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

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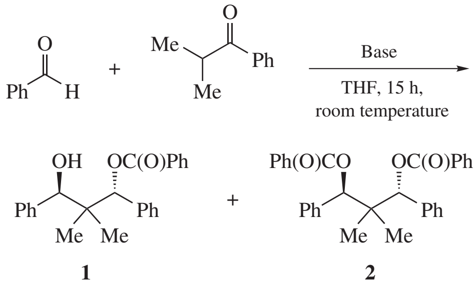
Sodium *tert*-butoxide promoted reaction between isobutyrophenone and excess (>4 mol) benzaldehyde gives *anti*-1,3-dibenzoyloxy-2,2-dimethyl-1,3-diphenylpropane, a product of sequential aldol–Tishchenko and Tishchenko reactions.

Aldol–Tishchenko reaction, an important sequential process of aldol reaction followed by the Tishchenko reduction primarily generating 1,3-glycol monoester,[1] is promoted by bases such as metal alkoxides, lithium amides in stoichiometric[2] or catalytic quantities.[3] Morken and co-workers showed LiOPr^i to be an efficient catalyst for highly diastereoselective (92% *de*) hetero aldol–Tishchenko reaction,[4] the lithium enolates having been generated from carbonyl compounds containing either secondary or primary α-hydrogen atoms. After the enolate was formed, a reversible aldolization step was thought to precede a rate-determining intramolecular hydride transfer reduction.[2(*b*)]

In the present study (Scheme 1),[†] we observed that lithium ethoxide and isopropoxide were unable to promote the reaction between isobutyrophenone and benzaldehyde even used in stoichiometric quantities (Table 1, entries 1 and 2).



Scheme 1

Apparently, this could be due to the poorer acidity of tertiary α-hydrogen atom in isobutyrophenone. Lithium *tert*-butoxide LiOBu^t being essentially stronger base was found to promote formation of the anticipated 1,3-glycol monoester **1**, being exclusively an *anti* isomer (under similar reaction conditions[5] some *syn* isomer was formed). The *anti*-configuration of compound **1** was established by X-ray crystallography (Figure 1).[‡]

Table 1 Base influence on the synthesis of compounds **1** and **2**.

Entry	Base	Base content[a] (mol%)	PhC(O)CHMe$_2$: PhCHO molar ratio	Yield[b] (%) anti-**1**	Yield[b] (%) anti-**2**
1	LiOEt	100	1 : 2.5	0	0
2	LiOPr^i	100	1 : 2.5	0	0
3	LiOBu^t	10	1 : 2.5	9 (18)[c]	0
4	LiOBu^t	100	1 : 2.5	71 (79)[d]	0
5	NaOPr^i	100	1 : 2.5	13	<5
6	NaOBu^t	20	1 : 2.5	5 (28)[e]	8 (34)[e]
7	NaOBu^t	100	1 : 4.5	0	94
8[f]	KOH	100	1 : 2.5	0	0

[a] With respect to PhC(O)CHMe$_2$. [b] Isolated yield after column chromatography. [c] With 20 mol% of LiOBu^t. [d] PhC(O)CHMe$_2$: PhCHO ratio of 1 : 4.5. [e] With 100 mol% of NaOBu^t. [f] Under reflux.

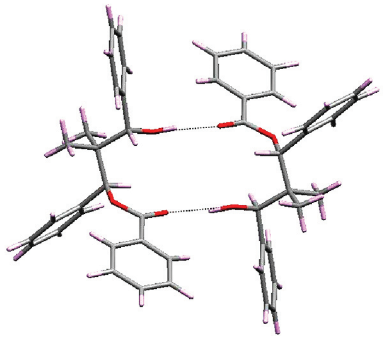


Figure 1 Molecular structure of compound **1**.

Unlike Morken's observation, LiOBu^t was required in stoichiometric quantity to obtain **1** in satisfactory yield (71%) (see

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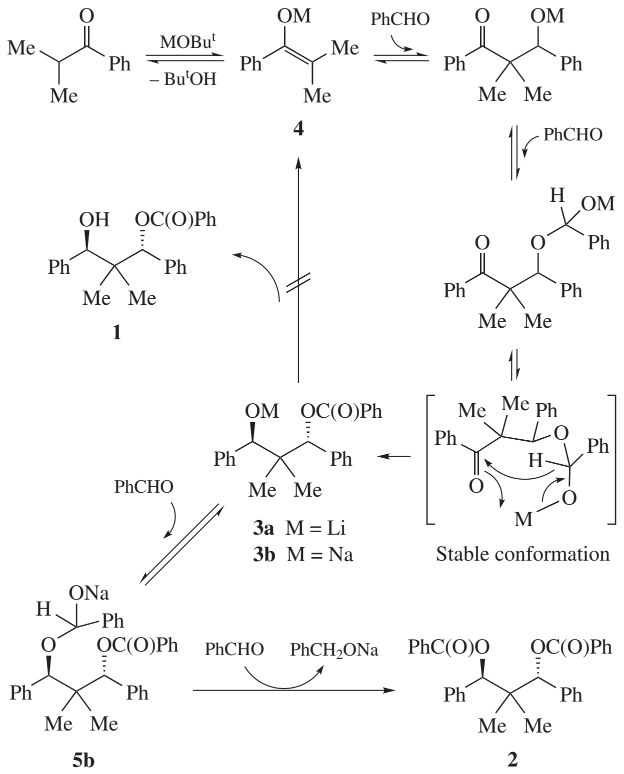
[†] For synthetic procedures and characteristics of compounds **1** and **2**, see Online Supplementary Materials.

[‡] *Crystal data for* **1**. Crystals of $C_{24}H_{24}O_3$ (M = 360.43) are triclinic, space group $P\bar{1}$, at 566(2) K: a = 8.450(8), b = 10.638(10) and c = 11.608(10) Å, α = 86.48(2)°, β = 77.402(18)°, γ = 74.363(16)°, V = 980.6(16) Å^3, Z = 2, d_{calc} = 1.221 g cm^{-3}, μ = 0.079 mm^{-1}, F(000) = 384. 7088 reflections were collected, from which 3425 unique reflections (R_{int} = 0.0885), 1.99° < θ < 25.00°. The structure was solved with a full-matrix least squares method on F^2, GOF = 0.835. Final R indices: R_1 = 0.1962, wR_2 = 0.1330 (for all reflections) and R_1 = 0.0562, wR_2 = 0.0962 [for reflections with $I > 2\sigma(I)$].

Crystal data for **2**. Crystals of $C_{31}H_{28}O_4$ (M = 371.63) are triclinic, space group $P\bar{1}$, at 566(2) K: a = 9.1460(11), b = 16.193(2) and c = 17.679(2) Å, α = 95.472(2)°, β = 90.034(2)°, γ = 104.379(2)°, V = 2523.9(5) Å^3, Z = 5, d_{calc} = 1.223 g cm^{-3}, μ = 0.080 mm^{-1}, F(000) = 984. 36 726 reflections were collected, from which 8865 unique reflections (R_{int} = 0.0569), 1.30° < θ < 25.00°. The structure was solved with a full-matrix least squares method on F^2, GOF = 1.221. Final R indices: R_1 = 0.1401, wR_2 = 0.2163 (for all reflections) and R_1 = 0.0963, wR_2 = 0.1970 [for reflections with $I > 2\sigma(I)$].

CCDC 919193 and 919194 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.



Scheme 2

Table 1, entry 4). Lowering its quantity to 20 and 10% diminished the yield of monoester **1** to 18 and 9%, respectively (entry 3). These results clearly indicate that LiOBu^t behaves like a stoichiometric reagent in this reaction. In another experiment, higher benzaldehyde and isobutyrophenone ratio (4.5 : 1) in the presence of stoichiometric quantity of LiOBu^t enhanced the yield of **1** to 79% (parentheses in entry 4).

We also examined the effect of alkali cation in the alkoxides. The increase in basicity from LiOPr^i to NaOPr^i also could not promote the reaction under catalytic (20 mol%) conditions but 13% yield of **1** was obtained using 1 equiv. of NaOPr^i from 2.5 : 1 ratio of benzaldehyde and isobutyrophenone (see Table 1, entry 5). To our surprise, an *anti*-1,3-glycol dibenzoate ester **2** was obtained as a product in the presence of 1 equiv. of NaOBu^t. Changing the ratio between benzaldehyde and isobutyrophenone from 2.5 : 1 to 4.5 : 1 raised the yield of diester **2** from 34 to 94% under the identical reaction conditions (entries 6 and 7). A plausible mechanism for this transformation is outlined in Scheme 2.

In Scheme 2, the catalytic cycle is breaking between the intermediate **3** and metal enolate **4** unlike the cases reported by Morken.[4] It is because of the fact that the intermediate **3** is a secondary metal alkoxide which can neither abstract the less acidic proton from isobutyrophenone nor equilibrate with *tert*-butanol to keep the cycle on. As a result, the process requires stoichiometric amounts of the base. From the above observation it can be stated that the nature of the substrate is very important for this reaction to be catalytic or stoichiometric. Moreover, the intermediate **3b**, when NaOBu^t is used as base, becomes a better nucleophile than **3a**. This better nucleophilic ability of sodium alkoxide **3b** explains the formation of diester **2**. The intermediate **3b** (see Scheme 2) attacks third benzaldehyde molecule rather than abstracting an acidic proton from surrounding source. This leads to intermediate **5b** which undergoes intermolecular Tishchenko reduction with the fourth benzaldehyde molecule resulting in diester **2** and benzyl alcohol (which was detected by GC). In whole, an initial aldol reaction is followed by intramolecular Tishchenko reduction which is followed by an intermolecular Tishchenko reduction in a sequential manner. This is a completely new observation in an aldol–Tishchenko reaction environment. In a control experiment, treatment of pure monoester **1** with NaOBu^t in THF does not give diester **2** and the corresponding diol, and it clearly nullifies the possibility of diester formation from two molecules of monoester **1** *via* transesterification. In support of the proposed mechanism, treatment of monoester **1** and two equivalents of benzaldehyde with sodium *tert*-butoxide afforded cleanly diester **2**. We have also performed one experiment taking KOH as the base but neither product **1** nor **2** were formed upon refluxing the reaction mixture for several hours (entry 8). The *anti*-configuration of product **2** has been established by X-ray crystallography (Figure 2).[‡]

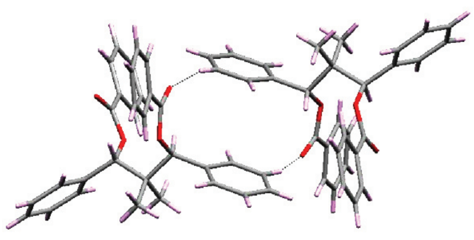


Figure 2 Molecular structure of compound **2**.

In conclusion, we have demonstrated the formation of 1,3-glycol dibenzoate from benzaldehyde and isobutyrophenone *via* a completely new tandem organic reactions, *i.e.* aldol–Tishchenko–Tishchenko reaction. We believe this new observation will be beneficial in respect to studies related to aldol–Tishchenko reaction.[6] Moreover, this reaction provides an easy access to a previously reported C_2-symmetric chiral 1,3-diol.[7] Further study with various benzaldehyde derivatives is underway in our laboratory.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.03.015.

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