



# Power ultrasound in metal-assisted synthesis: From classical Barbier-like reactions to click chemistry

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## ABSTRACT

The search for more efficient and greener synthetic procedures to obtain highly functionalized chemical structures has always found in metal-assisted reactions a noteworthy strategy. All these reactions fall in the main domain of sonochemistry; in fact few techniques can compete with power ultrasound in so efficiently activating a metal surface, thus enhancing and accelerating its subsequent reaction with an organic substrate. Young researchers will certainly benefit from the rich literature and past experience of several pioneers who have, since the early eighties, laid the foundations of modern sonochemical synthetic protocols. Herein we provide a concise overview that describes how ultrasound acts in such a way as to make it a fundamental tool in improving the classical one-step coupling promoted by zero-valent metal species, usually referred to as Barbier-like reactions. From early hallmarks to recent accomplishments, especially the latest Cu-catalyzed alkyne-azide reaction (the so-called Click reaction), intended to be a universal ligation in chemistry and biology; we highlight the role and crucial effects of sonication on these processes.

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## 1. Introduction and background

Synthetic protocols involving metals and organometallic reagents have long been a favourite and rewarding topic in sonochemistry. The majority of such studies have been focused on heterogeneous metal reactions. This is partly because of the synthetic usefulness of these transformations and partly due to the search for milder and faster procedures in organic synthesis. The interaction of acoustic waves with a heterogeneous reaction mixture is not merely an improved way of achieving agitation as it involves complex physico-chemical phenomena starting from the dispersion of materials in a finely divided form. Ultrasound (US) has been recognised as a key technique for green and sustainable synthetic processes, allowing the use of non-activated metals and crude reagents as well as aqueous media [1].

### 1.1. A piece of history

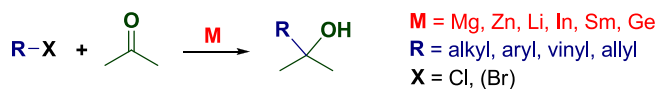
Philippe François Antoine Barbier (1848–1922) is considered to be the father of organometallic chemistry. By the end of the 19th century, while working in Lyon, he and his doctoral student and assistant François-Auguste Victor Grignard (1871–1935) decided

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to replace zinc with magnesium in the one-step synthesis of alcohols involving organic halides and carbonyl compounds [2]. Magnesium largely improved this protocol, but results were often variable and not always satisfactory. Both, mentor and student subsequently turned their attention to a less direct approach involving the initial preparation of the organomagnesium halide followed by its reaction with the carbonyl substrate. This two-step protocol, developed by Grignard in his doctoral thesis (1901) proved to be successful in most cases, a work for which he was later awarded the Nobel Prize in Chemistry (1912). The direct and attractive coupling (Scheme 1) is referred to as the Barbier reaction. This transformation may be induced not only by Mg and Zn, but also by other metals, enabling in addition numerous structural variations in the starting materials [3]. In general, aldehydes are more reactive than ketones and chlorides are more reluctant to undergo coupling than bromides and other leaving groups.

It is worth noting that the first report on cavitation was also published at that time by Thornycroft and Barnaby. They noticed that the propeller of a battleship was pitted and eroded by micro-bubbles generated during the rapid motion of the propeller blade immersed in water [4]. Later, Rayleigh published a mathematical model describing a cavitation event in an incompressible fluid concluding that the erosion on a propeller surface is caused by the pressure, turbulence and heat generated during the implosion of the cavitation bubbles [5]. In spite of this early findings, a more



**Scheme 1.** The Barbier reaction.

systematic study on metallic surface activation and erosion under ultrasonic waves [6] and, particularly in the area of metal-assisted sonochemistry started more than half century later. In 1950, Renaud reported that certain organometallics could be rapidly prepared in non-dried solvents, with inactivated metals, using simple ultrasonic cleaning baths [7].

## 2. The renaissance of Barbier reactions and the pioneering sonochemical approach

The development of Barbier-type reactions has been a long-awaited event. This is not surprising if one considers that the success of this reaction largely depends on the nature of the zero-valent metal and its degree of activation. Bulk metals, even if finely divided, are unwilling participants in synthetic transformations. The reason lies in a general and complex phenomenon collectively denoted as *passivation* wherein an external coating of varied chemical nature prevents further reaction. This also applies to the more reactive group 1 and 2 metals, which undergo rapid oxidation. Thus, magnesium oxide, a common passivation agent, is even harder than magnesium itself and difficult to break by mechanical stress. Accordingly, the popularization of the otherwise appealing Barbier reactions (metals are generally less toxic than other metal derivatives) was only possible with the advent of reliable and efficient activation methods [8].

In the early 1980s, Jean-Louis Luche and his team in Grenoble revisited Renaud's observations and systematically explored the application of ultrasound to organometallic reactions involving Ni, Li, Zn and Cu. Luche and Damiano described the facile sonochemical preparation of organolithium and Grignard reagents and their Barbier-type coupling with carbonyls [9]. In that decade the studies on the applications of sonochemistry in metal-assisted synthesis developed spectacularly as documented by books [10] and reviews [11]. Later on the green aspects of the sonochemical approach were reviewed and discussed by Cintas and Luche [12]. Petrier and Luche described the synthesis of homoallylic alcohols from the zinc-mediated addition of allyl chlorides and bromides to aldehydes or ketones in aqueous media. The yields of sonochemical reactions in the presence of either a radical scavenger (styrene) or promoter ( $\text{CCl}_4$ ) remained essentially unaffected. The positive

results obtained with allylic halides could not be achieved with other halides such as benzyl and butyl bromides [13]. Luche and co-workers also described the fast preparation of several organozinc derivatives under US irradiation in anhydrous solvents [14]. Their addition to  $\alpha$ -enones with catalytic nickel acetylacetonate, leads to  $\beta$ -alkylated ketones, a valuable alternative to the classic organocopper methods, whose sonochemical version was equally reported by Luche et al. [15]. As a model reaction for a systematic study under various sonochemical conditions, they chose: benzaldehyde, *n*-heptyl bromide and lithium. This showed that the rate of formation of 1-phenyloctanol strongly depends on the intensity of the ultrasonic waves and the temperature [16].

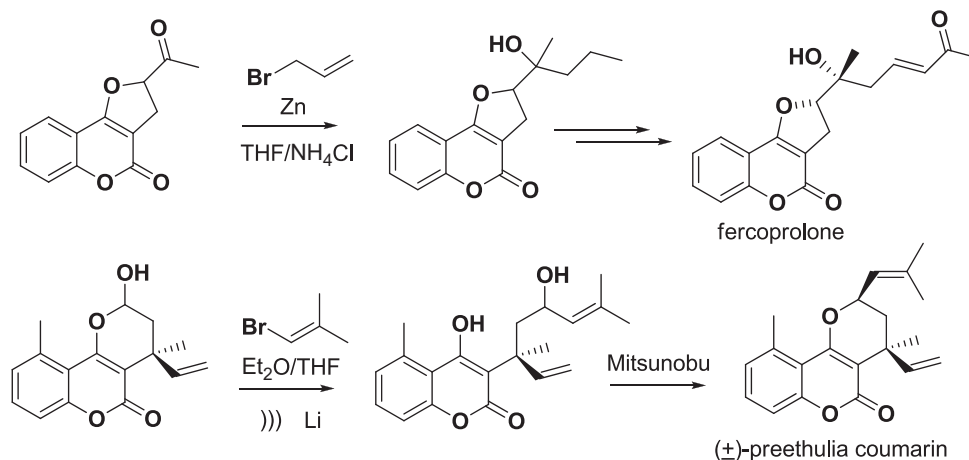
In 1982 Han and Boudjouk were able to dramatically increase the yields and rates of Reformatsky reactions under sonication [17], a finding that was subsequently exploited to prepare  $\beta$ -lactams from ethyl bromoacetate and a diaryl Schiff base [18].

## 3. Recent developments

We have often resorted to Barbier-like reactions in the synthesis of natural products, and when necessary under sonochemical conditions. We shall report one of these here; a step in the total synthesis of two naturally occurring coumarins, the furocoumarin fercoprolone [19] and the pyranocoumarin preethuliacoumarin [20] (Scheme 2). The following scheme shows the allylation of a furocoumarin derivative bearing a methylketone fragment to obtain the corresponding homoallylic alcohol (*i.e.*, 2,3-dihydro-2-(1-hydroxy-1-methylbut-3-enyl)-4*H*-furo[3,2-*c*]benzopyran-4-one) and the norprenylation of an hemiacetalic coumarin by treatment with 2-methyl-1-propenyllithium under US to give a *ca* 2:1 pair of diastereomeric alcohols.

As thoroughly discussed by Cintas in a preliminary review [21] and often updated by others [22], indium has rapidly gained wide popularity since its introduction for Barbier-type reactions in the late eighties [23]. We studied the Barbier allylindation of 1*H*-indole-3-carboxaldehyde in the presence of azoles (*e.g.*, pyrazoles and imidazole) under aqueous conditions. The subsequent dehydration and nucleophilic addition were combined in a convergent, one-pot process for the synthesis of a variety of indole derivatives (Scheme 3). Sonication dramatically reduced the reaction times without significantly affecting the yield [24].

Furthermore the In-assisted Barbier-like reaction was exploited in the enantioselective synthesis of natural convolutamydine A [25] and in a three-component one-pot domino reaction combining the allylindation of 1*H*-indole-3-carbaldehyde with the dehydrative alkylation of stabilized C-nucleophiles (*e.g.*, electron-rich



**Scheme 2.** Barbier-like reactions in the synthesis of coumarin derivatives.

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