Aldol–Tishchenko Reaction of α-Oxyketones. Diastereoselective Synthesis of 1,2,3-Triol Derivatives

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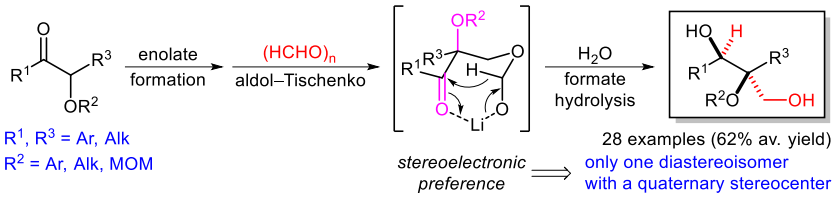
To the memory of Prof. Dr. V. Snieckus



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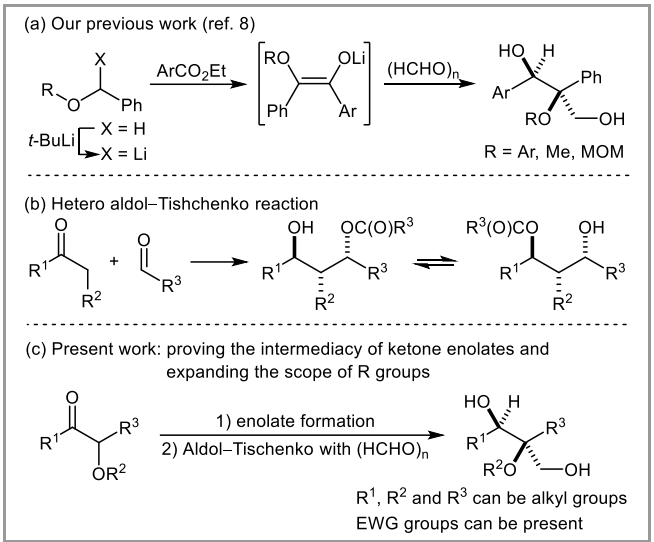
Abstract α-Oxyketones, easily accessible by conventional routes, can be selectively deprotonated generating an enolate intermediate, which upon treatment with paraformaldehyde undergoes an aldol–Tishchenko reaction, leading to relevant 1,2,3-triol fragments in a totally diastereoselective manner. The excellent stereocontrol in the generation of a quaternary stereocenter is attributed to stereoelectronic effects in the Evans intermediate. This methodology allows overcoming some limitations of our previously reported strategy, based on the reaction of α-lithiobenzyl ethers with esters and paraformaldehyde, broadening the scope of the obtained polyols. Synthetic applications of this process include the preparation of a new dilignol model and some functionalized oxetanes.

Key words aldol–Tishchenko, enolates, α-oxyketones, polyol derivatives, diastereoselectivity, oxetanes

In the last years, we have been interested in the study of α-oxygenated organolithiums,[1] despite their tendency to undergo α-eliminations[2] or Wittig rearrangements,[3] due to their potential for the preparation of functionalized oxygenated compounds.[4] In this field we have reported that aryl α-lithiobenzyl ethers, generated by α-lithiation at low temperature, are stable enough against Wittig rearrangement to allow their functionalization with selected electrophiles.[5] Only other selected benzyl ethers can also be effectively α-lithiated and further functionalized.[6] When studying the reactivity of aryl α-lithiobenzyl ethers we found that their treatment with aromatic carboxylic esters provided ketones instead of the expected tertiary alcohols, likely due to a subsequent α-deprotonation of the initially generated ketone by the ethoxide byproduct.[7] More recently, we have taken advantage of this process by merging the α-lithiation of benzyl ethers with the aldol–Tishchenko reaction to synthesize polyols in a diastereoselective manner (Scheme 1, a).[8]

In the hetero-aldol–Tishchenko reaction, a ketone enolate reacts with an excess of aldehyde to form 1,2-*anti*, 1,3-*anti* 1,3-diol monoesters (Scheme 1, b).[9] Lithium amides like LDA, LiHDMS or LTMP are typically employed for the enolate generation, usually at –78 °C in THF. Subsequent addition of the aldehyde, and further warming, trigger the Tishchenko pathway with high diastereoselectivity.[10] However, almost no examples for this reaction have been described starting from acyclic ketones bearing a tertiary stereocenter at the α-position, which would be highly interesting due to the possibility of constructing a quaternary stereocenter in a stereocontrolled way.[11] In this context, paraformaldehyde, which is the polymeric form of formaldehyde and one of the most useful C1 electrophilic reagents,[12] has been used in the crossed aldol–Cannizzaro reaction with aldehydes.[13] On the other hand, hydroxymethylated products, without further reduction, are usually obtained with ketones.[14]

Continuing our studies in this research field, the hypothesis that a ketone enolate could be involved in the tandem process for the synthesis of 1,2,3-triol derivatives from simple α-lithiated benzyl ethers (Scheme 1, a), inspired us to develop the hetero-aldol–Tishchenko reaction of α-oxyketones with paraformaldehyde (Scheme 1, c). The success of this methodology, apart from supporting our previous mechanistic proposal, would also expand the scope of polyols that can be prepared since the previous limitations of the reaction with α-lithiobenzyl ethers could be surpassed, i.e. only selected benzyl ethers and aromatic carboxylic esters can be employed and EWG or bromine substituents are not tolerated due to the use of *t*-BuLi as metallating agent. Herein, we would like to report our results that successfully expand our previously described methodology.[8]

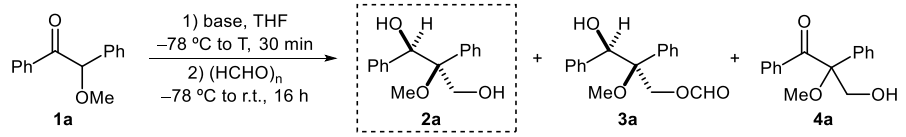


Scheme 1 (a) Previous results in the diastereoselective access to 1,2,3-triol derivatives bearing a quaternary stereocenter by merging α-lithiation of benzyl ethers and the aldol–Tishchenko reaction. (b) Synthesis of 1,2-*anti*, 1,3-*anti* 1,3-diol 1-monoester through hetero aldol–Tishchenko reaction. (c) Present work.

To explore the feasibility of this proposal, we selected commercially available benzoin methyl ether (**1a**) as the model compound. A series of experiments was carried out to identify the best reaction conditions, mainly regarding the base and its amount for the initial deprotonation, whereas the second step, the reaction with paraformaldehyde, was already established in our previous work[8] (Table 1). Initial experiments were performed with LDA as the metallating agent (entries 1–3). Two equivalents of this base were required to achieve complete conversion, avoiding the presence of the hydroxymethylated intermediate **4a**. Gratifyingly, the employment of lithium hexamethyldisilazide (LiHMDS) gave rise selectively to the 1,3-diol **2a** with an 86% yield (entry 4). Surprisingly, the expected formate **3a** was not observed, thus implying that a subsequent hydrolysis had taken place. In addition, we also checked that the enolate formation could also take place at lower temperatures (entries 5 and 6). Due to the catalytic role of the base in the aldol–Tishchenko reaction, subsequent assays were performed decreasing the amount of LiHMDS (entries 7–9). The number of base equivalents could be reduced to 0.3 without an adverse effect on the conversion, although the formate **3a** was also obtained along with 1,3-diol **2a**. This fact seems to show that an excess of the amide could favor the hydrolysis of the initially generated **3a** to **2a** without the need of a subsequent basic treatment. As an alternative to LiHMDS, the corresponding Na- or K-hexamethyldisilazides also resulted in being useful for this transformation, although slightly lower yields were obtained (entries 10 and 11). Therefore, to selectively obtain free 1,3-diol derivative **2a**, avoiding the need for subsequent hydrolysis of the formate group, the conditions from entry 6 were chosen (LiHDMS, 1 equiv, –78 °C).

After establishing the best reaction conditions for the synthesis of triol derivative **2a** from **1a**, a wide variety of α-alkoxy and α-aryloxyketones **1** was prepared using conventional synthetic methodologies (Table 2).[15] Whereas α-aryloxyketones **1d-p,s-w** were efficiently prepared from the corresponding α-halo ketones by a conventional Williamson reaction (method A, entries 4–16, 19–23), the α-alkoxyketones were synthesized employing alternative strategies. In this sense, the α-alkylation reaction of readily accessible 2-methoxyacetophenone with haloalkanes provided access to α-methoxyketones **1q,r** (entries 17 and 18). Finally, aliphatic ketones **1x-z** were produced by the reaction of an adequate organometallic reagent with the corresponding Weinreb amide derived from readily available ethyl lactate or mandelate (entries 24–26). The combination of these three different methods provides access to a plethora of α-alkoxy and α-aryloxyketones **1** in a straightway manner and in good yields.[15]

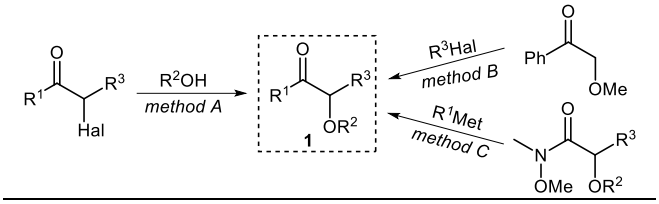
Table 1 Optimization Study[a]



Entry	Base (equiv)	T (°C)	Conv. (%)[b]	Ratio of **2a**/**3a**/**4a**[b]	Yield of **2a** (%)[c]
1	LDA (1)	r.t.	75	2:0:1	–[d]
2	LDA (1.5)	r.t.	90	4:0:1	–[d]
3	LDA (2)	r.t.	100	10:1:0	73
4	LiHMDS (1)	r.t.	100	1:0:0	86
5	LiHMDS (1)	–45	100	1:0:0	85
6	LiHMDS (1)	–78	100	1:0:0	87
7	LiHMDS (0.5)	r.t.	100	4:1:0	66
8	LiHMDS (0.3)	r.t.	100	2:1:0	54
9	LiHMDS (0.1)	r.t.	77	3:1,6:1	–[d]
10	NaHMDS (1.1)	r.t.	100	1:0:0	79
11	KHMDS (1.1)	r.t.	100	1:0:0	77

[a] Reaction conditions: **1a** (113 mg, 0.5 mmol), base, THF (3 mL).
[b] Determined by ^{1}H NMR analysis.
[c] Yield of isolated product **2a** after flash column chromatography.
[d] Not determined.

Table 2 Synthesis of Starting α-OxyKetones **1**.[a]

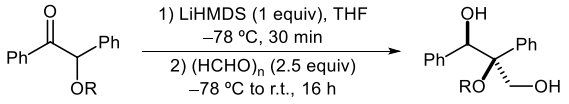


Entry	Ketone	R^1	R^2	R^3	Method[b]
1	**1a**	Ph	Me	Ph	–[c]
2	**1b**	Ph	Et	Ph	–[c]
3	**1c**	Ph	*i*-Pr	Ph	–[c]
4	**1d**	Ph	Ph	Ph	A
5	**1e**	Ph	2-$MeOC_6H_4$	Ph	A
6	**1f**	Ph	2,3-$(MeO)_2C_6H_3$	Ph	A
7	**1g**	Ph	4-$(EtO_2C)C_6H_4$	Ph	A
8	**1h**	Ph	Ph	Me	A
9	**1i**	Ph	1-Naphthyl	Me	A
10	**1j**	Ph	4-$MeOC_6H_4$	Me	A
11	**1k**	Ph	2-*i*-PrC_6H_4	Me	A
12	**1l**	Ph	2,6-$Me_2C_6H_3$	Me	A
13	**1m**	Ph	4-ClC_6H_4	Me	A
14	**1n**	Ph	2-BrC_6H_4	Me	A
15	**1o**	Ph	2,4-$F_2C_6H_3$	Me	A
16	**1p**	Ph	2-CNC_6H_4	Me	A
17	**1q**	Ph	Me	Et	B
18	**1r**	Ph	Me	$CH_2CH{=}CH_2$	B
19	**1s**	Ph	Ph	Et	A
20	**1t**	Ph	4-$MeOC_6H_4$	Et	A
21	**1y**	Ph	Ph	*i*-Pr	A
22	**1v**	Ph	4-$MeOC_6H_4$	*i*-Pr	A
23	**1w**	Ph	4-$MeOC_6H_4$	CH_2Ph	A
24	**1x**	Cy	Et	Me	C
25	**1y**	Cy	Me	Ph	C
26	**1z**	*c*-C_3H_5	Me	Ph	C

[a] See Supporting Information for details about the preparation and characterization of starting ketones **1**. [b] Method A: reaction of α-haloketones with phenols; Method B: α-alkylation of α-methoxyacetophenone; Method C: reaction of organometallics with the Weinreb amides derived from *O*-alkyl ethyl lactate and mandelate. [c] Commercially available.

Firstly, α-oxygen-functionalized benzyl phenyl ketones **1a-g** were used as starting materials (Table 3). α-Alkoxyketones **1a-c** provided high yields of the corresponding triol derivatives **2a-c** (entries 1–3). It is important to note that final products **2** bearing alkyl groups other than methyl cannot be accessible by the reactions of α-lithiobenzyl ethers with carboxylic esters and formaldehyde, due to more favorable competitive pathways such as β-elimination or Wittig rearrangement of alkyl α-lithiobenzyl ethers that prevent subsequent functionalization.[16] Moreover, the process resulted in being synthetically useful for subsequent transformations as shown with the gram-scale preparation of **2a** and **2b**. On the other hand, α-aryloxy ketones **1d-g** also provided the expected final triol derivatives **2d-g** under the same reaction conditions (entries 4–7). Interestingly, apart from alkoxy-functionalized aryl groups as substituents of the oxygen atom (entries 5 and 6), aryloxy groups bearing an electron-withdrawing group like ethoxycarbonyl, which would be completely incompatible with the α-lithiation strategy, are also tolerated under the reaction conditions (entry 7).

Table 3 Synthesis of Triol Derivatives **2a-g** from Benzyl Phenyl Ketones **1a-g**.[a]

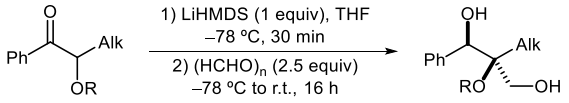


Entry	Ketone	Product	R	Yield (%)[b]
1	**1a**	**2a**	Me	87 (88)[c]
3	**1b**	**2b**	Et	83 (82)[c]
3	**1c**	**2c**	*i*-Pr	35[d]
4	**1d**	**2d**	Ph	70
5	**1e**	**2e**	2-$MeOC_6H_4$	61
6	**1f**	**2f**	2,3-$(MeO)_2C_6H_3$	57
7	**1g**	**2g**	4-$(EtO_2C)C_6H_4$	50

[a] Reaction conditions: ketone **1** (1 mmol), LiHMDS (1 mL of a 1 M solution in THF, 1 mmol), $(HCHO)_n$ (75 mg, 2.5 mmol), THF (4 mL). [b] Yield of isolated product **2** after flash column chromatography referred to the corresponding starting ketone **1**. [c] Yield referred to 10 mmol-scale reactions. [d] ca. 15% of the corresponding **3c** was also obtained.

One of the main limitations of our previously developed methodology[8] for the synthesis of triol derivatives **2** was that the R^3 substituent (see Scheme 1) could be only a phenyl group, as only the lithiation of benzyl ethers proceeds satisfactorily. For this reason, we turned our attention to α-oxygenated alkyl phenyl ketones **1h-w** that will provide polyols **2h-w** with an alkyl group at C-2 (Table 4). Starting from commercially available α-bromopropiohenone, a selection of α-aryloxyketones **1h-p** were synthesized and subjected to the established conditions to trigger the aldol–Tishchenko reaction (entries 1–9). A remarkable variety in the aryloxy moiety could be present in the starting ketone, including those with both electron-withdrawing and donating groups and even with a bromo (entry 7), a *m*-difluoro (entry 8), or a cyano (entry 9) substituents that would be incompatible with the *t*-BuLi required for the α-lithiation strategy.

Table 4 Synthesis of Triol Derivatives **2h-w** from Alkyl Phenyl Ketones **1h-w**.[a]

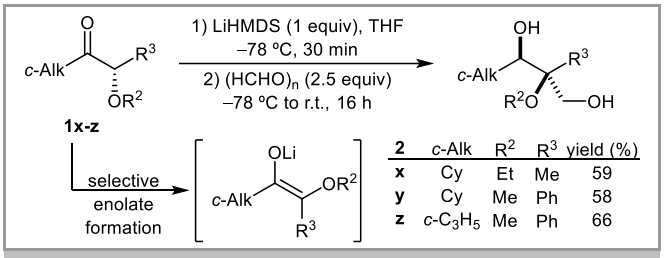


Entry	Ketone	Product	R	Alk	Yield (%)[b]
1	**1h**	**2h**	Ph	Me	68
2	**1i**	**2i**	1-Naphthyl	Me	63
3	**1j**	**2j**	4-$MeOC_6H_4$	Me	74
4	**1k**	**2k**	2-*i*-PrC_6H_4	Me	58
5	**1l**	**2l**	2,6-$Me_2C_6H_3$	Me	56
6	**1m**	**2m**	4-ClC_6H_4	Me	61
7	**1n**	**2n**	2-BrC_6H_4	Me	52
8	**1o**	**2o**	2,4-$F_2C_6H_3$	Me	55
9	**1p**	**2p**	2-NCC_6H_4	Me	40
10	**1q**	**2q**	Me	Et	67
11	**1r**	**2r**	Me	$CH_2CH{=}CH_2$	69
12	**1s**	**2s**	Ph	Et	65
13	**1t**	**2t**	4-$MeOC_6H_4$	Et	70
14	**1u**	**2u**	Ph	*i*-Pr	55
15	**1v**	**2v**	4-$MeOC_6H_4$	*i*-Pr	58
16	**1w**	**2w**	4-$MeOC_6H_4$	CH_2Ph	64[c]

[a] Reaction conditions: ketone **1** (1 mmol), LiHMDS (1 mL of a 1 M solution in THF, 1 mmol), $(HCHO)_n$ (75 mg, 2.5 mmol), THF (4 mL). [b] Yield of isolated product **2** after flash column chromatography referred to the corresponding starting ketone **1**. [c] Yield corresponds to the addition of **2w** (38%) and **3w** (26%).

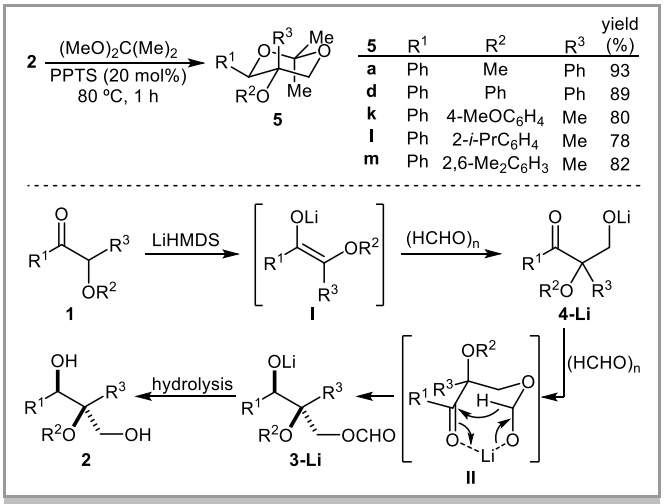
Additionally, α-methoxy substituted ketones **1q-r** also undergo the desired reaction (entries 10 and 11). Finally, other different alkyl groups, apart from methyl, at C-2 were studied (entries 10–16). Remarkably, branched alkyl (entries 14 and 15), or more challenging allyl (entry 11), as well as benzyl substituents (entry 16) are well-tolerated.

Another major drawback of the α-lithiation strategy was that R^1 substituent (see Scheme 1, a) is restricted to arenes due to the obligatory use of (hetero)aromatic carboxylic esters as electrophilic reagents because with alkylic ones the α-lithiobenzyl ether mainly undergoes protonation. In this sense, the alternative methodology herein reported is compatible with alkyl groups at this position (Scheme 2). Although exploratory essays with a butyl-substituted ketone did not provide satisfactory results,[17] interestingly, we found that cycloalkyl α-alkoxyalkyl ketones **1x-z** undergo regioselective enolate formation upon deprotonation at the tertiary α-alkoxy substituted position. Further reaction of this enolate intermediate with paraformaldehyde affords the triol derivatives **2x-z** in good yields and again with excellent stereocontrol in the process.



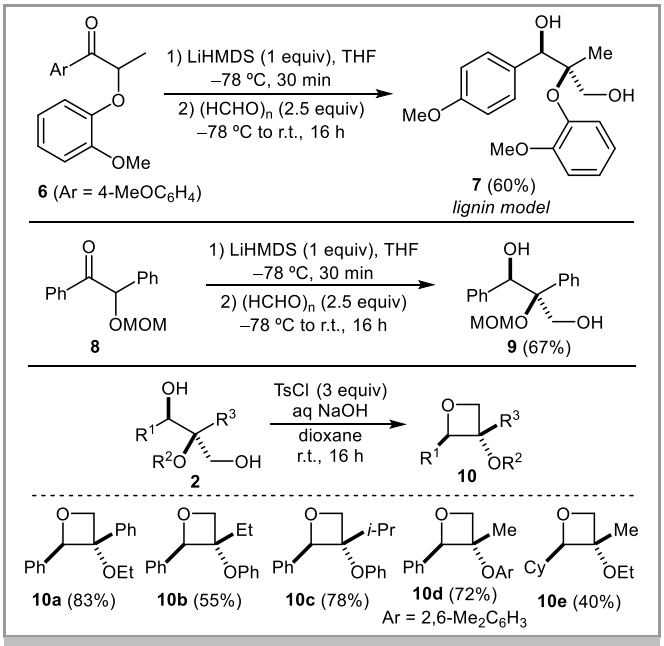
Scheme 2 Preparation of triol derivatives **2x-z** from dialkyl ketones **1x-z**.

To establish the relative stereochemistry of the obtained 1,3-diols **2** a selection of 1,3-dioxanes **5** were easily synthesized in high yields by reaction with acetone dimethyl acetal and a catalytic amount of pyridinium *p*-toluenesulfonate (Scheme 3). Their NMR analysis allowed us to assign the relative configuration of the stereocenters in **2**. A plausible mechanism for this transformation is also depicted in Scheme 3. The gathered evidence suggests that upon reaction with LiHMDS, the enolate intermediate **I** is formed preferentially. The addition of a molecule of formaldehyde generates the alkoxide **4-Li**, whose protonated form was previously observed in some experiments (see Table 1). The reaction with a second molecule of formaldehyde enables the formation of the classical aldol–Tishchenko hemiacetal intermediate **II**, which exhibits the appropriate orientation to evolve through hydride transfer ([3,3] bond reorganization), giving rise to Tishchenko adduct **3-Li**. Finally, the hydrolysis provides the 1,3-diol product **2**, in which the formate group has also been removed without the need for additional base. The stereoelectronic preference for the conformation of Evans intermediate **II** in which the oxygenated substituent, the best donor lone pair or bond, is antiperiplanar to the best acceptor bond, the carbonyl, determines the relative stereochemistry in the final product. It is worthy to highlight the exquisite stereocontrol in the generation of a quaternary stereocenter at the C-2 position.



Scheme 3 Preparation of selected 1,3-dioxanes **5**. Stereochemical assignment of selected diols **2** and mechanistic proposal.

Furthermore, to demonstrate the potential of the developed methodology, we applied this strategy to synthesize the new 1,3-dilignol model **7** with a β-O-4 linkage,[18] which presents the 2-position blocked with a methyl group[19] and could be useful for comparative studies toward lignin valorization (Scheme 4).[20] To our delight, compound **7** was satisfactorily obtained under the optimized reaction conditions from easily available α-aryloxy ketone **6**. In addition, the presence of an easily removable group on the oxygen of the starting α-oxyketone (R in Table 3) could be of great interest. For this reason, we tried the reaction with MOM-protected benzoin **8** and, gratifyingly, the expected 1,2,3-triol derivative **9** was obtained in good yield (Scheme 4). Finally, as it was demonstrated in our previous work,[8] the obtained 1,3-diols serve as an excellent platform for the synthesis of the relevant oxetane moiety.[20] The broader scope observed for the aldol–Tishchenko reaction of α-oxyketones with paraformaldehyde also renders in a wider variety of oxetanes **10**, allowing the substitution in α-position even with a cycloalkyl group (**10e**).



Scheme 4 Synthesis of the lignin model **7**, MOM-protected triol **9** and oxetanes **10**.

In conclusion, stereodefined acyclic polyhydroxylated fragments have been easily synthesized in good yields from simple α-oxyketones. This methodology, consisting of the hetero-aldol–Tishchenko reaction of α-alkoxy and α-aryloxyketones with paraformaldehyde, assembles two consecutive stereogenic centers, including a quaternary one, with complete stereocontrol. This strategy has allowed us to circumvent several limitations encountered with our previous strategy, based on α-lithiation of benzyl ethers and further reaction with carboxylic esters and formaldehyde, regarding the substituent nature in the starting materials. This has led to a considerably extended variety of the available 1,2,3-diol derivatives, with no change in the previously reported diastereoselectivity.

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All reactions involving air-sensitive compounds were carried out under a N_2 atmosphere (99.99%). All glassware was oven-dried (120 °C), evacuated and purged with nitrogen. All common reagents and solvents were obtained from commercial suppliers and used without any further purification. Flash column chromatography was carried out on silica gel 60, 230–240 mesh. TLC was performed on aluminium-backed plates coated with silica gel 60 with F254 indicator; the chromatograms were visualized under ultraviolet light and/or by staining with a Ce/Mo reagent and subsequent heating. R_f values are reported on silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-Plus (300 MHz ^{1}H; 75.4 MHz ^{13}C) or Bruker Avance (300 MHz ^{1}H; 75.4 MHz ^{13}C) spectrometers at room temperature. The chemical shifts (δ) are reported in ppm using residual solvent peak as reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). High-resolution mass spectra (HRMS) were obtained on an Agilent 6545 Q-TOF mass spectrometer using electrospray ionization (ESI). Melting points were measured on a Gallenkamp apparatus using open capillary tubes. For the synthesis of starting ethers **1** see Supporting Information.

General Procedure for Triol Derivatives 2, 7 and 9

To an oven-dried Schlenk flask under nitrogen 1 mmol of the corresponding α-oxy ketone **1** and anhydrous THF (4 mL) were added. The mixture was cooled to –78 °C and LiHDMS (1 equiv of a 1 M solution in THF) was added. The reaction was allowed to react for 30 min at this temperature. Then, paraformaldehyde (2.5 equiv) was added. After 10 min the mixture was warmed up to r.t. and it was allowed to react overnight. The reaction was quenched with water (10 mL). The mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Pure products **2**, **7** and **9** were isolated by silica gel flash column chromatography (eluent: hexane/EtOAc, from 5:1 to 1:1). Triol derivatives **2a,d,e** were reported in our previous work.[8]

(*1R*,2S)-2-Ethoxy-1,2-diphenylpropane-1,3-diol (2b)**

White solid; yield: 225 mg (83%); mp 149–151 °C; R_f = 0.10 (hexane/EtOAc, 4:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.10 (m, 6H), 7.03–6.95 (m, 2H), 6.87–6.79 (m, 2H), 4.95 (s, 1H), 4.30 (d, *J* = 12.3 Hz, 1H), 3.95 (dd, *J* = 12.3, 1.6 Hz, 1H), 3.79–3.22 (m, 4H), 1.29 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 138.8 (C), 137.7 (C), 128.2 (2 × CH), 128.0 (CH), 127.8 (CH), 127.6 (2 × CH), 127.3 (2 × CH), 127.0 (2 × CH), 82.9 (CH), 82.0 (C), 61.4 (CH_2), 58.6(CH_2), 15.7 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{22}NaO_3$: 309.1461; found: 309.1465.

(*1R*,2S)-2-Isopropoxy-1,2-diphenylpropane-1,3-diol (2c)**

Colorless oil; yield: 100 mg (35%); R_f = 0.16 (hexane/EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 3H), 7.19–7.08 (m, 5H), 6.84–6.78 (m, 2H), 5.03 (s, 1H), 4.24 (d, *J* = 12.2 Hz, 1H), 4.01 (dd, *J* = 12.2, 1.8 Hz, 1H), 3.83 (hept, *J* = 6.1 Hz, 1H), 3.61 (bs, 2H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.06 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 139.8 (C), 137.7 (C), 128.1 (CH), 128.0 (2 × CH), 127.7 (CH), 127.6 (2 × CH), 127.5 (2 × CH), 127.0 (2 × CH), 83.1 (CH), 82.2 (C), 67.1 (CH), 62.0 (CH_2), 24.7 (CH_3), 24.6 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{20}NaO_3$: 295.1305; found: 295.1308.

(1*R,2*S**)-2-(2,3-Dimethoxyphenoxy)-1,2-diphenylpropane-1,3-diol (2f)**

Colorless solid; yield: 160 mg (57%); mp 117–119 °C; R_f = 0.10 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.13 (m, 8H), 6.98 (d, *J* = 6.5 Hz, 2H), 6.69 (t, *J* = 8.4 Hz, 1H), 6.60 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.13 (dd, *J* = 8.4, 1.4 Hz, 1H), 5.41 (s, 1H), 4.65 (bs, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.10 (d, *J* = 12.8 Hz, 1H), 4.08 (s, 3H), 3.87 (bs, 1H), 3.87 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 153.7 (C), 149.1 (C), 141.1 (C), 138.7 (C), 138.4 (C), 128.1 (CH), 127.9 (4 × CH), 127.6 (CH), 127.5 (2 × CH), 127.4 (2 × CH), 123.4 (CH), 114.1 (CH), 107.1 (CH), 87.5 (C), 80.9 (CH), 61.6 (CH_2), 61.3 (CH_3), 56.0 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{24}NaO_5$: 403.1516; found: 403.1521.

Ethyl 4-(((1*R,2*S**)-1,3-dihydroxy-1,2-diphenylpropan-2-yl)oxy)benzoate (2g)**

Colorless solid; yield: 196 mg (50%); mp 145–147 °C; R_f = 0.32 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.9 Hz, 2H), 7.33–7.17 (m, 6H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 6.8 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 5.33 (d, *J* = 3.0 Hz, 1H), 4.63 (dd, *J* = 12.6, 4.3 Hz, 1H), 4.40-4.28 (m, 3H), 3.47 (d, *J* = 3.0 Hz, 1H), 2.89 (dd, *J* = 7.3, 4.3 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 166.4 (C), 159.3 (C), 137.9 (C), 137.6 (C), 131.1 (2 × CH), 128.35 (CH), 128.30 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 127.5 (2 × CH), 126.9 (2 × CH), 123.8 (C), 118.6 (2 × CH), 85.7 (C), 81.0 (CH), 60.8 (CH_2), 14.4 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{24}H_{24}NaO_5$: 415.1516; found: 415.1517.

(1*R,2*S**)-2-Methyl-2-phenoxy-1-phenylpropane-1,3-diol (2h)**

Colorless oil; yield: 175 mg (68%); R_f = 0.24 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.45 (m, 2H), 7.41–7.28 (m, 5H), 7.16–7.08 (m, 1H), 7.05–6.94 (m, 2H), 5.04 (s, 1H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.63 (d, *J* = 12.1 Hz, 1H), 3.52 (bs, 2H), 0.91 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 153.8 (C), 139.8 (C), 129.3 (2 × CH), 128.0 (CH), 127.9 (2 × CH), 127.9 (2 × CH), 124.5 (2 × CH), 124.4 (CH), 84.1 (C), 78.2 (CH), 65.4 (CH_2), 17.5 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{18}NaO_3$: 281.1148; found: 281.1148.

(1*R,2*S**)-2-Methyl-2-(naphthalen-1-yloxy)-1-phenylpropane-1,3-diol (2i)**

Pale yellow oil; 194 mg (63%); R_f = 0.11 (hexane/EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.64–7.56 (m, 3H), 7.50–7.36 (m, 6H), 7.24 (d, *J* = 7.6 Hz, 1H), 5.34 (s, 1H), 3.99 (d, *J* = 12.2 Hz, 1H), 3.91–3.87 (m, 2H), 3.27 (bs, 1H), 0.99 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 150.3 (C), 139.9 (C), 134.9 (C), 130.3 (C), 128.2 (2 × CH), 128.1 (3 × CH), 127.8 (CH), 126.2 (CH), 125.7 (CH), 125.7 (CH), 124.0 (CH), 122.9 (CH), 118.6 (CH), 85.2 (CH), 78.5 (C), 65.4 (CH_2), 17.1 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{20}NaO_3$: 331.1305; found: 331.1308.

(1*R,2*S**)-2-(4-Methoxyphenoxy)-2-methyl-1-phenylpropane-1,3-diol (2j)**

Colorless solid; 213 mg (74%); mp 84–86 °C; R_f = 0.27 (hexane/EtOAc, 40:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2H), 7.40–7.35 (m, 3H), 6.97–6.94 (m, 2H), 6.82–6.79 (m, 2H), 5.01 (s, 1H), 3.85 (d, *J* = 12.1 Hz, 1H), 3.79 (s, 3H), 3.60 (d, *J* = 12.1 Hz, 1H), 3.39 (bs, 2H), 0.90 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 156.4 (C), 147.1 (C), 139.8 (C), 128.1 (2 × CH), 128.0 (CH), 127.8 (2 × CH), 125.4 (2 × CH), 114.3 (2 × CH), 83.8 (C), 78.5 (CH), 65.3 (CH_2), 55.6 (CH_3), 17.6 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{20}NaO_4$: 311.1254; found: 311.1257.

(1*R,2*S**)-2-(2-Isopropylphenoxy)-2-methyl-1-phenylpropane-1,3-diol (2k)**

Colorless oil; 174 mg (58%); R_f = 0.19 (hexane/EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.43–7.35 (m, 3H), 7.29–7.26 (m, 1H), 7.13–7.08 (m, 3H), 5.19 (s, 1H), 3.93 (d, *J* = 12.1 Hz, 1H), 3.80–3.76 (m, 2H), 3.12–3.03 (m, 2H), 1.13 (dd, *J* = 6.9, 2.3 Hz, 3H), 1.11 (dd, *J* = 6.9, 2.3 Hz, 3H), 1.00 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 151.0 (C), 142.9 (C), 139.9 (C), 128.04 (4 × CH), 127.97 (CH), 126.6 (CH), 126.3 (CH), 124.1 (CH), 123.0 (CH), 84.2 (C), 78.3 (CH), 65.4 (CH_2), 26.0 (CH), 24.1 (CH_3), 23.2 (CH_3), 16.6 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{24}NaO_3$: 323.1618; found: 323.1624.

(1*R,2*S**)-2-(2,6-Dimethylphenoxy)-2-methyl-1-phenylpropane-1,3-diol (2l)**

Yellow oil; 160 mg (56%); R_f = 0.43 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.49 (m, 2H), 7.41–7.31 (m, 3H), 7.05–6.92 (m, 3H), 5.24 (s, 1H), 3.91 (s, 1H), 3.82–3.68 (m, 2H), 3.03 (s, 1H), 2.35 (s, 6H), 0.90 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 152.4 (C), 139.7 (C), 133.2 (CH), 129.3 (2 × CH), 128.3 (2 × CH), 128.1 (CH), 127.7 (2 × CH), 124.1 (CH), 85.4 (C), 81.5 (CH), 66.6 (CH_2), 18.6 (2 × CH_3), 17.5 (CH_3).

HRMS (ESI-TOF): could not be recorded.

(1*R,2*S**)-2-(4-Chlorophenoxy)-2-methyl-1-phenylpropane-1,3-diol (2m)**

Yellow solid; 178 mg (61%); mp 86–88 °C; R_f = 0.23 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.37 (m, 5H), 7.26 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.04 (s, 1H), 3.87 (d, *J* = 12.2 Hz, 1H), 3.62 (d, *J* = 12.2 Hz, 1H), 3.41 (bs, 1H), 2.94 (bs, 1H), 0.94 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 152.5 (C), 139.5 (C), 129.8 (C), 129.4 (2 × CH), 128.3 (3 × CH), 127.8 (2 × CH), 125.9 (2 × CH), 84.5 (C), 78.8 (CH), 65.3 (CH_2), 17.7 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{17}ClNaO_3$: 315.0758; found: 315.0763.

(1*R,2*S**)-2-(2-Bromophenoxy)-2-methyl-1-phenylpropane-1,3-diol (2n)**

Colorless oil; 173 mg (52%); R_f = 0.42 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.53–7.50 (m, 2H), 7.40–7.35 (m, 3H), 7.23–7.20 (m, 1H), 7.06–6.97 (m, 2H), 5.19 (s, 1H), 3.94 (d, *J* = 12.3 Hz, 1H), 3.71 (d, *J* = 12.3 Hz, 1H), 3.51 (bs, 1H), 2.99 (bs, 1H), 1.11 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 151.7 (C), 139.3 (C), 133.5 (CH), 128.5 (CH), 128.3 (2 × CH), 128.2 (CH), 127.9 (2 × CH), 125.2 (CH), 124.7 (CH), 118.6 (C), 87.1 (C), 79.0 (CH), 65.6 (CH_2), 17.6 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{17}BrNaO_3$: 359.0253; found: 359.0254.

(1*R,2*S**)-2-(2,4-Difluorophenoxy)-2-methyl-1-phenylpropane-1,3-diol (2o)**

Colorless oil; 162 mg (55%); R_f = 0.10 (hexane/EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 2H), 7.41–7.31 (m, 3H), 7.00–6.91 (m, 1H), 6.89–6.80 (m, 1H), 6.77–6.70 (m, 1H), 5.06 (s, 1H), 3.87 (d, *J* = 12.4 Hz, 1H), 3.60 (d, *J* = 12.4 Hz, 1H), 3.20 (bs, 2H), 0.92 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 157.8 (C, ddd, *J* = 183.2, 170.6, 11.7 Hz), 139.5 (C), 137.69 (C, dd, *J* = 11.4, 3.8 Hz), 128.2 (2 × CH), 127.9 (2 × CH), 127.47 (CH, dd, *J* = 9.6, 2.0 Hz), 111.13 (CH, dd, *J* = 22.4, 3.8 Hz), 104.8 (CH, dd, *J* = 26.6, 24.1 Hz), 86.1 (C), 78.0 (CH), 65.3 (CH_2), 16.9 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{16}F_2NaO_3$: 317.0960; found: 317.0960.

2-(((1*R,2*S**)-1,3-Dihydroxy-2-methyl-1-phenylpropan-2-yl)oxy)benzonitrile (2p)**

Colorless oil; 113 mg (40%); R_f = 0.30 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.52–7.46 (m, 3H), 7.39–7.36 (m, 3H), 7.16 (td, *J* = 7.7, 6.6 Hz, 2H), 5.17 (d, *J* = 2.4 Hz, 1H), 3.93 (dd, *J* = 12.4, 2.4 Hz, 1H), 3.80–3.71 (m, 2H), 3.35 (bs, 1H), 1.12 (s, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 157.3 (C), 139.3 (CH), 134.0 (CH), 133.3 (CH), 128.2 (2 × CH), 127.9 (2 × CH), 124.0 (CH), 123.9 (CH), 117.7 (C), 108.6 (C), 87.4 (C), 78.6 (CH), 65.5 (CH_2), 17.8 (CH_3).

HRMS (ESI-TOF): [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_3$: 306.1101; found: 306.1109.

(1*R,2*S**)-2-Ethyl-2-methoxy-1-phenylpropane-1,3-diol (2q)**

Colorless solid; 141 mg (67%); mp 75–77 °C; R_f = 0.20 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.30 (m, 5H), 4.90 (s, 1H), 3.64–3.59 (m, 4H), 3.42 (s, 3H), 1.41–1.21 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 140.0 (C), 128.3 (2 × CH), 127.9 (CH), 127.4 (2 × CH), 79.7 (C), 77.7 (CH), 63.5 (CH_2), 49.6 (CH_3), 21.9 (CH_2), 7.0 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{18}NaO_3$: 233.1148; found: 233.1144.

(1*R,2*S**)-2-Allyl-2-methoxy-1-phenylpropane-1,3-diol (2r)**

Colorless solid; 153 mg (69%); mp 86–88 °C; R_f = 0.19 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.31 (m, 5H), 5.86–5.75 (m, 1H), 5.15–5.10 (m, 2H), 4.89 (s, 1H), 3.69–3.61 (m, 4H), 3.45 (s, 3H), 2.21–2.02 (m, 2H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 139.9 (C), 132.5 (CH), 128.2 (2 × CH), 127.9 (CH), 127.6 (2 × CH), 118.5 (CH_2), 79.4 (C), 77.6 (CH), 63.7 (CH_2), 50.0 (CH_3), 34.0 (CH_2).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{18}NaO_3$: 245.1148; found: 245.1148.

(1*R,2*S**)-2-Ethyl-2-phenoxy-1-phenylpropane-1,3-diol (2s)**

White solid; 177 mg (65%); mp 71–73 °C; R_f = 0.12 (hexane/EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.44 (m, 2H), 7.39–7.24 (m, 5H), 7.22–7.08 (m, 3H), 5.02 (d, *J* = 4.6 Hz, 1H), 4.26 (d, *J* = 2.7 Hz, 1H), 3.76–3.67 (m, 2H), 3.50 (s, 1H), 1.42 (q, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 154.4 (C), 139.9 (C), 129.3 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 127.7 (2 × CH), 123.9 (CH), 123.6 (2 × CH), 85.5 (C), 77.7 (CH), 64.1 (CH_2), 24.0 (CH_2), 7.8 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{20}NaO_3$: 295.1305; found: 295.1303.

(1*R,2*S**)-2-Ethyl-2-(4-methoxyphenoxy)-1-phenylpropane-1,3-diol (2t)**

Colorless oil; 211 mg (70%); R_f = 0.20 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.6 Hz, 2H), 7.38–7.33 (m, 3H), 7.14 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.01 (s, 1H), 3.80 (s, 3H), 3.75 (d, *J* = 12.4 Hz, 1H), 3.68 (d, *J* = 12.4 Hz, 1H), 3.56–3.49 (m, 2H), 1.39 (q, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 156.1 (C), 147.5 (C), 139.9 (C), 128.3 (2 × CH), 128.0 (CH), 127.7 (2 × CH), 124.8 (2 × CH), 114.4 (2 × CH), 85.4 (C), 77.8 (CH), 64.1 (CH_2), 55.6 (CH_3), 23.9 (CH_2), 7.8 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{22}NaO_4$: 325.1410; found: 325.1407.

(1*R,2*S**)-2-Isopropyl-2-phenoxy-1-phenylpropane-1,3-diol (2u)**

Colorless oil; 157 mg (55%); R_f = 0.10 (hexane/EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.56 (m, 2H), 7.45–7.34 (m, 7H), 7.20–7.13 (m, 1H), 5.24 (d, *J* = 4.8 Hz, 1H), 3.95 (dd, *J* = 13.1, 3.9 Hz, 1H), 3.81 (ddd, *J* = 13.1, 7.7, 1.1 Hz, 1H), 3.56 (d, *J* = 4.8 Hz, 1H), 2.82 (dd, *J* = 7.7, 3.9 Hz, 1H), 2.12 (hept, *J* = 7.0 Hz, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 155.2 (C), 134.0 (C), 129.4 (2 × CH), 128.4 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 123.8 (CH), 123.6 (2 × CH), 87.6 (C), 77.4 (CH), 63.3 (CH_2), 31.1 (CH), 17.7 (2 × CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{22}NaO_3$: 309.1461; found: 309.1452.

(1*R,2*S**)-2-Isopropyl-2-(4-methoxyphenoxy)-1-phenylpropane-1,3-diol (2v)**

Orange oil; 183 mg (58%); R_f = 0.10 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.56 (m, 2H), 7.44–7.36 (m, 3H), 7.26 (d, *J* = 9.2 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 5.18 (s, 1H), 3.90 (d, *J* = 12.9 Hz, 1H), 3.81 (s, 3H), 3.73 (d, *J* = 12.9 Hz, 1H), 2.04 (hept, *J* = 7.0 Hz, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 156.1 (C), 148.3 (C), 139.9 (C), 128.5 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 124.8 (2 × CH), 114.5 (2 × CH), 87.4 (C), 77.5 (CH), 63.4 (CH_2), 55.6 (CH_3), 30.9 (CH), 17.7 (2 x CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{24}NaO_4$: 339.1567; found: 339.1557.

(1*R,2*S**)-2-Benzyl-2-(4-methoxyphenoxy)-1-phenylpropane-1,3-diol (2w)**

Colorless solid (138 mg, 38% yield); mp 119–121 °C; R_f = 0.11 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 10H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 4.90 (d, *J* = 4.2 Hz, 1H), 3.80 (s, 3H), 3.74 (bs, 1H), 3.53 (s, 2H), 3.17 (d, *J* = 13.7 Hz, 1H), 2.92 (d, *J* = 13.7 Hz, 1H), 2.30 (d, *J* = 4.2 Hz, 1H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 156.1 (C), 148.2 (C), 140.2 (C), 136.8 (C), 130.7 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 128.0 (CH), 126.6 (CH), 124.8 (2 × CH), 114.4 (2 × CH), 85.7 (C), 75.8 (CH), 64.3 (CH_2), 55.5 (CH_3), 37.3 (CH_2).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{24}NaO_4$: 387.1567; found: 387.1575.

(1*R,2*S**)-1-Cyclohexyl-2-ethoxy-2-methylpropane-1,3-diol (2x)**

Colorless oil; 128 mg (59%); R_f = 0.26 (hexane/EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.67 (d, *J* = 11.7 Hz, 1H), 3.57 (d, *J* = 11.7 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 2H), 3.40 (d, *J* = 4.3 Hz, 1H), 2.94–2.88 (m, 2H), 1.89–1.44 (m, 6H), 1.26–1.09 (m, 11H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 79.2 (C), 79.1 (CH), 65.4 (CH_2), 56.7 (CH_2), 39.2 (CH_3), 32.5 (CH_2), 28.3 (CH_2), 26.7 (CH_2), 26.4 (2 × CH_2), 16.8 (CH_3), 16.0 (CH_3).

HRMS (ESI-TOF): [M + H]$^+$ calcd for $C_{12}H_{25}O_3$: 217.1798; found: 217.1798.

(1*R,2*S**)-(1-Cyclohexyl-2-methoxy-2-phenylpropane-1,3-diol (2y)**

Colorless oil (153 mg, 58%); R_f = 0.47 (hexane/EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.28 (m, 5H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.20 (dd, *J* = 12.3, 1.7 Hz, 1H), 3.73 (dd, *J* = 4.0, 1.7 Hz, 1H), 3.20 (s, 3H), 3.18 (bs, 1H), 3.16 (bs, 1H), 1.76–1.40 (m, 5H), 1.21–1.02 (m, 6H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 139.1 (C), 128.5 (2 × CH), 128.0 (CH), 127.0 (2 × CH), 83.5 (CH), 81.3 (C), 61.8 (CH_2), 50.2 (CH_3), 38.3 (CH), 32.7 (CH_2), 27.6 (CH_2), 26.6 (CH_2), 26.3 (2 × CH_2).

HRMS (ESI-TOF): [M + Na]$^+$ calcd for $C_{16}H_{24}NaO_3$: 287.1618; found: 287.1617.

(1*R,2*S**)-1-Cyclopropyl-2-methoxy-2-phenylpropane-1,3-diol (2z)**

Colorless solid (147 mg, 66% yield); mp 78–80 °C; R_f = 0.23 (hexane/EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5H), 4.76 (dd, *J* = 12.2, 2.5 Hz, 1H), 4.18 (dd, *J* = 11.7, 8.2 Hz, 1H), 3.51 (dd, *J* = 12.2, 2.5 Hz, 1H), 3.41 (bs, 1H), 3.39 (bs, 1H), 3.27 (s, 3H), 0.80–0.78 (m, 1H), 0.46–0.36 (m, 2H), 0.26–0.21 (m, 1H), 0.24-–0.26 (m, 1H).

^{13}C NMR (75.4 MHz, $CDCl_3$): *δ* = 139.3 (C), 128.4 (CH), 127.8 (2 × CH), 126.9 (2 × CH), 82.8 (CH), 81.9 (C), 61.7 (CH_2), 50.6 (CH_3), 11.8 (CH), 3.0 (CH_3), 1.7 (CH_3).

HRMS (ESI-TOF): [M + Na]$^+$ calcd for $C_{13}H_{18}NaO_3$: 245.1148; found: 245.1148.

(1*R,2*S**)-2-(2-Methoxyphenoxy)-1-(4-methoxyphenyl)-2-methylpropane-1,3-diol (7)**

Colorless solid (191 mg, 60% yield); mp 111–113 °C; R_f = 0.28 (hexane/EtOAc, 1:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.6 Hz, 2H), 7.13–7.09 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.97–6.87 (m, 4H), 4.95 (s, 1H), 3.94 (d, *J* = 11.9 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.48 (d, *J* = 11.9 Hz, 1H), 1.01 (s, 3H), the OH signals do not appear.

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ = 159.2 (C), 153.4 (C), 143.0 (C), 131.9 (C), 128.9 (2 × CH), 126.2 (CH), 125.1 (CH), 121.2 (CH), 113.4 (2 × CH), 112.1 (CH), 86.6 (C), 77.1 (CH), 65.3 (CH_2), 55.9 (CH_3), 55.3 (CH_3), 17.2 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{22}NaO_5$: 341.1359; found: 341.1359.

(1*R,2*S**)-2-(Methoxymethoxy)-1,2-diphenylpropane-1,3-diol (9)**

Colorless solid (193 mg, 67% yield); mp 104–106 °C; R_f = 0.41 (hexane/EtOAc, 1:1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.33–7.24 (m, 3H), 7.21–7.04 (m, 5H), 6.89–6.83 (m, 2H), 5.04 (d, *J* = 4.5 Hz, 1H), 4.79 (d, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 7.2 Hz, 1H), 4.42 (dd, *J* = 13.2, 7.7 Hz, 1H), 4.03 (dd, *J* = 13.2, 6.9 Hz, 1H), 3.86–3.78 (m, 1H), 3.77–3.69 (m, 1H), 3.55 (s, 3H).

^{13}C-NMR (75.4 MHz, $CDCl_3$) δ = 139.1 (C), 137.9 (C), 128.1 (2 × CH), 128.0 (CH), 127.9 (2 × CH), 127.8 (2 × CH), 127.5 (CH), 127.3 (2 × CH), 92.6 (CH_2), 86.0 (C), 79.8 (CH), 62.3 (CH_2), 56.3 (CH_3).

HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{20}NaO_4$: 311.1254; found: 311.1258.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References

(1) Perna, F. M.; Salomone, A.; Capriati, V. In *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*; Luisi, R.; Capriati, V., Eds.; Wiley-VCH, **2014**, Ch. 6, pp 153-189.

(2) For the carbenoid nature of α-functionalized organolithiums, see: (a) Capriati, V.; Florio, S. *Chem. Eur. J.* **2010**, *16*, 4152. (b) Pace, V.; Castoldi, L.; Monticelli, S.; Rui, M.; Collina, S. *Synlett* **2017**, *28*, 879. (c) Castoldi, L.; Monticelli, S.; Senatore, R.; Ielo, L.; Pace. V. *Chem. Commun.* **2018**, *54*, 6692. (d) Ielo, L.; Pillari, V.; Miele, M.; Castiglione, D.; Pace, V. *Synlett* **2021**, *32*, 551. For a selected recent report, see: (e) Cocco, A.; Rubanu, M. G.; Sechi, M. L.; Frongia, A.; Mastrorilli, P.; Degennaro, L.; Colella, M.; Luisi, R.; Secci, F. *Org. Biomol. Chem.* **2021**, *19*, 1945.

(3) For a recent review, see: Wang, F.; Wang, J.; Zhang, Y.; Yang, J. *Tetrahedron* **2020**, *76*, 130857.

(4) For our previous work with oxygen-functionalized organolithiums, see: (a) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C.; Trabada, M. *Org. Lett.* **2002**, 4, 1587. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. *Org. Lett.* **2002**, 4, 2225. (c) Sanz, R.; Miguel, D.; Martínez, A.; Pérez, A. *J. Org. Chem.* **2006**, *71*, 4024. For other reports, see, for instance: (d) Dammacco, M.; Degennaro, L.; Florio, S.; Luisi, R.; Musio, B.; Altomare, A. *J. Org. Chem.* **2009**, *74*, 6319.

(5) (a) Velasco, R.; Feberero, C.; Sanz, R. *Org. Lett.* **2015**, *17*, 4416. (b) Sedano, C.; Velasco, R.; Suárez-Pantiga, S.; Sanz, R. *Org. Lett.* **2020**, *22*, 6365.

(6) Lithiation of benzyl methyl ether: (a) Azzena, U.; Demartis, S.; Fiori, M. G.; Pisano, L. *Tetrahedron Lett.* **1995**, *36*, 5641. Lithiation of benzyl methoxymethyl ether: (b) Azzena, U.; Pisano, L.; Mocci, S. *J. Organomet. Chem.* **2009**, *694*, 3619.

(7) Velasco, R.; Silva-López, C.; Nieto-Faza, O.; Sanz, R. *Chem. Eur. J.* **2016**, *22*, 15058.

(8) Sedano, C.; Velasco, R.; Suárez-Pantiga, S.; Sanz, R. *Org. Lett.* **2020**, *22*, 8070.

(9) (a) Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713. (b) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779. (c) Koskinen, A. M. P.; Kataja, A. O. *Org. React.* **2015**, *86*, 105.

(10) See, for instance: (a) Baramee, A.; Chaichit, N.; Intawee, P.; Thebtaranonth, C.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Conmmun.* **1991**, 1016. (b) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674. (c) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427. For examples of the enantioselective aldol–Tishchenko reaction, see: (d) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782. (e) Horiuchi, Y.; Gnanadesikan, V.; Ohshima, T.; Masu, H.; Katagiri, K.; Sei, Y.; Yamaguchi, K.; Shibasaki, M. *Chem. Eur. J.* **2005**, *11*, 5195. (f) Mlynarski, J.; Rakiel, B.; Stodulski, M.; Suszczyńska, A.; Frelek, J. *Chem. Eur. J.* **2006**, *12*, 8158. (g) Stodulski, M.; Mamiska, A.; Mlynarski, J. *Tetrahedron: Asymmetry* **2011**, *22*, 464. (h) Ichibakase, T.; Nakajima, M. *Org. Lett.* **2011**, *13*, 1579

(11) (a) Ichibakase, T.; Kaneko, T.; Orito, Y.; Kotani, S.; Nakajima, M. *Tetrahedron* **2012**, *68*, 4210. For the enantioselective aldol–Tishchenko reaction of cyclic α-fluoroketones, see: (b) Asano, T.; Kotani, S.; Nakajima, M. *Org. Lett.* **2019**, *21*, 4192.

(12) (a) Li, W.; Xu, X.-F. *Adv. Synth. Catal.* **2015**, *357*, 3393. (b) Liu, C.; Huang, W.; Zhang, J.; Rao, Z.; Gu, Y.; Jérôme, F. *Green Chem.* **2021**, *23*, 1447.

(13) See, for instance: (a) Mohapatra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 6031. (b) Reddy, P. S.; Sharma, G. V. M. *Synthesis* **2014**, 1532.

(14) See, for instance: (a) Ouchi, T.; Arita, Y.; Imoto, M. *Polym. J.* **1976**, *8*, 477. (b) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236. (c)Liu, C.; Shen, M.; Lai, B.; Taheri, A.; Gu, Y. *ACS Comb. Sci.* **2014**, *16*, 652.

(15) See Supporting Information for details.

(16) Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* **1968**, 6759. See also ref. (6a)

(17) The reaction of 2-ethoxyheptan-3-one (**SM11**) under the established conditions only afforded unidentified products. See Supporting Information for details.

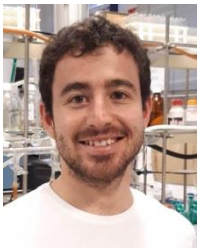
(18) For a related dilignol compound, see: Rinesch, T.; Mottweiler, J.; Puche, M.; Concepción, P.; Corma, A.; Bolm, C. *ACS Sustainable Chem. Eng.* **2017**, *5*, 9818.

(19) For the preparation of dilignol β-O-4 type model compounds, see: (a) Buendia, J.; Mottweiler, J.; Bolm, C. *Chem. Eur. J.* **2011**, *17*, 13877. (b) Dias, R. M. P.; de Oliveira, G. P.; Burtoloso, C. B. *Org. Biomol. Chem.* **2020**, *18*, 4815.

(20) (a) Kärkäs, M. D.; Matsuura, B. S.; Monos, T. M.; Magallanes, G.; Stephenson, C. R. J. *Org. Biomol. Chem.* **2016**, *14*, 1853. (b) Gillet, S.; Aguedo, M.; Petitjean, L.; Morais, A. R. C.; da Costa Lopes, A. M.; Lukasik, R. M.; Anastas, P. T. *Green Chem.* **2017**, *19*, 4200. (c) Das, A.; König, B. *Green Chem.* **2018**, *20*, 4844.

(21) (a) Burkhard, J. A.; Wuitschik, G.; Roger-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (b) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257. (c) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. *Chem. Rev.* **2016**, *116*, 12150.

Biosketches

	**Carlos Sedano** was born in Tardajos (Burgos), Spain in 1994. He graduated from the University of Burgos in 2016 and received his M.Sc. in Chemistry in 2017. Currently, he is a 4th year Ph.D. student working under guidance of Prof. Sanz. His research interests include new synthetic methodologies with organolithium compounds and their usefulness in stereoselective processes.
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