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A Convenient and General Iron-Catalyzed Hydrosilylation of Aldehydes

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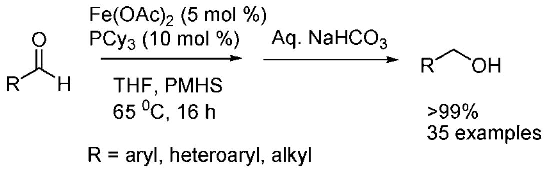
ABSTRACT



A general and highly chemoselective hydrosilylation of aldehydes using iron catalysts is reported. $Fe(OAc)_2$ in the presence of tricyclohexylphosphine as ligand and polymethylhydrosiloxane (PMHS) as an economical hydride source forms an efficient catalyst system for the hydrosilylation of a variety of aldehydes. Aryl, heteroaryl, alkyl and α,β-unsaturated aldehydes are successfully reduced to the corresponding primary alcohols. Broad substrate scope and high tolerance against several functional groups make the process synthetically useful.

Within the field of metal catalyzed organic transformations, hydrosilylation of carbon−carbon and carbon heteroatom bonds are valuable alternatives to hydrogenation as well as transfer hydrogenation reactions.[1] While hydrosilanes are inert toward nonactivated carbonyl compounds, a considerable number of transition metal complexes are known to act as catalysts for hydrosilylations. In the past especially the hydrosilylation of ketones has been studied.[2]

Although numerous methods are available for the reduction of aldehydes, drawbacks such as poor selectivity, the highly sensitive or pyrophoric nature of the reagents, or the toxicity and cost of metal catalyst, create the demand for more sustainable methods.[3] Hence, the development of selective but less expensive and environmentally more benign catalysts is a prime goal in this area. In this regard, iron is the most inexpensive and a relatively nontoxic transition metal.[4] Despite many obvious advantages, iron catalysis remained undeveloped compared to other transition metals such as Rh, Ru, Pd, and Ir, etc. Recently, we have successfully demonstrated the use of iron-based catalysts for biomimetic transfer hydrogenations,[5] hydrogenation of ketones,[6] epoxidation of olefins,[7] and other useful catalytic reactions.[8] On the basis

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[1] For recent reviews on chemo- and enantioselective hydrosilylation: (a) Carpentier, J.-F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, 913−936. (b) Nishiyama, H. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 182−191. (c) Nishiyama, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: 1999; Chapter 6.3. (d) Ohkuma, T.; Noyori, R. *Comp. Asym. Catal. Supp.* **2004**, *1*, 55−71. (e) Riant, O.; Mosterai, N.; Courmarcel, J. *Synthesis* **2004**, 2943.

[2] (a) Nishiyama, H.; Furuta, A. *Chem. Commun.* **2007**, *7*, 760−762. (b) Diez-Gonzalez, S.; Scott, N. M.; Nolan, S. P. *Organometallics* **2006**, *25*, 2355−2358.

[3] Existing methods for reduction of aldehydes using hydride-based reagents: (a) Krishnamurthy, S. J. *J. Org. Chem.* **1981**, *46*, 4628. (b) Hecker, S. J; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586. Recent examples for hydrosilylation of aldehydes using silver: (c) Wile, B. M.; Stradiotto, M. *Chem. Commun.* **2006**, 4104−4106. Using gold complexes: (d) Lantos, D.; Contel, M.; Sanz, S.; Bodor, A.; Horvath, I. T. *J. Organomet. Chem.* **2007**, *692*, 1799−1805. Using Stryker's reagent: (e) Lipshutz, B. H.; Chrisman, W.; Noson, K. *J. Organomet. Chem.* **2001**, *624*, 367−371. Using BINOL-Zr complex see: (f) Lorca, M.; Kuhn, D.; Kurosu, M. *Tetrahedron Lett.* **2001**, *42*, 6243−6246 and references cited therein. Use of $P(MeNCH_2CH_2)_3N$: (g) Wang, Z.; Wroblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 8021−8023. Using $NaBH_4$: (h) Nutaitis, C. F.; Bernardo, J. E., *J. Org. Chem.* **1989**, *54*, 5629−5630 and references cited therein.

[4] For a recent review on iron catalysis see: Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254.

[5] Enthaler, S.; Erre, G.; Tse, M. K.; Junge, K.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8095−8099.

[6] Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chem. Asian J.* **2006**, *1*, 598−604.

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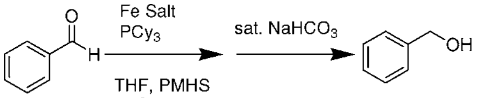
of these results we became interested in the iron-catalyzed hydrosilylation of carbonyl compounds.

Here, we report for the first time our investigations, which result in a highly chemoselective reduction of aldehydes with broad substrate scope.

As shown in Table 1, several commercially available iron salts were tested in the presence of tricyclohexyl-phosphine as a ligand and polymethylhydrosiloxan (PMHS)[9] for the hydrosilylation of benzaldehyde. In this model reaction benzaldehyde is converted to (polymeric) silyl ether intermediates, which upon basic workup afforded benzyl alcohol. At 65 °C $Fe(OAc)_2$ and $Fe(BF_4)_2 \cdot 6H_2O$ proved to be most reactive (Table 1, entries 2, 3, and 13). Iron perchlorate (hydrate) gave benzyl alcohol in moderate yield (57%) at higher catalyst loading (15 mol %, 20 mol % ligand) and temperature (85 °C). Other iron salts of Fe(II) as well as Fe(III) showed very little or no activity (Table 1, entries 6−9, 12, 14−16). $Fe(OAc)_2$ was chosen for further studies as it is easy to handle, for example, can be handled/weighed in air. There was no conversion when the reaction was carried out at room temperature using $Fe(OAc)_2/PCy_3$/PMHS system.

Table 1. Iron-Catalyzed Hydrosilylation of Benzaldehyde[a]



1a **1b**

entry	catalyst	temp (°C)	yield (%)[b]
1	$Fe(acac)_2$	65	18
2	$Fe(OAc)_2$	65	90[c]
3	$Fe(OAc)_2$	65	98
4	$Fe(OAc)_2$	rt	0
5	$Fe(OAc)_2$	50	75
6	$FeCl_2$	65	10
7	FeI_2	65	0
8	FeF_2	65	2
9	$FeCl_3$ (anhydrous)	65	25
10	$Fe(ClO_4)_3$	65	10
11	$Fe(ClO_4)_3$	85	57[d]
12	Fe(III)citrate	65	<1
13	$Fe(BF_4)_2.6H_2O$	65	92
14	$Fe(acac)_3$	65	5
15	$FeBr_2$	65	15
16	$Fe(OSO_2CF_3)_2$	65	21

[a] Reactions were conducted with benzaldehyde (0.5 mmol), unless stated, iron salt (5 mol %), PCy_3 (10 mol %) in THF (2 mL) using PMHS (3 equiv), for 16 h. [b] Determined by GC-FID using diethylene glycol dimethyl ether as an internal standard. [c] Reaction run using 5 mol % ligand. [d] Reaction run using 15 mol % catalyst and 20 mol % ligand.

Further screening of ligands (Table 2) revealed that a more basic phosphine is required for good conversion (e.g., Table 2, entries 1−4 and 6), although to our surprise the hindered di-1-adamantyl-*n*-butylphosphine does not show any reactivity (Table 2, entry 9). Use of other mono- or bidentate ligands showed very little or no activity at all. Among the tested hydrosilanes, diethoxymethylsilane and phenylsilane gave good yields of benzyl alcohol via formation of the corresponding silyl ether intermediates (Table 2, entries 2−4).[10] The most inexpensive polymeric hydrosilane, PMHS (3 equiv) proved to be ideal for this catalyst system. Moreover, diethoxymethylsilane gave similar results (95%, 4 h, Table 2, entry 2).

Table 2. Hydrosilylation of Benzaldehyde Using $Fe(OAc)_2$[a]

entry	ligand	silane	yield(%)[b]
1	PCy_3	PMHS	98
2	PCy_3	$(EtO)_2MeSiH$	95[c]
3	PCy_3	Ph_2SiH_2	64
4	PCy_3	$PhSiH_3$	83
5	PCy_3	Ph_2MeSiH	<1
6	$^tBu_3P$	PMHS	61
7	2-(Di-*tert*-butylphosphino)-1-phenyl-1*H*-pyrrole	PMHS	10
8	PPh_3	PMHS	9
9	Di-1-adamantyl-*n*-butyl-phosphine	PMHS	<1
10	DPPC	PMHS	15
11	DPPM	PMHS	2
12	DPPE	PMHS	3

[a] Unless otherwise stated, the reactions were performed at 65 °C for 16 h with benzaldehyde (0.5 mmol) in THF (2 mL) using silane (1.6 equiv) or PMHS (3 equiv). Iron catalyst 5 mol % and ligand 10 mol % were used. [b] Yield of **1b** determined by GC-FID using diethyleneglycol dimethyl ether as an internal standard. DPPC, 1,2-bis(diphenyl-phosphino)cyclohexane; DPPM, bis(diphenylphosphino)methane; DPPE, bis(diphenylphosphino)ethane. [c] Reaction was run for 4 h.

The order of reactivity of hydrosilanes with the present catalyst system is observed as PMHS ≥ $(EtO)_2MeSiH$ > $PhSiH_3$ > Ph_2SiH_2 > Ph_2MeSiH (Table 2, entries 1−5). After optimization, we were able to demonstrate the generality of our practical hydrosilylation with several aromatic aldehydes (Table 3).

The duration of the reaction was unoptimized; however, no product was formed in the first 3 h in the case of benzaldehyde (monitored by GC for entries 1, 3−5). In most

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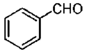
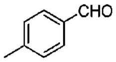
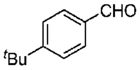
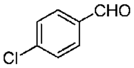
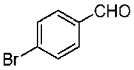
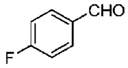
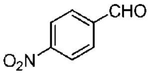
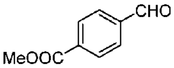
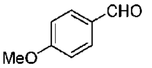
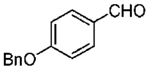
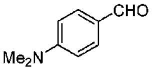
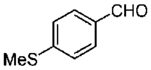
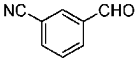
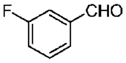
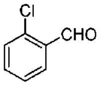
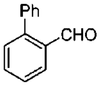
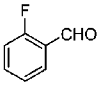
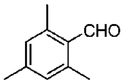
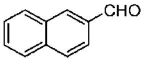
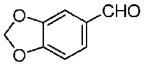
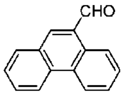
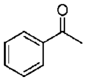
(7) (a) Anilkumar, G.; Bitterlich, B.; Gelalcha, F. G.; Tse, M. K.; Beller, M. *Chem. Commun.* **2007**, 289−291. (b) Bitterlich, B.; Anilkumar, G.; Gelalcha, F. G.; Spilker, B.; Grotevendt, A.; Jackstell, R.; Tse, M. K.; Beller, M. *Chem. Asian J.* **2007**, *2*, 521−529. (c) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem, Int. Ed.* **2007**, *46*, 7293−7296.

(8) (a) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19−22. (b) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913−3917.

(9) PMHS was discovered as a stoichiometric reductant with reduced toxicity and reagent cost: (a) Barr, K. J.; Berki, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323. For a review on PMHS see: (b) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381−3391. For the use of PMHS in hydrosilylation (c) Mimoun, H. *J. Org. Chem.* **1999**, *64*, 2582−2589. The first example of iron with PMHS in the presence of $NaBH_4$ for the reduction of carbonyl: (d) Mimoun, H. Patent WO 96/12694, Firmenich S. A., 1995. (e) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713−715. (f) Jurkauskas, V.; Sadighi, P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417−2420.

(10) According to GC−MS analysis of the reaction mixture the corresponding silyl ethers (*m*/*z* = 240, 290, 214; Table 2, entries 2−4, respectively) were detected. Ph_2MeSiH was inert under the present reaction conditions.

Table 3. Iron-Catalyzed Hydrosilylation[a]

entry	aldehyde	product	yield(%)[b]
1		**1b**	93
2		**2b**	91
3		**3b**	97[c]
4		**4b**	87[c]
5		**5b**	82
6		**6b**	72
7		**7b**	87
8		**8b**	>99[c]
9		**9b**	91[d]
10		**10b**	90
11		**11b**	98[c]
12		**12b**	87[c]
13		**13b**	87
14		**14b**	78
15		**15b**	87[c]
16		**16b**	96[c]
17		**17b**	81[c]
18		**18b**	78[c]
19		**19b**	93
20		**20b**	91
21		**21b**	86
22		**22b**	82

[a] For experimental procedure see Supporting Information. [b] Yield refers to isolated products with purity >95% by GC and NMR. Unless otherwise stated the remainder is essentially the starting material. [c] Conversion of 100% determined by GC. [d] Work up with CsF (1 mmol), 1 M TBAF in THF solution (1 mL).

cases the reaction was complete within 16 h resulting in a black precipitate of the iron catalyst. There is almost no reaction in the absence of either $\mathrm{Fe(OAc)_2}$ or $\mathrm{PCy_3}$ or both even at 85 °C (<5% conversion) in the case of benzaldehyde. Applying the optimized procedure several functionalized benzaldehydes were reduced with excellent chemoselectivity.[11] Functional groups that are susceptible to reduction, for example, Cl, Br, F, $\mathrm{NO_2}$, COOMe,[12] CN, and *O*-benzyl, remained unchanged during the reaction (Table 3, entries 4−10, 13).[13] Substitution at the ortho, meta or para position of the aryl ring did not hamper the reactivity. However, in the case of 4-nitrobenzaldehyde, 4-amino benzyl alcohol was detected only in a trace amount (Table 3, entry 7).[14] Electron-rich as well as electron-deficient groups on the aryl ring did not show any significant influence on the performance of the catalyst. Sterically demanding substrates (Table 3, entries 16−19, 21, respectively) are converted almost quantitatively to afford the corresponding primary alcohols in good to excellent yields (78−96%). In a few cases different silicon species were detected by GC−MS analysis of the reaction mixture with higher molecular weight resulting from the decomposition of PMHS.[15] Those silicon compounds are easily removed during column chromatography to obtain the desired products with high purity (>95% judged by GC and NMR).

Acetophenone is also reduced to the corresponding secondary alcohol, **22b** in good yield under the standard conditions (82% yield). As an obvious observation, in a competitive experiment when a mixture of 4-tolylaldehyde and 4-tolylacetophenone was reacted with PMHS in the presence of the catalyst system the aldehyde was reduced preferably in the first 6 h in 76% yield, whereas the ketone substrate was not reactive. When this reaction was continued the aldehyde was consumed completely giving a 96% yield of *p*-tolylmethanol **2b** and 21% of 1-*p*-tolylethanol **23b**.[16]

Notably, the present catalyst system can be applied successfully to the reduction of heteroaromatic aldehydes. Synthetically useful examples such as pyridine, quinoline, furan, and thiophene carbaldehyde (Table 4, entries 1−5) are converted to the corresponding primary alcohols again in good to excellent yields (80−92%).

In general, aliphatic aldehydes are more challenging substrates for metal-catalyzed reductions. In the present case

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(11) Recently, Nishiyama et al. demonstrated elegantly the catalytic application of iron with TMEDA and $\mathrm{(EtO)_2MeSiH}$ for reduction of ketones, including an example of *p*-anisaldehyde with 97% yield. However, detailed scope and limitations for various aldehydes remained to be studied; see ref 2a.

(12) PMHS in the presence of $\mathrm{Ti(O^iPr)_4}$ is used for hydrosilylation of esters to primary alcohols: Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1995**, *60*, 7884−7890. However, the ester group did not react with the present iron catalyst.

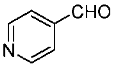
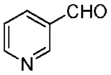
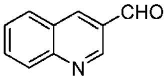
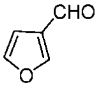
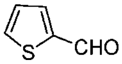
(13) For the Meerwein−Ponndorf−Verley (MPV) reduction of activated aldehydes using $\mathrm{Zr(O^iPr)_4}$ see: Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31.

(14) Interestingly, PMHS along with $\mathrm{Pd(OAc)_2}$/aq KF system is developed for the reduction of nitro groups: Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Org. Lett.* **2005**, *7*, 5087−5090.

(15) In the present case the compounds with *m/z*: 299, 399, 373, and 269 are observed. Degradation of PMHS by reactions with $\mathrm{Ti(O^iPr)_4}$ gave a product with *m/z* 220, see ref 11; this is not seen in the present case.

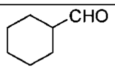
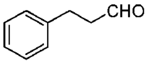
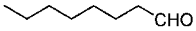
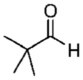
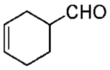
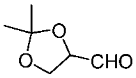
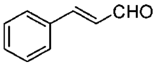
(16) Upon basic workup, the reaction was monitored by GC-FID using diethylene glycol dimethyl ether as an internal standard.

Table 4. Iron-Catalyzed Hydrosilylation of Heteroaromatic Aldehydes[a]

entry	aldehyde	product	Yield (%)[b]
1		**24b**	80[c]
2		**25b**	92[c]
3		**26b**	82
4		**27b**	90[c]
5		**28b**	81

[a] For experimental procedure see Supporting Information. [b] Yields refer to isolated products with purity >95% by GC and NMR. Unless otherwise stated the remainder is essentially the starting material. [c] Reaction produced 100% conversion determined by GC.

Table 5. Iron-Catalyzed Hydrosilylation of Aliphatic and α,*β*-Unsaturated Aldehydes[a]

entry	aldehyde	Product	Yield (%)[b]
1		**29b**	64[c]
2		**30b**	90[c,d]
3		**31b**	71[c,e]
4		**32b**	62[c]
5		**33b**	80[c,d]
6		**34b**	60
7		**35b**	82

[a] For experimental procedure see Supporting Information. [b] Yields refer to isolated pure products. Unless otherwise stated the remainder is essentially the starting material. [c] Reaction produced 100% conversion determined by GC. [d] Reaction was conducted at 80 °C for 3 h. [e] Reaction was conducted for 3 h using $(EtO)_2MeSiH$.

cyclic as well as acyclic aliphatic aldehydes are also reduced in good yields (Table 5, entries 1−6, 60−90%). Quantitative conversion of aldehydes **30a**−**33a** was observed within 3 h (Table 5, entries 2−5). The acetonide moiety of **34a** was stable under the reaction conditions (Table 5, entries 6) to afford a moderate yield of glycerol **34b** (60%). Furthermore, *trans*-cinnamaldehyde was converted to cinnamyl alcohol exclusively (82%). No sign of 1,4-reduction was detected[17] (Table 5, entry 7).

In summary, a general and highly chemoselective method for hydrosilylation of aldehydes has been developed using ferrous acetate and tricyclohexylphosphine as the catalyst system. PMHS as a stable, nontoxic, and easy to handle reducing agent proved to be a highly efficient hydride source. Alternatively, diethoxymethylsilane can be used for clean transformation within shorter reaction time (16 vs 4 h).

The iron catalyst and the reagents are readily available and inexpensive. The novel catalyst system works well for aryl, heteroaryl, and alkyl aldehydes to afford the corresponding primary alcohols in high yields. On the basis of the simplicity, inexpense, and tolerance of a diverse set of common organic functional groups we believe the present catalyst system will serve as a promising tool for organic chemists. Further effort directed toward the asymmetric version of the present process to ketones is in progress.

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Supporting Information Available: General experimental procedure, ^1H and ^{13}C NMR data, corresponding NMR spectra of isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Reduction of unsaturated carbonyl compounds using $NaBH_4$ provide allylic alcohols with significant amount of saturated alcohols; see ref 3h.