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An Efficient Approach to Chiral Ferrocene-Based Secondary Alcohols *via* Asymmetric Hydrogenation of Ferrocenyl Ketones

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Abstract: P-Phos-ruthenium-DPEN precatalysts have been found to be efficient for the asymmetric hydrogenation of various ferrocenyl ketones. The use of (*R*)-xylyl-P-PhosRuCl$_2$(*R*,*R*)-DPEN generated chiral ferrocenylethanol in 99.3% e.e. with >99% conversion in a 150-g scale.

Keywords: asymmetric catalysis; ferrocenyl ketone; homogeneous catalysis; hydrogenation; P-Phos; ruthenium

Introduction

Chiral ferrocene-based ligands have been extensively studied in asymmetric catalytic reactions.[1] Some of the most efficient chiral ferrocene ligands include BoPhoz,[2] Josiphos,[3] TaniaPhos,[4] Walphos,[5] PPFA,[6] Ferriphos,[7] Pigiphos,[8] Trap[9], etc. These ligands share a common intermediate, namely Ugi's amine **3** (Figure 1), a compound first prepared in 1970.[10a] The classical access to optically pure **3** is through laborious resolution of its racemic mixture.[10] Alternatively, attempts employing chiral auxiliaries have been made to synthesize Ugi's amine. For example, Togni's group reported a method whereby lithiated, diastereomeric or enantiomeric monosubstituted fulvene reacted with Cp*Fe(acac) to generate a Ugi's amine analogue.[11] A similar approach was introduced by Hayashi et al. using chiral cyclopentadienyllithium generated from 6-(dimethylamino)fulvene in the presence (−)-sparteine.[12]

Given that nucleophilic substitution at the chiral α-carbon attached directly to the ferrocene proceeds with stereoretention,[10] some catalytic methods under non-reducing conditions such as asymmetric arylation of ferrocenecarboxaldehyde,[13] (−)-sparteine/Pd-mediated aerobic oxidative kinetic resolution[14,15] and stereoselective enzymatic acylation of racemic **2**[16] have been explored in attempts to synthesize optically pure **2**, a precursor to Ugi's amine. However, acquisition of both enantiomers of **2** is often difficult using these methods due to the unavailability of the antipodic catalyst. Whilst homogeneous CBS (Corey–Bakshi–Shibata) reduction of metallocenyl ketones appears to overcome this shortcoming, providing the corresponding secondary alcohols in excellent yields and enantioselectivities,[17] an undesirably high level of catalyst loading of up to 30–60 mol % is needed. It is therefore an expensive way to obtain a large quantity of the Ugi-type amine, especially, if the unnatural (+)-proline is used.

Since its discovery by Noyori and co-workers,[18] the asymmetric catalytic hydrogenation of prochiral ketones with [(diphosphine)RuCl$_2$(diamine)] has quickly become a method of choice for the synthesis of simple chiral secondary alcohols. When applied to ferrocenyl ketones (Table 1), the best result hitherto reported is when (*S*)-SDP is used as the diphosphine and (*R*,*R*)-DPEN as the diamine.[19] Recently, we have initiated a program to broaden the diversity of chiral ferrocenyl ligands design.[20] In order to accomplish this, a large amount of Ugi's amine is required as an important intermediate. This paper describes our attempt to synthesize chiral ferrocenyl alcohols **2** *via* enantioselective hydrogenation of ferrocenyl ketones using Ru(II) catalysts containing the P-Phos ligand.[24]

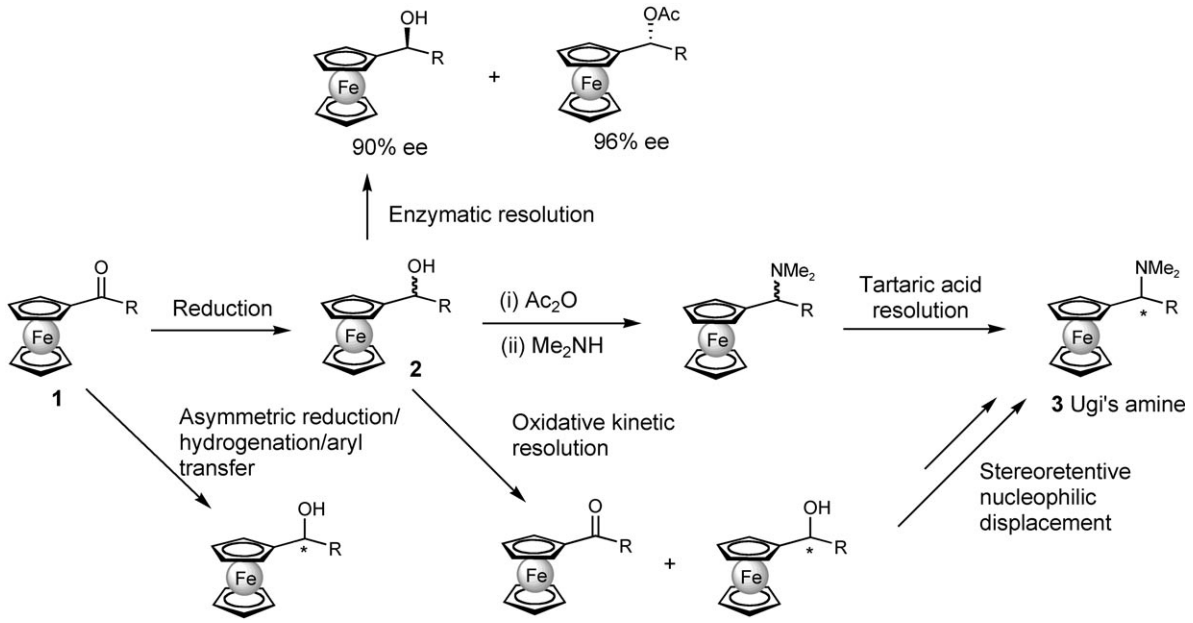


Figure 1.

Table 1. Enantioselective catalytic hydrogenation of ferrocenyl ketones.[a]

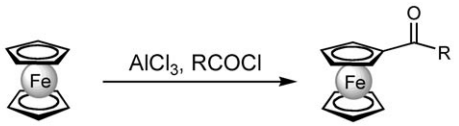
Entry	R of **1**	Catalyst	S/C	ee [%]	Conversion [%]	Configuration
1	Me	A	5000	98	100	*S*
2	Me	B	1000	92	>99	*R*
3	Me	C	[b]	87	[b]	*S*
4	Ph	D	2000	95	100	*S*
5	Ph	E	[b]	45	[b]	*S*

[a] General operation temperatures (T) ranged from 18–24 °C.
[b] Data unavailable.
Catalysts A = [((*S*)-Xylyl-SDP)$RuCl_2$((*R*,*R*)-DPEN)];[19] B = ([((*R*)-Xylyl-PhanePhos)$RuCl_2$((*S*,*S*)-DPEN)];[21] C = [((*R*)-Tol-BINAP)$RuCl_2$((*S*)-DAIPEN)];[22] D = [((*S*)-Tol-BINAP)$RuCl_2$((*S*)-DAIPEN)];[23] E = ([((*S*)-Xylyl-BINAP)$RuCl_2$((*S*)-DAIPEN)].[23]

Results and Discussion

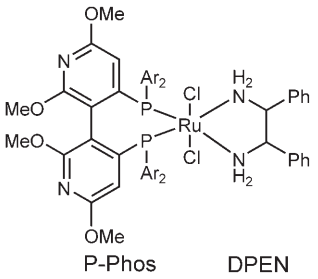
The reaction of ferrocene with various acid chlorides under classical Friedel–Crafts conditions afforded ferrocenyl ketones **1a**–**h** in generally acceptable yields (Scheme 1).[25] Acetyl chloride reacted most readily with ferrocene to give an excellent yield of the corresponding ketone. Benzoyl, naphthoyl and heteroaroyl chlorides all gave good to excellent yields. It was noted that substituted benzoyl chlorides reacted relatively less efficiently with ferrocene.

To investigate the effects of various phosphorus substituents on the activity and the enantioselectivity in the hydrogenation of ferrocenyl ketones, different P-Phos ligands (Figure 2) were screened using **1a** as a model substrate. As shown in Table 2, the parent P-Phos, irrespective to its configuration, gave poor conversion and selectivity whereas *RSS*-**9** provided full conversion but mediocre selectivity at a substrate-to-catalyst ratio



1a R = CH_3 (97%) **1e** R = 1-Naphthyl (86%)
1b R = Ph (86%) **1f** R = 2-Naphthyl (90%)
1c R = 2-MeO-C_6H_4 (70%) **1g** R = 2-Furyl (94%)
1d R = 4-Br-C_6H_4 (50%) **1h** R = 2-Thienyl (76%)

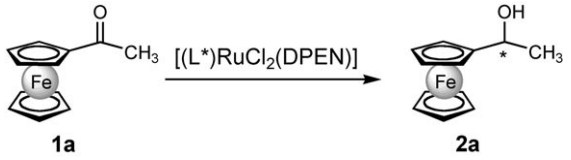
Scheme 1. Fridel–Crafts acylation of ferrocenyl ketones.



SSS-**5**: (*S*)-P-Phos, Ar = Ph; (*S*,*S*)-DPEN
SRR-**6**: (*S*)-P-Phos, Ar = Ph; (*R*,*R*)-DPEN
SRR-**7**: (*S*)-Xylyl-P-Phos, Ar = 3,5-$Me_2C_6H_3$; (*R*,*R*)-DPEN
RRR-**8**: (*R*)-Xylyl-P-Phos, Ar = 3,5-$Me_2C_6H_3$; (*R*,*R*)-DPEN
RSS-**9**: (*R*)-Tol-P-Phos, Ar = 4-MeC_6H_4; (*S*,*S*)-DPEN
RRR-**10**: (*R*)-Tol-P-Phos, Ar = 4-MeC_6H_4; (*R*,*R*)-DPEN

Figure 2.

Table 2. Initial catalyst screening using [(P-Phos)$RuCl_2$(DPEN)] system.[a]



1a **2a**

Catalyst	Alcohol Product **2a**		
	Conversion [%][b]	ee [%][b]	Configuration
SSS-**5**	19	76.5	*R*
SRR-**6**	20	35.7	*S*
SRR-**7**	>99	90.1	*R*
RRR-**8**	>99	99.4	*S*
RSS-**9**	>99	38.1	*R*
RRR-**10**[c]	98	77.5	*S*

[a] Standard conditions: sample size = 0.55–0.56 mmol; [sub] = 0.23–0.31 M; solvent = *i*-PrOH; S/C = 5000; base = KO-*t*-Bu; S/B = 50; H_2 pressure = 50 bar; *T* = room temperature.
[b] Determined by HPLC.
[c] S/C = 1000.

(S/C) of 5000. The results improved dramatically with the use of *SRR*-**7** and *RRR*-**8** under identical conditions leading to 90.1% ee and 99.4% ee, respectively. The latter value represents the best result so far attained for the synthesis of chiral **2a** catalytically without the need for further enrichment *via* recrystallization.

Having found the most suitable P-Phos ligand, we then turned our attention to the determination of an optimal catalyst loading based on a balanced consideration between reaction rate and selectivity. This exercise was applied to both *SRR*-**7** (Table 3) and *RRR*-**8** (Table 4). When the reaction time was fixed at 15 h and the concentration of substrate at 0.55–0.60 M, a successive two-fold decrease of *SRR*-**7**'s loading brought about an abrupt diminution in conversion, but with no significant

Table 3. S/C ratio tuning using *SRR*-**7**. [a]

S/C	Conversion [%][b]	ee [%][b]
5000	>99	89.9
10000	>99	88.0
25000	73	91.3
50000	50	91.6
100000	6.4	90.8
200000	0.9	89.0

[a] Standard conditions: substrate = **1a**; sample size = 44–48 μmol; [sub] = 0.55–0.6 M; solvent = *i*-PrOH; base = KO-*t*-Bu; substrate-to-base ratio = 50; H_2 pressure = 50 bar; *T* = room temperature; time = 15 h. The configuration of product **2a** is *R*.
[b] Determined by HPLC.

Table 4. S/C ratio tuning using *RRR*-**8**.[a]

S/C	Conversion [%][b]	ee [%][b]
5000	99	99.1
10000	82	99.2
15000	39	98.8
25000	19	98.7
30000	17	98.8
35000	7.7	97.7

[a] Standard conditions: substrate = **1a**; sample size = 0.22–0.23 mmol; [sub] = 0.55–0.6 M; solvent = *i*-PrOH; S/C = 5000; base = KO-*t*-Bu; S/B = 50; H_2 pressure = 50 bar; *T* = room temperature; time = 15 h. The configuration of product **2a** is *S*.
[b] Determined by HPLC.

erosion of product ee. In the case of *RRR*-**8**, a similar trend was observed. In comparison of both diastereomeric catalysts, the hydrogenation using *SRR*-**7** shows faster reactivity according to the S/C ratio of the 50% conversion. The conversion of the hydrogenation catalyzed by *RRR*-**8** was found to be complete by changing the substrate concentration to 1.5 M and allowing the reaction to take place at room temperature over 48 h at an S/C ratio of 40,000. Gratifyingly, this protocol was further up-scaled successfully to a 150-gram level using a Parr 4520 series stirred reactor with the resulting alcohol reaching the same level of ee (99.3%) even at S/C = 100,000, practically thereby setting the stage for applications. In comparison, the use of Xylyl-Binap-Ru-Daipan gave 90.8% ee when S/C was increased up to 1000.[26]

Subsequently, we attempted to extend the above methodology to different aryl and heteroaryl ferrocenyl ketones. Unfortunately, hydrogenation of these substrates in the presence of *RRR*-**8** led to both poor enantioselectivity and conversion under the same conditions as delineated for the foregoing experiments. In a similar context, the analogous Xylyl-BINAP catalyst also gave inferior results in the case of benzoylferrocene (Table 1,

Table 5. Asymmetric hydrogenation of ferrocenyl aryl/heteroaryl ketones **1b**–**h** to ferrocenyl alcohols **2b**–**h** using *RRR*-**10**.[a]

Entry	Substrate	Time [h]	ee [%][d]	Conversion [%][d]	Configuration
1[b]	**1b**	15	89	99	(*R*)/(−)
2[b]	**1c**	15	97	94	(−)
3	**1d**	182	73	37	(−)
4	**1e**	15	98	90	(−)
5[b]	**1f**	15	83	94	(−)
6	**1g**	15	41	73	n.d.[c]
7[b]	**1h**	15	68	93	n.d.[c]

[a] Standard conditions: sample size = 28–37 μmol; [sub] = 0.23–0.31 M; solvent = *i*-PrOH; S/C = 1000; base = KO-*t*-Bu; S/B = 50; H_2 pressure = 50 bar; *T* = room temperature.
[b] Average of two experiments.
[c] Not determined because the sample was very susceptible to decomposition.
[d] Determined by HPLC.

entry 5).[22] In a parallel experiment, the sterically less hindered *RRR*-**10** effected the reaction relatively more smoothly (Table 5). As for the aryl and heteroaryl substrates, the conversions were generally excellent while the ees were moderate to excellent (41–98%). Clearly, there were delicate and subtle matching and mismatching effects between the substituents on the phosphorus ligand and the structure of the ferrocenyl ketone substrate.

Conclusion

In conclusion, a facile, efficient and highly enantioselective method for the synthesis of enantiomerically pure **2a** and analogous chiral ferrocenyl alcohols has been developed. It was found that *RRR*-**8** was the best precatalyst for the hydrogenation of acetylferrocene (**1a**) with up to >99% ee whereas *RRR*-**10** was more appropriate for the hydrogenation of aryl/heteroaryl ferrocenyl ketones with up to 98% ee.

Experimental Section

General Remarks

Unless otherwise indicated, all reactions were carried out in an inert atmosphere glovebox or under a nitrogen atmosphere. Melting points were measured using an Electrothermal 9100 apparatus in capillaries and the data are uncorrected. NMR spectra were recorded on a Varian 500 MHz Fourier transform spectrometer. ^{1}H and ^{13}C NMR spectra were recorded relative to residual protiated solvent; a positive value of the chemical shift denotes a resonance downfield from TMS. Mass analyses were performed on a Finnigan model Mat 95 ST mass spectrometer. High-performance liquid chromatography (HPLC) analyses were performed using a Hewlett-Packard model HP 1050/1100 LC interfaced to an HP 1050 series computer workstation and Waters™ 600 using a variety of optically active columns (Daicel Chiracel AS-H, Chiracel AS, or Chiracel AD-H). Optical rotations were measured on a Perkin-Elmer model 341 polarimeter at 20 °C. The solid prochiral ferrocenyl ketones were recrystallized before use and all other chemicals were purchased from commercial suppliers and used without further purification. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. Dichloromethane was freshly distilled from calcium hydride under nitrogen. All reactions were monitored by analytical thin-layer chromatography (TLC) on Merck aluminum-precoated plates of silica gel 60 F_{254} with detection by spraying with 5% (w/v) dodecamolybdophosphoric acid in ethanol or 5% (w/v) ninhydrin in ethanol and subsequent heating. E. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. Hydrogenation reactions were carried out using Parr 4714 bomb and Parr 4520 series stirred reactor.

General Procedure for Friedel–Crafts acylation of Ferrocene

$AlCl_3$ was added portion-wise into a solution of ferrocene and acyl chloride (1.1 equivs.) in dichloromethane at 0 °C and the solution was allowed to warm up to room temperature and stirred overnight. The solution was then added slowly into a saturated $NaHCO_3$ solution cooled in an ice-bath. The mixture was extracted with diethyl ether (30 mL × 3). The combined organic solution was further washed with water (50 mL × 3), brine (50 mL × 3), dried over anhydrous $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography gave the corresponding ferrocenyl alcohol.

General Preparation of [(P-Phos)RuCl$_2$(DPEN)] Precatalyst[27]

$[RuCl_2(p\text{-cymeme})]_2$ (4.1 mg, 6.7μmol) and (*R*)-XylylPPhos (10.6 mg, 14.5 μmol) in degassed DMF (0.5 mL) were stirred at 100 °C for 10 min to form a reddish brown solution. After cooling to room temperature, a solution of (*R*,*R*)-DPEN (4.3 mg, 13.7 μmol) in degassed DMF (0.5 mL) was added to the reaction mixture and stirring continued for 3 h. The solvent was removed under reduced pressure and the crude residue was used directly without any further purification.[25]

Standard Procedure for Asymmetric Hydrogenation of Ferrocenyl Ketones

A stock solution of the ruthenium precatalyst in 2-propanol, ferrocenyl ketone, 2-propanol and $(CH_3)_3COK$ solution in 2-propanol were added to a stainless steel autoclave under a nitrogen atmosphere. The whole system was purged with hydrogen before being pressurized to 50 bar. The reaction mixture was stirred at room temperature for 15 h, after which the unreacted hydrogen was released slowly and carefully. The conversion and enantiomeric excess of ferrocenyl alcohol were determined by HPLC immediately without further purification. Analytical samples were purified by flash column chromatography.

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