HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2018 April 19.

Published in final edited form as:

J Am Chem Soc. 2017 April 19; 139(15): 5313–5316. doi:10.1021/jacs.7b02389.

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

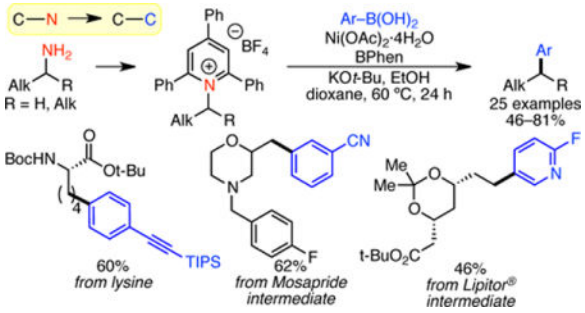
Corey H. Basch, **Jennie Liao**, **Jianyu Xu**, **Jacob J. Piane**, and **Mary P. Watson***

Department of Chemistry & Biochemistry, University of Delaware, Newark, Delaware 19716, United States

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.

Graphical Abstract



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

***Corresponding Author:** mpwatson@udel.edu.

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

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]

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 transformations 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).

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 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]

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank NIH R01 GM111820, UD for University Graduate (CHB) and Summer Scholars (JP) Fellowships, and the Plastino Alumni Undergraduate Research Fellowship program (JP). Data were acquired at UD on instruments obtained with assistance of NSF and NIH funding (NSF CHE0421224, CHE1229234, CHE0840401, and CHE1048367; NIH P20 GM104316, P20 GM103541, and S10 OD016267).

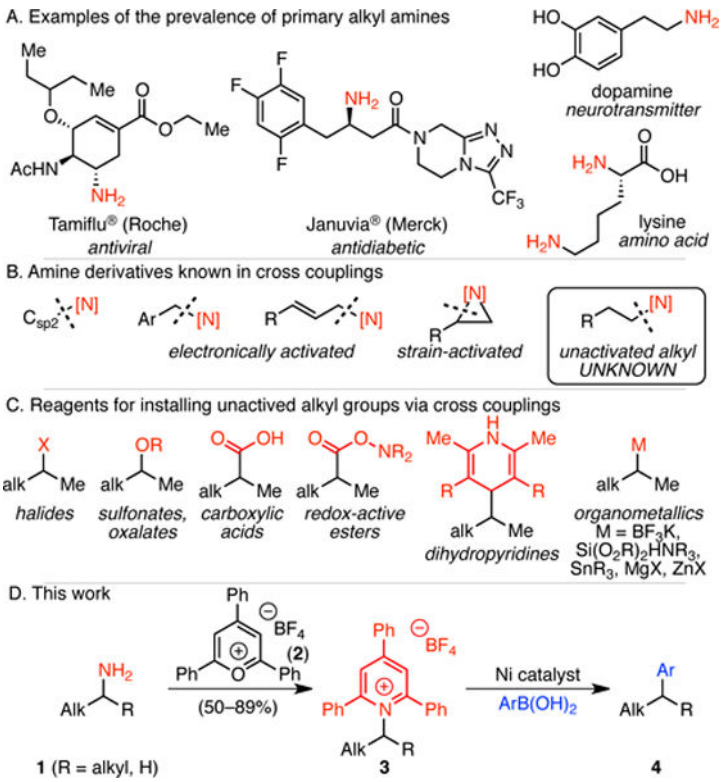
References

1. (a) Ruiz-Castillo P, Buchwald SL. Chem Rev. 2016; 116:12564. [PubMed: 27689804] (b) McGrath NA, Brichacek M, Njardarson JT. J Chem Educ. 2010; 87:1348.(c) Liu Y, Ge H. Nat Chem. 2017; 9:26.
2. Ouyang K, Hao W, Zhang WX, Xi Z. Chem Rev. 2015; 115:12045. [PubMed: 26423200]
3. (a) Blakey S, MacMillan D. J Am Chem Soc. 2003; 125:6046. [PubMed: 12785821] (b) Buszek KR, Brown N. Org Lett. 2007; 9:707. [PubMed: 17253706] (c) Hie L, Baker EL, Anthony SM, Desrosiers JN, Senanayake C, Garg NK. Angew Chem, Int Ed. 2016; 55:15129.(d) Meng G, Szostak M. Org Lett. 2016; 18:796. [PubMed: 26855279] (e) Peng C, Wang Y, Wang J. J Am Chem Soc. 2008; 130:1566. [PubMed: 18186640] (f) Shi S, Meng G, Szostak M. Angew Chem, Int Ed. 2016; 55:6959.(g) Simmons BJ, Weires NA, Dander JE, Garg NK. ACS Catalysis. 2016; 6:3176.(h) Tobisu M, Nakamura K, Chatani N. J Am Chem Soc. 2014; 136:5587. [PubMed: 24684671] (i) Weires NA, Baker EL, Garg NK. Nat Chem. 2016; 8:75. [PubMed: 26673267] (j) Wu G, Deng Y, Wu C, Zhang Y, Wang J. Angew Chem, Int Ed. 2014; 53:10510.
4. (a) Maity P, Shacklady-McAtee DM, Yap GPA, Sirianni ER, Watson MP. J Am Chem Soc. 2013; 135:280. [PubMed: 23268734] (b) Shacklady-McAtee DM, Roberts KM, Basch CH, Song Y-G, Watson MP. Tetrahedron. 2014; 70:4257. [PubMed: 25364060] (c) Basch CH, Cobb KM, Watson MP. Org Lett. 2016; 18:136. [PubMed: 26679212] (d) Hu J, Sun H, Cai W, Pu X, Zhang Y, Shi Z. J Org Chem. 2016; 81:14. [PubMed: 26628255] (e) Huang CY, Doyle AG. J Am Chem Soc. 2012; 134:9541. [PubMed: 22414150] (f) Li MB, Wang Y, Tian SK. Angew Chem, Int Ed. 2012; 51:2968. (g) Moragas T, Gaydou M, Martin R. Angewandte Chemie. 2016; 128:5137.(h) Zhang H, Hagihara S, Itami K. Chem Eur J. 2015; 21:16796. [PubMed: 26435307] (i) Moragas T, Gaydou M, Martin R. Angew Chem, Int Ed. 2016; 55:5053.(j) Jensen KL, Standley EA, Jamison TF. J Am Chem Soc. 2014; 136:11145. [PubMed: 25055180]
5. Tasker SZ, Standley EA, Jamison TF. Nature. 2014; 509:299. [PubMed: 24828188]
6. (a) Tsuji T, Yorimitsu H, Oshima K. Angew Chem, Int Ed. 2002; 41:4137.(b) Zhou JS, Fu GC. J Am Chem Soc. 2003; 125:14726. [PubMed: 14640646] (c) Gonzalez-Bobes F, Fu GC. J Am Chem Soc. 2006; 128:5360. [PubMed: 16620105] (d) Firmansjah L, Fu GC. J Am Chem Soc. 2007; 129:11340. [PubMed: 17718496] (e) Saito B, Fu GC. J Am Chem Soc. 2007; 129:9602. [PubMed: 17628067] (f) Strotman NA, Sommer S, Fu GC. Angew Chem, Int Ed. 2007; 46:3556.(g) Saito B, Fu GC. J Am Chem Soc. 2008; 130:6694. [PubMed: 18447357] (h) Hatakeyama T, Nakagawa N, Nakamura M. Org Lett. 2009; 11:4496. [PubMed: 19757826] (i) Owston NA, Fu GC. J Am Chem Soc. 2010; 132:11908. [PubMed: 20701271] (j) Lu Z, Wilsily A, Fu GC. J Am Chem Soc. 2011; 133:8154. [PubMed: 21553917] (k) Dudnik AS, Fu GC. J Am Chem Soc. 2012; 134:10693. [PubMed: 22668072] (l) Ito H, Kubota K. Org Lett. 2012; 14:890. [PubMed: 22260229] (m) Wilsily A, Tramutola F, Owston NA, Fu GC. J Am Chem Soc. 2012; 134:5794. [PubMed: 22443409] (n) Yang

CT, Zhang ZQ, Liang J, Liu JH, Lu XY, Chen HH, Liu L. J Am Chem Soc. 2012; 134:11124. [PubMed: 22734716] (o) Cordier CJ, Lundgren RJ, Fu GC. J Am Chem Soc. 2013; 135:10946. [PubMed: 23869442] (p) Zultanski SL, Fu GC. J Am Chem Soc. 2013; 135:624. [PubMed: 23281960] (q) Bose SK, Fucke K, Liu L, Steel PG, Marder TB. Angew Chem, Int Ed. 2014; 53:1799.(r) Choi J, Martin-Gago P, Fu GC. J Am Chem Soc. 2014; 136:12161. [PubMed: 25127186] (s) Liang Y, Fu GC. J Am Chem Soc. 2015; 137:9523. [PubMed: 26203662] (t) Ratani TS, Bachman S, Fu GC, Peters JC. J Am Chem Soc. 2015; 137:13902. [PubMed: 26491957] (u) Wang X, Wang S, Xue W, Gong H. J Am Chem Soc. 2015; 137:11562. [PubMed: 26325479] (v) Zhang P, Le CC, MacMillan DW. J Am Chem Soc. 2016; 138:8084. [PubMed: 27263662] (w) Zhou J, Fu GC. J Am Chem Soc. 2004; 126:1340. [PubMed: 14759182]

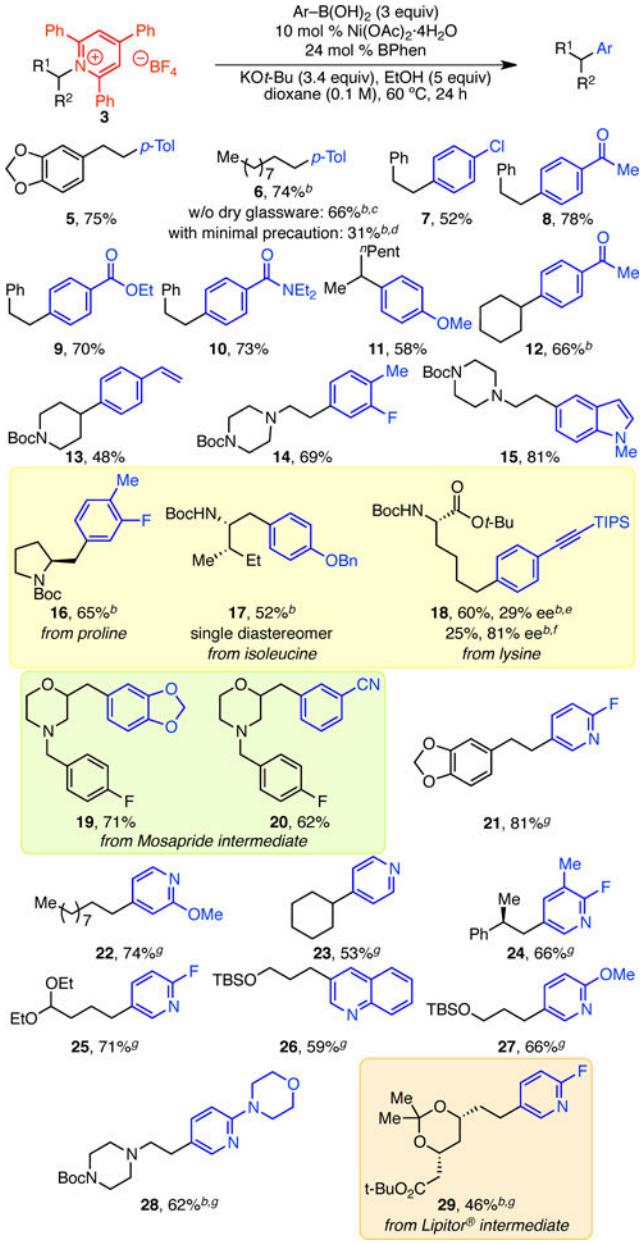
7. (a) Liang Z, Xue W, Lin K, Gong H. Org Lett. 2014; 16:5620. [PubMed: 25333482] (b) Liu JH, Yang CT, Lu XY, Zhang ZQ, Xu L, Cui M, Lu X, Xiao B, Fu Y, Liu L. Chem Eur J. 2014; 20:15334. [PubMed: 25308802] (c) Molander GA, Traister KM, O'Neill BT. J Org Chem. 2015; 80:2907. [PubMed: 25711834]
8. (a) Joshi-Pangu A, Wang CY, Biscoe MR. J Am Chem Soc. 2011; 133:8478. [PubMed: 21553878] (b) Lohre C, Dröge T, Wang C, Glorius F. Chem Eur J. 2011; 17:6052. [PubMed: 21509842] (c) Thapa S, Kafle A, Gurung SK, Montoya A, Riedel P, Giri R. Angew Chem, Int Ed. 2015; 54:8236. (d) Wang CY, Derosa J, Biscoe MR. Chem Sci. 2015; 6:5105. [PubMed: 26388985]
9. (a) Nawrat CC, Jamison CR, Slutskyy Y, MacMillan DWC, Overman LE. J Am Chem Soc. 2015; 137:11270. [PubMed: 26322524] (b) Zhang X, MacMillan DW. J Am Chem Soc. 2016; 138:13862.
10. (a) Johnston CP, Smith RT, Allmendinger S, MacMillan DW. Nature. 2016; 536:322. [PubMed: 27535536] (b) Zuo Z, Ahneman DT, Chu L, Terrett JA, Doyle AG, MacMillan DWC. Science. 2014; 345:437. [PubMed: 24903563]
11. Gutiérrez-Bonet Á, Tellis JC, Matsui JK, Vara BA, Molander GA. ACS Catalysis. 2016; 6:8004. [PubMed: 27990318]
12. (a) Tellis JC, Primer DN, Molander GA. Science. 2014; 345:433. [PubMed: 24903560] (b) Primer DN, Karakaya I, Tellis JC, Molander GA. J Am Chem Soc. 2015; 137:2195. [PubMed: 25650892] (c) Yamashita Y, Tellis JC, Molander GA. Proc Natl Acad Sci USA. 2015; 112:12026. [PubMed: 26371299] (d) Tellis JC, Amani J, Molander GA. Org Lett. 2016; 18:2994. [PubMed: 27265019] (e) Tellis JC, Kelly CB, Primer DN, Jouffroy M, Patel NR, Molander GA. Acc Chem Res. 2016; 49:1429. [PubMed: 27379472]
13. (a) Jouffroy M, Primer DN, Molander GA. J Am Chem Soc. 2016; 138:475. [PubMed: 26704168] (b) Patel NR, Kelly CB, Jouffroy M, Molander GA. Org Lett. 2016; 18:764. [PubMed: 26828317] (c) Patel NR, Molander GA. J Org Chem. 2016; 81:7271. [PubMed: 27258090] (d) Vara BA, Jouffroy M, Molander GA. Chem Sci. 2017; 8:530. [PubMed: 28451200]
14. (a) Cornella J, Edwards JT, Qin T, Kawamura S, Wang J, Pan CM, Gianatassio R, Schmidt M, Eastgate MD, Baran PS. J Am Chem Soc. 2016; 138:2174. [PubMed: 26835704] (b) Huihui KM, Caputo JA, Melchor Z, Olivares AM, Spiewak AM, Johnson KA, DiBenedetto TA, Kim S, Ackerman LK, Weix DJ. J Am Chem Soc. 2016; 138:5016. [PubMed: 27029833] (c) Qin T, Cornella J, Li C, Malins LR, Edwards JT, Kawamura S, Maxwell BD, Eastgate MD, Baran PS. Science. 2016; 352:801. [PubMed: 27103669] (d) Toriyama F, Cornella J, Wimmer L, Chen TG, Dixon DD, Creech G, Baran PS. J Am Chem Soc. 2016; 138:11132. [PubMed: 27548696] (e) Wang J, Qin T, Chen TG, Wimmer L, Edwards JT, Cornella J, Vokits B, Shaw SA, Baran PS. Angew Chem, Int Ed. 2016; 55:9676.
15. (a) Katritzky AR, De Ville G, Patel RC. Tetrahedron. 1981; 37:25.(b) Bapat JB, Blade RJ, Boulton AJ, Epsztajn J, Katrizky AR, Lewis J, Molina-Buendia P, Nie PL, Ramsden CA. Tetrahedron Lett. 1976; 31:2691.(c) Katrizky AR, Marson CM. Angew Chem, Int Ed. 1984; 23:420.
16. See Supporting Information
17. (a) Kearney AM, Vanderwal CD. Angew Chem, Int Ed. 2006; 45:7803.(b) Sun Z, Yu S, Ding Z, Ma D. J Am Chem Soc. 2007; 129:9300. [PubMed: 17625864] (c) Black DA, Beveridge RE, Arndtsen BA. J Org Chem. 2008; 73:1906. [PubMed: 18215063] (d) Chau ST, Lutz JP, Wu K, Doyle AG. Angew Chem, Int Ed. 2013; 52:9153.(e) Lutz JP, Chau ST, Doyle AG. Chem Sci. 2016; 7:4105. [PubMed: 28058106]
18. Said SA, Fiksdahl A. Tetrahedron Asym. 2001; 12:1947.
19. Vinyl pyridinium salts have been used in Pd-catalyzed cross couplings. See ref. 3b.

20. Maluenda I, Navarro O. Molecules. 2015; 20:7528. [PubMed: 25919276]
21. Ohshima T, Hayashi Y, Agura K, Fujii Y, Yoshiyama A, Mashima K. Chem Commun. 2012; 48:5434.
22. Kato S, Morie T, Yoshida N. Chem Pharm Bull. 1995; 43:699. [PubMed: 7600620]
23. Roth, BD. US 4,681,893. 1987.
24. Álvaro M, Formentín P, García H, Palomares E, Sabater MJ. J Org Chem. 2002; 67:5184. [PubMed: 12126404]
25. Greulich TW, Daniliuc CG, Studer A. Org Lett. 2015; 17:254. [PubMed: 25541887]
26. (a) Biswas S, Weix DJ. J Am Chem Soc. 2013; 135:16192. [PubMed: 23952217] (b) Breitenfeld J, Ruiz J, Wodrich MD, Hu X. J Am Chem Soc. 2013; 135:12004. [PubMed: 23865460] (c) Hu X. Chem Sci. 2011; 2:1867.(d) Jones GD, Martin JL, McFarland C, Allen OR, Hall RE, Haley AD, Brandon RJ, Konovalova T, Desrochers PJ, Pulay P, Vicic DA. J Am Chem Soc. 2006; 128:13175. [PubMed: 17017797] (e) Lin X, Phillips DL. J Org Chem. 2008; 73:3680. [PubMed: 18410144] (f) Powell DA, Fu GC. J Am Chem Soc. 2004; 126:7788. [PubMed: 15212521] (g) Schley ND, Fu GC. J Am Chem Soc. 2014; 136:16588. [PubMed: 25402209] (h) Zheng B, Tang F, Luo J, Schultz JW, Rath NP, Mirica LM. J Am Chem Soc. 2014; 136:6499. [PubMed: 24712743]



Scheme 1.

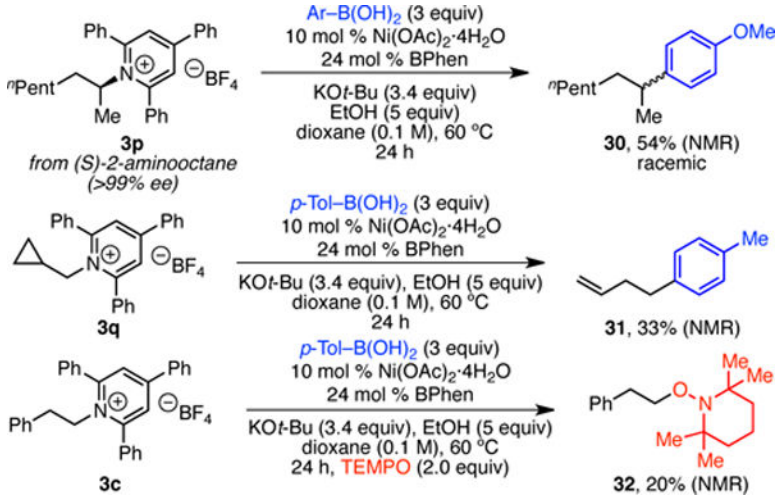
Alkyl amines and their potential in the context of cross-coupling reactions



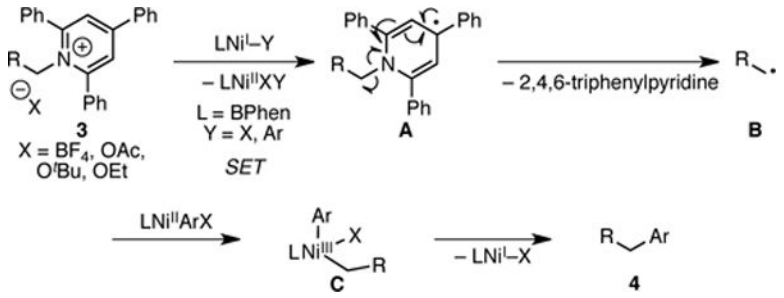
Scheme 2.

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).



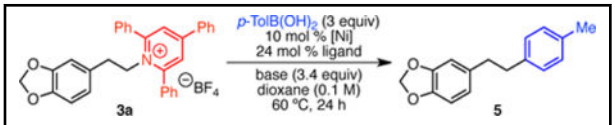
Scheme 3.
Mechanistic experiments



Scheme 4.
Mechanistic proposal

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.