Asymmetric Catalytic Reduction of Ketones with Hypervalent Trialkoxysilanes

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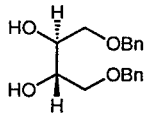
Abstract: The catalytic asymmetric reduction of different ketones[1] with transient hypervalent silicon hydrides is described. Trialkoxysilanes, upon activation by a small amount of a chiral nucleophile, underwent addition to the carbonyl group, forming the corresponding silyl protected alcohols, which were cleaved during the workup to give the enantiomerically enriched product alcohols. A brief screening of the reaction parameters and the results are summarized below.

Trialkoxysilanes **1** may react with various nucleophiles to generate pentacoordinate, "hypervalent", hydrosilicates **2.** The reducing properties of these species are well established, especially towards ketones.[2-5] An extended mechanistical model with a chiral alkoxide as the nucleophile and acetophenone **3** as the ketone is outlined in Scheme 1.

With regards to asymmetric synthesis an interesting observation was made in 1988 by Hosomi *et al*, since the authors established for the first time, both the use of lithium alkoxides as catalysts and demonstrated that the dilithio salts of some chiral diols or β-aminoalcohols catalyzed the asymmetric reduction of aromatic ketones by the trialkoxysilanes **1**.[6] The dilithio salt of **9**, for example, in a stoichiometric amount promoted the reduction of isobutyrophenone at 0°C with up to 69% ee, and moreover the dilithiosalt of *(S)*-phenylalaninol (0.4% eq) catalyzed the reduction of acetophenone at room temperature with up to 49% ee.[7]



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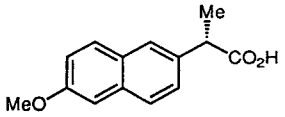

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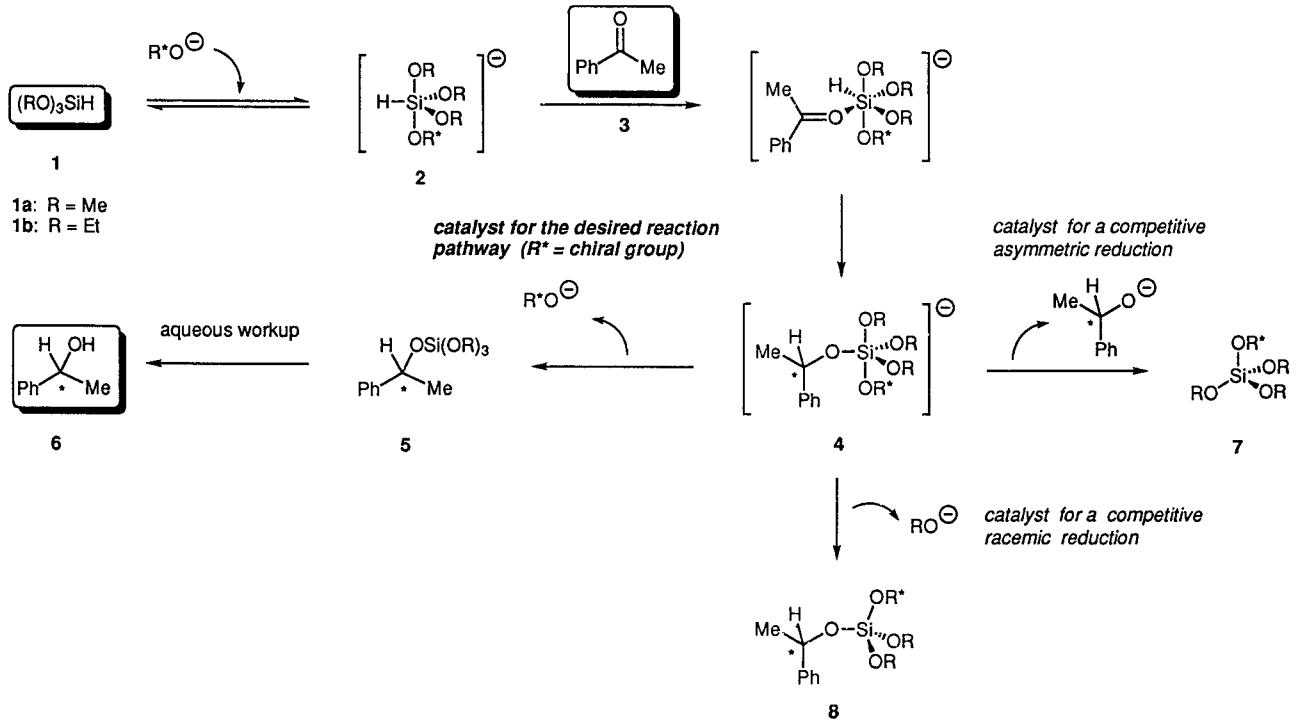
Scheme 2

We now wish to report the discovery and development of some other catalyst systems which can give excellent catalytic activity and quite good enantioselectivity. A preliminary screening of various chiral catalysts was performed with acetophenone **3** as the model system, and THF as the solvent. Interestingly, we could not detect any reaction at -78°C, in contrast to Hosomi's results, but mixing the components at this temperature and then warming to room temperature overnight gave, after aqueous workup, the phenethyl alcohol **6**. In the reductions with **1a** and 1 mol% of lithio salts of cinchonidine, menthol, mandelic acid (disalt) or binol **11a**[8] (mono or disalt, Scheme 3), for example, good yields of **6** were obtained, but the ee's were inferior to 8%. The use of 5 mol% of lithio thiophenolate gave a quantitative yield, but the combination of thiophenol and diisopropylethylamine as the base was completely inactive. The replacement of **1a** by the less toxic **1b** gave lower yields, while a quantitative yield of phenethyl alcohol **6** (racemic) was obtained with 5 mol% of the lithium salt of *(R)*-naproxen **10**. Similarly *(R)*-binol **11a** (mono salt) gave 62% of alcohol **6** (4% ee). The next step in the screening was the replacement of THF by ether, which



Scheme 1

Table 1. Effect of TMEDA as additive for the reduction of acetophenone

Entry	Solvent	$(RO)_3SiH$	Conditions [a]	Yield(%)[b]	ee(%)[c]
1	THF	**1a**	6h, -78°C then 20°C overnight	88	0
2	Et_2O	**1b**	6h, 0°C then 20°C overnight	33	31
3	Et_2O/TMEDA 2:1	**1b**	24h, 0°C	50	64
4	THF/TMEDA 2:1	**1b**	24h, 0°C	52	33
5	Et_2O/TMEDA	**1b**	24h, 0°C	46	63

a) 5 mol% of monolithio salt of *(R)*-**11a** as catalyst. If not otherwise stated : 1 eq silane **1**, 2 eq of additive (TMEDA etc.). b) Isolated yield after chromatography on silica gel (pentane/ether =3.1). c) Measured by hplc on a Daicel OD-H column (*n*-hexane/*i*-PrOH = 9:1), *(S)* configuration for phenethyl alcohol **6**

Table 2. Reduction of different ketones

Entry	Ketone	Conditions[a]	Yield(%)[b]	ee(%)[c]
1	Acetophenone	6h, 0°C	80	61 *(S)*
2	1-Acetylnaphthalene	24h, 0°C[f]	67	77 *(S)*
3	Isobutyrophenone	24h, 0°C	60	81 *(S)*
4	2',4',6'-Trimethylacetophenone	24h, 0°C[f]	57	90 *(R)*
5	α-Tetralone	24h, 0°C[f]	39	93 *(R)*
6	Benzylideneacetone	24h, 20°C	91	57 *(R)*
7	4-Phenyl-2-butanone	24h, 0°C	74	46 *(R)*
8	Methyl benzoylpropionate	24h, 0°C	63	65 *(S)* [e]
9	2'-Bromoacetophenone	24h, 0°C	91	66 *(S)*
10	4'-Methylbenzophenone	24h, 0°C	74	0
11	4'-Trifluoromethylbenzophenone	24h, 0°C	90	0

a) $(MeO)_3SiH$ unless stated. Reaction with 5 mol% of the monolithio salt of *(R)*-**11a** as catalyst and 1 eq of silane in ether/TMEDA=30:1, unless otherwise stated. b) Isolated yields, after chromatography on silica gel (pentane/ether=2:1 to 5:1) c) Measured by hplc on a Daicel-OD-H column (*n*-hexane/*i*-PrOH=9:1 to 99:1). d) $(EtO)_3SiH$. e) Poor separation by hplc. f) 10 mol% of *(R)*-**11a**, 5 mol% of *n*-BuLi

Table 3. Experiments to optimize the reduction of acetophenone

Entry	Catalyst[a]	Experimental conditions[b]	Yield(%)[c]	ee(%)[d]
1	*(R)*-Binol **11a**	48h, 0°C, Et_2O[e]	59	7 *(R)*
2	*(R)*-Binol **11a**	12h, 0°C, Et_2O/TMEDA=2:1[e]	53	48 *(S)*
3	*(R)*-Binol phosphoric acid **14**	48h, -22°C, THF[e]	37	6 *(R)*
4	*(R)*-Binol **11a**	24h, 20°C, Et_2O/TMEDA=2:1[e]	50	64 *(S)*
5	*(R)*-Binol **11a**	24h, 20°C[e]	46	63 *(S)*
6	Aluminium - *(R)*-Binol-complex[13]	24h, 20°C, Et_2O or THF[e]	0	-
8	*(R)*-2,2'-Dimethyl-binol **11b**	24h, -20°C,	87	26 *(R)*
9	*(R)*-Methoxythiobinol **13**	24h, 20°C,	22	37 *(R)*
10	*(R)*-Binol **11a**	8h, 0°C, 10 mol% catalyst	91	58 *(S)*
11	*(R)*-Binol **11a**	8h, 0°C, 20 mol% catalyst	96	59 *(S)*
12	*(R)*-Binol **11a**	24h, 0°C, additional 5 mol% *(R)*-binol **11a** from the beginning	92	70 *(S)*
13	*(R)*-Binol **11a**	24h, 0°C, additional 5 mol% *(R)*-binol **11a** after catalyst preparation	90	70 *(S)*
14	*(R)*-Binol **11a**	24h, 0°C, no TMEDA, additional 5 mol% *(R)*-binol **11a** from the beginning	47	52 *(S)*
15	*(R)*-Hydrobinol **12**	24h, 0°C,	47	40 *(S)*
17	*(R)*-Binol **11a**	24h, 0°C, additional 10 mol% cinchonidine	91	66 *(S)*

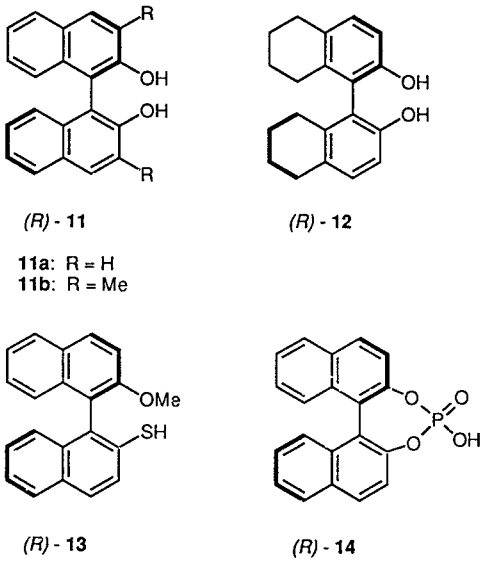
a) Monolithio salt of binol and derivatives (except entry 6), 5 mol% catalyst. b) In ether/TMEDA=30:1, 1 eq of $(MeO)_3SiH$, unless stated otherwise. c) Isolated yield after chromatography on silica gel (pentane/ether = 3:1). d) Measured by hplc on a Daicel-OD-H column. e) $(EtO)_3SiH$

afforded a significant increase in the enantioselectivity [21% ee *(S)*], but with a drop in the chemical yield (24%). Since it is known that the aggregation of organolithio compounds has a strong effect on their reactivity,[9] some experiments with or without an additional cosolvent were performed, which showed that *the use of TMEDA as cosolvent not only increased the yield but also the enantioselectivity.*

Table 1 collects data concerning the influence of solvents on the yields and ee's for the reduction of acetophenone in the presence of 5 mol% of *(R)*-binol (monolithio salt). In pure THF only racemic alcohol **6** was obtained, while 33% ee was observed with THF/TMEDA (entries 1 and 3). Pure Et_2O gave 31% ee, and Et_2O/TMEDA within these experiments up to 64% ee (entries 2, 4 and 5). Other solvents or additives were less effective.

A systematic screening of ketones was then made by selecting the best conditions (ether/TMEDA), with the monolithium salt of *(R)*-binol as catalyst (5 mol%); the results are listed in Table 2. It is interesting to see that, with this system, steric effects seem to be much more important than electronic effects. On the one hand there is a significant increase of the enantioselectivity with the increase of steric hindrance around the carbonyl function - shown by the sequence acetophenone, naphthophenone, isobutyrophenone and 2',4',6'-trimethylacetophenone which gave 61, 77, 80 and 90% ee for the corresponding alcohols (entries 1, 2, 3 and 4). On the other hand, the two prochiral benzophenones (entries 10 and 11) were reduced in high yield but gave racemic alcohols. The highest ee so far observed was for the reduction of α-tetralone, 93% (entry 5). There was no reduction of phenylacetone or benzoylacetone, and the reduction of acetophenone in a 1:1 mixture with phenylacetone also failed, presumably because of protonation and hence deactivation of the catalyst by these readily enolizable compounds.

In Table 3 are indicated various experiments performed to further optimize the reduction for the model system acetophenone **3**, catalyzed by the monolithium salt of *(R)*-binol and derivatives. This compound was chosen since it was found to be superior to all other catalysts.



(R) - **11** *(R)* - **12**

11a: R = H
11b: R = Me

(R) - **13** *(R)* - **14**

Scheme 3

As pointed out in Scheme 1, the chiral nucleophile is liberated during the catalytic cycle, together with the formation of the corresponding trialkoxysilyl protected alcohol. Since the nucleophile is generally also an alcoholate, two more reaction pathways are possible, depending on the basicity and steric demands of the alcoholates involved. Because of the much lower pKa value of phenols, compared to aliphatic alcohols, and also the steric demand of the binol skeleton, the latter should be the best leaving group at this point, thus directing the catalytic reduction in the desired way. Structural modifications of the binol skeleton afforded important changes (entries 7,8 and 9). Thus the *(R)*-tetrahydrobinol **12**[10] gave lower ee's under the standard reaction conditions, and the inversion of configuration of alcohol **6** was observed when *(R)*-2,2'-dimethylbinol **11b**[11] or *(R)*-methoxythiobinol **13**[12] were used as catalyst precursors.

The proper experimental conditions are also crucial for the "fine-tuning" in order to combine high yield and good enantioselectivity. For some of the ketones the reaction proceeded very slowly, and then deactivation of the catalyst system was observed. On the other hand the use of "chiral activators",[13] for example an additional 5 mol% of *(R)*-binol **11a**, provided high yields and better ee's for acetophenone **3** (entries 11 and 12), and it will be interesting to see if these conditions can be applied successfully to the ketones mentioned before. Obviously a tuning of the catalyst structure should be possible to enhance the enantioselectivity, and is currently under investigation, as well as a mechanistic study.

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References and Notes

(1) For a recent general reference to the stereoselectivity of the reduction of carbonyl groups see: Brunner, H. "Formation of C-H Bonds by Reduction of Carbonyl Groups", *Houben-Weyl* **1996**, E21, Vol. 7 of the Workbench Edition, p. 3945-4197, Eds.: Helmchen, G., Hoffmann, R. W., Mulzer, J.,Schaumann, E., Thieme Verlag Stuttgart 1996.

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(15) **Typical experimental procedure** (example: acetophenone)**:** *First we have to recall that triethoxysilane* **1b** *and especially trimethoxysilane* **1a** *are rather toxic compounds and therefore* **care should be taken**. *Both are commercially available (Aldrich) and can be handled without problems via syringe-technique.*
43 mg (0.15 mmol, 5 mol%) of *(R)*-Binol **11a** were dissolved in 30 mL of dry ether under argon. At room temperature 0.10 mL (≈ 0.15 mmol, ≈ 1.5 mol/L in hexane) *n*-butyl lithium were added slowly and the resulting suspension stirred for 10 min, cooled to 0°C, and then 1.0 mL (≈ 6 mmol, 2 eq.) TMEDA was added and again stirred for 10 min, then 0.40 mL (3 mmol, 1 eq., 95%) trimethoxysilane **1a** were added, stirred 10 min and finally 0.35 mL (3 mmol, 1 eq.) acetophenone **3** were added and the reaction mixture kept at 0°C for 6h. The reaction was quenched by adding 20 mL of 0.1 mol/L sodium hydrogencarbonate solution and stirred vigorously for 30 min at room temperature, then transferred into a separatory funnel and extracted with ether (3 times 50 mL). The ether was removed without drying and the resulting crude product was purified by column chromatography on silica gel with pentane/ether (3:1) immediately after (*longer standing of the crude product at this stage resulted in gel formation and more difficult workup and lower yields*) to give 295 mg (2.41 mmol) *(S)*-phenethyl alcohol **6** as a colorless liquid (80.3 % yield based on acetophenone **3** - entry 1, Table 2). The ee for this example was 61% (hplc on a Daicel OD-H column, *n*-hexane/*i*-PrOH 9:1, flow 0.5 mL/min, *(R)*-**6**: 11.9 min, *(S)*-**6**: 13.3 min, absolute configuration previously assigned by measurement of the optical rotation).