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Oxidative Dimerization of Lithium-Enolates of Esters Promoted by TitaniumTetrachloride†

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Oxidative dimerization of lithium ester enoalates is effectively promoted by $TiCl_4$, which serves as a new and efficient synthetic method. Mechanistic study indicates that the reaction proceeds via a radical-like mechanism, but it is not a free radical process.

Dimerization of the lithium-enolates of ketones and esters gives 1,4-diketones and 1,4-diesters, respectively, which are useful intermediates in organic synthesis. It is known that Cu(II) salts can promote the dimerization of ester enolates and ketone enolates, giving the corresponding 1,4-diesters (succinates) and 1,4-diketones, respectively, in reasonable yields.[1-3] It has also been shown that iodine can promote the dimerization of dilithium-enolates of carboxylic acids to the corresponding 1,4-dicarboxylic acids (succinic acids) in good to excellent yields.[4,5] Renaud and Fox reported supporting evidence for the existence of both radical and inoic paths in this reaction.[5] Silver (I)-promoted dimerization of the dilithium-enolates of α,β-unsaturated carboxylic acids has been reported to give γ–γ and α–γ (ca. 1:1) coupling products in fair to good yields.[6] It has been shown that silyl enol ethers of ketones dimerize in the presence of Ag_2O to form the corresponding 1,4-diketones.[7] As in the Cu(II)-promoted reactions of ketone lithium-enolates,[2] the yield of the reaction is highly sensitive to substituent at the α-position of the ketone although $Cu(OTf)_2$ works well for α-*mono*substituted ketones.[3] We have reported that ketene silyl acetals (KSAs) underegoes smooth oxidative dimierization in the presence of $TiCl_4$ to give succinates in high yields regardless of the substitution pattern at the α-position of starting esters.[8] The reaction was assumed to proceed via homocoupling of ester radicals generated from Ti(IV) ester enolates (Scheme 1). We have also demonstrated that the oxidative dimerization of vinylketene silyl acetals promoted by $TiCl_4$ proceeds with good to high regioselectivity, affording $\gamma(E),\gamma(E)$-products as the predominant dimer,[9] which implies an important role of Ti(IV) - ester enolate intermediates rather than free radicals to account for the observed regioselectivity. If the $TiCl_4$-promoted dimerization of KSAs and VKSAs involves Ti(IV) - ester enolate species, it may be possible to generate the same species by the direct transmetallation of lithium enolates to Ti(IV) enolates (Scheme 1). In fact, we have found that a similar dimerization takes place by the reaction of lithium ester enolates with $TiCl_4$. We will describe in this communication new and facile $TiCl_4$-promoted homodimerizations of lithium ester enolates, which is, to the best of our knowledge, the first example of homogeneous dimerization of enolates promoted by early transition metal species.

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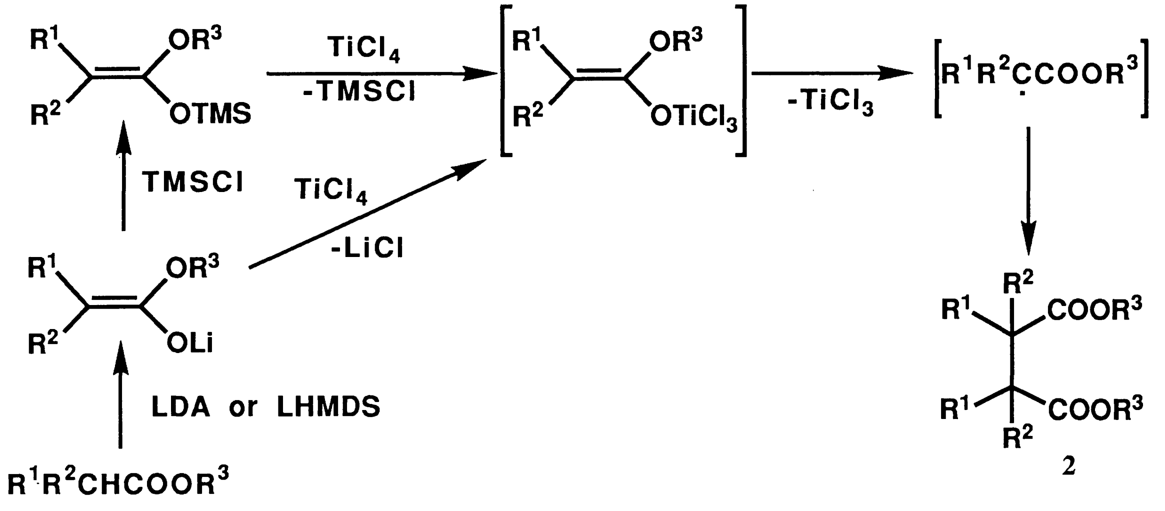
†Dedicated to Dr. Osamu Simamura, Professor Emeritus of The University of Tokyo, and Former President of Sagami Chemical Research Center, on the occasion of his 80th Birthday.



Scheme 1.

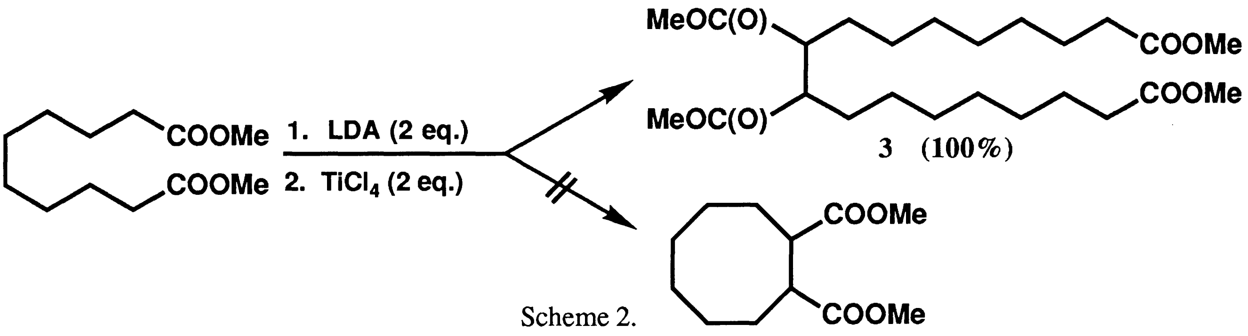
Typically, an ester **1** is allowed to react with LDA at -78 °C in THF, generating a lithum ester enolate to which is added one equivalent of $TiCl_4$ in dichloromethane at the same temperature. The reaction is either quenched at -78 °C or at room temperature with aqueous NH_4Cl or Na_2CO_3. The reaction mixture is extracted with EtOAc, centrifuged, washed with brine, passed through a pad of celite, dried over anhydrous $MgSO_4$, and the solvent removed to give succinates **2**. Esters **1** with monoalkyl, dialkyl, α-phenoxy, and α-benzyloxy substitutents reacted smoothly to afford the corresponding dimers **2**, i.e., succinates, in good to nearly quantitative yield. Typical results are shown in Table 1.

Table 1. Oxidative dimerization of simple esters through lithium ester enolate - $TiCl_4$ system[a)]

Entry	Ester **1**			Conditions[b)]	Yield of **2**/%[c)]
	R^1	R^2	R^3		
1	Me	Me	Me	A	80
2	^iPr	H	Et	B	96
3	$PhCH_2O$	H	Me	A	60
4	$PhCH_2O$	H	^iPr	A	98
5	PhO	H	Me	A	52

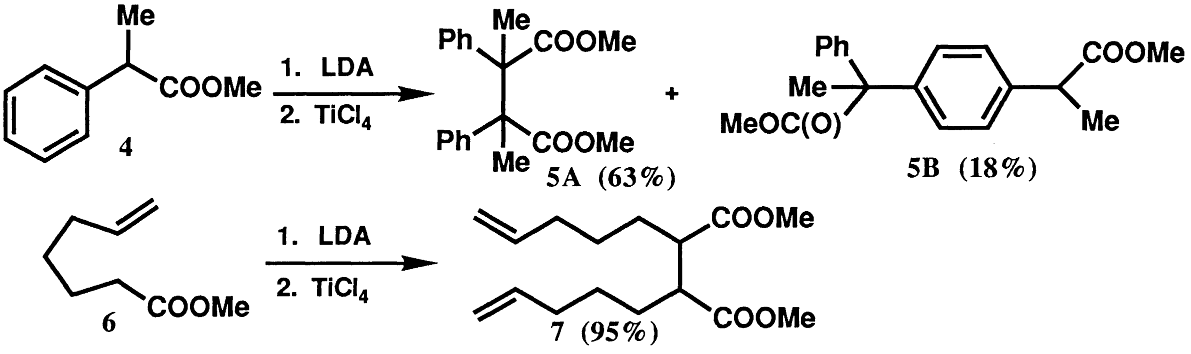
[a)] All reactions were run with 4.0 mmol of ester, 4.0 mmol of LDA, and 4.0 mmol of $TiCl_4$ (4.0 ml of 1M solution in CH_2Cl_2) in 20 ml of THF. [b)] Condition A: the reaction and quenching were carried out at -78 °C; Condition B: the reaction was run at -78 °C for 1 h and the mixture was gradually warmed to room temperature (12 h) and quenched. [c)] Isolated yield. Product is a mixture of racemic and meso isomers except for Entry 1.

An attempted intramolecular coupling giving a cyclooctane-1,2-dicarboxylate with two equivalents each of LDA and $TiCl_4$ in a high dilution condition ($5x10^{-3}M$) resulted in the formation of the linear tetraester **3** in a quantitative yield which was formed via intermolecular dimerization (Scheme 2).



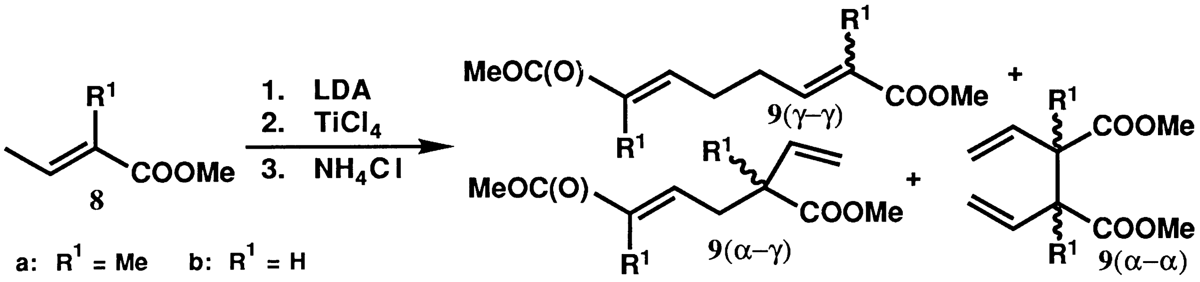
Scheme 2.

In order to obtain mechanistic insight of the reaction, especially the radical nature of the process, we carried out the dimerization of methyl 2-phenylpropionate (**4**) and methyl 6-heptenoate (**6**) (Scheme 3), which have been used as "*in situ* radical trap".5) The reaction with **4** gave a 3.5:1 mixture of the usual dimer **5A** and the unsymmetrical dimer **5B** in which coupling took place at the para position of one of the ester **4** moiety. The formation of **5B** (minor product) can be ascribed to a radical process.5) In fact, in the oxidative dimerizations promoted by I_2 and electrolysis, Renaud and Fox observed the formation of unsymmetrical dimer **5B** as the major product,5) i.e., **5A**:**5B** = 1:1.7 for the I_2-promoted reaction and 1:2.5 for the electrolysis.5) This result may imply less radical nature of the $TiCl_4$-promoted reaction. The reaction with **6** gave the usual dimer **7** in 95% yield and no cyclized product was detected, which is supposed to be formed via facile radical cyclization of a hexenyl radical intermediate if any free radical process *were* involved.



Scheme 3.

It should be noted that (i) $BF_3.OEt_2$ and $SnCl_4$ do not promote this oxidative dimerization of lithium ester enolates at all (no reaction took place with lithium ester enolates), (ii) $ZrCl_4$ does not promote the dimerization either, but acts as a Lewis acid to promote Claisen condensation of esters under the standard reaction conditions (LDA, -78°C, then $ZrCl_4$), and (iii) this $TiCl_4$-promoted dimerization of lithium enolates is applicable only for esters and not for ketones and amides. α,β-Unsaturated esters **8** also dimerize to give a mixture of diesters **9** under the same reaction conditions (Scheme 4). Typical results are listed in Table 2. As Table 2 shows, this dimerization exhibits only low regioselectivity, which forms a sharp contrast to the regioselective $TiCl_4$-promoted dimerizations of VKSAs, which give always **9**(γ-γ) as the predominant product **9**. Substantial formation of α-α dimer, **9**(α-α), is also characteristic to this reaction (Entries 2 and 3). It is noteworthy that this reaction gives **9**(α-γ) as the major product and the use of LHMDS as the base instead of LDA increased the α-γ/γ-γ ratio to 4. This fact suggests that the amines generated in this reaction, i.e., HN^iPr_2 and $HN(TMS)_2$, interact with the intermediate Ti(IV)-enolate species to effect the regioselectivity of the coupling.



Scheme 4.

Table 2. Oxidative dimerization of α,β-unsaturated esters through lithium ester enolate - $TiCl_4$ system[a)]

Entry	Ester	Base	Yield/%[b)]	Product ratio[c)]			(γ-γ):(α-γ)
				9(γ-γ)	9(α-γ)	9α-α)	
1	**8a**	LDA	94	55	45	---	1.2:1
2	**8b**	LDA	65	29	59	12	1:2
3	**8b**	LHMDS	50	14	57	29	1:4

[a)] For reaction conditions, see Table 1 footnote a). [b)] Isolated yield. [c)] Determined by GLC analysis.

Further study on the mechanism of this reaction and the applications to organic synthesis is actively underway.

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