

Role of Titanium Reagents in Carbonyl Compounds Reactions

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Abstract This article describes some important organic reactions catalyzed by different titanium-reagents. Combinatorial approach and green procedures involving the use of titanium reagents with other transition-metals (such as Sm, Pd, Sn and Zn) in photochemical procedures, and with the auxiliary techniques like microwaves for environmental friendly reaction conditions, are also discussed.

Keywords Aldehydes, Barbier Type Allylations, Ketones, Photochemical, Titanium Reagents

1. Introduction

Transition metals are known to catalyze organic reactions, ever since Sabatier and Sendrens reported conversion of alkenes into an alkane by hydrogenation in presence of Raney Nickel. Allyltitanium complexes have proven to be capable of reacting with carbonyl compounds with considerable chemo-, regio-, diastereo-, and even enantioselectivity. Among others, reagents based on titanium metal, which are easily generated from commercial Ti(IV) precursors, catalyze several reactions such as Barbier type allylations, intramolecular crotylations (cyclizations), coupling reactions, condensation, furylation and prenylations of a wide range of aldehydes and ketones, to name a few.[1]

This review explores the recent literature and describes organic synthesis, applications and developments in mechanistic understanding of titanium reagents mediated various reactions of carbonyl compounds. Attempt has been made to describe some recent synthetic applications and developments in mechanistic understanding of titanium - mediated reductive coupling of carbonyl compounds such as allylation, furylation, and reductive coupling and addition reactions.

2. Allylation Reactions

Although the challenges of solvent-free and highly concentrated asymmetric catalysis are significant, they are outweighed by the potential environmental and economical

benefits. In response to these challenges, some research groups have examined catalytic asymmetric reactions under solvent-free and highly concentrated conditions.[2] Catalytic asymmetric additions of carbon-based nucleophiles to carbonyl groups constitute a substantial class of C-C bond-forming reactions that are of great value in synthetic organic chemistry.[3] In comparison to aldehydes, additions to ketones have been shown to be more difficult due to their reduced reactivity and lower binding affinity to metals. With this view in mind researchers have worked in the field of catalytic asymmetric additions of carbon-based nucleophiles to ketones, including the allylation of ketones. [4] Kim *et al.* have reported catalytic asymmetric allylation of ketones with high enantioselectivity.[5] (Scheme 1)

Kim group were the first to observe catalytic asymmetric methallylation of ketones.[6] They have developed an (H_8 -BINOLate)Ti based catalyst for the asymmetric methallylation of ketones and (H_8 -BINOLate)Ti + tetra methallyl stannane in acetonitrile to afford tertiary homoallylic alcohols in fair-to-excellent yields (55-99%) with fair-to-high enantioselectivities (46-90%). Ozonolysis of the resulting products renders access to chiral α -hydroxy ketones. Kim *et al.* have also studied the addition of tetraallylstannane to a variety of ketones in CH_2Cl_2 with high enantioselectivities.[7] Good -to -high levels of enantioselectivity have been reported for a range of substrates. Enantioenriched tertiary homoallylic alcohol has also been converted to α -hydroxy ketones.

Catalytic asymmetric allylation of ketones under highly concentrated reaction conditions with a catalyst generated from titanium tetraisopropoxide and BINOL(1:2 ratios) in the presence of isopropanol, is reported.[8] This catalyst promotes the addition of tetraallylstannane to a range of ketones to produce tertiary homoallylic alcohols in excellent yield (80-99%) with high enantioselectivities (79-

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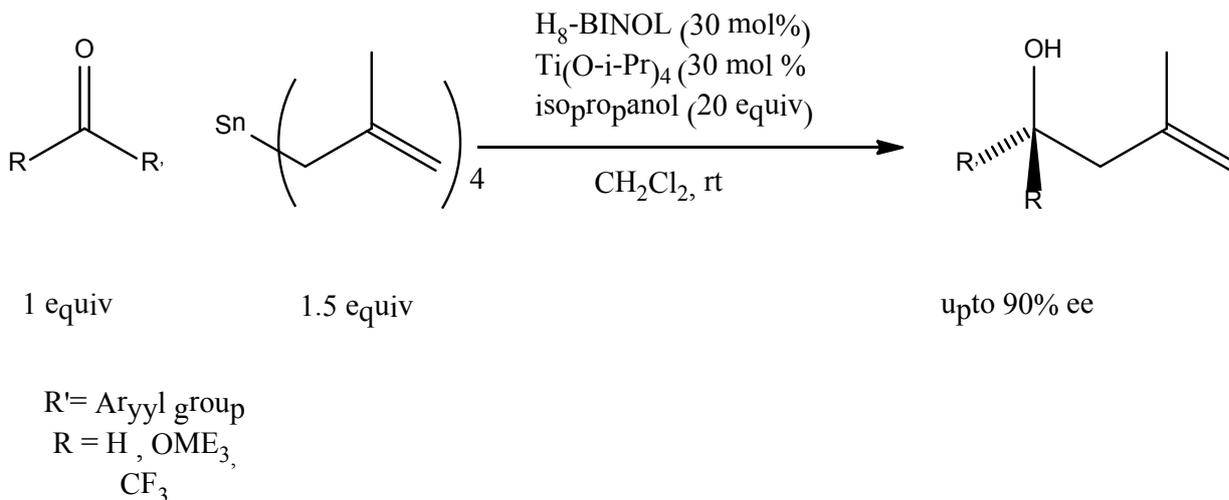
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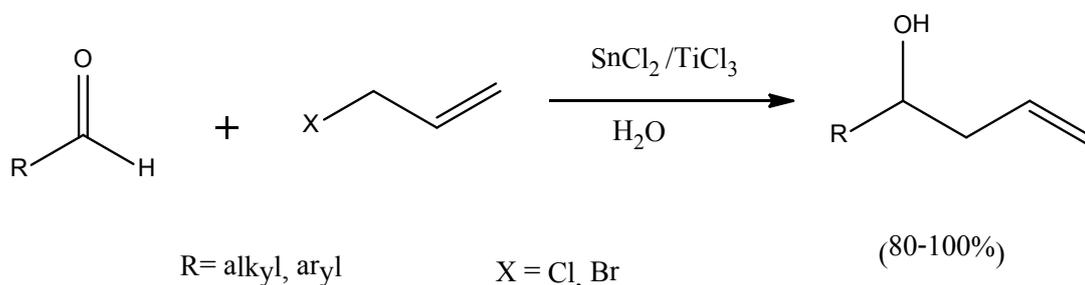
95%). The resulting homoallylic alcohols can also be deoxidized *in situ* using tert-butyl hydroperoxide (TBHP) to afford cyclic epoxy alcohols in high yield (84-87%). Tan *et al.* have demonstrated carbonyl allylation reaction mediated by $\text{SnCl}_2/\text{TiCl}_3$ in water.[9] The reaction is very competent and easy to run, can be conveniently scaled up for both laboratory as well as industrial synthesis. (Scheme 2)

The catalytic asymmetric vinylation of ketone is more challenging transformation, owing to the major difference in reactivity between aldehydes and ketones. This reaction has attracted significant attention from many research

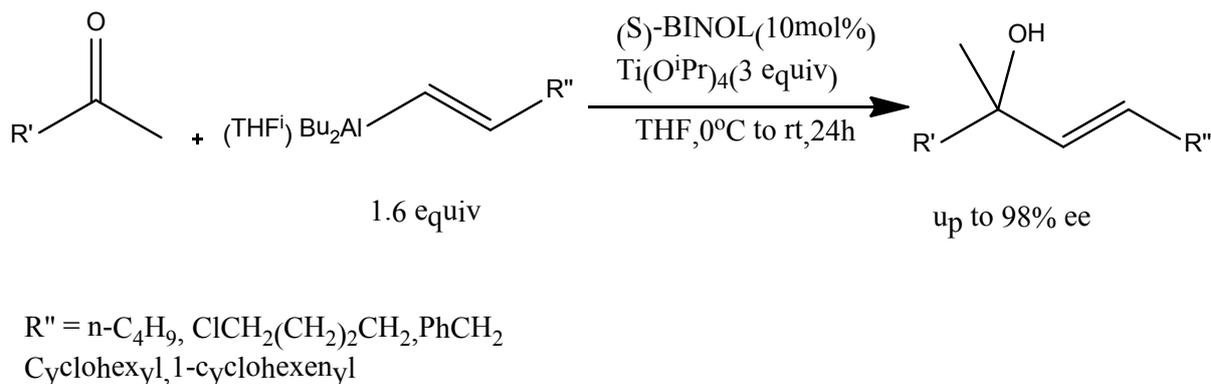
groups. Highly enantioselective catalysts for the vinylation of aldehydes have been developed by Oppolzer,[10] and others.[11] Biradar and Gau have reported asymmetric addition of vinyl group to ketones using vinylaluminum reagents catalyzed by $\text{Ti}(\text{O}i\text{Pr})_4$ (prepared *in situ*) complexes of (*S*)-BINOL to afford diversified tertiary allylic alcohols.[12] They examined varieties of aromatic ketones bearing either an electron-donating or an electron withdrawing substituent on the aromatic ring to give products in excellent enantioselectivities up to 98%. (Scheme 3)



Scheme 1. Asymmetric allylation of ketones



Scheme 2. Carbonyl allylation reaction mediated by $\text{SnCl}_2/\text{TiCl}_3$



Scheme 3. Vinylation of ketones using vinylaluminum reagents

3. Reduction Reactions

The reduction of aldehydes and ketones to alcohols involving the use of a range of metal hydrides, frequently in conjunction with titanium (IV) salts or other metals with Lewis acidity has been widely studied. Clerici and Porta group reported the free-radical decomposition of arene - diazonium salts catalyzed by aqueous $TiCl_3$, in the presence of aldehydes and anilines proceeds to secondary amines. They have also proposed a mechanism in which the aryl radical adds to the C-atom of the intermediate protonated imine.[13] Kosal and coworkers demonstrated that Cp_2TiCl_2 can be used as an effective catalyst for the conjugate reduction of α , β -unsaturated carbonyl compounds. [14] (Scheme 4)

Chen *et al.* used a titanium-based catalytic system of (S)-BINOL that catalyzed the addition of $AlAr_3(THF)$ to a wide variety of ketones affording tertiary alcohols with excellent stereocontrol.[15] Aqueous acidic $TiCl_3$ solution promptly reduces cyclic aliphatic ketones to the corresponding thermodynamically less stable axial alcohols when aqueous NH_3 is used instead of NaOH as a coexisting base to obtain a pH of 10-11.[16] Concurrently, a simple and quick procedure for the almost quantitative reduction of aromatic aldehydes, ketones, diketones and oxo aldehydes to alcohols by use of $TiCl_3/NH_3$ in aqueous methanol solution, has been reported.[17] Walsh *et al.* demonstrated the asymmetric $MeTi(OiPr)_3$ addition to aldehydes at 0 °C catalyzed by 20 mol % $Ti(BINOLate)(OiPr)_2$, affording secondary alcohol in ~50%. [18] In another study, Cozzi and Alesi described a titanium phenylacetylide addition reaction to ketones in the presence of 10 mol % (*R*)-BINOL conducted at temperatures below 15 °C. The reaction gives chiral propargyl alcohols in modest yields with moderate to good enantioselectivities. [19]

TiO_2 catalyzed reactions have used to reduce different functions in moderate to high yields. TiO_2 -catalyzed photochemical reduction of pyruvate to lactate, nitro and nitroso-compounds to amines, bis(2-dipyridyl)-disulfide to 2-mercaptopyridine, and aldehydes to alcohols have been reported. [20] 1,2-Diketones, camphorquinone and 1-phenyl-1,2-propanedione, are converted to the corresponding α -hydroxyketones in moderate to good yields by TiO_2 -catalyzed photochemical reactions in deoxygenated alcoholic media. [21] Sharghi and Sarvari reported a one-pot, solvent free procedure for the conversion of aldehydes and ketones to their respective amides in the presence of $NH_2OH \cdot HCl$ and TiO_2 , but with long reaction times. [22]

Clerici research group have reported that *tert*-butoxyl radical, generated by the aqueous $Ti(III)/TBHP$ system, abstracts an H atom from alcoholic cosolvents (EtOH, *i*PrOH), leading to α -hydroxyalkyl radicals that reduce aromatic aldehydes to the corresponding 1,2-diols. [23] Aromatic aldehydes having electron-donating groups are

easily converted into their respective nitriles using $NH_2OH \cdot HCl$ and TiO_2 under microwave irradiation, while those bearing an electron-withdrawing group give the corresponding oximes. [24]

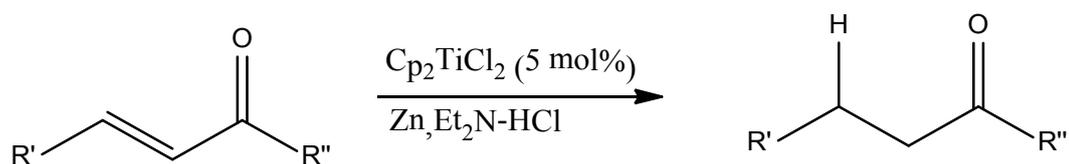
4. Barbier-type Reactions

Phillipe Barbier reported a coupling reaction between a ketone (6-methyl-5-hepten-2-one) and an alkyl halide (CH_3I) in the presence of a stoichiometric quantity of magnesium metal, thus establishing the basis for the one step C-C bond-forming process currently known as the Barbier reaction. [25] Titanocene (III) complexes (such as $[TiClCp_2]$) and others might be used in a Barbier-type strategy to transform allyl halides into allyl radicals, which would subsequently, react with a carbonyl compound present in the medium. [26] Regio- and stereoselective addition of crotyl metals to carbonyl compounds permits the introduction of two new adjacent stereogenic centers in only one step, which is a significant process in organic synthesis. [27] In Barbier-type protocols, the crotyl metal intermediates are generated *in situ* from the crotyl halide and the corresponding metal. [28] Thus, for example, Barbier-type protocols based on Zn, [29] Cd, [30] Sn, [31] amongst other have been developed. Cp_2TiCl , a mild single-electron transfer (SET) reagent extensively studied by RajanBabu [32], and Gansauer [33] were able to promote mild, chemo- and regioselective allylation, prenylation, and propargylation reactions of aldehydes.

$TiCl_3$ can also efficiently catalyze the $SnCl_2$ -mediated Barbier reaction. [34] Clerici *et al.* found that an aqueous $TiCl_3/NH_3$ system can reduce aldehydes and ketones to alcohols. [35] Pastori *et al.* have reported a one-pot multicomponent free radical synthesis of quaternary α -aminoamides promoted by an acidic $TiCl_4/Zn/H_2O_2$ system. [36] (Scheme 5)

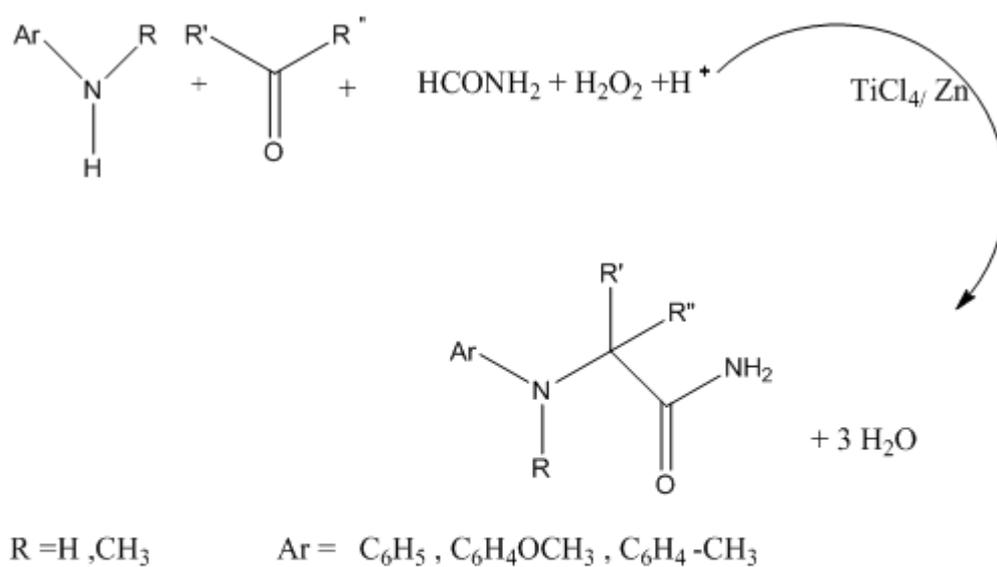
Barbier-type reaction among carbonyl compounds and activated alkyl halides can also be accomplished at room temperature, under really mild conditions using titanocene (III) complexes as catalysts. [37] Chiral titanocene leads to optically active compounds in 50-80% yield (Scheme 6)

$Ti(III)$ -induced free-radical decomposition of a phenyldiazonium salt (initiated by phenyl radical iodine-atom abstraction from alkyl iodides) leads to a one-pot selective alkyl radical addition to the C-atom of imines generated *in situ* under aqueous acidic conditions. Sanz, and coworkers reported a novel procedure for the crotylation of a wide range of aldehydes and ketones promoted by the titanocene(III) complex under mild reaction conditions that are compatible with many functional groups. [38] (Scheme 7) Interestingly, a single change in the reaction conditions (temperature and addition of LiBr) allowed the selective production of γ -adducts in high yield and stereoselectivity in which anti isomer was formed predominantly.



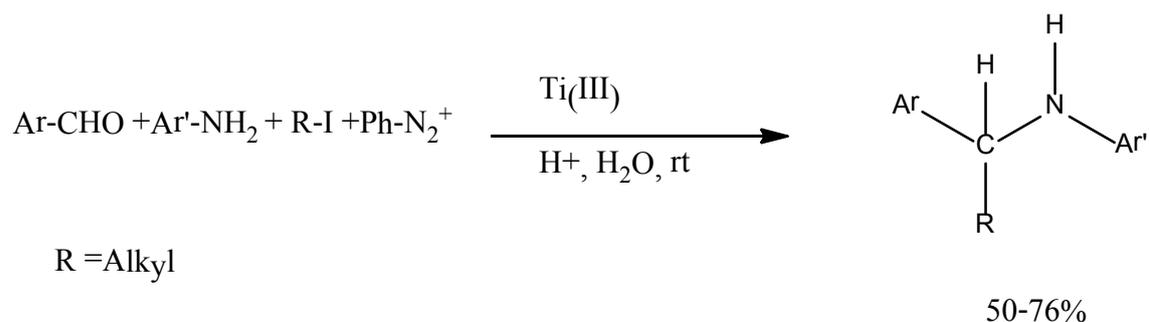
R''=H, Ph, Me
R'=Aryl, substituted aryl

Scheme 4. Reduction of α, β -unsaturated carbonyl using Cp_2TiCl_2

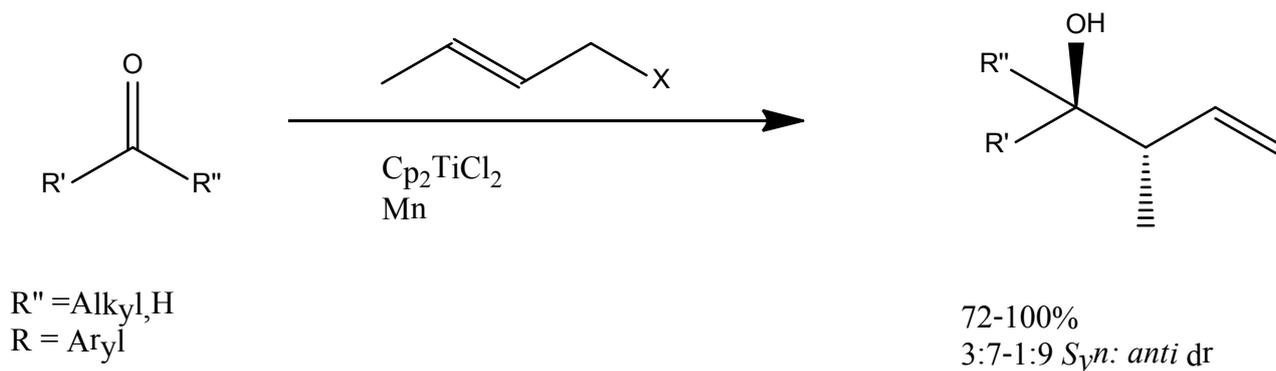


R' = H, Alkyl
R'' = alkyl, H

Scheme 5. Synthesis of quaternary α -Aminoamide



Scheme 6. Barbier-type reaction among carbonyl compounds and activated alkyl halides



Scheme 7. Titanocene(III)- mediated Barbier-type crotylation of carbonyl group

5. Addition Reactions

The enantioselective addition of organometallic reagents to ketones is one of the most popular and powerful method to generate chiral alcohols. 1,1'-Bi-2-naphthol (BINOL) - $\text{Ti}(\text{O}^i\text{Pr})_4$ system for the asymmetric alkyne addition to aldehydes established unsuitable for propiolate addition.[39] Pu and coworkers used 1,1-bi-2-naphthol (BINOL,2)/ $\text{Ti}(\text{O}^i\text{Pr})_4/\text{Et}_2\text{Zn}$ to catalyze the highly enantioselective addition of terminal alkynes with a broad range of substrates, including alkyl, aryl, and unsaturated aldehydes.[40]

Wang reported the use of a β -sulfonamide ligand in combination with ZnEt_2 and $\text{Ti}(\text{O}^i\text{Pr})_4$ for the addition of methyl propiolate to aromatic aldehydes.[41] Trost *et al.* reported the use of β -sulfonamide ligand in combination with ZnEt_2 and $\text{Ti}(\text{O}^i\text{Pr})_4$ for the addition of methyl propiolate to aromatic aldehydes.[42] Zhou *et al.* reported that organoaluminum compounds were effective reagents in asymmetric additions to organic carbonyl compounds affording secondary and tertiary alcohols in excellent enantioselectivities.[43] Zhou *et al.* reported novel direct asymmetric 3-furyl addition of (3-furyl) $\text{Ti}(\text{O}^i\text{Pr})_3$ to ketones using 10 mol % titanium catalyst of (*S*)-BINOL.[44] (Scheme 8)

This catalytic system affords products in good to excellent yields with high degree of enantioselectivities of 90% for most aromatic ketones bearing either an electron-donating or an electron-withdrawing substituent on the aromatic ring. The catalytic system also applied to α , β -unsaturated ketones and α or β -halophenones afforded products in good yields with high enantioselectivities. Asymmetric addition of Grignard reagents to aldehydes is a potent C-C bond formation reaction to generate chiral secondary alcohols with numerous biological activities.[45] Wang and coworkers reported highly catalytic asymmetric addition of deactivated alkyl Grignard reagents to aldehydes.[46] Highly reactive RMgBr reagents were effectively deactivated by bis[2-(*N,N*-dimethylamino)ethyl] ether and then were employed in the highly enantioselective addition of Grignard reagents to aldehydes. The reaction was catalyzed by the complex of commercially available (*S*)-BINOL and $\text{Ti}(\text{O}^i\text{Pr})_4$ under mild conditions.

Compared with the other observed Grignard reagents, alkyl Grignard reagents exhibited higher enantioselectivity >99% yield. (Scheme 9)

Turlingto *et al.* have observed that 3, 3-bisanisyl substituted BINOL ligand found to catalyze the alkyl propiolate addition to aliphatic aldehydes in the presence of ZnEt_2 and $\text{Ti}(\text{O}^i\text{Pr})_4$ at room temperature with excellent enantioselectivity (89-97%).[47] This system's effectiveness for aliphatic substrates under simple and mild reaction conditions makes it especially useful, as no system has been shown to afford high enantioselectivities for a wide range of aliphatic aldehydes. Wang *et al.* reported that β -sulfonamide alcohol, $\text{Ti}(\text{O}^i\text{Pr})_4$, Et_2Zn , and tertiary amine base (R^3N), effectively catalyzes the enantioselective addition of various terminal alkynes including alkynes to aldehydes in good yields with excellent enantioselectivities.[48]

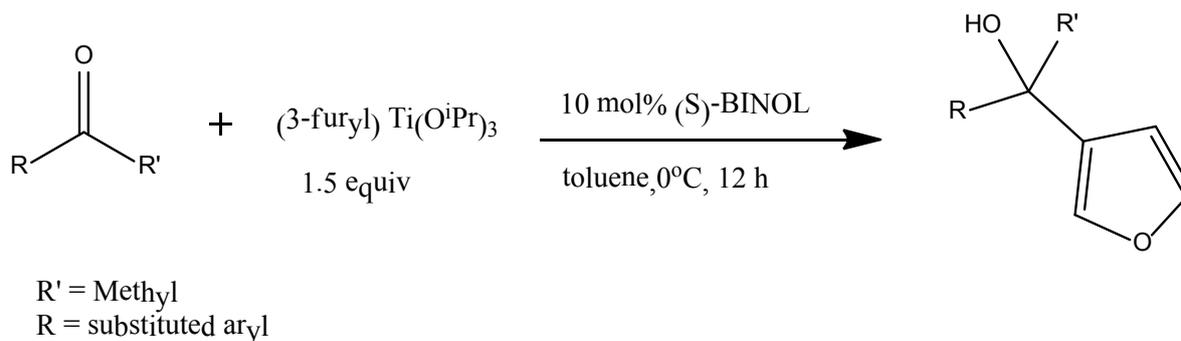
6. Condensation Reactions

Pastori *et al.* reported the first asymmetric heterocyclic condensation of the Danishefsky's diene with per(poly) fluoro aldehyde catalysed by a chiral Lewis acid prepared from binaphthol and titanium isopropoxide.[49] (Scheme 10) A particularly attractive feature of this approach was that a large variety of asymmetric dihydropyrones was directly accessible in unprecedentedly high level of enantiomeric excess giving synthetic access to F-alkyl pyranosic compounds with potential liquid crystal properties.[50]

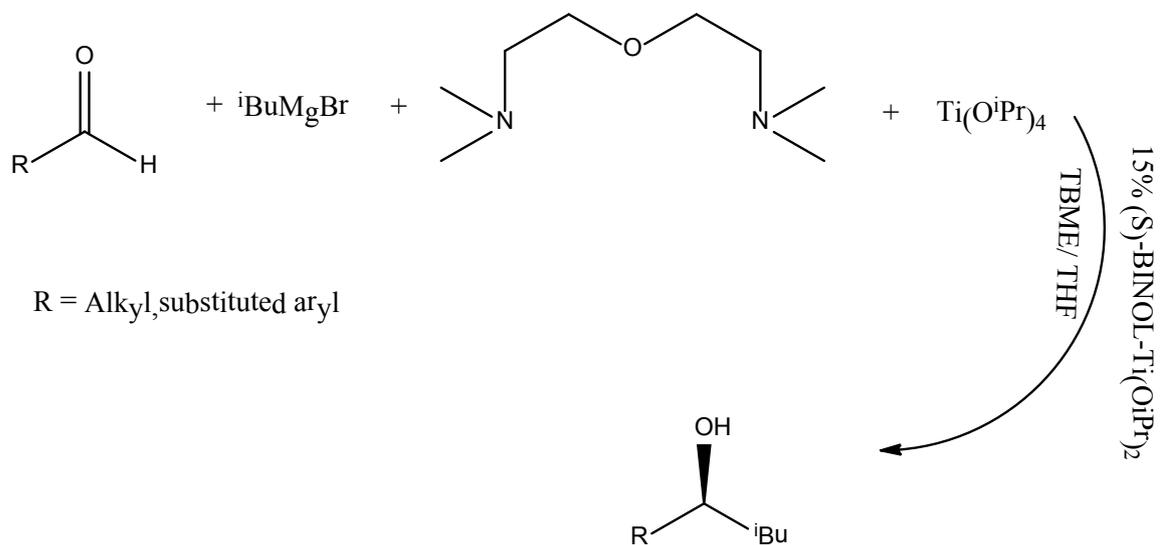
Clerici *et al.* observed that methyl phenylglyoxylate, aniline and aromatic aldehydes, on treatment with TiCl_3 / pyridine in anhydrous THF at room temperature, undergo rapid condensation to produce *syn*- β -amino- α -hydroxyesters.[51] Iranpoor and Zeynizadeh observed that catalytic reactions and found that $\text{TiCl}_3\text{SO}_3\text{CF}_3$ can act as a very efficient catalyst for cross-aldol condensation reaction of cycloalkanones with aromatic aldehydes without any self-condensation of ketones.[52] They further reported efficient cross-aldol condensation of cycloalkanone with various aromatic aldehydes catalyzed with $\text{TiCl}_3\text{SO}_3\text{CF}_3$ at room temperature in excellent yields. Easy procedure and simple work-up and ease of easy handling of

TiCl₃.SO₃CF₃. as a solid Titanium (IV) compound make this reagent a very suitable catalyst for such type of reactions.[53] Sarvari and coworkers have demonstrated a very simple and highly efficient method for the condensation of aromatic and heteroaromatic carbonyl compounds with various active methylene compounds using TiO₂ in solvent free conditions to give Knoevenagel

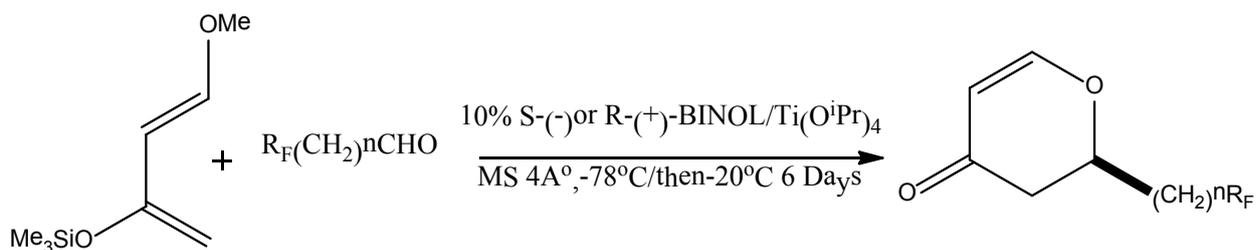
condensation products in excellent yields.[54] (Scheme 11) With the increasing tight legislation on the release of waste and use of toxic substrates as a measure to control environmental pollution, the nontoxic nature of TiO₂ and solvent free condition employed in the present protocol make it “environmentally friendly” and suitable for industrial application.



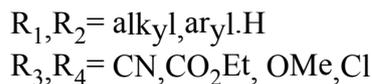
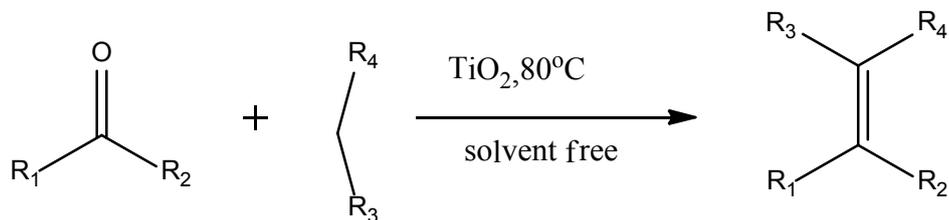
Scheme 8. Asymmetric furylation of ketones using titanium catalyst of (S)-BINOL



Scheme 9. Asymmetric additions of Grignard reagents to aldehydes

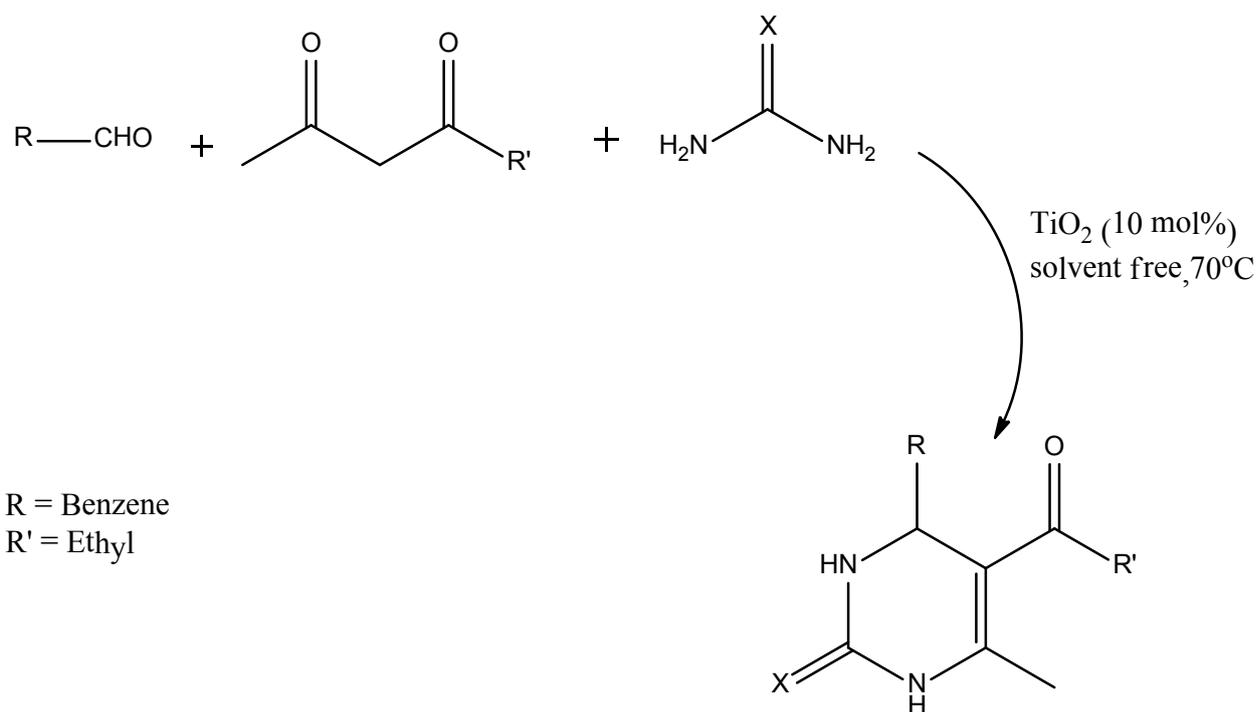


Scheme 10. Asymmetric heterocyclo condensation of the Danishefsky's diene and per(poly)fluoro aldehyde



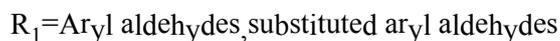
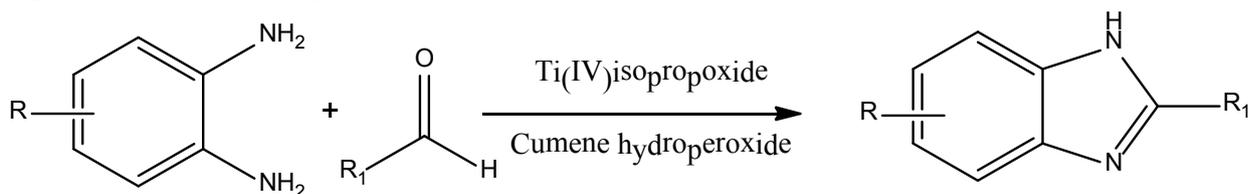
Scheme 11. Condensation of carbonyl compound under solvent free condition

Kassae *et al.* reported three-component, one-pot condensation for the synthesis of dihydropyrimidin-2(1H)-ones/thiones through a three-component condensation of 1,3-dicarbonyl compounds, aldehydes, and urea, using commercially available Titania (TiO_2) as a heterogeneous and recyclable catalyst under neutral and solvent-free conditions.[55] This method provides efficient, facile, and environmentally acceptable modification of Biginellis reaction. (Scheme 12)

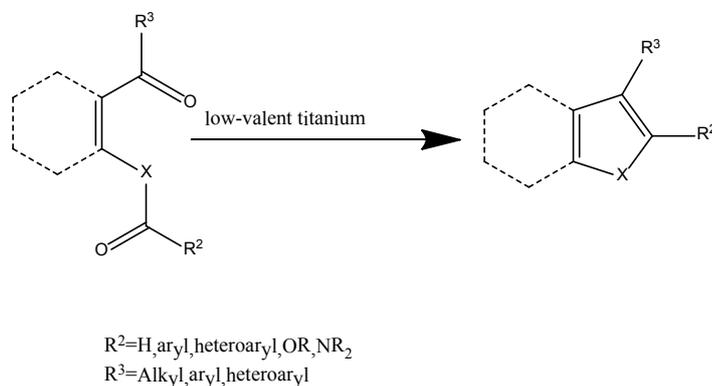


Scheme 12. Synthesis of dihydropyrimidin-2(1H)-ones/thiones by TiO_2

Havaldar *et al.* reported one-pot condensation of o-phenylenediamine with aldehyde using a mixture of Ti(IV) isopropoxide and cumene hydroperoxide.[56] (Scheme 13)



Scheme 13. Synthesis of 2-substituted benzimidazoles using a mixture of Ti(IV)isopropoxide and cumene hydroperoxide



Scheme 14. Reductive cyclization for the synthesis of heterocyclics, X = O, NR

7. Reductive Coupling Reactions

The use of titanium reagent to mediate reductive coupling of organic functional groups has steadily grown in importance in organic and organometallic synthesis. Synthesis of Bicyclo[6.3.0] undecene skeleton characteristic of some cyclooctanoids by an intramolecular reductive coupling of carbonyls promoted by low-valent Titanium was reported.[57] by Lima and Corricab. The methodology relies on an intramolecular reductive coupling of a dialdehyde promoted by low valent titanium to construct the eight-membered ring. The Lewis acid catalyzed reaction of nucleophiles with aldehyde constitutes an important part of organic synthesis, since it frequently results in stereoselective carbon-carbon bond formation in conformationally non rigid open-chain compounds.[58] The reductive coupling of methyl phenylglyoxylate with aromatic and aliphatic aldehydes promoted by TiCl_3/Py system in anhydrous THF, affords α , β -dihydroxyester in good yields and high *syn*-diastereoselectivity (up to 85%).[59]

The scope of low-valent titanium chemistry extends beyond the classical reductive dimerization of aldehydes and ketones to alkenes (McMurry reaction).[60] Titanium efficiently promotes the intramolecular coupling of carbonyl groups of distinctly different redox potentials. This has opened a new and flexible entry into hetero aromatic compounds such as furans, benzo(b)furans, pyrroles and indoles by reductive cyclization of oxo-ester or oxo-amides[61] (Scheme 14) Synthesis of indole derivatives namely Secofascaplysin, Indolopyridocoline and Endothelin – receptor antagonist is reported by Furstner.[62]

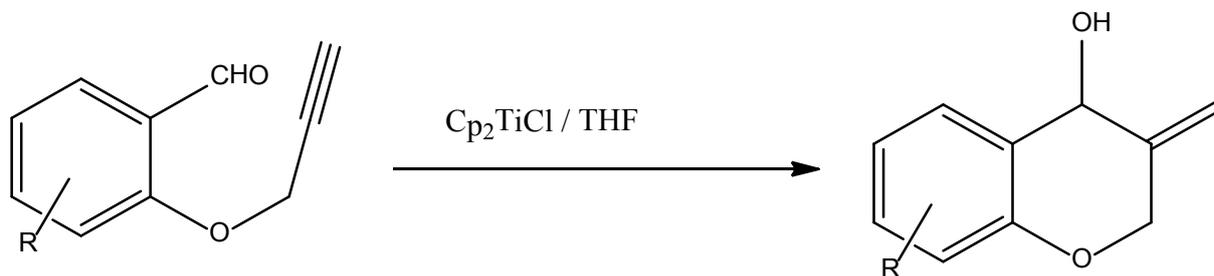
The reductive coupling of aromatic aldehydes showed *threo*-selectivity ranging from (*threo/erythro*) = 66:34 to 75:25 under catalyzed conditions using $\text{Cp}_2\text{Ti}(\text{Ph})\text{Cl}/\text{Zn} / \text{Me}_3\text{SiCl}$. [63] This method is also applicable to aliphatic aldehydes, but the diastereomeric ratios were lower than those for the aromatic aldehydes. Chiara *et al.* reported that titanocene chloride efficiently promotes the intramolecular reductive cross coupling of highly functionalized 4-oxiranylaldehydes and 4-oxiranyl ketones derived from

readily available hexoses affording branched cyclopentitols with good stereoselectivity.[64]

8. Pinacol Coupling Reactions

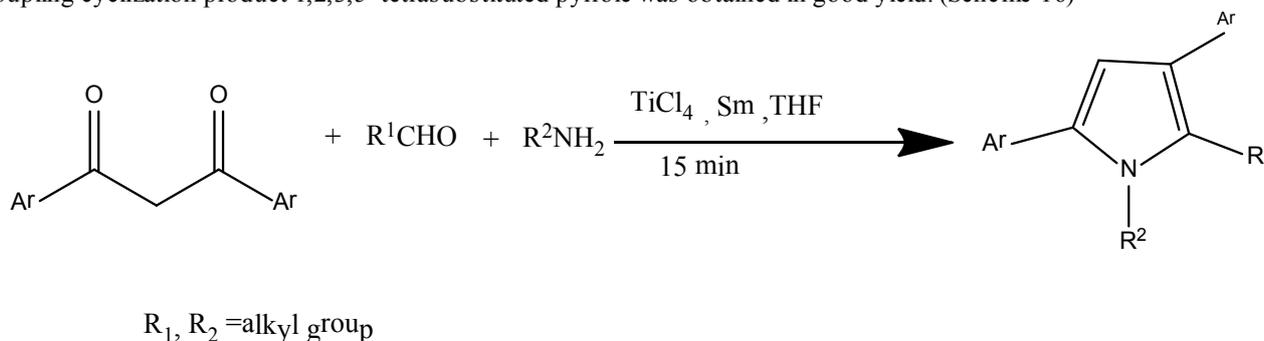
Pinacol coupling has been employed as a key step in the synthesis of natural products and pharmaceuticals.[65] Cp_2TiCl has become a useful reagent in organic synthesis. Under anhydrous conditions Cp_2TiCl promotes and catalyzes the pinacol coupling of aromatic and α,β -unsaturated aldehydes.[66] Aromatic aldehyde with Cp_2TiCl in the presence of water, gives a mixture of reduction and pinacol coupling product.[67] Estevez research group reported stereocontrolled coupling between aldehydes and conjugated alkenals mediated by $\text{Ti}(\text{III})/\text{H}_2\text{O}$. [68]

Earlier investigations by Clerici research group showed that an aqueous TiCl_3 solution promotes pinacolization of aromatic aldehydes only in strong basic medium but not under acidic conditions.[69] In the presence of water, titanocene(III) complexes promote a stereoselective C-C bond-forming reaction that provides gamma-lactols by radical coupling between aldehydes and conjugated alkenals. The method is useful for both intermolecular reactions and cyclizations. The procedure can be carried out enantioselectively at room temperature under mild conditions and is useful for both intermolecular reactions and cyclizations using chiral Titanocene catalysts. Diastereoselective inter- and intra-molecular pinacol coupling of aldehydes have been reported using a Titanium (III) complex.[70] Jana and Roy have developed a method to synthesize benzopyrans by radical cyclization of aromatic carbonyl compounds using Titanium (III) chloride as the radical initiator.[71] The radical initiator (Cp_2TiCl) is prepared *in situ* from commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF under argon. (Scheme 15) Intermolecular coupling product is the major product when Cp_2TiCl was added in the normal way. However, slow addition of carbonyl compound to the reagent (Cp_2TiCl) yields the cyclized product in good yield without any of the coupling product.



Scheme 15. Radical promoted cyclization of aromatic carbonyl compounds using Cp_2TiCl

Dou *et al.* reported highly regioselective synthesis of polysubstituted pyrroles through three component reaction induced by low valent titanium.[72] 1,3-diketone, aldehydes and amines were treated with the low-valent titanium reagent prepared from Titanium(IV) chloride and Samarium powder in anhydrous THF at room temperature under nitrogen atmosphere, the coupling cyclization product 1,2,3,5- tetrasubstituted pyrrole was obtained in good yield. (Scheme 16)



Scheme 16. Synthesis of three component polysubstituted pyrroles

The above method can be applied not only to the aromatic aldehydes with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl and alkoxy groups) but also to heterocyclic and aliphatic aldehydes under the same conditions. This method has the advantage of high regioselectivity, easily accessible starting materials, short reaction time, high yields, and convenient manipulation.

9. McMurry Reactions

McMurry reaction has served as a key step in numerous synthesis of natural carbonyl compounds because of its effectiveness. TiCl_4 -Zn-THF system has been utilized to promote McMurry cross coupling of ferrocenyl and ruthenocenyl ketones with appropriate ketones to give good yields of mixtures of *E* and *Z* isomers of alkenes which function as key precursors for the preparation of a series of ferrocifens and ruthenocifens (ferrocene and ruthenocene derivatives based on the structure of the breast cancer drug tamoxifen) [73] Microwave heating has also been applied in high yield synthesis of alkenes by TiCl_4 - Zn mediated McMurry coupling of aromatic aldehydes and ketones.[74] Unfortunately, simple aliphatic aldehydes and ketones such as pentanal and cyclohexanone did not give well defined reactions. The pronounced effect of solvent in controlling the stereochemistry of the McMurry reaction has also been studied.[75] The TiCl_3 -Li-naphthalene-THF reagent promotes McMurry coupling of aromatic and aliphatic

aldehydes and ketones at ambient temperature and produces the corresponding alkenes in good yields.

10. Conclusions

In recent years, a number of significant advances have been made toward the development of efficient and economical protocols. For achieving this transformation with substantial emphasis has been placed on the use of Titanium reagents. New reactions have been developed in recent years to provide greener and improved pathways towards preparation of organic and pharmaceutical compounds. The newer organic reactions are being reported considering technical improvements and increasing number of applications in the organic synthesis arena. Synthesis of some new natural products have also been achieved using titanium reagents catalyzed reactions leading to their synthesis in a facile manner compared to conventional methods of organic synthesis involving chemical reactions using different chemical reagents.

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