SYNLETT Spotlight 75

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

Titanium Tetraisopropoxide

Compiled by Óscar López

Óscar López was born in Seville (Spain) in 1976 and studied chemistry in the University of Seville, where he received his diploma in 1999. He is currently finishing his PhD studies at the same University, in the Department of Organic Chemistry, under the supervision of Professor José G. Fernández-Bolaños. His research field is new synthetic approaches to carbohydrate-derived thio-ureas, isoureas, ureas, and selenoureas.

Departamento Química Orgánica, Facultad Química, Universidad Sevilla, Apartado 553, 41071 Sevilla, Spain
E-mail: osc-lopez@mixmail.com

Introduction

Titanium tetraisopropoxide is a mild Lewis acid that has been extensively used as a catalyst in organic synthesis, specially in those reactions involving asymmetric inductions,¹ such as Sharpless epoxidation, additions to carbonyl compounds, and oxidations; its catalytic activity in

asymmetric synthesis is based on the formation of complexes with chiral auxiliaries.² Its mild nature enables the use of this catalyst in the presence of some acid-sensitive functional groups, such as acetonides, OTBDMS, and lactams.

Titanium tetraisopropoxide is a non-expensive catalyst, commercially available as a low-melting point solid.

Abstracts

(A) $\text{Ti}(i\text{-PrO})_4$ is a mild catalyst for transesterification reactions; it is used in macrolide synthesis to facilitate ring size equilibration.³ For instance, macrolide **1** was transformed⁴ into **2** by treatment with $\text{Ti}(i\text{-PrO})_4$ and this macrolide was used in the synthesis of Scytophycin C.

(B) $\text{Ti}(i\text{-PrO})_4$ has been used in the selective oxidation of sulfides to sulfoxides. An asymmetric oxidation of sulfides with high enantioselectivity has been reported⁵ using (*R*)-(+)-BINOL as the chiral auxiliary and $\text{Ti}(i\text{-PrO})_4$ as catalyst. Recently, some $\text{Ti}(i\text{-PrO})_4$ derivatives supported on silica have been investigated⁶ as catalysts for these oxidation reactions.

(C) Sharpless asymmetric epoxidation of allylic alcohols using *tert*-butyl hydroperoxide, diethyl tartrate, and $\text{Ti}(i\text{-PrO})_4$ is the key step in the preparation of many products of synthetic and biological interest.⁷ The reaction usually takes place with good yield and high stereoselectivity. Sharpless epoxidation conditions have been used to prepare the phenylalkylamine motif of several calcium channel blockers, such as verapamil and emopamil.⁸

(D) A dimethylsulfide–Ti(*i*-PrO)₄ mixture has been used to reduce hydroperoxides,⁹ obtained by photooxygenation of olefins. The reaction takes place at room temperature in 10 minutes with a high yield (93%).

(E) Ti(*i*-PrO)₄ enables the opening of 2,3-epoxy alcohols in the presence of nucleophiles. This occurs usually in high regioselectivity, as the ring-opening normally takes place at C-3. By this type of reaction, chiral benzosultams¹⁰ and amino acid derivatives¹¹ have been obtained. This reaction can also be extended to 2,3-epoxycarboxylic acids and amides.

(F) Titanium-derived complexes can be used to catalyze aldol-Tishchenko reaction to afford stereoselectively 1,3-*anti*-diol monoesters. Mahrwald et al.¹² reported the one-pot synthesis of these compounds using a titanium ate complex, obtained in situ by mixing equimolecular amounts of Ti(*i*-PrO)₄ and BuLi. The reaction took place at room temperature with high *anti*-stereoselectivity.

(G) Ti(*i*-PrO)₄ has been used, together with a chiral ligand, in the preparation of optically active cyanohydrins via asymmetric trimethylsilylcyanation of aldehydes¹³ or ketones.¹⁴ In particular, the chiral Ti(IV) salen complex **17** has been used¹⁵ in the preparation of fluoroepinephrine derivatives with high enantioselectivity.

(H) The title compound can be used¹⁶ to catalyze the addition of alkyl groups to aldehydes and ketones, an area where much effort has been devoted. This reaction was studied by Walsh et al. using bis(sulfonamido) or BINOL/ Ti(*i*-PrO)₄ complexes, applied to aldehydes,¹⁷ ketones¹⁸ and α,β-unsaturated ketones.¹⁹ In the case of **18**, the reaction is totally chemoselective, as no conjugate addition compound was detected.

Chan et al. have reported²⁰ the preparation of chiral propargylic alcohols via enantioselective alkynylation of aldehydes using BINOL/ Ti(*i*-PrO)₄ catalysts.

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