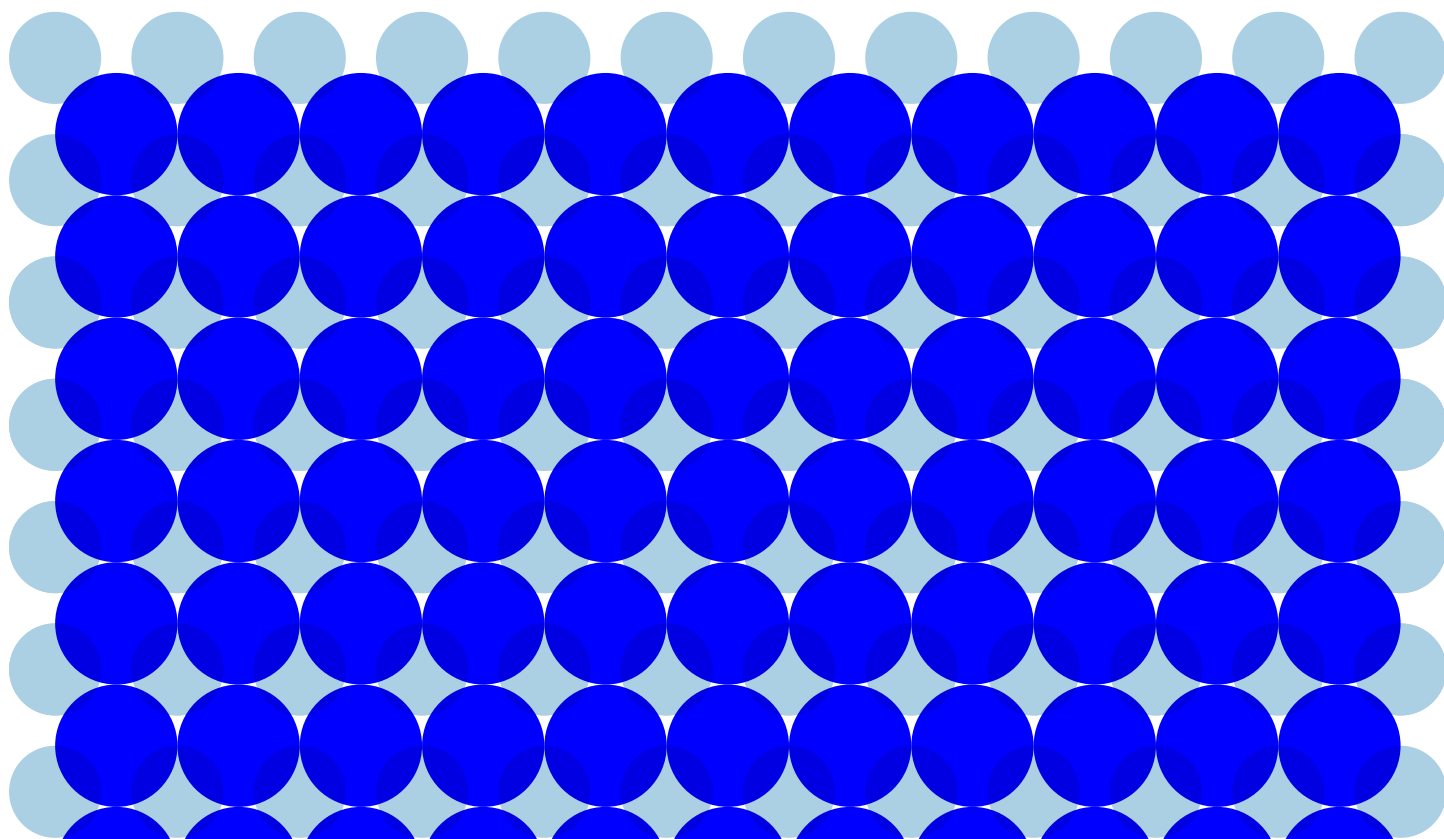


# Sustainable Twist to a Long-Established Process: 'Knocking Out' Copper(I) Chloride in Grignard Reactions

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In line with the May 2023 white paper, this edition is once again tackling sustainability. By aligning its vision and strategy (net zero by 2050), to its expertise, the Arxada team revamped a well-known transformation, the Grignard reaction, which is broadly used in the chemical industry and finds application in various sectors. Ultimately, this novel version of a Grignard reaction can be performed without copper, hence avoiding the formation of toxic wastes.

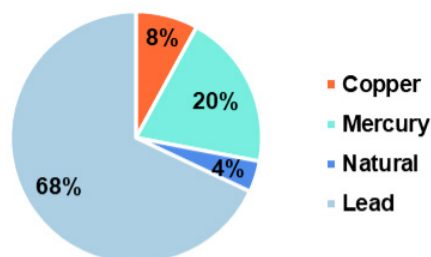


## Sustainable Twist to a Long-Established Process: 'Knocking Out' Copper(I) Chloride in Grignard Reactions

Grignard reactions are widely applied in large-scale chemical processes and often require the use of metal-based catalysts such as copper salts which have a high toxicity for aquatic life with devastating and long-lasting effects. Thus, the avoidance of copper in chemical processes is a sustainable measure to prevent negative impact on aqueous ecosystems. This study demonstrates that carboxylic acid anhydrides can be used as highly selective electrophiles in Grignard reactions to introduce ketone substituents on aromatic compounds. In contrast to acetyl chloride, high selectivity and yields are achievable without addition of copper(I) chloride as catalyst. Performing processes based on Grignard reactions with acid anhydrides as electrophiles can reduce the ecological impact of copper to aquatic life.

Since decades, copper(I) salts are industry-standard catalysts and reagents to facilitate and increase the selectivity in organic reactions.<sup>1</sup> In most cases, the copper catalysts form species involving a copper-carbon bond, which acts as a nucleophile reacting with an electrophilic center. However, the use of copper(I) salts in large-scale industrial processes is accompanied by very high cost and exhibit high toxicity towards aquatic life with devastating and persistent consequences.<sup>2</sup> Previous reports indicated that only 4% of heavy metal influx in the oceans are of natural origin, whilst copper has the third largest share of man-made heavy metal pollution, after lead and mercury (Figure 1).<sup>3</sup>

Figure 1. Graphical illustration of the major heavy metal influxes in oceans.



With almost 10%, copper has the third largest share in causing heavy metal pollution in the oceans.

Due to its significant toxicity,<sup>4</sup> a sustainable and responsible large scale industrial process has to remove copper from any wastewater streams.<sup>5</sup> For this, a variety of different technologies are available use of adsorbent materials,<sup>6</sup> cementation,<sup>7</sup> membrane filtration,<sup>8</sup> as well as electrochemical<sup>9</sup> and photocatalytic methods<sup>10</sup>), but the applicability and efficiency of each approach is highly dependent on the concentration and type of copper species in the respective streams.<sup>5</sup> These wastes or the corresponding copper removal procedure significantly contribute to the overall production costs. Thus, the most sustainable and economic way to tackle the problem is to develop processes based on alternative chemical routes not requiring the use of heavy metal catalysts.

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<sup>3</sup> <https://www.slideshare.net/FarhanHameedGeoPhysics/sea-water-pollution>.

<sup>4</sup> <https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15986/6/2/1>.

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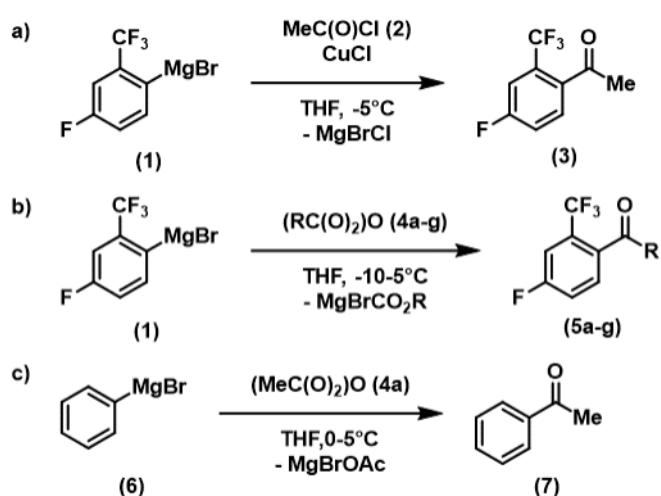
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For large scale industrial processes, Grignard reactions are both challenging, due to the high reactivity and limited stability of the Grignard reagents, and highly attractive, as they offer relatively cheap access to active carbon nucleophiles for carbon-carbon bonds obtainment.<sup>11</sup>

Compared to organolithium reagents, organomagnesium compounds are significantly more economical but also exhibit different reactivity. Various pathways can be considered to approach aromatic ketones using Grignard reactions (Scheme 1).

*Scheme 1. Reaction pathways to introduce ketone functions to aromatic compounds via Grignard reactions.*

a) Copper(I) chloride catalyzed Grignard reaction of (1) with acetyl chloride (2); b) Grignard reaction of (1) with different carboxylic acid anhydrides (4) (a = Me, b = Et, c = *i*-Pr, d = *n*-Pr, e = *t*-Bu, f = Ph, g = CF<sub>3</sub>); c) Grignard reaction of (6) with acetic anhydride (4a).



A traditional access uses acid chlorides due to their ascribed high reactivity.<sup>12</sup> In Scheme 1a, 4-fluoro-2-(trifluoromethyl)acetophenone (3) is synthesized from the corresponding Grignard reagent (1) (4-fluoro-2-(trifluoromethyl)phenyl)magnesium bromide) with acetyl chloride (2) in the presence of catalytic amounts of copper(I) chloride.

As Arxada constantly strive to make its processes both more cost efficient and more sustainable, one key target is the replacement of critical substances. To avoid the expensive waste treatments and the negative environmental impact related to copper, alternative reactants to introduce ketone functions via Grignard reactions were studied (Scheme 1).

*Table 1. Overview for the Grignard reaction of (1) and (5) with AcCl (2) and various carboxylic acid anhydrides (4a-g).*

Substrate	Reactant	Reaction Temp.	Yield	Catalyst (eq)
(1)	(2)	-5°C	93-95%	CuCl (0.03)
(1)	(4a)	-5°C	94%	CuCl (0.03)
(1)	(4a)	-5°C	99%	-
(1)	(4a)	0°C	100%	-
(1)	(4a)	5°C	99%	-
(1)	(4a)	25°C	70%	-
(1)	(4b)	5°C	89%	-
(1)	(4c)	5°C	85%	-
(1)	(4d)	5°C	99%	-
(1)	(4e)	5°C	94%	-
(1)	(4f)	5°C	98%	-
(1)	(4g)	5°C	73%	-
(5)	(4a)	5°C	11%	-
(5)	(4a)	-10°C	86%	-

Reactions were performed in semi-batch mode by parallel dosage of (1) and the respective reactant. Isolated yield (average over 5 runs).

In the absence of CuCl, the reaction shows a limited selectivity towards the desired product with accumulation of the Grignard reagent resulting in lower yields and increased side-product formation. This not only complicates the work-up and purification process, but the observed Grignard reagent accumulation is associated with significant process safety risk for large scale production. In the presence of catalytic amounts of CuCl, the reaction proceeds smoothly with appreciable high yields above 90% if the reaction temperature is kept below -5°C.

<sup>11</sup> a) Grignard, V., Sur quelques nouvelles combinaisons organométalliques du magnésium et leur application à des synthèses d'alcools et d'hydrocarbures (On some new organometallic compounds of magnesium and their application to syntheses of alcohols and hydrocarbons). *Compt. Rend. Hebd. Séances Acad. Sci.* 1900, 130, 1322-1325; b) Yamamoto, Y.; Asao, N., Selective reactions using allylic metals. *Chem. Rev.* 1993, 93 (6), 2207-2293. <https://doi.org/10.1021/cr00022a010>; c) Yus, M.; González-Gómez, J. C.; Foubelo, F., Diastereoselective allylation of carbonyl compounds and imines: application to the synthesis of natural products. *Chem. Rev.* 2013, 113 (7), 5595-5698. <https://doi.org/10.1021/cr400008h>.

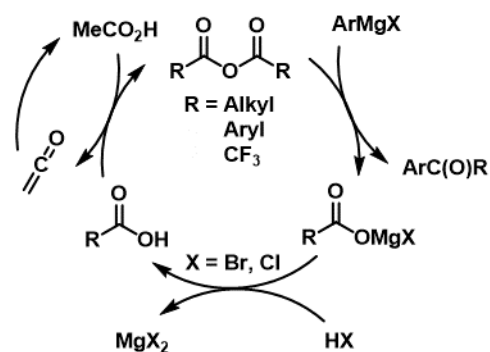
<sup>12</sup> a) Gilman, H.; Nelson, J. F., Relative reactivities of organometallic compounds. IX. cadmium. *Recl. Trav. Chim. Pays-Bas* 1936, 55 (6), 518-530. <https://doi.org/10.1002/recl.19360550607>; b) Amri, H.; Villieras, J., Alkylation d'acetates de cyclenols fonctionnels (5 et 6 chainons) par les reactifs de grignard et les enolates lithiens catalysees (ou non) par les sels de cuivre (I). *Synthese rapide de la (±) mitsugashiwalactone*. *Tetrahedron Lett.* 1987, 28 (45), 5521-5524. [https://doi.org/10.1016/S0040-4039\(00\)96769-8](https://doi.org/10.1016/S0040-4039(00)96769-8); c) Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H., Addition of Grignard reagents to aryl acid chlorides: an efficient synthesis of aryl ketones. *Org. Lett.* 2005, 7 (25), 5593-5595. <https://doi.org/10.1021/ol052150q>.

With the optimized reaction conditions, acetic anhydride not only equals but outperforms the copper catalyzed acetyl chloride variant (Scheme 1b and Table 1). The use of acetic anhydride as electrophile results in equal yields as acetyl chloride in the presence of copper chloride, also featuring a similar side-product profile with the presence of homo-coupled species. However, contrary to the Grignard reaction with (2), the reaction with acetic anhydride proceeds smoothly in the absence of copper chloride without any accumulation of the Grignard reagent. Even more beneficial, the yield significantly increases as substantially less side-products are formed. A further beneficial aspect, very important for large scale processes, is the improved tolerance for higher temperatures. The data suggest, that the reaction with (4a) can be run in a temperature range from -5 to 5 °C with almost quantitative yields. At higher temperatures, the yield starts to drop significantly as the formed ketone (5a) starts to further react with (1) and/or (4a) still present in the reaction mixture to form a variety of side-products.

To challenge the limits of this strategy/approach, six other carboxylic acid anhydrides were assessed as potential electrophiles (Scheme 1b and Table 1). As shown relatively constant high yields were achieved, using similar reaction conditions. To proof that this procedure is generally applicable and not only restricted to electron pure aromatic Grignard reagents like (1), the reaction between phenylmagnesium bromide (6) and (4a) was used as model. At 5°C only low yields of 11% are achieved, as the formed product (7) readily undergoes follow-up side reactions. However, by running the reaction at -10°C, the side reactions can be restricted and a substantial yield increase to 86% is achieved. Therefore, the results suggest that carboxylic acid anhydrides can more broadly be considered to replace acyl chlorides as electrophiles and therewith avoid the use of copper(I) chloride as catalyst in this type of Grignard reactions.

One might rightfully argue, that the proposed process creates a new waste problem, especially if fluorinated anhydrides are used. As a sustainable industrial process does not end with the product isolation, a procedure to recover the respective carboxylate salts out of the waste streams was also developed (Scheme 2).

Scheme 2. Illustration of a potential process cycle including the carboxylate recovery and magnesium halide salt recovery as value stream.



The magnesium halide carboxylate salt formed in the Grignard reaction, can be transferred by acidification into the magnesium halides such as  $\text{MgBr}_2$  and  $\text{MgCl}_2$ , which can be isolated as additional value stream. The recovered carboxylic acid can then be converted in the respective anhydrides by reaction with ketene. In combination with a suitable solvent recycling concept for THF, it is possible to run this type of Grignard reactions with high atom economy and close to zero waste.

To summarize, the Arxada's team demonstrated that carboxylic acid anhydrides can be used as highly selective electrophiles in Grignard reactions to introduce ketone substituents on aromatic compounds. This study shows that in contrast to acetyl chloride, high selectivity and yields are achievable without copper(I) chloride addition as catalyst. In consequence, the use of carboxylic anhydrides can contribute to minimize future copper accumulation and input in aqueous ecosystems. Furthermore, in absence of copper ions or other additives, the procedure allows a closed value cycle with high atom economy and extremely low waste streams. The combination of all of these features makes this process not only sustainable, but also highly economically attractive.

**In conclusion, a more sustainable process was established around Grignard chemistry. The discussed transformation appears to be versatile, high-yielding, and running with mild conditions. In favorable cases, this Grignard reaction could even reach zero waste. This successful implementation was possible thanks to passionate people with a shared vision and commitment towards continuous improvement & sustainability, as well as Arxada's customers trust into better solutions.**

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