

Efficient Cross-Coupling of Aryl Chlorides with Aryl Grignard Reagents (Kumada Reaction) Mediated by a Palladium/Imidazolium Chloride System

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Palladium-catalyzed cross-coupling reactions of aryl halides or halide equivalents with organometallic reagents have been demonstrated to be a highly effective and practical method for the formation of C–C bonds.¹ The use of aryl chlorides as chemical feedstock in coupling chemistry has proven difficult but would economically benefit a number of industrial processes.^{2,3} In 1972, Kumada and Tamao⁴ and Corriu⁵ reported independently that the reaction of Grignard reagents with alkenyl or aryl halides (Kumada reaction) could be catalyzed by Ni(II) complexes. The Pd-catalyzed Kumada reaction was first reported by Murahashi⁶ in 1975. To the best of our knowledge, no successful coupling has ever been reported involving unactivated aryl chlorides and an aryl Grignard reagent.⁷ Several reports have recently appeared dealing with phosphine-modified palladium- or nickel-mediated coupling reactions which employ inexpensive aryl chlorides as substrates.⁸

Nucleophilic *N*-heterocyclic carbenes, or so-called “phosphine-mimics”, have attracted considerable attention as possible alternatives for the widely used phosphine ligands in homogeneous catalysis.^{9,10} The primary advantage of these ligands appears to be that they do not dissociate from the metal center, as a result an excess of the ligand is not required to prevent aggregation of

Table 1. Cross-Coupling of Chlorotoluene with Phenylmagnesium Bromide under Various Conditions

entry	L	solvent	temp (°C)	time (h)	yield ^a (%)
1	IMes	Et ₂ O/THF	45	20	35
2	IPr	Et ₂ O/THF	45	20	97
3	IPr	toluene/THF	80	20	10
4	IPr	THF	80	5	86
5	none	dioxane/THF	80	3	0
6	IMes	dioxane/THF	80	3	41
7	IPr	dioxane/THF	80	3	99

^a Isolated yields are the average of two runs.

the catalyst to yield the bulk metal.¹⁰ The use of these ligands in palladium-catalyzed Heck reactions,¹¹ rhodium carbene complexes in hydrosilylation¹² and ruthenium carbene catalysts in olefin metathesis,^{13,14a} has opened new opportunities in catalysis.

Recently, we examined the solution calorimetry of transition metal centered ligand substitution involving nucleophilic *N*-heterocyclic carbenes.¹⁴ This class of ligands exhibits a considerable stabilizing effect in organometallic systems.^{10,15} An understanding of ligand stereoelectronic effects provided by the thermochemical investigations led to the use of this ligand class in a ring-opening/closing metathesis system.^{14a} This ligand class has recently been employed by Herrmann and co-workers in Suzuki cross-coupling involving aryl bromides and activated aryl chlorides.¹⁶ We recently reported the Suzuki cross-coupling reactions of aryl chlorides and arylboronic acids employing Pd₂(dba)₃ or Pd(OAc)₂/imidazolium salts as the catalyst system.¹⁷ Considering that aryl boronic acids and other organometallic reagents used in this type of C–C coupling are generally made from the corresponding Grignard or lithium reagents,¹⁸ it would prove valuable to find a general method for Kumada coupling. Herein, we wish to report the first successful example of Kumada coupling using a variety of aryl chlorides as substrates.

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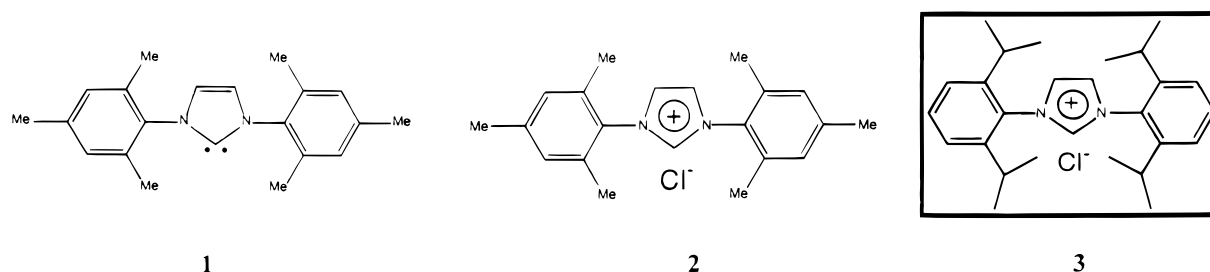
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Scheme 1



Based on our recent success with IMesHCl^{14,19} (IMes = bis(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene) in Suzuki coupling of aryl chlorides with arylboronic acids,¹⁷ we employed a similar protocol for Kumada coupling. In our initial experiment, Pd₂(dba)₃/IMesHCl (**2**) was used as the catalyst precursor. In Suzuki coupling, the carbene ligand IMes (**1**) can be generated in situ by use of a strong base, Cs₂CO₃. The presence of phenylmagnesium bromide (1.0 M solution in THF) in Kumada coupling allows for use of a slight excess of the Grignard reagent to form **1** from **2**. When 4-chlorotoluene is reacted with phenylmagnesium bromide using this catalytic system in Et₂O at 45 °C for 20 h, the product 4-phenyltoluene is isolated in 35% yield (Table 1, entry 1).

Since the use of bulky ligands may improve catalytic performance in this C–C coupling procedure,^{7c,g,8b,c,e,17} a new carbene salt, IPrHCl (**3**, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), recently explored in our lab,²⁰ was employed in this reaction. When the same reaction is carried out with **3**, the coupling product 4-phenyltoluene is isolated in 99% yield (Table 1, entry 2). This result is consistent with Arduengo's²¹ and our studies^{14,20} which explain the ligand steric and electronic properties of this family of ligands. The ligands are excellent donors and therefore facilitate the oxidative addition of aryl halides and the sterics at the ortho position of the imidazolyl aryl groups cause a destabilization of the groups ready to reductively eliminate. Further study showed that using dioxane as the cosolvent and heating the reaction mixture at 80 °C gave excellent yield of product in 3 h (Table 1, entry 7), while the reaction in toluene/THF and THF required longer reaction time and led to lower yields (Table 1, entries 3 and 4).

A survey of catalytic cross-coupling of arylhalides with arylmagnesium bromides using IPrHCl (**3**) is provided in Table 2. Reactions were faster for aryl bromides and iodides (Table 2, entries 3, 8, and 10) than that of aryl chlorides. As in similar coupling reactions, the significant challenge in the practical Kumada reaction is the tolerance of a variety of functional groups.^{22,7j} Those halides bearing methoxy (Table 2, entries 4 and 10–14) or even hydroxy²³ (Table 2, entries 8 and 9) groups react with Grignard reagents to form biaryls in excellent yields. When methyl 4-bromobenzoate was used, methyl 4-phenylbenzoate was isolated in 69% yield (Table 2, entry 7), although more complicated byproducts are formed when the less reactive chloro analogue was used. Although sterically hindered substrates are often problematic,^{8h,i,17} the ortho-substituted 2-fluoro- or 2,4,6-trimethyl phenylmagnesium bromides coupled with 4-chloroanisole without any difficulty. When ortho substituents were present in aryl chlorides, good yields were obtained by using a slight excess of Grignard reagent (1.8 instead of 1.2 equiv). However, the coupling of 2-chloro-*m*-xylene or 2-bromomesitylene with mesitylmagnesium bromide failed because of steric congestion around both reactive centers. Homocoupling products of Grignard

Table 2. Palladium/Imidazolium Salt-Catalyzed Cross-Coupling Aryl Halides with Aryl Grignard Reagents^a

entry	Ar-X	Ar'	time (h)	yield (%) ^b
1	4-MeC ₆ H ₄ -Cl	C ₆ H ₅	3	99
2	4-MeC ₆ H ₄ -Cl	C ₆ H ₅	3	96 ^c
3	4-MeC ₆ H ₄ -Br	C ₆ H ₅	1	99
4	4-MeOC ₆ H ₄ -Cl	C ₆ H ₅	3	97
5	2, 5-(Me) ₂ C ₆ H ₃ -Cl	C ₆ H ₅	3	85
6	2, 6-(Me) ₂ C ₆ H ₃ -Cl	C ₆ H ₅	5	87 ^d
7	4-MeO ₂ CC ₆ H ₄ -Br	C ₆ H ₅	5	69
8	4-HOC ₆ H ₄ -I	C ₆ H ₅	3	96 ^e
9	4-HOC ₆ H ₄ -Cl	C ₆ H ₅	5	95 ^e
10	6-MeO-Np-2-Br	C ₆ H ₅	1	98
11	4-MeOC ₆ H ₄ -Cl	4-MeC ₆ H ₄	3	99
12	4-MeOC ₆ H ₄ -Cl	3-MeC ₆ H ₄	3	83
13	4-MeOC ₆ H ₄ -Cl	2-FC ₆ H ₄	3	99
14	4-MeOC ₆ H ₄ -Cl	2,4,6-(Me) ₃ C ₆ H ₂	3	95
15	2,6-(Me) ₂ C ₆ H ₃ -Cl	2,4,6-(Me) ₃ C ₆ H ₂	24	0
16	2,4,6-(Me) ₃ C ₆ H ₂ -Br	2,4,6-(Me) ₃ C ₆ H ₂	24	0

^a The reactions were carried out according to the conditions indicated by the above equation; 1.2 equiv of PhMgBr (1.0 M solution in THF) used unless otherwise stated. ^b Isolated yields (average of two runs) after flash chromatography. ^c 2.0 mol % of Pd(OAc)₂ used instead of 1.0 mol % of Pd₂(dba)₃. ^d 1.8 equiv of phenylmagnesium bromide was used. ^e 2.5 equiv of phenylmagnesium bromide was used.

reagent were observed in all other reactions as minor products with the exception of mesitylmagnesium bromide where no homocoupling is observed.

While the mechanism remains to be elucidated, it seems apparent at least that diarylpalladium intermediates are involved in this reaction.⁷ⁱ At some point the steric bulk of the ligand becomes more important than its electron donor contribution, as IPr is a poorer donor²⁴ than IMes but results in more effective couplings.

In conclusion, we present a general methodology for the Kumada reaction. The methodology proves effective for unactivated aryl chlorides, aryl bromides, and aryl iodides by simply employing Pd(0) or Pd(II) and an imidazolium chloride as the catalytic precursor. Development of improved protocols for this²⁵ and related C–C bond coupling reactions is ongoing.

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Supporting Information Available: Experimental procedures (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) While this manuscript was being reviewed, we determined that 1 equiv of the IPr-HCl salt could be used leading to similar isolated yields in approximately half the time. A full report of this improvement is forthcoming.