Communication

Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C–N Bond Activation

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Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C–N Bond Activation

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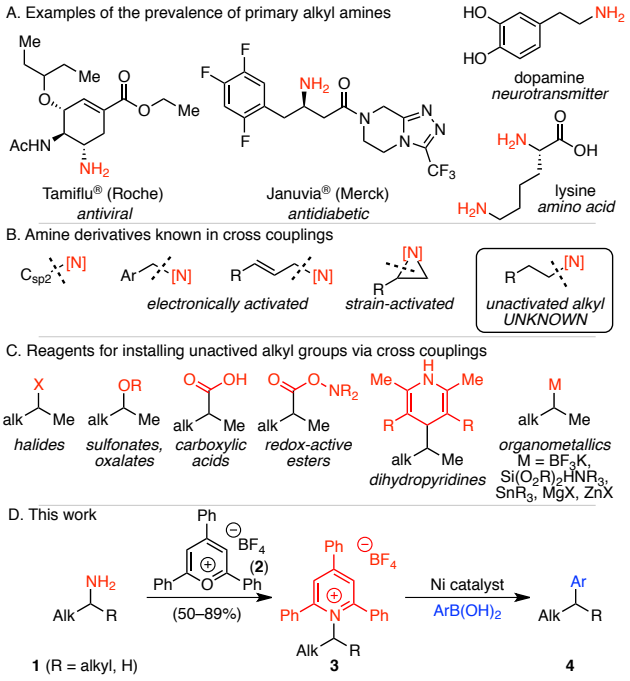
Supporting Information Placeholder

ABSTRACT: We developed a strategy to harness alkyl amines as alkylating agents via C–N bond activation. This Suzuki–Miyaura cross coupling of alkyl pyridinium salts, readily formed from primary amines, is the first example of a metal-catalyzed cross coupling via C–N bond activation of an amine with an *unactivated* alkyl group. This reaction enjoys broad scope and functional group tolerance. Primary and secondary alkyl groups can be installed. Preliminary studies suggest a Ni^{I}/Ni^{III} catalytic cycle.

Primary amines are prevalent across a wide range of molecules, from simple building blocks and synthetic intermediates, to biomolecules, drugs, and natural products (Scheme 1A).[1] The amino (NH_2) group is easily installed, is amenable to late-stage functionalization, and offers advantages such as purification via acid/base extraction. Although these benefits are well appreciated in the synthesis of nitrogen-containing products, alkyl amines have yet to be broadly recognized as alkylating agents. We envisioned that this underutilized reactivity of alkyl amines could be unlocked via metal-catalyzed C–N bond activation in a cross coupling. However, few cross couplings employ amine derivatives (Scheme 1B).[2] Cross couplings have been achieved via cleavage of various C_{sp2}–N bonds.[3] For C_{sp3}–N bonds, electronically activated (benzylic and allylic) and strain-activated (aziridinyl) C–N bonds have been employed.[4] However, there are no cross couplings of an alkyl amine derivative with an *unactivated* alkyl group.

In contrast, intense efforts have identified other reagents to install alkyl groups lacking activation (Scheme 1C).[5] Following pioneering developments with alkyl halides,[6] pseudohalides,[6n, 7] and organometallic nucleophiles,[8] dual photoredox/nickel catalysis has enabled use of oxalates,[9] carboxylic acids,[10] 1,4-dihydropyridines,[11] organoboronates,[12] and organosilicates.[13] Redox-active esters are also potent alkylating agents without need for a photocatalyst.[14]

Scheme 1. Alkyl amines and their potential in the context of cross-coupling reactions

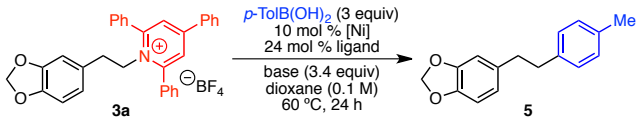


Cross coupling an alkyl amine derivative would offer exciting complimentary opportunities in synthesis and late-stage functionalization. Our previous efforts toward C–N activation relied on benzylic trimethylammonium salts, in which chemoselectivity for the benzylic C–N bond is achieved via electronic activation.[4a-c] Due to the similarity of the alkyl groups and diminished reactivity of non-benzylic C–N bonds, activation of nonbenzylic alkyl amines required a new strategy. Toward this goal, we were drawn to Katritzky pyridinium salts (**3**, Scheme 1D).[3b, 15] These air- and moisture-stable solids are easily prepared in a single step via condensation of a primary amine with commercially available 2,4,6-triphenylpyrylium tetrafluoroborate.[16] Unlike pyridinium cations lacking 2,6-substitution, which undergo addition to the pyridinium ring,[17] these pyridinium salts have been employed as alkyl electrophiles in non-metal-catalyzed trans-

formations via S_N2[18] or radical mechanisms.[15a,19] We envisioned that they would also serve as alkyl electrophiles in metal-catalyzed cross couplings, particularly Suzuki–Miyaura reactions with commercially available and functional group tolerant aryl boronic acids.[20] Herein, we report the first example of a metal-catalyzed cross coupling via C–N bond activation of an amine derivative with an *unactivated* alkyl group. This reaction enjoys broad scope and functional group tolerance in the alkyl pyridinium and (hetero)aryl boronic acid. Both primary and secondary alkyl groups can be installed.

Optimization began with the cross coupling of pyridinium **3a** and *p*-tolylboronic acid. Conditions similar to those for benzyl trimethylammonium triflates gave only 6% yield (Table 1, entry 1).[4a] However, with bathophenanthroline (BPhen) as ligand, the yield increased (entry 2). KO^{t}Bu as base also led to improvement (entry 3). The use of inexpensive, air- and moisture-stable $Ni(OAc)_2{\cdot}4H_2O$ gave increased yield, enabling set-up without an inert atmosphere glovebox (entry 4). Further improvement was realized by premixing $Ni(OAc)_2{\cdot}4H_2O$ and BPhen before the reaction (entry 5). Suspecting solubility was important, EtOH was added, giving 81% yield (entry 6). Not surprisingly, KOEt can be used (entry 7). $Ni(OAc)_2{\cdot}4H_2O$, BPhen, and KO^{t}Bu are necessary (entries 8, 9, and 11). Replacing BPhen with bipy decreases yield (entry 10), as does K_3PO_4 instead of KO^{t}Bu (entry 12).

Table 1. Optimization[a]



entry	[Ni]	ligand	base	yield (%)[b]
1	$Ni(cod)_2$	PPh_2Cy	K_3PO_4	6
2	$Ni(cod)_2$	BPhen	K_3PO_4	21
3	$Ni(cod)_2$	BPhen	KO^{t}Bu	24
4	$Ni(OAc)_2{\cdot}4H_2O$	BPhen	KO^{t}Bu	39
5[c]	$Ni(OAc)_2{\cdot}4H_2O$	BPhen	KO^{t}Bu	52
6[c,d]	$Ni(OAc)_2{\cdot}4H_2O$	BPhen	KO^{t}Bu	81
7[c,d]	$Ni(OAc)_2{\cdot}4H_2O$	BPhen	KOEt	68
8[c,d]	–	BPhen	KO^{t}Bu	0
9[c,d]	$Ni(OAc)_2{\cdot}4H_2O$	–	KO^{t}Bu	0
10[c,d]	$Ni(OAc)_2{\cdot}4H_2O$	bipy	KO^{t}Bu	54
11[c,d]	$Ni(OAc)_2{\cdot}4H_2O$	BPhen	–	0
12[c,d]	$Ni(OAc)_2{\cdot}4H_2O$	BPhen	K_3PO_4	3

[a] Conditions: pyridinium salt **3a** (0.1 mmol), [Ni] (10 mol %), ligand (24 mol %), *p*-TolB(OH)$_2$ (3.0 equiv), base (3.4 equiv), dioxane (0.1 M), 60 °C, 24 h. [b] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Two mixtures (Vial 1: [Ni], BPhen, dioxane. Vial 2: *p*-TolB(OH)$_2$, KO^{t}Bu, EtOH, dioxane. **3a** in either vial.) were stirred for 1 h before combining. [d] EtOH (5 equiv) added.

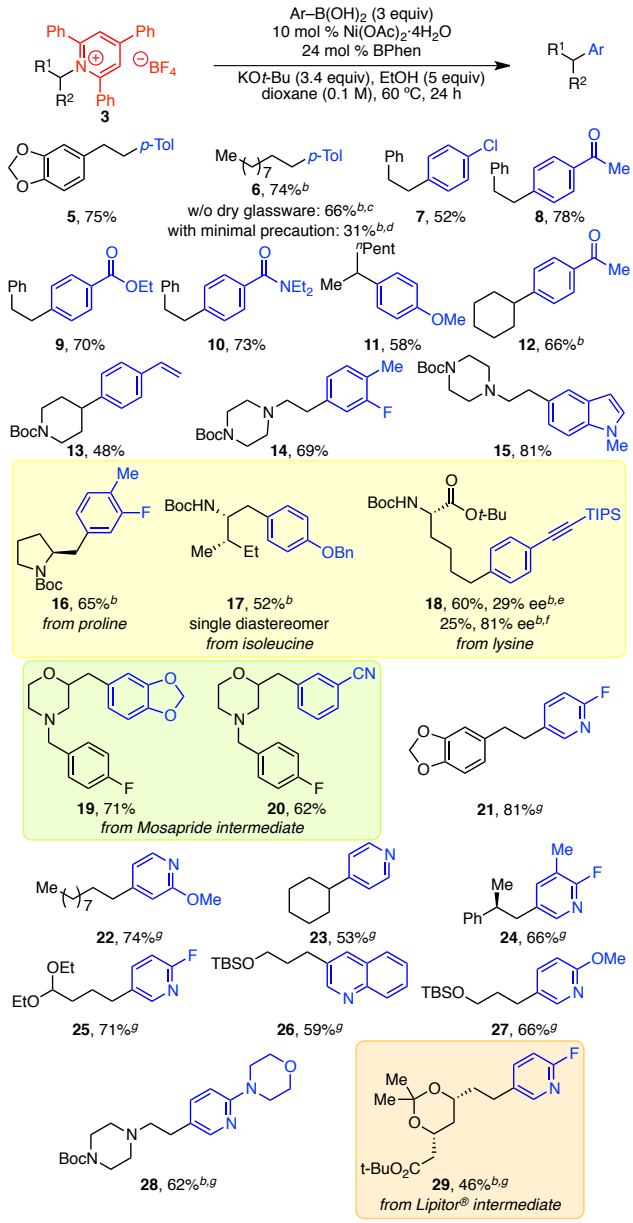
Under optimized conditions, we observed broad scope of alkyl pyridinium salts (Scheme 2). The reaction is somewhat tolerant of moisture and can be set up without oven-dried glassware, but low yield was observed when only minimal precautions were taken against air and moisture (**6**).[16] Both primary and secondary (cyclic and acyclic) alkyl groups work. β-Substituted alkyl groups can be installed, including enantioenriched examples with β-stereocenters (**17**). Many functional groups, including ethers, silyl ethers, acetals, and esters, were well tolerated. Excitingly, unlike trimethylammonium substrates, this strategy is selective for primary amines; pyridinium formation and cross coupling does not affect tertiary or Boc-protected amines. Heterocycles, including piperidines, piperazines, and morpholine, can be used.

Several products demonstrate the utility of this chemistry to create novel, potentially bioactive compounds from natural or synthetic molecules (Scheme 2). Products **16** and **17** are derived from proline and isoleucine, respectively. The synthesis of **17**, which required only 4 steps from *N*-Boc isoleucine, is representative of the ease of synthesis enabled by this cross coupling. Cross coupling of the amino side chain of *N*-Boc lysine also proceeded in good yield, albeit poor conservation of ee (**18**). However, a much higher ee, but lower yield, was observed with the use of an acidic additive, suggesting conditions can be identified to solve this problem.[21] Products **19** and **20** are derived from an amine intermediate in the synthesis of Mosapride, a treatment for gastrointestinal disorders.[22] Product **29** derives from an amine intermediate used in the synthesis of Lipitor®, an anti-cholesterol drug.[23]

Broad scope was also achieved with the aryl boronic acid. Various functionalities were tolerated, including aryl chlorides (**7**) and fluorides (**14**, **16**), methyl ketones (**8**, **12**), esters (**9**), amides (**10**), ethers (**11**, **17**), alkenes (**13**), silyl-protected alkynes (**18**), acetals (**19**), and nitriles (**20**). Given the prevalence of heterocycles in bioactive molecules, we investigated heteroarylboronic acids. *N*-Methyl indole was easily installed (**15**). Pyridyl boronic acids can also be used under slightly altered conditions (**21**–**29**). Both 3- and 4-pyridyl groups work, including those with fluoride, ether, and morpholino substituents. Notably, 2-fluoropyridines **21**, **25**, and **29** are primed for elaboration via S_NAr chemistry. Unsubstituted pyridyl was also successful (**23**).

This cross coupling could proceed via a $Ni^{0/II}$ or $Ni^{I/III}$ cycle. A $Ni^{0/II}$ mechanism would involve two-electron oxidative addition (S_N1 or S_N2), whereas a $Ni^{I/III}$ cycle would proceed via single-electron transfer (SET) from a Ni^I intermediate to the pyridinium. Although pyridinium salts undergo S_N2 reactions,[18] they are also single-electron acceptors,[15a] and have been exploited as photosensitizers[24] and sources of nitrogen radicals.[25] Also, cross coupling of **3p**, prepared from(*S*)-2-aminooctane, resulted in racemic **30**; cross coupling of

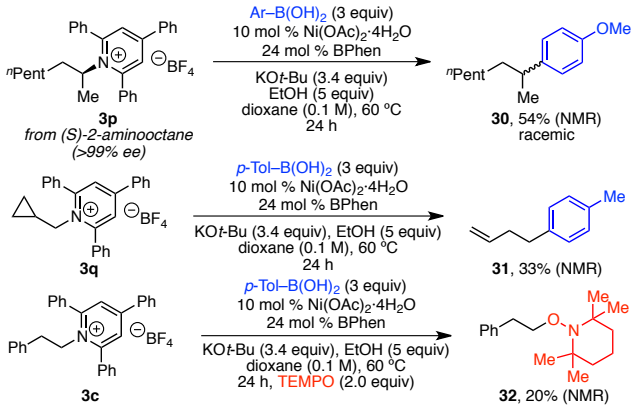
Scheme 2. Reaction scope



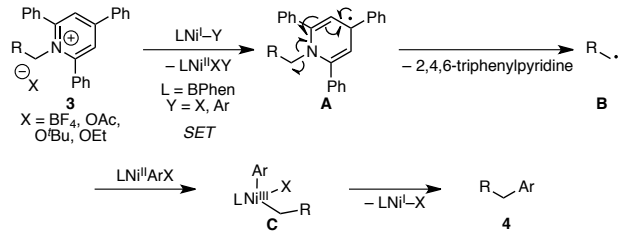
[a] Conditions: pyridinium salt **3** (1.0 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (10 mol %), BPhen (24 mol %), $ArB(OH)_2$ (3.0 equiv), KO*t*-Bu (3.4 equiv), EtOH (5 equiv), dioxane (0.1 M), 60 °C, 24 h. Average isolated yields (±6%) from duplicate experiments. [b] Single experiment. [c] Glassware not oven-dried before use. [d] Minimal precautions to protect from air and moisture (see Supporting Information). [e] 0.5-mmol scale. [f] 0.05-mmol scale. *p*-$(CF_3)C_6H_4OH$ (2 equiv) added. Yield determined by ^1H NMR using 1,3,5-$(OMe)_3C_6H_3$ as internal standard. [g] 12 mol % BPhen, dioxane (0.025 M).

cyclopropane **3q** gave ring-opened **31**; and addition of TEMPO provided trapped product **32** (Scheme 3). These results, the superiority of bipyridyl ligands, which are often employed in $Ni^{I/III}$ catalysis,[5] and the fact that Ni^{II} precursors outcompete Ni^0 suggest a SET mechanism (Scheme 4). Similarly to redox-active esters, pyridinium **3** undergoes SET with a Ni(I) intermediate, triggering fragmentation to give alkyl radical **B**, which recombines with an arylnickel(II) intermediate to give Ni^{III} species **C**. Reductive elimination provides **4**. Both monometallic "transmetallation-first" and radical chain bimetallic SET oxidative addition are known; we cannot currently distinguish these possibilities.[6w, 26]

Scheme 3. Mechanistic experiments



Scheme 4. Mechanistic proposal



In sum, we developed a nickel-catalyzed cross coupling of alkyl pyridinium salts with aryl boronic acids. When combined with efficient formation of pyridinium salts from primary amines, this method enables transformation of primary alkyl amines to alkyl arenes. This reaction is the first cross coupling to install unactivated alkyl groups via C–N bond activation. Additional highlights include selectivity for primary amines, broad scope for primary and secondary alkyl groups, and wide tolerance of functional groups and heterocycles. Mechanistic experiments suggest a $Ni^{I/III}$ cycle. Current efforts are underway to expand the scope and utility of this chemistry, which we hope will find broad use in synthesis and late-stage functionalization of alkyl amines.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental details and data (PDF)

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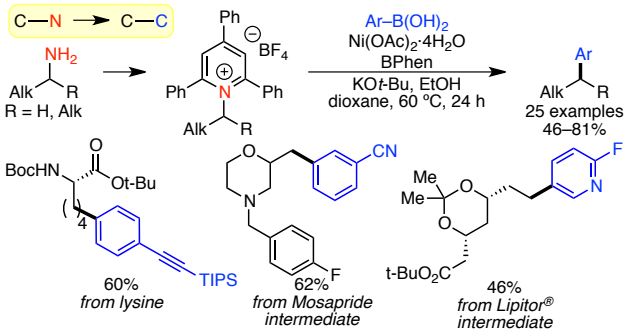
C—N → C—C
NH2
Alk
R
R = H, Alk
Ph
BF4
Ph
N
Ph
Alk
R
Ar–B(OH)2
Ni(OAc)2·4H2O
BPhen
KOt-Bu, EtOH
dioxane, 60 °C, 24 h
Ar
Alk
R
25 examples
46–81%
BocHN
O
Ot-Bu
4
TIPS
60%
from lysine
O
N
CN
F
62%
from Mosapride
intermediate
Me
Me
O
O
t-BuO2C
F
N
46%
from Lipitor®
intermediate