Non-chelation-controlled Nucleophilic Addition to Chiral α-Siloxyketones

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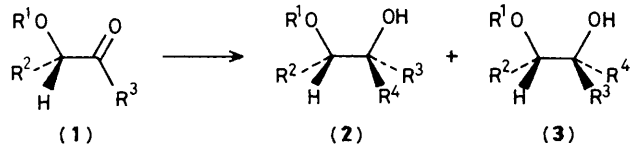
Non-chelation-controlled Grignard-like and aldol additions to *O*-silyl protected α-hydroxyketones are possible for the first time using titanium reagents of reduced Lewis-acidity.

The problem of chelation- or non-chelation-controlled nucleophilic additions to α-chiral α-alkoxyaldehydes has been largely solved, the reagents of choice often being organotitanium compounds of high or low Lewis-acidity, respectively.[1] For example, α-benzyloxypropanal (**1**; $R^1 = CH_2Ph$, $R^2 = Me$, $R^3 = H$) reacts with $[MeTiCl_3]$ to form the chelation-controlled adduct *via* a five-membered intermediate chelate, whereas the less Lewis-acidic analogue $[MeTi(OCHMe_2)_3]$ allows entry into the non-chelation-controlled manifold.[2] Apparently, α-alkoxyaldehydes do not form intermediate chelates with the latter reagents, thereby allowing the phenomena involved in the Felkin–Anh or Cornforth models

Table 1. Diastereoselective additions to ketones (**1**).

Ketone	Reagent	Temp./time (°C) (h)	Solvent	Yield (%)	(**2**) : (**3**)[a]
(**1a**)	[$MeTi(OCHMe_2)_3$]	22/48	CH_2Cl_2	97	>99 : <1
(**1a**)	[MeMgCl]	−78/2	Et_2O	85	>99 : <1
(**1a**)	[MeLi]	−78/2	THF[c]	90	60 : 40
(**1a**)	[MeLi]/[$TiCl_4$]	0/4	Et_2O	85	95 : 5
(**1b**)	[$MeTi(OCHMe_2)_3$]	22/48	neat	80[b]	<1 : >99
(**1b**)	[MeMgCl]	−78/2	Et_2O	78	60 : 40
(**1b**)	[MeLi]/[$TiCl_4$]	−10/3	Et_2O	78	85 : 15
(**1c**)	[$MeTi(OCHMe_2)_3$]	22/24	neat	72	78 : 22
(**1c**)	[MeLi]/[$TiCl_4$]	−10/2	Et_2O	79	81 : 19
(**1d**)	[$MeTi(OCHMe_2)_3$]	22/48	neat	80	<1 : >99
(**1d**)	[MeLi]/[$TiCl_4$]	−10/2	Et_2O	72	31 : 69
(**1b**)	[$(CH_2{=}CHCH_2)Ti(OCHMe_2)_3$]	−78/2	THF	87	<1 : >99
(**1b**)	[$(CH_2{=}CHCH_2)Ti(OCHMe_2)_4$][MgCl]	−78/2	THF	88	<1 : >99
(**1b**)	[$(CH_2{=}CHCH_2)MgCl$]	−78/2	THF	90	10 : 90

[a] In the case of Me_3Si protective groups (**1c**), acidic workup affords the diols (**2**)/(**3**) (R^1 = H). In the case of (**1d**), the products (**2**)/(**3**) retain the $Bu^t(Me_2)Si$ protective group during such workup. [b] Typical procedure: [$MeTi(OCHMe_2)_3$] (1.7 g; 7 mmol), prepared according to standard procedure (M. T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Peter, R. Ostarek, and S. Maus, *Chem. Ber.*, 1985, **118**, 1421) is added to ketone (**1b**) (1.1 g; 5 mmol) under an atmosphere of dry nitrogen in the absence of any solvent at room temperature. After stirring for 48 h, diethyl ether (*ca.* 30 ml) is added followed by workup with saturated NH_4F solution (*ca.* 20 ml). Dilute HCl is also suitable. After extraction and drying over $MgSO_4$, the solvent is stripped off and the residue distilled using a Kugelrohr apparatus (95 °C/0.1 Torr) to yield 0.93 g (80%) of pure {**3**; R^1 = $Bu^t(Me_2)Si$, R^2 = R^4 = Me, R^3 = Et}. Allyltitanium reagents and titanium enolates are much more reactive and should be treated with ketones in a solvent (see also Table 2). [c] THF = tetrahydrofuran.



(**1**) (**2**) (**3**)

a; R^1 = CH_2Ph, R^2 = Me, R^3 = Et
b; R^1 = $Bu^t(Me_2)Si$, R^2 = Me, R^3 = Et
c; R^1 = Me_3Si, R^2 = Me, R^3 = Et
d; R^1 = $Bu^t(Me_2)Si$, R^2 = R^3 = Ph

to operate.[1] In the analogous ketone series (**1a**; R^3 = alkyl or aryl),† simple Grignard reagents are known to provide chelation-controlled products,[1,3] but no method to reverse this diastereofacial selectivity has been reported to date.[1] This communication describes a solution to this problem.

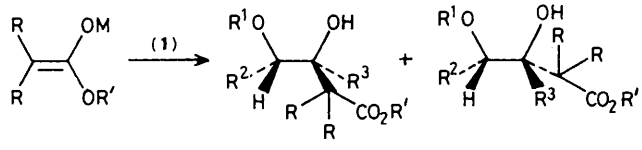
Expecting the α-benzyloxyketones to behave analogously to the aldehydes, we treated (**1a**) with [$MeTi(OCHMe_2)_3$]. To our surprise, the sole product turned out to be the chelation-controlled diastereoisomer (**2**) (Table 1), just as in the reactions of [MeMgCl] and [$MeTiCl_3$]. Thus, the two oxygen functionalities in (**1a**) constitute an efficient bidentate ligand even when [$MeTi(OCHMe_2)_3$] is used. In order to prevent such chelation, we employed the bulky t-butyldimethylsilyl protective group.[4] Indeed, complete non-chelation-control in the reaction of (**1b**) with [$MeTi(OCHMe_2)_3$] was observed: (**2b**) : (**3b**) = <1 : >99.[5] Table 1 documents the generality of our approach.‡ It can be seen that a bulky silyl protective group *and* a titanium reagent of fairly low Lewis-acidity are prerequisites for efficient non-chelation-control. Interestingly, the use of the trimethylsilyl group leads to a surprising degree of chelation-control. Thus, steric factors appear to be more important than any electronic effect that might originate from the silyl group.

In the aldol additions of ester enolates (**4**), the task of non-chelation-control is not quite as formidable, *i.e.*, trimethylsilyl or even benzyl protective groups are sufficiently

Table 2. Aldol additions to ketones (**1**).

Ketone	Reagent	Temp./time (°C) (h)	Yield[a] (%)	(**5**) : (**6**)
(**1a**)	(**4a**)	−78/2	67	10 : 90
(**1a**)	(**4b**)	−78/2	68	<1 : >99
(**1a**)	(**4c**)	−78/2	75	15 : 85
(**1b**)	(**4a**)	22/20	60	<1 : >99
(**1b**)	(**4b**)	22/20	60	<1 : >99
(**1b**)	(**4c**)	−78/2	79	11 : 89
(**1c**)	(**4a**)	−78/3	65	<1 : >99
(**1c**)	(**4b**)	−78/3	61	<1 : >99
(**1c**)	(**4c**)	−78/2	82	21 : 79
(**1d**)	(**4c**)	−78/2	78	<1 : >99
(**1b**)	(**4d**)	−40/3	79	19 : 81
(**1b**)	(**4e**)	−40/3	85	<1 : >99
(**1b**)	(**4f**)	−78/1	88	21 : 79

[a] All reactions were performed in THF and worked up with 2 M HCl. Under these conditions ketones (**1c**) lead to the 3-hydroxy-γ-butyrolactones corresponding to (**5**)/(**6**). See also footnote§.



(**4**) (**5**) (**6**)

a; R = Me, M = $Ti(OCHMe_2)_3$, R′ = Me
b; R = Me, M = $Ti(NEt_2)_3$, R′ = Me
c; R = Me, M = Li, R′ = Me
d; R = H, M = $Ti(OCHMe_2)_3$, R′ = Et
e; R = H, M = $Ti(NEt_2)_3$, R′ = Et
f; R = H, M = Li, R′ = Et

† In testing diastereofacial selectivity, racemic ketones were employed leading to racemic products. Only one enantiomeric form is arbitrarily shown.

‡ Configurational assignments[5] in methyl additions were made by deprotection of (**2**)/(**3**) and comparison of the diols with those obtained by OsO_4-induced *cis*-hydroxylation of (*Z*)- and (*E*)-3-methylpent-2-ene. For the allyl additions, (**2**)/(**3**) were deprotected and the diols converted into the acetonides, with which nuclear Overhauser enhancement (n.O.e.) experiments were performed in order to ascertain the relative configuration.

bulky in certain cases, and occasionally even lithium enolates provide non-chelation-controlled aldols (**6**) exclusively.§ Nonetheless, it is again the combination of a silyl protective group and a titanium reagent of fairly low Lewis-acidity which constitutes the most general method (Table 2).[5]

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§ Configurational assignments in the addition reactions of (**4a—c**) were made by deprotection leading to the 2,2-dimethyl-3-ethyl-3-hydroxy-4-methyl-γ-butyrolactones which were *O*-methylated and then studied by n.O.e. For the addition reactions of (**4d—f**) tentative assignment was made on the basis of analogous chemical behaviour.

References

1 Review: M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 556; see also M. T. Reetz, 'Organotitanium Reagents in Organic Synthesis,' Springer–Verlag, Berlin, 1986.
2 M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, and R. Steinbach, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 989; *Angew. Chem. Suppl.*, 1983, 1511.
3 W. C. Still and J. H. McDonald, *Tetrahedron Lett.*, 1980, **21**, 1031; D. C. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, 1959, **81**, 2748.
4 The t-butyldiphenylsilyl protective group has been employed in the non-chelation-controlled reduction of α-hydroxyketones: L. E. Overman and R. J. McCready, *Tetrahedron Lett.*, 1982, **23**, 2355; T. Nakata, T. Tanaka, and T. Oishi, *ibid.*, 1983, **24**, 2653; L. E. Overman and S. W. Goldstein, *J. Am. Chem. Soc.*, 1984, **106**, 5360.
5 M. Hüllmann, Dissertation, Universität Marburg, 1986.