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

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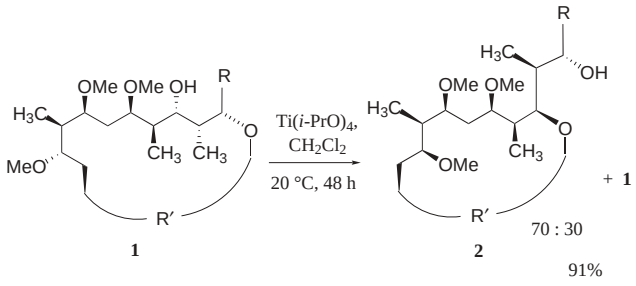
Introduction

Titaniun 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.

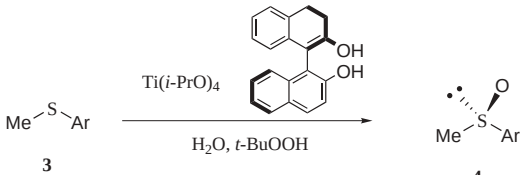
Abstracts

(A) Ti(*i*-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 transformed[4] into **2** by treatment with Ti(*i*-PrO)$_4$ and this macrolide was used in the synthesis of Scytophycin C.



1 **2**

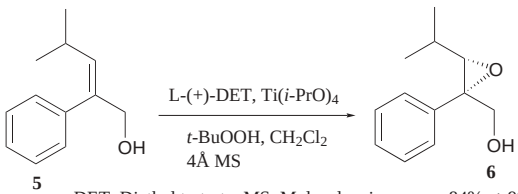
(B) Ti(*i*-PrO)$_4$ has been used in the selective oxidation of sulfides to sulfoxides. An asymmetric oxidation of sulfides with high enantioselectivity has been reported[5] using (*R*)-(+)-BINOL as the chiral auxiliary and Ti(*i*-PrO)$_4$ as catalyst. Recently, some Ti(*i*-PrO)$_4$ derivatives supported on silica have been investigated[6] as catalysts for these oxidation reactions.



3 **4**

Ar	Yield (%)	ee
p-Tol	44	96
Ph	28	96
p-BrC$_6$H$_4$	39	96

(C) Sharpless asymmetric epoxidation of allylic alcohols using *tert*-butyl hydroperoxide, diethyl tartrate, and Ti(*i*-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]

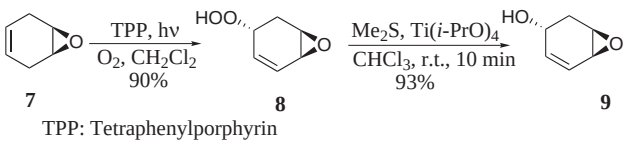


5 **6**

DET: Diethyl tartrate; MS: Molecular sieves 84%, >99% ee

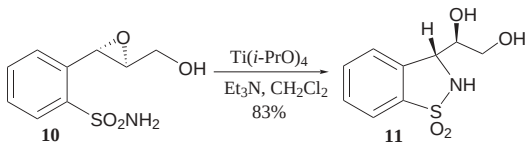
SYNLETT 2003, No. 14, pp 2261–2262
Advanced online publication: 29.10.2003
DOI: 10.1055/s-2003-42111; Art ID: V08203st

(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%).

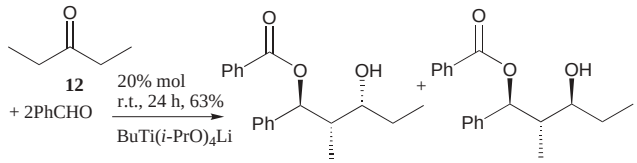


TPP: Tetraphenylporphyrin

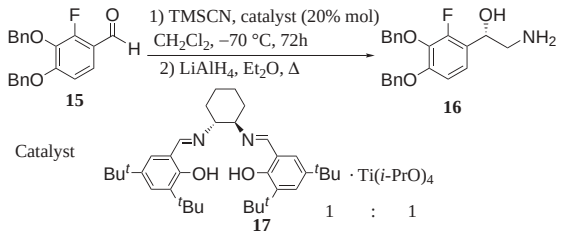
(E) Ti(*i*-PrO)$_4$ enables the opening of 2,3-epoxy alcohols in the presence of nucleophiles. This occurs usually in high regioselectivity, as the ring-opening normally takes place at C-3. By this type of reaction, chiral benzosultams[10] and amino acid derivatives[11] have been obtained. This reaction 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.

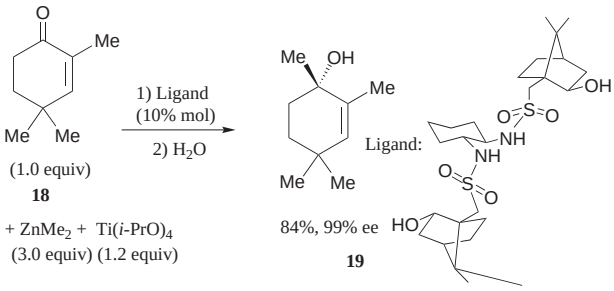


(G) Ti(*i*-PrO)$_4$ has been used, together with a chiral ligand, in the preparation of optically active cyanohydrins via asymmetric trimethylsilylcyanation of aldehydes[13] or ketones.[14] In particular, the chiral Ti(IV) salen complex **17** has been used[15] in the preparation of fluoroepinephrine derivatives with high enantioselectivity.



(H) The title compound can be used[16] 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] ketones[18] 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 reported[20] the preparation of chiral propargylic alcohols via enantioselective alkynylation of aldehydes using BINOL/ Ti(*i*-PrO)$_4$ catalysts.



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