Iron Catalysis

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Asymmetric Iron-Catalyzed Hydrosilane Reduction of Ketones: Effect of Zinc Metal upon the Absolute Configuration**

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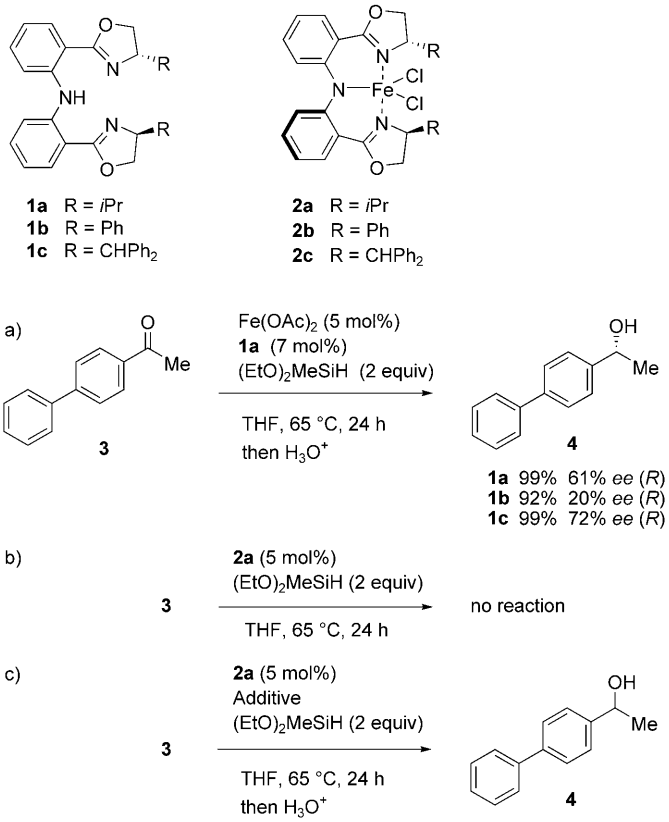
Optically active organic molecules are key compounds for the pharmaceutical and materials industries. In the synthesis of these molecules, the asymmetric synthesis of a single enantiomer has been realized using single chiral reagents or catalysts as each enantiomer usually has a different biological activity. Therefore when a particular enantiomer is required it can be readily synthesized from one of two antipodal reagents. However, both a molecule and its antipode are not commonly available from natural organic compounds such as amino acids or carbohydrates. Therefore, where possible, it would be desirable for both enantiomers of a product to be produced using reagents with a single chiral source. To do this would require the fine-tuning of the chiral reagents or reaction conditions.[1] Some examples have recently been reported in which the product chirality can be changed by changing the metal[2–4] or ligand substituents on the catalyst,[5–9] as well as substrate substituents[10] and additives.[11] During research on environmentally benign iron catalysts for asymmetric reduction using hydrosilanes, we have found that optically active (*S*,*S*)-bis(oxazolinylphenyl)amine [(*S*,*S*)-BOPA] iron catalysts can act as efficient catalysts.[12–14] Herein we report on the highly enantioselective hydrosilane reduction of ketones with (*S*,*S*)-BOPA/$FeCl_2$ complexes, and describe the unique phenomenon of the effect of zinc metal upon the absolute configuration of the products.

We have previously reported on the asymmetric hydrosilylation of methyl 4-phenylphenyl ketone (**3**) using a combination catalyst of $Fe(OAc)_2$ (5 mol%) and **1a** (7 mol%), which gave the corresponding alcohol product **4** with 61% *ee* and *R* as the absolute configuration (Scheme 1a); similar results were obtained with **1b** [20% *ee* (*R*)] and **1c** [72% *ee* (*R*)].[13] In addition, although the complex **2a** could be obtained as a green solid and its molecular structure was confirmed by X-ray analysis,[13] it did not show any catalytic activity for the hydrosilylation of ketones using $(EtO)_2MeSiH$ (Scheme 1b). Therefore, we continued to search for a more efficient catalyst system derived from complex **2a** and an appropriate activator, such as a base or metal (Scheme 1c).



Scheme 1. Hydrosilane reduction of **3** using a) $Fe(OAc)_2$/**1a**, b) **2a**, and c) **2a** + additive.

We started by screening appropriate activators for Fe complexes **2**. The complex **2** was treated with various additives and subsequent addition of hydrosilane at 65 °C. Silver salts did not work efficiently as activators (Table 1, entries 1 and 2). Sodium acetate and *tert*-butoxide activated **2a** to produce the alcohol **4** with 57% *ee* and 55% *ee* (*R* absolute configuration), respectively (Table 1, entries 3 and 4). Cu and Mn powder did not show any catalyst activation (Table 1, entries 5 and 6). Although Mg efficiently activated the complex to promote the reduction, giving 92% yield, it gave a low *ee* value of 15% (*R*; Table 1, entry 7). Gratifyingly, Zn powder (6 mol%) efficiently promoted the catalysis to give 60% product yield after reacting for 24 hours at 65 °C

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Table 1: Asymmetric hydrosilane reduction with **2a** or Zn salts in the presence of various additives.[a]

Entry	Cat., Additive (mol%)	*t* [h]	Yield [%] (recov. **3** [%])	*ee* [%]
1	**2a**, AgOAc (9)	24	n.r.	–
2	**2a**, $AgBF_4$ (9)	24	n.r.	–
3	**2a**, NaOAc (9)	24	97	57 (*R*)
4	**2a**, NaO*t*Bu (9)	24	99	55 (*R*)
5	**2a**, Cu (10)	48	n.r.	
6	**2a**, Mn (10)	24	n.r.	
7	**2a**, Mg (10)	24	92	15 (*R*)
8	**2a**, Zn (6)	24	60 (40)	44 (*S*)
9	**2a**, Zn (6)	48	97	41 (*S*)
10	**2a**, Zn (6), **1a** (7)	48	n.r.	
11	**2a**, $ZnEt_2$ (5)	24	64 (36)	33 (*S*)
12	**2a**, $ZnCl_2$ (4.5)	24	n.r.	
13[b]	–, $ZnCl_2$ (5)	24	97	–
14[b]	–, $ZnCl_2$ (5), **1a** (7)	48	n.r.	
15[b]	–, $Zn(OAc)_2$ (5), **1a** (7)	48	96 (3)	21 (*R*)
16	–, $Fe(OAc)_2$ (5), **1a** (6), Zn (8)	48	83 (17)	23 (*R*)
17	**2b**, Zn (6)	48	67 (32)	21 (*S*)
18	**2c**, Zn (6)	48	98 (2)	65 (*S*)

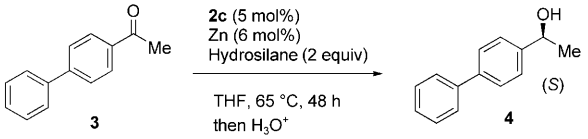
[a] Reaction conditions: Cat. **2a** (5 mol%), **3** (0.5 mmol), $(EtO)_2MeSiH$ (1 mmol), THF (1.5 mL), 65 °C, then H_3O^+. All reported yields are of the isolated product. [b] **3** (1 mmol), THF (3 mL), 65 °C.

(Table 1, entry 8), and surprisingly the product alcohol **4** had an absolute configuration of *S* (44% *ee*). The reaction that was run for 48 hours produced **4** in 97% yield and 41% *ee* (Table 1, entry 9), and the addition of extra **1a** (7 mol%) negated the effect of the zinc metal (Table 1, entry 10). When diethylzinc (5 mol%) was used instead of Zn, it activated the complex **2a**, giving predominantly the *S* enantiomer with 33% *ee* (Table 1, entry 11). However, using $ZnCl_2$ (4.5 mol%) as an additive showed no activation (Table 1, entry 12). Although $ZnCl_2$ itself was found to promote the reaction, giving the alcohol in 97% yield but as a racemic mixture (Table 1, entry 13),[15,16] the combination of **1a** and $ZnCl_2$ did not work as a catalyst (Table 1, entry 14). However, the combination of $Zn(OAc)_2$ and **1a** did promote the reaction, giving 96% yield of the alcohol **4** with an *R* configuration in 21% *ee* (Table 1, entry 15). The addition of Zn powder to the catalyst generated in situ from $Fe(OAc)_2$ and **1a** decreased the enantioselectivity to 23% *ee* compared to 61% *ee* obtained without the Zn powder (Scheme 1a versus Table 1, entry 16). The use of other complexes, such as **2b** and **2c**, in combination with zinc powder (6 mol%) were also effective, giving the *S* enantiomer in 21% *ee* and 65% *ee*, respectively (Table 1, entries 17 and 18).

We have successfully activated the Fe complexes **2** by the addition of a small amount of zinc powder at 65 °C. Not only does the catalyst combination promote hydrosilylation of the ketone but it also results in a change in the absolute configuration of the products. The experiments shown in entries 10 and 12–14 in Table 1 ruled out the possibility that only the zinc bearing the chiral ligand was involved in the asymmetric induction. These findings imply that a combined Fe/Zn complex may serve as the catalyst or that the Fe and Zn atoms take part in the reaction simultaneously. At this point, we cannot specify which hydride metal species, Fe–H or Z–H, is involved. It may also be possible that a hydride is directly transferred from the hydrosilane.

Other hydrosilanes, including $(EtO)_3SiH$, Ph_3SiH, and Ph_2SiH_2, were tested with the catalyst **2c** and exhibited similar activities, giving 65–71% *ee* with the same absolute configuration (*S*) as that obtained with $(EtO)_2MeSiH$ (Table 2). Thus, the observed effect of a change in the absolute configuration of the product was not influenced by the hydrosilanes.

Table 2: Asymmetric hydrosilane reduction with various hydrosilanes.[a]

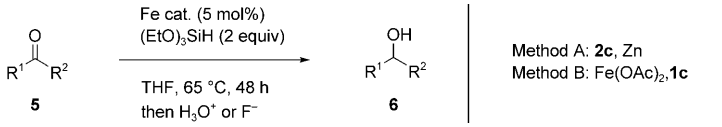


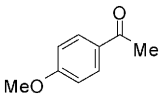
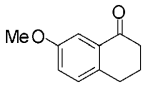
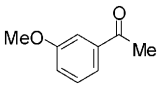
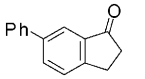
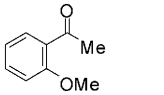
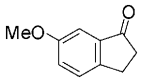
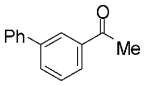
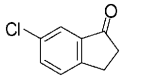
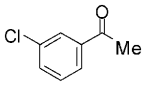
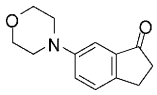
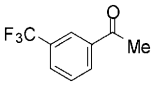
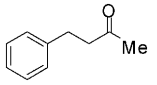
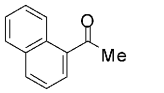
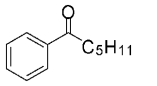
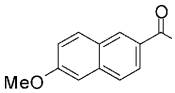
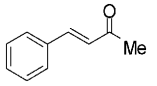
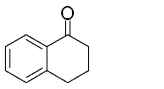
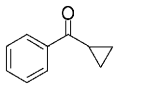
Entry	Hydrosilane	Yield [%] (recov. **3** [%])	*ee* [%]
1	$(EtO)_2MeSiH$	98 (2)	65 (*S*)
2	$(EtO)_3SiH$	99	71 (*S*)
3	Ph_3SiH	97	67 (*S*)
4[b]	Ph_2SiH_2	92 (2)	70 (*S*)
5	Ph_2MeSiH	n.r.	–

[a] Reaction conditions: Cat. **2c** (5 mol%), **3** (0.5 mmol), hydrosilane (1 mmol), THF (1.5 mL), 65 °C, 48 h, then H_3O^+. All reported yields are of the isolated product. [b] 72 h.

The reduction of other ketones was carried out using two different methods (Methods A and B) so as to compare the resulting enantioselectivity (Table 3); for the results of Method B, some previous data are cited. Methyl ketones bearing substituted phenyl groups resulted in the formation of the corresponding *S*-configured secondary alcohols in high yields (Table 3, entries 1–6). Naphthalenyl ketones **5g** and **5h** were reduced with 75% *ee* (*S*) and 82% *ee* (*S*), respectively (Table 3, entries 7 and 8). Tetralone derivatives **5i** and **5j** also gave the *S* as the absolute configuration with 80% *ee* and 83% *ee*, respectively (Table 3, entries 9 and 10). Interestingly, the substituted indanone derivatives **5k**–**5n** were reduced to the *S*-configured product with up to 95% *ee* (Table 3, entries 11–14). Methyl phenethyl ketone (**5o**) was also converted into an *S*-configured secondary alcohol with 33% *ee* (Table 3, entry 15). Thus, by using Method A, all ketones were reduced to the corresponding alcohols as *S* enantiomers, which is the opposite configuration to that obtained by using Method B. In the case of benzalacetone **5q**, a 1,2-reduction preferentially proceeded to give the corresponding secondary alcohol in 87% yield with 60% *ee* (Table 3, entry 17). The reduction of 2,4,6-trimethylphenyl methyl ketone as a bulky ketone did not proceed with the iron complex **2c**. Although the reduction of cyclopropyl phenyl ketone (**5r**) is very slow, probably a result if the steric hindrance, it gives 40% of the corresponding secondary alcohol and no ring-opening product is obtained (Table 3, entry 18). This fact indicates that the reduction did not proceed by a radical mechanism.[17] The exceptions to the trend were ketones **5g**, **5o**, and **5r**, which resulted in the

Table 3: Substrate scope and limitations.



Entry	Ketone		Method A[a] Yield [%]	*ee* [%]	Abs. config.	Method B[b] Yield [%]	*ee* [%]	Abs. config.	Entry	Ketone		Method A[a] Yield [%]	*ee* [%]	Abs. config.	Method B[b] Yield [%]	*ee* [%]	Abs. config.
1		**5a**	99	63	*S*	98	78	*R*[c]	10		**5j**	99	83	*S*	92	90	*R*[d]
2		**5b**	99	76	*S*	99	54	*R*[c]	11		**5k**	99	94	*S*	91	89	*R*[d]
3		**5c**	99	36	*S*	95	50	*R*[c]	12		**5l**	99	95	*S*	97	90	*R*[d]
4		**5d**	99	78	*S*	99	58	*R*[c]	13		**5m**	99	81	*S*	93	86	*R*[d]
5		**5e**	99	74	*S*	99	56	*R*[c]	14		**5n**	99	95	*S*[e]	97	89	*R*[d,f]
6		**5f**	99	55	*S*	99	40	*R*[d]	15		**5o**	99	33	*S*	94	35	*S*[d]
7		**5g**	99	75	*S*	93	22	*S*[c]	16		**5p**	98	1	*S*	88	58	*R*[c]
8		**5h**	99	82	*S*	99	71	*R*[c]	17		**5q**	87	60	*S*	57	15	*R*[d]
9		**5i**	99	80	*S*	99	85	*R*[d]	18		**5r**	40	32	*S*[e]	40	18	*S*[d,e]

[a] Method A: Cat. **2c** (0.025 mmol, 5 mol%), **5** (0.5 mmol), $(EtO)_3SiH$ (1 mmol), THF (1.5 mL), 65 °C, 48 h, then H_3O^+ or F^-. All reported yields are of the isolated product. [b] Method B: $Fe(OAc)_2$ (2 mol%), **1c** (3 mol%), **5** (1.0 mmol), $(EtO)_2MeSiH$ (2.0 mmol), THF (3 mL), 65 °C, 24 h, then H_3O^+ or F^-. All reported yields are of the isolated product. [c] These data are quoted from Ref. [13]. [d] These data were obtained under Method B. [e] Reaction time, 96 h. [f] Reaction time, 48 h.

formation of products having the same absolute configuration (*S*) when reacted using either of the methods.

To find out what happens in the initial activation of **2a**, we monitored the reaction by UV/Vis spectroscopy. The initial solution of **2a** in THF was green in color (Figure 1a), and upon treatment of **2a** with Zn powder at room temperature, the color changed to yellow (Figure 1b). In the UV/Vis spectra of **2a**, this color change corresponded with the disappearance of a peak at 631 nm (Figure 1c) and the observation of a new peak at 432 nm (Figure 1d).

The magnetic susceptibility in solution was measured using the Evans method.[18] The effective magnetic moment, μ_{eff}, of **2a** measured at 20 °C in [D_8]THF/cyclohexane (10:1) was 5.9 μ_B, which is within the range for a high-spin Fe^{III} complex. In contrast, the effective magnetic moment of the orange solution obtained after the reaction of **2a** with Zn was 4.8 μ_B. This value implies the formation of a high-spin Fe^{II} complex assuming that the product has a mononuclear structure. As such, we consider that Zn serves as a reducing agent for reduction of Fe^{III} to Fe^{II}.

The reaction mechanism of the hydrosilane reduction has not yet been clarified, and the active catalyst in the catalytic cycle remains ill-defined. Additional studies to detect the active species and determine the transition-state model for enantiofacial discrimination in the presence, or absence of zinc powder are in progress.

In summary, we have described the use of unique iron catalysts with chiral BOPA ligands for the enantioselective hydrosilane reduction of ketones. The combination of the complex **2** and zinc afforded predominantly the *S*-configured alcohols, whereas the $Fe(OAc)_2$/**1** system gave the *R*-configured products. Notably, the BOPA/iron catalysts presented herein can access both enantiomers from a single chiral source by the addition of a small amount of zinc powder.

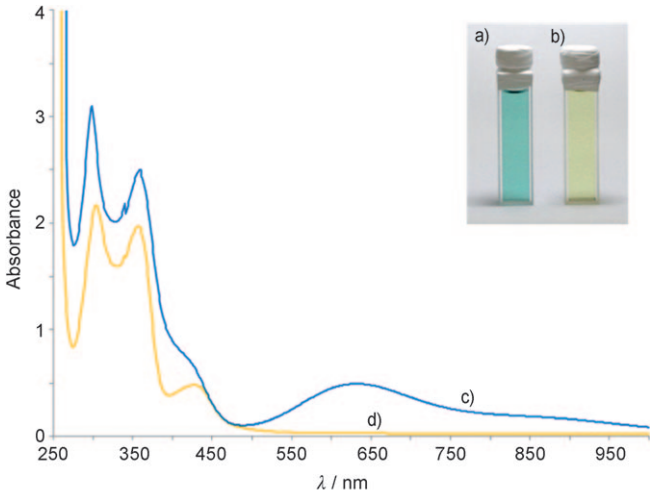


Figure 1. THF solution of a) **2a** ($c = 2.0\times10^{-4}$ M) and b) **2a** + 8.3 equiv of Zn ($c = 1.8\times10^{-4}$ M) in UV cells. UV/Vis spectra of c) **2** (THF, $c = 2.0\times10^{-4}$ M) and d) **2** + 8.3 equiv of Zn (THF, $c = 1.8\times10^{-4}$ M).

Experimental Section

Reduction of 6-methoxy-2,3-dihydro-1*H*-inden-1-one (**51**; Table 3, entry 12, Method A): Ketone **51** (81.1 mg, 0.50 mmol), **2c** (19.1 mg, 0.025 mmol, 5.0 mol%), and zinc powder (2.0 mg, 0.030 mmol, 6.0 mol%) were placed in a two-necked test tube and THF (1.5 mL) was added under argon. The mixture was stirred at 65°C for 1 h. $(EtO)_3SiH$ (164 mg, 1.0 mmol, 2 equiv) was then added, and the mixture was stirred at 65°C for an additional 48 h. Consumption of the ketone was monitored by TLC analysis (ethyl acetate/*n*-hexane = 1:3). The reaction mixture was treated with TBAF (1 mol L^{-1} in THF, 1 mL), KF (2.0 mmol), and MeOH (1.0 mL), and then extracted with ethyl acetate (2 × 25 mL). The extract was washed with brine, dried over anhydrous sodium sulfonate, and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:20 to 1:3) to give the secondary alcohol **61** [(*S*)-6-methoxy-2,3-dihydro-1*H*-inden-1-ol; 82 mg, 0.499 mmol, 99% yield] as a colorless oil; analysis, CHIRALPAK OD-H (*n*-hexane/2-propanol = 99:1, 1.0 mL min^{-1}), 42.7 min (*S*), 50.1 min (*R*), area = 97.5:2.5, 95% *ee* (*S*); $[\alpha]_D^{25} = 20.8$ deg cm^3 g^{-1} dm^{-1} ($c = 1.0$, $CHCl_3$), Lit:[19] $[\alpha]_D^{23} = -20.0$ deg cm^3 g^{-1} dm^{-1} ($c = 0.5$, $CHCl_3$), 94% *ee* for *R*. IR (film): $\tilde{\nu} = 3344$ (broad), 2941, 1614, 1490, 1255, 1186, 1035, 894 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.75$ (s; 1H), 1.90–2.01 (m; 1H), 2.47–2.58 (m; 1H), 2.71–2.81 (m; 1H), 2.94–3.03 (m; 1H), 3.82 (s; 3H), 5.18–5.22 (m; 1H), 6.83 (dd, J(H,H) = 2.4, 8.4 Hz; 1H), 6.96 (d, J(H,H) = 2.4 Hz; 1H), 7.15 ppm (d, J(H,H) = 8.4 Hz; 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.1$, 36.6, 55.5, 76.5, 108.6, 114.8, 125.3, 134.8, 146.1, 158.6 ppm.

Reduction of 6-methoxy-2,3-dihydro-1*H*-inden-1-one (**51**; Table 3, entry 12, Method B): $Fe(OAc)_2$ (3.5 mg, 0.02 mmol, 2 mol%) and **1c** (19.2 mg, 0.03 mmol, 3 mol%) were used as the catalyst. The ketone **51** (162 mg, 1.0 mmol) and $(EtO)_2MeSiH$ (268 mg, 2.0 mmol, 2 equiv) were added to a THF solution (3.0 mL) containing the catalyst (argon atmosphere) and reacted at 65°C for 24 h. After a workup similar to that described in Method A, the secondary alcohol **61** (164 mg, 0.97 mmol, 97% yield) was obtained; analysis, CHIRALPAK OD-H (*n*-hexane/2-propanol = 99:1, 1.0 mL min^{-1}), 42.6 min (*S*), 47.3 min (*R*), area = 5.2:94.8, 90% *ee* (*R*); $[\alpha]_D^{25} = -19.3$ deg cm^3 g^{-1} dm^{-1} ($c = 1.0$, $CHCl_3$).

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