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Transforming Benzylic Amines into Diarylmethanes: Cross-Couplings of Benzylic Pyridinium Salts via C−N Bond Activation

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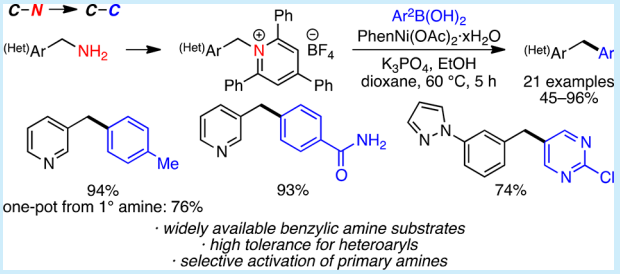
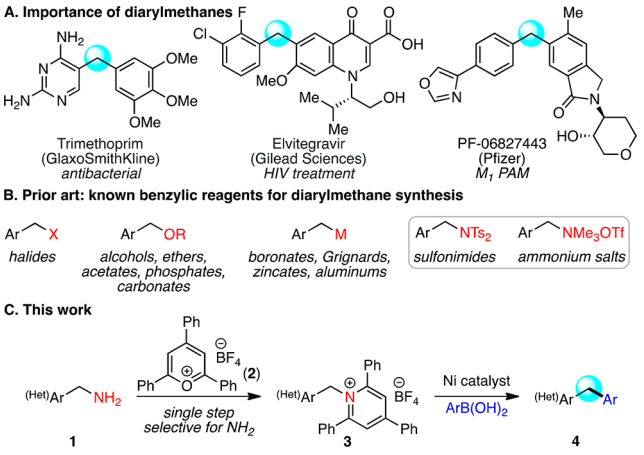
Supporting Information

ABSTRACT: A nickel-catalyzed cross-coupling of benzylic pyridinium salts with arylboronic acids was developed. Coupled with chemoselective pyridinium formation, this method allows benzyl primary amines to be efficiently converted to di(hetero)-arylmethanes. Excellent heteroaryl and functional group tolerance is observed, and a one-pot procedure enables benzylic amines to be converted to diarylmethanes directly.



Diarylmethanes are an important motif in pharmaceuticals, including antibacterial, anti-HIV, and antitumor agents (Scheme 1A).[1] In our own work, we have identified diarylmethanes such as PF-06827443 as subtype-selective positive allosteric modulators (PAMs) of the muscarinic M_1 receptor.[2] Following a common approach, the diarylmethane was formed using a palladium-catalyzed cross-coupling of a benzylic chloride to an arylboronic ester. In addition to benzylic halides,[3] benzylic alcohol derivatives[4] and metal-based benzylic nucleophiles[5] are frequently used in cross-couplings to form diarylmethanes (Scheme 1B).[6]

Scheme 1. Importance of Diarylmethanes and Cross-Coupling Approaches for Their Synthesis



In contrast, benzylic amine derivatives have only sparingly been investigated as electrophiles in cross-coupling arylations. Tian and Rhee demonstrated that benzylic sulfonimides can be employed in copper- or palladium-catalyzed arylations.[7] We and others have also shown that benzylic ammonium salts are suitable substrates for cross-couplings with aryl boronic acids.[8−10] However, conversion of benzylic primary amines to sulfonimides or ammonium salts requires two steps and can limit the inclusion of basic heteroatoms elsewhere in the substrate. These constraints restrict the utility of these cross-couplings, particularly in the context of drug discovery.

We believe that the lack of methods to harness benzylic amines in cross-couplings is a missed opportunity in the toolbox of reactions for drug discovery. Benzylic amines are generally inexpensive and widely available. They can be easily synthesized[11] and can often be purified without chromatography. As a case study for their availability versus more common substrates for cross-couplings, 5208 benzylic primary amines are present in the internal Pfizer chemical store, in contrast to only 1843 benzylic chlorides and 1020 benzylic bromides.

We have recently reported that Katritzky pyridinium salts are effective in nickel-catalyzed cross-couplings with arylboronic acids.[12] This work focused on alkyl amines with unactivated alkyl groups (nonbenzylic, nonallylic, not strained). Initial studies suggested that these reactions likely proceed via an alkyl radical formed via single-electron transfer (SET) from a Ni^I intermediate to the pyridinium ring, initiating C−N bond fragmentation.[13] Based on this mechanistic hypothesis, cross-coupling of a benzylic pyridinium salt (**3**) should also be feasible, given that a stabilized benzylic radical will be formed in this key step.[14] Herein, we report a nickel-catalyzed cross-coupling of benzylic pyridinium salts with aryl boronic acids to form diarylmethanes (Scheme 1C). This method is highly amenable to both electron-poor and electron-rich heteroaromatics. In

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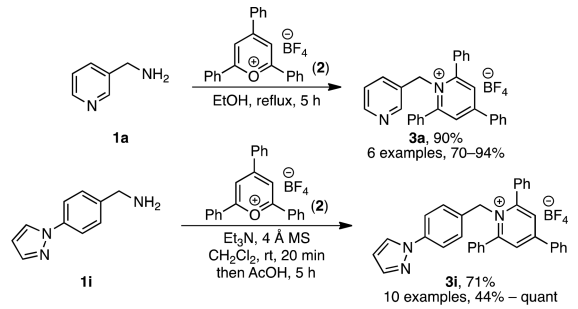
addition, the synthesis of the pyridinium salt requires only a single step from the primary amine and is compatible with other basic groups in the substrate.[15] Furthermore, electron-poor benzylic amines can be directly transformed to diarylmethanes via a one-pot pyridinium formation/cross-coupling sequence.

Given the importance of nitrogen-containing heterocycles in pharmaceutials,[16] we selected pyridylpyridinium salt **3a** as the model substrate. Pyridinium **3a** was formed in 90% yield via the condensation of amine **1a** with commercially available 2,4,6-triphenylpyrrilium tetrafluoroborate **2** (Scheme 2). Other

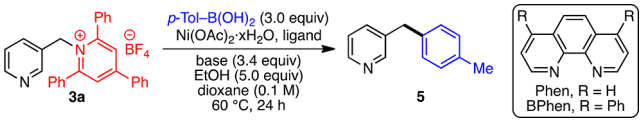
Scheme 2. Synthesis of Benzylic Pyridinium Salts



amines with electron-poor heteroaryl groups were also prepared via this method. For benzylic amines with electron-rich aromatic groups, the use of EtOH as solvent resulted in the formation of the undesired benzylic ether, via substitution of the more labile pyridinium with EtOH. This issue was circumvented by forming the pyridinium salt in CH_2Cl_2. These pyridinium salts are stable when stored as solids for at least 9 months.

With pyridinium salt **3a** in hand, we optimized its cross-coupling with *p*-Tol-B(OH)$_2$. Under conditions optimized for nonbenzylic pyridinium salts, diarylmethane **5** was formed in 66% yield (see Table 1, entry 1). Bathophenanthroline (BPhen)

Table 1. Optimization[a]



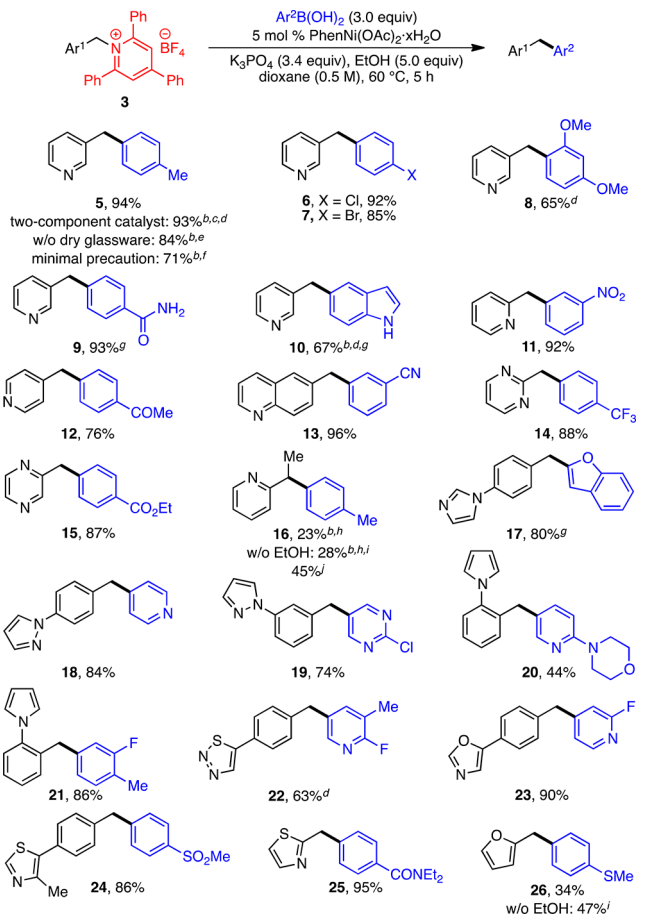
entry	[Ni] (mol %)/ligand (mol %)	base	yield[b] (%)
1[c]	$Ni(OAc)_2{\cdot}4H_2O$ (10)/BPhen (24)	KO^{t}Bu	66
2[c]	$Ni(OAc)_2{\cdot}4H_2O$ (10)/Phen (12)	KO^{t}Bu	59
3[c]	$Ni(OAc)_2{\cdot}4H_2O$ (10)/Phen (12)	K_3PO_4	93
4[c]	Phen (12)	K_3PO_4	0
5[c]	$Ni(OAc)_2{\cdot}4H_2O$ (10)	K_3PO_4	0
6[c]	none	K_3PO_4	0
7[c]	$Ni(OAc)_2{\cdot}4H_2O$ (10)/Phen (12)	none	0
8	$PhenNi(OAc)_2{\cdot}xH_2O$ (10)	K_3PO_4	93
9	$PhenNi(OAc)_2{\cdot}xH_2O$ (5)	K_3PO_4	93
10[d]	$PhenNi(OAc)_2{\cdot}xH_2O$ (5)	K_3PO_4	93
11[d,e]	$PhenNi(OAc)_2{\cdot}xH_2O$ (5)	K_3PO_4	98
12[e,f]	$PhenNi(OAc)_2{\cdot}xH_2O$ (5)	K_3PO_4	68

[a]Conditions: pyridinium salt **3a** (0.10 mmol), *p*-Tol-B(OH)$_2$ (3.0 equiv), [Ni], ligand, base (3.4 equiv), EtOH (5.0 equiv), dioxane (0.1 M), 60 °C, 24 h, unless noted otherwise. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]Two mixtures (Vial 1: [Ni], ligand, dioxane. Vial 2: *p*-TolB(OH)$_2$, base, EtOH, dioxane. Pyridinium **3a** in either vial) stirred for 1 h before being combined. [d]5 h. [e]0.5 M. [f]*p*-Tol-Bpin (3.0 equiv), 16 h.

could be replaced with the less-expensive phenanthroline (Phen), with only a slight reduction in yield (Table 1, entry 2). By changing the base to K_3PO_4, 93% yield was achieved (Table 1, entry 3). Control studies confirmed that the cross-coupling relied upon [Ni], Phen, and base (Table 1, entries 4–7). The use of a single-component catalyst, $PhenNi(OAc)_2{\cdot}xH_2O$, which is easily prepared in a single step, provided 93% yield (Table 1, entry 8), enabled lower catalyst loading (Table 1, entry 9), and prevented the need for premixing the catalyst components for 1 h before combining with the other reagents. By increasing the concentration of **3a** to 0.5 M, the time could be reduced (Table 1, entry 11). Finally, the pinacol boronic ester can also be used, further increasing the versatility of this transformation (Table 1, entry 12).

A wide range of benzylic pyridinium salts successfully underwent the cross-coupling (see Scheme 3). Model product **5** was isolated in 94% yield on 1 mmol scale. Use of 10 mol % $Ni(OAc)_2{\cdot}4H_2O$ and 12 mol % Phen also resulted in high yield;

Scheme 3. Scope[a]



[a]Conditions: pyridinium salt **3** (1.0 mmol), $PhenNi(OAc)_2{\cdot}xH_2O$ (5 mol %), ArB(OH)$_2$ (3.0 equiv), K_3PO_4 (3.4 equiv), EtOH (5 equiv), dioxane (0.5 M), 60 °C, 5 h. Average isolated yields (±5%) from duplicate experiments. [b]Single experiment. [c]10 mol % $Ni(OAc)_2{\cdot}4H_2O$, 12 mol % Phen. [d]24 h. [e]Glassware was not oven-dried. [f]Minimal precautions to protect from air and moisture. See the Supporting Information. [g]3:1 dioxane:DMSO. [h]0.1 mmol scale. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [i]EtOH omitted. [j]Conditions: 3 g (1.0 mmol) pyridinium salt, $Ni(OAc)_2{\cdot}4H_2O$ (10 mol %), 4,4′-ditBuBipy (12 mol %), *p*-Tol-B(OH)$_2$ (3.0 equiv), K_3PO_4 (3.4 equiv), dioxane (0.1 M), 60 °C, 24 h.

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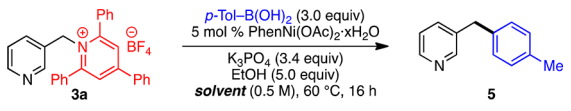
this protocol can be used when preparation of the single-component catalyst is less convenient. To test the sensitivity, the reaction was performed without oven-dried glassware and without precautions against air or moisture. In both cases, good yields were still obtained. Other electron-poor heteroaryls were also well-tolerated, including 2-pyridine (**11**), 4-pyridine (**12**), quinoline (**13**), pyrimidine (**14**), and pyrazine (**15**). Various electron-rich heteroaryls were also tolerated, including imidazole (**17**), pyrazole (**18**, **19**), pyrrole (**20**, **21**), thiadiazole (**22**), oxazole (**23**), and thiazole (**24**, **25**). Furan-derived pyridinium salts were competent as well, providing **26** in 34% yield, along with undesired ethyl ether byproduct. By eliminating EtOH, the yield improved to 47%. When solubility of the pyridinium salt or boronic acid was low, 3:1 dioxane/DMSO was used. In most cases, little homocoupling of the benzylic pyridiniums or arylboronic acid was observed, but in some lower-yielding examples, significant protodeborylation was seen (e.g., **20**).

Secondary benzylic pyridinium salts were also examined. However, diarylethane **16** was formed in only 23% yield. Omission of EtOH only slightly increased the yield. A brief screen of ligands demonstrated that the use of 4,4′-ditBuBipy increased the yield to 45%. Triphenylpyridine was only formed in ~60% in this reaction, suggesting that C−N bond cleavage was sluggish. Note that a deactivating electron-poor aryl substituent is required for pyridinium formation from secondary benzylic amines; the pyridinium salt of α-methylbenzylamine could not be isolated or formed in situ.

For the aryl boronic acid, broad tolerance for functional groups and heteroaryls was observed, including aryl chlorides (**6**, **19**), fluorides (**21**, **22**) and even bromides (**7**), ethers (**8**, **20**), amides (**9**, **25**), nitroarenes (**11**), ketones (**12**), nitriles (**13**), trifluoromethyls (**14**), esters (**15**), tertiary amines (**20**), sulfones (**24**), and thioethers (**26**). Both electron-rich and electron-poor heteroaryls can be used, including indole (**10**), benzofuran (**17**), pyridine (**18**, **20**, **22**, **23**), and pyrazine (**19**). Notably, many of the pyridines are poised for further elaboration via S_NAr chemistry.

Cognizant that poor solubility can be limiting for some substrates, we tested the tolerance of this reaction to various solvents (see Table 2). A wide range of solvents can be used. Lower yields were observed when DMSO and DMF were used, but these yields were still of high synthetic utility. EtOH can be used, although only for pyridinium salts with electron-poor heteroaryls, which do not undergo substitution with EtOH (Table 2, entry 9).

Table 2. Wide Solvent Tolerance[a]

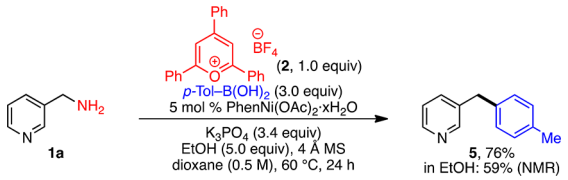


entry	solvent	yield[b] (%)	entry	solvent	yield[b] (%)
1	CH_2Cl_2	83	6	MeCN	91
2	PhMe	94	7	DMSO	62
3	2-Me-THF	96	8	DMF	61
4	Et_2O	90	9[c]	EtOH	77[d]
5	CPME	96			

[a]Conditions: pyridinium salt **3** (0.10 mmol), PhenNi$(OAc)_2\cdot xH_2O$ (5 mol %), $ArB(OH)_2$ (3.0 equiv), K_3PO_4 (3.4 equiv), EtOH (5 equiv), solvent (0.5 M), 60 °C, 16 h. [b]Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]24 h. [d]Isolated yield.

The robustness to various solvents presented the opportunity to combine the pyridinium formation and cross-coupling in a one-pot operation. Noting that EtOH can be used for both pyridinium formation and cross-coupling, we treated primary amine **1a** with pyrrilium salt **2**, PhenNi$(OAc)_2\cdot xH_2O$, *p*-Tol-$B(OH)_2$, and K_3PO_4 in EtOH, and observed a 59% yield of the cross-coupling product (see Scheme 4). By using dioxane and

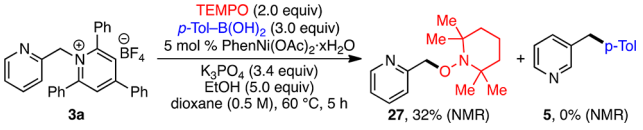
Scheme 4. One-Pot Transformation



only 5 equiv of EtOH in the presence of 4 Å molecular sieves, 76% isolated yield was achieved. Notably, this is not a two-step, one-pot procedure: all reagents were added simultaneously at the beginning of the reaction.

We hypothesize that this reaction proceeds via a $Ni^{I/III}$ catalytic cycle. Although further experiments are needed to confirm the nickel species, a radical trapping experiment supports the intermediacy of a benzylic radical.[14] When TEMPO was added to the cross-coupling of pyridinium **3a**, known TEMPO adduct **27** was produced in 32% yield (see Scheme 5).[17] Cross-coupled product **5** was not observed.

Scheme 5. Radical Trapping Experiment



In summary, we have developed a nickel-catalyzed Suzuki–Miyaura cross-coupling of benzylic pyridinium salts with aryl boronic acids. Via benzylic pyridinium intermediates, this reaction enables efficient conversion of widely available benzylic amines to diarylmethanes, which is a prevalent motif in pharmaceuticals and other bioactive molecules. Importantly, this reaction is amenable to heteroaryl substitution on both coupling partners, as well as a wide range of functional groups. Finally, for benzylic pyridinium salts with electron-poor aryl groups, a one-pot procedure was developed to facilitate the use of this chemistry in synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01062.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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