Titanium Reagents in Heterocyclic Synthesis

Hari Om¹, Pratibha Choudhary¹, Poonam Devi¹*, Varun Sharma²

¹Department of Chemistry, Deenbandhu Chhotu Ram University of Science and Technology, Murthal (Sonipat), 131039, India
²Department of Chemistry, Hindu College, University of Delhi, Delhi, 110007, India

Abstract This review confronts the diversity and selectivity of titanium reagents that mediate heterocyclic synthesis. Applications of different titanium based reagents in various organic reactions leading to the formation of heterocyclic compounds are discussed. Among others, epoxide-opening arene annulations, intramolecular coupling of carbonyl groups intermolecular hydroamination, intramolecular aza-Heck, regioselective synthesis of indoles, anti-Markovnikov hydration of internal and terminal alkynes, and the synthesis of polyarylpyrroles under microwave conditions, are reviewed.

Keywords Heterocyclic, Hydroamination, Polyarylpyrroles, Regioselective, Titanium

1. Introduction

Transition metals mediated reactions are one of the most attractive methods in synthetic organic chemistry.[1] These metals catalyzed reactions offer promising range of selectivities such as chemoselectivity, regiosselectivity, diastereoselectivity, enantioselectivity and atom economy, among others. A wide range of heterocycles are now accessible following novel and efficient pathways based on intramolecular cross-coupling of functional groups. Titanium is widely used among the various transition metals employed for the synthesis of heterocyclic compounds. Pinacol and McMurry coupling reactions are the most powerful methods for constructing carbon-carbon bonds and have served as the key step in the synthesis of various heterocyclics, natural products and pharmaceutically active compounds.[2] Synthesis of substituted pyrroles from alkynes, imines, and carbon monoxide via an organotitanium intermediate or from alkynes, nitriles, imines, and titanium-imine complexes have been reported.[3,4] The indole ring system is a crucial structure in drug discovery and has become an essential component in many pharmaceutically active compounds. Regioselectively substituted pyroles represent indispensable structural motifs of biologically active natural products and molecular sensors.[5]

This review explores the recent literature, and describes organic synthesis applications and developments in mechanistic understanding of heterocyclic synthesis catalyzed by different titanium reagents such as TiCl₄, Cp₂TiCl₂, Cp₂TiMe₂, TiCl₄-BINOL, TiO₂, and Ti(IV)-isopropoxide.

2. Titanium (IV) Chloride

Titanium chlorides are the most important and much widely used catalyst for different synthetic applications. McMurry coupling reaction has extended the scope of low-valent titanium chemistry beyond the classical reductive dimerization of aldehydes and ketones to alkenes.[6] Titanium chloride promotes the intramolecular coupling of carbonyl groups of distinctly different redox potentials competently. 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 as depicted in the Scheme 1.[7-9]

![Scheme 1: Reductive cyclization for the synthesis of heterocyclics, X = O, NR](image)

A user friendly procedure for intermolecular hydroamination reactions which employs inexpensive and readily available TiCl₄ has been reported.[10] Ackermann and coworker used TiCl₄/t-BuNH₂ as catalyst for hydroamination based Fisher Indole synthesis. The reaction commenced with the addition of 1,1-disubstituted hydrazines onto aryl and alkyl-substituted alkynes catalyzed by the addition of t-BuNH₂ to a solution of TiCl₄ in toluene competently.[11] (Scheme 2) In this process, hydrazine is directly converted to the indole derivative.
Similarly, Abbiati et al. have reported TiCl4/t-BuNH2 mediated hydroamination/annulations reaction of α-keto-acetylenes.[12] The hydroamination of unsymmetrically substituted alkynes proceed with excellent regioselectivity with a single regioisomer. Ackermann group have also reported another titanium chloride based regioselective synthesis of indoles. This reaction begins with a user friendly TiCl4 catalyzed intermolecular hydroamination of 2-chloroaniline and a subsequent palladium catalyzed intramolecularaza-Heck reaction. 2-chlorophenyl substituted enamine is formed in one-pot procedure (Scheme 3).[13] Unsymmetric al substituted alkynes enable the synthesis of diversely functionalized indoles with regioselectivity.

However, more selective anti-Markovnikov hydration of internal and terminal alkynes was attained using more sterically hindered amines. The synthesis of substituted pyroles from 1,3-diketones and imines at room temperature using TiCl4/Zn or TiCl4/Sm in anhydrous THF is reported.[23] Later on highly regioselective synthesis of substituted pyroles utilizing low-valent titanium reagent was reported.[24]

Rao et al. have accounted facile one-pot synthesis of polyarylpyroles from 2-butene and but-2-yne-1,4-diones under microwave conditions.[25] Substituted pyroles are obtained in good yields via the novel coupling cyclization reaction of 1,3-diketones with imines promoted by low-valent titanium reagent. Synthesis of substituted pyroles from 1,3-diketones and imines has been performed at room temperature using TiCl4/Zn or TiCl4/Sm in anhydrous THF.[26,27] Similarly, Dou and coworkers have reported the synthesis of highly regioslective polysubstituted pyroles through three component reaction induced by low-valent titanium.[28] 1,3-diketone, aldehydes and amines are treated with the low-valent titanium reagent prepared from Titanium (IV) chloride and Samarium powder in anhydrous THF at room temperature under a nitrogen atmosphere. The cyclization product (1,2,3,5-tetra-substituted pyrrole) is obtained in good yield. (Scheme 5)
nols through a reaction sequence comprising dehydration, intermolecular hydroamination, [1,5]H-sigmatropic shift and intramolecular nucleophilic substitution. (Scheme 6)

**Scheme 6.** Titanium catalyzed synthesis of pyrrole using α-haloalkynols

Duan *et al.* achieved a total synthesis of cicerfuran, a naturally occurring benzofuran compound using a simple procedure and readily available reagents.[30] This synthetic approach promotes the scope of cross McMurry reaction and provide a novel approach for the facile synthesis of 2-arylbenzofurans. In another paper, Abbiati and coworkers have described a TiCl$_4$/t-BuNH$_2$-mediated synthesis of pyrrolo[1,2-α]indole-2-carbaldehydes, starting from 2-acyl-1-propargyl-1H-indoles under mild reaction conditions.[31] (Scheme 7)

**Scheme 7.** Synthesis of pyrrolo-[1,2-α] indole-2-carbaldehydes

Application of TiCl$_4$ as catalyst extends to the synthesis of aromatic thiazoles. 2-Arylbenzothiazole has been prepared from bis-(2-benzalaminophenyl)disulfide using titanium tetrachloride and samarium powder in anhydrous tetrahydrofuran (Scheme 8).[32] Disulfides give the expected products either bearing electron-withdrawing groups (such as halide) or electron-donating groups (such as alkyl and alkoxy groups) under the same reaction conditions with moderate to good yields. The electronic nature of the substituent has no significant effects on this reaction.

**Scheme 8.** Synthesis of 2-Arylbenzothiazole

3. **Cp$_2$TiCl$_2$**

Titanocene chloride is a well-known reagent for generating carbon-centred radicals from epoxides. Diastereoselective inter- and intramolecular pinacol couplings of aldehydes have been reported using a titanium(III) complex.[33,34] Zhou and Hirao reported catalytic reductive cyclization of olefinic iodoethers by use of Cp$_2$TiCl$_2$ in the presence of Mn and Me$_3$SiCl.[35] (Scheme 9) This protocol provides a versatile method for the selective formation of multisubstituted tetrahydrofurans. In the absence of Cp$_2$TiCl$_2$, this reaction led to a much lower yield.

**Scheme 9.** Preparation of multi-substituted tetrahydrofuran

Diastereoselective inter- and intramolecular pinacol coupling of aldehydes have been reported using a titanium(III) complex.[36] 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.[37] The radical initiator (Cp$_2$TiCl) is prepared \emph{in situ} from commercially available titanocene dichloride (Cp$_2$TiCl$_2$) and zinc dust in THF under argon. (Scheme 10) Intramolecular coupling product is the major product when Cp$_2$TiCl was added in the normal way. However, slow addition of carbonyl compound to the reagent (Cp$_2$TiCl) yields the cyclized product in good yield without any of the coupling product.

**Scheme 10.** Radical cyclization of aromatic carbonyl compounds using Cp$_2$TiCl promoted

Wipf and Maciejewski have developed a novel titanocene (III) chloride catalyzed epoxide-opening arene annulation that affords 3,3-disubstituted indolines. 3 mol % of titanocene dichloride and stoichiometric manganese tolerate a range of substituents on the aromatic ring.[38] This methodology can be extended to other five-membered heterocycles as demonstrated by the preparation of a 3,3-disubstituted 5-azaindoline. (Scheme 11)
In another paper, Maciejewski and Wipf reported the conversion of N-epoxyalkylanilines into indolines catalyzed by Titanocene (III) Chloride.[39] The reaction proceeds through Curtius rearrangement of the known carboxylic acid followed by subsequent trapping of the intermediate isocyanate with benzyl alcohol affording the Cbz-protected aminopyridine in 33% yield over 3 steps. (Scheme 12) Subsequent methallylation and epoxidation using m-CPBA led to epoxide, which on treatment with catalytic titanocene(III) chloride in the presence of stoichiometric manganese powder, provided an intermediate 4,6-dichloro-5-azaindoline. Further conversion of this intermediate with Pd/C under an atmosphere of H₂ gave azaindoline in 52% yield over 2 steps.

**Scheme 12. Preparation of 5-azaindolene**

**Scheme 13. One-pot synthesis of cyclic amines from aminalkynes by Cp₂TiMe₂ catalyzed intramolecular hydroamination and subsequent reduction**

Indoles have also been synthesized via alkylidenation of acylphenyldrazides using phosphoranes and the Petasis reagent, followed by in situ thermal rearrangement of the product enehydrazines. The Petasis reagent provides an essentially neutral equivalent of the [acid-catalysed] Fischer indole synthesis with acyl phenylhydrazides as starting substrates.[45] (Scheme 14) Alkylidene triphenyl-phosphoranes convert aryl phenylhydrazide to indoles, but acyl phenylhydrazides derived from aliphatic carboxylic acids undergo a Brunner reaction to form indolin-2-ones.

**Scheme 14. Synthesis of substituted indole from acyl phenyldrazides**

4. **Cp₂TiMe₂**

Petasis reagent (dimethyltitanocene, Cp₂TiMe₂) has proven to be very effective for the methylation of esters. [40,41] Cp₂TiCl₂ also serves as a precursor for the synthesis of Cp₂TiMe₂. A new synthetic entry to the 1,4-dihydroquinoline nucleus involves dimethyltitanocene catalysed methylation of N-(alkoxycarbonyl)amides derived from 2-allylanilines, followed by ring-closing metathesis of the resulting enamides.[42,43] Bytschkov and Doye have reported intra-molecular hydroamination/cyclization of aminoalkynes catalyzed by Cp₂TiMe₂.[44] This catalyst has been found a competent catalyst for the intramolecular hydroamination/cyclization of aminoalkynes. The hydroamination reactions proceed smoothly in the presence of 5.0 mol% Cp₂TiMe₂ at 100–110°C to give five- and six-membered cyclic imines within 4–6 hours. After subsequent reduction with zinc-modified NaBH₃CN at room temperature cyclic amines can be isolated in good yields. In combination with an imine reduction, the intramolecular hydroamination reactions can be used for a convenient one-pot synthesis of cyclic amines from aminoalkynes. (Scheme 13)

5. **TiCl₄-BINOL**

Zhao and coworkers have reported a simple and efficient catalytic enantioselective hetero-Diels–Alder reaction between (E)-4-methoxy-2-trimethylsiloxy-penta-1,3-diene and aromatic aldehydes catalyzed by TiCl₄-(R)-BINOL catalytic system using sodium alcoholates as additives. Aromatic aldehydes were used and provided relative product yield (61-88%) yields and with good to excellent enantioselectivities.[46] Yu et al. reported asymmetric synthesis of 2,6-substituted dihydropyrones catalyzed by 3-monosubstituted and 3,3-bisubstituted BINOL titanium complexes where asymmetric hetero-Diels–Alder (HDA) reactions of aromatic aldehydes with Danishefsky’s diene derivative were carried out smoothly in the presence of the Ti(IV)–(R)-BINOL (1:1.2) complex to give the corresponding chiral 2,6-disubstituted dihydropyrones under mild conditions.[47] Aromatic aldehydes afford the corresponding products in moderate yields (up to 72%) with good enantioselectivities (up to 80% ee). Aromatic aldehydes afforded the corresponding products in moderate yields (up to 72 %) with good enantioselectivities (up to 80% ee).
Highly enantioselective hetero-Diels-Alder reaction of trans-1-Methoxy-2-methyl-3-trimethylsiloxybuta-1,3-diene with aromatic and aliphatic aldehydes catalyzed by 3-substituted BINOL-TiO₂ complex are reported.[48] 3-Diphenylhydroxymethyl-substituted BINOL-titanium complex (prepared in situ) is found to be a highly efficient catalyst for hetero-Diels-Alder reaction of diene with both aromatic and aliphatic aldehydes to give 2,5-disubstituted dihydropyrone in up to 99% yield and 99% ee. (Scheme 15)

R)-BINOL-Ti(OiPr)₄ complex displayed high enantioselectivity in the asymmetric HDA reaction of diene with both aromatic and aliphatic aldehydes. Majumder and coworkers reported titanium-catalyzed 3-component coupling of primary amine, alkyne, and isonitrile followed by treatment with hydrazines provides pyrazoles in a one-pot procedure. This new procedure has significant flexibility. [49]

6. Miscellaneous Reagents

Park et al. reported a one-pot synthesis of 4-ethoxy-1,2,3,4-tetrahydroquinoline from a heterogeneous solution of nitroarene, ethanol and TiO₂ upon irradiation by UV light.[50] (Scheme 16)

Kassae et al. reported three-component, one-pot condensation for the synthesis of dihydropyrimidin-2(1H)-ones/thiones ones through a three-component condensation of 1,3-dicarbonyl compounds, aldehydes, and urea, using commercially available titania (TiO₂) as heterogeneous and recyclable catalyst under neutral and solvent-free conditions.[51] This method provides efficient, facile, and environmentally acceptable modification of Biginellis reaction. (Scheme 17)

Havaldar et al. synthesize various 2-substituted benzimidazoles in one pot by condensation of o-phenylenediamines with an appropriate aldehyde using a mixture of Titanium (IV) isopropoxide and cumene hydroperoxide.[52] (Scheme 18)

7. Conclusions

Transition metal mediated reactions are one of the most attractive methods in synthetic organic chemistry. Analysis of a variety of titanium reagents in heterocyclic synthesis has revealed that their efficiency strongly depends on the nature of the active titanium species and the experimental conditions. The reasons that explain the interest shown by many researchers includes, among others, regio- and stereochemical control of the reaction, together with the mildness of the experimental conditions which include the use of catalytic quantities of titanium.

The rapid access to indoles as well as the selection of environmentally benign and chemoselective methods are the major goals in heterocyclic synthesis using titanium reagents based catalysts. The exploration for new annulations and heterocyclization procedures is a very competitive and determined research field. Many organic reactions catalyzed by titanium reagents are presented involving the use of transition-metal complexes (especially palladium complexes, but many other transition- and main-group metals and their complexes are continuously being studied and introduced in the chemistry of heterocycles, thermal reactions, photochemical procedures, solid-support synthesis for a combinatorial approach, green procedures with the auxiliary techniques of microwaves and ultrasound for environmentally friendly reaction conditions.

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