DOI: 10.1002/anie.200803730

Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents**

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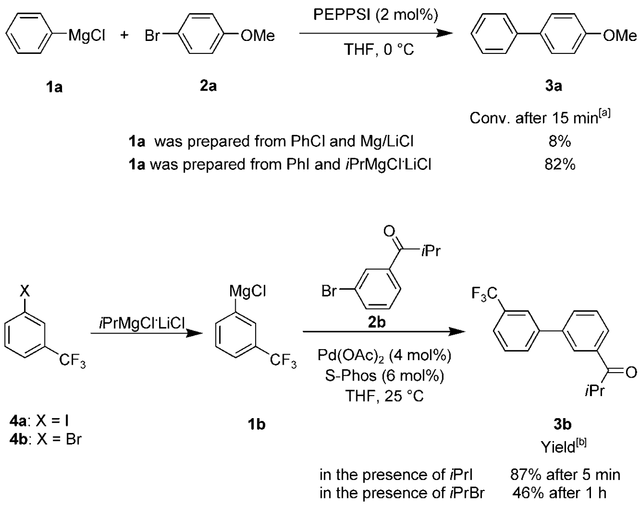
In memory of Jay K. Kochi

The Kumada cross-coupling allows direct Pd-catalyzed carbon–carbon bond formation between unsaturated halides and organomagnesium reagents (without further transmetalation steps)[1,2] and is therefore a highly atom-economical cross-coupling reaction.[3] Most of these cross-couplings follow a standard mechanism (oxidative addition, ligand exchange, reductive elimination),[4] although an alternative pathway is possible, as was shown by Kambe et al. for Kumada cross-couplings in the presence of dienes.[5] Recently, Buchwald and co-workers have shown that when an appropriate phosphine ligand[6] and low temperatures are used, functionalized aryl and heteroaryl iodides undergo a smooth cross-coupling with functionalized arylmagnesium halides.[7,8]

Herein, we wish to report a new radical catalysis which makes it possible to perform a Kumada cross-coupling using aryl bromides at room temperature within a few minutes in the presence of an alkyl iodide. In preliminary experiments we observed that the reaction of PhMgCl (**1a**), prepared by the insertion of magnesium in the presence of lithium chloride,[9] reacts slowly with 4-bromoanisole (**2a**) in the presence of $Pd(OAc)_2$ and S-Phos (S-Phos = 2-dicyclohexylphosphanyl-2′,6′dimethoxyphenyl)[10] or PEPPSI (PEPPSI = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride),[11] leading to 4-methoxybiphenyl (**3a**). A conversion of only 8% was observed at 0°C after 15 minutes. In strong contrast, the reaction of PhMgCl (**1a**), prepared by I/Mg exchange using *i*PrMgCl·LiCl,[12] provided **3a** with 82% conversion after 15 minutes (Scheme 1, top). This difference was attributed to the presence of 1.1 equivalents of *i*PrI obtained as a side product in the I/Mg exchange. Thus, the cross-coupling of arylmagnesium halide **1b**, prepared from 3-iodobenzotrifluoride (**4a**) by I/Mg exchange with the bromoaryl ketone **2b**, furnished the functionalized biphenyl **3b** within 5 min at 25°C as a single product (87% yield, Scheme 1, bottom). Interestingly, when the Grignard reagent **1b** was prepared from the corresponding aryl bromide **4b** by Br/Mg exchange, no acceleration was observed and the biphenyl **3b** was isolated in only 46% yield after 1 hour.[13] This demonstrates the accelerating effect of *i*PrI. We have found that a range of alkyl iodides such as MeI, 1-iodoadamantane, neopentyl iodide, and cyclohexyl iodide give similar rate enhancement.[14] In subsequent experiments, however, we used isopropyl iodide (1.1–1.2 equiv),[15] since it is produced in the I/Mg exchange and since the above-mentioned iodides displayed comparable catalytic activity.



Scheme 1. Accelerating effect of *i*PrI in the Kumada coupling reaction. [a] Conversion determined by GC using tetradecane as the internal standard. [b] Yield of isolated, analytically pure product.

As shown in the bottom equation of Scheme 1, the presence of *i*PrI considerably enhances the functional-group tolerance of this Kumada cross-coupling. By using this procedure, a range of functionalized arylmagnesium species were efficiently coupled with functionalized aryl and heteroaryl bromides. Thus, the reaction of 3-trifluoromethylphenylmagnesium chloride (**1b**, 1.1 equiv) with 2-bromobenzonitrile (**2c**, 1.0 equiv) in the presence of PEPPSI (2 mol%) provided the coupling product **3c** within 5 minutes at 25°C in 92% yield (Table 1, entry 1). Interestingly, this method can be extended to functionalized arylmagnesium reagents having low stability at room temperature. Thus, the ester-substituted organomagnesium compound **1c** (1.1 equiv),[16] prepared by I/Mg exchange at −20°C,[11] reacted with the functionalized bromobenzenes **2d** and **2e** (1.0 equiv) in the presence of $Pd(OAc)_2$ (2 mol%) and S-Phos (3 mol%) or PEPPSI (2 mol%)[17] to afford the biphenyls **3d** and **3e** in 82 and

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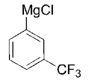
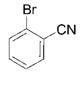
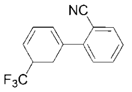
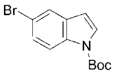
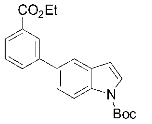
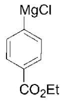
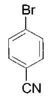
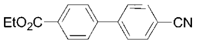
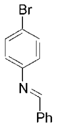
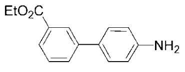
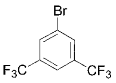
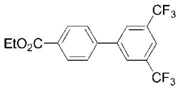
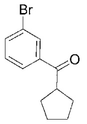
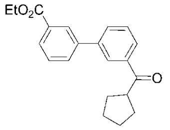
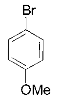
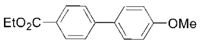
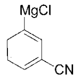
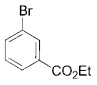
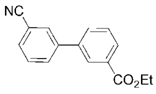
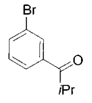
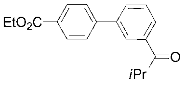
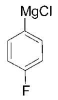
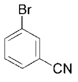
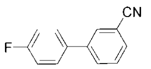
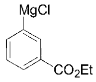
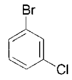
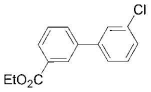
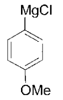
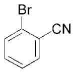
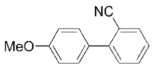
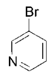
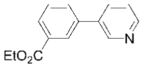
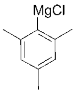
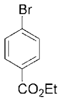
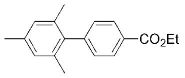
[**] We thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (DFG), and SFB 749 for financial support. We also thank Chemetall GmbH (Frankfurt), Evonik GmbH (Hanau), W. C. Heraeus GmbH (Hanau), and BASF AG (Ludwigshafen) for generous gifts of chemicals.

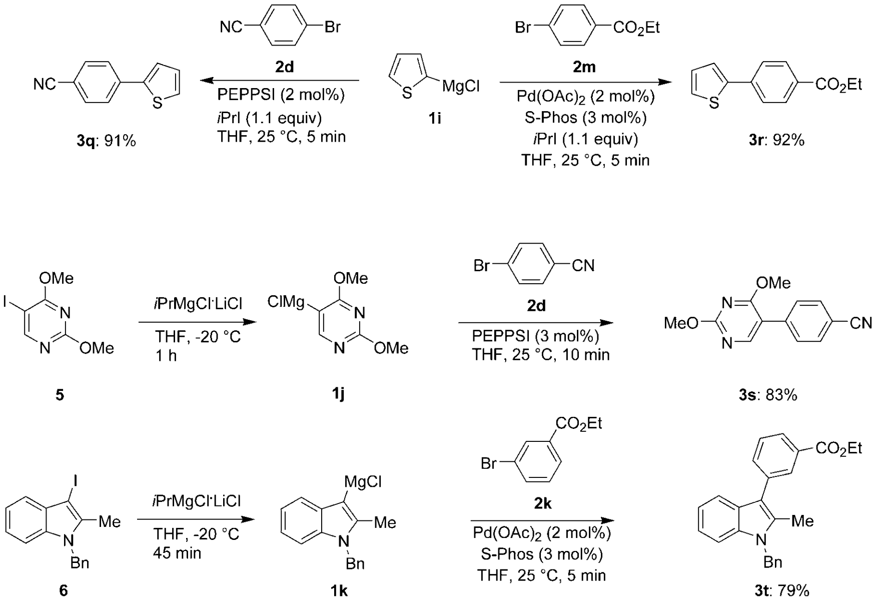
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803730.

Table 1: Products of type **3** obtained by the cross-coupling of functionalized arylmagnesium reagents **1** and aryl bromides **2** in the presence of *i*PrI.[a]

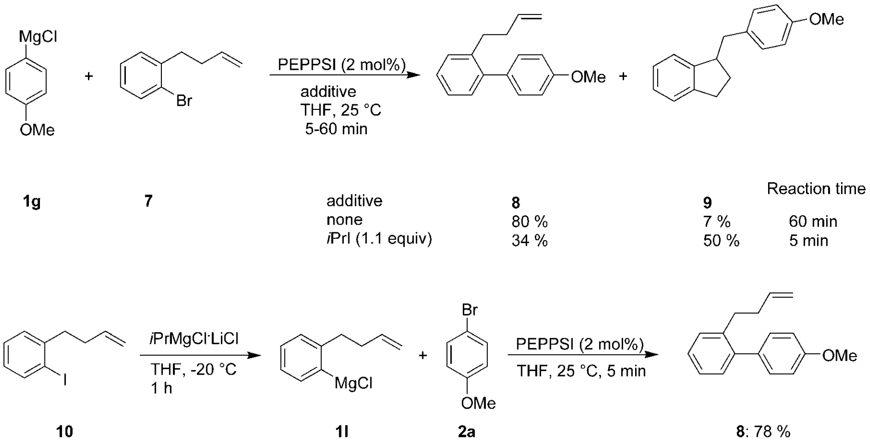
Entry	Magnesium reagent	Aryl bromide	Product	Yield [%][b]	Entry	Magnesium reagent	Aryl bromide	Product	Yield [%][b]
1	 **1b**	 **2c**	 **3c**	92[c]	8	**1d**	 **2h**	 **3j**	74[d]
2	 **1c**	 **2d**	 **3d**	84[d]	9	**1d**	 **2i**	 **3k**	86[d,g]
3	**1c**	 **2e**	 **3e**	82[c]	10	**1d**	 **2j**	 **3l**	82[e]
4	**1c**	 **2a**	 **3f**	78[d]	11	 **1e**	 **2k**	 **3m**	77[f]
5	**1c**	 **2b**	 **3g**	75[e]	12	 **1f**	 **2l**	 **3n**	84[c]
6	 **1d**	 **2f**	 **3h**	79[c]	13	 **1g**	 **2c**	 **3o**	98[c]
7	**1d**	 **2g**	 **3i**	83[f]	14	 **1h**	 **2m**	 **3p**	92[c]

[a] Reaction for 5 min at 25 °C. [b] Yield of isolated, analytically pure product. [c] 2% PEPPSI was used as catalyst. [d] 2 mol% Pd(OAc)$_2$ and 3 mol% S-Phos were used as the catalyst. [e] 4 mol% Pd(OAc)$_2$ and 6 mol% S-Phos were used as the catalyst. [f] 3 mol% PEPPSI was used as the catalyst. [g] After hydrolysis with 2 M HCl.

84% yield, respectively (Table 1, entries 2 and 3). Similarly, electron-rich 4-bromoanisole (**2a**) and the bromoaryl ketone **2b** could be coupled with the magnesium reagent **1c** (1.1 and 1.2 equiv) to furnish the desired products **3f** and **3g** in 75 and 78% yield, respectively (Table 1, entries 4 and 5). The reaction of 1-bromo-3-chlorobenzene (**2f**) with the functionalized Grignard reagent **1d** proceeded chemoselectively and afforded the chlorobiphenyl derivative **3h** in 79% yield (Table 1, entry 6). The heteroaryl bromides **2g** and **2h** also reacted with the ester-substituted organomagnesium compound **1d** leading to the functionalized pyridine **3i** and indole **3j** in 74 and 83% yield, respectively (Table 1, entries 7 and 8). The cross-coupling of **1d** and the imine **2i** led to the aniline **3k** in 86% yield after acidic hydrolysis (Table 1, entry 9). Sensitive substrates like the bromoaryl ketone **2j** were perfectly tolerated in this reaction. The reaction of **1d**



Scheme 2. Kumada couplings of heteroarylmagnesium reagents in the presence of *i*PrI.



additive	8	9	Reaction time
none	80 %	7 %	60 min
*i*PrI (1.1 equiv)	34 %	50 %	5 min

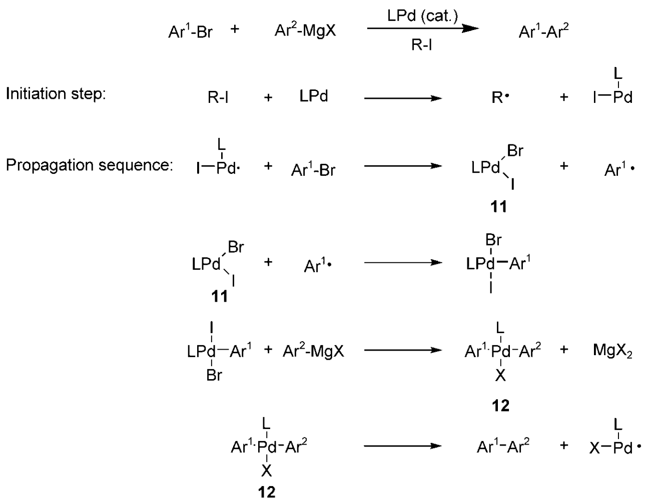
Scheme 3. Cross-couplings of substrates **1l** and **7**, which bears a remote double bond.

(1.2 equiv) with the bromoaryl ketone **2j** (1.0 equiv) furnished the polyfunctional biphenyl **3l** in 82% yield (Table 1, entry 10). Several other functionalized Grignard reagents were suitable for the cross-coupling procedure. Thus, 3-cyanophenylmagnesium chloride (**1e**) coupled with ethyl 3-bromobenzoate (**2k**) gave **3m** in 77% yield (Table 1, entry 11). Similarly, the reaction of 4-fluorophenylmagnesium chloride (**1f**) and the electron-rich 4-methoxyphenylmagnesium chloride (**1g**) with the bromobenzonitriles **2l** and **2c** afforded the biphenyls **3n** and **3o** in 84% and 98% yield, respectively (Table 1, entries 12 and 13). Also, the sterically hindered mesitylmagnesium reagent **1h** reacted with the ester-substituted aryl bromide **2m**, leading to the biphenyl **3p** in 92% yield (Table 1, entry 14).

Encouraged by these results, we applied several heteroarylmagnesium compounds in the *i*PrI-accelerated Kumada coupling. Thus, 1-thienylmagnesium chloride (**1i**, 1.1 equiv) reacted smoothly with the aryl bromides **2d** and **2m** (1.1 equiv), and the functionalized thiophenes **3q** and **3r** were obtained in 91% and 92% yield, respectively (Scheme 2). By using the heteroarylmagnesium reagents **1j** and **1k**, prepared from pyrimidine **5** and indole **6** by I/Mg exchange, the arylated heterocycles **3s** and **3t** were obtained in 83% and 79% yield after the reaction with aryl bromides **2d** and **2k** (Scheme 2).

Since various alkyl halides such as methyl iodide or neopentyl iodide lead to a similar rate acceleration whereas no rate acceleration was observed with aryl triflates,[18] we suspected a radical mechanism for the cross-coupling catalysis based on the pioneering contributions of Hegedus, Kochi, and Osborn.[19,20] We therefore submitted the bromobenzene derivative **7**, which bears a remote double bond, to the cross-coupling conditions. We obtained a mixture of the cyclized product **9** (50% yield) and the noncyclized product **8** (34% yield), which supports a radical intermediate.[21] We verified that an organopalladium(II) intermediate of the type [Ar^{1}PdAr^2] does not likely lead to the cyclized product **9** since the use of a Grignard reagent **1l** bearing a remote double bond did not lead to a cyclization product but provided, after cross-coupling with **2a**, only the biphenyl **8** (90% yield, Scheme 3).

On the basis of these results we propose the mechanism shown in Scheme 4. The palladium(0) catalyst [LPd^0] reacts in an initiation step with



Scheme 4. Tentative mechanism of the palladium-catalyzed cross-coupling between an aryl bromide and an arylmagnesium reagent by a radical path.

the alkyl iodide RI, affording the radical R$^\bullet$ and the palladium(I) intermediate [LPdI] (**11**). Previous reports from the Curran and Suzuki groups as well as from our laboratory have demonstrated that alkyl iodides react by a radical path with Pd^0 complexes (or Ni^0 complexes) and Et$_2$Zn.[22] Similarly, the reaction of the palladium(I) intermediate **11** with the aryl bromide Ar^1–Br furnishes an aryl radical Ar$^{1\bullet}$, which may undergo a ring closure in the presence of a remote double bond (see Scheme 3). The trapping of this aryl radical with [LPdX$_2$] results in the formation of the Pd^{III} intermediate [Ar^{1}PdL(I)(Br)], which after ligand exchange with Ar^{2}MgBr provides the diarylpalladium(III) halide **12**. Reductive elimination of **12** furnishes the cross-coupling product Ar^1–Ar^2 and regenerates the Pd^I radical chain carrier.

In summary, we have found that the *i*PrI-accelerated Kumada cross-coupling allows the rapid reaction of a wide range of functionalized aryl- and heteroarylmagnesium reagents with aryl bromides. Since the transmetalation of readily available Grignard reagents to zinc or boron intermediates can be avoided, this is a more atom-economical[3] variant of the Kumada cross-coupling reaction. Extension of this radical catalysis is currently underway in our laboratories.

Experimental Section

Typical procedure: Preparation of **3b**: A solution of *i*PrMgCl·LiCl (3.5 mL, 3.78 mmol, 1.08 M in THF) was cooled to −20 °C, and **4a** (3.6 mmol, 980 mg) was added. The reaction mixture was stirred for 30 min at this temperature. Then, the Grignard reagent **1b** was slowly added by means of a Teflon cannula to a solution of **2b** (681 mg, 3 mmol), Pd(OAc)$_2$ (27.6 mg, 0.12 mmol), and S-Phos (73.8 mg, 0.18 mmol) in THF (3 mL). The resulting mixture was stirred for 5 min at 25 °C. Then the reaction mixture was quenched with a saturated NH$_4$Cl solution and extracted with diethyl ether. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and concentrated to dryness. Purification of the crude residue by flash chromatography (pentane/diethyl ether 97:3) yielded **3b** as a colorless oil (768 mg, 87 %).

Received: July 30, 2008

Keywords: cross-coupling · homogeneous catalysis · organomagnesium compounds · palladium · radicals

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[14] The addition of the alkyl iodide after the preparation of the Grignard reagent had the same effect. See the Supporting Information for further details.

[15] Catalytic amounts of the alkyl iodide resulted in the decomposition of the catalyst prior to complete consumption of the starting aryl bromide.

[16] The arylmagnesium reagent **1c** is only stable below −20 °C and decomposes at 25 °C within 10 min.

[17] As no general rule could be found for the selection of the best Pd catalyst, each reaction was tested with both catalyst systems.

[18] Under the conditions described by Buchwald et al. (low temperature, THF/toluene) similar yields and reaction times were obtained (see Ref. [7] for details). However, when the reaction was performed at 25 °C in THF/toluene, several by-products were obtained (typically < 5 % by GC–MS analysis) that arose from radical reactions of toluene.

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