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Negishi coupling of 2-pyridylzinc bromide—paradigm shift in cross-coupling chemistry?

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ABSTRACT

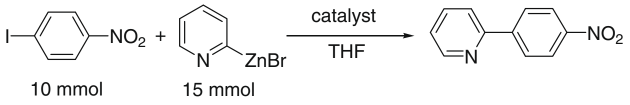
The efficient cross-coupling of 2-pyridylzinc bromide with functionalized aryl halides has been accomplished by a simple and highly efficient protocol. To the best of our knowledge, we report the first shelf life study of 2-pyridylzinc bromide which confirms the excellent stability of this compound and underlines the synthetic value of organozinc reagents in the cross-coupling reactions of sensitive heterocyclic nucleophiles on academic and commercial scale.

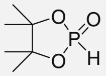
The introduction of a 2-pyridyl moiety by cross-coupling reactions into functionalized organic molecules displays a challenging and important transformation in organic synthesis. Several pharmaceutically relevant molecules, agrochemicals, and natural products contain 2-pyridyl scaffolds.[1] Despite the groundbreaking discoveries in the field of transition metal-catalyzed carbon–carbon bond forming reactions, the scope for cross-coupling of 2-pyridyl-nucleophiles is still limited.[2] The reason for this methodological lag is based on the fact, that 2-pyridyl nucleophiles often suffer from low stability, short shelf life or have to be generated under elaborate reaction conditions at low temperatures.[3,4] To circumvent unstable organometallic intermediates, novel direct arylation reactions of pyridine derivatives with aryl halides and unactivated arenes have been reported.[4]

Furthermore, several research groups made important progress to accomplish Suzuki reactions of 2-pyridyl nucleophiles.[5] Buchwald reported a new cross-coupling reaction of lithium triisopropyl-2-pyridylborates with aryl bromides and aryl chlorides.[6] The borate was synthesized in two steps from the corresponding 2-bromopyridine by lithium-halogen exchange and reaction of the organometallic intermediate with triisopropylborate. The novel protocol employs air stable phosphine oxide ligands in combination with $Pd_2(dba)_3$ as a *pre*-catalyst. Although yields are high, the lithium triisopropyl-2-pyridylborates were described as somewhat air-sensitive. Likewise, Li and Shen reported cross-coupling reactions of 2-pyridylboronic esters with aryl bromides using palladium phosphine chloride and oxide catalysts under Suzuki conditions.[7] The method requires careful optimization of the applied base and gives the desired biaryl in moderate to good yields. Burk and coworkers developed an elegant approach to generate an air stable MIDA-protected 2-pyridyl boronate derivative.[8] However, the synthesis of the 2-pyridyl MIDA boronate is difficult and the overall yield was 27%. The applied catalyst system consisting of $Pd_2(dba)_3$, SPhos, and $Cu(OAc)_2$ in the presence of K_2CO_3 in DMF/IPA at 100 °C provides the desired cross-coupling products in good yields up to 79%. Since organozinc halides were introduced by Negishi for cross-coupling applications in the 1970s,[9] his group,[10] Knochel,[11] Rieke,[12] Fu,[13] Buchwald[14] and others have developed very powerful procedures to open this technology to a broad variety of applications. Recently, Kappe described two examples for the cross-coupling of 2-pyridylzinc chloride with aryl chlorides in the presence of $Pd_2dba_3/Bu_3P{\cdot}HBF_4$ as a catalyst under microwave conditions in good yields.[15] Although pyridylzinc halides have been used in organic synthesis, to the best of our knowledge, no stability data of 2-pyridylzinc halides is available and cross-coupling reactions with this nucleophile are under-represented.[16]

In order to evaluate the potential of 2-pyridylzinc halide nucleophiles for organic synthesis and in particular for Negishi cross-coupling reactions in more detail, we started our studies with

Table 1
Catalyst screening



Entry	Catalyst	Mol %	Time (h)	Temp (°C)	Conversion % (GC)
1	$Pd(PPh_3)_4$	2.5	24	rt	98
2	$Pd(PPh_3)_4$	1.0	24	rt	100
3	$Pd(PPh_3)_4$	0.1	24	rt	25
4	$Pd(PPh_3)_4$	0.01	24	rt	1.4
5	$Pd(PPh_3)_4$	0.1	24	65	97
6	PEPPSI	2.5	24	rt	95
7	$Pd_2(dba)_3$	2.5	24	rt	0
		5			

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E-mail address: Andreas.Leitner@basf.com (A. Leitner).

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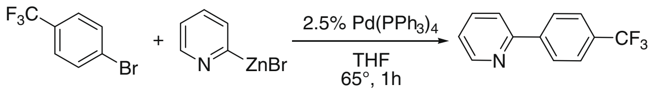
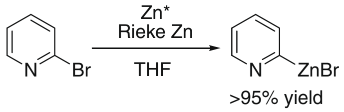
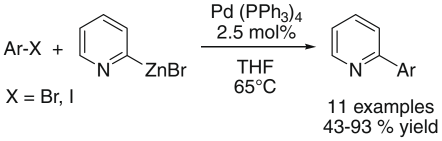
Table 2
Stability and reactivity study



Entry	Storage time (month at room temperature)	Conversion % (GC)
1	0	>99
2	12	>99



Scheme 1.



Scheme 2.

the conversion of 4-iodonitrobenzene in the presence of 1.5 equiv of 2-pyridylzinc bromide and different palladium *pre*-catalysts in THF (Table 1). $Pd(PPh_3)_4$ emerged as an excellent catalyst for this transformation and without further optimization of reaction conditions, conversions >95% were obtained in the first trials (Table 1, entries 1–3).

At reflux, a catalyst loading of 0.1% $Pd(PPh_3)_4$, which correlates to a useful technical turn over number of 1000, gave a conversion of 97% in 24 h. PEPPSI showed a comparable high reactivity to $Pd(PPh_3)_4$ (Table 1, entry 6).[17] An in situ catalyst system based on $Pd_2(dba)_3$ in presence of a pinacolephospholane ligand, which was recently used by several groups for the cross-coupling of aryl chlorides, showed no conversion (Table 1, entry 7).[18]

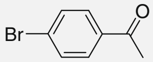
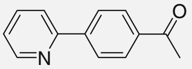
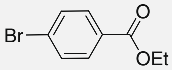
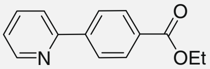
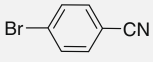
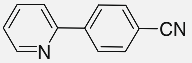
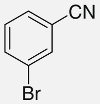
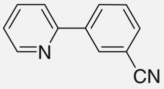
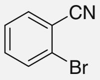
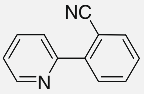
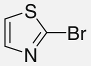
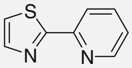
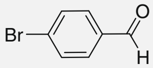
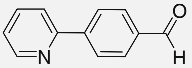
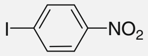
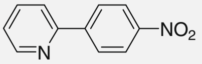
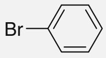
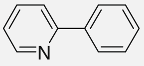
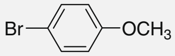
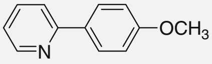
As depicted in Table 2, 2-pyridylzinc bromide turned out to be very stable as a solution in THF under nitrogen. The cross-coupling with a newly synthesized reagent (0.98 mol/l) and an aged compound (12 month at room temperature) of the same batch showed no significant difference in reactivity and full conversion of 4-bromobenzotrifluoride was obtained within 1 h in both cases.

Most important, insignificant amounts of decomposition products in the aged material were detected by gas chromatography. To the best of our knowledge, this is the first report about the long-term stability of a 2-pyridylzinc reagent.[19] As compared to other nucleophiles, 2-pyridylzinc bromide can be prepared by the Rieke technology[12] in one step. This pathway provides the product solution in THF (IM) with yields >95% and prevents a multistep synthesis (see Scheme 1).

We were able to produce 2-pyridylzinc bromide on multi-kilogram scale by this process.

Having these promising stability data and the convenient one-step synthesis with a high yield in hand, we evaluated the scope of the Negishi coupling with 2-pyridylzinc bromide in more detail to get comprehensive information about the value of this technol-

Table 3
Palladium-catalyzed cross-coupling reactions of aryl halides with 2-pyridylzinc bromide[c]

Entry	Substrate	Catalyst[b] (mol %)	Reaction time (h)/temperature (°C)	Product	Yield[a] (%)
1		2.5%	16/65		>90 (GC)
2		2.5%	16/65		98 (GC)
3		2.5%	16/65		91
4		2.5%	16/65		93
5		2.5%	24/65		66
6		2.5%	1/65		43
7		2.5%	1/65		60
8		2.5%	1/65		88
9		2.5%	4/65		85
10		2.5%	4/65		82

[a] Isolated yields unless stated otherwise. Reactions conducted in THF on 10 mmol scale.
[b] Catalyst loadings are not optimized.
[c] 2-Pyridylzinc bromide was prepared as 1 M solution in THF by BASF.

ogy (Scheme 2). As outlined in Table 3, aryl bromides and -iodides bearing functional groups like an enolizable methyl ketone, ester, nitrile, aldehyde, and ether or nitro group undergo Negishi cross-coupling in high conversions and yields in the presence of Pd(PPh$_3$)$_4$. No broad catalyst or additive screening was required to accomplish these results. The substitution pattern of the aryl halide had no significant impact on the reaction rate. For example, 2-, 3-, and 4-bromo benzonitrile were coupled with comparable high reaction rates providing the final product in isolated yields up to 93% (Table 3, entries 3–5). 2-Bromo-thiazole was converted into the cross-coupling product within 1 h reaction time and the product was isolated in 43% yield (Table 3, entry 6). Electron neutral bromobenzene as well as the electron rich 4-bromo-anisol provided the biaryl product in 85% and 82% isolated yields (Table 3, entries 9 and 10).[20]

In summary, we have demonstrated the high value of 2-pyridylzinc nucleophiles for cross-coupling chemistry. The excellent stability of 2-pyridylzinc bromide, the tolerance to sensitive-functional groups and its simple one step, high yield synthesis can lead to a paradigm shift in the cross-coupling of this important nucleophile. Apart from stability data, we demonstrated the application in cross-coupling reactions of aryl bromides and iodides. The developed Negishi cross-coupling protocol does not require careful optimization of reaction conditions, additives, and catalysts for the selected substrate scope. Currently we are working on the extension of this technology to aryl chlorides which will be reported in due course.

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20. *General procedure: 4-(2-pyridyl)nitrobenzene* (Table 2, *entry 8*). In a glove box, Pd(PPh$_3$)$_4$ (0.29 g, 0.25 mmol), 4-iodonitrobenzene (2.49 g, 10 mmol), and THF (3 mL) were filled into a 50 mL 2-necked round-bottomed flask with magnetic stir bar. The mixture was stirred for 0.5 h at room temperature resulting in a yellow-orange slurry. Next, 2-pyridylzinc bromide (15 mL, 15 mmol 1 M solution in THF) was added by syringe and the flask was sealed with rubber septa. The reaction mixture was heated at 65 °C for 1 h. The resulting blood-red to black solution was cooled to room temperature, and aqueous HCl was added (3.0 M; 10 mL). Aqueous NaOH (25 wt %, 10 ml) was added followed by an extraction of the product with Et$_2$O (3×30 mL), washed with 10 mL of saturated aqueous KCl, dried over MgSO$_4$, and concentrated, resulting in a light brown solid. The solid was dissolved in THF and recrystallized from cold hexane. Vacuum filtration furnished 1.88 g (88%) of the title compound as a tan-colored powder. ^{1}H NMR (CDCl$_3$, 300 MHz): 8.76 (d, 1H, J = 4.95 Hz), 8.33 (d, 2H, J = 8.98 Hz), 8.19 (H, J = 9.01 Hz), 7.82 (m, 2H), 7.35 (m, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz) 155.1, 150.3, 148.4, 145.5, 137.4, 127.9, 124.2, 123.8, 121.5.Compound is also described in the following publication: Prasad, A. S. B.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237–7254.