Merging α-Lithiation and Aldol-Tishchenko Reaction to Construct Polyols from Benzyl Ethers

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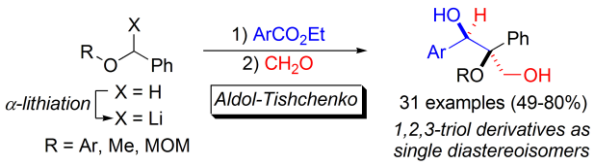
Supporting Information Placeholder

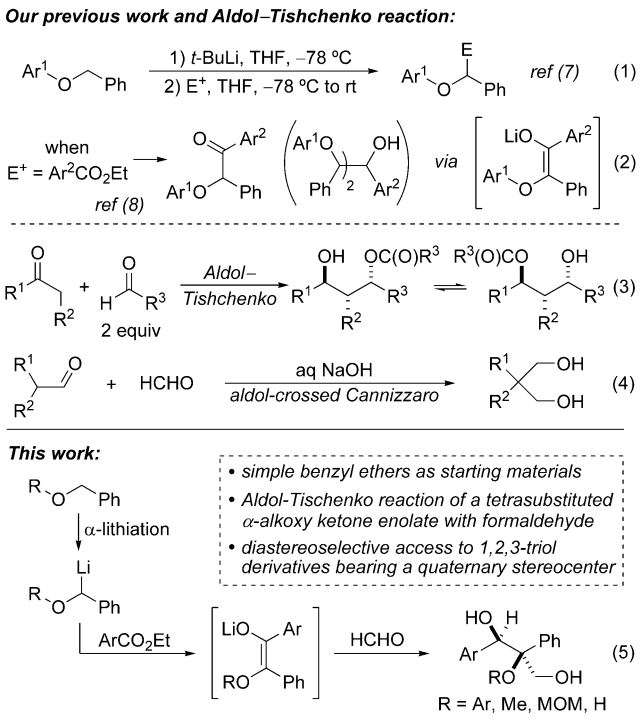


ABSTRACT: α-Lithiobenzyl ethers, generated by selective α-lithiation, undergo an Aldol-Tishchenko reaction upon treatment with carboxylic esters and paraformaldehyde. The reaction of the organolithium with the carboxylate generates an intermediate enolate that, after formaldehyde addition, affords 1,2,3-triol derivatives in a straightforward and one-pot manner. These products are obtained as single diastereoisomers bearing a quaternary stereocenter. The complete diastereocontrol of the Aldol-Tishchenko process is attributed to stereoelectronic preferences in the transition state.

α-Lithiated oxygen-substituted compounds,[1] though carbenoids in nature,[2] are useful reagents for accessing functionalized oxygenated compounds. Although α-lithiated benzyl ethers are easily accessible by deprotonation with highly basic alkyllithiums[3] or by Sn–Li exchange,[4] their synthetic usefulness is limited by competitive processes like eliminations or Wittig rearrangements.[5] Following our interest in the preparation and applications of oxygen-functionalized organolithiums,[6] we have reported that aryl α-lithiobenzyl ethers, generated from α-lithiation with *t*-BuLi at low temperature, can be functionalized with electrophilic reagents avoiding the previously described [1,2]-Wittig rearrangement (Scheme 1, eq 1).[7] In the study of the reactivity of these α-oxygenated organolithiums we found that their reactions with aromatic carboxylic esters gave rise to ketones rather than the expected tertiary alcohols. This behavior was likely due to the in-situ formation of an enolate, by the fast deprotonation of the ketone with the ethoxide byproduct (Scheme 1, eq 2).[8]

On the other hand, the classical Aldol–Tishchenko reaction leads to the trimerization of an enolizable aldehyde, under basic conditions, affording a 1,3-*anti*-diol monoester.[9] Particularly, ketone enolates react with an excess of aldehyde to form 1,3-*anti*-diol monoesters in a hetero-Aldol–Tishchenko reaction that is a powerful, one step methodology for creating up to three contiguous stereocenters, even in an enantioselective way in the presence of chiral catalysts (Scheme 1, eq 3).[10] Nevertheless, very few examples of acyclic ketones with a tertiary stereocenter at the α-position, thus leading to the construction of quaternary stereocenter, have been reported.[11] A related transformation is the aldol condensation of aliphatic aldehydes with formaldehyde followed by a crossed Cannizzaro reaction to give *gem*-dihydroxymethyl derivatives (Scheme 1, eq 4).[12] However, with related ketones formaldehyde typically affords hydroxymethylated products.[13] It is also worthy to note that formaldehyde is one of the most important C1 electrophiles in organic synthesis.[14]

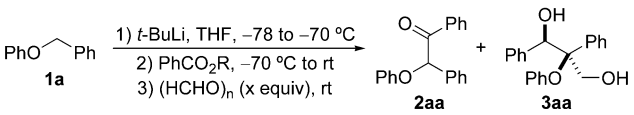
Scheme 1. Previous Results in the Reaction of Aryl α-Lithiobenzyl Ethers with Carboxylates and Present Work



Considering an enolate as a plausible and potentially useful intermediate from the reactions of α-lithiobenzyl ethers with carboxylates,[8] we envisaged that its treatment with an aldehyde[15] could trigger an Aldol-Tishchenko reaction, though the diastereoselectivity of the process could not be clearly predicted due to the generation of a quaternary stereocenter (Scheme 1, eq 5). Herein, we report how the α-lithiation of simple benzyl ethers could be merged with the powerful Aldol-Tishchenko reaction allowing access to interesting triol derivatives in a complete diastereoselective manner in one single operational step.[16]

We selected benzyl phenyl ether **1a** as model substrate and, as we had previously reported, its α-lithiation with a slight excess of *t*-BuLi and further reaction with ethyl benzoate gives rise after hydrolysis to the α-phenoxy ketone **2aa** (Table 1, entry 1). When paraformaldehyde (1,1 equiv) was added before the hydrolysis, a different compound was observed, although significant decomposition was also detected (entry 2). This compound was initially assigned to the triol derivative **3aa**, arising from an Aldol-Tishchenko reaction. Remarkably, it was generated as a single diastereoisomer. Looking for improving its formation, a higher amount of paraformaldehyde was found to be required (entries 3 and 4). Under the optimal conditions (entry 4), we decided to test other benzoates as electrophiles to determine if the lithium alkoxide, released from the reaction of **1a-Li** with the ester, plays a non-innocent role in the formation of the intermediate enolate from ketone **2aa**. Whereas methyl benzoate afforded a similar result (entry 5), isopropyl and benzyl benzoates provide lower yields of **3aa** (entries 6 and 7), and phenyl benzoate only led to decomposition (entry 8). Thus, methyl and ethyl carboxylates were selected as the optimal partners.

Table 1. Conditions for the Reaction of α-Lithiated 1a with Benzoates and Formaldehyde[a]

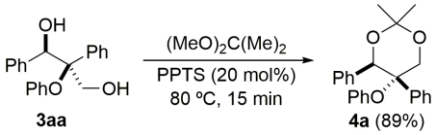


entry	R	x[b]	product	yield (%)[d]
1	Et	0	**2aa**	79 (73)
2	Et	1.1	**3aa**	(21)
3	Et	2	**3aa**	(58)
4	Et	2.5	**3aa**	74 (70)
5	Me	2.5	**3aa**	70
6	*i*-Pr	2.5	**3aa**	39
7	Bn	2.5	**3aa**	53
8	Ph	2.5	–[e]	–

[a] Reaction conditions: **1a** (0.5 mmol), *t*-BuLi (0.65 mmol, 30 min), $PhCO_2R$ (0.65 mmol, 1 h), $(HCHO)_n$ (x equiv, 2 h); paraformaldehyde was used as HCHO source. [b] Equiv of paraformaldehyde referred to **1a**. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] NMR yield using 1,3,5-trimethoxybenzene as internal standard. In brackets isolated yield. [e] Decomposition was observed without any identified product.

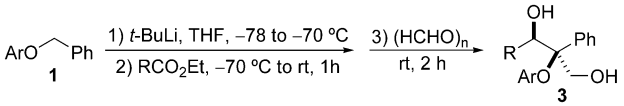
The complete characterization and stereochemical assignment of **3aa** were carried out by its transformation into the ketal derivative **4a** through reaction with an acetone equivalent under acid-catalysis (Scheme 2). The NMR analysis of **4a** supports the proposed Aldol-Tishchenko product and lets us know the relative configuration of the stereocenters in **3aa**.

Scheme 2. Stereochemical Assignment of 3aa. Synthesis of 1,3-Dioxane 4a



With an efficient protocol in place to obtain a triol derivative like **3aa**, we surveyed the scope of this reaction with a selection of easily available aryl benzyl ethers **1** and different esters (Table 2). Using benzyl phenyl ether **1a** a wide variety of (hetero)aromatic carboxylates was evaluated to demonstrate the applicability of this strategy for accessing functionalized 2-phenoxy-1,3-diol derivatives **3** (entries 1–9). Aromatic esters bearing electron-donating or electron-withdrawing groups at different positions, as well as a heteroaromatic ester, gave rise to the corresponding triol derivatives **3aa-ai** in good yields. The use of an aliphatic ester, such as ethyl isobutyrate, led to the corresponding product **3aj** in a lower yield, along with starting ether **1a**, likely due to competitive α-proton abstraction, and some unidentified side-products (entry 10). Other functionalized aryl benzyl ethers **1b-i**, possessing different groups at the *ortho*, *meta*, or *para* positions of the aryl moiety, also showed the same reactivity as the parent ether **1a** affording, after α-lithiation and reaction with ethyl *p*-fluorobenzoate or ethyl benzoate and formaldehyde, the corresponding 2-aryloxy-1,3-diol derivatives **3** also in high yields (entries 11–18). In this way, we were able to prepare triol derivatives **3** being functionalized in both aromatic rings.

Table 2. Reactions of α-Lithiated Aryl Benzyl Ethers 1 with (Hetero)aromatic Carboxylates and Formaldehyde[a]



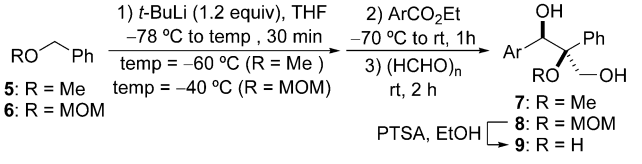
entry	ether	Ar	R	product	yield (%)[b]
1	**1a**	Ph	Ph	**3aa**	70
2	**1a**	Ph	1-Naphthyl	**3ab**	61
3	**1a**	Ph	4-(MeO)C_6H_4	**3ac**	75
4	**1a**	Ph	2-(MeO)C_6H_4	**3ad**	60
5	**1a**	Ph	4-FC_6H_4	**3ae**	72
6	**1a**	Ph	4-BrC_6H_4	**3af**	70
7	**1a**	Ph	2-ClC_6H_4	**3ag**	75
8	**1a**	Ph	3-ClC_6H_4	**3ah**	73
9	**1a**	Ph	2-Thienyl	**3ai**	67
10	**1a**	Ph	*i*-Pr	**3aj**	25

11	**1b**	4-(MeO)C_6H_4	4-FC_6H_4	**3be**	66
12	**1c**	4-ClC_6H_4	4-FC_6H_4	**3ce**	80
13	**1d**	4-(*t*-Bu)C_6H_4	4-FC_6H_4	**3de**	74
14	**1e**	4-PhC_6H_4	4-FC_6H_4	**3ee**	65
15	**1f**	3-(CF_3)C_6H_4	4-FC_6H_4	**3fe**	67
16	**1g**	2-(*i*-Pr)C_6H_4	Ph	**3ga**	64
17	**1h**	2-(MeO)C_6H_4	Ph	**3ha**	61
18	**1i**	2-Naphthyl	4-FC_6H_4	**3ie**	62

[a] Reaction conditions: **1** (0.5–1 mmol), *t*-BuLi (1.3 equiv, 30 min), RCO_2Et (1.3 equiv mmol, 1 h), $(HCHO)_n$ (2.5 equiv, 2 h). [b] Isolated yield referred to the starting ether **1**.

Azzena and co-workers had described the direct metalation of methoxy and methoxymethyl benzyl ethers **5** and **6**, showing that the corresponding α-alkoxy-substituted benzyllithium derivatives could be reacted with electrophiles prior to undergo Wittig rearrangement.[17] In order to minimize the amount of the carboxylic ester employed as electrophile, which is influenced by the excess of base required for the metalation, a revision of the reaction conditions initially reported for the α-lithiation of both alkoxy benzyl ethers **5** and **6** was carried out (see Supporting Information). Gratifyingly, treatment of the α-lithiobenzyl ethers derived from **5** and **6**, under the same conditions previously described for **1**, led to the expected Aldol-Tishchenko products, the 2-alkoxy-1,3-diols **7** and **8** as single diastereoisomers (Table 3, entries 1–13). A selection of aromatic carboxylates was assayed with both alkyl benzyl ethers giving rise to triol derivatives **7** and **8** in moderate to good yields, although mainly from **5** lower yields were obtained than those from aryl benzyl ethers **1**. Moreover, if crude 2-methoxymethyloxy-1,3-diol derivatives **8** are treated with acid the corresponding 1,2,3-triol products **9** can be easily obtained (entries 14–16). The relative stereochemistry of the obtained 1,3-diols **7** and **8** was found to be the same as that of 1,3-diols **3**, as shown by NMR analysis of the 1,3-dioxanes **4b** and **4c** (Scheme 3).

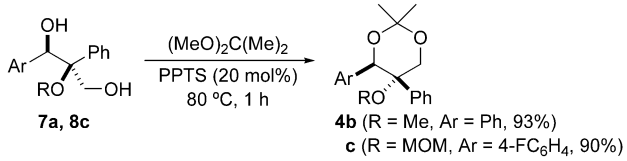
Table 3. Synthesis of 2-Alkoxy and 2-Hydroxy 1,3-Diol Derivatives 7-9 from Alkoxy Benzyl Ethers 5 and 6[a]



entry	starting ether	Ar	product	yield (%)[b]
1	**5**	Ph	**7a**	69
2	**5**	1-Naphthyl	**7b**	57
3	**5**	4-FC_6H_4	**7c**	49
4	**5**	4-BrC_6H_4	**7d**	50
5	**5**	2-ClC_6H_4	**7e**	58
6	**6**	Ph	**8a**	55
7	**6**	1-Naphthyl	**8b**	60
8	**6**	4-FC_6H_4	**8c**	68
9	**6**	4-BrC_6H_4	**8d**	50
10	**6**	2-ClC_6H_4	**8e**	60
11	**6**	3-ClC_6H_4	**8f**	75
12	**6**	2-FC_6H_4	**8g**	61
13	**6**	4-$CF_3C_6H_4$	**8h**	63
14[c]	**6**	1-Naphthyl	**9b**	52
15[c]	**6**	4-FC_6H_4	**9c**	62
16[c]	**6**	2-ClC_6H_4	**9e**	56

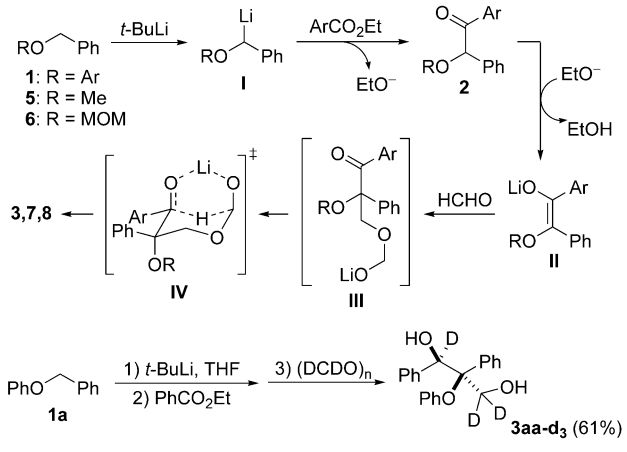
[a] Reaction conditions: **5** or **6** (1 mmol), *t*-BuLi (1.2 mmol, 30 min), $ArCO_2Et$ (1.2 mmol, 1 h), $(HCHO)_n$ (2.5 mmol, 2 h). [b] Yield of isolated product referred to starting ether **5** or **6**. [c] The corresponding crude products **8** were treated with PTSA (1 equiv) in EtOH at 60 ºC for 4 h.

Scheme 3. Synthesis of 1,3-Dioxanes 4b,c



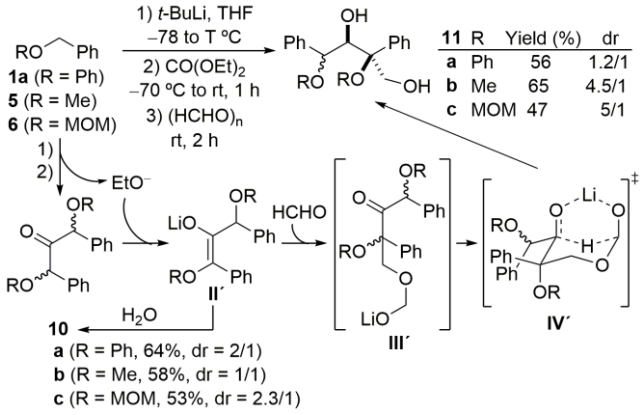
Our mechanistic proposal to account for the formation of triol derivatives **3**, **7**, and **8** from α-lithiobenzyl ethers **I** is shown in Scheme 4. According to our previous results, a ketone **2** is generated after the reaction of **I** with the carboxylate, which undergoes in-situ deprotonation with the alkoxide byproduct leading to enolate **II**. Its reaction with two molecules of formaldehyde affords the intermediate hemiacetal **III** that evolves to the final products by intramolecular hydride transfer via the transition state **IV**. The relative stereochemistry of the triol derivatives corresponds to an arrangement in which the C-2 alkoxy or aryloxy group is located in an axial position. This fact could be attributed to a stereoelectronic preference for the conformation in which the oxygenated substituent, the best donor lone pair or bond, is antiperiplanar to the best acceptor bond, the ketone group. In addition, we have carried out the reaction of **1a** using paraformaldehyde-d_2 isolating trideuterated **3aa-d_3**, thus further supporting our proposal (Scheme 4).

Scheme 4. Mechanistic Proposal



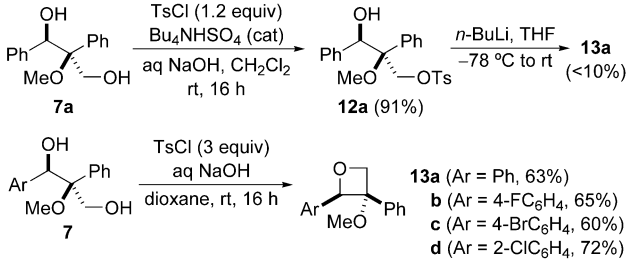
Then, we turned our attention to the use of diethyl carbonate, easily accessible from CO_2,[18] as a C1 synthon carboxylate partner[19] for the herein reported methodology. First, we found that its reaction with the α-lithiobenzyl ethers generated from **1a**, **5** and **6** led, after hydrolysis, to the bis(α-alkoxy)benzyl ketones **10**, which were obtained as variable mixtures of diastereoisomers that could be isolated independently (Scheme 5). Their formation was also explained by assuming that the generation of the corresponding enolates **II´** is faster than the third addition of the organolithium that would give rise to the tertiary alcohol. Then, when formaldehyde was added prior to hydrolysis the tetraol derivatives **11** were obtained in moderate to good yields as mixtures of diastereoisomers, though **11b,c** with remarkable selectivity. In accordance with our mechanistic proposal, the relative stereochemistry of C-2 and C-3 in the 2,4-diphenylbutane-1,3-diols **11** is completely controlled by the Aldol-Tishchenko transition state **IV´** (Scheme 5).

Scheme 5. Reactions of α-Lithiated Benzyl Ethers with Diethyl Carbonate. Synthesis of Ketones 10 and Tetraol Derivatives 11



Due to the interest of the oxetane motif in medicinal chemistry as a surrogate for lipophilic *gem*-dimethyl or labile carbonyl groups as well as its potential usefulness for further synthetic transformations,[20] we planned to synthesize functionalized oxetanes from the prepared 1,3-diol derivatives. As the intramolecular Williamson etherification is one of the most general strategies for the synthesis of oxetanes,[21] first, we prepared the primary monotosylate **12a** from 1,3-diol derivative **7a** (Scheme 6). Then, we attempted to synthesize oxetane **13a** by its treatment with *n*-BuLi.[21a] However, a very low yield of the desired oxetane was obtained. Looking for a suitable, as well as one-pot procedure, process we found that the reaction of a variety of 1,3-diols **7** with an excess of tosyl chloride in the presence of base led to the desired oxetanes **13** in moderate to good yields, presumably via an initial sulfonation of the primary alcohol with subsequent alkylation of the secondary hydroxy group (Scheme 6).[22] In addition, the relative stereochemistry of the final oxetanes further supports the one proposed from the 1,3-dioxane derivatives **4**.

Scheme 6. Synthesis of Oxetanes 13 from Triol Derivatives 7



In summary, we have described an efficient highly diastereoselective protocol to synthesize polyol derivatives in one single operational step from simple and easily available benzyl ethers involving α-lithiation, carboxylate addition and Aldol-Tishchenko reaction. The C–H bond functionalization of the benzyl ethers takes place selectively through α-lithiation at low temperature, thus avoiding the expected [1,2]-Wittig rearrangement. After a fine-tuning of the reaction conditions, the α-lithiobenzyl ethers generated were successfully engaged in reaction addition to carboxylates. Then the *in situ* produced enolate evolves through a second C–C bond-forming reaction to the desired polyols after Aldol-Tishchenko reaction upon addition of formaldehyde. This method has revealed efficient to obtain challenging quaternary carbons, which are found to commonly participate in retro-Aldol reaction. Under the established reaction conditions, no noticeable retro-Aldol reaction was observed. Interestingly, diethyl carbonate was also demonstrated to act as carboxylate equivalent in the process allowing the addition of two equivalents of α-lithiobenzyl ethers providing access to tetraol derivatives after Aldol-Tishchenko reaction. Remarkably, the triol derivatives obtained in a diastereoselective manner are excellent building blocks for the synthesis of valuable compounds, such as functionalized oxetanes that can be obtained in only two operational steps from simple starting materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org/doi/10.1021/acs.orglett.

Full experimental procedures, characterization data, and copies of NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa**, **3aa-d$_3$**, **3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ag**, **3ah**, **3ai**, **3be**, **3ce**, **3de**, **3ee**, **3fe**, **3ga**, **3ha**, **3ie**, **4a**, **4b**, **4c**, **5-d**, **6-d**, **7a**, **7b**, **7c**, **7d**, **7e**, **8a**, **8b**, **8c**, **8d**, **8e**, **8f**, **8g**, **8h**, **9b**, **9c**, **9e**, **10a-diast1**, **10a-diast2**, **10b-diast1**, **10b-diast2**, **10c-diast1**, **10c-diast2**, **11a**, **11b**, **11c**, **12a**, **13a**, **13b**, **13c**, **13d**, **14** (ZIP)

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Notes

The authors declare no competing interest.

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