ORGANIC LETTERS

2008
Vol. 10, No. 13
2765−2768

Negishi Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents

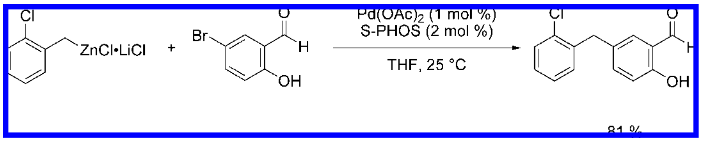
Georg Manolikakes, Matthias A. Schade, Carmen Muñoz Hernandez, Herbert Mayr, and Paul Knochel*

Department Chemie and Biochemie, Ludwig-Maximilians-Universität,
Butenandtstrasse 5-13, 81377 München, Germany

paul.knochel@cup.uni-muenchen.de

Received April 18, 2008

ABSTRACT

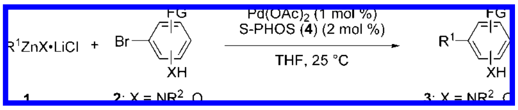


A wide range of polyfunctional aryl, heteroaryl, alkyl, and benzylic zinc reagents were coupled with unsaturated halides bearing an acidic NH or OH function, using Pd(OAc)$_2$ (1 mol %) and S-Phos (2 mol %) as catalyst without the need of protecting groups.

Pd-catalyzed cross-couplings that allow linking of unsaturated molecular fragments are of central importance in synthetic organic chemistry. The resulting products are highly relevant for applications in the pharmaceutical or agrochemical industry, as well as for the preparation of new materials.[1] The most popular Pd-catalyzed cross-coupling, the Suzuki cross-coupling, uses as substrates boronic acids or derivatives[2] and is compatible with many functional groups, especially with functional groups bearing relatively acidic hydrogens such as amines,[3] anilines,[4] alcohols,[5] or heterocyclic NH groups.[6] Due to the covalent nature of the C−B bond of boronic acids, these cross-couplings proceed as a rule under harsher conditions as the corresponding cross-couplings using organozincs (Negishi cross-couplings).[7]

Although organozinc reagents are reactive toward acidic hydrogens, herein we report reaction conditions and a catalytic system allowing an efficient cross-coupling between various organozinc reagents (**1**) and a broad range of aryl halides bearing relatively acidic NH or OH groups of type **2**, leading to polyfunctional products of type **3** (Scheme 1).

Scheme 1. Pd-Catalyzed Cross-Couplings between Functionalized Zinc Reagents and Aromatic Substrates Bearing an Acidic NH or OH Function



Preliminary experiments show that a range of active catalyst systems[8] allow the cross-coupling of arylzinc halides with various bromoanilines. However, we have found that S-Phos

---

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, 2004. (b) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, 1995. (c) *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Beller, M., Bolm, M., Eds.; Wiley-VCH: Weinheim, 1998. (d) Miyaura, N., Ed. Cross-Coupling Reactions. A Practical Guide *Top. Curr. Chem.* 2002, 219.

(2) (a) Miyaura, N.; Suzuki, A. *Chem. Rec.* **1995**, *95*, 2457. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (c) Wolfe, J. P.; Buchwald, S. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (d) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (e) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

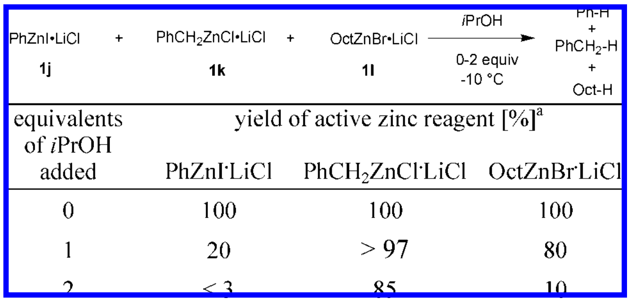
(3) Villard, A.-L.; Warrington, B. R.; Ladlow, M *J. Comb. Chem.* **2004**, *6*, 611.

(4) Miura, Y.; Oka, H.; Momoki, M. *Synthesis* **1995**, *11*, 1419.

10.1021/ol8009013 CCC: $40.75

(**4**), introduced by Buchwald,[9] affords reproducible results for a broad range of substrates under mild conditions. Thus, the reaction of 4-cyanophenylzinc iodide (**1a**, 1.2 equiv) with 2-amino-5-bromobenzoic acid methyl ester (**2a**, 1.0 equiv) in the presence of $Pd(OAc)_2$ (1 mol %) and S-Phos (**4**, 2 mol %) provides the desired cross-coupling product **3a** within 2 h at 25 °C in 98% isolated yield (entry 1 of Table 1). The relatively acidic NH_2 protons[10] of **2a** do not disturb the cross-coupling reaction, which obviously occurs faster than the competitive deprotonation of the aniline **2a** with the zinc reagent **1a**. The use of S-Phos (**4**) as ligand is crucial and allows a generalization of these results to various zinc reagents. Thus, the arylzinc iodide **1b** prepared by the direct insertion of zinc in the presence of LiCl[11] reacts smoothly with the bromoanilines **2b** within 2 h at 25 °C, leading to the biphenyl aniline **3b** in 87% yield (entry 2). Interestingly, this behavior can be extended to functionalized *alkylzinc bromides* prepared similarly by direct zinc insertion.[11] Thus, the cyano- and ester-substituted alkylzinc bromides **1c** and **1d** (1.2 equiv) react with the bromoanilines **2a** and **2c** (1.0 equiv), affording the substituted anilines **3c** and **3d** in 98% and 73% yield (2 h, 25 °C, entries 3 and 4). In addition, the functionalized benzylic zinc reagent **1e**, prepared by direct zinc insertion into benzylic chlorides,[12] reacts with the bromide **2c** in 1 h at 25 °C, leading to the diarylmethane **3e** in 88% yield (entry 5). In the case of the secondary amine **2d**, the cross-coupling occurs also satisfactorily. The deprotonation of these less acidic amines ($pK_a \sim 40$)[10] is not a concern; however, we have observed a palladium catalyst desactivation due to the high donor ability of these amines. The reaction temperature has therefore to be increased to 65 °C (16 h), providing the polyfunctional amine **3f** in 78% yield (entry 6). 5-Bromoindole (**2e**) was also suitable for the cross-coupling procedure, leading to the arylated indoles **3g** and **3h** in 85% and 94% yield (25 °C, 1 h, entries 7 and 8).[13] Encouraged by these results, we have investigated various unsaturated bromides bearing an alcohol function. To evaluate the kinetic basicity of various types of zinc reagents with alcohols, we have treated an equimolar mixture of PhZnI•LiCl (**1j**), $PhCH_2ZnCl$•LiCl (**1k**), and OctZnBr•LiCl (**1 L**) with various amounts of 2-propanol (Scheme 2).

Scheme 2. Selective Protonation of Organozinc Reagents[a]



equivalents of *i*PrOH added	yield of active zinc reagent [%][a]		
	PhZnI·LiCl	$PhCH_2ZnCl$·LiCl	OctZnBr·LiCl
0	100	100	100
1	20	> 97	80
2	< 3	85	10

[a] Yields are determined by quenching with CuCN/allyl bromide in THF and GC analysis with *n*-tetradecane as internal standard.

Interestingly, we have observed that a chemoselective protonation occurs. Thus, after the addition of 1 equiv of *i*-PrOH at −10 °C, 80% of PhZnI•LiCl (**1j**) and 20% of OctZnBr•LiCl (**1 L**) were protonated, whereas almost no protonation of $PhCH_2ZnCl$•LiCl (**1k**) was observed. After the addition of the second equivalent of *i*-PrOH, the protonation of more than 97% of PhZnI•LiCl (**1j**) and 90% of OctZnBr•LiCl (**1l**) was observed. These results indicate the relative kinetic basicity of zinc reagents: arylzinc halide > alkylzinc halide > benzylzinc halide.[14]

Thus, adding 2-chlorobenzylzinc chloride (**1f**, 1.2 equiv) slowly over 90 min (via syringe pump) to a solution of 4-bromobenzyl alcohol (**2f**, 1.0 equiv), $Pd(OAc)_2$ (1 mol %), and S-Phos (**4**, 2 mol %) led to the cross-coupling product **3i** in 98% yield (entry 9 of Table 1). The slow addition of the zinc reagent was crucial for obtaining a high yield. Also, the aniline derivative **2g** and the substituted indole **2h**, bearing relatively acidic NH and OH protons, react with the benzylzinc chlorides **1g** and **1h**, leading to the coupling products **3j** and **3k** in 64% and 72% yield (entries 10 and 11). To our delight, even more acidic phenolic protons were tolerated by our protocol. Adding 2-chlorobenzylzinc chloride (**1f**, 1.3 equiv) slowly (over 90 min) to a solution of 4-bromophenol (**2i**, 1 equiv), $Pd(OAc)_2$ (1 mol %), and S-Phos (**4**, 2 mol %) provided the phenol **3l** in 98% yield (entry 12). Similarly, the benzylzinc chlorides **1f** and **1i** react smoothly with 5-bromosalicylaldehyde (**2j**), leading to the polyfunctional phenols **3m** and **3n** in 81% and 73% yield (entries 13 and 14). The more basic arylzinc reagents **1a** and **1b** reacted only with the sterically hindered tertiary iodobenzyl alcohol **2k**, furnishing the biaryls **3o** and **3p** in 78% and 87% yield (entries 15 and 16). The less basic alkylzinc bromide **1c** could be coupled with the less hindered secondary iodobenzyl alcohol **2i**, leading to the benzylic alcohol

---

(5) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. C. *Chem. Eur. J.* **2006**, *12*, 4407.

(6) Prieto, M.; Zurita, E.; Rosa, E.; Munoz, L.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* **2004**, *69*, 6812.

(7) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Zeng, X.; Quian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259.

(8) Using $Ni(acac)_2$ (2 mol %)/bipyridine (3 mol %), some substrates could be coupled at elevated temperature with similar yields.

(9) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844. (c) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096. (d) Biscoe, M. R.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7232. (e) Other ligands tested gave lower yields.

(10) Typical pK_a values (in DMSO) for anilines range between 20−30; for a comprehensive compilation of pK_a data, see http://www.chem.wisc.edu/areas/reich/pkatable/index.htmand references cited therein.

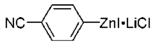
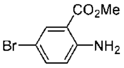
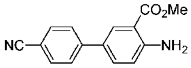
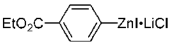
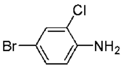
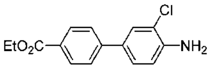
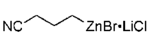
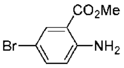
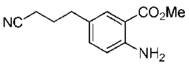
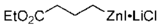
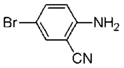
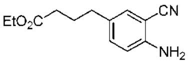
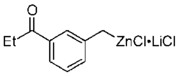
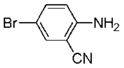
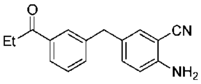
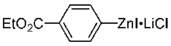
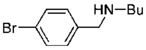
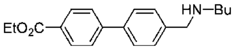
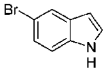
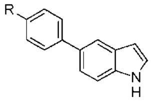
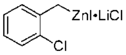
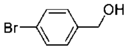
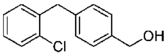
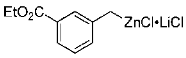
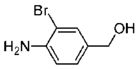
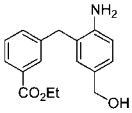
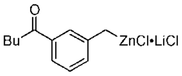
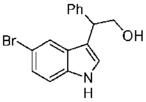
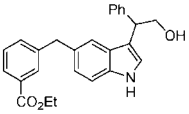
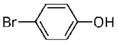
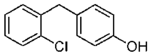
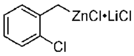
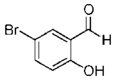
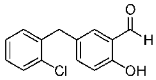
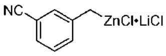
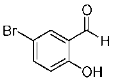
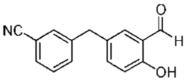
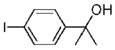
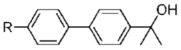
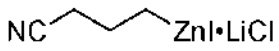
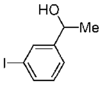
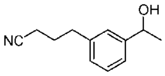
(11) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

(12) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107.

(13) However, for the coupling of 5-bromoindole (**2j**), the zinc reagents **1a** and **1b** had to be prepared by transmetalation from the corresponding magnesium reagents. Control experiments have revealed accelerated cross-coupling reactions in the presence of magnesium salts. For the preparation of organomagnesium reagents, see:(a) Knochel, P.; Gommermann, N.; Kneisel, F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

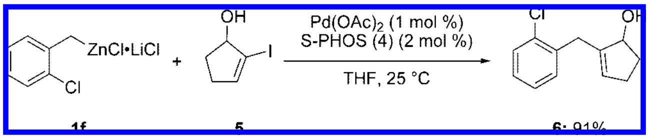
(14) (a) For the reactivity of 1,1-bimetallic species toward protonation, see also: Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1043.

Table 1. Pd-Catalyzed Cross-Couplings between Functionalized Zinc Reagents and Aromatic Substrates Bearing an Acidic NH or OH Function

entry	zinc reagent of type **1**	aryl halide of type **2**	product of type **3**	reaction time (h)[a]	yield (%)[b]
1	 **1a**	 **2a**	 **3a**	2	98
2	 **1b**	 **2b**	 **3b**	2	87
3	 **1c**	 **2a**	 **3c**	2	98
4	 **1d**	 **2c**	 **3d**	2	73
5	 **1e**	 **2c**	 **3e**	1	88
6	 **1b**	 **2d**	 **3f**	16[c]	78
7	**1a**	 **2e**	 **3g** R = CN	1	85
8	**1b**	**2e**	**3h** R = CO_2Et	1	94
9	 **1f**	 **2f**	 **3i**	2.5	98
10	 **1g**	 **2g**	 **3j**	2.5	64
11	 **1h**	 **2h**	 **3k**	2.5	72
12	 **1f**	 **2i**	 **3l**	2.5	98
13	 **1f**	 **2j**	 **3m**	2.5	81
14	 **1i**	 **2j**	 **3n**	2.5	73
15	**1a**	 **2k**	 **3o** R = CN	2.5	78
16	**1b**	**2k**	**3p** R = CO_2Et	2.5	87
17	 **1c**	 **2i**	 **3q**	2.5	88

[a] Reaction time at 25 °C. [b] Isolated yield of analytically pure product. [c] Reaction temperature 65 °C.

Scheme 3. Pd-Catalyzed Cross-Couplings between the Functionalized Benzylic Zinc Reagent (**1m**) and the Cyclopentyl Iodide **5** Bearing an Acidic OH Function



1f **5** **6**: 91%

3q in 88% yield (entry 17). In addition, 2-iodocyclopent-2-enol (**5**) could be coupled with 2-chlorobenzylzinc chloride (**1f**, 1.2 equiv, slow addition over 90 min) to afford the functionalized unsaturated alcohol **6** in 91% yield (Scheme 3).

Acknowledgment. We thank the SFB 749 (DFG) for a financial support. We thank Umicore AG (Angleur, Belgium) for the generous gift of zinc powder. We also thank Chemetall GmbH (Frankfurt), Evonik Industries AG (Hanau), and BASF AG (Ludwigshafen) for the generous gift of chemicals.

Supporting Information Available: Experimental procedures and full characterization of all compounds. This information is available free of charge via Internet at http://pubs.acs.org.

OL8009013