

STUDIES OF THE STABILITY AND REACTIVITY OF SUBSTITUTED VINYL TITANIUM TRIISOPROPOXIDES

Robert K. Boeckman, Jr.^{*} and Kenneth J. O'Connor

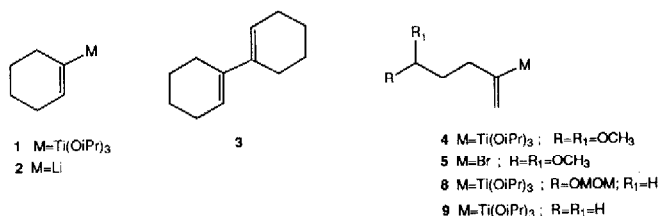
Department of Chemistry
University of Rochester
Rochester, New York 14627

Summary: The stability and reactivity of vinyl titanium triisopropoxides having a variety of substitution patterns has been explored. These reagents when prepared in Et₂O have proven to be more stable than expected based on prior reports, and they exhibit sufficient reactivity at temperatures where they are stable (-78° → -60°C) to undergo highly chemoselective addition to a structurally diverse group of aldehydes in fair to excellent yields. However, stereoselectivity obtained upon attempted chelation controlled addition to α and β -alkoxy aldehydes is modest.

Vinyl organometallic reagents occupy a central role in the construction of a wide array of organic compounds.¹ However, based on early reports, vinyl titanium reagents were presumed to be insufficiently stable to prove useful due to rapid reductive elimination to dienes,²⁻⁴ a property which is not shared by the related vinyl zirconium reagents.⁵ Nevertheless, the ligand tunable Lewis acidity of titanium would appear to potentially provide a particularly effective template for chelation controlled stereoselection in acyclic systems.^{3,4} Still examined the use of diorganocuprate reagents for this purpose and observed good levels of stereoselection in additions to β alkoxy aldehydes for all cases except the vinyl reagent.⁶ Thus, we set out to determine if, in general, vinyl titanium reagents were sufficiently stable for use, and if enhanced levels of stereoselection in addition to chiral aldehydes would be observed.⁷

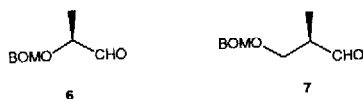
We first examined the tendency of **1** to undergo reductive dimerization, which had been previously reported to occur rapidly.³ Indeed, generation of **1** from **2** (prepared by halogen-metal exchange of 1-bromocyclohexene with *t*BuLi in either Et₂O or THF at -78°C) and ClTi(OiPr)₃ as usual and measurement of the amount of reductive

dimerization which had occurred by NMR showed that **1** (in Et_2O) was quantitatively converted to diene **3** after 6h at 0°C . Dimerization was observed to be substantially faster in THF (complete after 2h at $\sim -50^\circ\text{C}$). While the foregoing is in accord with prior reports, we were gratified to find that reductive dimerization of **1** was nearly completely suppressed at temperatures $\leq -60^\circ\text{C}$ in Et_2O . Thus, vinyl titanium triisopropoxide reagents can, in principle, be effectively employed in Et_2O at temperatures lower than $\sim -60^\circ\text{C}$.



The stability of the vinyl titanium triisopropoxides is also dependant on the degree of substitution present in the vinyl residue. For example, the 1,1-disubstituted reagent **4** (prepared from **5** and $t\text{BuLi}$ in Et_2O) showed minimal ($\leq 10\%$) reductive dimerization at temperatures as high as 23°C over 12h. However, the integrity of the reagent with respect to reaction with electrophiles was not determined under these conditions. We have noted that other as yet undefined pathways can result in decomposition of the reagents **1** and **4** at temperatures above $\sim -60^\circ\text{C}$ leading to significant reduction in the yields upon reaction with electrophiles. We have prepared vinyl titanium triisopropoxide reagents possessing all possible substitution patterns in the vinyl residue, and found comparable levels of reagent stability (with respect to reductive dimerization) in Et_2O at temperatures $\leq \sim -60^\circ\text{C}$ (Table 1).

As shown in Table 1, addition of 1,1-, *trans* 1,2-, and relatively unhindered trisubstituted vinyl residues occurs with good facility to reactive aldehydes (50-85% yields) at -78°C .⁴ The chemoselectivity of **4** for aldehydes was complete both when a competition experiment was employed (benzaldehyde/acetophenone),⁵ and when 6-oxohexanal was employed as the substrate (53% yield) which confirms that the reagents are indeed trialkoxytitanium species. Although addition to benzaldehyde occurred smoothly in the case of the *cis* 1,2-, and more hindered trisubstituted cases (60-85%), in these instances, significant reduction in yield occurred when an enolizable aldehyde was employed.



Turning to the question of stereoselectivity, reaction of **4** with α or β alkoxy aldehydes **6** and **7** was rather disappointing in that limited (1-3:1) levels of diastereoselectivity were observed (Table 1). We also examined

Table 1

Entry	Reagent ^a	Product	Yield (%)
1			75
2	.		67
3	.		65
4	.		75 ^b T/E= 3:1
5	.		75 ^c T/E= 1:1
6			77
7	.		70
8			85
9	.		85
10			60
11			75
12	.		40

^aR = isopropyl^bBased on recovered starting material (40% conversion)^cBased on recovered starting material (42% conversion)

the question of participation of the remote ether oxygen atoms in internal chelation. No evidence for the participation of such chelates could be found since reagents **8** and **9** were comparably stable and afforded essentially identical levels of stereoselection in additions to **6** and **7** when compared to **4**.

Thus, the reported lack of stability of vinyl titanium trialkoxides can be overcome by use of Et₂O and working at sufficiently low temperatures ($\leq -60^{\circ}\text{C}$). They exhibit excellent chemoselectivity and moderate reactivity with aldehydes. *Problems experienced in previous studies may have stemmed in part from the surprising lack of reactivity.* Since the trialkoxytitanium group apparently shows a low tendency to be involved in chelation,²⁻⁴ it would appear exploration of the stability and reactivity of substituted vinyl chloroalkoxytitanium reagents is warranted to determine their potential to effect chelation controlled addition to chiral α and β alkoxy aldehydes.

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REFERENCES

1. Stowell, J. C. "Carbanions in Organic Chemistry" John Wiley, New York, 1979.
2. Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostanek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421; Reetz, M. T.; Kessler, K.; Schmidtberger, S.; Wendroth, B.; Steinbach, R. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 989.
3. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556.
4. Reetz, M. T. *Topics in Current Chemistry* **1982**, *106*, 3.
5. Seebach, D.; Weidmann, B.; Maycock, C. *Helv. Chim. Acta* **1981**, *64*, 1552; Seebach, D.; Weidmann, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31.
6. Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1035; Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1031.
7. The addition of the parent vinyl titanium triisopropoxide to a chiral α,β dialkoxyaldehyde was reported after our studies were underway: Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.
8. A solution (1.5M) of t-butyllithium (5mmol) in hexane was cooled to -78°C under N₂ and the vinyl bromide (2.5mmol) in 3 mL of freshly distilled Et₂O was added dropwise over 5 min. An immediate precipitate of LiBr was formed, and the mixture was stirred at -78°C for 20 min. A 1M solution of ClTi(OiPr)₃ (2.5 mL) in hexanes was then added and the solution, which turned brown immediately, was stirred for 20 min. The aldehyde (1 mmol) was added and the reaction mixture stirred at -78°C until the disappearance of the aldehyde was apparent by TLC (8 h maximum). After quenching into sat. NH₄Cl/Et₂O (33 mL, 1:10), the Et₂O layer was decanted. Two fresh portions of Et₂O were similarly employed to complete extraction of the product(s). The combined ethereal solutions were dried, concentrated, and the residue purified by chromatography (SiO₂) to afford the expected alcohol.

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