Tetrahedron 64 (2008) 7225–7233

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

Shyam M. Rele *,†, Sandip K. Nayak *, Subrata Chattopadhyay *

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

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.

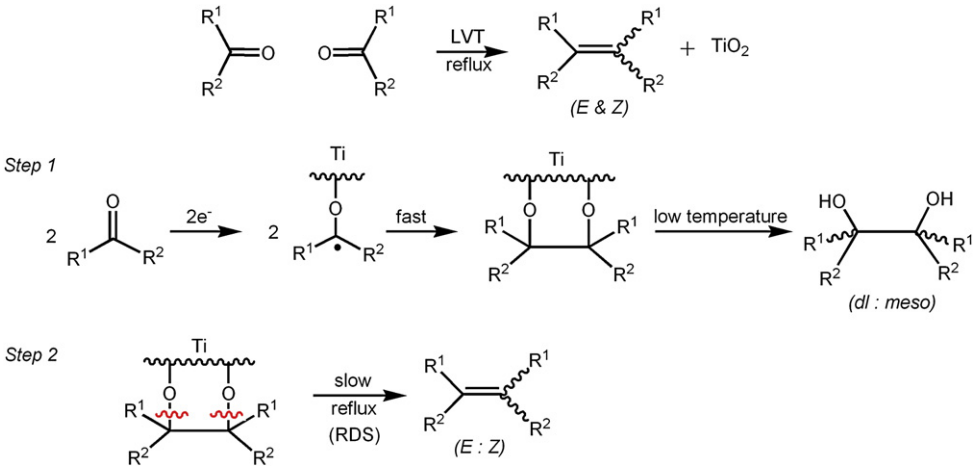
1. Introduction

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 (ΔH=−225.8 kcal/mol) and reducing power ($Ti \rightarrow Ti^{+2} + 2e^-$; 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 systems[6] to complex natural products including paclitaxel.[7]

The LVT-induced reductive deoxygenation of carbonyls to olefins takes place in two successive steps[1] (Scheme 1): (i) reductive dimerization of the starting ketone or aldehyde via electron transfer (ketyl anion radical) to form a carbon–carbon bond (titanium pinacolates) 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 pinacols (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 pinacols to olefins (step 2) is rather unique to LVT reagents. The extrusion of oxygen by titanium (oxophilic) from the pinacolates 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 pinacols), 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

* Corresponding authors. Tel.: +1 626 404 6144; fax: +1 626 305 9094 (S.M.R.).
E-mail addresses: shyamrele@yahoo.com, shyamrele@gmail.com (S.M. Rele), sknayak@magnum.barc.ernet.in (S.K. Nayak), schatt@apsara.barc.ernet.in (S. Chattopadhyay).
† Present address: 129 N. Hill Avenue, Ste 104, Pasadena, CA 91106, USA.

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.084



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 work[3] on the rational design of organometallic reagents in electron transfer processes, it has been shown by us[3] and others[4] 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 [$TiMgCl_2 \cdot x$THF] 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]

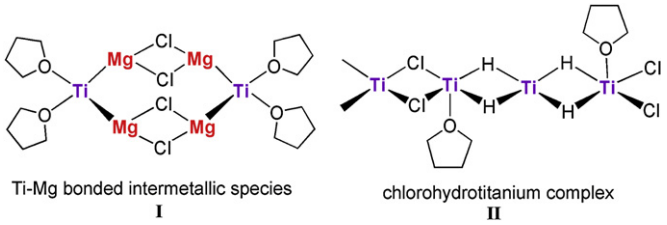


Figure 1. Intermetallic (inorganic Grignard) and metal hydride species generated from different LVT preparations.

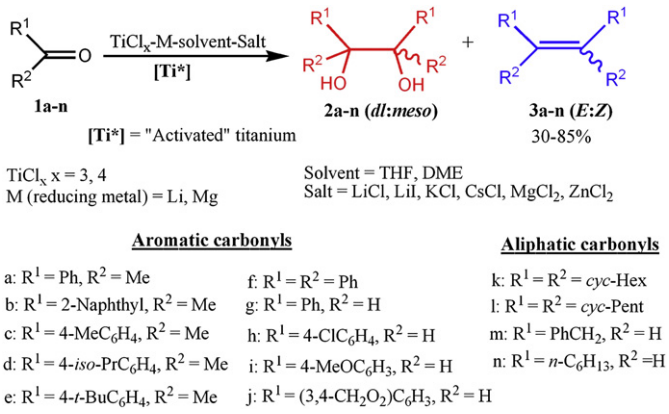
These results strongly indicate that depending on the reducing agent used, a significant proportion of the free salt produced in situ during the generation of the active LVT species is consumed in the formation of the reactive intermetallic species which is chemically bound to the low-valent titanium 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

agents) as ligand-tuning control elements in modulating and enhancing the reactivity of LVT reagents. Significantly, the chemically engineered 'salt-activated' LVT reagent(s) performs the diastereoselective C–C bond formation in McMurry's carbonyl coupling and other SET-induced reactions not only efficiently and at enhanced reaction rates, but also at ambient temperatures and in improved yields, thereby presenting an emerging paradigm critical to actualizing the preparative potential in LVT chemistry in SET reactions.

2. Results and discussion

2.1. 'Salt-activated'[3b] LVT reagents: influence of metal salts on the preparation and reactivity of activated LVT reagents and the stereochemical outcome in McMurry olefination

In the present studies, $TiCl_3$–Li–THF (McMurry reagent) and $TiCl_3$–Mg–THF (Tyrlik's reagent) were selected as the LVT-source on the grounds of their unique reactivity toward carbonyl coupling reactions. A set of 'activated' LVT reagents were generated in situ by external addition of alkali metal/alkaline earth metal salts/amphoteric salts to the preformed low-valent titanium species obtained from the above systems and the potential of these salted LVT reagents in McMurry olefination was then investigated. Reductive dimerization of acetophenone (**1a**) to 2,3-diphenyl-2-butene (**3a**) (Scheme 2) was chosen as the model reaction to optimize the influence of salted LVT reagent and the results are summarized in Table 1.



Scheme 2. McMurry olefination via salted LVT reagents.

Conventional McMurry olefination using $TiCl_3$–Li–THF (reagent **A**)[12] and $TiCl_3$–Mg–THF (reagent **B**)[9,13] afforded only the pinacol **2a** (87–89% yield) at ambient temperatures, while the stilbene **3a** was isolated as the predominant product (≥85% yield) only after prolonged (16 h) refluxing (Table 1, entries 1, 2, 10, 11).[12] In contrast, reaction of **1a** with reagent **A**–$MgCl_2$ (2 equiv) furnished the stilbene **3a** (25%) along with the pinacol **2a** (62%) even at ambient temperature in 16 h (Table 1, entry 3), clearly indicating the positive influence of external salt addition ($MgCl_2$) on the activity of the reagent **A**. Addition of excess amount of $MgCl_2$ (8 equiv) did not show any significant change (Table 1, entry 4) on the diastereomeric outcome of the products (**2a**/**3a**) formed. Based on these preliminary observations, an extensive study on the conversion of **1a** to **3a** was carried out using different electropositive mono-/divalent metal salts with varying size/charge such as CsCl, KCl, LiI and $ZnCl_2$. Surprisingly, as indicated by the results in Table 1, the more electropositive metal salts KCl and CsCl enhanced the activity of reagent **A** significantly. For example, addition of CsCl to the LVT preparation (reagent **A**) led to the formation of **3a** in appreciable yield (65%) (Table 1, entry 6), while addition of KCl under identical conditions

Table 1
Influence of salts on the reactivity of LVT reagents and its outcome on the reductive coupling of acetophenone (**1a**) to stilbene (**3a**)

Entry	Reagent[a]	Salt[b]	Temp (°C)/ time (h)	Product yields[c,d] (%)	
				Pinacol **2a** (*dl*:*meso*)	Stilbene **3a** (*E*:*Z*)[3a,c]
1	**A**	Nil	25/16.0	89 (75:25)	Trace
2	**A**	Nil	Reflux/16.0	—	87 (75:25)
3	**A**	$MgCl_2$	25/16.0	62 (70:30)	25 (65:35)
4	**A**	$MgCl_2$[e]	25/16.0	64 (62:38)	22 (62:38)
5	**A**	LiI	25/16.0	75 (80:20)	Trace
6	**A**	CsCl	25/2.0	—	65 (75:30)
7	**A**	KCl	25/2.0	—	82 (85:15)
8	**C**	KCl	25/2.0	No reaction	
9	**A**	$ZnCl_2$	25/16.0	45 (74:26)	32 (32:68)
10	**B**	Nil	25/16.0	85	—
11	**B**	Nil	Reflux/16.0	Trace	85 (76:24)
12	**B**	LiCl	25/16.0	25	52 (44:56)
13	**B**	CsCl	25/16.0	55	36 (51:49)
14	**B**	KCl	25/16.0	18	65 (40:60)
15	**B**	$ZnCl_2$	25/16.0	57	30 (20:80)
16	**D**	KCl	25/2.0	—	86 (65:35)

[a] Reagent **A**: $TiCl_3$–Li–THF; reagent **B**: $TiCl_3$–Mg–THF (Tyrlik's reagent); reagent **C**: $TiCl_3$–Li–DME; reagent **D**: $TiCl_4$–Li–THF.
[b] Amount of salt used: 2 equiv.
[c] All yields refer to isolated products (purity >95%, analyzed by ^{1}H NMR).
[d] Stereochemical assignments (calculation of *E*:*Z* and *dl*:*meso* ratio) were made by ^{1}H NMR and by comparison of spectroscopic data to that reported in the literature.[3a,c,14] For **3a**: ^{1}H NMR δ (ppm) 1.86 (*E*) and 2.16 (*Z*) (2s, 6H), 7.0–7.3 (m, 10H).
[e] Amount of salt used: 8 equiv.

at ambient temperature resulted in a facile dimerization affording **3a** within 2 h in very high yield (82%) (Table 1, entry 7) with no trace of pinacol. Changing the titanium salt from trichloride to tetrachloride ($TiCl_4$) in the salt-activated LVT preparation ($TiCl_4$–Li–THF–KCl, reagent **D**) had marginal influence on the pinacol to stilbene product balance with stilbene **3a** obtained as the sole product (Table 1, entry 16). Furthermore, the influence of divalent amphoteric salt like $ZnCl_2$ on the activation of LVT preparation was observed to be less efficient with both pinacol **2a** and stilbene **3a** being produced in moderate yields (Table 1, entry 9). While 2 equiv of salt was sufficient for optimum LVT activation (cf. entries 3 and 4), the LVT reagent was insignificantly affected by the nature of the anionic part (LiI) of the added salt (Table 1, entry 5). However, the effect of the reaction medium was more dramatic on the product outcome. For example, DME-solvated salted LVT ($TiCl_3$–Li–DME–KCl) rendered the reagent ineffective by completely suppressing the C–C bond formation (pinacolization) even at room temperature resulting in quantitative recovery of the unreacted substrate **1a** (Table 1, entry 8). Analogous reactions studying the influence of salts on reagent **B** ($TiCl_3$–Mg system) again indicated that the best results were observed when KCl was used as the metal salt (Table 1, entry 14), albeit less efficiently in comparison to reagent **A**–KCl system. Thus, reaction of **1a** with reagent **B**–KCl while exhibiting pronounced reactivity furnished **3a** (65%) at ambient temperature (16 h) (Table 1, entry 14); the same reaction when carried out without the addition of salt (reagent **B**) afforded solely the pinacol **2a** (85%) over the same period of time (Table 1, entry 10).[9,13] Based on all the above observations, reagent **A**–KCl (2 equiv) was primarily used as the reagent of choice for McMurry olefination and other SET reactions. Moreover, the above results clearly demonstrate the dramatic influence of exogenously added metal salts on the preformed LVT reagents in enhancing their reactivity in McMurry reaction (C–C bond formation).

2.1.1. *Diastereoselectivity and steric course of stilbene formation*

The stereoselectivity during McMurry olefination is a function of the number of interdependent variables, such as solvent, the nature

of the active reagent (valences etc.), external auxiliaries, temperature, and steric bulk of the groups.[1–3] The study of the stereochemical outcome (*E*/*Z*) of the olefination with the above salted LVT reagents (Table 1) was revealing. In general, use of the salted reagent **A** and reagent **D** (alkali metal Li-based reductant) led to preferential formation of *E*-**3a** isomer as the major product (Table 1, entries 3, 4, 6, 7, and 16). Surprisingly, a complete reversal in stereoselectivity was observed on addition of a divalent ampholyte $ZnCl_2$ (reagent **A**–$ZnCl_2$ combination), affording *Z*-**3a** as the predominant product (Table 1, entry 9). Moreover, the preponderance of *E*-**3a** olefination was augmented in case of reagent **A**–KCl (*E*:*Z* 85:15) by carrying out the reaction at ambient temperature (Table 1, entry 7) in comparison to the conversion of **1a** to **3a** under prolonged reflux (16 h) when reagent **A** was solely used (*E*:*Z* 75:25) (Table 1, entry 2). Subtle variation in the preparation of LVT reagent ($TiCl_3$ replaced $TiCl_4$) although resulted in comparable stilbene formation, ~24% loss in *E*:*Z* stereoselectivity (*E*:*Z* 85:15 to *E*:*Z* 65:35) was observed in the case of KCl-activated $TiCl_4$ reagent (Table 1, see entries 7 and 16). In contrast, when the salt-modified LVT reagents derived from Tyrlik's reagent ($TiCl_3$–Mg–THF, alkali earth metal-based reductant) were employed, the *Z*-**3a** isomer was preferentially obtained over the *E*-**3a** isomer (Table 1, entries 12–15). The influence of salts on the diastereoselectivity bias of **3a** when reacted with reagent **A** (Li as reductant) and reagent **B** (Mg as reductant) is consistent with our earlier finding involving generation of reactive LVT species obtained by reducing $TiCl_3$ with in situ formed chemically redox metal–arene systems acting as the soluble organic reductants.[3a] Specifically, while the LVT reagents derived from $TiCl_3$–Mg–arenes–THF (bivalent akaline earth metal reductant) showed similar bias toward the formation of the *Z*-**3a** stilbene, a complete reversal in stereoselectivity (*E*-**3a** diastereomer) was observed by switching over to monovalent alkali metal–arene-based reductants ($TiCl_3$–Li–arenes–THF). Our results summarized in Table 1 demonstrate that the stereochemical outcome of the products is amenable to tuning by judicious design of reagents and reaction conditions (salts, ligands/auxiliaries). The ratio of *E*- and *Z*-**3a** stilbene was determined by ^{1}H NMR spectroscopy,[3a,c,14] where the NMR spectrum showed two characteristic peaks at 1.86 and 2.16 ppm corresponding to the *E*- and *Z*-stilbene stereoisomers,[3a,c] respectively (m/z=M^+ 208.09).

2.1.2. Generality and selectivity

To explore the generality and scope of the reagent **A**–KCl, experiments were carried out using a variety of substituted aryl carbonyls, such as aryl alkyl ketones (Table 2, entries 1–4), aryl aldehydes (Table 2, entries 6–9), and a diaryl ketone (Table 2, entry 5) (Scheme 2). In all the cases, the respective olefins were obtained smoothly at room temperature and in good yields (65–85%) as the exclusive products (see Table 2). Significantly, functional groups such as halogen, aryl-OMe, and methylenedioxy (Table 2, entries 7–9), which are otherwise cleaved under refluxing conditions,[3f,15] remained unaffected during olefination at ambient (low) temperatures, ensuring excellent chemoselectivity in the McMurry olefination. Moreover, the activated reagent **A**–KCl exhibited diastereoselective bias toward the predominant formation of the respective *E*-stilbenes as the major product based on ^{1}H NMR spectroscopy.[3a,c,14]

One of the striking limitations of the McMurry reaction has been its inability to effectively couple aliphatic carbonyls to olefins.[16] The relatively strong alkyl–oxygen bonds in the intermediate pinacolates[16] require prolonged refluxing for the required deoxygenation to occur. Even then, the yields of the product olefins are often unsatisfactory. However, the low propensity of alicyclic ketones (**1k**, **1l**) and aliphatic aldehydes (**1m**, **1n**) (Table 3, entries 1–4) to couple was greatly augmented using reagent **A**–KCl combination. As such, reductive dimerization of alicyclic ketones (**1k**, **1l**) and aldehydes (**1m**, **1n**) to their respective olefins (**3k**–**n**) was accomplished at ambient temperature in yields almost comparable to olefins obtained from aromatic substrates (see Scheme 2, Table 3).

2.2. One-pot synthesis of phenanthrenes

Previously, a short one-step synthesis of phenanthrenes (**6a**) from *o*-alkoxy aromatic aldehydes/ketones (**4a**) was developed in our laboratory, albeit in poor yield and after prolonged heating (36%, 16 h reflux).[3f] Mechanistically, the synthesis involves multiple steps in tandem, viz., (i) preferential formation of the *Z*-stilbene (an apriori condition for phenanthrene formation) followed by (ii) *ortho* dealkoxylation (determining factor) of the aryl alkyl ether functionality in *Z*-stilbene to generate the aryl radical and its subsequent C–C coupling leading to ring cyclization (Scheme 3). In the present work, the applicability and efficiency of the various salt-activated LVT preparations in the synthesis of phenanthrenes were explored.

2′-Methoxypropiophenone (**4a**) was chosen as the model substrate to investigate the influence of salted LVT reagents. When **4a** was subjected to coupling with Tyrlik's reagent $TiCl_3$–Mg–THF (reagent **B**), stilbene **5a** [2,3-bis-(2′-methoxyphenyl)-hex-3-ene] was isolated as the sole product obtained under refluxing conditions (Table 4, entry 1).[3f] However, coupling of **4a** using a salted $TiCl_3$–Mg–THF (reagent **B**–LiCl), afforded 9,10-diethyl phenanthrene **6a** in 17–20% yield along with the stilbene **5a** (65%) (Table 4, entries 3 and 4). Interestingly, addition of sub-stoichiometric amount of Li metal as a co-reductant with Mg (Table 4, entry 5) in reagent **B** furnished **6a** in 30% yield ($TiCl_3$/Li=1:1.65, $TiCl_3$/Mg=1:0.85). This implies that the McMurry salt component in the form of the more electropositive Li either as a co-reductant or in its salt form (LiCl) drives the dealkoxylation–ring cyclization process post *E*-/*Z*-stilbene formation generating phenanthrene **6a**. The proposed hypothesis was corroborated when substituting the reducing metal Mg in reagent **B** by the more electropositive reductant Li (reagent **A**) afforded the phenanthrene **6a** as the sole product in 36% yield (Table 4, entry 2).[3f] Consequently, the salted reagent **A**, in comparison to Mg-based LVT reagents, showed more pronounced effect on the phenanthrene synthesis. Thus, while the ketone **4a**

Table 2
Reagent **A**–KCl (2 equiv) induced facile McMurry olefination of aromatic carbonyls

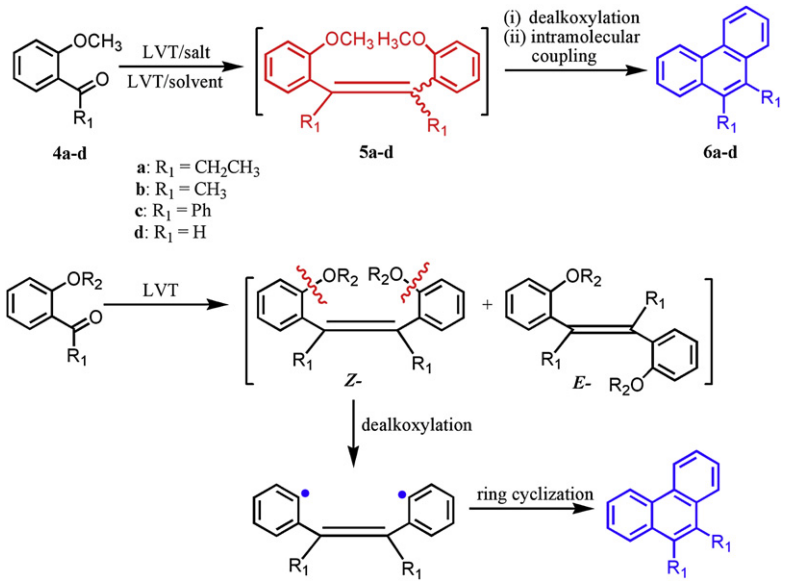
Entry	Substrate	Temp (°C)/time (h)	Product[3a,c,14]	Product yields (%) (*E*:*Z*)[a,b]
1	**1b**	25/6.0	**3b**	68 (72:28)
2	**1c**	25/3.0	**3c**	82 (65:35)
3	**1d**	25/10.0	**3d**	75 (80:20)
4	**1e**	25/10.0	**3e**	78 (75:25)
5	**1f**	25/5.0	**3f**	75
6	**1g**	25/2.0	**3g**	85 (90:10)
7	**1h**	25/2.5	**3h**	65 (92:8)
8	**1i**	25/14.0	**3i**	64 (85:15)
9	**1j**	25/12.0	**3j**	65 (100 *E*)

[a] Isolated yields of pure products, fully characterized by IR and ^{1}H NMR spectra.
[b] Diastereoisomeric ratios of olefins were determined by 200 MHz NMR and comparing with literature data.[3a,c]

Table 3
Low temperature reductive duplication of aliphatic carbonyls with reagent **A**–KCl

Entry	Substrate	Temp (°C)/time (h)	Product[3a,c]	Yield[a] (%)
1	**1k**	25/2.0	**3k**	70
2	**1l**	25/2.0	**3l**	68
3	**1m**	25/6.0	**3m**	76
4	**1n**	25/18.0	**3n**	52

[a] Isolated yields of pure products, fully characterized by IR and ^{1}H NMR (200 MHz) spectra.[3a,c]



Scheme 3. LVT-mediated one-pot synthesis of phenanthrenes.

Table 4
Reductive deoxygenation–reductive dealkoxylation–cyclization of *o*-alkoxy aromatic aldehyde–ketone by salt/solvating ligand-activated low-valent titanium

Entry	Reagent	Salt/metal/solvent	Product (yield %)[a]	
			E:*Z*[b]	Phenanthrene[3f]
1	**B**	Nil	**5a**, 85	—
2	**A**	Nil	—	**6a**, 36
3	**B**	LiCl	**5a**, 65 (80:20)	**6a**, 17
4	**B**	LiCl[c]	**5a**, 60 (68:22)	**6a**, 20
5	**B**	Li[d]	**5a**, 65 (55:45)	**6a**, 35
6	**A**	KCl	—	**6a**, 81
7	**A**	CsCl	—	**6a**, 84
8	**C**	Nil	**5a**, 75	
9	**C**	THF[e]		**6a**, 75
10	**A**	I_2	**5a**, 35 (60:40)	**6a**, 25
11	**A**	Naphthalene	**5a**, 33 (58:42)	**6a**, 30
12	**A**	CsCl	—	**6b**, 82
13	**A**	KCl	—	**6c**, 75
14	**A**	KCl	—	**6d**, 73

[a] All yields refer to isolated products purified by preparative thin layer or column chromatography (purity >95%, analyzed by ^{1}H NMR).
[b] Stereochemical assignments (*E*:*Z*) were made by ^{1}H NMR and by comparison of spectroscopic data to that reported in the literature.[3f] For **5a**[3f] ^{1}H NMR δ (ppm) (200 MHz, $CDCl_3$) 1.76 (t, 6H, CH_3), 2.36 (q, 4H, CH_2), 3.66 and 3.73 (s, 6H, OCH_3), 6.46–8.1 (m, 8H). For **6a**[3f] ^{1}H NMR δ ppm (200 MHz, $CDCl_3$) 1.32 (t, 6H, CH_3), 3.21 (q, 4H, CH_2), 7.36–8.6 (m, 8H).
[c] Amount of salt used: 8 equiv.
[d] Sub-stoichiometric amounts of Li and Mg were used as co-reductant ($TiCl_3$/Li=1:1.65, $TiCl_3$/Mg=1:0.85).
[e] 1:1 v/v ratio of anhydrous THF and DME.

yielded **6a** in 36% yield (Table 4, entry 2) with reagent **A** alone,[3f] in combination with either KCl or CsCl, a 2.5–3.0-fold jump in reactivity of the LVT reagent was observed furnishing **6a** in vastly improved yields of 81 and 84%, respectively (Table 4, entries 6 and 7) with no trace of **5a** or dealkoxylated alkene. Characterization of **6a** by proton NMR showed the clear disappearance of the methoxy signals (3.66 and 3.73 ppm for *E*-**5a**:*Z*-**5a**) with distinct resonance signals for CH_3 (1.32 ppm, triplet) and CH_2 (3.21 ppm, quartet) along with Ar peaks corresponding to 9,10-diethyl phenanthrene skeleton (*m*/*z* M^+ 234.12).

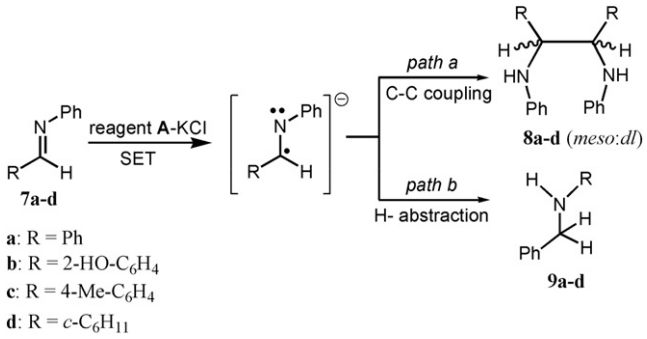
From the above results, it is evident that metal salts exert not only a dramatic influence on modulating the coordination sphere and the reactivity of the LVT reagents but also on the stereoselectivity and final product outcome. Notably, the ability of reagent **A**–KCl to cleave *o*-methoxy group in the resultant stilbene under prolonged refluxing conditions to generate phenanthrenes **6a** is in contrast to the reductive coupling of *p*-methoxy acetophenone using the same reagent (see Table 2, entry 8) where the methoxy group was retained under milder ambient conditions. Similarly, the reduction potential of several other LVT formulations (data not shown) was also screened for different LVT preparations such as $TiCl_3$–ZnCu–THF, $TiCl_3$–Zn–Li–THF which essentially produced stilbene **5a** as the major product. This was expected considering the lower reduction potential of Zn (E^{0+}=−0.71 V) in comparison to that of Li (E^{0+}=−3.047 V) and Mg (E^{0+}=−2.37 V).

In order to examine the influence of solvating medium (ligand exchange effect) in modulating the reactivity of the LVT preparations, an unusual solvent/ligand effect was observed. Substituting the solvating ligand THF in reagent **A** with slightly stronger electron-pair donor coordinating solvent DME (reagent **C**) proceeded only up to the stilbene stage without any dealkoxylation under prolonged heating (Table 4, entry 8).[3f] Surprisingly, the same reaction when carried out using equimolar amounts of THF as co-solvent with DME (1:1, v/v) ($[Ti^*]\cdot(DME)_{x-y}(THF)_y$) furnished the phenanthrene **6a** as the sole product in a significantly high yield of 75% (Table 4, entry 9). While the influence of coordinated ligand exchange effect on the reactivity of the resultant LVT species and the formation of **6a** is inexplicable at this juncture, an observation reported by Matsubara et al. suggests that addition of THF as a co-solvent to an inert $(TiCl_3)_n$–$(amine)_m$ cluster afforded monomeric $[TiCl_3(amine)_{1-2}(THF)_{1-2}]$ particles augmenting its reactivity in enantioselective pinacol coupling reactions from 40% to 58%.[17] Similar reactions using various 1:1 combinations of ethereal and aprotic solvents like THF/dioxan, THF/CH_3CN either resulted in quantitative recovery of substrate (complete arrest) or afforded the pinacol as was observed in case of THF/CH_2Cl_2 (unpublished results). The efficacy of the salted reagents vis-à-vis those of I_2-activated LVT and naphthalene-activated LVT reagents developed earlier from our laboratory was also explored.[3a,c] As compared to the present salted LVT formulation (reagent **A**–KCl), the reactivity of these two LVT preparations (reagent **A**–I_2, reagent **A**–naphthalene) in the synthesis of **6a** was less pronounced (25% and 30%) which also afforded the stilbene **5a** in 33% and 38% yield, respectively (Table 4, entries 10 and 11). Application of this methodology to

other *o*-alkoxy aromatic ketones and aldehydes (**4b**–**d**) as substrates expectedly furnished the corresponding phenanthrenes **6b**–**d** (Table 4, entries 12–14), thereby demonstrating the generality of the reaction. All the above observations clearly demonstrate the chemoselective nature of salted/solvated LVT reagents where small differences in the steric environment (electron density) around the native titanium can tip the balance in favor of less shielded reaction site and an energetically favorable product leading to enhanced selectivities under redox potential control.

2.3. Imino-pinacol coupling

Vicinal diamines find extensive applications in radiopharmaceuticals and as complexing agents and chiral auxiliaries.[18] In view of their frequent occurrence in natural products and medicinal compounds, we have earlier developed an LVT-mediated synthesis of them via an imino-pinacol coupling reaction.[19] In principle, the intermediate can undergo dimerization to diamines **8a** by bimolecular process (*path a*) or can be quenched by hydrogen from the medium to give unimolecularly reduced amines **9a** (*path b*). In this study, the utility of the KCl-activated reagent **A** for the coupling of imino substrates was also explored (Scheme 4).



Scheme 4. Reagent **A**–KCl-mediated imino-pinacol coupling.

The effect of the reagent **A**–KCl[3b] on the imino-pinacol reaction was noteworthy as coupling of the imine **7a** with the salted reagent was complete in just 20 min at ambient temperature affording the vicinal diamine **8a** (*dl*:*meso*=80:20) in 65% yield. However, competitive unimolecular reduction also produced *N*-benzyl aniline (**9a**) in an appreciable amount (30%) (Table 5, entry 3). A comparable yield (~62–68%) of **8a** was obtained with reagent **A** or reagent **B** alone albeit after a much longer reaction time (~2.5–3.5 h) (Table 5, entries 1 and 2).[19] In comparison, the same reaction when carried out using naphthalene-activated LVT reagent developed in our laboratory afforded the imino-pinacol coupling product **8a**, albeit less efficiently than the salt-activated LVT reagent (Table 5, entry 4).[3a] The ratio of *dl*- and *meso*-**8a** isomers was calculated on the basis of ^{1}H NMR which clearly indicated the presence of singlet resonance signals at 4.72 and 5.12 ppm corresponding to the methine (–CH) protons in addition to the aromatic peaks at 6.7–7.3 ppm (20H). Likewise, coupling of the imines **7b**, **7c** and **7d** in the presence of reagent **A**–KCl proceeded smoothly producing the vicinal diamines **8b**, **8c** and **8d**, respectively, in appreciable yields along with their respective monoamines as byproducts (Table 5, entries 5, 6, and 7). Thus, while the salted reagent **A** accelerated the imino-pinacol coupling to vicinal diamines, the high reactivity of the LVT reagent also resulted in competitive unimolecular reductions.

Table 5
Reagent **A**–KCl-mediated dimerization of aldimines at 25 °C to generate vicinal diamines

Entry	Reagent	Time[a] (h)	Product(s)[19] (% yields, *dl*:*meso*)[b]
1	$TiCl_3$–Mg–THF (**B**)	3.5	**8a** (62)
2	$TiCl_3$–Li–THF (**A**)	2.5	**8a** (68, 75:25)
3	**A**–KCl	0.33	**8a** (65%, 80:20), **9a** (30%)
4	**A**–naphthalene (0.25 equiv)	0.5	**8a** (45%), **9a** (30%)
5	**A**–KCl	1.0	**8b** (70%), **9b** (18%)
6	**A**–KCl	1.5	**8c** (68%, 78:22), **9c** (20%)
7	**A**–KCl	2.0	**8d** (72%), **9d** (15%)

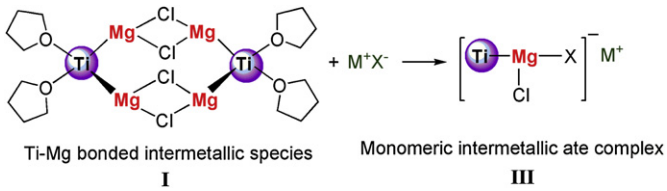
[a] All the reactions were carried out at ambient temperature (25 °C).
[b] All yields refer to isolated products (preparative thin layer or column chromatography), analyzed by ^{1}H NMR, IR, and MS. Stereochemical assignments (*dl*:*meso*) were made by ^{1}H NMR and by comparison of spectroscopic data to that reported in the literature.[19] For **8a**[19]: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 4.12 (br s, D_2O exchangeable), 4.72 (s, 1H, *dl*), 5.12 (s, 1H, *meso*), 6.64–7.31 (m, 20H).

2.4. Mechanistic aspects

A mechanistic hypothesis for the high reactivity exhibited by the salted LVT formulations described herein is mainly based on the rational assessment and interpretation of the results obtained by judicious incorporation of various salts as auxiliaries into the LVT reagent prepared from $TiCl_3$/1.5 Mg/THF (Tyrlik's reagent) and $TiCl_3$/3.3 Li/THF (McMurry's reagent), during a series of C–C bond forming SET-induced reactions. Due to the labile nature of Ti species, McMurry reagents may exist in structurally different forms and subtle changes in the reagent preparation of LVT can have a significant impact on its reactivity, selectivity, and performance. The ambiguity which surrounds the mechanistic interpretation and molecular level characterization of the active Ti species, including its oxidation state, is mainly due to the oxophilic and in situ generated multiphase and heterogeneous nature of these reagents, and therefore, still under debate. Conventionally, heterogeneous suspended colloidal slurries of activated Ti are obtained by refluxing $TiCl_3$/$TiCl_4$ with reductants (Li/Mg/$LiALH_4$/Zn) in an ethereal solvent (THF, DME, dioxan).[1,2,9] Studies by Bogdanovic et al. on some of these systems suggests the formation of bimetallic Ti–metal bond surrounded by solvent ligands as the active species (**I**).[2,10] Addition of metal salt to this preformed intermetallic LVT suspension resulted in a slight effervescence indicating the exothermic nature of the reaction and the possible ligand displacement from the coordination site of Ti. It is important to note that on reflux (1 h), the resultant salt-activated LVT system afforded black, uniform, and viscous slurries (homogeneous but not transparent), unlike traditional LVT reagents. While the nature and morphology of the salted LVT active species present in the intermetallic cocktail are unknown, the enhanced reactivity of the salted LVT reagent prepared could be rationalized on the basis of a soluble/homogeneous model due to the possible electronic modification and monomerization of the LVT species.

Owing to the existence of a definite Ti–Mg/Ti–Li bond (as seen in **I**), Ti is likely to assume higher electron density (compared to metallic Ti) when one considers the more electropositive character of Mg/Li. Exchanging the existing bound $MgCl_2$/LiCl salt component in the bimetallic Ti–Mg/Ti–Li species by the more electropositive metal salts with larger ionic size (KCl, CsCl) further augments the electron density on the active titanium center in Ti–KCl/CsCl reagents while exhibiting varying reducing activities. Consequently, by virtue of their larger ionic size, we anticipate that K^+/Cs^+ ions in comparison to Li^+/Mg^{+2} are likely to inhibit the uniform dimeric intermetallic cluster formation in LVT preparations (as seen in **I**) affording the monomeric LVT species (like **III**) with greater reactivity and selectivity. Presumably, the formation of highly reactive, viscous, and more homogeneously soluble LVT slurries observed could therefore be a direct manifestation of the monomerization and electronic modification of the LVT center caused

due to the exogenous addition of salts which possibly segregates/breaks the bimetallic LVT clusters formed (Scheme 5) to generate a highly reactive electron rich 'monomeric ate' complexes (**III**). The following explanation is further reinforced by analogous 'salt effect' on activation and solubility of Grignard reagents[20,21] and chromium(II) species.[22] Furthermore, a recent example involving the reaction of Fe(II) salt ($FeCl_2$) in THF with inorganic Grignard species **I** derived from $TiCl_3$–Mg–THF system resulting in the in situ formation of a highly active intermetallic phase of Ti–Fe validates our proposed theory.[1c] While the reactivity and stability of transition metal complexes are mutually exclusive, these aspects vary considerably in various low-valent metal–ligand/auxiliary systems depending on the ability of the metal center to accept (activation) or donate (passive) electrons.[3a–d,4] In principle, the apparent lack of vacant d orbitals in alkali/alkaline earth metal ions restricts the synergistic ability of electron rich low-valent titanium (more reactive) to back-donate the excess electrons, as was observed in case of *N*-heterocycles such as pyridine (Chatt–Dewar–Duncunson model),[23] wherein the pyridine-deactivated LVT complex completely suppressed the deoxygenation of the pinacolate intermediate.[3d,g] Simply put, incorporation of electropositive metal salts while enhancing the electron density/Lewis acid character of the native Ti center also alters its redox potential thereby augmenting the reactivity and accelerating the reaction rates of LVT-mediated stereoselective C–C bond formation in electron transfer processes.



Scheme 5. Monomerization of clustered bimetallic LVT species (inorganic Grignard) on external addition of metal salts.

This clearly suggests that important structural differences likely exist between the mechanism of action of salt-activated uniformly homogeneous LVT complexes and conventional heterogeneous LVT suspensions. The smooth accelerated stereoselective dimerization of carbonyls/imines under facile conditions to the respective olefins/vicinal diamines (**3a**–**n**/**8a**–**d**) even at ambient temperatures or formation of phenanthrenes (**6a**–**d**) in high yield could only possibly be explained by considering activation of the LVT species through monomerization and ligation with the metal salts as proposed above. This argument is also substantiated by the fact that the conventional McMurry reagents (reagents **A** and **B**) produce only the 1,2-diols at room temperature. Moreover, the diastereoselectivity bias toward a particular product (*E*/*Z* or *dl*/*meso*) in titanium-mediated SET reactions is greatly influenced by modification of steric and electronic properties of ancillary ligands/auxiliaries. Specifically, while reagent **A** predominantly produced *E*-stilbene (electropositive alkali metal reductant, Li), a complete reversal in diastereoselectivity (*Z*-stilbene as major product) was observed when reagent **B** (bivalent alkaline earth metal reductant, Mg) was employed (Tables 1 and 2). This pronounced diastereoselectivity bias observed in case of reductive deoxygenation of aromatic ketones/aldehydes could be a direct result of combined ligand exchange effect of auxiliary (salt), reductant, and solvent coordinated to the metal center. Additionally, the high phenanthrene yield obtained from these salted reagents is directly related to the stereochemical outcome of the most favored (sterically and energetically) intermediate *Z*-stilbene (over *E*-stilbene) thereby promoting the process of demethoxylation and subsequent ring cyclization. To this end, metal salts as promoters perform the dual role of not only modulating the activity of the LVT reagents but also effecting the electron transfer interactions between substrate and the active LVT species thereby governing the product diastereoisomeric ratio under redox potential control.

3. Conclusion

Discovering new reagents for old reactions is crucial to the development of sustainable chemical processes as well as for broadening the spectrum of synthetic methodologies. In situ regulation of the LVT-mediated electron transfer process allows selective generation of radicals which have a significant influence on the reactivity/passivity of these reagents facilitating stereoselective product formation under redox control. Significantly, the McMurry reaction when conducted using the salt-activated LVT reagents augmented the reductive dimerization of carbonyls (aromatic/aliphatic substrates) to olefins at ambient (low) temperatures. In addition, one-pot synthesis of biologically relevant vicinal diamines and phenanthrenes in good yields enhanced the scope and utility of the protocol. The accelerated reaction rates observed in the various SET transformations unequivocally establish the profound influence of metal salts as one of the critical parameters for the 'activation' of LVT reagents under redox conditions. Mechanistically, we envisage that the reaction of metal salts with the LVT reagents possibly results in the formation of highly reactive and homogeneous monomeric intermetallic Ti complex. The synergism between the additives, along with the unique properties exhibited by LVT species has thus culminated in the strategical design and development of new titanium formulations possessing varying degrees of reducing activity. The exceptional performance of some of the salt-activated LVT reagents while facilitating significant improvement in the old McMurry reaction and other C–C bond forming SET transformations provides new impetus for organometallic preparative chemistry. This work may therefore redefine the rationale for fine-tuning the reactivity of LVT reagents (and organometallic reagents, in general) to generate soluble reductant systems with well-defined oxidation states, thereby enhancing the scope of the SET reactions leading to the discovery of new and selective synthetic transformations.

4. Experimental section

4.1. General methods

General information regarding instruments, techniques, and source of chemicals used is the same as mentioned in our previous publications.[3,5a,15a,b] Lithium rods cut into small pieces were used for the reduction of titanium chlorides. All the products **3a**–**n**, **6a**–**d**, **8a**–**d**, **2a**, **5a**, **9a**–**d** are known compounds and all yields refer to isolated products purified by preparative thin layer or column chromatography (purity >95%) analyzed by mp, ^{1}H NMR, IR in comparison with known literature data (for product details see Supplementary data).

4.2. McMurry olefination via reductive deoxygenation

*4.2.1. General procedure for metal salt-activated LVT-induced reductive deoxygenation of aromatic and aliphatic carbonyls (**1a**–**n**) to corresponding olefins (**3a**–**n**)*

To a mixture of anhydrous $TiCl_3$ (10 mmol, 1.55 g) in dry THF or DME (50 ml) in a three-necked flask, reducing metal (Li: 33 mmol, 0.231 g/Mg: 17 mmol, 0.408 g) was added and refluxed (3 h) under Ar. With time, the violet color of the reaction suspension changed and gradually got converted to a black colloidal slurry. (Note: in case of Mg as reducing agent, a brownish black homogeneous slurry

of the LVT reagent was obtained. With Li, black, finely particulated heterogeneous slurry of LVT was produced along with a few suspended pieces of unreacted Li on the surface of the slurry.) After attaining room temperature, addition of annhydrous metal halide (2.0–8.0 equiv of $TiCl_3$) to this preformed LVT reagent resulted in slow effervescence indicating the exothermic nature of the reaction. The resultant formulation was then refluxed for an additional 1 h and then cooled to room temperature affording viscous, non-transparent homogeneous slurry. (With anhydrous $MgCl_2$, LiCl, CsCl, KCl, black slurries were obtained, while annhydrous LiI and $ZnCl_2$ provide brownish black slurry. Use of anhydrous LiCl, $MgCl_2$, $ZnCl_2$ resulted in brisk effervescence in comparison to CsCl and KCl salts.) Carbonyl substrates **1a**–**n** (2.5 mmol) in dry THF or DME (5 ml) were added to activated LVT reagent with continued stirring at room temperature. The reaction was monitored at regular intervals (TLC) and on completion; the reaction was quenched with water and diluted with hexane. The mixture was thoroughly extracted with hexane/ethylacetate (70:30) mixture and the extract passed through Celite. After repeated washings (five times), the organic portion was pooled together, washed with water and brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded the crude product which was subjected to preparative TLC (SiO_2 gel, 5% EtOAc/hexane) furnishing the olefins **3a**–**n** (mixture of cis and trans isomers) along with vicinal diols **2a** (pinacols) wherever reported. All the product stilbenes **3a**–**n** and pinacol **2a** reported are known compounds for which references have been cited in the text and tables.

4.3. Phenanthrene synthesis via reductive deoxygenation and reductive dealkoxylation

*4.3.1. Representative procedure for one-pot synthesis of 9,10-dialkylphenanthrenes (**6a**–**d**) by salt-activated LVT reagent*

Titanium trichloride (10 mmol, 1.55 g) was added to a dry flask containing Li pieces (33 mmol, 0.231 g)/Mg (17 mmol, 0.408 g) in dry THF (50 ml). The mixture was refluxed for 3 h, cooled to room temperature, and anhydrous metal halides like LiCl, KCl, CsCl (2–8 equiv) were added. The mixture was then refluxed for an additional 1 h, *o*-alkoxy aromatic aldehydes/ketones **4a**–**d** (2.5 mmol, 410 mg) in 5 ml THF (and/or DME) were added to the activated LVT species and refluxed for additional 16 h. After completion (TLC), it was allowed to attain room temperature, diluted with hexane/ethylacetate (70:30) mixture, quenched with saturated solution of NH_4Cl, and passed through Celite. The collective organic eluent was washed with water and brine, and dried. Concentration of the organic extract afforded the crude product which was subsequently purified by preparative TLC (SiO_2 gel, 2.5% EtOAc/hexane) furnishing the phenanthrene derivatives **6a**–**d** and/or the olefins **5a**–**d**. Comparison of the spectral data of the reaction products with those of authentic samples confirmed the presence of these compounds. All the product phenanthrenes **6a**–**d**[3f] and stilbene **5a**[3f] reported are known compounds for which references have been cited in the text in the Supplementary data.

4.4. Imino-pinacol coupling reaction

*4.4.1. Typical procedure for reductive dimerization of aldimines to vicinal diamines using reagent **A**–KCl*

A mixture of $TiCl_3$ (6.25 mmol, 964 mg) and freshly cut Li pieces (20.6 mmol, 144 mg), in dry THF was refluxed (3 h) in an inert atmosphere of Ar. The reduced LVT reagent so prepared was then allowed to cool to room temperature. Addition of KCl (2 equiv of $TiCl_3$) to this active mixture resulted in very slow effervescence indicating the slightly exothermic nature of the reaction. The resulting slurry was then further refluxed for an additional 1 h which on cooling to the room temperature afforded a thick black activated slurry. An appropriate amount of aldimine **7a**–**d** was added (2.5 mmol, 5 ml THF) and was stirred at room temperature till all the starting compound disappeared (monitored by TLC). After completion, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with hexane/ethylacetate mixture (60:40) and passed through a Celite bed. The collective organic fractions so obtained were washed with water, brine and dried (Na_2SO_4). Concentration of the dried organic solvent afforded the crude reaction product which was further purified using preparative TLC (SiO_2 gel, 5% EtOAc+hexane) which furnished the respective vicinal diamines **8a**–**d** along with the mono-reduced amines (**9a**–**d**). The products are known compounds and were characterized by IR, NMR, MS, physical constants, and also by comparison with authentic samples.

Acknowledgements

S.M.R. is grateful to the Department of Atomic Energy, Government of India, for a Senior Research Fellowship (1998–2000).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.084.

References and notes

1. For excellent reviews on the synthetic applications of low-valent titanium reagents, see: (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513; (b) Lenoir, D. *Synthesis* **1989**, 883; (c) Furstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2442; (d) Dushin, R. G. *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, p 1071; (e) Ladipo, F. *Curr. Org. Chem.* **2006**, *10*, 965; (f) Ephritikhine, M.; Villiers, C. *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, 2004; p 223.
2. For different recipes for the generation of activated LVT reagents, see: (a) Cintas, P. *Activated Metals in Organic Synthesis*; CRC: Boca Raton, 1996; (b) Lectka, T. *Active Metal – Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1996; pp 85–131.
3. (a) Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* **2001**, *66*, 2990; (b) Rele, S.; Chattopadhyay, S.; Nayak, S. K. *Tetrahedron Lett.* **2001**, *42*, 9093; (c) Talukdar, S.; Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 4925; (d) Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, *118*, 5932; (e) Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1991**, *56*, 1940; (f) Banerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1991**, 1432; (g) Talukdar, S.; Nayak, S. K.; Banerji, A. *Fullurene Sci. Technol.* **1995**, *3*, 327; (h) Nayak, S. K.; Kadam, S.; Talukdar, S.; Banerji, A. *J. Indian Inst. Sci.* **1994**, *74*, 401; (i) Kadam, S. M.; Nayak, S. K.; Banerji, A. *Synth. Commun.* **1995**, *25*, 135; (j) Mayekar, N. V.; Chattopadhyay, S.; Nayak, S. K. *Synthesis* **2003**, 2041; (k) Mayekar, N. V.; Chattopadhyay, S.; Nayak, S. K. *Lett. Org. Chem.* **2004**, *1*, 203.
4. (a) Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. *J. Org. Chem.* **1997**, *62*, 4566; (b) Mukaiyama, T.; Kagayama, A.; Shiina, I. *Chem. Lett.* **1998**, 1107; (c) Ganauser, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101.
5. (a) Nayak, S. K.; Banerji, A. *J. Chem. Soc., Chem. Commun.* **1990**, 150; (b) Furstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991; (c) Furstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7328; (d) Furstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468; (e) Furstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215.
6. (a) Furstner, A.; Seidel, G. *Synthesis* **1995**, 63; (b) Furstner, A.; Seidel, G.; Kopiske, C.; Kruger, C.; Mynott, R. *Liebigs Ann.* **1996**, 655.
7. (a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannnan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630; (b) Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634; (c) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645.
8. (a) Wang, L.; Zhang, Y. *Synth. Commun.* **1998**, *28*, 3991; (b) Nishiyama, Y.; Shinomiya, E.; Kimura, S.; Itoh, K.; Sonoda, N. *Tetrahedron Lett.* **1998**, *39*, 3705; (c) Wang, L.; Zhang, Y. *Tetrahedron* **1998**, *37*, 11129; (d) Ascham, F. R.; Carroll, K. M. *J. Org. Chem.* **1993**, *58*, 7328; (e) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 3867; (f) Akane, N.; Hayano, T. H.; Kusui, H.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 7904; (g) Szymoniak, J.; Besancon, J.; Moise, C. *Tetrahedron* **1992**, *48*, 3867; (h) Szymoniak, J.; Besancon, J.; Moise, C. *Tetrahedron* **1994**, *50*, 2841; (i) Immamoto, T.; Kusumoto, T.; Hatanaka, Y.; Yokoyama, M. *Tetrahedron Lett.* **1982**, *23*, 1353; (j) Wang, C.; Pana, Y.; Wu, A. *Tetrahedron* **2007**, *63*, 429; (k) Pederson, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014; (l) Xu, X. L.; Hirao, T. *J. Org. Chem.* **2005**, *70*, 8594; (m) Hirao, T. *Synlett* **1999**, 175; (n) Ueda, T.; Kanomata, N.; Machida, H. *Org. Lett.* **2005**, *7*, 2365; (o) See Ref. 17.

9. Dams, R.; Malinowski, M.; Westdorp, I.; Geise, Y. H. *J. Org. Chem.* **1982**, *47*, 248.
10. (a) Aleandri, L. E.; Bogdanovic, B.; Gaidies, A.; Jones, D. J.; Liao, S.; Michalowicz, A.; Roziere, J.; Schott, A. *J. Organomet. Chem.* **1993**, *459*, 87; Related references: (b) Bogdanovic, B.; Bolte, A. *J. Organomet. Chem.* **1995**, *502*, 109; (c) Aleandri, L.; Becke, S.; Bogdanovic, B.; Jones, D. J.; Roziere, J. *J. Organomet. Chem.* **1994**, *472*, 97.
11. The concept of salt effect on reaction rates is explained in Sykes, P. *The Search for Organic Reaction Pathways*; Longman: London, 1972; p 31. Addition of neutral salts is known to influence the resultant ionic strength of the medium (positive salt effect) significantly modulating the rates of many reactions in which the charge is concentrated or dispersed. Also see Refs. 20 and 21.
12. (a) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255; (b) McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169; (c) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942.
13. Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147.
14. Isomeric ratio of **3a** is established using spectroscopic data, see: Andersson, P. G. *Tetrahedron Lett.* **1994**, *35*, 2609.
15. (a) Talukdar, S.; Banerji, A. *Synth. Commun.* **1996**, *26*, 1051; (b) Talukdar, S.; Banerji, A. *Synth. Commun.* **1995**, *25*, 813; (c) Tyrlik, S.; Wolochowicz, I. *J. Chem. Soc., Chem. Commun.* **1975**, 781.
16. McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249.
17. Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem. Soc.* **2001**, *123*, 1503.
18. Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
19. Talukdar, S.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 3468 and references therein.
20. Rieke, R. D.; Bales, S. F. *J. Am. Chem. Soc.* **1974**, *96*, 1775. Many organic halides due to their low propensity for reaction with ordinary Mg turnings use activated [Mg*] during formation of Grignard reagents. Rieke and co-workers in their pioneering work have suggested that alkali salts play an important role in inducing high reactivity of Mg. The addition of simple alkali salts or Lewis bases like KI, prior to the reduction of anhydrous $MgCl_2$ with K in refluxing THF, afforded a reactive black activated Mg (Mg*) powder ($MgCl_2+KI+K \rightarrow Mg^{*}\cdot KCl$). Scanning electron microscopy (SEM) has shown this Mg* to be a sponge-like material with much smaller particle size. The apparent association of KCl and Mg metal and its subsequent reaction with the organic halide (RX) was reported to afford an 'ate' complex ($R–X+Mg^{*}\cdot KCl \rightarrow [R–Mg–(Cl)X]K^{+}$). The reactivity of the Mg so produced was assessed by addition of a number of metal salts (LiCl, LiF, NaCl, NaI, CsI, KCl, KI, $MgSO_4$, $CuSO_4$, NaBr, $ZnBr_2$, etc.). Salts like NaI, KI, $ZnBr_2$, etc., were found to exhibit an activating effect on the reactivity of Mg prepared from $MgCl_2$–K–THF. In contrast, other salts (KF, $CuSO_4$, etc) had a deactivating effect, while the use of NaF, NaCl, LiF, LiCl, KCl essentially gave the same results as the control reaction.
21. Transition metal Grignards with generalized formula $[M^1(MgCl)_m]$ are known to react with metal halides M^2X in a molar ratio of n:m in coordinating solvents generating highly reactive alloys and intermetallics of composition $M^1{}_nM^2{}_m$. In a similar fashion the reaction of $[M^1(MgCl)_m]$ with its corresponding metal chloride (M^1Cl) can be employed as a method for preparation of finely divided metal powders $(m+n)M^1$. We anticipate a similar mechanism taking place on exogenous administration of metal salts to the preformed LVT reagents (reagents **A** and **B**) which breaks the uniform and ordered dimeric intermetallic cluster resulting in the formation of a highly reactive intermetallic monomeric 'ate' donor complex.
22. See: (a) Wessjohann, L.; Gunter, S. *Synthesis* **1999**, 1; (b) Wessjohann, L.; Gabriel, T. J. *J. Org. Chem.* **1997**, *62*, 3772. The overall reactivity of such organometallic preparations, in general, is dependent on their solubility in the reaction medium. For example, $CrCl_2$ is poorly soluble in THF and tends to associate in this medium and shows poor reactivity which can be augmented by the addition of LiI. The increased reactivity has been attributed to the enhanced solubility and possibly electronic modification and monomerization of $CrCl_2$.
23. (a) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939; (b) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, C71.