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i-PrI Acceleration of Negishi Cross-Coupling Reactions

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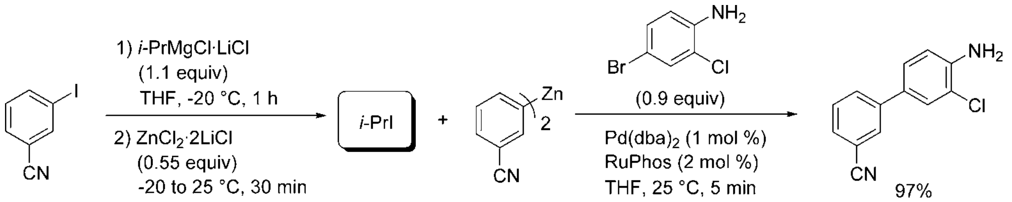
ABSTRACT



The Negishi cross-coupling of arylzinc reagents with various bromoanilines is accelerated by the presence of *i*-PrI (1 equiv) and furnished the expected biaryls within 5−12 min reaction time at 25 °C. Arylzinc reagents can also be cross-coupled under these conditions with a range of aryl bromides bearing an enolizable ester or acidic benzylic protons.

The Suzuki and the Negishi cross-coupling reactions are the most powerful and widely used methods for making $C_{sp2}-C_{sp2}$ bonds.[1] In contrast to organoboronates (Suzuki reaction), organozinc reagents usually undergo cross-couplings under very mild conditions; however, arylboronates are usually air- and water-stable reagents.[2] Recently, we reported that primary and secondary amines, alcohols, phenols and amides are compatible with the Negishi cross-coupling conditions, when the zinc reagent is slowly added (over 90 min) to the electrophile.[3] Furthermore, we reported a new *i*-PrI-accelerated Kumada cross-coupling, allowing a reaction of aryl bromides and magnesium reagents within 5−10 min.[4] A radical reaction pathway has been proposed for this reaction.[4,5] Herein, we report that the Negishi cross-coupling can similarly be accelerated by the presence of *i*-PrI. These new reaction conditions allow the use of aryl bromides bearing various acidic protons without the need of protection.

Thus, a Br/Mg exchange on 3-bromobenzonitrile (**1a**) and subsequent transmetalation with the THF-soluble complex $ZnCl_2 \cdot 2LiCl$[6] afforded the diarylzinc reagent **2** (Scheme 1). Negishi cross-coupling of **2** with 4-bromoaniline (**3a**) in the presence of $Pd(dba)_2$ (1 mol %) and RuPhos[7] (2 mol %) gave only 37% conversion after 10 min at 25 °C. However,

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[1] (a) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, 1998. (c) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, 1995. (d) Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009. (e) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545.

[2] (a) Negishi, E.; King, A. O.; Okudado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (d) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532. (e) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380. (f) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756. (g) Zeng, X.; Quian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259.

[3] (a) Manolikakes, G.; Dong, Z.; Mayr, H.; Li, J.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 1324. (b) Manolikakes, G.; Schade, M. A.; Munoz Hernandez, C.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765. (c) Manolikakes, G.; Munoz Hernandez, C.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422.

[4] Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205.

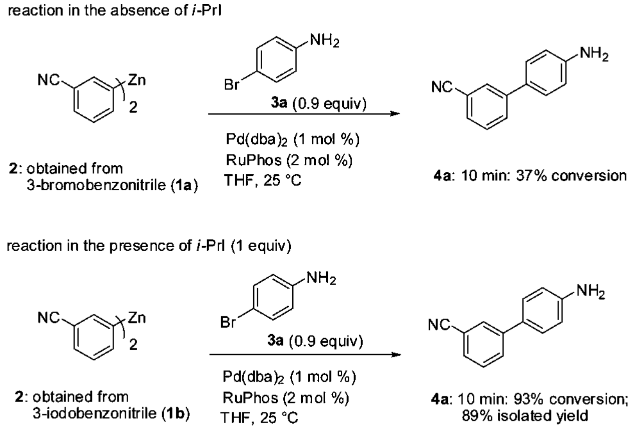
[5] (a) Corey, E. J.; Semmelhack, M. F.; Hegedus, L. S. *J. Am. Chem. Soc.* **1968**, *90*, 2416. (b) Corey, E. J.; Semmelhack, M. F.; Hegedus, L. S. *J. Am. Chem. Soc.* **1968**, *90*, 2417. (c) Hegedus, L. S.; Waterman, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 6789. (d) Hegedus, L. S.; Miller, L. L. *J. Am. Chem. Soc.* **1975**, *97*, 459. (e) Hegedus, L. S.; Thompson, D. H. P. *J. Am. Chem. Soc.* **1985**, *107*, 5663. (f) Elson, I. H.; Morrell, D. G.; Kochi, J. K. *J. Organomet. Chem.* **1975**, *84*, C7. (g) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319. (h) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547. (i) Labinger, J. A.; Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 7908. (j) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7145. (k) Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7832.

[6] The presence of LiCl from $ZnCl_2 \cdot 2LiCl$ leads to an additional rate enhancement.

[7] For aryl−aryl Negishi cross-coupling reactions using RuPhos, see: Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

10.1021/ol1007026

Scheme 1. Negishi Cross-Coupling of Zinc Reagents with Aryl Bromides Accelerated by *i*-PrI

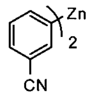
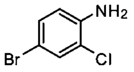
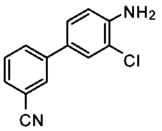
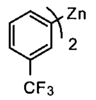
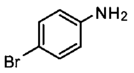
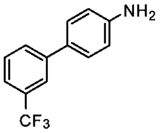
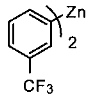
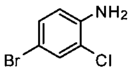
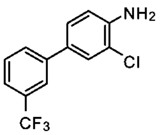
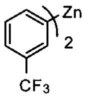
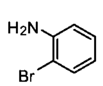
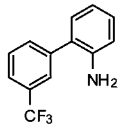
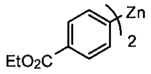
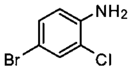
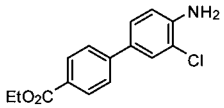
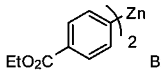
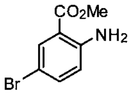
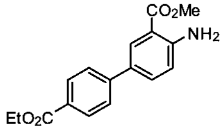
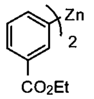
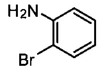
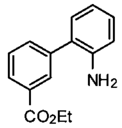
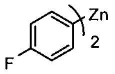
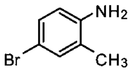
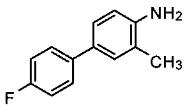
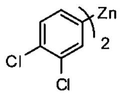
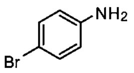
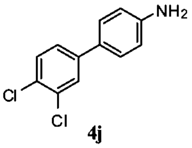


when the same reaction is performed with the diarylzinc **2**, generated from the corresponding 3-iodobenzonitrile (**1b**), full conversion was obtained after 10 min, and the desired biaryl **4a** was isolated in 89% yield. Other alkyl iodides gave also an acceleration in this reaction. However, this effect strongly depends on the nature of the used alkyl halide. Secondary alkyl iodides gave the best results.[8] The same rate enhancement can also be achieved by addition of *i*-PrI (1.1 equiv) to a Grignard reagent obtained by Br/Mg-exchange and subsequent transmetalation with the THF-soluble complex $ZnCl_2$•2LiCl.

Encouraged by these results, we studied the scope of this new protocol, emphasizing the compatibility with amines and various other functional groups bearing acidic protons. Thus, the reaction of bis(3-cyanophenyl)zinc (**2b**) with 4-bromo-2-chloroaniline (**3b**) in the presence of $Pd(dba)_2$ (1 mol %) and RuPhos[7] (2 mol %) furnished the biphenyl **4b** within 5 min at 25 °C in 97% yield (Table 1, entry 1). In a similar manner, 1-iodo-3-(trifluoromethyl)benzene was converted to the corresponding biarylzinc **2c**. This reagent was successfully coupled with various bromoanilines **3a**,**b**, furnishing the amines (**4c**,**d**) in 89−92% yield (entries 2 and 3). Furthermore, the zinc compound **2c** was reacted with the sterically hindered 2-bromoaniline (**3c**), providing the biaryl **4e** within 10 min in 80% yield (entry 4). Interestingly, this reaction also proceeds smoothly at larger scales (10 mmol), furnishing the aniline derivative **4e** after the same reaction time in 81% yield.

This procedure was extended to functionalized zinc reagents bearing an ester function. This may be of practical interest since the corresponding magnesium reagents show a low stability at room temperature. Therefore, the zinc species **2d** was chemoselectively coupled with 4-bromo-2-chloroaniline (**3b**), affording the chlorobiphenyl derivative **4f** in 91% yield (entry 5). After reaction of **2d** with the

Table 1. Palladium-Catalyzed Cross-Coupling of Zinc Reagents **2** with Aniline Derivatives of Type **3**

entry	substrate	electrophile	product	yield (%)[a]
1	 **2b**	 **3b**	 **4b**	97[b]
2	 **2c**	 **3a**	 **4c**	92[b]
3	 **2c**	 **3b**	 **4d**	89[b]
4	 **2c**	 **3c**	 **4e**	80[b, e] 81[b, c, e]
5	 **2d**	 **3b**	 **4f**	91[b]
6	 **2d**	 **3d**	 **4g**	94[b, e]
7	 **2e**	 **3c**	 **4h**	79[b,e]
8	 **2f**	 **3e**	 **4i**	94[e,f]
9	 **2g**	 **3a**	 **4j**	76[d]

[a] Isolated, analytically pure product. Reaction conditions: 5 min at 25 °C. [b] The zinc reagent was obtained by an I/Mg exchange and subsequent transmetalation with $ZnCl_2$•2LiCl (0.55 equiv). [c] The reaction was performed on a 10 mmol scale. [d] The zinc reagent was obtained by a Br/Mg exchange and subsequent transmetalation with $ZnCl_2$•2LiCl (0.55 equiv) and addition of *i*-PrI (1.1 equiv). [e] 10 min reaction time. [f] The zinc reagent was obtained after a Br/Mg insertion and subsequent transmetalation with $ZnCl_2$•2LiCl (0.55 equiv) and addition of *i*-PrI (1.1 equiv).

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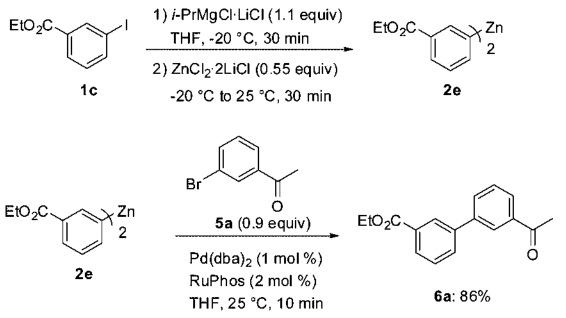
(8) The use of the other secondary alkyl iodides instead of *i*-PrI led to comparable conversions. *n*-BuI and cHexI gave under similar conditions after 10 min 88% and 85% conversion, respectively. In contrast, MeI resulted in a conversion of 18%.

methyl ester derivative **3d** the corresponding biaryl **4g** was obtained in 94% yield (entry 6). 2-Bromoaniline (**3c**) was reacted with the ester-substituted organozinc compound **2e**, furnishing the aniline derivative **4h** within 10 min in 79% yield (entry 7). Additionally, we have applied this procedure to zinc reagents prepared by transmetalation from the corresponding arylmagnesium bromides. Thus, the reaction of the zinc reagent **2f** in the presence of *i*-PrI (1.1 equiv) with 4-bromo-2-methylaniline (**3e**) gave within 10 min the amine **4i** in 94% yield (entry 8). In a similar sequence, the reaction of the dichlorophenylzinc reagent **2g** with 4-bromoaniline (**3a**) furnished the biaryl **4j** in 76% yield (entry 9).

We used also this protocol for the reaction of enolizable bromoaryl ketones. Therefore, ethyl 3-iodobenzoate (**1c**) was smoothly exchanged using *i*PrMgCl•LiCl (30 min, −20 °C). Transmetalation with $ZnCl_2$•2LiCl (0.55 equiv) furnished the diarylzinc **2e** (Scheme 2). Subsequent palladium-catalyzed cross-coupling with 3-bromoacetophenone (**5a**) yielded the biaryl ketone **6a** in 86% yield.

Scheme 2. Negishi Cross-Coupling of a Biarylzinc Reagent **2e** with 3-Bromoacetophenone (**5a**)



By applying this procedure, various arylzinc reagents were efficiently coupled with several bromoaryl ketones. Thus, the reaction of **2d** with 4-bromovalerophenone (**5b**) furnished the ester **6b** in 92% yield (Table 2, entry 1). Furthermore, the Pd-catalyzed cross-couplings of the zinc compounds **2c** and **2h** with 3-bromoacetophenone (**5a**) resulted in the biaryls **6c**,**d** in 85−86% yield (entries 2 and 3). The coupling of **2b** with the sterically hindered 3-bromo-4-fluoropropiophenone (**5c**) gave the desired product **6e** within 12 min in 73% yield (entry 4). This reaction was also applicable toward the reaction of zinc reagents obtained from the corresponding arylmagnesium bromides and addition of *i*-PrI (1.1 equiv). Thus, the reaction of **2f** in the presence of *i*-PrI, Pd(dba)$_2$, and RuPhos with various bromoarylketones provided the biaryls **6f**−**h** in 91% yield (entries 5−7).

Scheme 3. Negishi Cross-Coupling of a Diarylzinc Reagent **2a** with (4-Bromophenyl)acetonitrile (**7a**)

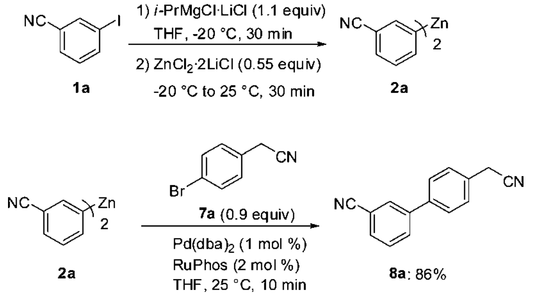
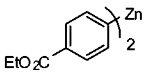
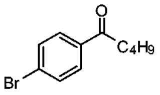
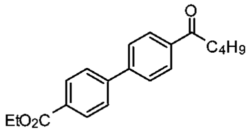
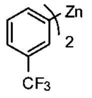
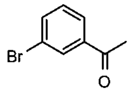
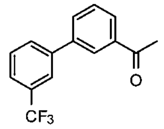
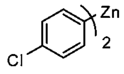
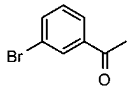
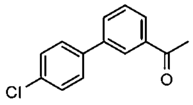
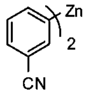
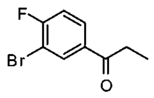
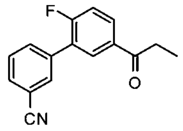
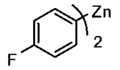
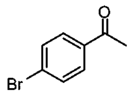
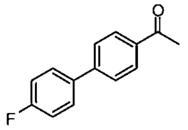
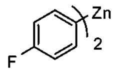
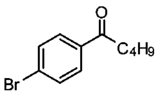
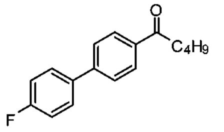
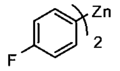
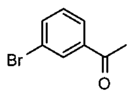
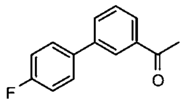


Table 2. Palladium-Catalyzed Cross-Coupling of Zinc Reagents **2** with Arylbromoketones of Type **5**

entry	substrate	electrophile	product, yield (%)[a]
1	 **2d**	 **5b**	 **6b** (92)[b]
2	 **2c**	 **5a**	 **6c** (86)[b]
3	 **2h**	 **5a**	 **6d** (85)[b]
4	 **2b**	 **5c**	 **6e** (73)[b,d]
5	 **2f**	 **5d**	 **6f** (91)[c]
6	 **2f**	 **5b**	 **6g** (91)[c]
7	 **2f**	 **5a**	 **6h** (91)[c]

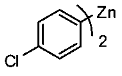
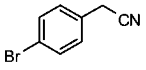
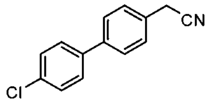
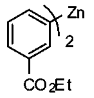
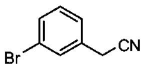
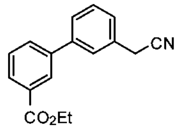
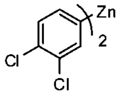
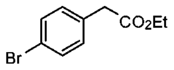
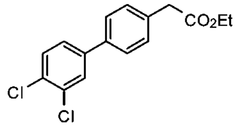
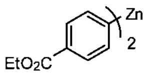
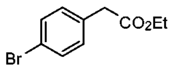
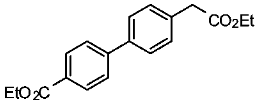
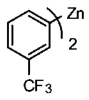
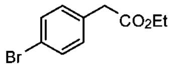
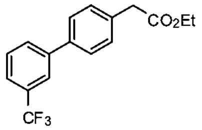
[a] Isolated, analytically pure product. Reaction conditions: 5 min at 25 °C. [b] The zinc reagent was obtained by an I/Mg exchange and subsequent transmetalation with $ZnCl_2$•2LiCl (0.55 equiv). [c] The zinc reagent was obtained after a Br/Mg insertion and subsequent transmetalation with $ZnCl_2$•2LiCl (0.55 equiv) and addition of *i*-PrI (1.1 equiv). [d] 12 min reaction time.

Furthermore, we used this method for the coupling of arylzinc reagents with aryl bromides bearing acidic benzylic protons. Thus, the I/Mg exchange of 3-iodobenzonitrile (**1a**) with *i*PrMgCl·LiCl and transmetalation with $ZnCl_2$·2LiCl (0.55 equiv) yielded the diarylzinc **2a** (Scheme 3).

Subsequent Pd(0)-catalyzed cross-coupling with (4-bromophenyl)acetonitrile (**7a**) furnished the dinitrile **8a** in 86% yield.

Also, the reaction of the chloroarylzinc reagent **2h** with **7a** yielded the biaryl **8b** in 97% yield (Table 3, entry 1).

Table 3. Cross-Coupling of Arylzinc Reagents with Various Aryl Bromides Bearing Acidic Benzylic Protons

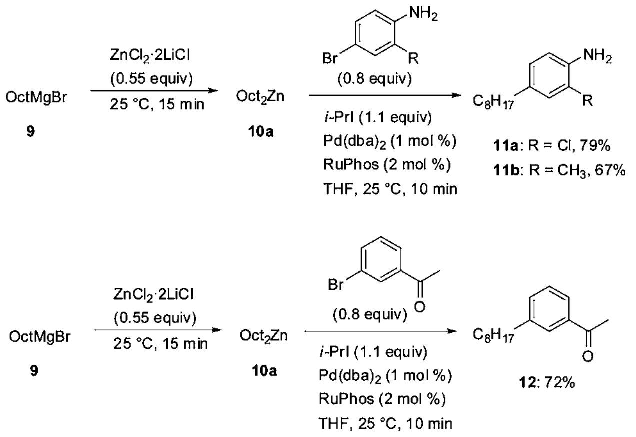
entry	substrate	electrophile	product, yield (%)[a]
1	 **2h**	 **7a**	 **8b** 97[b]
2	 **2e**	 **7b**	 **8c** 89[b]
3	 **2g**	 **7c**	 **8d** 83[c]
4	 **2d**	 **7c**	 **8e** 85[b]
5	 **2c**	 **7c**	 **8f** 94[b]

[a] Isolated, analytically pure product. Reaction conditions: 5 min at 25 °C. [b] The zinc reagent was obtained by an I/Mg exchange and subsequent transmetalation with $ZnCl_2$·2LiCl (0.55 equiv). [c] The zinc reagent was obtained by a Br/Mg exchange and subsequent transmetalation with $ZnCl_2$·2LiCl (0.55 equiv) and addition of *i*-PrI (1.1 equiv).

Furthermore, the coupling of the zinc compound **2e** bearing an ester function with (3-bromophenyl)acetonitrile (**7b**) provided the desired product **8c** in 89% yield (entry 2). The reaction of the dichlorophenylzinc reagent **8d** with (4-bromophenyl)acetic acid ethyl ester (**7c**) in the presence of *i*-PrI leads to the dichlorobiaryl **8d** in 83% yield (entry 3). The coupling of the zinc compounds **2c**,**d** with aryl bromide **7c** furnished the esters **8e**,**f** in 85−94% yield.

This protocol was extended to alkylzinc reagents. Thus, OctMgBr (**9**) was smoothly transmetalated with $ZnCl_2$·2LiCl (0.55 equiv) furnishing Oct_2Zn (**10a**). Subsequent Pd-catalyzed cross-coupling in the presence of *i*-PrI with various bromoanilines provided within 10 min the amines **11a**,**b** in 67−79% yield. In a similar manner, the reaction of **10a** with 3-bromoacetophenone (**5a**) furnished within 10 min the ketone **12** in 72% yield (Scheme 4).

Scheme 4. Cross-Coupling of an Alkylzinc Reagent with Various Aryl Bromides Bearing Acidic Protons



In conclusion, we have reported a new protocol for the Negishi cross-coupling of organozinc reagents with aryl bromides bearing acidic protons in the presence of *i*-PrI and an active Pd-catalyst system such as RuPhos, enhancing the yield of application of this valuable ligand.[7] This new procedure allows remarkably fast coupling reactions, thereby allowing in several cases to avoid protecting groups.

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Note Added after ASAP Publication. The abstract graphic contained an error in the version published ASAP May 18, 2010; the correct version reposted May 21, 2010.

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

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