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Aldol-Tischenko-Tischenko reaction: sodium-*tert*-butoxide-mediated one step formation of 1,3-glycol diester from benzaldehyde and isobutyrophenone

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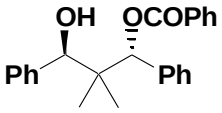
Synthetic Procedure

Representative procedure for lithium-*tert*-butoxide mediated aldol-Tishchenko reaction: synthesis of *anti*-(±)-3-hydroxy-2,2-dimethyl-1,3-diphenylpropylbenzoate 1.

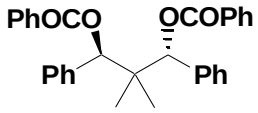


A 25 ml flame-dried flask was charged with freshly dried *tert*-butanol (0.22 g, 3 mmol) and 2 ml dry THF under argon atmosphere. 1.3M cyclohexane solution of Bu^nLi (2.3 ml, 3 mmol) was added dropwise with stirring to the solution. Isobutyrophenone (0.44 g, 3 mmol) was then added and the mixture was stirred for 10 min. Benzaldehyde (1.43 g, 13.5 mmol) dissolved in anhydrous THF (5 ml) was added dropwise for 20 min. The mixture was stirred for 15 h, then quenched by the addition of 25 ml 0.5N HCl and extracted with ethyl acetate (1 x 60 ml). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (100-200 mesh) using ethyl acetate−light petroleum as the eluent to obtain **1** as a white solid. (0.85 g, 79%), mp 138−139 ^oC; R_f (10% EtOAc/PE) 0.32; IR ($CHCl_3$): 3610, 1720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.80 (s, 3H, -C**H**$_3$), 0.87 (s, 3H, -C**H**$_3$), 2.97 (d, *J* 3.41Hz, 1H, -O**H**), 4.755 (d, 3.29 Hz, 1H, -C**H**Ph), 6.37 (s, 1H, -C**H**Ph), 7.22-7.64 (m, 13H, -**H**$_{Ar.}$), 8.10-8.18 (m, 2H, -**H**$_{Ar.}$); ^{13}C NMR ($CDCl_3$): δ

17.8, 19.2, 42.9, 76.9, 80.0, 127.3, 127.4, 127.7, 128.1, 128.2, 128.5, 129.6, 130.2, 133.1, 137.9, 141.1, 166.0. Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 80.13; H, 6.56.

Preparation of stock solution of 1M sodium alkoxides in THF. To a suspension of NaH (0.48 g, 20 mmol) in anhydrous THF (20 ml), 20 mmol freshly dried alcohol (EtOH or Pr^iOH or Bu^tOH) was added and stirred till hydrogen evolution ceased. The heterogeneous mixture was allowed to settle. The clear supernatant solution of sodium alkoxides were estimated by acidimetry and used for aldol-Tishchenko-Tishchenko reaction.

Representative procedure for sodium-*tert*-butoxide mediated aldol-Tishchenko-Tishchenko reaction: synthesis of *anti*-(±)-2,2-dimethyl-1,3-diphenylpropyl-1,3-dibenzoate 2.



A 25 ml flame-dried flask was charged with 1M $NaOBu^t$ (3 ml) under argon atmosphere. Isobutyrophenone (0.44 g, 3 mmol) was then added dropwise and the mixture was stirred for 10 min. Next, benzaldehyde (1.43 g, 13.5 mmol) dissolved in anhydrous THF (10 ml) was added dropwise for 20 min. The mixture was stirred overnight (15 h), quenched by the addition of 25 ml 0.5N HCl and extracted with ethyl acetate (1 x 60 ml). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (100-200 mesh) using ethyl acetate−light petroleum as the eluent to obtain diester **2** as white solid (1.31 g, 94%), mp 226−228 ^oC; R_f (10% EtOAc/PE) 0.44; IR ($CHCl_3$): 1722 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 6H, -C**H**$_3$), 6.15 (s, 2H, -C**H**Ph), 7.23-7.54 (m, 16H, $\mathbf{H}_{Ar.}$), 7.99-8.11 (m, 4H, $\mathbf{H}_{Ar.}$); ^{13}C NMR ($CDCl_3$): δ 19.6, 42.3, 79.3, 127.8, 128.0, 128.3, 129.6, 130.4, 132.9, 137.9, 165.2. Anal. Calcd for $C_{24}H_{24}O_3$: C, 80.15; H, 6.07. Found: C, 80.15; H, 5.81.

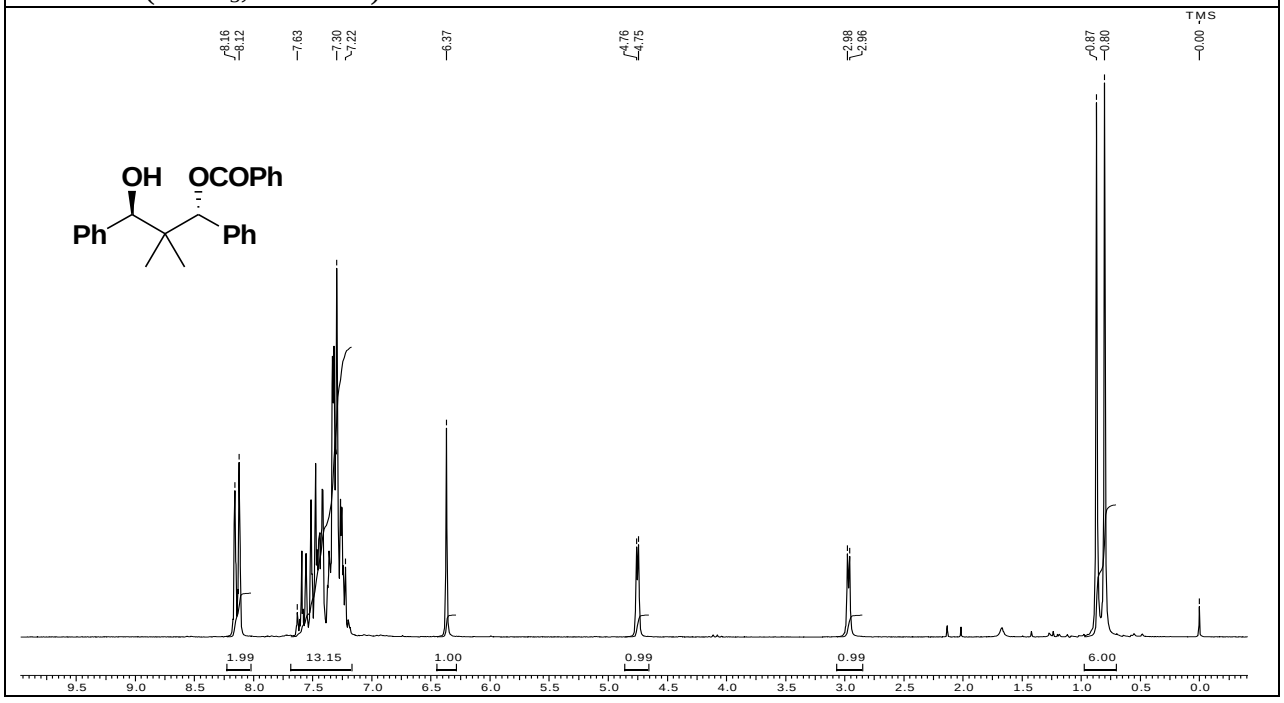
CIF data for crystalographic analysis of compound **1**.

Empirical formula	$C_{24}H_{24}O_3$
Formula weight	360.43
Temperature	566(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.450(8) Å α = 86.48(2)°.
	b = 10.638(10)Å β = 77.402(18)°.
	c = 11.608(10)Å γ = 74.363(16)°.
Volume	980.6(16) $Å^3$
Z, Calculated density	2, 1.221 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	384
Crystal size	0.20 x 0.13 x 0.04 mm
Theta range for data collection	1.99 to 25.00 deg.
Limiting indices	-10<=h<=10, -12<=k<=12, -13<=l<=13
Reflections collected / unique	7088 / 3425 [R(int) = 0.0885]
Completeness to theta = 25.00	99.0 %
Max. and min. transmission	0.9968 and 0.9843
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3425 / 0 / 340
Goodness-of-fit on F^2	0.835
Final R indices [I>2sigma(I)]	R1 = 0.0562, wR2 = 0.0962
R indices (all data)	R1 = 0.1962, wR2 = 0.1330
Largest diff. peak and hole	0.163 and -0.157 $e.Å^{-3}$

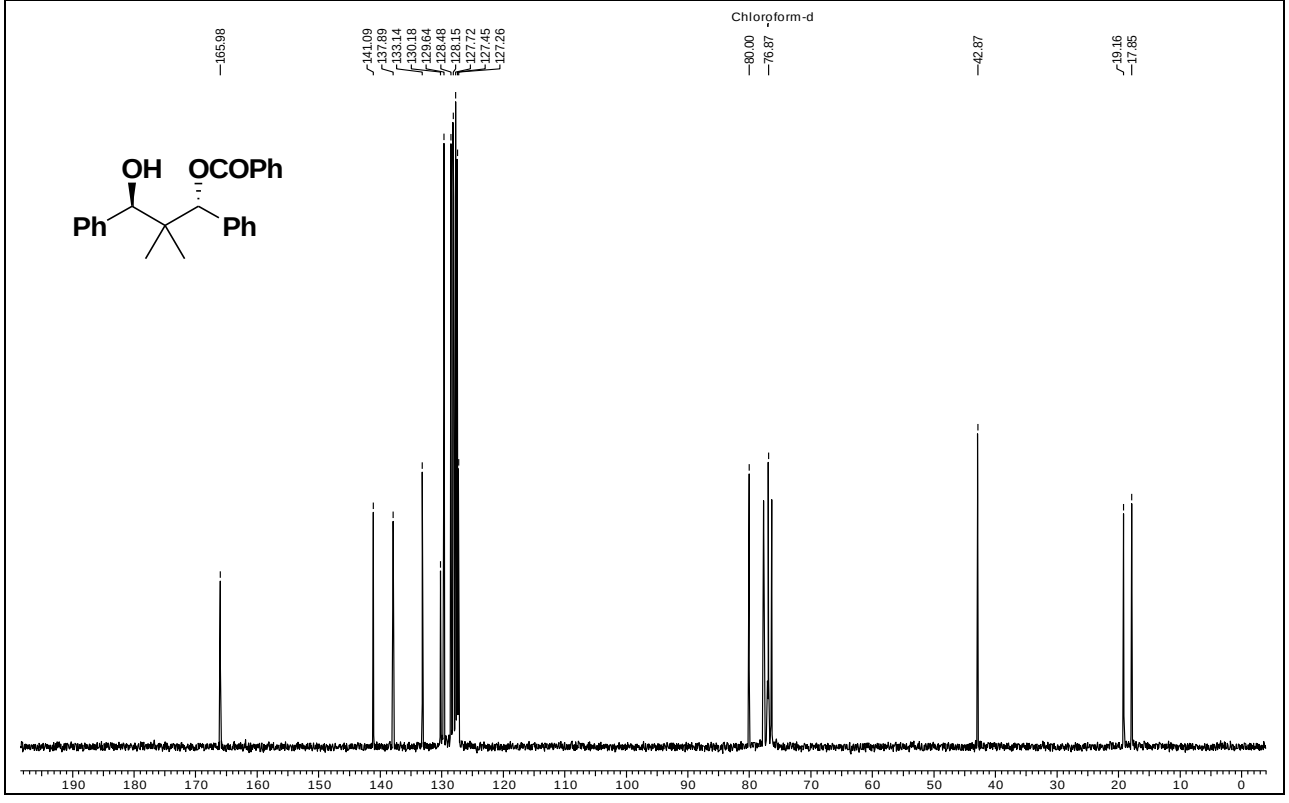
CIF data for crystallographic analysis of compound **2**.

Empirical formula	$C_{31}H_{28}O_4$
Formula weight	371.63
Temperature	566(2) K
Wavelength	0.71073 Å
Crystal system, space group	TRICLINIC, P-1
Unit cell dimensions	a = 9.1460(11) Å α = 95.472(2)°.
	b = 16.193(2) Å β = 90.034(2)°.
	c = 17.679(2) A γ = 104.379(2)°.
Volume	2523.9(5) $Å^3$
Z, Calculated density	5, 1.223 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	984
Crystal size	0.34 x 0.24 x 0.09 mm
Theta range for data collection	1.30 to 25.00 deg.
Limiting indices	-10<=h<=10, -19<=k<=19, -21<=l<=21
Reflections collected / unique	36726 / 8865 [R(int) = 0.0569]
Completeness to theta = 25.00	99.7 %
Max. and min. transmission	0.9928 and 0.9734
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8865 / 0 / 635
Goodness-of-fit on F^2	1.221
Final R indices [I>2sigma(I)]	R1 = 0.0963, wR2 = 0.1970
R indices (all data)	R1 = 0.1401, wR2 = 0.2163
Largest diff. peak and hole	0.229 and -0.165 e. $Å^{-3}$

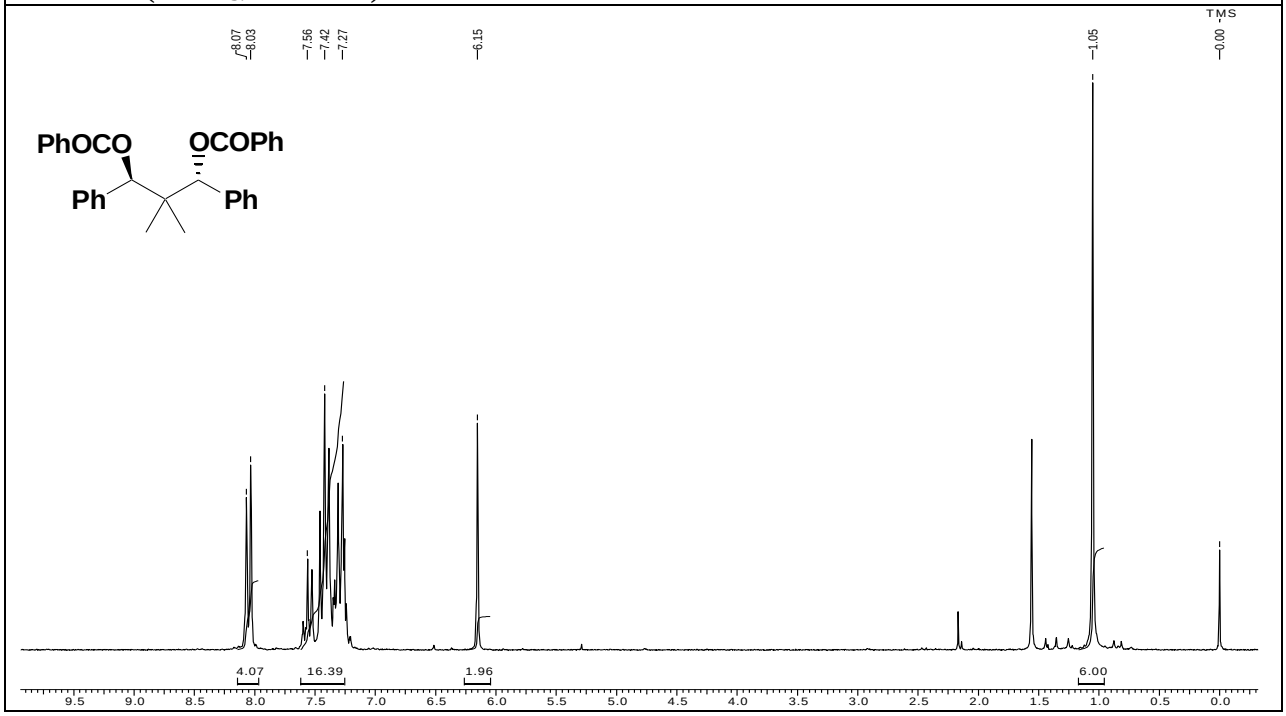
^{1}H-NMR ($CDCl_3$, 200MHz)



^{13}C-NMR ($CDCl_3$, 50.32MHz)



^{1}H-NMR ($CDCl_3$, 200MHz)



^{13}C-NMR ($CDCl_3$, 50.32MHz)