

Iron-Catalyzed Enantioselective Hydrosilylation of Ketones**

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Dedicated to Professor Wolfgang A. Herrmann on the occasion of his 60th birthday

Noteworthy efforts have been devoted to the development of efficient catalytic asymmetric reductions employing benign and environmentally available biometals such as iron, zinc, and copper. The preparation of enantiomerically pure secondary alcohols is of special significance because these intermediates constitute valuable building blocks for the manufacture of pharmaceuticals, agrochemicals, and advanced materials.^[1] Catalytic asymmetric hydrogenation of prochiral ketones is the most direct route to optically active alcohols,^[2] however, hydrosilylation of carbon–carbon and carbon–heteroatom bonds is a promising alternative to asymmetric hydrogenation because of the mild conditions and operational simplicity.^[3]

The earliest reports on hydrosilylation appeared three decades ago,^[4] and known asymmetric hydrosilylations of prochiral ketones rely on precious metals such as rhodium,^[5] ruthenium,^[6] and iridium.^[7] Less expensive metals such as titanium,^[8] zinc,^[9] tin,^[10] and copper^[11] have also been explored. Each method has its virtues as well as its limitations. The limitations include either the cost of the metal catalyst, the toxicity of the residual metal in the product, the operational difficulties (e.g. low temperatures ranging from –50 to –70 °C), or the use of complex ligand systems.

Recently, we started a program to develop more sustainable catalysts by replacing precious metals with nonprecious metals. In accord with the concept of “cheap metals for noble tasks”,^[12] the possible uses of iron catalysts are especially attractive.^[13] Iron is the second most abundant metal available and plays an important role in biology.^[14] Despite the many advantages and recent attention^[15] to iron catalysis, it remains undeveloped compared to other transition metals (e.g. Ru, Rh, Pd, and Ir etc.), particularly in the field of asymmetric catalysis. To the best of our knowledge there is only one report by Nishiyama and Furuta^[16] on the development of iron-catalyzed asymmetric hydrosilylation. They used multi-dentate nitrogen ligands and reported enantioselectivities of up to 79%. The scope of this work can be expanded; herein,

we disclose our results on an improved and general iron-catalyzed asymmetric hydrosilylation of ketones (Table 1).

Our recent study on the hydrosilylation of aldehydes revealed that Fe(OAc)₂ in the presence of electron-rich

Table 1: Ligand screening for the asymmetric hydrosilylation of acetophenone with Fe(OAc)₂–ligand.^[a]

Entry	Ligand	Yield ^[b] [%]	ee ^[c] [%]
1	(S)-binap	> 99	1
2	(R)-(S)-josiphos	74	1
3	(S,S)-diop	27	14
4	(S,S)-chiraphos	5	0
5	(S)-quinap	96	8
6	(S,S)-deguphos	68	7
7	(R)-binaphane	78	5
8	(R,R)-Me-duphos	92	69 (S)
9	(S,S)-Et-duphos	> 99	77 (R)
10	(S,S)-iPr-duphos	99	7
11	(S,S)-Me-duphos	> 99	75 (R)

[a] General conditions: Fe(OAc)₂ (5 mol %), ligand (10 mol %), acetophenone (0.5 mmol), (EtO)₂MeSiH (2 equiv), THF (2 mL), 65 °C. Absolute configuration of the secondary alcohol was determined by comparison of the optical rotation to reported values (see Supporting Information). (S,S)-diop = (4S,5S)-(–)-4,5-bis(diphenylphosphino)methyl-2,2-dimethyl-1,3-dioxolane; (S,S)-chiraphos = (2S,3S)-(–)-bis(diphenylphosphino)butane; (R)-binaphane = (R,R)-(–)-1,2-bis[(R)-4,5-dihydro-3H-binaphtho[1,2-c:2',1'-e]phosphino]benzene. [b] Determined by GC-FID methods with diethyleneglycol dimethyl ether as an internal standard. FID = flame ionization detection. [c] Determined by GC methods with a chiral column.

phosphine ligands and hydrosilanes forms an active catalyst.^[17] On the basis of these findings we turned our attention to the asymmetric reduction of ketones.

Initially, several chiral ligands were tested for the reduction of acetophenone to 1-phenylethanol by using a given set of conditions and selected phosphines (Table 1 and Figure 1). Privileged ligands such as (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((S)-binap), (R)-1-[(S)-2-diphenylphosphino]ferrocenyl]ethylidicyclohexylphosphine ((R)-(S)-josiphos), (S)-1-[2-(diphenylphosphino)-1-naphthyl]isoquinoline ((S)-quinap), (S,S)-1-benzyl-3,4-bis-(diphenylphosphino)pyrrolidine ((S,S)-deguphos), and binaphthyl derived systems, such as **L1** and **L2**, gave good to excellent conversions of acetophenone (68–99 %), but poor enantioselectivities (0–14 % ee). A 25 % ee is observed for **L3**, indicating the need for a more basic phosphorus atom to give increased

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

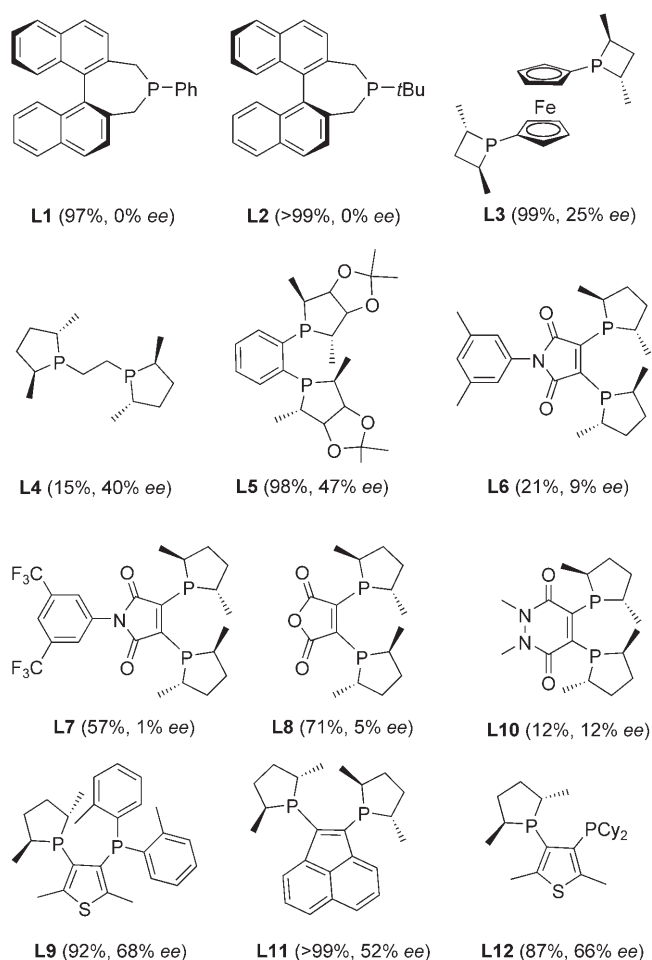


Figure 1. Selected chiral phosphine ligands (conversion and *ee* values). Reactions were carried out at 65 °C (**L1–L9**) and room temperature (**L10–L12**). Cy = cyclohexyl.

enantioselectivities. Additional screening of duphos systems^[18] (Table 1, entries 8–11) and related ligands **L4–L12** (Figure 1) showed that the steric bulk of the ligand was crucial in terms of enantioselectivity. A yield of greater than 99 % and *ee* values up to 77 % are obtained by using 1,2-bis((2*S*,5*S*)-2,5-diethyl-phospholano)benzene ((*S,S*)-Et-duphos) (Table 1, entry 9). The absolute configuration of product **2a** is opposite to that of the chiral ligand.

Notably, variations in the aryl backbone of ligands **L4** and **L6–L9**, or modifications of the phospholane ring (**L5**) lowered the enantioselectivity significantly. 1,2-Bis((2*S*,5*S*)-2,5-dimethyl-phospholano)-benzene ((*S,S*)-Me-duphos) was chosen for additional optimization because of the price and the ease of handling the parent ligand. To our surprise, even FeCl₃ gave a substantial conversion (68 %) of acetophenone, but with moderate enantioselectivity (49 % *ee*) (Table 2, entry 5).

No reaction was observed for either FeCl₂ or FeCl₃ when used in the presence of a silver salt additive (Table 2, entries 2 and 6). Surprisingly, one of the most common iron–carbonyl complexes, Fe₃(CO)₁₂, led to a respectable *ee* value (Table 2, entry 8). Among the salts tested, Fe(OAc)₂ was found to be optimal in terms of conversion and enantioselectivity.

Table 2: Asymmetric hydrosilylation of acetophenone by using (*S,S*)-Me-duphos.^[a]

Entry	Metal precursor	Conversion ^[b] [%]	<i>ee</i> ^[c] [%]
1	FeCl ₂	< 5	5
2	FeCl ₂ /AgBF ₄	10	0
3	FeI ₂	89	21
4	FeF ₂	15	41
5	FeCl ₃	68	49
6	FeCl ₃ /AgBF ₄	< 5	0
7	Fe(acac) ₃	14	40
8	Fe ₃ (CO) ₁₂	15	66
9	Fe(BF ₄) ₂ ·6 H ₂ O	> 99	5
10	Fe(OAc) ₂	> 99	75
11	Fe(OSO ₂ CF ₃) ₂	17	20

[a] General conditions: Fe catalyst (5 mol %), (*S,S*)-Me-duphos (10 mol %), acetophenone (0.5 mmol), (EtO)₂MeSiH (2 equiv), THF (2 mL). [b] Determined by GC-FID methods with diethyleneglycol dimethyl ether as an internal standard. [c] Determined by GC methods with a chiral column.

Having a suitable metal/ligand combination in hand, we surveyed different hydride sources and found that both (EtO)₂MeSiH and the more economical poly(methylhydroxysilane) (PMHS) have similar reactivity and selectivity (compare Table 1, entry 11 to Table 3 entry 1).^[19] In general,

Table 3: Asymmetric hydrosilylation of acetophenone with different solvents and hydrosilanes.^[a]

Entry	Silane	Solvent	<i>T</i> [°C]	Conv. ^[b] [%]	<i>ee</i> ^[c] [%]
1 ^[d]	PMHS	THF	65	> 99	75 ^[d]
2	Ph ₂ SiH ₂	THF	65	22	12
3	PhSiH ₃	THF	65	32	1
4	TMDS	THF	65	54	76
5	(EtO) ₂ MeSiH	THF	RT	88	79
6 ^[d,e]	PMHS	THF	RT	27	76
7 ^[f]	PMHS	THF	RT	81	76
8	(EtO) ₂ MeSiH	Et ₂ O	40	> 99	75
9	(EtO) ₂ MeSiH	<i>n</i> hexane	65	96	73
10	(EtO) ₂ MeSiH	DCM	65	> 99	74
11	(EtO) ₂ MeSiH	toluene	100	99	74
12	(EtO) ₂ MeSiH	THF-MeOH ^[g]	50	8	80
13	(EtO) ₂ MeSiH	THF- <i>t</i> BuOH ^[h]	65	43	80

[a] Unless stated otherwise reactions were run with acetophenone (0.5 mmol), Fe(OAc)₂ (5 mol %), (*S,S*)-Me-duphos (10 mol %), silane (2 equiv) for 16 h. [b] Determined by GC-FID methods with diethyleneglycol dimethyl ether as an internal standard. [c] Determined by GC methods with a chiral column. [d] Used PMHS (2.5 equiv). [e] Reaction run for 32 h. [f] Used excess of PMHS (4 equiv). [g] MeOH (1 mol %). [h] *t*BuOH (1 mol %). TMDS = 1,1,3,3-tetramethyldisilane.

we observed a small temperature effect on the selectivity of the catalyst. Typically, when the reaction is carried out at room temperature the conversion is lowered slightly (100 versus 88 %) and the *ee* values increase slightly (75 versus 79 % *ee*, Table 3, entry 5). Advantageously, there is no solvent effect on the reaction because the hydrosilylation works well in most of the common organic solvents such as ethers (diethyl ether), alkanes (*n*hexane), haloalkanes (dichloromethane), and arenes (toluene) (Table 3, entries 8–11). The

Table 4: Scope of the Fe-catalyzed asymmetric hydrosilylation.^[a]

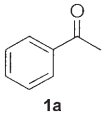
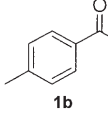
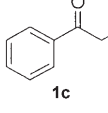
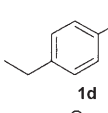
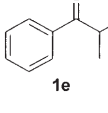
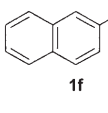
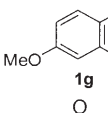
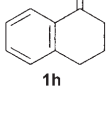
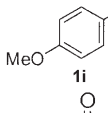
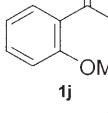
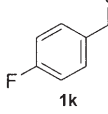
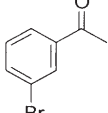
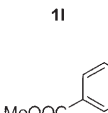
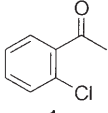
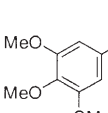
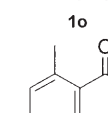
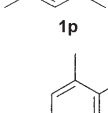
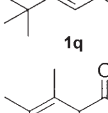
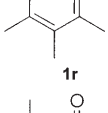
Entry	Ketone	T [°C]	t [h]	Yield ^[b] [%]	ee ^[c] [%]
1		RT 65 100	48 2 1	80 85 ^[d] 82 ^[d]	79 75 75 ^[e]
2		RT	32	90	81
3		RT 65	32 16	61 93	78 74
4		RT	96	> 99 ^[d]	82
5		RT	48	52	67
6		RT 65	32 16	93 ^[d] 81 ^[d]	70 66
7		RT	48	86	79 ^[f]
8		RT	32	72	75
9		85	4	76 ^[e]	78 ^[f]
10		RT 65	32 16	80 95	77 ^[f] 74 ^[f]
11		RT	38	85	62
12		85	2	90	49 ^[e]
13		RT	32	93	48 ^[f]

Table 4: (Continued)

Entry	Ketone	T [°C]	t [h]	Yield ^[b] [%]	ee ^[c] [%]
14		85	2	71	55 ^[e]
15		RT	32	84	89 ^[f]
16		RT 65 65	48 20 20	76 94 ^[d] > 99 ^[d]	99 98 99 ^[e]
17		65	24	78	99 ^[e]
18		65	24	45	99 ^[e]
19		65	16	60	51 ^[h]

[a] Unless stated otherwise see the experimental section for general conditions. For entries 4 and 6, the reaction was quenched before completion. Absolute configuration of secondary alcohols was determined to be *R* by comparison of optical rotation with reported values (see Supporting Information). RT = room temperature. [b] Yield of isolated pure product. [c] Determined by GC/HPLC methods with a chiral column. [d] Conversion of more than 99% (GC). [e] Reaction in toluene. [f] Work-up with saturated NaHCO₃. [g] Used PMHS (4 equiv). [h] Used (EtO)₂MeSiH (3.5 equiv).

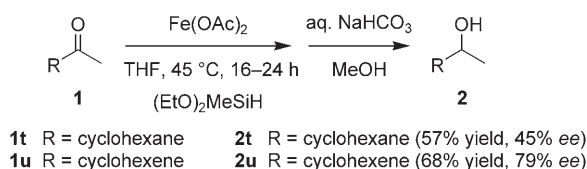
addition of protic solvents such MeOH and water to the reaction mixture showed no effect on the *ee* value, but the conversion is significantly decreased (Table 3, entries 12 and 13).

After the optimized conditions were established, we studied the scope and the limitations of the present reaction protocol (Table 4). Several aryl ketones reacted at room temperature, but nevertheless, reactions at 100 °C gave similar yields of the desired product within 1 hour and with marginal loss in enantioselectivity. In contrast to the elegant work of Nishiyama et al.,^[17] formation of the corresponding silyl enol ether is not detected after full conversion. In our reactions the silyl ether of the corresponding secondary alcohol is the only product observed before hydrolysis. For acetophenones with alkyl groups on both the arene ring or the α -position we observe comparable enantioselectivities (67–82 %). The *ee* value is influenced by the electronic nature of the aryl substituents (Table 4, entries 1–10) with electron-donating substituents gave a higher selectivity than electron-withdraw-

ing substituents (compare ketones **1i**, **1j**, and **1o** with **1k**, **1l**, **1m**, and **1n**).^[20]

Interestingly, sterically hindered aryl ketones gave the best enantioselectivities. The reaction of **1p** led to a remarkable 99% *ee* (Table 4, entry 16). Notably, the selectivity does not decrease at 65 °C or when using PMHS as the reductant. To the best of our knowledge this is the highest enantioselectivity obtained for an iron-catalyzed reduction. An excellent enantioselectivity is also obtained for the reduction of ketone **1q** (99% *ee*). Similarly, fully substituted acetophenone **1r** (to our knowledge studied for the first time in the hydrosilylation reactions) gave the corresponding secondary alcohol in greater than 99% *ee*.

Despite the wide applications of optically active benzhydrol derivatives in the synthesis of pharmaceuticals, asymmetric hydrosilylation of unsymmetrical benzophenones remains a challenge.^[21] Thus, we studied the reduction of 2-methyl benzophenone. The reaction proceeded smoothly to give 2-methylbenzhydrol in 60% yield and 51% *ee*, indicating the possibility of broadening the scope of the present iron catalysis (Table 4, entry 19). Finally, we performed some initial hydrosilylations of challenging dialkyl ketones (Scheme 1). Here, cyclohexylmethyl ketone is reduced to



Scheme 1. Iron-catalyzed asymmetric hydrosilylation of alkyl and α,β -unsaturated ketones.

the corresponding alcohol in 45% *ee*, which is superior to previously reported Ru^[6b] and Ti^[8] catalysts (43 and 23% *ee*, respectively). Also, conjugated ketone **1u** is reduced to corresponding allylic alcohol **2u** in 79% *ee*.^[22]

In summary, we have demonstrated for the first time that high enantioselectivity (up to 99% *ee*) can be achieved in the Fe-catalyzed hydrosilylation of ketones. Good to excellent enantioselectivities are obtained for electronically rich and sterically hindered aryl ketones. In addition, diaryl and dialkyl ketones were converted into the corresponding alcohols in good to excellent enantioselectivities (up to 79% *ee*). As an additional advantage of the present catalytic system, activating agents or additives are not needed. We believe that the present investigation is an important step towards general asymmetric reductions with iron catalysts.

Experimental Section

General procedure: A 10-mL oven dried Schlenk tube containing a stir bar was charged with Fe(OAc)₂ (8.7 mg, 0.05 mmol) and (*S,S*)-Me-duphos (28 mg, 0.1 mmol). Anhydrous THF (3 mL) and the ketone (1 mmol) were added after purging the Schlenk tube with argon (argon/vacuum three cycles). The reaction mixture was stirred in a preheated oil bath at 65 °C for 10–15 min until an orange-colored solution was observed. The reaction tube was removed from the oil bath and then (EtO)₂MeSiH (0.18 mL, 2 equiv) or PMHS (0.24 mL, 4

equiv) was added by a syringe under argon. The reaction mixture was stirred for the time indicated in Table 4 at room temperature (unless stated otherwise) and cooled to 0 °C. Then diglyme (80 μ L) as a GC standard (for GC analysis), MeOH (1 mL), and 2 M NaOH (1 mL) or saturated aqueous solution of NaHCO₃ (2 mL, in case of methoxy substituted compounds or dialkyl ketones) were added with vigorous stirring (Caution: The reaction mixture bubbled briefly but vigorously upon the addition of the base). The reaction mixture was stirred for an additional hour (or until the organic layer changed from colorless to pale yellow) at room temperature and was then extracted with diethyl ether (3 $\times$ 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered (an aliquot was removed for GC analysis), and concentrated in vacuo. The residue was purified by silica gel column chromatography by using an ethyl acetate/nhexane solvent mixture (20 to 40%) to afford the desired product.

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