Reactions of 2-Lithio- and 2-Titano-methyl-quinoline Reagents: The Necessity of using an Excess of Titanating Agents in adjusting Molecular Recognition

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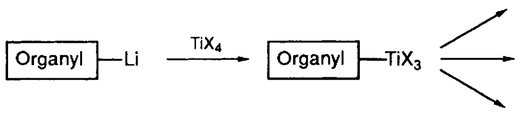
The extremely reactive and unselective 2-lithiomethyl-quinoline **1** can be titanated with an excess of $Ti(OPr^i)_4$ or $ClTi(OPr^i)_3$ to produce titanium analogues which react chemoselectively with carbonyl compounds.

The titanation (Scheme 1) of classical carbanions generally increases chemo-, regio- and stereo-selectivity.[1] Since the electronic and steric nature of the ligands X at titanium can be varied,[1,2] such metal exchange makes it possible to introduce ligand effects into 'carbanion chemistry.' Indeed, this concept not only works well for titanium, it has also been extended to other transition metals.[1,3] Although in most cases a 1 : 1 ratio of carbanion precursor to titanating agent suffices, the use of an excess of reagent has been reported to increase stereoselectivity in one rare case.[4] Here we report that the titanation of

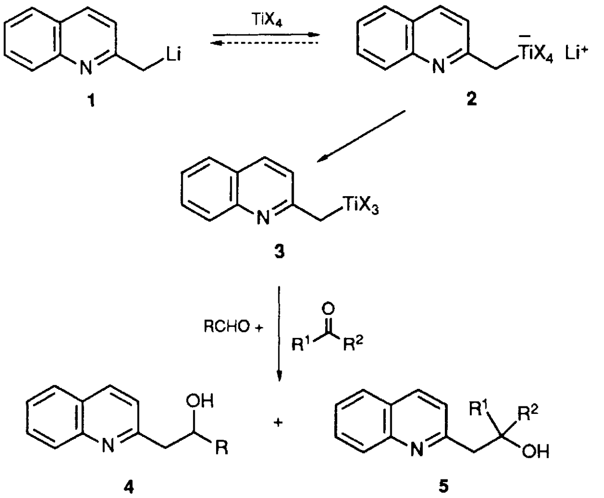
Table 1 Chemoselectivity in reactions of metallomethyl-quinoline reagents[a]

Entry	Transmetallating agent (amount)[b]	R	R[1]	R[2]	**4**:**5**	Conversion (%)
1	—[c]	Ph	Ph	Me	60:40	93
2	$ClTi(OPr^i)_3$ (1)	Ph	Ph	Me	77:23	94
3	$ClTi(OPr^i)_3$ (2)	Ph	Ph	Me	96:4	92
4	$ClTi(OPr^i)_3$ (3)	Ph	Ph	Me	>99:<1	65
5	$Ti(OPr^i)_4$ (1)	Ph	Ph	Me	89:11	73
6	$Ti(OPr^i)_4$ (2)	Ph	Ph	Me	>99:<1	68
7	$ClTi(NEt_2)_3$ (1)	Ph	Ph	Me	71:29	80
8	$TiCl_4$ (1)	Ph	Ph	Me	73:27	89
9	$TiCl_4$ (2)	Ph	Ph	Me	74:25	67
10	—[c]	n-C_6H_{13}	Me	n-C_5H_{11}	80:20	96
11	$ClTi(OPr^i)_3$ (2)	n-C_6H_{13}	Me	n-C_5H_{11}	>99:<1	87
12	$Ti(OPr^i)_4$ (2)	n-C_6H_{13}	Me	n-C_5H_{11}	>99:<1	96
13	$MnCl_2$[d] (2)	n-C_6H_{13}	Me	n-C_6H_{13}	83:17	70
14	—[c]	n-C_6H_{13}	Ph	Me	36:64	94
15	$Ti(OPr^i)_4$	n-C_6H_{13}	Ph	Me	>99:<1	73

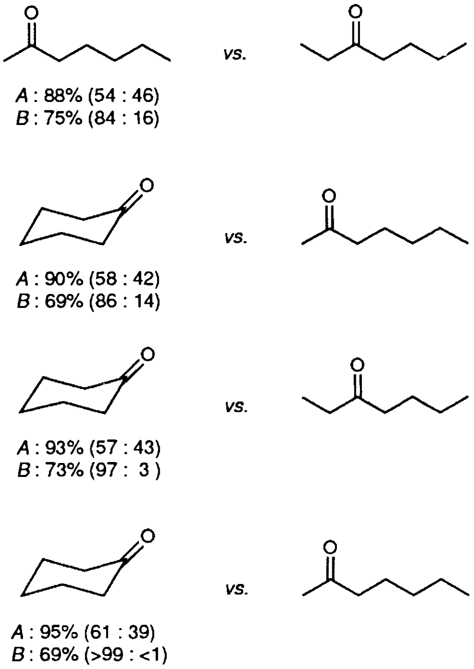
[a] In ether at −78 °C. [b] Equiv. of transmetallating agent with respect to **1** in parentheses. [c] Reagent **1** was used. [d] Tetrahydrofuran as solvent.



Scheme 1



Scheme 2



Scheme 3 Competition experiments with two ketones. Yields are given for: *A*, reactions with reagent **1**; and *B*, reactions with reagent **1** + $Ti(OPr^i)_4$; numbers in parentheses are the ratios of the two alcohols produced

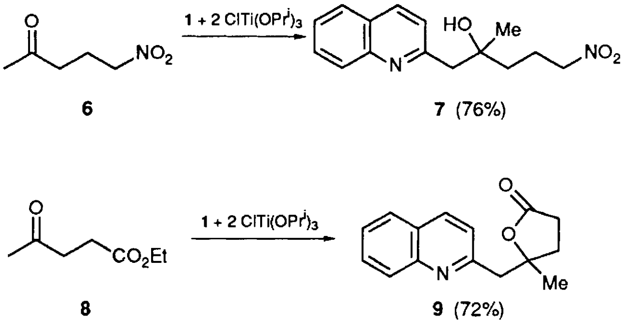
the extremely reactive 2-lithiomethylquinoline **1** with various titanating agents increases chemoselectivity in carbonyl addition reactions dramatically, provided that an excess of TiX_4 is used.

Aldehyde–ketone differentiation, being a sensitive test of chemoselectivity,[1] was first explored by the reaction of 1 : 1 mixtures of aldehydes and ketones with reagents **1**-TiX_4 at −78 °C in competition experiments (Scheme 2). The results show that the lithium reagent **1** reacts essentially chemorandomly and that titanation results in moderate to high degrees of aldehyde selectivity. This is related to the fact that the Ti–C bond is less polar than the Li–C analogue, and that the bulky ligands at titanium give rise to steric interactions in the transition state.[1] Significantly, the degree of aldehyde-selectivity depends upon the amount of titanating agent, $ClTi(OPr^i)_3$ or $Ti(OPr^i)_4$ used (Table 1, entries 2–6). The use of two to three equivalents of $ClTi(OPr^i)_3$ or two equivalents of $Ti(OPr^i)_4$ constitutes the method of choice. The phenomenon behind these reactivity patterns is difficult to define. In the case of $Ti(OPr^i)_4$ the initial (reversible?) formation of ate complexes[1,5] **2** is likely, which may collapse to the neutral triisopropoxy reagent **3** (X = $\mathrm{OPr^i}$) by the action of additional $\mathrm{Ti(OPr^i)_4}$. In the case of $\mathrm{ClTi(OPr^i)_3}$ the analogous process would mean that the corresponding ate complex **2** contains a chloride as a ligand at titanium which is abstracted by the additional Lewis acid $\mathrm{ClTi(OPr^i)_3}$. Either the ate complexes are less chemoselective than the neutral reagents **3**, or a small amount reverts back to the unselective lithium reagent **1**. Finally, the trichlorotitanium reagent **3** (X = Cl) is, as expected,† much more reactive and consequently less selective (Table 1, entries 8–9), just like the manganese[6] analogue (entry 13).

Using two equivalents of $\mathrm{Ti(OPr^i)_4}$, the possibility of ketone–ketone discrimination was also explored. Indeed, small to moderate differences in steric shielding of the substituents of the ketones lead to significant molecular recognition, the smaller ketones reacting faster (Scheme 3).

Finally, compatibility with additional functionality was tested. Whereas the lithium reagent **1** reacts with the nitro-ketone **6** and the keto-ester **8** at −78 °C to produce fairly complex mixtures of products (<40% of desired adducts), prior addition of two equivalents of titanating agents results in well behaved reagents. In the case of **8** the primary adduct cyclizes[7] to the lactone **9** (Scheme 4).

In summary, we have shown that reactivity and selectivity of the extremely indiscriminate carbanion **1** can be modulated by titanation with two or three equivalents of $\mathrm{ClTi(OPr^i)_3}$ or $\mathrm{Ti(OPr^i)_4}$. The fact that an excess of titanating agent is essential should be kept in mind whenever similar chemoselectivity problems arise in other situations.[9]‡§



Scheme 4

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† Organyltitanium trichlorides are generally more reactive than the analogous triisopropoxides; see ref. 1.

‡ Typical procedure: a solution of n-butyllithium (3.13 ml of a 1.6 mol $\mathrm{dm^{-3}}$ n-hexane solution; 5.0 mmol) in dry ether (50 ml) was slowly treated with 2-methylquinoline (6.8 ml; 5 mmol) at 0 °C under dry $\mathrm{N_2}$. After 20 min the soln. was cooled to −30 °C, treated with chlorotriisopropoxytitanium[7] (2.9 g, 11 mmol) in melted form or as an ether soln., stirred for 0.5 h and cooled to −78 °C. 5-Nitropentan-2-one (**6**; 650 mg, 5.0 mmol) was slowly added and the mixture stirred for 3 h, during which time the temperature rose to −30 °C. The mixture was poured on saturated aqueous $\mathrm{NH_4F}$ and extracted several times with ether. The combined ether phases were dried over $\mathrm{K_2CO_3}$, and evaporated, and the residue filtered through silica gel and recrystallized from toluene. After storing in a drying pistol over paraffin chips at 50 °C, 1.04 g (76%) of analytically pure white crystals of **7**, m.p. 69–70 °C, were obtained. For the competition experiments, the reagents (one part) were transferred into 1 : 1 mixtures of carbonyl compounds.

§ Preliminary NMR studies of **1**–$\mathrm{TiX_4}$ have not been successful, so that nothing is currently known about the structure of the titanium reagents. Formulae **2** and **3** are simply formal pictures; nitrogen may well serve as an internal ligand. It is not clear when to expect the necessity of using an excess of titanating agent in the case of other carbanions not studied so far.