OL | Organic Letters

pubs.acs.org/OrgLett Letter

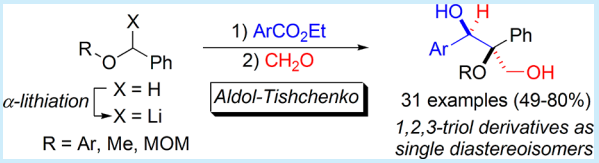
Merging α-Lithiation and Aldol-Tishchenko Reaction to Construct Polyols from Benzyl Ethers

Carlos Sedano, Rocío Velasco, Samuel Suárez-Pantiga, and Roberto Sanz*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03014 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

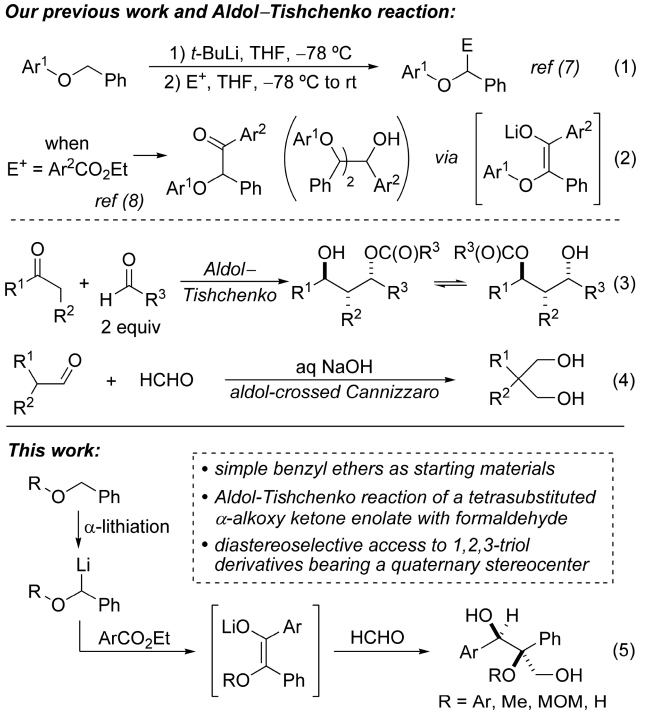
ABSTRACT: α-Lithiobenzyl ethers, generated by selective α-lithiation, undergo an aldol-Tishchenko reaction upon treatment with carboxylic esters and paraformaldehyde. The reaction of the organolithium with the carboxylate generates an intermediate enolate that, after formaldehyde addition, affords 1,2,3-triol 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 can be easily accessed 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 temperatures, 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 contrary, the classical aldol-Tishchenko reaction leads to the trimerization of an enolizable aldehyde, under basic conditions, affording a 1,3-*anti*-diol monoester.[9] In particular, 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 noteworthy 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 the Work Presented Here

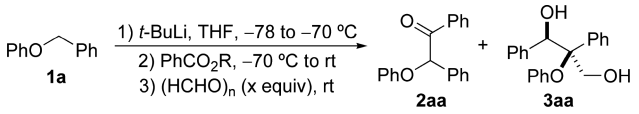


Received: September 9, 2020

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 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 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 triol derivative **3aa**, arising from an aldol-Tishchenko reaction. Remarkably, it was generated as a single diastereoisomer. Looking to improve its formation, we found a larger amount of paraformaldehyde 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, respectively), and phenyl benzoate led to only 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]

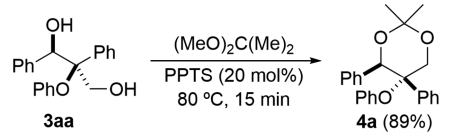


entry	R	x[b]	product	yield (%)[c]
1	Et	0	**2aa**	79 (73)
2	Et	1.1	**3aa**	(21)
3	Et	2	**3aa**	(58)
4	Et	2.5	**3aa**	74 (70)
5	Me	2.5	**3aa**	70
6	*i*-Pr	2.5	**3aa**	39
7	Bn	2.5	**3aa**	53
8	Ph	2.5	–[d]	–

[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 used as the HCHO source. [b]Equivalents of paraformaldehyde referenced to **1a**. [c]NMR yield using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses. [d]Decomposition was observed without any identified product.

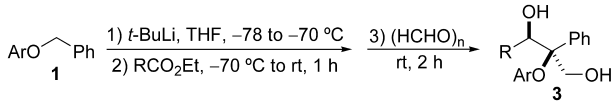
The complete characterization and stereochemical assignment of **3aa** were carried out by its transformation into ketal derivative **4a** through reaction with an acetone equivalent under acid catalysis (Scheme 2). The NMR analysis of **4a** supports the proposed aldol-Tishchenko product and lets us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

Scheme 2. Stereochemical Assignment of 3aa and 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

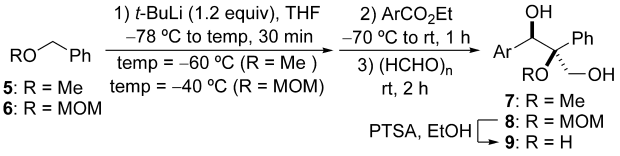
[a]Reaction conditions: **1** (0.5–1 mmol), *t*-BuLi (1.3 equiv, 30 min), RCO_2Et (1.3 equiv mmol, 1 h), $(HCHO)_n$ (2.5 equiv, 2 h). [b]Isolated yield referenced to starting ether **1**.

Azzena and co-workers had described the direct metalation of methyl and methoxymethyl benzyl ethers **5** and **6**, showing

https://dx.doi.org/10.1021/acs.orglett.0c03014
Org. Lett. XXXX, XXX, XXX−XXX

that the corresponding α-alkoxy-substituted benzyllithium derivatives could be reacted with electrophiles prior to undergo Wittig rearrangement.[17] To minimize the amount of the carboxylic ester employed as an electrophile, which is influenced by the excess of the base required for the metalation, a revision of the reaction conditions initially reported for the α-lithiation of both alkyl benzyl ethers **5** and **6** was carried out (see the 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, 2-alkoxy-1,3-diols **7** and **8**, respectively, 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 compared to 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 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]

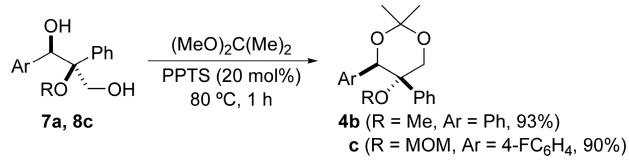


entry	starting ether	Ar	product	yield (%)[b]
1	**5**	Ph	**7a**	69
2	**5**	1-naphthyl	**7b**	57
3	**5**	4-FC_6H_4	**7c**	49
4	**5**	4-BrC_6H_4	**7d**	50
5	**5**	2-ClC_6H_4	**7e**	58
6	**6**	Ph	**8a**	55
7	**6**	1-naphthyl	**8b**	60
8	**6**	4-FC_6H_4	**8c**	68
9	**6**	4-BrC_6H_4	**8d**	50
10	**6**	2-ClC_6H_4	**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

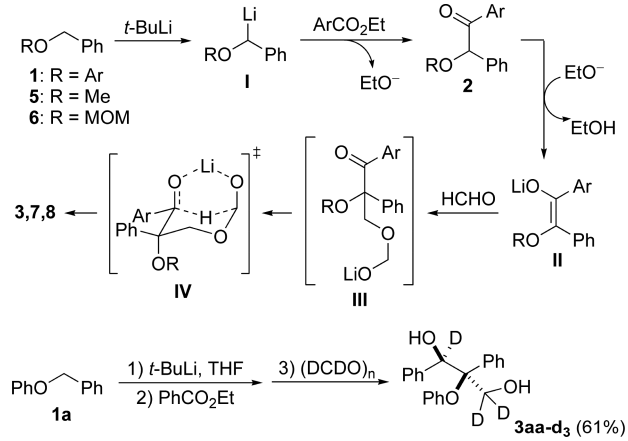
[a]Reaction conditions: **5** or **6** (1 mmol), *t*-BuLi (1.2 mmol, 30 min), $ArCO_2Et$ (1.2 mmol, 1 h), $(HCHO)_n$ (2.5 mmol, 2 h). [b]Yield of the isolated product referenced to starting ether **5** or **6**. [c]Corresponding crude products **8** were treated with PTSA (1 equiv) in EtOH at 60 °C for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

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 intermediate hemiacetal **III** that evolves to the final products by intramolecular hydride transfer via 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 3. Synthesis of 1,3-Dioxanes 4b and 4c

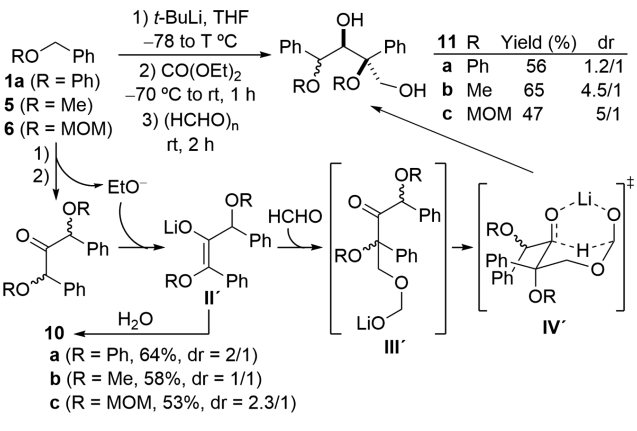


Scheme 4. Mechanistic Proposal



Then, we turned our attention to the use of diethyl carbonate, which can be easily accessed from CO_2,[18] as a C1 synthon carboxylate partner[19] for the methodology reported herein. First, we found that its reaction with the α-lithiobenzyl ethers generated from **1a**, **5**, and **6** led, after hydrolysis, to 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

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

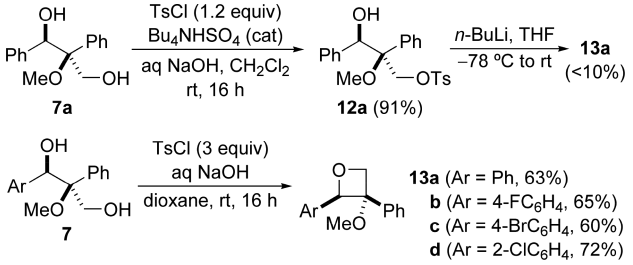


https://dx.doi.org/10.1021/acs.orglett.0c03014
Org. Lett. XXXX, XXX, XXX−XXX

by assuming that the generation of 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, tetraol derivatives **11** were obtained in moderate to good yields as mixtures of diastereoisomers, though **11b** and **11c** 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 aldol-Tishchenko transition state **IV′** (Scheme 5).

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 primary monotosylate **12a** from 1,3-diol derivative **7a** (Scheme 6). Then, we attempted to synthesize oxetane **13a** by

Scheme 6. Synthesis of Oxetanes 13 from Triol Derivatives 7



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 that proposed from 1,3-dioxane derivatives **4**.

In summary, we have described an efficient highly diastereoselective protocol to synthesize polyol derivatives in one 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 temperatures, 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 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 been revealed to be efficient for obtaining 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 2 equiv 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 https://pubs.acs.org/doi/10.1021/acs.orglett.0c03014.

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**, and **14** (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Roberto Sanz − *Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain;* orcid.org/0000-0003-2830-0892; Email: rsd@ubu.es

Authors

Carlos Sedano − *Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain*

Rocío Velasco − *Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain*

Samuel Suárez-Pantiga − *Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain;* orcid.org/0000-0002-4249-7807

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03014

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge Ministerio de Ciencia e Innovación and FEDER (CTQ2016-75023-C2-1-P) and Junta de Castilla y León and FEDER (BU291P18) for financial support. S.S.-P. thanks Junta de Castilla y León and FEDER for a postdoctoral contract. C.S. thanks Ministerio de Educación for an FPU predoctoral contract.

■ 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; Chapter 6, pp 153−189.

(2) (a) Capriati, V.; Florio, S. Anatomy of Long-Lasting Love Affairs with Lithium Carbenoids: Past and Present Status and Future Prospects. *Chem. - Eur. J.* **2010**, *16*, 4152−4162. (b) Pace, V.; Castoldi, L.; Monticelli, S.; Rui, M.; Collina, S. New Perspectives in Lithium Carbenoid Mediated Homologations. *Synlett* **2017**, *28*, 879−888. (c) Castoldi, L.; Monticelli, S.; Senatore, R.; Ielo, L.; Pace, V.

Homologation chemistry with nucleophilic α-substituted organometallic reagents: chemocontrol, new concepts and (solved) challenges. *Chem. Commun.* **2018**, *54*, 6692−6704.

(3) (a) Wittig, G.; Löhmann, L. Über die kationtrope Isomerisation gewisser Benzyläther bei Einwirkung von Phenyl-lithium. *Justus Liebigs Ann. Chem.* **1942**, *550*, 260−268. (b) Garst, J. F.; Smith, C. D. Wittig rearrangements of aralkyl alkyl ethers. *J. Am. Chem. Soc.* **1976**, *98*, 1526−1537. (c) Pace, V.; Murgia, I.; Westermayer, S.; Langer, T.; Holzer, W. Highly efficient synthesis of functionalized α-oxyketones *via* Weinreb amides homologation with α-oxygenated organolithiums. *Chem. Commun.* **2016**, *52*, 7584−7587. For α-lithiations of oxygen heterocycles, see: (d) Perna, F. M.; Salomone, A.; Capriati, V. Recent Developments in the Lithiation Reactions of Oxygen Heterocycles. *Adv. Heterocycl. Chem.* **2016**, *118*, 91−127.

(4) (a) Still, W. C. Stannylation/Destannylation. Preparation of α-Alkoxy Organolithium Reagents and Synthesis of Dendrolasin via a Carbinyl Carbanion Equivalent. *J. Am. Chem. Soc.* **1978**, *100*, 1481−1487. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. Physical Properties and Synthetic Utility of α-Alkoxyorganolithium Species as Studied through Ligand Selectivity in Tin-Lithium Exchange. *J. Am. Chem. Soc.* **1988**, *110*, 842−853.

(5) Review: (a) Wang, F.; Wang, J.; Zhang, Y.; Yang, J. The [1,2]- and [1,4]-Wittig rearrangement. *Tetrahedron* **2020**, *76*, 130857. For selected synthetic applications, see: (b) Tomooka, K.; Yamamoto, K.; Nakai, T. Enantioselective [1,2] Wittig Rearrangement Using an External Chiral Ligand. *Angew. Chem., Int. Ed.* **1999**, *38*, 3741−3743. (c) Bertrand, M. B.; Wolfe, J. P. Tandem Wittig Rearrangement/Aldol Reactions for the Synthesis of Glycolate Aldols. *Org. Lett.* **2006**, *8*, 4661−4663. (d) Nakano, T.; Soeta, T.; Endo, K.; Inomata, K.; Ukaji, Y. Stereoselective Synthesis of (2*Z*,4*E*)-2,4-Pentadien−ols via Sequential 1,4-Elimination Reaction and [1,2]-Wittig Rearrangement Starting from (*E*)-4-Alkoxy-2-butenyl Benzoates. *J. Org. Chem.* **2013**, *78*, 12654−12661.

(6) (a) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C.; Trabada, M. On the Reactivity of *o*-Lithioaryl Ethers: Tandem Anion Translocation and Wittig Rearrangement. *Org. Lett.* **2002**, *4*, 1587−1590. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. Diastereo-Enantioselective Carbolithiation of Allyl *o*-Lithioaryl Ethers. New Chiral Cyclopropane Derivatives. *Org. Lett.* **2002**, *4*, 2225−2228. (c) Sanz, R.; Miguel, D.; Martínez, A.; Pérez, A. New Synthesis of 2-Aryl-3-Substituted Benzo[*b*]furans from Benzyl 2-Halophenyl Ethers. *J. Org. Chem.* **2006**, *71*, 4024−4027.

(7) (a) Velasco, R.; Feberero, C.; Sanz, R. α-Lithiated Aryl Benzyl Ethers: Inhibition of [1,2]-Wittig Rearrangement and Application to the Synthesis of Benzo[*b*]furan Derivatives. *Org. Lett.* **2015**, *17*, 4416−4419. (b) Sedano, C.; Velasco, R.; Feberero, C.; Suárez-Pantiga, S.; Sanz, R. α-Lithiobenzyloxy as a Directed Metalation Group in *ortho*-Lithiation Reactions. *Org. Lett.* **2020**, *22*, 6365−6369.

(8) Velasco, R.; Silva-López, C.; Nieto-Faza, O.; Sanz, R. Exploring the Reactivity of α-Lithiated Aryl Benzyl Ethers: Inhibition of the [1,2]-Wittig Rearrangement and the Mechanistic Proposal Revisited. *Chem. - Eur. J.* **2016**, *22*, 15058−15068.

(9) Kulpinski, M. S.; Nord, F. F. Essential steps in the catalytic condensation of aldehydes; new synthesis of glycol esters. *J. Org. Chem.* **1943**, *8*, 256−270.

(10) See, for instance: (a) Baramee, A.; Chaichit, N.; Intawee, P.; Thebtaranonth, C.; Thebtaranonth, Y. Meerwein-Ponndorf-Verley Reaction of α-Ketoepoxides. A Stereocontrolled One-step Synthesis of Epoxy-1,3-diol Monoesters. *J. Chem. Soc., Chem. Commun.* **1991**, 1016−1017. (b) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. Tandem Aldol-Tishchenko Reactions of Lithium Enolates: A Highly Stereoselective Method for Diol and Triol Synthesis. *J. Org. Chem.* **1997**, *62*, 5674−5675. (c) Mascarenhas, C. M.; Duffey, M. O.; Liu, S.-Y.; Morken, J. P. Simple Metal Alkoxides as Effective Catalysts for the Hetero-Aldol−Tishchenko Reaction. *Org. Lett.* **1999**, *1*, 1427−1429. (d) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. Direct Catalytic Asymmetric Aldol-Tishchenko Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 7782−7783. (e) Stodulski, M.; Maminska, A.; Mlynarski, J. Asymmetric aldol-Tishchenko reaction catalyzed by Yb-complexes with basic amino acid-derived ligands. *Tetrahedron: Asymmetry* **2011**, *22*, 464−467. (f) Ichibakase, T.; Nakajima, M. Direct Enantioselective Aldol−Tishchenko Reaction Catalyzed by Chiral Lithium Diphenylbinaphtholate. *Org. Lett.* **2011**, *13*, 1579−1581. (g) Asano, T.; Kotani, S.; Nakajima, M. Stereoselective Synthesis of 2-Fluoro-1,3-Diols via Lithium Binaphtholate-Catalyzed Aldol−Tishchenko Reaction. *Org. Lett.* **2019**, *21*, 4192−4196. For a review, see: (h) Mahrwald, R. The Aldol-Tishchenko Reaction: A Tool in Stereoselective Synthesis. *Curr. Org. Chem.* **2003**, *7*, 1713−1723.

(11) Ichibakase, T.; Kaneko, T.; Orito, Y.; Kotani, S.; Nakajima, M. Construction of quaternary carbon centers by a base-catalyzed enantioselective aldol reaction and related reactions of trimethoxysilyl enol ethers. *Tetrahedron* **2012**, *68*, 4210−4224.

(12) See, for instance: (a) Bruns, K.; Conrad, J.; Steigel, A. Stereochemistry of cyclic compounds−I: Synthesis and configurational assignment of diastereomeric 2,4-dioxaspiro[5.5]undec-8-enes. *Tetrahedron* **1979**, *35*, 2523−2530. (b) Youssefyeh, R. D.; Verheyden, J. P. H.; Moffatt, J. G. 4'-Substituted Nucleosides. 4. Synthesis of Some 4'-Hydroxymethyl Nucleosides. *J. Org. Chem.* **1979**, *44*, 1301−1309. (c) Mohapatra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. Synthesis of the spiro fused β-lactone-γ-lactam segment of oxazolomycin. *Tetrahedron Lett.* **2006**, *47*, 6031−6035.

(13) (a) Ouchi, T.; Arita, Y.; Imoto, M. Resins from Formaldehyde. CIV. Hydroxymethylation of Diisopropyl Ketone with Formaldehyde. *Polym. J.* **1976**, *8*, 477−479. (b) Ozasa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. Aldol Synthesis with an Aqueous Solution of Formalin. *Synlett* **2003**, 2219−2221. (c) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. Catalytic Asymmetric Hydroxymethylation of Silicon Enolates Using an Aqueous Solution of Formaldehyde with a Chiral Scandium Complex. *J. Am. Chem. Soc.* **2004**, *126*, 12236−12237. (d) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. Bismuth Triflate-Chiral Bipyridine Complexes as Water-Compatible Chiral Lewis Acids. *Org. Lett.* **2005**, *7*, 4729−4731. (e) Pasternak, M.; Paradowska, J.; Rogozinska, M.; Mlynarski, J. Direct asymmetric α-hydroxymethylation of ketones in homogeneous aqueous solvents. *Tetrahedron Lett.* **2010**, *51*, 4088−4090. (f) Liu, C.; Shen, M.; Lai, B.; Taheri, A.; Gu, Y. Condition-Determined Multicomponent Reactions of 1,3-Dicarbonyl Compounds and Formaldehyde. *ACS Comb. Sci.* **2014**, *16*, 652−660.

(14) Li, W.; Wu, X.-F. The Applications of (Para)formaldehyde in Metal-Catalyzed Organic Synthesis. *Adv. Synth. Catal.* **2015**, *357*, 3393−3418.

(15) After a brief initial screening that formaldehyde was the only aldehyde that provides good results in the proposed sequence. The use of an aromatic aldehyde like *p*-chlorobenzaldehyde leads to the intermediate ketone, what indicates that no reaction occurs between the enolate and this aldehyde, likely due to steric encumbrance.

(16) For an example of an aldol-Tishchenko reaction that is initiated from a lithiated enol carbamate, see: (a) Shterenberg, A.; Haimov, E.; Smirnov, P.; Marek, I. Convergent and flexible approach to stereodefined polyhydroxylated fragments. *Tetrahedron* **2018**, *74*, 6761−6768. For the synthesis of related triol derivatives, see: (b) Takahashi, K.; Ogata, M. Stereochemistry of the Ring Opening of Chiral Epoxides Derived from Allylic Alcohols Having Two Substituted-Phenyl Groups. *J. Org. Chem.* **1987**, *52*, 1877−1880.

(17) Lithiation of benzyl methyl ether: (a) Azzena, U.; Demartis, S.; Fiori, M. G.; Pisano, L. Metalation of Arylmethyl Methyl Ethers and Connection with Their Reductive Electrophilic Substitution. *Tetrahedron Lett.* **1995**, *36*, 5641−5644. (b) Azzena, U.; Pilo, L.; Sechi, A. Metalation of Arylmethyl Alkyl Ethers. *Tetrahedron* **1998**, *54*, 12389−12398. Lithiation of benzyl methoxymethyl ethers: (c) Azzena, U.; Pisano, L.; Mocci, S. Direct metalation of methoxymethyl arylmethyl ethers: A tin-free approach to the generation of α-alkoxyalkoxy-substituted aryllithiums. *J. Organomet. Chem.* **2009**, *694*, 3619−3625.

(18) Shukla, K.; Srivastava, V. C. Diethyl carbonate: critical review of synthesis routes, catalysts used and engineering aspects. *RSC Adv.* **2016**, *6*, 32624−32645.

https://dx.doi.org/10.1021/acs.orglett.0c03014
Org. Lett. XXXX, XXX, XXX−XXX

(19) For a review of the reactivity of dialkyl cabonates, see: (a) Tundo, P.; Musolino, M.; Aricò, F. The reactions of dimethyl carbonate and its derivatives. *Green Chem.* **2018**, *20*, 28−85. For the direct synthesis of ketones by reaction of organometallic compounds with carbonates, see: (b) Hurst, T. E.; Deichert, J. A.; Kapeniak, L.; Lee, R.; Harris, J.; Jessop, P. G.; Snieckus, V. Sodium Methyl Carbonate as an Effective C1 Synthon. Synthesis of Carboxylic Acids, Benzophenones, and Unsymmetrical Ketones. *Org. Lett.* **2019**, *21*, 3882−3885.

(20) (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. Oxetanes as Versatile Elements in Drug Discovery and Synthesis. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052−9067. (b) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257−8322. (c) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **2016**, *116*, 12150−12233.

(21) See, for instance: (a) Guo, Y.-A.; Lee, W.; Krische, M. J. Enantioselective Synthesis of Oxetanes Bearing All-Carbon Quaternary Stereocenters via Iridium-Catalyzed C−C Bond-Forming Transfer Hydrogenation. *Chem. - Eur. J.* **2017**, *23*, 2557−2559. (b) Nicolle, S. M.; Nortcliffe, A.; Bartrum, H. E.; Lewis, W.; Hayes, C. J.; Moody, C. J. C−H Insertion as a key step to spiro-oxetanes, scaffolds for drug discovery. *Chem. - Eur. J.* **2017**, *23*, 13623−13627.

(22) The preparation of the corresponding oxetanes from **3** was not possible due to competitive Grob fragmentation of the intermediate into an aldehyde and an enol ether **14** (see the Supporting Information for further details).

https://dx.doi.org/10.1021/acs.orglett.0c03014
Org. Lett. XXXX, XXX, XXX−XXX