# Titanate-Mediated Transesterifications with Functionalized Substrates

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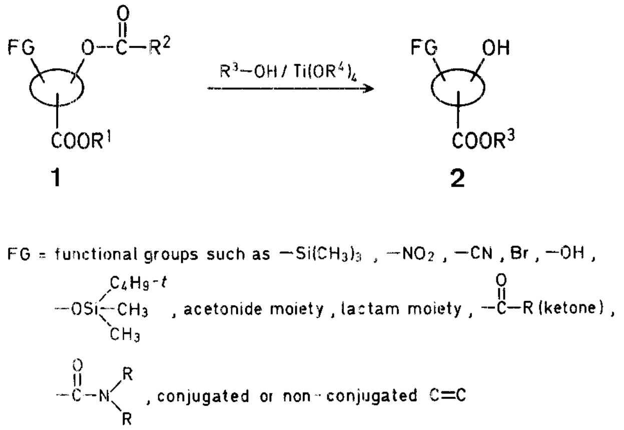
The chemical industry offers titanates as cheap bulk chemicals for various applications[a]. A literature search, inspection of the eight volumes of Fieser's *Reagents*, and discussions with many colleagues have revealed that titanate-mediated transesterifications are described almost exclusively in patents[2] and that this method is essentially unknown in synthetic laboratories[3]. We would therefore like to present here our recent experiences with transesterifications of esters bearing additional functional groups.

When esters of the type **1** containing functional groups are treated with titanium(IV) alkoxides [tetraalkyl titanates, $Ti(OR^4)_4$] in alcohols ($R^3$—OH) as solvents, acyl-protected carbinol functions (—O—CO—$R^2$) in the substrate are deprotected while the ester groups —COOR$^1$ are transesterified by the alcohol. Since the alcohol $R^3$—OH is used in excess, the group $R^4$ in the titanate need not necessarily be identical with $R^3$.



FG = functional groups such as $-Si(CH_3)_3$, $-NO_2$, $-CN$, Br, $-OH$, $-OSi(CH_3)_2C_4H_9\text{-}t$, acetonide moiety, lactam moiety, $-C(=O)-R$ (ketone), $-C(=O)-NR_2$, conjugated or non-conjugated C=C

Because of the low solubility of tetramethyl titanate, methyl esters can not be prepared. The accompanying Table shows the examples which we have carried out so far, and some representative procedures are given below.

This transesterification method is extremely mild. It is compatible with a large variety of functional groups, both in the acid and in the alcohol components (see FG under Scheme). Thus, *α*- and *β*-hetero-substituted alkanoic esters can be converted without *α*-substitution or *α,β*-elimination; the *t*-butyldimethylsilyl protective group (e.g. in **1g**) remains unaffected; on the other hand, no acetal or enol ether formation takes place when a keto group is present; nitrile, amide, and even *β*-lactam groups survive the transesterification; neither alkyl- and arylnitro functions nor aliphatic bromides interfere with the reaction; *t*-butyl esters can be made only in poor yields (<20%) but can be transesterified; benzyl esters can also be made, and carbamic acid esters can be transesterified. Chiral centers are not affected by the transesterification conditions (see Table). Attempts to obtain an allyl ester from an ethyl ester have hitherto been unsuccessful because of the instability of allyl alcohols.

The product esters **2** are at least 95% pure (according to $^1$H-N.M.R. analysis). Obviously, the method is based on a thermodynamic equilibrium so that the amount of starting material in the product ester can be further decreased, if desired, by using a larger excess of the alcohol, i.e., using lower concentrations of the ester **1** to be transesterified.

The surprising selectivity and mildness of the present method is undoubtedly due to the essentially neutral conditions during the reaction and also during aqueous work-up when the titanate is hydrolyzed to give $(TiO_2)_{aq}$ and $R^4$—OH; for neutral work-up, see the acetonide **2m** in the Table and the procedure below; another method of work-up is treatment of the reaction mixture with saturated aqueous potassium fluoride: if the product of transesterification is not too acid-sensitive, work-up with 1 normal hydrochloric acid is simpler.

The titanate-mediated transesterification might turn out to be the method of choice in many synthetic situations; it should not remain hidden in the patent literature.

The use of dried solvents is not necessary; we used 96% ethanol and commercial unpurified isopropanol as well as the absolute solvents with equal results. The boiling points given in the procedures and in the Table refer to air-bath temperatures during Kugelrohr distillation.

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[a] Thus, advertisements of two major manufacturers state: "... reliable supply and delivery, whether you need tank trucks, drums, or 40 lb. pails"[1a] or "Anwendungsgebiete: Katalysatoren für Ver- und Umesterungen"[1b].

0039-7881/82/0232-0138 $ 03.00

**Table.** Tetraalkyl Titanate-Mediated Transesterifications (**1**→**2**)

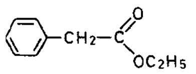
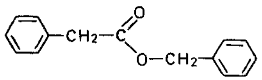
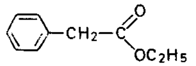
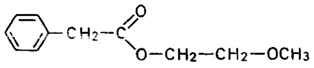
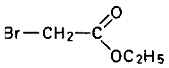
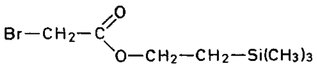
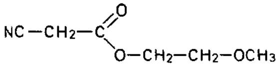
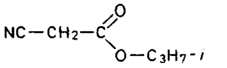
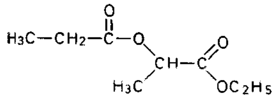
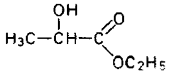
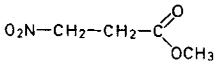
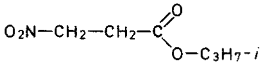
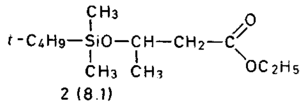
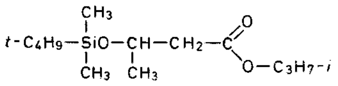
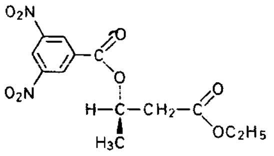
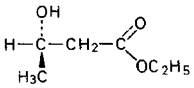
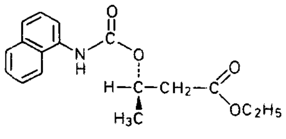
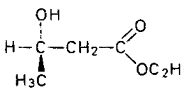
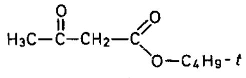
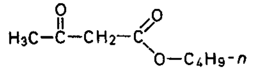
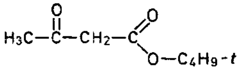
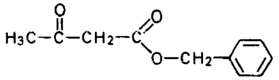
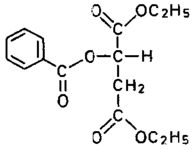
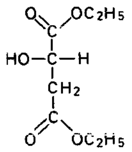
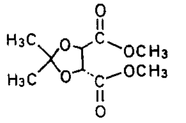
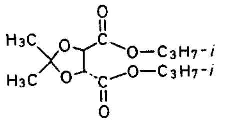
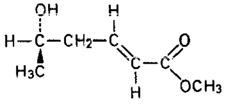
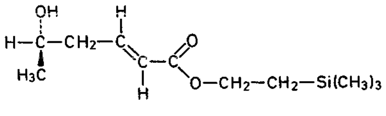
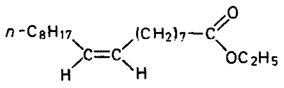
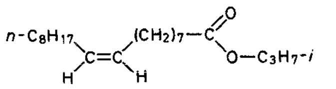
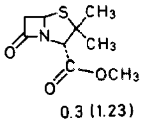
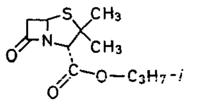
| | **1** Amount [g (mmol)] | | **2**[a] | Reaction Conditions | | | Yield [%] | b.p./torr [°C], and $[\alpha]_D$ | Molecular Formula or b.p./torr [°C] reported |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Alcohol (Solvent) (ml) | Titanate (molar Ratio titanate: **1**) | Time [h], Temperature [°C] | | | |
| **a** | <br>2 (12.2) | → |  | $C_6H_5-CH_2-OH$<br>(40) | $Ti(OC_2H_5)_4$<br>(0.36) | 15, 110° | 85 | 240°/7 | 166°/4[5a] |
| **b** | <br>2 (12.2) | → |  | $H_3CO-CH_2-CH_2-OH$<br>(40) | $Ti(OC_2H_5)_4$<br>(0.36) | 15, 125° | 99[c] | 120°/0.02 | $C_{11}H_{14}O_3$<br>(194.3) |
| **c** | <br>0.5 (3) | → |  | $(H_3C)_3Si-CH_2-CH_2-OH$<br>(10) | $Ti(OC_2H_5)_4$<br>(0.29) | 6, 100° | 71 | 50°/0.01 | $C_7H_{15}BrO_2Si$[b]<br>(239.2) |
| **d** | <br>5 (35) | → |  | $i\text{-}C_3H_7-OH$<br>(100) | $Ti(OC_2H_5)_4$<br>(0.31) | 6, 82° | 77 | 82°/6[d] | 205°[5b] |
| **e** | <br>2 (11.5) | → |  | $C_2H_5-OH$<br>(30) | $Ti(OC_2H_5)_4$<br>(0.38) | 6, 78° | 60 | $[\alpha]_D^{25}$: −10.14°<br>(neat) | 70°/36[5c]; $[\alpha]_D^{25}$:<br>−10.33° |
| **f** | <br>2 (15) | → |  | $i\text{-}C_3H_7-OH$<br>(15) | $Ti(OC_3H_7\text{-}i)_4$<br>(0.23) | 17, 82° | 50 | 105°/0.2 | $C_6H_{11}NO_4$[b]<br>(161.2) |
| **g** | <br>2 (8.1) | → |  | $i\text{-}C_3H_7-OH$<br>(30) | $Ti(OC_3H_7\text{-}i)_4$<br>(0.43) | 6, 82° | 83 | 125°/9 | $C_{13}H_{28}O_3Si$[b]<br>(260.5) |
| **h** | <br>0.83 (2.55) | → |  | $C_2H_5-OH$<br>(25) | $Ti(OC_2H_5)_4$<br>(0.3) | 96, 78° | 90 | 78°/11<br>$[\alpha]_D^{25}$: 43°<br>(c 1.0, $CHCl_3$) | 75–76°/12[5d] |
| **i** | <br>2 (6.6) | → |  | $C_2H_5-OH$<br>(40) | $Ti(OC_2H_5)_4$<br>(0.6) | 120, 130°, 5 atm | 30–45[c] | 78°/11<br>$[\alpha]_D^{25}$: 40.9°<br>(c 1.02, $CHCl_3$) | |

**Table.** Continued

| | 1<br>Amount<br>[g (mmol)] | 2[a] | Reaction Conditions | | | Yield [%] | b.p./torr [°C], and $[\alpha]_D$ | Molecular Formula or b.p./torr [°C] reported |
|---|---|---|---|---|---|---|---|---|
| | | | Alcohol (Solvent) (ml) | Titanate (molar Ratio titanate: 1) | Time [h], Temperature [°C] | | | |
| j |  10 (63.2) | ⟶  | $n$-$C_4H_9$—OH<br>(100) | $Ti(OC_2H_5)_4$<br>(0.21) | 8, 117° | 78[f] | 90-93°/12 | 83-85°/12[5c] |
| k |  10 (63.2) | ⟶  | $C_6H_5$—$CH_2$—OH<br>(200) | $Ti(OC_2H_5)_4$<br>(0.35) | 15, 100° | 56 | 160°/0.1 | 156-159°/0.1[4] |
| l |  2 (6.8) | ⟶  | $C_2H_5$—OH<br>(50) | $Ti(OC_2H_5)_4$<br>(0.64) | 6.5, 78° | 63 | 90°/0.01 | 144°/23[5f] |
| m |  2 (9.2) | ⟶  | $i$-$C_3H_7$—OH<br>(2 × 50) | $Ti(OC_3H_7$-$i)$<br>(~0.05) | 3, 70° | 91 | 80°/0.001<br>(m.p. 42-42.7°) | $C_{13}H_{22}O_6$[b]<br>(274.3) |
| n |  0.5 (3.47) | ⟶  | $(H_3C)_3Si$—$CH_2$—$CH_2$—OH<br>(10) | $Ti(OC_2H_5)_4$<br>(0.25) | 6, 100° | 74 | 150°/0.04 | $C_{11}H_{22}O_3Si$[b]<br>(230.4) |
| o |  2 (6.44) | ⟶  | $i$-$C_3H_7$—OH<br>(50) | $Ti(OC_3H_7$-$i)_4$<br>(0.55) | 8, 82° | 98 | 190°/0.1 | 218°/16[5g] |
| p |  0.3 (1.23) | ⟶  | $i$-$C_3H_7$—OH<br>(2 × 20) | $Ti(OC_3H_7$-$i)_4$<br>(1.8) | 4, 82° | 91 | $[\alpha]_D^{25}$: +224°<br>($c$ 0.65, $CHCl_3$) | $C_{11}H_{17}NO_3S$[b]<br>(243.3) |

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[a] The $^1H$-N.M.R. spectra are compatible with the product structures shown. Purities were better than 95% (Exception: **2b**).

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.34; H, ±0.07; N, ±0.10; Br, 0.31.

[c] Ratio starting material (**1b**): product (**2b**) = 13 : 87.

[d] I.R. ($CHCl_3$): $\nu = 2263\ cm^{-1}$ (C≡N).

[e] According to $^1H$-N.M.R. analysis, the crude ethyl 3-hydroxybutanoate **2i** contained the high-boiling ethyl 1-naphthylcarbamate which remained as residue after distillation of ester **2i**.

[f] Ratio starting material (**1j**): product (**2j**) = 1.3 : 98.7.

### Isopropyl 3-(*t*-Butyldimethylsiloxy)-butanoate (2g) from the Ethyl Ester (1g); Typical Procedure:

Ethyl 3-(*t*-butyldimethylsiloxy)-butanoate (**1g**; 2 g, 8.1 mmol) is dissolved in isopropanol (30 ml), tetraisopropyl titanate (1 g, 3.5 mmol) is added, and the mixture is heated to reflux temperature for 6 h. It is then cooled to ~45 °C, quenched with 1 normal hydrochloric acid (50 ml) (temporary turbidity is observed), and extracted with pentane (2 x 150 ml). The organic extract is washed with saturated aqueous sodium hydrogen carbonate (30 ml), dried with magnesium sulfate, and evaporated at 60 °C under reduced pressure to remove solvent and residual isopropanol; yield of **2g**: 1.745 g (83%); b.p. 125 °C/9 torr. The product is pure according to $^1$H-N.M.R. and T.L.C. analysis (Alox N, dichloromethane/pentane 1/1; iodine, $R_F = 0.6$).

| | | | |
|---|---|---|---|
| $C_{13}H_{28}O_3Si$ | calc. | C 59.95 | H 10.84 |
| (260.5) | found | 59.81 | 10.81 |

$^1$H-N.M.R. (CDCl$_3$/TMS, 90 MHz): $\delta = 5.0$ [hept, 1 H, O—C$\underline{H}$(CH$_3$)$_2$]; 4.25 (sext, 1 H, 3-H); 2.35 (d of d, 2 H, CO—CH$_2$); 1.25-1.05 [2 d, 9 H, 4,4,4-H$_3$ + O—CH(C$\underline{H}_3$)$_2$]; 0.85-0.7 [m, 9 H, SiC(C$\underline{H}_3$)$_3$]; 0.1 ppm [2 s, 6 H, Si(CH$_3$)$_2$].

### Diethyl (*S*)-(–)-Malate (2l) from Diethyl (*S*)-(–)-*O*-Benzoylmalate (1l):

Diethyl (*S*)-(–)-*O*-benzoylmalate (**1l**), $[\alpha]_D^{25}$: –4.0° (neat, 1 cm cell), is prepared from (*S*)-(–)-diethyl malate, $[\alpha]_D^{25}$: –9.3° (neat, 0.1 cm cell). The ester **1l** (2 g, 6.79 mmol) is dissolved in absolute ethanol (50 ml), tetraethyl titanate (1 g, 4.4 mmol) is added, and the mixture is heated at reflux temperature for 6.5 h. It is then cooled to ~40 °C, quenched with 1 normal hydrochloric acid (30 ml) (temporary turbidity is observed), and extracted with ether (3 x 100 ml). The organic extract is washed with saturated aqueous sodium hydrogen carbonate (30 ml), dried with magnesium sulfate, and evaporated at 20 °C under reduced pressure to remove solvent and residual ethanol. The residue which consists of **2l** and ethyl benzoate is distilled in vacuo to give *ethyl benzoate* (0.98 g, 96%; b.p. 55 °C/0.01 torr) and pure **2l**; yield: 0.81 g (63%); b.p. 90 °C/0.01 torr (Ref.$^{5f}$, b.p. 144 °C/23 torr); $[\alpha]_D^{25}$: –9.3° (neat, 0.1 cm cell) (cf. optical rotation of starting diethyl malate).

$^1$H-N.M.R. (CDCl$_3$/TMS, 90 MHz): $\delta = 4.6$-4.0 (m, 5 H, 2-H + 2 COOC$\underline{H}_2$—CH$_3$); 3.35 (d, 1 H, OH); 2.8 (d, 2 H, 3,3-H$_2$); 1.26, 1.3 ppm (2 t, 6 H, 2 COOCH$_2$—C$\underline{H}_3$).

### Diisopropyl (2*S*,3*S*)-2,3-*O*-Isopropylidenetartrate (2m) from the Dimethyl Ester (1m):

To a solution of dimethyl (2*S*,3*S*)-2,3-*O*-isopropylidenetartrate (**1m**; 2 g, 9.2 mmol) in absolute isopropanol (50 ml) is added a catalytic amount of tetraisopropyl titanate (~100 mg) and the mixture is stirred at 70 °C for 2 h. The solvent is then evaporated and the residue heated at 70 °C with more isopropanol (50 ml) for 1 h. The solvent is again evaporated and the residue distilled in the Kugelrohr to give a colorless viscous liquid (2.6 g). Crystallization from ether/hexane affords **2m**; yield: 2.3 g (91%); b.p. 80 °C/0.001 torr; m.p. 42.0–42.7 °C; $[\alpha]_D^{r.t.}$: +40.8° (*c* 3.80, chloroform).

| | | | |
|---|---|---|---|
| $C_{13}H_{22}O_6$ | calc. | C 56.92 | H 8.08 |
| (274.3) | found | 56.81 | 8.13 |

M.S.: *m/e* = 259 (M$^+$ – 15, 60), 217 (16), 87 (20), 75 (26), 145 (100), 85 (10), 59 (31), 43 (31).

I.R. (KBr): $\nu = 2980$ (m), 1755 (s), 1730 (s), 1468 (w), 1455 (w), 1385 (m), 1375 (m), 1330 (w, broad), 1280 (w), 1210 (s, broad), 1145 (w), 1105 (s), 965 (m, broad), 870 (m), 935 cm$^{-1}$ (m).

$^1$H-N.M.R. (CDCl$_3$/TMS, 90 MHz): $\delta = 5.11$ [sept, 2 H, 2 OC$\underline{H}$(CH$_3$)$_2$]; 4.66 (s, 2 H, 2-H, 3-H); 1.47 [s, 6 H, O—C(C$\underline{H}_3$)$_2$—O]; 1.27 ppm [d, 12 H, 2 OCH(C$\underline{H}_3$)$_2$].

### Benzyl Acetoacetate (2k) from *t*-Butyl Acetoacetate (1k); Typical Procedure:

To a solution of *t*-butyl acetoacetate (**1k**; 10 g, 63.2 mmol) in benzyl alcohol (200 ml) is added tetraethyl titanate (5 g, 22 mmol) and the mixture is heated at 100 °C overnight. The cooled (~45 °C) mixture is quenched with 1 normal hydrochloric acid (100 ml) and extracted with ether/pentane (1/1; 700 ml). The organic extract is washed with saturated aqueous sodium hydrogen carbonate (100 ml) and saturated sodium chloride solution (100 ml), and dried with magnesium sulfate. The solvent is evaporated (65 °C/0.1 torr for benzyl alcohol) and the residue distilled in vacuo to give **2k**; yield: 6.83 g (56%): b.p. 160 °C/0.1 torr (Ref.$^4$, b.p. 156–159 °C/0.1 torr).

$^1$H-N.M.R. (CDCl$_3$/TMS, 90 MHz): $\delta = 7.4$ (s, 5 H$_{arom}$); 5.15 (s, 2 H, O—C$\underline{H}_2$—C$_6$H$_5$); 3.5 (s, 2 H, 2,2-H$_2$); 2.25 ppm (s, 3 H, 4,4,4-H$_3$).

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[1] 1 kg of tetraisopropyl titanate costs ~$ 5.— (50 kg), or $ 4.— (1000 kg).
(a) DuPont (Wilmington, Del., U.S.A.).
(b) Dynamit Nobel (Troisdorf, Germany).

[2] Three early patents referred to in *Chemical Abstracts:*
A. F. E. Sims, J. Southwood, *Brit. Patent* 960005 (1964), Distillers Co.; *C. A.* **61**, 4223 (1964).
*Neth. Patent Appl.* 6404085, 6406196 (1965), Chemische Werke Witten GmbH; *C. A.* **63**, 545, 2932 (1965).
A complete list is available in a brochure *Titansäure-ester,* from: Dynamit Nobel AG, D-5210 Troisdorf, Germany.

[3] Exceptions:
T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **102,** 5974 (1980).
B. E. Rossiter, T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **103,** 464 (1981).
E. J. Corey, S.-I. Hashimoto, A. E. Barton, *J. Am. Chem. Soc.* **103,** 721 (1981).
T. Mukaiyama, *Angew. Chem.* **89,** 858 (1977); *Angew. Chem. Int. Ed. Engl.* **16,** 817 (1977).

[4] R. B. Baker, R. E. Schaub, M. V. Querry, J. H. Williams, *J. Org. Chem.* **17,** 77 (1952).

[5] *Beilsteins Handbuch der Organischen Chemie:*
a: E III, **9,** 2183; b: E III, **2,** 1632; c: E III, **3,** 449; d: E IV, **3,** 762; e: E IV, **3,** 1536; f: E IV, **3,** 1126; g: E IV, **2,** 1653.