2-Arylallyl as a new protecting group for amines, amides and alcohols†

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Amines, amides and ethers containing 2-arylallyl groups are selectively and easily deprotected with *tert*-butyllithium. This transformation probably involves a carbolithiation reaction of the styrenyl moiety followed by a β-elimination process.

Protecting groups (PGs) play an important role in multi-step processes in synthetic organic chemistry.[1] So, there is continuing demand for more varied, robust, economical and/or chemically differentiable PGs. Between the plethora of alternatives, the use of allylic PGs, which are stable under both acidic and basic conditions, for the protection of amines and alcohols will become more common provided that more effective procedures for the removal of the allyl-type groups become available.[2,3] In general, two strategies have been used for the removal of allylic PGs of amines and ethers: a two-step process in which the double bond of the allyl moiety is isomerised and single-step procedures employing a variety of conditions.[4] In this context, Bailey *et al.* have reported the *O*-deallylation of allyl ethers by treatment of a hydrocarbon solution of the ether with *t*-BuLi at 0 °C.[5] However, this procedure is not useful for the cleavage of allylamines[6] and the relatively high temperature needed prevents the use of this method with functionalised substrates.

We have recently studied the reactivity of some allyl 2-lithioaryl ethers and we have found different results depending on the allyl moiety and the conditions of the reactions.[7] Searching for new carbolithiation processes, we found that 2-arylallyl 2-lithioaryl ethers undergo intermolecular attack by *t*-BuLi instead of intramolecular carbolithiation. This fact is supported by the known intermolecular addition of *t*-BuLi to α-methylstyrenes that takes place at −78 °C in hydrocarbon solvents in the presence of ethers or tertiary amines as ligands affording a tertiary benzylic carbanion.[8] It is also known that styrene derivatives easily undergo carbolithiation reactions due to the favoured formation of a benzylic anion.[9] We now report that 2-arylallyl groups are useful PGs for amines, amides and alcohols due to their efficient single-step removal with *t*-BuLi.

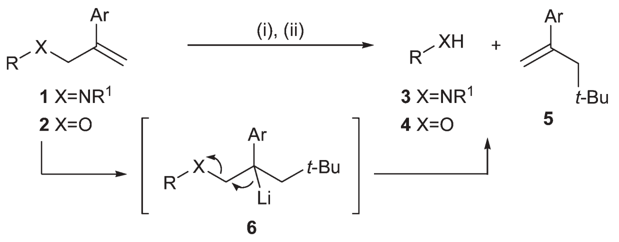
Protected amines **1** were efficiently prepared by alkylation of the corresponding primary or secondary amine or amide **3** with α-bromomethylstyrene[10] or with 2-*p*-tolylallyl mesylate.[11] The deprotection step was achieved by treatment of a solution of different amines **1** in THF (*ca.* 1 mL per mmol of starting substrate) with *t*-BuLi (1 equiv) at −78 °C and further evolution to 0 °C to afford, after hydrolysis and extractive workup, essentially pure amines **3** along with α-neopentyl styrene derivative **5** (Scheme 1 and Table 1, entries 1–10).

The following conclusions can be inferred from Table 1. Regardless of the electronic nature of the amines, the reactions take place with specific removal of the 2-arylallyl group even in the presence of allyl (Table 1, entries 2, 4, 6) or benzyl groups (Table 1, entry 3). Also, a fluorine atom could be present in the amine moiety (Table 1, entry 4). Interestingly, with secondary amines such as **1e** and **1g** (Table 1, entries 5 and 7), the reactions proceeded smoothly, provided that 2 equiv of *t*-BuLi were used in order to first deprotonate the acidic N–H. A cyclic amine like piperidine derivative **1h** was also attempted and the reaction proceeded without any problems (Table 1, entry 8). We next examined the reaction of *N*-2-arylallyl five-membered nitrogen hetero-aromatic compounds. As shown in entries 9–10 (Table 1), the deprotection of *N*-2-phenylallylimidazole (**1i**) and *N*-2-*p*-tolylallylindole (**1j**) occurred without difficulty to give the corresponding N–H products in satisfactory yields.

Due to the poor electrophilic nature of the amide group, we next turned our attention to the possibility of using the 2-phenylallyl group as a protecting group for amides. So, we prepared a series of benzamides (**1k–m**), sulfonamides (**1n–p**) and pivalamides (**1q–s**) from aniline, benzylamine and allylamine.

Similarly, as described for amines, amides undergo facile and efficient removal of the 2-arylallyl group under treatment with *t*-BuLi (1 equiv) in THF from −78 to 0 °C to give the corresponding secondary amides (Scheme 1 and Table 1, entries 11–19). Only in the case of amide **1k** the deprotection was not essentially quantitative, probably due to partial deprotonation of the phenyl ring. However, addition of 2 equiv of *t*-BuLi solves the problem. In all cases, the deprotection takes place selectively on the 2-arylallyl group.

Moreover, we have also found that amines and amides protected with two 2-arylallyl groups can be easily deprotected to give the corresponding primary amines and amides. So, when bis-(*N*-2-arylallyl)amines **1t, u** or amides **1v, w** were treated with *t*-BuLi (2 equiv) under the same reaction conditions as described above, the two 2-arylallyl groups were efficiently removed and the



Scheme 1 Deprotection of 2-arylallyl amines and amides **1** and ethers **2**. Reagents and conditions: (i) *t*-BuLi, THF, −78 to 0 °C for X = NR$_1$ and −78 °C for X = O; (ii) H_2O.

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† Electronic supplementary information (ESI) available: experimental procedures and characterization data for all compounds. See http://www.rsc.org/suppdata/cc/b4/b414966a/
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Table 1 Cleavage of *N*-2-arylallylamines and amides **1**

Entry	Starting amine	R	R[1]	Ar	Product	Yield (%)[a]
1	**1a**	Ph	Me	*p*-Tol	**3a**	86
2	**1b**	Ph	Allyl	*p*-Tol	**3b**	84
3	**1c**	Bn	Bn	*p*-Tol	**3c**	82
4	**1d**	$2\text{-FC}_6\text{H}_4$	Allyl	*p*-Tol	**3d**	84
5[b]	**1e**	*p*-Tol	H	*p*-Tol	**3e**	82
6	**1f**	Allyl	Allyl	Ph	**3f**	79
7[b]	**1g**	Bn	H	Ph	**3g**	83
8	**1h**	$–(CH_2)_5–$		Ph	**3h**	80
9	**1i**	Imidazole[c]		Ph	**3i**	78
10	**1j**	Indole[c]		*p*-Tol	**3j**	81
11[b]	**1k**	PhCO	Ph	Ph	**3k**	69
12	**1l**	PhCO	Allyl	Ph	**3l**	91
13	**1m**	PhCO	Bn	Ph	**3m**	73
14	**1n**	Ts	Ph	Ph	**3n**	80
15	**1o**	Ts	Allyl	Ph	**3o**	86
16	**1p**	Ts	Bn	Ph	**3p**	95
17	**1q**	*t*-BuCO	Ph	Ph	**3q**	78
18	**1r**	*t*-BuCO	Allyl	Ph	**3r**	84
19	**1s**	*t*-BuCO	Bn	Ph	**3s**	86
20	**1t**	*p*-Tol	G[d]	*p*-Tol	**3e**	81
21	**1u**	Bn	G[d]	*p*-Tol	**3g**	83
22	**1v**	PhCO	G[e]	Ph	$PhCONH_2$	80
23	**1w**	$PhSO_2$	G[e]	Ph	$PhSO_2NH_2$	78

[a] Isolated yield based on the starting amine or amide **1**. [b] 2 equiv of *t*-BuLi were used. [c] The nitrogen atom is also included. [d] G = 2-(*p*-tolyl)allyl. [e] G = 2-phenylallyl

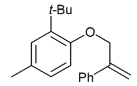
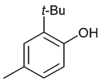
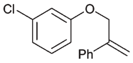
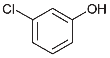
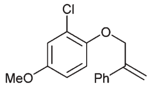
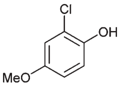
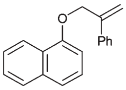
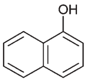
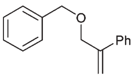
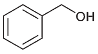
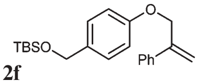
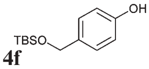
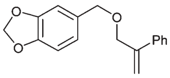
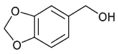
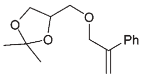
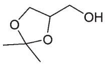
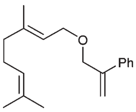
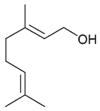
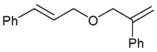
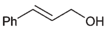
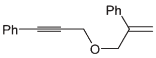
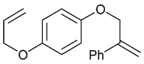
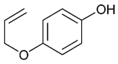
corresponding primary amine **3e, g** or amide (benzamide or phenylsulfonamide) was recovered in a good yield (Table 1).

The excellent results described above prompted us to investigate the possibility of applying the same protecting group to alcohols. Our studies began with the preparation of a series of 2-phenylallyl ethers **2**. Their syntheses were easily achieved by alkylation of the corresponding alcohol or phenol with α-bromomethylstyrene under standard Williamson conditions. The reactions were carried out by treating a THF solution of the starting ether **2** with *t*-BuLi (1 equiv) at −78 °C for 30 min affording, after the addition of aqueous acid followed by extractive workup, essentially pure alcohols **4** along with styrene derivative **5** (Scheme 1).

It is worth noting that whereas allyl ethers on treatment with *t*-BuLi in THF afford a mixture of products, including those derived from Wittig rearrangements,[5] the same reaction with 2-arylallyl ethers gives rise selectively to the removal of the protecting group. Moreover, with this allylic moiety, the reaction takes place at −78 °C. Some representative examples of the deprotection of 2-phenylallyl ethers are summarised in Table 2.

2-Phenylallyl ethers derived from phenols or naphthols (Table 2, entries 1–4) are cleaved cleanly and in excellent yield. Of particular significance are the reactions shown in entries 2 and 3 where chloro and methoxy groups, even in a *m*-relationship, are tolerated under these conditions. It is also significant that the 2-phenylallyl group may be selectively cleaved in the presence of benzyloxy or siloxy groups (Table 2, entries 5–6). Acetal functionalities can also be present in the molecule (Table 2, entries 7–8). Related allylic or propargylic groups such as cinnamyl or 3-phenyl-2-propinyl (Table 2, entries 9–11) are not affected allowing high chemoselectivity. Moreover, in the hydroquinone derivative **2l** that possesses the two O–H protected with allyl and 2-arylallyl groups respectively, our method allows the selective deprotection of the 2-phenylallyl group (Table 2, entry 12).

Table 2 Cleavage of 2-phenylallyl ethers **2**

Entry	Ether[a]	Product	Yield (%)[a]
1	 **2a**	 **4a**	88
2	 **2b**	 **4b**	91
3	 **2c**	 **4c**	90
4	 **2d**	 **4d**	94
5	 **2e**	 **4e**	97
6	 **2f**	 **4f**	87
7	 **2g**	 **4g**	89
8[b]	 **2h**	 **4h**	75
9	 **2i**	 **4i**	95
10	 **2j**	 **4j**	90
11[b]	 **2k**	 **4k**	83
12	 **2l**	 **4l**	86

[a] Isolated yield based on ethers **2**. [b] Reactions were carried out in Et_2O.

The reaction could involve an intermolecular addition of *t*-BuLi onto the styrenyl moiety giving rise to the β-substituted organolithium intermediate **6**.[12] Subsequent β-elimination would generate, after hydrolysis, the corresponding amines or amides **3** or alcohols **4**. Isolation of compound **5**, easily separated from **3** or **4** by column chromatography, supports our mechanistic proposal.

In conclusion, we have described and developed a new protecting allyl-type group, 2-arylallyl, for amines, amides and alcohols. The methodology described here is general, selective, and operationally simple.[13] Moreover, this procedure allows the selective deprotection of the 2-arylallyl group in the presence of other allyl protected functionalities. The mechanism of the cleavage reaction most likely involves an intermolecular carbolithiation of the styrenyl moiety followed by a spontaneous β-elimination process. Considering the synthetic availability and chemostability of our 2-arylallyl protecting group and the highly efficient method for its removal, this methodology is believed to find wide applications in many synthetic programs.

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