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

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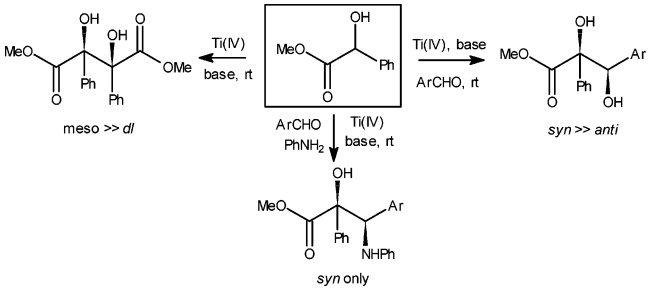
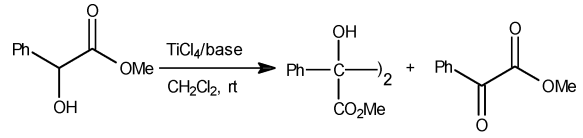


Methyl mandelate undergoes quantitative oxidative homocoupling on treatment with $TiCl_4$/amine at room temperature. In the presence of ArCHO, quantitative *syn*-diastereoselective aldol condensation takes over the dimerization, whereas exclusive Mannich-type *syn*-diastereoselective reaction is observed in the presence of both ArCHO and $PhNH_2$. The subsequent reactions of the title intermediate do not depend on how it is generated.

Scattered examples of Li-enolate and silylenol ether[1] 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 $TiCl_3$/pyridine/THF reduction of methyl phenylglyoxylate **1**, in the presence of aldehydes or imines (formed in situ), undergoes aldol[3] or direct Mannich-type[4] 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 the heterolytic cleavage of Ti(IV)-chelated diol **B**, affording **C** and the starting **1**.[5]

TABLE 1. Oxidative Coupling of 2 under Different Experimental Conditions



entry (method)[b]	molar ratio **2**	$TiCl_4$	base	yield (%)[a] **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 (ref 3)[d]				59 (92:8)	−

[a] Material balance ≥95%; quant means ^{1}H NMR purity of the crude residue is ≥95%; the remainder to 100% is the starting material **2**; yields and isomer ratios are calculated from the peak area of the $COOCH_3$ 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 $TiCl_4$ to **2** followed by the base addition (5 min). Method ii: addition of the base (10 min) to **2** followed by $TiCl_4$ addition (5 min.). [c] DIPEA instead of TEA was used. [d] From **1**/$TiCl_3$/pyridine/THF.

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 $TiCl_4$/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 CH_2Cl_2 solution of **2** and $TiCl_4$ (1 equiv each), dimer **3** is formed in quantitative yield after NH_4Cl 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 $TiCl_4$ slightly improved the *meso*/*dl* ratio (entry 5).

The reaction conditions that involve reverse order of addition (TEA followed by $TiCl_4$, 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-

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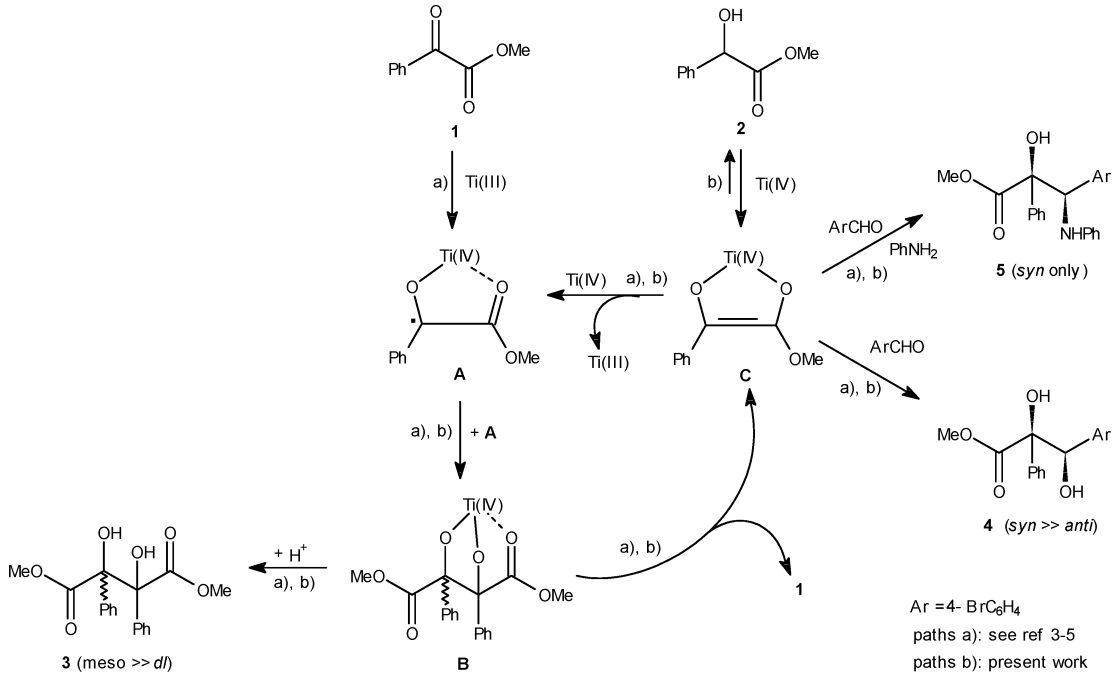
SCHEME 1



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.

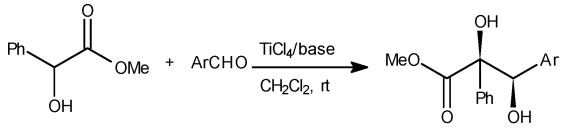
In a control experiment it was found that 68% of **3**-*meso*, under conditions of entry 7, is converted to **1** (47%), **2** (10%), and **3**-*dl* (9%), whereas it is recovered unchanged under conditions of entry 4. Last, it must be stressed that no traces of products derived from $TiCl_4$-amine oxidation were detected.[6]

Aldol Addition of 2 vs Homocoupling. When equimolar amounts of **2**, 4-bromobenzaldehyde, and $TiCl_4$ 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 $TiCl_4$ was employed (entry 3), but the *syn*/*anti* ratio increased to 98:2. The order of $TiCl_4$ 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 $TiCl_4$/amine at room temperature. Most related methods require low temperatures and hydroxy-protected substrates.[7] At low temperature, it is critical that $TiCl_4$ complexation of the enolizable substrate precedes the amine addition, which, otherwise, irreversibly complexes with $TiCl_4$.[7] We found that no aldol condensation of **2** by $TiCl_4$/TEA occurs at −40 °C, thus the $TiCl_4$−TEA complexation at room temperature is readily reversible and, as a consequence, the order of reagent addition must no longer be strictly followed.

TABLE 2. Aldol Addition of 2 with 4-Bromobenzaldehyde under Different Experimental Conditions



entry (method)[b]	molar ratio **2**	ArCHO	$TiCl_4$	base	yield (%)[a] **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. $COOCH_3$ 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 $TiCl_4$. Method iv: $TiCl_4$ 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**/$TiCl_3$/pyridine/THF.

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

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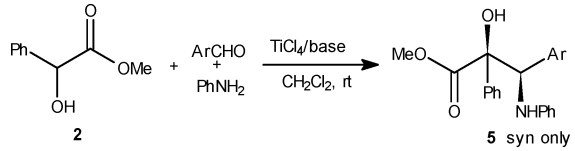
TABLE 3. *Syn*-Diastereoselective Direct Mannich-Type Condensation of 2 under Different Experimental Conditions



entry (method)[b]	molar ratio 2	ArCHO	$PhNH_2$	$TiCl_4$	base	yield (%)[a] 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. $COOCH_3$ proton singlets (δ, ppm): **5**-*syn*, 3.82; **2**, 3.74. [b] Method v: slow addition (6 min) of $TiCl_4$ to **2**, ArCHO, $PhNH_2$, and TEA in CH_2Cl_2 solution; Method vi: slow addition (6 min) of $TiCl_4$ to a THF solution of **2**, ArCHO, $PhNH_2$, and pyridine. [c] Isolated yield in parentheses. [d] From **1**/$TiCl_3$/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 formation[8] 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**/$TiCl_4$ (entries 1−4), with the reactivity of **C**, indirectly formed from **1**/$TiCl_3$/pyridine/THF,[4] we performed the Mannich type condensation starting from **2**/$TiCl_4$/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) $TiCl_4$ is easier to handle than $TiCl_3$, (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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