JOC Article

Palladium- and Nickel-Catalyzed Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Protons with Organozinc Reagents

Georg Manolikakes,[†] Carmen Muñoz Hernandez,[‡] Matthias A. Schade,[†] Albrecht Metzger,[†]
and Paul Knochel*,[†]

*Department Chemie and Biochemie, Ludwig-Maximilians-Universität, Butenandtstr. 5-13,
81377 Munich, Germany, and Facultad de Ciencias, Universidad de Málaga, Campus de Teatinos s/n,
29071 Málaga, Spain*

knoch@cup.uni-muenchen.de

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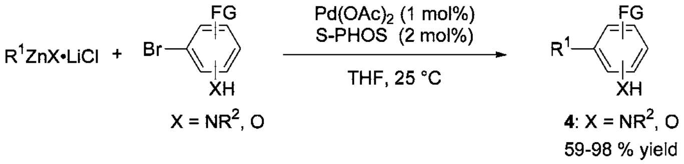

A wide range of polyfunctional aryl, heteroaryl, alkyl, and benzylic zinc reagents were coupled with unsaturated aryl halides bearing an acidic NH or OH proton, using $Pd(OAc)_2$ (1 mol %) and S-Phos (2 mol %) as catalyst without the need of protecting groups. A similar nickel-catalyzed reaction is described. The relative kinetic basicity of organozinc compounds as well as their stability toward acidic protons is also described.

1. Introduction

Palladium- or nickel-catalyzed carbon−carbon bond forming reactions between organometallic reagents and unsaturated halides are important methods in modern synthetic organic chemistry. The resulting products are highly relevant for applications in the pharmaceutical and agrochemical industry, as well as for the preparation of new materials or natural products.[1] Among the possible nucleophilic substrates, organoboronic acids and derivatives are used most widely.[2] Despite the widespread use of organoboron reagents for Suzuki−Miyaura couplings and the advantages associated with these reagents, such as commercial availability, air stablility, and especially their tolerance of relatively acidic protons,[3] difficulties concerning their tendency to form boroxines and competitive protodeboronation remain.[4] Also, due to the covalent nature of the C−B bond of boronic acids, these cross-couplings proceed as a rule under harsher conditions compared to the corresponding Negishi cross-couplings using organozinc compounds.[5] Recently, we have found reaction conditions and a catalytic system allowing the cross-coupling of organozinc reagents with unsaturated halides bearing relatively acidic hydrogens, without the use of protecting groups.[6] No excess of the organozinc reagent and no additional base for deprotonation of the acidic proton prior to the coupling were necessary. Herein, we wish to report the scope and limitations of this cross-coupling reaction as well as the corresponding nickel-catalyzed version of this reaction.

2. Results and Discussion

Palladium-Catalyzed Cross-Coupling Reaction. First, we have examined the palladium-catalyzed cross-coupling of or-

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* Address correspondence to this author. Fax: (+49) 89-2180-77680.

[†] Ludwig-Maximilians-Universität.

[‡] Universidad de Málaga.

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

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(3) (a) Villard, A.-L.; Warrington, B. R.; Ladlow, M. *J. Comb. Chem.* **2004**, *6*, 611. (b) Miura, Y.; Oka, H.; Momoki, M. *Synthesis* **1995**, *11*, 1419. (c) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. C. *Chem.—Eur. J.* **2006**, *12*, 4407. (d) Prieto, M.; Zurita, E.; Rosa, E.; Munoz, L.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* **2004**, *69*, 6812.

(4) For selected examples highlighting the problems with the use of organoboron reagents, see: (a) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362. (b) Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655. (c) Wanatabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

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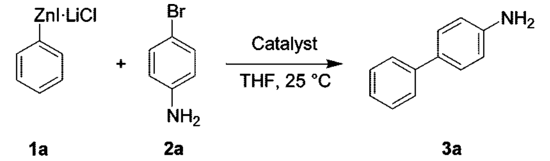
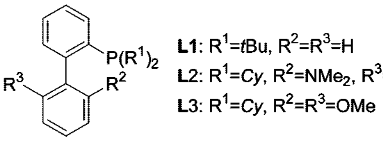
10.1021/jo8015852 CCC: $40.75

TABLE 1. Screening of Various Palladium−Ligand Systems for the Cross-Coupling of Unprotected Aniline 2a



entry	catalyst system	yield [%][a]
1	Pd(PPh$_3$)$_4$ (2 mol%)	-
2	Pd(dba) (2 mol%)/tfp (4 mol%)	9
	Pd(dba) (2 mol%)/PCy$_3$ (4 mol%)	15
3	PEPPSI (2 mol%)	17
4	Pd(OAc)$_2$ (1 mol%)/**L1** (2 mol%)	70
5	Pd(OAc)$_2$ (1 mol%)/**L2** (2 mol%)	57
6	Pd(OAc)$_2$ (1 mol%)/**L3** (2 mol%)	96 (93)[b]
7	Pd(OAc)$_2$ (1 mol%)/**L3** (2 mol%)	17[c]



[a] Yields were determined by GC analysis with tetradecane as internal standard. [b] Isolated yield of analytically pure product. [c] 4-Chloroaniline was used as electrophile.

ganozinc reagents with aryl bromides in the presence of acidic hydrogens. The reaction of phenylzinc iodide (**1a**, 1.2 equiv), prepared by direct zinc insertion in the presence of LiCl,[7] with 4-bromoaniline (**2a**, 1.0 equiv) was chosen as model system. Various ligands were tested (Table 1). Several phosphines, such as PPh$_3$, tri-(2-furyl)-phosphine (tfp) or PCy$_3$, gave low yields of aniline **3a** (<20%, entries 1−3). Similar yields were obtained with N-heterocyclic carbene ligands, for example, PEPPSI (entry 4).[8] Electron-rich biaryl phosphines **L1**−**L3**, introduced by Buchwald,[9] displayed the highest activity for this reaction, and biphenyl **3a** was obtained in moderate to high yields (57−96% yield, entries 4−6). In this class of ligands, S-Phos[10] (**L3**) was identified as the most promising, leading to **3a** in 96% yield (entry 6). Even with the most active catalyst system (Pd(OAc)$_2$/**L3**), aryl chlorides were not suitable. The reaction of phenylzinc iodide (**1a**, 1.2 equiv) with 4-chloroaniline furnished biphenyl **3a** in only 17% yield, indicating a quantitative deprotonation of the aniline prior to the coupling reaction.

Using Pd(OAc)$_2$/**L3** as catalytic system, a broad range of functionalized arylzinc reagents reacted with various bromoanilines within 1−3 h at 25 °C in good to excellent yields (Table 2, entries 1−15). Zinc compounds bearing ester, cyano, or trifluoromethyl groups were suitable for the palladium catalysis and afforded the corresponding polyfunctional anilines in 72−98% yield (Table 2, entries 5−12). Also, 3-pyridylzinc iodide (**1f**) reacted with the bromoanilines **2c**, **2i**, and **2j**, leading to the products **3n**, **3o**, and **3p** (70−98% yield, entries 13−15). In the case of primary or secondary amines, such as the benzylamines **4a** and **4b**, the cross-coupling occurred satisfactorily. The deprotonation of these less acidic amines (pK_a ~ 40[11]) was not a concern; however, we have observed a palladium catalyst deactivation, due to the high donor ability of these amines. The reaction temperature has therefore to be increased to 65 °C (3−16 h), providing the polyfunctional amines **5a**−**5f** in 61−97% yield (entries 16−21). Interestingly, alkylzinc bromides, prepared by direct zinc insertion in alkyl bromides,[7] were suitable for the palladium-catalyzed cross-coupling. Thus, octylzinc bromide (**1g**) and the functionalized alkylzinc compounds **1h** and **1i** reacted with various bromoanilines within 1−3 h at 25 °C, leading to the polyfuctional anilines **3q**−**3w** in 71−98% yield (entries 22−28). Also, functionalized benzylic zinc reagents, prepared by the direct zinc insertion into benzylic chlorides,[12] undergo a cross-coupling with various aryl bromides in 1−3 h at 25 °C, leading to the diarylmethanes **3x**−**3ae** in 73−98% yield (entries 29−36). The polyfunctional pyridine **3ae**, a useful intermediate for the synthesis of HIV integrase inhibitors,[13] was obtained in 92% yield (entry 36) by the reaction of 4-fluorobenzylzinc chloride (**1n**) with bromopyridine **2l**.

Unprotected indoles are also suitable electrophiles under the reaction conditions described above. Thus, the reaction of 5-bromoindole (**6**) with the benzylzinc reagent **1m** gave the expected product **7a** in 71% yield (Scheme 1). Similarly, alkyl- or arylzinc[14] halides react with the unprotected indole **6**, furnishing the functionalized indoles **7b**−**7e** in 85−98% yield (Scheme 1).

Interestingly, more acidic OH protons were tolerated as well by our protocol. Thus, slowly adding phenylzinc iodide (**1a**, 1.2 equiv) over 90 min (via syringe pump) to a solution of the sterically hindered tertiary iodobenzyl alcohol **8a** (1.0 equiv), Pd(OAc)$_2$ (1 mol %) and **L3** (2 mol %) led to the cross-coupling product **10a** in 95% yield (Table 3, entry 1). The slow addition of the zinc reagent was crucial for obtaining a high yield. The functionalized arylzinc reagents **1b** and **1c** also react with the iodide **8a** and gave the biaryls **10b** and **10c** in 78 and 87% yield (entries 2 and 3). By using bromobenzyl alcohol **8b** as electrophile, the cross-coupling product **10c** was obtained in

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(7) The preparation of the zinc reagent by transmetalation from the corresponding organomagnesium or organolithium compound led to similar results. For the preperation via direct zinc insertion, see: Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

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(9) (a) Altman, R. A.; Buchwald, S. L. *Nat. Protoc.* **2007**, *2*, 3115. (b) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096. (c) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(10) S-Phos (**L3**) was purchased from Strem or prepared according to: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(11) Typical pK_a values (in DMSO) for anilines range between 20 and 30, for amines ~40; for a comprehensive compilation of pK_a data see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm and references cited therein.

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

(13) Boros, E. E.; Burova, S. A.; Erickson, G. A.; Johns, B. A.; Koble, C. S.; Kurose, N.; Sharp, M. J.; Tabet, E. A.; Thompson, J. B.; Toczko, M. A. *Org. Process Res. Dev.* **2007**, *11*, 899.

(14) However, for the coupling of 5-bromoindole (**7**), the zinc reagents **1a**, **1g**, and **1h** 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) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

TABLE 2. Palladium-Catalyzed Cross-Coupling of Anilines of Type 2 and Amines of Type 4[a]

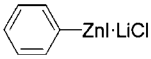
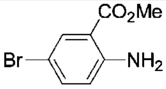
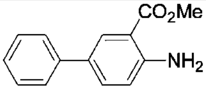
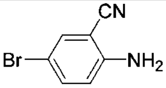
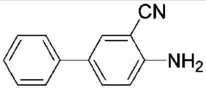
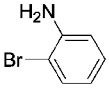
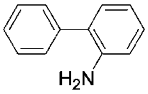
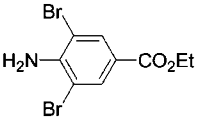
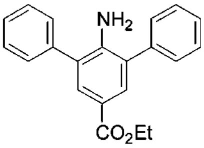
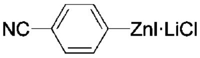
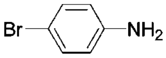
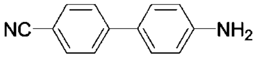
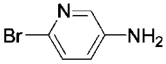
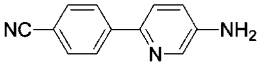
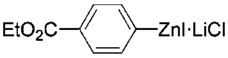
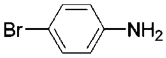
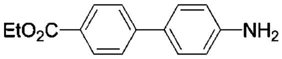
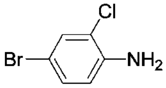
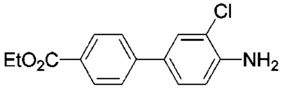
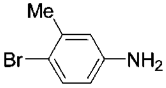
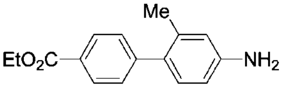
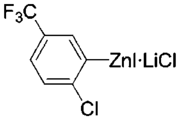
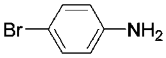
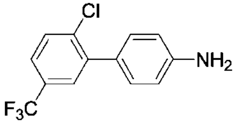
entry	zinc reagent	aryl bromide	product	time [h], T [°C]	yield [%][b]
				2, 25	94
1	**1a**	**2b**	**3b**		
				3, 25	81
2	**1a**	**2c**	**3c**		
				3, 25	67
3	**1a**	**2d**	**3d**		
				2, 25	53^{c}
4	**1a**	**2e**	**3e**		
				2, 25	96
5	**1b**	**2a**	**3f**		
				2, 25	82
6	**1b**	**2f**	**3g**		
				1, 25	88
7	**1c**	**2a**	**3h**		
				2, 25	87
8	**1c**	**2g**	**3i**		
				3, 25	72
9	**1c**	**2h**	**3j**		
				2, 25	79^{d}
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TABLE 2. Continued

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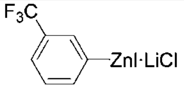
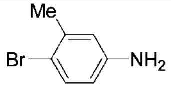
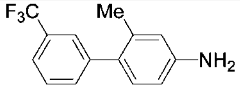
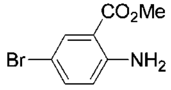
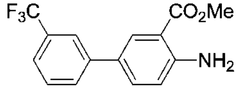
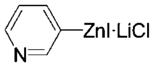
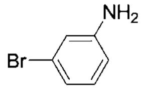
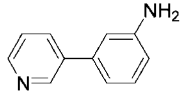
				2, 25	93
11	**1e**	**2h**	**3l**		
				2, 25	98
12	**1e**	**2b**	**3m**		
				2, 25	98
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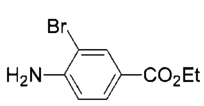
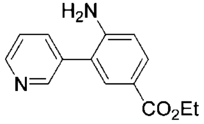
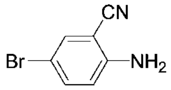
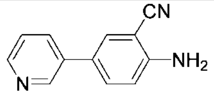
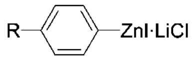
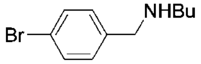
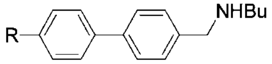
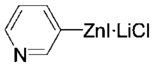
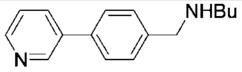
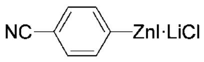
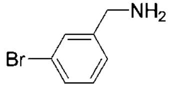
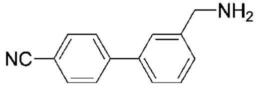
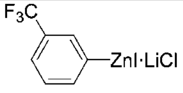
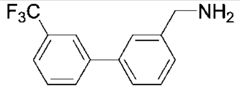
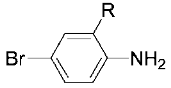
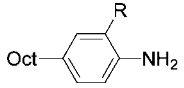
				2, 25	70
14	**1f**	**2j**	**3o**		
				2, 25	87
15	**1f**	**2c**	**3p**		
					
16	**1a**: R = H	**4a**	**5a**: R = H	4, 65	72
17	**1b**: R = CN	**4a**	**5b**: R = CN	17, 65	74
18	**1c**: R = CO_2Et	**4a**	**5c**: R = CO_2Et	16, 65	78
				3, 65	71
19	**1f**	**4a**	**5d**		
				3, 65	97
20	**1b**	**4b**	**5e**		
				3, 65	61
21	**1e**	**4b**	**5f**		
	OctZnBr·LiCl				
22	**1g**	**2a**: R = H	**3q**: R = H	2, 25	92

TABLE 2. Continued

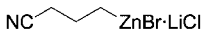
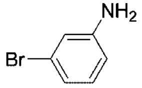
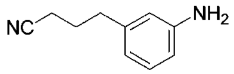
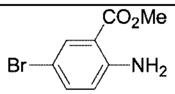
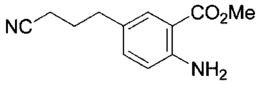
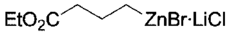
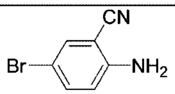
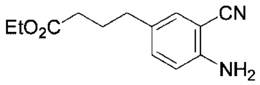
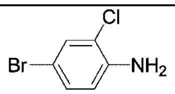
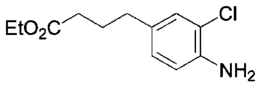
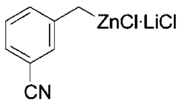
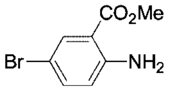
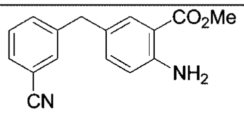
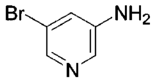
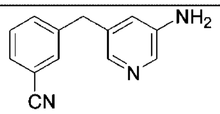
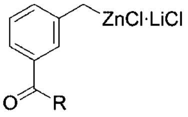
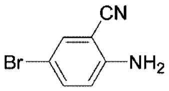
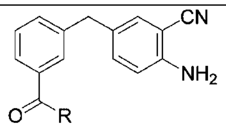
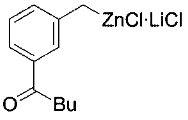
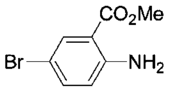
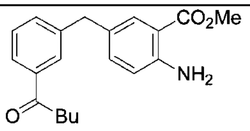
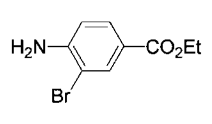
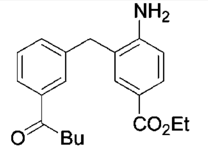
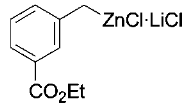
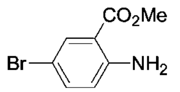
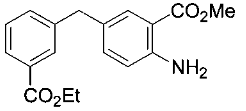
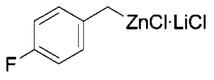
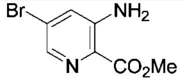
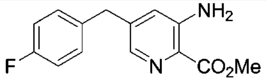
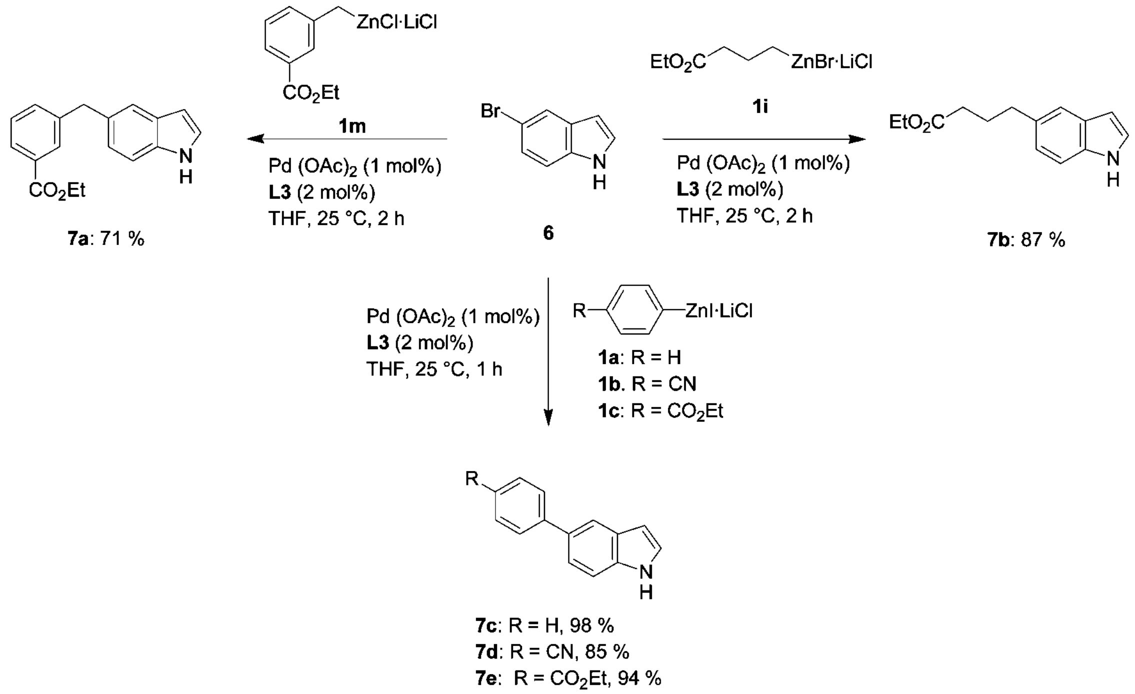
entry	zinc reagent	aryl bromide	product	time [h], T [°C]	yield [%][b]
23	**1g**	**2b**: R = CO_2Me	**3r**: R = CO_2Me	2, 25	85
24	**1g**	**2c**: R = CN	**3s**: R = CN	2, 25	78
				1.5, 25	95
25	**1h**	**2i**	**3t**		
				2, 25	98
26	**1h**	**2b**	**3u**		
				2, 25	73
27	**1i**	**2c**	**3v**		
				3, 25	71
28	**1i**	**2g**	**3w**		
				3, 25	86
29	**1j**	**2b**	**3x**		
				3, 25	90
30	**1j**	**2k**	**3y**		
					
31	**1k**: R = Et	**2c**	**3z**: R = Et	1, 25	88
32	**1l**: R = *n*Bu	**2c**	**3aa** : R = *n*Bu	1, 25	90
				2, 25	98
33	**1l**	**2b**	**3ab**		

TABLE 2. Continued

entry	zinc reagent	aryl bromide	product	time [h], T [°C]	yield [%][b]
				2, 25	73
34	**1l**	**2g**	**3ac**		
				2, 25	97
35	**1m**	**2b**	**3ad**		
				1.5, 25	92
36	**1n**	**2l**	**3ae**		

[a] Reaction conditions: 3.0 mmol of aryl bromide, 3.6 mmol of zinc reagent, Pd(OAc)$_2$ (1 mol %), **L3** (2 mol %). [b] Isolated yield of analytically pure product. [c] 7.2 mmol of the zinc reagent was used. [d] The zinc reagent was added slowly over 90 min via syringe pump.

SCHEME 1. Palladium-Catalyzed Cross-Coupling of Unprotected Indole 6[a]



[a] Reaction conditions: 3.0 mmol of indole **6**, 3.6 mmol of zinc reagent, Pd(OAc)$_2$ (1 mol %), **L3** (2 mol %).

73% yield (entry 4). Similarly, the sterically hindered diphenylmethanol **8c** reacted with the arylzinc iodides **1b** and **1c**, leading to the products **10d** and **10e** in 91 and 81% yield (entries 5 and 6). In the case of the less reactive aryl bromide **8d**, the biphenyl **10e** was obtained in only 40% yield (entry 7). The alkylzinc bromides **1h** and **1i** reacted with the less hindered secondary alcohols **8e** and **8f** and with the primary iodobenzyl alcohol **8g**, furnishing the functionalized benzylic alcohols in 59−88% yield (entries 8−11). Interestingly, various functionalized benzylzinc chlorides could be coupled with 4-bromoben-

TABLE 3. Palladium-Catalyzed Cross-Coupling of Alcohols of Type 8 and Phenols of Type 9[a]

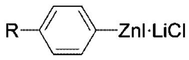
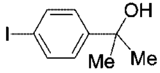
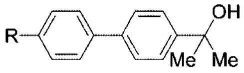
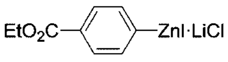
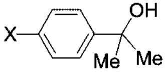
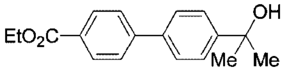
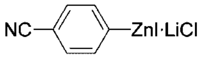
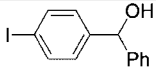
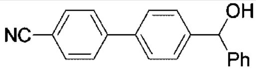
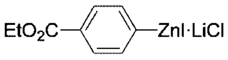
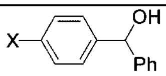
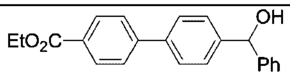
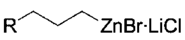
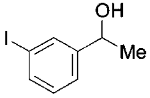
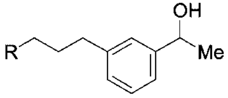
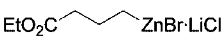
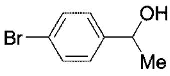
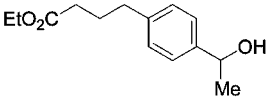
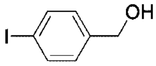
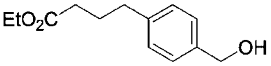
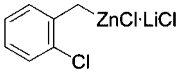
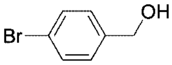
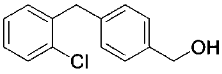
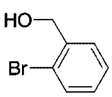
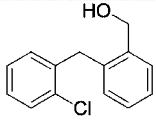
entry	zinc reagent	aryl halide	product	time [h], T [°C]	yield [%][b]
					
1	**1a**: R = H	**8a**	**10a**: R = H	2.5, 25	95
2	**1b**: R = CN	**8a**	**10b**: R = CN	2.5, 25	78
					
3	**1c**	**8a**: X = I	**10c**	2.5, 25	87
4	**1c**	**8b**: X = Br	**10c**	2.5, 25	73
				2.5, 25	91
5	**1b**	**8c**	**10d**		
					
6	**1c**	**8c**: X = I	**10e**	2.5, 25	81
7	**1c**	**8d**: X = Br	**10e**	2.5, 25	40
					
8	**1h**: R = CN	**8e**	**10f**	2.5, 25	88
9	**1i**: R = CO_2Et	**8e**	**10g**	2.5, 25	59
				2.5, 25	70
10	**1i**	**8f**	**10h**		
				2.5, 25	65
11	**1i**	**8g**	**10i**		
				2.5, 25	98
12	**1o**	**8h**	**10j**		
				2.5, 25	0
13	**1o**	**8i**	**10k**		

TABLE 3. Continued

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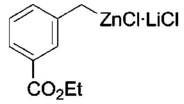
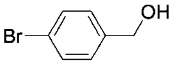
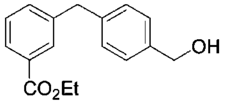
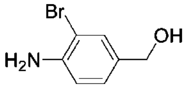
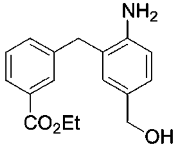
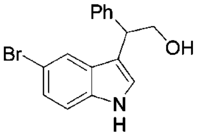
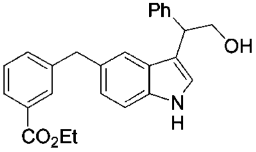
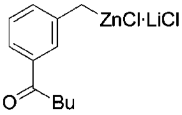
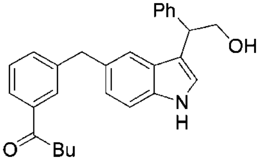
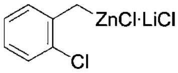
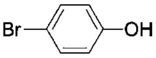
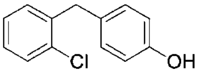
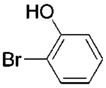
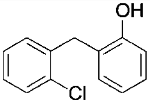
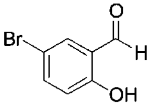
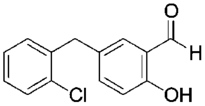
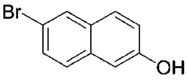
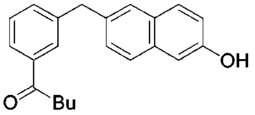
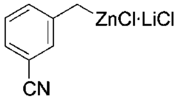
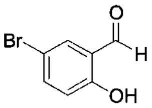
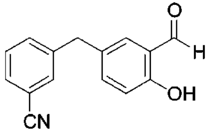
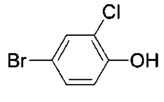
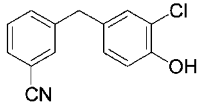
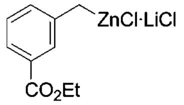
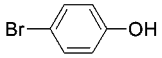
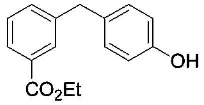
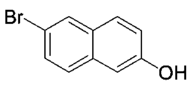
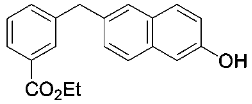
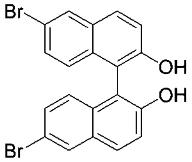
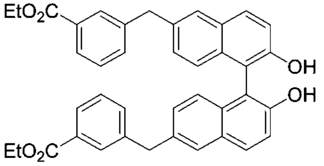
				2.5, 25	94
14	**1m**	**8h**	**10l**		
				2.5, 25	64
15	**1m**	**8i**	**10m**		
				2.5, 25	85
16	**1m**	**8j**	**10n**		
				2.5, 25	72
17	**1l**	**8j**	**10o**		
				2.5, 25	98
18	**1o**	**9a**	**11a**		
				2.5, 25	82
19	**1o**	**9b**	**11b**		
				2.5, 25	81
20	**1o**	**9c**	**11c**		
				2.5, 25	82
21	**1l**	**9d**	**11d**		
				2.5, 25	73
22	**1j**	**9c**	**11e**		

TABLE 3. Continued

entry	zinc reagent	aryl halide	product	time [h], T [°C]	yield [%][b]
				2.5, 25	82
23	**1j**	**9e**	**11f**		
				2.5, 25	89
24	**1m**	**9a**	**11g**		
				2.5, 25	96
25	**1m**	**9d**	**11h**		
				2.5, 25	76[c]
26	**1m**	**9f**	**11i**		

[a] Reaction conditions: 2.0 mmol of aryl halide, 2.4−2.6 mmol of zinc reagent, Pd(OAc)$_2$ (1 mol %), **L3** (2 mol %). [b] Isolated yield of analytically pure product. [c] 5.2 mmol of the zinc reagent was used.

zyl alcohol **8h** or the aryl bromides **8j** and **8k**, bearing relatively acidic NH and OH protons, leading to the products **10j**−**10o** in 64−98% yield (entries 12, 14−17). However, with 2-bromobenzyl alcohol, no coupling product was observed, probably due to an intramolecular coordination of the OH function. To our delight, benzylzinc reagents tolerated even more acidic phenolic protons. When we added 2-chlorobenzylzinc chloride (**1o**, 1.3 equiv) slowly (over 90 min) to a solution of 4-bromophenol (**9a**, 1.0 equiv), Pd(OAc)$_2$ (1 mol %) and **L3** (2 mol %) provided the phenol **11a** in 98% yield (entry 18). Similarly, various functionalized benzylic zinc chlorides react smoothly with various bromophenols and bromonaphthol (**9a**−**9e**), resulting in the formation of the corresponding diarylmethanes **11b**−**11h** in 73−96% yield (entries 19−26). Remarkably, 5,5′-dibromobinaphthol **9f**, a common intermediate for various BINOL-based ligands,[15] is compatible with the cross-coupling conditions, and the reaction with the benzylic zinc reagent **1m** (2.6 equiv) furnished binol **11i** in 76% yield (entry 26).

Alkenyl halides, bearing relatively acidic protons, could be coupled using the standard protocol. Thus, the reaction of phenylzinc iodide (**1a**) with the alkenyl bromide **12a**, bearing an acidic NH proton, provided the aniline **13a** in 61% yield (Table 4, entry 1). Also, the functionalized arylzinc iodide **1b**, alkylzinc bromide **1h**, and benzylzinc chlorides **1j** and **1m** react with the 2-bromoallylic amine **12a**, leading to the allylic amines **13b**−**13d** in 75−81% yield (entries 2−4). More acidic OH functions were only tolerated if benzylic zinc reagents were used. Thus, when benzylzinc chloride (**1q**, 1.2 equiv) was added slowly over 90 min (via syringe pump) to a solution containing Pd(OAc)$_2$ (1 mol %), **L3** (2 mol %) and 3-bromoallyl alcohol **12b** (1.0 equiv) afforded the allylic alcohol **13e** in 65% yield (entry 5). Similarly, the cross-coupling reactions of the cycloalkenyl iodide **12c** with benzylic zinc compounds **1o** furnished the unsaturated alcohols **13f** (91% yield, entry 6).

Since the pK_a of terminal alkynes is similar to the pK_a of anilines,[11] we have examined their behavior toward zinc reagents in the cross-coupling reaction. Competitive deprotonation was not a concern, and the palladium-catalyzed reaction [1 mol % of Pd(OAc)$_2$ and 2 mol % of **L3**) of phenylzinc iodide (1.2 equiv of **1a**) with the aryl bromide **14a** (1.0 equiv), bearing an ethynyl function, furnished the biphenyl **15a** in 74% yield (Scheme 2). Other aryl- or heteroarylzinc iodides, such as **1c** and **1f**, provided the corresponding alkynes **15b** and **15d** in 70 and 76% yield. Also the 3-cyanopropylzinc bromide (**1h**) reacted

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(15) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.

TABLE 4. Palladium-Catalyzed Cross-Coupling of Alkenyl Halides of Type 12[a]

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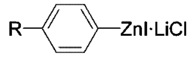
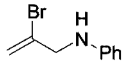
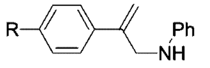
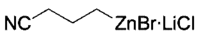
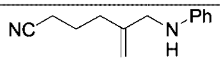
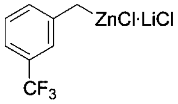
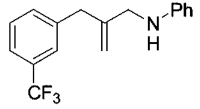
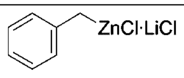
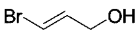
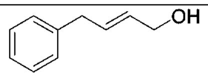
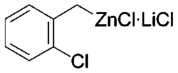
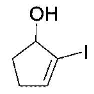
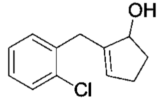
					
1	**1a**: R = H	**12a**	**13a**: R = H	5, 25	61
2	**1c**: R = CO_2Et	**12a**	**13b**: R = CO_2Et	7, 25	75
				2, 25	87
3	**1h**	**12a**	**13c**		
				8, 25	75
4	**1p**	**12a**	**13d**		
				2.5, 25	65[c]
5	**1q**	**12b**	**13e**		
				2.5, 25	91[c]
6	**1o**	**12c**	**13f**		

[a] Reaction conditions: 2.0 mmol of aryl halide, 2.4 mmol of zinc reagent, $Pd(OAc)_2$ (1 mol %), **L3** (2 mol %). [b] Isolated yield of analytically pure product. [c] The zinc reagent was slowly added over 90 min via syringe pump.

with 2-bromophenylacetylene (**14a**), leading to the phenylacetylene derivative **15c** in 77% yield.

Nickel-Catalyzed Cross-Coupling Reaction. We have also examined the use of nickel, which is cheaper and intrinsically more active than palladium in cross-couplings.[16] The reaction of phenylzinc iodide, prepared by the direct zinc insertion[7] (**1a**, 1.2 equiv), with 4-bromoaniline (**2a**, 1.0 equiv) was chosen as the test reaction (Table 5). Preliminary studies showed that the slow addition of the zinc reagent **1a** (via syringe pump over 90 min) was crucial for obtaining high yields of the aniline **3a**. The best results together with complete consumption of the aryl bromide **2a** were obtained by using either PPh_3 or 2,2′-bipyridine, furnishing the biphenyl **3a** in 62 and 77% yield (Table 5, entries 1 and 2). Other phosphines, such as 1,2-bis(diphenylphosphino)ethane (dppe) or tris(2-furyl)phosphine (tfp), gave only yields of <20% (entries 3 and 4), presumably due to competitive deprotonation of the aniline **2a** prior to the cross-coupling reaction. Similar results were obtained with phenanthroline, N-heterocyclic carbene (IPr·HCl = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene hydrochloride), or diethyl phosphite.[17]

Using the optimized conditions (2 mol % of $Ni(acac)_2$, 3 mol % of 2,2′-bipyridine, slow addition of the zinc reagent), bromoaniline **2a** reacted with phenylzinc iodide (**1a**) leading to the biphenyl **3a** in 75% isolated yield (2 h, 25 °C, Table 6, entry 1). Similarly, the functionalized bromoanilines **2b**−**2d** reacted with **1a** within 2−3 h at 25 °C, leading to the biphenyl amines **3b**−**3d** in 75−85% yield (entries 2−4). In the case of the secondary amine **2e**, which is less acidic than anilines,[11] the reaction temperature had to be increased to 60 °C, and the amine **3e** was obtained in 71% yield after 2 h (entry 5). Also, functionalized benzylic zinc reagents, prepared by direct zinc insertion in the presence of LiCl,[12] could be used in this cross-coupling reaction, although the procedure had to be modified. A combination of $Ni(acac)_2$ (2.5 mol %) and PPh_3 (10 mol %) as catalyst system, together with an elevated reaction temperature (60 °C) and a slow addition of the zinc reagent, turned

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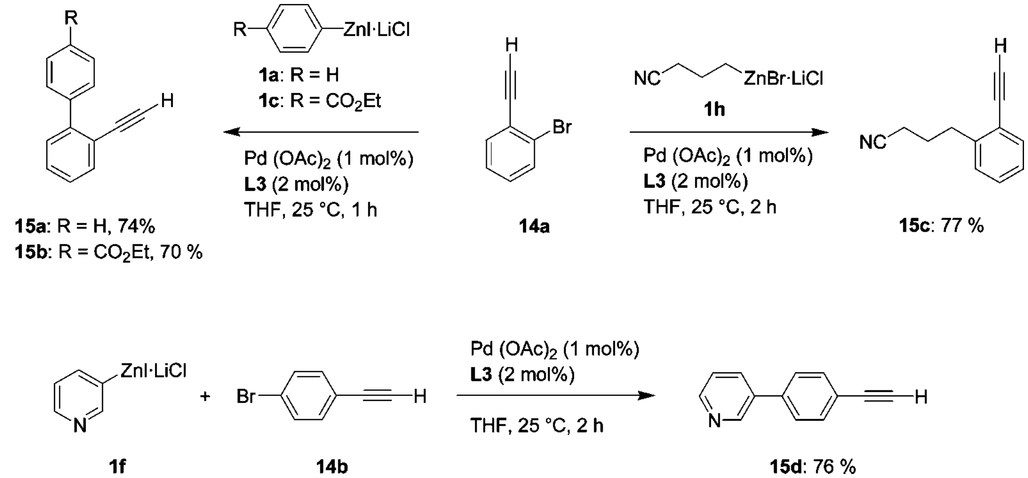
[16] (a) Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529. (b) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544. (c) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387.

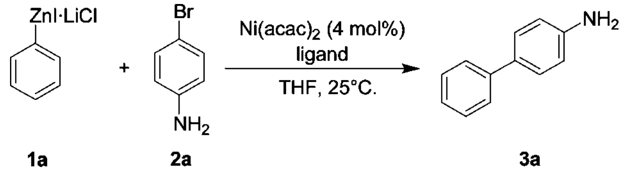
[17] Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871.

SCHEME 2. Cross-Coupling of Bromoethynylbenzene 14a and 14b[a]



[a] Reaction conditions: 2.0 mmol of aryl bromide, 2.4 mmol of zinc reagent, $Pd(OAc)_2$ (1 mol %), **L3** (2 mol %).

TABLE 5. Screening of Various Nickel−Ligand Systems for the Negishi Cross-Coupling of Unprotected Aniline (2a)



entry	ligand	yield [%][a,b]
1	PPh_3 (8 mol %)	62
2	2,2′-bipyridine (3 mol %)[c]	77
3	tfp (8 mol %)	17
4	dppe (6 mol %)	12
5	1,10-phenanthroline (6 mol %)	18
6	IPr·HCl (4 mol %)	16
7	$(EtO)_2P(O)H$ (8 mol %)	15

[a] Yields were determined by GC analysis with tetradecane as internal standard. [b] Slow addition of the zinc reagent over 90 min with a syringe pump. [c] $Ni(acac)_2$ (2 mol %) was used instead.

out to be superior compared to the conditions used for arylzinc halides. Thus, the benzylic zinc chlorides **1j**−**1q** reacted with the aryl bromides **2a**−**2h** within 2 h, affording the functionalized diarylmethanes **3af**−**3am** in 60−90% yield (entries 6−13).

Although the nickel-catalyzed reaction afforded high yields combined with the use of cheap nickel and ligands,[18] it displayed several disadvantages. Functionalized *aryl*zinc compounds were not suitable and led to low yields (typically <20%). Also it was difficult to predict if a chosen combination of zinc reagent and aryl bromide would afford the desired product in satisfactory yields.

Basicity of Organozinc Reagents. In order to understand the chemoselectivity of the different zinc reagents toward aryl halides, bearing acidic OH protons, we next examined their relative basicity and also their stability in the presence of relatively acidic hydrogens. To evaluate the relative basicity of various types of organozinc compounds, we have treated an equimolar mixture of PhZnI·LiCl (**1a**), OctZnBr·LiCl (**1g**), and $PhCH_2ZnCl·LiCl$ (**1q**) with various amounts of *i*PrOH (Scheme 3). 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 (**1a**) and 20% of OctZnBr·LiCl (**1g**) were protonated, whereas almost no protonation of $PhCH_2ZnCl·LiCl$ (**1q**) was observed. After the addition of the second equivalent of *i*PrOH, the protonation of more than 97% of PhZnI·LiCl (**1a**) and 90% of OctZnBr·LiCl (**1g**) was observed. These results indicate the relative kinetic basicity of zinc reagents: arylzinc halide > alkylzinc halide > benzylzinc halide.[19]

In order to investigate the reactivity of organozinc compounds with acidic protons, these organometallics were treated with an equimolar amount of an amine or an alcohol.[20] Thus, *n*-butylamine was added to a solution of PhZnI·LiCl (**1a**), OctZnBr·LiCl (**1g**), or $PhCH_2ZnCl·LiCl$ (**1q**) in THF (Figure 1). In the case of this comparatively weak acid, all three zinc reagents are quite unreactive. After 24 h, only 25% of PhZnI·LiCl (**1a**) is protonated. The less basic alkylzinc bromide **1g** led to only 8% of protonation, and almost no protonation of benzylzinc chloride (**1q**) occurred (98% of active zinc reagent). These stabilities are in accordance with the results obtained in the cross-coupling reactions with primary and secondary amines (Table 1, entries 16−20), where long reaction times still led to full conversion of the aryl bromides prior to the protonation of the zinc reagents.

In a second experiment, PhZnI·LiCl (**1a**), OctZnBr·LiCl (**1g**), or $PhCH_2ZnCl·LiCl$ (**1q**) was treated with an equimolar amount of aniline (Figure 1). The addition of aniline to phenylzinc iodide (**1a**) resulted in a relatively fast protonation. After 15 min, already more than 50% of the corresponding zinc reagent was protonated. In comparison, only 33% of alkylzinc bromide **1g** and 6% of benzylzinc chloride **1q** were protonated after 4 h. Noteworthy is also the long-term stability of the benzylic zinc reagent **1q**. After 1 day of stirring at 25 °C, there is still 73% of the active zinc reagent present, as confirmed by quenching with CuCN/allyl bromide (0% for **1a**, 14% for **1g**).

The same experiment with *i*PrOH as proton source led to a rapid protonation of all three organozinc compounds (Figure 3). PhZnI·LiCl (**1a**) was protonated immediately (0% of active zinc reagent after 30 s) and 73% of OctZnBr·LiCl (**1g**) was

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(18) $Ni(acac)_2$ (0.48 euro/g), $Pd(OAc)_2$ (29.40 euro/g), 2,2′-bipyridine (0.83 euro/g), and PPh_3 (0.07 euro/g) were purchased from Alfa Aesar, **L3** (139.50 euro/g) from Strem.

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

(20) For the preparation of zinc and copper organometallics bearing acidic hydrogens, see: Knoess, H. P.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974.

TABLE 6. Nickel-Catalyzed Cross-Coupling of Anilines of Type 2 and Amines of Type 4[a]

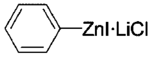
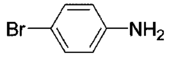
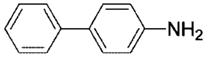
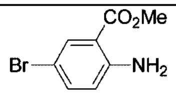
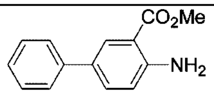
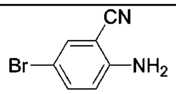
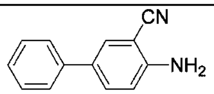
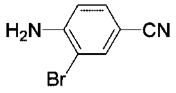
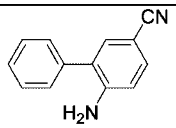
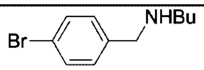
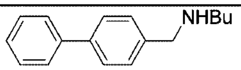
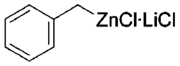
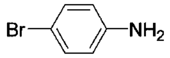
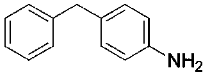
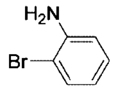
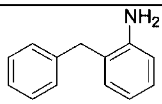
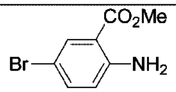
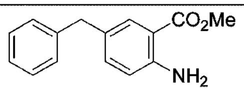
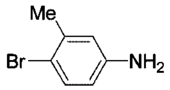
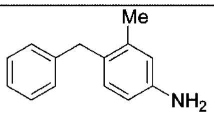
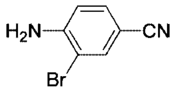
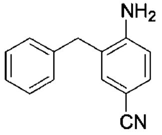
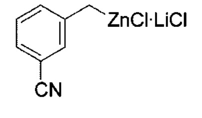
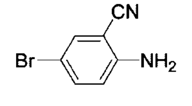
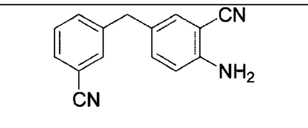
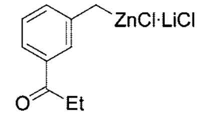
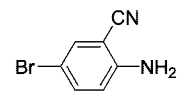
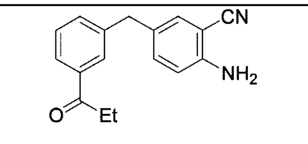
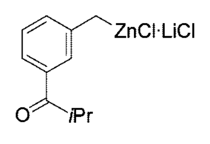
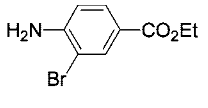
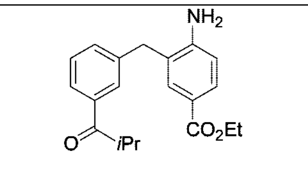
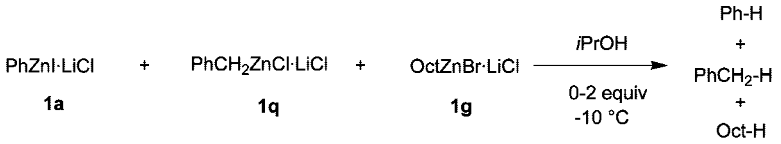
entry	zinc reagent	aryl bromide	product	time [h], T [°C]	yield [%][b]
1				2, 25	75[c]
	1a	**2a**	**3a**		
				2, 25	78[c]
2	**1a**	**2b**	**3b**		
				3, 25	85[c]
3	**1a**	**2c**	**3c**		
				3, 25	75[c]
4	**1a**	**2m**	**3af**		
				2, 65	71[c]
5	**1a**	**4a**	**5a**		
				2, 65	90[d]
6	**1q**	**2a**	**3ag**		
				2, 65	75[d]
7	**1q**	**2d**	**3ah**		
				2, 65	77[d]
8	**1q**	**2b**	**3ai**		
				2, 65	79[d]
9	**1q**	**2h**	**3aj**		
				2, 65	84[d]
10	**1q**	**2m**	**3ak**		

TABLE 6. Continued

entry	zinc reagent	aryl bromide	product	time [h], T [°C]	yield $[\%]^{b}$
				2, 65	81^{d}
11	**1j**	**2c**	**3al**		
				2, 65	86^{d}
12	**1k**	**2c**	**3z**		
				2, 65	60^{d}
13	**1r**	**2g**	**3am**		

[a] Reaction conditions: 3.0 mmol of aryl bromide, 3.6 mmol of zinc reagent, catalyst as mentioned, slow addition of the zinc reagent over 90 min via syringe pump and stirred for an additional time. [b] Isolated yield of analytically pure product. [c] $Ni(acac)_2$ (2 mol %), 2,2′-bipyridine (3 mol %). [d] $Ni(acac)_2$ (2.5 mol %), PPh_3 (10 mol %).

SCHEME 3. Selective Protonation of Organozinc Reagents[a]



$$\underset{\mathbf{1a}}{PhZnI{\cdot}LiCl} + \underset{\mathbf{1q}}{PhCH_2ZnCl{\cdot}LiCl} + \underset{\mathbf{1g}}{OctZnBr{\cdot}LiCl} \xrightarrow[\text{0-2 equiv, -10 °C}]{i\text{PrOH}} Ph\text{-}H + PhCH_2\text{-}H + Oct\text{-}H$$

Amount of *i*PrOH added	Yield of active zinc reagent $[\%]^{a}$		
	PhZnI·LiCl (**1a**)	OctZnBr·LiCl (**1g**)	$PhCH_2ZnCl{\cdot}LiCl$ (**1q**)
0	100	100	100
1	20	80	> 97
2	< 3	10	85

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

protonated after 5 min; $PhCH_2ZnCl{\cdot}LiCl$ (**1q**) was slightly more stable and after 15 min still 55% of the active zinc reagent was detected. These results can explain the quite different reactivity of the three zinc reagents with various aryl halides, bearing acidic OH functions (Table 3). The strongly basic arylzinc reagents can only be coupled with sterically hindered alcohols, and better yields can be obtained with more reactive aryl iodides, whereas alkylzinc bromides also tolerate less hindered alcohol functions. The least basic benzylic zinc reagents even tolerate more acidic phenolic protons. Using phenol as protons source led to an instant hydrolysis of phenylzinc iodide (**1a**) and octylzinc bromide (**1g**, 0% of the active zinc reagent was observed after 30 s). Although ca. 70% of $PhCH_2ZnCl{\cdot}LiCl$ (**1q**) was protonated with phenol after 30 s, the stability seems to be sufficient to undergo cross-coupling reaction prior to the capture of a proton if the concentration of the reactive palladium species is high enough to react with the benzylic zinc compound.

These results indicate the same relative kinetic basicity: arylzinc halide > alkylzinc halide > benzylzinc halide.[21] The reason for this different relative basicity of organozinc reagents

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[21] Using OctZnI·LiCl or $PhCH_2ZnCl{\cdot}LiCl$ led to similar results.

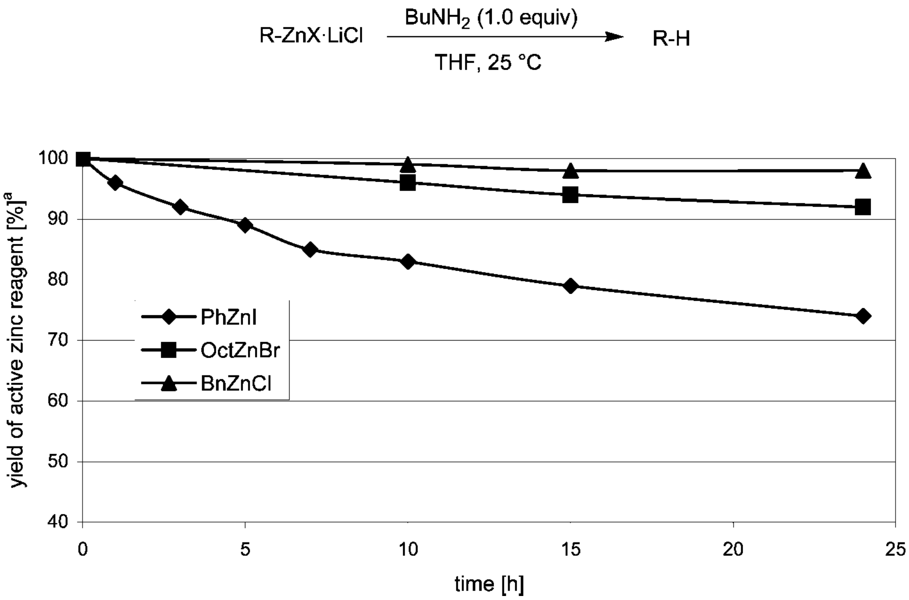

FIGURE 1. Relative reaction rates of organozinc reagents with *n*-butylamine. Yields are determined by quenching with CuCN/allyl bromide in THF and GC analysis with tetradecane as internal standard.

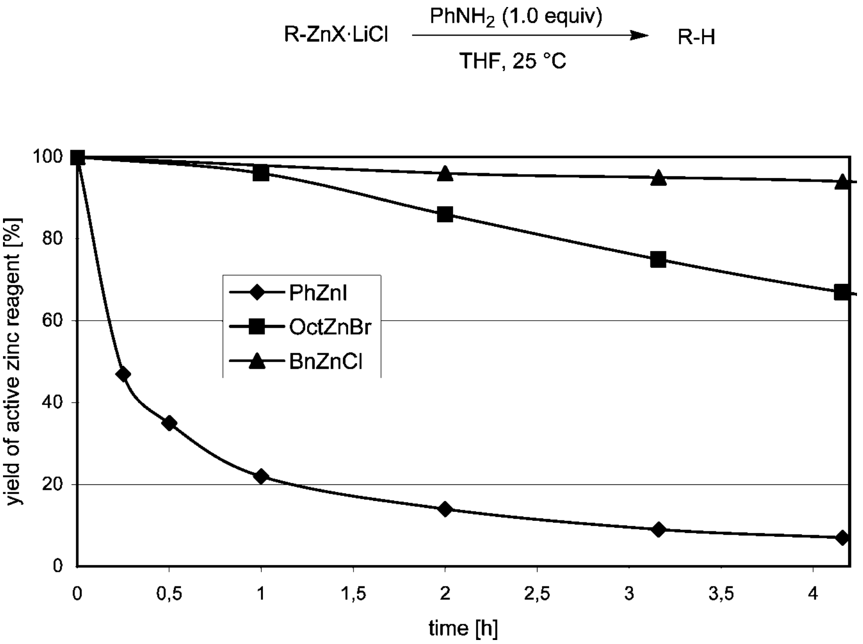

FIGURE 2. Stability of organozinc reagents toward aniline. Yields are determined by quenching with CuCN/allyl bromide in THF and GC analysis with tetradecane as internal standard.

compared to those of carbanions or organolithium compounds (alkyl > aryl > benzyl)[22] may result from different aggregation of zinc and lithium reagents.

3. Conclusion

In summary, we have developed a general and efficient palladium-catalyzed protocol for the cross-coupling of organozinc reagents with unsaturated aryl halides in the presence of relatively acidic protons. No protection or deprotonation by an additional base prior to the coupling reaction of these acidic protons is required. The reaction has a broad substrate scope and could be even applied to bromophenols. Additionally, we reported a nickel-catalyzed version of this reaction with a smaller substrate scope, but more economical. We have also investigated the relative basicity of the used zinc reagents and their stability toward acidic protons. The relative kinetic basicity of the organozinc compounds was found to be arylzinc halide > alkylzinc halide > benzylic zinc halide.

4. Experimental Section

General Considerations. All reactions were carried out under nitrogen using standard Schlenk techniques. Reactions were monitored by gas chromatography (GC and GC−MS) or thin layer chromatography. Yields refer to the isolated yields of compounds estimated to be >97% pure, as determined by ^{1}H NMR. Melting points are uncorrected. Solvents were dried according to the commonly used procedures. All ligands were prepared according

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[22] *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, UK, 2002.

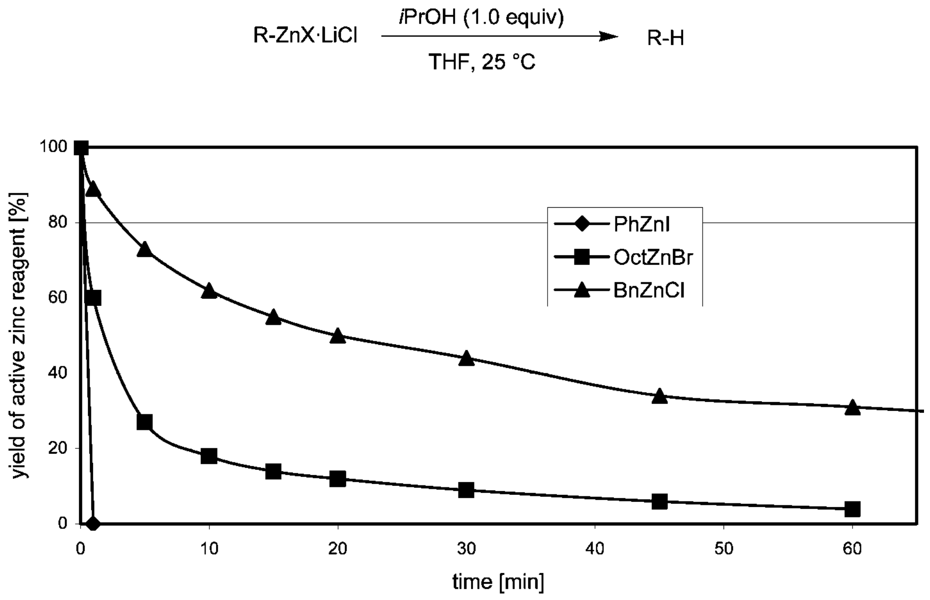

FIGURE 3. Reactivity of organozinc reagents with *i*PrOH. Yields are determined by quenching with CuCN/allyl bromide in THF and GC analysis with tetradecane as internal standard.

to literature procedures mentioned above. All the starting materials were purchased from commercial sources and used without further purification.

Typical Procedure 1 (Cross-Coupling with a Bromoaniline): Preparation of 4′-Aminobiphenyl-4-carbonitrile (3f): A dry and argon flushed 20 mL Schlenk tube was charged with 4-bromoaniline (**2a**, 516 mg, 3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), S-Phos (**L3**, 24.6 mg, 0.06 mmol), and THF (2 mL). After stirring the reaction mixture for 5 min, 4-cyanophenylzinc iodide (**1g**, 3.8 mL, 0.95 M in THF, 3.6 mmol) was added. The reaction mixture was stirred for 2 h at 25 °C. Then, the reaction mixture was quenched with a saturated aq NH_4Cl solution and extracted with ether (3 × 25 mL). The combined organic phases are washed with an aq thiourea solution and dried (Na_2SO_4). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 7:3) yielded 4′-aminobiphenyl-4-carbonitrile (**3f**) as a light yellow solid (559 mg, 96% yield): mp 181.0−183.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 7.67−7.58 (m, 4H), 7.41 (ddd, J = 8.2, 1.5, 0.4 Hz, 2H), 6.76 (ddd, J = 8.2, 1.5, 0.4 Hz, 2H), 3.87 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ = 147.2, 145.5, 132.5, 129.0, 128.2, 126.6, 119.3, 115.3, 109.5; MS (EI, 70 eV) m/z (%) 194 (34) [M^+], 166 (44), 140 (29), 97 (14), 77 (11).

Typical Procedure 2 (Cross-Coupling with a Bromoalcohol): Preparation of [4-(2-Chlorobenzyl)phenyl]methanol (10j): A dry and argon flushed 20 mL Schlenk-tube was charged with 4-bromobenzyl alcohol (**8h**, 374 mg, 2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), S-Phos (**L3**, 16.4 mg, 0.04 mmol), and THF (2 mL). After stirring the reaction mixture for 5 min, 2-chlorobenzylzinc chloride (**1o**, 2.6 mL, 0.92 M in THF, 2.4 mmol) was added slowly over 90 min with a syringe pump. The reaction mixture was stirred for 1 h at 25 °C. Then, the reaction mixture was quenched with a saturated aq NH_4Cl solution and extracted with ether (3 × 25 mL). The combined organic phases are washed with an aq thiourea solution and dried over Na_2SO_4. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane/ether 9:1) yielded [4-(2-chlorobenzyl)phenyl]methanol (**10j**) as a colorless solid (456 mg, 98% yield): mp 78.1−80.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 7.39−7.34 (m, 1H), 7.30−7.27 (m, 2H), 7.22−7.10 (m, 5H), 4.65 (s, 2H), 4.10 (s, 2H), 1.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ = 139.0, 138.8, 138.5, 134.2, 131.0, 129.5, 129.1, 127.7, 127.2, 126.8, 65.2, 38.9; HRMS m/z calcd for $C_{14}H_{13}ClO$ 232.0655, found 232.0647; MS (EI, 70 eV) m/z (%) 232 (87) [M^+], 201 (44), 179(24), 165 (100), 107 (94); IR (cm^{-1}) 3301 (m), 3049 (w), 3012 (w), 2914 (w), 2865 (w), 1514 (m), 1469 (m), 1443 (m), 1421 (m), 1344 (w), 1292 (w), 1210 (w), 1048 (m), 1033 (s), 1018 (s), 995 (m), 911 (m).

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

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