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Low-valent titanium: New synthetic applications

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Abstract

During the course of our work on the synthesis of bioactive compounds, new low-valent titanium (LVT)-mediated reactions were discovered. These include: i) a short synthesis of oxygen heterocycles *via* intramolecular reductive deoxygenation between ketone and ester functions in aromatic systems, ii) an unusual *ortho*-hydroxyl-assisted reduction/isomerisation of aromatic alkenes, iii) reductive dealkoxylation of aryl alkyl ethers, iv) one-pot synthesis of polycyclic aromatic hydrocarbons from *o*-alkoxy aromatic aldehydes/ketones involving reductive deoxygenation, reductive dealkoxylation and intramolecular C–C coupling in *tandem*, v) a novel approach to the deprotection of allyl, propargyl and benzyl ethers of alcohols and phenols and N-benzyl/allyl amines, and vi) modulation of the activity of LVT reagent by nitrogen heterocycles. Mechanism and synthetic implications of these reactions are discussed.

Key words: Low-valent titanium, benzofurans, polycyclic aromatic hydrocarbons, deprotection, reduction, isomerisation.

1. Introduction

Transition metal-mediated synthetic transformations are increasingly used in modern synthetic organic chemistry. Steric and electronic factors of the ligands regulate the reactivity of the transition metals. Development of several new strategies which are otherwise impossible by conventional methods show the promise they hold in organic synthesis. Amongst the 3d-block transition metals, titanium is less explored compared to other members. The high oxophilicity of low-valent titanium (LVT)[1] reagents has been extensively exploited in the C–C bond formation involving reductive coupling of carbonyl and dicarbonyl to alkenes and cycloalkenes which is generally referred to as McMurry reaction[2] (Scheme 1). During the course of our studies on the synthesis of bioactive compounds, in addition to carbonyl coupling reactions, several new applications of LVT [Ti(O) and Ti(II)] were discovered. A brief account of our recent work on the synthetic utility of LVT is presented here.

2. Intramolecular reductive deoxygenation in aromatic ketoesters

Benzofuran derivatives occur widely in nature and some of them are known to possess pharmacodynamic properties[3]. An LVT-mediated short synthesis of benzofurans h

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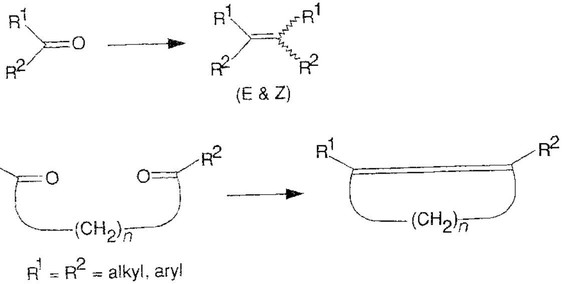
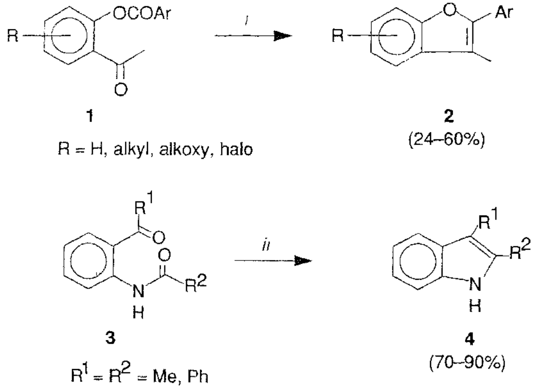


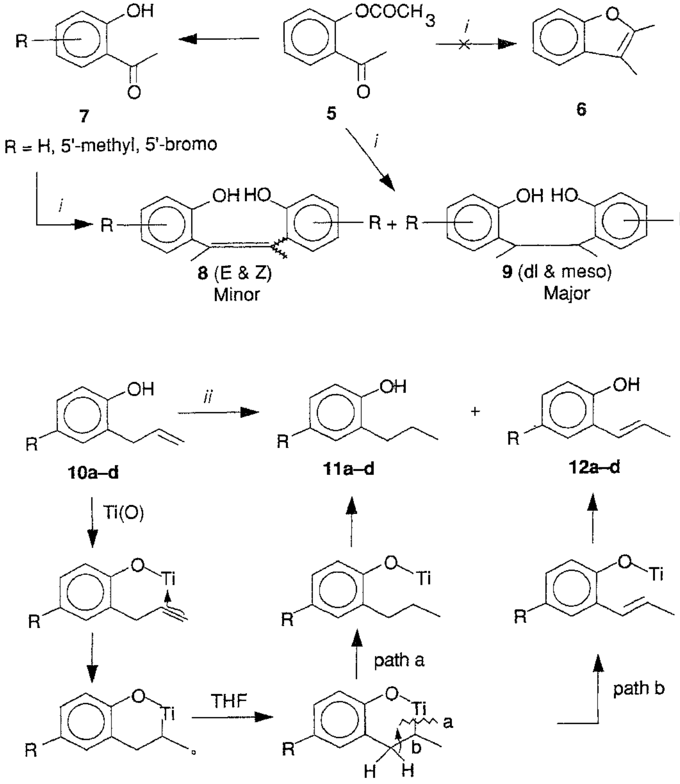
SCHEME 1. Inter- and intramolecular reductive deoxygenations.

been developed in our laboratory. Retrosynthetically, an intramolecular reductive deoxygenation between the ketone and ester groups of *o*-aroyloxyacetophenone would lead to the formation of five-membered oxygen heterocycles. Mukaiyama's reagent ($TiCl_4$–Zn), which is known to couple aromatic carbonyls, was selected for the study. Thus, treatment of 2′-benzoyloxyacetophenone (**1**: R=H, Ar=Ph) with Ti(II) reagent



Reagents and conditions: (i) $TiCl_4$/Zn, dioxane/reflux, (ii) Ti on graphite, THF/reflux.

SCHEME 2. Intramolecular reductive deoxygenation reactions.



	R	11	12
		Yield %	
a	H	53	—
b	Me	31	23
c	OMe	25	28
d	Ph	27	28

Reagents and conditions: (i) $TiCl_4$/Zn, dioxane/reflux, (ii) $TiCl_3$/Mg, THF/reflux.

SCHEME 3. *ortho*-Hydroxyl-assisted reduction/isomerisation of aromatic alkenes.

prepared from $TiCl_4$–Zn in dioxane under refluxing condition gave 3-methyl-2-phenylbenzofuran (**2**: R=H, Ar=Ph) in 55% yield (Scheme 2)[4]. The scope of this methodology has been illustrated by the synthesis of a series of alkyl, alkoxy and halo-substituted benzofurans.

The method has the potential for the synthesis of other heterocycles also. Independently, Furstner and Jumbam[5] have prepared furans and indoles using similar approach using Ti on graphite. Thus, reaction of 2-acylamidobenzophenones (**3**: R^1=Ph, R^2=Me) on treatment with Ti on graphite yielded 2-methyl-3-phenylindole (**4**: R^1=Ph, R^2=Me) in good yield (Scheme 2)[5].

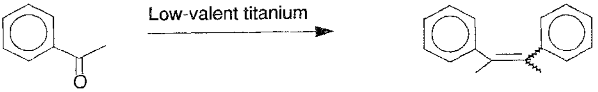
3. Unusual *ortho*-hydroxyl-assisted reduction of aromatic alkenes

In our attempts to extend the above protocol to the synthesis of 2,3-dialkylbenzo[b]furans, it was logical to use 2′-acetoxyacetophenone (**5**) as substrate. To our surprise, 2,3-dimethylbenzo[b]furan (**6**) was not formed but diarylalkane (**9**: R=H) was obtained as the major product along with minor amounts of the corresponding alkene (**8**: R=H) (Scheme 3). Same products were also obtained when *o*-hydroxyacetophenone (**7**: R=H) was used as substrate which showed the hydrolysis of acetoxy functions under reaction conditions. Reduction of stilbene double bond did not take place in aromatic carbonyls lacking *o*-hydroxy group[6]. The mechanism for the reduction of double bond can be explained by the coordination of π-bond to sterically close titanium. In order to investigate the mechanism of this unusual reduction, 2-allylphenol (**10a**) was chosen as a model substrate since the allyl double bond and hydroxyl group were suitably placed for possible coordination with LVT. Thus, when a reaction was carried out with **10a**, smooth reduction of double bond occurred furnishing 2-propylphenol (**11a**) (Scheme 3). To explore the scope of this reduction, experiments were carried out with a variety 2-allylphenols. In the case of substituted 2-allylphenols (**10b-d**), however, the reaction led to a mixture of reduced (**11b-d**) as well as isomerised products[7] (**12b-d**).

To explain this novel reduction/isomerisation, a mechanism has been proposed as given in Scheme 3. A carbon radical generated as a result of formation of six-membered titanium complex is quenched by the hydrogen radical from the solvent (THF). Finally, the cleavage of the Ti–C bond (path a) resulted in the formation of reduced product while β-cleavage (path b) led to the formation of the isomerised product.

4. A new approach to the synthesis of polycyclic aroamtic hydrocarbons (PAH)

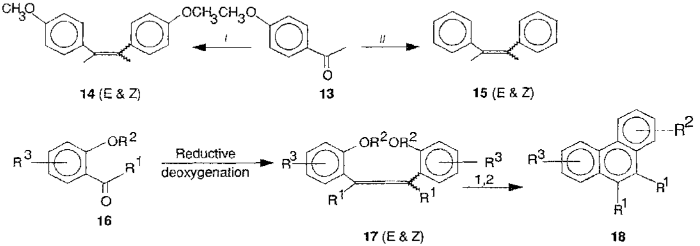
Recently, we have established that solvents have profound effect on the LVT-mediated reductive deoxygenation reaction[8] (Scheme 4). Thus, in dimethoxyethane (DME) expected reductive coupling of 4′-methoxyacetophenone (**13**) to 4,4′-dimethoxy-α,α'-dimethylstilbene (**14**) was obtained when LVT reagent was prepared by the reduction of $TiCl_3$ with Li. However, the reaction took an entirely different course when tetrahydrofuran (THF) was used as solvent. Besides reductive coupling, an unprecedented reductive dealkoxylation was observed with LVT reagent prepared from $TiCl_3$ and Li in THF resulting in the formation of α, α'-dimethylstilbene (**15**) (Scheme 5). This observation is in contrast to the reported compatibility of ether



Reagent	*Conditions*	*E(%)*	*Z(%)*
$TiCl_3$–Li–DME	Reflux, 16 h	83	9
$TiCl_3$–Li–THF	–do–	25	64

SCHEME 4. Influence of solvents on reductive deoxygenation.

functionalities under LVT conditions[2]. The mechanism of this cleavage probably involves SET from Ti to the ether to form a radical anion which dissociates into arene radical and alkoxide anion. The arene radical is quenched by THF, a potential source of hydrogen radical. From the retrosynthetic point of view, *o*-alkoxy aromatic aldehydes/ketones could serve as appropriate substrates for the synthesis of phenanthrenes if reductive deoxygenation, reductive dealkoxylation and intramolecular C–C coupling between radicals could occur in *tandem*. Therefore, a reaction was carried out with *o*-methoxyacetophenone (**16a**) and Ti(O) ($TiCl_3$–Li–THF). It was gratifying to find the formation of 9,10-dimethylphenanthrene (**18a**) as the sole isolable product[9] (Scheme 5). Intermediacy of dimethoxystilbene (**17a**) in the formation of **18a** from **16a** was demonstrated by the direct conversion of **17a** to **18a**.



a: R^1=R^2=Me, R^3=H
b: R^1=R^3=H, R^2=Me
c: R^1=Me, R^2=Et, R^3=H
d: R^1=R^2=Me, R^3=5–Me

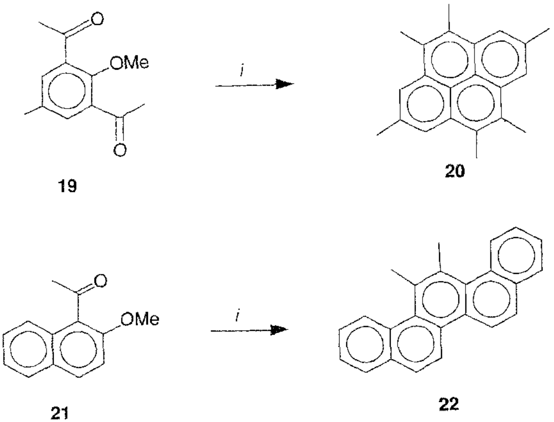
(1) Reductive dealkoxylation, and (2) Intramolecular C–C coupling.

18a: R^1=Me, R^2=R^3=H
18b: R^1=R^2=R^3=H
18c: R^1=Me, R^2=2–Me, R^3=7–Me

Reagents and conditions: (1) $TiCl_3$/Li, DME/reflux; (2) $TiCl_3$/Li, THF/reflux.

SCHEME 5. Reductive dealkoxylation of aryl alkyl ethers and intramolecular C–C coupling.

The above protocol has been successfully used in the synthesis of several PAHs. Treatment of aromatic substrate with alkoxy group flanked by two keto groups offer possibility of multiple C–C bond formations. Indeed, this was achieved by the preparation of 2,4,5,7,9,10-hexamethylpyrene (**20**) from 2,6-diacetyl-4-methylanisole (**19**), which represents simultaneous formation of three C–C bonds. Thus, tetracyclic aromatic systems could be obtained from monocyclic aromatic compounds. Similarly, the use of 1-acetyl-2-methoxynaphthalene (**21**) with LVT yielded a pentacyclic PAH, *i.e.*, 13,14-dimethylpicene (**22**) (Scheme 6).



Reagents and conditions: (i) $TiCl_3$/Li, THF/reflux.

SCHEME 6. One-pot synthesis of polycyclic aromatic hydrocarbons.

However, in spite of its elegance, the method suffers from poor yields, restricting its synthetic utility. Therefore, attempts were made to modulate the activity of LVT reagents.

5. Influence of nitrogen bases on the reactivity of LVT

The reactivity of LVT is known to be dependent on its oxidation state and method of preparation[11] (reducing agents and coordinating solvents). The effects of ligands on the activity of transition metals is well documented[12]. Since reactivity and stability of transition metal complexes are mutually exclusive, the stable complexes of LVT are expected to be less reactive. In view of the greater ability of nitrogen-containing ligands to form stronger complexes with 3d-block transition metals as compared to oxygen analogs, the effects of organic bases on the activity of LVT were studied.

The 3d-block transition metals in their reduced states are usually rich in electrons (soft acids). Further, donation of oxygen lone pair (THF) to the vacant 3d-orbitals of the metal is expected to increase their electron density, thereby reducing the stability of the complex. However, back donation of the electrons from the filled metal orbitals to the vacant orbitals of the ligand will contribute to the stability of the metal complex. To test this hypothesis, pyridine which possesses σ-donor hetero atom (N) as well as empty π^*-orbital for back bonding was used as a model ligand. Thus, the addition of pyridine (0.3 eq with respect to $TiCl_3$) to LVT in the reaction of **16a**, the yield of **18a** improved from 36 to 82% (Scheme 5) (Table I, entries 1,2). Other organic bases such as quinoline, 4-N,N-dimethylaminopyridine (DMAP), N,N-diethylaniline, etc., also improved the yields of **18a** though to a lesser extent (Table I, entries 3–5).

Table I

Influence of organic bases on LVT-induced synthesis of 9,10-dimethylphenanthrene (18a)

Entry	*Substrate*	*Reagent*	*Conditions*	*% Yield of product(s)* **17a**	 **18a**
1	**16a**	$TiCl_3$–Li–THF	Reflux, 16 h	–	36
2	**16a**	$TiCl_3$–Li–THF–pyridine(0.3 eq)	–do–	–	82
3	**16a**	$TiCl_3$–Li–THF–quinoline(0.3 eq)	–do–	–	47
4	**16a**	$TiCl_3$–Li–THF–DMAP(0.3 eq)	–do–	6	52
5	**16a**	$TiCl_3$–Li–THF–N,N′–diethylaniline(0.3 eq)	–do–	35	43

In order to investigate the influence of pyridine-stabilized LVT on other substrates, different *ortho*-alkoxy aromatic aldehydes and ketones such as *o*-ethoxyacetophenone (**16c**), *o*-methoxybenzaldehyde (**16b**) and 2′-methoxy-5′-methylacetophenone (**16d**) were used when the corresponding phenanthrenes (**18a-c**) were obtained (Scheme 5) in moderate to high yields, respectively[13] (Table II).

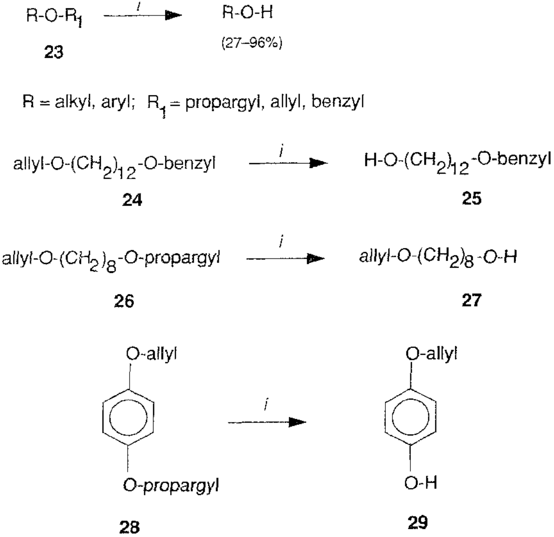
Table II

Comparison of yields in LVT-induced synthesis of phenanthrenes with/without pyridine

Substrate	*Reagent*	*Conditions*	*Product (Yield %)*
16b	$TiCl_3$–Li–THF	Reflux, 16 h.	**18b** (25)
16c	–do–	–do–	**18a** (38)
16d	–do–	–do–	**18c** (38)
16b	$TiCl_3$–Li–THF–py(0.3 eq)	–do–	**18b** (48)
16c	–do–	–do–	**18a** (80)
16d	–do–	–do–	**18c** (70)

6. A new approach to deprotection of allyl, benzyl and propargyl ethers

Unlike aryl alkyl ethers, dialkyl ethers such as 1-methoxydecane (**23**; R=*n*-decyl, R^1=methyl)) did not undergo either demethylation or demethoxylation with LVT ($TiCl_3$–Li–THF). However, in the cases of alkyl allyl ethers, regiospecific cleavage of allyl-oxygen bonds occurred readily. Similarly, debenzylation was observed by the above LVT reagent[14]. Of the several reagents tried, LVT prepared by the reduction of $TiCl_3$ with Mg in THF gave most satisfactory results for deallylation of a variety of aliphatic, alicyclic and aromatic allyl ethers (Scheme 7). However, this reagent gave poor yield for debenzylation of ethers. This difference in reactivity has been utilised in the selective deallylation of 1-allyloxy-12-benzyloxy dodecane (**24**) to 12-benzyloxy-dodecan-1-ol (**25**).



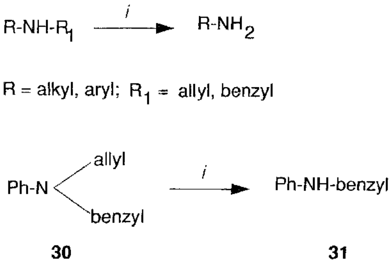
Reagents and conditions: (i) $TiCl_3$/Mg, THF/reflux.

SCHEME 7 Deprotection of different ethers.

The deallylation/debenzylation possibly proceeds *via* oxidative addition of Ti(O) to the O-allyl/benzyl bond followed by cleavage of Ti–O bond. The selectivities of the cleavages could be explained by the differential stabilities of the intermediate n^3-complexes. n^3-Allyl complexes are stabler than the corresponding benzyl complexes. According to this argument, the propargyl group should give stabler complexes compared to allyl complexes. Based on this consideration propargyl ethers are expected to undergo more facile deprotection. Indeed, 1-propargyloxyhexadecane on treatment with LVT ($TiCl_3$–Mg–THF) gave 1-hexadecanol within 30 minutes in 72% yield. Regioselective cleavage of propargyl ethers in the presence of allyl and benzyl ethers was also investigated. Mixed ethers such as 1-allyloxy-8-propargyloxyoctane (**26**) and 1-allyloxy-4-propargyloxybenzene (**28**) were smoothly converted into 8-allyloxyoctan-1-ol (**27**) and 4-allyloxyphenol (**29**), respectively (Scheme 7)[15].

7. Cleavage of N-allyl/benzyl bonds

As a logical extension of the deprotection of allyl/benzyl/propargyl ethers it was of interest to study the effect of LVT on allyl and benzyl amines. The N–C bonds are expected to be less susceptible to the cleavage as compared to O–C bonds due to the lower electronegativity of nitrogen than that of oxygen. Indeed, deprotection of N-allyl diphenyl amine required 16 h refluxing for completion of reaction whereas 2-allyloxynaphthalene could be deallylated in only 5 h. As in the case of ethers, N-allyl bond could be cleaved in the presence of N-benzyl bonds in mixed amines[16] by LVT ($TiCl_3$–Li–THF) as demonstrated by the smooth conversion of N-allyl-N-benzylaniline (**30**) to N-benzylaniline (**31**) (Scheme 8). Moreover, chemoselective deprotection of allyl ethers in the presence of allyl amines could be achieved by LVT reagents.



Reagents and conditions: (i) $TiCl_3$/Li, THF/reflux.

SCHEME 8. Reductive cleavage of allyl/benzyl amines.

8. Conclusions

Low-valent titanium complexes have been extensively used for varied types of reductive coupling reactions. We have, however, demonstrated a novel type of intramolecular reductive deoxygenation in aromatic keto esters. Based on this, a new synthesis of oxygen heterocycles has been developed. An unusual reductive dealkoxylation of aryl alkyl ethers was also observed which led to the formulation of a one-pot synthesis of polycyclic aromatic hydrocarbons. Beside C–C coupling reactions, we report the power of low-valent titanium reagents in the reductive cleavage of different C–O and C–N bonds. This has resulted in the development of a new approach to deprotection of allyl/propargyl/benzyl ethers as well as N-allyl/benzyl amines. An unprecedented reduction/isomerisation of alkenes *ortho* to phenols was also observed. We look forward to many more novel applications of LVT in organic synthesis.

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