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PYRIDINYLZINC HALIDES BY OXIDATIVE ADDITION OF ACTIVE ZINC WITH HALOPYRIDINES

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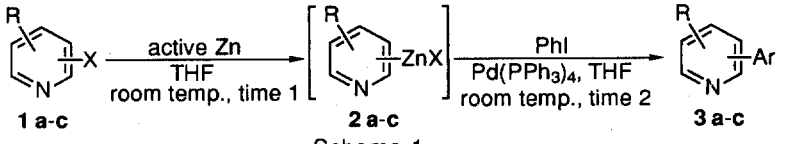
Abstract: The oxidative addition of active zinc to bromo- and iodopyridines gave pyridinylzinc halides which were coupled with aryl halide or benzoyl chloride in the presence of a palladium catalyst.

Arylzinc halides are versatile reagents to introduce various carbon functionalized substituents into aromatic nuclei. Unlike aryllithiums or arylmagnesium halides, the reagents are known to be soft and intact to functional groups such as alkoxy-carbonyl and cyano groups. The advantage in synthetic chemistry mentioned above, however, may be lost when the zinc reagents are prepared traditionally by metal-exchage reactions of aryllithiums or arylmagnesium halides with zinc halides. Recently, Knochel *et al.*[1] and Rieke *et al.*[2] reported the direct synthesis of arylzinc halides by the oxidative addition of active zinc with aryl halides. However, there is no report dealing with the direct formation of π-electron-deficient heteroarylzinc halides from the heteroaryl halides, although the zinc reagents such as pyridinylzinc halides have been prepared from the corresponding lithium derivatives.[3]

Here, we report the first direct preparation of pyridinylzinc halides from halopyridines and active zinc, and the palladium-catalyzed cross-coupling reaction of the reagents with iodobenzene and benzoyl chloride or benzoic anhydride.

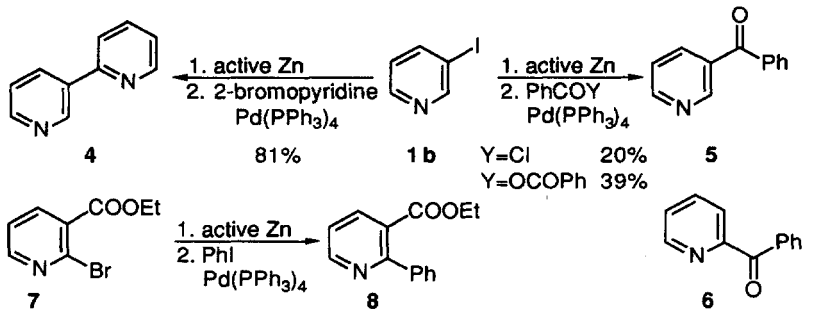


1 a-c **2 a-c** **3 a-c**

Scheme 1

Table I Palladium-Catalyzed Cross-Coupling Reaction of Pyridinylzinc Halides with Iodobenzene

Substrate (1)			Ratio	Reaction time 1	Reaction time 2	Product	Yield
No.	X	R	PhI/**1**	(h)	(h)	(**3**)	(%)
1 a	2-Br	H	2	4.5	19	**3 a**	54
1 a	2-Br	H	0.5	4	41	**3 a**	76
1 b	3-I	H	2	1.5	44	**3 b**	47
1 b	3-I	H	0.5	1.5	48	**3 b**	75
1 c	4-I	2,6-diMe	2	5	41	**3 c**	55
1 c	4-I	2,6-diMe	0.5	5	51	**3 c**	65



Scheme 2

2-Bromopyridine (**1 a**) was treated in tetrahydrofuran with active zinc prepared by Rieke's method[2] at room temperature to give 2-pyridinylzinc bromide (**2 a**) which reacted with iodobenzene in the presence of tetrakis(triphenylphosphine)palladium at room temperature to afford 2-phenylpyridine (**3 a**) in 75% yield[4]. Similarly, 3-phenylpyridine (**3 b**) and 2,6-dimethyl-4-phenylpyridine (**3 c**) were obtained from the palladium-catalyzed cross-coupling reaction of iodobenzene with the corresponding pyridinylzinc iodides (**2 b,c**) prepared from iodopyridines (**1 b,c**) and active zinc.

The palladium-catalyzed cross-coupling reaction of 3-pyridinylzinc iodide (**2 b**) and 2-pyridinylzinc bromide (**2 a**) with benzoyl chloride or benzoic anhydride afforded 3-pyridinyl phenyl ketone (**5**) in 20 and 39% and 2-pyridinyl phenyl ketone (**6**) in 48 and 18% yields , respectively.

An interesting feature of the present method is that the unsymmetrical biheteroaryls can easily be synthesized. For example, 2, 3'-bipyridine (**4**) was synthesized from **1 b** in 81% yield. Furthermore, preparation of pyridinylzinc bromide with ethoxycarbonyl group was realized, and ethyl 2-bromo-3-pyridine-carboxylate (**7**) was converted to ethyl 2-phenyl-3-pyridinecarboxylate (**8**) via the palladium-catalyzed cross-coupling reaction.

References and Notes

1. T. N. Majid and P. Knochel, *Tetrahedron Lett.*, 1990, **31**, 4413.
2. L. Zhu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, 1991, **56**, 1445.
3. *a*) E. Negishi, F.-T. Luo, F. Frisbee, and H.Matsusita, *Heterocycles*, 1982, **18**, 117; *b*) A. S. Bell, D.A.Roberts, K. S. Ruddock, *Synthesis*, 1987, 843; *c*) D. A. Roberts, K. S. Ruddock, G. H. R. Samuels, and M. S. Stefaniak, *J. Med. Chem.*,1988, **31**, 2048.

4. Typical Procedure---2-Phenylpyrdine (**3 a**)—All operations were performed under an argon atmosphere. A mixture of naphthalene (3.07 g, 24 mmol) and lithium (84 mg, 12 mmol) in dry THF (5 ml) was stirred at room temperature for 12 h, followed by addition of an 1M THF solution of $ZnCl_2$ (6.6 ml, 6.6 mmol) during 15 min. The mixture was centrifuged (3,500 rpm, 20 min), and the supernatant was discarded. The remained active zinc was suspended in dry THF (4 ml) followed by addition of 2-bromopyridine (**1 a**) (316 mg, 2 mmol). The mixture was stirred at room temperature for 4 h. The mixture was centrifuged (3,500 rpm, 20 min), and the supernatant was transformed to another flask. To the THF solution containing 2-pyridinylzinc bromide (**2 a**), was added iodobenzene (204 mg, 1 mmol) and $Pd(PPh_3)_4$. The whole mixture was stirred at room temperature for 41 h. The reaction was quenched with aq. NH_4Cl, and the THF was removed in vacuo. The residue was partitioned with H_2O and $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was purified by silica gel column chromatography using hexane-AcOEt (10:1) as an eluent to give 2-phenylpyridine (**3 a**).

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