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New developments in enantioselective hydrogenation

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Abstract. A broad variety of atropisomeric biphenyl diphosphines have been synthesized via optically active 6,6'-dimethoxybiphenyl-2,2'-diyl-bis(diphenyl phosphonates), -bis(phosphonic dichlorides), -bis(phosphonous dichlorides) and -bis(primary diphosphines). The usefulness of diphosphine variety in enantioselective hydrogenation was demonstrated by application to substrates of unconventional and unprecedented type such as an α-pyridyl ketone, γ-keto olefins, an α-pyrone and an enol ether of a β-keto lactam. Enantioselectivities and rates in these hydrogenations were markedly influenced by the electronic and steric properties of the diphosphine ligands. Of particular utility were the biphenyl diphosphines with α-furyl and 3,5-di-*t*-butylphenyl groups on the P atoms. A synthesis of a tetrasulfonated biphenyl diphosphine carrying the sulfonato substituents in the *para* position of the P-phenyl rings has also been developed. Ruthenium catalysts derived from this ligand proved highly efficient for several enantioselective hydrogenations in aqueous systems.

1. Introduction

The enantioselective hydrogenation of prochiral C=C, C=O and C=N double bonds constitutes a powerful, technically and economically viable tool to establish chirality at stereogenic tertiary carbon atoms (1). In the application of such methodology to the synthesis of biologically active molecules, process research chemists in industry are facing, as a rule, the task of developing processes for substrates of precisely defined structure. Moreover, these substrates quite often do not belong to the standard structural classes known to be amenable to enantioselective hydrogenation. In such a situation, and in view of the increasingly limited development time frames, it is important to have available broad libraries of chiral ligands and catalysts for rapid catalyst screening and thus efficient process development. Therefore, development of chemistry which allows the rapid generation of a diversity of sterically and electronically differing diphosphine ligand analogues is highly desirable from an industrial viewpoint. Such chemistry will be presented, and the usefulness of ligand diversity will be demonstrated with the development of successful enantioselective hydrogenation processes for substrates of unprecedented structural type. Moreover, an application to the rational synthesis of a new tetrasulfonated diphosphine ligand and its use in enantioselective hydrogenations in water will be reported.

2. Generation of diphosphine diversity in the atropisomeric biphenyl series

Atropisomeric diphosphines of the BINAP type have found widespread use in metal-catalyzed reactions due to their spectacular ability to induce asymmetry (2). In particular, BINAP type diphosphines belong to the most useful ligands for enantioselective hydrogenations. Therefore, the generation of diphosphine diversity in this class appeared particularly attractive. Synthetically, BINAP **1a** and analogues thereof are accessible via reaction of phosphinous or phosphinic acid derivatives (e.g. R_2PCl or $R_2P(O)Cl$) with a dimetalated binaphthyl species derived from a binaphthalene dihalide (3), or by Ni-catalyzed reaction of a secondary phosphine with binaphthol ditriflate (4), the resolution being undertaken either at the diamino or dihydroxy precursor stage or at the bis(phosphine oxide) stage (*Fig. 1*). Similar strategies have been applied by us and others for the synthesis of atropisomeric diphosphines in the biphenyl series (BIPHEMP **2a** (5), BICHEP **2b** (6), MeOBIPHEP **3a** (7)). In the case of **3a**, phosphinoylation was performed at the monoaryl stage and the biphenyl system subsequently built up via an *ortho*-lithiation/iodination Ullmann reaction protocol (6).

With respect to the rapid synthesis of a multitude of analogues of such ligands, the established synthetic routes have some disadvantages. Specifically, the phosphinous or phosphinic acid derivatives or the secondary phosphines have to be synthesized separately for each case (typically starting from a phosphorus trihalide) which adds steps and which can be difficult for more complex structures. Moreover, in the case of the phosphine oxide routes, individual resolution procedures have to be elaborated for each new derivative.

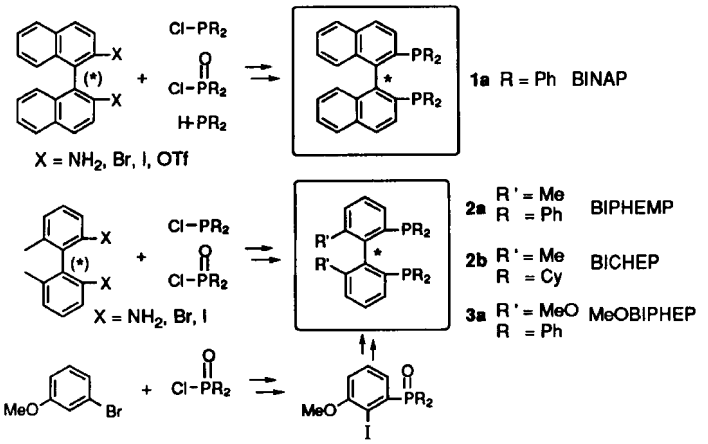


Fig. 1. Established routes to atropisomeric diphosphines

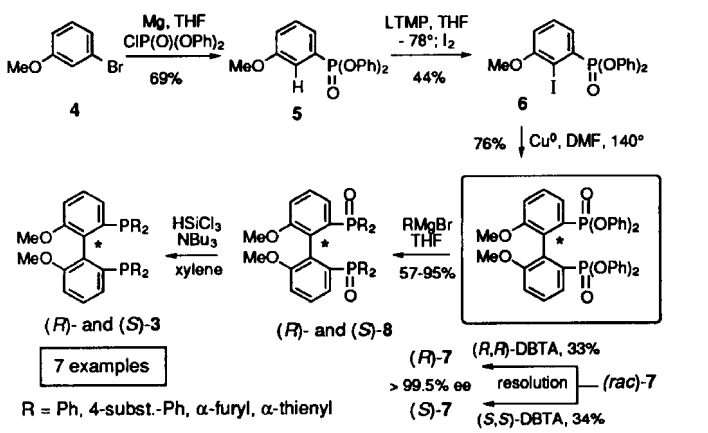


Fig. 2. Bis(diphenyl phosphonate) route

Complementary chemistry has now been developed which avoids the requisite separate formation of the phosphinic or phosphinous moieties and the individual resolutions. It is based on the generation of optically active 6,6'-dimethoxybiphenyl-2,2'-diyl-bis(phosphonic or phosphonous acid) derivatives or -bis(primary phosphines) as pivotal intermediates. These intermediates allow the incorporation of the R substituents of the PR_2 moieties at a very late stage, i.e. in the penultimate or final step (8). In our first approach (*Fig. 2*), the bis(diphenyl phosphonate) (*rac*)-**7** was synthesized via an *ortho*-lithiation/iodination Ullmann reaction sequence (cf. 7). Resolution of (*rac*)-**7** was readily achieved with dibenzoyltartaric acid (DBTA) via the (*R*)-**7**/(*R,R*)-DBTA and the (*S*)-**7**/(*S,S*)-DBTA complexes. Thus *rac*-**7** displays the same resolution behaviour as the bis(phosphine oxide) MeOBIPHEPO (7). Reaction of (*R*)- or (*S*)-**7** with Grignard reagents afforded bis(phosphine oxides) (*R*)- and (*S*)-**8** in good yields. Trichlorosilane reduction then produced the diphosphines (*R*)- and (*S*)-**3**. In this way, MeOBIPHEP **3a** itself and various analogues carrying 4-monosubstituted phenyl, α-furyl or α-thienyl groups could be prepared. Biphenyl stereochemistry was completely retained in these two-step conversions. From a practical point of view however, the moderate yields in the three-step synthesis of (*rac*)-**7** rendered this route less useful for larger-scale preparations. In addition, the route was not suitable for the synthesis of alkyl MeOBIPHEP analogues.

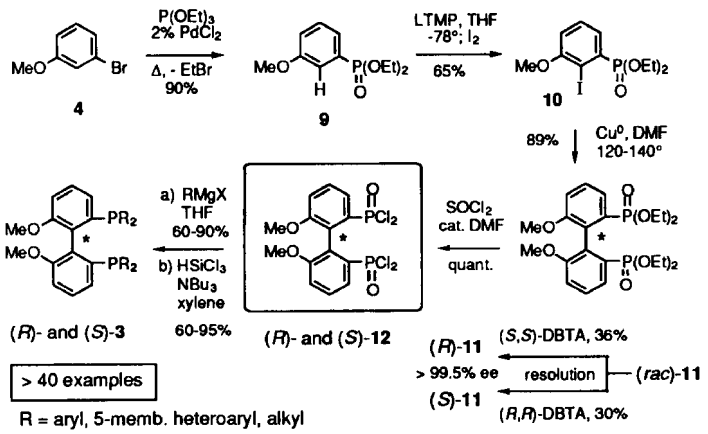


Fig. 3. Bis(phosphonic dichloride) route

A superior solution which eluded the shortcomings of the bis(diphenyl phosphonate) route was found with the bis(phosphonic dichloride) route shown in *Fig. 3*. Synthesis and resolution of the racemic bis(diethyl phosphonate) (*rac*)-**11** proceeds exceedingly well. Surprisingly, the stereochemical mode of association with DBTA is reverse to the bis(diphenyl phosphonate) series (shown by X-ray analysis of the (*S*)-**11**/(*R,R*)-DBTA complex). The bis(diethyl phosphonates) **11** are not reactive enough for complete tetrasubstitution with Grignard reagents. However, the bis(phosphonic dichlorides) **12**, which are readily obtained from **11** by thionyl chloride treatment (9), underwent smooth tetrasubstitution with a wide variety of 3- and 4-monosubstituted, 3,5-disubstituted, and 3,4,5-trisubstituted phenyl Grignard reagents, as well as with 5-membered heteroaryl Grignard reagents and with primary and secondary alkyl Grignard reagents. Even *ortho*-substituted phenyl Grignard reagents, i.e. dibenzothiophen-4-ylmagnesium bromide and *ortho*-anisylmagnesium chloride reacted satisfactorily. All the bis(phosphine oxides) thus obtained with the exception of electronically deactivated compounds and the *ortho*-anisyl compound were readily reduced to the diphosphines **3**. Again, substitution and reduction proceeded with complete retention of the biphenyl stereochemistry. Unoptimized yields in each of the steps typically ranged from 60 to 95%. By this route over 40 MeOBIPHEP analogues were prepared.

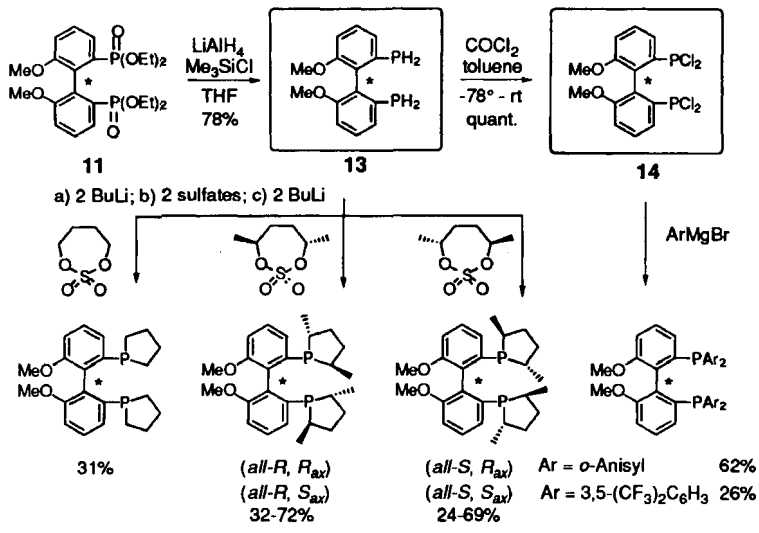


Fig. 4. Bis(primary phosphine) and (phosphonous dichloride) routes

The order of substitution and reduction could also be reversed as shown in *Fig. 4*. Thus, reduction of the optically active bis(diethyl phosphonates) **11** with $LiAlH_4/Me_3SiCl$ (8b) afforded the surprisingly stable bis(primary phosphines) **13** which were converted into the bis(phosphonous dichlorides) **14** with complete retention of the biphenyl stereochemistry. Substitution with Grignard reagents then provided directly the diphosphines. This method is particularly useful for diphosphines which are difficult or impossible to obtain by reduction of bis(phosphine oxides), e.g. the *o*-anisyl MeOBIPHEP analogue. The bis(primary phosphines) **13** themselves constitute also valuable optically active intermediates for the preparation of diphosphines via alkylation strategies. Thus, five phospholane MeOBIPHEP analogues were prepared starting from **13** by application of the cyclic sulfate methodology of Burk (10).

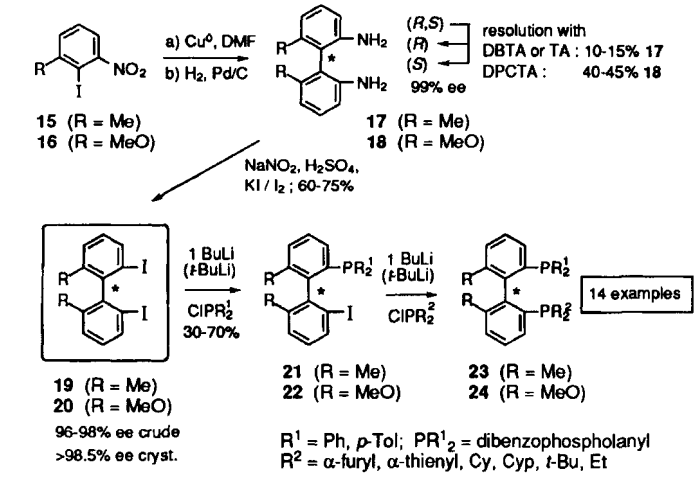


Fig. 5. Diiodide route to unsymmetrical biphenyl diphosphines

Finally, the synthesis of unsymmetrical biphenyl diphosphines starting from optically active diiodides **19** and **20** was addressed (*Fig. 5*), applying the sequential monolithiation/monophosphination principle demonstrated previously by Murdoch (3c) in the binaphthyl and by Achiwa (5d) in the racemic biphenyl series. Instrumental to our approach proved an efficient resolution of the diamine **18** using O,O'-di(phenylcarbamoyl)tartaric acid (DPCTA) as resolving agent (11) and the development of an improved procedure for the conversion of the diamines **17** and **18** into the diiodides **19** and **20** (12). A number of unsymmetrical diphosphine ligands **23** and **24** thus were prepared. Obviously, strategies involving phosphonate chemistry can also be envisioned for the synthesis of such ligands.

Overall, over 60 new ligands have been prepared in the biphenyl series, many of them in both enantiomeric series and in larger amounts (13). The usefulness of such ligand diversity will now be demonstrated with some enantioselective hydrogenation examples from recent process research projects.

3. Enantioselective hydrogenation of new substrate types

Mefloquine (Lariam®) (*rac* -**26**), an antimalarial drug, is manufactured by a route which involves in the last step a heterogeneous hydrogenation of the α-pyridyl ketone **25** (14) (*Fig. 6*). We have investigated the enantioselective hydrogenation of **25** as an entry into the optically active series. So far, enantioselective metal-catalyzed hydrogenations of α-pyridyl ketones have not been described (15).

Neutral Rh(I) complexes containing atropisomeric diphosphine ligands emerged as the most promising catalysts for the hydrogenation of **25** to the alcohol **27** (*Figs. 6 and 7*). The parent diphosphines BINAP, BIPHEMP and MeOBIPHEP afforded fair ee's (61-71%), but reactions were slow. Electron-releasing substituents in the 4- and/or in the 3,5-positions of the P-phenyl groups markedly increased both the rate and the enantioselectivity of the hydrogenation. Electron-withdrawing substituents led to complete loss of hydrogenation activity. Similar electronic effects had been observed previously in dehydroamino acid hydrogenations (16). Further enhancement of the P-basicity by introduction of P-alkyl groups led to further improvements (17). The optimal ligand was an unsymmetrical one, containing one dicyclohexylphosphino

and one diphenylphosphino moiety, which afforded 92% ee. The process with this ligand was scrutinized by variation of the halide ligand, solvent, concentration, pressure and temperature. In the final process a molar substrate/catalyst ratio (S/C) of 6400 could be realized, corresponding to an average turnover frequency (TOF) (18) of 320 h^{-1}. Crystallization of (*R*)- or (*S*)-**27** to optical purity and subsequent heterogeneous hydrogenation of the pyridine nucleus allowed the preparation of both enantiomers of **26** (19). The same catalyst afforded ee's of 64% and 12% in the hydrogenation of 2- and 3-benzoylpyridine, respectively. The hydrogenation with this catalyst does not appear to be general for 2-acylpyridines, since 2-acetylpyridine was reduced to the alcohol with 15% ee only.

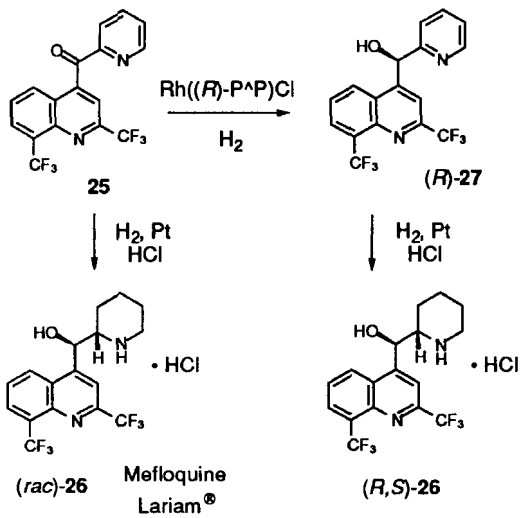
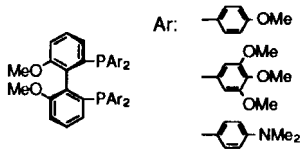
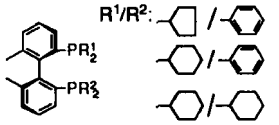


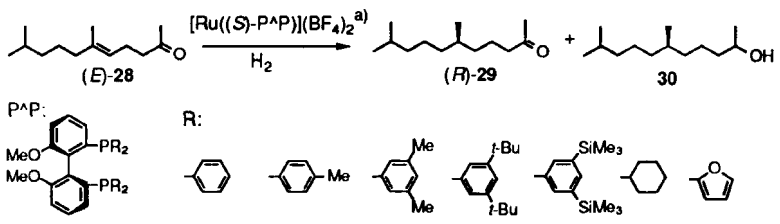
Fig. 6. Synthesis of (rac)- and (R,S)-Mefloquine

(P^P)-Ligand		% ee	% conv. (1 h)
(*R*)-BINAP (*R*-**1a**)		64	3
(*R*)-BIPHEMP (*R*-**2a**)		61	5
(*R*)-MeOBIPHEP (*R*-**3a**)		71	10
	Ar: OMe	70	35
	3,5-(OMe)2	85	44
	3,4,5-(OMe)3	68	76
	R^1/R^2: Ph/Ph	68	63
	1-Naphthyl/Ph	92	86
	1-Naphthyl/1-Naphthyl	78	75

S/C 200, toluene, c = 1%, 60°C, 60 bar.

Fig. 7. Ligand effects in the enantioselective hydrogenation of 25

The Ru-BINAP catalyzed enantioselective hydrogenation of allylic alcohols (e.g. geraniol, nerol and tetrahydrofarnesol) (20) constituted a veritable breakthrough in view of the development of a synthesis of (*R,R,R*)-α-tocopherol and the preparation of terpenoid fragrance compounds. We have investigated the enantioselective hydrogenation of **dihydrogeranylacetone (28)**, which is readily accessible from intermediates of our current vitamin chemistry, as an alternative entry into the (*R,R,R*)-α-tocopherol side chain chemistry. Such a hydrogenation would require chemoselective reduction of the trisubstituted olefinic double bond in the presence of the C=O double bond. Precedents for the hydrogenation of a trisubstituted olefin with an oxo or oxy substituent in the γ-position are not known. In particular, it has been stated that bishomogeraniol, having the same 1,4-relationship between C=C and C-O bond, was inert under Ru-BINAP catalysis (20). On the other hand, ketones carrying oxygen or amino functionalities in the γ-position have been successfully hydrogenated (21).



% **29** b)	97	80	69	33	35	3	**98**
% **30**	3	20	28	65	65	96	2
% ee (*R*)-**29**	77 c)	75	54	89	**91**	73	**91**

a) S/C 200-400, MeOH/CH_2Cl_2, c = 10%, rt, 35 bar, 18 h, conv. > 90%.
b) Ketone **29** and ca. 10-20% of dimethyl acetal.
c) (*S*)-BINAP 91 / 5; 64% ee.

Fig. 8. Dihydrogeranylacetone hydrogenation: Chemo- and enantioselectivity

Hydrogenation of (*E*)-**28** with bis(cationic) Ru-(*S*)-BINAP and (*S*)-MeOBIPHEP catalysts afforded ketone (*R*)-**29** with high chemoselectivitiy but with ee's of only 64 and 77%, respectively (*Fig. 8*). Substitution of the MeOBIPHEP P-phenyl rings with electron-releasing groups enhanced the rates and led to concomitant reduction of the C=O group to give the alcohol **30**. In the case of the 3,5-di-*t*-butyl and 3,5-bis(trimethylsilyl) analogues ee's of 89 and 91% at C(6) were achieved, but the major product was alcohol **30**. The cyclohexyl-MeOBIPHEP ligand produced even more overreduction. Eventually, the MeOBIPHEP analogue containing four α-furyl groups as P substituents, the first member of a chiral diphosphine carrying 5-membered heterocyclic substituents (13b), proved superior; hydrogenation of the olefinic double bond proceeded with high chemo- and high enantioselectivity. The ee of 91% could be

further improved to 94% using an unsymmetrical ligand containing one di-(α-furyl)phosphino and one diphenylphosphino moiety (22).

Hydrogenation of (*Z*)-**28** afforded the same ee's but with the opposite sense of asymmetry (*Fig. 9*). The hydrogenation procedure was also successfully applied to the isoprenoid homologues (*R,E*)-**31** and (*R,Z*)-**31.** Enantioselective hydrogenations of the related substrates geranylacetone (*E*)-**32**, the dimethyl acetal (*E*)-**33** and the alcohol (*E, rac*)-**34** proceeded in a similar way as the hydrogenation of (*E*)-**28.** In the case of geranylacetone (*E*)-**32**, only little preference for the hydrogenation of the central double bond was observed. Direction and magnitude of the asymmetric inductions in the hydrogenations of substrates **28** and **31-34** imply that the Ru catalyst differentiates the C(5) enantioface of the double bond, the (*S*)-catalyst favouring the *si* face at C(5). Thus the same stereochemical relationships are operative as those in the geraniol and nerol hydrogenations (20) (*Fig. 10*). Asymmetric inductions in these hydrogenations were determined by GC diastereoisomer analysis of the ketone derived diisopropyl L-tartrate acetals (23).

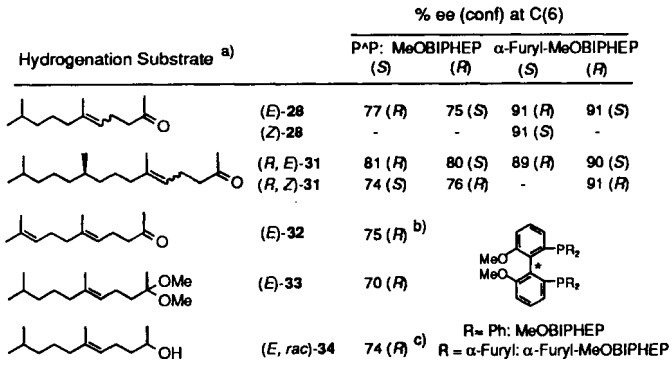


Fig. 9. Enantioselective hydrogenation of γ-oxo and γ-oxy olefins

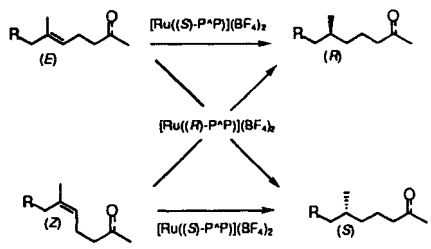


Fig. 10. Stereochemical relationships

The reasons for the superiority of the α-furyl containing phosphines in these hydrogenations are unclear at the moment. An X-ray structure determination of the Ru diacetato complex of (*R*)-α-furyl-MeOBIPHEP did reveal only small differences in comparison to the corresponding phenyl analogue. Subtle steric and perhaps also electronic effects may play a role. It is noteworthy, that β-furyl and α-thienyl containing ligands were less effective.

Tetrahydrolipstatin (38) (*Fig. 11*), a potent inhibitor of pancreatic lipase (24), is currently under clinical evaluation as an antiobesity drug. Synthetically, tetrahydrolipstatin is accessible via the δ-lactone (*S,S,R*)-**37**, which in turn is obtained by heterogeneous hydrogenation of dihydropyrone (*R*)-**36** (25). An asymmetric hydrogenation of prochiral α-pyrone **35** to either (*R*)-**36** or (*S,S,R*)-**37** would provide an attractive entry into the optically active series.

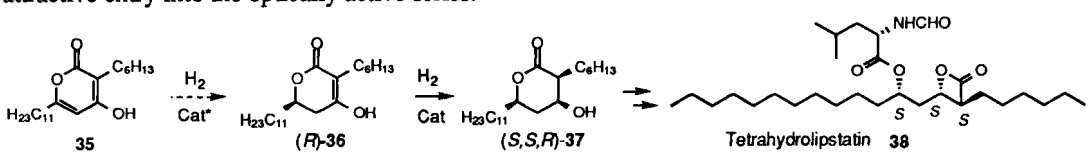
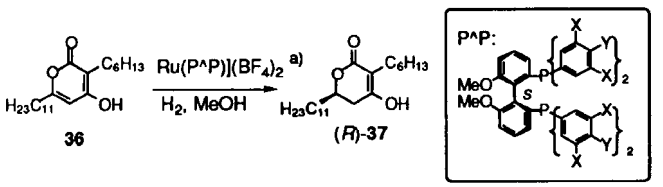


Fig. 11. Pyrone hydrogenation approach to tetrahydrolipstatin

Heterogeneous asymmetric reduction of **35** with the Harada/Izumi catalyst Raney-Ni/tartaric acid/NaBr (26) was slow and afforded (*S,S,R*)-**37** in only 17% ee. Bis(cationic) Ru complexes of MeOBIPHEP diphosphine ligands, however, allowed a remarkably selective hydrogenation of the trisubstituted double bond of **35** to afford dihydropyrone **36** (27). Again, for achieving a high ee and particularly for achieving a reasonable TOF, electron-releasing substituents on the P-phenyl rings were required (*Fig. 12*). Among the best ligands in terms of activity was the 3,5-dimethyl-4-dimethylamino MeOBIPHEP analogue, while one of the most enantioselective ones was the 3,5-di-*t*-butyl MeOBIPHEP analogue, which afforded 93% ee in methanolic solvent. In an optimized process, hydrogenation of **35** with Ru((*S*)-di-*t*-Bu-MeOBIPHEP)$(BF_4)_2$ in isopropanol afforded (*R*)-**36** of 96% ee in 97% yield. The hydrogenation of **35** represents the first example of a regio- and highly enantioselective reduction of an α-pyrone and, in a more general sense, of an endocyclic enol ester type double bond. Only one example of an endocyclic enol ester hydrogenation, which afforded a low 20% ee, has been reported so far (28). Enol lactones with exocyclic methylene moieties (28) and acyclic enol acetates (10) on the other hand are known to undergo enantioselective hydrogenation with high enantioselectivity.



X	H	H	Me	*t*-Bu	Me_3Si	Me	OMe	*t*-Bu
Y	H	Me	H	H	H	NMe_2	OMe	OMe
% conv.	<1 b)	3 b)	10	84	54	97	93	54
% ee	nd	86	86	93	91	89	90	94

a) S/C 1000, c = 15%, 60°, 60 bar, 20 h; b) S/C 25-100.

Fig. 12. Pyrone hydrogenation: Ligand effects

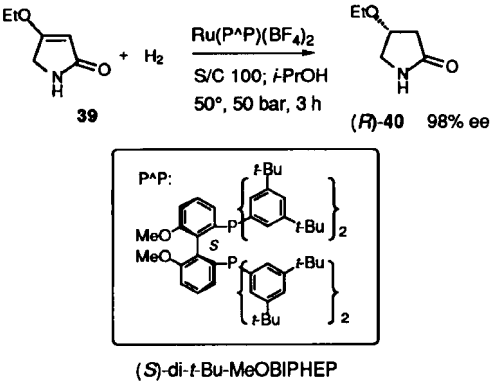


Fig. 13. Pyrrolinone hydrogenation

Interestingly, the Ru((*S*)-di-*t*-Bu-MeOBIPHEP)$(BF_4)_2$ catalyst proved very efficient also in the enantioselective hydrogenation of an enol ether of a β-keto lactam. Thus 3-ethoxypyrrolinone **39** was hydrogenated with this catalyst in alcoholic solvents to (*R*)-**40** with ee's of 92-98%, isopropanol again being the optimal solvent (*Fig. 13*). Surprisingly, the corresponding N-benzyl derivative was a poor substrate. The enantioselective hydrogenation of enol ethers of this type has no precedent in the literature. In both the α-pyrone and the enol ether cases the Ru((*S*)-di-*t*-Bu-MeOBIPHEP) catalyst performs the hydrogenation from the *si*-face of the sp^2-C(H) atom.

4. Water solubilization of an atropisomeric hydrogenation catalyst

The water solubilization of atropisomeric diphosphine ligands represents a challenging but potentially very rewarding endeavour in view of the broad applicability of catalysts derived from these ligands in asymmetric synthesis. In fact, sulfonation approaches for the synthesis of water-soluble BINAP ligands have been reported. The Takasago group has described the preparation of 5,5'-disulfonato-BINAP (29) by sulfonation of BINAP, and its application in the Ru-catalyzed hydrogenation of ethyl acetoacetate in water (91% ee). Wan & Davis (30) have reported the sulfonation of BINAP to produce mainly a tetrasulfonated BINAP ligand having sulfonato groups in the *meta* positions of the four P-phenyl rings. They also reported the application of this ligand in the Rh-catalyzed hydrogenation of 2-acetamido acrylic acid in water (up to 70% ee) and in the Ru-catalyzed triphase hydrogenation of didehydro-Naproxen (70-96% ee). The sulfonation of (racemic) 2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthalene and applications in propylene hydroformylation have also been described (31).

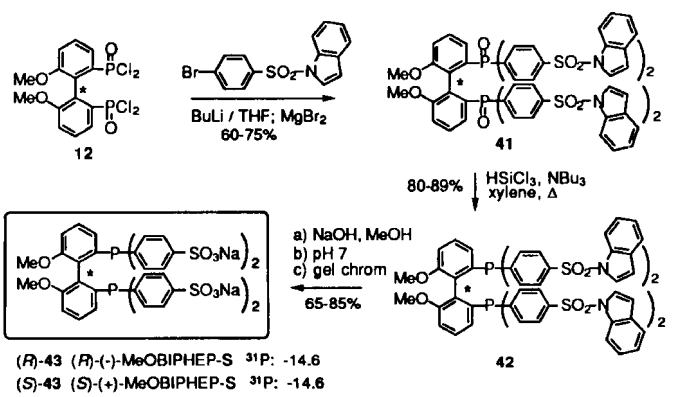
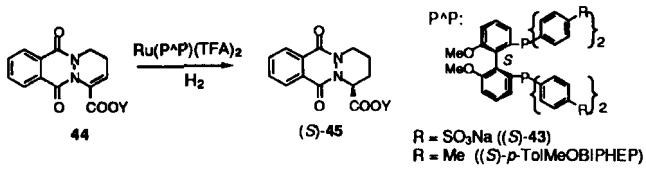


Fig. 14. Synthesis of the water-soluble MeOBIPHEP-S diphosphine

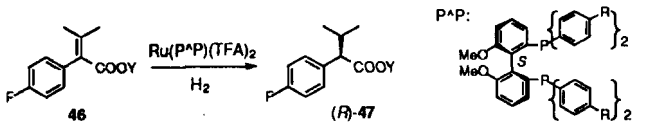
Here we disclose the synthesis of a new, tetrasulfonated biphenyl diphosphine ligand, which carries sulfonato groups in the *para* position of each of the four P-phenyl groups, i.e. of the ligand MeOBIPHEP-S **43** (*Fig. 14*) (32). The *para* position for attachment of the sulfonato group was chosen in order to minimize possible steric interactions of the sulfonato group with the inner ligand sphere of a co-ordinated metal, and thus to retain the enantioselectivity of the non-sulfonated catalyst. Catalysts derived from diphosphines with sulfonato groups in the *meta* positions often show lower enantioselectivities in hydrogenations in aqueous systems as compared to their parent systems. In addition, the degree of sulfonation may also influence the enantioselectivity of the catalyst (33).

The synthesis of the MeOBIPHEP-S diphosphines **43** was accomplished in ca. 45% overall yield starting from bis(phosphonic dichlorides) **12** via the Grignard substitution/reduction protocol shown in *Fig. 14*. The sulfonato group was masked during the synthesis as a sulfonamide. The indolylsulfonyl group was chosen due to its stability under the conditions of the Grignard reaction and the phosphine oxide reduction step, and because of its ready hydrolysis under mild alkaline conditions. To our knowledge, the diphosphines **43** are the first examples of optically active diphosphines with *para*-sulfonated phenyl groups.



Y	(P^P)-Ligand R	S/C	solvent	p [bar]	temp [°C]	ee [%]	TOF [h⁻¹]
NEt_3H	SO_3Na	10'000	H_2O	40	60	> 99	480
Na	SO_3Na	2'000	H_2O	40	60	98.5	48
NEt_3H	Me	40'000	MeOH	40	100	95-97	13'000
NEt_3H	Me	20'000	MeOH / H_2O 9:1	7	60	> 99	830

Fig. 15. Hydrogenation of unsaturated acid 44



Y	(P^P)-Ligand R	S/C	solvent	p [bar]	temp [°C]	ee [%]	TOF [h⁻¹]
NEt_3H	SO_3Na	1'000	H_2O	60	20	84	48
Na	SO_3Na	1'000	H_2O	60	20	80	48
NEt_3H	H [a]	1'000	MeOH	60	20	88	40
H	H	1'000	MeOH	60	20	84 [b]	42

a) Catalyst: Ru((*S*)-BIPHEMP)(OAc)$_2$. b) 96% ee at 180 bar.

Fig. 16. Hydrogenation of unsaturated acid 46

Rh(I) and Ru(II) complexes derived from MeOBIPHEP-S were synthesized in the usual way (34). In exploratory hydrogenation experiments with standard substrates, **43** showed promising results. The Ru-catalyzed hydrogenation of methyl acetoacetate in methanol afforded 93% ee. Geraniol, under non-optimized conditions, afforded citronellol of 98% ee in an ethyl acetate/water two-phase system.

In two applications, both in the context of the synthesis of pharmaceutical intermediates, the potential of the sulfonated ligand became evident. Thus the sodium or triethylammonium salts of the unsaturated acids **44** (*Fig. 15*) and **46** (*Fig. 16*) could be hydrogenated in water with high S/C ratios (1000 to 10'000) and with high ee's (98.5-99% and 80-84%, respectively). These enantioselectivities are the same as those obtained in hydrogenations in methanol with the non-sulfonated ligands. The first example is particularly intriguing with the very high S/C ratio of 10'000; this corresponds to an average TOF of ca. 480 h^{-1}. In the case of substrate **46**, the catalyst TOF in water is the same as that of the non-sulfonated catalyst in methanol (42-48 h^{-1}). Thus, the diphosphine **43** shows excellent potential for enantioselective hydrogenations in aqueous systems. It also provides a tool for in-depth studies of the influence of the sulfonation pattern on catalyst enantioselectivity and activity.

5. Conclusions

The successful hydrogenations described above suggest that the width of substrate types amenable to enantioselective hydrogenation may be much larger than previously thought. In particular, steric and electronic tuning of the diphosphine ligand proved to be a highly successful means to achieve excellent catalyst performance also in the hydrogenation of unconventional substrates. In this respect, the establishment of ligand diversity, as demonstrated here for the biphenyl series, has truly found its utility, and has proven instrumental for rapid enantioselective hydrogenation process research and development. The new synthetic methodology to generate ligand diversity has opened up also a novel entry into the field of water soluble catalysts.

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