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A Very Simple, Highly Stereoselective and Modular Synthesis of Ferrocene-Based P-Chiral Phosphine Ligands

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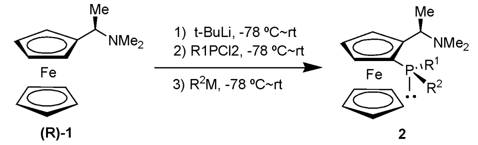
Ferrocene-based ligands provide an important subset of chiral phosphines,[1] and several families with subtle structural variations, such as Josiphos,[2] Taniaphos,[3] Mandyphos,[4] Walphos,[5] Trap,[6] and BoPhoz,[7] have been developed in the past few years. Most of these ligands incorporate both carbon-centered chirality and planar chirality, and they have been proven to be highly effective in numerous asymmetric reactions. In stark contrast, much less attention has been paid to P-chiral phosphines bearing ferrocenyl groups, although, in theory, they are highly likely to provide a superior class of ligands for asymmetric catalysis by virtue of bringing the chiral environment into the closest possible proximity to the catalytic center. The paucity of examples undoubtedly reflects the difficulties in synthesis of P-chiral phosphines.[8]

Almost all of the documented ferrocene-based planar chiral phosphine ligands are synthesized by chiral group-directed diastereoselective *ortho*-lithiation[9] or enantioselective lithiation[10] followed by reaction with a *monochloro*phosphine. We envisioned that ferrocene-based P-chiral phosphines could be synthesized by reaction of a *dichloro*phosphine with a chiral lithiated ferrocene, followed by a second organometallic reagent. Herein we report a first example of highly stereoselective and modular synthesis of ferrocene-based P-chiral phosphine ligands using this simple and straightforward strategy.

Enantiopure *N*,*N*-dimethyl-1-ferrocenylethylamine (Ugi's amine) is readily available[11] and provided a suitable starting material for our investigations. Thus, (*R*)-Ugi's amine **1** was lithiated with *t*-BuLi, followed by reaction with $PhPCl_2$ and then reacted with *o*-anisyllithium unexpectedly (and most pleasingly!) to afford a single diastereomer (R_C,S_{Fc},S_P)-**2a** (as judged by ^1H NMR and ^{31}P NMR spectroscopy) in 91% yield (Table 1).[12] The absolute configuration of the product (R_C,S_{Fc},S_P)-**2a** was determined by single-crystal X-ray diffraction analysis. Similarly, the naphthalene derivative (R_C,S_{Fc},S_P)-**2b** was prepared as a single diastereomer in 89% yield. Recrystallization of (R_C,S_{Fc},S_P)-**2b** proved to be difficult as it is very soluble in every solvent tested. By way of contrast, its epimer, (R_C,S_{Fc},R_P)-**2c**, is almost insoluble in hot hexane and is easily prepared from (R_C,S_{Fc},S_P)-**2b** by crystallization induced asymmetric transformation. The absolute configuration of (R_C,S_{Fc},R_P)-**2c** was determined by single-crystal X-ray diffraction analysis.

Table 1. Synthesis of Ferrocene-Based P-Chiral Phosphines



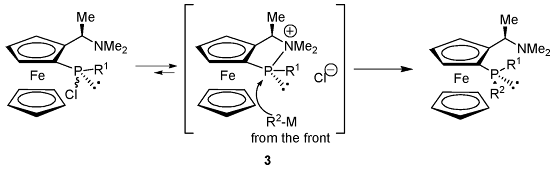
entry	R^1	R^2	M	yield (%)	product	configuration
1	Ph	*o*-An	Li	91	**2a**	(R_C,S_{Fc},S_P)
2	Ph	1-Np	Li	89	**2b**	(R_C,S_{Fc},S_P)
3	Ph	1-Np	MgBr	83	**2b**	(R_C,S_{Fc},S_P)
4	1-Np	Ph		78	**2c**[a]	(R_C,S_{Fc},R_P)
5	Ph	2-Np	MgBr	87	**2d**	(R_C,S_{Fc},S_P)
6	Ph	2-Biph	Li	94	**2e**	(R_C,S_{Fc},S_P)
7	Cy	Ph	MgBr	95	**2f**	(R_C,S_{Fc},S_P)
8	Ph	Cy	MgCl	92	**2g**	(R_C,S_{Fc},R_P)
9	Ph	Me	MgBr	89	**2h**	(R_C,S_{Fc},R_P)
10	*t*-Bu	Me	Li	86	**2i**	(R_C,S_{Fc},R_P)

[a] (R_C,S_{Fc},R_P)-**2c** was prepared from (R_C,S_{Fc},S_P)-**2b** by crystallization induced asymmetric transformation (CIAT).

This new synthetic methodology is highly modular. The scope of the above reaction was extended by using different dichlorophosphines R^1PCl_2 and organometallic compounds R^2M (Table 1) to provide a variety of ferrocene-based P-chiral phosphines each as a single diastereomer in high yield. Replacement of the lithium reagent with the corresponding Grignard reagent gave similar results (entry 2 vs entry 3). More importantly, the two diastereomers with the opposite configuration at the phosphorus atom can be prepared simply by exchanging R^1 and R^2 in R^1PCl_2 and R^2M (entry 7 vs entry 8). The absolute configuration of each compound in the series **2d**−**2i** was inferred from the established stereochemistry of **2a** and **2c**. We have also extended the scope of this reaction by using other ferrocenyllithium species generated using, initially, the classical chiral group directed *ortho*-lithiation, and the results will be reported elsewhere.

The stereochemistry and high diastereoselectivity of this reaction can be explained by the following plausible reaction mechanism (Scheme 1). For the substrates bearing groups which are strong Lewis bases (such as the dimethylamino unit in Ugi's amine), a five-membered ring quaternary ammonium salt intermediate, such as **3**, is formed and then the organometallic compound RM attacks from the front (as portrayed) to give the products.

Scheme 1



Compound **2** is useful as a starting point for expanding the range of novel compounds of potential utility. Thus several new families of ferrocene-based phosphine ligands, combining phosphorus chirality and other chiralities, such as P-chiral phosphine−aminophosphine ligands **4a**−**e**, P-chiral phosphine−phosphoramidite ligands **5a**,**b**,**d**, and P-chiral 1,3-bisphosphine ligands **6a**−**e** (Scheme 2), can be prepared easily by similar methods to those used for the preparation of Josiphos[4] and BoPhoz.[9] It should be noted that epimerization at the phosphorus stereocenter occurred when the transformations were performed at elevated temperature. Fortu-

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Scheme 2

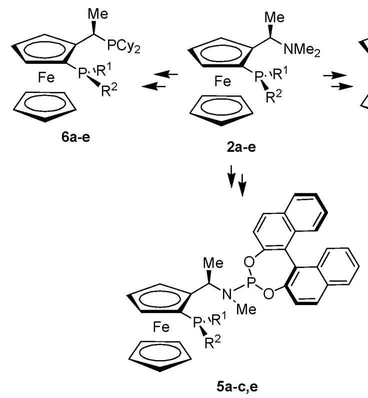

Table 2. Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives

$$\mathrm{R\!-\!CH{=}C(NHAc)CO_2Me} \xrightarrow[\text{solvent, rt}]{\mathrm{H_2,\ L^*\text{-}Rh(COD)_2T_fO\ (0.5\ mol\%)}} \mathrm{R\!-\!CH_2\!-\!CH(NHAc)CO_2Me}$$

entry	L*	R	solvent	H_2 (psi)	time (h)	conv. (%)	ee (%)
1	BoPhoz	H	THF	50	2.5	99	94.5
2	**4b**	H	THF	50	2.5	**100**	**98.3**
3	**4c**	H	THF	50	2.5	100	92.3
5	BoPhoz	H	MeOH	50	2.5	91.4	81.1
6	**4b**	H	MeOH	50	2.5	**100**	>**99**
7	**4c**	H	MeOH	50	2.5	84.5	90.3
8	BoPhoz	Ph	THF	100	2	100	95.7
10	**4b**	Ph	THF	100	2	100	**97.0**
11	**4c**	Ph	THF	100	2	100	92.4

nately, most of transformations can be carried out at room temperature, with no evidence of any epimerization.

The preliminary results of asymmetric hydrogenation of two α-dehydroamino acid derivatives catalyzed by Rh complexes prepared from the new ligands show that the introduction of P-chirality in ferrocene-based phosphine ligands enhances the enantioselective discrimination produced by the catalyst when a cooperative effect operates among the planar chirality, carbon chirality, and the chirality at phosphorus (Table 2). The activities and enantioselectivities of the matched ligand (R_{C},S_{Fc},S_{P})-**4b** are higher than that of BoPhoz (entry 1 vs entry 2 and entry 8 vs entry 10), while the mismatched ligand (R_{C},S_{Fc},R_{P})-**4c** is less active and enantioselective than BoPhoz (entry 1 vs entry 3 and entry 8 vs entry 11). Interestingly, the matched ligand (R_{C},S_{Fc},S_{P})-**4b** seems to be particularly suitable for hydrogenation conducted in methanol (entry 5 vs entry 6).

In summary, a very simple, highly stereoselective synthesis of ferrocene-based P-chiral phosphine ligands has been developed. This new methodology offers modular construction of ligands and hence generates many possibilities for modifying the structure of these ferrocene-based phosphines. Indeed, on the basis of this new method, several new families of ferrocene-based phosphine ligands combining phosphorus chirality and other chiralities have been prepared. The preliminary results from some asymmetric hydrogenation reactions show that the introduction of P-chirality into well-known ferrocene-based phosphine ligands enhances the enantioselective discrimination produced by the corresponding Rh catalyst when a matching among the planar chirality, carbon chirality, and the chirality at phosphorus exists.

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Supporting Information Available: Experimental procedures and confirmation of the absolute configuration of (R_{C},S_{Fc},S_{P})-**2a**, (R_{C},S_{Fc},R_{P})-**2c**, (R_{C},S_{Fc},S_{P})-**2a**, and (R_{C},S_{Fc},S_{P})-**6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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