



Highly active salted low-valent titanium reagents for various SET induced reactions

Shyam Rele, Subrata Chattopadhyay and Sandip K. Nayak*

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India

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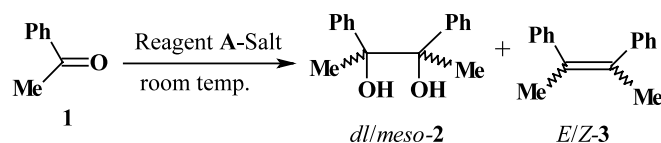
Abstract—External addition of inorganic salts (Group I and II metal halides) to the preformed low-valent titanium reagent **A** ($\text{TiCl}_3\text{-Li-THF}$) dramatically enhanced its activity. The new reagents were used to carry out various SET reactions including McMurry's olefination at a faster rate even at ambient temperature. © 2001 Published by Elsevier Science Ltd.

Low-valent titanium (LVT) reagent-mediated McMurry coupling is a key reaction in organic synthesis.^{1–3} However, olefin synthesis by this reaction requires higher temperatures^{1,2} especially with aliphatic substrates,⁴ which might be detrimental for compounds possessing thermolabile functionalities. This warrants activation of the LVT reagents, which we have earlier accomplished by changing the ligand environment or addition of chemical redox agents leading to some new LVT preparations.⁵ Considering the formation of intermetallic Ti–metal bonds between Ti and inorganic salts,⁶ we envisaged that external addition of an inorganic salt might be an alternative for LVT activation. This communication constitutes the first report on the activation of LVT reagents by addition of inorganic salts and their use in various single electron transfer (SET) reactions including the McMurry coupling.

The 'salted' LVT reagents used for the study were prepared by refluxing a mixture of the preformed LVT reagent **A** [$\text{TiCl}_3\text{-Li-THF}$] and various metal salts for 1 h. The new reagents, obtained as viscous and uniform slurries (unlike conventional LVT reagents), were used for various organic transformations as discussed below.

McMurry olefination: Reductive dimerization of acetophenone (**1**) to 2,3-diphenyl-2-butene (**3**) (Scheme 1) was chosen as the model reaction to optimize the influence of salted LVT reagent and the results are summarized in Table 1. The reagent **A** as such, afforded the pinacol **2** (89%) (Table 1, entry 1) at ambient temperature, while the stilbene **3** (87%) could be

obtained only after prolonged (16 h) refluxing (Table 1, entry 2). In contrast, reaction of **1** with reagent **A**/ MgCl_2 (2 equiv.) furnished the stilbene **3** (25%) along with the pinacol **2** (62%) even at ambient temperature in 16 h (Table 1, entry 3), clearly indicating the positive effect of MgCl_2 on the activity of the reagent **A**. As



Scheme 1.

Table 1. Effect of salts on the LVT reagent **A** ($\text{TiCl}_3\text{-Li-THF}$) in the reductive coupling of acetophenone (**1**)

Entry	Salt ^a	Product yields (%) ^b	
		Pinacol 2 (<i>dl:meso</i>)	Stilbene 3 (<i>E:Z</i>)
1	Nil	89 (75:25)	Trace
2	Nil ^c	–	87 (75:25)
3	MgCl_2	62 (70:30)	25 (65:35)
4	MgCl_2^{d}	64 (62:38)	22 (62:38)
5	LiI	75 (80:20)	Trace
6	CsCl^{e}	–	65 (70:30)
7	KCl^{e}	–	82 (85:15)
8	ZnCl_2	45 (74:26)	32 (32:68)

^a 2 equiv. of salt were used.

^b Isolated yields.

^c The reaction was carried out at reflux temp., in other cases the reaction temp. was 25°C.

^d 8 equiv. of salt were used.

^e The reaction was over in 2 h, in other cases the reaction period was 16 h.

* Corresponding author. E-mail: sknayak@magnum.barc.ernet.in

Table 2. Effect of KCl (2 equiv.) on reagent **A** in various SET reactions

Entry	Substrate	Time (h)	Products ^a (% yields)
1	Cyclohexanone (4a)	2	5a (70)
2	Cyclopentanone (4b)	2	5b (68)
3	PhCH=NPh (6a)	0.33	7a (65) + 8a (30)
4	2-OHC ₆ H ₄ CH=NPh (6b)	1	7b (70) + 8b (18)
5	Ph ₂ N-Allyl (9) ^b	18	Ph ₂ NH (10) (80)

^a Isolated yields.

^b The reaction was carried out at 60°C, in other cases the reaction temp. was 25°C.

indicated by the results in Table 1, the salts of more electropositive metals (CsCl and KCl) increased the activity of reagent **A** most, leading to the formation of **3** in appreciable yields within 2 h at ambient temperature (entries 6 and 7), while activation with an amphoteric salt like ZnCl₂ was moderate when both pinacol **2** and stilbene **3** were produced in moderate yields (entry 8). Two equiv. of salt were sufficient for optimum activation (cf. entries 3 and 4) which was insignificantly affected by the nature of the anionic part of the added salt (Table 1, entry 5). Hence, reagent **A**–KCl (2 equiv.) was primarily used for other SET reactions. Use of the salted reagent **A** did not change the stereoselectivity of olefination and *E*-**3** was the major product (Table 1, entries 2–4, 6 and 7) except with the ZnCl₂–reagent **A** combination, where *Z*-**3** was formed (Table 1, entry 8) predominantly. The ratio of *E*- and *Z*-stilbenes **3** was determined by ¹H NMR spectroscopy.^{5b,7}

The reagent **A**–KCl combination could also carry out coupling of the otherwise sluggish aliphatic substrates like **4a** and **4b** at ambient temperature to furnish the olefins **5a** and **5b** respectively in good yields (Table 2, entries 1 and 2) thereby, enhancing the utility of the salted reagent **A**.

Apparently, exchange of existing LiCl in the intermetallic Ti–LiCl complex of the reagent **A** by the more electropositive metal salts (KCl, CsCl) increases the electron density on Ti in Ti–KCl/CsCl leading to the higher activity of the LVT reagent. In addition, exogenous addition of

metal salts might possibly segregate the intermetallic cluster to monomeric ate complexes thereby increasing its solubility and leading to activation as was reported with Grignard reagents⁸ and chromium(II) species.⁹

Miscellaneous SET reactions: Like carbonyls, imines can also be coupled (imino-pinacol coupling) with LVT reagents¹⁰ to 1,2-diamines which are useful ligands in radiopharmaceuticals^{11a} as well as in asymmetric synthesis.^{11b,c} The effect of the salted reagent **A** on the imino-pinacol reaction was also noteworthy as coupling of the imine **6a** with KCl–reagent **A** was complete in just 20 min at ambient temperature affording the vicinal diamine **7a** (*dl:meso* = 80:20) in 65% yield along with the unimolecularly reduced product **8a** (30%) (Table 2, entry 3). A comparable yield (68%) of **7a** was obtained with reagent **A** alone albeit after a much longer time (2.5 h). Likewise, coupling of the imine **6b** in the presence of KCl–reagent **A** produced the vicinal diamine **7b** (70%) and the monoamine **8b** (18%) within 1 h (Table 2, entry 4).

Besides reductive coupling, LVT reagents are also equally efficient in the deprotection of protected alcohols and amines.¹² The KCl–reagent **A** combination also showed its potential for deallylation of *N*-allyl amines. Thus, deprotection of the tertiary amine **9** could be carried out easily with the salted reagent at reflux temperature producing diphenylamine (**10**) in 80% yield (Table 2, entry 5). In contrast reagent **A**, under similar reaction conditions, furnished the amine **10** in 68% yield only.

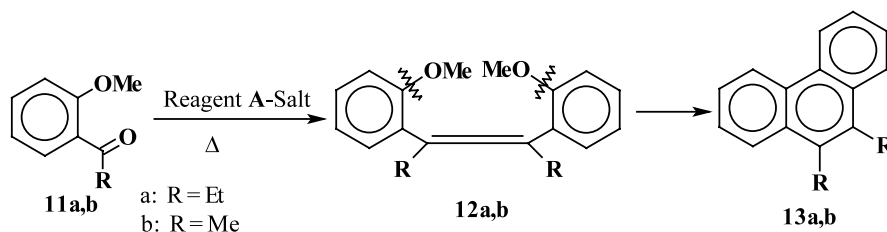
**Scheme 2.**

Table 3. Synthesis of phenanthrenes with salted LVT reagents

Entry	Reagent	Substrate	Product (% yields) ^a
1	Reagent B	11a	12a (87)
2	Reagent B–LiCl	11a	12a (65)+13a (17)
3	Reagent B–LiCl ^b	11a	12a (60)+13a (20)
4	Reagent A	11a	13a (36)
5	Reagent A–KCl	11a	13a (81)
6	Reagent A–CsCl	11a	13a (84)
7	Reagent A–CsCl	11b	13b (82)

^a Isolated yields.

^b The reaction was carried out with 8 equiv. salt, in other cases 2 equiv. salt were used.

Phenanthrenes synthesis: Previously, a one-pot synthesis of phenanthrenes from *ortho*-alkoxy aromatic aldehydes/ketones was developed in this laboratory.¹³ The synthesis involved multiple steps *in tandem* of which the dealkoxylation step was found to be unique for the reagent A. To see the influence of the salted LVT reagent on the above reaction, a model substrate, 2'-methoxypropiophenone (**11a**) was subjected to coupling with a salted Tyrlik's reagent [TiCl₃–Mg–THF (reagent B)¹⁴/LiCl (2 equiv.)], when the phenanthrene **13a** was obtained (Scheme 2) in 17% yield along with the stilbene **12a** (65%) (Table 3, entry 2). Further increase in the amount of LiCl (8 equiv.) improved the yield of **13a** marginally (Table 3, entry 3). Under similar conditions, the reagent B alone furnished the stilbene **12a** only (Table 3, entry 1) from which the salt-mediated activation of LVT reagents was evident.

As expected, the salted reagent A showed more pronounced effect in phenanthrene synthesis. Thus, while the ketone **11a** yielded **13a** in 36% yield (Table 3, entry 4) with reagent A alone, in combination with either KCl or CsCl, it furnished **13a** in vastly improved yields (81 and 84%, respectively) (Table 3, entries 5 and 6). Likewise, reaction of 2'-methoxyacetophenone (**11b**) with CsCl–reagent A furnished the phenanthrene **13b** in 82% yield (Table 3, entry 7).

In conclusion, a novel and simple protocol for activation of the LVT species by exogenous addition of inorganic salts is reported. Besides being economic, the method ensures easier product isolation as it does not involve introduction of any organic additive. The new

reagents carry out all the reactions attributed to LVT species more efficiently and at ambient temperature.

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