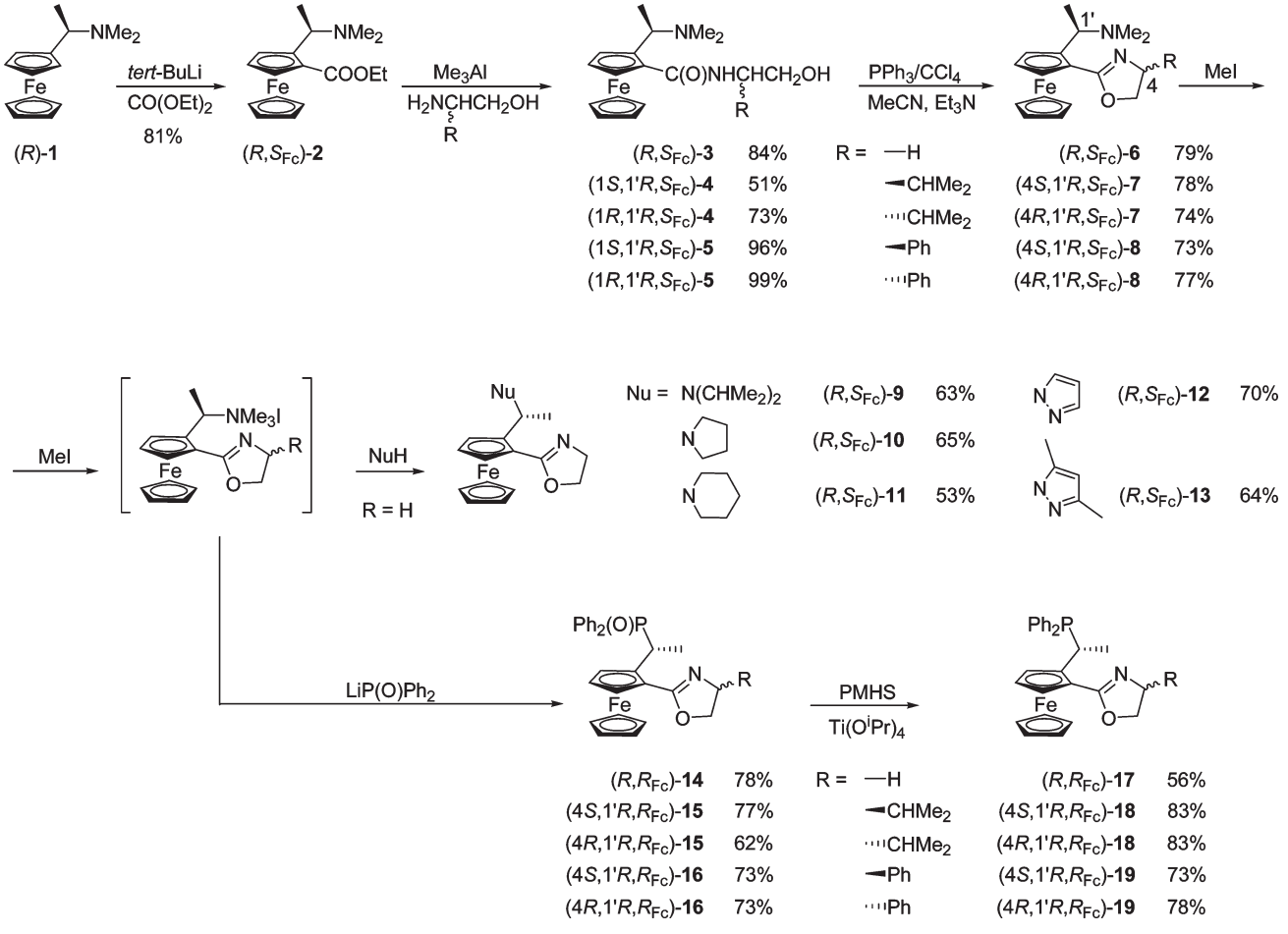
Furthermore, the ammonium salt of **6** could be transformed with diphenylphosphinyllithium to the phosphinyl-substituted derivative (R,R_{Fc})-**14**.[24] Reduction of this phosphine oxide with polymethylhydrosiloxane in the presence of titanium isopropoxide[25] gave the phosphinooxazoline (R,R_{Fc})-**17**. On the basis of this reaction sequence the aminooxazolines **7** and **8** were also transformed into phosphineoxides ($4S,1'R,R_{Fc}$)-**15**, ($4R,1'R,R_{Fc}$)-**15**, ($4S,1'R,R_{Fc}$)-**16**, and ($4R,1'R,R_{Fc}$)-**16** and subsequently to the phosphinooxazolines ($4S,1'R,R_{Fc}$)-**18**, ($4R,1'R,R_{Fc}$)-**18**, ($4S,1'R,R_{Fc}$)-**19**, and ($4R,1'R,R_{Fc}$)-**19**.

In summary, this highly flexible reaction sequence can be used to access amino- and pyrazolyl-substituted oxazolines from Ugi's amine in four steps, while for the preparation of phosphinooxazolines

Scheme 1. Synthesis Routes for Josiphos- and FOXAP-Type Ligands



Scheme 2



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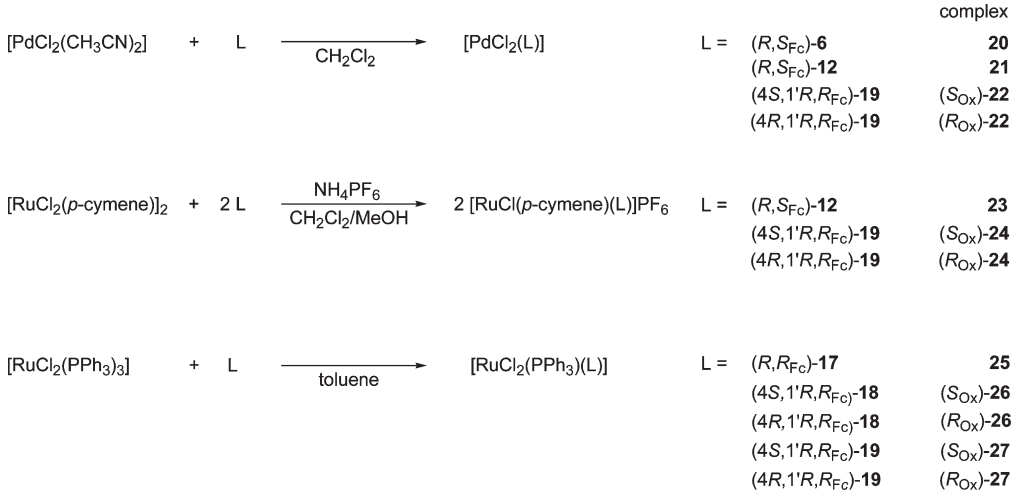
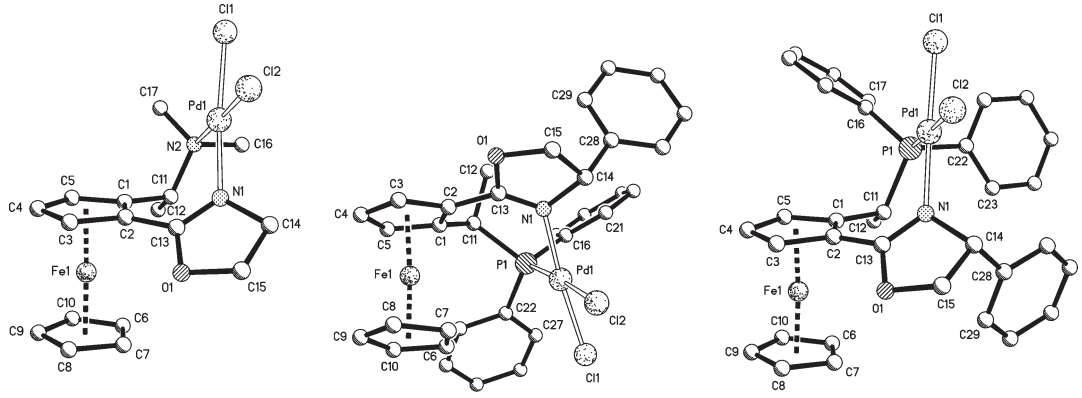
Scheme 3. Preparation of Palladium and Ruthenium Complexes 20−27





20, [L = (*R*,S_{Fc})-**6**] (S_{Ox})-**22**, [L = (4*S*,1′*R*,R_{Fc})-**19**] (R_{Ox})-**22**, [L = (4*R*,1′*R*,R_{Fc})-**19**]

Figure 1. Molecular structures of the complexes [$PdCl_2$(L)] (H-atoms omitted for clarity; assignment of absolute configuration: 4 refers to configuration at C14, 1′ to C11).

five steps are needed. Selection of the appropriate amino alcohol in the second step determines the oxazoline substitution pattern, while in the fourth step a variety of nucleophiles can be attached to the ethyl side chain.

Synthesis and Structural Features of Pd and Ru Complexes of Ligands (*R*,S_{Fc})-6, (*R*,S_{Fc})-12, (4*S*,1′*R*,R_{Fc})-19, and (4*R*,1′*R*,R_{Fc})-19. Ferrocenyloxazoline derivatives have frequently been used as ligands in enantioselective transition metal catalysts. For this purpose the metals Pd and Ru are mainly used (to a lesser extent Rh and Ir have been applied),[4] but coordination compounds of other metals such as Os,[26] Pt,[27] Cu,[28] Au,[29] Zn,[30] and Hg[31] have also been explored. Palladium complexes of ferrocenyloxazolines have been used as catalyst precursors for a number of reactions including allylic alkylations,[7k,10c,13] Heck reactions,[11] aza Claisen rearrangements,[32] Grignard cross-coupling,[5b,10] and Suzuki reactions,[33] while ruthenium complexes have found applications in hydrogenations,[7] hydrogen transfer,[7k,8] and hydrosilylation reactions.[5d,7k,9]

In order to study the complexation behavior of our newly synthesized ligands, palladium dichloride complexes [$PdCl_2$(L)] of oxazolines (*R*,S_{Fc})-**6**, (*R*,S_{Fc})-**12**, (4*S*,1′*R*,R_{Fc})-**19**, and (4*R*,1′*R*,R_{Fc})-**19** and ruthenium *p*-cymene complexes [RuCl(*p*-cymene)(L)]PF_6 of ligands (*R*,S_{Fc})-**12**, (4*S*,1′*R*,R_{Fc})-**19**, and (4*R*,1′*R*,R_{Fc})-**19** were prepared (Scheme 3). The palladium complexes **20**, **21**, (S_{Ox})-**22**, and (R_{Ox})-**22** were obtained by reacting the appropriate ligands (**6**, **12**, **19**) with [$PdCl_2$-(CH_3CN)$_2$], while reaction of ligands **12** and **19** with the ruthenium dimer [$RuCl_2$(*p*-cymene)]$_2$ and subsequent treatment of the reaction mixture with ammonium hexafluorophosphate gave the cationic ruthenium complexes **23**, (S_{Ox})-**24**, and (R_{Ox})-**24**. It should be mentioned that in the latter reaction for each ligand two diastereomeric complexes with different configurations at ruthenium might be expected. In fact, for all three ligands only one diastereomer was isolated.

From the three palladium complexes **20**, (S_{Ox})-**22**, and (R_{Ox})-**22** [$PdCl_2$(L)] [L = (*R*,S_{Fc})-**6**, (4*S*,1′*R*,R_{Fc})-**19**, (4*R*,1′*R*,R_{Fc})-**19**] and the three ruthenium complexes **23**, (S_{Ox})-**24**, and (R_{Ox})-**24** [RuCl(*p*-cymene)(L)]PF_6 [L = (*R*,S_{Fc})-**12**, (4*S*,1′*R*,R_{Fc})-**19**, (4*R*,1′*R*,R_{Fc})-**19**] suitable single crystals were obtained, and their molecular structures in the solid state were studied by X-ray

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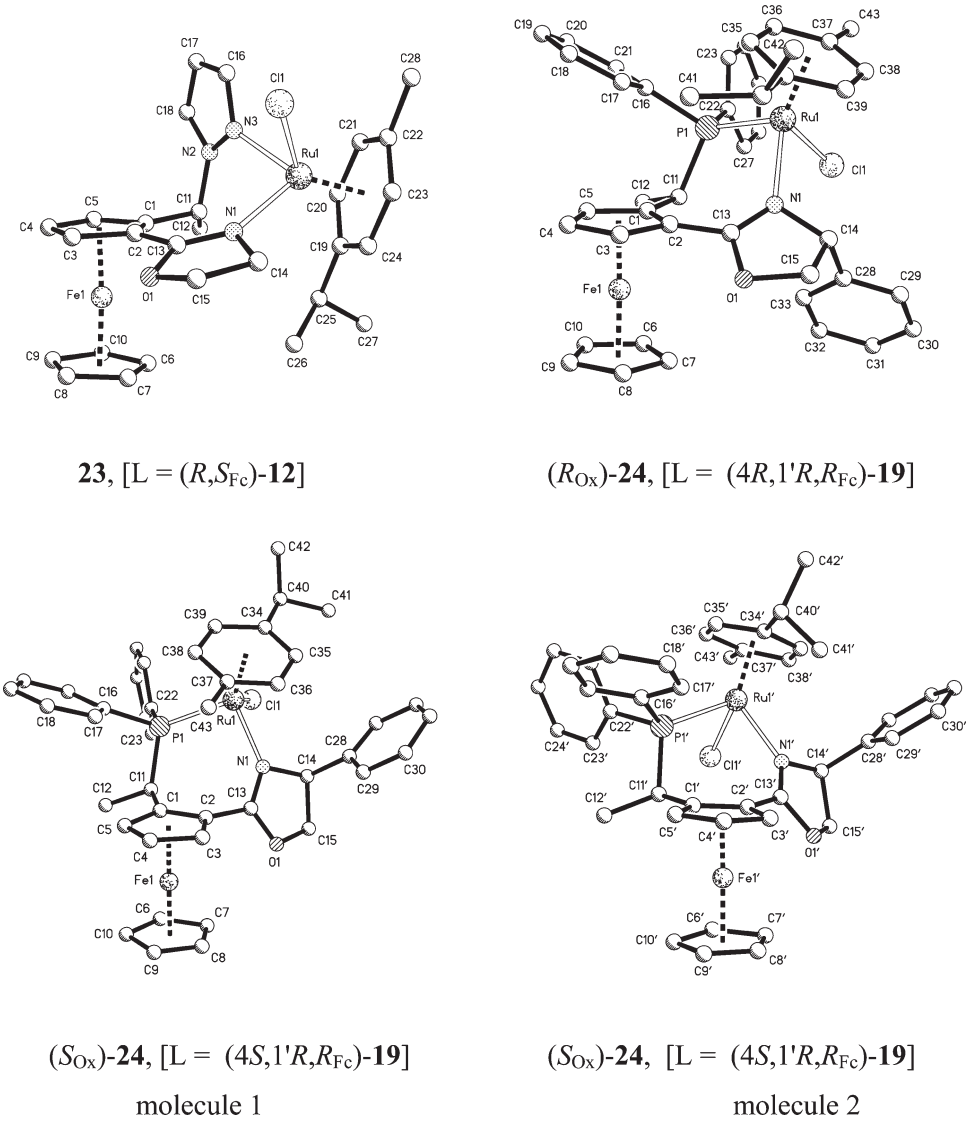

Figure 2. Molecular structures of complexes $[RuCl(p\text{-cymene})(L)]PF_6$ (H-atoms omitted for clarity; assignment of absolute configuration: 4 refers to configuration at C14, 1′ to C11).

diffraction. Details of these X-ray crystallography studies are given in Table S1 of the Experimental Section (see Supporting Information). 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, and selected geometrical data are given in Tables 1 and 2.

In all complexes the ligands are bidentate, forming square-planar palladium dichloride complexes and three-legged piano stool-type ruthenium complexes. All palladium complexes co-crystallized with one or two equivalents of $CHCl_3$, which in each case show close contacts (nonclassical C−H···Cl bonds) with one or both chlorides of the palladium dichloride unit. The atoms coordinated to palladium form an approximately square-planar arrangement that deviates only slightly from planarity (rms deviations from planarity between 0.008 and 0.064 Å). The N−Pd−N or N−Pd−P bond angles are within a narrow range of 93.9−94.9° (Table 1). As expected, in complex **20** the *trans*-influence caused by the oxazoline nitrogen is stronger than that of the amino nitrogen, while in the case of the phosphino-oxazolines the phosphino-phosphorus shows a stronger *trans*-influence than the oxazoline nitrogen. Interestingly, the arrangements of the respective oxazoline nitrogen N1 and atoms directly connected to it (Pd1, C13, C14) deviate significantly from planarity, a trend that is especially pronounced in complex (S_{Ox})-**22** (N 0.228 Å above the plane defined by Pd1, C13, C14). In complexes **20** and (R_{Ox})-**22** the $PdCl_2$ unit is located above the ferrocene Cp^1 ring (*exo* position), an arrangement that places the side chain methyl carbon C12 below Cp^1 (Cp^1 = C1 through C5, Cp^2 = C6 through C10).

In the palladium complexes of ligand **19** gross overall structural changes are observed on changing the configuration at the oxazoline position 4 from *R* to *S*. In complex (R_{Ox})-**22** the palladium dichloride unit is located above Cp^1 (*exo* arrangement), whereas in complex (S_{Ox})-**22** this unit is found below Cp^1 (*endo* arrangement). This change also results in a reorientation of the ethyl side chain.

In all piano stool-type ruthenium half-sandwich complexes **23**, (S_{Ox})-**24** and (R_{Ox})-**24**, $[RuCl(p\text{-cymene})(L)]PF_6$ [L = (R,S_{Fc})-**12**, $(4S,1'R,R_{Fc})$-**19**, and $(4R,1'R,R_{Fc})$-**19**], the coordinated

Table 1. Geometric Parameters of Complexes $[PdCl_2(L)]$

	complex **20** [L = (R,S_{Fc})-**6**]	complex (S_{Ox})-**22** [L = (4S,1′R,R_{Fc})-**19**]	complex (R_{Ox})-**22** [L = (4R,1′R,R_{Fc})-**19**]
		Distances (Å)	
Pd−Cl(*trans*-$N(CH_3)_2$), (tr-P)	2.299	2.372	2.378
Pd−Cl(tr. Ox)	2.310	2.281	2.291
Pd−$N(N(CH_3)_2)$, (P)	2.138	2.241	2.234
Pd−N(Ox)	2.027	2.045	2.044
Cl−$HCCl_3$	(tr-Ox) 2.48	(tr-P) 2.48/2.94	(tr-P) 2.65/2.95 (tr-P) 2.75/3.07
		Bond Angles (deg)	
N−Pd−N, N−Pd−P	94.2	94.9	93.9
Cl−Pd−Cl	87.5	89.3	90.0
		Tilt Angle (deg)	
Cp^1/Cp^2	1.8	4.4	3.8
		Normal Distance from Mean Plane (Å)	
Cp^1−$CHCH_3$	−0.783	1.829	−0.682
Cp^1−$CHCH_3$	−0.063	0.376	−0.052
Cp^1−$N(CH_3)_2$, −PPh_2	1.327	−0.786	1.645
Cp^1−N(Ox)	0.633	−0.262	0.705
Cp^1−Pd	2.332	−1.820	2.508
Cp^1−Cl(tr. Ox)	4.375	−3.602	4.578
Cp^1−Cl(tr. $N(CH_3)_2$), (tr-P)	3.429	−3.014	3.456
N(Ox) pl of **Pd**, NCH_2, **C**=N	−0.158	0.228	−0.150

Table 2. Geometric Parameters of Complexes $[RuCl(p\text{-cymene})(L)]PF_6$

		complex (S_{Ox})-**24** [L = (4S,1′R,R_{Fc})-**19**]		
	complex **23** [L = (R,S_{Fc})-**12**]	molecule 1	molecule 2	complex (R_{Ox})-**24** [L = (4R,1′R,R_{Fc})-**19**]
		Distance (Å)		
Ru−Cl	2.392	2.40	2.40	2.379
Ru−N(pz), −PPh_2	2.117	2.41	2.37	2.349
Ru−N(Ox)	2.161	2.11	2.14	2.143
Cl−CH_3(Cy)	3.269	5.86	3.30	3.415
Cl−CH(Cy)	5.780	3.32	5.89	5.623
		Angles (deg)		
N−Ru−N, N−Ru−P	91.4	92.7	96.9	94.4
Cl−Ru−N(Py), Cl−Ru−P	84.4	84.7	82.3	85.6
Cl−Ru−N(Ox)	82.3	82.0	80.5	82.5
		Tilt Angle (deg)		
Cp^1/Cp^2	3.7	1.8	2.7	1.8
Cp^1/cymene	105.2	26.6	19.7	24.2
		Normal Distance from Mean Plane (Å)		
Cp^1−$CHCH_3$	−0.509	−0.47	−0.50	−0.376
Cp^1−$CHCH_3$	0.133	0.11	0.06	0.042
Cp^1−N(Py), −PPh_2	2.199	1.87	1.79	1.767
Cp^1−N(Ox)	0.209	0.92	0.92	0.458
Cp^1−Ru	1.264	2.81	2.47	2.273
Cp^1−Cl	3.002	2.16	0.69	0.892
N(Ox) pl of **Ru**, NCH_2, **C**=N	−0.074	−0.06	0.05	−0.135

ruthenium and chloride Cl1 are positioned above Cp^1, while the side-chain methyl carbon C12 is located below Cp^1. Interestingly, reaction of the dimer $[RuCl_2(p\text{-cymene})]_2$ with ligand (R,S_{Fc})-**12** and NH_4PF_6 leads to the formation of complex **23** with the

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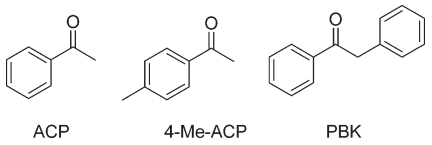

Figure 3. Ketones used as substrates in catalytic hydrogenations.

R configuration at ruthenium, while with both ligands **19** complexes with the *S* configuration at ruthenium were obtained.

In complexes (R_{Ru})-[RuCl(*p*-cymene)((*R*,S_{Fc})-**12**)]PF_6 (**23**) and (S_{Ru})-[RuCl(*p*-cymene)((4*R*,1′*R*,R_{Fc})-**19**)]PF_6 ((R_{Ox})-**24**) the *p*-cymene units are oriented in such a way that their respective methyl carbon (C28 and C43) is positioned in proximity to chloride Cl1. In contrast to the palladium and ruthenium complexes described so far, complex (S_{Ru})-[RuCl(*p*-cymene)-((4*S*,1′*R*,R_{Fc})-**19**)]PF_6 ((S_{Ox})-**24**) crystallizes with two molecules in the asymmetric unit, and these differ mainly in the orientation of their *p*-cymene units. In one molecule the *p*-cymene methyl carbon C43 is located close to chloride Cl1, while in the second molecule the *p*-cymene unit is rotated around the Ru−arene bond by approximately 180°, which brings the isopropyl methine carbon C40′ in proximity to Cl1′.

Superposition of the molecular structures of complexes (R_{Ox})-**24** with both molecules of (S_{Ox})-**24** showed that, unlike the case of the analogous palladium complexes, a change in the configuration of the oxazoline carbon 4 from 4*R* to 4*S* does not cause significant structural changes to the molecular backbone.

Synthesis of Neutral, Five-Coordinate Ruthenium Complexes of Ligands 17−19 and Their Use in Catalytic Asymmetric Hydrogenations of Ketones. Reaction of phosphinooxazoline ligands **17**−**19** with [$RuCl_2(PPh_3)_3$] in toluene at rt led to the isolation of green complexes **25**−**27** of molecular formula [$RuCl_2(PPh_3)$(L)] (Scheme 3). These complexes were screened in catalytic hydrogenations of three ketones using a customized Symyx high-throughput screening system (for substrates see Figure 3). Typical results are listed in Table 3 (for detailed reaction conditions see Supporting Information).

All hydrogenations were carried out with isolated and fully characterized catalyst precursors. Reactions were run under hydrogen gas at a pressure of 25 bar, at a substrate to catalyst ratio of 25:1, and at a temperature of 25 °C. 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,[34] 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.[7h]

For all ketones used as substrates [acetophenone (ACP), 4-methylacetophenone (4-Me-ACP), and phenyl benzyl ketone (PBK)] catalyst systems and reaction conditions were identified that transformed the substrates with quantitative or nearly quantitative conversion into products with an enantiomeric excess ranging from 97% ee (4-Me-ACP) to 99% ee (ACP and PBK).

On using acetophenone as the substrate, all solvent/base systems tested gave excellent results (Table 3, entries 1−3, 6−8, 12), with the toluene/H_2O/K_2CO_3 system performing slightly better than the toluene/H_2O/NaOH system (99% versus 97% ee; entries 2 and 7). The best conditions for the hydrogenation of 4-Me-ACP also involved the use of toluene/H_2O. As with acetophenone the influence of the base was found to be rather small (97% versus 95% ee; entries 17 and 22). 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 (entries 37 and 32), giving quantitative conversion and a product enantiomeric excess of 99% ee (entry 37).

Table 3. Results Obtained in the Hydrogenation of Ketones with Complexes 25−27 [$RuCl_2(PPh_3)$(17−19)][a]

entry	substrate	[$RuCl_2$ (PPh_3)(L)]	solvent	base	conv	% ee[b]	abs conf[c]
1	ACP	**25**	toluene, H_2O	K_2CO_3	99	95	*S*
2	ACP	(R_{Ox})-**26**	toluene, H_2O	K_2CO_3	99	99	*S*
3	ACP	(R_{Ox})-**27**	toluene, H_2O	K_2CO_3	99	98	*S*
4	ACP	(S_{Ox})-**26**	toluene, H_2O	K_2CO_3	99	44	*R*
5	ACP	(S_{Ox})-**27**	toluene, H_2O	K_2CO_3	99	49	*R*
6	ACP	**25**	toluene, H_2O	NaOH	99	94	*S*
7	ACP	(R_{Ox})-**26**	toluene, H_2O	NaOH	99	97	*S*
8	ACP	(R_{Ox})-**27**	toluene, H_2O	NaOH	99	96	*S*
9	ACP	(S_{Ox})-**26**	toluene, H_2O	NaOH	99	43	*R*
10	ACP	(S_{Ox})-**27**	toluene, H_2O	NaOH	99	47	*R*
11	ACP	**25**	*i*-PrOH	KO*t*-Bu	96	75	*S*
12	ACP	(R_{Ox})-**26**	*i*-PrOH	KO*t*-Bu	95	94	*S*
13	ACP	(R_{Ox})-**27**	*i*-PrOH	KO*t*-Bu	94	89	*S*
14	ACP	(S_{Ox})-**26**	*i*-PrOH	KO*t*-Bu	95	58	*R*
15	ACP	(S_{Ox})-**27**	*i*-PrOH	KO*t*-Bu	95	62	*R*
16	4-Me-ACP	**25**	toluene, H_2O	K_2CO_3	100	88	*S*
17	4-Me-ACP	(R_{Ox})-**26**	toluene, H_2O	K_2CO_3	100	97	*S*
18	4-Me-ACP	(R_{Ox})-**27**	toluene, H_2O	K_2CO_3	100	97	*S*
19	4-Me-ACP	(S_{Ox})-**26**	toluene, H_2O	K_2CO_3	88	20	*R*
20	4-Me-ACP	(S_{Ox})-**27**	toluene, H_2O	K_2CO_3	99	28	*R*
21	4-Me-ACP	**25**	toluene, H_2O	NaOH	100	80	*S*
22	4-Me-ACP	(R_{Ox})-**26**	toluene, H_2O	NaOH	99	95	*S*
23	4-Me-ACP	(R_{Ox})-**27**	toluene, H_2O	NaOH	99	90	*S*
24	4-Me-ACP	(S_{Ox})-**26**	toluene, H_2O	NaOH	99	20	*R*
25	4-Me-ACP	(S_{Ox})-**27**	toluene, H_2O	NaOH	99	27	*R*
26	4-Me-ACP	**25**	*i*-PrOH	KO*t*-Bu	99	56	*S*
27	4-Me-ACP	(R_{Ox})-**26**	*i*-PrOH	KO*t*-Bu	98	88	*S*
28	4-Me-ACP	(R_{Ox})-**27**	*i*-PrOH	KO*t*-Bu	100	79	*S*
29	4-Me-ACP	(S_{Ox})-**26**	*i*-PrOH	KO*t*-Bu	98	35	*R*
30	4-Me-ACP	(S_{Ox})-**27**	*i*-PrOH	KO*t*-Bu	99	49	*R*
31	PBK	**25**	toluene, H_2O	NaOH	59	68	*S*
32	PBK	(R_{Ox})-**26**	toluene, H_2O	NaOH	74	85	*S*
33	PBK	(R_{Ox})-**27**	toluene, H_2O	NaOH	61	85	*S*
34	PBK	(S_{Ox})-**26**	toluene, H_2O	NaOH	34	50	*R*
35	PBK	(S_{Ox})-**27**	toluene, H_2O	NaOH	98	50	*R*
36	PBK	**25**	*i*-PrOH	KO*t*-Bu	100	74	*S*
37	PBK	(R_{Ox})-**26**	*i*-PrOH	KO*t*-Bu	100	99	*S*
38	PBK	(R_{Ox})-**27**	*i*-PrOH	KO*t*-Bu	100	93	*S*
39	PBK	(S_{Ox})-**26**	*i*-PrOH	KO*t*-Bu	100	38	*R*
40	PBK	(S_{Ox})-**27**	*i*-PrOH	KO*t*-Bu	100	45	*R*

[a] Reaction conditions: 41.67 μmol of substrate in 500 μL of solvent, 1.67 μmol of catalyst precursor (S/C = 25:1); $p(H_2)$ 25 bar, *T* 25 °C, reaction time 16 h. [b] Determined by ACP: GC, Supelco ChiralDex 110; 4-Me-ACP: HPLC, Daicel Chiralcel OB-H; PBK: HPLC, Daicel Chiralcel OD-H. [c] ACP: GC of authentic sample; 4-Me-ACP: HPLC (ref 35); PBK: HPLC of authentic sample.

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As one might expect, the product enantioselectivity depends strongly on the ligand substitution pattern as well as on the relative configuration. Ligands **17**, **18**, and **19** differ only in their oxazoline unit in that the oxazoline unit of ligand **17** is unsubstituted, whereas ligands **18** bear an isopropyl and ligands **19** a phenyl group at the oxazoline position 4. For each type of ligand (**18** and **19**) two diastereomers with either an *R* or *S* configuration at the oxazoline carbon 4 were tested [e.g., (4*R*,1′*R*,R_{Fc})-**18** and (4*S*,1′*R*,R_{Fc})-**18**].

With respect to the ligand substitution pattern and relative configuration, the results obtained in the hydrogenation test reactions show highly consistent trends. For all three substrates tested the highest enantioselectivities were obtained with the isopropyl-substituted ligand (4*R*,1′*R*,R_{Fc})-**18** with an *R* configuration at the oxazoline unit (entries 2, 17, 37). The phenyl-substituted ligand (4*R*,1′*R*,R_{Fc})-**19**, which also has an *R* configuration at the oxazoline unit, gave identical conversions, and in this case the product enantiomeric excess either was identical (4-Me-ACP, entries 17 and 18) or only dropped to a very small extent (e.g., 99% versus 98% ee; entries 2 and 3). However, the corresponding *S*-configured ligands (4*S*,1′*R*,R_{Fc})-**18** and (4*S*,1′*R*,R_{Fc})-**19** led not only to a significant drop in the product enantiomeric excess but also to a change in the product absolute configuration as compared to ligands with an *R* configuration (e.g., entries 2 and 3 versus 4 and 5; 17/18 versus 19/20; 37/38 versus 39/40). Surprisingly, on using acetophenone as the substrate, the unsubstituted oxazoline ligand (*R*,R_{Fc})-**17** also gave excellent results (99% conversion and 95% ee; entry 1).

As mentioned above, when ligands with *R* configuration at the oxazoline unit and *R* configuration at ferrocene were used [e.g., ligand (4*R*,1′*R*,R_{Fc})-**18** in the form of complex (R_{Ox})-**26**], all three substrates (ACP, 4-Me-ACP, and PBK) were transformed into product alcohols with an *S* absolute configuration (Table 3). The same dependence of ligand and product configuration was reported for the original FOXAP ligands (Chart 1).[8b] For example, when acetophenone was hydrogenated under comparable conditions with the use of complex [$RuCl_2(PPh_3)$-((*S*,S_{Fc})-**A**)] [ligand **A**: *S* configuration at the oxazoline unit and *S* configuration at ferrocene], a product with an *R* absolute configuration was obtained. These observations suggest for the hydrogenation of acetophenone and similar substrates that for both ligands of type **A** and ligands of type **18** the combination of *S* configuration at the oxazoline unit and *S* configuration at ferrocene induces an *R* absolute configuration of the product.

As already pointed out, changing the configuration of ligands **18** and **19** at the oxazoline unit from *R* to *S* while leaving the *R* ferrocene configuration identical [e.g., (4*R*,1′*R*,R_{Fc})-**18** → (4*S*,1′*R*,R_{Fc})-**18**; complexes (R_{Ox})-**26** → (S_{Ox})-**26**, Table 3, entries 2/4] leads to a change of product configuration from *S* to *R*. A similar behavior has been described for FOXAP ligand (*S*,S_{Fc})-**B** and its diastereomer (*S*,R_{Fc})-**B** (Chart 1).[7i] In the iridium-catalyzed enantioselective hydrogenation of 2-methylquinoline both diastereomers of **B** led to product of the same absolute configuration. As a consequence, like for ligands **18** and **19**, a change of the oxazoline configuration of ligand **B** [(*S*,S_{Fc})-**B** → (*R*,S_{Fc})-**B**] results in a change of product configuration. It is obvious that with respect to enantioselective induction in the hydrogenation of acetophenone and similar substrates FOXAP ligands and our newly developed analogues act in a highly comparable manner.

In summary, for all three substrates tested, reaction conditions could be identified that gave products in high conversion and excellent enantiomeric excess [ACP: 99% ee (entry 2), 4-Me-ACP: 97% ee (entry 17), PBK: 99% ee (entry 37)]. In all cases the highest enantioselectivities were obtained with the isopropyl-substituted ligand (4*R*,1′*R*,R_{Fc})-**18**. Replacement of the isopropyl with a phenyl substituent [(4*R*,1′*R*,R_{Fc})-**19**] resulted in either the same or only slightly lower product enantiomeric excess, while the use of ligands with an *S*-configured oxazoline unit led not only to a significant drop in the product enantiomeric excess but also to a change in the product absolute configuration. It is worth mentioning that a change in the oxazoline substituent from isopropyl to phenyl resulted in less marked changes in the hydrogenation results than a change in the absolute configuration at the oxazoline carbon 4.

SUMMARY

A very general and highly modular synthesis of ferrocenyl oxazolines, all of which are based on a ferrocenylethyl backbone, has been developed. Starting from *N*,*N*-dimethylaminoethyl ferrocene (Ugi's amine) differently substituted ferrocenyloxazolines were built up in a three-step sequence. After quaternization of the dimethylamino nitrogen the former dimethylamino group could be replaced by a variety of nucleophiles bearing amino, pyrazolyl, or phosphino substituents. The synthetic route not only allows the easy variation of the type of side-chain substituents but also provides easy access to differently substituted oxazoline units. Three palladium and three ruthenium complexes of representative amino-, pyrazolyl-, and phosphino-substituted ligands were studied by X-ray diffraction. A comparison of the molecular structures of palladium dichloride complexes of diastereomeric phosphinooxazoline ligands [(4*S*,1′*R*,R_{Fc})-**19** and (4*R*,1′*R*,R_{Fc})-**19**] revealed that changing the configuration at the oxazoline unit at position 4 leads to significant overall changes of the complex geometry in the solid state. In the ruthenium arene complexes, besides the position of the oxazoline substituent, such gross overall changes were not observed.

Five-coordinate, neutral Ru(II) complexes [$RuCl_2(PPh_3)(L)$] of five phosphineoxazoline ligands were prepared and tested using a high-throughput screening system in the hydrogenation of three ketones. Three ligands delivered products with quantitative conversion and with excellent enantiomeric excess of 97−99% ee. The product enantiomeric excess and the product absolute configuration were found to be highly dependent on the relative configuration of the ligands used.

At present applications of the newly developed ligands in ruthenium-catalyzed transfer hydrogenation and hydrogenation of ketones are being explored.

ASSOCIATED CONTENT

Supporting Information. Text giving full experimental descriptions and spectroscopic data for all newly synthesized ligands and complexes. Crystallographic and geometric data for three palladium and three ruthenium complexes of the type [$PdCl_2(L)$] and [$RuCl(p\text{-cymene})(L)]PF_6$, respectively, 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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