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Deaminative Reductive Cross-Electrophile Couplings of Alkylpyridinium Salts and Aryl Bromides

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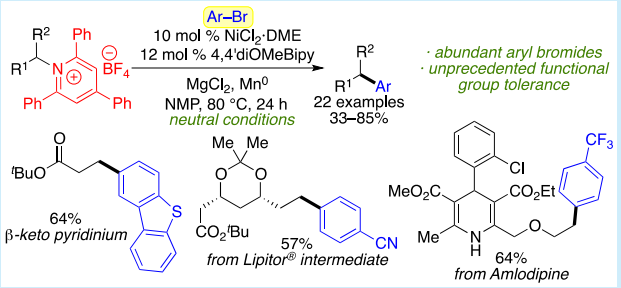
Supporting Information

ABSTRACT: A nickel-catalyzed reductive cross-coupling of alkylpyridinium salts and aryl bromides has been developed using Mn as the reductant. Both primary and secondary alkylpyridinium salts can be used, and high functional group and heterocycle tolerance is observed, including for protic groups. Mechanistic studies indicate the formation of an alkyl radical, and controlling its fate was key to the success of this reaction.



The increasing prevalence of sp^3-hybridized carbons in pharmaceuticals, along with their presence in natural products and other targets, has spurred exciting innovations in the development of reagents and methods for the incorporation of alkyl groups.[1,2] Methods that harness ubiquitous functional groups in cross-couplings provide opportunities to exploit previously untapped feedstocks and for late-stage functionalization.[3] Our efforts focus on methods that enable alkyl primary amines to be transformed into alkyl electrophiles. Alkyl amines are prevalent in molecules ranging from simple starting materials to complex natural products and drug candidates.[1b,4] They are easy to prepare, stable, and broadly compatible with many functional groups, allowing them to be carried deep into a synthetic sequence particularly when protected.[4c,d] From the perspective of medicinal discovery, alkyl amines are present in pharmaceutical libraries in vast numbers and offer considerable diversity. For example, Pfizer's internal chemical inventory has >47 000 alkyl primary amines (vs <30 000 primary and secondary alkyl halides).

We identified that alkyl amines, including those with *unactivated* alkyl groups, can become effective reagents for cross-couplings via conversion to Katritzky pyridinium salts.[5−7,5c,d,8,9] These Katritzky pyridinium salts are easily prepared in a single step from the primary amine, are air- and moisture-stable, and are convenient to purify. Their formation is selective for primary amines, allowing other Lewis basic groups to be tolerated in the substrate. We demonstrated a nickel-catalyzed Suzuki−Miyaura arylation of alkylpyridinium salts to form $C(sp^3)-C(sp^2)$ bonds, the first example of using an unactivated alkyl amine derivative in a cross-coupling.[5a] Since our discovery, we and others have continued to develop this underappreciated class of reagents.[5,10]

Although the use of aryl boronic acids presents control over the arylation regioselectivity, it also presents limitations. Due to the basic conditions required for boronic acid activation, pyridinium salts with β-electron-withdrawing groups undergo elimination, and other protic groups are also problematic. An excess (3.0 equiv) of the aryl boronic acid is required.[5a] Third, aryl boronic acids must be prepared from aryl halides, adding steps and limiting opportunities for efficient parallel synthesis. Finally, the availability of aryl boronic acids is much more limited than aryl bromides. In contrast to only 6200 (het)aryl boronic acids and esters, there are >56 000 (het)aryl bromides in Pfizer's inventory. Similar constraints limit the potential of any organometallic coupling partner. Thus, a method for direct use of aryl bromides would be of high value.

Despite the exquisite methods developed for reductive couplings of other alkyl electrophiles,[3d,g,11] it was unclear if the reduction of the pyridinium cation and potential side reactions of the alkyl radical intermediate could be controlled in the presence of a stoichiometric reductant. Overcoming these challenges, we report conditions for the efficient coupling of alkyl pyridinium salts with aryl bromides (Scheme 1). This method uses abundant and diverse aryl bromides and approximately equimolar amounts of alkyl pyridinium salt and aryl bromide, and the neutral conditions allow exceptional scope of pyridinium salts, particularly those with base-sensitive functional groups. During the preparation of this manuscript, Han and Rueping reported couplings of alkylpyridinium salts and aryl iodides.[12] These reports demonstrate feasibility of a reductive coupling. However, it is important to note that aryl iodides are less available than aryl boronic acids and esters; for

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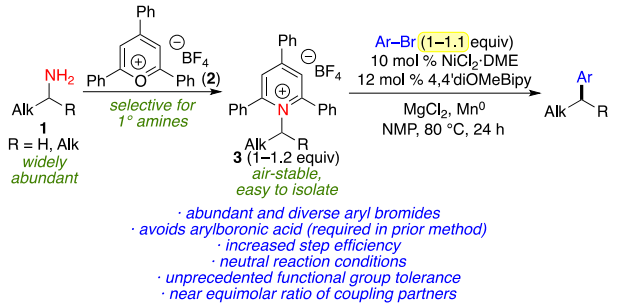
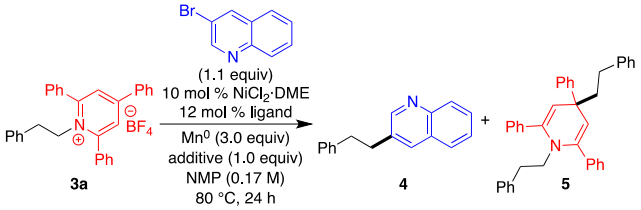
Scheme 1. Reductive Coupling of Alkyl Pyridinium Salts and Aryl Bromides



example, less than 300 (het)aryl iodides are in Pfizer's internal inventory, making these methods of limited utility for the incorporation of diverse and readily available aryl groups.

In an effort to optimize conditions for the incorporation of heteroaryls, we selected the reductive coupling of pyridinium salt **3a** and 3-bromoquinoline for optimization. To maximize the utility of this reaction for the use of precious alkyl amines and/or precious aryl bromides, we prioritized conditions that would allow approximately equimolar amounts of alkyl pyridinium salt and aryl halide to be used. Using $NiBr_2$·DME and 4,4′-di^{t}BuBipy, a promising 9% yield was observed with Zn as the reductant (Table 1, entry 1). However, dihydropyridine **5** was a major competing product, likely arising from addition of the alkyl radical intermediate to another equivalent of **3a**. Changing the reductant to Mn^0 gave increased yield (entry 2). Further improvement was observed with the addition of LiCl or $MgCl_2$, by changing the solvent to NMP and by reducing concentration (entries 3–5). These additives may accelerate reduction of the Ni^{II} intermediates or assist in activating the surface of the Mn^0.[13] Under these conditions, the equivalents of Mn^0 could be reduced (entry 6). Hypothesizing that an electron-rich ligand was necessary to promote single-electron transfer (SET) to the pyridinium cation, we found that 4,4′-diOMeBipy provided an even higher yield of 74% (entry 7). Because the aryl halide is often the precious component, we investigated conditions with aryl bromide as the limiting reagent and observed 85% isolated yield (1.2 equiv of pyridinium **3a**, entry 8). Control experiments confirmed that $NiCl_2$·DME, ligand, and Mn^0 are required (entries 9–11 and 13) and that $MgCl_2$ still provides a beneficial effect (entry 12). With minimal precaution taken to exclude air and moisture (set up under air, no drying of glassware or solvents), 53% yield is observed (entry 14).

Table 1. Optimization of Primary Alkyl Pyridinium Salt[a]

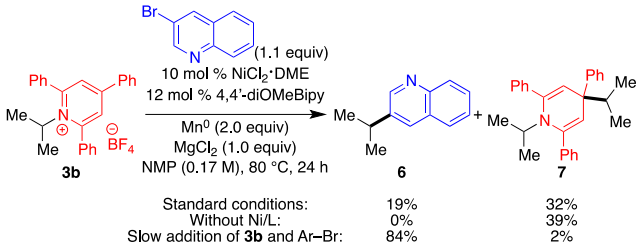


entry	ligand	additive	yield (%)[b] 4	5	Ar–Ar
1[c,d]	4,4′-di^{t}BuBipy	–	9	24	5
2[d]	4,4′-di^{t}BuBipy	–	26	25	4
3[d]	4,4′-di^{t}BuBipy	LiCl	54	14	4
4	4,4′-di^{t}BuBipy	LiCl	60	12	10
5	4,4′-di^{t}BuBipy	$MgCl_2$	65	8	15
6[e]	4,4′-di^{t}BuBipy	$MgCl_2$	67	6	17
7[e]	4,4′-diOMeBipy	$MgCl_2$	74	7	15
8[e,f]	4,4′-diOMeBipy	$MgCl_2$	85[g]	n.d.	n.d.
9[e,f,h]	4,4′-diOMeBipy	$MgCl_2$	0	36	0
10[e,f]	none	$MgCl_2$	0	16	14
11[e,f,h]	none	$MgCl_2$	0	30	0
12[e,f]	4,4′-diOMeBipy	–	50	24	12
13[f,i]	4,4′-diOMeBipy	$MgCl_2$	0	0	0
14[e,f,j]	4,4′-diOMeBipy	$MgCl_2$	53[g]	n.d.	n.d.

[a]Conditions: pyridinium salt **3a** (0.10 mmol), 3-bromoquinoline (1.1 equiv), $NiCl_2$·DME (10 mol %), ligand (12 mol %), Mn^0 (3.0 equiv), additive (0 or 1.0 equiv), NMP (0.17 M), 80 °C, 24 h, unless noted otherwise. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Zn^0 instead of Mn^0. [d]$NiBr_2$·DME (10 mol %), DMA (0.33 M). [e]Mn^0 (2.0 equiv). [f]**3a** (1.2 equiv), 3-bromoquinoline (1.0 equiv). [g]1.0 mmol scale. Isolated yield. [h]No $NiCl_2$·DME. [i]No Mn^0. [j]Minimal precautions to protect from air and moisture. n.d. = not determined.

With these conditions in hand, we turned to the reductive coupling of secondary alkylpyridinium salts. Disappointingly, only 19% yield of product **6** was observed, and dihydropyridine **7** was formed in 32% yield (Scheme 2). In the absence of Ni catalyst, product **7** is formed in 39% yield, indicating a noncatalyzed competitive pathway for the production of the isopropyl radical via direct reduction by Mn^0. Hypothesizing that **7** forms from addition of the isopropyl radical to pyridinium cation **3b** instead of combination with a Ni(II) intermediate (see mechanism discussion below), we proposed that maintaining a low concentration of pyridinium cation vs Ni catalyst would prevent formation of **7** and give higher yield of **6**. Indeed, slow addition of a solution of **3b** and aryl bromide resulted in a much improved 84% yield.[14]

Scheme 2. Optimization of Secondary Alkyl Pyridinium Salt[a]



[a]Conditions: pyridinium salt **3b** (0.50 mmol), 3-bromoquinoline (1.1 equiv), $NiCl_2$·DME (10 mol %), 4,4′-diOMeBipy (12 mol %), Mn^0 (2.0 equiv), $MgCl_2$ (1.0 equiv), NMP (0.17 M), 80 °C, 24 h, unless noted otherwise. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

These optimized conditions proved general for a wide range of alkyl pyridinium salts and aryl bromides (Scheme 3). Primary and secondary alkyl pyridinium salts underwent coupling in good yield, as did a benzylic pyridinium salt (**15**). Even a quaternary carbon can be formed via cross-coupling of a tertiary alkyl pyridinium salt, albeit in 35% yield (**20**). Pyridinium salts with more bulky tertiary alkyls cannot be prepared due to hindrance of the 2,6-diphenyls. In addition to general exploration of functional group tolerance, we were particularly interested in substrates that failed under the basic conditions of our Suzuki–Miyaura arylation.[5a] Excitingly,

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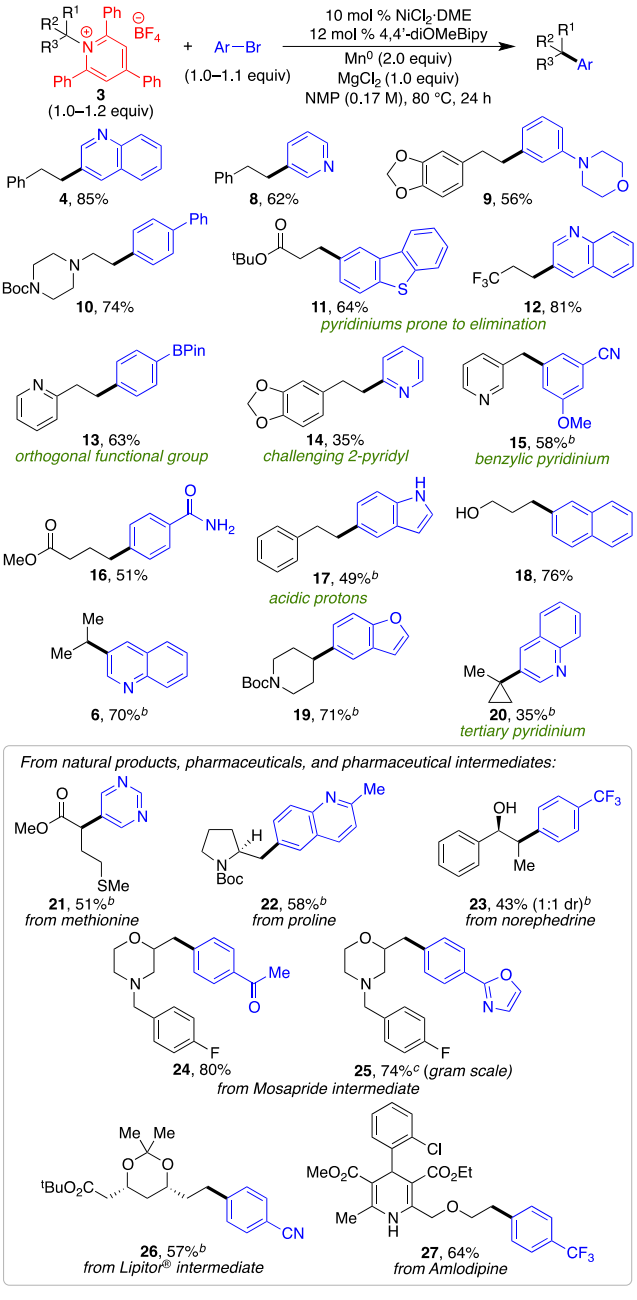
Scheme 3. Substrate Scope[a]



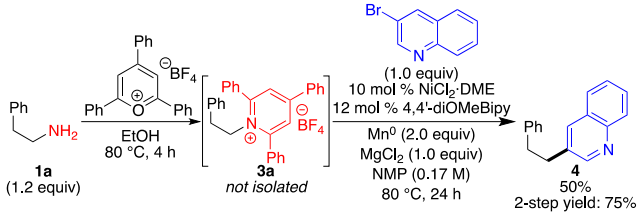
[a]Conditions: pyridinium salt **3** (1.2 mmol), aryl bromide (1.0 mmol), $NiCl_2$·DME (10 mol %), 4,4′-dimethoxy-2,2′-bipyridine (12 mol %), Mn^0 (2.0 equiv), $MgCl_2$ (1.0 equiv), NMP (0.17 M), 80 °C, 24 h. Average isolated yields (±5%) from duplicate experiments. [b]Slow addition of pyridinium salt **3** (1.0 mmol) and aryl bromide (1.1 mmol). [c]4.0 mmol scale, single experiment.

pyridinium salts with β-electron-withdrawing groups are effective substrates (**11** and **12**); elimination is not observed under these mild, neutral conditions. Protic functional groups (primary amide, indole, alcohol, and dihydropyridine) were also well tolerated (**16**–**18**, **23**, and **27**). Successful pyridinium formation and arylation of a number of natural product and pharmaceutically relevant alkyl amines highlight another advantage of using alkyl amines as precursors for late-stage functionalization. For example, pyridinium salts derived from amino acids (**21**, **22**) and amino alcohols (**23**) can be utilized. Amine intermediates used in the synthesis of the pharmaceuticals mosapride and Lipitor can also be arylated (**24**–**26**).[15] Notably, the arylation to form **25** was successful on the gram scale, demonstrating the scalability of this chemistry. Finally, arylation of the pharmaceutical amlodipine provides a dramatic example of the functional groups tolerated under these mild reaction conditions (**27**).[16]

We also observed excellent scope with respect to the aryl bromide. Aryl boronate esters (**13**) can be incorporated into the products. The use of 2-pyridyl bromide enabled the challenging 2-pyridyl group to be installed (**14**), highlighting another advantage over using an aryl boronic acid.[17] A range of other heteroaryl bromides were also effective, including quinolyl (**4**, **6**, **12**, **20**, **22**), 3-pyridyl (**8**), dibenzothiophenyl (**11**), benzofuranyl (**19**), and pyrimidyl (**21**). 3-Pyridyl iodide and chloride provided <10% yield.[18] Aryl bromides with *ortho* substitution, electron-donating groups, and some complex heteroaryls provided low yields.[19] Saturated heterocycles, including morpholines **9**, **24**, and **25**, piperazine **10**, piperidine **19**, pyrrolidine **22**, ketal **26**, and dihydropyridine **27**, were also tolerated. Additional functional groups compatible with this method include dioxalane (**9**, **14**), Boc-protected amines (**10**, **19**, **22**), esters (**11**, **16**, **21**, **26**, **27**), trifluoromethyls (**12**, **23**, **27**), nitriles (**15**, **26**), ethers (**15**, **27**), thioethers (**21**), isoxazoles (**25**), and aryl chlorides (**27**). However, these conditions fail for alkyl or alkynyl bromides.

We also investigated one-pot transformations of amine to arylalkane. Although simultaneous addition of pyrilium salt, aryl bromide, catalyst, and other reagents failed, telescoping pyridinium formation and cross-coupling provided 50% yield (Scheme 4). This yield is lower than when pyridinium salt **3a** is isolated (75%), but this protocol may be advantageous in certain cases, such as parallel synthesis.

Scheme 4. Telescoped Pyridinium Formation and Cross-Coupling



This reaction likely proceeds via a mechanism analogous to reductive cross-couplings of alkyl halides with aryl halides (Scheme 5A).[20] Oxidative addition of aryl bromide to a Ni^0 intermediate generates an arylnickel(II) bromide. Single-electron transfer (SET) from a Ni^I intermediate to the pyridinium salt generates a neutral pyridyl radical, which then fragments to give alkyl radical **28**. Alkyl radical **28** may also form via reduction by Mn^0, particularly for secondary alkylpyridinium salts. Combination of radical **28** with an arylnickel(II) intermediate delivers Ni^{III} species **29**. Reductive elimination then releases product **30** and regenerates a Ni^I intermediate. In support of the oxidative addition of the aryl bromide, 24% yield of product **4** is observed when tetrakis(dimethylamino)ethylene (TDAE) is used in place of Mn^0, suggesting an arylmanganese intermediate is not required (Scheme 5B). The intermediacy of alkyl radical **28** is consistent with the observed opening of cyclopropylmethylpyridinium **3s** and the formation of TEMPO-trapped adduct **32**

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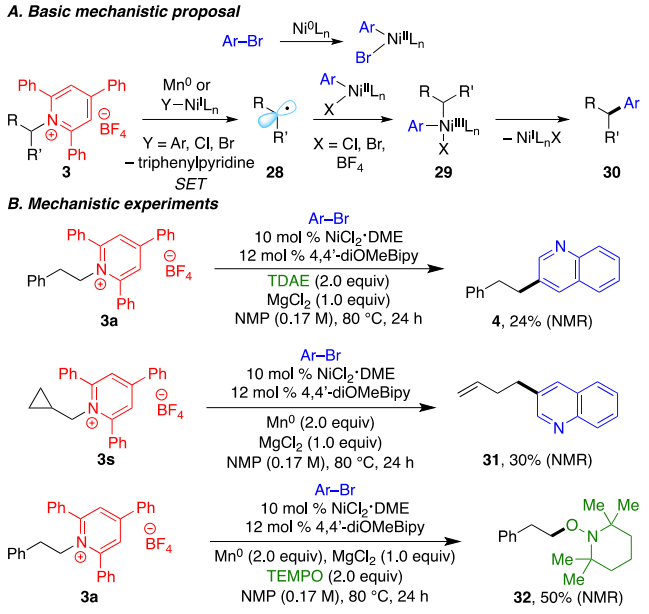
Scheme 5. Mechanism and Supporting Experiments



when TEMPO is added to the reaction. However, we cannot yet distinguish between a radical-chain bimetallic pathway and a radical-rebound pathway.[21]

In summary, we have developed a nickel-catalyzed reductive cross-coupling of alkyl pyridinium salts and aryl bromides. Given the abundance and diversity of alkyl amines and (het)aryl bromides available and the mild conditions, this method enables access to an exceptional variety of products, including those with protic and other base-sensitive functional groups. The success of this method, and the ability to use primary, secondary, and one tertiary alkyl pyridinium salts, relied on controlling the relative concentration of pyridinium salt to shuttle the alkyl radical intermediate along the desired catalytic cycle.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01014.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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