

TiCl₄ in Stereoselective Synthesis

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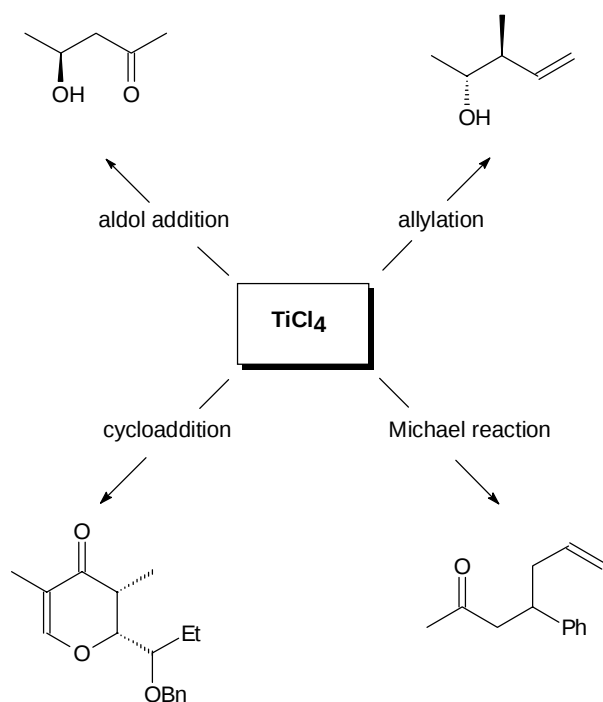
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TiCl₄ is a hygroscopic liquid (*m.p.* –24 °C; *b.p.* 136 °C). It is commercially available as a standard solution (dichloromethane, toluene), as a pure liquid or a hygroscopic TiCl₄–THF-complex.

TiCl₄ has been established for use as a reagent in a wide range of organic reactions, including low-valent titanium species with carbonyl compounds [1], especially the McMurry-reaction [2] and its catalytic versions [3], titanium–carbene mediated reactions, in particular methylenation of carbonyl compounds [4] and cyclopropanation of alkenes [5], Friedel–Crafts reactions [6], formylation reactions [7], Friedel–Crafts acylations [8], acetalization [9] and thioacetalization [10] of carbonyl compounds, Knoevenagel reaction [11], glycosidation/nucleoside synthesis [12] and alkylation of carbonyl compounds [13]. For further reviews of the utilization of TiCl₄ see also [14].



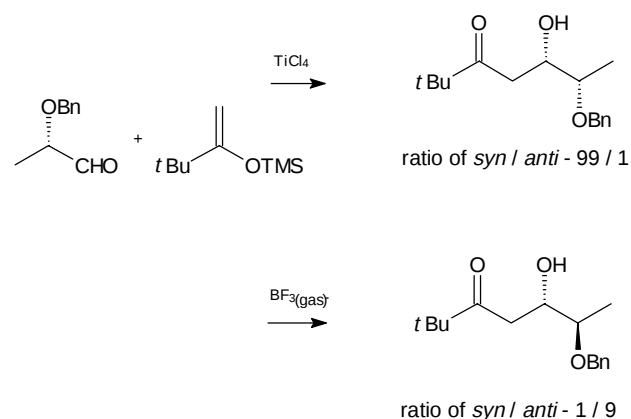
Scheme 1 Typical stereocontrolled reactions of TiCl₄

Possibly the most important application of TiCl₄ in organic synthesis is its use in stereoselective reactions. TiCl₄ possesses high affinity to oxygenated functional groups and acts as a chelating Lewis-acid. By careful choosing substrates and reaction conditions a preparatively useful control of stereoselectivity has been obtained.

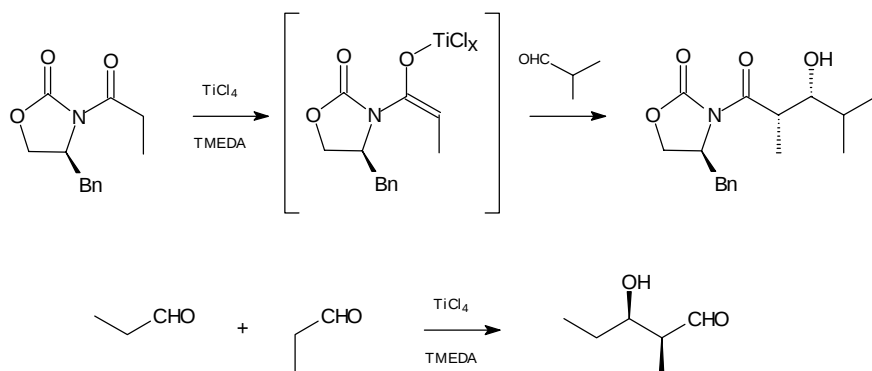
TiCl₄ or other related titanocene chlorides have also been used as starting material for the synthesis of active chiral titanium species. For methods synthesizing titanium complexes starting with titanium halogenides see reference [15].

1. Aldol Addition

TiCl₄ appears to be one of the most used Lewis acid in aldol additions. TiCl₄ itself acts as a Lewis acid catalyst in the so-called Mukaiyama reaction. It activates carbonyl functions, promoting nucleophilic attack by silyl enol ethers. For reviews of this reaction (stereochemical outcome, reaction conditions, choice of Lewis acids etc.) see reference [16]. An impressive example of 1,2-asymmetric induction and chelation control through the use of TiCl₄ [17] and nonchelation control in aldol addition using BF₃ [18] is shown in Scheme 2.

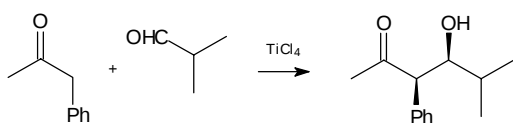


Scheme 2 Chelated and nonchelated 1,2-asymmetric induction in aldol addition

**Scheme 3** Titanium enolates in aldol additions

Titanium enolate-intermediates in aldol additions were prepared by reactions of TiCl_4 and nucleophiles in the presence of base. High *syn*-selectivity were observed in reactions of chiral oxazolidin-2-ones with aldehydes [19] and aldol additions of aldehydes with enolizable aldehydes [20] (Scheme 3).

Carbonyl compounds can also react in aldol addition without activation in the presence of Lewis acids. Various aldehydes and ketones react in the presence of substoichiometric amounts of TiCl_4 and in the *absence* of bases in high degree of *syn*-selectivity [21] and regioselectivity [22] (Scheme 4).

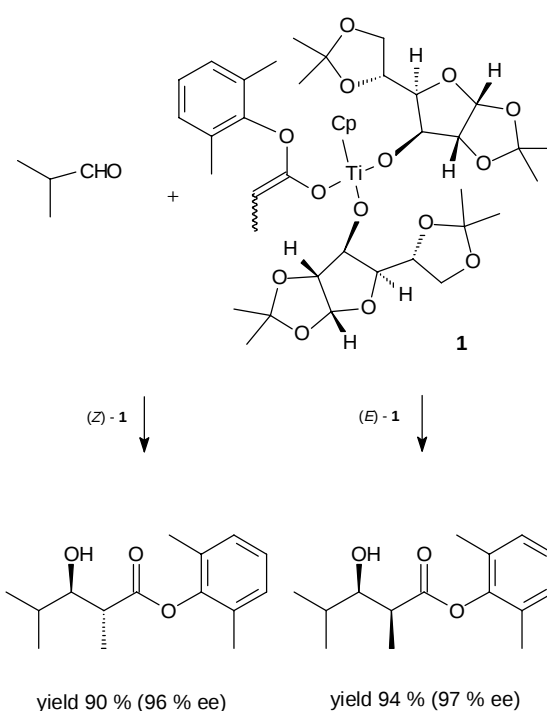
**Scheme 4** Regioselectivity in TiCl_4 -mediated aldol addition

Chiral titanium enolates have been used in eqimolecular aldol addition reactions [23]. The titanium complexes were prepared on the basis of titanocene halogenides and diacetone-glucose (DAG) or tartaric acid-derivates (TADDOL). By careful choice of reaction conditions, high enantio-meric excesses were observed in acetate and propionate aldol additions. Thermodynamical equilibration of the reaction mixture results in mostly *anti*-products (using titanium complex *Z*-1), whereas by kinetically controlled reactions, high *syn*-selectivity of the isolated aldols were found (titanium complex *E*-1 was used) (Scheme 5) [24].

2. Allylation

Allylsilanes react in the presence of TiCl_4 with electrophiles in the same manner as silyl enol ether do in the Mukaiyama reaction. An very illustrating example is represented in Scheme 6. Different stereochemical outcomes resulted by using TiCl_4 (chelation control) or BF_3 (nonchelation control) as Lewis acids in this reaction [25].

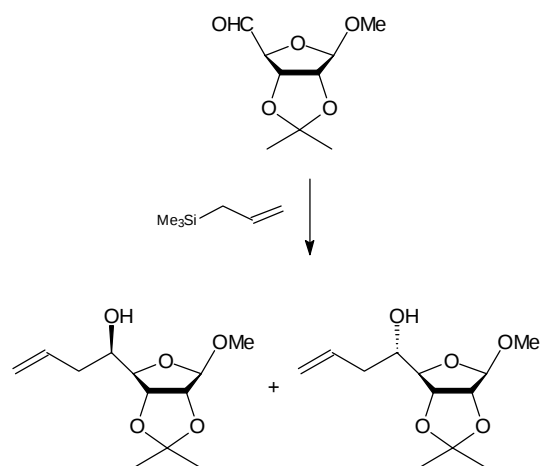
An analogous aldol addition result is observed by treating chiral electrophiles with chiral allylsilanes; the inherent dia-

**Scheme 5** Enantioselective aldol addition

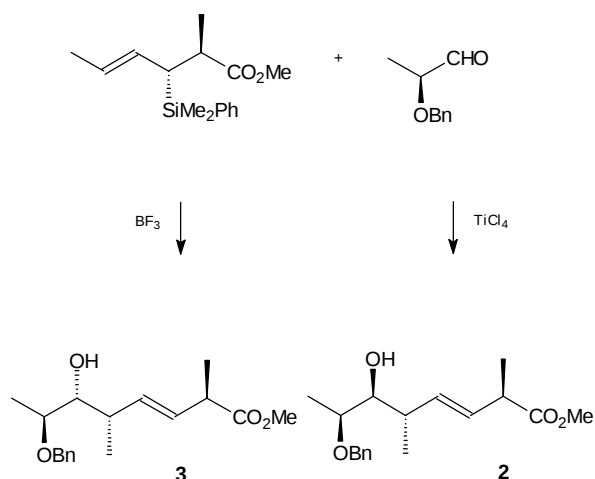
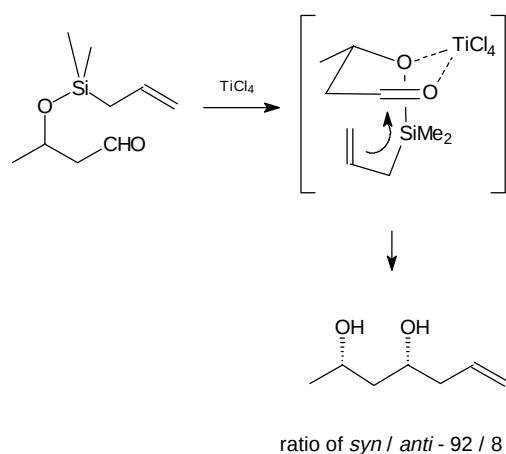
stereofacial preferences of the two reactants may reinforce one another (matched pair) or oppose one another (mismatched pair). An impressive example of different stereochemical results by using chelating or nonchelating Lewis acids is shown in Scheme 7. The homoallylic alcohol **2** is the matched product of reactions in the presence of chelating Lewis acid, whereas alcohol **3** is the matched product of reactions using nonchelating Lewis acid like BF_3 [26].

Intramolecular delivery of allyl groups was reported. The allyl group of the silyl ether attacks the carbonyl function in an axial manner as shown in the transition structure (Scheme 8), leading to a high *syn*-diastereoselectivity [27].

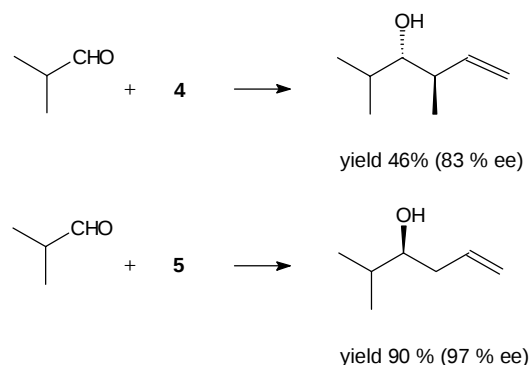
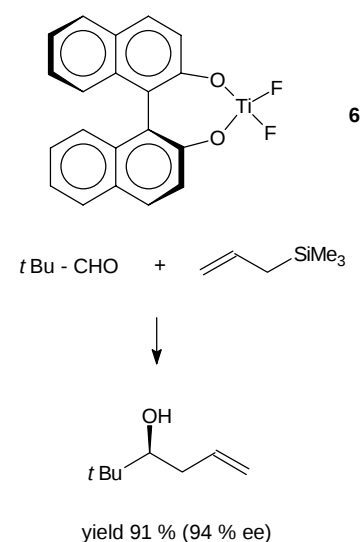
A comprehensive overview of these reaction of allylsilanes was given by Fleming *et al.* [28]. Attempts to introduce chiral informations by means of a chiral substituent at silicon (*i. e.* using chiral allylsilanes) are not generalizable [29]. This



BF ₃	95	:	5
TiCl ₄	9	:	91

Scheme 6 Chelation and nonchelation control in allylation**Scheme 7** Double stereodifferentiation in allylation**Scheme 8** Stereoselective intramolecular delivery of allyl groups

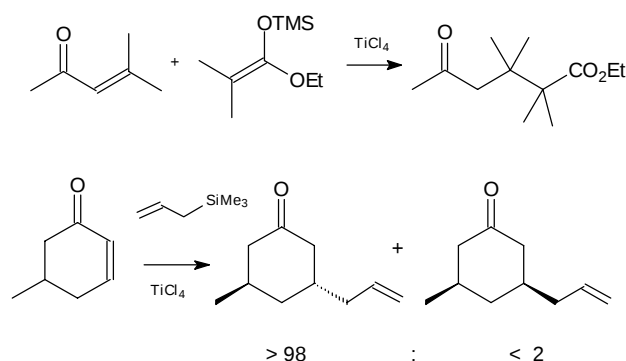
problem was elucidated for the first time by the Duthaler group [23] by using chiral allyltitanium reagents **4** and **5** for this reaction. Isopropylidene-derivatives of glucose (DAG) or diols derived from tataric acid (TADDOL) were used as ligands to introduce chiral informations. High enantioselectivities were observed in this equimolecular process (Scheme 9).

**Scheme 9** Enantioselective allylation**Scheme 10** Catalytic, enantioselective allylation

Enantioselective and catalytic versions of these reactions were reported by Carreira et al. [30]. The catalyst **6** derived from *S*-BINOL and TiF_4 was used. By using 10 mol% of the catalyst in the reaction of allylsilane with pivalaldehyde 94% *ee* was observed (Scheme 10).

3 Michael Reaction

TiCl_4 is known to promote additions of silyl enol ethers as well as allylsilanes to enone systems. The reactions proceed under very mild conditions. The addition of allylsilanes to enones is known as the Sakurai reaction. An overview of this



Scheme 11 Addition of silyl enol ether and allylsilane (Sakurai reaction) to Enones

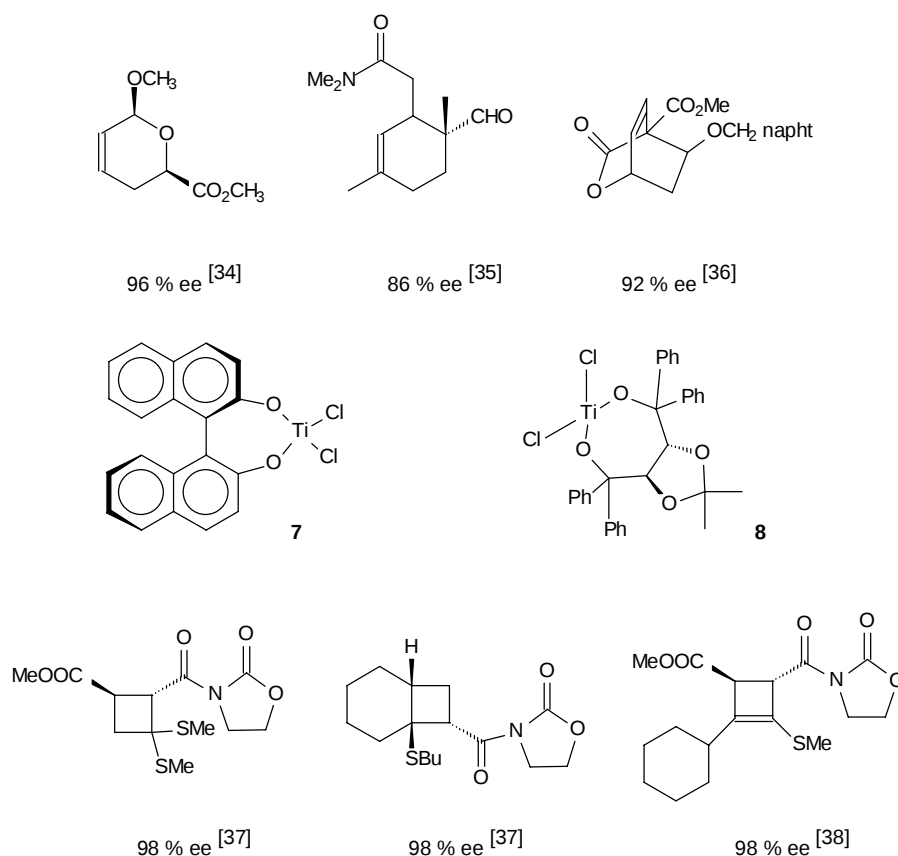
reaction is given in reference [31]. Examples of this two reaction types are shown in Scheme 11 [32, 33].

4. Cycloaddition

Titanium-complexes have also been used as Lewis acid catalysts in cycloaddition reactions. Outstanding examples for [4+2] and [2+2] cycloadditions are shown in Scheme 12. The BINOL-complex **7** and TADDOL-derived titanium complex **8** were prepared from $\text{Cl}_2\text{Ti}(\text{O}i\text{-Pr})_2$ and the corresponding ligands.

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Scheme 12 Enantioselective cycloaddition

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