Ligand Design

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ChenPhos: Highly Modular P-Stereogenic C_1-Symmetric Diphosphine Ligands for the Efficient Asymmetric Hydrogenation of α-Substituted Cinnamic Acids

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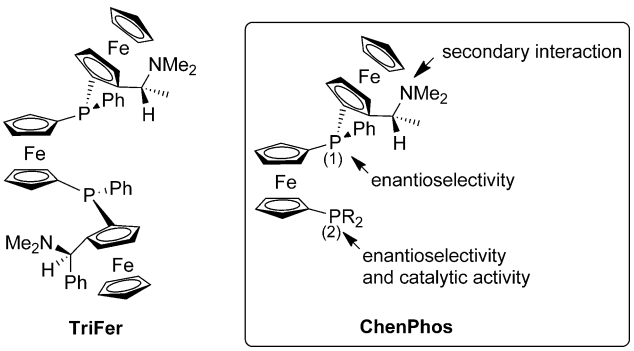
Over four decades, tremendous effort has been devoted to the design and synthesis of chiral phosphine ligands that can provide high enantioselectivity and high reactivity in asymmetric catalysis.[1] Since the discovery of the diop ligand by Kagan and Dang in 1971,[2] the concept of C_2 symmetry has been a very popular design motive for chiral diphosphine ligands (probably as a result of the huge success of ligands such as dipamp, binap, MeO-biphep, and Duphos, as well as the ease of synthesis).[3] Indeed, a large number of diphosphine ligands with C_2 symmetry have been developed for highly efficient asymmetric hydrogenation reactions of various olefins, ketones, and imines.[4] Despite impressive progress in this field, the design of structurally novel, readily accessible, operationally convenient, and efficient chiral phosphine ligands remains a formidable task. The complexity of most catalytic processes precludes a purely rational approach based on mechanistic and structural criteria. Therefore, most new chiral catalysts are still found empirically, with chance, intuition, and systematic screening all playing important roles. Even though, when the mechanism of a certain reaction, such as rhodium-catalyzed hydrogenation,[5] is well-established, at most the semirational design of new ligands is possible. General experience is that small structural alterations can lead to significant, unpredictable changes in catalysis. For this reason, ideally, a new ligand should be readily accessible through a synthetic route that allows the straightforward variation of structural and electronic features and optimization for a specific application.

Previously, we described the first C_2-symmetric diphosphine that combines carbon- and phosphorus-centered chirality and planar chirality: TriFer (Scheme 1). Although its high enantioselectivity in the asymmetric hydrogenation of α-substituted cinnamic acids was unprecedented,[6] the synthesis of TriFer was very difficult to scale up because reasonable diastereoselectivity was only possible under very strict conditions; the catalyst activity and productivity were still unsatisfactory, since complete conversion was only possible at a relatively low ratio of substrate to catalyst. Furthermore,



Scheme 1. Comparison of the TriFer and ChenPhos ligands.

the modularity of the TriFer ligand is restricted by the availability of dichlorophosphines. For practical applications in industry, not only very high enantioselectivity, but also the productivity (turnover number, TON) and activity (turnover frequency, TOF) of catalysts as well as the accessibility and modularity of ligands are also crucial issues.[7] Herein, we report a new, very simple and efficient synthesis of ferrocene-based P-stereogenic phosphines on the basis of thermal epimerization through pyramidal inversion as the key step, as well as a novel, readily accessible and highly modular family of C_1-symmetric P-chiral diphosphine ligands, ChenPhos[8] (Scheme 1), which show extremely high enantioselectivity, activity, and productivity for the rhodium-catalyzed asymmetric hydrogenation of α-substituted cinnamic acids.

ChenPhos was designed on the basis of various facts and hypotheses. According to the plausible mechanism of the asymmetric hydrogenation of α-substituted cinnamic acids under the catalysis of a TriFer–Rh complex,[6] we anticipated that one dimethylamino group may be enough for the secondary interaction between the catalyst and the substrate. A current trend in the design of chiral diphosphane ligands is the differentiation of the electronic and/or the steric properties of the phosphorus donors.[9] As pointed out by Achiwa and co-workers,[10] the intermediates in the catalytic cycle of the asymmetric hydrogenation are nonsymmetrical, and, consequently, the two phosphino groups interact with a metal-bound substrate in an electronically and sterically different manner. Indeed, the presence of nonequivalent phosphorus centers, in particular the replacement of one of the diphenylphosphine units in a C_2-symmetric diphosphine with a more electron rich dicyclohexylphosphanyl group, often results in improved catalyst activity and a significant but unpredictable change in enantioselectivity.[11,12] Our design of

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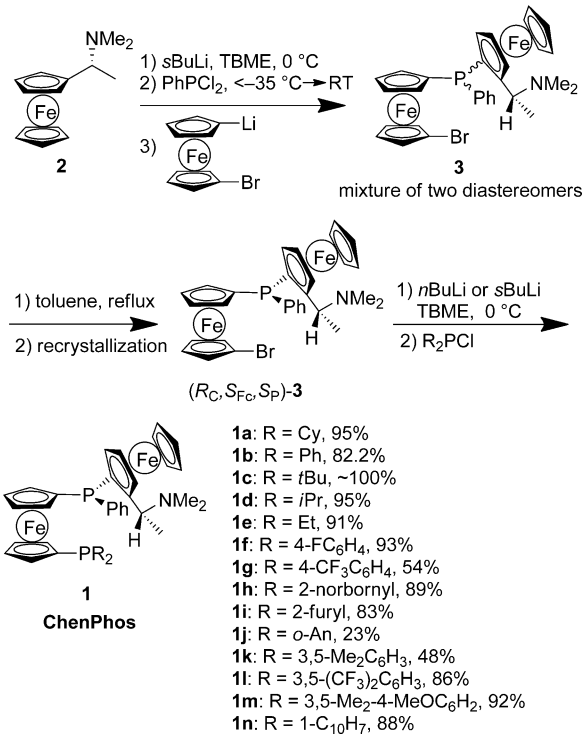
the highly modular ChenPhos ligands involves: 1) the 2-(1-*N*,*N*-dimethylaminoethyl)ferrocenyl group on P^1 for the secondary interaction between catalyst and substrate; 2) the stereogenic phosphorus center P^1 for high enantioselectivity; 3) the introduction of bulky and electron-rich R groups on P^2 for the enhancement of catalytic activity by the strengthened d–σ* interaction (acceleration of the oxidative addition of molecular hydrogen), and, possibly, enantioselectivity by the rigid chelation of rhodium with electron-deficient olefins. This modification greatly improves the modularity of the ligand and makes ChenPhos C_1-symmetric (Scheme 1).

We previously reported a very simple, highly diastereoselective strategy for building up ferrocene ligands with P-chiral phosphine group(s): the treatment of a dichlorophosphine first with a chiral lithiated ferrocene and then with a second organometallic reagent.[13] This straightforward method gives almost perfect diastereoselectivity with simple alkyl and aryl organometallic reagents. However, the diastereoselectivity was variable (often low) when the second organometallic reagent was derived from another ferrocene derivative, as in the synthesis of ChenPhos. Fortunately, we were able to develop another very simple and efficient synthesis of ferrocene-based P-chiral phosphines for the preparation of ChenPhos on the basis of thermal epimerization through pyramidal inversion as the key step.[14]

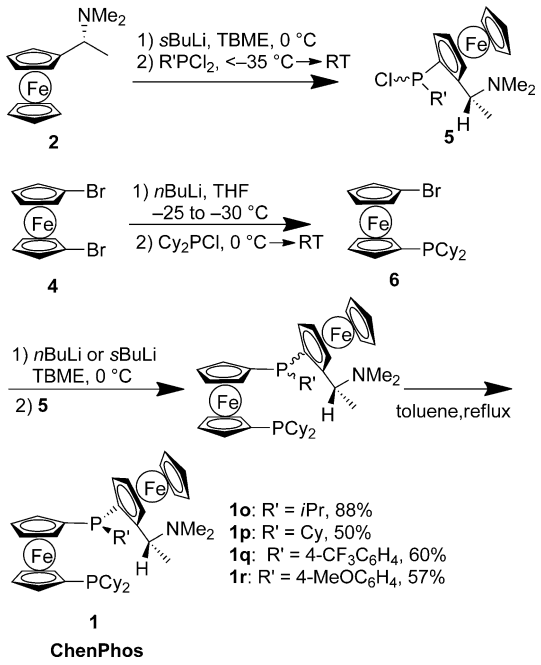
Two synthetic routes were investigated for the preparation of ChenPhos. In route 1, the chiral P^1 group, (R_C,S_{Fc},S_P)-1-[2-(1-*N*,*N*-dimethylaminoethyl)ferrocen-1-yl]phenylphosphanyl, was first introduced (Scheme 2). Thus, the Ugi amine (*R*)-**2** was lithiated with *s*BuLi (0 °C, 1.5 h) and then treated first with $PhPCl_2$ (> −35 °C, 10 min, then RT, 1.5 h) and then with



Scheme 2. Synthesis of ChenPhos (route 1). *o*-An = *o*-anisidyl, Cy = cyclohexyl, TBME = *tert*-butyl methyl ether.

1-lithio-1′-bromoferrocene, generated from 1,1′-dibromoferrocene by monolithiation with *n*BuLi in THF (between −25 and −30 °C, 3 h), to afford a mixture of (R_C,S_{Fc},S_P)-**3** and (R_C,S_{Fc},R_P)-**3**. A solution of the product mixture in toluene was heated at reflux for 4 h to promote epimerization. Fortunately, the thermodynamically more stable diastereomer was the desired intermediate (R_C,S_{Fc},S_P)-**3**, which could be isolated as a single diastereomer in 59% yield by recrystallization from EtOH. Lithiation of (R_C,S_{Fc},S_P)-**3**, followed by treatment with a diaryl or dialkyl chlorophosphine, R_2PCl, normally gave the desired ChenPhos ligands **1a**–**n** in high yield. ChenPhos **1a** was also prepared efficiently by lithiation of a mixture of (R_C,S_{Fc},S_P)-**3** and (R_C,S_{Fc},R_P)-**3**, treatment with Cy_2PCl, and then thermal epimerization.

In route 2, the achiral P^2 group, Cy_2P, was first introduced (Scheme 3). Thus, 1,1′-dibromoferrocene (**4**) was selectively monolithiated with *n*BuLi in THF (between −25 and −30 °C, 3 h) and treated with Cy_2PCl (0 °C, 10 min, then RT, 1.5 h) to



Scheme 3. Synthesis of ChenPhos (route 2).

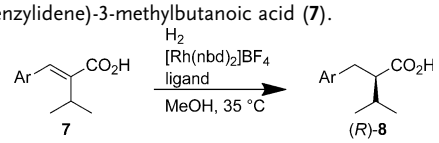
give **6** in 85% yield. Lithiation of **6**, followed by treatment with a monochlorophosphine **5**, which was prepared by lithiation of the Ugi amine (*R*)-**2** with *s*BuLi (0 °C, 1.5 h) and then treatment with an aryl or alkyl dichlorophosphine $R'PCl_2$ (< −35 °C, 10 min, then RT, 1.5 h), afforded ChenPhos as a mixture of two diastereomers. The desired ChenPhos ligands **1o**–**r** were obtained in high yield after thermal epimerization of the diastereomeric mixtures.

The synthesis of ChenPhos is very economical and simple, since it can be completed without the purification of intermediates ("one-pot" synthesis, ca. 60% overall yield) for both routes (see the Supporting Information). Also, the synthesis is highly modular; the R and R′ groups can be any aryl or alkyl group that tolerates lithiation and a Grignard reaction. The absolute configuration of (R_C,S_{Fc},S_P)-**1a** was

confirmed by single-crystal X-ray diffraction analysis. Importantly, ChenPhos ligands are extremely insensitive to air oxidation; for example, the ^{1}H and ^{31}P NMR spectra of ligand (R_C,S_{Fc},S_P)-**1a** remained unchanged when this ligand was heated as a solid for three days at 75 °C in air or when it was stored as a non-degassed solution in EtOAc/EtOH for 6 months at room temperature. Ligand **1a** was readily synthesized on a kilogram scale in a one-pot synthesis.

The efficiency of Rh–ChenPhos complexes as catalysts was investigated in the enantioselective hydrogenation of (*E*)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid (**7**): a key step in the production of the renin inhibitor aliskiren[6,15,16] (Table 1). All ligands with bulky and

Table 1: Asymmetric hydrogenation of (*E*)-2-(3-(3-methoxypropoxy)-4-methoxybenzylidene)-3-methylbutanoic acid (**7**).



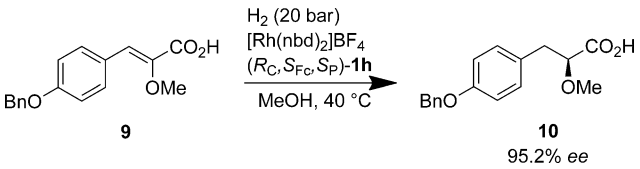
7 (*R*)-**8**

Ar = 3-(3-methoxypropoxy)-4-methoxyphenyl

Ligand	S/C	$p(H_2)$ [bar]	*t* [h]	Conversion [%]	*ee* [%]
1a	8500	50	5	100	99.2
1b	2000	50	22	99	87.4
1c	5000	60	20.5	100	97.5
1h	12000	50	3.5	49.3	99.2
1p	8500	60	20	99	21.4
1a	12000	50	3.5	95	99.0
TriFer	12000	50	3.5	14	99.5

electron-rich R groups on P^2 showed high enantioselectivity and activity. Typically, the product **8** was formed with less than 90% *ee* when R was an aryl group (e.g. **1b**, 87.4% *ee*); whereas up to > 99% *ee* was observed when R was a bulky and electron-rich alkyl group (see the Supporting Information).[17] The enantioselectivity of **1a** (R = Cy) was slightly lower than that of TriFer (99.2 versus 99.5% *ee*); however, importantly, **1a** is much more active and productive. When **7** was hydrogenated with a hydrogen pressure of 50 bar at 35 °C in MeOH for 3.5 h with a molar substrate/catalyst ratio (S/C) of 12000, conversion was 95% with the **1a**–Rh complex, whereas under identical conditions, TriFer gave only 14% conversion. Interestingly, the product was formed with 99.2% *ee* when ligand **1h** (R = 2-norbornyl) was used, even though this ligand existed as a mixture of at least four diastereomers (as confirmed by ^{31}P NMR spectroscopy) owing to the presence of racemic *exo*/*endo* 2-norbornyl groups. In accord with our design concept, the dramatic increase in the activity of ligand **1a** seems to be due to the introduction of two nonequivalent phosphorus centers and an electron-rich dicyclohexylphosphanyl group. Cy-TriFer, formed by the replacement of both phenyl rings of TriFer with cyclohexyl groups, indeed showed enhanced activity, but not to the same extent as ligand **1a**. Strangely, ligand **1p**, with two nonequivalent but electron-rich phosphorus centers (with three cyclohexyl groups), gave a very poor result in the hydrogenation (21.4% *ee*). The introduction of a bulky and electron-rich phosphino group might strengthen the d–σ* interaction and accelerate the oxidative addition of molecular hydrogen. Considering both enantioselectivity and activity, **1a** is the best-performing ChenPhos ligand prepared so far.

ChenPhos was also highly effective in the asymmetric hydrogenation of 3-aryl 2-alkoxy acrylic acids: a key step in the synthesis of some PPAR agonists (PPAR = peroxisome proliferator-activated receptor). For example, in the Rh-catalyzed hydrogenation of (*E*)-3-(4-benzyloxyphenyl)-2-methoxyacrylic acid (**9**), the use of **1h** led to the product **10** with 95.2% *ee* (Scheme 4).



9 **10**
95.2% *ee*

Scheme 4. Asymmetric hydrogenation of (*E*)-3-(4-benzyloxyphenyl)-2-methoxyacrylic acid. Bn = benzyl, nbd = norbornadiene.

As observed for TriFer,[6] the high enantioselectivity of ligand **1a** in the Rh-catalyzed asymmetric hydrogenation of α-substituted cinnamic acids is due to a secondary electrostatic interaction of the dimethylamino group of the ligand with the carboxylate unit of the substrate. Ligand **1t** (in which the dimethylamino group present in **1a** is replaced with a methoxy group) was not effective for the Rh-catalyzed hydrogenation of **7** (**8** was formed with 44% *ee*) owing to the lack of this secondary interaction, although it is a perfect ligand for the hydrogenation of the standard substrate methyl 2-acetamidoacrylate (the product was formed with > 99.9% *ee*; see the Supporting Information). Furthermore, all ChenPhos ligands were almost inactive in the Rh-catalyzed hydrogenation of the corresponding esters of **7** and **9**.

Preliminary screening of the scope of application of ChenPhos indicated that the ligand gives active Rh catalysts (for C=C hydrogenation), Ru catalysts (for C=O hydrogenation), and Ir catalysts (for C=N hydrogenation; see the Supporting Information); however, no optimization efforts have been made so far.

In conclusion, ChenPhos was designed by replacing one 2-(1-dimethylaminoethyl)ferrocenyl(phenyl)phosphanyl group of TriFer with a bulky, electron-rich phosphanyl group. This change was found to dramatically enhance the catalytic activity of the corresponding rhodium complexes, the enantioselectivity of which remained high. The synthesis of ChenPhos on the basis of thermal epimerization through pyramidal inversion as the key step is economical and simple. ChenPhos meets all requirements of a ligand of practical relevance: it is readily accessible, extremely air-stable, and exhibits very high enantioselectivity, activity, and productivity in asymmetric catalytic reactions. Furthermore, because of its high modularity, ChenPhos has the potential for very broad application.

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