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α-Lithiated Aryl Benzyl Ethers: Inhibition of [1,2]-Wittig Rearrangement and Application to the Synthesis of Benzo[*b*]furan Derivatives

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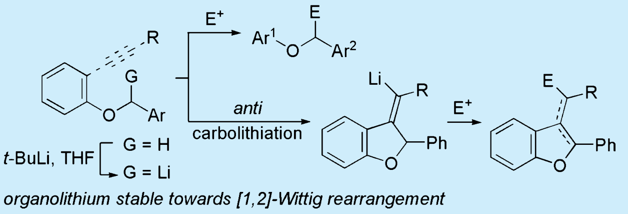
Supporting Information

ABSTRACT: The use of *t*-BuLi at low temperature selectively leads to α-lithiation of benzyl phenyl ether generating a stable organolithium, which can be efficiently trapped with a variety of selected electrophiles prior to suffering the expected [1,2]-Wittig rearrangement. In the case of (*o*-alkynyl)phenyl benzyl ethers, the intermediate α-aryloxyorganolithium undergoes an unexpected *anti* intramolecular carbolithiation reaction leading to functionalized benzo[*b*]furan derivatives.



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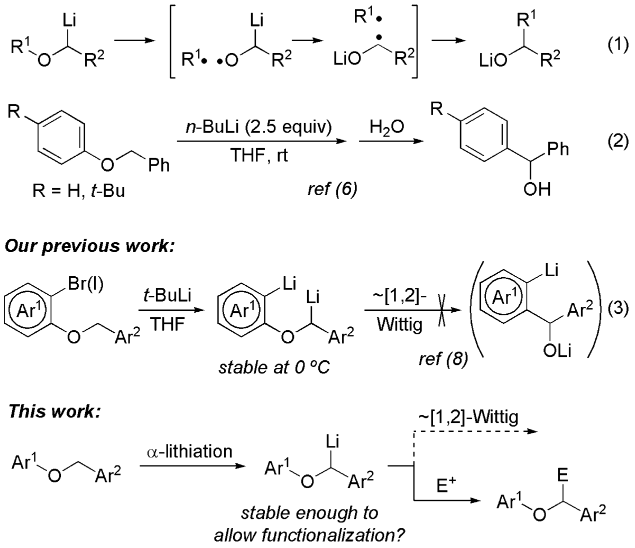
α-Alkoxyorganolithiums, usually generated by deprotonation of ethers[1] or by Sn–Li exchange,[2] are generally unstable undergoing either elimination or Wittig rearrangements.[3] For the [1,2] variant of the Wittig rearrangement,[4] the use of allyl or benzyl ethers allows the migrating group to be benzylic, secondary, or primary alkyl, but not methyl. This reluctance of the methyl group to undergo migration has allowed the trapping of α-lithiobenzyl methyl ether with electrophiles.[5] In this context, it would be highly interesting to find a way to avoid the Wittig rearrangement and allow functionalization of other α-lithiobenzyl ethers. The most accepted mechanism for the [1,2]-Wittig rearrangement is a two-stage process that involves the homolysis of the α-anion intermediate and subsequent recombination of the radical and radical anion fragment. This proposal mainly satisfies the observed migratory aptitude for the R^1 groups (Scheme 1, eq 1). However, the migration of aryl groups from aryl benzyl ethers has received much less attention (Scheme 1, eq 2).[6]

Our interest in this field[7] led us to report that α-lithiobenzyl *o*-lithiophenyl ethers, generated from benzyl 2-halophenyl ethers, do not undergo Wittig rearrangement probably due to the reluctance of the *o*-lithiophenoxy ring to migrate (Scheme 1, eq 3).[8] At this point, we thought about the possibility of inhibiting the Wittig rearrangement from aryl α-lithiobenzyl ethers without the requirement of the additional lithium atom at the aryl ring. With all these results in mind, and considering the unexplored potential synthetic usefulness of aryl α-lithiobenzyl ethers,[9] we proposed to study the α-lithiation of aryl benzyl ethers with the aim of finding suitable conditions in which these anionic intermediates were stable enough to avoid the Wittig rearrangement (Scheme 1). In this paper, we report the successful generation of α-lithiated aryl benzyl ethers and their functionalization with selected electrophiles, including intramolecular *anti* carbolithiation reactions onto unactivated C–C triple bonds to generate benzo[*b*]furan derivatives.

Scheme 1. Previous Work and Proposed α-Lithiation of Aryl Benzyl Ethers



We selected benzyl phenyl ether **1a** as model substrate and performed the metalation reaction under the conditions reported by Eisch et al. As expected, a complete conversion to diphenylmethanol **3a** takes place by using BuLi at 0 °C, in agreement with their results (Scheme 2).[6a] In order to generate the lithiated intermediate **2a** at a lower temperature, we decided to use a stronger base (*t*-BuLi). Gratifyingly, deuteriated ether **4a** was selectively and almost quantitatively obtained by reacting **1a** with a slight excess of *t*-BuLi at −78 °C (Scheme 2). This result

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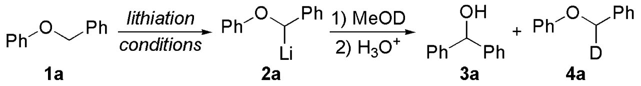
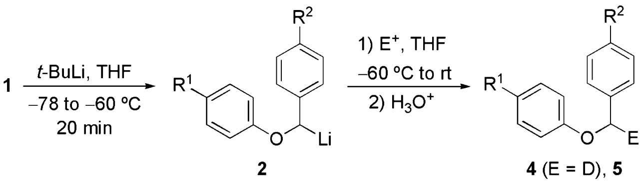
Scheme 2. α-Lithiation of Benzyl Phenyl Ether 1a



n-BuLi (2.5 equiv), THF, 0 °C, 90 min 1 / 0
t-BuLi (1.3 equiv), THF, −78 °C, 20 min 0 / 1
t-BuLi (1.3 equiv), THF, −30 °C, 20 min 1 / 15

Table 1. Reaction of Aryl α-Lithiobenzyl Ethers 2 with Electrophiles: Synthesis of Funtionalized Ethers 5

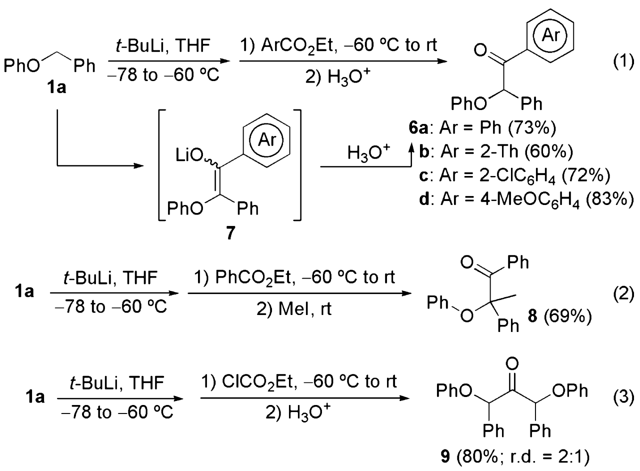


entry	1	R^1	R^2	4, 5	E	yield[a] (%)
1	**1a**	H	H	**4a**	D	96
2	**1a**	H	H	**5aa**	Me	95
3	**1a**	H	H	**5ab**	$CH_2CH{=}CH_2$	88
4	**1a**	H	H	**5ac**	$SiMe_3$	95
5	**1a**	H	H	**5ad**	$SnBu_3$	62
6	**1a**	H	H	**5ae**[b]	$CH(OH)(4\text{-}ClC_6H_4)$	79
7	**1a**	H	H	**5af**[c]	CH(OH)*i*-Pr	71
8	**1a**	H	H	**5ag**	$C(OH)Ph_2$	81
9	**1a**	H	H	**5ah**[d]	C(OH)PrPh	78
10	**1a**	H	H	**5ai**[e]	$C(OH)(2\text{-}Th)c\text{-}C_3H_5$	79
11	**1a**	H	H	**5aj**[b]	CH(Ph)NHPh	65
12	**1a**	H	H	**5ak**[f]	$CH{-}(CH_2)_4CH(OH){-}$	95
13	**1b**	Cl	H	**4b**	D	97
14	**1b**	Cl	H	**5ba**[b]	CH(OH)*i*-Pr	83
15	**1c**	OMe	H	**4c**	D	90
16	**1c**	OMe	H	**5ca**[f]	$CH{-}(CH_2)_4CH(OH){-}$	88
17	**1d**	H	Cl	**4d**	D	94
18	**1d**	H	Cl	**5da**	Et	92
19	**1e**[g]	H	OMe	**4e**[h]	D	93
20	**1e**[g]	H	OMe	**5ea**	$C(OH)Ph_2$	70

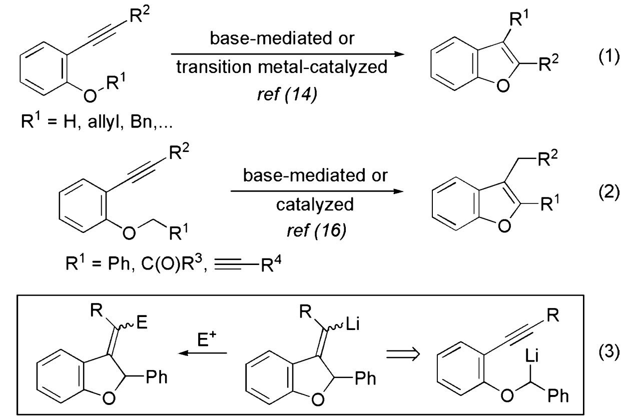
[a] Yield of isolated product referred to starting ether **1**. [b] Obtained as a 1:1 mixture of diastereoisomers. [c] Obtained as a 1.25:1 mixture of diastereoisomers. The major one could be isolated in pure form. [d] Obtained as 4:1 mixture of diastereoisomers. [e] Obtained as 3.3:1 mixture of diastereoisomers. [f] Cyclohexene oxide as electrophile. **5ak** and **5ca** were obtained as a ca. 1.5:1 mixture of diastereoisomers. [g] Lithiation was carried out from −78 to −35 °C. [h] ~92%-D incorporation.

shows that simply by decrease of the temperature, the [1,2]-Wittig rearrangement can be suppressed. We also studied the stability of intermediate α-alkoxyorganolithium **2a** by gradually increasing the reaction temperature, finding that the [1,2]-Wittig rearrangement initiates at ca. −30 °C (Scheme 2). In addition, when the lithiation reaction of **1a** was carried out in Et_2O, it was not until −30 °C that complete lithiation took place, implying that in this solvent organolithium **2a** is stable at higher temperatures than when using THF.[10] With this study, we have shown how **1a** can be efficiently and selectively lithiated at low temperature in THF to generate organolithium intermediate **2a**, which remains stable up to ca. −30 °C.

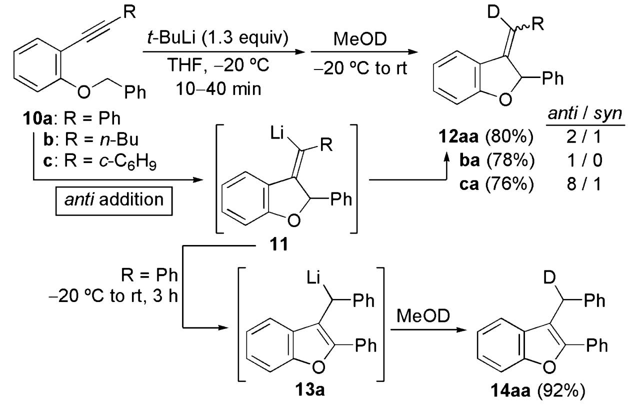
Scheme 3. Reaction of α-Lithiobenzyl Phenyl Ether 2a with Caboxylic Esters: Synthesis of Ketones 6, 8, and 9



Scheme 4. Intramolecular Cyclization of *o*-Alkynylphenyl Ethers and Proposed Intramolecular Carbolithiation



Scheme 5. Intramolecular *anti*-Carbolithiation of *o*-(Alkynyl)aryl Benzyl Ethers 10



These optimized lithiation conditions were used to prepare a variety of α-functionalized aryl benzyl ethers **5aa**−**5ak** after electrophilic quenching (Table 1, entries 2−12). Addition of alkyl halides gave high yields of the corresponding α-alkylated ethers (entries 2 and 3). In the same way, the use of TMSCl or Bu_3SnCl resulted in the production of functionalized ethers **5ac** and **5ad** (entries 4 and 5). Typical carbonyl electrophiles such as aldehydes (entries 6 and 7) and ketones (entries 8−10) gave the

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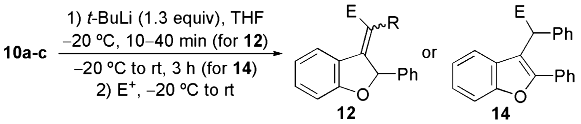
Table 2. Synthesis of Benzo[*b*]furan Derivatives 12 and 14



entry	10	R	E^+	prod.	E	yield[a] (%)
1	**10a**	Ph	I_2	**12ab**[b]	I	86
2	**10a**	Ph	Me_3SiCl	**12ac**[b]	$SiMe_3$	84
3	**10a**	Ph	Me_3SnCl	**12ad**[b]	$SnMe_3$	80
4	**10b**	*n*-Bu	4-ClC_6H_4CHO	**12bb**[c]	C(H)OH(4-ClC_6H_4)	71
5	**10c**	*c*-C_6H_9	Me_2CO	**12cb**[d]	C(OH)Me_2	70
6	**10a**	Ph	Me_3SiCl	**14ab**	$SiMe_3$	72
7	**10a**	Ph	$CH_2{=}CHCH_2Br$	**14ac**	$CH_2CH{=}CH_2$	85
8	**10a**	Ph	Me_2CO	**14ad**	C(OH)Me_2	82
9	**10a**	Ph	PhCHO	**14ae**[c]	CH(OH)Ph	70
10	**10a**	Ph	$ClCO_2Et$	**14af**	CO_2Et	60
11	**10a**	Ph	(*p*-TolS)$_2$	**14ag**	S(*p*-Tol)	78

[a] Yield of isolated product after column chromatography referred to starting ether **10**. [b] Obtained as a ca. 1.2–2:1 mixture of geometrical isomers. [c] Obtained as a mixture of diastereoisomers. [d] Obtained as ca. 1:1 mixture of geometrical isomers.

corresponding hydroxyl-functionalized ethers in high yields. The process was also amenable to an imine or an epoxide as electrophiles, giving rise to products **5aj** and **5ak**, respectively (entries 11 and 12). In all cases, when two stereogenic centers are generated, the final compound is obtained as a variable mixture of diastereoisomers.

We have also investigated the metalation and functionalization of other aryl benzyl ethers **1b–e** related to the parent benzyl phenyl ether **1a**. Benzyl ethers **1b**,**c** bearing a chloro or a methoxy substituent at the *para* position of the aryl moiety undergo selective benzylic deprotonation on treatment with *t*-BuLi, and the corresponding α-lithiated species **2b**,**c** can be trapped with selected electrophiles (entries 13–16). In the same way, starting ethers **1d**,**e** substituted at *para* position of the benzylic moiety were also tried and the corresponding α-deuteriated or α-functionalized benzyl ethers **4** and **5** were obtained (entries 17–20). Only with ether **1e**, possessing a 4-methoxybenzyl group, a significant increase in the reaction temperature was required to reach an almost complete lithiation.[11] This fact is likely due to the lower acidity of the benzylic hydrogen imposed by the *p*-methoxy group.

Surprisingly, when ethyl benzoate was tested as electrophile, the aromatic ketone **6a** was selectively obtained instead of the expected tertiary alcohol, independently of the amount of the ester added to **2a**. This result was general for a selection of esters derived from aromatic acids, allowing the synthesis of ketones **6** in good yields (Scheme 3, eq 1).[12] To account for this unexpected result, we propose that the initially formed ketone **6** undergoes deprotonation by the lithium ethoxide generated in the first step, leading to the corresponding enolate **7**, which remains intact prior to hydrolysis. Our proposal was supported by the fact that, upon addition of methyl iodide, prior to aqueous workup, ketone **8** bearing an α-quaternary center was isolated (Scheme 3, eq 2). Moreover, the addition of ethyl chloroformate as the electrophilic partner afforded α,α′-difunctionalized ketone **9** as a 2:1 mixture of diastereoisomers in high yield (Scheme 3, eq 3). Interestingly, this ketone was always selectively obtained irrespective of the stoichiometry of the reactants.

Due to the interest in benzo[*b*]furan derivatives, a wide variety of approaches for their synthesis have been reported.[13] One of the most useful methodologies involves the intramolecular cyclization of *o*-(alkynyl)phenyl ethers or *o*-alkynylphenols by formation of a C–O bond. Several transition metal-catalyzed or base-mediated processes have been described in the last years (Scheme 4, eq 1).[14] However, just a few reports for accessing the benzo[*b*]furan skeleton have appeared involving the C2–C3 bond formation as an alternative methodology.[15] Most of them are related to base-mediated or catalyzed cyclizations of *o*-(alkynyl)phenyl benzyl ethers. Although this transition metal-free approach is highly interesting, developed procedures do not allow further functionalization of the generated benzofuran derivative, thus representing a drawback of these methodologies (Scheme 4, eq 2).[16] Taking advantage of the easy and efficient lithiation that we had developed, we envisaged that an α-lithiated *o*-(alkynyl)phenyl benzyl ether could undergo an intramolecular carbolithiation[17] giving rise to a new organolithium intermediate, which could be further functionalized with electrophiles (Scheme 4, eq 3).

o-(Alkynyl)phenyl benzyl ether **10a** was the chosen model to initiate the study of the proposed intramolecular carbolithiation reaction. In this case, it was necessary to raise the temperature to −20 °C in order to complete lithiation at the α-position and subsequent cyclization, obtaining product **12aa** as a mixture of geometrical isomers (Scheme 5). When performing this optimization study,[18] we noticed that deuteriated **10a** at the α-position was never obtained, which demonstrates that the lithiation is slower than the carbolithiation reaction. Based on previous reports about the cyclization of acetylenic organolithiums,[19] the addition of the C–Li unit to the triple bond to produce a 5-membered ring was expected to proceed in a syn fashion, and depending on the stability of the formed vinyllithium, it could undergo a cis–trans isomerization afterward. Unsurprisingly, compound **12aa** was obtained as a mixture of *Z* and *E* isomers. However, alkyl-substituted vinyllithiums are known to be configurationally stable, so the isolation of deuteriated dihydrobenzofuran **12ba** as a single geometrical *Z* isomer was really unexpected, meaning that an anti addition of the C–Li bond to the alkyne had taken place in the former case as well.[20] Furthermore, benzyl ether **10c**, bearing a cyclohex-1-enyl substituent, also undergoes an anti addition, although without complete selectivity, probably due to the configurational instability of the resulting vinyllithium, as in the case of the phenyl substituent (Scheme 5). Although an anti carbolithiation of propargyl *o*-lithioaryl ethers has been

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reported,[21] in that specific case an interaction of a heteroatom located at the terminal position of the alkyne with the lithium atom seems to be the cause for the observed anti addition.[22]

On the other hand, we also checked that when the reaction temperature is raised to rt, the intermediate organolithium **11a** (R = Ph) smoothly undergoes isomerization giving rise to the deuteriated benzofuran derivative **14aa** after deuteriolysis in high yield (Scheme 5).[23]

To further demonstrate the utility of this new carbolithiation reaction in the synthesis of benzofuran derivatives, a variety of representative electrophiles were used for trapping the intermediate organolithiums **11** or **13a** (Table 2). Functionalized dihydrobenzofurans **12** were obtained in average to good yields as mixtures of geometrical isomers except in the case of **12bb** bearing R = *n*-Bu (entries 1−5). The scope of the reaction was further explored by synthesizing a selection of 3-benzyl-2-arylbenzo[*b*]furan derivatives **14ab−ag** using different electrophiles (entries 6−11).

In summary, easily available aryl benzyl ethers have been shown to be selectively α-lithiated at low temperature, being stable enough to avoid the expected [1,2]-Wittig rearrangement. The α-aryloxy benzyllithiums generated can be trapped with a wide range of electrophiles. Starting from *o*-(alkynyl)phenyl benzyl ethers, an intramolecular carbolithiation is triggered after α-lithiation providing a direct entry to functionalized 2-arylbenzo[*b*]furan derivatives. Moreover, the addition takes place in an unexpected anti fashion representing the first example of an anti carbolithiation of an unactivated triple bond without coordination of the lithium cation and the terminal substituent of the alkyne.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01964.

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

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Notes

The authors declare no competing financial interest.

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(10) See Supporting Information for a detailed study of the α-lithiation of ether **1a**.

(11) Increasing the reaction temperature over −35 °C to force complete lithiation leads to the competitive formation of diarylmethanol **3e** derived from [1,2]-Wittig rearrangement.

(12) Nevertheless, when an aliphatic ester such as ethyl isobutyrate was used, the reaction resulted in a mixture of the corresponding ketone and tertiary alcohol.

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(23) Vinyllithium intermediates **11b,c** did not isomerize at rt before undergoing decomposition after extended reaction time.