

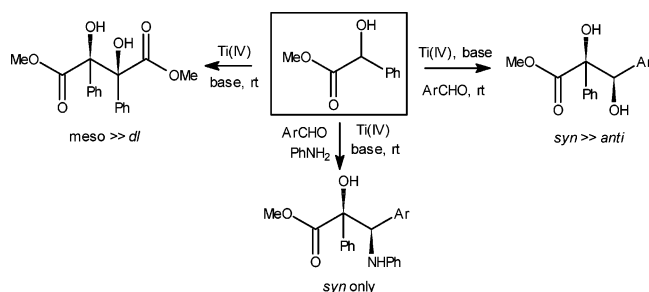
## Reactivity of Methyl Mandelate–Ti(IV)-enediolate: Oxidative Homocoupling versus Aldol and Direct Mannich-Type *Syn*-Diastereoselective Condensation

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Methyl mandelate undergoes quantitative oxidative homocoupling on treatment with  $\text{TiCl}_4$ /amine at room temperature. In the presence of  $\text{ArCHO}$ , quantitative *syn*-diastereoselective aldol condensation takes over the dimerization, whereas exclusive Mannich-type *syn*-diastereoselective reaction is observed in the presence of both  $\text{ArCHO}$  and  $\text{PhNH}_2$ . The subsequent reactions of the title intermediate do not depend on how it is generated.

Scattered examples of Li-enolate and silylenol ether<sup>1</sup> homocoupling promoted by  $\text{TiCl}_4$  have been reported. More recently, oxidative coupling of simple Ti(IV)-enolates from phenylacetic acid derivatives have appeared.<sup>2</sup> Since Ti(IV)-enolates can play an important role in carbon–carbon bond formation, understanding all aspects of their reactivities is an important goal.

In the course of our studies, we have found that  $\text{TiCl}_4$ /pyridine/THF reduction of methyl phenylglyoxylate **1**, in the presence of aldehydes or imines (formed in situ), undergoes aldol<sup>3</sup> or direct Mannich-type<sup>4</sup> condensations. According to the mechanism of Scheme 1 (paths a), we suggested Ti(IV)-enediolate **C**<sup>3,4</sup> to be the reactive intermediate. Ti(III)-reductive dimerization of **1**, via coupling of the intermediate radical **A**, is followed in tandem by

(1) (a) Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, *23*, 2009–2012. (b) Wallace, I. H. M.; Chan, T. H. *Tetrahedron* **1983**, *39*, 847–853. (c) Ojima, I.; Brandstadter, S. M.; Donovan, R. *Chem. Lett.* **1992**, 1591–1594.

(2) (a) Matsamura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809–2811. (b) Kise, N.; Kumada, K.; Terao, Y.; Ueda, N. *Tetrahedron* **1998**, *54*, 2697–2708.

(3) Clerici, A.; Clerici, L.; Malpezzi, L.; Porta, O. *Tetrahedron* **1995**, *51*, 13385–13400.

(4) Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1995**, *36*, 5955–5958.

TABLE 1. Oxidative Coupling of **2** under Different Experimental Conditions

entry (method) <sup>b</sup>	molar ratio			yield (%) <sup>a</sup>	
	<b>2</b>	$\text{TiCl}_4$	base	<b>3</b> ( <i>meso/dl</i> )	<b>1</b>
1 (i)	1	1	–	no reaction	
2 (i)	1	1	1	9 (83:17)	–
3 (i)	1	1	2	62 (80:20)	–
4 (i)	1	1	3	quant (83:17)	–
5 (i)	1	2	3	quant (95:5)	–
6 (i) <sup>c</sup>	1	1	3	60 (83:17)	–
7 (ii)	1	1	3	14 (only <i>meso</i> )	30
8 (ref 3) <sup>d</sup>				59 (92:8)	–

<sup>a</sup> Material balance  $\geq 95\%$ ; quant means <sup>1</sup>H NMR purity of the crude residue is  $\geq 95\%$ ; the remainder to 100% is the starting material **2**; yields and isomer ratios are calculated from the peak area of the  $\text{COOCH}_3$  proton singlets ( $\delta$ , ppm): **3-meso**, 3.85; **3-dl**, 3.79; **2**, 3.74; **1**, 3.98. <sup>b</sup> Method i: slow addition (15 min) of  $\text{TiCl}_4$  to **2** followed by the base addition (5 min). Method ii: addition of the base (10 min) to **2** followed by  $\text{TiCl}_4$  addition (5 min.). <sup>c</sup> DIPEA instead of TEA was used. <sup>d</sup> From **1**/ $\text{TiCl}_3$ /pyridine/THF.

the heterolytic cleavage of Ti(IV)-chelated diol **B**, affording **C** and the starting **1**.<sup>5</sup>

In the absence of any reactive partner, both **1** and **C** are partially recycled to **A**, the former by Ti(III) reduction and the latter by Ti(IV) oxidation affording dimethyl 2,3-dihydroxy-2,3-diphenylbutanedioate **3** (59%; *meso/dl*, 98:2) and **2** (6%).<sup>3</sup> Conversely, in the presence of a suitable electrophile, **C** is drained from the cycle to afford **4** or **5**.<sup>3–5</sup>

We now report our preliminary results on the reactivity of **C** when it is directly generated from methyl mandelate **2** and  $\text{TiCl}_4$ /TEA (or DIPEA, *N,N*-diisopropylethylamine) at room temperature (Scheme 1, paths b). The results obtained, either in the absence or in the presence of electrophiles, show that the chemo- and stereoselectivity of **C** generated by the previous and the present methods are quite similar.

**Oxidative Coupling of 2.** When 3 equiv of TEA was added to a  $\text{CH}_2\text{Cl}_2$  solution of **2** and  $\text{TiCl}_4$  (1 equiv each), dimer **3** is formed in quantitative yield after  $\text{NH}_4\text{Cl}$  hydrolysis of **B**. The amount of TEA strictly controlled the yield of **3** (Table 1, method i, entries 1–4), whereas the use of DIPEA resulted in a lower yield (entry 6). Two equivalents of  $\text{TiCl}_4$  slightly improved the *meso/dl* ratio (entry 5).

The reaction conditions that involve reverse order of addition (TEA followed by  $\text{TiCl}_4$ , method ii, entry 7) furnished **1** as the main oxidation product. Both products distribution (formation of **3** and **1**) and stereoselectivity (only **3-meso**) observed are in accord with the radical mechanism shown in Scheme 1 (paths b).

The Ti(IV)-enolate **C**, once formed from **2**, is oxidized, via metal to ligand electron transfer (ET), to the stabi-

(5) Clerici, A.; Clerici, L.; Porta, O. *J. Org. Chem.* **1995**, *60*, 480–481.



**TABLE 3.** *Syn*-Diastereoselective Direct Mannich-Type Condensation of **2** under Different Experimental Conditions

entry (method) <sup>b</sup>	molar ratio					yield (%) <sup>a</sup> <b>5</b>
	<b>2</b>	ArCHO	PhNH <sub>2</sub>	TiCl <sub>4</sub>	base	
1 (v)	1	1	1	1	2	50
2 (v)	1	1	1.5	1	2	55
3 (v)	1	1	1.5	1.5	2	56
4 (v)	1	1	1.5	2	2	70 (60) <sup>c</sup>
5 (vi)	1	1	1.5	1.5	2	71 (62) <sup>c</sup>
6 (ref 4) <sup>d</sup>						61 <sup>c</sup>

<sup>a</sup> See footnote *a* of Table 1. COOCH<sub>3</sub> proton singlets ( $\delta$ , ppm): **5-syn**, 3.82; **2**, 3.74. <sup>b</sup> Method v: slow addition (6 min) of TiCl<sub>4</sub> to **2**, ArCHO, PhNH<sub>2</sub>, and TEA in CH<sub>2</sub>Cl<sub>2</sub> solution; Method vi: slow addition (6 min) of TiCl<sub>4</sub> to a THF solution of **2**, ArCHO, PhNH<sub>2</sub>, and pyridine. <sup>c</sup> Isolated yield in parentheses. <sup>d</sup> From **1**/TiCl<sub>3</sub>/pyridine/THF.

oxidative dimerization products were observed and *syn*- $\alpha$ -hydroxy- $\beta$ -amino ester **5** was the sole product and the only detectable isomer (Table 3, method v, entries 1–4).

However, by performing the reaction in the presence of an excess of aldehyde (4-bromobenzaldehyde/aniline, 2:1 molar ratio), the aldol product **4** was obtained in 90% yield. This result, along with the ones of entries 1–4, would indicate that the Ti(IV)-catalyzed imine formation<sup>8</sup> is faster than the concurrent aldolization and that addition of **C** is faster to an aldehyde than to an imine.

To carefully compare the reactivity of **C**, directly formed from **2**/TiCl<sub>4</sub> (entries 1–4), with the reactivity of

**C**, indirectly formed from **1**/TiCl<sub>3</sub>/pyridine/THF,<sup>4</sup> we performed the Mannich type condensation starting from **2**/TiCl<sub>4</sub>/pyridine/THF also (entry 5) and, as predicted by the proposed mechanism, the yield and diastereoselectivity were similar (compare entries 4–6).

In recent years,<sup>9</sup> the synthesis of  $\beta$ -amino- $\alpha$ -hydroxy acids has attracted much attention due to their occurrence in many biologically relevant compounds (taxol side chain is a representative example). The results herein reported demonstrate the significance of titanium salts as useful reagents in *syn*-diastereoselective synthesis of this class of compounds. It remains to be seen whether this very simple approach is to be successful in enantioselective synthesis with chiral  $\alpha$ -hydroxy derivatives. Current studies toward this goal are underway.

In conclusion, the present investigation has demonstrated that the reactivity of **C** does not depend on how it is generated and, at the same time, supports our previous mechanistic hypothesis. This new method is synthetically more attractive than the former since (a) TiCl<sub>4</sub> is easier to handle than TiCl<sub>3</sub>, (b) strictly anhydrous solvents are not required, (c) many  $\alpha$ -hydroxy esters are commercially available materials and more stable than the corresponding  $\alpha$ -keto esters, and (d) for comparable yields of products (**3**, **4**, and **5**) half the amount of metal salt is required.

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**Supporting Information Available:** General experimental details, full purification, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(8) Ti(IV) has been shown to facilitate the formation of enamines and imines in anhydrous solvents. (a) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213–214. (b) Weingarten, H.; Chupp, J. P.; White, W. A. *J. Org. Chem.* **1967**, *32*, 3246–3249. (c) Carlson, R.; Larson, U.; Hansson, L. *Acta Scand.* **1992**, *46*, 1211–1213.

(9) (a) Roers, R. R.; Verdine, G. L. *Tetrahedron Lett.* **2001**, *42*, 3563–3565. (b) Kudyba, I.; Raczko, J.; Jurczak, J. *Tetrahedron Lett.* **2003**, *44*, 8685–8687 and references quoted therein.