



Salt/ligand-activated low-valent titanium formulations: the ‘salt effect’ on diastereoselective carbon–carbon bond forming SET reactions

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ARTICLE INFO

Article history:

Received 14 April 2008

Received in revised form 14 May 2008

Accepted 16 May 2008

Available online 21 May 2008

Keywords:

Low-valent titanium

Activation

Deoxygenation

Electron transfer

Inorganic Grignard

Monomerization

ABSTRACT

A comprehensive study on the influence of exogenously added electropositive metal salts as promoters/secondary activators on preformed LVT species has resulted in the construction of highly efficient low-valent titanium (LVT) reagents. These salt-activated LVT reagents while exhibiting enhanced chemoselectivity and diastereoselectivity accelerated the reductive olefination rates of aromatic and aliphatic carbonyls under ambient temperature conditions and in much reduced reaction times. The versatility of the salted reagent was further explored in other single electron transfer reactions, namely, imino-pinacol couplings and one-pot synthesis of phenanthrenes from *o*-alkoxy aromatic carbonyls. We envisage that, in contrast to multiphase heterogeneous colloidal slurries, salt-activated LVT reagents afforded uniformly viscous homogeneous slurries generating a highly reactive monomeric intermetallic LVT complex. Continued judicious exploration of the emerging paradigms by studying the influence of external ligands/auxiliaries/redox agents on LVT reagents, and organometallics in general, will be critical to widen the scope and utility of the classical McMurry reaction and other SET reactions.

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1. Introduction

Designing of reagents with appropriate reactivity or improving the existing methodologies for selective organic transformations is an important domain of organometallic chemistry. For the transition metal-based reagents in general, and for low-valent titanium (LVT) in particular,^{1–4} it is widely known that the reactivity, reproducibility, and stereochemistry of reaction products vary greatly with the source of the metal, its method of preparation, and the experimental conditions. Due to the unique features of high oxophilicity ($\Delta H = -225.8$ kcal/mol) and reducing power ($\text{Ti} \rightarrow \text{Ti}^{+2} + 2\text{e}^-$; $E^{0+} = 1.63$ V), low-valent titanium (LVT) reagents have gained widespread acceptance in organic synthesis.^{1–7} In particular, the remarkable scope of LVT reagents to effect reductive coupling of carbonyls (McMurry reaction) has resulted in a variety of applications such as synthesis of strained olefins,¹ heterocyclic compounds,⁵ and macrocyclic ring systems⁶ to complex natural products including paclitaxel.⁷

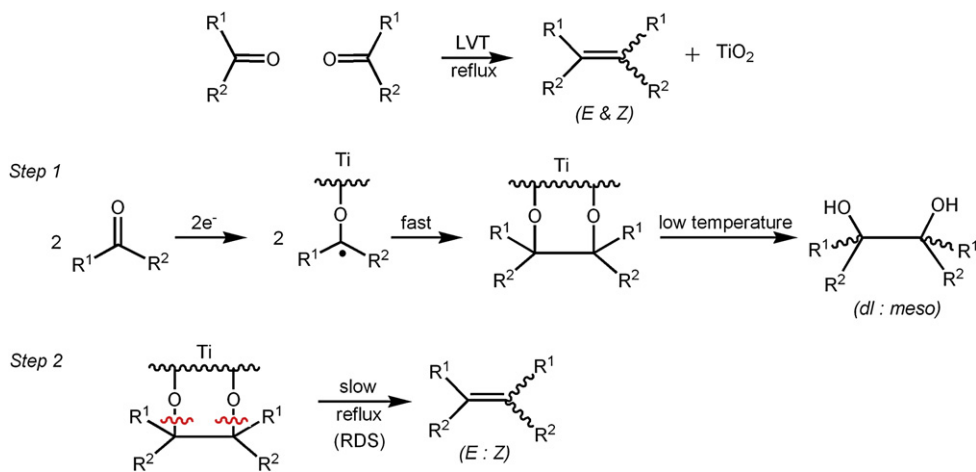
The LVT-induced reductive deoxygenation of carbonyls to olefins takes place in two successive steps¹ (Scheme 1): (i) reductive

dimerization of the starting ketone or aldehyde via electron transfer (ketyl anion radical) to form a carbon–carbon bond (titanium pinacولات) and (ii) subsequent deoxygenation of the 1,2-diolate intermediate involving cleavage of the carbon–oxygen bonds to give the alkene (rate determining step) along with the thermodynamically stable Ti-oxides (TiO_2). While the dimerization of carbonyls to generate the pinacولات (step 1) has been accomplished with a variety of reducing metals (Zr, Sn, Sm, Nb, Ce, In, V),⁸ including LVT,^{1–7} deoxygenation of pinacولات to olefins (step 2) is rather unique to LVT reagents. The extrusion of oxygen by titanium (oxophilic) from the pinacولات necessitates the use of solvent-reflux temperatures and prolonged reaction times affording the alkene. While many of the otherwise reducible functionalities survive the McMurry reaction at low temperatures (which predominantly generates pinacولات), the incompatibility of several functionalities under the refluxing reaction conditions limits its applications. These drawbacks apparently restrict the utility of LVT reagents in the case of oxygenated complex natural products with semicompatible functionalities, where the introduction of olefinic double bonds is achieved in two steps via initial pinacolization at lower temperatures followed by deoxygenation through indirect milder methods.¹ For the synthesis of olefins at lower temperatures, the ‘activation’ of LVT species therefore becomes imperative. Moreover, the intrinsic tendency of the reactive metals toward deactivation necessitates further depassivation or secondary activation.² Thus, the motivation to generate new LVT reagent(s) which not only possesses enhanced reactivity (due to activation) but is

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Scheme 1. Classical mechanism of C–C bond formation in LVT-mediated reductive deoxygenation of aldehyde/ketone.

also capable of direct one-step olefination at ambient/low temperatures would serve as ideal low-valent formulations in titanium-induced single electron transfer (SET) reactions.

Besides the native state of the metal, the stability, tendency for aggregation, and the reactivity of LVT reagents are highly dependent on the coordinating solvents/auxiliaries and the stability of the complexes formed in situ which in turn are influenced by the steric and electronic factors. Consequently, the addition or subtraction of electron(s) can dramatically alter the redox potential of the native titanium species, and therefore, the type of chemistry the generated active or passive metal center (Ti) might mediate. To this end, in continuation of our earlier work³ on the rational design of organometallic reagents in electron transfer processes, it has been shown by us³ and others⁴ that the reducing ability of LVT-based reagents can be rationally tuned by the simple addition of co-solvents, external ligands (π -acid species such as pyridine, triphenylphosphine, and fullerenes), and chemical redox agents (arenes, I_2 , salts).³ While the surrounding electronic environment is at the heart of LVT chemistry, the actual reactive metal species responsible for the chemical transformation and its genesis has been put to considerable debate.

Conventionally, LVT reagents have been prepared using Rieke's protocol involving reduction of titanium halides with an alkali metal (lithium, sodium, or potassium) in an ethereal or hydrocarbon solvent.² Based on ESR studies involving stoichiometric reaction of $TiCl_3$ with various reducing agents (Li, Mg, $LiAlH_4$) in THF (Rieke type activation process), Geise et al. proposed the formation of finely suspended Ti species in zero-valent state adsorbed on the precipitated inorganic salt byproducts ($LiCl$, $MgCl_2$).⁹ However, Bogdanovic et al. suggested that the actual scenario involving the generation of activated LVT species in McMurry olefination is far more complex and involves the stepwise formation of bimetallic inorganic Grignard reagents as the active species highlighting the crucial role of in situ released salts.^{1c,2b,10} For example, studies involving Tyrlik's reagent ($TiCl_3$ -Mg-THF) produced a highly soluble, covalently bonded paramagnetic Ti–Mg species (Ti–Mg– Cl_x bimetallic complex) coordinated to the solvent molecules. The reaction involved the initial formation of $[TiMgCl_2 \cdot xTHF]$ which further reacts with the excess Mg giving 1 mol of $Ti(MgCl_2)THF$ (I), the actual reducing species, along with 0.5 mol of free $MgCl_2$ (Fig. 1). Analogous ESCA studies by Bogdanovic and his co-workers on McMurry reagent ($TiCl_3$ - $LiAlH_4$ -THF) have revealed the formation of Ti(II) chlorohydride $[HTiCl(THF)_{\sim 0.5}]$ (II) as the active LVT species.^{2b,10}

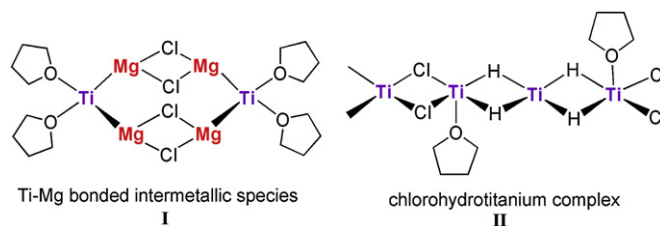


Figure 1. Intermetallic (inorganic Grignard) and metal hydride species generated from different LVT preparations.

These results strongly indicate that depending on the reducing agent used, a significant proportion of the free salt produced in situ during the generation of the active LVT species is consumed in the formation of the reactive intermetallic species which is chemically bound to the low-valent titanium nucleus (Ti–Mg/Ti–H/Ti–Li bonded bimetallic complex). Significantly, the active titanium species generated by each method may therefore differ not only in its reducing and Lewis acid properties but also in the surface bound ligands, morphology, aggregation and formal oxidation state (redox state). The low-valent Ti metal center thus emerges as a tunable functionality whose redox properties and reactivity could therefore be modulated and/or controlled by the exogenous addition of metal salts (salt tuning) and/or mixture of solvating ligands (solvent–ligand tuning). Addition of neutral salts as promoters has been known to enhance the Lewis acidity of active metal center and the resultant ionic strength of the medium, thereby influencing the rates of many organometallic electron transfer reactions (salt effect).¹¹ All told, since single electron transfer is an elementary reaction step in LVT-mediated reductive transformations, modulation of the LVT-mediated redox process by judicious incorporation of metal salts (as promoters) may not only dramatically augment the reactivity and selectivity of the C–C bond formation in McMurry olefination and other SET reactions, but may also provide an alternative route to 'activation' of LVT reagents under redox potential control. Despite the significance of in situ generated salts in LVT preparations, the direct influence of electropositive metal salts (mono-, bivalent) as promoters on the reactivity of LVT-based reagents has not received much attention, and is therefore, long overdue. In continuation of our preliminary work on salted LVT reagents,^{3b} the present investigation is a comprehensive study on the influence of exogenously added metal salts/solvents (redox

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