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Chelation-Controlled Protocol for the Diastereoselective Reduction of Ketones

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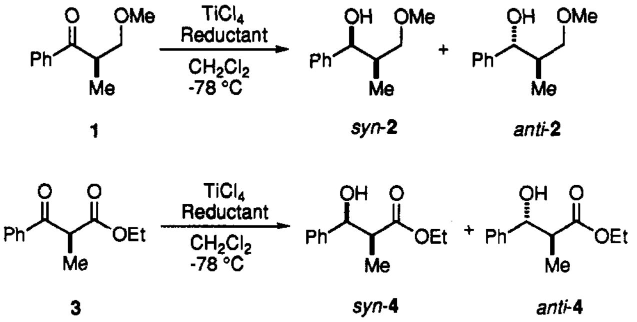
Summary: A new chelation-controlled, α-chiral ketone reduction protocol is presented based on titanium tetrachloride and a wide variety of reducing agents. Features of the proposed intermediate titanium chelates necessary to obtain high diastereoselectivity are discussed.

The components necessary for chelation control are well understood: chelate formation between a Lewis acid and substrate that activates and organizes followed by addition of a nucleophile.[1] This has been applied with great success in diastereoselective additions to substituted aldehydes using carbon nucleophiles (e.g., allylsilanes, allylstannanes, R_2Zn, enol–silanes) and Lewis acids capable of bis-ligation (e.g., $TiCl_4$, $SnCl_4$, $MgCl_2$). A similar two-component approach to tackle the widely studied problem of diastereoselective acyclic ketone reduction,[2] however, has seen little attention,[3] although the Lewis acid/nucleophile $Zn(BH_4)_2$ should be noted.[4] In this paper, we report a convenient method for the chelation-controlled, diastereoselective reduction of α-chiral acyclic ketones using a wide variety of reducing agents in conjunction with titanium tetrachloride. The structural features necessary in substrates to achieve high levels of diastereocontrol are discussed.

After some optimization, the following conditions proved to be effective: ketone (1.0 equiv) is treated with $TiCl_4$[5] (1.0 equiv) in CH_2Cl_2 at −78 °C for 10 min followed by addition of the reductant (1.0 equiv). The application of these conditions to two representative ketones capable of chelation employing a variety of reducing agents is shown in Table 1.[6] These data are striking in several regards. First, the level of diastereocontrol is uniformly high. Second, only 9-BBN of the CH_2Cl_2-soluble reducing agents attempted to date has failed to give product alcohol.[7] Third, both electrophilic (borane, DIBAL-H) and nucleophilic (borohydride) reducing agents can be used. Fourth, reagents that require ketone activation for reduction to occur (e.g., $Me_3N–BH_3$ and pyridine–BH_3) as well as reagents that do not (t-$BuNH_2–BH_3$ and $Me_4N{\cdot}BH_4$) can be employed.

Table 1. Reduction of β-Alkoxy Ketone 1 and β-Keto Ester 3 with $TiCl_4$ and Various Reductants[a]



reductant	ketone	ratio (syn:anti)[b]	yield (%)
$Et_4N{\cdot}NCBH_3$[c]	1	98:2	87
t-$BuNH_2–BH_3$	1	96:4	89
$Me_3N–BH_3$	1	>99:1	84
$Me_4N{\cdot}BH_4$	1	>99:1	93
THF–BH_3	1	>99:1	72
pyridine–BH_3	1	98:2	87
DIBAL-H[d]	1	94:6	88
$Et_4N{\cdot}NCBH_3$[c]	3	96:4	96
t-$BuNH_2–BH_3$	3	94:6	81
$Me_3N–BH_3$	3	>99:1	88
$Bu_4N{\cdot}BH_4$	3	>99:1	84
THF–BH_3	3	>99:1	80
pyridine–BH_3	3	>99:1	91
DIBAL-H[d]	3	97:3	80

[a] General experimental procedure of ref 6 used. [b] Diastereomer ratios were measured by GLC or ^1H NMR. [c] 1.2 equiv of $TiCl_4$ was used. [d] 2.0 equiv of DIBAL-H was used.

A number of substrates that might be subject to chelation control were treated with $Et_4N{\cdot}NCBH_3$[8] and $TiCl_4$ (Table 2). The presumed chelate intermediates involved 5-, 6-, and possibly 7-membered rings[9] and led generally to useful levels of diastereoselectivity. In particular, a number of hydroxyl-protected derivatives of a common β-hydroxy ketone were evaluated. Methoxymethyl, benzyl, and *tert*-butyldiphenylsilyl ethers proved effective, while *p*-methoxybenzyl and *tert*-butyldimethylsilyl ethers were labile under the reaction conditions.[10] The level of diastereocontrol achieved with the *tert*-butyldiphenylsilyl ether example is notable. Silyl ethers are recognized generally for their poor coordinating and chelating abilities[11] with few exceptions.[12]

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[1] Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984,** *23,* 556–569. Reetz, M. T. *Acc. Chem. Res.* **1993,** *26,* 462–468.

[2] (a) Greeves, N. In *Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 8, pp 7–14. (b) Nógrádi, M. *Stereoselective Synthesis*; VCH: New York, 1986; pp 131–148. (c) Rahman, A.-u.; Shah, Z. *Stereoselective Synthesis in Organic Chemistry*; Springer-Verlag: New York, 1993; pp 162–174.

[3] (a) Thieme, P. C.; Sauter, H.; Reissenweber, G. *Chem. Ber.* **1988,** *121,* 1059–1062. (b) Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991,** *32,* 6147–6150. (c) Elliot, J.; Hall, D.; Warren, S. *Tetrahedron Lett.* **1989,** *30,* 601–604. (d) Maier, G.; Seipp, U.; Boese, R. *Tetrahedron Lett.* **1987,** *28,* 4515–4516.

[4] Nakata, T.; Oishi, T. *Acc. Chem. Res.* **1984,** *17,* 338–344.

[5] $SnCl_4$ can be substituted for $TiCl_4$. In the case of $Et_4N{\cdot}NCBH_3$, 1.2 equiv of $TiCl_4$ must be used.

[6] General experimental procedure: In a dry, three-necked, round-bottomed flask was placed 1.0 mmol of ketone and 10 mL of dry CH_2Cl_2 under N_2. The reaction vessel was chilled to −78 °C and $TiCl_4$ (1.2 mmol, 0.132 mL) added quickly. Soon thereafter, the reductant (1.0 mmol) is added over a 1-min period. For liquid reductants or purchased reductant solutions, direct addition by syringe was employed. For solid reductants, a CH_2Cl_2 solution (5 mL) was generated and added slowly by syringe. After 10 min at −78 °C, the reaction was quenched with 1 N HCl and slowly warmed to 20 °C. The reaction mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with water and then brine, dried (anhyd Na_2SO_4), and concentrated *in vacuo* to give material that upon chromatography afforded the corresponding alcohol. In those cases where quaternary ammonium salts were used, the initial CH_2Cl_2 extracts were concentrated and then partitioned between water and Et_2O, with the resulting ethereal extracts taken through the workup described above.

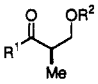
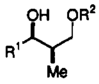
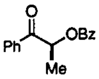
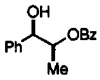
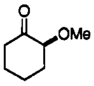
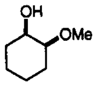
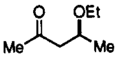
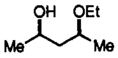
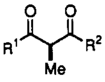
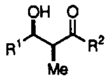
[7] With 9-BBN, no reduction was observed. Ethereal solvents can be used, but the resulting ratios are depressed compared to CH_2Cl_2.

[8] Repasky, J. E.; Weidig, C.; Kelly, H. C. *Syn. React. Inorg. Metal-Org. Chem.* **1975,** *5,* 337–345. $Bu_4N{\cdot}NCBH_3$ is also effective; see: Hutchins, R. O.; Kandasamy, D. *J. Am. Chem. Soc.* **1973,** *95,* 6131–6133.

[9] 2-(Benzoyloxy)propiophenone (Table 2) presumably forms a seven-membered chelate.

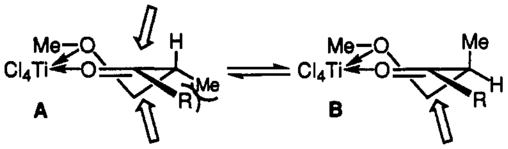
0022-3263/94/1959-0705$04.50/0

Table 2. Reduction of Ketones by $TiCl_4$ and $Et_4N{\cdot}NCBH_3$[a]

substrate	syn diastereomer	R^1	R^2	combined yield (%)	syn: anti[b]
		Ph	MOM	86	98:2
		Ph	Bn	94	96:4
		Ph	TBDPS	84	92:8
		t-Bu	Me	89	97:3
		Me	Me	90	58:42
				91	89:11
				91	94:6
					78:22
		*t*-Bu	OEt	91	98:2
		Me	Piperidyl	92	98:2

[a] General experimental procedure of ref 6 used with 1.2 equiv of $TiCl_4$. [b] Diastereomer ratios were measured by GLC or ^1H NMR.

As would be expected, substrates that are selectively reduced by $Zn(BH_4)_2$ are also selectively reduced by the system reported here. While good selectivity involving 5-membered chelates is not unexpected given their well-defined conformation,[13] the lack of selectivity with the presumed six-membered chelates derived from 4-methoxy-3-methyl-2-butanone and 4-methoxy-2-pentanone demanded further explanation (see Table 2). In studies similar to those of Keck and co-workers concerning chelates of β-alkoxy aldehydes,[14] we have examined by ^1H NMR six-membered, $TiCl_4$–ketone chelates. These studies suggest that the position of the equilibrium between conformers **A** and **B** determines reduction selectivity,[15] rather than differences in coordinating ability as suggested by Nakata and Oishi for $Zn(BH_4)_2$.[4] When R is small, conformer **A** is favored; it displays no clear facial biasing of the ketone, and low selectivity is a consequence. When R is large or an sp^2-hybridized center, conformer **B** is favored because it avoids the steric interaction then present in conformer **A**, leading to a facial biasing of the ketone and preferred formation of the syn reduction product. Like considerations predict the selectivity observed with other ketone reductions involving six-membered chelates.



In summary, the two-component approach to chelation control can be applied to diasteroselective ketone reduction. The wide range of reductants that can be employed in this method dramatically expands the number of nucleophiles that may be used in chelation-controlled processes.[16] An understanding of chelate conformation is critical in predicing the level of reduction diastereocontrol with six-membered ketone chelates. Extending these observations is the subject of ongoing studies.

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Supplementary Material Available: Synthesis and characterization of substrates as well as ^1H NMR for all reduction products (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(10) With acid-sensitive protecting groups, changing the order of addition described in the general experimental procedure (ref 6) was advantageous; namely, $TiCl_4$ and $Et_4N{\cdot}NCBH_3$ were combined, and then ketone was added. In the case of the *tert*-butyldimethylsilyl ether, an 87% yield of protected and deprotected product in a 1:1.1 ratio was obtained.

(11) See the following and references cited therein: Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697–703.

(12) Sharma, V.; Simard, M.; Wuest, J. D. *Inorg. Chem.* **1991**, *30*, 579–581. Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130–6131.

(13) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881–5884.

(14) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847–3849. Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480–5482.

(15) This argument assumes that there is no great difference in the activation barriers associated with nucleophile attack at unhindered carbonyl faces of conformers **A** and **B**.

(16) We have briefly examined carbon nucleophiles and found that Et_2Zn and $AlMe_3$ add to $TiCl_4$ chelates to ketones **1** and **3**. Selectivity was >99:1 with yields of 83–89%.