SYNLETT Spotlight 260

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

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

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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-demethylpierrezin 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

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