

0040-4039(95)00983-3

Palladium(0)/LiCl Promoted Cross-Coupling Reaction of (4-Pyridyl)stannanes and Aromatic Bromides: Easy Access to Poly(4-pyridyl)-Substituted Aromatics

Makoto Fujita,* Hiroko Oka, and Katsuyuki Ogura*

Department of Applied Chemistry, Faculty of Engineering, Chiba University 1-33 Yayoicho, Inageku, Chiba 263, Japan

Abstract: A PdCl₂(PPh₃)₂/LiCl catalyst effectively promoted the cross-coupling reaction of trimethyl(4-pyridyl)stannane and aromatic polybromides to offer easy access to poly(4-pyridyl)-substituted aromatic compounds.

In addition to sustained interest in pyridyl-containing compounds in view of their unique biological¹ and physical properties,² newly and rapidly increasing use of polypyridyl-substituted aromatics ((Py)_nAr) as essential components for supramolecular synthesis^{3,4} prompted us to search for an efficient Py-Mtl + X-Ar type cross-coupling reaction (route *a* in eq 1; Py = pyridyl).^{5,6} An umpoled route *b* is less effective for (Py)_nAr synthesis because of the need for troublesome polymetallic species Py(Mtl)_n. Despite many examples

Py-Mtl + X-Ar
$$\xrightarrow{a}$$
 Py-Ar \xleftarrow{b} **Py-X + Mtl-Ar** (1)

of the route *b* reaction,⁵ however, there are fewer reports on the route *a* reaction.⁶ In particular, only one example has appeared for the cross-coupling reaction of a (4-pyridyl) metal with aryl halides.^{6a} In this example, the coupling of a (4-pyridyl) stannane and a heteroaromatic bromide was promoted by a Pd(PPh₃)₄ catalyst, but the reaction required somewhat forced conditions and common aryl bromides were not examined.⁷ After making a careful examination of the reaction conditions, we found a remarkable salt effect of LiCl on this coupling reaction. Although there are a few reports on LiCl/Pd(0) promoted cross-coupling reactions,^{8,9} the salt effect has been never examined in the coupling reaction with aromatic bromides which usually give the coupled products in excellent yields. We now report highly efficient access to (poly)pyridyl-substituted aromatic compounds via the cross-coupling reaction of trimethyl(4-pyridyl)stannane (1)¹⁰ and aromatic (poly)bromides promoted by a PdCl₂(PPh₃)₂/LiCl catalyst (eq 2).

$$N \longrightarrow SnMe_3 + Ar(Br)_n \xrightarrow{PdCl_2(PPh_3)_2} (N \longrightarrow Ar (2))$$

The following reaction procedure is representative: $PdCl_2(PPh_3)_2$ (0.02 mmol) and LiCl (1.5 mmol) were added to a toluene solution (5 mL) of 1 (0.36 mmol) and bromobenzene (0.30 mmol), and the mixture was stirred for 71 h under reflux. The usual workup and purification by column chromatography afforded 4phenylpyridine (2) in 79% yield. In the absence of LiCl, the yield decreased to 34%. Employment of iodobenzene did not significantly improve the yield (82%). The reaction using tributyl(4-pyridyl)stannane was inferior even in the presence of LiCl to give 2 in 44% yield. $PdCl_2(PPh_3)_2$ was more effective than $PdCl_2(dppp)$ or $Pd(PPh_3)_4$. The reactions employing other 4-pyridylmetal reagents involving Li, MgX, or ZnX as the metal failed probably because of their insolubility.





^aAll compounds were prepared by the reaction of 1 and the corresponding aromatic (poly)bromides with PdCl₂(PPh₃)₂/LiCl catalyst (toluene, 110 °C, 2-5 d). Dashed lines indicate the bonds newly developed by the present cross-coupling reaction. The ratio of the reagents are as follows: for the syntheses of **3-8**, **1** : dibromide : PdCl₂(PPh₃)₂ : LiCl = 3 : 1 : 0.1 : 10; for the syntheses of **9-11**, **1** : tribromide : PdCl₂(PPh₃)₂ : LiCl = 4.5 : 1 : 0.15 : 15; for the synthesis of **12**, **1** : tetrabromide : PdCl₂(PPh₃)₂ : LiCl = 6.0 : 1 : 0.2 : 20. ^bYields in the absence of LiCl. ^cR form, $[\alpha]_D$ -20.4 (c = 0.5, CHCl₃). ^dR form, $[\alpha]_D$ -155 (c = 0.26, CHCl₃).

The salt effect of LiCl was more enhanced in the synthesis of polypyridyl-substituted compounds. For example, 1,3,5-tris(4-pyridyl)benzene (9) was obtained in 90% yield from 1 and 1,3,5-tribromobenzene in contrast to the poor result (7% yield) of a control experiment without LiCl. Selected results are summarized in Table 1. In addition to simple bis(4-pyridyl)-substituted aromatics (3-6), optically active derivatives containing a binaphthyl unit (7 and 8) were easily accessible. Furthermore, tris- and tetrakis(4-pyridyl)-substituted aromatics (9-12) were prepared similarly. Supramolecular self-assembly using these polypyridine compounds has been successfully studied in our laboratory.

It is interesting that the LiCl effect was also observed in a typical Stille's biaryl synthesis.⁹ Although Stille's standard conditions⁹ gave biphenyl according to eq 3 in fair yield (75%), the addition of LiCl dramatically increased the yield up to >99%. According to Stille's interpretation for the LiCl effect in the cross-coupling reaction of organostannanes and aromatic (or vinylic) triflates, LiCl accelerates the transmetallation step by replacing an inert Pd-O bond with an active Pd-Cl bond for transmetallation.^{8b} Since our reaction does not involve an inert bond in the intermediate, another mechanism is apparently involved for the acceleration of the reaction by LiCl.¹³



This work was financially supported by the Grant-in-Aid for Scientific Research on Priority Area of Reactive Organometallics from the Ministry of Education, Science and Culture, Japan.

References and Notes

- 1. For a review: Newcome, G. R.; Paudler, W. W. Contemporary Heterocyclic Chemistry; John Wiely: New York, 1982.
- Yamamoto, T.; Maruyama, T.; Zhou, Z.; Ito, T.; Fukuda, T.; Yoneda, Y.; Begum, F.; Ikeda, T.; Sasaki, S.; Takezoe, H.; Fukuda, A.; Kubota, K. J. Am. Chem. Soc. 1994, 116, 4832-4845.
- 3. For a review, see the following. Fabbrizzi, L.; Poggi, A., Eds. Transition Metals in Supramolecular Chemistry; Kluwer: Dordrecht, 1994.
- (a) Constable, E. C. Tetrahedron 1992, 48, 10013-10059. (b) Constable, E. C.; Hannon, M. J.; Smith, D. R. Tetrahedron Lett. 1994, 35, 6657-6660. (c) Potts, K. T.; Raiford, K. A. G.; Keshavarz-K, M. J. Am. Chem. Soc., 1993, 115, 2793-2807. (d) Baxter, P.; Lehn, J.-M.; DeCian, A. Angew. Chem., Int. Ed. Engl. 1993, 32, 69-72. (e) Youinou, M.-T.; Rahmouni, N.; Fischer, J.; Osborn, J. A. Angew. Chem., Int. Ed. Engl. 1992, 31, 733-735. (f) Lehn, J.-M.; Rigault, A. Angew. Chem., Int. Ed. Engl. 1992, 31, 733-735. (f) Lehn, J.-M.; Rigault, A. Angew. Chem., Int. Ed. Engl. 1988, 27, 1095-1097. (g) Fujita, M.; Ibukuro, F.; Hagihara, H.; Ogura, K. Nature 1994, 367, 720-723. (h) Baxter, P. N. W.; Lehn, J.-M.; Fischer, J.; Youinou, M.-T. Angew. Chem., Int. Ed. Engl., 1994, 33, 2284-2287. (i) Fujita, M.; Nagao, S.; Ogura, K. J. Am. Chem. Soc., 1995, 117, 1649-1650.
- 5. A review for the synthesis of heterocycles via cross-coupling reactions: Kalinin, V. N. Synthesis 1992, 413-432.
- 6. Examples of the cross-coupling reaction of Py-metals: (a) Trimethyl(2-, 3-, or 4-pyridyl)stannane with heteroaromatics: Yamamoto, Y.; Azuma, Y.; Mitoh, H. Synthesis 1986, 564-565. (b) 2- or 3-

(Trimethylstannyl)pyridine with aromatic halides: Bailey, T. R. Tetrahedron Lett. 1986, 27, 4407-4410. Malm, J.; Björk, P.; Gronowitz, S.; Hörnfeldt, A.-B. Tetrahedron Lett. 1992, 33, 2199-2202. (c) 2-(or 3-)Pyridylzinc chloride with heteroaromatics: Bell, A. S.; Roberts, D. A.; Ruddock, K. S. Synthesis 1987, 843-844. Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J. J. Med. Chem. 1986, 29, 2427-2432. (d) 3-Pyridylboranes with aromatic bromides: Ishikura, M.; Kamada, M.; Terashima, M. Heterocycles 1984, 22, 265-268. Ishikura, M.; Kamada, M.; Terashima, M. Synthesis 1984, 936-938. (e) 3- or 4-Pyridylboranes with vinylic bromides: Ishikura, M.; Kamada, M.; Ohta, T.; Terashima, M. Heterocycles 1984, 22, 2475-2478. (f) Constable, E. C.; Elder, S. M.; Healy, J.; Tocher, D. A. J. Chem. Soc., Dalton Trans 1990, 1669-1674.

- 7. Interestingly, 2- and 3-stannylpyridines were shown to effectively couple with bromobenzene under standard Stille's conditions.
- (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. J. Am. Chem. Soc. 1984, 106, 4630-4632. (b) Scott, W. J.; McMurry, J. E. Acc. Chem. Res. 1988, 21, 47-54. (c) Tsuji, Y.; Kajita, S.; Isobe, S.; Funato, M. J. Org. Chem. 1993, 58, 3607-3608. (d) Cummins, C. H. Tetrahedron Lett. 1994, 35, 857-860.
- 9. A leading review for the cross-coupling of organostannanes: Stille, J. K. Angew. Chem. Int., Ed. Engl. 1986, 25, 508-524.
- 10. (a) Preparation of 1: Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 1731-1737. Alternatively, we prepared this compound from 4-pyridyllithium¹¹ and trimethylstannyl chloride.
- 11. Minn, F. L.; Trichilo, C. L.; Hurt, C. R.; Filipescu, N. J. Am. Chem. Soc. 1970, 92, 3600-3610.
- 12. Physical properties of new compounds: Bis[(4-pyridyl)phenyl] ether (6): mp 147-148 °C; ¹H NMR $(270 \text{ MHz, CDCl}_3) \delta 8.66 \text{ (d-like, } J = 6.3 \text{ Hz, 4 H)}, 7.66 \text{ (d, } J = 8.6 \text{ Hz, 4 H)}, 7.50 \text{ (d-like, } J = 6.3 \text{ Hz}, 4 \text{ H}), 7.50 \text{ (d-like, } J = 6.3 \text{ Hz}, 4 \text{ H}), 7.50 \text{ (d-like, } J = 6.3 \text{ Hz}, 4 \text{ H}), 7.50 \text{ (d-like, } J = 6.3 \text{ Hz}, 4 \text{ H}), 7.50 \text{ (d-like, } J = 6.3 \text{ Hz}, 4 \text{ H}), 7.50 \text{ (d-like, } J = 6.3 \text{ Hz}, 4 \text{ H}), 7.50 \text{ (d-like, } J = 6.3 \text{ Hz}, 4 \text{ Hz}$ Hz, 4 H), 7.17 (d, J = 8.6 Hz, 4 H); IR (KBr) 1593, 1518, 1486, 1286, 1228, 811 cm⁻¹; Anal. (C₂₂H₁₆N₂O•0.2H₂O): C, H, N. (*R*)-2,2'-Dimethoxy-3,3'-di(4-pyridyl)-1,1'-binaphthyl (7): mp 89.5-90 °C; $[\alpha]^{25}$ -20.4 (c 0.5, CHCl₃); ¹H NMR (270 MHz, CDCl₃) δ 8.71 (d-like, J = 6.2 Hz, 4 H), 8.03 (s, 2 H), 7.95 (d, J = 7.9 Hz, 2 H), 7.72 (d-like, J = 6.2 Hz, 4 H), 7.46 (t-like, J = 7.9 Hz, 4 H), 7.32 (t-like, J = 7.9 Hz, 4 H), 7.21 (d, J = 7.9 Hz, 2 H), 3.19 (s, 6 H); IR (KBr) 1600, 1404, 753 cm⁻¹; HRMS (FAB) m/z calcd for C₃₂H₂₄N₂O₂: 468.1827, found 468.1836. (R)-2,2'-Dimethoxy-6,6'-di(4-pyridyl)-1,1'-binaphthyl (8): mp 232-233 °C; [a]D²⁵ -157 (c 1.0, CHCl₃); ¹H NMR $(270 \text{ MHz}, \text{CDCl}_3) \delta 8.64 \text{ (d-like}, J = 6.3 \text{ Hz}, 4 \text{ H}), 8.16 \text{ (d}, J = 2.0 \text{ Hz}, 2 \text{ H}), 8.07 \text{ (d}, J = 9.0 \text{ Hz}, 2 \text{ H})$ H), 7.57 (d-like, J = 6.3 Hz, 4 H), 7.52 (d, J = 9.0 Hz, 2 H), 7.49 (dd, 2 H, J = 2.0, 9.6 Hz), 7.23 (d, J = 9.6 Hz, 2 H), 3.80 (s, 6 H); IR (KBr) 1593, 1492, 1253, 815 cm⁻¹; Anal. (C₃₂H₂₂N₂O₂•0.5H₂O): C, H, N. 1,3,5-Tris(4-pyridyl)benzene (9): mp >300 °C; ¹H NMR (270 MHz, CDCl₃) δ 8.76 (dlike, J = 5.9 Hz, 6 H), 7.92 (s, 3 H), 7.61 (d-like, J = 5.9 Hz, 6 H); IR (KBr) 1588, 813 cm⁻¹; HRMS (FAB) m/z calcd for C₂₁H₁₆N₃ (M+H): 310.1344, found 310.1343. 1,3,5-Tris[4-(4-pyridyl)phenyl]benzene (10): mp >300 °C; ¹H NMR (270 MHz, CDCl₃) δ 8.71 (d-like, J = 5.9 Hz, 6 H), 7.91 (s, 3 H), 7.86 (d, J = 8.6 Hz, 6 H), 7.80 (d, J = 8.6 Hz, 6 H), 7.59 (d-like, J = 5.9 Hz, 6 H); IR (KBr) 1590, 806 cm⁻¹; HRMS (FAB) m/z calcd for C₃₉H₂₈N₃ (M+H): 538.2283, found 538.2281. 2,4,6-Tris[4-(4-pyridyl)phenyl]-1,3,5-triazine (11): mp 261-263 °C, ¹H NMR (270 MHz, CDCl₃-CD₃OD) δ 8.63 (d, J = 6.0 Hz, 6 H), 8.03 (d, J = 8.6 Hz, 6 H), 7.79(d, J = 8.2 Hz, 6 H), 7.69 (d, J = 6.3 Hz, 6 H); IR 1595, 822 cm⁻¹; Anal. $(C_{36}H_{24}N_6 \cdot 4H_2O):$ C, H, N. 1,2,4,5-Tetrakis(4pyridyl)benzene (12): mp >300 °C; ¹H NMR (270 MHz, CDCl₃) δ 8.55 (d-like, J = 5.9 Hz, 8 H), 7.54 (s, 2 H), 7.13 (d-like, J = 5.9 Hz, 8 H); IR (KBr) 1590, 1409, 820 cm⁻¹. Anal. (C₂₆H₁₈N₄• 0.1H2O): C, H, N.
- 13. Nucleophilic attack of chloride ion on organostannanes may produce reactive hypervalent species. Compare the F⁻/Pd(0)-promoted cross-coupling of organosilicon compounds in which hypervalent silicates are the active species: Hatanaka, Y.; Hiyama, T. Synlett **1991**, 845-853 and references cited therein.