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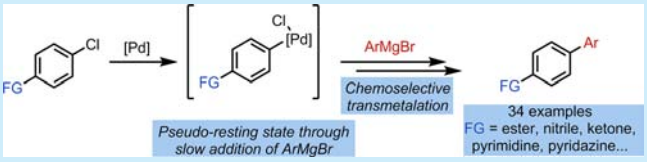
Inherent vs Apparent Chemoselectivity in the Kumada–Corriu Cross-Coupling Reaction

XiYe Hua, Jeanne Masson-Makdissi, Ryan J. Sullivan, and Stephen G. Newman*

Centre for Catalysis Research and Innovation, Department of Chemistry and Biomolecular Sciences, University of Ottawa, 10 Marie-Curie, Ottawa, Ontario, Canada, K1N 6N5

Supporting Information

ABSTRACT: The Kumada–Corriu reaction is a powerful tool for C–C bond formation, but is seldom utilized due to perceived chemoselectivity issues. Herein, we demonstrate that high-yielding couplings can occur in the presence of many electrophilic and heterocyclic functional groups. Our strategy is mechanically based, matching oxidative addition rates with the rate of syringe pump addition of the Grignard reagent. The mechanistic reason for the effectiveness of this strategy is uncovered by continuous-infusion ESI-MS studies.

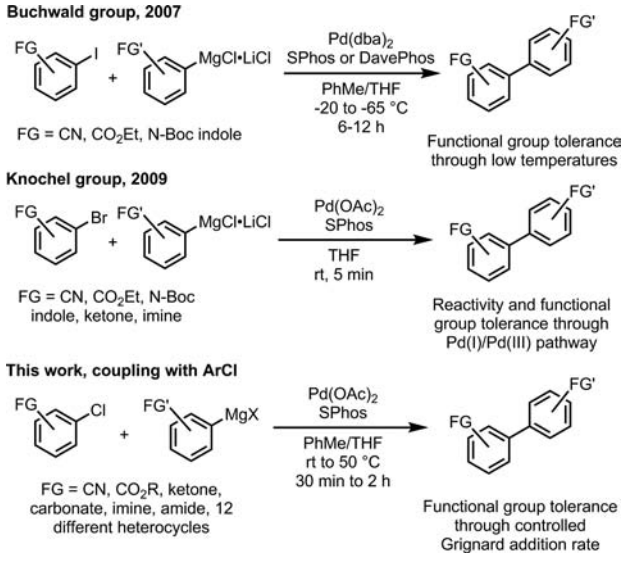


The Ni- and Pd-catalyzed reaction of aryl halides with Grignard reagents, discovered in the laboratories of Kumada and Corriu in 1972, is a pioneering example of cross-coupling.[1] This discovery inspired the exploration of milder nucleophilic coupling partners, including organozinc (Negishi reaction), organotin (Stille), organoboron (Suzuki–Miyaura), and organosilicon (Hiyama) reagents. These more functional group tolerant transformations have overshadowed Kumada–Corriu reactions in complex molecules synthesis.[2] Nonetheless, the use of Grignard reagents as coupling partners offers some significant advantages such as inexpensive and reliable access from aryl halides via metal–halogen exchange or direct insertion of Mg[3] and rapid transmetalation during coupling.[4]

Toward the goal of expanding the scope of the Pd-catalyzed Kumada–Corriu coupling, Buchwald and Martin reported the coupling of sensitive aryl iodides with a highly active Pd/SPhos catalytic system that allowed the reaction to proceed at temperatures as low as −65 °C (Scheme 1).[5] Later, Manolikakes and Knochel reported a catalyst system that allowed rapid coupling of sensitive aryl bromides at room temperature.[6] These accomplishments suggest that some of the fear and avoidance of Kumada–Corriu couplings is unwarranted: If the reaction can be performed sufficiently quickly or at low temperature, a useful reaction scope can be realized.[7] Mechanistically, this suggests that the Grignard nucleophile is capable of chemoselectively transmetalating the Pd(II) catalytic intermediate in lieu of nucleophilic addition to some sensitive functional groups.

In this work, we demonstrate a general and simple strategy to perform Pd-catalyzed Kumada-Corriu couplings that exploits the inherently high chemoselectivity of transmetalation over undesired side reactivity of the Grignard reagent. Our strategy involves controlled, slow addition of the Grignard to the reaction mixture at a rate that approximately matches the oxidative addition step. This ensures a Pd(II) intermediate is always present as a pseudo-resting state and allows transmetalation to compete kinetically against undesired side reactions of the Grignard with sensitive functional groups. To demonstrate the strength of this method, we use a simple solvent and catalyst system with commercial Grignard reagents. Aryl chlorides are utilized as the starting material to illustrate that these strong C–X bonds, which require long reaction times and elevated temperatures, can be coupled chemoselectively.[8] This report represents the most thorough demonstration of Pd-catalyzed Kumada–Corriu coupling of aryl chlorides and the most in-depth study of chemoselectivity issues with Grignard reagents. It is complementary to existing methods for base metal-catalyzed chemoselective coupling, particularly of alkyl halides.[9] Furthermore, syringe pump addition is a very common technique in catalysis,

Scheme 1. Chemoselective Palladium-Catalyzed Kumada–Corriu Coupling Reactions



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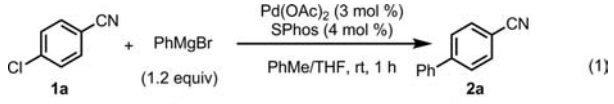
but is seldom mechanistically explained.[10] To our knowledge, this is the first report to demonstrate how simple mechanical reaction manipulation can be done to alter a catalyst resting state for the purpose of enhancing chemoselectivity in cross-coupling.

At the outset of our investigation, a robustness screen[11] was performed on the Kumada–Corriu coupling of aryl chlorides developed by Nolan and co-workers.[12] Additives that contained an alkyne, ether, thioether, benzofuran, benzothiophene, and some others were well tolerated (see Table S1, Supporting Information). In contrast, incompatible additives included those bearing carbonyl, imine, nitro, and nitrile functional groups as well as a wide range of nitrogen-containing heterocycles (pyridine, pyrazine, pyrimidine, imidazole, and protected indole, imidazole, and pyrrole) and acidic molecules.[13] Given the importance of these functional groups and heterocycles in complex molecule synthesis, it is not surprising that the direct use of Grignard reagents in cross-coupling reactions has been overshadowed by less sensitive organozinc, tin, boron, and silicon reagents. Additives bearing acidic protons were also incompatible in the reaction, but could be recovered upon workup.

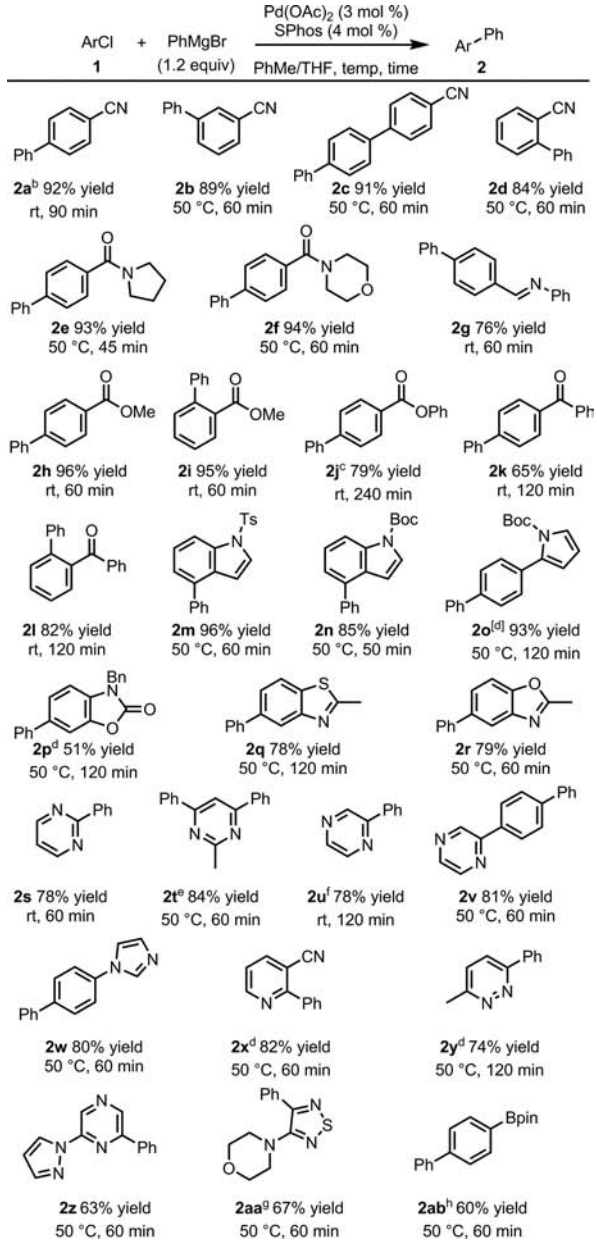
With a better idea of the types of functional groups that are incompatible in traditional Kumada–Corriu reactions, we began exploring the hypothesis that transmetalation can outcompete undesired side reactions if oxidative addition to form the Pd(II) intermediate is not prohibitively slow. Initial exploration of our strategy focused on the coupling of aryl chlorides bearing nitrile groups. After preliminary screening, we identified $Pd(OAc)_2$ (3 mol %) and SPhos (4 mol %) to be a simple, effective catalyst system with toluene as the solvent and 1.2 equiv of PhMgBr. Using 4-chlorobenzonitrile (**1a**) as a reactant at room temperature with a 1 h reaction time, a drastic effect on yield was observed with different addition rates of the Grignard reagent (eq 1). A



similar trend was observed for other aryl chlorides bearing sensitive functional groups, with less electron-deficient aryl chlorides requiring the Grignard to be added over even longer periods (see Supporting Information).

Satisfied that high chemoselectivity was obtainable in the Kumada–Corriu cross-coupling reaction of nitrile-bearing substrates by controlling the addition rate of the Grignard reagent, a diverse range of aryl chlorides featuring incompatible functional groups identified from the robustness screen were investigated (Scheme 2). Various nitrile (**2a–d**), amide (**2e**, **f**), imine (**2g**), ester (**2h–j**), ketone (**2k**, **l**), tosyl (**2m**), and carbamate-containing products (**2n–p**) could be coupled chemoselectively with moderate to excellent yields. Heterocycles that were identified as incompatible were next explored, with benzothiazole (**2q**), benzoxazole (**2r**), and many heterocycles bearing multiple nitrogen atoms (**2s–z**) found to be tolerated with a controlled rate of addition. In all cases, fast addition of the Grignard reagent provided poor yields. Substrates containing thiadiazole (**2aa**) and boronate ester (**2ab**) functional groups could be coupled with a 67% and 60% yield, respectively. These two species were not evaluated in the robustness screen, and slow addition of the Grignard reagent provided only a modest improvement, suggesting that they are not particularly prone to side reactions. For each of these entries, the addition rate and

Scheme 2. Scope of Sensitive Aryl Chlorides[a]



[a]Grignard added over the duration of the reaction time. Isolated yield (0.2 mmol scale). Unless otherwise noted, yields were <20% if Grignard added over 20 s. [b]85% yield on 2 mmol scale. 84% yield with temp = 50 °C, time = 120 min. [c]60% yield with temp = 50 °C, time = 120 min. [d]6 mol % $Pd(OAc)_2$, 8 mol % SPhos were used. [e]2.4 equiv of PhMgBr used for double coupling reaction. [f]63% yield with temp = 50 °C, time = 120 min. [g]56% yield with Grignard added over 20 s. [h]32% yield with Grignard added over 20 s.

temperature were optimized to be as fast and mild as possible to maximize yield as well as to note relationships between structural differences and optimal reaction conditions. There was a small but significant detriment to yield when running reactions at a higher temperature and longer time than necessary. Using the most aggressive reaction conditions (50 °C, Grignard added over 2 h) resulted in an 8% to 19% decreased yield for some substrates (**2a**, **j**, **u**) compared to the optimized temperature and addition rate. These conditions should thus be considered a good starting point

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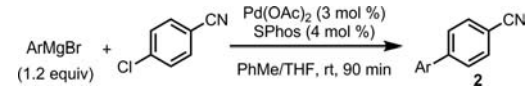
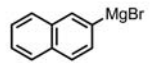
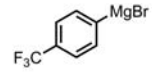
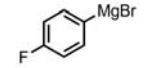
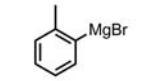
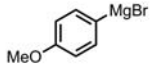
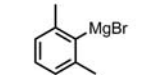
when utilizing new starting materials, but may require further optimization to maximize yield.

Variation of the sterics and electronics of the Grignard reagents were found to have very little influence on the reaction yield, and did not require reoptimization of reaction temperature or time (Table 1). The only exception was found with highly sterically

Table 1. Scope of Grignard Reagents



entry	ArMgBr	yield (%)[a]	entry	ArMgBr	yield (%)[a]
1		85 **2ac**	4		81 **2af**
2		98 **2ad**	5		85 **2ag**
3		99 **2ae**	6		8[b] **2ah**

[a]Isolated yield. [b]Yield determined by ^{1}H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard.

hindered 2,6-dimethylphenylmagnesium bromide, which provided only an 8% yield of biaryl **2ah**.[14] Analysis of the reaction mixture revealed a 33% yield of the imine-bearing side product resulting from addition of the Grignard to the nitrile, suggesting that transmetalation is more heavily impacted by steric bulk than the side reaction.[15]

The mechanistic hypothesis for the greatly increased yield upon controlled addition of the Grignard reagent is that the Pd(II) oxidative addition species ArPdCl must always be present to consume the Grignard via the transmetalation pathway, thereby preventing side product formation (Figure 1A). If the Grignard is added faster than the ArPdCl species is formed, then the inherently high reactivity of the Grignard will result in quenching of the excess reagent by reaction with the sensitive functional group on the starting material or product. To provide further support for this hypothesis, real-time mass spectrometric analysis[16] was undertaken to track oxidative addition intermediate **3**. When PhMgBr was added over the course of only 5 min, a Pd-containing species was initially observed at m/z = 618, representing the loss of chloride from Pd(II) intermediate **3** (Figure 1B). However, this signal rapidly depleted as the Grignard was added, while imines **5a** and **5b** were observed. In contrast, when the experiment was run with the Grignard reagent slowly added over 1 h, Pd(II) intermediate **3** was present during the entire course of the reaction (Figure 1C). Small amounts of side product **5a** were formed only during the initial induction period, suggesting that this side reaction does not occur provided a significant amount of **3** is present for chemoselective transmetalation.[17]

Slowly adding a nucleophile to a reaction is a very common technique in catalysis; however, mechanistic explanations are seldom investigated.[10] The real time ESI-MS monitoring study was also extended to the Pd catalyzed coupling of organolithium reagents with aryl halides reported by Feringa and co-workers,[10h,i] a transformation that also necessitates slow addition of the nucleophile coupling partner to achieve high yields (Supporting Information, Figure S9). The same observation of ArPdCl depletion when the nucleophile was added too quickly was

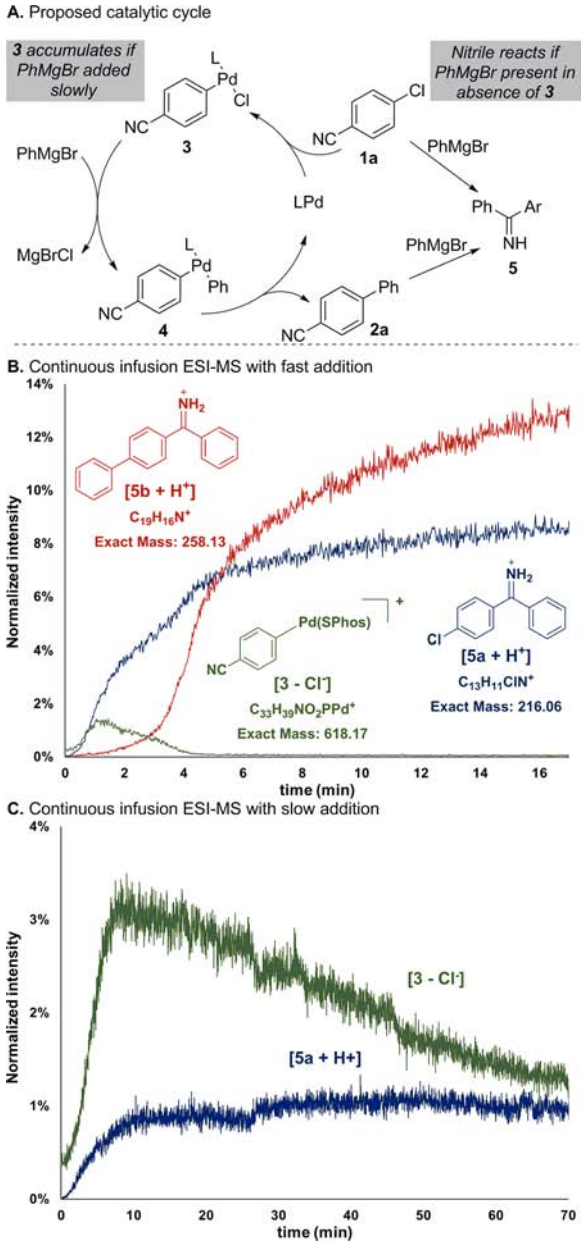


Figure 1. (A) Mechanistic interpretation of selectivity. (B) Real time mass spectrometric monitoring with PhMgBr added over 5 min. Intensity represents the height of the most abundant isotope peak normalized to the total ion current from m/z = 100 to 800. (C) PhMgBr added over 1 h.

observed, confirming that the principle of matching reagent addition rate to reactive intermediate formation is not limited to the Kumada−Corriu coupling but is more widely applicable.

In summary, we have developed a simple, highly effective strategy to overcome functional group tolerance issues in the Kumada−Corriu reaction by adding the Grignard dropwise over the duration of the reaction. This provides access to the inherent chemoselectivity of transmetalation over other undesirable side reactions. Biaryls containing nitriles, esters, ketones, amides, sensitive protecting groups, and heterocycles such as pyrazine, imidazole, and benzothiazole are accessible in high yield. The mechanistic hypothesis that the accumulation of Pd(II) intermediates following oxidative addition is responsible for the enhanced yields upon slow addition of the Grignard is corroborated by continuous infusion ESI-MS studies. This

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concept is shown to be applicable to other chemistry in the literature, namely the direct use of organolithium reagents in cross-coupling. Given that the ultimate source of chemoselectivity comes from the relative rate of transmetalation in comparison with potential side reactions, further improvement of this method is anticipated with more study into the parameters that influence either of these rates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02631.

Experimental procedures, characterization of organic molecules, optimization tables, robustness screen data, scope limitations, electrospray mass spectrometry experiments (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stephen.newman@uottawa.ca.

Notes

The authors declare no competing financial interest.

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(14) The use of sp^3-hybridized nucleophiles was also highly challenging. See: Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(15) In addition to poor chemoselectivity with these challenging Grignard reagents, aryl chlorides bearing a nitro, aldehyde, pyridine *N*-oxide, and some other functional groups could not be efficiently coupled. All unsuccessful examples are provided in Figure S6 of the Supporting Information.

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(17) Similar results were obtained when monitoring the synthesis of **2r**, wherein the consumption of starting material and formation of desired product could be followed over the course of the reaction (see Supporting Information Figure S8).

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