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Engaging Alkenes and Alkynes in Deaminative Alkyl–Alkyl and Alkyl–Vinyl Cross-Couplings of Alkylpyridinium Salts

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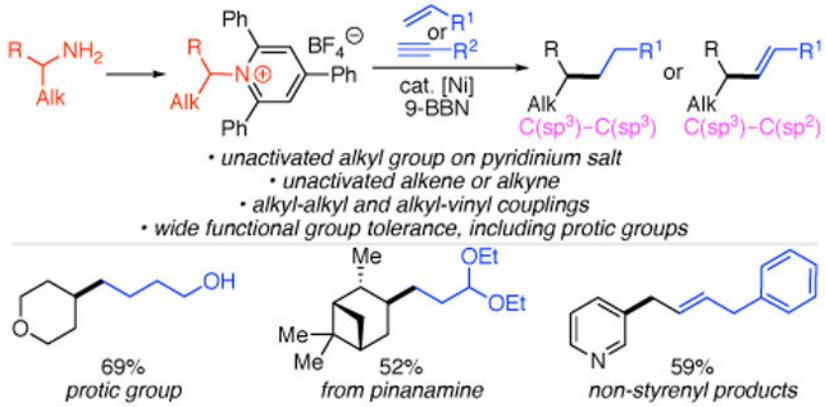
Abstract

An alkyl–alkyl cross-coupling of alkylpyridinium salts and organoboranes, formed *in situ* via hydroboration of alkenes, has been developed. This method utilizes the abundance of both alkyl amine precursors and alkenes to form C(sp^3)—C(sp^3) bonds. This strategy is also effective with alkynes, enabling a C(sp^3)—C(sp^2) cross-coupling. Under these mild conditions, a broad range of functional groups, including protic groups, is tolerated. As seen with previous alkylpyridinium cross-couplings, mechanistic studies support an alkyl radical intermediate.

Graphical Abstract



Alkyl amines are inexpensive and widely abundant feedstock chemicals, making them ideal precursors for further functionalization.[1] The amino group is also present in many advanced intermediates and products, enabling opportunities for late-stage derivatization.[1-2] Although reactions of both simple and complex alkyl amines have classically centered on the preparation of nitrogen-conaining products, deaminative reactions via C—N bond activation of Katritzky pyridinium salts **3** have emerged as useful transformations of the highly versatile amino functional group.[3] Specifically, we and others have developed arylations,[4]

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Supporting Information
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Experimental details and data (PDF)

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vinylations,[5] alkynylations,[6] allylations,[7] and borylations[8] of pyridinium salts. However, deaminative *alkylation* of pyridinium salts to form C(sp^3)—C(sp^3) bonds remains limited, despite the potential of such reactions as a powerful, albeit noncanonical, disconnection in synthesis, particularly if both starting materials can arise from ubiquitous substrate classes. Towards such a deaminative alkylation, we reported a Negishi alkylation of alkyl pyridinium salts (Scheme 1A).[9] Although this cross-coupling tolerated primary and secondary alkyl pyridinium salts and a range of functional groups, the harsh conditions prevented the use of benzylic pyridinium salts and base-sensitive functional groups. Han, Wang, and Yan recently reported several examples of reductive alkylation, but these were limited to forging C—C bonds between primary alkyl groups.[4g] We thus pursued the use of an alternative, milder nucleophilic partner to provide broad scope in both primary and secondary alkyl pyridiniums, as well as excellent functional group tolerance. In particular, we envisioned that the use of alkyl-boranes, generated *in situ* via hydroboration of simple alkenes, would fulfill our requirement for mild, neutral conditions and also enable the use of abundant alkenes as starting materials.[10]

Other groups have also utilized alkenes in alkylations of alkylpyridinium salts. Glorius and Aggarwal reported photocatalytic generation of alkyl radicals, which were subsequently trapped with either styrenes or electron-poor alkenes (Scheme 1A).[11,12] However, these reactions are limited to activated alkenes, as well as activated alkyl groups on the pyridinium salt for Glorius's three-component coupling. While this manuscript was in preparation, Martin published a cross-coupling of alkylpyridinium salts with alkenes, reduced *in situ* with a silane.[13] Herein, we report our development of an alkyl–alkyl cross-coupling of alkylpyridinium salts with alkenes, including unactivated examples, via *in situ* formation of organoboranes. These conditions also enable vinylation when alkyne starting materials are used.

We selected the reaction of pyridinium salt **3a** and commercially available acrolein acetal for our initial studies. We used (9-BBN) as our hydroboration agent based on its high hydroboration regioselectivities and precedent in the use of this type of alkylborane in other cross-couplings.[10, 14] Our initial studies focused on examining both ligand and base in the cross-coupling of pyridinium **3a** and preformed alkylborane using high-throughput experimentation (HTE) techniques (scale: 8.3 μmol pyridinium **3a**). We used a combination of $Ni(acac)_2$ and $Ni(cod)_2$ to ensure successful *in situ* formation of Ni(I).[15] Among the 36 ligands examined, 2,6-bis(pyrazol-1-yl)pyridine (1-bpp) provided the best yield of desired product **6**.[16] In addition, we found that only KF provided product of the eight activating agents tested. Using 1-bpp and KF, quantitative yield of **6** was observed on HTE scale. When we applied these conditions to a 0.1 mmol-scale experiment, however, only 16% yield was observed (Table 1, entry 1). Under these conditions, we found that the use of air-stable $NiCl_2$·DME provided a comparable, albeit low, yield (entry 2), and thus switched to this simpler catalyst system to determine why yields were inconsistent between the HTE and 0.1-mmol scale reactions. In our HTE campaign, we used spray-dried and carefully sieved KF, but had used only oven-dried KF in the 0.1-mmol experiments. By switching to spray-dried and sieved KF on 0.1-mmol scale, yield increased substantially (entry 3). With $Ni(acac)_2$, an even higher yield of 67% was observed (entry 4). Notably, other fluoride

sources, such as CsF, resulted in a significant drop in yield (entry 5). Under these conditions, the equivalents of $(9\text{-BBN})_2$, alkene, and base could be decreased without lowering the yield (entry 6). Considering the sensitivity of the yield to the fluoride activator, we hypothesized that efficient formation of the boronate via fluoride co-ordination to the organoborane was critical. To promote formation of this intermediate, KF was added in the hydroboration step; by combining $(9\text{-BBN})_2$, alkene, and KF at 60 °C before the addition of the other reagents, we increased the yield to 95% (entry 7). Control experiments showed the importance of this pre-ligation and the need for both nickel and base in this reaction (entries 8–10).

Under these optimized conditions, a variety of both primary and secondary alkylpyridinium salts were successfully alkylated. Notably, although benzylic pyridinium salts failed under our previous, more basic Negishi alkylation conditions,[9] benzylic pyridinium salts (**11–13**) worked under these conditions.[17] This method also shows high tolerance for a variety of functional groups on the pyridinium salt, including acetals (**7**), protected amines (**8**), esters (**10**), ethers (**6**, **14–19**, **22**, **24**, **25**), tertiary amines (**25**), and aryl fluorides (**25**). These examples include base-sensitive substrates, such as the pyridinium salt of a β-amino ester (**10**). Our previous Negishi coupling failed for these types of substrates.[9] Pyridinium salts containing a range of heterocycles also underwent alkylation in good yields: azetidines (**8**), pyridines (**9**), pyrimidines (**12**), pyrroles (**13**), pyrans (**6**, **14–19**), and morpholines (**25**). With a diastereomerically pure pyridinium salt prepared from cyclohexane amino ether (**22**), a 1:1 ratio of diasteromeric products was isolated, consistent with a radical intermediate. With a more constrained system (**23**), a single diastereomer of product was isolated. To highlight the utility of this method for late-stage functionalization of amines, pharmaceutical intermediates and natural products were investigated. Both pinanamine and mexilitine were successfully alkylated (**23**, **24**).[18] Alkylation of the pyridinium salt derived from an amine intermediate in the Mosapride synthesis also worked well (**25**).[19]

On the alkene side, broad functional group tolerance was also observed, including acetals (**6–13**, **20**, **22–25**), ethers (**18**, **21**), and aryl fluorides (**17**). Notably, unprotected alcohols (**19**) are even tolerated, highlighting the mild conditions and representing a significant advance over our previous Negishi conditions.[9] In addition to aliphatic alkenes, styrenes can also be used in this chemistry (**15**, **21**). We were also pleased to find that allylic arenes can serve as the alkene partner (**17**, **18**); alkene isomerization did not pose a major problem. Unfortunately, however, 1,1- and 1,2-disubstituted alkenes were not effective in this reaction.

While investigating the scope of this alkylation method, we were also intrigued by the possibility of starting with a simple alkyne. We have previously reported the vinylation of benzylic pyridinium salts with vinyl boronic acids,[5a] and installation of styrenyl groups can also be accomplished with boronic acids or via a Heck-type reaction.[5b-d] Excitingly, our hydroboration/cross-coupling conditions can be applied to alkyne substrates, providing a vinylated product. The functional group tolerance includes ethers (**26–29**), aryl bromides (**27**), nitriles (**28**), phthalimides (**29**). Notably, this vinylation is successful with nonbenzylic pyridinium salts and can install non-styrenyl vinyl groups (**30**), complimenting the methods previously developed.

Similar to previously developed pyridinium cross-couplings,[3d, 4a] we propose that this reaction proceeds through a single-electron transfer (SET) from a Ni(0) or Ni(I) intermediate to the alkyl pyridinium salt. Fragmentation of the neutral pyridyl radical gives an alkyl radical, which can recombine with a Ni(I) or Ni(II) intermediate to provide the product after reductive elimination. Consistent with the formation of an alkyl radical, TEMPO adduct **31** is observed upon addition of TEMPO, and cyclopropane **3q** underwent ring-opening (Scheme 4).

In summary, we have developed a nickel-catalyzed alkyl–alkyl cross-coupling of alkyl pyridinium salts with alkenes, via organoborane intermediates. This method harnesses ubiquitous functional groups (amines and alkenes) in both partners, and is successful even with unactivated alkenes. In addition, this method can also be applied to alkynes to effectively provide the vinylation of unactivated pyridinium salts. Broad functional group tolerance, including benzylic pyridinium salts and protic functional groups, is seen with both of these methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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16. See Supporting Information.

17. Only primary benzylic pyridinium salts can be prepared effectively; secondary benzylic pyridinium salts decompose upon synthesis. See reference 4b.

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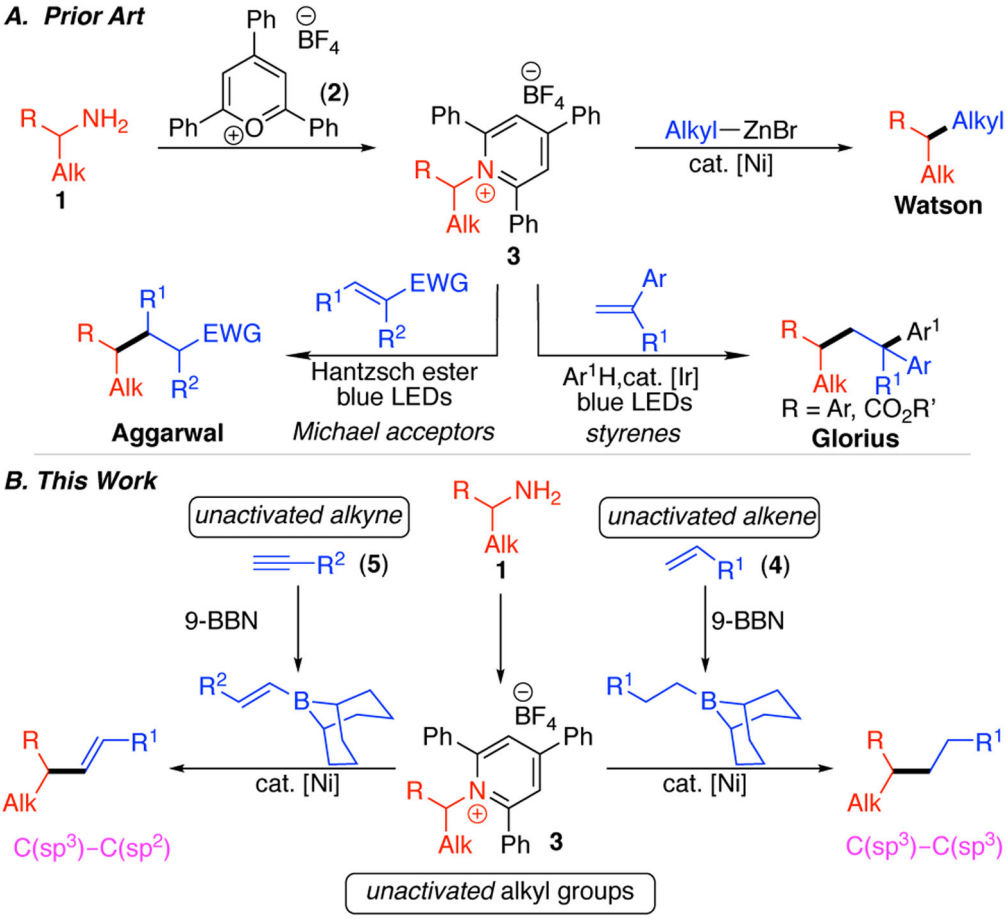
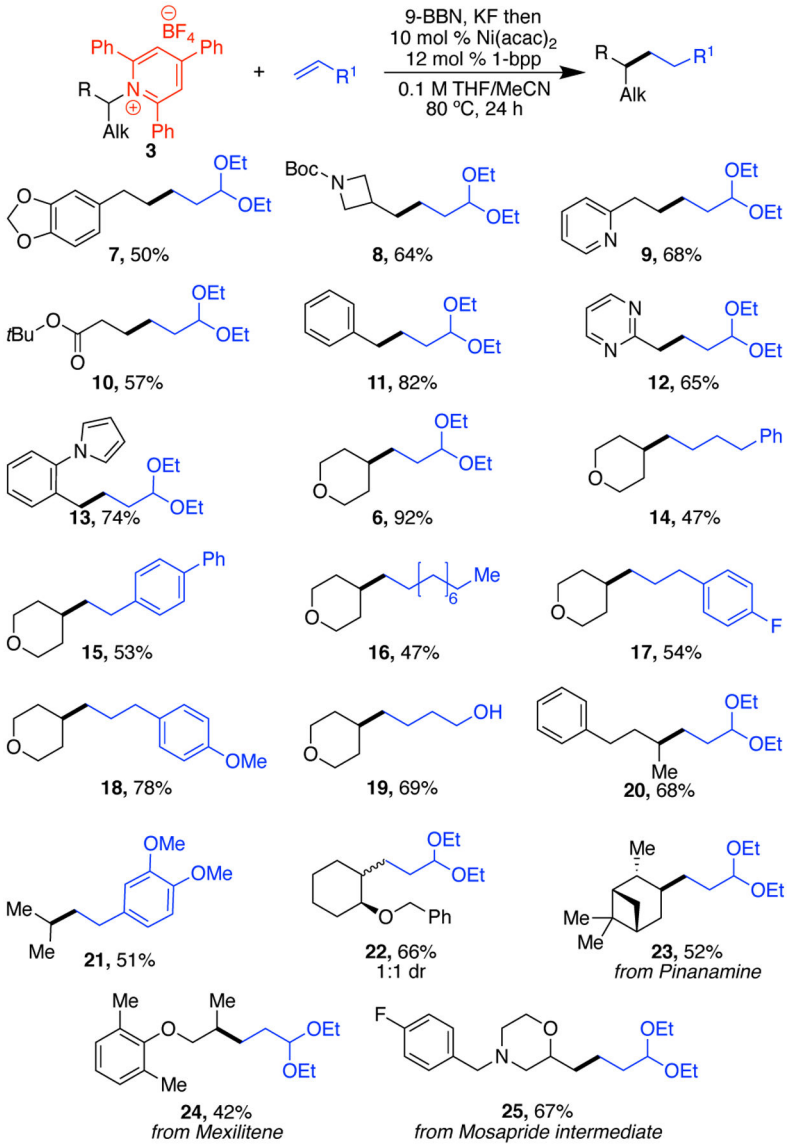
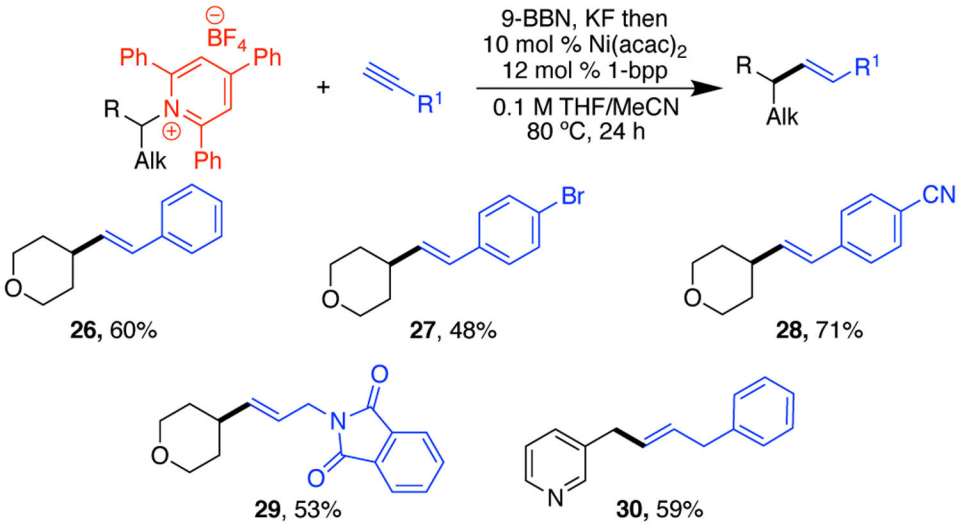


Scheme 1.
Deaminative Alkyl–Alkyl Couplings



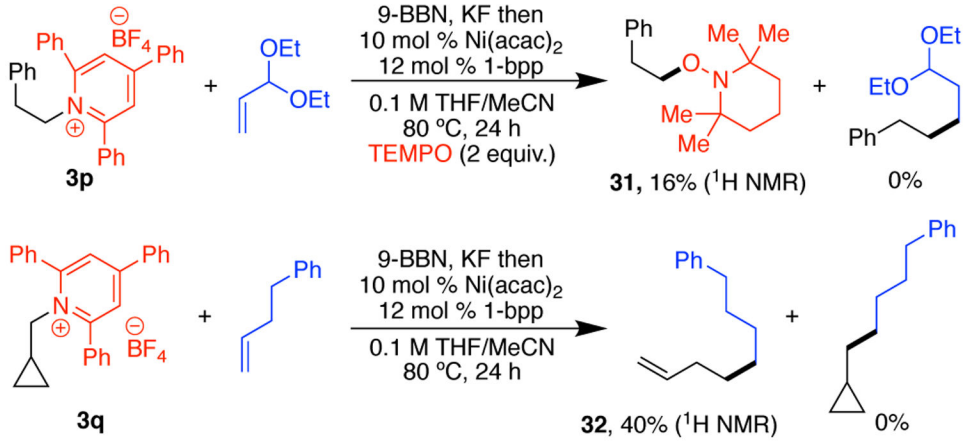
Scheme 2. Scope of alkyl–alkyl coupling[a]

[a] Conditions: alkene (2.5 equiv), 9-BBN (0.5 M in THF, 2.5 equiv), KF (2.75 equiv), then pyridinium salt **3** (1.0 mmol, 1.0 equiv), [Ni] (10 mol %), 1-bpp (12 mol %), MeCN (0.5 mL), 80 °C, 24 h. Average isolated yield of duplicate experiments (±4%).



Scheme 3. Vinylation Scope[a]

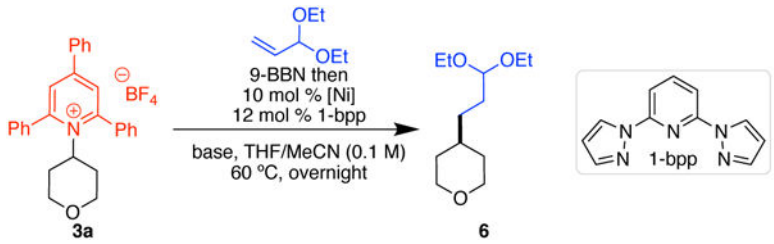
[a] Conditions: alkene (2.5 equiv), 9-BBN (0.5 M in THF, 2.5 equiv), KF (2.75 equiv), then pyridinium salt **3** (1.0 mmol, 1.0 equiv), [Ni] (10 mol %), 1-bpp (12 mol %), MeCN (0.5 mL), 80 °C, 24 h.



Scheme 4.
Mechanistic studies

Table 1.

Optimization[a]



entry	[Ni]	Base	yield (%)[b]
1	$Ni(cod)_2/Ni(acac)_2$	KF	16
2[c,d]	$NiCl_2$·DME	KF	12
3[d,e]	$NiCl_2$·DME	KF	55
4[d,e]	$Ni(acac)_2$	KF	67
5[d]	$Ni(acac)_2$	CsF	30
6[d,e,f]	$Ni(acac)_2$	KF	68
7[d,e,f,g]	$Ni(acac)_2$	KF	95
8[e,f,g]	$Ni(acac)_2$	KF	81
9[e,f,g]	None	KF	7
10[e,f,g]	$Ni(acac)_2$	none	n.d.[h]

[a]Conditions: alkene (3.0 equiv) and 9-BBN (0.5 M in THF, 3.0 equiv), then pyridinium salt **3a** (0.10 mmol, 1.0 equiv), [Ni] (10 mol %), ligand (12 mol %), KF (3.3 equiv), 3:2 THF:MeCN (0.1 M), 60 °C, 24 h, unless noted otherwise.

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

[c]KF oven-dried.

[d]Nickel and 1-bpp stirred for 15 min in MeCN before addition to other reagents.

[e]KF spray-dried, oven-dried, and sieved.

[f]9-BBN (0.5 M in THF, 2.5 equiv), alkene (2.5 equiv), KF (2.5 equiv), 1:1 THF:MeCN (0.1 M).

[g]9-BBN, KF, and alkene heated at 60 °C for 30 min before addition of other reagents.

[h]n.d. = not detected.