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Influence of External Ligands and Auxiliaries on the Reactivity of Low-Valent Titanium in McMurry Reaction: Selectivity and Mechanistic Profile

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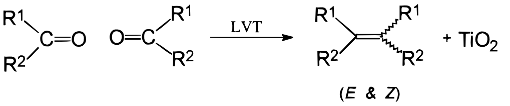
Abstract: Influence of various external ligands/auxiliaries on the reductive carbonyl coupling reactions mediated by low-valent titanium (LVT) reagents (McMurry coupling) has been explored. The LVT species generated from Tyrlik's $TiCl_3$−Mg−THF system has been selected for the reactivity-tuning trials. Our studies show that incorporation of about 10 equiv of pyridine (a π-acceptor ligand) with respect to $TiCl_3$ to the THF solvated LVT reagent could arrest the reductive dimerization of acetophenone at the intermediate pinacol stage. Modulation of the LVT-species by covalently-binding monohydroxy, 1,2- and 1,3-dihydroxy auxiliaries also resisted deoxygenation completely to give the pinacols in higher yields and better diastereoselectivity, as compared to pyridine-modified LVT system. Amongst these modified reagents, the LVT−catechol (1:1) system was found to be the most efficient combination for total pinacolization of aromatic carbonyl compounds, even under refluxing conditions. The actual titanium reagent responsible for this transformation is proposed to be a Ti(II) complex formed *in situ*. Further enhancement of stereoselectivity (*threo*-selectivity) of the pinacols has been achieved by carrying out the reactions with LVT-complexes modified by a variety of covalently-linking auxiliaries at low temperatures. The results demonstrate that by the judicious incorporation of various ligands/auxiliaries into LVT reagents it is possible to widen the scope and applicability of the classical McMurry reaction.

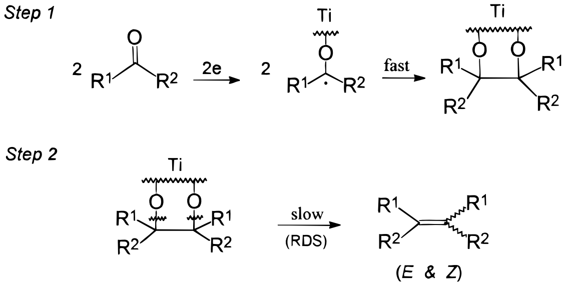
1. Introduction

The immense synthetic potential of reductive coupling of carbonyl compounds by low-valent titanium (LVT) reagents (McMurry reaction) has been exemplified by a variety of applications ranging from the preparation of simple symmetrical alkenes[1−4] to the strategic construction of an eight-membered ring during the synthesis of the anticancer drug *taxol* by Nicolaou and co-workers.[5] Furthermore, recent reports on the syntheses of various heterocyclic compounds,[6] the first acylsilane couplings,[7] and the synthesis of macrocyclic compounds like archaebacterial membrane lipids[8] *etc.* serve as ample evidences for the wide applicability of the classical McMurry reaction. The reaction, in general, is operationally simple and provides an easy, one-flask synthetic strategy to difficultly accessible olefins (eq 1).[9−13]



(1)

Scheme 1. Classical Mechanism of LVT Mediated Reductive Deoxygenation of Aldehyde/Ketone



The LVT-induced reductive deoxygenation of carbonyls to olefins takes place in two successive steps (Scheme 1): (i) reductive dimerization of the starting ketone or aldehyde to form a carbon−carbon bond and (ii) deoxygenation of the 1,2-diolate intermediate to give the alkene, which is the rate determining step of the reaction. The first step in this reaction involves transfer of an electron to the carbonyl group yielding an anion radical (ketyl) which dimerizes to 1,2-diolates.[11] The deoxygenation of the pinacolate involving cleavage of the carbon−

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oxygen bonds resulted in the formation of olefin and oxide coated titanium.

The carbon−oxygen bond cleavage (step 2, Scheme 1) has been found to be more facile in aromatic carbonyls as compared to aliphatic ones. This can be attributed to the relatively weak benzyl−oxygen bond in comparison to the alkyl−oxygen bond[14] of the intermediate 1,2-diolates. This is evidenced by the predominant formation of alkenes with aromatic systems and 1,2-diols with aliphatic systems, during the reactions at room temperature. Besides the native state of the metal, the activity of LVT reagents is also dependent on the coordinating solvents and the stability of the complexes formed *in situ*. For example, diethyl ether-solvated LVT is less reactive compared to that prepared in THF, while the use of stronger coordinating solvents like pyridine or cyclopentadiene causes the complete arrest of the reaction.[15a] However, no systematic study on the effects of ligands on the reactivity of LVT species has been reported so far.

The present studies on reactivity modulation stems from our previous observations on LVT mediated reactions. We have demonstrated that by the choice of appropriate solvents it is possible to control the stereochemistry of the products formed during the carbonyl coupling reactions.[16] It was also noticed that the dealkoxylation of aryl alkyl ethers took place with the unique reagent, *i.e.*, $TiCl_3$/Li/THF, while similar reagent system like $TiCl_3$/Li/DME was ineffective for this reaction.[17a] However, addition of catalytic amounts of pyridine[17b] or fullerenes[17c] to THF-solvated LVT resulted in increased yields of the reaction products. The dramatic effect exerted by pyridine prompted us to undertake a detailed investigation on the influence of various external ligands/auxiliaries on the reactivity of LVT reagents. We envisaged that, by incorporating appropriate additives/ligands, it should be possible to enhance the synthetic scope of LVT reagents.

In the present studies, Tyrlik's reagent ($TiCl_3$/Mg/THF) was selected as the LVT- source on the grounds of its unique reactivity toward carbonyl coupling reactions.[15] It has been suggested that an inorganic Grignard reagent $[Ti(MgCl_2)\cdot n\mathrm{THF}]$[18] is the actual reducing species present in the above LVT-system, and therefore it was the reagent of choice for a series of stoichiometric studies.

Even though, the use of tertiary amines as additives to LVT systems has precedence in the literature,[19] systematic study on the influence of external agents on the LVT-reactivity has not been attempted. Our approach in the selection of the ligands (additives) for the reactivity modulation, however, has been made on the lines of classical complexation theory. It is well-known that the reactivity and stability of transition metal complexes are mutually exclusive, and hence the stable complexes of LVT are expected to be less reactive. In view of the greater ability of nitrogen heterocycles to form stronger coordination complexes with 3*d*-block metals, the effect of an organic base pyridine on the activity of LVT has been explored. The 3*d*-block transition metals in their reduced states are rich in electrons (soft acids). Thus the coordination of pyridine to LVT, *i.e.*, donation of electrons by nitrogen-lone-pair to the vacant 3*d*-orbitals of the metal, is expected to increase the electron density at the metal center. However, the back donation of the electrons from the filled *d*-orbitals of the metal to the vacant orbitals of pyridine will contribute to the stability of the metal complex (Chatt−Dewar−Duncunson model).[20,21] In effect, the reactivity, *i.e.*, electron donating capacity of the metal can be controlled by the judicious incorporation of such an external ligand into the metal complex.[22] Based on these considerations, covalent complexes with auxiliaries having mono- and dihydroxy functionalities (where the metal undergoes change in oxidation states) are also expected to show reduced activity.

Table 1. Modulation of the Reactivity of LVT by Pyridine Incorporation in the Reductive Coupling of Acetophenone (**1a**)[a]

run	$TiCl_3$:pyridine	rxn temp[b] °C	conversion of **1a** (%)	product balance **2a** (%)	**3a** (%)
1	1:0	25	85	50	10
2	1:1	25	82	23	35
3	1:2	25	91	13	47
4	1:4	25	92	11	48
5	1:6	25	96	9	54
6	1:6	reflux	75	7	47
7	1:10	25	98	trace	76[c]
8	1:10	reflux	53	14	77
9	1:50	25	83	trace	63

[a] Low-valent titanium reagent was generated from $TiCl_3$/Mg (1.5 equiv)/THF. $TiCl_3$−**1a** ratio was kept at 1:1 in all the cases. [b] The reaction mixture was stirred at room temperature and/or refluxed for 16 h after the addition of **1a** in all the trials. [c] *dl/meso* ratio was found to be 2.03.

This paper presents the results of our studies on the effects of (i) π-acceptor ligands and (ii) mono- and dihydroxy auxiliaries and a 1,3-diketone on the reactivity of LVT reagent during the reductive duplication of aromatic carbonyl compounds. Reductive coupling of acetophenone was chosen as the model reaction. A plausible mechanistic model has been formulated based on the results obtained from a series of stoichiometric experiments.

2. Results and Discussion

Reductive Coupling of Acetophenone by Pyridine-Modified Low-Valent Titanium Reagent. Based on our earlier work on the effect of various nitrogenous bases on the reactivity of LVT reagent for dealkoxylation of aryl alkyl ethers,[17b] pyridine was selected for the present studies on account of its high efficacy and easy availability. The LVT generated from $TiCl_3$ and 1.5 equiv of Mg metal in THF was treated with increasing amounts of pyridine, keeping a constant THF-volume. The reductive dimerization of acetophenone (**1a**) was carried out mainly at room temperature (25 °C). The results of the experiments with pyridine are summarized in Table 1. A control reaction (Scheme 2) performed without any external additives afforded a mixture of α,α′-dimethyl stilbene (**2a**) and 2,3-diphenylbutan-2,3-diol (**3a**) in a product balance of 50 and 10%, respectively (Table 1, run 1). Addition of 1 equiv of pyridine to LVT system brought down the yield of **2a** to almost half

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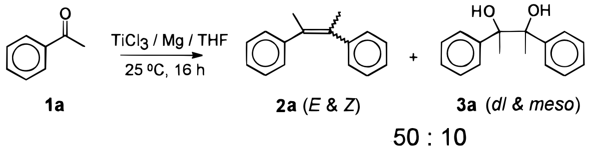
Scheme 2



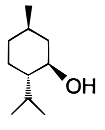
(*i.e.*, 23%), while **3a** was obtained in 35% yield (Table 1, run 2). The ligand effect became more pronounced as the amounts of pyridine were increased stoichiometrically (runs 3 and 4). A six-fold excess of pyridine led to a preferential formation of **3a** (**2a:3a** = 9:54) at room temperature (run 5). With further increase in the amount of pyridine (ten-fold excess), the olefin **2a** was obtained only in traces, while the yield of diol **3a** increased to 76% (run 7). Thus, progressive increase in the amounts of pyridine resulted in concomitant increase in the yield of **3a**. There was marginal change in the yields of the reaction products up to the addition of 50 equiv of pyridine (run 9). Earlier, it has been reported that when pyridine alone was used as solvent, the reaction did not occur at all,[15a] and **2a** was the sole product when THF was used instead. Thus, it has been established that by judicious addition of pyridine to the THF-solvated LVT, the activity of the latter can be modulated to furnish preferentially the diol **3a**.

The effect of another π-acceptor, PPh$_3$, on the reactivity of LVT has also been studied. Thus, addition of 2 equiv of PPh$_3$ (with respect to TiCl$_3$) to the THF solvated LVT reagent yielded **3a** in 48% yield (*dl*/*meso* = 2.94) as the sole product under the same reaction conditions. Compared to pyridine, use of PPh$_3$ suffered from operational shortcomings due to its high molecular weight and difficulty in separation from the reaction mixture.

From the foregoing experiments, it is clear that the activity of LVT species with the same oxidation states is highly dependent on the coordinating ligands.

Reductive Coupling Mediated by LVT Modified by Covalently Binding Auxiliaries. The stability, tendency for aggregation, and the reactivity of LVT reagents are highly influenced by the steric and electronic factors. Titanium when covalently bonded to auxiliaries undergoes change in oxidation states with a considerable difference in the electronic environment around the metal. Therefore, a number of experiments were carried out using mono- and dihydroxy auxiliaries for the reactivity modulation studies.

Menthol (**4**), ethylene glycol (**5**), and 1,2:5,6-di-*O*-cyclohexylidine-D-mannitol (**6**) were used as external auxiliaries for the preliminary trials. Carefully controlled stoichiometric procedures have been adopted for all the trials (Table 2). When the reaction was carried out with the addition of a molar equiv of **4** to the LVT reagent system, followed by the addition of 1 equiv of **1a** at room temperature, a mixture of **3a** (67%) along with 25% of **2a** was isolated (Table 2, run 1). However, use of two equiv of **4** furnished **3a** as the sole product (run 2). The substantial reduction in the yield of **2a**, compared to the control reaction where no auxiliary was used (run 11), represents the pronounced influence exerted by **4** on the reactivity of LVT. Use of diol **6**, derived from mannitol, as the auxiliary afforded excellent (97%) conversion of **1a** and **3a** was isolated in 94% yield (run 5). However, much reduced product turnover (30% conversion), even lower than the control reaction (run 11), was observed when **5** was used as the auxiliary molecule (run 3). This could be due to deoxygenation of **5** by LVT to ethylene gas, evolution of which was observed during the reaction. Heating of the reaction mixture resulted in further decrease in the conversion of acetophenone (run 4). This conjecture gained credence when it was observed that the use of 2,2-dimethyl-1,3-propanediol (**7**), where the deoxygenation is rather difficult, afforded 71% of the pinacol **3a**, and the auxiliary was recovered unchanged (run 6). These observations led us to explore aromatic 1,2-diol, catechol (**8**), as the auxiliary unit. Indeed, use of LVT-catechol reagent resulted in 62% conversion of **1a** at room temperature (25 °C), and **3a** was isolated in 97% yield (*dl*/*meso* = 4.27) (run 7). When the same reaction was carried out at lower temperature (0−25 °C), yield of **3a** was less, but better selectivity (*dl*/*meso* = 5.98) was observed (run 9). Use of acetyl acetone (**9**) as an auxiliary unit did not show much conversion possibly due to the stability of the resulting complex through pronounced chelation (run 10). Heating of the reaction mixture also did not improve the yields. Thus, amongst the above auxiliaries, **6**, **7**, and **8** were found to be efficient in controlling the reactivity of the low-valent titanium species. Besides affording **3a** as the sole product, the use of **8** offered operational advantages due to the ease of separation (by base) and recovery of auxiliary from the reaction mixture.



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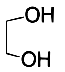

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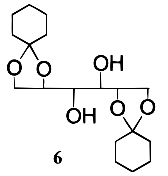

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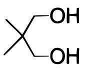
Table 2. Effect of Hydroxy Auxiliaries on the Reactivity of LVT toward the Reductive Coupling of Acetophenone (**1a**)

				product balance	
run[a]	auxiliary	rxn temp (°C)	% conversion of **1a**	**2a** (%)	**3a** (%) (*dl*/*meso*)
1	**4**	25	97	25	67 (4.33)
2	**4**[b]	25	50	trace	88 (4.19)
3	**5**	25	30		87 (4.20)
4	**5**	reflux, 25[c]	22		85 (1.87)
5	**6**	25	97		94 (3.33)
6	**7**	25	84		71 (4.28)
7	**8**	25	62		97 (4.27)
8	**8**[b]	25	59		43 (4.97)
9	**8**	0−25[d]	60		69 (5.98)
10	**9**	25	50		60 (3.08)
11	**Nil**	25	85	50	10 (1.66)

[a] TiCl$_3$:**1a** ratio was kept 1:1 in all experiments, and the reaction mixture was stirred at room temperature and/or refluxed for 16 h after the addition of **1a** in all the trials. [b] Two equiv of auxiliaries were used. [c] The reaction mixture was refluxed for 1 h after the addition of the auxiliary. [d] **1a** was added at 0 °C, stirred for 3 h, and slowly allowed to reach 25 °C; and then stirred for 16 h.



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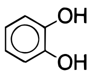

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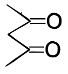

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To optimize the efficacy of LVT-catechol complex, a Ti−auxiliary−ketone ratio of 2:2:1 was used for the reductive dimerization of various carbonyl compounds at 25 °C (Table 3). Using this reagent system, acetophenone (**1a**) and benzaldehyde (**1b**) underwent 100% conversion with 95% and 82% yields of pinacols, respectively (Table 3, runs 1 and 2). At the same time, sterically bulky aromatic ketones such as benzophenone (**1c**), *o*-methoxyacetophenone (**1d**), and valerophenone (**1e**) furnished the corresponding 1,2-diols in poor yield (10−39%) (runs 3, 4, and 5). This can be attributed to the influence of the steric bulk of the substrate during the dimerization process.

Total Pinacolization of Aromatic Carbonyl Compounds with TiCl$_3$−Mg−THF−Catechol Reagent at Higher Temperature. The efficient construction of pinacols as strategic synthetic intermediates is of great importance as exemplified by the preparation of various biologically active compounds such

Table 3. Reductive Dimerization of Various Ketone/Aldehyde by Using Catechol−LVT−Complex[a] at 25 °C (Scheme 3)

run	substrate	ketone converted (%)	yield of the pinacol (%)
1	**1a**	100	95[b]
2	**1b**	100	82[b]
3	**1c**	66	39[b]
4	**1d**	25	10[c]
5	**1e**	29	20[d]

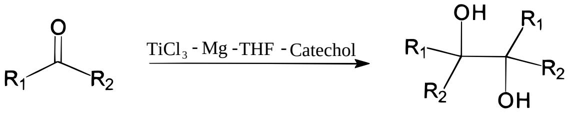
[a] $TiCl_3$−catechol−substrate ratio was maintained at 2:2:1, and the reaction mixture was stirred at room temperature (25 °C) for 16 h after the addition of respective carbonyl compounds in all the trials. [b] Reference 32. [c] Reference 38. [d] Reference 39.

Table 4. Reductive Dimerization of Carbonyl Compounds with LVT−Catechol Reagent at Higher Temperature (Scheme 3)

run	substrate	auxiliary[a]	rxn temp °C (time, h)	% yield of pinacol[b] (*dl*/*meso*)[c]	% yield of alkene[b]
1	**1a**	8	80 (1)	86 (3.35)	
2	**1b**		25 (0.5)	29 (0.73)	43
3	**1b**		80 (0.5)		62
4	**1b**	8	80 (0.5)	76 (1.16)	
5	**1f**		80 (1)	27 (3.50)	42
6	**1f**	8	80 (1)	82 (4.60)	
7	**1g**	8	80 (1)	71 (4.35)	
8	**1h**	8	80 (1)	87 (2.27)	
9	**1i**	8	80 (1)	77 (0.54)	
10	**1j**	8	80 (1)	72 (2.51)	
11	**1k**	8	80 (1)	62 (0.74)[d]	

[a] $TiCl_3$−substrate−auxiliary ratio was kept at 1:1:1 in all the trials. [b] Products were characterized by spectral data (IR, ^{1}HNMR). [c] *dl:meso* assignments were made according to ref 32. [d] 26% of **1k** was recovered.

Scheme 3



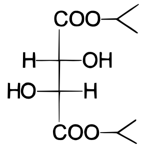
1a - k **3a -k** *(dl & meso)*

a: $R_1 = C_6H_5$; $R_2 = CH_3$
b: $R_1 = C_6H_5$; $R_2 = H$
c: $R_1 = R_2 = C_6H_5$
d R_1 = 2-$MeOC_6H_4$; $R_2 = CH_3$
e: $R_1 = C_6H_5$, $R_2 = C_4H_9$
f: R_1 = 4-$MeOC_6H_4$; $R_2 = CH_3$
g: R_1 = 3,4-(O-CH_2-O)C_6H_3; R_2 = H
h: R_1 = 2-Napthyl; $R_2 = CH_3$
i: R_1 = 2-ClC_6H_4; R_2 = H
j: R_1 = 3-$MeOC_6H_4$; $R_2 = CH_3$
k: R_1 = 4-ClC_6H_4; R_2 = H

as sarcophytol[6b] and taxol.[5] Among the wide range of reagents, *viz.*, Mg-MgI_2,[23] Al-Hg,[24] Al-KOH,[25] Ce/I_2,[26] SmI_2,[27] $TiCl_4$-Mg(Hg),[28] aqueous $TiCl_3$,[29] *n*-Bu_3SnH,[30] which have been employed for pinacolizations, titanium based reagents are of special importance. In the light of the observations with $TiCl_3$−Mg−THF−catechol, the possibility of total and rapid pinacolization of various aromatic carbonyl compounds at higher temperatures were undertaken (Table 4, Scheme 3). Interestingly, when a mixture of acetophenone (**1a**) and catechol-modified LVT reagent (in 1:1 ratio) was refluxed (80 °C, 1 h), the conversion was better than the room temperature reaction, and pinacol **3a** was obtained as the sole product in high yield (86%) without even a trace of stilbene **2a** (Table 4, run 1). While improving the yield and reaction time, no significant reduction in the diastereoselectivity was observed as compared to the trial carried out at room temperature (Table 2, run, 7). Similarly, reaction of benzaldehyde (**1b**) with LVT at room temperature (0.5 h) without incorporating catechol yielded a mixture of 1,2-diphenyl-1,2-ethanediol (**3b**) and stilbene (**2b**) (Table 4, run 2). However, when the same reaction was carried out under reflux (80 °C, 0.5 h) in the absence of catechol, **2b** was obtained as the sole product (run 3). Expectedly, the use of catechol-LVT reagent afforded **3b** as the sole product in 76% yield under refluxing conditions (0.5 h) (run 4). *Incidentally, this is the first report of LVT-mediated total pinacolization of aromatic carbonyl compounds at higher temperatures.*

To explore the synthetic scope of LVT-catechol reagent, various aromatic carbonyl compounds such as 4′-methoxyacetophenone (**1f**), 3,4-(methylenedioxy)benzaldehyde (**1g**), 2-acetylnaphthalene (**1h**), 2-chlorobenzaldehyde (**1i**), 3′-methoxyacetophenone (**1j**), and 4-chlorobenzaldehyde (**1k**) (Scheme 3) were used as substrates, and in all the cases corresponding pinacols were obtained in good to excellent yields (62−87%) under the above reaction conditions (Table 4). In general, the aldehydes gave lesser diastereoselectivity as compared to ketones.

Enhancement of *threo*-Selectivity by Modification of LVT with Various Auxiliaries and Temperature Control. Stereoselectivity in pinacolization is highly desirable phenomenon as *threo*-1,2-diols have, after resolution, frequently been used as auxiliaries in asymmetric syntheses.[31] Although, a number of methods have been developed for the reductive duplication of carbonyl compounds,[28,32] *threo*-selective pinacolization has been found only with stannylene precursors,[33] $NbCl_3$(DME),[34] "active-titanium(III) reagent" prepared from $TiCl_4$ and *n*-BuLi,[35] or with cyclopentadienyl-bound titanium(III) reagent derived from Cp_2TiCl_2 and *sec*-BuMgCl.[36] Highly pH-controlled pinacolizations mediated by aqueous-$TiCl_3$ gave only moderate *threo*-selectivity (*dl*/*meso* = 2 to 3.2).[29] Our results, summarized in Table 2 (runs 7 and 9), reveal that as the temperature is lowered, though the extent of conversion goes down, the *threo*-selectivity of the 1,2-diols increased. To optimize the selectivity, low-temperature reactions were carried out with **4**, **6**, and **8** along with some additional auxiliaries such as (+)-diisopropyl tartrate (**10**), L-proline (**11**), and L-prolinol (**12**) (Table 5).



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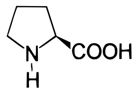

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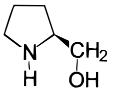

12

Stereoselectivity (*dl/meso* ratio) of the pinacols was analyzed by NMR spectroscopy of chromatographically homogeneous diastereomeric mixtures. Though the conversion was not high, excellent stereoselection could be obtained by using **4** and **12**

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Table 5. Reductive Duplication of Acetophenone (**1a**) Using Auxiliary-Modified LVT at Low Temperatures[a]

run	auxiliary	conversion of **1a** (%)	yield of **3a** (%)[b]	ratio[c] *dl/meso*
1	**4**	38	78	8.43
2	**6**	45	100	5.68
3	**8**	98	91	6.10
4	**10**	92	90	4.45
5	**11**	56	81	2.40
6	**12**	57	60	7.72

[a] All reactions were carried out at the temperature range of −70 to 25 °C, and $TiCl_3$:auxiliary:**1a** ratio was kept 1:1:0.5 in all the trials except in run 1 where 1:2:0.5 ratio was used. [b] Yields were calculated on the basis of reacted **1a**. [c] Diastereoselectivity was determined by 200 MHz NMR spectroscopy.

as auxiliaries at low temperatures (Table 5, runs 1 and 6) (see Experimental Section). The pinacols with *dl/meso* ratios, as high as 8.43 and 7.72 respectively, were obtained using these auxiliaries. More interestingly, use of catechol (**8**) resulted in the conversion of the ketone to pinacol in high yield (91%) with significant improvement in *threo*-selectivity (*dl/meso* = *6.10*) (run 3). Even though, **10** had given better conversion under the present temperature range, it exhibited a lower *dl/meso* ratio (4.45) (run 4).

Mechanistic Considerations. Preparation and use of several low-valent titanium reagents by the reduction of titanium halides ($TiCl_3$ and $TiCl_4$) with strong reducing agents such as K, Li, Mg, Zn, $LiAlH_4$, *etc*. have been reported in the literature.[37] However, the reactivities of these reagents were found to be dependent on their methods of preparation as discussed earlier. Identification of the "active species" responsible for chemical transformations in these LVT reagents are still under debate. The ambiguity which surrounds the mechanistic interpretation is mainly due to the heterogeneous and oxophilic nature of these reagents. Our interpretation described herein are mainly based on the results obtained by the stoichiometric incorporation of various ligands/auxiliaries into the LVT reagent prepared from $TiCl_3$/1.5 Mg/THF (Tyrlik's reagent), during a series of carbonyl coupling reactions.

Based on ESR studies, Geise *et al*. have proposed that the reduction of $TiCl_3$ with 1.5 equiv of Mg in THF under reflux (3 h) (Rieke type activation process) leads to the formation of a suspension of titanium species in zero-valent state.[15a] A recent study by Bogdanovic *et al*. suggests that in the McMurry reaction with Tyrlik's reagent, a bimetallic "inorganic Grignard" reagent [$TiMgCl_2(THF)_x$] is involved as the active species (eq 2).[18]

$$\mathrm{TiCl_3 + 1.5Mg + THF \rightarrow \underset{[\mathbf{A}]}{[TiMgCl_2(THF)_x]_p} + 0.5MgCl_2(THF)_2} \quad (2)$$

Because of the existence of a definite Ti−Mg bond in [**A**], Ti is likely to assume higher electron density (compared to metallic Ti) when one considers the more electropositive character of Mg. This might also explain our earlier observation of higher reactivity of $TiCl_3$/Li/THF in the reductive dealkoxylation of aryl alkyl ethers,[17a] because of the higher electropositivity of Li as compared to that of Mg in $TiCl_3$/Mg/THF system.

The incorporation of pyridine, by the displacement of THF from the coordination site on Ti in [**A**], is expected to reduce the net electron density around Ti due to back donation of metal electrons to the vacant orbitals of pyridine. Consequently, complexes of type [**B**] (eq 3) with different Ti/pyridine/THF ratios are expected to exhibit varying reducing activities as exemplified by the results in Table 1. Thus, addition of pyridine up to 10 equiv with respect to $TiCl_3$ suppresses the deoxygenation of the pinacolate intermediate (step 2, Scheme 1). Though weak, the ligand-exchange effects operating here can influence the reactivity of LVT species to a reasonable extent.

$$[\mathbf{A}] + y\mathrm{Py} \rightleftharpoons \underset{[\mathbf{B}]}{\mathrm{TiMgCl_2{\cdot}(THF)_{x-y}(Py)_y}} + y\mathrm{THF} \quad (3)$$

The highly electron rich and oxophilic nature of Ti in the complex [**A**] is likely to undergo oxidation to Ti(II) alkoxide [**C**] in the presence of alcohol *via* a hydride intermediate as shown in eq 4. In other words, 2 equiv of monohydroxy alcohol or 1 equiv of a diol are required for complete conversion of [**A**] to [**C**]. The reactivity or electron donating ability of titanium in [**C**] is definitely lower than that in complex [**A**]. This is evidenced by the fact that the reductive dimerization of acetophenone (**1a**) by [**A**] furnished the olefin **2a** as the major product (eq 5), while addition of 2 equiv of menthol (**4**) or 1 equiv of catechol to [**A**] yielded **3a** as the only product (eqs 7 and 8). Expectedly, use of 1 equiv of **4** provided a mixture of **2a** (25%) and **3a** (67%) (eq 6). The uncomplexed [**A**] (almost 50%) is believed to be responsible for the deoxygenation of **3a** to **2a** (Table 2, run 1) in this case.

$$[\mathbf{A}] + \mathrm{2ROH \rightarrow [H_2Ti(OR)_2MgCl_2{\cdot}(THF)_y] \rightarrow \underset{[\mathbf{C}]}{Ti(OR)_2{\cdot}MgCl_2{\cdot}(THF)_z} + H_2\uparrow} \quad (4)$$

$$[\mathbf{A}] + \mathbf{1a} \rightarrow \mathbf{2a}\ (\text{major}) + \mathbf{3a}\ (\text{minor}) \quad (5)$$

$$[\mathbf{A}] + 1\ \text{menthol} + \mathbf{1a} \rightarrow 0.5\ \mathrm{Ti^{II}}\ (\text{O}-\text{menthyl})_2 + 0.5\ [\text{A}] \rightarrow \mathbf{2a}\ (\text{minor}) + \mathbf{3a}\ (\text{major}) \quad (6)$$

$$[\mathbf{A}] + 2\ \text{menthol} + \mathbf{1a} \rightarrow \mathrm{Ti^{II}}\ (\text{O-menthyl})_2 \rightarrow \mathbf{3a}\ (\text{only}) \quad (7)$$

$$[\mathbf{A}] + 1\ \text{catechol} + \mathbf{1a} \rightarrow \mathrm{Ti^{II}}\ (\text{catechol}) \rightarrow \mathbf{3a}\ (\text{only}) \quad (8)$$

The pronounced *threo*-selectivity during the pinacolizations could be ascribed to the bulkiness of the resultant Ti-complex formed as a result of the combined effect of the auxiliary, $MgCl_2$, and the solvent coordinated to the metal.[36] A very probable situation involving the formation of complex [**D**] is diagramatically shown in Scheme 4. Most likely, the transition state tends to orient the bulkier substituents away from one another so as to keep the steric forces a minimum. The use of chiral auxiliaries, however, imparted no significant asymmetric induction in the purified *dl*-isomers obtained by crystallization from the *dl-meso* mixture.

3. Conclusions

The reactivity of low-valent titanium (LVT) reagents in carbonyl coupling reactions largely depends on the choice of reducing metals, solvents, and the oxidation state of the resulting metallic species. Reductive coupling of aromatic carbonyl compounds mediated by LVT reagents usually lead to the preferential formation of stilbenes at room temperature. In the present study, we have demonstrated that by the addition of various external agents, it is possible to design LVT reagents of variable reactivities. Reductive coupling of acteophenone with Tyrlik's LVT-system ($TiCl_3$/Mg/THF) has been selected as the model reaction for a series of reactivity-control experi-

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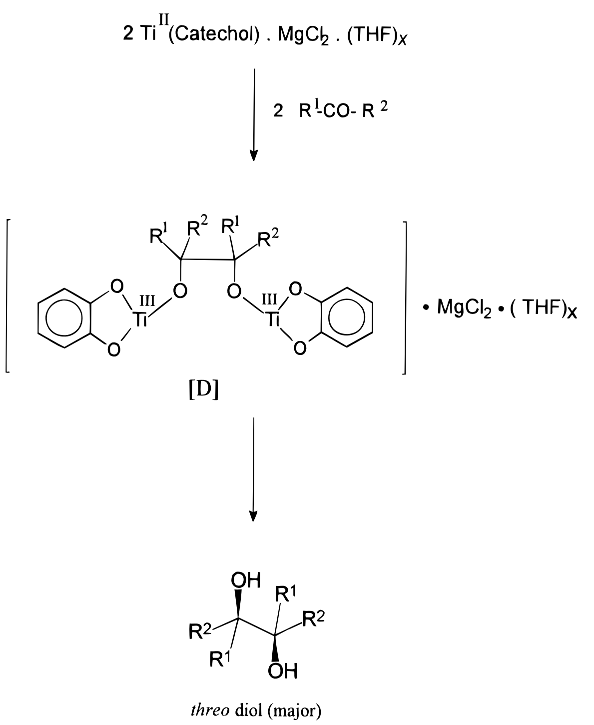
Scheme 4



ments. Modulation of LVT has been effected in two different ways: (i) by reducing the electron density of Ti center by displacing THF by pyridine or triphenylphosphine, both having σ-donating and π-accepting properties, and (ii) by changing the oxidation state of the metal atom by the incorporation of various covalent-bond-forming auxiliaries like mono- and diols, 1,3-diketone, amino acid, amino alcohol, *etc*.

Incorporation of about 10 equiv of pyridine to the THF-solvated complex could arrest the reductive dimerization of acetophenone at the intermediate 1,2-diol stage. Stoichiometric incorporation of covalently-linking hydroxylated auxiliaries also afforded 1,2-diols as the sole products with appreciable diastereoselectivity (*threo*-selectivity)). Further enhancement of *threo*-selectivity in 1,2-diol formation has been achieved by carrying out the reactions at low temperatures. The stereocontrol of the reaction is governed by the nature of the ligands used. Amongst the modified LVT reagents, the LVT-catechol system was found to be efficient for *total pinacolizations even under refluxing conditions*.

Our observations on the behavior of modified LVT reagents further elaborate the scope, limitations, and applicability of the classical McMurry reaction. More significantly, the present study provides important guidelines for the reactivity-modulation of various low valent metal-based reagents and thereby widening their synthetic scope.

4. Experimental Section

Infrared spectra were run on a Perkin-Elmer spectrophotometer (Model 783). ^{1}H NMR spectra were recorded on a Varian EM 360 (60 MHz) or Bruker AC-200 (200 MHz) spectrometer using CDCl$_3$ with TMS as an internal standard. Mass spectra were obtained on a Shimadzu QP 1000A mass spectrometer.

TiCl$_3$ and Mg turnings were purchased from Aldrich Chemical Co., U.S.A. Rigorous anhydrous conditions were maintained during the reactions. THF was distilled freshly from benzophenone-sodium ketyl. All operations were carried out under an atmosphere of dry argon.

Typical Procedure for the Reductive Coupling of Acetophenone with LVT-Pyridine System. In a typical experiment, a dry argon-filled, three-necked, round-bottom flask was charged with dry THF (40 mL), titanium(III) chloride (1.54 g, 10 mmol), and Mg-turnings (362 mg, 15 mmol). The mixture was refluxed for 3 h with stirring during which the color of the reaction mixture changed from violet to black. The black slurry thus obtained was cooled to ambient temperature and required amount of dry pyridine was added in a single lot. Stirring continued for 1 h and then a solution of acetophenone (10 mmol) in THF (5 mL) was added. After stirring at room temperature (25 °C) for 16 h, the reaction mixture was diluted with diethyl ether, quenched with cold saturated solution of NH$_4$Cl, and then passed through a small bed of Celite on a sintered glass filter to remove inorganic salts. The filtrate was extracted with ether, washed with 2 N HCl and water, and then dried (Na$_2$SO$_4$). Removal of the solvent and subsequent column chromatography over silica gel (100−200 mesh) yielded the products (Table 1).

Typical Procedure for Reductive Coupling of Acetophenone by Modified LVT Reagent by Mono-, Dihydroxy, and 1,3-Diketone Auxiliaries. A solution of required amount of the ligand was added *via* a syringe to the black suspension of the LVT reagent prepared as described earlier. A rapid evolution of H$_2$ gas was observed on addition of the auxiliary. The mixture was stirred at 25 °C for 1 h, and then a solution of **1a** (1 equiv) in THF was added to it. Stirring was continued at 25 °C for an additional 16 h under a gentle stream of argon. The reaction mixture was worked up in the usual way to isolate the products (Table 2).

Typical Experiment with Catechol−Titanium Complex for the Pinacolization Reactions at Room Temperature (25 °C). In these experiments, the LVT species generated from TiCl$_3$/Mg/THF was treated with equimolar amount of catechol and stirred for 0.5 h at 25 °C. Appropriate aldehyde/ketone (0.5 equiv) was then added to the reagent and then stirred at 25 °C for 16 h. Usual workup (by alkali wash) followed by column chromatography (SiO$_2$) afforded the products as reported in Table 3.

Typical Experiment with Catechol−Titanium Complex for the Pinacolization at Higher Temperature (80 °C). In these experiments, LVT species generated from TiCl$_3$/Mg/THF, was treated with equimolar amount of catechol and stirred for 0.5 h at 25 °C. One equiv of ketone/aldehyde (TiCl$_3$: substrate = 1:1) was then added, and the reaction mixture was refluxed (80 °C) for specified time. The usual workup afforded the products as reported in Table 4.

Typical Procedure for Reductive Coupling of Acetophenone with Modified LVT at Low Temperatures. LVT reagent was prepared as described above. A solution of the auxiliary (1 equiv) in THF was introduced into the LVT system (except that of **11** which was added directly because of its insolubility in THF and 2 equiv of **4** was used) and stirred at room temperature for 1 h. The reaction mixture was then cooled to −70 °C, and THF solution of **1a** (0.5 equiv) was added dropwise. The reaction mixture was stirred for 3 h at −70 °C and then allowed to reach room temperature (25 °C) over a period of 3 h. The stirring was continued for 16 h and the usual workup followed by column chromatography on silica gel (100−200 mesh) afforded the products as mentioned in Table 5.

NMR Measurements. 200 MHz ^{1}H NMR spectra assignments were used for the determination of *dl*/*meso* ratio of the pinacols obtained. Chromatographically purified homogeneous diastereomeric mixture was used for the analysis. Assignments were made by comparing the relative heights of methyl signals at δ 1.5 and 1.6, respectively, for *dl* and *meso* isomers, as reported by Fürstner *et al*.[32]

Product Balances. The product balances were calculated based on the percentage of conversion of ketone/aldehyde to corresponding stilbene/pinacol. All the reactions were carried out at least twice for concordant values. Products were characterized by IR, ^{1}H NMR, and mass spectral data.

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Supporting Information Available: Experimental data for **3f−k** (1 page). See any current masthead page for ordering and Internet access instructions.

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