Metal-catalyzed Cross-coupling Reactions

Edited by François Diederich and Peter J. Stang

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Dedicated to the memory of
Professor ***John K. Stille****,*
one of the pioneers of
modern cross-coupling reactions

Foreword

Carbon-carbon bond-forming reactions are arguably the most important processes in chemistry, as they represent key steps in the building of more complex molecules from simple precursors. In the past 50–100 years, organic chemists have developed a plethora of reactions for carbon-carbon bond formation between molecules with saturated sp^3 C-atoms. However, until the discovery and development of metal-mediated cross-coupling reactions, starting in the 1970s, there were no simple, general *direct* methodologies known for carbon-carbon bond formation between unsaturated species such as vinyl, aryl, and alkynyl moieties. In other words, carbon-carbon bond formation between sp and sp^2 C-atom centers was often difficult and tedious. In the intervening 25 years, a wide variety of cross-coupling methodologies have been developed and cross-coupling reactions have emerged among the most powerful and useful synthetic tools in chemistry.

Metal-catalyzed cross-coupling reactions are extensively employed in a wide range of areas of preparative organic chemistry, from the synthesis of complex natural products to supramolecular chemistry and materials science. For example, the formation of new carbon-rich polymers and networks by acetylenic molecular scaffolding, the development of many abiotic receptors, and the preparation of many dendrimers depends heavily on modern cross-coupling methodologies. In fact, in the 1990s one can hardly open a chemical journal in the broad area of organic chemistry or materials science that does not contain several examples of cross-coupling reactions.

Many of the metal-mediated cross-coupling reactions discussed in this book follow a similar mechanistic scheme. The general features of the catalytic cycles are currently quite well understood and involve an oxidative addition-transmetallation-reductive elimination sequence. The reaction is initiated by the oxidative addition of the electrophile to the zero-valent metal. The most widely used active catalysts are diverse Ni(0) and Pd(0) complexes with organic triflates or halides (mostly iodides or bromides; rarely chlorides) as the electrophilic partners. A wide variety of organometallic reagents (organo-boron-aluminum, -copper, -zirconium, -silicon, -tin, etc.) serve as nucleophiles. However, the details of the individual steps, and in particular the transmetallation process, are less well understood and the reaction pathways are highly dependent upon the specific organometallic nucleophiles as well as reaction conditions.

In this multi-authored monograph, a dozen experts and leaders in the field bring the reader up to date by documenting and critically analyzing current developments and uses of metal-catalyzed cross-coupling reactions. The various methodologies involving organo-silicon, -copper, -tin, -zinc, -zirconium, -aluminum, and -boron reagents, as well as the diverse uses of 1,4-additions to 1,3-dienes, carbometallations, and carbonylations, in natural product synthesis are covered. Emphasis is placed upon key developments and important advances, which are illustrated with attractive and useful examples. Carefully chosen references guide the reader through the extensive literature in the field. A particularly attractive and useful feature, that enhances the practical value of this monograph, is the inclusion of key synthetic protocols, in experimental format, chosen for broad utility and application.

We anticipate that this monograph will be of value to both expert and novice practitioners in the area of metal-catalyzed cross-coupling reactions. We hope that it will further stimulate both the development and applications of this enormously useful and already widely employed reactivity principle in all fields of chemistry involving synthesis depending upon carbon-carbon bond formation.

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February 1997

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1 Palladium- or Nickel-catalyzed Cross-coupling with Organometals Containing Zinc, Magnesium, Aluminum, and Zirconium

Ei-ichi Negishi, Fang Liu

1.1 Introduction

The cross-coupling reaction of organometallic reagents with organic halides and related electrophiles represents one of the most straightforward methods for carbon-carbon bond formation (Scheme 1-1). Despite its inherent simplicity and significance, however, its synthetic utility was very limited until the mid-1960s. Mainly Grignard reagents and organolithiums were used in earlier examples. In such cases, organic halides are mostly limited to alkyl (C_{sp^3}) halides. Furthermore, the use of organometals containing Mg and Li is often complicated and limited by their generally low chemoselectivity. Although advances in organocopper chemistry [1] over the past three decades have solved many of the difficulties associated with the use of Grignard reagents and organolithiums, a number of other problems have remained unsolved.

$$R^1{-}M + R^2{-}X \longrightarrow R^1{-}R^2 + M{-}X$$

Scheme 1-1

In 1972, Kumada [2] and Corriu [3] independently reported that the reaction of Grignard reagents with alkenyl or aryl halides could be markedly catalyzed by Ni-phosphine complexes, e.g., $Cl_2Ni(PPh_3)_2$. Although many other transition-metal-catalyzed reactions of Grignard reagents with organic halides without the use of phosphines were known, the so-called Kharasch-type reactions [4], with the exception of the Cu-catalyzed procedures [5,6], were not well suited for cross-coupling due to various complications, including extensive cross-homo scrambling.

The discovery of Pd-catalyzed cross-coupling was somewhat more subtle and evolutionary. During the 1975-1976 period, several groups of workers including the present authors' group published various results involving Pd-phosphine complexes. Thus, Cassar [7] reported the Pd-catalyzed cross-coupling reaction of aryl bromides and iodides with sodium acetylides generated in situ by mixing terminal alkynes with NaOMe in DMF (Scheme 1-2). The corresponding reaction using a Ni-phosphine complex did not proceed catalytically. Similar reactions of alkynes, where the countercations in active species were most probably ammonium and/or Cu^+, were also reported by Heck [8] and Sonogashira [9] (Scheme 1-2).

$$\mathrm{PhC{\equiv}CH + RX \xrightarrow[\text{[7]}]{\substack{\text{cat. Pd(PPh}_3)_n \\ \text{NaOMe, DMF}}} PhC{\equiv}CR}$$

RX = PhI (95%), $\mathrm{H_2C{=}CHBr}$ (52%), $\mathrm{PhCH{=}CHBr}$ (89%)

$$\mathrm{R^1C{\equiv}CH \quad + \quad R^2X \xrightarrow[\text{[8]}]{\substack{\text{cat. Pd(OAc)}_2\text{(PPh}_3)_2 \\ \text{Et}_3\text{N}}} R^1C{\equiv}CR^2}$$

R^1	R^2X	yield (%)
Ph	PhI	73
$\mathrm{H_2C{=}C(Me)}$	PhI	71
Ph	$\mathrm{H_2C{=}C(Me)Br}$	88
t-Bu	$p\text{-}\mathrm{NO_2C_6H_4Br}$	88

$$\mathrm{R^1C{\equiv}CH \quad + \quad R^2X \xrightarrow[\text{[9]}]{\substack{\text{cat. Pd(PPh}_3)_n \\ \text{cat. CuI, Et}_2\text{NH}}} R^1C{\equiv}CR^2}$$

R^1	R^2X	yield (%)
Ph	PhI	90
$\mathrm{HOCH_2}$	PhI	80
Ph	$\mathrm{H_2C{=}CHBr}$	91
$\mathrm{HOCH_2}$	$\mathrm{H_2C{=}CHBr}$	40

Scheme 1-2

Murahashi [10,11] reported the Pd-catalyzed version of the Kumada-Corriu reaction of Grignard reagents, and demonstrated highly stereospecific transformations of (*E*)- and (*Z*)-bromostyrenes into methyl-, vinyl-, and aryl-substituted derivatives (Scheme 1-3). Similar Pd-catalyzed reactions of methyl-, aryl-, and benzylmagnesium bromides were also reported by Fauvarque [12] and Ishikawa [13]. In these three studies Grignard reagents were the only organometals used catalytically, and organolithiums appeared to be unsatisfactory in the catalytic sense [10,11].

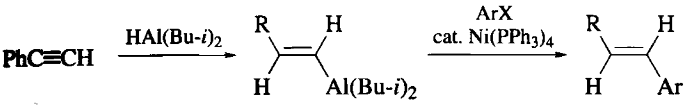
$$\mathrm{PhCH{=}CHBr + RMgX \xrightarrow{\text{cat. Pd(PPh}_3)_n} PhCH{=}CHR}$$

RMgX = MeMgI (100%), $\mathrm{H_2C{=}CHMgBr}$ (81%), *p*-MePhMgBr (86%)

Scheme 1-3

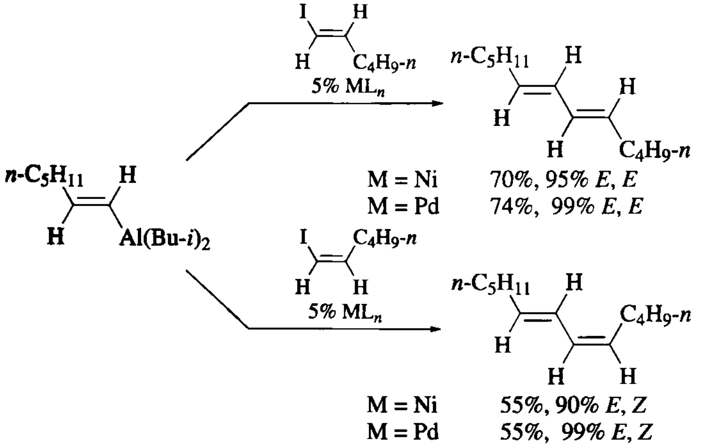
The authors' group reported that alkenylalanes generated in situ by hydroalumination of alkynes could be employed in the Ni-catalyzed alkenyl-aryl coupling [14], demonstrating, for the first time, (i) a hydrometallation cross-coupling tandem process and (ii) the use of countercations other than highly electropositive alkaline metals or Mg in the cross-coupling-catalyzed by Ni-phosphine complexes (Scheme 1-4). The Ni-catalyzed alkenylalane cross-coupling was shown to be applicable to the synthesis of conjugated dienes as well [15]

(Scheme 1-5). In this study, however, it was discovered that Pd-phosphine catalysts were more highly stereospecific and hence distinctly superior to the corresponding Ni-phosphine catalysts. This reaction provided some prototypical examples of efficient, general, and highly stereospecific synthesis of various types of conjugated dienes. In the studies mentioned above, alkenylboranes and alkenylborates were used initially, but the results were unsatisfactory, even though later studies by the authors' group showed that alkenylborates were, in fact, satisfactory in some cases [16]. However, the widespread use of alkenylboron derivatives in the Pd-catalyzed cross-coupling is based on the later development of the Suzuki protocol [17,18].



R	ArX	yield (%)
n-Bu	PhBr	85
n-Bu	1-NaphBr	93
Cyclohexyl	*p*-MeC_6H_4Br	75

Scheme 1-4



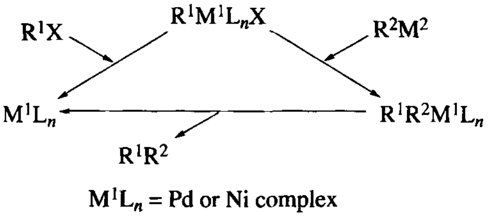
Scheme 1-5

Collectively, the above-mentioned studies reported during 1975 and 1976 not only established the feasibility of the Pd-catalyzed cross-coupling but also suggested the potential superiority of Pd catalysts over Ni catalysts in many instances. In this chapter, some noteworthy aspects of the Pd- or Ni-catalyzed cross-coupling reactions of organometals containing Zn, Mg, Al, and Zr will be discussed with emphasis on the Pd-catalyzed cross-coupling reactions of organozincs, sometimes referred to as the Negishi cross-coupling. In so doing, the authors will have to severely and unduly curtail discussion of the Ni-catalyzed cross-coupling, especially the pioneering and systematic investigation, mainly in the 1970s, by Kumada, Tamao, and their co-workers [19,20] as well as studies of the Pd-catalyzed cross-coupling reactions of Grignard reagents, most notably a systematic investigation by Linstrumelle since 1978 [21–25]. It should be noted that the early investigations mentioned above have paved the way to later developments of the Pd-catalyzed cross-coupling reactions of other organometals containing B [17,18], Sn [26–31], Cu [32,33], and even Si [34–37], as discussed in other chapters in this book.

1.2 Systematic Survey of Palladium- or Nickel-catalyzed Cross-coupling

1.2.1 Scope with Respect to Metal Counterions and Inhibition of Catalysis by Organolithiums

In several papers [2,7,8,10,14,15] published by 1976 the following generic three-step mechanism for the Pd- or Ni-catalyzed cross-coupling was suggested, although few supporting mechanistic and structural data were provided (Scheme 1-6).



Scheme 1-6

According to this mechanism, the only role of organometallic reagents is to transfer an organic group onto organopalladium or organonickel intermediates. Once diorganylpalladium or diorganylnickel intermediates are formed, their reductive elimination to produce the desired cross-coupling products with the regeneration of active Pd or Ni complexes as well as their subsequent oxidative addition with organic halides should proceed essentially independently of the organometals used. This, in turn, suggested that the Pd- or Ni-catalyzed cross-coupling should be quite general with respect to metal counterions. Indeed, the above discussed shift from Mg to Al was made with this simplistic notion in mind. With encouragement from the findings shown in Schemes 1-4 and 1-5, a systematic screening of metal counterions was then undertaken. To this end, the cross-coupling reaction between alkynylmetals and aryl halides was chosen, as these classes of compounds were widely and readily available. Some of the favourable results are summarized in Table 1-1 [38].

The results indicate the following.

1. 1-Heptynylmetals containing Zn, B, and Sn led to the desired products in excellent yields. Under the conditions used, their relative reactivity order was Zn>Sn>B.

Table 1-1 Pd-catalyzed reaction of 1-heptynylmetals with *o*-tolyl iodides

$$n\text{-PentC}\equiv\text{CM} + o\text{-Tol-I} \xrightarrow[\text{THF}]{5\%\ \text{Pd(PPh}_3)_n} n\text{-PentC}\equiv\text{CTol-}o$$

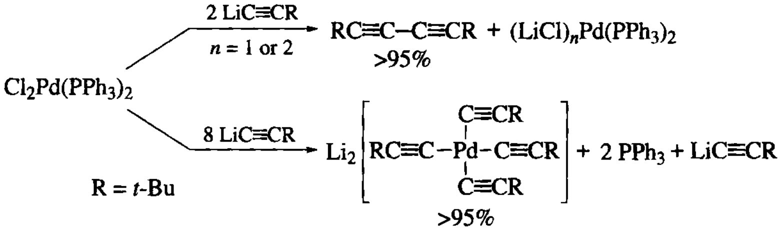
M	Time (h)[a]	Product yield (%)	Starting material (%)
Li	24	3	80
Na	24[b]	58	41
MgBr	24	49	33
ZnCl	1	91	8
$B(n\text{-}Bu)_3$	3	10	76
$B(n\text{-}Bu)_3$	1[b]	92	5
$Al(i\text{-}Bu)_2$	3	49	46
$Al(i\text{-}Bu)_2(n\text{-}Bu)$	1	38	10
$Sn(n\text{-}Bu)_3$	6	83	6

[a] The reaction was run at 20–22 °C unless otherwise stated. [b] Reflux.

2. 1-Heptynyllithium was unsatisfactory, while 1-heptynylmetals containing Na, Mg, and Al led to moderate yields of the desired products. However, more recent results [39] indicate that those containing Mg can be satisfactorily employed.
3. Although not listed in Table 1-1, 1-heptynylmetals containing HgCl and $SiMe_3$ did not produce the desired products in detectable yields. The latter appeared to be totally unreactive under the reaction conditions.

The results obtained with 1-heptynylmetals containing Zn, B, and Sn provided some prototypical examples of the Pd-catalyzed cross-coupling involving these metals. To our knowledge, the reaction of 1-heptynylborate represents the first example of the Pd-catalyzed cross-coupling reaction of organoboron compounds. It is interesting to note that Zn, B, and Sn are currently the three most widely used and satisfactory metals. It should also be emphasized that organometals containing Zn, B, and Sn are by themselves relatively unreactive towards common electrophiles, making their Pd-catalyzed cross-coupling chemoselective in the usual sense. For further discussions of the Pd-catalyzed cross-coupling of organometals containing B [17,18] and Sn [26–31], readers are referred to the corresponding chapters in this book and reviews cited above. In addition to the three metals mentioned above, Mg, Al, Zr (*vide infra*), and Cu have also been successfully employed in Pd-catalyzed cross-coupling. Thus, synthetic chemists have at their disposal at least seven metals to be considered for this purpose, and selection of the most appropriate metal for a given synthetic task has become very important. For the application of organocoppers, readers are referred to Chapter 5 in this book. In view of the low ionic nature of the C—Si bond, it is not surprising that 1-heptynyl(trimethyl)silane was unreactive. However, later studies by other workers, notably Kikukawa [34–36] and Hiyama [37], have shown that even organosilanes can be successfully used in Pd-catalyzed cross-coupling. In cases where some unique advantages associated with the organosilane-based procedures can be found, they may prove useful. For this subject, Chapter 10 in this book should be consulted.

Although their causes are unclear, the difficulties associated with Hg compounds may be attributable to undesirable redox reactions with Pd. Initially more puzzling was the inability of 1-heptynyllithium to participate in Pd-catalyzed cross-coupling. Similar difficulties were encountered in an earlier study by Murahashi [10,11], and it appears that organolithiums as a class, are generally unsatisfactory, although some exceptions are known [11]. The reasons for the difficulties associated with organolithiums are still not very clear. In a limited number of cases, however, they have been attributed to the excessively high reactivity of organolithiums leading to inhibition of Pd catalysts. Specifically, the stoichiometric reaction of $Cl_2Pd(PPh_3)_2$ with two equivalents of LiC≡CR, where R = *t*-Bu, proceeds at least as fast as the corresponding reaction of BrZnC≡CR to give RC≡CC≡CR in >95% yield. Yet, the use of eight equivalents of LiC≡CR to simulate catalytic conditions leads to the formation of a Pd complex best represented by $Li_2[Pd(C{\equiv}CR)_4]$ in >95% yield with concomitant release of PPh_3 but without the production of RC≡CC≡CR in more than a trace amount [40] (Scheme1-7).



Scheme 1-7

1.2.2 Cross-coupling between Two Unsaturated Carbon Groups

1.2.2.1 Palladium-catalyzed cross-coupling involving alkynylmetals and related alkynyl nucleophiles: alkynyl-aryl, alkynyl-alkenyl, and alkynyl-alkynyl coupling

Several studies discussed earlier [7–9,38] as well as others published in the 1970s [42,43] have firmly established that the Pd-catalyzed alkynyl-aryl and alkynyl-alkenyl coupling reactions involving several counterions, especially Cu^+ [9] and Zn^{2+} [38,41,42], are the methods of choice for the synthesis of arylated alkynes and conjugated enynes [43]. For convenience, the first of the two hyphenated organic groups to form the adjective refers to the organometal or nucleophile, while the second one corresponds to the electrophile. The Sonogashira protocol [9] involving both Cu and Pd catalysts offers a highly convenient procedure. On the other hand, the use of alkynylzincs provides a direct route to terminal alkynes that has not been readily achieved by other methods (Scheme 1-8). It has been repeatedly observed that the corresponding reactions using similarly structured Ni complexes, e.g., $[NiCl_2(PPh_3)_2]$, are complicated by side reactions, such as alkyne oligomerization, and that they tend not to permit clean and high-yielding synthesis of the desired alkynes.