Ti(O*i*Pr)$_4$ in Stereoselective Synthesis

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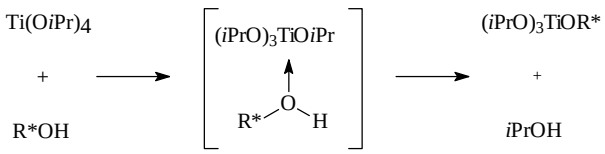
Contents

Titanium(IV) reagents play an important role in both dia- and enantioselective syntheses. Due to their mild Lewis-acid character, these compounds are able to complex with carbonyl oxygen or are involved in the reaction by transmetallation or ligand exchange processes.

Many of these compounds are synthesized by ligand exchange on titanium(IV) chloride or on titanium(IV) alkoxides. In the latter case, alkoxide ligands are substituted with alcohols. The more volatile alcohol can be displaced by evaporation. Titanium(IV) isopropoxide is therefore most often used due to the ease of formation and removal of 2-propanol (Scheme 1). For a review of synthetically useful titanium complexes see [1].



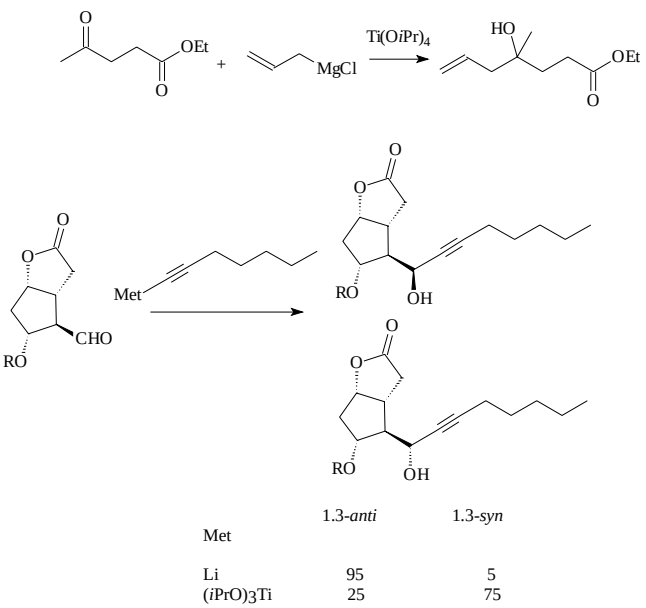
Scheme 1

Titanium(IV) isopropoxide is a flammable, nontoxic, moisture-sensitive liquid (*m.p.* 18–20 °C; *b.p.* 218 °C/10 mm) and is soluble in a wide range of solvents, including ethers, organohalides, alcohols and benzenes. Titanium(IV) alkoxides have been used in several reactions, *i.e.* transesterification [2], lactamization [3], Meerwein-Ponndorf-Verley-reduction [4], aldol condensation [5], cycloaddition [6], and have been employed in hydroxypropanation [7].

The aim of this article is to give a brief overview of several stereoselective reactions in which titanium(IV) isopropoxide acts either as a starting material for the synthesis of a corresponding catalyst or as a reagent in the formation of an active titanium species. Most applications of titanium(IV) isopropoxide have been found in carbanion chemistry and oxidation processes. Only the most representative examples are decribed.

1. Alkylation

Among the most common reactions for this purpose, the addition of an organometallic reagent to a carbonyl compound is one of the most fundamental operations for the synthesis of organic molecules. A wide range of organometallics react with Ti(O*i*Pr)$_4$ to form an active organotitanium reagent or titanatespecies [8]. These titanium ate complexes may differ significantly in their stereochemical and regiochemical reactivity from those of their starting organometallics (typical examples for ester/ketone differentiation of an allylmagnesium –titanium ate complex [9] and stereoselectivity of an alkynyl titanium reagent [10] are given in Scheme 2; see also 1,4-addition of α,β-unsaturated ketones in the presence of titanium ate complexes [11]).



Met	1.3-*anti*	1.3-*syn*
Li	95	5
(*i*PrO)$_3$Ti	25	75

Scheme 2

Successful applications of chiral titanium catalysts in enantioselective alkyl-transfer reactions were achieved by the use of dialkylzinc reagents [12]. Ohno was one of the first who utilized catalyst **1**, derived from bis-trifluoromethyl-sulfona-

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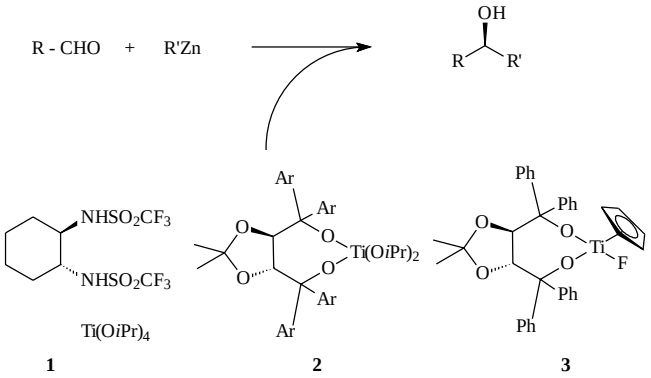
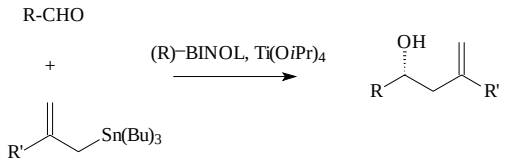
mide and Ti(O*i*Pr)$_4$ [13]. Seebach *et al*. employed the chiral diisopropoxytitanium-TADDOLates **2** for these alkylation additions [14]. The Duthaler group improved this procedure by using the fluorinated cyclopentadienyl-titanium complex **3** (Scheme 3) [15].



Scheme 3

2. Allylation

A catalytic, enantioselective approach to homoallyl alcohols using allyl stannanes and the well-known BINOL/Ti(O*i*Pr)$_4$ system (Scheme 4) is described by Brückner *et al*. [see 16 and references cited in].



Scheme 4

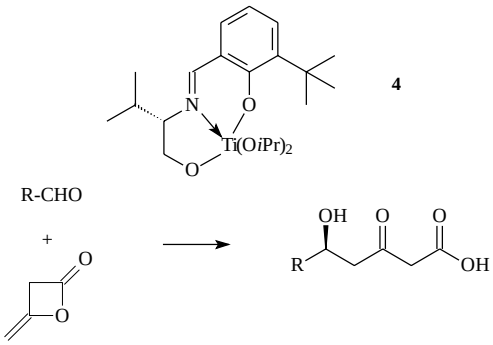
Highly enantioselective titanium allylation processes were described by Duthaler *et al*. However, the titanium complexes used in these reactions were obtained by the reaction of CpTiCl$_3$ and diacetone glucose (DAG) or TADDOLates [1, 17, 21].

3. Aldol Addition

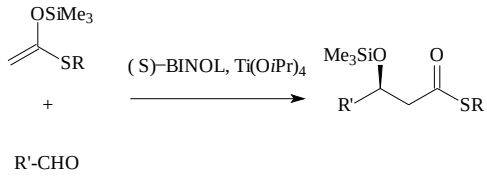
Most of this work was performed in the field of the catalytic and enantioselective execution of aldol additions. Oguni *et al*. reported in 1994 an enantioselective "acetate" aldol addition, catalyzed by the tridentate catalyst **4** as shown in Scheme 5 [18].

At the same time, two groups independently used the proven BINOL/Ti(O*i*Pr)$_4$ system in "acetate" thioester Mukaiyama-aldol additions. The silylated aldol products were obtained in a high degree of enantioselectivity by treating ketene silylacetals with aldehydes (Scheme 6) [19].

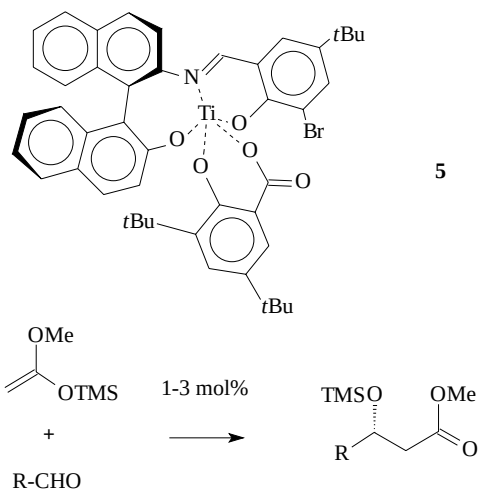
A combination of the catalysts used in Scheme 5 and 6 were designed by the group of Carreira. High enantioselectivities were obtained by using only 2 mol% of the catalyst **5** in "acetate" Mukaiyama-aldol addition (Scheme 7) [20].



Scheme 5



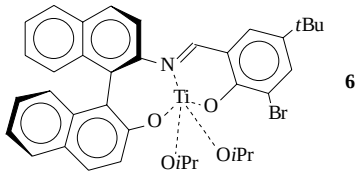
Scheme 6



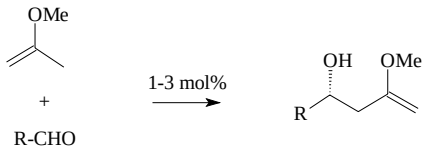
Scheme 7

4. Ene-Type Reactions

A synthetic equivalent to the described Mukaiyama reaction is represented by the ene-type reaction. In this case, an aldehyde is treated with an enol ether containing an allylic hydrogen atom. An outstanding example is represented in Scheme 8. High enantioselectivities were obtained by using 1–2 mol%



6

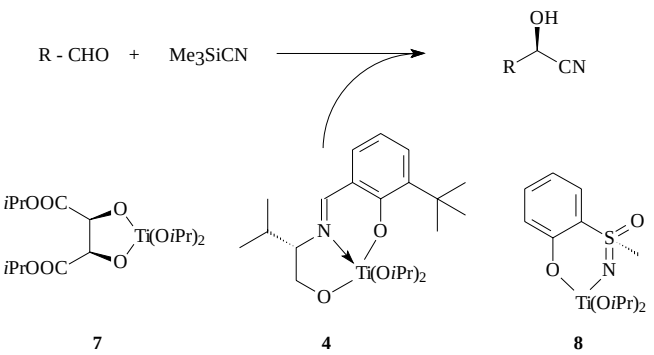


Scheme 8

of the catalyst **6**. Methoxypropene served as the ene-component and was used as a solvent at the same time [22].

5. Enantioselective Addition of Cyanide

Trialkylsilylcyanides were added enantioselectively to aldehydes in the presence of chiral titanium complexes. Several ligands were used for this purpose. Again, the most outstanding examples are represented in Scheme 9. 20 mol% of **7** (the so-called Sharpless catalyst) [23] or of the chiral Schiff base **4** [24] or even equimolar amounts of the ligand system **8** [25] are necessary to produce the product in high yields with good enantioselectivities.



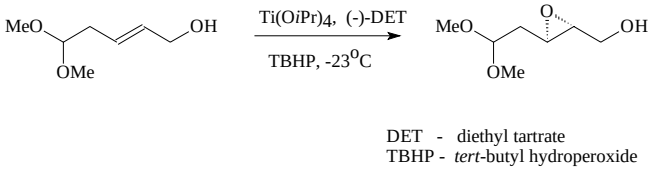
7 **4** **8**

Scheme 9

A lot of work has been accomplished in the field of enantioselective epoxidation and oxidation processes by means of chiral titanium complexes.

6. Epoxidation

In 1980, Katsuki and Sharpless were the first who established a real enantioselective, catalytic epoxidation process for a wide range of allylic alcohols. They used a combination of titanium alkoxides, mostly Ti(O*i*Pr)$_4$, and optically active dialkyl tartrates for achieving high enantioselectivities in these reactions (Scheme 10 [26]).



DET - diethyl tartrate
TBHP - *tert*-butyl hydroperoxide

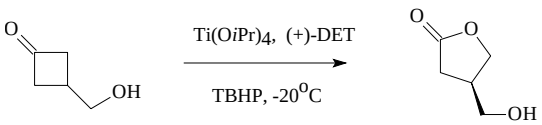
Scheme 10

Later on, numerous publications dealt with the further development of this important reaction, especially in the field of natural product synthesis [for a review see 27].

7. Bayer-Villiger Oxidation

Recently, the asymmetric oxidation of racemic cyclobutanones has been described. The reaction was carried out under Sharpless-conditions. In the very first investigation, the authors obtained only moderate enantioselectivities (Scheme 11) [28].

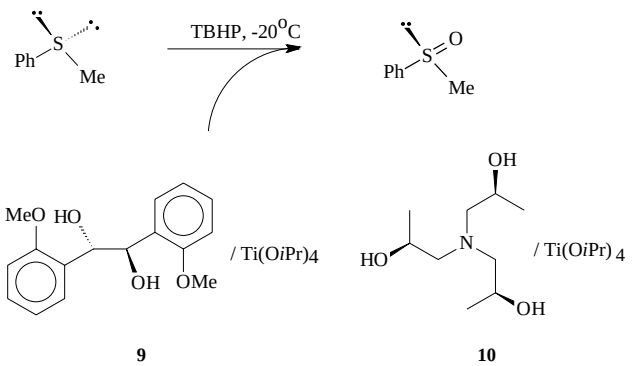
Chiral lactones were observed with a high degree of enantioselelectivity by asymmetric oxydation of tricyclic ketones [29].



Scheme 11

8. Asymmetric Sulfoxidation

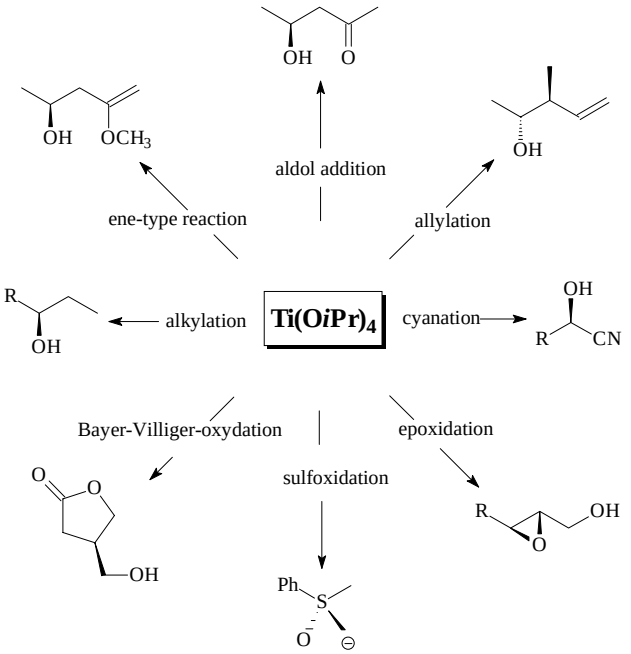
Chiral sulfoxides were obtained by suitable modifications of Sharpless oxidation conditions of the corresponding sulfides. The catalyst systems DET/Ti(O*i*Pr)$_4$ [30], BINOL/Ti(O*i*Pr)$_4$ [31], 1.2-diol **9**/Ti(O*i*Pr)$_4$ [32] and the trialkanolamines **10**/Ti(O*i*Pr)$_4$ [33] were used for this pupose (Scheme 12). The results are detailed in a main review [34].



9 **10**

Scheme 12

In summary, titanium (IV) isopropoxide is utilized for a variety of stereoselective processes. Due to its ease of handling and formation it is an ideal precursor for the synthesis of chiral catalytic systems used in stereoselective C–C bond formation and oxidation processes (Scheme 13).



Scheme 13

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