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Ruthenium complexes of phosphine–aminophosphine ligands

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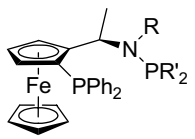
Abstract—Ruthenium complexes of phosphinoferrocenylaminophosphine ligands (BoPhoz™ ligands) have been prepared by combining the ligands with tris(triphenylphosphine)ruthenium dichloride and precipitating the complexes. The optimal species exhibit high enantioselectivities for the asymmetric hydrogenation of functionalized ketones, particularly β-ketoesters.

Asymmetric catalysis is a powerful technology for generating single enantiomer materials. Asymmetric hydrogenation is perhaps the most useful asymmetric reaction, as it utilizes an inexpensive reagent (hydrogen) with an often relatively inexpensive unsaturated substrate to afford a high value single enantiomer product. Of particular interest has been the asymmetric hydrogenation of functionalized ketones to afford the corresponding chiral alcohols.[1] Within this area, the hydrogenation of β-ketoesters has found the widest application, as the resulting β-hydroxyesters can be utilized for the preparation of a variety of materials, including pharmaceuticals[2] and chiral polymers.[3] The most effective catalysts for the asymmetric hydrogenation of β-ketoesters are ruthenium complexes prepared from axially chiral ligands, as first demonstrated with the BINAP ligand.[4] This methodology has found wide use for the preparation of a wide variety of chiral β-hydroxyesters in high enantiomeric purity. We have recently described a series of phosphine–aminophosphine ligands **1** that afford excellent activities and enantioselectivities as rhodium complexes for the asymmetric hydrogenation of dehydroamino acids, itaconates, and α-ketoesters,[5] and were interested in determining the viability of ruthenium complexes of these ligands for asymmetric catalysis.



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There are a number of methods available for the preparation of ruthenium complexes of bidentate phosphine ligands. Unfortunately, many of the methods use strong acid or base during the preparation, conditions that are not compatible with ligands **1**. Other potential precursors, such as dichloro(benzene)ruthenium(II) dimer and dichloro(*p*-cymene)ruthenium(II) dimer, afforded catalytically inactive materials with ligands **1**. A notable exception was the procedure developed by Mezetti and co-workers, which involves the exchange of two triphenylphosphine moieties of dichlorotris(triphenylphosphine)ruthenium(II) for a chelating bis-phosphine.[6] This methodology is perhaps the simplest process for the preparation of a catalytically active material, as it involves just a single step from readily available materials and utilizes no harsh reagents.

Combining ligands **1** with dichlorotris(triphenylphosphine)ruthenium(II) in dichloromethane overnight afforded ruthenium complexes **2**, which were isolated as air-stable green precipitates by dilution of the reaction mixture with isopropanol and removal of the dichloromethane under reduced pressure. The complexes prepared are indicated below. The antipodal complexes have also been prepared using the enantiomer of **1**.

These materials were examined for the asymmetric hydrogenation of a variety of β-ketoesters as indicated in Figure 1, with the results obtained detailed in Table 1.

The ruthenium complexes **2** showed a wide variety of reactivities and selectivities depending upon the

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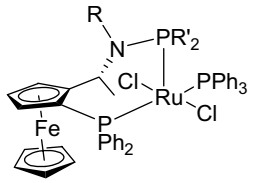
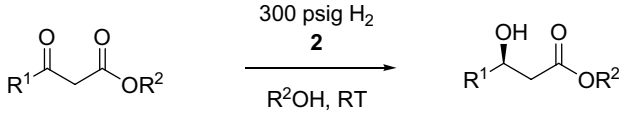


2

a: R = Me, R' = Ph
b: R = H, R' = Ph
c: R = Et, R' = Ph
d: R = CH_2Ph, R' = Ph
e: R = Me, R' = cyclohexyl
f: R = Me, R' = Et
g: R = Me, R' = i-Pr
h: R = Me, R' = 3,5-Me_2Ph
i: R = Me, R' = 4-MeOPh
j: R = Me, R' = 3-FPh
k: R = Me, R' = 4-FPh
m: R = Me, R' = 3,4-F_2Ph
n: R = Me, R' = 3,4-Cl_2Ph
o: R = Me, R' = 3,5-F_2Ph
p: R = Me, R' = 3,5-Cl_2Ph
q: R = Me, R' = PhO
r: R = Me, R' = 4-MeOPhO
s: R = Me, R' = 4-CF_3PhO
t: R = Me, R' = *R*-BINOL
u: R = Me, R' = *S*-BINOL

substituents on the aminophosphine portion of ligands **1**. The results with complex **2a** (from ligand **1a**) can be employed as a baseline, as this ligand has fairly generic



3 **4**

a: $R^1 = R^2 = Me$
b: $R^1 = Me$, $R^2 = Et$
c: $R^1 = Et$, $R^2 = Me$
d: $R^1 = Ph$, $R^2 = Et$

Figure 1. Asymmetric hydrogenation reactions.

Table 1. Asymmetric hydrogenation of β-ketoesters **3** with complex **2**[a]

Entry	2	% ee (% Conversion)			
		4a	**4b**	**4c**	**4d**
1	**a**	90.7 (100)	88.6 (100)	89.4 (100)	56.8 (70)
2	**b**	45.4 (82)	47.6 (73)	29.2 (1)	60.6 (14)
3	**c**	76.2 (100)	71.6 (85)	82.0 (91)	33.0 (60)
4	**d**	62.2 (100)	48.6 (90)	52.8 (87)	54.6 (39)
5	**e**	16.4 (65)[b]	52.2 (17)[b]	45.0 (11)[b]	87.2 (26)[b]
6	**f**	24.1 (51)[b]	59.6 (58)[b]	37.2 (93)[b]	1.8 (13)[b]
7	**g**	57.2 (25)[b]	49.2 (7)[b]	36.4 (6)[b]	75.6 (17)[b]
8	**h**	82.5 (100)	81.7 (100)	79.3 (100)	83.0 (37)
9	**i**	85.4 (97)	92.7 (34)	84.9 (24)	63.3 (43)
10	**j**	92.9 (100)	92.7 (100)	94.3 (100)	80.1 (99)
11	**k**	89.6 (100)	91.6 (100)	91.9 (98)	70.3 (91)
12	**m**	93.9 (99)	95.0 (100)	95.3 (100)	94.9 (99)
13	**n**	87.9 (100)	94.0 (59)	89.7 (100)	91.3 (87)
14	**o**	84.4 (100)	92.5 (100)	86.1 (100)	95.0 (6)
15	**p**	64.5 (100)	63.4 (40)	64.4 (90)	92.6 (33)
16	**q**	17.3 (99)	31.5 (79)	15.7 (93)	58.2 (39)
17	**r**	17.2 (99)	10.7 (36)	21.8 (45)	82.8 (2)[b]
18	**s**	11.5 (25)	nd (<1)	17.2 (2)	65.7 (16)[b]
19	**t**	0.4 (80)	2.3 (55)	1.1 (91)	38.2 (15)[b]
20	**u**	3.5 (100)	2.7 (68)	1.7 (96)	1.2 (5)[b]

[a] Reactions were run for 6 h at rt under 300 psig hydrogen using 0.5 mol % catalyst. nd indicates the result was not determined.
[b] Enantioselectivity reversal was observed.

substitution and afforded the best results for rhodium-catalyzed hydrogenations. Complex **2a** afforded good enantioselectivities for the hydrogenation of β-ketoesters **3a–c**, but poorer selectivity for the more challenging phenyl-substituted species **3d**. Changing the size of the alkyl group on the nitrogen (either smaller or larger) had a decidedly negative effect on the enantioselectivities (entries 2–4). Converting the aminophosphine of **1** to a phosphoramidite resulted in extremely poor enantioselectivities for β-ketoester hydrogenations (entries 16–20). In particular, the BINOL derived species **2t** and **2u** afforded the poorest enantioselectivities, a reversal of the excellent results obtained with some of these species for rhodium-catalyzed reactions.[5c,7]

Modification of the aryl groups of the aminophosphine of **1** had a significant effect on the selectivities of the reactions. Complexes with electron-donating aryl species on the phosphorus afforded slightly poorer results than **2a** (entries 8 and 9). In contrast, electron-withdrawing aryl substituents on the aminophosphine afforded good to excellent enantioselectivities and high reactivities (entries 10–15). The optimum results were obtained with a 3,4-difluorophenyl group as R′ (entry 12, **2m**), affording the overall highest enantioselectivities, even for the demanding phenyl-substituted substrate **3d**.

Of particular note are complexes **2e**, **2f**, and **2g**, which have alkyl groups on the phosphorus of the aminophosphine. These complexes afforded products with reversed (albeit moderate) enantioselectivities. Although the reason for this is not well understood, it is likely due to sterics rather than electronics, as other electron-donating phosphines did not show this reversal.

A pronounced improvement in enantioselectivity was observed for the asymmetric hydrogenations upon switching the solvent from methanol to ethanol for a number of catalysts (Table 2). This effect was in general most evident with the best catalysts. However, reduced activity was also often observed in ethanol as compared to methanol, and was more pronounced in going to higher alcohol solvents (*n*-propanol, isopropanol, *n*-butanol), although these solvents also afforded higher enantioselectivities than the reactions in methanol.

There was also interest in applying these complexes to the asymmetric hydrogenation of halo-substituted

Table 2. Solvent effects on asymmetric hydrogenation of **3a** and **3c** with complex **2**[a]

Entry	2	% ee (% Conversion)			
		4a (MeOH)	**4a** (EtOH)	**4c** (MeOH)	**4c** (EtOH)
1	**a**	90.7 (100)	90.8 (58)	89.4 (100)	91.4 (48)
2	**i**	85.4 (97)	94.0 (60)	84.9 (24)	93.4 (41)
3	**j**	92.9 (100)	94.2 (100)	94.3 (100)	94.0 (68)
4	**k**	89.6 (100)	94.2 (90)	91.8 (98)	94.6 (79)
5	**m**	93.9 (99)	96.0 (100)	95.3 (100)	95.4 (100)
6	**n**	87.9 (100)	94.6 (74)	89.7 (100)	84.6 (1)
7	**o**	84.4 (100)	96.6 (44)	86.1 (100)	93.8 (34)

[a] Reactions were run for 6 h at ambient temperature under 300 psig hydrogen using 0.5 mol % catalyst.

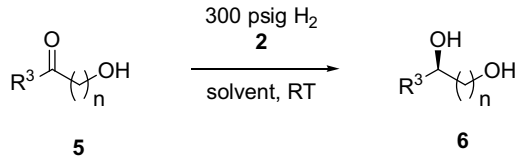


Figure 2. Asymmetric hydrogenation of hydroxyketones **5**.

Table 3. Asymmetric hydrogenation of hydroxyketones **5** with complex **2**[a]

Entry	**2**	R^3	*n*	Solvent	ee (%)
1	**a**	Et	1	MeOH	85.6
2	**a**	Et	1	EtOH	86.6
3	**m**	Et	1	MeOH	87.4
4	**m**	Et	1	EtOH	88.8
5	**m**	Me	2	MeOH	81.8
6	**m**	Ph	1	EtOH	77.6

[a] Reactions were run for 6 h at ambient temperature under 300 psig hydrogen using 0.5 mol % catalyst.

β-diketones (**3**, $R^1 = XCH_2$). Surprisingly, the hydrogenation of these substrates with complexes **2** afforded uniformly poor reactivities and enantioselectivities. This anomaly is unfortunate, as the products of these reactions have great utility for the preparation of a number of biologically active materials.[2]

Complexes **2** were examined for the asymmetric hydrogenation of other functionalized ketones. Positive results were obtained for the hydrogenation of hydroxy-substituted ketones. As shown in Figure 2 and Table 3, various α- and β-hydroxyketones **5** were hydrogenated with complexes **2** with good enantioselectivities. Although these selectivities are not as high as those obtained with the β-ketoesters, these reactions do afford synthetically interesting chiral diols in reasonably high enantiomeric purity.

Thus, we have found that ruthenium complexes of phosphine–aminophosphine ligands, prepared in a single simple step from dichlorotris(triphenylphosphine)ruthenium(II), afford good to high enantioselectivities for the asymmetric hydrogenation of functionalized ketones, particularly β-ketoesters. The complex with two 3,4-difluorophenyl substituents on the phosphorus of the aminophosphine affords the highest enantioselectivities (and good reactivities) for these transformations.

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