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Pd-Catalyzed Kumada−Corriu Cross-Coupling Reactions at Low Temperatures Allow the Use of Knochel-type Grignard Reagents

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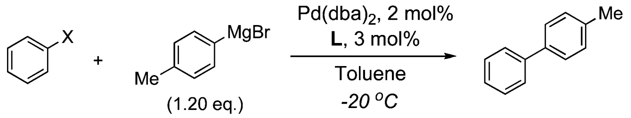
The discovery of the Kumada−Corriu reaction,[1] followed shortly by the work of Murahashi,[2] established the use of nickel and palladium catalysts for the cross-coupling of Grignard reagents with aryl and vinyl halides. Issues with functional group compatibility, however, encouraged the development of alternate protocols with less nucleophilic coupling reagents.[3] Still, the use of aryl (and vinyl) boronic acids, zinc halides, stannanes, and silicates is less direct and experimentally straightforward than employing organomagnesium halides.[4]

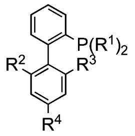
Knochel has pioneered the development of methods for the preparation of functionalized Grignard reagents.[5] In most instances, however, these compounds cannot be used directly in cross-coupling procedures because of their instability at the temperatures required for these reactions.[6] Herein, we present our initial studies on the development of a Pd-catalyzed Kumada−Corriu cross-coupling process[7] that can be conducted at temperatures ranging from -20 to -65 °C and that tolerates the presence of a wide variety of functional groups, in either coupling partner.

We initially focused our efforts on the reaction of aryl triflates with Grignard reagents since we felt that transmetalation might be the rate-limiting step at low temperature (Table 1). The effects of palladium precatalyst, solvent, temperature, and ligand were systematically examined. After some experimentation, it was determined that a catalyst using ligand **L3**[8] provided the best results in toluene (0.25 M) at -20 °C (entry 4).[9] Subsequently, we found that the corresponding aryl iodides were superior substrates and provided the desired cross-coupling product in essentially quantitative yield (entry 8).[9] This fact likely suggests that oxidative addition and not transmetalation is the rate-limiting step under this protocol.[10]

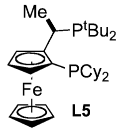
Table 1. Screening of Ligands for Kumada−Corriu Reactions



entry	X	L	time (h)	yield[a] (%)
1	OTf	PCy$_3$	10	26
2	OTf	**L1**	10	34
3	OTf	**L2**	10	27
4	OTf	**L3**	10	79
5	OTf	**L4**	10	53
6	OTf	XantPhos	10	41
7	OTf	**L5**	10	3
8	I	**L3**	6	98
9	I	**-**	6	1



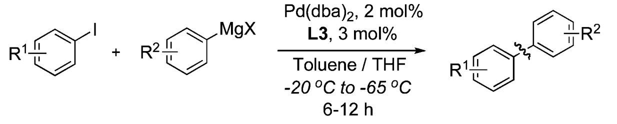
R^1=Cy; R^2=R^3=R^4=^{i}Pr, **L1**
R^1=Cy; R^2=R^3=OMe; R^4=H, **L2**
R^1=Cy; R^2=NMe$_2$; R^3=R^4=H, **L3**
R^1=^{t}Bu; R^2=NMe$_2$; R^3=R^4=H, **L4**

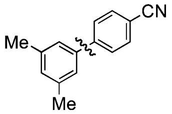
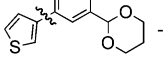
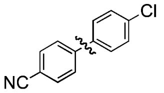
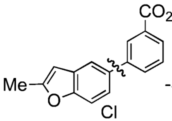
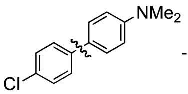
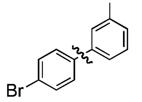
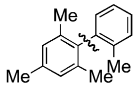
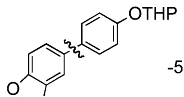
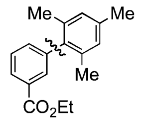
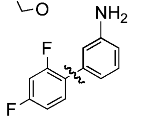


L5

[a] GC yields using dodecane as internal standard.

Table 2. Pd-Catalyzed Kumada−Corriu Reactions of Aryl Iodides with Grignard Reagents[a]



entry	product	T(°C)	yield(%)[b]	entry	product	T(°C)	yield(%)[b]
1		-20	91%	6		-20	86%
2		-50	86%	7		-30	91%[c]
3		-65	93%	8		-30	72%[d]
4		-65	91%	9		-50	88%
5		-30	93%	10		-20	85%[d,e]

[a] Reaction conditions: aryl iodide (1.0 mmol), Pd(dba)$_2$ (2 mol %), **L3** (3 mol %), arylmagnesium halide (1.20 mmol) in toluene (0.25 M) at -20 °C under Ar. [b] Isolated yields are an average of two runs. [c] **L2** (3 mol %) was used. [d] Pd(dba)$_2$ (3 mol %) and **L3** (4 mol %) were used. [e] 3-Bis(trimethylsilyl)amino phenylmagnesium bromide was used.

Encouraged by these initial findings, we examined the scope of this transformation. The results of this investigation are summarized in Table 2. Functionalized aryl Grignard reagents were prepared via Knochel's I/Mg-exchange method[5b] and used in situ (entries 1, 2, and 6−9).[11] As shown, our version of the Pd-catalyzed Kumada−Corriu cross-coupling reaction manifests a broad substrate scope. For example, *ortho*-, *meta*- and *para*-substituted biaryls could all be efficiently prepared. In addition, a variety of functional groups were tolerated, including nitriles (entries 1 and 2), amines (entries 3 and 10), esters (entries 5 and 7), heterocycles (entries 6 and 7), and a benzylic acetal (entry 6). This process could also be employed for challenging cross-coupling reactions at -50 °C (entries 2 and 9) or at -65 °C (entry 3), as well as for the construction of a tri-*ortho*-substituted biaryl (entry 4). To the best of our knowledge, no other Pd-catalyzed biaryl-forming reactions have been accomplished at such temperatures.[12,13] Moreover, the process showed excellent chemoselectivity toward aryl halide substituents, as chlorides (entries 2, 3, and 8), fluorides (entry 10), and even bromides (entry 8) were tolerated, making them available, in many

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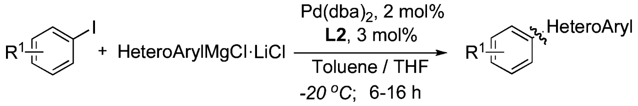
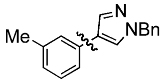
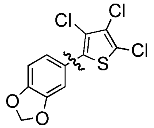
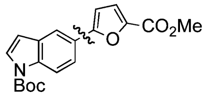
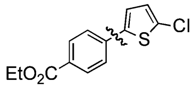
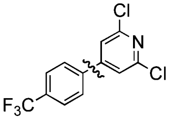
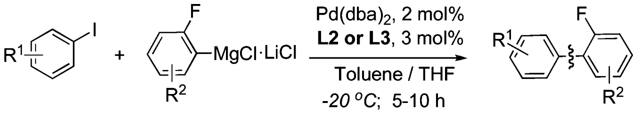
Table 3. Pd-Catalyzed Kumada−Corriu Reactions of Aryl Iodides with Heteroaryl Grignard Reagents[a]

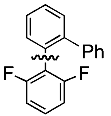
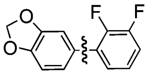
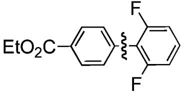
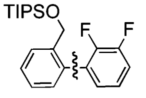
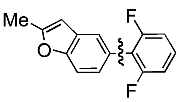
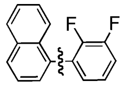


entry	product	yield(%)[b]	entry	product	yield(%)[b]
1		84%	4		73%
2		86%			
3		83%	5		55%

[a] Reaction conditions: as in Table 2, using **L2** as ligand. [b] Isolated yields are an average of two runs.

Table 4. Pd-Catalyzed Kumada−Corriu Reactions of Aryl Iodides with 2,*n*-Difluorophenylmagnesium Grignard Reagents[a]



entry	product	yield(%)[b]	entry	product	yield(%)[b]
1		81%	4		93%
2		78%[c]	5		96%
3		91%[c]	6		91%

[a] Reaction conditions: as in Table 2, using **L2** as ligand. [b] Isolated yields are an average of two runs. [c] **L3** (3 mol %) was used.

instances, for further functionalization via conventional cross-coupling techniques.

Table 3 shows representative examples of the Pd-catalyzed Kumada−Corriu reaction with functionalized heteroaryl Grignard reagents.[5a] While the reaction conditions were essentially identical to those in Table 2, the use of **L2** gave better results than did **L3**; at present, we have no explanation for this behavior. In this manner, cross-coupling products bearing pyrazole (entry 1), furan (entry 2), thiophene (entries 3 and 4), or pyridine (entry 5)[14] moieties were all isolated in moderate to good yields. Again, high levels of chemoselectivity were observed, leaving esters, N-Boc amides, acetals, and heteroaryl chlorides intact.

Electron-deficient arylboronic acids such as *ortho*-fluoro derivatives are often poor substrates in Suzuki−Miyaura reactions because of their low reactivity in the transmetalation process and higher tendency to homocouple.[15] Although we anticipated that the higher reactivity of Grignard reagents would overcome the difficulty of the transmetalation step, these organometallic species are unstable at ambient temperatures, decomposing via benzyne and other pathways. We were pleased to find using our conditions this did not occur. Table 4 shows the results for several *ortho*-fluoro-substituted Grignard reagents that were successfully combined with aryl iodides bearing an ester (entry 2), heteroaryl substituents (entry 3), an acetal (entry 4), or a silyl ether (entry 5) in high yield. In particular, the utilization of 2,6-difluoroaryl metal derivatives in cross-coupling methodology has been quite difficult;[16] with the present method, a variety of heretofore inaccessible 2,6-difluorobiaryls are now readily available.

In summary, a highly efficient process for the Pd-catalyzed Kumada−Corriu reaction that proceeds at temperatures ranging from −20 to −65 °C has been developed. The stability and reactivity of polyfunctionalized Grignard reagents at such temperatures along with the tolerance of our protocol toward a wide variety of functional groups allow for the synthesis of a broad spectrum of valuable compounds, including heterocyclic biaryls and polyfluoro biaryls. Further investigations into this and related methods are ongoing in our laboratories.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, *144*. (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

(2) Yamamura, M.; Moritani, I.; Murahashi, S.-I. *J. Organomet. Chem.* **1975**, *91*, C39.

(3) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(4) (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (d) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

(5) For recent reviews, see: (a) Hiriyakkanavar, I.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(6) For some exceptions, see: (a) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron* **2002**, *58*, 4429. (b) Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, 1008. (c) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 5717.

(7) For recent selected publications on Kumada−Corriu reactions, see: (a) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem.*—*Eur. J.* **2007**, *13*, 150. (b) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364. (c) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216. (d) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889.

(8) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789.

(9) For experimental details and the use of other ligands, see Supporting Information.

(10) (a) For a mechanistic study of the oxidative addition of aryl iodides and aryl triflates to palladium catalysts, see: Alcazar-Roman, L. M.; Hartwig, J. F. *Organometallics* **2002**, *21*, 491. (b) As oxidative addition appears to be rate limiting, reactions with aryl bromides and aryl chlorides are slower. Further work to allow the use of these substrates is currently in progress.

(11) I/Mg exchange was performed using ^{i}PrMgCl−LiCl. The use of ^{i}PrMgBr resulted in similar yields of the final biaryl compounds. Thus, we do not believe, as suggested by one reviewer, that LiCl is important in our Pd-catalyzed chemistry.

(12) While this paper was in preparation, a report describing a single example of a Pd-catalyzed Kumada−Corriu reaction with an unactivated aryl halide at −20 °C was reported; see ref 7a.

(13) For some examples of Pd-catalyzed Kumada−Corriu reactions with activated heteroaryl halides at −40 °C, see refs 6a and 6c.

(14) The reaction using 2- and 3-pyridylmagnesium reagents resulted in lower conversion of the aryl iodides (0−30% in most cases).

(15) (a) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087. (b) Thiemann, T.; Umeno, K.; Ohira, D.; Inohae, E.; Sawada, T.; Mataka, S. *New J. Chem.* **1999**, *23*, 1067.

(16) For an example of cross-coupling reaction of potassium 2,6-difluorophenyltrifluoroborate with 4-bromobenzonitrile, see: Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

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