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Nickel-catalyzed cross-electrophile coupling of 2-chloropyridines with alkyl bromides

Daniel A. Everson, **Joseph A. Buonomo**, and **Daniel J. Weix**
Department of Chemistry, University of Rochester, Rochester, NY 14627-0216 USA. Fax: 1-585-276-0205

Daniel J. Weix: daniel.weix@rochester.edu

Abstract

The synthesis of 2-alkylated pyridines by the nickel-catalyzed cross-coupling of two different electrophiles, 2-chloropyridines with alkyl bromides, is described. Compared to our previously published conditions for aryl halides, this method uses the different, more rigid bathophenanthroline ligand and is conducted at high concentration in DMF solvent. The method displays promising functional group compatibility and the conditions are orthogonal to the Stille coupling.

Keywords

Nickel; catalysis; pyridine; electrophile; cross-coupling

Alkylated pyridines represent an important class of azines that have appeared in launched drugs such as Nexium, used to treat acid reflux,[1] and Lunesta, used in the treatment of insomnia.[2] While 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 compared to 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 is the cross-coupling of 2-halogenated pyridines with alkyl organometallic reagents such as tri-alkyl aluminum reagents,[7] alkyl Grignard reagents,[8] and alkyl zinc reagents (Scheme 1A).[9]

In addition to the challenges associated with pyridine substrates, all of the approaches listed above require the synthesis of functionalized organometallic reagents. Besides the additional steps, organometallic reagents can also limit functional-group compatibility. For example, the most general approaches to 2-alkylated pyridines are the Fe[8b, c, 10] and Ni[8a, 8d, 11] catalyzed coupling of alkyl Grignard reagents with 2-halogenated pyridines (Scheme 1A,

Correspondence to: Daniel J. Weix, daniel.weix@rochester.edu.

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[M] = MgX). The synthesis of the Grignard reagents adds an extra step, and the high reactivity of alkyl Grignard reagents places limitations on electrophilic and acidic functional groups. The anionic Mg-C bond also causes problems with β-elimination of leaving groups.[12] While methods for the synthesis of functionalized Grignard reagents have advanced considerably,[13] it would be easier to avoid the challenge entirely.

One underexplored approach that avoids organometallic reagent synthesis is the direct cross-coupling of 2-halopyridines ($C\delta^+$) with alkyl halides ($C\delta^+$) (Scheme 1B). While we,[14] and others[15, 16, 17] have made great progress on cross-coupling methods that catalytically join two electrophiles, the best reported yield for pyridine alkylation is only 26% (for 6-methyl-2-chloropyridine).[14a] While Gong reported the alkylation of 8-bromoquinoline in good yield (96%), the one alkylation of 2-bromopyridine afforded 38% of the desired product, and no 2-chloropyridines were examined.[15c] We present here our progress towards a more general solution for 2-halopyridine alkylation.

Optimization for the cross-coupling of 2-chloropyridine (**1a**) with ethyl 4-bromobutyrate (**2a**) to give **3a** yielded the conditions in Table 1 (See SI Table S1 for product distribution data). Comparable yields were obtained at substrate concentrations ranging from 0.25–1.7 M, but concentrations higher than 1.7 M resulted in gells that complicated workup and provided inconsistent results. To ensure complete conversion of **1a**, reactions were conducted with a slight excess of alkyl halide. Reactions run with equimolar amounts of each reagent or a slight excess of **1a** provided similar results (Table 1 entries 3–4).

Several ligands were examined, but bathophenanthroline (**4**) provided the highest yields of cross-coupled product **3a**. Substitution of **4** for the less expensive 1,10-phenanthroline (**5**) does produce product in appreciable yield and should be considered in process applications where ligand cost can become a limiting factor (Table 1, entry 1 vs. 5). Other bi-dentate imine ligands gave lower yield (Table 1, entries 6–7), the tri-dentate imine ligand 4,4′,4″-tri-*tert*-butyl-2,2′,:6′,2″-terpyridine (**8**) gave a very low yield of alkylated pyridine and favored dimerization of **2a** instead.[14c] Replacing $NiBr_2 \cdot 3H_2O$ with $NiCl_2$(glyme) gave similar results (entries 1 and 9), while other nickel sources ($NiI_2 \cdot xH_2O$, NiI_2, $NiBr_2$, $NiCl_2$) resulted in lower yields (35–58% yield). Lowering the temperature to 20 °C resulted in slow reactions and partial conversion of starting materials, while raising the temperature to 60 or 80 °C decreased selectivity for **3a** (entries 1 and 10). The higher temperature reactions displayed an increase in hydrodehalogenated 2-chloropyridine (entries 11 and 12). Solvents other than DMF (DMA, DMPU, NMP, NEP, THF) resulted in either poor selectivity for **3a**, partial conversion after 24 h, or both (4–45% yield). Lastly, the use of Zn^0 or $Al^0/PbBr_2$[18] in place of Mn^0 as the reducing agent resulted in lower yield and selectivity for **3a** (entries 13 and 14). Specifically, the use of Zn^0 quickly produced hydrodehalogenated 2-chloropyridine, possibly through direct insertion of Zn^0 into the C-Cl bond followed by protonation, and this in turn resulted in dimerization of **2a** once **1a** was consumed. The use of $Al^0/PbBr_2$ gave only the dimer product of **2a** with almost no conversion of **1a** (entry 15).

To examine the scope of this new method, several different alkyl halides were coupled with **1a** to give 2-alkylated pyridines (Table 2). Unfunctionalized alkyl bromides coupled with 2-chloropyridine efficiently under the optimized conditions giving **3b** in 72% yield (Table 2,

entry 2). As we discovered during optimization, alkyl bromides bearing ester functionality couple efficiently (Table 2, entry 1), and those bearing a Boc-protected primary amine also coupled well (Table 2, entry 3). An alkyl bromide with a tri-substituted olefin gave a lower yield (Table 2, entry 4), consistent with the challenge we observed in coupling this bromide with bromobenzene.[14a]

In addition to these primary halides, cyclohexyl bromide (**2e**) coupled in reasonable yield showing the promise of this method to couple secondary alkyl bromides, which are challenging substrates because of their propensity for β-hydrogen elimination (Table 2, entry 5).

An alkyl bromide bearing a β-silyloxy leaving group (**2f**) also coupled in reasonable yield if a higher catalyst loading was used (10 mol %, Table 2, entry 6). The corresponding organometallic reagent ($TBSOCH_2CH_2$-[M]) is prone to β-elimination and presents a particular challenge.[12] In our case, the parent alkane of **2f** was the predominant by-product rather than the β-elimination product. The product, **3f**, is a precursor to enediynes of tetrahydropyridine that exhibit antitumor activity.[19]

The synthetically useful tri-butyltin group on the pyridyl chloride (**1b**) was tolerated with no observable de-stannylation (Table 2, entry 7). The tri-butyl tin functional group can be used in subsequent steps for poly functionalization of the pyridine core with the well-established Stille reaction.[20]

Finally, electronics on the pyridine core were briefly explored. The coupling of 2-chloro-4-*tert*-butylpyridine (**1c**) with **2a** provided a 50% yield of the desired alkylated pyridine (Table 2, entry 8). Electron-poor pyridine **1d** was plagued by long induction periods and long reaction times that allowed for competing side reactions that resulted in a low yield (27%) without additives. Halogen exchange that converted the alkyl bromide to the much less reactive alkyl chloride was the major competing reaction. The yield of **3i** could be improved from 27% to 46% by the addition of catalytic amounts (25 mol%) of sodium iodide that converted the alkyl chloride into alkyl iodide in situ,[14c] and the addition of catalytic amounts (10 mol%) of azobisisobutyronitrile, AIBN, reduced the reaction time from 48 to 19 h. The observation that a radical initiator, AIBN, significantly decreased the reaction time is suggestive of a mechanism that contains radical steps. AIBN may decrease reaction times by generating alkyl radicals.

With the exception of **3f** the major challenge to overcome in the cross-coupling reactions of 2-chloropyridines with alkyl bromides is competing dimerization of the alkyl bromide (See SI, Table S2, which contains product distribution data and the structures of 9–13). The synthesis of **3i** that employed AIBN as an additive to decrease the reaction time exhibited poor mass balance, only 50% with respect to the alkyl bromide, and only 41% with respect to the chloropyridine (See SI, Table S2). Unproductive side reactions with AIBN may account for the missing mass, but no such products were identified by GC analysis of crude reaction mixtures. The propensity of these coupling reactions to, in some cases, be selective for alkyl bromide dimerization over the cross-coupling reaction suggests the chemistry of nickel terpyridine complexes.[14c, 15g] Nickel complexes (**14**) or (**15**), formed under these

conditions, might have similar reactivity to terpyridine nickel complexes, such as (**16**),[21] that are efficient alkyl dimerization catalysts (Figure 1).[14c]

Our success with AIBN made us consider the possibility that Minisci chemistry,[22] and not cross-electrophile coupling, was responsible for the observed products (Scheme 2). However, no product (**3a** or **3i**) are formed in reactions performed with added AIBN but no nickel. In fact, the addition of AIBN lowered the yield of **3a** (Table 2, entry 1 vs. Scheme 2) because of increased alkyl dimerization, consistent with the over-production of alkyl radicals being detrimental.

Pyridines halogenated at the 3- or 4-postion do not currently couple in acceptable yields under the reaction conditions developed here (eq. 1). Similarly, a few other heterocycles that were examined also did not couple in high yield (2-chlorothiophene, 2-chlorobenzo[*d*]oxazole, 2-chloro-1*H*-benzo[*d*]imidazole, and 2-bromopyrazine). New reaction conditions and catalysts for these couplings are an active area of research in our lab.

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

General Experimental Procedure

In a well-ventilated fume hood, a 15 mL round bottom flask equipped with a Teflon coated magnetic stir bar was charged with $NiBr_2 \bullet 3H_2O$ (40.9 mg, 0.150 mmol, 0.05 equiv), bathophenanthroline (49.9 mg, 0.150 mmol, 0.05 equiv), DMF (2.0 mL), and alkyl bromide (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 homogenous solution resulted (approx. 20 min). Once homogeneity was achieved the vessel was removed from the heat. The 2-halogenated pyridine (3.00 mmol, 1.00 equiv) and Mn^0 (−325 mesh, 330 mg, 6.00 mmol, 2.00 equiv) were added, after which, the vessel was resealed with the septum, purged with argon gas, and heated again to 40 °C for the duration of the reaction. Reaction progress was monitored by GC analysis of aliquots of crude reaction mixture. In general the reactions turn dark brown or black in color when complete. Upon completion the reaction was cooled to room temperature, diluted with ether (10 mL) and filtered through a short pad of Celite 545 (approx. $1'' \times 1'' \times 1''$) that had been wetted with ether (approx. 10 mL) to remove metal salts. The celite pad was washed with additional ether (2 × 10 mL). The filtrate was transferred to a separatory funnel and washed with 1M aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was washed with additional ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude products were purified by silica gel flash column chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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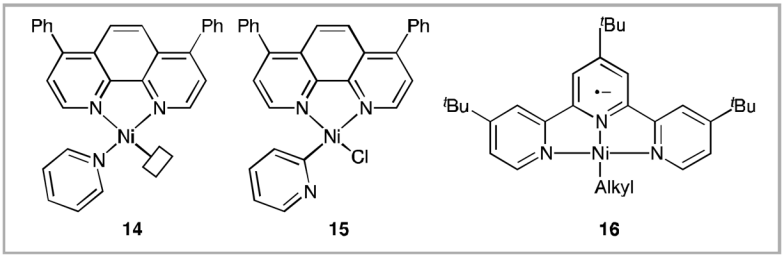
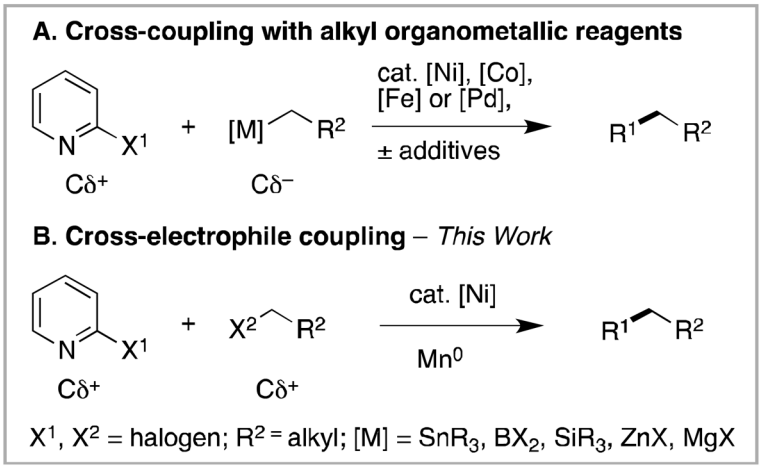
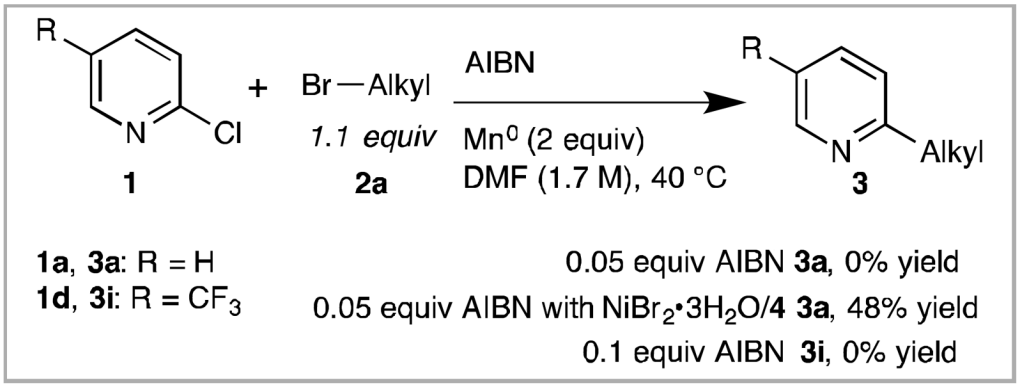


Figure 1.
Postulated nickel complexes and terpyridine complex **16**.

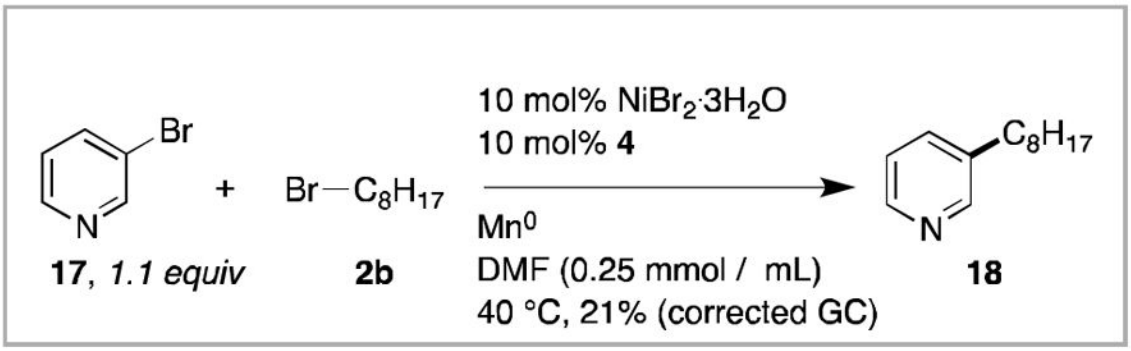


Scheme 1.

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



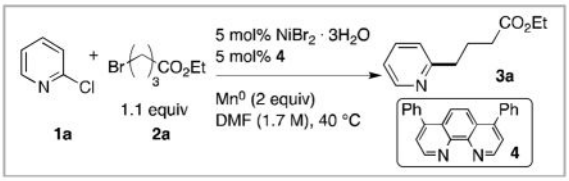
Scheme 2.
Reactions with AIBN require nickel to form cross-product.



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

Table 1

Optimization results for the cross-coupling of 2-chloropyridine (**1a**) with ethyl 4-bromobutyrate (**2a**).[a]



Entry	Change from above 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**) in place of **4**	64
6	4,4′-di-*t*-butyl-2,2′-bipyridine (**6**) in place of **4**	66
7	4,4′-di-methoxy-butyl-2,2′-bipyridine (**7**) in place of **4**	69
8	4,4′,4″-tri-*tert*-butyl-2,2′,:6′,2″-terpyridine (**8**) in place of **4**	15
9	$NiCl_2$(glyme) in place 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 in place of DMF	15[d]
14	Zn^0 (<10 μm) in place of Mn^0	19[e]
15	$Al^0/PbBr_2$ in place of Mn^0	2[e,g]

[a] 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 for 4–22 h.

[b] GC yield corrected vs. dodecane internal standard.

[c] Isolated yield.

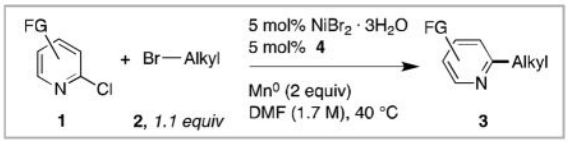
[d] Observed partial conversion of starting material at 24 h.

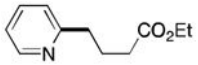
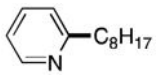
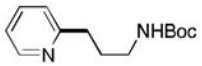
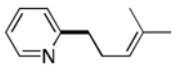
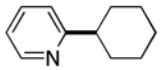
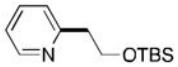
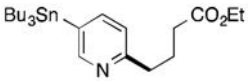
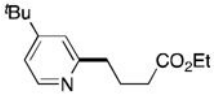
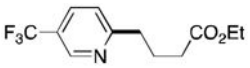
[e] Major coupled product was the alkyl dimer.

[f] No reaction of **2a** was observed.

Table 2

Scope of the electrophile cross-coupling of 2-chloropyridines with alkyl halides.[a]



Entry	Py-Cl (1)	Alkyl-X (2)	Product (3)	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: Reaction conditions: DMF (1 mL), $NiBr_2 \cdot 3H_2O$ (0.15 mmol), **4** (0.15 mmol), chloropyridine (3.00 mmol), alkyl bromide (3.30 mmol), and Mn^0 (6.00 mmol) were added to a 1 dram vial on the bench top and heated under air for 4–22 h.

[b] Yield of isolated and purified product.

[c] Reaction run with 10 mol% $NiBr_2 \cdot 3H_2O$/**4**, yield 65% at 5 mol%.

[d] Reaction run on 0.75 mmol scale with 1.1 equiv **1a** and 10 mol% $NiBr_2 \cdot H_2O$/**4**.

[e] Reaction run with 2 equiv **2e**, yield was 33% with 1.1 equiv.

[f] Reaction run with 10 mol% $NiBr_2 \cdot 3H_2O$/**4**, yield is 37% with 5 mol%.

[g] Reaction run with 10 mol% $NiBr_2 \cdot 3H_2O$/**4**, 25 mol% NaI, and 10 mol% AIBN as additives, yield under standard conditions was 27%.