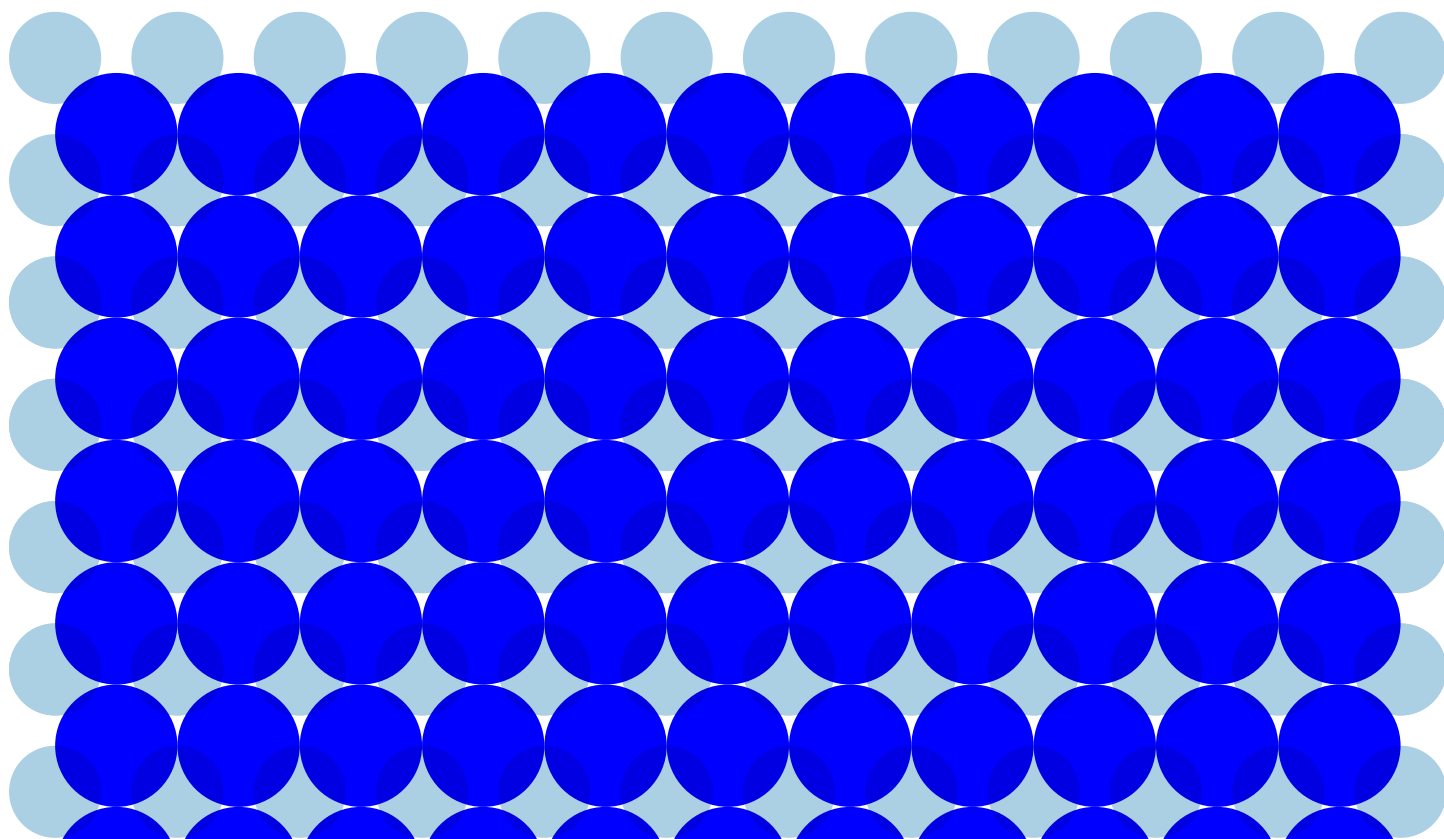


Would you dare to handle timeless and reactive Grignard nucleophiles to react them with diketene?

Dr. Katarzyna Palica, Dr. Leonardo Kleebauer,
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Have you ever considered making a Grignard reaction on a large scale, or truncated your synthesis by using it? This carbon-carbon bond formation methodology often relies on elevated temperature near the solvent's boiling point, hence requiring careful monitoring to avoid reactants building up due to a delayed initiation. Moreover, when reacting the Grignard species with instable electrophiles like diketene, extra measures are necessary when it comes to safety and undesired water. This elegant reaction between diketene and Grignard reagents necessitates the ability to fine-tune reaction conditions together with a careful control to avoid side reactions, experience in scaling-up, and of course, backward integration to access the needed diketene.

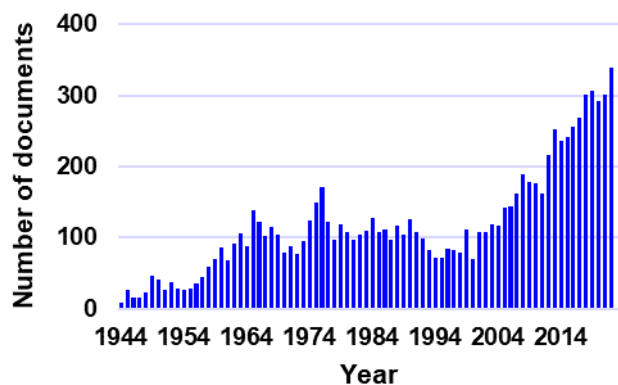


Would you dare to handle timeless and reactive Grignard nucleophiles to react them with diketene?

Combining the handling of Grignard reagents and diketene requires expertise into two different but quite specific fields, ultimately leading to the introduction of a 3-methylenepropanoic acid moiety onto carbon nucleophilic species. Arxada CDMO is proud to stand out as one manufacturer able to handle both for creating carbon-carbon bonds. The on-site backward integration provides the otherwise not transportable diketene, while years of expertise can unlock challenging Grignard's chemistry.

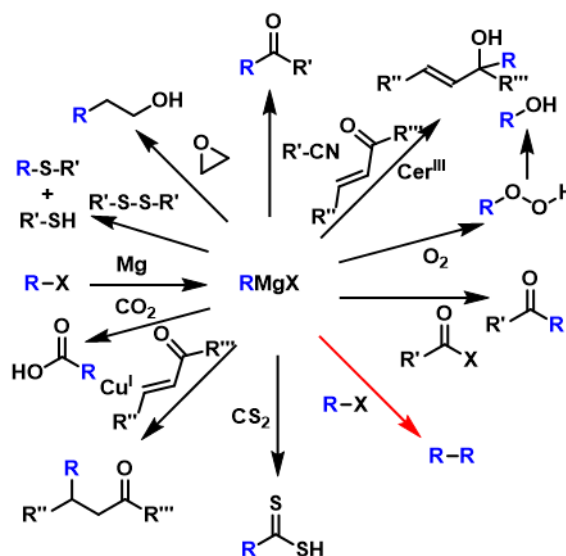
Over the last vicennium, the number of patents per year mentioning the Grignard reaction has continuously increased, from 26 in 1945 to 339 in 2022 (Figure 1).¹

Figure 1. Trend of the Grignard reaction related patents.



This increase shows a raising interest into Grignard reactions, as already highlighted in 1910 when its “creator” was awarded a Nobel prize, 12 years after describing his discoveries.² Since Dr. Grignard was among the pioneers in employing nucleophilic carbon species as reactants, instead of the more commonly utilized electrophilic carbon species, it held a distinctive position.³ Ultimately, the power of the Grignard's methodology lies in the uniqueness of the carbon based reagents to form carbon-carbon bonds, unlocking access to various motifs (Figure 2).

Figure 2. Broad scope of electrophiles reacting with Grignard reagents.



Grignard reagents are organomagnesium compounds that can be seen as reagents bearing a nucleophilic carbon. Their preparation involves metallic magnesium and encounters two main challenges. Firstly, the preparation requires the complete exclusion of water. Secondly, there's a need to minimize side reactions (such as the Wurtz coupling, see Figure 2 in red). Both can be overcome thanks to low reaction temperatures, low halide concentrations, control of the reaction rates, and/or the need for a large surface area of magnesium.

Aside from the Grignard species, similar nucleophilic reagents (ie bearing a nucleophilic carbon) often need to be prepared in advance from an electrophilic carbon functionalities, through a Umpolung-like transformation, for which only a limited number of methods are available.⁴ One could for example cite the Seebach Umpolung approach (Figure 3), the Stetter Reaction (using cyanide as a catalyst), and *N*-heterocyclic carbene (NHC) catalyzed methods.

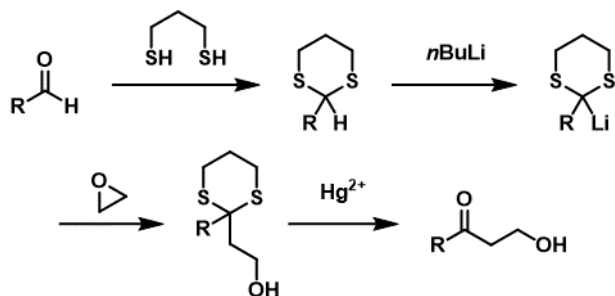
¹ Scifinder search for Grignard patents, performed in September 2023.

² V. Grignard, *Compt. Rend.* **1900**, *130*, 1322.

³ R. M. Peltzer, J. Gauss, O. Eisenstein, M. Cascella, *J. Am. Chem. Soc.* **2020**, *142*, 6, 2984-2994.

⁴ D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239-258; S. Wang, B. König, *Angew. Chem. Int. Ed.* **2021**, *133*, 40, 21792-21802.

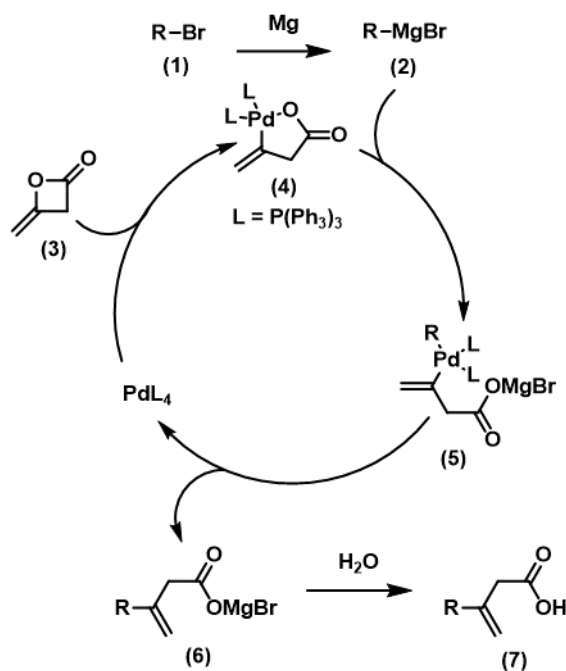
Figure 3. Typical reaction pathway of a Seebach Umpolung reaction.



However, these methods usually require more complex reagents compared to the commonly used magnesium in Grignard reactions, leading to additional synthetic steps, particularly in the case of the Umpolung approach. Furthermore, when considering the range of electrophiles that can react with Grignard reagents, the Stetter reaction is limited to Michael acceptors as reaction partners. In contrast, organometallic Grignard-like reagents exhibit a broader scope of reactivity, allowing them to interact with various electrophiles, including epoxides, ketones, and nitriles, enabling chemists to rapidly synthesize complex organic molecules (Figure 2).

One elegant way to make use of the nucleophilic Grignard versatile reactivity is by reacting them with diketene as an electrophile. While such an electrophilic reactant can be seen as difficult to handle, due to its high reactivity, or challenging to procure, due to its inability to be transported, it afforded a unique opportunity to introduce the 3-methylenepropanoic acid moiety when combined with organomagnesium species, together with a metal catalyst (Figure 4).

Figure 4. Reaction mechanism of palladium catalyzed Grignard reaction of diketene.



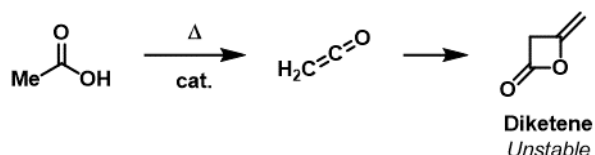
In agreement with the current scientific assumption, the reaction mechanism starts with the oxidative addition of palladium (Pd^0L_4) on diketene (3), to form a palladacycle (4).⁵ This cyclic derivative then reacts with the Grignard reagent (2) to deliver the intermediate (5), via transmetalation. A reductive elimination finally delivers the salt (6), that itself leads to the final carboxylic acid (7) after hydrolysis. It is interesting to note that the palladium catalyst can often be substituted with catalysts based on iron, nickel, or cobalt.⁶ This adaptability makes the reaction flexible, allowing for adjustments tailored to individual applications and required trace profiles.

This unique combination, ie the reaction between a Grignard reagent and diketene together with a metal catalyst, requires the collaboration with a CDMO able to handle both of these reactive species, and a manufacturer able to produce the needed diketene as a starting point (as it cannot be transported). The Visp Arxada's facility presents itself as an ideal partner since a continuous production of diketene is carried out on site, by dehydrating acetic acid (Figure 5). Under strictly controlled conditions, the resulting ketene can then undergo dimerization at room temperature, forming diketene.

⁵ Y. Abe, H. Goto, M. Sato, T. Kato, *Chem. Pharm. Bull.*, **1983**, 31, 3, 1106-1111.

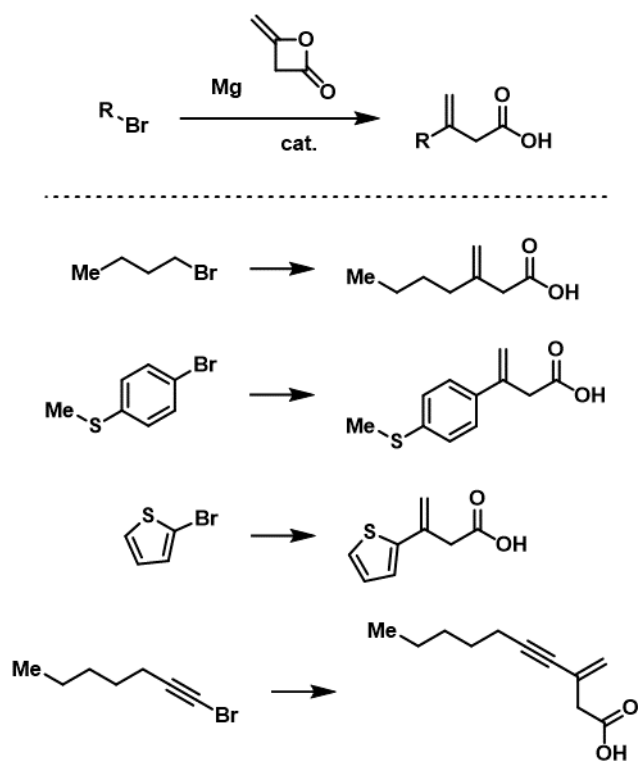
⁶ T. Fujisawa, T. Sato, Y. Gotoh, M. Kawashima, T. Kawara, *Bull. Chem. Soc. Jpn.*, **1982**, 55, 3555-3559.

Figure 5. Diketene formation path.



While quite specific, this metal catalyzed 3-methylenepropanoic acid introduction from a Grignard reagent and diketene, happened to be broad when it comes to the organomagnesium species. Hence, a wide range of substrates with different functional groups can be deployed, including but not limited to, halide- alkanes, aromatics, heterocycles, and alkynes (Figure 6).⁷

Figure 6. Introduction of the 3-methylenepropanoic acid motif on a wide range of reagents via palladium catalyzed Grignard reactions.



To conclude, Arxada CDMO is able to produce both Grignard reagents and diketene, allowing for the formation of carbon-carbon bonds to obtain various derivatives including the 3-methylenepropanoic acid moieties. Despite the specific examples treated in this white paper and extracted from the literature, thanks to versatility of the Grignard reagents that can be used, a person skilled in the art would quickly recognize the broadness of the method, that can be developed to perform into Arxada Visp multi-purpose assets. Last but not least, the 3-methylenepropanoic acid moiety would offer many derivatization opportunities via its alkene or carboxylic acid functions.

⁷ Z. Yao, G. Li, Y. Zhou, D. Xue, *Adv. Synth. Catal.* **2003**, 365, 2, 1615-4150.

In summary, the 3-methylenepropanoic acid motif can be synthesized through Grignard reaction from a diketene stream, up to multi-tons at the Arxada Visp site. The uniqueness of this methodology highlight the need to partner with an experience and backward integrated producer. Finally, these 3-methylenepropanoic acid derivatives also serve as excellent starting materials for subsequent derivatizations.

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Our offer

- Experience in developing and using organometallic species
- Quick introduction of the 3-methylenepropanoic acid moiety
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