Chemoselective *in situ* Protection of Aldehydes and Ketones using Titanium Tetrakis(dialkylamides)

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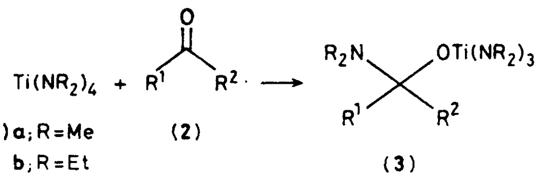
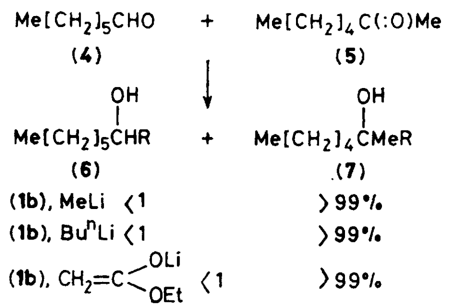
Titanium tetrakis(dialkylamides) are chemoselective protective agents for carbonyl compounds, so that such reactions as Grignard and aldol additions can be induced to occur at ketone groups in the presence of aldehydes in a one-pot procedure.

Although numerous protective groups[1] for aldehydes and ketones are currently known, notably acetals and thioacetals, several drawbacks persist. (a) If a molecule contains two or more carbonyl groups, protection of one function with the complete exclusion of the other is not always possible. (b) In protective group methodology three-step sequences are



Scheme 1



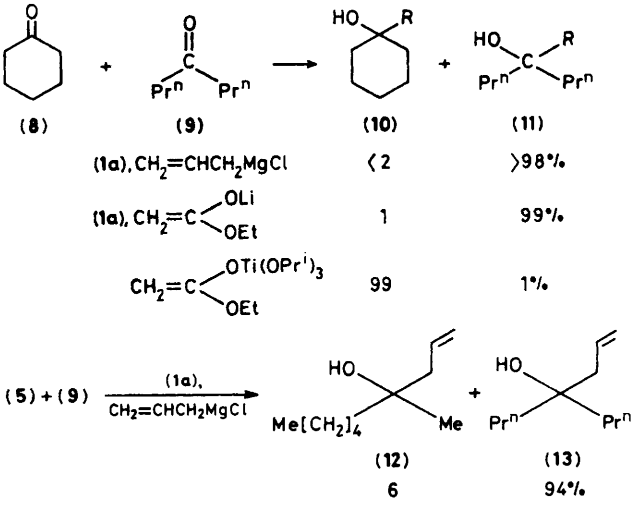
Scheme 2

generally required: protection, reaction, and deprotection. (c) Conditions for deprotection may be stringent, sometimes requiring toxic reagents (*e.g.*, Hg or Cd salts in case of thioacetals). We have discovered that titanium tetrakis(dialkylamides)[2] (**1**) are excellent reagents for *in situ*[3] protection of aldehydes and ketones (**2**) to form adducts (**3**), which readily revert back to (**2**) upon aqueous work-up. Aldehydes react considerably faster than ketones, so that in systems containing both functional groups complete chemoselective blocking of the former results. Addition of RMgX, RLi, $LiCH_2CN$, or enolates to ketones in the presence of aldehydes is therefore possible in a one-pot procedure.[4] This methodology also allows for controlled delivery of the above nucleophiles to sterically more hindered carbonyl sites (Scheme 1).

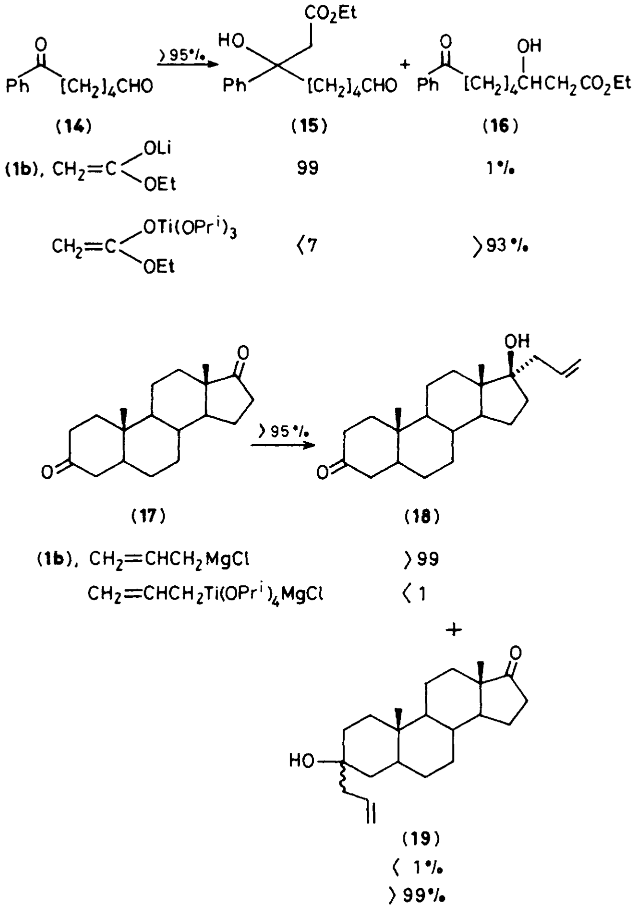
Addition of (**1b**) (1 equiv.; −78 °C) to a 1 : 1 mixture of n-heptanal (**4**) and heptan-2-one (**5**) resulted in complete protection of the former,† since the reaction of methyl-lithium, n-butyl-lithium, and the lithium enolate derived from ethyl acetate followed by aqueous work-up afforded essentially only the ketone adducts (**7**) (>90% conversion) and the starting aldehyde (**4**). Similar selectivities were obtained using other aldehyde–ketone pairs such as benzaldehyde–acetophenone in combination with the above and other carbanions (*e.g.*, $LiCH_2CN$ and allylmagnesium chloride) (Scheme 2).

Reagent (**1a**) turned out to be more reactive, since the reaction with a 1 : 1 mixture of (**4**) and (**5**) resulted in complete protection of *both* carbonyl compounds, more than one amino-group being rapidly transferred and no reaction occurring with carbanions. Use of only 0.5 equiv. of (**1a**) restored the selectivity to ketones in reactions with n-butyl-lithium and other carbon nucleophiles. This means that transfer of the second and third amino-group is slower, *i.e.*, the oxygenophilicity[5] of the reagent is somewhat tempered as more amino-groups are substituted by alkoxy-moieties.

Upon testing potential ketone–ketone discrimination, we discovered that the addition of (**1b**) requires higher temperatures (*ca.* −30 °C), at which the adducts (**3**) begin to fragment.[6] In contrast, (**1a**) proved to be reactive and selective at −50 °C, as shown by the examples in Scheme 3.



Scheme 3



Scheme 4

The principles which evolve from these intermolecular competition experiments apply to keto-aldehydes, dialdehydes, or diketones. It should be noted that in all these cases the use of organotitanium reagents[7] resulted in essentially complete aldehyde selectivity or in preferred attack at less hindered carbonyl sites, which means that the two methods are complementary (*e.g.* Scheme 4).

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† The addition of (**1a**) or (**1b**) to benzaldehyde was monitored by ^1H n.m.r. spectroscopy. Rapid and complete disappearance of the aldehyde proton-signal was observed as well as new signals in accord with the proposed adduct (**3**). Similar effects were recorded for aliphatic aldehydes.

In a typical experiment, (**1b**) (1 equiv.) was added to a 1 : 1 mixture of aldehyde and ketone (or keto-aldehyde) in tetrahydrofuran (THF) at −78 °C. The mixture was allowed to warm to −50 °C during 1 h, and alkyl-lithium reagents or enolates were added at that temperature. It is important not to let the temperature rise above −35 °C during the reactions. Aqueous work-up (*e.g.*, dil. HCl) follows. In the case of ketone–ketone selectivity, (**1a**) (1 equiv.) was used at −50 °C analogously.

Initial experiments utilizing $ClTi(NR_2)_3$, $(C_5H_5)Ti(NR_2)_3$, and $Zr(NR_2)_4$ show similar trends, although the reactions are generally not as clean. We are currently testing other metal amides such as those of magnesium, zinc, vanadium, and manganese.‡

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‡ *Added in proof:* $Mn(NEt_2)_2$ is a very mild protecting agent, transferring both of the amino groups onto the aldehyde function so that complete ketone selectivity in reactions with carbanions is observed (>90% conversion). Discrimination between two different ketone groups is also pronounced.

References

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3 Recently, a method for the *in situ* protection of aldehydes using lithium morpholide has been described which cannot be utilized for ketones owing to undesired enolization: D. L. Comins and J. D. Brown, *Tetrahedron Lett.*, 1981, 4213; D. L. Comins, J. D. Brown, and N. B. Mantlo, *ibid.*, 1982, 3979.

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5 Mean bond energies: Ti–O (115 kcal/mol), Ti–N (81 kcal/mol) (1 cal = 4.184 J): M. F. Lappert, D. S. Patil, and J. B. Pedley, *J. Chem. Soc., Chem. Commun.*, 1975, 830.

6 Enamine formation occurs: see also H. Weingarten and W. A. White, *J. Org. Chem.*, 1966, **31**, 4041.

7 Review: M. T. Reetz, *Top. Curr. Chem*, 1982, **106**, 1; see also B. Weidmann and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 31.