

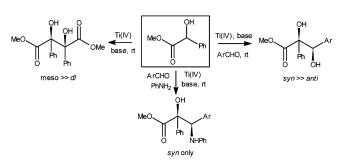
Reactivity of Methyl Mandelate-Ti(IV)-enediolate: Oxidative Homocoupling versus Aldol and Direct Mannich-Type Syn-Diastereoselective Condensation

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Methyl mandelate undergoes quantitative oxidative homocoupling on treatment with $TiCl_4$ /amine at room temperature. In the presence of ArCHO, quantitative *syn*-diastereoselective aldol condensation takes over the dimerization, whereas exclusive Mannich-type *syn*-diastereoselective reaction is observed in the presence of both ArCHO and PhNH₂. The subsequent reactions of the title intermediate do not depend on how it is generated.

Scattered examples of Li-enolate and silylenol ether¹ homocoupling promoted by $TiCl_4$ have been reported. More recently, oxidative coupling of simple Ti(IV)-enolates from phenylacetic acid derivatives have appeared.² 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 TiCl₃/ pyridine/THF reduction of methyl phenylglyoxylate 1, in the presence of aldehydes or imines (formed in situ), undergoes aldol³ or direct Mannich-type⁴ condensations. According to the mechanism of Scheme 1 (paths a), we suggested Ti(IV)-enediolate $C^{3,4}$ to be the reactive intermediate. Ti(III)-reductive dimerization of 1, via coupling of the intermediate radical **A**, is followed in tandem by TABLE 1. Oxidative Coupling of 2 under DifferentExperimental Conditions

	`OMe −	TiCl₄/base CH₂Cl₂, rt	OH │ PhC │ CO; 3)Me	
entry	molar ratio			yield (%) ^a		
$(method)^b$	2	${ m TiCl}_4$	base	3 (meso/dl)	1	
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) ^c	1	1	3	60 (83:17)	_	
7 (ii)	1	1	3	14 (only meso)	30	
$8 (\mathrm{ref}3)^d$				59 (92:8)	-	

^a Material balance \geq 95%; quant means ¹H 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 COOCH₃ proton singlets (δ , ppm): **3**-meso, 3.85; **3**-dl, 3.79; **2**, 3.74; **1**, 3.98. ^b Method i: slow addition (15 min) of TiCl₄ to **2** followed by the base addition (5 min). Method ii: addition of the base (10 min) to **2** followed by TiCl₄ addition (5 min.). ^c DIPEA instead of TEA was used. ^d From **1**/TiCl₃/pyridine/THF.

the heterolytic cleavage of Ti(IV)-chelated diol **B**, affording **C** and the starting $\mathbf{1}^{.5}$

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%).³ Conversely, in the presence of a suitable electrophile, C is drained from the cycle to afford 4 or $5.^{3-5}$

We now report our preliminary results on the reactivity of **C** when it is directly generated from methyl mandelate **2** and TiCl₄/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 CH_2Cl_2 solution of **2** and $TiCl_4$ (1 equiv each), dimer **3** is formed in quantitative yield after NH₄Cl 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 TiCl₄ slightly improved the *meso/dl* ratio (entry 5).

The reaction conditions that involve reverse order of addition (TEA followed by TiCl₄, 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-

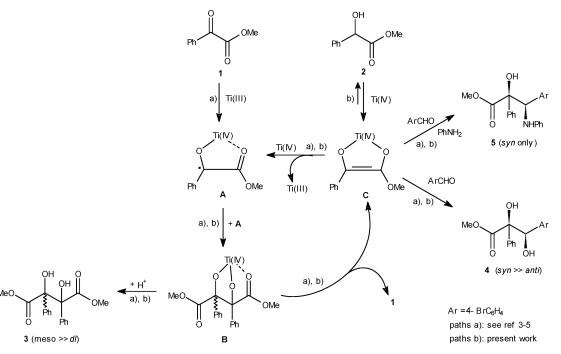
^{(1) (}a) Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, *23*, 2009–2012.
(b) Wallace, I. H. M.; Chan, T. H. *Tetrahedron* **1983**, *39*, 847–853. (c) Ojima, I.; Brandstadter, S. M.; Donovan, R. *Chem. Lett.* **1992**, 1591–1594.

 ^{(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.

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



lized capto-dative radical **A**, which, under acidic conditions from the beginning (method i), couples at the less hindered side to give predominantly **3**-meso. Under basic conditions from the beginning (method ii), Ti(IV)-chelated diol **B**, once formed, undergoes heterolytic cleavage to **1** and **C**, which is partially recycled.

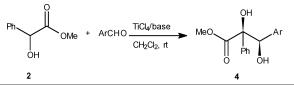
In a control experiment it was found that 68% of **3**-meso, under conditions of entry 7, is converted to **1** (47%), **2** (10%), and **3**-dl (9%), whereas it is recovered unchanged under conditions of entry 4. Last, it must be stressed that no traces of products derived from TiCl₄-amine oxidation were detected.⁶

Aldol Addition of 2 vs Homocoupling. When equimolar amounts of 2, 4-bromobenzaldehyde, and TiCl₄ were allowed to react at room temperature for 30 min in the presence of 2 equiv of TEA or DIPEA, syn-diastereoselective condensation of C with the aldehyde occurred and α,β -dihydroxy ester 4 was formed in quantitative yield (Table 2, method iii, entries 2 and 4). Longer reaction time (2-4 h) did not change the diastereoselectivity.

Oxidative coupling of **2** partially competed (17% of 3) with aldol condensation (83% of 4) only when 2 equiv of TiCl₄ was employed (entry 3), but the *syn/anti* ratio increased to 98:2. The order of TiCl₄ and amine addition did not significantly decrease the yield of **4** (entry 5, method iv).

To the best of our knowledge there are no previous reports of aldol condensation of unprotected α -hydroxy ester promoted by TiCl₄/amine at room temperature. Most related methods require low temperatures and hydroxy-protected substrates.⁷ At low temperature, it is critical that TiCl₄ complexation of the enolizable substrate precedes the amine addition, which, otherwise,

TABLE 2.Aldol Addition of 2 with4-Bromobenzaldehyde under Different ExperimentalConditions



entry		mola	vield (%) ^a		
$(method)^b$	2	ArCHO	${ m TiCl}_4$	base	4 (syn:anti)
1 (iii)	1	1	1	1	<5
2 (iii)	1	1	1	2	quant (83:17)
3 (iii)	1	1	2	2	$83 (98:2)^c$
4 (iii) ^d	1	1	1	2	quant (87:13)
5 (iv)	1	1	1	2	80 (90:10)
$6 (ref 3)^{e}$					85 (96:4)

^{*a*} See footnote *a* of Table 1. COOCH₃ proton singlets (δ , ppm): 4-*syn*, 3.85; 4-*anti*, 3.67; 2, 3.74. ^{*b*} Method iii: the base was slowly added (6 min) to 2, ArCHO, and TiCl₄. Method iv: TiCl₄ was slowly added (5 min) to 2, ArCHO, and the base. ^{*c*} 17% of 3 was also formed. ^{*d*} DIPEA instead of TEA is used. ^{*e*} From 1/TiCl₃/pyridine/ THF.

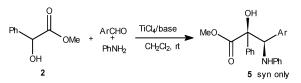
irreversibly complexes with TiCl₄.⁷ We found that no aldol condensation of **2** by TiCl₄/TEA occurs at -40 °C, thus the TiCl₄-TEA complexation at room temperature is readily reversible and, as a consequence, the order of reagent addition must no longer be strictly followed.

Direct Syn-Diastereoselective Mannich-Type Reaction of 2 vs Aldol Condensation. When $TiCl_4$ was added at room temperature to a CH_2Cl_2 solution of 2 and TEA containing 4-bromobenzaldehyde and aniline in a 1:1 or 1:1.5 molar ratio, neither aldol addition nor

^{(6) (}a) Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron Lett.* **2004**, *45*, 1825–1827 and references quoted therein. (b) Periasamy, M.; Sriniva, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577–7580.

^{(7) (}a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Lombardi Borgia, A. J. Org. Chem. 1992, 57, 6339–6342. (b) Adrian, J. C., Jr.; Borkin, L.; Fox, R. J.; Chick, J. E.; Hunter, A. D.; Nicklow, R. A. J. Org. Chem. 2000, 65, 6264–6267. (c) Crimmins, M. T.; McDougall, P. J. Org. Lett. 2003, 5, 591–594.

TABLE 3. Syn-Diastereoselective Direct Mannich-TypeCondensation of 2 under Different ExperimentalConditions



entry (method) ^b			vield (%) ^a			
	2	ArCHO	$PhNH_2$	${ m TiCl}_4$	base	5
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	$70 \ (60)^c$
5 (vi)	1	1	1.5	1.5	2	$71 (62)^c$
$6 (ref 4)^d$						61^c

^{*a*} See footnote *a* of Table 1. COOCH₃ proton singlets (δ , ppm): **5**-syn, 3.82; **2**, 3.74. ^{*b*} Method v: slow addition (6 min) of TiCl₄ to **2**, ArCHO, PhNH₂, and TEA in CH₂Cl₂ solution; Method vi: slow addition (6 min) of TiCl₄ to a THF solution of **2**, ArCHO, PhNH₂, and pyridine. ^{*c*} Isolated yield in parentheses. ^{*d*} From **1**/TiCl₃/ pyridine/THF.

oxidative dimerization products were observed and syn- α -hydroxy- β -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 formation⁸ 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 $2/\text{TiCl}_4$ (entries 1–4), with the reactivity of

C, indirectly formed from $1/\text{TiCl}_3/\text{pyridine/THF}$,⁴ we performed the Mannich type condensation starting from $2/\text{TiCl}_4/\text{pyridine/THF}$ also (entry 5) and, as predicted by the proposed mechanism, the yield and diastereoselectivity were similar (compare entries 4-6).

In recent years,⁹ the synthesis of β -amino- α -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 α -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) TiCl₄ is easier to handle than TiCl₃, (b) strictly anhydrous solvents are not required, (c) many α -hydroxy esters are commercially available materials and more stable than the corresponding α -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 fo 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.