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Grignard reagents and Copper

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1 Introduction

Transition metal-catalyzed cross-coupling reactions involving organic halides or pseudohalides with organometallic Grignard reagents are among the most important method allowing for the C–C bond formation [1–4]. Since their discovery at the beginning of the last century [5], these reactions found a considerable amount of applications in organic synthesis either at the laboratory or at the industrial scale. In fact, the key to the success lied on the association of Grignard reagents with transition metal catalysts which greatly increased their application field. Since the work of Kharasch [6–8], who presented the first studies in this field, a large number of cross-coupling methods involving a variety of transition metal complexes as catalysts have been described. The Kumada-Corriu reaction [9, 10], usually corresponding to the nickel- or palladium-catalyzed coupling of electrophiles such as aryl or vinyl halides with Grignard reagents, represents one of the best examples of such a successful combination. Other transition metals are able to promote this reaction and it is also the case, in a general point of view, for the coupling of various families of Grignard reagents with different types of electrophiles which can be catalyzed by Ni-, Pd-, Fe-, Co-, Mn-, Cu-based complexes and to a less extend by Cr-, Zr- or Ti-based complexes. We will focus in this chapter on copper (Cu)-catalyzed cross-couplings of saturated and unsaturated electrophiles with Grignard reagents.

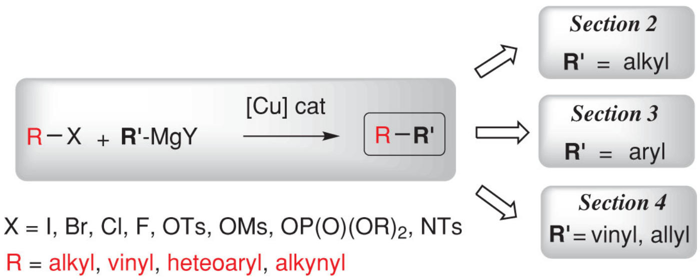

Figure 1: Cu-catalyzed coupling reactions involving organic halides or pseudohalides with organometallic Grignard reagents.

The sections are organized according to the type of Grignard reagent involved: thus the first two sections are dedicated respectively to alkyl- and aryl Grignard reagents and the third and last section discusses the less widespread Grignard reagents such as vinyl, allyl and propargyl derivatives. In every case, the starting electrophile and nucleophile components are respectively highlighted in red (R) and in black bold (**R'**).

2 Coupling reactions from alkyl Grignard reagents (R'MgX)

2.1 Coupling of alkyl Grignard reagents with alkyl halides or pseudo-halides derivatives (RX)

In his seminal work, Kharasch reported, in 1943, the Co-, Cr- and to a lesser extent Cu-catalyzed cross-coupling of vinyl halides with phenylmagnesium bromide (PhMgBr) [11]. However his catalytic systems did not succeed

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to be extended to the crosscoupling of alkyl Grignard reagents or alkyl halides due to the formation of homo-coupling and/or disproportionation products [8]. While the possibility of efficiently performing the coupling of alkyl halides with Grignard reagents only appeared in the past decade when metals such as nickel, palladium or iron catalysts were used [4], the corresponding copper-catalyzed cross-coupling of alkyl Grignard reagents with alkyl halides was reported by Noller [12] in 1964 and in the 1970s by Tamura and Kochi (Figure 2) [13–15]. This coupling employed CuBr2 or Li2CuCl4 as precatalysts in THF at low temperature to form, in high yields, cross-coupling products from primary alkyl bromides and iodides with various Grignard reagents.

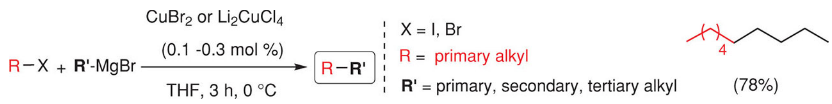


Figure 2: Cu-catalyzed coupling of primary alkyl bromide or iodides with alkyl Grignard reagents [13–15].

After these breakthroughs, in 1974, Schlosser demonstrated the efficiency of low catalytic amounts of Li2CuCl4 (0.3–0.5 mol %) to promote, in very simple experimental conditions, the coupling of tosylate derivatives (aryl and primary alkyl tosylates) with primary and tertiary Grignard reagents (Figure 3).

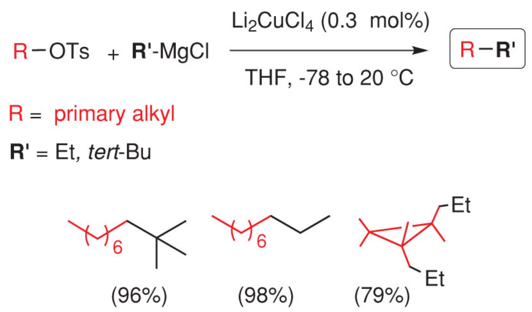


Figure 3: Cu-catalyzed coupling of primary alkyl toylates with alkyl Grignard reagents [16, 17].

Later on, some interesting but isolated examples, were reported respectively by Nunomoto (1983) and Stratton (1995). The former employed catalytic amounts of Li_2CuCl_4 used by Kochi and Schlosser to couple the *n*-octyl iodide with a secondary alkyl Grignard reagent (*i*PrMgBr). This system also found a wider application with the synthesis of 2-functionnally substituted 1,3-butadienes from the corresponding coupling of 1,3-butadien-2-ylmagnesium chloride with primary functionalized alkyl iodides and bromides [18]. The second author presented a symmetrical coupling procedure combining di-halide substrates (X-R-X), magnesium turnings and Li_2CuCl_3 as the precatalyst, allowing for the synthesis of some di-haloalkanes (X-R-R-X) potentially interesting as precursors for the synthesis of insect pheromones or fatty acid-ester [19].

In 1997, Burns *et al*. discovered a new copper-based catalytic system ($CuBr.Me_2S$. LiBr.PhSLi) soluble in the reaction solvent (THF) which was efficient at 0–18°C for the coupling of primary alkyl electrophiles (X = I, Br, OTs) with primary alkyl Grignard reagents (Figure 4). The presence of a thiol (Me_2S) and further addition of HMPA (hexamethylphosphoramide, 6 % v/v) stabilized the Grignard catalytic system, thus allowing the reaction to proceed at higher temperature and the scope of the coupling could be broaden. For example, secondary tosylates or challenging mesylates react with primary Grignard reagents while primary tosylates couple with secondary or tertiary Grignard reagents. Interestingly, this method extended to the C–alkyl—C–aryl bond formation has been applied by the authors to the synthesis of *exo*-metacyclophanes (homologues of exocalix[4]arenes) [20, 21].

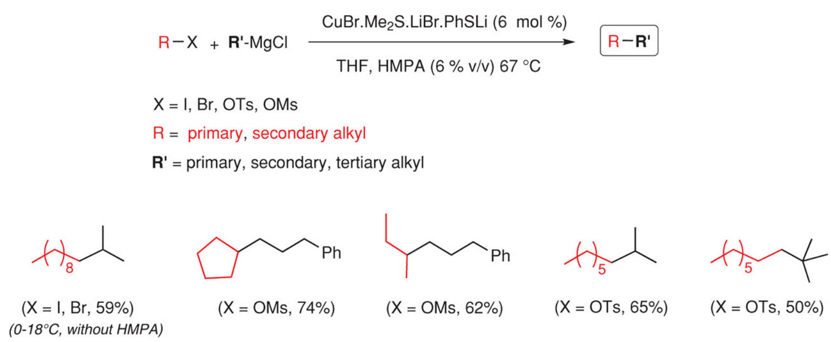


Figure 4: Cu-catalyzed coupling involving primary or secondary alkyl toylates or mesylates and alkyl Grignard reagents [20, 21].

In 1998, Van Koten *et al*. described a copper/manganese (CuCl/[Mn],Y = Cl_2Li) co-catalyzed coupling of *n*-primary or secondary alkyl bromides with primary, secondary, and tertiary alkyl magnesium chlorides (Figure 5) [22]. The reactions take place in a very short reaction time (15 min) probably *via* the formation of a transmetalation product intermedite ([Mn]; Y = **R'**) prior the cross-coupling product itself.

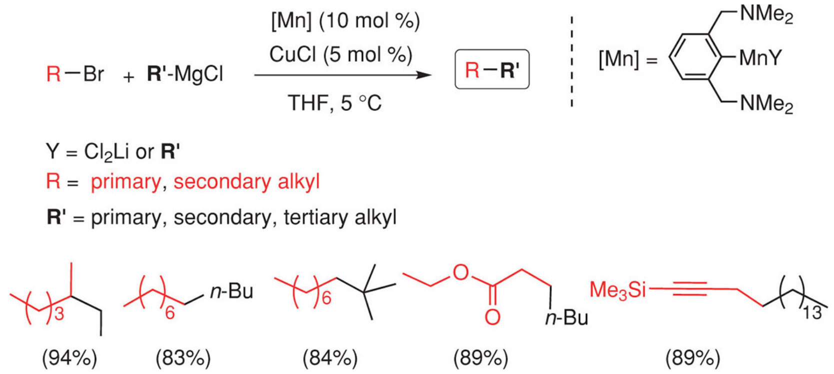


Figure 5: Cu/Mn-catalyzed coupling involving primary functionalized or secondary alkyl bromides and alkyl Grignard reagents [22].

In 2000, Cahiez *et al*. reported the copper-catalyzed alkylation of alkyl Grignard reagents using the traditional CuCl or Li2CuCl4 salts as the precatalysts (Figure 6). Under mild conditions (THF, 20°C), primary alkyl halides (X = I, Br, OTs) functionalized by an ester, an amide, a nitrile or a keto group could react with various Grignard reagents including the most challenging tertiary alkyl ones. The key to the success of this coupling relies on the presence of NMP (*N*-methyl pyrrolidinone) as the solvent, which prevents side reactions and the restriction of functionality usually observed in cross-coupling involving organometallic compounds. The authors have shown that the addition of NMP could however not be efficient enough to allow the coupling from challenging alkyl chlorides or secondary and tertiary alkyl halides [23].

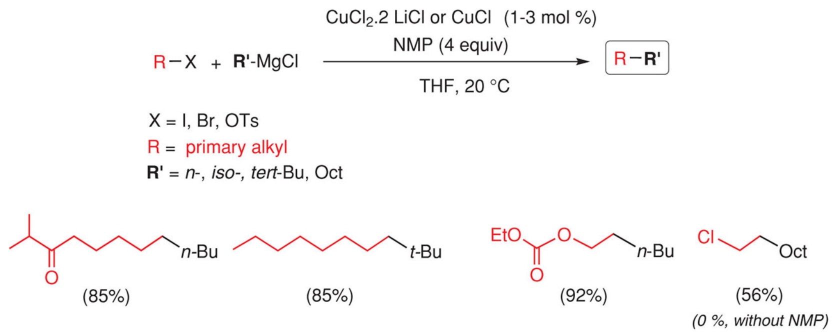


Figure 6: Cu-catalyzed coupling of primary alkyl halides with alkyl Grignard reagents in the presence of the solvent NMP [23].

In 2002, Kambe *et al*. described a nickel-catalyzed Kumada-Corriu type coupling [9, 10] performed in the presence of a catalytic to a stoichiometric amount of butadiene as the additive [24]. The latter allowed the formation of coupling products, obtained from alkyl bromides or tosylates, in good yields. In the absence of the butadiene, reduction and elimination products were mostly obtained. A similar positive impact was observed for the related palladium-catalyzed coupling of alkyl halides with alkyl Grignard reagents [25, 26]. Applied to the copper catalysis ($CuCl_2$), the addition of butadiene which is supposed to stabilize an active species of the copper, also improved the system performance. Thus, the first example of a metal-catalyzed cross-coupling of unreactive and non-activated alkyl fluorides with Grignard reagent of alkyl (and also aryl) type, was reported (Figure 7, eq. 1) [27]. It is worth noting that the observed reactivity order (R-Cl<R-F<R-Br) could not be reasonably explained in terms of bond energies of the alkyl halides. The same year, these authors expanded the application field of their catalytic copper/1,3-butadiene system to the cross-coupling of unactivated secondary alkyl iodides with primary alkyl Grignard reagents (Figure 7, eq. 2) [28]. After the first reports of Burns and Van Koten involving the coupling of secondary alkyl halides with Grignard reagents [20–22], only few results were reported in this field.

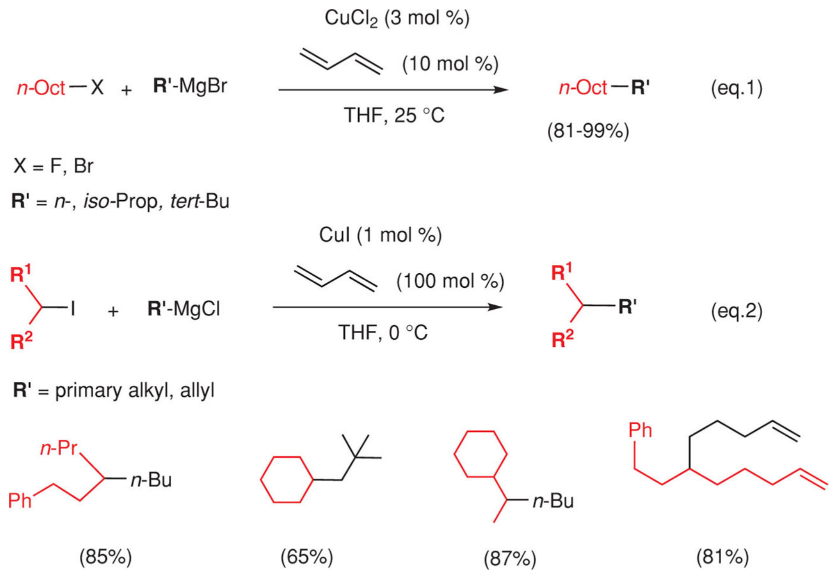


Figure 7: Cu-catalyzed coupling of alkyl Grignard reagents in the presence of butadiene with primary alkyl fluorides or bromides (eq. 1) and secondary alkyl iodides (eq. 2) [27].

As a variation of their protocol, the same authors disclosed that the coupling of alkyl Grignard reagents with primary alkyl chlorides, less efficient (3 % yield) than alkyl fluorides in the presence of butadiene, proceeded efficiently when the copper catalyst was assisted by another additive, the 1-phenylpropyne (Figure 8) [29, 30]. Taking advantage of the difference of reactivity between bromo- and chloroalkyl electrophiles, interesting highly site-selective sequential cross-coupling involving two different alkyl Grignard reagents was performed from a chlorobromoalkane.

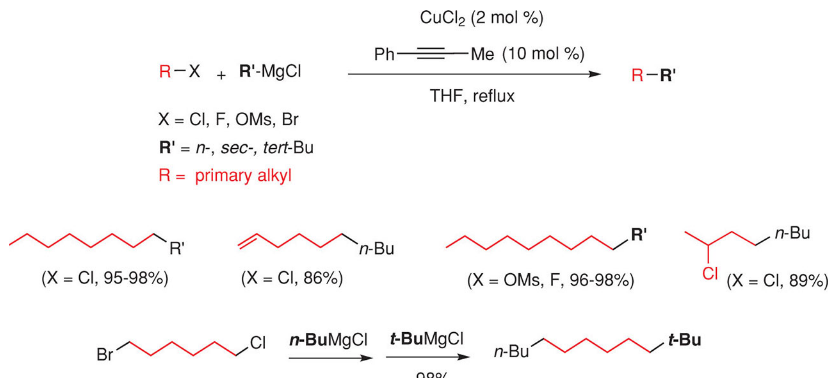


Figure 8: Cu-catalyzed coupling of primary alkyl chloride with alkyl Grignard reagents, [29, 30] in the presence of 1-phenylpropyne as additive.

In a remarkable way, in the presence of an alkyne or a diene as an additive, very high TON (up to 10_6) and TOFs (around 10_4 h_{-1}) were attained, as illustrated below by the copper-catalyzed cross-coupling of *n*-butyl magnesium chloride with 2-(4-bromobutyl)thiophene (Figure 9) [31].

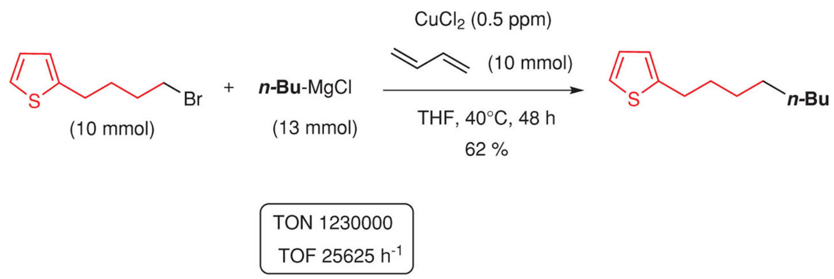


Figure 9: Cu-catalyzed coupling of primary alkyl bromide with alkyl Grignard reagents with very high TON and TOFs (Kambe *et al.*).

Chung and co-workers also used an alkyne (1-phenylpropyne) as an additive for the coupling of primary alkyl bromides or chlorides with primary-, secondary- or tertiaryalkyl Grignard reagents in the presence of copper or copper oxide nanoparticles (Cu NPs) catalysts [32]. The Cu NPs employed in this study are commercially available and can be reused five times without any loss of activity (TON = 49).

Kambe and coworkers have proposed catalytic pathways to describe the coppercatalyzed alkyl–alkyl cross-coupling and also the side reactions potentially able to lower the selectivity in the expected products (Figure 10) [31, 33]. The catalyst of the reaction, **A**, generated from a copper salt (CuCl or $CuCl_2$), a ligand **L** of butadienyl or alkyne type and one equivalent of **R′** MgX, would react with a second equivalent of the Grignard reagent to form a dialkyl cuprate intermediate **B**. The latter in the presence of the alkyl halide could allow the formation of a new intermediate **C** *via* a nucleophilic substitution. By a reductive elimination of *cis*-oriented alkyl partners, the expected product could be expelled and the catalyst **A** regenerated. The presence in the medium of the ligand **L** is a key factor to the selectivity for the expected coupling product. Coordinated to the copper, the ligand **L** strongly or fully disfavors the β-elimination pathway by blocking the β-hydride elimination from **A** and probably also by accelerating the competitive formation of the cuprate **B**. Thus, in the absence of **L** several side reactions are possible among which: (i) a β-hydrogen elimination from Cu**R′** leading to an alkene and CuH; (ii) a reaction of this latter with an alkyl halide to give an alkane and CuX and (iii) after formation of a Cu(0) from disproportionation of CuH and/or CuX, reaction of the former with an alkyl halide and β-hydrogen elimination leading to the formation of a new alkene (Figure 10).

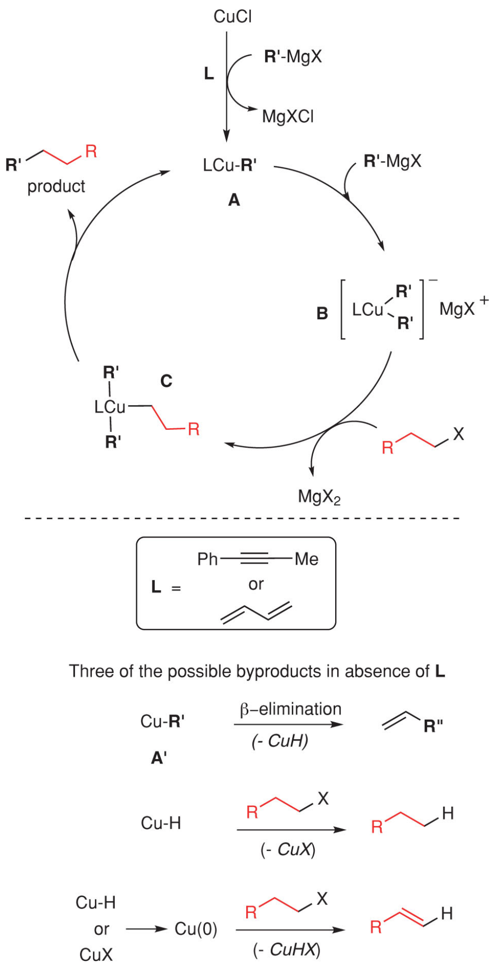


Figure 10: A possible mechanism for the coupling of primary alkyl halide with alkyl Grignard reagents [31, 33]. Role of the ligand **L** and possible byproducts.

Whereas the copper-catalyzed coupling from primary alkyl halides is well described, the coupling involving secondary alkyl electrophiles, first described by Burns et Van Koten (*vide infra*) [20–22], has been scarcely reported. In 2012, Liu *et al*. presented a method also based on a copper catalytic system, allowing for this difficult crosscoupling of non-activated secondary alkyl halides (X = Br) and pseudohalides (X = OTs) with alkyl Grignard reagents (Figure 11). Since this reaction can result in the formation of tertiary carbons and stereogenic centers, it is potentially more interesting than the related one involving primary alkyl electrophiles. Additionally, the authors addressed the even more challenging coupling involving secondary alkyl electrophiles with secondary or tertiary alkyl nucleophiles (Grignard reagents). The method requires the presence of two types of additives, tetramethylene diamine (TMEDA) and LiOMe used respectively in catalytic and stoichiometric amounts. The reaction proceeds by a S_N2 mechanism with inversion of configuration as illustrated by the stereocontroled C–C bond formation resulting from the coupling of chiral tosylates (obtained from the related chiral alcohols) such as for example, cyclohexyl magnesium bromide (ee = 98–99%) [34].

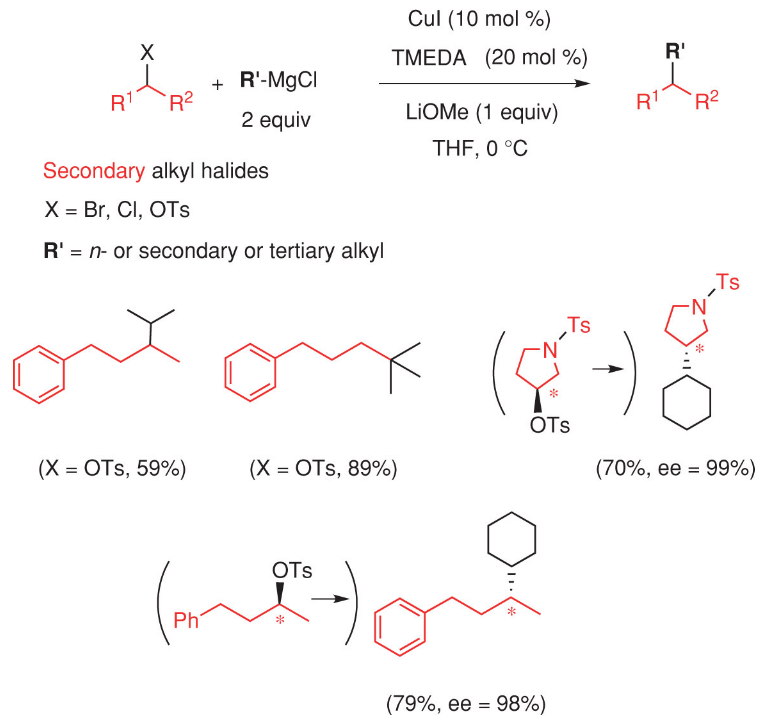


Figure 11: Cu-catalyzed coupling of secondary alkyl halides with secondary or tertiary alkyl Grignard reagents [34]. Stereocontrolled C–C bond formation.

Hu *et al*. described, in 2012, a method for the cross-coupling of non-activated and functionalized primary alkyl halides and tosylates with secondary and tertiary Grignard reagents (Figure 12). A wide scope was reported. The attempts to develop an enantioselective coupling in the presence of chiral ligands were not successful [35].

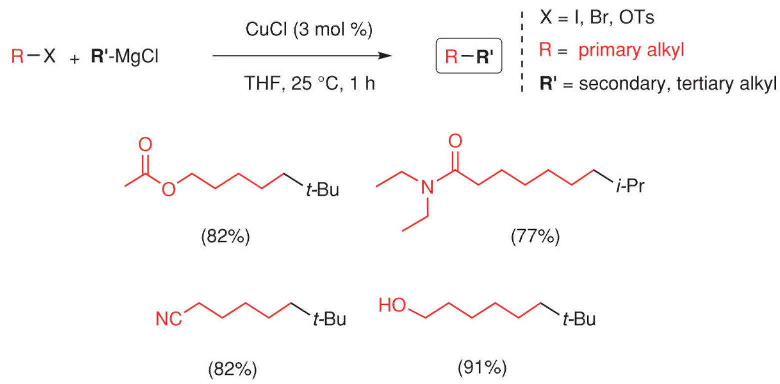


Figure 12: Cu-catalyzed coupling of functionalized primary alkyl halides and tosylates with secondary or tertiary alkyl Grignard reagents [35].

Recently, Matsuoka *et al*., based on the Kambe method [29], have reported the preparation of selectively isotope cluster-labeled long-chain fatty acids, *via* two consecutive copper-catalyzed cross-couplings of alkyl tosylates intermediates with alkyl magnesium bromides (Figure 13) [36]. These NMR- and IR-active molecules of stearic acid type are interesting to determine the conformation of an alkyl chain of lipidic biomolecules upon interaction with proteins.

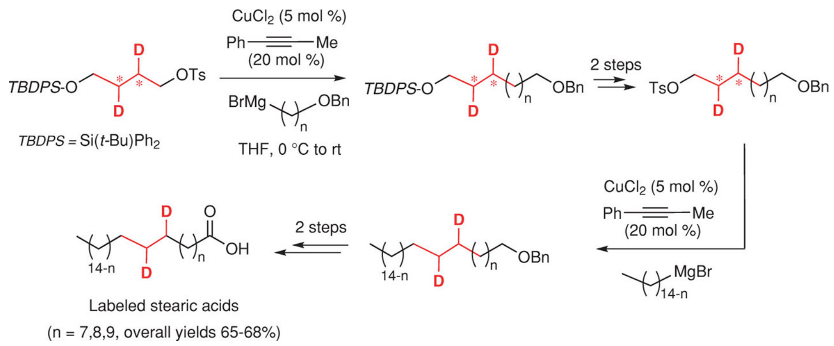


Figure 13: Consecutive Cu-catalyzed cross-couplings of alkyl tosylates with alkyl magnesium bromides. Synthesis of stearic acids [36].

2.2 Coupling of alkyl Grignard reagents with vinyl halides or pseudo-halides derivatives (RX)

As early as 1943, Kharasch and coworkers reported the ability of copper chloride (5 mol %) to promote the coupling of PhMgBr and vinyl bromide. Using CuCl (5 mol %) only resulted in poor product yield (11 %) and cobalt-based catalysts revealed much more efficient in this reaction [37]. Later on, more efficient copper-based systems were described. For example, Bäckwall and coworkers proposed a very general copper-catalyzed coupling reaction of dien-2-yl triflates with a wide array of alkyl- and also allyl- or aryl Grignard reagents (Figure 14) [38]. The resulting 2-substituted 1,3-dienes were obtained in good to excellent yields in the presence of copper iodide (1–10 mol %) in THF at low temperature (–20 to 0 °C). The same group applied this method in the total synthesis of paenilactone A especially used in the treatment of abdominal pain [39].

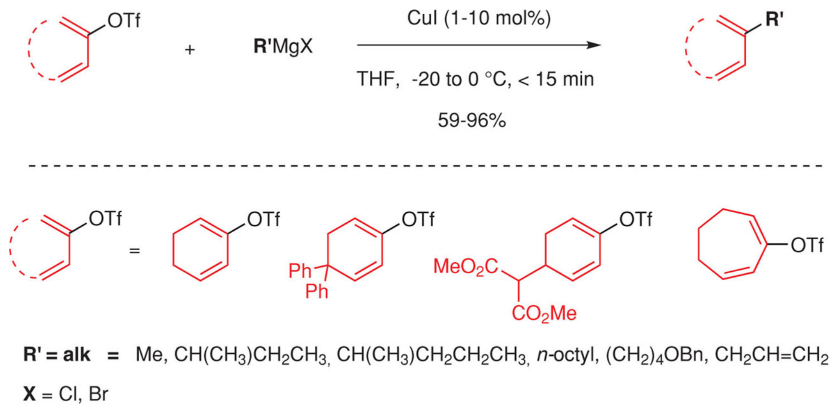


Figure 14: Cu-catalyzed cross-couplings between alkyl Grignard reagents and dien-2-yl triflates [38].

2.3 Coupling of alkyl Grignard reagents with heteroaryl halidesderivatives (RX)

It is worth noting that copper-catalyzed cross-couplings involving alkyl Grignard reagents and aryl or heteroaryl halides are very rare in the literature. For example, Hinterman and coworkers reported a copper-based catalytic system (CuI, 3–10 mol %) allowing the reaction between a wide range of heterocyclic electrophiles and bulky tertiary magnesium halides including dimethylalkyl, cycloaliphatic and cage-like Grignard reagents (Figure 15) [40]. The cross-couplings selectively converted dichloroazacycles into monosubstituted monochloroazacycles and trichloroazacycles into either monosubstituted dichloroazacycles or disubstituted monochloroazacycles. All these extremely sterically hindered and highly functionalized targets, difficult to access otherwise, can be obtained in fair to excellent yields (51–95 % with one exception at 15 %) under mild reaction conditions.

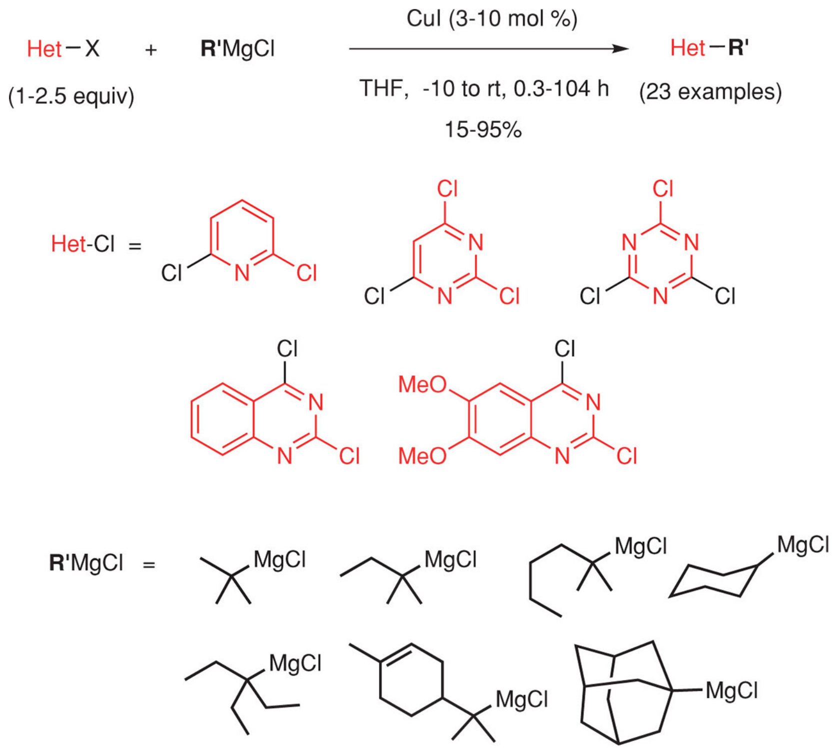


Figure 15: Cu-catalyzed cross-couplings between heteroaryl chlorides and alkyl Grignard reagents [40].

2.4 Coupling of alkyl Grignard reagents with alkynyl halides or pseudo-halides derivatives (RX)

Until very recently, no method allowing the cross-couplings of alkynyl halides with aryl or alkyl Grignard reagents, in the presence of catalytic amounts of copper has been reported. In 2010, Cahiez and coworkers were the first authors to propose a copper-based catalytic system composed of copper(II) chloride (3 mol %) and NMP (4 mol %) able to promote the alkynylation of a wide array of alkyl Grignard reagents in THF at 0 °C (Figure 16) [41]. The addition of NMP as a co-catalyst allowed to significantly increase the yield in the coupling products (Figure 16, eq. 1), for example from 73 % to 91 % for the coupling of *n*-butyl magnesium bromide and heptynyl bromide. Noteworthy, this additive was not necessary when aromatic haloalkynes (e.g. phenylacetylene) and alkyl Grignard reagents were used as the coupling partners (Figure 16, eq. 2).

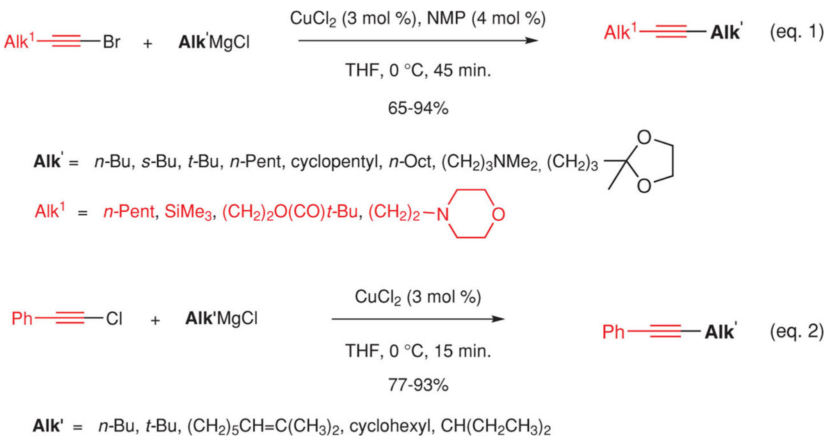


Figure 16: Copper-catalyzed cross-couplings between alkyl Grignard reagents and alkylnyl-alkyl or alkynyl-aryl halides [41].

For these cross-couplings, the authors proposed a catalytic cycle (Figure 17) involving: (i) the formation of the catalytic active species **D** from R′MgX and the copper precursor (CuCl2 here); ii) the reaction of **D** with the Grignard reagent to form cuprate **E**; (iii) the reaction of **E** with the haloalkyne to form a vinylcopper reagent **G** *via* the complex **F/F′**. Formally, **G** results from a reductive elimination from the metallacyclopropene **F′** and (iv) the *ß*-halogen elimination leading to the expected substituted product **H** and the regeneration of the catalytic active species **D**. This putative mechanism is consistent with the observations and with the catalytic cycles proposed for other copper-catalyzed cross-couplings of Grignard reagents and organic halides.

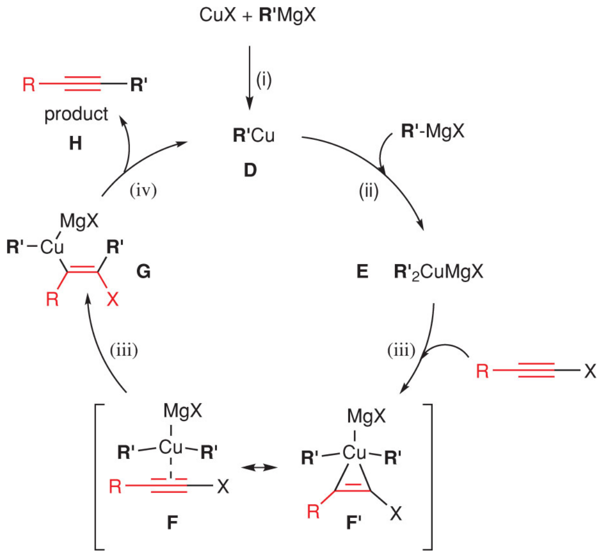


Figure 17: Mechanism proposed by Cahiez *et al.* for the couplings between alkyl Grignard reagents and alkylnyl derivatives [41].

2.5 Coupling of alkyl Grignard reagents with allylic substrates

Alkyl Grignard reagents are involved in numerous couplings with allylic substrates (halides or esters including acetates, perfluorobenzoates, sulfonates, phosphates, etc.), under copper catalysis (Figure 18) [42]. Such reactions involve the allylic rearrangements (S_N2' substitution) and are stereoselective [43, 44]. The reaction conditions can be tuned to obtain the branched isomer as the major compound and the association of chiral ligands to copper catalyst allows high enantioselectivity. From a mechanistic point of view, π-allylic copper complexes seem to be involved. Even if they display a great synthetic potential and represent a very active research field [43, 44], these transformations will not be discussed in deep details in this chapter. Indeed, they cannot be considered as cross-couplings, defined as σ-bond metathesis reactions between a nucleophilic and an electrophilic reagent [2].

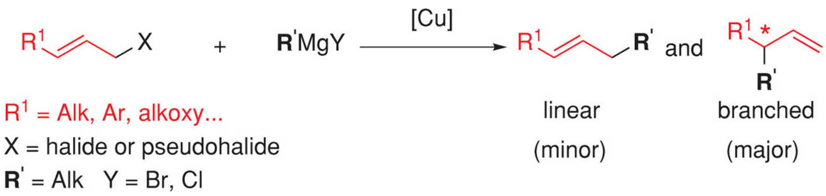


Figure 18: Particular case of allylic alkylations.

3 Coupling reactions of aryl Grignard reagents [1, 2, 45]

3.1 Coupling of aryl Grignard reagents with alkyl derivatives

3.1.1 Coupling with alkyl halides or pseudo-halides (triflates, mesylates,...)

On the whole, aryl nucleophiles are generally less reactive than their alkyl counterparts in cross-couplings with alkyl halides and pseudohalides, the sp_2-hybridized carbon atom being less nucleophilic [1]. Therefore, there are few examples of cross-couplings involving aryl Grignard reagents compared to the alkyl ones. The effect of copper salts on the cross-couplings of aryl Grignard reagents with organic halides has been disclosed by Tamura and Kochi in 1971 [13]. Shortly afterwards, in 1974, Schlosser and coworkers reported the first cross-coupling involving the phenyl magnesium bromide and primary alkyl sulfonates in the presence of di-lithium tetrachlorocuprate [Li_2CuCl_4] (0.2–0.5 mol %) as the catalyst [17]. The reaction proceeded smoothly in THF at room temperature or below and this method could be successfully applied to the preparation of several natural products [46–48]. It is worth noting that the copper(I) counterpart of this precursor, CuCl.2LiCl, can also be used with at least the same efficiency [19]. The scope of this reaction was next broadened by Burns and coworkers who proposed, in 1997, a more complex catalytic system composed of $CuBr.SMe_2$ (6 mol %), LiSPh and LiBr to promote the cross-coupling of primary and secondary alkyl sulfonates (tosylates and mesylates) with various aryl Grignard reagents in a THF/HMPA mixture (94:6, v/v) at 67 °C [20]. This method was successfully applied for the synthesis of natural products [49] or for the construction of cyclophosphane architectures [21] with a broad field of applications as secondary and tertiary alkyl Grignard reagents could also be alkylated.

Couplings involving alkyl halides instead of sulfonates as the alkylating partners were also proposed. In 1986, Nishimura and coworkers demonstrated the ability of copper bromide (5 mol %) to promote couplings of phenyl or 2-naphthyl magnesium bromide and α,ω-dibromoalkanes with either one or two bromides being selectively replaced in a refluxing THF/HMPA mixture [50]. This method was used by Bruice and coworkers to prepare bulky key building blocks in the synthesis of porphyrin derivatives [51]. In 1996, Fuchikami and coworkers reported cross-couplings between β-perfluoroalkyl-substituted alkyl bromides with the phenyl magnesium chloride in the presence of copper iodide (3–6 mol %) [52]. Soon after, Cahiez *et al*. showed that dilithium tetrachlorocuprate [Li_2CuCl_4] (3 mol %) could efficiently catalyze the coupling of octyl bromide and phenyl magnesium bromide under mild conditions (room temperature, short reaction time, Figure 19, eq. 1) [23]. Surprisingly, the addition of the polar co-solvent NMP inhibited the reaction although this additive is known to accelerate the parent cross-coupling of alkyl Grignard reagents mentioned above.

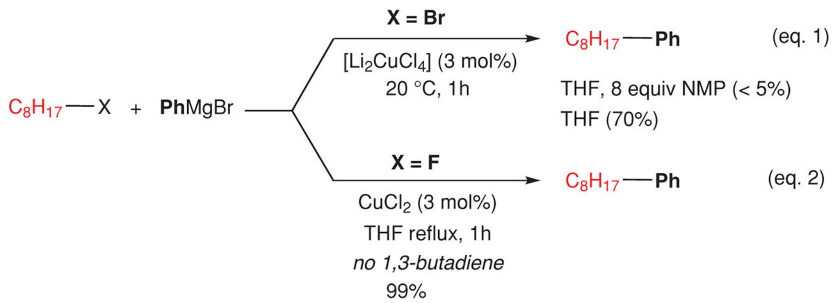


Figure 19: Copper-catalyzed Kumada coupling by Cahiez et al. (eq. 1) [23] and Terao, Kambe *et al*. (eq. 2) [27].

In 2003, Terao, Kambe and co-workers described the copper-catalyzed cross-coupling of octyl fluoride with phenyl magnesium bromide (Figure 19, eq. 2) [27] Contrary to the case of their parent alkyl–alkyl cross-coupling protocol (cf Figure 7), the reactions were not accelerated by the addition of 1,3-butadiene. The reactivity of alkyl halides decreased in the order F > Br » Cl, a trend that cannot be rationalized by considering the bond energies of the alkyl halides. No clear explanation was given for this effect by the authors.

Later, in 2007, Terao, Kambe and co-workers showed that alkyl chlorides could efficiently react with aryl Grignard reagents in the presence of $CuCl_2$ (2 mol %) and 1-phenylpropyne (10 mol %) as the additive in refluxing THF (Figure 20) [29]. The copper-catalyzed reaction was shown to proceed *via* a S_N2-type mechanism by realizing a radical-clock study and 2D-labeled experiments. The method was also efficient starting from primary alkyl bromides and mesylates.

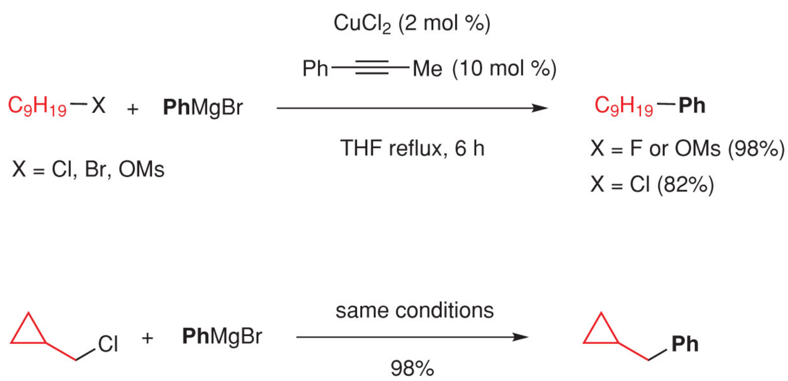


Figure 20: Copper-catalyzed couplings of alkyl chlorides, bromides and mesylates with PhMgBr [29].

A general method was recently published by Kobayashi and coworkers (Table 1) [53]. Alkyl bromides, iodides and tosylates can react with a wide range of aryl Grignard reagents in the presence of copper iodide and lithium chloride as a co-catalyst under mild conditions and within short reaction times (<2 h). Lithium chloride was shown to accelerate the reaction which is in total accordance with the well-known efficiency of the dilithium tetrachlorocuprate [Li_2CuCl_4] [17, 19] and other catalytic systems including lithium-based additives (LiSPh/LiBr) in analogous cross-couplings [20]. Regarding the Grignard partner, the scope mainly includes aryl magnesium bromides (one example with PhMgCl, [Table 1, entry 2]) potentially substituted by electron-donating (Me, OMe) (Table 1, entries 5–10) or more electron-withdrawing groups (F) (Table 1, entry 11). Bulky substrates involving *ortho*-substituents (Me or OMe) could also be successfully used as arylating agents and the corresponding products were obtained in high yields (85–91 %) (Table 1, entries 8–10). Regarding the alkyl partner, bromides (Table 1, entries 1, 2, 5–11), iodides (Table 1, entries 3, 13, 14) and tosylates (Table 1, entry 4) act as effective leaving groups while alkyl chlorides were unreactive under the same conditions (Table 1, entry 12). Noteworthy, the method can allow the arylation of alkyl bromides possessing sensitive functional substituents such as cyanides or esters (Table 1, entries 13, 14). The high amounts of copper precursor (30 mol %) and LiCl (200 mol %) required to get products in good yields constitute however the major drawback of this coupling. Interestingly, the authors demonstrated that the coupling of 3,5-dimethyl magnesium bromide and bromopentane could be successfully catalyzed by only 5 mol % of CuI (Table 1, entry 7, note d), the expected coupling product, a key intermediate in the preparation of cannabinoids, was obtained in 82% yield (instead of 86% by using 30 mol % of the same copper catalyst). Curiously, the extension of such improvement to other cross-couplings was not reported.

$$\text{Alk—X} + \text{ArMgY} \xrightarrow[\text{THF, rt, 1-2 h}]{\text{CuI (30 mol \%), LiCl (200 mol \%)}} \text{Alk—Ar} \qquad X = \text{Br, Cl, I, OTs};\ Y = \text{Br, Cl}$$

Table 1 Copper-catalyzed cross-couplings of aryl Grignard reagents with alkyl pseudo-halides.[1] [53]

Entry	Ar	Y	Alk	X	Yield (%)
1	**Ph**	Br	Ph-$(CH_2)_3$	Br	100[2]
2	**Ph**	Cl	Ph-$(CH_2)_3$	Br	100[3]
3	**Ph**	Br	Ph-$(CH_2)_3$	I	100[4]
4	**Ph**	Br	Ph-$(CH_2)_3$	OTs	100[5]
5	**4-Me-C_6H_4**	Br	Ph-$(CH_2)_3$	Br	91[6]
6	**4-OMe-C_6H_4**	Br	Ph-$(CH_2)_3$	Br	87[7]
7	**3,5-OMe$_2$-C_6H_3**	Br	C5H11	Br	86[89]
8	**2-Me-C_6H_4**	Br	Ph-$(CH_2)_3$	Br	91[10]
9	**2-OMe-C_6H_4**	Br	Ph-$(CH_2)_3$	Br	87[11]
10	**2,6-Me$_2$-C_6H_3**	Br	Ph-$(CH_2)_3$	Br	85[12]
11	**4-F-C_6H_4**	Br	Ph-$(CH_2)_3$	Br	89[13]
12	**Ph**	Br	Ph-$(CH_2)_3$	Cl	0
13	**Ph**	Br	NC-$(CH_2)_3$	I	83[14]
14	**Ph**	Br	EtO_2C-$(CH_2)_3$	I	76[15]

The cross-couplings between benzylic electrophiles and aryl organometallics is a powerful method to prepare dissymmetric biarymethanes, moieties present in many biologically active compounds and drugs [54]. Noteworthy, Brandsma and coworkers reported that benzyl bromide and chloride reacted with phenyl magnesium bromide under copper catalysis (1 mol % CuBr). Interestingly, in these cross-couplings, palladium and nickel catalysts revealed much less efficient than the copper catalyst [55].

3.1.2 Coupling with alkyl phosphates

Besides benzylic halides, the reactivities and selectivities of other benzylic electrophiles have been investigated. Therefore, Knochel and coworkers reported in 2006 a general method for the arylation of highly reactive benzylic phosphates, readily available from the corresponding alcohols, by aryl Grignard reagents (Figure 21) [56]. The catalytic system, composed of copper chloride (10 mol %), triethyl phosphite (20 mol %) and tetrabutylammonium iodide (10 mol %), was able to efficiently promote various cross-couplings in dimethylether at 60 °C. The triethylphosphite was necessary to stabilize the arylcopper reagents. Electron-poor and electron-rich aryl Grignard reagents as well as magnesiated indoles underwent alkylation with functionalized benzylic and heterocyclic phosphates in good to excellent yields. This method, allowing for the formation of highly functionalized carbocyclic and heterocyclic biarylmethanes in the presence of a catalytic amount of cheap copper chloride, offers an attractive alternative to the corresponding palladium-catalyzed cross-couplings. It was successfully applied, as the key step, to synthesize the antibiotic thimethoprim (overall yield: 52 %).

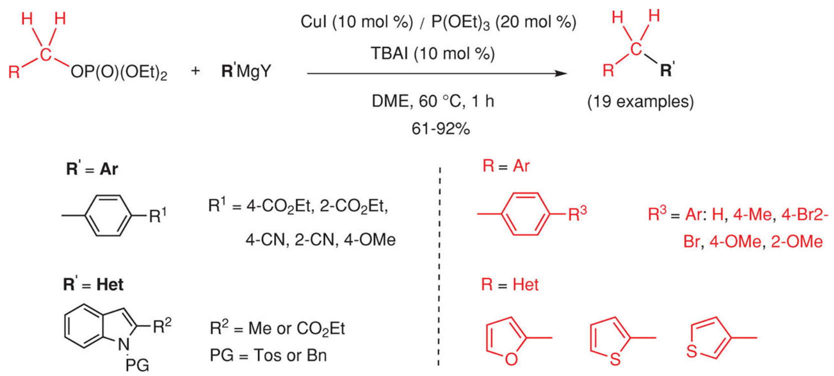


Figure 21: Cross-couplings between aryl Grignard reagents and benzylic phosphates [56].

3.1.3 Coupling with alkyl sulfonalides and sulfonimides

Along the same lines, Tian and coworkers demonstrated in 2011 that Grignard reagents, and in particular aryls, were able to cleave the sp^3 carbon-nitrogen bonds of sulfonyl-activated benzylic, allylic, and propargylic amines in the presence of copper iodide (5 mol %) in refluxing THF (Table 2) [57]. Cross-couplings involving a large panel of double *p*-toluenesulfonyl-activated primary alkyl amines (R-CH2-NTs2, R'.=.Ts) and aryl Grignard reagents proceeded in very high yields with the tolerance of a wide range of functional groups such as halide, alkenes, alkynes, benzyl ethers and allyl ethers (Table 2, entries 1–18). Concerning the scope of Grignard reagent, mainly phenyl and electron-rich aryl groups (including bulky 2-tolyl) were shown to participate to the cross-couplings. Single *p*-toluenesulfonyl-activated secondary allylic and propargylic amines (Table 2, entries 19–20) and *p*-toluenesulfonyl-activated α-branched amines (Table 3) could also act as alkylating agents able to react with aryl magnesium bromides and chlorides under the same conditions. In the latter case, enantioenriched sulfonimide (Table 3, entry 4) and sulfonamide (Table 3, entry 5) were arylated with aryl Grignard reagents. Whatever the substrate, a configurational inversion of the chiral centers was observed which is in accordance with the occurrence of an S_N2-type mechanism in these cross-couplings. Moreover, epimerization of the sulfonamide occurred under the reaction conditions whereas the sulfonamides gave rise to a single isomer without loss of optical purity. Noteworthy, the authors also reported several examples of cross-couplings involving alkyl or allyl magnesium halides in the same publication. The method described by Tian and coworkers is therefore very broad in scope and the necessity to prepare the electrophilic alkyl partner can be seen as its main disadvantage.

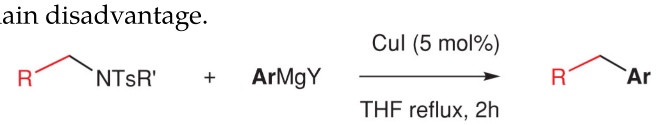


Table 2 Cu-catalyzed cross-couplings of aryl Grignard reagents with sulfonimides and sulfonamides.[16] [57]

Entry	Ar	Y	R	R	Time (h)	Yield (%)[17]
1	**Ph**	Br	4-OMe-C_6H_4	Ts	2	93
2	**Ph**	Br	2-OMe-C_6H_4	Ts	2	88
3	**Ph**	Br	1-heptynyl	Ts	2	88
4	**4-OMe-C_6H_4**	Br	Ph	Ts	2	75
5	**4-OMe-C_6H_4**	Br	4-Br-C_6H_4	Ts	2	72
6	**4-OMe-C_6H_4**	Br	4-Cl-C_6H_4	Ts	2	65
7	**4-OMe-C_6H_4**	Br	4-F-C_6H_4	Ts	2	74
8	**4-OMe-C_6H_4**	Br	1-naphtyl	Ts	2	74
9	**4-OMe-C_6H_4**	Br	2-furyl	Ts	2	80
10	**4-OMe-C_6H_4**	Br	2-thienyl	Ts	2	86
11	**4-OMe-C_6H_4**	Br	CH2=CH	Ts	1	97
12	**4-OMe-C_6H_4**	Br	(E)-PhCH=CH	Ts	1	96
13	**4-OMe-C_6H_4**	Br	Me_2C=CH	Ts	1	99
14	**4-OMe-C_6H_4**	Br	CH_2=C(Me)	Ts	1	96
15	**2-Me-C_6H_4**	Cl	4-OMe-C_6H_4	Ts	2	92
16	**2-Me-C_6H_4**	Cl	(E)-BnOCH_2CH=CH[18]	Ts	1	83[19]

17	**2-Me-C_6H_4**	Cl	(Z)-$BnOCH_2CH{=}CH$[20]	Ts	1	85[21]
18	**2-Me-C_6H_4**	Cl	phenylethynyl	Ts	2	90
19	**4-OMe-C_6H_4**	Br	(*E*)-PhCH=CH	CH2Ph	2	63
20	**2-Me-C_6H_4**	Cl	Ph-CC	Me	2	77

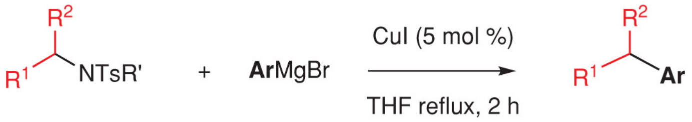
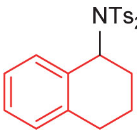
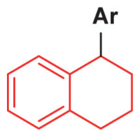
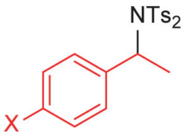
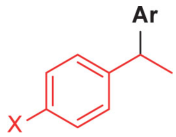
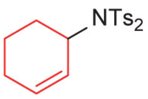
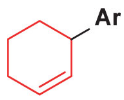
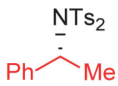
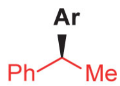
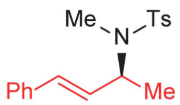
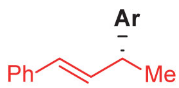


Table 3 Copper-catalyzed cross-couplings of aryl Grignard reagents with *p*-toluene-sulfonyl-activated a-branched amines.[22] [57]

Entry	Ar	Starting Amine (ee)	Product	Yield (%)[23]
1	**4-OMe-C6H4**			**75**
2	**4-OMe-C6H4**			(X = Cl, 58) (X = F, 59)
3	**4-OMe-C6H4**			93
4	**4-OMe-C6H4**	 (ee = 99 %)	 (ee = 44 %)	93
5	**Ph**	 (ee = 95 %)	 (ee = 95 %)	88

More unusual Grignard reagents were also used as the coupling partners in C–C bond forming reactions. For example, Yorimitsu, Oshima and coworkers demonstrated that copper(II) triflate efficiently catalyzed the cross-coupling of cyclopentadienyl Grignard reagents with various electrophiles in mild reaction conditions (diethylether, 25 °C, 3 h) [58].

3.2 Coupling of aryl Grignard reagents with vinyl derivatives

Bäckwall method, described above and allowing the coupling of vinyl triflates with alkyl Grignard reagents (Figure 14), was also used in the coupling of various aryl magnesium bromides with vinyl triflates (Figure 22) [38]. The expected functionalized dienes were obtained in very good yields regardless of the substituent present on the aromatic ring.

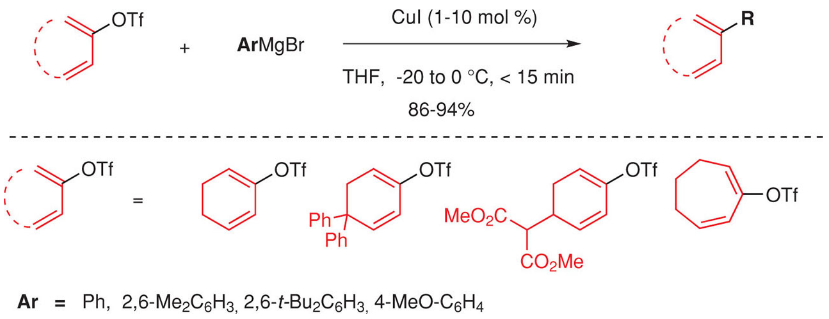


Figure 22: Cross-couplings between aryl Grignard reagents and dien-2-yl triflates [38].

3.3 Coupling of aryl Grignard reagents with alkynyl derivatives

Cahiez *et al*. system described above and allowing the coupling of a wide range of alkynyl halides with alkyl Grignard reagents (Figure 16) is also efficient to promote the coupling of aryl magnesium bromides with alkynyl halides (Figure 23). The expected compounds were obtained in good to very good yields under very mild conditions [41].

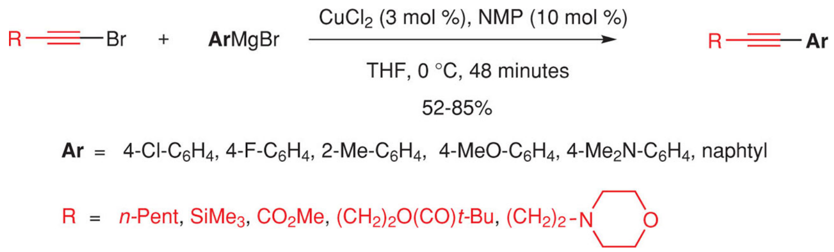


Figure 23: Copper-catalyzed cross-couplings between aryl Grignard reagents and alkylnyl halides [41].

4 Coupling reactions of other Grignard reagents

4.1 Coupling reactions of vinyl Grignard reagents

Coupling of vinyl Grignard reagents and various alkyl halides or pseudohalides were also reported in the literature. In 1981, Nunomoto and coworkers demonstrated that copper iodide (20 mol %) was able to promote the coupling of 1,3-butadien-2-yl-magnesium chloride with alkyl halides [59]. Shortly afterwards, the same authors succeeded in decreasing the copper amounts by replacing CuI by Li_2CuCl_4 (1–5 mol %), which efficiently and selectively catalyzed the cross-coupling of the same vinyl Grignard reagent with primary alkyl iodides and bromides in THF (20–65 °C). The expected 2-substituted 1,3-dienes were obtained in fair to very good yields (Figure 24) [18]. Fleming and coworkers also showed that CuBr (10 mol %) was able to catalyze the vinylation of ω-bromonitriles by the same Grignard reagent (1,3-butadien-2-yl-magnesium chloride) under analogous reaction conditions [60]. Vinyl magnesium bromide could also be used, however, with much lower efficiency. Noteworthy, the systems reported by Fuchikami [52] and Burns [20] allowing the coupling of aryl Grignard reagents with alkyl halides and sulfonates, respectively were also able to afford the vinylation of these alkyl substrates by vinyl magnesium bromide.

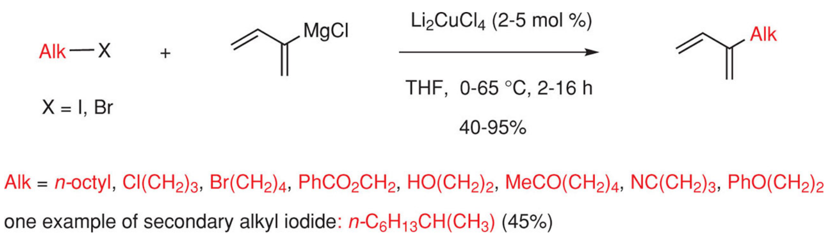


Figure 24: Cross-couplings between 1,3-butadien-2-ylmagnesium chloride with alkyl iodides and bromides [18].

4.2 Coupling reactions of allyl Grignard reagents

Allyl Grignard reagents can also participate to a cross-coupling with various alkyl halides, including secondary and tertiary ones, in the presence of copper catalysts [19, 28, 61]. Noteworthy, the precursor [Li_2CuCl_4] (20 mol %) was successfully applied by Wang and co-workers at Novartis for the cross-coupling of allyl magnesium bromide and 1-bromo-4-chlorobutane on kilogram scale (Figure 25) [62]. This reaction, leading to the expected product in high yield (83 %), constituted the first step in the multi-step synthesis of an HCV NS3 protease inhibitor.

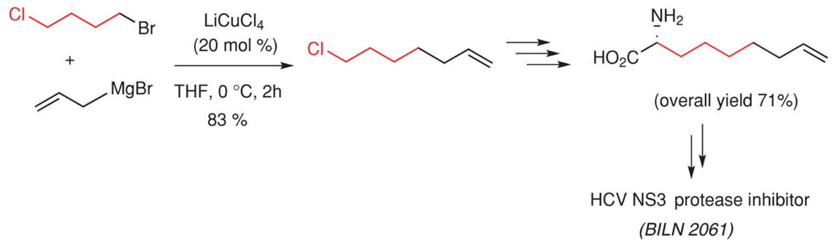


Figure 25: Cross coupling of allyl magnesium bromide and 1-bromo-4-chlorobutane on kilogram scale [62].

5 Conclusion

Even if palladium, nickel and iron are often recognized as metals of choice to promote a lot of existing C–C cross-couplings, one have to remind that organocuprates were the first to perform cross-coupling reactions. Although, for a long time they often required stoichiometric amounts of metal [2, 63]. Today, very efficient and general copper-catalyzed protocols allowing the couplings of Grignard reagents (mainly alkyl, aryl, allyl, vinyl) and organic halides or pseudohalides (mainly alkyl, allyl, vinyl, alkynyl) have emerged and it became possible to reach very high TONs and TOFs [31]. In some cases, copper and palladium can be complementary, thus allowing for chemoselective subtitutions. For example, palladium-based catalysts favor the substitution of aryl halides while copper systems rather prefer the substitution of alkyl halides [59]. The mechanisms involved in most of these copper-catalyzed C–C bond forming reactions remain however not clear and a better comprehension of the processes will probably constitute the key to develop even more efficient Cu-promoted transformations.

Acknowledgements

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Notes

1 Conditions: ArMgX / AlkY (1.5:1), CuI (30 mol %), LiCl (2 equiv), THF, room temperature, 2 h.
2 Yields determined by ^{1}H NMR spectroscopy using anisole as an internal standard.
3 Yields determined by ^{1}H NMR spectroscopy using anisole as an internal standard.
4 Yields determined by ^{1}H NMR spectroscopy using anisole as an internal standard.
5 Yields determined by ^{1}H NMR spectroscopy using anisole as an internal standard.
6 Isolated yield.
7 Isolated yield.
8 Isolated yield.
9 55–60.°C. 82 % with 5 mol % CuI instead of 30 mol % at 55–60.°C.
10 Isolated yield.
11 Isolated yield.
12 Isolated yield.
13 Isolated yield.
14 Isolated yield.
15 Isolated yield.
16 Conditions: **Ar** MgY / AlkX (1.2:1), CuI (5 mol %), THF, 70 °C, 1–2.h.
17 Isolated yield.
18 *E/Z* = 98:2.
19 *E/Z* = 98:2.

20 E/Z = 5:95.
21 E/Z = 5:95.
22 Conditions: ArMgY / AlkX (1.2:1), CuI (5 mol %), THF, 70 °C, 1–2.h.
23 Isolated yield.

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