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On the Reactivity of *o*-Lithioaryl Ethers: Tandem Anion Translocation and Wittig Rearrangement

José Barluenga,*,† Francisco J. Fañanás,† Roberto Sanz,‡ César Marcos,‡ and Marta Trabada‡

Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al C.S.I.C. Julián Clavería, 8, Universidad de Oviedo, 33071 Oviedo, Spain, and Departamento de Química, Área de Química Orgánica, Facultad de Ciencias, Pza. Missael Bañuelos s/n, Universidad de Burgos, 09001 Burgos, Spain

barluenga@sauron.quimica.uniovi.es

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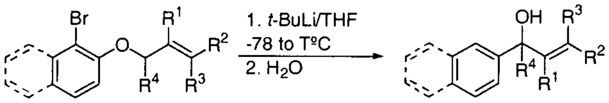
ABSTRACT



Allyl and benzyl 2-lithioaryl ethers, generated by bromine–lithium exchange in THF, undergo a new tandem anion translocation-[1,2]-Wittig rearrangement allowing the isolation of the corresponding benzylic alcohols.

The "anion translocation" reaction, in which an organolithium compound formed under kinetic control undergoes an inter- or intramolecular proton transfer, offers an easy entry to new organolithium compounds that are difficult to obtain following the traditional lithiation methods.[1] α-Oxygen carbanions are unstable[2] and usually undergo protophilic cleavage (elimination) or [1,2]-Wittig rearrangement,[3] which consists of the isomerization of these carbanions to metal alkoxides.[4] In most of the examples of [1,2]-Wittig rearrangement the migrating groups are alkyl and benzyl, and the migration of vinyl[5] and aryl groups[6] is not so common. Another feature of this kind of rearrangement is the presence in the starting ether, in most of the cases, of a group that can stabilize the negative charge in a position α to the oxygen.[7] In general, the yields of this process are moderate, and harsh conditions are often employed. The mechanism traditionally accepted for the [1,2]-Wittig rearrangement involves the homolysis of an α-anion intermediate followed by recombination of the radical and radical anion fragments.[8] Despite many mechanistic studies, synthetic applications[9] of the [1,2]-Wittig rearrangement have remained limited, mainly because of the rather low yields and the restricted range of

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[†] Universidad de Oviedo.

[‡] Universidad de Burgos.

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[2] The α-carbanion of an alkyl benzyl ether is able to add to a carbonyl moiety in the alkyl chain without Wittig rearrangement or protophilic decomposition: Matsumoto, M.; Watanabe, N.; Ishikawa, A.; Murakami, H. *Chem. Commun.* **1997**, 2395−2396.

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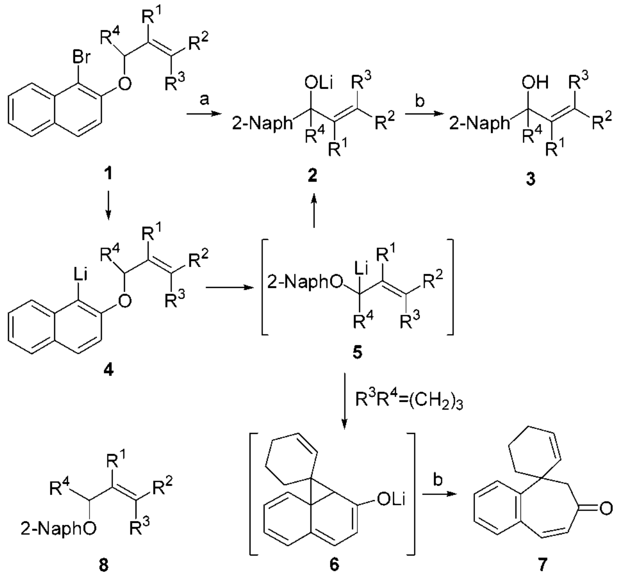
substrates.[10] On the other hand, we have recently described that cuprates derived from 2-lithiophenyl allyl ethers undergo a Claisen-type rearrangement with retention of the regio- and stereochemistry.[11] In the context of the research of new reactivities of this kind of substrates, we now report the transformation of 2-lithioaryl allyl and benzyl ethers into allyl and benzyl alcohol derivatives through a tandem anion translocation-[1,2]-Wittig rearrangement.

The treatment of different allyl and benzyl 1-bromo-2-naphthyl ethers **1** with 2 equiv of *tert*-butyllithium in THF at −78 °C afforded, after warming to different temperatures and subsequent hydrolysis, the benzylic alcohols **3** in moderate to good yields along with variable amounts of other compounds, depending on the starting material (Scheme 1 and Table 1).[12] The formation of the resulting products could be explained by assuming that the initial organolithium compounds **4**, generated by bromine−lithium exchange,[13] undergo an anion translocation process generating new anions **5**, which suffer a [1,2]-Wittig rearrangement to afford the alkoxides **2**, which upon hydrolysis allow the isolation of alcohols **3**. The temperature at which the translocation takes place was determined for each lithiated ether **4** by the deuteriolysis of aliquots and analysis by GC−MS.

Scheme 1[a]



[a] Reagents and conditions: (a) *t*-BuLi (2 equiv), THF, −78 to *T* °C; (b) H_2O.

Table 1. Rearranged Alcohols **3** from Naphthyl Ethers **1**

starting ether	R^1	R^2	R^3	R^4	T (°C)/ time (h)	product	yield (%)[a]
1a	H	H	H	H	−30/3	**3a**	81
1b	Me	H	H	H	−30/3	**3b**	82
1c[b]	H	Me	H	H	0/12	**3c**[c]	72[d]
1d	H	Me	H	Me	0/12	**3d**	61[e]
1e	H	H	−(CH$_2$)$_3$−		0/12	**3e**	23[f]
1f	−(CH)$_4$−		H	H	−30/3	**3f**	83
1g	−(CH)$_4$−		H	Me	−30/12	**3g**	78

[a] Isolated yield based on the starting ether **1**. [b] A 4:1 mixture of *E*/*Z*-isomers. [c] *E*-isomer (>95% by ^{1}H NMR). [d] Ether **8c** (15%) was also obtained. [e] Ether **8d** (22%) and *β*-naphthol (14%) were also obtained. [f] Ether **8e** (51%) and ketone **7** (20%) were also isolated.

From the results summarized in Table 1 it can be concluded that the temperature at which the reactions occur is related to the ability of the allyl or benzyl fragment to stabilize the negative charge in **5**. So with allyl, methallyl, or benzyl ethers **1a,b,f** the anion translocation takes place at −30 °C, whereas with α- and/or *γ*-substituted ethers **1c−e** it occurs at 0 °C. Probably as a result of this increase in the reaction temperature, a competitive protonation of the intermediate anions **4** or **5** by the solvent, giving the corresponding naphthyl ether **8c−e**, could explain the lower yield of **3c−e**. Furthermore, we have observed that starting from α-substituted benzyl ether **1g** the reaction also proceeds at −30 °C but to be completed it needs longer times (12 h) compared to the analogous benzyl ether derivative **1f**. These results show that substitution at the α- or *γ*-position of the starting allyl or benzyl ether delays the anion translocation. Moreover, the presence of an allyl or benzyl substituent in the starting ether is necessary to promote the anion translocation process, as was demonstrated by the fact that 1-bromo-2-naphthyl methyl ether does not undergo the tandem reactions described, probably because of the lack of a group that stabilizes the α anion to the oxygen.

With respect to the nature of the allyl fragment some other considerations could also be made. The reaction works efficiently for all kinds of allyl and benzyl moieties tested except for the case of cyclohexenyl ether **1e**, where a mixture of α,*β*-unsaturated ketone **7**, debrominated ether **8e**, and alcohol **3e** was obtained. The formation of the unexpected spiro-derivative **7** could be explained by taking into account that intermediate organolithium **5** could undergo an α-elimination process leading to carbenoid reactions. In this case a cyclopropanation of a double bond of the aromatic ring is assumed, affording intermediate **6**, which rearranges to the more stable benzo-fused cycloheptenone derivative **7** after hydrolysis. This fact and the formation of *β*-naphthol in the reaction of ether **1d** supports the idea that the α-elimination competes with the Wittig rearrangement in those cases where less stable tertiary carbanions, such as **5d,e**, are formed. Although **5g** is also a tertiary carbanion, formation of *β*-naphthol is not observed with ether **1g**, probably because of its benzylic character that stabilizes it. Interestingly, with crotyl ether **1c** the tandem sequence affords alcohol **3c** as almost isomerically pure *E*-alkene (20:1 by ^{1}H NMR) despite the fact that the starting ether is a 4:1 mixture of *E* and *Z*-diastereoisomers. This fact could be explained by assuming

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[10] Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann./Recueil* **1997**, 1275−1281.

[11] Barluenga, J.; Sanz, R.; Fañanás, F. J. *Tetrahedron Lett.* **1997**, *38*, 6103−6106.

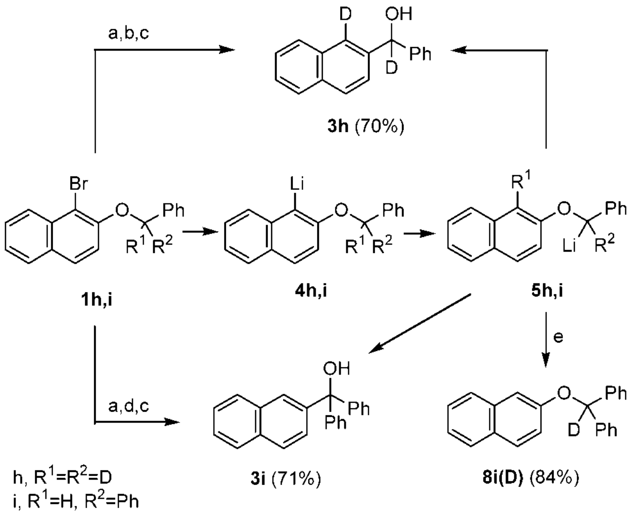
[12] Alcohols **3**, derived from a Wittig rearrangement, could also be obtained from the corresponding *β*-naphthyl ethers without the bromine atom by treatment with *t*-BuLi (1 equiv).

[13] Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785−2812.

that intermediate organolithiums **5** are allyloxy carbanions and the *E*,*Z*-mixture of **5c** can therefore be transformed into the more stable *E*-isomer through an allylic rearrangement.

To support the proposed mechanism of an anion translocation, inter- or intramolecular, we prepared the deuterium-labeled ether **1h**, by reduction of methyl benzoate with lithium aluminum deuteride, chlorination[14] of the resulting alcohol, and further alkylation with 1-bromo-2-naphthol. When this substrate was used as starting material the dideuterated alcohol **3h** was obtained, showing that the deuterium−lithium exchange takes place in the intermediate **4h**, leading to the benzyllithium derivative **5h**. Further [1,2]-Wittig rearrangement of **5h** affords the alcohol **3h** after hydrolysis (Scheme 2). We have also observed that although the intermediate **4f**, derived from benzyl ether **1f**, undergoes the anion translocation at −30 °C in 3 h (see Table 1), the lithiated intermediate **4h** is completely stable in these reaction conditions and its evolution to the final product **3h** is observed at 0 °C in 3 h. In addition, with diphenylmethyl ether **1i** the hydrogen−lithium exchange takes place at −78 °C, probably as a result of the additional stabilization introduced by the second phenyl group in **4i** (Scheme 2). In contrast with the rest of the ethers **1**, the corresponding translocated anion **5i** is stable and could be deuterated to afford ether **8i(D)** in 84% yield. If the reaction mixture is allowed to reach room temperature for 3 h the corresponding rearranged alcohol **3i** is obtained in 71% yield after hydrolysis.

Scheme 2[a]



[a] Reagents and conditions: (a) *t*-BuLi (2 equiv), THF, −78 °C; (b) 0 °C, 3 h; (c) H_2O; (d) rt, 3 h; (e) D_2O, −78 °C.

To establish the inter- or intramolecular nature of the anion translocation process, several experiments were performed with varying concentrations of the starting ether **1b** in THF, under the same temperature conditions. In this way, different ratios of the rearranged alcohol **3b** and the hydrolyzed ether **8b** were obtained, depending on the concentration (Table 2). These results seem to indicate that the anion translocation is intermolecular as shown by the decrease in the ratio of the rearranged product **3b** with an increase of the dilution. Also, crossover experiments were carried out in order to know about the intermolecularity of this process. So, a 1:1 mixture of lithium derivatives **4a** and **4h** was allowed to warm from −78 to 20 °C to obtain alcohols **3a** and **3h**. The lack of incorporation of deuterium in **3a** could be due to the different temperatures at which the translocation takes place in organolithiums **4a** and **4h** (see above). However, a more successful experiment was accomplished when a 1:1 mixture of allyl β-naphthyl ether and organolithium compound **4h** was allowed to react at −30 °C for 3 h, affording a mixture of alcohol **3a** and unreacted allyl β-naphthyl ether besides the hydrolyzed ether derived from **4h**. This result also supports the intermolecular nature of the translocaction.

Table 2. Effect of Concentration in the Reaction of **1b**

concentration (mmol of **1b**/mL THF)	ratio **3b:8b**[b]
1/30	1:6.5
1/10	3:1
1.5/10	3.3:1
1/3	7.5:1

[a] The reaction was carried out from −78 to 20 °C for 2 h. [b] The overall yield was about 95% in all the examples.

To extend the scope of this process we investigated the reaction of 2-bromophenyl allyl and benzyl ethers **9**. So, treatment of **9** with 2 equiv of *tert*-butyllithium at −78 °C in THF afforded the organolithium compounds **10**, which after warming to 0 °C and further stirring for 3 h led to a mixture of compounds **12**, **13**, and **14** in different ratio, depending on the R^1 and R^2 substituents in the allyl moiety of **9** (Scheme 3).

It is important to note that organolithium compounds **10** are stable at −30 °C, in contrast to the related intermediates **4** derived from naphthyl ethers **1**, and it is necessary to warm the reaction mixture to 0 °C and stir it for 3 h to obtain the final products. This increase in the reaction temperature could be the reason these phenyl ethers undergo the tandem anion translocation-Wittig rearrangement less efficiently than the naphthyl derivatives. The formation of these compounds could be again explained through the intermediate α-oxygenated organolithium **11** generated from **10** by an anion translocation process. When $R^1 = R^2 = H$ (pathway a), a competitive intramolecular carbolithiation followed by a γ-elimination, as described by Bailey,[15] took place, and the corresponding *o*-cyclopropylphenol **13a** was obtained along with the expected alcohol **12a** in a 2.5:1 ratio (63% overall

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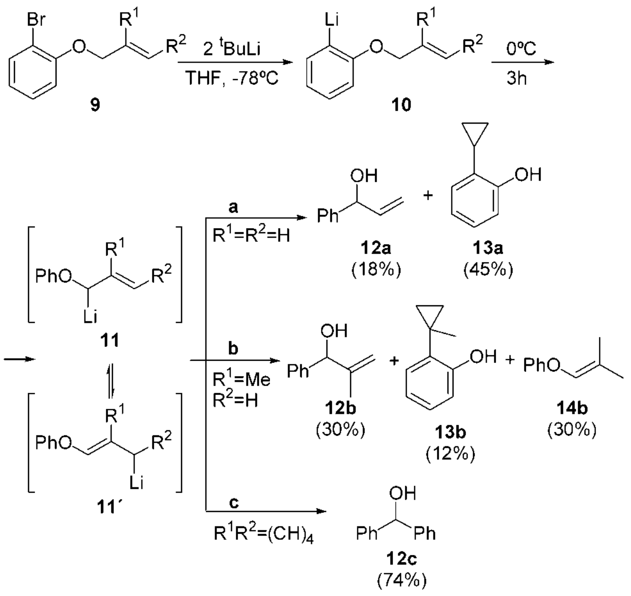
(14) The chlorination was carried out with thionyl chloride and 1*H*-benzotriazole following the procedure described by Chaudhari, S. S.; Akamanchi, K. G. *Synlett* **1999**, 1763−1765.

(15) An isomerization of 2-(2-propenoxy)phenyllithium to afford 2-(cyclopropyl)phenol in 40% yield has been reported: Bailey, W. F.; Punzalan, E. R. *Tetrahedron Lett.* **1996**, *37*, 5435−5436.

Scheme 3



yield). However, when $R^1 = Me$ and $R^2 = H$ (pathway b) the intermediate **10b** afforded an equimolecular mixture of alcohol **12b** and enol ether **14b** (60% overall yield), derived from the translocated organolithium **11b**, together with a small amount (12%) of the corresponding cyclopropyl derivative **13b**. The unexpected formation of **14b** also supports that α-oxygenated anions **11** are intermediates in these reactions because its formation could be explained by hydrolysis of intermediate **11'b**, generated by an allylic rearrangement in **11b**.[16] The formation of **14b** only in this case could be due to the additional stabilization of the resulting olefin by the methyl group at the R^1 position. The best result in the rearranged alcohol was obtained in pathway c, starting from benzyl 2-bromophenyl ether, which affords the expected diphenylmethanol **12c** in 74%. In this case the formation of the corresponding products **13** and **14** is not possible.

In summary, we have described a new tandem anion translocation-Wittig rearrangement on *o*-lithioaryl ethers that have a moiety able to stabilize a carbanion at the position adjacent to the oxygen. The final products are the corresponding allylic or benzylic alcohols, and this sequence points to the potential development of anion translocation as a new synthetic strategy in organic chemistry.

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Supporting Information Available: Experimental procedures, characterization data for all compounds, and 2D-NMR spectra for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] (a) Still, W. C.; Macdonald T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561−5563. (b) Still, W. C.; Macdonald T. L. *J. Org. Chem.* **1976**, *41*, 3620−3622.