Asymmetric Catalysis

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Stereoselective Synthesis of Ferrocene-Based C_2-Symmetric Diphosphine Ligands: Application to the Highly Enantioselective Hydrogenation of α-Substituted Cinnamic Acids

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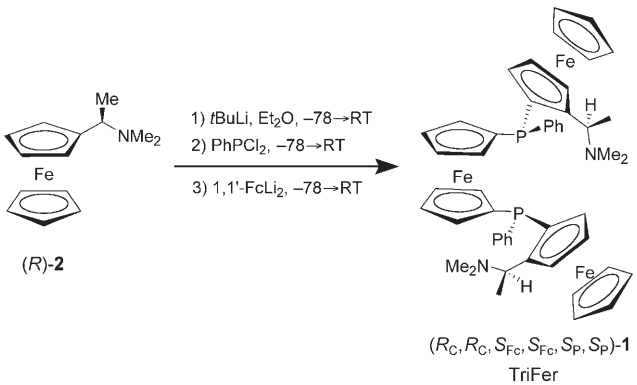
Optically active phosphine ligands, especially C_2-symmetric diphosphine ligands, have played an important role in various metal-catalyzed asymmetric transformations, and numerous phosphine ligands have been prepared for the development of effective catalytic asymmetric processes.[1] Dramatic results from Knowles and co-workers with the C_2-symmetric P-chiral ligand 1,2-ethanediylbis[(2-methoxyphenyl)phenylphosphane] (dipamp) for Rh-catalyzed hydrogenations opened up this field of asymmetric catalysis.[2] However, it took nearly two decades for other groups to develop efficient methods to prepare C_2-symmetric P-chiral diphosphine ligands, largely as a result of the synthetic difficulties in the construction of the P-chiral P centers.[3,4] Nevertheless, some C_2-symmetric P-chiral diphosphine ligands, such as BisP*,[4a] MiniPhos,[4b] TangPhos,[4c] DiSquareP*,[4d] DuanPhos,[4e] and QuinoxP*,[4f] which exhibit almost perfect enantioselectivity in some Rh-catalyzed asymmetric hydrogenations, have been developed recently. However, a major drawback in many of the requisite synthetic methods (developed by the groups of Imamoto,[3a] Jugé,[3b] Corey,[3c] Evans,[3e] and Livinghouse[3g]) is that either only one enantiomer of the ligand is readily accessible owing to the nature of the chiral auxiliaries used in the formation of the chiral center or there is a need for tedious diastereomeric derivatization, separation, and deprotection sequences.

Ferrocene-based phosphine ligands are well documented.[5] They are more amenable to asymmetric catalysis than many other types of chiral ligands as a result of their easy accessibility and derivatization as well as special electronic and steric properties. Indeed, several families of ferrocene-based phosphine ligands with subtle structural variations have been developed in the last few years. Most of these ligands incorporate both C-centered chirality and planar chirality, and they have proved to be highly effective in numerous asymmetric reactions. In stark contrast, much less attention has been paid to P-chiral phosphines that bear ferrocenyl groups,[3k,l,5] doubtless as a result of the previous difficulties in their synthesis. Very recently, we reported a highly stereoselective and modular synthesis of ferrocene-based P-chiral phosphine ligands using a simple and straightforward strategy, that is, reaction of a chiral organometallic reagent with a dichlorophosphine, followed by a second organometallic reagent; several families of new ferrocene-based P-chiral phosphine ligands have been developed.[6] Herein, we describe the highly stereoselective synthesis of a new ferrocene-based C_2-symmetric diphosphine ligand **1** (TriFer). To the best of our knowledge, ligand **1** is the first class of C_2-symmetric diphosphine that combines C-centered, P-centered, and planar chirality. Most importantly, unprecedented enantioselectivities have been achieved with ligand **1** for the Rh-catalyzed asymmetric hydrogenation of α-substituted cinnamic acids, a class of very important substrates for which efficient asymmetric reduction procedures are eagerly sought.

Both enantiomers of **1** can be prepared from the readily available *R* and *S* enantiomers of Ugi's amine (**2**) in only one step, in good yield, and with excellent stereoselectivity (Scheme 1). Thus, Ugi's amine (*R*)-**2** was lithiated with *t*BuLi (−78 °C, 10 min, then room temperature, 1.5 h) and then treated with $PhPCl_2$ (−78 °C, 10 min, then room temper-



Scheme 1. Preparation of ligand **1**.

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Supporting information, including details on the preparation of ligands and substrates, general hydrogenation procedure, and determination of *ee* values, for this article is available on the WWW under http://www.angewandte.org or from the author.

ature, 1.5 h) followed by 1,1′-dilithioferrocene (1,1′-$FcLi_2$) generated from 1,1′-dibromoferrocene by lithiation (−78 °C→RT, overnight) to afford a mixture of (R_C,R_C,S_{Fc},S_{Fc},S_P,S_P)-**1** and the *meso* compound (R_C,R_C,S_{Fc},S_{Fc},S_P,R_P)-**1** (≈95:5 ratio as judged by ^{1}H NMR and ^{31}P NMR spectroscopy) in 84% yield. Pure (R_C,R_C,S_{Fc},S_{Fc},S_P,S_P)-**1** could be easily obtained by crystallization from MeOH. Its enantiomer, (S_C,S_C,R_{Fc},R_{Fc},R_P,R_P)-**1**, was obtained from Ugi's amine (*S*)-**2**. The absolute configuration of the product (S_C,S_C,R_{Fc},R_{Fc},R_P,R_P)-**1** was confirmed by single-crystal X-ray diffraction analysis. Ligand **1** shows good air stability; (R_C,R_C,S_{Fc},S_{Fc},S_P,S_P)-**1** did not show any changes in its ^{1}H or ^{31}P NMR spectra even after being stored for about two years under air at room temperature.

The prescribed generation of 1,1′-$FcLi_2$ from 1,1′-dibromoferrocene is crucial for the highly stereoselective synthesis of (R_C,R_C,S_{Fc},S_{Fc},S_P,S_P)-**1**, as the configuration of the P centers could be reversed by changing the reaction conditions, namely by replacement of 1,1′-$FcLi_2$ with 1,1′-$FcLi_2$–TMEDA complex (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine). Thus, following lithiation of Ugi's amine (*R*)-**2** and treatment of the Li compound with $PhPCl_2$ as described above and subsequent addition of 1,1′-$FcLi_2$–TMEDA complex and stirring for 1 h at room temperature, a mixture of diastereomer (R_C,R_C,S_{Fc},S_{Fc},R_P,R_P)-**1** and the *meso* compound (R_C,R_C,S_{Fc},S_{Fc},S_P,R_P)-**1** was obtained in about 9:1 ratio in 93% yield.

The stereochemistry and high stereoselectivity in the formation of ligand **1** under the standard reaction conditions are consistent with our proposed reaction mechanism,[6a] which involves the cyclic intermediate **3** (Figure 1). The

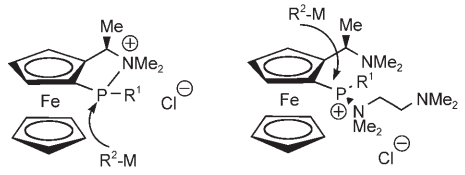

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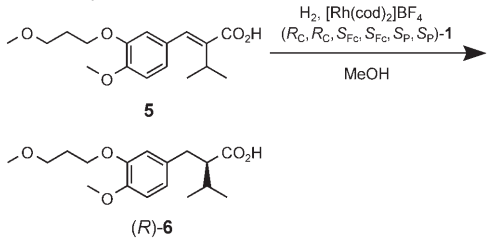
Figure 1. Intermediates in the formation of **1**.

influence of using the 1,1′-$FcLi_2$–TMEDA complex on the resultant stereochemistry of ligand **1** is also accommodated by this mechanism. Hence, when 1,1′-$FcLi_2$ is replaced with 1,1′-$FcLi_2$–TMEDA complex, the more basic TMEDA breaks the ring intermediate **3** to form intermediate **4**. For the reactions at ambient temperature, the intermediate **4** is fully formed and leads to (R_C,R_C,S_{Fc},S_{Fc},R_P,R_P)-**1** highly stereoselectively.

Chiral α-substituted dihydrocinnamic acid derivatives are key intermediates in the synthesis of several bioactive compounds, including renin inhibitors,[7] β-secretase inhibitors,[8] enkephalinase inhibitors,[9] opioid antagonists,[10] and peroxisome proliferator-activated receptors (PPAR) agonists.[11] Nowadays, significant progress has been achieved in asymmetric hydrogenation of a wide range of unsaturated substrates, but the enantioselective hydrogenation of α-substituted cinnamic acids remains a challenge.[12] Thus, the efficiency of ligand **1** in the enantioselective hydrogenation of α-substituted cinnamic acids catalyzed by Rh complexes was first investigated using (*E*)-2-[3-(3-methoxypropoxy)-4-methoxybenzylidene]-3-methylbutanoic acid (**5**) as the substrate, as this is an industrially relevant compound which is known to be difficult to hydrogenate with high enantioselectivity.[7,12c] Hydrogenation of **5** in the presence of a Rh catalyst, generated in situ from $[Rh(cod)_2]BF_4$ (0.1 mol%; cod = cycloocta-1,5-diene) and ligand **1** (1.1 equiv with respect to Rh) in MeOH, gave optically active (*R*)-**6**, a key intermediate in the synthesis of renin inhibitor Aliskiren, with unprecedented enantioselectivities of up to 99.6% *ee* (Table 1). Importantly, for reactions at higher substrate

Table 1: Enantioselective hydrogenations on butanoic acid **5** using (R_C,R_C,S_{Fc},S_{Fc},R_P,R_P)-**1**.[a]



Entry	S/C	*T* [°C]	[Substrate] [M]	*t* [h]	*ee* [%]
1	500	40	0.16	13	99.6
2	500	65	0.16	5	99.3
3	1000	40	0.55	4	98.6
4	2000	60	0.55	4	98.4

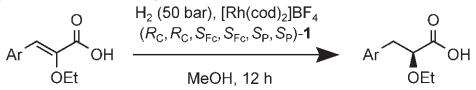
[a] The reactions were carried out under 50 bar H_2 pressure with over 99% conversion in all cases.

concentrations, substrate-to-catalyst (S/C) ratios and temperature seem to have only a marginal effect on *ee* values. The enantioselectivities obtained here for product **6** exceed the reported values for Rh-catalyzed hydrogenations using Walphos (95% *ee*)[7] and Monophos (90% *ee*).[12c] Thus, TriFer is the most enantioselective ligand in the asymmetric hydrogenation of **5** so far reported.

Recently, the synthesis of optically enriched α-alkoxy dihydrocinnamic acids has attracted significant attention as a result of their potential usefulness as PPAR agonists in the treatment of type 2 diabetes and dislepedimia.[11] Investigations have been carried out on the synthesis of these materials through resolution[13] and enzymatic[14] and enantioselective catalytic procedures.[15] The Rh-catalyzed enantioselective hydrogenation of 3-aryl-2-ethoxyacrylic acids **7** is usually extremely difficult.[15] However, gratifyingly, TriFer is highly effective in the Rh-catalyzed enantioselective hydrogenation of these acrylic acids, displaying unprecedented enantioselectivities and leading to products with 95–98% *ee* (Table 2).

A secondary interaction of the ligand with the substrate[16] could account for the high enantioselectivity and activity of TriFer in the Rh-catalyzed asymmetric hydrogenation of α-substituted cinnamic acids. The generally accepted mechanism of enantioselective hydrogenation catalyzed by a Rh complex involves coordination of a substrate to the solvated Rh complex to form a chelate catalyst–substrate complex **9**

Table 2: Enantioselective hydrogenations on 3-aryl-2-ethoxyacrylic acids **7** using (R_C,R_C,S_{Fc},S_{Fc},R_P,R_P)-**1**.[a]



Entry	Aryl group	S/C	*T* [°C]	[Substrate] [M]	*ee* [%]
1	3-methoxyphenyl	500	40	0.41	95.2
2	3-methoxyphenyl	1000	40	0.82	94.6
3	4-cyanophenyl	500	35	0.50	98.0
4	4-cyanophenyl	500	55	0.50	96.5
5	2-thienyl	500	50	0.41	95.0
6	3-thienyl	1000	55	0.41	96.5
7	3-benzyloxy-4-methoxyphenyl	500	50	0.50	97.6
8	3-benzyloxy-4-methoxyphenyl	2000	50	0.40	96.2

[a] Over 99% conversion for all reactions.

(Figure 2), in which the C=C bond and the carbonyl O atom at the β position interact with the Rh^I center.[17] To obtain high enantioselectivity and activity, it is essential that there is a

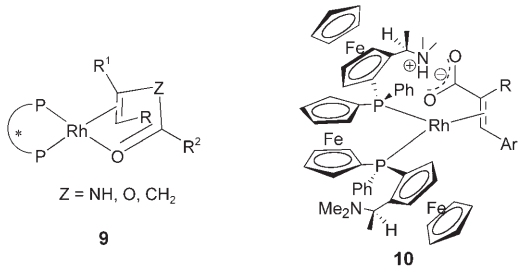


Figure 2. Substrate–catalyst complex in the asymmetric hydrogenation.

second functional group such as carbonyl group at the β position to the C=C bond that is capable of chelation with the metal and result in a ring system that stabilizes the reactive intermediate. Unlike enamides, enol acetates, and itaconates, α-substituted cinnamic acids lack such functionality at the β position to coordinate with the metal, and so most known chiral diphosphine ligands give low enantioselectivities and activities for the Rh-catalyzed asymmetric hydrogenation of α-substituted cinnamic acids. However, in the **1**–Rh–substrate complex **10**, the dimethylamino moiety would serve to have a secondary interaction with the substrate, that is, an electrostatic interaction with the carboxylate unit of the substrate, and establish the multisite recognition of the substrate by the Rh complex that leads to high enantioselectivity and activity. In accord with this postulate, ligand **1** is almost inactive for the Rh-catalyzed hydrogenation of the corresponding esters of **5** or **7**.

The origin of the enantioselectivity is accounted for on the basis of the well-known quadrant rule.[18] When looking at the **1**–Rh complex from the side, the two equatorial 2-(dimethylaminoethyl)ferrocen-1-yl groups spatially occupy and thus block two opposite quadrants. In the case of (R_C,R_C,S_{Fc},S_{Fc},S_P,S_P)-**1**, two equatorial 2-(dimethylaminoethyl)ferrocen-1-yl groups shield the second and the fourth quadrants. During a reaction, a substrate approaches the metal so as to minimize steric interactions with the equatorial 2-(dimethylaminoethyl)ferrocen-1-yl groups. Figure 3 illustrates the favored and disfavored transition states for the asymmetric hydrogenation of α-substituted cinnamic acids catalyzed by the (R_C,R_C,S_{Fc},S_{Fc},S_P,S_P)-**1**–Rh complex. Transition state TS-2 suffers from steric repulsion between the aryl group of the substrate and an equatorial 2-(dimethylaminoethyl)ferrocen-1-yl group. In transition state TS-1, this steric repulsion is avoided and allows the reaction to proceed, yielding the enantiomer as shown in Figure 3 as the major product.

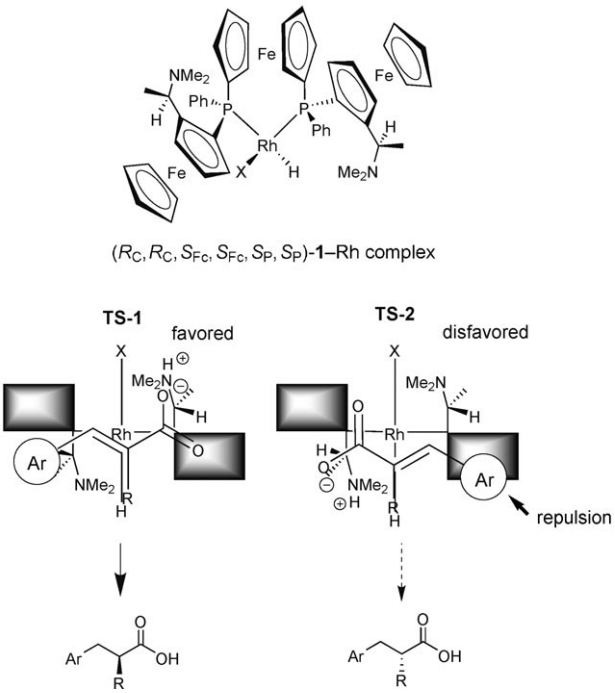


Figure 3. Transition-state models for the asymmetric hydrogenation of α-substituted cinnamic acids catalyzed by the (R_C,R_C,S_{Fc},S_{Fc},S_P,S_P)-**1**–Rh complex.

In conclusion, a new class of ferrocene-based C_2-symmetric P-chiral diphosphine ligand (Trifer) has been developed and applied in the highly enantioselective hydrogenation of α-substituted cinnamic acids with *ee* values of up to 99.6% obtained. TriFer is the most enantioselective ligand so far reported, probably owing to an influential secondary electrostatic interaction of the dimethylamino group of the ligand with the carboxylate unit of the substrate.

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