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A general route to pyridine-modified salicylaldehydes via Suzuki coupling

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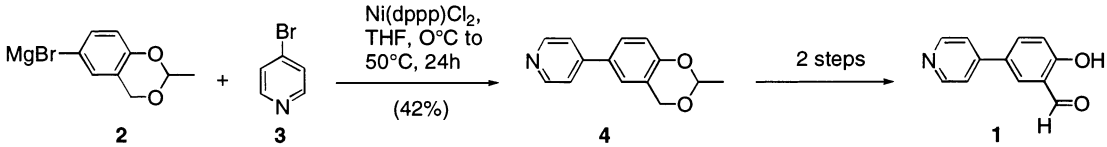
Abstract—An efficient method for the preparation of 5-(3-pyridyl)- and 5-(4-pyridyl)salicylaldehydes by the palladium-catalyzed cross-coupling reaction of either 4-pyridylboronic acid or diethyl-(3-pyridyl)borane and bromosalicylaldehydes is described.

Our interest in the design of cyclic supramolecular structures of the Fujita[1,2] and Stang[3] varieties led us to investigate the synthesis of a bifunctional salen template containing pendant Lewis base groups. Our primary target was a salen-type ligand featuring a pair of 5,5′-pyridyl groups oriented at 180° with respect to each other that we envisioned would have the potential to be used as 'edges' in the construction of a supramolecular complex. It was thought that this highly functionalized ligand could be synthesized by reacting a 5-(4-pyridyl)salicylaldehyde (**1**) with a vicinal diamine. Since salicylaldehydes containing a pyridyl functionality were not known, we decided to explore the synthetic possibilities for introducing pyridyl substituents.

We set out to prepare a variety of pyridylsalicylaldehydes by a Ni- or Pd-mediated cross-coupling approach. Because we wanted to access a variety of substituted salen ligands in the most efficient manner, our strategy emphasized the use of a single easily accessible pyridyl-substituted coupling agent in conjunction with several 3-substituted salicylaldehydes. A review of the literature revealed a number of such methods that might be applicable for the synthesis of the targeted heterobiaryl framework, including Ni- or Pd-catalyzed coupling of halopyridines and arylmetallic compounds (Mg, Zn),[4] the Pd-catalyzed cross-coupling of stannylpyridines and aryl halides,[5] and the Pd-catalyzed coupling of pyridylboranes and aryl halides.[6] Yet, after each of these methods gave disappointing results in our laboratory, we were left searching for better ways to synthesize the desired 3- and 4-arylpyridines.

Our first attempt at preparing the 5-(4-pyridyl)salicylaldehyde **1** involved a Ni-catalyzed cross-coupling between aryl Grignard **2**[7] and 4-bromopyridine **3** to produce the heterobiaryl product **4** (Eq. (1)). Even though we took great care in the procedure, including titrating the Grignard reagent and taking several steps to ensure that the 4-bromopyridine was dry after free-basing,[8] we were unable to obtain yields greater than 42% for the coupling. In addition to using $Ni(dppp)Cl_2$ as a catalyst, we also tried $Ni(dppe)Cl_2$, $Ni(dppf)Cl_2$, and $Ni(PPh_3)_2Cl_2$ but were not able improve on our initial yields. Since others have reported similar problems due to the well-known instability of 4-halopyridines,[4,9–11] we decided to seek other means for the synthesis of **4**. Although the reverse Ni-catalyzed cross-coupling could, in theory, be accomplished, the nucleophilicity of the necessary reagent, 4-pyridylmagnesium bromide, has been shown to be significantly weaker than that of typical phenyl or alkyl Grignard reagents.[12] Furthermore, 4-pyridylmagnesium



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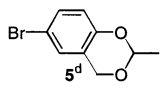
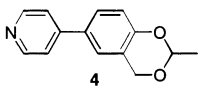
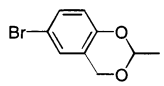
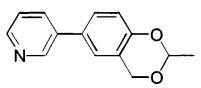
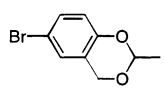
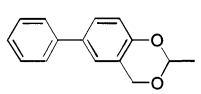
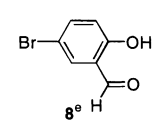
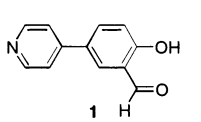
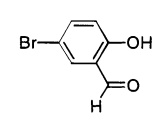
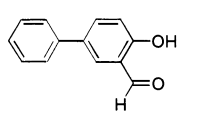
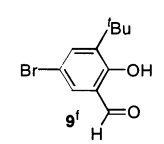
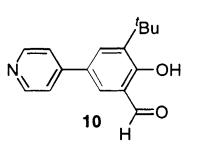
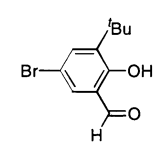
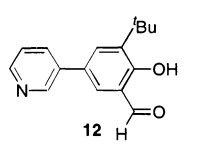
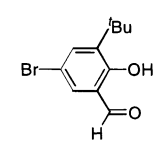
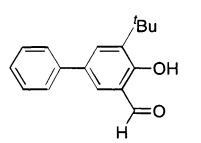
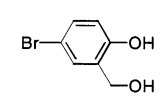
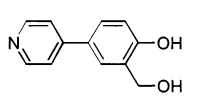
bromide must be obtained through a transmetalation procedure with ethyl or phenylmagnesium bromide,[12–14] leaving a halide as a byproduct that could potentially interfere in the subsequent coupling reaction.

Next, we investigated the Pd-catalyzed coupling of aryl halide **5** and tributyl-(4-pyridyl)stannane **6**[15] as a way to prepare the heterobiaryl product **4** (Eq. (2)). Using $Pd(PPh_3)_4$ as a catalyst, we were able to achieve yields of only 28%. When we used $Pd_2(dba)_3$ with $(2\text{-furyl})_3P$ in THF,[16] we were able to improve the yield only slightly to 32%. While we were aware that there have been reports of the successful use of trimethyl-(4-pyridyl)stannane in cross-coupling reactions,[17] we ruled out this reagent due to the unnecessary risks associated with handling the trimethylstannane reagents.

Table 1. Formation of aryl pyridines

$$Ar'B(R)_2 + ArB \xrightarrow{\text{Pd catalyst}} Ar'\text{–}Ar$$

Halide	Method	Product	Yield (%)[g]	IR / NMR DATA
 **5**[d]	A[a]	 **4**	74	^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, 2H, *J* = 5.5 Hz), 7.43 (dd, 1H, *J* = 8.3, 2.4 Hz), 7.41 (d, 2H, *J* = 5.5 Hz), 7.24 (d, 1H, *J* = 2.4 Hz), 6.94 (d, 1H, *J* = 8.3 Hz), 5.22 (q, 1H, *J* = 5.1 Hz), 5.04 and 4.88 (ABq, 2H, *J* = 14.6 Hz), 1.57 (d, 3H, *J* = 5.1 Hz).
	B[b]		71	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.52 (dd, 1H, *J* = 5.0, 1.6 Hz), 7.78 (d, 1H, *J* = 8.0 Hz), 7.36 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.31 (dd, 1H, *J* = 8.0, 5.0 Hz), 7.16 (s, 1H), 6.93 (d, 1H, *J* = 8.4 Hz), 5.20 (q, 1H, *J* = 5.2 Hz), 5.02 and 4.87 (ABq , 2H, *J* = 14.8 Hz), 1.56 (d, 3H, *J* = 5.2 Hz).
	C[c]		87	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.33 (m, 5H), 7.47 (d, 1H, *J* = 8.4 Hz), 7.22 (s, 1H), 6.96 (d, 1H, *J* = 8.4 Hz), 5.23 (q, 1H, *J* = 5.2 Hz), 5.07 and 4.93 (ABq, 2H, *J* = 14.0 Hz), 1.62 (d, 3H, *J* = 5.2 Hz).
 **8**[e]	A	 **1**	67	IR (KBr, υ_{CO}) : 1649 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 10.17 (s, 1H), 8.59 (d, 2H, *J* = 5.3 Hz), 8.18 (d, 1H, *J* = 2.5 Hz), 8.01 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.75 (d, 2H, *J* = 5.3 Hz), 7.12 (d, 1H, *J* = 9.0 Hz)
	C		75	IR (KBr, υ_{CO}) : 1648 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.04 (s, 1H), 9.98 (s, 1H), 7.73 (s, 1H), 7.59-7.36 (m, 5H), 7.57 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 8.0 Hz).
 **9**[f]	A	 **10**	66	IR (KBr, υ_{CO}) : 1646 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.94 (s, 1H), 9.99 (s, 1H), 8.67 (d, 2H, *J* = 4.7 Hz), 7.81 (s, 1H), 7.70 (s, 1H), 7.49 (d, 2H, *J* = 4.7 Hz), 1.49 (s, 9H).
	B	 **12**	64	IR (KBr, υ_{CO}) : 1650 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 (s, 1H), 9.98 (s, 1H), 8.84 (s, 1H), 8.61 (d, 1H, *J* = 4.5 Hz), 7.88 (d, 1H, *J* = 7.9 Hz), 7.73 (d, 1H, *J* = 1.7 Hz), 7.62 (d, 1H, *J* = 1.7 Hz), 7.41 (dd, 1H, *J* = 7.9, 4.5 Hz), 1.48 (s, 9H).
	C		78	IR (KBr, υ_{CO}) : 1652 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.85 (s, 1H), 9.97 (s, 1H), 7.81 (d, 1H, *J* = 1.4 Hz), 7.62 (d, 1H, *J* = 1.4 Hz), 7.6-7.37 (m, 5H), 1.52 (s, 9H).
	A		57	^{1}H NMR (500 MHz, CD_3OD): δ 8.47 (d, 2H, *J* = 4.9 Hz), 7.72 (d, 1H, *J* = 2.0Hz), 7.65 (d, 2H, *J* = 4.9 Hz), 7.54 (dd, 1H, *J* = 8.6, 2.0 Hz), 6.89 (d, 1H, *J* = 8.6 Hz), 4.72 (s, 2H).

[a] 4-Pyridylboronic acid (1.1 equiv.), Na_2CO_3 (1.5 equiv.), $Pd(dppf)Cl_2$ (0.05 equiv.) refluxed for 3–5 h in N_2-degassed DME:H_2O (3:1) v/v), TLC analyzed.

[b] Diethyl-(4-pyridl)borane (1.1 equiv.), NaOH (3 equiv.), Bu_4NBr (0.5 equiv.), $Pd(PPh_3)_4$(0.05 equiv., refluxed for 3–5 h in THF, TLC analyzed.

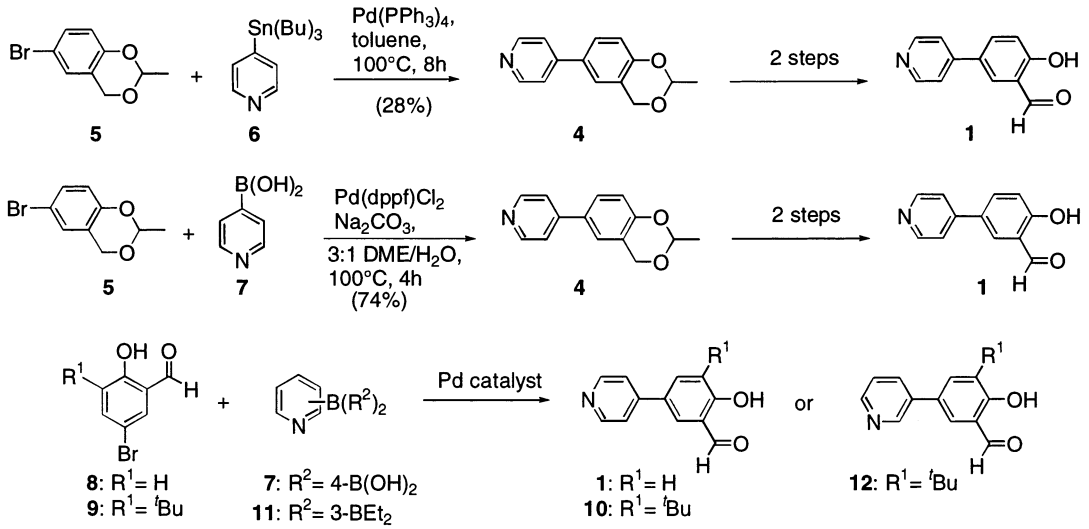
[c] Phenylboronic acid (1.1 equiv.), Na_2CO_3 (1.5 equiv.), $Pd(dppf)Cl_2$ (0.05 equiv.) refluxed for 3–5 h in N_2-degassed DME:H_2O (3:1) v/v), followed by TLC.

[d] Prepared by literature procedure.[23]

[e] Available from Aldrich.

[f] Prepared by literature procedure.[24]

[g] Yields are given for pure products isolated by flash chromatography on silica gel.



(2)

(3)

(4)

Finally, we decided to examine the Pd-catalyzed cross-coupling reactions of aryl halide **5** with organoboron reagents as a way to prepare **4**. We decided on this coupling direction because it would allow us to synthesize a series of salicylaldehydes from a single pyridylborane.[18] We initially planned to use diethyl-(4-pyridyl)borane as a coupling reagent. However, the preparation of this compound proved to be difficult, as we were unable to reproduce the results of a literature procedure.[6] While we were eventually able to make diethyl-(4-pyridyl)borane using an alternative procedure,[19] the crude yield was a disappointing 41%. As a result, we turned to the commercially available 4-pyridylboronic acid **7**.[20] We were pleased that the $Pd(dppf)Cl_2$-catalyzed cross-coupling reaction between **7** and aryl halide **5** provided heterobiaryl compound **4** in 74% yield (Eq. (3) and Table 1). The coupled product **4** could then be converted to the targeted salicylaldehyde **1** using a two-step procedure consisting of deprotection of the hydroxymethyl group followed by oxidation to the aldehyde.

Even more gratifying was the fact that salicylaldehyde **1** could also be obtained directly through the $Pd(dppf)Cl_2$-catalyzed cross-coupling reaction between bromoaldehyde **8** and boronic acid **7** in 67% yield (Eq. (4)). Thus, this methodology enabled us to prepare the target biaryl compound in a single step. This method could be readily applied to a variety of bromosalicylaldehydes such as **9**, which produced the biaryl aldehyde **10** in 66% yield.[21]

Furthermore, we found that the $Pd(PPh_3)_4$-catalyzed coupling reaction between diethyl-(3-pyridyl)borane **11** and aryl halide **9** was a good way to access 5-(3-pyridyl)salicylaldehydes such as **12** in 64% yield. The reagent, diethyl-(3-pyridyl)borane **11**, is easier to prepare than the 4-substituted isomer and is also commercially available. Results for the Pd-catalyzed cross-coupling reactions forming various 3- and 4-arylpyridines are summarized in Table 1. Reactions of each aryl halide with phenylboronic acid are shown for comparison. As expected, the yields in the latter reactions are slightly higher due to the fact that pyridyl boron reagents are known to undergo more facile protodeboronation.[22]

In conclusion, we have shown that the Pd-catalyzed cross-coupling reaction between either 4-pyridylboronic acid or diethyl-(3-pyridyl)borane and bromosalicylaldehydes can provide direct access to a variety of highly functionalized 3- and 4-arylpyridines. This procedure is quite versatile and makes use of commercially available organoboron reagents.

Acknowledgements

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18. We note that the opposite coupling chemistry between an arylboronic acid and a halopyridine has been reported, see: Zhang, H.; Kwong, F. Y.; Tian, Y.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 6886–6890.
19. This procedure involved the reaction of the lithium salt of 4-iodopyridine with diethylmethoxyborane.
20. 4-Pyridylboronic acid is commercially available from Frontier Scientific chemical company.
21. Preparation of **10**: A mixture of salicylaldehyde **9** (10.5 g, 40.7 mmol), boronic acid **7** (5.0 g, 40.7 mmol), Na_2CO_3 (10.5 g, 40.7 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (1.7 g, 2 mmol) was stirred in DME/H_2O (3:1 v/v, 80 mL, degassed with N_2) at (100°C) for 4 h. After cooling to rt, the reaction contents were poured into H_2O (250 mL). The aqueous mixture was extracted with CH_2Cl_2 (3×75 mL) and the combined extracts were dried over Na_2SO_4 before being concentrated under reduced pressure. The crude aldehyde was purified by flash chromatography on silica gel [Et_2O eluent, 9×20 cm silica] to provide the 6.9 g of **10**. A white solid (mp 95–96°C). Yield = 66%. IR (KBr): 3041, 2959, 2946, 2861, 1646, 1457, 1441, 1396, 1335, 1272, 1253, 1164, 1022, 890, 802, 646 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 11.94 (s, 1H), 9.99 (s, 1H), 8.67 (d, 2H, $J = 4.7$ Hz), 7.81 (s, 1H), 7.70 (s, 1H), 7.49 (d, 2H, $J = 4.7$ Hz), 1.49 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 197.1, 162.0, 150.5, 147.2, 139.5, 132.6, 130.3, 129.2, 121.1, 120.9, 35.2, 29.2. EIMS (m/z): 255 (M^+, 46), 240 (M^+–Me, 100), 212 (36), 172 (13). HRMS (EI): exact mass calcd for $[C_{16}H_{17}NO_2]^+$: 255.1259. Found: 255.1256. Anal. calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.27; H, 6.73, N, 5.39.
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