



Metal mediated solvent free synthesis of homoallylic alcohols

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In, Bi, Cu and Zn metals mediate the allylation of various carbonyl compounds under solvent free conditions. Controlling the exothermic nature of these reactions, to prevent decomposition of starting materials, results in good to excellent yields of the corresponding homoallylic alcohols.

Introduction

Developing more benign synthetic procedures in chemical synthesis is important in moving towards sustainable technologies, as part of the rapidly emerging field of green chemistry.¹ In reducing the amount of waste, energy usage, and the use of volatile, toxic and flammable solvents, several approaches are available including avoiding the use of organic solvents for the reaction media.¹ Replacement media include non-volatile and recyclable ionic liquids,² H₂O,³ supercritical CO₂,⁴ polyethylene and polypropylene glycol.⁵ An alternative approach avoids the use of a reaction medium as the so-called 'solvent free' or 'solventless' reaction.^{6,7}

There are several advantages associated with the use of a solvent free system over the use of organic solvent. These include; (i) there is no reaction media to collect, dispose of or purify and recycle, (ii) on a laboratory, preparative scale, there is often no need for specialised equipment, (iii) extensive and expensive purification procedures such as chromatography can often be avoided due to the formation of sufficiently pure compounds, (iv) greater selectivity is often observed, (v) reaction times can be rapid, often with increased yields and lower energy usage,^{6,7} and (vi) economic considerations, since cost savings can be associated with the lack of solvents requiring disposal or recycling. Not surprisingly solvent free synthesis has recently drawn attention from the wider synthetic community. Reactions epitomizing the simplicity, versatility, high yielding and selective nature of solvent free systems include: aldol condensations,⁸ sequential aldol and Michael additions,⁹ Stobbe condensations,¹⁰ *O*-silylation of alcohols with silyl chlorides¹¹ and clay catalysed syntheses of trans-chalcones.¹²

A potential criticism of the solvent free approach, which are inhibiting its widespread introduction into routine synthesis, is the possibility of producing 'hot spots', which can lead to runaway reactions and consequently the increased likelihood of unwanted side reactions.⁵ Thus, measurement of heat of reaction in solvent free systems is important, as is effective heat dissipation. If highly exothermic reactions are identified, which are otherwise suited to solventless conditions, the problem could be addressed through advanced reactor design.⁶

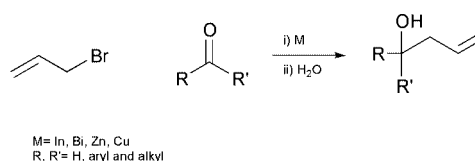
Recently, considerable attention has been given to the development of Barbier–Grignard type reactions in aqueous media using In, Zn and Sn.^{3,13,14} Although these reactions can be classed as environmentally benign, the utilisation of aqueous media places several limitations on synthesis including; (i) the inability to carry out moisture sensitive processes such as the allylation of imines and commonly used reagents which are

inherently moisture sensitive,¹⁵ such as lithium amides and Grignard reagents, and (ii) the requirement of acidic or ultrasonic activators to produce significant yields when using mediators having a high disposition to form oxides on their surface such as Mg.¹⁶

Herein, we explore Barbier–Grignard type reactions under solvent free conditions, monitoring their exothermic behaviour and seeking controlling factors, which can alleviate the generation of excessive heat and the consequent decomposition of starting materials. Our studies involved a solventless, one-pot system employing In, Bi, Zn, and Cu as mediators in the allylation of various carbonyl compounds to give the corresponding homoallylic alcohols, Scheme 1. Traditionally, volatile organic solvents have been used as 'heat sinks'.⁶ Furthermore, we find in these systems the lack of unwanted side products, such as the pinacol and Wurtz coupled compounds.

Experimental

A typical experiment involved the addition of the carbonyl compound (5 mmol) to a suspension of the allyl bromide (7.25



Scheme 1

Green Context

The simplification of reaction protocols, minimising the use of auxiliaries, is an important paradigm in green chemistry. Working without solvent gives the potential for a simpler process, smaller plants, and reduces a major source of VOCs, eliminates the energy costs of removal, recycling and eventual disposal of waste solvent. However, the role of the solvent must be taken into account, and thus it is important to control mixing and exotherms if an acceptable process is to be achieved. The work here demonstrates that this is indeed possible for coupling reactions using a series of metals. Thus, the formation of homoallylic alcohols can be achieved under solventless conditions. *DJM*

mmol) and the commercially available metal powder (5 mmol) in a sealed, 50 ml, round-bottomed flask. The mixture was allowed to react *via* rapid stirring or sonication, at or below room temperature, before quenching with water (*ca.* 0.5 ml). Specific conditions and yields are given in Tables 1 and 2.

Results and discussion

A major consideration in choosing a reactive metal as a mediator in allylation reactions has been its first ionization potential (1st IP), more specifically their similarity to the most reactive alkali metals (Li = 5.39, Na = 5.14) and Mg (= 7.65). The assumption is that greater reactivity can arise from low electron transfer energies and thus higher yields will result from metals with low 1st IPs.¹⁷ Metal mediators investigated herein all have relatively low 1st IPs, (Table 1)¹⁸ in principle favouring single electron transfer (SET) processes in these reactions, (Scheme 2) and it was expected that the reactivity and subsequent yields of the various mediators would closely adhere to trends in the 1st IPs. Surprisingly this was not the case. Those with the highest 1st IPs, notably Zn, required the reaction to be performed at 0 °C to prevent the decomposition of the starting materials, whereas In, with its relatively low 1st IP, produced no such decomposition when reactions were carried out at room temperature, so long as quenching was performed within 3 h of initiation. By varying reaction conditions, (Table 1) for all the

Table 1 First ionization potentials (1st IP) and reactions conditions for In, Bi, Cu and Zn¹⁸

Metal	1st IP/eV	Reaction conditions
In	5.70	Required quenching within 3 h
Bi	5.28	Kept at or below room temperature for 3 h before quenching
Cu	7.73	Sonicated for 24 h before quenching
Zn	9.39	Kept on ice for 3 h before quenching

Table 2 Isolated yields for allylation reactions of various carbonyl compounds in the presence of In, Bi, Cu or Zn

Carbonyl compound	Metal	Allylbromide: aldehyde/ketone: metal ratio	Yield ^a (%)
PhCHO	In	1.5:1:1	97
PhCHO	Bi	1.5:1:1	94
PhCHO	Cu	1.5:1:1	0
PhCHO	Zn	1.5:1:1	80
2-HOC ₆ H ₄ CHO	In	1.5:1:1	92
2-HOC ₆ H ₄ CHO	Bi	1.5:1:1	81
2-HOC ₆ H ₄ CHO	Zn	1.5:1:1	68
2-MeOC ₆ H ₄ CHO	In	1.5:1:1	78
2-MeOC ₆ H ₄ CHO	Bi	1.5:1:1	0
4-MeOC ₆ H ₄ CHO	Bi	1.5:1:1	0
4-MeOC ₆ H ₄ CHO	Bi	1.5:1:1	Decomposition ^b
2-MeOC ₆ H ₄ CHO	Zn	1.5:1:1	56
PhCH=CHCHO	In	1.5:1:1	86
PhCH=CHCHO	Bi	1.5:1:1	15
PhCH=CHCHO	Zn	1.5:1:1	51
MeCHO	In	1.5:1:1	33
Ph(Me)C=O	In	1.5:1:1	67 ^c
Ph(Me)C=O	In	2:1:1.5	85
MeCOCH ₂ COMe	In	2:1:1.5	28 ^d
Ph ₂ C=O	In	2:1:1.5	0
Me ₂ C=O	In	2:1:1.5	0
Ph(Me)C=O	Bi	2:1:1.5	0
Ph(Me)C=O	Bi/In (95/5)	2:1:1	<10 ^c
Ph(Me)C=O	Zn	1.5:1:1	17
Ph(Me)C=O	Cu	1.5:1:1	0

^a All products gave satisfactory IR, ¹H NMR and GC. ^b Reaction performed at room temperature ^c Estimated by ¹H NMR and GC. ^d MeCOCH₂C-Me(OH)CH₂CH=CH₂ only; estimated by ¹H NMR and GC/MS.

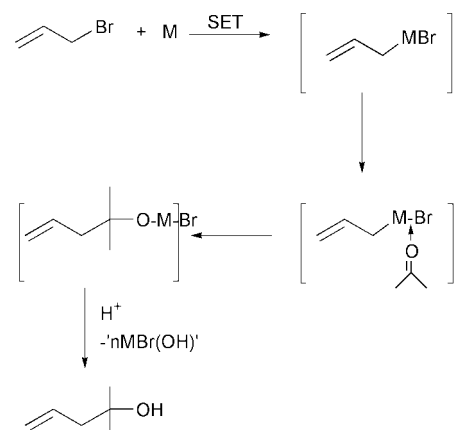
metals, decomposition of starting materials previously observed in solvent free systems in the cases of In and Zn was prevented.¹⁹

These findings suggest that the ability of a metal to mediate the allylation of carbonyl species is not solely governed by the ability of the metal to participate in SET processes, as previously postulated.⁹ Rather the success of the mediators (judged by the reaction time and subsequent yield) may be also determined by; (i) the ease with which the metal inserts into a C–X bond and its predisposition, or lack thereof, to form a C–M bond in generating the intermediate **1**, (ii) the formation of the alkoxide species **2** and bond energy considerations of the transition from M–C to M–O bonds, and (iii) the dependency of the rate of quenching of the enolate M–O bond strength.

Careful control of the exothermic allylations of the carbonyl compounds studied resulted in good to excellent yields of the target allylic alcohol, (Table 2). Bi metal gave good yields for aromatic aldehydes (80–94%), which are comparable to those produced in equivalent reactions performed in a solvent.²⁰ However, in the case of –OMe substituted aromatic and aliphatic aldehydes little to no homoallylic alcohol was obtained. These observations can be rationalized by the nature of the R groups of the aldehydes. The aliphatic and *para*-OMe groups are known electron-donating groups, whilst the relatively weak electronegative nature of the *ortho*-OMe prevents attack because of its inability to stabilize the carbonyl group *via* hydrogen bonding and also steric hindrance. Another important observation was that when the allylation of the –OMe substituted aromatic aldehydes was repeated at room temperature, the decomposition of starting materials still occurred, indicating that the exothermic nature of these systems is largely attributed to the insertion of the metal into the C–X bond. In the case of acetophenone little or no homoallylic alcohol was produced even in the presence of a catalytic amount of In (5%), as has been observed for *in situ* reactions performed in DMF.²⁰ This can be related to the reduced reactivity of the carbonyl groups of ketones.

With its relatively low 1st IP, Cu was expected to result in the formation of allylic alcohols with relative ease. However, the allylic copper intermediate was not observed in these reactions, even with sonication. Thus more forcing conditions are necessary, such as generating an allylic copper species *via* allyl Grignard reagent and CuI,²¹ to counteract the relatively noble character of metallic copper, with a full sub-shell of d orbitals involved in metallic bonding.²² Nevertheless, our observation further supports the formation of an M–C organometallic intermediate as an important factor in such reactions.

With Zn acting as the mediator, no acidic, ultrasonic or Zn/Cu couple system was required to activate the metal powder. This contrasts with previous allylations utilising Zn, which were performed in organic solvents other than THF.²³ Once the



Scheme 2 † Variable/unknown oxidation states.

decomposition of starting materials was alleviated, by carrying out the reaction at *ca.* 0 °C, high yields were obtained. Indeed, yields in the range from 50–80% were achieved for both aliphatic and aromatic aldehydes, whilst evidence of the allylic alcohol, generated from acetophenone was also noted.

With In metal, excellent yields were obtained for both aliphatic and aromatic aldehydes (85–97%). In the case of acetophenone yields were improved, by *ca.* 20%, by increasing the ratio of allyl bromide and In to the ketone. Decreased yields were observed for the diketone, acetylacetone, with the monoallylation product resulting. This indicates the presence of a larger excess of allyl bromide and In may be required to produce the di-substituted ketone, with only 1.5 equivalents of the allylic In species being generated *in situ*. Reactions involving ketones with bulky substituents, such as benzophenone and di-isopropyl ketones did not produce the corresponding homoallylic alcohols, indicating steric hindrance prevents attack of the carbonyl group. A noteworthy observation is that there was no evidence of the possible side products such as the pinacol or Wurtz coupling.

Successfully controlling the exothermic nature of the allylation of carbonyl compounds makes the solvent free approach to the synthesis of homoallylic alcohols a viable synthetic procedure. Although, the nature of the allylic metallic species is not clear at this stage, we assume its ability to be generated is a crucial factor in determining the suitability for metals in such reactions. Investigations into the characteristics of such intermediates and the development of solvent free protocol for air- and moisture-sensitive procedures are currently in progress.

Acknowledgments

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