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Preparation of π-Deficient Heteroarylzinc Halides by Oxidative Addition of Active Zinc and Its Palladium-Catalyzed Reaction[1]

Takao Sakamoto,* Yoshinori Kondo, Naoko Murata, and Hiroshi Yamanaka

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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Abstract The oxidative addition of active zinc to iodo- and bromo-substituted π-deficient heteroarenes such as pyridine, pyrimidine, and quinoline gave the corresponding heteroarylzinc halides which were transformed to the arylated and benzoylated derivatives by palladium-catalyzed reaction

As summarized in the recent review,[2] arylzinc halides are useful reagents for transition metal-catalyzed reaction to introduce carbon substituents into aromatic nuclei The reagents have an enough nucleophilicity for carbon-carbon bond formation reaction by the palladium-catalyzed reaction of aryl, alkenyl, or acyl halide, but they are intact to functional groups such as alkoxycarbonyl and cyano groups

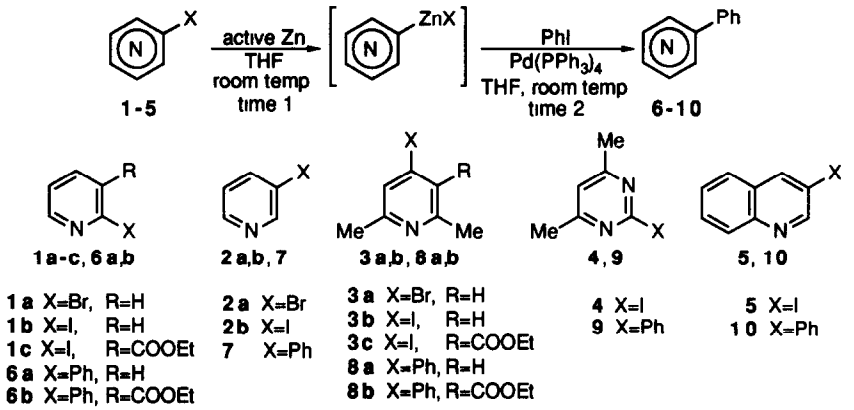
In general, the zinc reagents are prepared by transmetalation reaction of aryllithium or arylmagnesium halides with zinc halides The preparation of the zinc reagents containing a carbonyl group by this method, however, lose the remarkable feature described above due to the strong affinity of lithium or magnesium reagents to carbonyl groups Although some π-deficient heteroarylzinc halides such as pyridinylzinc halides can be synthesized by the traditional method, there is no general preparative method of the heteroarylzinc halides because of lack of the corresponding lithium or magnesium reagents

Recently, Knochel *et al* [3] and Rieke *et al* [4] reported the direct synthesis of arylzinc halides by the oxidative addition of active zinc with aryl halides [5] This method has a value to make synthesis of arylzinc halides containing a carbonyl group possible

Here, we reported the first direct preparation of π-deficient heteroarylzinc halides from the corresponding heteroaryl halides with active zinc, and the palladium-catalyzed arylation and benzoylation of the zinc reagents

2-Iodopyridine (**1b**) was treated in tetrahydrofuran (THF) with active zinc prepared by Rieke's method[4]

at room temperature for 5 h to give 2-pyridinylzinc iodide which reacted with iodobenzene in the presence of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] at room temperature for 66 h to afford 2-phenylpyridine (**6a**) in 77% yield Similarly, 3-phenylpyridine (**7**), 2,6-dimethyl-4-phenylpyridine (**8a**), 4,6-dimethyl-2-phenylpyrimidine (**9**), and 3-phenylquinoline (**10**) were obtained from the palladium-catalyzed cross-coupling reaction of iodobenzene with the corresponding heteroarylzinc iodides prepared from the heteroaryl iodides (**2b**, **3b**, **4**, and **5**) and active zinc



Scheme 1

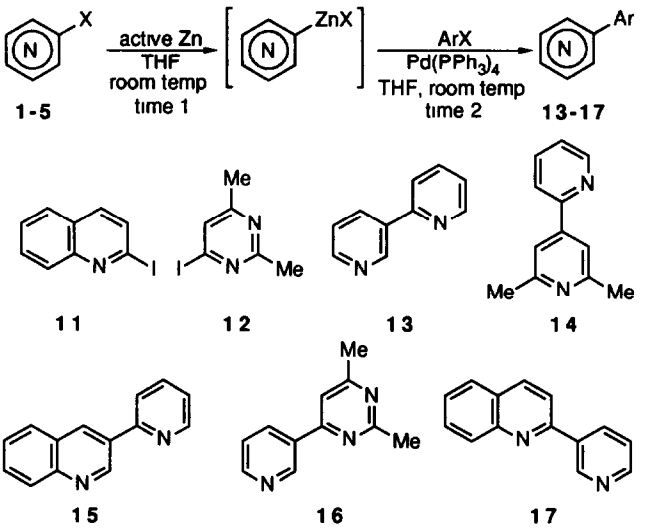
Table I Palladium-Catalyzed Cross-Coupling Reaction of Heteroarylzinc Halides with Iodobenzene

Substrate No	Reaction time 1 (h)	Ratio PhI/Substrate	Reaction time 2 (h)	Product No	Yield (%)
1a	4 5	2	19	**6a**	54
1a	4	0 5	41	**6a**	76
1b	3	2	14	**6a**	48
1b	5	0 5	66	**6a**	77
1c	4	0 5	18[a]	**6b**	82
2a	27	2	70	**7**	8
2b	1 5	2	44	**7**	47
2b	1 5	0 5	48	**7**	75
3a	1 5	2	45	**8a**	31
3b	5	2	41	**8a**	55
3b	5	0 5	41	**8a**	65
3c	1 5	0 5	45	**8b**	80
4	6	2	41	**9**	26
5	1 5	0 5	47	**10**	96

a) Under reflux

Alkoxycarbonyl-substituted pyridinylzinc halides such as ethyl 2-iodopyridine-3-carboxylate (**1c**) and ethyl 4-iodo-2,6-dimethylpyridine-3-carboxylate (**3c**) yielded the corresponding zinc reagents and coupled with iodobenzene to give the phenylated products (**6b** and **8b**) in good yields

An interesting feature of the reaction is that the unsymmetrical biheteroarenes can easily be synthesized. As shown in Table II, bipyridines (**13** and **14**), pyridinylquinolines (**15** and **17**), and a pyridinylpyrimidine (**16**) were synthesized in 60-84% yields by preferable matching of heteroarylzinc halides and heteroaryl halides



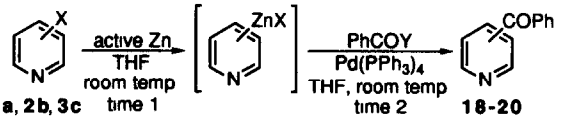
Scheme 2

Table II Palladium-Catalyzed Cross-Coupling Reaction of Heteroarylzinc Halides with Heteroaryl Halides

Substrate No	Reaction time 1 (h)	ArX No	Ratio ArX/Substrate	Reaction time 2 (h)	Product No	Yield (%)
1a	4	**2b**	0 7	45	**13**	23
1a	5	**3b**	0 5	44	**14**	72
1a	4	**5**	0 5	43	**15**	53
2b	2	**1a**	0 5	48	**13**	81
2b	1	**12**	0 5	43	**16**	84
2b	1	**11**	0 5	45	**17**	73
3b	6	**1a**	0 5	44	**14**	67
5	3	**1a**	2	67	**15**	60

Since it is well known that pyridines can not be acylated under Friedel-Crafts conditions, we studied the preparation of acylpyridines from the pyridinylzinc halides The palladium-catalyzed cross-coupling reaction of 2-pyridinylzinc bromide with benzoyl chloride or benzoic anhydride afforded phenyl 2-pyridinyl ketone (**18**) in 41 or 18% yield The results are not satisfactory but we hope general synthetic method of acylheteroarenes would be established by use of heteroarylzinc halides

Table III Palladium-Catalyzed Benzoylation of Pyridinylzinc Halides



Substrate No	Reaction time 1 (h)	Y	Reaction time 2 (h)	Product No	Yield (%)
1a	5	Cl	46	**18**	41
1a	4	OCOPh	42	**18**	18
2b	1	Cl	43 5	**19**	20
2b	1	OCOPh	63	**19**	39
3c	6	Cl	64	**20**	56
3c	6 5	OCOPh	48	**20**	12

Experimental

General Comments

Melting points are uncorrected Boiling points and sublimation points are bath temperature of Kugelrohr apparatus IR spectra were measured on a JASCO IR-A1 spectrophotometer ^{1}H-NMR spectra were recorded on a JEOL PMX-60 (60 MHz) spectrometer using tetramethylsilane as an internal standard Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz) The following abbreviations are used s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, dt=double triplet, m=multiplet Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a JEOL JMS-PX303 spectrometer

Materials

$Pd(PPh_3)_4$ in THF suspension was prepared by addition of BuLi (2 eq) in hexane to a THF suspension of $Pd(PPh_3)Cl_2$ (1 eq) and PPh_3 (2 eq) at room temperature 1 M THF solution of $ZnCl_2$ was prepared as follows $ZnCl_2$ (0 1 mol) contained in a 100ml-round bottomed flask was heated to melt on free frame under reduced pressure, cooled to room temperature, and dissolved in dry THF (100 ml) under

argon atmosphere THF was freshly distilled before use from sodium-benzophenone under argon atmosphere

Ethyl 2-Iodopyridine-3-carboxylate (1c)

A mixture of ethyl 2-chloropyridine-3-carboxylate (0 95 g, 5 1 mmol), NaI (7 5 g, 50 mmol), *p*-toluenesulfonic acid (190 mg, 5 1 mmol), and 2-butanone (10 ml) was refluxed for 40 h The mixture was diluted with water and extracted with $CHCl_3$ The $CHCl_3$ extract was washed with aq $Na_2S_2O_3$ and dried over $MgSO_4$ After evaporation of the $CHCl_3$, the residue was distilled to remove the starting material and purified by silica gel column chromatography using Et_2O as an eluent to give colorless needles which were recrystallized from hexane Yield 0 46 g (33%) mp 69℃ ^{1}H-NMR ($CDCl_3$) δ (ppm) 1 58 (3H, t, *J*=7), 4 37 (2H, q, *J*=7), 7 30 (1H, dd, *J*=7, 2), 7 96 (1H, dd, *J*=7, 2) 8 40 (1H, *J*=4, 2) IR ($CHCl_3$) cm^{-1} 1728 MS *m/z* (relative intensity) 277 (M^+, 100), 232 (26), 204 (18), 150 (60), 127 (9), 122 (79), 106 (23), 94 (40), 78 (32), 77 (42) *Anal* Calcd for $C_8H_8INO_2$ C, 34 68, H, 2 91, N, 5 05 Found C, 34 69, H, 2 87, N, 5 10

General Procedure for the Preparation of Heteroarylzinc Halides

All operations were performed under 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 1M THF solution of $ZnCl_2$ (6 6 ml, 6 6 mmol) during 15 min The mixture was centrifuged (3500 rpm) for 20 min, add the supernatant was discarded The remained active zinc was suspended in dry THF (4 ml) followed by addition of of an aryl halide (2 mmol) The mixture was stirred at room temperature for an appropriate time shown in Tables and centrifuged (3500 rpm) for 20 min The supernatant was transferred to another flask

General Procedure for the Palladium-Catalyzed Reaction of Heteroarylzinc Halides with Heteroaryl Halides or Benzoylating Reagents

To the THF (3 ml) solution containing a heteroarylzinc halide (1 mmol) was added an aryl halide (0 5 mmol) or a benzoylating reagent (0 5 mmol) in dry THF (2 ml) and $Pd(PPh_3)_4$ (0 5 mol%) The whole mixture was stirred at room temperature The reaction was quenched with NH_4Cl, and the THF was removed *in vacuo* The residue was partitioned between H_2O and $CHCl_3$ The crude product obtained from the $CHCl_3$ extract was purified by silica gel column chromatography using hexane-AcOEt as an eluent followed by distillation, recrystallization, or sublimation to give a pure product

2-Phenylpyridine (6a) Colorless liquid, bp 130-150℃/16 mmHg (bath temp)

[lit [6] bp 270-272°C] ^{1}H-NMR ($CDCl_3$) 7 1-7 6 (4H, m), 7 6-7 8 (2H, m), 7 9-8 1 (2H, m), 8 6-8 8 (1H, m) MS *m/z* (relative intensity) 155 (M^+, 100), 127 (12), 102 (3) HRMS Calcd for $C_{11}H_9N$ 155 0735 Found 155 0736

Ethyl 2-Phenylpyridine-3-carboxylate (6b) Colorless liquid, bp 120-130°C/3 mmHg (bath temp) ^{1}H-NMR ($CDCl_3$) 1 07 (3H, t, *J*=6 0), 4 15 (2H, q, *J*=6 0), 7 3-7 7 (6H, m), 8 10 (1H, dd, *J*=2 0, 7), 8 76 (1H, dd, *J*=2 0, 5) IR ($CHCl_3$) cm^{-1} 1718 MS *m/z* (relative intensity) 227 (M^+, 5 77), 198 (2 88), 183 (30 95), 155 (100 0), 154 (51 57), 17 (21.45), 117 (2 28), 106 (3 53), 77 (9 44), 63 (2 38) HRMS Calcd for $C_{14}H_{13}NO_2$ 227 0946 Found 227 0939

3-Phenylpyridine (7) Colorless liquid, bp 100-110°C/5 mmHg (bath temp) [lit [7] bp 273-278°C] ^{1}H-NMR ($CDCl_3$) 7 2-7 7 (6H, m), 7 90 (1H, dt, *J*=8 0, 2 0), 8 61 (1H, dd, *J*=4 2, 2 0), 8 88 (1H, d, *J*=2 0) MS *m/z* (relative intensity) 155 (M^+, 100), 127 (11 99), 115 (2 52), 102 (7 54), 77 (5 75) HRMS Calcd for $C_{11}H_9N$ 155 0735 Found 155 0734

2,6-Dimethyl-4-phenylpyridine (8a) Colorless solid, sublimation point 100-115°C/23 mmHg (bath temp), mp 60-61°C ^{1}H-NMR ($CDCl_3$) 2 58 (6H, s), 7 18 (2H, s), 7 3-7 8 (5H, m) MS *m/z* (relative intensity) 183 (M^+, 100), 167 (7), 153 (3), 141 (10) HRMS Calcd for $C_{13}H_{13}N$ 183 1047 Found 183 1042 *Anal* Calcd for $C_{13}H_{13}N$ C, 85 21, H, 7 15, N, 7 64 Found C, 85 40, H, 7 16, N, 7 62

Ethyl 2,6-Dimethyl-4-phenylpyridine-3-carboxylate (8b) Colorless liquid, bp 110-130°C/3 mmHg (bath temp) ^{1}H-NMR ($CDCl_3$) 1 00 (3H, t, *J*=7 0), 2 60 (3H, s), 2 63 (3H, s), 4 32 (2H, q, *J*=7 0), 7 04 (1H, s), 7 41 (5H, s) IR ($CHCl_3$) cm^{-1} 1722 MS *m/z* (relative intensity) 255 (M^+, 56 56), 240 (3 03), 237 (3 66), 227 (6 44), 226 (6 19), 211 (19 50), 210 (100), 209 (23 08), 196 (2 67), 182 (11 63) HRMS Calcd for $C_{16}H_{17}NO_2$ 255 1259 Found 255 1246

4,6-Dimethyl-2-phenylpyrimidine (9) Colorless needles, sublimation point 100-115°C/23 mmHg (bath temp), mp 79-80°C [lit [8] mp 83-84°C] ^{1}H-NMR ($CDCl_3$) 2 54 (6H, s), 6 93 (1H, s), 7 4-7 7 (3H, m), 8 4-8 7 (2H, m) MS *m/z* (relative intensity) 185 (M^++1, 15 89), 184 (M^+, 100), 183 (6 37), 169 (19 40), 169 (19 40), 143 (1 59),128 (1 95), 104 (19 89), 103 (24 33), 92 (3 56), 77 (5 90) HRMS Calcd for $C_{12}H_{12}N_2$ 184 0999 Found 184 0997

3-Phenylquinoline (10) Colorless liquid, bp 160-170°C/1 6 mmHg (bath temp), picrate mp [lit [9] mp 51-53°C] ^{1}H-NMR ($CDCl_3$) 7 3-8 1 (9H, m), 8 30 (1H, d, *J*=2 0), 9 22 (1H, d, *J*=2 0) MS *m/z*

(relative intensity) 206 (M^++1, 17 87), 205 (M^+, 100), 204 (46 79),176 (9 15),151 (4 11), 102 (5 11), 89 (4 75), 88 (4 56), 76 (7 49) HRMS Calcd for $C_{15}H_{11}N$ 205 0891 Found 205 0886

2,3'-Bipyridine (13) Colorless liquid, bp 110-130℃/5 mmHg (bath temp), [lit [10] bp 106℃/1 mmHg] ^{1}H-NMR ($CDCl_3$) 7 2-7 6 (2H, m), 7 7-7 9 (2H, m), 8 35 (1H, dt, *J*=8 0, 2 0), 8 6-8 9 (2H, m), 9 21 (1H, d, *J*=3 0) MS *m/z* (relative intensity) 156 (M^+, 100), 129 (8 26), 103 (6 33), 76 (6 63) HRMS Calcd for $C_{10}H_8N_2$ 156 0687 Found 156 0689

4-(Pyridin-2-yl)-2,6-dimethylpyridine (14) Colorless liquid, bp 115-125℃/3 mmHg (bath temp), [lit [11] bp 180-183℃/27 mmHg] ^{1}H-NMR ($CDCl_3$) 2 60 (6H, s), 7 2-7 5 (1H, m), 7 54 (2H, s), 7 7-7 9 (2H, m), 8 6-8 8 (1H, m) MS *m/z* (relative intensity) 185 (M^++1, 15 68), 184 (M^+, 100), 183 (23 86), 169 (10 97), 156 (1 58), 143 (5 05), 142 (7 59), 141 (4 51), 117 (2 38), 91 (2 29) HRMS Calcd for $C_{12}H_{12}N_2$ 184 1000 Found 184 1000

3-(Pyridin-2-yl)quinoline (15) Colorless needles, sublimation point 120-130℃/25 mmHg (bath temp), mp 101-102℃ [lit [9] mp 99-100℃] ^{1}H-NMR ($CDCl_3$) 7 1-8 3 (7H, m), 8 7-8 8 (2H, m), 9 5-9 6 (1H, m) MS *m/z* (relative intensity) 207 (M^++1, 16 33), 206 (M^+, 100), 205 (56 14), 180(6 42), 178 (4 53), 151 (4 69), 104 (16 92), 103 (12 41), 89 (4 49), 78 (12 92) HRMS Calcd for $C_{14}H_{10}N_2$ 206 0844 Found 206 0852

4-(Pyridin-3-yl)-2,6-dimethylpyrimidine (16) Colorless liquid, bp 140-150℃/3 mmHg (bath temp) ^{1}H-NMR ($CDCl_3$) 2 56 (3H, s), 2 74 (3H, s), 7 3-7 5 (3H, m), 8 35 (1H, dt, *J*=8 0, 2 0), 8 68 (1H, dd, *J*=4 0, 2 0), 9 20 (1H, d, *J*=2 0) MS *m/z* (relative intensity) 186 (M^++1, 14 95), 185 (M^+, 100), 184 (26 64), 170 (2 81), 159 (5 74), 156 (2 84), 144 (19 47), 129 (6 40), 117 (2 40), 103 (14 34) HRMS Calcd for $C_{11}H_{11}N_3$ 185 0952 Found 185 0985

2-(Pyridin-3-yl)quinoline (17) Colorless needles, sublimation point 135-150℃/2 mmHg (bath temp), mp 66-67℃ [lit [9] mp 70-71℃] ^{1}H-NMR ($CDCl_3$) 7 1-7 9 (5H, m), 8 0-8 7 (4H, m), 9 22 (1H, d, *J*=2 0) MS *m/z* (relative intensity) 207 (M^++1, 18 05), 206 (M^+, 100), 205 (62 39), 180 (21 58), 178 (8 88), 154 (6 67), 129 (8 26), 128 (13 12), 103 (14 87), 89 (12 09) HRMS Calcd for $C_{14}H_{10}N_2$ 206 0843 Found 206 0842

Phenyl 2-Pyridinyl Ketone (18) Colorless needles, bp 105-115℃/2 mmHg (bath temp) [lit [12] bp 166-169℃/10 mmHg] ^{1}H-NMR ($CDCl_3$) δ (ppm) 7 3-7 7 (4H, m), 7 7-8 2 (4H, m), 8 7-8 8 (1H, m) IR ($CHCl_3$) cm^{-1} 1671 MS *m/z* (relative intensity) 183 (M^+, 48), 182 (58), 155 (74), 105 (100)

HRMS Calcd for $C_{12}H_9NO$ 183 0684 Found 183 0658

Phenyl 3-Pyridinyl Ketone (19) Colorless needles, bp 135-140°C/3 mmHg (bath temp) [lit [12] bp 156-157°C/7 mmHg] ^{1}H-NMR ($CDCl_3$) 7 3-8 0 (6H, m), 8 13 (1H, dt, *J*=8 0, 2 0), 8 81 (1H, dd, *J*=5 0, 2 0), 8 99 (1H, d, *J*=2 0) IR ($CHCl_3$) cm^{-1} 1655 MS *m/z* (relative intensity) 183 (M^+, 92), 154 (5), 127 (3), 105 (100), 77 (69) HRMS Calcd for $C_{12}H_9NO$ 183 0684 Found 183 0689

2,6-Dimethylpyridin-4-yl Phenyl Ketone (20) Colorless solid, sublimation point 120-140°C/18 mmHg (bath temp), mp 82-83°C ^{1}H-NMR ($CDCl_3$) 2 60 (6H, s), 7 23 (2H, s), 7 4-7 9 (5H, m) IR ($CHCl_3$) cm^{-1} 1665 MS *m/z* (relative intensity) 211 (M^+, 50), 105 (100), 77 (30) HRMS Calcd for $C_{14}H_{13}NO$ 211 0996 Found 211 0971 *Anal* Calcd for $C_{14}H_{13}NO$ C, 79 59, H, 6 20, N, 6 63 Found C, 79 54, H, 6 15, N, 6 50

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