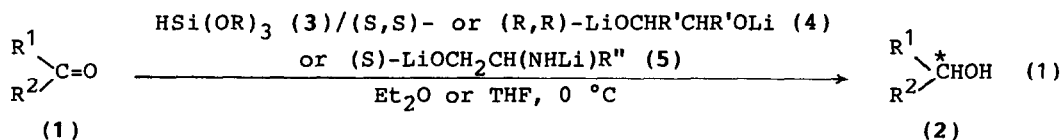


PENTACO-ORDINATE ORGANOSILICON COMPOUNDS IN SYNTHESIS: ASYMMETRIC REDUCTION OF CARBONYL COMPOUNDS WITH HYDROSILANES CATALYZED BY CHIRAL BASES

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Summary: Reduction of carbonyl compounds with trialkoxysilane can be readily catalyzed by alkoxides of alkali metal. A considerable high asymmetric induction takes place by use of optically active diolates or even N-lithio 2-amino alcoholates derived from optically active amino acid as a catalyst.

Recently much attention has been directed to the asymmetric and stereoselective synthesis of alcohols by the reduction of ketones using metal hydrides.¹ Hydrosilylation of ketones followed by hydrolysis may be useful and convenient method to achieve this purpose. Indeed tri-substituted silanes,² readily available and easily handled, are shown to be reducing reagents with the aid of acid,³ fluoride ion,⁴ and transition metal complexes.⁵ We have recently demonstrated that an active pentaco-ordinate hydride species derived from an trialkoxy-substituted silane (3) and an alkali metal alkoxide (4), especially lithium pinacolates, reduces aldehydes and ketones (1) chemo- and stereo-selectively to give the corresponding alcohols (2).⁶ In the course of our studies on the use of highly co-ordinate organosilicon compounds in organic synthesis,⁷ we have found that new enantioselective hydrosilylation of ketones with a pentaco-ordinate hydrosilane can be achieved by use of a trialkoxysilane and an optically active lithium alcoholate. (eq. 1)



In addition to the previous work in which a stoichiometric amount of a metal alkoxide was used as a promoter,⁶ we have found that the reduction proceeds very smoothly even by a catalytic amount of the base. Thus the reduction of acetophenone (1 mmol) was attained by treatment with trimethoxysilane (1.5 mmol)-dilithium pinacolate (0.08 mmol) in tetrahydrofuran (THF) in 98 % yield. Moreover it has been found that the lithium alcoholates derived from various 2-amino alcohols such as diethanol amine, 2-dimethylaminoethanol and 2-amino-2-methyl-1-propanol are also efficient catalysts for the reduction. The yields towards a variety of aromatic ketones were usually 75-100 % even by use of 0.004 equivalent of the catalyst at room temperature.

Table 1. Asymmetric reduction of ketones (1) using HSi(OMe)_3 (3) and (S,S)- or (R,R)- LiOCHR'R'CHOLi (4)^a

| Entry | Ketone (1) | Diolate (4) | % Yield ^b | %ee ^{c,d} |
|-------|---------------------------------------|---|----------------------|----------------------|
| 1 | PhCOCH_3 (1a) | (R,R)-4a ($\text{R}'=\text{CH}_3$) | 41 | 22 |
| 2 | 1a | (S,S)-4b ($\text{R}'=\text{CH}_2\text{OCH}_3$) | 66 | 40 |
| 3 | 1a | (S,S)-4c ($\text{R}'=\text{CH}_2\text{OCH}_2\text{Ph}$) | 78 | 44 |
| 4 | $\text{PhCOCH}_2\text{CH}_3$ (1b) | 4a | 52 | 36 |
| 5 | 1b | 4b | 70 | 53 |
| 6 | 1b | 4b | 61 ^e | 58 |
| 7 | 1b | 4c | 66 | 54 (47) ^f |
| 8 | 1b | (S,S)-4d ($\text{R}'=\text{CONMe}_2$) | 64 | 42 |
| 9 | $\text{PhCO(CH}_2)_2\text{CH}_3$ (1c) | 4a | 67 | 36 |
| 10 | 1c | 4b | 67 | 66 |
| 11 | 1c | 4c | 71 | 62 |
| 12 | $\text{PhCOCH(CH}_3)_2$ (1d) | 4a | 48 | 44 |
| 13 | 1d | 4b | 63 | 69 |
| 14 | 1d | 4c | 55 | 69 |
| 15 | $\text{PhCO(CH}_2)_3\text{CH}_3$ (1e) | 4a | 51 | 44 |
| 16 | 1e | 4b | 59 | 63 |
| 17 | 1e | 4c | 64 | 55 |

^aReactions were carried out in a system of 1 (0.5 mmol), 3 (0.6 mmol), and 4 (1.2 mmol) at 0 °C for 15–20 h in THF. ^bYield after isolation by TLC. ^cDetermined by ^1H NMR or HPLC after the conversion to the corresponding Mosher's esters. ^dAbsolute configuration was (R). ^eIn Et_2O . ^fDetermined by optical rotation. $[\alpha]_D^{20} +21.4^\circ$ (c 4.4, CHCl_3). $[\alpha]_D^{25} -45.45^\circ$ (c 5.15, CHCl_3) for the pure (S) configuration: R. H. Rickard and J. Kenyon, J. Chem. Soc., 1911, 45.

In an extension of these new evidences, we next tried the reaction of trimethoxysilane with a ketone in the presence of a dilithium salt of optically active diol (4). The reduction proceeded very smoothly in anhydrous ethereal solvent at 0 °C to afford optically active alcohol after acid hydrolysis. The results are shown in Table 1.

A variety of aromatic ketones can be reduced by trimethoxysilane (3) promoted by optically active dilithium diolate (4) which was readily prepared from diethyl L-(+)-tartrate.⁸ The enantioselectivity in this system was 40–69 %ee for the diolate (4). As the asymmetric sources, we further used lithium salts of optically active 2-amino alcohols which were readily prepared by the reduction of readily available amino acids.¹⁰ The results are summarized in Table 2.

The efficiency of the asymmetric induction was considerably high at low temperature, though the chemical yield was not necessarily satisfactory. It should be emphasized that the reduction proceeded very smoothly by the use of a catalytic amount of the promoter without any decreasing of both the chemical yield and the asymmetric induction. Thus (R)-1-phenylethyl alcohol was

Table 2. Asymmetric reduction of ketones using trimethoxysilane (3) and lithium salt (5) of 2-amino alcohol (6)^a

| Entry | Ketone (1) | 2-Amino alcohol (6) | % Yield ^b | %ee ^{c,d} |
|-------|--|---|----------------------|----------------------|
| 1 | PhCOCH ₃ (1a) | (S)-Phenylalaninol (6a) | 62 | 44 |
| 2 | 1a | 6a ^e | 62 | 77 |
| 3 | 1a | 6a ^f | 89 | 44 |
| 4 | 1a | 6a ^{f,g} | 75 | 49 |
| 5 | 1a | 6a ^{f,h} | 42 | 48 |
| 6 | 1a | (S)-Prolinol (6b) ^f | 89 | 52 |
| 7 | 1a | 6b ^{f,i} | 100 | 49 |
| 8 | 1a | (S)-Valinol (6c) ^f | 99 | 49 |
| 9 | 1a | (S)-1,1-Diphenylvalinol (6d) ^f | 87 | 48 |
| 10 | PhCOCH ₂ CH ₃ (1b) | 6a ^e | 44 | 72 |
| 11 | 1b | 6a ^f | 88 | 32 |
| 12 | 1b | 6b ^f | 85 | 45 |
| 13 | PhCO(CH ₂) ₂ CH ₃ (1c) | 6a | 52 | 12 |
| 14 | 1c | 6a ^e | 27 | 84 (79) ^j |
| 15 | PhCOCH(CH ₃) ₂ (1d) | 6a | 55 | 18 |
| 16 | PhCO(CH ₂) ₃ CH ₃ (1e) | 6a | 55 | 17 |
| 17 | 1e | 6a ^e | 12 | 84 |

^aReactions were carried out in a system of 1 (0.5 mmol), 3 (0.6 mmol), and 4 (1.2 mmol) at rt for 3 h in THF, unless otherwise noted. ^bYield after isolation by TLC. ^cDetermined by ¹HNMR and HPLC after the conversion to the corresponding Mosher's esters. ^dAbsolute configuration was (R). ^eAt -78°C, overnight. ^fA catalytic amount (0.004 equiv.) of 6 was used. ^gHSi(OEt)₃ was used. ^hHSiMe(OEt)₂ was used. ⁱAt -78°C, overnight. ^jDetermined by optical rotation. $[\alpha]_D^{25} +28.0^\circ$ (c 2.0, PhH). $[\alpha]_D^{25} +35.7^\circ$ (c 3, PhH) for the pure (R) configuration: J. -P. Mazaleyrat and D. J. Cram, J. Am. Chem. Soc., 103, 4585 (1981).

obtained in the similar %ee by the reduction of acetophenone in the presence of a catalytic amount of a lithium salt of (S)-phenylalaninol. Triethoxysilane and diethoxymethylsilane can also be used as reducing reagents, the chemical yield being rather low.

Further study is required before the mechanistic details of these reactions can be fully understood. However, in contrast with the relatively low efficiency for the asymmetric induction using optically active hydrosilanes¹¹ or an asymmetric hydrosilylation of ketones catalyzed by rhodium-chiral phosphine complexes,⁵ the present reaction provides a novel route to asymmetric reduction of ketones to optically active alcohols.

In a typical procedure the lithium salt (5) was prepared from the optically active 2-amino alcohol (6) (0.004 mmol) and n-butyllithium (0.008 mmol) in THF (5 ml) at 0 °C. To this solution was added to a solution of the ketone (1) (1.0 mmol) and methoxysilane (134 mg, 1.5 mmol) in THF (15 ml) at 0 °C. The resulting mixture was stirred at the same temperature. Diethyl ether (20

ml) and hydrochloric acid (1 M, 10 ml) were then added and the mixture was stirred for 1 h. Usual work-up and preparative thin layer chromatography on silica gel gave the pure alcohol (2). The α of 2 was determined by HPLC or NMR analysis after conversion to the Mosher's esters.¹²

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References and Notes

- For reviews, M. Nogradi, "Stereoselective Synthesis," VCH, Weinheim, 1986, pp. 53-148; H. Haubenstock, *Top. Stereochem.*, **14**, 231 (1982).
- For reviews, E. Colvin, "Silicon in Organic Synthesis," Butterworths, London, 1981, Chap 21, pp. 325-336; W. P. Weber, "Silicon Reagents for Organic Synthesis," Springer-Verlag, Berlin, 1983, Chap 17 and 18, pp. 273-297.
- D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, **1974**, 633.
- J. Boyer, R. J. P. Corriu, R. Perz, and C. Reye, *Tetrahedron*, **37**, 2165 (1981); R. J. P. Corriu, R. Perz, and C. Reye, *ibid.*, **39**, 999 (1983); M. Fujita and T. Hiyama, *J. Am. Chem. Soc.*, **106**, 4629 (1984); *ibid.*, **107**, 8294 (1985).
- For a review, see I. Ojima, K. Yamamoto, and M. Kumada, "Aspects of Homogeneous Catalysis," D. Reidel, ed., Dordrecht, Vol. 3, 1977. I. Ojima and Y. Nagai, *Chem. Lett.*, **1973**, 541; *Idem*, *ibid.*, **1974**, 223; R. J. P. Corriu and J. J. E. Moreau, *J. Organomet. Chem.*, **85**, 19 (1975); K. Yamamoto, T. Hayashi, and M. Kumada, *ibid.*, **54**, C45 (1973).
- A. Hosomi, H. Hayashida, S. Kohra, and Y. Tominaga, *J. Chem. Soc., Chem. Commun.*, **1986**, 1411. See also M. Kira, K. Sato, and H. Sakurai, *J. Org. Chem.*, **52**, 948 (1987).
- A. Hosomi, S. Kohra, and Y. Tominaga, *Chem. Pharm. Bull.*, **35**, 2155 (1987); *J. Chem. Soc., Chem. Commun.*, in press.
- 4a**: $[\alpha]_D^{26} -12.5^\circ$ (neat). After L-(+)-tartaric acid, $[\alpha]_D^{20} 12.8^\circ$ (c 20, H₂O), was esterified and acetonized with 2,2-dimethoxypropane-MeOH catalyzed by p-TsOH, reduction with LiAlH₄, alkylation with MeI and PhCH₂Cl, and hydrolysis, successively, give **4b** and **4c**, respectively. **4b**: bp 75°C (1 mmHg); mp 28-30°C; $[\alpha]_D^{24} -6.0^\circ$ (c 1.0, Et₂O), $[\alpha]_D^{30} -11^\circ$ (c 4.7, MeOH), lit.^{9a} $[\alpha]_D -2.5^\circ$ (c 1.9, MeOH). **4c**: mp 52-55°C; $[\alpha]_D^{24} -11^\circ$ (c 1.0, Et₂O), $[\alpha]_D^{30} -13^\circ$ (c 4.9, CHCl₃), lit.^{9b} $[\alpha]_D -5.5^\circ$ (c 5.0, CHCl₃). The amide **4d** was prepared by the reaction of diethyl tartrate and dimethylamine in EtOH.^{9c} **4d**: mp 189-190°C; $[\alpha]_D^{21} +45^\circ$ (c 3.0, EtOH), lit.^{9c} mp 189-190°C; $[\alpha]_D +43^\circ$ (c 3.0, EtOH).
- (a) M. Schmidt, R. Amstutz, G. Crass, and D. Seebach, *Chem. Ber.*, **113**, 1691 (1980); (b) T. Matui and K. Koga, *Chem. Pharm. Bull.*, **27**, 2295 (1979); (c) D. Seebach, H.-O. Kalinowski, W. Langer, G. Crass, E.-M. Wilka, *Org. Synth.*, **61**, 24 (1983).
- 6a**: $[\alpha]_D^{20} -27.1^\circ$ (c 1.06, EtOH); **6b**: $[\alpha]_D^{20} +29.7^\circ$ (c 1.13, PhH); **6c**: $[\alpha]_D^{25} +14.7^\circ$ (c 10, EtOH); **6d**: $[\alpha]_D^{25} -138.0^\circ$ (c 1.98, CHCl₃). H. Seki, K. Koga, H. Matsuo, A. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.*, **13**, 995 (1965); D. Enders and H. Eichenmayer, *Chem. Ber.*, **112**, 2933 (1979); S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, A. Hirao, S. Nakahama, *J. Chem. Soc., Perkin Trans. I*, **1985**, 2039 and references cited therein.
- J. L. Fry and M. A. McAdam, *Tetrahedron Lett.*, **25**, 5859 (1984).
- S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973); J. P. Dirlam, D. A. Clark, and J. J. Hecker, *ibid.*, **51**, 4920 (1986).

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