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10 examples, 30-73% yield

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A mild copper catalyzed method for the selective deprotection of aryl allyl ethers

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ABSTRACT

Copper boryl reagents enable the selective cleavage of aryl allyl ethers to the corresponding phenols in good to moderate yields.

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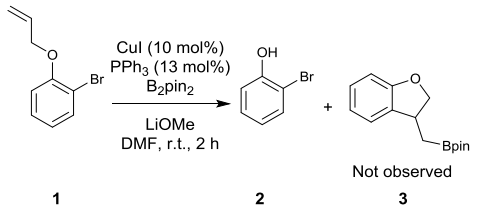
1. Introduction

Allyl ethers serve as useful protecting groups for alcohols, owing to their stability under a wide pH and a variety of reaction conditions. This allows them to be used in orthogonal protecting group strategies and many procedures have been established for their removal.[1-5] Whilst these methods give the corresponding alcohols in high yields and show good functional group tolerance, the vast majority employ catalysts based on palladium and rhodium. Due to ever increasing cost and diminishing availability, there is considerable current interest in efforts to substitute processes mediated by palladium group metals (such as cross couplings) with more readily available transition metals.[6-10] In this paper we describe a new copper mediated process for the selective deprotection of aryl allyl ethers that is orthogonal to classic palladium-mediated methods, operationally simple and occurs under mild conditions with good functional group tolerance.

2. Results and discussion

As a component of a study into the C-X borylation of aryl and alkyl halides,[11] we attempted the borylation of allyl protected bromophenol **1** (Scheme 1). In this reaction, a solution of the

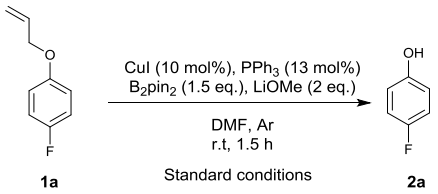


Scheme 1 Attempted borylation resulting in cleavage of the allyl ether

substrate in DMF was added to a mixture of CuI, LiOMe, PPh_3 and B_2pin_2. The reaction rapidly darkened and after ~2 h complete consumption of the starting material was observed by TLC. Surprisingly, no evidence for the expected borylated product could be obtained but rather formation of 2-bromophenol was observed. This suggested that this reagent combination might represent a simple and convenient alternative to the commonly used methods for cleavage of allyl ethers based on palladium complexes. Pleasingly, applying the same conditions to 4-fluorophenylallyl ether (**1a**) afforded the parent phenol (**2a**) in good yield (71%) after only 1 h at room temperature. Further examination of the reaction variables (Table 1) revealed that the presence of the diboron reagent is essential (Entry 2), with no reaction occurring in the absence of this component. The reaction can be run using just stoichiometric amounts of B_2pin_2 but this requires rigorous exclusion of air and moisture (reaction was run in a glove–box), thus it proves more pragmatic to use 1.5 equivalents B_2pin_2. Under these conditions the reaction can be run open to air with minimal / no loss in yield suggesting that the excess diboron reagent may serve to sequester trace oxygen and preserve the catalytically active species. Similarly, the base is important, with LiOMe proving to be the most effective (Entries 4-9). This suggests that the formation of a Bpin-OMe adduct may be necessary for the reaction to proceed. In the absence of the metal catalyst the reaction progresses very slowly (Entry 10). This effect was not due to presence of trace precious metal in the copper source as control reactions using Pd(0) and Pd(II) (Entries 13 and 14) only gave limited conversion, comparable to background reactivity. The role of the phosphine remains unclear but the presence of this component is important (Entry 17). It is possible that the ligand helps to stabilise the metal catalyst potentially, given the heterogeneous nature of the reaction mixture, as nanoparticles. However, addition of mercury to the reaction mixture had no adverse effect on the yield. In keeping with C-X borylation processes using similar reagent combinations, DMF was found to be the optimal solvent (Entries 20 and 21).

Having determined optimal conditions, we then examined the substrate scope (Table 2). Initial exploration of a set of phenyl allyl ethers revealed that electron deficient phenols were deprotected most readily whilst very electron rich substrates were only cleaved slowly and in low yields (**1c** and **1d**). In these cases a complex reaction mixture resulted with hydroboration of the alkene being one minor isolable product. These results suggested that the pKa of the alkoxide/phenoxide was critical. Consistent with this hypothesis, alkyl allyl ethers did not perform well in the reaction (**1h** and **1r**) and allyl amines were stable to the reaction conditions (**1l**). Steric bulk on the aromatic ring is well tolerated but the presence of a terminal methyl group on the alkene (**1g**) prevents the reaction from occurring.

Table 1 Screening Conditions

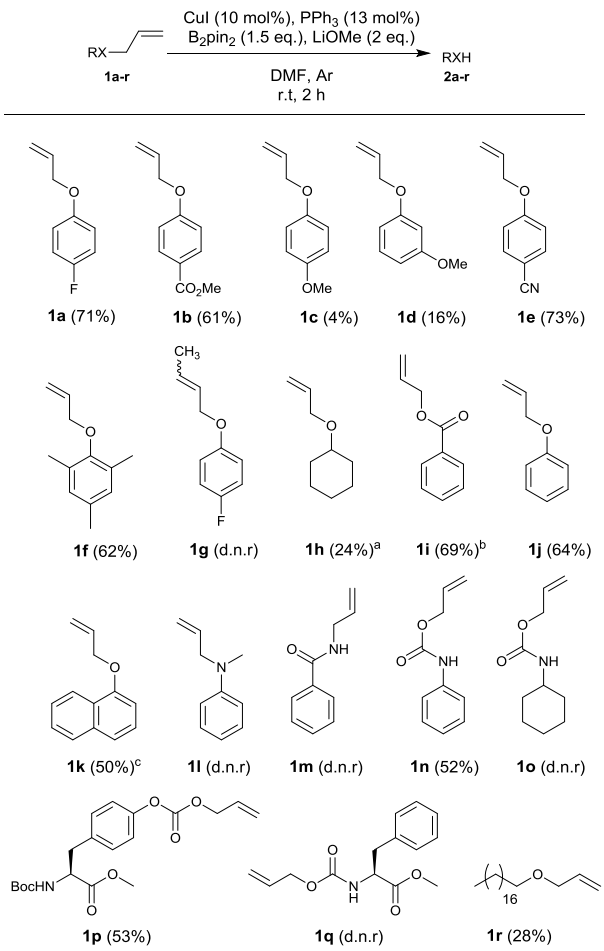


Entry	Change from standard conditions	% yield after 1.5 h (GC)
1	None	80
2	No B_2pin_2	0
3	1 eq. B_2pin_2 (glove box)	76
4	LiO^tBu	62
5	KO^tBu	s.m isomerism[a]
6	NaO^tBu	55
7	K_2CO_3	65
8	CsF	59
9	No base	0
10	No metal	15
11	CuCl	62
12	$CuCl_2$	61
13	$Pd(PPh_3)_4$	35[b]
14	$PdCl_2(PPh_3)_2$	12[b]
15	$ZnCl_2$	14
16	$MgCl_2$	5
17	No ligand	trace
18	Xantphos ligand	78
19	$P(^nBu)_3$ ligand	72
20	THF solvent	trace
21	MeCN solvent	20

GC-MS yields calculated using mesitylene as an internal standard; a) to the corresponding vinyl ether; b) 5 mol% Pd catalyst was used

Surprisingly, in view of the pKa correlation for phenoxides, whilst allyl esters are viable substrates the rate of reaction is significantly slower than for simple phenols. Alloc ethers are cleaved (**1p**) as are alloc carbamates of anilines (**1n**). Given these results, it was surprising to discover that *N*-alloc phenylalanine was resistant to this cleavage protocol (**1q**). This observation suggested that this new copper mediated deallylation may have use in selective deprotection strategies for peptide chemistry. As proof of concept, dipeptide **4** bearing both an *N*-terminal alloc group and an *O*-allyl tyrosine residue was subjected to the cleavage conditions (Scheme 2). Whilst the cleavage reaction requires further optimisation, it was pleasing to observe that treatment with the CuI-B_2pin_2 combination selectively cleaved

Table 2 Substrate scope



Yields quoted represent that of purified isolated products; d.n.r. = did not react; a) after 26 h with coelution of PPh_3; b) after 5 h; c) after oxidation to remove boron impurities

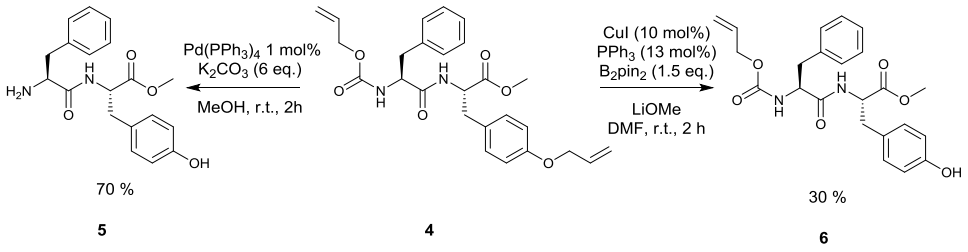
the tyrosine allyl ether. In contrast, treatment of the same dipeptide with Pd resulted in cleavage of the *N*-alloc group after 30 minutes, followed by subsequent deprotection of the *O*-allyl ether after 2 h reaction time.

Mechanistic considerations

The mechanism of this transformation remains an ongoing question. Similar copper boryl reagent combinations to those described in this report have been shown to promote a diverse array of transformations, including the hydroboration of alkenes and alkynes,[12-16] the borylation of aldehydes and imines, β-borylation of α,β-unsaturated carbonyl compounds[13, 17-21] and a variety of C-X borylations to generate aryl, alkyl and allyl boronates.[11, 22-28] Of these, the current reaction has closest parallels with the last of these transformations for which an S_N2' type displacement is commonly invoked.[29] In line with this, GCMS analysis of the crude reaction mixture reveals the presence of a signal with *m/z* = 168 corresponding to the formation of allyl-Bpin as a byproduct. In a series of elegant studies,[24, 29-33] Ito has provided compelling evidence for Cu-Bpin complexes adding to alkenes to afford η^1-Cu alkyl complexes which in this case would then undergo fragmentation to generate the observed phenoxide and allyl-Bpin. Alternatively, McQuade and coworkers using electron poor allyl aryl ethers as the leaving group in combination with a chiral copper-NHC/B_2pin_2 system to generate chiral allyl boronates proposed formation of an η^3-complex between copper and the allylic system.[34] In all these possibilities the observed regiochemistry of copper-boryl addition differs to that of copper catalysed hydroboration[18] and it may be that the heteroatom co-ordinates to the copper directing it towards the carbon closest to the oxygen thus facilitating elimination.[35] In some cases, small amounts of the alternative 'hydroboration' regiochemistry could be detected, presumably arising from protodemetallation of the corresponding B-boryl copper which cannot undergo fragmentation. However, the possibility of competing hydroboration using HBpin generated during the reaction cannot be completely discounted.[16] Whilst these pathways are consistent with the observation of higher reactivity of electron deficient aryl arenes compared with their more electron rich analogues, the lower reactivity of other allyl derivatives with better leaving groups (lower pKa), notably carboxylate, would suggest otherwise.

A final possibility is that the reaction occurs by a single electron transfer (SET) process. The observed selectivities are paralleled by those obtained for the reductive cleavage of allyl ethers using a SmI_2/water/amine reagent combination[36] in which alkyl allyl ethers reacted more slowly than their aryl counterparts and N-allyl amines were not cleaved. Moreover, as with **1g** (Table 2), a terminal methyl substituent prevented the reaction from occurring. However, counter to this proposal, our attempts to inhibit the reaction by the addition of radical scavengers (cyclohexadiene or dihydroanthracene) had no effect on the reaction of fluorophenyl ether **1a**.

3. Conclusions



Scheme 2 Selective removal of an allyl ether in the presence of an alloc protected amine

Copper boryl complexes provide a new approach for the cleavage of allyl ethers and related functional groups. The reaction proceeds under mild conditions, giving the deprotected products in good to moderate yields and presents a simple alternative to existing methods, avoiding the use of expensive palladium group metal catalysts. Furthermore, aryl allyl ethers can be selectively cleaved in the presence of *N*-alloc protected

aliphatic amines, providing an opportunity for orthogonal deprotection strategies.

4. Acknowledgments

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37. *Typical procedure for deallylation experiments*: To a round bottomed flask/microwave vial containing a magnetic stirrer bar was added CuI (0.1 eq.), PPh_3 (0.13 eq.), LiOMe (2 eq.) and B_2pin_2 (1.5 eq.). The vessel was capped and via syringe was added a solution of the allyl ether (1 mmol, 1 eq.) in anhydrous DMF (0.5 M). The reaction mixture was left to stir at room temperature (1.5 – 6 h). After completion, the crude mixture was diluted with EtOAc and filtered through Celite®, washing with EtOAc. The filtrate was washed 3 times with water and once with brine then dried over magnesium sulfate and concentrated *in vacuo*. The crude mixture was purified by column chromatography (ethyl acetate:hexanes) to give the desired product, spectroscopically identical in all respects with an authentic sample. In some cases, coelution of boron containing impurities with the products was observed; in these cases oxidation of the crude reaction mixture with oxone facilitated purification.