α-Lithiobenzyloxy as a Directed Metalation Group in *ortho*-Lithiation Reactions

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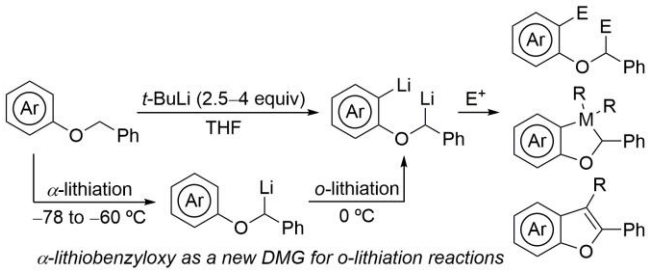
Supporting Information Placeholder



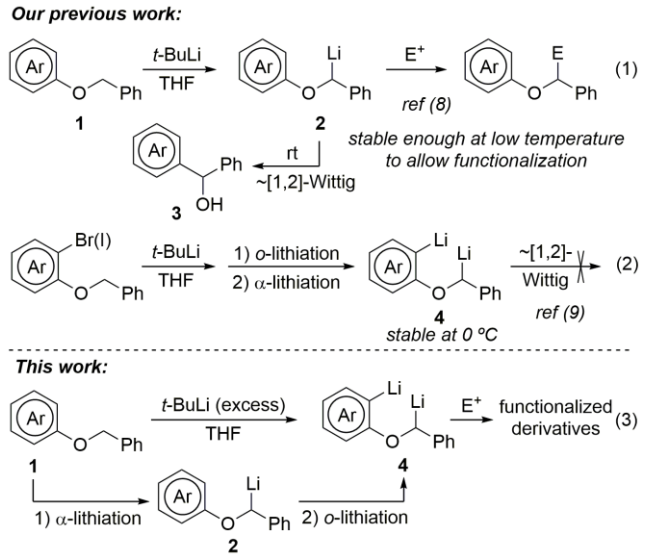
ABSTRACT: The α-lithiobenzyloxy group, easily generated from aryl benzyl ethers by selective α-lithiation with *t*-BuLi at low temperature, behaves as a directed metalation group (DMG) providing a straight access to *o*-lithiophenyl α-lithiobenzyl ethers. This *ortho*-directing effect is reinforced in substrates bearing an additional methoxy group at the *meta* position. The generated dianions can be reacted with a selection of electrophiles including carboxylic esters and dihalosilanes or germanes, which afford interesting benzofuran, sila(germa)dihydrobenzofuran and silachroman derivatives from simple aryl benzyl ethers.

Oxygenated organolithium compounds are useful intermediates for the preparation of functionalized molecules containing oxygen.[1] In this field, α-oxygen-functionalized organolithiums present an ambiphilic behavior as nucleophiles or electrophiles, which makes them to be considered carbenoids, in the same way that α-lithiated halogens,[2] and also complicate the reactivity of these species.[3] Although lithiation α to oxygen is unfavorable due to antibonding interactions of the oxygen´s lone pairs with the C–Li bond, the presence of an aryl (or vinyl) group on the side chain helps to stabilize the α-oxygenated organolithium through Li–π interactions. Thus, deprotonations of benzyl ethers are easily achieved by their treatment with more basic Csp^3-based organolithiums.[4] Alternatively, α-lithiated ethers can also be prepared by Sn–Li exchange.[5] Nevertheless, non-stabilized acyclic α-alkoxy organolithiums are generally unstable undergoing either elimination or Wittig rearrangements, which lead to lithium alkoxides through the isomerization of these carbanions.[6] In this field, we reported that aryl α-lithiobenzyl ethers could be generated by anion translocation from benzyl *o*-lithioaryl ethers and subsequently undergo [1,2]-Wittig rearrangement.[7] More recently, we have described that these aryl α-lithiobenzyl ethers **2**, generated by selective α-lithiation of aryl benzyl ethers **1**, resulted to be stable enough at low temperatures allowing their functionalization by preventing the Wittig rearrangement that would lead to benzhydrols **3** (Scheme 1, eq 1).[8] In addition, we have also found that benzyl 2-halophenyl ethers afford α-lithiobenzyl *o*-lithiophenyl ethers **4**, avoiding competitive Wittig rearrangement likely due to the reluctance of the *o*-lithiophenoxy ring to migrate (Scheme 1, eq 2).[9]

On the other hand, directed *ortho*-metalation (DoM) is a powerful method for the synthesis of *ortho*-functionalized arenes, which otherwise are significantly more challenging to prepare by classical routes such as electrophilic aromatic substitutions and hydrogen nucleophilic aromatic substitutions that typically present significant drawbacks concerning regioselectivity.[10] Alternatively, D*o*M ensures very high regioselectivity for the *ortho*-functionalization of arenes bearing a suitable directed metalation group (DMG).[11] Although a wide variety of DMGs has been described, many of them possess some limitations mainly related to the additional steps required to install and further remove them. Among oxygen-based DMGs[12] the *O*-carbamate developed by Snieckus is probably the most useful one, affording a wide number of applications.[13] An interesting variation in this chemistry is the one in which the DMG could be a versatile functional group for subsequent manipulations, or the DMG itself could be considered a useful functional group.[14] Thus, one of the main research efforts in the field has been devoted to the discovery of new DMGs.[15]

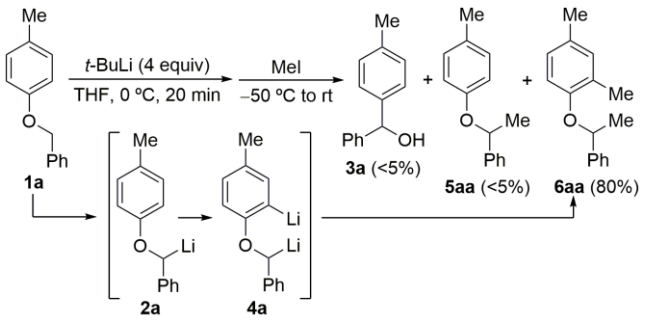
As established above, benzylic ethers easily undergo benzylic lithiation and so, they cannot be employed as DMGs.[16] Nonetheless, herein, we report that the α-lithiobenzyloxy group behaves as an effective oxygen-based DMG for aryl systems providing a straightforward methodology for the regioselective *o*,α-difunctionalization of simple aryl benzyl ethers (Scheme 1, eq 3).

Scheme 1. Previous Work and Proposed *o*-Lithiation of Aryl α-Lithiobenzyl Ethers



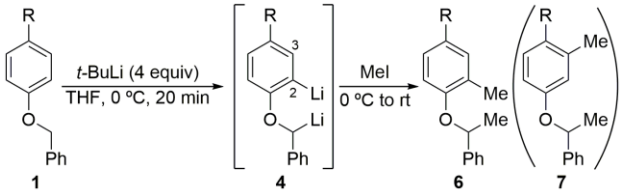
We selected benzyl *p*-tolyl ether **1a** as model substrate due to its higher reluctance to undergo Wittig rearrangement once the corresponding α-lithiobenzyl ether **2a** was generated, compared with benzyl phenyl ether.[8b] After a thorough study for the regioselective dilithiation process, optimal conditions for model substrate **1a** were established as 4 equiv of *t*-BuLi in THF at 0 ºC for 20 minutes (for further details, see Supporting Information).[17] Under these conditions, only minor amounts of competitive Wittig rearranged product **3a** and monofunctionalized **5aa** were obtained (Scheme 2).

Scheme 2. Optimized Conditions for the Dilithiation of Benzyl *p*-Tolyl Ether 1a



To roughly establish the relative strength of the α-lithiobenzyloxy group as DMG, we also decided to investigate the metalation and functionalization of different aryl benzyl ethers **1b-j** further substituted at the *para*-position of the aryl fragment (Table 1). Benzyl *p*-halophenyl ethers **1b,c** as well as benzyl *p*-(dimethylamino)phenyl ether **1d**, undergo regioselective *o*-lithiation at C2, the nearest position to the α-lithiobenzyl group, providing dimethylated derivatives **6ba-da** after treatment with methyl iodide (entries 1–3). We then turned our attention to study the relative activation ability of different oxygen-based DMGs. The obtained results with benzyl ethers **1e,f** suggest that the α-lithiobenzyloxy group is stronger than methoxy or isopropoxy groups, although the methoxy-functionalized benzyl ether **1e** gave rise to small amounts of regioisomeric dimethylated ether **7ea** (entries 4 and 5). Surprisingly, with benzyl 4-phenoxyphenyl ether **1g** selective dilithiation could not be achieved irrespective of the equivalents of *t*-BuLi employed (entry 6),[18] in its place a complete and regioselective trilithiation reaction was observed by using excess of base (see Scheme 3). In addition, other benzylic DMGs such as dimethylaminomethyl and hydroxymethyl were also surpassed by the α-lithiobenzyloxy group in ethers **1h** and **1i** (entries 7 and 8). On the other hand, not unexpectedly, lithiation of *N*,*N*-diethyl-4-benzyloxybenzamide **1j** took place selectively at C3 instead of at C2 (entry 9). With this intramolecular lithiation competition experiments, α-lithiobenzyloxy was found to outperform halogens, dimethylamino, and alkoxy groups as well as hydroxymethyl and dimethylaminomethyl groups.

Table 1. Competitive *ortho*-Directing Groups. Substituents Effects on the Regioselectivity of the *ortho*-Lithiation



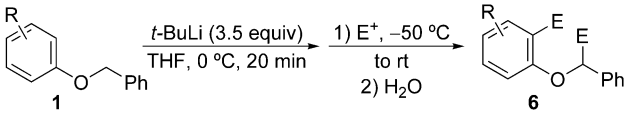
entry	1	R	Product	C_2/C_3[a]	yield (%)[b]
1[c,d]	**1b**	Cl	**6ba**	1/0	74
2[c]	**1c**	F	**6ca**	1/0	76
3	**1d**	NMe_2	**6da**	1/0	77
4[c]	**1e**	OMe	**6ea**	10/1	70
5[c]	**1f**	O*i*-Pr	**6fa**	1/0	80
6	**1g**	OPh	–[e]	–	–
7	**1h**	CH_2NMe_2	**6ha**	12/1	71[f]
8[g]	**1i**	CH_2OH	**6ia**	1/0	57[f]
9	**1j**	$CONEt_2$	**7ja**	<1/15	50

[a]Regioisomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Yield of isolated product referred to starting ether **1**. [c]*t*-BuLi (3.5 equiv) was used. [d]Carried out at –10 ºC. [e]A trimethylated derivative appears at the same time than the dimethylated one by using more than 2.5 equiv of base. [f]A ~5/1 ratio of the corresponding products **6** and benzhydrols **3** was obtained. [g] *t*-BuLi (6 equiv) was used.

With the optimized dilithiation conditions, a variety of α,*o*-difunctionalized aryl benzyl ethers **6ab-6ae** was prepared from **1a** by using selected electrophilic reagents (Table 2, entries 1–4). Starting benzyl phenyl ethers bearing halogen (**1b,c**), or dimethylamino (**1d**) substituents, were also successfully difunctionalized with high yields (entries 5–9). As above mentioned, the dilithiation of benzyl 4-methoxyphenyl ether **1e** was not completely regioselective leading to the corresponding difunctionalized derivatives **6ec** and **6ee** with trace amounts of their regioisomers **7** (entries 10 and 11). This issue was nicely solved by using benzyl 4-isopropoxyphenyl ether **1f** that allowed the preparation of difunctionalized derivatives **6fb-fe** in good to high yields (entries 12–15). Interestingly, the

dilithiation/functionalization sequence for benzyl 2-methoxyphenyl ether **1k** proved to be highly regioselective leading almost exclusively to difunctionalized ethers **6ka-ke** (entries 16–19). Finally, with the parent benzyl phenyl ether **1l** the [1,2]-Wittig rearrangement resulted to be competitive with the *o*-lithiation process leading to a mixture of the desired dimethylated or dideuterated ethers **6la** or **6lb** and diphenylmethanol (**3l**) (entries 20 and 21), even by performing the reaction at lower temperature.[19]

Table 2. Synthesis of Difunctionalized Aryl Benzyl Ethers 6

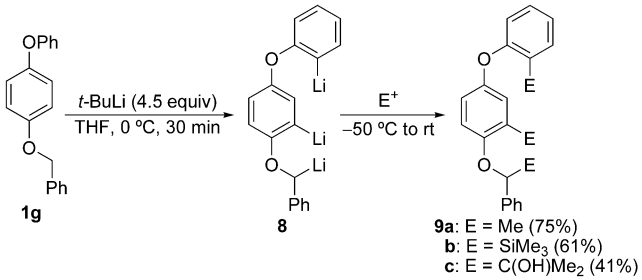


entry	**1**	R	Product	E	yield (%)[a]
1[b]	**1a**	4-Me	**6ab**	D	83
2[b]	**1a**	4-Me	**6ac**	$SiMe_3$	72
3[b]	**1a**	4-Me	**6ad**	$SnBu_3$	60
4[b]	**1a**	4-Me	**6ae**	$C(OH)Me_2$	59
5[c]	**1b**	4-Cl	**6bb**	D	77
6[c]	**1b**	4-Cl	**6bc**	$SiMe_3$	71
7[c]	**1b**	4-Cl	**6be**	$C(OH)Me_2$	60
8	**1c**	4-F	**6cc**	$SiMe_3$	69
9[b]	**1d**	4-NMe_2	**6dc**	$SiMe_3$	83
10	**1e**	4-MeO	**6ec**	$SiMe_3$	66[d]
11	**1e**	4-MeO	**6ee**	$C(OH)Me_2$	60[d]
12	**1f**	4-*i*-PrO	**6fb**	D	95
13	**1f**	4-*i*-PrO	**6fc**	$SiMe_3$	80
14	**1f**	4-*i*-PrO	**6fd**	$SnBu_3$	61
15	**1f**	4-*i*-PrO	**6fe**	$C(OH)Me_2$	68
16	**1k**	2-MeO	**6ka**	Me	74[e]
17	**1k**	2-MeO	**6kb**	D	78
18	**1k**	2-MeO	**6kc**	$SiMe_3$	70[e]
19	**1k**	2-MeO	**6ke**	$C(OH)Me_2$	55
20[f]	**1l**	H	**6la**	Me	64[g]
21[f]	**1l**	H	**6lb**	D	68[g]

[a]Yield of isolated product referred to starting ether **1**. [b]*t*-BuLi (4 equiv) was used. [c]Carried out at –10 °C. [d]Isolated along with minor amounts of the regioisomeric ethers **7ec** and **7ee**. [e]Isolated with trace amounts of other regioisomer. [f]Carried out at –15 °C for 5 h. [g]Diphenylmethanol (**3l**) was also formed (~15%)

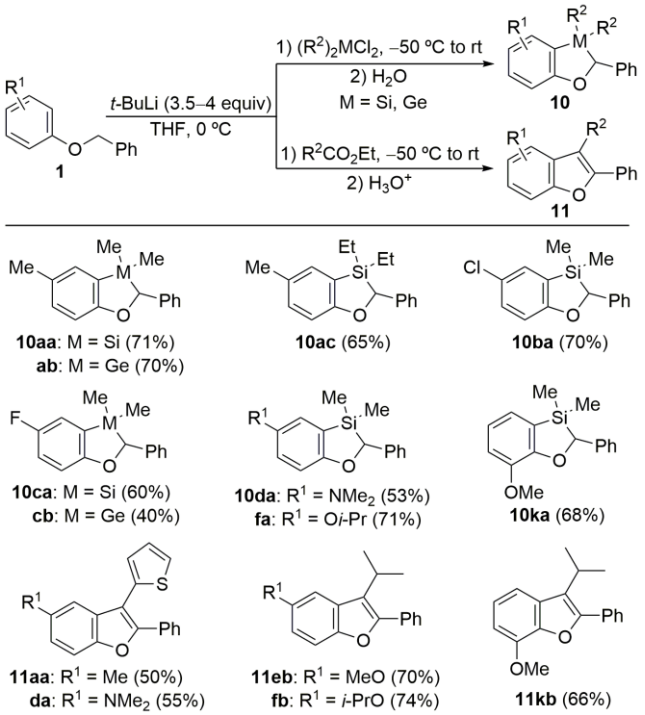
As shown in Table 1 (entry 6), the dilithiation of benzyl 4-phenoxyphenyl ether **1g** was not selective since a competitive lithiation of the phenoxy group was observed.[20] Gratifyingly, by using an excess of *t*-BuLi, the regioselective and complete trilithiation of ether **1g** was achieved. The trilithiated ether **8** was further functionalized by its treatment with selected electrophiles leading to trifunctionalized ethers **9** in moderate to high yields (Scheme 3).

Scheme 3. Trilithiation of Benzyl 4-Phenoxyphenyl Ether 1g. Synthesis of Trifunctionalized Ethers 9



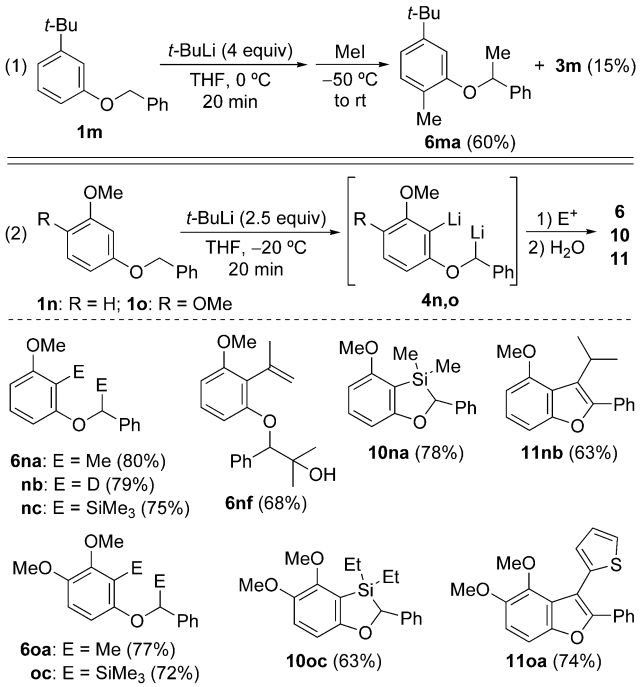
Taking advantage of the 1,4-relationship of dianions **4**, we turned our attention to test the possibility of generating *O*-heterocyclic derivatives. For this purpose, different bis-electrophilic reagents were made to react with the previously prepared dianions **4** (Scheme 4). Considering the relevance of silylated heterocycles, due to the potential effect of C–Si switch on the biological properties of drugs,[21] and the lack of general procedures for their synthesis with tetraorganosilicon moieties,[22] we decided to use silicon and germanium dichlorides as electrophiles. Interestingly, sila- and germa-dihydrobenzofurans **10** were obtained in moderate to high yield, with the benzenoid fragment of these silylated and germylated heterocycles being functionalized with halogens, alkoxy or dimethylamino groups, which are initially present in the starting aryl benzyl ethers **1**. On the other hand, the reaction of dianions **4** with carboxylic esters afforded, after an acidic hydrolysis, to benzo[*b*]furan derivatives **11**.[9] Both heteroaromatic as well as alkylic carboxylic esters could be employed leading to the corresponding benzofurans **11** in moderate to high yields (Scheme 4).

Scheme 4. Synthesis of Oxametallacycles 10 and 2-Phenyl-3-Substituted Benzo[*b*]furans 11 from Aryl Benzyl Ethers 1



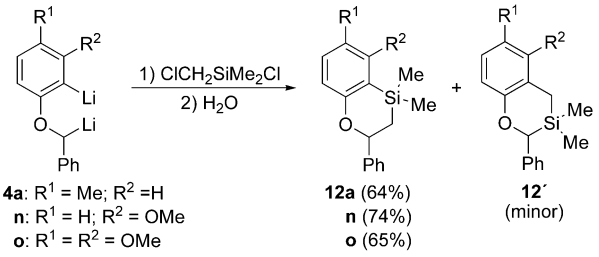
The steric effect of a large alkyl group at one of the meta positions was evaluated with 3-*t*-butylphenyl benzyl ether **1m** resulting in a complete regiocontrol of the *o*-lithiation in favor of the least congested ortho position as demonstrated with the preparation of **6ma**. As it was observed with **1l**, the Wittig rearrangement was partially competitive (Scheme 5, eq 1). On the other hand, a synergetic action of the alkoxy and α-lithiobenzyloxy groups in the stabilization of the corresponding dianions **4n,o** could explain the lower amount of base required for the complete dilithiation of ethers **1n,o**. In this way, a selection of difunctionalized benzyl 3-methoxyaryl ethers **6** as well as oxasilacycles **10** and benzofurans **11** was efficiently synthesized in high yields (Scheme 5, eq 2).[23]

Scheme 5. Steric and Cooperative Effects in the *α*- and *o*-Lithiation of Benzyl 3-Substituted Aryl Ethers 1m-o



Finally, in the seek of determining if there was a difference in the nucleophilicity of both lithiated positions (*ortho*- and α-positions), chloro(chloromethyl)dimethylsilane was employed as electrophile, since it has two differentiated electrophilic centers. As it is shown in Scheme 6, the reaction of selected dianions **4** with this electrophilic reagent, led to the regioselective formation of silachromans **12**, in which the silicon atom is attached to the aromatic ring. This selectivity could be the result of a combination of the expected higher nucleophilicity and basicity of the *o*-lithiated aromatic ring (since it is the second position to be lithiated), and the greater electrophilicity of the chlorosilane entity compared to the chloromethyl one. However, this selectivity was not complete as minor amounts of the regioisomeric benzoxasilines **12´** were also formed (Scheme 6).[24]

Scheme 6. Reactions of Selected Dianions 4 with $ClCH_2SiMe_2Cl$. Synthesis of Silachromans 12



In summary, the DMG ability of the α-lithiobenzyloxy group in D*o*M chemistry has been described. Through a comparative study we have established the directing power of this group for regioselective *o*-lithiation, which was found to be comparable or stronger to that of other alkoxy groups and halogens as well as dimethylaminomethyl. The D*o*M capability of the α-lithiobenzyloxy group provides a straightforward convenient access to a variety of cores such as difunctionalized ethers, benzo[*b*]furans, oxasilacycles and oxagermacycles from unfuctionalized starting materials, surpassing in terms of atom economy the previous reports based on the use of benzyl 2-haloaryl ethers. Finally, this C–H bond double functionalization strategy was successfully applied to the synthesis of silachromans with a high degree of regioselectivity, which demonstrates that both lithiated positions own a differential reactivity.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data, and copies of NMR spectra. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds **1a-o**, **3m**, **5aa**, **5ga**, **5la**, **6aa**, **6ab**, **6ac**, **6ad**, **6ae**, **6ba**, **6bb**, **6bc**, **6be**, **6ca**, **6cc**, **6da**, **6dc**, **6ea**, **6ec**, **6ee**, **6fa**, **6fb**, **6fc**, **6fd**, **6fe**, **6ha**, **6ia**, **6ka**, **6kb**, **6kc**, **6ke**, **6la**, **6lb**, **6ma**, **6na**, **6nb**, **6nc**, **6nf**, **6oa**, **6oc**, **7ja**, **9a**, **9b**, **9c**, **10aa**, **10ab**, **10ac**, **10ba**, **10ca**, **10cb**, **10da**, **10fa**, **10ka**, **10na**, **10oc**, **11aa**, **11da**, **11eb**, **11fb**, **11kb**, **11nb**, **11oa**, **12'o**, **12a**, **12n**, **12o**.This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing interest.

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