Nickel-Catalyzed Cross-Electrophile Coupling of 2-Chloropyridines with Alkyl Bromides

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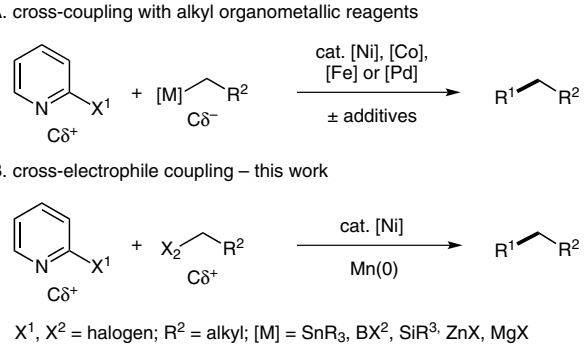
Abstract: The synthesis of 2-alkylated pyridines by the nickel-catalyzed cross-coupling of two electrophiles, a 2-chloropyridine and an alkyl bromide, is described. Compared with our previously published conditions for aryl halides, this method uses a different, more rigid, bathophenanthroline ligand and is conducted at high concentration in *N*,*N*-dimethylformamide as solvent. The method displays promising functional group compatibility and the conditions are orthogonal to those for the Stille coupling.

Key words: nickel, catalysis, alkylations, pyridines, cross-coupling

Alkylated pyridines represent an important class of azines that have appeared in several launched drugs such as esomeprazole (Nexium), used to treat acid reflux,[1] and eszopiclone (Lunesta), used in the treatment of insomnia.[2] Whereas the Suzuki–Miyaura reaction ($C\delta^- + C\delta^+$) is the dominant cross-coupling reaction used in both the discovery and production of pharmaceuticals,[3] the coupling of heteroarenes is generally more challenging than that of aryl halides.[4] For example, 2-pyridylboronic acid esters are difficult to synthesize and handle.[5] In general, the cross-coupling of an alkyl halide with a pyridyl organometallic reagent (diorganozinc or tin reagent) remains challenging.[6] A more developed approach involves the cross-coupling of 2-halopyridines with alkyl organometallic reagents, such as trialkylaluminum reagents,[7] alkyl Grignard reagents,[8] or alkylzinc reagents (Scheme 1, A).[9]



Scheme 1 Comparison of cross-coupling of alkyl organometallic reagents (A) with cross-electrophile coupling (B)

In addition to the challenges associated with pyridine substrates, all of the approaches described above require the synthesis of functionalized organometallic reagents. Besides the additional steps required for their preparation, organometallic reagents have limited functional-group compatibility. For example, the most-general approaches to 2-alkylpyridines are the iron-catalyzed[8b,c,10] and nickel-catalyzed[8a,d,11] coupling of alkyl Grignard reagents with 2-halopyridines (Scheme 1, A; [M] = MgX). The synthesis of the Grignard reagents adds an extra step, and the high reactivity of alkyl Grignard reagents places limitations on the choice of electrophilic and acidic functional groups. The anionic Mg–C bond also causes problems with β-elimination of leaving groups.[12] Although methods for the synthesis of functionalized Grignard reagents have advanced considerably,[13] it would be easier to avoid this problem entirely.

One underexplored approach that avoids the need to synthesize organometallic reagents is the direct cross-coupling of 2-halopyridines ($C\delta^+$) with alkyl halides ($C\delta^+$) (Scheme 1, B). Although we[14] and others[15–17] have made great progress on cross-coupling methods for catalytically joining two electrophiles, the best reported yield for pyridine alkylation is only 26% (for 2-chloro-6-methylpyridine).[14a] Whereas Gong and co-workers reported the alkylation of 8-bromoquinoline in good yield (96%), their one alkylation of 2-bromopyridine gave only 38% of the desired product, and they did not examine the reaction of 2-chloropyridines.[15c] We present here our progress towards a more general method for the alkylation of 2-halopyridines.

Studies on the cross-coupling of 2-chloropyridine (**1a**) with ethyl 4-bromobutanoate (**2a**) to give ethyl 4-pyridin-2-ylbutanoate (**3a**) identified the optimal conditions shown in Table 1 (See Supplementary Information, Table S1 for product-distribution data). Comparable yields were obtained at substrate concentrations ranging from 0.25 M to 1.7 M, but concentrations higher than 1.7 M produced gels that complicated workup and gave inconsistent results. To ensure complete conversion of **1a**, reactions were conducted with a slight excess of the alkyl bromide **2a**. Reactions performed with equimolar amounts of each reactant or with a slight excess of **1a** provided similar results (Table 1; entries 3 and 4).

Several ligands were examined, but bathophenanthroline (**4**; 4,7-diphenyl-1,10-phenanthroline) gave the highest yields of the cross-coupled product **3a**. Substitution of **4**

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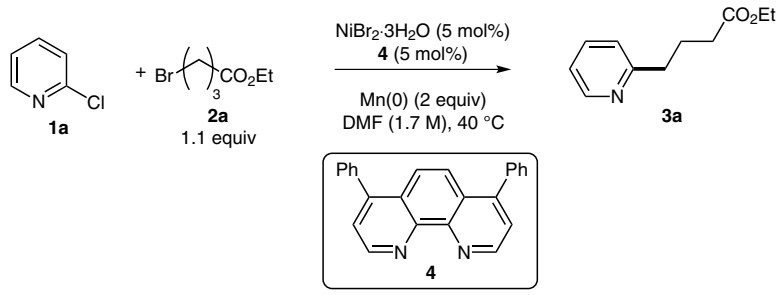
for less-expensive 1,10-phenanthroline (**5**) gave the product in an appreciable yield and this should be considered in process applications where ligand cost might be a limiting factor (Table 1, entries 1 and 5). Other bidentate imine ligands gave lower yields (entries 6 and 7). The tridentate imine ligand 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (**8**) gave a very low yield of **3a** and favored the dimerization of **2a** instead.[14c] Replacement of nickel(II) bromide trihydrate with nickel chloride–glyme gave similar results (entries 1 and 9), whereas other nickel sources produced lower yields (35–58%). Lowering the temperature to 20 °C resulted in slow reactions and partial conversion of the starting materials (entry 10), whereas raising the temperature to 60 or 80 °C decreased selectivity toward **3a** (entries 11 and 12). Reactions at these higher temperatures resulted in more hydrodehalogenation of 2-chloropyridine. The use of solvents other than *N*,*N*-dimethylformamide resulted in poor selectivity toward **3a**, partial conversion after 24 hours, or both (4–45% yield). Lastly, the use of zinc(0) or aluminum(0)–lead(II) bromide[18] instead of manganese(0) as the reducing agent resulted in a lower yield and a lower selectivity toward **3a** (entries 13 and 14). Specifically, the use of zinc(0) rapidly resulted in hydrodehalogenation of 2-chloropyridine, possibly through direct insertion of zinc(0) into the C–Cl bond with subsequent protonation; this, in turn, resulted in dimerization of **2a** once **1a** was consumed. The use of aluminum(0)–lead(II) bromide gave the dimer product of **2a** exclusively, with almost no conversion of **1a** (entry 15).

To examine the scope of this new method, we coupled several different alkyl halides with 2-chloropyridine (**1a**) to give 2-alkylated pyridines (Table 2). Nonfunctional-

Table 1 Results of Optimization of the Cross-Coupling of 2-Chloropyridine (**1a**) with Ethyl 4-Bromobutanoate (**2a**)

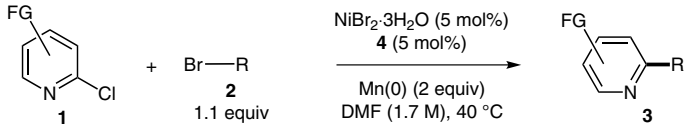


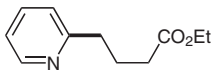
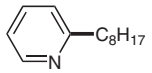
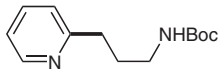
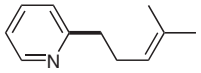
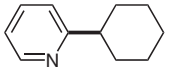
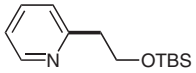
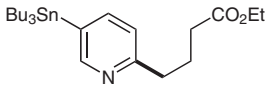
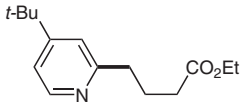
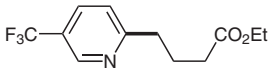
Entry[a]	Changes from standard conditions	Yield[b] (%)
1	none	82
2	10 mol% $NiBr_2·3H_2O$/**4**	74[c]
3	1 equiv each **1a** and **2a**	78
4	1.1 equiv **1a**	71
5	1,10-phenanthroline (**5**) instead of **4**	64
6	4,4′-di-*tert*-butyl-2,2′-bipyridine (**6**) instead of **4**	66
7	4,4′-dimethoxy-2,2′-bipyridine (**7**) instead of **4**	69
8	4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (**8**) instead of **4**	15
9	$NiCl_2$(glyme) instead of $NiBr_2·3H_2O$	79
10	reaction run at 20 °C	55[c]
11	reaction run at 60 °C	70[c]
12	reaction run at 80 °C	62[c]
13	25% DMA in THF instead of DMF	15[d]
14	Zn(0) (<10 μm) instead of Mn(0)	19[e]
15	Al(0)/$PbBr_2$ instead of Mn(0)	2[e,f]

[a] Standard reaction conditions: DMF (1 mL), $NiBr_2·3H_2O$ (0.15 mmol), **1a** (3.00 mmol), **2a** (3.30 mmol), ligand (0.15 mmol), and Mn(0) (6.00 mmol) were added to a 1 dram vial on the bench top and heated under air at 40 °C for 4–22 h.
[b] Yield by GC (corrected) with dodecane as internal standard.
[c] Isolated yield.
[d] Partial conversion of starting material after 24 h.
[e] The major coupled product was the alkyl dimer.
[f] No reaction of **1a** was observed.

ized 1-bromooctane (**2b**) coupled with 2-chloropyridine efficiently under the optimized conditions to give 2-octylpyridine (**3b**) in 72% yield (entry 2). As we had discovered during the optimization process, an alkyl bromide bearing an ester group coupled efficiently (entry 1) as did one bearing a *tert*-butoxycarbonyl-protected primary amine (entry 3). An alkyl bromide containing a tri-substituted olefin group gave a lower yield (entry 4), consistent with a problem that we observed in coupling this bromide with bromobenzene.[14a]

Table 2 Scope of the Electrophile Cross-Coupling of 2-Chloropyridines with Alkyl Halides



Entry[a]	Reactants		Product	Yield[b] (%)
1	**1a**	**2a**	 **3a**	72
2	**1a**	**2b**	 **3b**	72[c]
3	**1a**	**2c**	 **3c**	60[d]
4	**1a**	**2d**	 **3d**	33[c]
5	**1a**	**2e**	 **3e**	48[e]
6	**1a**	**2f**	 **3f**	45[f]
7	**1b**	**2a**	 **3g**	48
8	**1c**	**2a**	 **3h**	50
9	**1d**	**2a**	 **3i**	46[g]

[a] Reaction conditions: Chloropyridine **1** (3.00 mmol), alkyl bromide **2** (3.30 mmol), Mn(0) (6.00 mmol), $NiBr_2 \cdot 3H_2O$ (0.15 mmol), ligand **4** (0.15 mmol), and DMF (1 mL) were added to a 15 ml round-bottom flask and heated for 4–22 h.
[b] Yield of isolated and purified product.
[c] 10 mol% $NiBr_2 \cdot 3H_2O$/**4**; the yield was 65% at 5 mol%.
[d] Reaction performed on 0.75 mmol scale with 1.1 equiv **1a** and 10 mol% $NiBr_2 \cdot H_2O$/**4**.
[e] Reaction performed with 2 equiv **2e**; the yield with 1.1 equiv was 33%.
[f] Reaction performed with 10 mol% $NiBr_2 \cdot 3H_2O$/**4**; the yield with 5 mol% was 37%.
[g] Reaction performed with 10 mol% $NiBr_2 \cdot 3H_2O$/**4**, 25 mol% NaI, and 10 mol% AIBN as additives; the yield under the standard conditions was 27%.

In addition to these primary halides, bromocyclohexane (**2e**) coupled in reasonable yield (Table 2, entry 5), showing that the method has promise for coupling of secondary alkyl bromides, which are challenging substrates because of their propensity to undergo β-hydrogen elimination. An alkyl bromide bearing a β-siloxy leaving group, **2f**, also coupled in reasonable yield if a higher catalyst loading of 10 mol% was used (entry 6). The corresponding organometallic reagent ($TBSOCH_2CH_2$-[M]) is prone to undergo β-elimination and presents a particular challenge.[12] In our case, the parent alkane of **2f** was the predominant byproduct rather than its β-elimination product. The product **3f** is a precursor to enediynes of tetrahydropyridine that exhibit antitumor activity.[19] The synthetically useful tributylstannyl group on the pyridyl chloride **1b** was tolerated with no observable destannylation (entry 7). The tributylstannyl functional group can be used in subsequent steps to achieve polyfunctionalization of the pyridine core by means of the well-established Stille reaction.[20]

Finally, we briefly explored the effects of electron density in the pyridine core. Coupling of 4-*tert*-butyl-2-chloropyridine (**1c**) with ethyl 4-bromobutanoate (**2a**) gave a 50% yield of the desired alkylated pyridine **3h** (Table 2, entry 8). The electron-deficient pyridine **1d** suffered from long induction periods and long reaction times that permitted competing side reactions to occur, resulting in a low yield (27%) in the absence of additives. Halogen exchange with conversion of the alkyl bromide into the much less reactive alkyl chloride was the major competing reaction. The yield of product **3i** could be improved from 27% to 46% by the addition of a catalytic amount (25 mol%) of sodium iodide, which converted the alkyl chloride into the corresponding alkyl iodide in situ;[14c] addition of a catalytic amount (10 mol%) of azobisisobutyronitrile (AIBN) reduced the reaction time from 48 to 19 h. The observation that the radical initiator AIBN significantly decreased the reaction time is suggestive of a mechanism that involves radicals. AIBN might decrease the reaction times by generating alkyl radicals.

With the exception of 2-{2-[*tert*-butyl(dimethyl)siloxy]ethyl}pyridine (**3f**), the major challenge to overcome in the cross-coupling reactions of 2-chloropyridines with alkyl bromides was competing dimerization of the alkyl bromide (See Supporting Information, Table S2, for product-distribution data and the structures of compounds **9**–**13**). The synthesis of ethyl 4-[5-(trifluoromethyl)pyridin-2-yl]butanoate (**3i)** in the presence of AIBN as an additive to decrease the reaction time showed a poor mass balance of only 50% with respect to the alkyl bromide and 41% with respect to the chloropyridine (See Supporting Information, Table S2). Unproductive side reactions with AIBN might account for the lost mass, but no such products could be identified by gas chromatographic analysis of the crude reaction mixtures. The propensity of some of these coupling reactions to show selectivity toward dimerization of the alkyl bromide over the cross-coupling reaction is reminiscent of the chemistry of nickel terpyridine complexes.[14c,15g] Nickel complexes **14** or **15** formed under these conditions might show similar reactivity to terpyridine nickel complexes, such as **16**,[21] which are efficient catalysts of alkyl dimerization reactions (Figure 1).[14c]

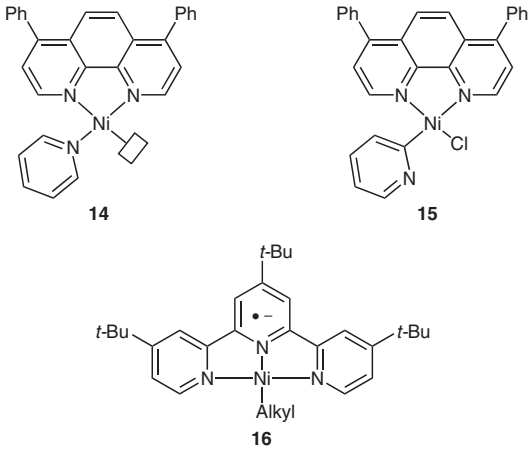
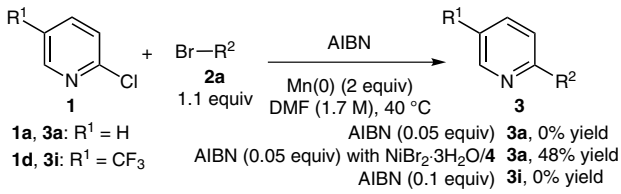


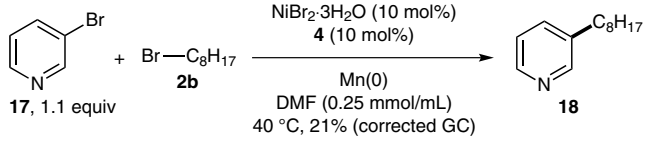
Figure 1 Postulated nickel complexes and terpyridine complex **16**

Our success with the use of AIBN made us consider the possibility that Minisci chemistry[22] rather than cross-electrophile coupling was responsible for the observed products (Scheme 2). However, neither of the products **3a** and **3i** was formed in reactions performed with added AIBN in the absence of nickel. In fact, the addition of AIBN lowered the yield of **3a** (Table 2, entry 1 and Scheme 2) as a result of increased alkyl dimerization, which is consistent with overproduction of alkyl radicals being detrimental to the reaction.



Scheme 2 Reactions with AIBN require nickel to form the cross-product

Pyridines halogenated at the 3- or 4-postion cannot currently be coupled in acceptable yields under the reaction conditions that we have developed (Scheme 3). Similarly, a few other heterocycles that were examined (2-chlorothiophene, 2-chlorobenzo[*d*]oxazole, 2-chloro-1*H*-benzo[*d*]imidazole, and 2-bromopyrazine) failed to couple in high yields. New reaction conditions and catalysts for coupling of these compounds are an active area of research in our laboratory.



Scheme 3 Electrophile cross-coupling of 3-bromopyridine (**17**) with 1-bromooctane (**2b**)

In summary, the cross-electrophile coupling approach to 2-alkylated pyridines permits the synthesis of functionalized molecules not readily accessible by coupling reactions of Grignard reagents. The products are obtained in a single step from easily available organic halides and 2-chloropyridines. Although future studies will seek to improve yields and expand the substrate scope, the current conditions should, already, prove helpful in synthesis.

Coupling of 2-Halopyridines 1 with Alkyl Bromides 2: General Procedure

In a well-ventilated fume hood, a 15 mL round-bottomed flask equipped with a Teflon-coated magnetic stirrer bar was charged with $NiBr_2 \cdot 3H_2O$ (40.9 mg, 0.150 mmol, 0.05 equiv), bathophenanthroline (**4**; 49.9 mg, 0.150 mmol, 0.05 equiv), DMF (2.0 mL), and alkyl bromide **2** (3.3 mmol, 1.1 equiv). The vessel was stoppered with a rubber septum and heated to 40 °C in a fume hood until a green homogeneous solution formed (~20 min). The vessel was then removed from the heat and 2-halopyridine **1** (3.00 mmol, 1.00 equiv) and manganese(0) (–325 mesh; 330 mg, 6.00 mmol, 2.00 equiv) were added. The vessel was resealed with the septum, purged with argon, and heated again to 40 °C while the progress of the reaction was monitored by GC analysis of aliquots of the crude reaction mixture. In general, the mixtures turned dark brown or black when the reaction was complete. Upon completion of the reaction, the mixture was cooled to r.t., diluted with Et_2O (10 mL), and filtered through a short pad of Celite 545 (approx. 1 × 1 × 1 inch) wetted with Et_2O (~10 mL) to remove metal salts. The Celite pad was washed with additional Et_2O (2 × 10 mL), and the filtrate was transferred to a separatory funnel and washed with 1 M aq NH_4Cl (10 mL). The layers were separated and the aqueous layer was washed with additional Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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