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Harnessing Alkyl Pyridinium Salts as Electrophiles in Deaminative Alkyl-Alkyl Cross-Couplings

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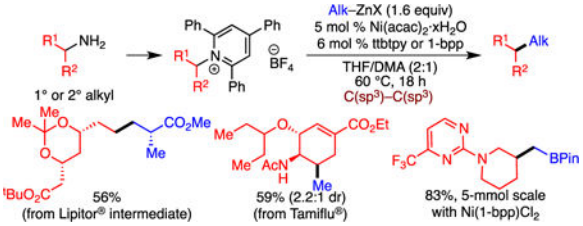
Abstract

A Negishi cross-coupling of alkyl pyridinium salts and alkylzinc halides has been developed. This is the first example of alkyl–alkyl bond formation via cross-coupling of an alkyl amine derivative with an unactivated alkyl group, and allows both primary and secondary alkyl pyridinium salts to react with primary alkylzinc halides with high functional group tolerance. When combined with formation of the pyridinium salts from primary amines, this method enables the non-canonical transformation of NH_2 groups into a wide range of alkyl substituents with broad functional group tolerance.

Graphical Abstract



Alkyl amines are abundant molecules ranging from simple starting materials to complex natural products and drug candidates.[1] As an example of their prevalence, a search of Pfizer's internal chemical store revealed over 47,000 alkyl primary amines vs. about 28,000 primary and secondary alkyl halides.[2] In addition, the use of alkyl amines as intermediates is advantageous, because they can be prepared directly and convergently with simultaneous formation of the amine and C–C bonds via classic reactions, such as Mannich, Petasis, Strecker, and others.[3] Due to their ubiquity, methods that allow alkyl amines to be converted into electrophiles for cross-coupling reactions present an exciting opportunity for development. However, the utilization of amine-derived alkyl electrophiles remains limited

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Notes

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ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and data (PDF)

with cross-couplings largely restricted to alkyl amine derivatives with electronic or strain activation of the C(sp^3)–N bond (Scheme 1A).[4,5,6] We recently overcame this limitation by developing a Suzuki–Miyaura arylation of Katritzky pyridinium salts, which are easily and selectively prepared from primary alkyl amines (Scheme 1B).[7,6m, 6n,5b, 8] This reaction was the first cross-coupling of an alkyl amine derivative with an *unactivated* alkyl group. Recognizing that our proposed alkyl radical intermediate could also be formed via photoredox catalysis, Glorius, Gryko, Aggarwal, Li and Shi then developed Minisci arylation, alkynylation, and borylations.[9] These exciting reports demonstrate the potential of alkyl pyridinium salts in synthesis, and offer avenues to convert ubiquitous NH_2 groups into C(sp^2) and C(sp) substituents. However, no current methods enable C(sp^3)–C(sp^3) formation via cleavage of these unactivated alkyl pyridinium salts.[10]

The prevalence of C(sp^3)–C(sp^3) bonds in bioactive molecules has led to intense efforts to develop methods to incorporate fully saturated C–C bonds in complex products.[11] In particular, Negishi cross-couplings have emerged as a reliable and functional group tolerant method.[6a, 6d, 12] Motivated by the myriad advantages of alkyl amine derivatives as alkyl electrophiles, we envisioned a Negishi cross-coupling for the generation of C(sp^3)–C(sp^3) bonds from alkyl pyridinium salts (Scheme 1C). However, despite the precedent with other alkyl electrophiles, we were concerned that competitive nucleophilic addition of the organozinc to the pyridinium ring and/or deprotonation of the acidic α-proton of the alkyl pyridinium salts would prevent the desired cross-coupling. Overcoming these challenges, we have developed the first example of alkyl–alkyl bond formation via cross-coupling of an alkyl amine derivative with an unactivated alkyl group. This method allows both primary and secondary alkyl pyridinium salts to react with primary alkylzinc halides with high functional group tolerance. In combination with efficient pyridinium formation, this reaction enables the non-canonical transformation of amino groups into alkyl substituents, providing unprecedented entry to complex, saturated organic frameworks via versatile and attractive amine intermediates.

We selected the cross-coupling of phenethyl pyridinium salt **1a** and commercially available (2-(1,3-dioxolan-2-yl)ethyl)zinc bromide for our initial studies. We prioritized the use of alkyl zinc halides, as opposed to dialkyl zinc reagents, due to their greater commercial availability, higher functional group tolerance, and ease of handling.[13] Using bathophenanthroline (BPhen), the optimal ligand for our Suzuki–Miyaura arylation, resulted in <20% yield. However, with $NiCl_2$·DME/4,4’,4’’-tri-*tert*-butyl terpyridine (ttbtpy) as catalyst and DMA as a polar co-solvent, 68% yield was observed (Table 1, entry 1).[14] Increasing the amount of organozinc halide further improved the yield (entry 2); however, more than 1.6 equivalents led to decreased product formation (see Supporting Information). The use of other redox non-innocent ligands also resulted in lower yields (entries 3–6). To maximize the practicality, less expensive Ni^{II} sources and lower catalyst loadings were examined. Although $NiCl_2$·$6H_2O$ was ineffective (entry 7), Ni(acac)$_2$·xH_2O gave slightly higher yields than $NiCl_2$·DME (entry 8). Lowering the Ni(acac)$_2$·xH_2O and ttbtpy loading to 5 and 6 mol %, furnished a similar yield (entry 9). Control experiments confirmed that both nickel and ligand are required (entries 10 and 11).

Although ttbtpy proved effective for primary alkyl pyridinium salts, only 18% yield was observed with secondary alkyl pyridinium salt **1b** (Table 1, entry 12). However, 2,6-bis(*N*-pyrazolyl)pyridine (1-bpp) promoted the cross-coupling with high efficiency (entry 14). This ligand has been used previously in Negishi cross-couplings, including those of bulky alkylzinc iodides.[12f, 12g] Notably, tpy also bested the more hindered ttbtpy (entries 12 vs. 13), suggesting that steric hindrance of the ligand may be primarily responsible for the success of 1-bpp.[12g]

Wide scope of primary and secondary alkyl pyridinium salts was observed (Scheme 2). Aryl and heteroaryl groups were tolerated, including thiophene (**4**), benzodioxole (**6**), pyridine (**7**), and pyrimidine (**15**). Products with saturated heterocycles, such as piperazine **5**, morpholine **16**, pyrans **9** and **13**, piperidines **11** and **15**, pyrrolidine **12**, and strained azetidine **8**, also formed in good yields. Highlighting the potential for late-stage functionalization, pyridinium salts of several drugs, pharmaceutical intermediates, and natural products underwent alkylation. Alkylations of the pyridinium salts of amine intermediates in the synthesis of the gastrointestinal drug Mosapride (**16**) and Lipitor (**18**–**20**) were effective.[15] A single diastereomer of **19** was observed, indicating that stereocenters bearing acidic protons are not epimerized. The unprotected carboxylic acid of **20** is tolerated in both the pyridinium formation and cross-coupling, demonstrating orthogonality of the amine and carboxylate groups, either of which can be used to generate alkyl radicals.[12h, 16] The pyridinium salts of natural *cis*-myrtanylamine (**17**), pinanamine (**21**), the anti-arrhythmic drug Mexiletine (**22**) and antiviral Tamiflu (**23**) also coupled well.[17] The cross-coupling of the Tamiflu pyridinium salt demonstrates that a high degree of steric hindrance and chemical complexity is tolerated. However, this method is limited to primary and secondary alkyl 2,4,6-triphenyl pyridinium salts, because we cannot yet form them from unconstrained tertiary alkyl amines.[9e] To simplify set-up, a single-component catalyst, Ni(1-bpp)Cl_2, can be used (see **11**, **15**).

Both commercial and prepared primary alkyl zinc halides proved effective (Scheme 2). We used Hou's method to generate organozinc reagents due to its high functional group tolerance.[18] In line with findings by Organ,[19] a salt additive was crucial for maintaining high reactivity of non-commercial organozinc reagents, with NBu_4I as the optimal additive.[20] Homemade organozinc halides were generated in DMA (no THF present). In terms of steric hindrance, β-branching is tolerated (**6**, **19**), including quaternary carbons (**13**). However, secondary and tertiary alkylzinc halides do not undergo the desired cross-coupling. Instead, a non-nickel-catalyzed addition to the 4-position of the pyridinium ring occurs.[21] Regarding functional group tolerance, various groups can be incorporated in the alkylzinc halide, including acetal (**2**, **3**, **9**, **20**), ester (**4, 16**, **19**), alkene (**5**, **17**), nitrile (**7**, **11**, **22**), trifluoromethyl (**12**), and oxetane (**13**). Notably, the pyridinium group couples preferentially in the presence of an alkyl chloride (**14**). Methylzinc iodide is also effective (**8**, **23**). When coupled with formation of the pyridinium salt, this strategy allows NH_2 to be replaced with a steric isostere CH_3, offering opportunities for efficient structure-activity relationship studies.[22] Finally, synthetically versatile α-methylpinacolboronate (CH_2Bpin) can also be installed (**10**, **15**, **21**). To our knowledge, this is the first example utilizing α-methylpinacolboronate zinc bromide in a Negishi cross-coupling.[23] Product **15** is formed in 83% yield on a 5-mmol

scale with the single-component catalyst. Further, we demonstrated the versatility of the newly installed Bpin by converting it to an alcohol (**22**),[6g] bromide (**23**),[24] and thiophene (**24**, Scheme 3).[25]

To facilitate use of this chemistry in parallel medicinal chemistry and other synthesis efforts, we developed conditions for the one-pot transformation of amines directly to the alkylated products. By increasing the equivalents of alkylzinc halide, similar yields were obtained in this one-pot procedure as the two-step method (Scheme 4). Notably, these conditions are not sequential addition; primary amine and pyrylium tetrafluoroborate are simply added in place of the pyridinium salt under the previous conditions.

In analogy to Negishi cross-couplings of other alkyl electrophiles, our arylation of alkyl pyridinium salts,[7, 12f, 12g] and other reactions of alkyl pyridinium salts,[9a, 9b, 26] we hypothesize that this reaction proceeds through single-electron transfer (SET) to the alkyl pyridinium salt from a Ni(I) intermediate or a Ni(II) cation with a reduced ligand.[12g] Fragmentation of the resulting neutral pyridyl radical then gives an alkyl radical, which recombines with a Ni(II) intermediate to then deliver the product. Consistent with an alkyl radical intermediate, we observe ring-opened **30** in the reaction of cyclopropylmethyl pyridinium salt and TEMPO-adduct **31** when TEMPO is added (Scheme 5). No cross-coupled product **2** is observed upon addition of TEMPO.

In summary, we have developed the first example of an alkyl–alkyl cross-coupling of alkyl amine derivatives with unactivated alkyl groups, specifically alkyl pyridinium salts. When combined with chemoselective pyridinium formation from primary amines, this Negishi reaction provides the ability to convert NH_2 into a range of alkyl groups with broad functional group tolerance. The reaction appears to proceed via an alkyl radical intermediate, likely generated after SET from a Ni species to the pyridinium cation. Future efforts will expand the scope of alkyl groups and pursue detailed mechanistic understanding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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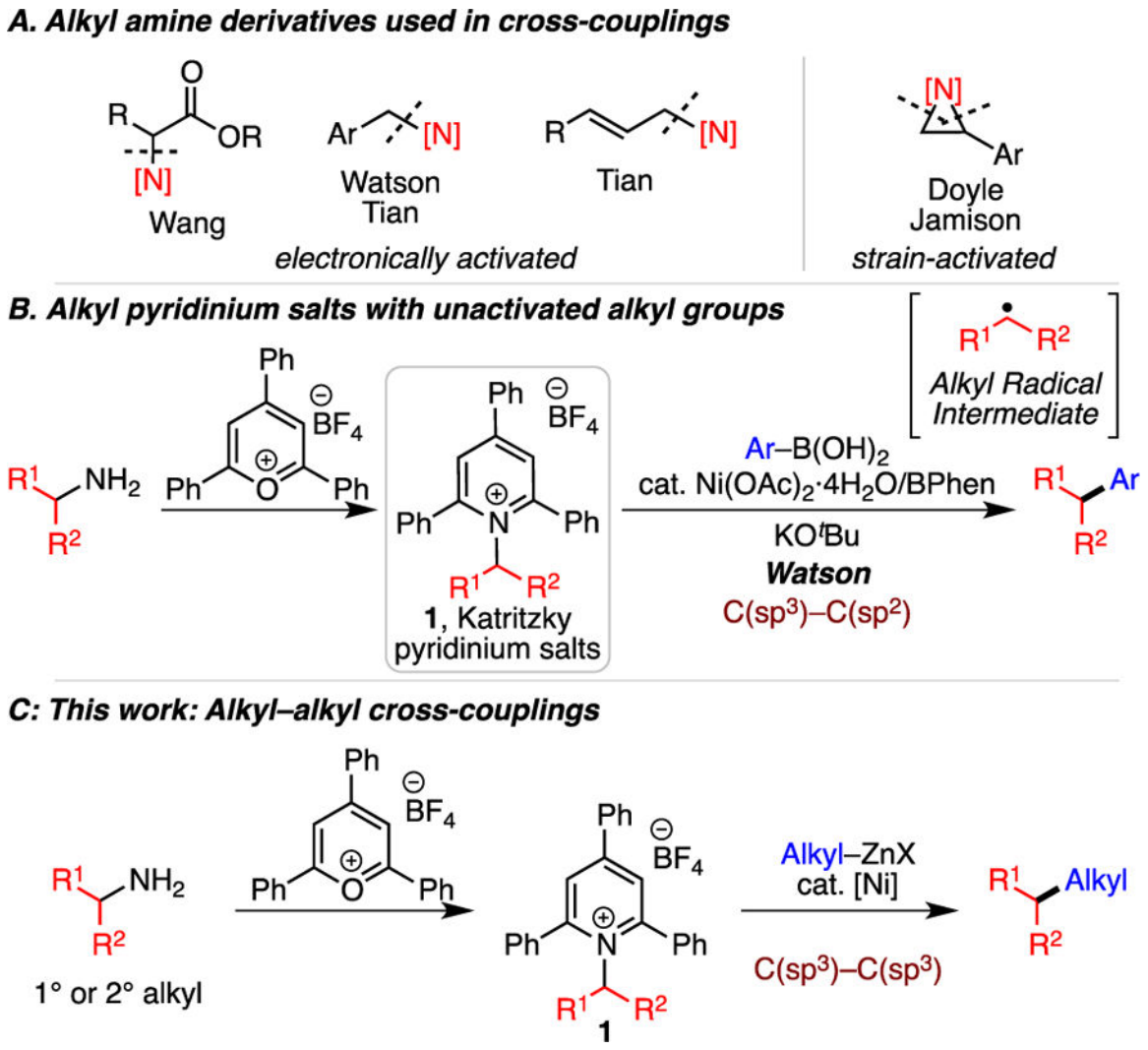
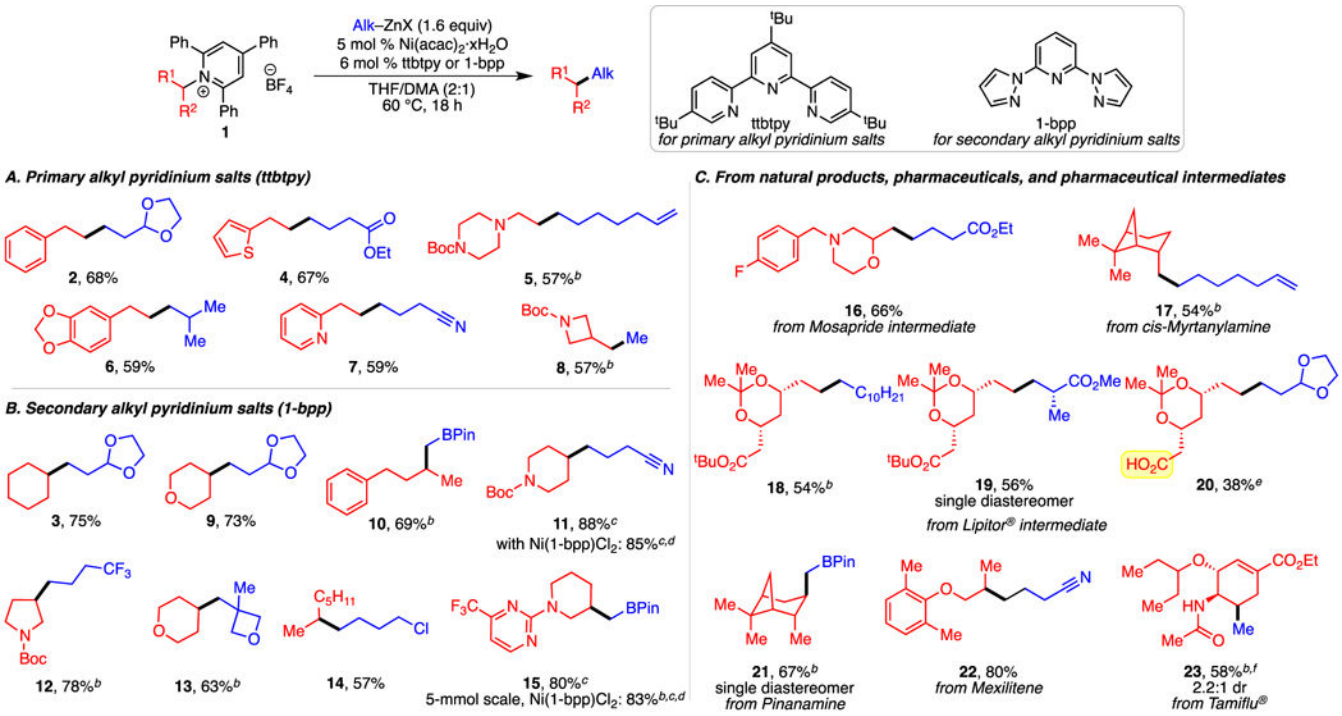
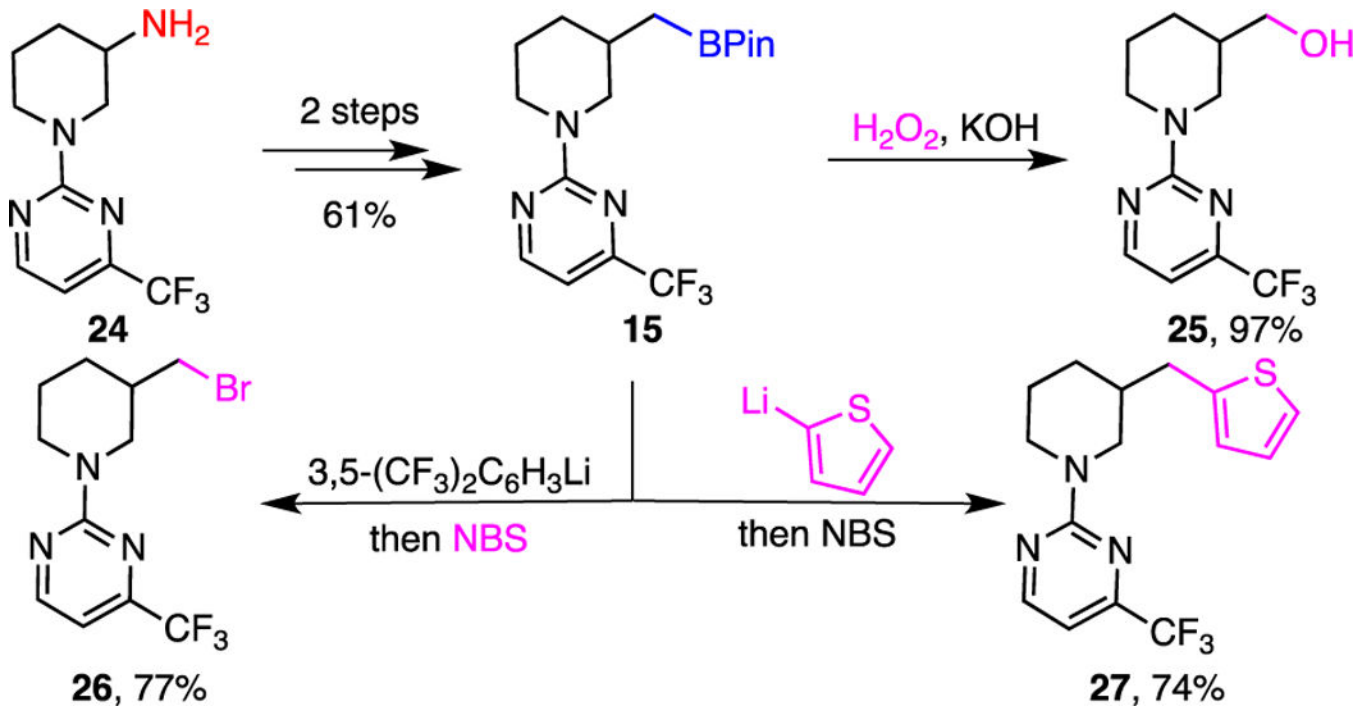


Scheme 1.
Alkyl amine derivatives in cross-coupling reactions.

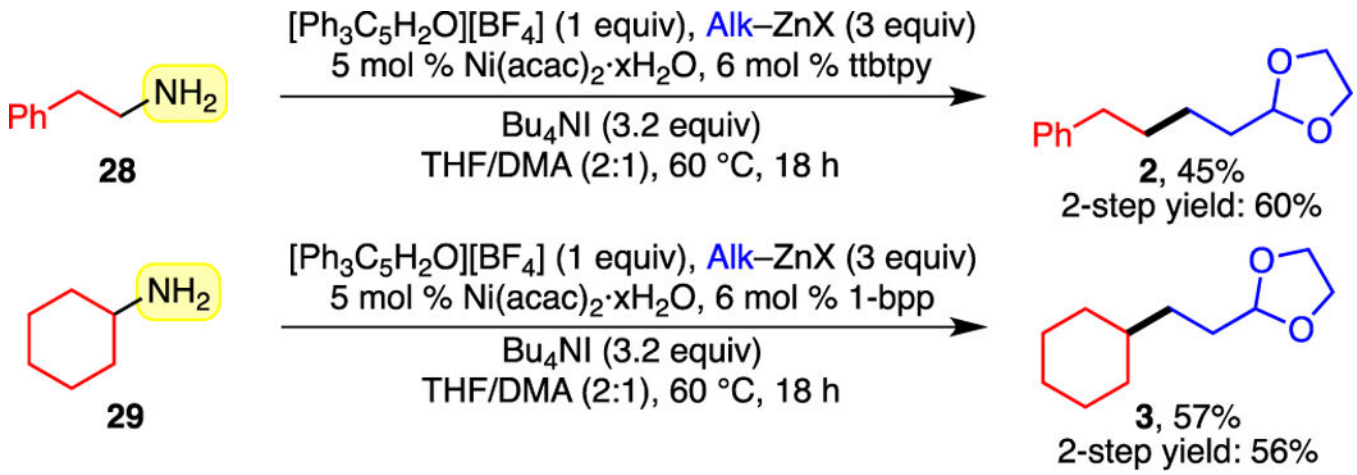


[a] Conditions: Pyridinium salt **1** (1 mmol), Ni(acac)$_2$·xH$_2$O (5 mol %), ttbtpy or 1-bpp (6 mol %), Alk–ZnX (X = Br or I, 1.6 equiv), THF/DMA (2:1, 0.2 M), 60 °C, 18 h. Average isolated yield (±4%) from duplicate experiments. [b] Alk–ZnX generated in DMA (no THF). NBu_4I (3.2 equiv) added. [c] Single experiment. [d] Ni(1-bpp)Cl$_2$ (5 mol %) as catalyst. [e] Alk–ZnX (3.0 equiv). [f] 0.5 mmol scale.

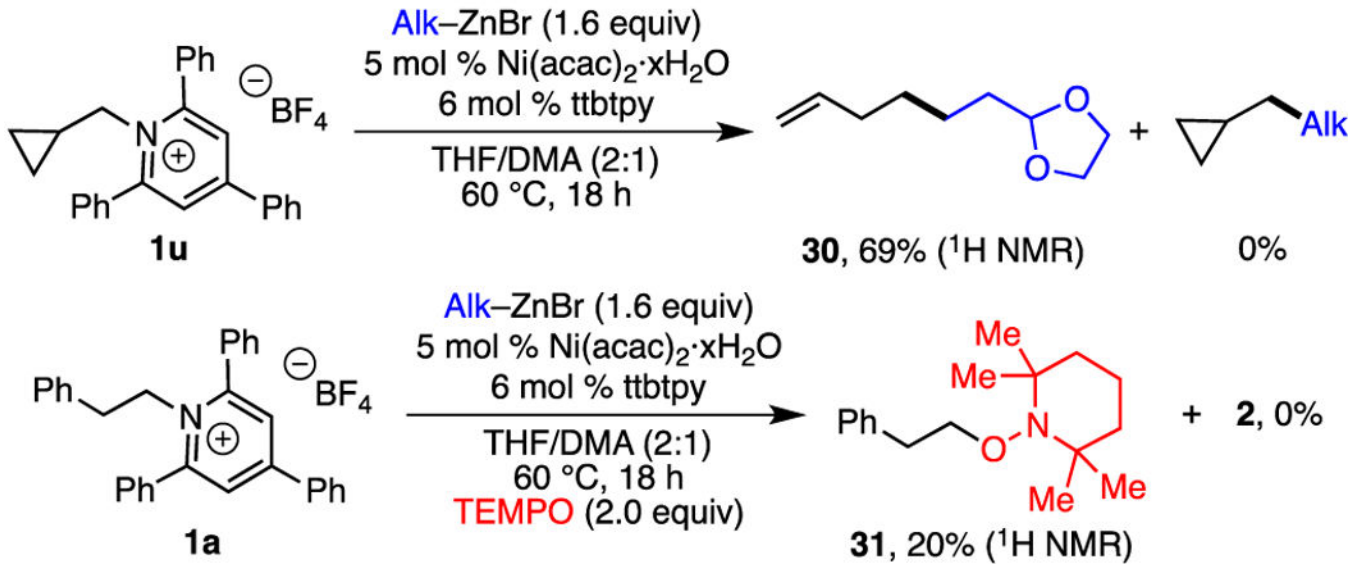
Scheme 2.
Reaction Scope[a]



Scheme 3.
Elaboration of Boronic Ester



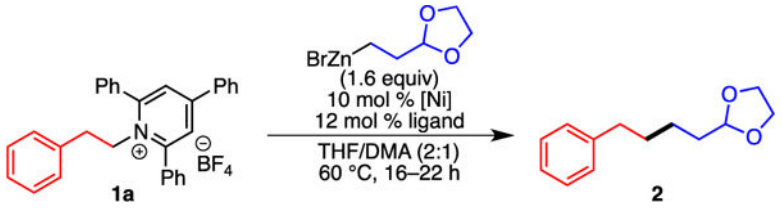
Scheme 4.
One-pot activation and cross-coupling



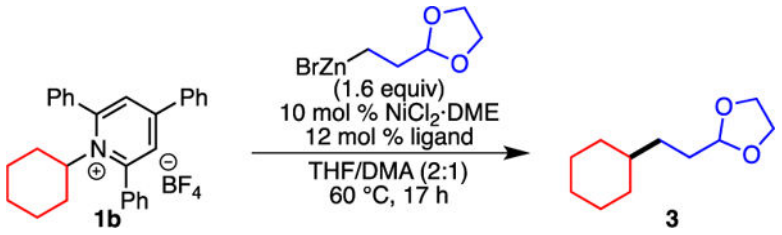
Scheme 5.
Support for Alkyl Radical Intermediate

Table 1.

Reaction Optimization[a]



entry	[Ni]	ligand	yield (%)[b]
1[c]	$NiCl_2$·DME	ttbtpy	68
2	$NiCl_2$·DME	ttbtpy	75
3	$NiCl_2$·DME	tpy	47
4	$NiCl_2$·DME	phen	14
5	$NiCl_2$·DME	dtbbpy	15
6	$NiCl_2$·DME	1-bpp	49
7	$NiCl_2$·$6H_2O$	ttbtpy	20
8	$Ni(acac)_2$·xH_2O	ttbtpy	81
9[d]	$Ni(acac)_2$·xH_2O	ttbtpy	80
10	none	ttbtpy	3
11	$Ni(acac)_2$·xH_2O	none	9



12	$NiCl_2$·DME	ttbtpy	18
13	$NiCl_2$·DME	tpy	68
14	$NiCl_2$·DME	1-bpp	83

[a]Conditions: Pyridinium salt **1a** (0.1 mmol), [Ni] (10 mol %), ligand (12 mol %), AlkZnBr (1.6 equiv), THF/DMA (2:1, 0.2 M), 60 °C, 16–22 h, unless noted otherwise.

[b]Determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as internal standard.

[c]AlkZnBr (1.4 equiv).

[d]5 mol % [Ni], 6 mol % ligand.