Masked allylic zinc reagents

Philip Jones, Nicolas Millot and Paul Knochel*

Fachbereich Chemie der Universität, Hans-Meerwein Strasse, D-35032 Marburg, Germany.
*E-mail: knochel@ps1515.chemie.uni-marburg.de*

The preparation of allylic zinc reagents using the fragmentation of sterically hindered tertiary homoallylic alcohols is described

The development and use of allylic organometallic reagents in synthesis has been an underlying theme of modern organic synthesis.[1,2] Despite the plethora of methods currently available for the introduction of allylic moieties into complex molecules several problems remain, most notably that of cross contamination of the product with the Wurtz coupling adduct. Secondly, there are the problems associated with generating stoichiometric amounts of inorganic salts and thirdly, the functionally group tolerance of the reagent due to the highly polar nature of most carbon–metal bonds.

There are several reports in the literature that the addition of allylic organometallics to electrophiles is reversible;[3–6] in particular one report by Miginiac has inspired us.[5a] Therefore it was rationalised that generation of a zinc alkoxide of a sterically hindered tertiary allyl alcohol would result in decomposition to the parent ketone and an allyl zinc reagent, which in the presence of a suitable electrophile could be utilised synthetically. Recently, Nokami has described a related allyl transfer reaction of homoallylic alcohols catalysed by tin(II) triflate which has caused us to disclose our results.[7]

Accordingly a series of tertiary homallylic alcohols **1a,b** were prepared. Treatment of the tertiary alcohol bearing two isopropyl groups **1a** first with Bu[n]Li and then with zinc bromide gave the zinc alkoxide. At room temperature no migration of the allyl group was observed in the presence of benzaldehyde, but after heating at reflux for 6 h the benzylic alcohol **2** could be isolated in 70% yield (Scheme 1). Clearly, as hypothesised the zinc alkoxide had fragmented *in situ* to give an allyl zinc reagent. The reaction could be improved by the addition of a polar co-solvent; after 6 h in a THF–HMPA mixture 98% of the secondary alcohol **2** was observed. Increasing the steric congestion around the zinc alkoxide also resulted in a faster reaction; by using two *tert*-butyl groups **1b** the migration was complete within 1 h at room temperature, resulting in 89% isolated yield of the secondary alcohol **2**.† In both cases, control experiments with lithium and magnesium alkoxides in the absence of zinc salts showed no migration of the allyl group.

Inspired by this reaction the compatibility of these reagents with a range of aldehydes and ketones was investigated (Table 1). Treatment of the zinc alkoxide with heptanal gave dec-1-en-4-ol in 83% yield (entry 1), whilst an α,β-unsaturated aldehyde was also tolerated (entry 2), giving exclusively the 1,2-addition product in 84% yield. In a similar manner, aldehydes bearing an
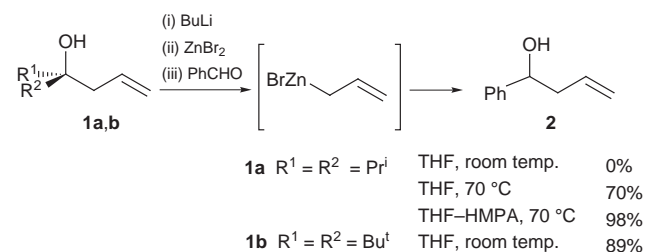
α-substituent reacted well, within 2 h at room temperature, to give the desired allylated product in good yields (entries 3 and 4). Transfer of the allyl group to a ketone required slightly longer reaction times, the reaction usually taking between 2 and 4 h at room temperature to go to completion. Reaction with cyclohexanone gave the allylated adduct in 82% (entry 5), while α,β-unsaturated ketones gave the desired products in reasonable yields (entries 6 and 7). α-Tetralone also reacted well to give the desired material in excellent yield (entry 8).
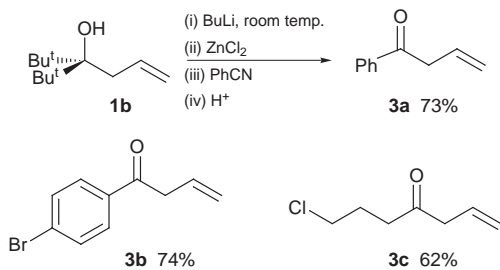
The reaction is not just limited to carbonyl compounds. It was discovered that nitriles also react well to give β,γ-unsaturated ketones in good yields (Scheme 2). Generation of the zinc alkoxide as previously and addition of the nitrile generates the corresponding imine, which upon hydrolysis liberates the ketones **3a–c** in good yield; both aromatic and enolisable nitriles reacted well.

β,γ-Unsaturated amines can also be prepared using these masked organozinc reagents through reaction with imines (Scheme 3). Addition of Bu[n]Li and then zinc chloride to a solution of the tertiary allyl alcohol **1b** in THF generates the
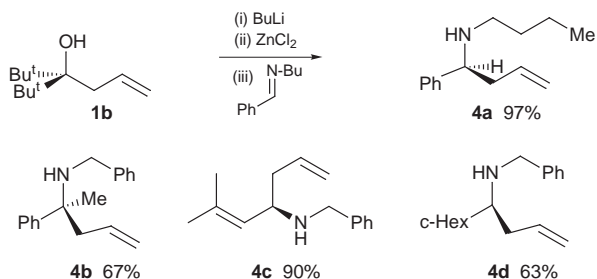
Table 1 Reaction of masked organozinc reagent **1b** with carbonyl compounds

Entry	Electrophile	Product	Yield (%)[a]
1	$C_6H_{13}CHO$	C_6H_{13} — OH	83
2	(prenal) CHO	OH	84
3	cyclohexyl-CHO	OH	82
4	Ph—CHO	Ph — OH	85[b]
5	cyclohexanone O	OH	82
6	enone O	OH	74
7	Ph—enone O	Ph — HO	73
8	α-tetralone O	OH	99

[a] Isolated yield of analytically pure products. [b] 3:1 mixture of *erythro*:*threo* isomers.

|	THF, room temp.	0%
1a R¹ = R² = Pr[i]	THF, 70 °C	70%
	THF–HMPA, 70 °C	98%
1b R¹ = R² = Bu[t]	THF, room temp.	89%

Scheme 1

Scheme 2

Scheme 3

zinc alkoxide that fragments in a retro-allylation reaction to give the allylzinc reagent *in situ*; in turn this reacts with benzylidene-butylamine to give the secondary amine **4a** in 97% yield. Reaction with benzyl(1-phenylethylidene)amine generates **4b** in 67% yield, whilst the α,β-unsaturated imine, benzyl(3-methylbut-2-enylidene)amine, reacts to give amine **4c** in 90% yield. The α-substituted imine benzyl(cyclohexyl)methylene-amine also reacted in 63% yield to give **4d**.

Carbozincation reactions are also possible using this approach with masked organozinc reagents, indeed reaction of the zinc alkoxide with trimethyl(prop-2-ynyloxy)silane at room temperature gives, within 2 h, the 1,4-diene **5** in 74% yield after hydrolysis (Scheme 4).
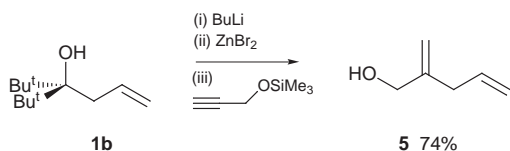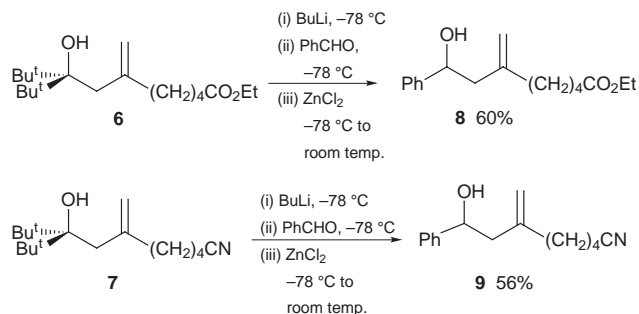
Scheme 4

Although we had eliminated the problems associated with Wurtz coupling, our reagents were not environmentally friendly, generating 1 equiv. of zinc waste; consequently we were delighted to discover that the reaction could be made to function using catalytic amounts of zinc salts—reduction to 50 mol% gave the benzylic alcohol **2** in 95% yield after 6 h, whilst further reductions to 10 mol% gave no loss in efficiency, with the secondary alcohol being isolated in 92%, again within 6 h (Scheme 5). However, all efforts to make the reaction catalytic in base have to date been unsuccessful.

Scheme 5

100 mol% 89%
50 mol% 95%
10 mol% 92%
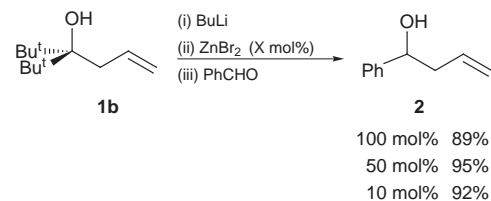
A further advantage with this concept is the ability of these reagents to tolerate functional groups, in a similar manner to other organozinc reagents.[8] The tertiary alcohols **6** and **7** were

Scheme 6

prepared[9] and treated with BuLi, benzaldehyde and zinc chloride at −78 °C, followed by warming the reaction mixture to room temperature. This gave the desired hydroxy ester **8** and hydroxy nitrile **9** in 60 and 56% yields, respectively.

In summary, we have developed a method for the generation of allylic organozinc reagents by exploiting a retro-addition reaction. This method avoids entirely the problem of Wurtz coupling during formation of the organometallic reagent. The reaction is also very general and addition to a range of electrophiles is possible. The mild conditions associated with this reaction also make it compatible with a range of functional groups and finally the reaction has been shown to be catalytic in zinc salts.[10]

Notes and references

† Typical procedure: Preparation of 1-phenylbut-3-en-1-ol **2**: A solution of Bu^{n}Li (2.71 mmol) in pentane (1.40 M, 1.94 ml) was added dropwise over 2 min to a stirred solution of 3-*tert*-butyl-2,2-dimethylhex-5-en-3-ol **1b** (500 mg, 2.71 mmol) in THF (4 ml) at 0 °C under argon. The resulting solution was then stirred for 15 min and a solution of zinc bromide (610 mg, 2.71 mmol) in THF (2 ml) was added, followed by benzaldehyde (275 μl, 2.71 mmol). The reaction was allowed to warm to room temperature and stirred for 1 h. Saturated aq. NH$_4$Cl solution (15 ml) was added and the resulting mixture was extracted with Et$_2$O (3 × 15 ml). The combined organic extracts were washed with brine (10 ml), dried and concentrated under reduced pressure to give a crude residue, which was purified by column chromatography on silica using 15% Et$_2$O–hexanes as eluent to give the desired alcohol **2** (356 mg, 89%) as a colourless oil.

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9 These reagents were prepared from 3-*tert*-butyl-2,2,5-trimethylhex-5-en-3-ol by NBS allylic bromination and displacement with the appropriate zinc-copper reagent (ref. 11).
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