

SYNLETT Spotlight 260

Synthetic Uses of Chlorotitanium(IV) Triisopropoxide in C–C(N) Bond Formation



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Compiled by Allan Patrick G. Macabeo

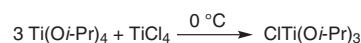
Allan Patrick G. Macabeo was born in Ilocos Sur, Philippines. He pursued his B.Sc. and M.Sc. degrees in chemistry at the University of Santo Tomas in Manila. He was involved in the isolation, structure elucidation, chemotaxonomy and derivatization of biologically active secondary metabolites from Philippine medicinal plants and marine sponges under the supervision of Professor Ma. Alicia M. Aguinaldo. At present, he is working as a DAAD scholar in the research group of Professor Dr. Oliver Reiser at the University of Regensburg, focusing on the stereoselective synthesis of bioactive butyrolactone marine natural products.

Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, 93053 Regensburg, Germany
E-mail: allanpatrick_m@yahoo.com

Introduction

Chlorotitanium(IV) isopropoxide, $\text{ClTi}(\text{O}i\text{-Pr})_3$, is a Lewis acid utilized in various synthetic procedures for carbon–carbon (or nitrogen) bond constructions. Its preparation involves the mixing of three equivalents of tetrakisopropoxytitanium and one equivalent of titanium(IV) chloride at 0 °C under a nitrogen atmosphere. Vacuum distillation of the crude product furnishes a syrupy liquid which turns into a solid at room temperature. It

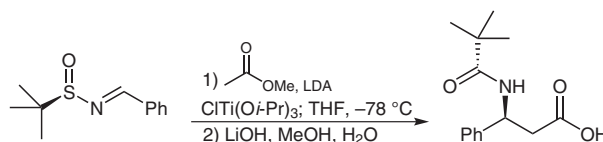
is soluble in *n*-pentane, toluene, THF and CH_2Cl_2 ; it is moisture-sensitive but can be kept under nitrogen for several months.¹ The reagent is used as a starting material for the synthesis of versatile alkyl- and aryltriisopropoxytitanium compounds that are more chemo- and stereoselective as compared to Grignard reagents.^{1,2}



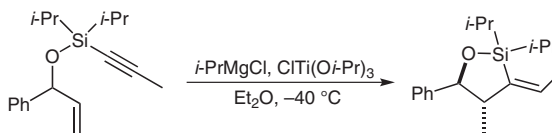
Scheme 1 Chemical preparation of $\text{ClTi}(\text{O}i\text{-Pr})_3$

Abstracts

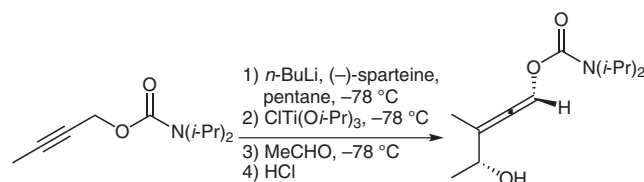
(A) Enolates with titanium as metal component formed by displacement of lithium with $\text{ClTi}(\text{O}i\text{-Pr})_3$ give a more covalent derivative that imposes high diastereoselectivity. The enolate was hypothesized to exist in equilibrium with lithium enolate and lithium-titanium-ate complex. It was found that increasing the stoichiometry of this reagent to two equivalents improves the reaction's diastereoselectivity. A recent application of this procedure has been the diastereoselective nucleophilic addition to *tert*-butanesulfinyl aldimines and ketimines to furnish β -amino acids with high enantiomeric purity.³



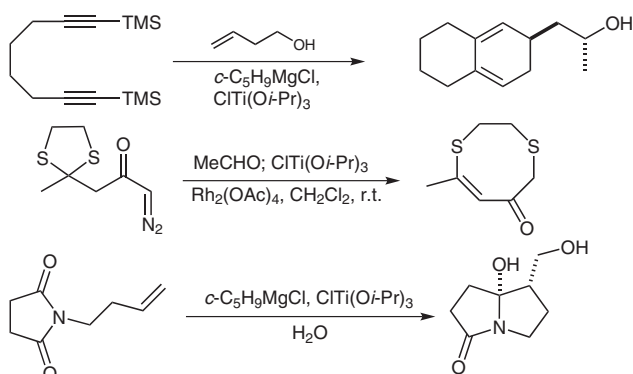
(B) Phillips and co-workers described the application of $\text{ClTi}(\text{O}i\text{-Pr})_3$ in the total synthesis of two cytotoxic metabolites, namely dictyostatin-1 and (–)-7-demethylpicricidin A₁, via cyclization of (silyloxy)enyne intermediates.⁴ In this transformation, the combination of $\text{ClTi}(\text{O}i\text{-Pr})_3$ and *i*-PrMgCl gives in situ $(\eta_2\text{-propene})\text{Ti}(\text{O}i\text{-Pr})_2$ which effects a highly diastereoselective 5-*exo*-trig cyclization.



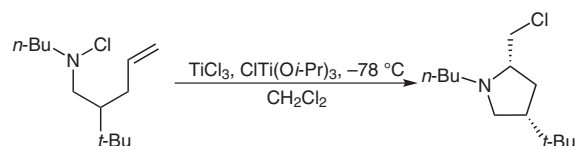
(C) Transmetalation of lithiated alkynyl carbamates with $\text{ClTi}(\text{O}i\text{-Pr})_3$ yields chiral allene and alk-3-en-5-yn-1-ol derivatives. Most notable in this reaction is the inversion process during the lithium–titanium exchange that occurs at the deprotonated prochiral center.⁵



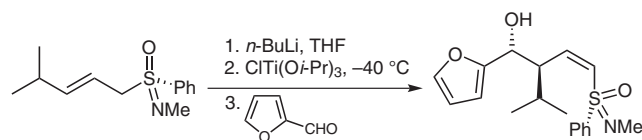
(D) Esters and amides in Kulinkovich reactions⁶ form titanacyclopropane intermediates after treatment with alkoxy-containing titanium reagents such as $\text{ClTi}(\text{O}i\text{-Pr})_3$ and alkyl Grignard reagents to provide cyclopropyl alcohols and amines.⁷ Many variants have been developed for this reaction and have given rise to the synthesis of various carbocycles,⁸ and heterocycles that contain sulfur⁹ and nitrogen.¹⁰



(E) Somfai et al. described that a mixture of $\text{ClTi}(\text{O}i\text{-Pr})_3$ and TiCl_3 in CH_2Cl_2 imposes high diastereoselection in the intramolecular annulation of cationic aminyl radicals in a radical chain fashion to furnish pyrrolidines.¹¹



(F) Gais et al. reported that transmetalation of lithiated allylsulfoximines with $\text{ClTi}(\text{O}i\text{-Pr})_3$ affords bis(allyl)-titanium complexes which react stereoselectively with aldehydes at the γ -position to furnish homoallylic alcohols. This methodology has been applied to the synthesis of unnatural amino acids and azaspirocycles.¹²



References

- (1) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1.
- (2) (a) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. (b) Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31.
- (3) (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (b) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722. (c) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.
- (4) (a) O'Neil, G. W.; Phillips, A. J. *Tetrahedron Lett.* **2004**, *45*, 4253. (b) Keaton, K. A.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 408.
- (5) (a) Schultz-Fademrecht, C.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2001**, *3*, 1221. (b) Chedid, R. B.; Brümmer, M.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Angew. Chem.* **2007**, *46*, 3131.
- (6) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789.
- (7) (a) Lee, J. C.; Sung, M. J.; Cha, J. K. *Tetrahedron Lett.* **2001**, *42*, 2059. (b) de Meijere, A.; Williams, C. M.; Kourdioukov, A.; Sviridov, S. V.; Chaplinski, V.; Kordes, M.; Savchenko, A. I.; Stratmann, C.; Noltemeyer, M. *Chem. Eur. J.* **2006**, *3789*. (c) Faler, C. A.; Joullié, M. M. *Org. Lett.* **2007**, *9*, 1987.
- (8) (a) Okamoto, S.; Subburaj, K.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 11244. (b) Sung, M. J.; Pang, J.-H.; Park, S.-B.; Cha, J. K. *Org. Lett.* **2003**, *5*, 2137. (c) Baktharaman, S.; Selvakumar, S.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4335.
- (9) Sawada, Y.; Oku, A. *J. Org. Chem.* **2004**, *69*, 2899.
- (10) (a) Cao, B.; Xiao, D.; Joullié, M. M. *Org. Lett.* **1999**, *1*, 1799. (b) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. H. *J. Org. Chem.* **1999**, *64*, 6771. (c) Kim, S.-H.; Park, S.; Choo, H.; Cha, J. H. *Tetrahedron Lett.* **2002**, *43*, 6657.
- (11) Hemmerling, M.; Sjöholm, A.; Somfai, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4091.
- (12) (a) Gais, H.-J.; Hainz, R.; Müller, H.; Bruns, P. R.; Giesen, N.; Raabe, G.; Runsick, J.; Nienstedt, S.; Decker, J.; Schleusner, M.; Hachtel, J.; Loo, R.; Woo, C.-W. *Eur. J. Org. Chem.* **2000**, 3973. (b) Tiwari, S. K.; Gais, H.-G.; Lindenmaier, A.; Babu, G. S.; Raabe, G.; Reddy, L. R.; Köhler, F.; Günter, M.; Koep, S.; Iska, V. B. R. *J. Am. Chem. Soc.* **2006**, *128*, 7360. (c) Köhler, F.; Gais, H.-J.; Raabe, G. *Org. Lett.* **2007**, *9*, 1231. (d) Adrien, A.; Gais, H.-G.; Köhler, F.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9*, 2155.