Chemo and enantioselective addition of grignard reagents to ketones and enolizable ketimines
Ortiz, Pablo

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 9:
Perspective: Overcoming the Limitations of Organometallic Reagents in 1,2-Addition Reactions
Several times throughout this thesis it has been emphasized the suitability of Grignard reagents as the ideal organometallics for 1,2 asymmetric addition to ketones and imines, and the claim can be further extended to 1,4 addition as well.[1] Their attractiveness derives from being commercially available or easy to prepare, safe to handle and economical, both in monetary and chemical terms (they transfer all the groups, contrary to organozinc or organoaluminium reagents). However, the use of these and other organometallics has some associated disadvantages: they require the use of dry atmosphere and solvents, often low temperatures for catalysis are needed and the functional group tolerance is limited (Scheme 1, a). The use of organometallics generated in situ could circumvent these problems, and a good example is a recent report on the chemoselective reaction of organolithium reagents using submillisecond mixing time in a chip reactor.[2] The set-up is innovative, but the concept of in situ formation of organometallic reagents is not new. In fact, Victor Grignard’s discovery was to split the reaction developed by his mentor, Philippe Barbier (Scheme 1, b).

**Scheme 1.** Grignard and Barbier-type reactions with carbonyl electrophiles.

In the latter, an organic halide reacts with a carbonyl electrophile in the presence of a metal (Mg, Al, Al, Zn, In and Sm among others) or their salts, via an organometallic formed in situ. Barbier-type chemistry can be carried out in aqueous media,[3] but there are important limitations in this chemistry, mainly the need of activated substrates: carbonyl electrophiles are generally aldehydes with few examples of ketones and the halides are typically allyl halides (Scheme 1, b). In contrast, pre-forming the Grignard reagent and performing the addition in a
separate step allows the use of less activated and broader set of substrates (Scheme 1, a). Only recently progress has been made in the use of more challenging alkyl and aryl halides for Barbier-type reaction, as reported by Li (Scheme 2, a).[4]

Arguably, the most appealing feature of Barbier-type reactions is the possibility of carrying them out in water. There is a growing interest in the chemical community on the possibility of using organometallic reagents in uncommon solvents, such as deep eutectic solvents, ionic liquids and water.[5] In this regard, one of the most impressive implementations of this concept was reported recently. García-Álvarez, Hevia et al. showed that chemoselective addition of organolithium and Grignard reagents to ketones in air and at room temperature is possible using deep eutectic solvents (DES) (Scheme 2, b).[6] According to the authors, the observed remarkable chemoselectivity can be rationalized by the formation of an halide-rich magnesiate from the quaternary ammonium salt, which have been previously shown to enhance the chemoselectivity in the addition to ketones.[7]

Scheme 2. Use of organometallics in uncommon solvents.

Often, when organic chemistry is claimed to be done in water, is actually on water, as the organic compounds do not dissolve in it and the reaction takes place on the surface.[8] In order to enhance the formation of two phases and compartmentalization of the organic compounds the formation of micelles can be sought.[9] In fact, in Li’s report on the Barbier-type arylation of aryl iodides in water Brij10 is used, which is an amphiphilic polyoxoethylene (Scheme 2, a). We reasoned
that if a Barbier-Grignard type reaction would take place, the more reactive organometallic formed in situ (organomagnesium instead of organozinc) might be able to attack an (activated) ketone (Table 1). First, we tested if the in situ formation of the Grignard reagent took place under typical anhydrous conditions (dry atmosphere and solvents). We found full conversion to the addition product (Table 1, entry 1) so the next step was to use solvent from the can (containing some water) and have the reaction done in open air. In this case there was no conversion at all, which can be attributed indeed to the presence of water from the solvent and the atmosphere (Table 1, entry 2). We envisioned adding a surfactant to help separating the water from the organic phase, and for that purpose BrijC10 was used. In addition, a more reactive isopropyl bromide was used in this case, although the increased steric hindrance could be a problem. To our disappointment, no conversion was observed. As sonication has been shown to promote the addition in “wet” Et\(\text{O}\), it was tried in the next reaction, together with warming up to speed up a possible formation of the Grignard reagent. Regrettably, once again only starting material was recovered (Table 1, entry 4).

**Table 1. Attempts for Barbier-Grignard type reaction.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R(^1)</th>
<th>R</th>
<th>Surfactant</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Conv. (%)[^{[a]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^{[b]}]</td>
<td>Me</td>
<td>Et</td>
<td>-</td>
<td>Et(\text{O}) (dry)</td>
<td>r.t.</td>
<td>full</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Et</td>
<td>-</td>
<td>Et(\text{O}) (non-dry)</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>iPr</td>
<td>BrijC10 (5%)</td>
<td>Et(\text{O}) (non-dry)</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>4[^{[d]}]</td>
<td>Me</td>
<td>iPr</td>
<td>BrijC10 (5%)</td>
<td>Et(\text{O}) (non-dry)</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>iPr</td>
<td>BrijC10 (5%)</td>
<td>H(\text{O})</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>6[^{[e]}]</td>
<td>Me</td>
<td>iPr</td>
<td>BrijC10 (5%)</td>
<td>Et(\text{O})/H(\text{O})</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>nBu</td>
<td>TPGS-750-M (2%)</td>
<td>H(\text{O})</td>
<td>r.t.</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: Carbonyl compound (0.1 mmol), 0.1 M. The reactions were carried out in open atmosphere. \[^{[a]}\] Conversion was measured by \(^1\)HNMR and GC-MS. \[^{[b]}\] Inert atmosphere (N\(_2\)) was used. \[^{[c]}\] The sample was sonicated for 60 minutes. Brij10 = Polyethylene glycol hexadecyl ether. TPGS-750-M = polyoxyethanyl-\(\alpha\)-tocopheryl succinate.

The surfactant was also tried directly in water, as reported in the original paper,\[^{[4b]}\] Neither in this case nor with a mixture of Et\(\text{O}\) and water conversion to the addition...
product was observed (Table 1, entries 5 and 6). Finally, a slightly different conditions were tried, based on a report by Lipshutz et al.[11] They could perform conjugate additions to enones with in situ generated copper reagents in water, using TPGS-750-M as a surfactant. We tried it for the addition to an aldehyde in this case, to be sure that the lower reactivity of a ketone compared to an aldehyde was not the problem of the set-up. Recovering the starting material supported our assumption that the organometallic reagent was not forming in our case (Table 1, entry 7). Some other less systematic experiments were also carried out with the aim of in situ forming organolithium or organocopper reagents in water and subsequent attack to an electrophile, but they invariably failed (not shown). Not seeing a hint, the project was abandoned. But the idea of overcoming the limitations of organometallic reagents did not vanish from my mind.

A more direct approach for the in situ formation and consecutive trapping of the organometallic formed is to perform a hydrometalation of alkenes/alkynes (Scheme 3, a). This has been elegantly shown by Fletcher et al. in the hydrozirconation of alkenes and subsequent asymmetric 1,4 addition to enones (Scheme 3, b).[12] However, although this methodology allows the reaction to be carried out at room temperature the other limitations typical of organometallic reagents (i.e. inert atmosphere and low functional group tolerance) remain. Moreover, an equimolar amount of Cp₂ZrHCl is needed. A greater step forward has come from the Buchwald group: they had developed an efficient catalytic asymmetric hydroamination of alkenes and alkynes catalyzed by Cu-H (Scheme 3, c).[13] The initial procedure required strict inert atmosphere conditions and the reaction had to be set up in the globe-box, but further optimization allowed it to carry out in open air, by pre-making the copper complex.[14] At this stage it attracted our attention as a viable method and we reasoned that the organocupper intermediate, instead of reacting with the amine, could be made to react with a carbon electrophile. We envisioned an asymmetric allylic substitution as a feasible catalytic cycle (Scheme 3, d) but when put into practice no addition product was observed. Few days after we started with the experiments a report on the same concept was disclosed by Buchwald et al.[15] After that report the catalytic asymmetric addition of alkene derived nucleophiles to ketones[16] and aldimines[17] was reported by the same group. Regrettably, all these carbon-carbon bond forming reactions are carried out now under inert atmosphere, in the globe box. Despite this drawback, the methodology developed by Buchwald represent a big step forward: alkenes can be
used as pronucleophiles, reactions are run at room temperature and functional group tolerance is good. Hopefully, future developments of this chemistry will remove the need of inert atmosphere and make it a more powerful tool.

a) Hydrometallation of alkenes/alkynes

\[
\text{R=CH} \quad \xrightarrow{\text{H-M}} \quad \text{R=CH} \quad \xrightarrow{\text{E}^+} \quad \text{R=E}
\]

b) Hydrozirconation of alkenes followed by ACA (Fletcher)

\[
\text{R=CH} \quad \xrightarrow{\text{Cp}_2\text{ZrHCl}} \quad \text{R=ZrCp}_2\text{Cl} \quad \xrightarrow{\text{Cu(I) L}^*} \quad \text{R=CH} \quad \xrightarrow{\text{Bn}_2\text{N}-\text{OBz}} \quad \text{R=CH}
\]

L* = (S)-DTBM-SEGPHOS

d) Idea for catalytic asymmetric hydroallylation of vinylarenes

\[
\text{(EtO)}_2\text{MeSiOBz} \quad \xrightarrow{\text{L}^*\text{CuH}} \quad \text{Ph=CH} \quad \xrightarrow{\text{CuL}^*} \quad \text{Ph=CH} \quad \xrightarrow{\text{CuOBz}} \quad \text{Ph=CH}
\]

Scheme 3. Hydrometallation of alkenes/alkynes and subsequent asymmetric additions. M = Metal. L* = Chiral ligand

The final goal of overcoming the limitations associated with organometallic reagents (water and oxygen free atmosphere, low temperatures and limited functional group tolerance) is to make their applicability broader. These restrictions
can be bothersome in a university lab, but truly limiting in industry. In this regard, one of the most interesting findings of this thesis was the compatibility of using substrates containing functional groups (vinyl, ester and cyano) in the Grignard addition to enolizable imines (Chapter 7). The presence of alcohols, acids or free amines in the substrate is a bigger challenge due to the negative charge that is formed after the excess Grignard reagents deprotonates them. Moreover, free amines and acids have low solubility in organic solvents commonly used in this chemistry. Having said that, I foresee that this will be possible in the future. Following on the topic of the addition of Grignard reagents to enolizable imines, I see it as a major advance. Not yet as an enabling technology, because in industry Ellman’s chiral auxiliary will still be preferred, but as a door opening for performing catalytic asymmetric addition to enolizable imines.

It should not be forgotten that in most university labs basic research is carried out, which is not immediately applicable to the industry settings. Fundamental research, contrary to applied research, is plagued with dead ends and failures but also with unexpected outcomes and surprises. Hence, I believe that scientific research should not be constrained to production of “useful” results. In the case of synthetic organic chemistry, the usefulness is considered developing methods, reactions and protocols related to industrially relevant molecules. Science should also pursue pure knowledge and understanding, explore unmapped areas, test how far can we go. Although the results from this type of research are generally not directly applicable, the findings can have an unforeseen application in the future. It happened with Marie Curie’s discovery of radium to cite a famous example, but I have witnessed myself one of this cases, which I find very illustrative. The products of the asymmetric addition of Grignard reagents to acylsilanes\(^{[18]}\) (Chapter 1) were described by the main author as “completely useless”, when asked about their application. He was probably right in the sense that they will not be incorporated into drug candidates. Nevertheless, beautiful chemistry has derived from those products (Chapters 3 and 4). But what could truly not be anticipated is that the use of a Lewis acid mixture to prevent reduction of the acylsilanes would start a whole new line of research in our group as a way of activating otherwise inert substrates\(^{[19]}\).
References


References


