An iron-catalysed hydrosilylation of ketones

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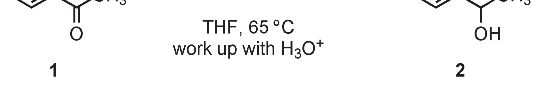
The combination of $Fe(OAc)_2$ and multi-nitrogen-based ligands such as *N,N,N′,N′*-tetramethyethylenediamine, bis-*tert*-butyl-bipyridine, or bis(oxazolinyl)pyridine can efficiently catalyse hydrosilylation of ketones to give the corresponding alcohols in high yields including asymmetric catalysis.

Use of iron as a catalyst core metal, being inexpensive and environmentally sound, has long been required in organic synthesis.[1] Recently, some efficient reactions with iron salts or complexes have been reported in terms of C–C bond formations such as coupling, cycloaddition or polymerization reactions. However, examples related to reduction are scarce and limited for alkene- or nitro-reductions.[2] As we have studied hydrosilylation of ketones with rhodium catalysts, we were greatly interested in finding a new iron catalyst for that purpose.[3,4] In this context, to the best of our knowledge, Brunner *et al.* described only one instance of hydrosilylation of acetophenone with Fe(Cp)(CO) complex under photo-irradiation.[5] Although much attention has been focused in this decade on copper or titanium catalysts as well as rhodium ones as the hydosilylation catalysts in both asymmetric and non-asymmetric reduction of ketones,[4,6–9] we have attempted to find a new iron-catalysed system. Very recently, iron-catalysed transfer hydrogenative reduction of ketones was reported by Beller *et al.* as an environmentally benign process.[10] Here, we disclose an efficient iron-catalysed hydrosilylation of ketones with several hydrosilanes as a versatile and valuable reduction method.

We examined several commercially available iron salts such as ferrous acetate, ferrous chloride, or ferrous and ferric acetylacetonato as candidate catalysts. First, we carried out the reduction of methyl 4-phenylphenyl ketone (**1**) as a probe substrate using ferrous acetate, $Fe(OAc)_2$, (5 mol%) and $(EtO)_2MeSiH$ (2 equiv.) in THF (3 mL) solution at 65 °C (Scheme 1). However, ferrous acetate changed to black precipitates by reaction with the hydrosilane to promote the reduction only in 6% yield (Table 1, run 1). Addition of bipyridine (bipy) and bis-*tert*-butyl-bipyridine (bipy-*tb*) (10 mol%) dramatically improved the yield to 90 and 85% of the alcohol **2**, respectively (run 2,3). Furthermore, an addition of *N,N,N′,N′*-tetramethylethylenediamine (tmeda) (10 mol%) eventually attained 94% yield for 20 h reaction time (run 4).†‡ The addition of the nitrogen-based additives made ferrous acetate readily soluble in THF by facile coordination to give a reddish brown solution, and the generated lower-valent iron species might efficiently act as catalysts. Polymethylhydrosilane (PMHS) also worked well as a hydrogen donor in the combination of ferrous acetate (run 5). Next, we adopted terdentate ligands such as bis(oxazolinyl)pyridine (pybox-*dm*)[11] and bisiminopyridine (bimpy).[12] The case of pybox-*dm* retarded the reduction somewhat but gave high yield 94% (run 7), whereas the reaction with bimpy was very slow (run 8). At room temperature, the catalysis was very slow. In addition, the active iron catalysts were very sensitive toward oxygen. The catalysis therefore should be used under an inert atmosphere. As other iron salts, $FeCl_2{\cdot}(H_2O)_4$, $Fe(acac)_2$, and $Fe(acac)_3$ (5 mol%) were examined with tmeda and $(EtO)_2MeSiH$ at 65 °C but resulted in no reduction or formation of only trace amounts of **2**. Probably, the iron catalysts decomposed in the failure cases, where by addition of $(EtO)_2MeSiH$ the color of the reaction mixtures turned to pale yellow from dark orange.



Scheme 1

Table 1 Iron-catalysed hydrosilylation of methyl 4-phenylphenyl ketone (**1**)[a]

Run	Ligand	Hydrosilane	Temp/time (°C/h)	Yield (%) **2** (recvd **1**)
1	—	$(EtO)_2MeSiH$	65/24	6 (94)
2	bipy	$(EtO)_2MeSiH$	65/24	90 (6)[b]
3	bipy-*tb*	$(EtO)_2MeSiH$	65/24	85 (6)[b]
4	tmeda	$(EtO)_2MeSiH$	65/20	94 (3)[b]
5	tmeda	PMHS	65/5	90 (2)[b]
6	tmeda	$(EtO)_3SiH$	65/24	65 (20)
7	pybox-*dm*	$(EtO)_2MeSiH$	65/34	95 (3)[b]
8	bimpy	$(EtO)_2MeSiH$	65/24	7 (93)

[a] Ketone (**1**) (1.0 mmol), $Fe(OAc)_2$ (5 mol%), ligand: bipy, bipy-*tb*, and tmeda (10 mol%), pybox-*dm* and bimpy (7 mol%), hydrosilane: $(EtO)_2MeSiH$ and $(EtO)_3SiH$ (2.0 mmol), PMHS (*ca.* 3.0 mmol), THF (3.0 mL). [b] Conversion of **1** was *ca.* 100%. Small amount of the ketone **1** was recovered by hydrolysis of the corresponding silyl ether derived from dehydrogenative silylation.

Under the optimized conditions, other aromatic ketones were reduced to the corresponding secondary alcohols in high yields at 65 °C (Table 2). Ether, ester, and bromide groups can tolerate the reduction conditions (run 2–5). In the cases of 1-acetonaphthone (**15**), α-tetralone (**19**), tetralone derivative **21**, and benzyl ketone **29**, the yields were decreased to 48–67% (run 7, 10–12, 13, 17) to form the corresponding silyl enol ether, which were recovered as the starting ketones. Use of pybox-*dm* slightly improved the yields for **16** and **20** up to 72% and 62%, respectively (run 8 and 11). Although the benzyl ketone **29** resulted in a lower yield, an aliphatic ketone 4-phenyl-2-butanone (**31**) was reduced in a good

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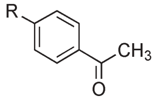
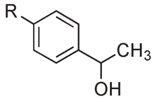
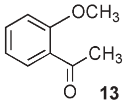
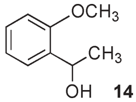
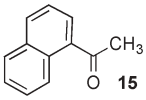
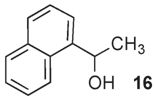
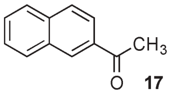
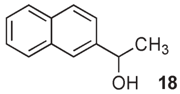
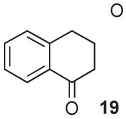
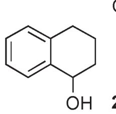
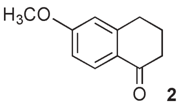
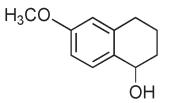
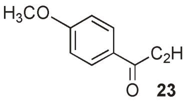
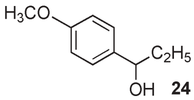
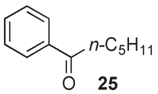
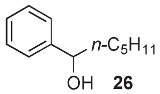
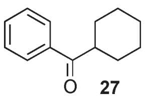
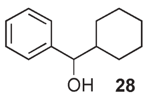
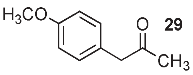
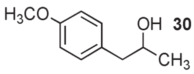
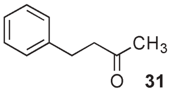
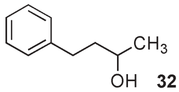
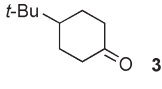
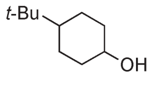
Table 2 Iron-catalysed hydrosilylation of other ketones[a]

Run	Ketone	Product	Yield (%) (recvd)
			
1	**3** R = H	**4** R = H	93 (2)
2	**5** R = OCH_3	**6** R = OCH_3	94 (4)[b]
3	**7** R = OPh	**8** R = OPh	90 (5)[b]
4	**9** R = CO_2CH_3	**10** R = CO_2CH_3	91 (5)
5	**11** R = Br	**12** R = Br	92 (3)
6	 **13**	 **14**	94 (2)[b]
7	 **15**	 **16**	67 (31)
8			72 (24)[c]
9	 **17**	 **18**	94 (3)
10	 **19**	 **20**	55 (42)
11			62 (32)[c]
12			50 (35)[d]
13	 **21**	 **22**	67 (28)[b]
14	 **23**	 **24**	91 (5)[b]
15	 **25**	 **26**	94 (2)
16	 **27**	 **28**	89 (10)
17	 **29**	 **30**	48 (51)
18	 **31**	 **32**	88 (5)
19	 **33**	 **34**	71 (23) *cis*:*trans* = 73:27

[a] Ketone (1.0 mmol), $Fe(OAc)_2$ (5 mol%), tmeda (10 mol%), $(EtO)_2MeSiH$ (2.0 mmol), THF (3.0 mL), 65 °C, 20∼24 h, work up with hydrochloric acid. Conversion was almost 100%. Some amount of the starting ketone was recovered by hydrolysis of the corresponding silyl ether derived from dehydrogenative silylation. [b] Work up with KF (2 mmol), TBAF (tetra-*n*-butylammonium fluoride (1.0 mL, 1 M in THF), 0 °C, 2 h. [c] In place of tmeda, pybox-*dm* (7 mol%) was used. [d] In place of tmeda, bipyridine (10 mol%) was used.

yield of 88% (run 18). 4-*tert*-Butylcyclohexanone (**33**) was *cis*-selectively reduced (run 19).

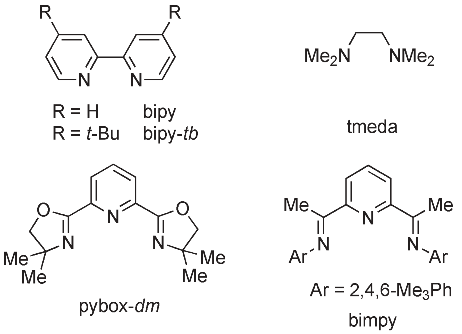


Fig. 1 Multi-nitrogen-based ligands.

We in turn examined asymmetric hydrosilylation of the ketone **1** using chiral tridentate bisoxazoline ligands (7 mol%) such as pybox-*bn* and bopa-*ip* and -*tb* in place of tmeda (Fig. 2).[13] Use of pybox-*bn* gave 37% ee of (*R*)-**2** in 93% yield. Interestingly, bopa-*ip* and *tb* increased the ee up to 57% and 79% for (*R*)-**2** [yield: 82% (65 °C, 24 h), 75% (65 °C, 48 h)], respectively.[14] The other ketones **17** and **25** were reduced in 65% ee for (*R*)-**18** (59% yield) and 59% ee for (*R*)-**26** (39% yield), respectively, at 65 °C for 48 h with $Fe(OAc)_2$ (5 mol%) and bopa-*tb* (7 mol%).§

Other findings are as follows: *p*-anisaldehyde **35** was smoothly reduced to the alcohol **36** in 97% yield. Benzalacetone (**37**) was reduced to the alcohol **38** in 80% yield accompanied with a small amount of conjugate reduction (1,4-reduction) product (4%). The conjugate reduction of ethyl cinnamate (**39**) was not observed.[15]¶

In conclusion, we have thus found a new catalytic system for hydrosilylation of ketones with ferrous acetate and nitrogen-based ligands as a convenient and environmentally benign method. We now have under way further study on efficient asymmetric reduction and reduction of other unsaturated substrates.

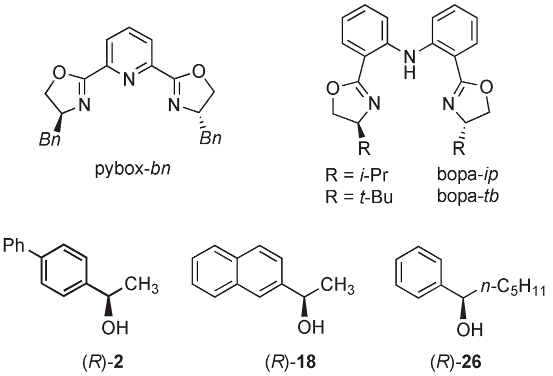


Fig. 2 Chiral ligands and product alcohols.

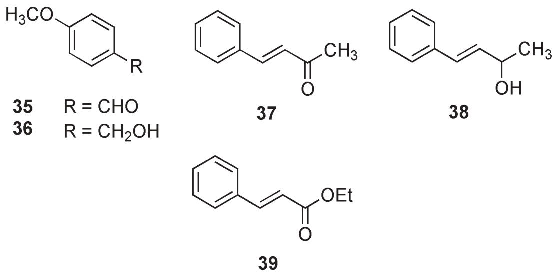


Fig. 3 Other substrates and products.

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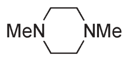
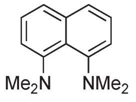
Notes and references

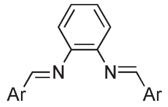
† By addition of other bidentate or tridentate nitrogen ligands, 1,4-dimethylpiperazine (dmp), proton sponge (bdmn), bisimine (bim-*meo*), and terpyridine (terpy), the reduction did not proceed or was very slow under the same condition. Use of Ph_2SiH_2 resulted in 76% yield of **2**, whereas with Et_2MeSiH there was no reduction.



dmp

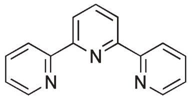


bdmn



Ar = 4-MeOPh

bim-*meo*



terpy

‡ **Typical procedure: reduction of methyl 4-phenylphenyl ketone (1)**: ferrous acetate (8.7 mg, 0.05 mmol) and the ketone (196 mg, 1.0 mmol) were placed in a flask. Under an argon atmosphere, absolute THF (3.0 mL) and TMEDA (*N,N,N′,N′*-tetramethylethylenediamine, 15 μL, 0.10 mmol) were added at room temperature. The mixture was stirred for 10 min. at 65 °C to give a reddish brown homogeneous solution. $(EtO)_2MeSiH$ (320 μL, 2.0 mmol) was then added by a syringe. The mixture was stirred for 20 h at 65 °C, and the reaction was monitored by TLC examination; hexane : ethyl acetate = 5 : 1, R_f = 0.40 for the ketone, 0.66 for silyl ether, and 0.14 for alcohol. At 0 °C, aq. HCl (2N, 2 mL) was added to quench the reaction. After stirred for 1 h, the mixture was extracted with ethyl acetate (10 mL x3), and the extract was washed with brine and aq. $NaHCO_3$ and was dried over Na_2SO_4. After concentration, the residue was purified by silica-gel column chromatography to give the desired alcohol (187 mg, 0.94 mmol) in 94% and the ketone (5.9 mg, 0.03 mmol).

§ Several chiral ligands were examined. Spartein and other bidentate bis(oxazoline) ligands gave low yields. BINAP (10 mol%) gave 54% yield of racemic **2** under the same reaction condition above described.

For analysis of (*R*)-**2**: CHIRALCEL OD (hex/ipa = 95 : 5, 0.8 mL min^{-1}), 17.8 min (*S*), 19.0 min (*R*), 79% ee; $[\alpha]_D^{23} = +33.8$ (*c* 0.75, $CHCl_3$); Lit,[16] $[\alpha]_D^{28} = -43.7$ (*c* 0.75, $CHCl_3$) for *S*. For (*R*)-**18**: CHIRALCEL OD (hex/ipa = 95 : 5, 0.8 mL min^{-1}), 21.9 min (*S*), 23.7 min (*R*), 65% ee; $[\alpha]_D^{23} = +31.7$ (*c* 1.0, $CHCl_3$); Lit,[17] $[\alpha]_D^{28} = +46$ (*c* 1.1, $CHCl_3$) for *R*. For (*R*)-**26**: CHIRALCEL OD-H (hex/ipa = 97 : 3, 0.8 mL min^{-1}), 14.0 min (*R*), 15,4 min (*S*), 59% ee; $[\alpha]_D^{23} = +20.8$ (*c* 1.0, $CHCl_3$); Lit,[16] $[\alpha]_D^{24} = -35.0$ (*c* 0.88, $CHCl_3$) for *S*.

¶ Under the standard conditions of Table 2, PhCH=NPh could be reduced at 65 °C in 75% yield with $Fe(OAc)_2$ and tmeda. The details will be reported in the near future. Several catalyst-combinations of $Fe(OAc)_2$ and nitrogen or oxygen ligands with PMHS have been reported not to give sufficient yields (<10%) for reduction of imines.[15]

1 C. Bolm, J. Legros, J. L. Paih and L. Zani, *Chem. Rev.*, 2004, **104**, 6217. For iron catalyzed cross coupling reactions, see: A. Fürstner and R. Martin, *Chem. Lett.*, 2005, 624.
2 S. C. Bart, E. Lobkovsky and P. J. Chirik, *J. Am. Chem. Soc.*, 2004, **126**, 13794; S. C. Bart, E. J. Hawrelak, E. Lobkovsky and P. J. Chirik, *Organometallics*, 2005, **24**, 5518; S. C. Bart, E. Lobkovsky, E. Bill and P. J. Chirik, *J. Am. Chem. Soc.*, 2006, **128**, 5302; E. J. Dalda and J. C. Peteres, *Inorg. Chem.*, 2004, **43**, 7474 and references sited therein.
3 Y. Kanazawa, Y. Tsuchiya, K. Kobayashi, T. Shiomi, J. Itoh, M. Kikuchi, Y. Yamamoto and H. Nishiyama, *Chem.–Eur. J.*, 2006, **12**, 63; Y. Tsuchiya, Y. Kanazawa, T. Shiomi, K. Kobayashi and H. Nishiyama, *Synlett*, 2004, 2493.
4 For review of hydrosilylation: H. Nishiyama, *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2004, chapt. 1.4.2, 182; H. Nishiyama and K. Itoh, *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, Weinheim, 2000, chapt. 2., 111; O. Riant, N. Mosterai and J. Courmarcel, *Synthesis*, 2004, 2943.
5 H. Brunner and K. Fisch, *J. Organomet. Chem.*, 1991, **412**, C11; H. Brunner and M. Rötzer, *J. Organomet. Chem.*, 1992, **425**, 119.
6 For copper catalysts: for examples, B. H. Lipshutz, K. Noson, W. Chrisman and A. Lower, *J. Am. Chem. Soc.*, 2003, **125**, 8779; B. H. Lipshutz, K. Noson and W. Chrisman, *J. Am. Chem. Soc.*, 2001, **123**, 12917; B. H. Lipshutz, A. Lower and K. Noson, *Org. Lett.*, 2002, **4**, 4045; B. H. Lipshutz and B. A. Frieman, *Angew. Chem., Int. Ed.*, 2005, **44**, 6345; J. Yun, D. Kim and H. Yun, *Chem. Commun.*, 2005, 5181; D.-W. Lee and J. Yun, *Tetrahedron Lett.*, 2004, **45**, 5415. For reduction of hindered ketones, S. Díez-González, H. Kauer, F. K. Zinn, E. D. Stevens and S. P. Nolan, *J. Org. Chem.*, 2005, **70**, 4784.
7 For titanium catalysts: X. Verdaguer, U. E. W. Lange, M. T. Reding and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 6784; X. Verdaguer, U. E. W. Lange and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 1998, **37**, 1103 and references sited in ref. 4*b*.
8 For rhodium catalysts: for examples, B. Tao and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 3892; V. César, S. Bellemin-Lapnnaz, H. Wadepohl and L. H. Gade, *Chem.–Eur. J.*, 2005, **11**, 2862.
9 For other metal catalysts: rhenium catalyst, J. J. Kennedy, K. A. Nolin, H. P. Gunterman and F. D. Toste, *J. Am. Chem. Soc.*, 2003, **125**, 4056; K. A. Nolin, R. W. Ahn and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 12462.Zinc catalyst, H. Mimoun, J. Y. S. Laumer, L. Giannini, R. Scopelliti and C. Floriani, *J. Am. Chem. Soc.*, 1999, **121**, 6158; V. Bette, A. Mortreux, C. W. Lehmann and J. F. Carpentier, *Chem. Commun.*, 2003, 332; V. Bette, A. Montreu, S. Savoia and J.-F. Carpentier, *Tetrahedron*, 2004, **60**, 2837; V. M. Mastranzo, L. Quintero, C. A. de Parrodi, E. Juaristi and P. J. Walsh, *Tetrahedron*, 2004, **60**, 1781; H. Ushio and K. Mikami, *Tetrahedron Lett.*, 2005, **46**, 2903.
10 S. Enthaler, B. Hagemann, G. Erre, K. Junge and M. Beller, *Chem.–Asian J.*, 2006, **1**, 598.
11 H. Nishiyama, M. Kondo, T. Nakamura and K. Itoh, *Organometallics*, 1991, **10**, 501. For a recent review, G. Desimoni, G. Faita and P. Quadreil, *Chem. Rev.*, 2003, **103**, 3119.
12 G. J. P. Britovsek, M. Bruce, V. C. Gibson, B. S. Kimberley, P. J. Maddox, S. Mastroianni, S. J. McTavish, C. Redshaw, G. A. Solan, S. Strömberg, A. J. P. White and D. J. Williams, *J. Am. Chem. Soc.*, 1999, **121**, 8728 see also ref. 2.
13 For bopa (bisoxazolinylphenylamine): H. A. McManus and P. J. Guiry, *J. Org. Chem.*, 2002, **67**, 8566; S.-F. Lu, D.-M. Du, S.-W. Zhang and J. Xu, *Tetrahedron: Asymmetry*, 2004, **15**, 3433; D.-M. Du, S.-F. Lu, T. Fang and J. Xu, *J. Org. Chem.*, 2005, **70**, 3712.
14 For absolute configuration and spectroscopic date of (*R*)-(+)-**2**: R. Kourist, J. Gonzákez-Sabín, R. Liz and F. Rebolledo, *Adv. Synth. Catal.*, 2005, **347**, 695; N. A. Salvi and S. Chattopadhyay, *Tetrahedron*, 2001, **57**, 2833.
15 T. Ireland, F. Fontanet and G.-G. Tchao, *Tetrahedron Lett.*, 2004, **45**, 4383.
16 N. A. Salvi and S. Chattopadhyay, *Tetrahedron*, 2001, **57**, 2833.
17 P. N. Liu, J. G. Deng, Y. Q. Tu and S. H. Wang, *Chem. Commun.*, 2004, 2070.