## Selective O-Deallylation of o-Allyloxyanisoles

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**Abstract:** *o*-Allyloxyanisoles are selectively and easily deallylated by treatment with *sec-* or *tert*-butyllithium at low temperature. The reaction is proposed to proceed through a tandem intermolecular carbolithiation– $\beta$ -elimination process, which can also be considered an S<sub>N</sub>2' attack of the organolithium on the allyl ether.

Key words: protecting groups, lithium, eliminations, phenols, ethers

The selective introduction and removal of protecting groups (PG) is of critical importance in many synthetic sequences.<sup>1</sup> For this reason, there is a continuing demand for more varied, robust, economical and/or chemically differentiable protecting groups. Protection of the hydroxyl functionality of phenols is required to prepare a number of compounds. The use of allylic PG, which are stable under both acidic and basic conditions, for the protection of alcohols will become more common provided that more effective procedures for the removal of the allyl groups become available.<sup>2</sup> In this context, we have described the 2-arylallyl group as a new PG for amines, amides, and alcohols.<sup>3</sup> In 1965 Broaddus reported the cleavage of several alkyl allyl ethers upon treatment with *n*-BuLi in a hydrocarbon solution at 70 °C leading to the lithium alkoxide and 1-heptene.<sup>4</sup> More recently, Bailey and coworkers described that this O-deallylation of allyl ethers could be carried out at room temperature by their treatment with t-BuLi.5

During the last years, we have studied the intramolecular carbolithiation of allyl *o*-lithioaryl ethers **2**, generated by bromine–lithium exchange from allyl *o*-bromophenyl ethers **1**, with different substituents at the allyl and the aryl moieties (R<sup>1</sup>, R<sup>2</sup> substituents).<sup>6</sup> 3-Functionalized 2,3-di-hydrobenzofurans **4** or *o*-cyclopropyl phenols **5** could be selectively obtained depending on the evolution of the 3-lithiomethyl-2,3-dihydrobenzofurans intermediates **3** (Scheme 1).<sup>6b,c</sup> In general, the presence of substituents at the R<sup>1</sup> and/or R<sup>2</sup> positions seems to inhibit the  $\gamma$ -elimination process that gives rise to the cyclopropyl derivatives **5**. However, we have recently observed that the treatment of allyl 2-bromo-6-methoxy-4-methylphenyl ether (**1a**) with *t*-BuLi in Et<sub>2</sub>O and TMEDA at low temperature, and further evolution to 0 °C, gives rise to a ca. 1:1 mixture of

SYNLETT 2008, No. 13, pp 1957–1960 Advanced online publication: 15.07.2008 DOI: 10.1055/s-2008-1077962; Art ID: D12908ST © Georg Thieme Verlag Stuttgart · New York cyclopropyl derivative **5a** (42% isolated yield) and 4methyl-2-methoxyphenol (**6a**, 35% isolated yield, Scheme 1). We thought that the presence of the methoxy group at the *ortho* position with respect to the allyloxy moiety could favor a competitive intermolecular carbolithiation reaction of *t*-BuLi onto the double bond, affording a  $\beta$ -oxygen-substituted organolithium intermediate such as **7a**. Subsequent  $\beta$ -elimination, in an analogous way as we have previously described for 2-arylallyl ethers,<sup>3</sup> would lead to 4-methylguaiacol (**6a**).



 $Scheme 1 \quad Competitive intramolecular carbolithiation reaction versus deallylation of allyl$ *o*-lithioaryl ether <math>2a

Due to the usefulness of *o*-methoxyphenols in organic synthesis,<sup>7</sup> and the current interest in the development of methods for their selective protection/deprotection,<sup>8</sup> we decided to initiate a systematic study in order to check if the allyl group removal was selective due to the *ortho*-directing effect of the methoxy group. Therefore, the reactivity of allyl phenyl ethers **8a** and **8b**,<sup>9</sup> which differ on the presence of a methoxy group, was studied with different organolithium reagents. We found that reactions of **8a** and **8b** under several conditions afforded a variable mixture of the corresponding deallylated products **6**, the deuteriated

derivatives **9** and **10**, and, in some cases, starting materials **8** (Scheme 2 and Table 1). Formation of deallylated phenols **6** could be explained, as described above, by intermolecular carbolithiation reaction of the organolithium reagent and subsequent  $\beta$ -elimination, which could also be formulated as a concerted process through **11** (Scheme 2). Generation of deuteriated enol ether derivatives **9** and  $\alpha$ -deuteriated ether derivatives **10** could be explained through competitive deprotonation of the starting ether **8** by the organolithium reagent that would lead to the allyllithium intermediate **12**.<sup>10</sup> Deuteration at both positions of the allyl moiety accounts for the formation of **9** and **10** (Scheme 2).



Scheme 2 Pathways for the reactions of ethers **8a**,**b** with organolithium reagents. Formation of phenols **6a**,**b** and deuteriated ethers **9a**,**b** and **10a**,**b** 

 Table 1
 Reactivity of 8a,b with Organolithium Reagents<sup>a</sup>

Entry	Starting ether	RLi	Solvent	Ratio of <b>6/9</b> + <b>10</b> <sup>b,c</sup>		
1	8a	n-BuLi	Et <sub>2</sub> O	d		
2	8a	s-BuLi	Et <sub>2</sub> O	1:2		
3	8a	t-BuLi	$Et_2O$	1.5:1		
4	8a	t-BuLi	THF	0:1		
5	8b	n-BuLi	Et <sub>2</sub> O	1:2.5 <sup>e</sup>		
6	8b	s-BuLi	Et <sub>2</sub> O	10:1		
7	8b	t-BuLi	Et <sub>2</sub> O	15:1		
8	8b	t-BuLi	THF	1:7		

<sup>a</sup> All reactions were carried out by treatment of **8** (1 mmol) in the corresponding solvent (10 mL), with the organolithium reagent (1.1 mmol) for 2 h at -78 °C.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude.

<sup>c</sup> In all the cases the isolated overall yield was higher than 85%.

<sup>d</sup> Starting ether **8a** was recovered without deuterium incorporation. <sup>e</sup> Starting ether **8b**, without deuterium incorporation, was the major product of the reaction mixture. Taking advantage of our finding with ether 1a, reactions were initially carried out with Et<sub>2</sub>O as solvent varying the nature of the organolithium reagent. As shown from Table 1 (entries 1-3), allyl phenyl ether 8a was only partially deallylated with s-BuLi or t-BuLi at low temperature using 10 mL of solvent per mmol of ether.<sup>11</sup> On the other hand, under the same reaction conditions, allyl omethoxyphenyl ether 8b was almost completely deallylated with these reagents (Table 1, entries 5-7). Not surprisingly, worse results were obtained for both ethers 8a,b when THF was used as solvent (Table 1, entries 4 and 8), being the deprotonation pathway favored over the carbolithiation one.<sup>12</sup> From this study we can conclude that the allyl removal from allyl phenyl ethers, by their reaction with s-BuLi or t-BuLi, is easier when the starting material contains a methoxy group in *ortho* position with respect to the allyloxy moiety. The coordination of the methoxy group with the organolithium reagent, which favors its approach to the double bond, probably facilitates the O-deallylation reaction.

Thus, we decided to explore the generality of the reaction by using different allyl *o*-methoxyphenyl ethers **8b–j** under the best reaction conditions previously established, that is, treatment of the ether with a slight excess of *s*-BuLi or *t*-BuLi in Et<sub>2</sub>O at -78 °C for 2 hours (Scheme 3 and Table 2).



Scheme 3 Selective deallylation reactions of ethers 8b-j

Allyl ethers **8b**,**c** derived from *o*-methoxyphenols or naphthols are cleanly cleaved to give the corresponding phenol derivatives in excellent yield (Table 2, entries 1 and 2). Interestingly, ethers **8d**,**e**, bearing fluoro or chloro substituents at the benzenoid moiety in a *m*-relationship with the methoxy group were successfully deallylated as shown in Table 2 (entries 3 and 4). However, bromo-substituted ether **8f** mainly underwent bromine–lithium exchange (Table 2, entry 5). It is also significant that the allyl group may be selectively cleaved in the presence of other typical protecting groups for ethers like benzyloxy or silyloxy groups (Table 2, entries 6 and 7). Also, an allyl group on the aromatic ring, like those occurring in ethers **8i**,**j**, were unaffected under the reaction conditions (Table 2, entries 8 and 9).

Considering the selectivity found for the allyl-group removal from *o*-allyloxy anisole derivatives **8b**–**j**, we decid-

 Table 2
 Selective Deallylation Reactions of Ethers 8b-j<sup>a</sup>

Entry	Ether	$\mathbb{R}^1$	R <sup>2</sup>	R <sup>3</sup>	$\mathbb{R}^4$	Product	Yield (%) <sup>b</sup>
1	8b	Me	Н	Н	<i>t</i> -Bu	6b	88
2	8c	-(CH) <sub>4</sub> -		Н	s-Bu	6c	95
3	8d	F	Н	Н	s-Bu	6d	86
4	8e	Cl	Н	Н	<i>t</i> -Bu	6e	90
5	8f	Br	Н	Н	s-Bu	_c	_
6	8g	CH <sub>2</sub> OBn	Н	Н	s-Bu	6g	80
7	8h	CH <sub>2</sub> OTBDMS	Н	Н	s-Bu	6h	87
8	8i	Allyl	Н	Н	<i>t</i> -Bu	6i	92
9	8j	Н	Н	Allyl	s-Bu	6j	80

<sup>a</sup> All reactions were carried out by treatment of **8** (1 mmol, 10 mL of  $Et_2O$ ) with *s*-BuLi or *t*-BuLi (1.1 mmol) for 2 h at -78 °C.

<sup>b</sup> Isolated yield.

<sup>c</sup> A bromine–lithium exchange occurred and *o*-methoxyphenol was mainly obtained.

ed to test if this methodology could be applied to the selective allyl-group removal from allyl *o*-methoxyphenyl ethers bearing other allyloxy unit in their structure. In fact, allyloxymethyl ether **8k** could be selectively deprotected as we only observed reaction at the allyloxy group in *ortho* position with respect to the methoxy group (Scheme 4). In the same way, ether **8l** also underwent selective O-deallylation reaction (Scheme 4). Finally, the 2-methoxyhydroquinone derivative **8m** that possesses the two hydroxyl groups protected with allyl groups was tested. To the best of our knowledge, direct selective monoalkylation of methoxyhydroquinone derivatives are usually prepared from Baeyer–Villiger oxidation of vanillin, that precludes the use of allyl



Scheme 4 Selective deallylation of bisallyloxy anisole derivatives **8k–m**; preparation of 4-allyloxyguaiacol (**6m**)

groups.<sup>14</sup> Gratifyingly, treatment of **8m** with *s*-BuLi or *t*-BuLi selectively afforded 4-allyloxy-2-methoxyphenol (**6m**) in high yield (Scheme 4), showing the high selectivity of this protecting-group removal and providing a useful method for the easy preparation of **6m** from 2-methoxyhydroquinone. Remarkably, no partial O-deallylation of the other allyloxy group in none of these bisallyloxy derivatives **8k**–**m** was observed under these reaction conditions.

Having successfully developed an efficient selective Odeallylation of *o*-allyloxyanisoles **8**, we finally checked the possibility of applying this methodology to the corresponding *o*-thioanisole derivatives. However, reaction of allyl *o*-methoxyphenyl thioether  $13^{15}$  with *t*-BuLi (or *s*-BuLi) in Et<sub>2</sub>O mainly afforded a mixture of deuteriated thioethers **14** and **15**, due to a predominant acid–base process (Scheme 5).<sup>16</sup> Furthermore, we were also interested in studying the reactivity of a related substrate possessing the methoxy group far away from the allyloxy moiety, as it is the case of allyl *o*-methoxymethylphenyl ether **16**. Its reaction with *t*-BuLi led to the almost exclusive abstraction of the allylic proton  $\alpha$  to the oxygen atom and, therefore, to the formation of a mixture of deuteriated ether **17** and enolether **18** after deuteriolysis (Scheme 5).<sup>17</sup>



Scheme 5 Attempts of allyl removal from related substrates 13 and 16

In summary, we have shown that the presence of an *ortho*methoxy group with respect to an allyloxy moiety allows the selective removal of the allyl group affording the corresponding guaiacol derivatives in high yields. The efficient two-step synthesis of unknown 4-allyloxyguaiacol (**6m**) from 2-methoxyhydroquinone, shows the high selectivity and potential applications of this methodology.

## General Procedure for the Selective Removal of the Allyl Group from Allyl *o*-Methoxyphenyl Ethers 8 – Synthesis of 4-Allyloxy-2-methoxyphenol (6m)

To a solution of 1,4-bis-allyloxy-2-methoxy-benzene (**8m**, 0.220 g, 1 mmol) in dry Et<sub>2</sub>O (10 mL), *t*-BuLi (0.73 mL of a 1.5 M solution in pentane, 1.1 mmol), or alternatively *s*-BuLi (0.77 mL of a 1.3 M solution in cyclohexane–hexane, 1.1 mmol), was added under nitrogen at -78 °C. The reaction was stirred at this temperature for 2 h, and then was quenched by the addition of MeOH (excess) at this

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temperature. The mixture was allowed to reach r.t., aq HCl (1 M, 10 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were dried with anhyd Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to afford **6m** (0.153 g, 85%) as a pale brown oil.  $R_f = 0.17$  (hexane–EtOAc, 5:1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 3.83$  (s, 3 H), 4.46 (dt, J = 5.3, 1.4 Hz, 2 H), 5.26 (dq, J = 10.4, 1.4 Hz, 1 H), 5.42–5.35 (m, 2 H, including OH), 6.09–5.98 (m, 1 H), 6.38 (dd, J = 8.7, 2.7 Hz, 1 H), 6.51 (d, J = 2.7 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 1 H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta = 55.7$  (CH<sub>3</sub>), 69.4 (CH<sub>2</sub>), 100.1 (CH), 105.2 (CH), 113.9 (CH), 117.5 (CH<sub>2</sub>), 133.4 (CH), 139.7 (C), 146.9 (C), 152.3 (C). LRMS (EI): m/z (%) = 180 (44) [M<sup>+</sup>], 139 (100). HRMS: m/z calcd for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>: 180.0786; found: 180.0784.

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- (15) Thioether **13** was prepared from 2-methoxythiophenol by its treatment with NaOH and allyl bromide in water.
- (16) A small amount of the expected 2-methoxythiophenol could be detected in the crude product of the reaction.
- (17) Although treatment of 16 with *s*-BuLi also afforded a mixture of 17 and 18 as main products, in this case 2-methoxymethyl phenol was also obtained as a minor product.