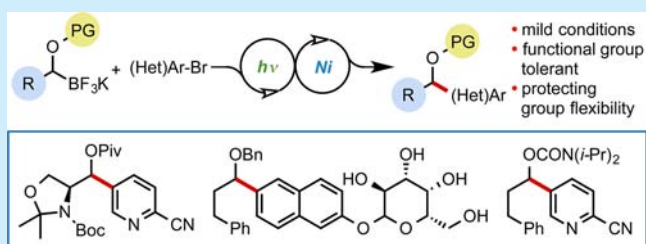


Single-Electron Transmetalation: Protecting-Group-Independent Synthesis of Secondary Benzylic Alcohol Derivatives via Photoredox/Nickel Dual Catalysis

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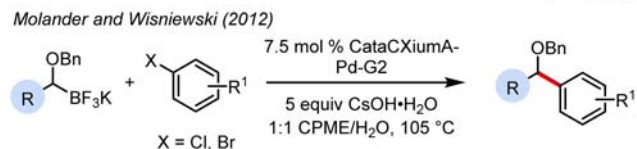
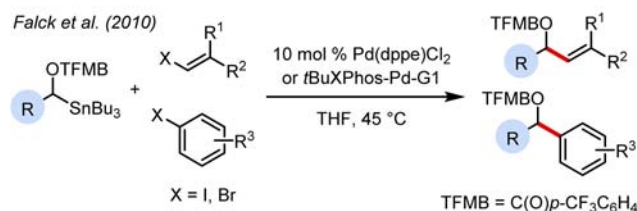
S Supporting Information

ABSTRACT: Protecting-group-independent cross-coupling of α -alkoxyalkyl- and α -acyloxyalkyltrifluoroborates with aryl and heteroaryl bromides is achieved through application of photoredox/nickel dual catalysis. Reactions occur under exceptionally mild conditions, with outstanding functional group compatibility and excellent observed tolerance of heteroarenes. This method offers expedient access to protected secondary benzylic alcohol motifs bearing benzyl, pivaloyl, and *N,N*-diisopropylcarbamoyl protecting groups.



The prominence of the secondary benzylic alcohol motif is clearly evident from its presence in biologically active compounds, both naturally and synthetically derived, and its utility as an intermediate in organic synthesis. Although accessible through a variety of retrosynthetic disconnections (most notably nucleophilic addition of organometallic reagents to aldehydes¹ and reduction of aryl-alkyl ketones²), few methods permit direct synthesis of a protected secondary benzylic alcohol without the intermediacy of an unprotected derivative. In cases where protection is required for subsequent manipulations, installation of the protecting group before assembly of the benzylic alcohol motif is more convergent than installation of the protecting group after fragment coupling. Furthermore, the “protected” (or otherwise alkylated, acylated, silylated, etc.) form may be desired for purposes of bioactivity and/or pharmacokinetic/pharmacodynamic properties or utility in subsequent reactions as a reactive functional group. Finally, the intermediacy of an unprotected benzylic alcohol can be problematic in cases wherein this intermediate would be prone to oxidation or other decomposition pathways.

Transition-metal-catalyzed cross-coupling of an α -alkoxyalkylmetallic reagent with an aryl halide represents an attractive manifold for the direct synthesis of protected secondary benzylic alcohol derivatives because of the commercial availability of structurally and electronically diverse aryl halides and the general modularity of cross-coupling methods. This disconnection has been realized through the efforts of Falck³ and Molander,⁴ who have reported the cross-coupling of α -alkoxyalkyltin and -boron nucleophiles, respectively, with aryl/alkenyl halides (see Figure 1). However, these methods are limited by moderate demonstrated functional group tolerance and inflexibility of the oxygen protecting group, wherein alkyltin reagents must bear a 4-trifluoromethylbenzoyl group, and a benzyl protecting group is

(A) Previously reported cross-couplings of α -alkoxyalkylmetallic reagents

(B) This work: unified strategy via photoredox/nickel dual catalysis

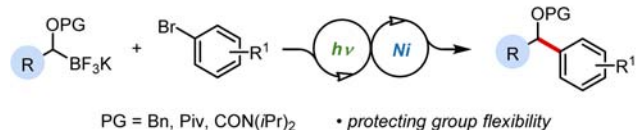


Figure 1. (A) Previously reported methods for direct synthesis of protected secondary benzylic alcohol derivatives via Pd catalysis. (B) Present report: photoredox/nickel dual catalytic cross-coupling of α -alkoxyalkyl- and α -acyloxyalkyltrifluoroborates with (hetero)aryl bromides.

required for trifluoroborate cross-coupling due to the strongly basic, high-temperature reaction conditions. These limitations restrict the utility of the reported methods because neither offers

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a general, protecting-group-independent approach to the synthesis of protected secondary benzylic alcohol derivatives.

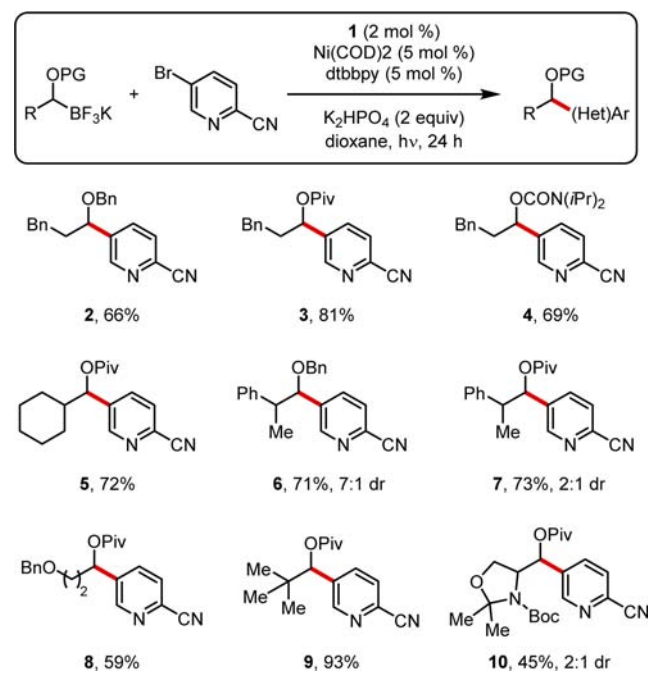
In view of the deficiencies of prior art, we sought to realize the goal of a protecting-group-independent synthesis of secondary benzylic alcohols through the application of photoredox/nickel dual catalysis. This paradigm has recently proven advantageous for the cross-coupling of various alkylboron and alkylsilicon reagents under extraordinarily mild conditions and with unprecedented levels of functional group tolerance.^{5–7} Although previous studies confirmed the feasibility of cross-coupling α -benzyloxyalkyltrifluoroborates,^{5a,8} it was unclear if the more electronically deactivated α -acyloxyalkyl derivatives would be reactive in this manifold.

Consistent with previous studies, a catalytic system of $\text{Ir}[\text{dFCF}_3\text{ppy}]_2(\text{bpy})\text{PF}_6$ **1**, $\text{Ni}(\text{COD})_2$, and dtbbpy proved most active in promoting the desired reactivity. Use of $\text{Ni}(\text{II})$ sources, such as $\text{NiCl}_2(\text{dme})$ or $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, is also possible, but a slight reduction in yield was typically observed (~5–20%). Although previous reactions of secondary α -benzyloxyalkyltrifluoroborates were performed in acetone or THF with 2,6-lutidine or 2,2,6,6-tetramethylpiperidine as additives,^{5a,8} the use of dioxane as a solvent and 2 equiv of K_2HPO_4 as an additive were found to be most broadly effective for the cross-coupling of secondary α -alkoxyalkyltrifluoroborates bearing benzyloxy, pivaloyl, and N,N -diisopropylcarbamoyl protecting groups. Notably, although the synthesis of these pivaloyl and N,N -diisopropylcarbamoyl-protected derivatives were reported previously,⁴ the present report is the first successful example of their cross-coupling. This success effectively highlights the unique strengths of the photoredox/nickel dual catalytic cross-coupling manifold relative to conventional Pd catalysis, wherein the strongly basic conditions required for cross-coupling resulted in decomposition of these hydrolytically unstable protecting groups. Contrasting the conditions previously reported for the cross-coupling of α -benzyloxyalkyltrifluoroborates (105 °C, 5 equiv of $\text{CsOH} \cdot \text{H}_2\text{O}$) with the conditions reported here for protecting-group-independent cross-coupling (room temperature, 2 equiv of K_2HPO_4) only further underscores these advantages.

These conditions were found to be widely effective for the cross-coupling of sterically and electronically diverse secondary α -alkoxyalkyl and α -acyloxyalkyltrifluoroborates, as summarized in Scheme 1. Notably, these starting materials are easily synthesized from commercially available aldehydes via a two-step procedure involving borylation to afford the α -hydroxyalkyltrifluoroborate followed by straightforward, base-mediated protection with the corresponding acyl halide or benzyl bromide. We chose to examine the scope of alkyltrifluoroborate tolerance with 3-bromo-5-cyanopyridine as a coupling partner in an effort to highlight the exceptional tolerance of this method for the cross-coupling of heteroaryl bromides. Substrates displaying simple alkyl chains were readily cross-coupled in good to very good yields as their benzyloxy (**2**), pivaloyl (**3**), and carbamoyl (**4**) derivatives. α -Branched substrates were also well-tolerated (**5–7**), including a sterically hindered α -*tert*-butyl substrate (**9**). Trifluoroborates containing stereocenters could be cross-coupled with moderate diastereoselection (**6, 7, 10**). Functional groups including benzyl ethers (**8**) and tertiary carbamates (**10**) were also well-tolerated.

We next turned our attention to examining the reaction scope with regard to the (hetero)aryl bromide partner (Scheme 2). Here, functional group tolerance far surpasses previous efforts in the cross-coupling of secondary α -alkoxyalkylmetallic reagents.

Scheme 1. Photoredox/Nickel Dual Catalytic Cross-Coupling of Various α -Alkoxyalkyl and α -Acyloxyalkyltrifluoroborates with 3-Bromo-5-cyanopyridine



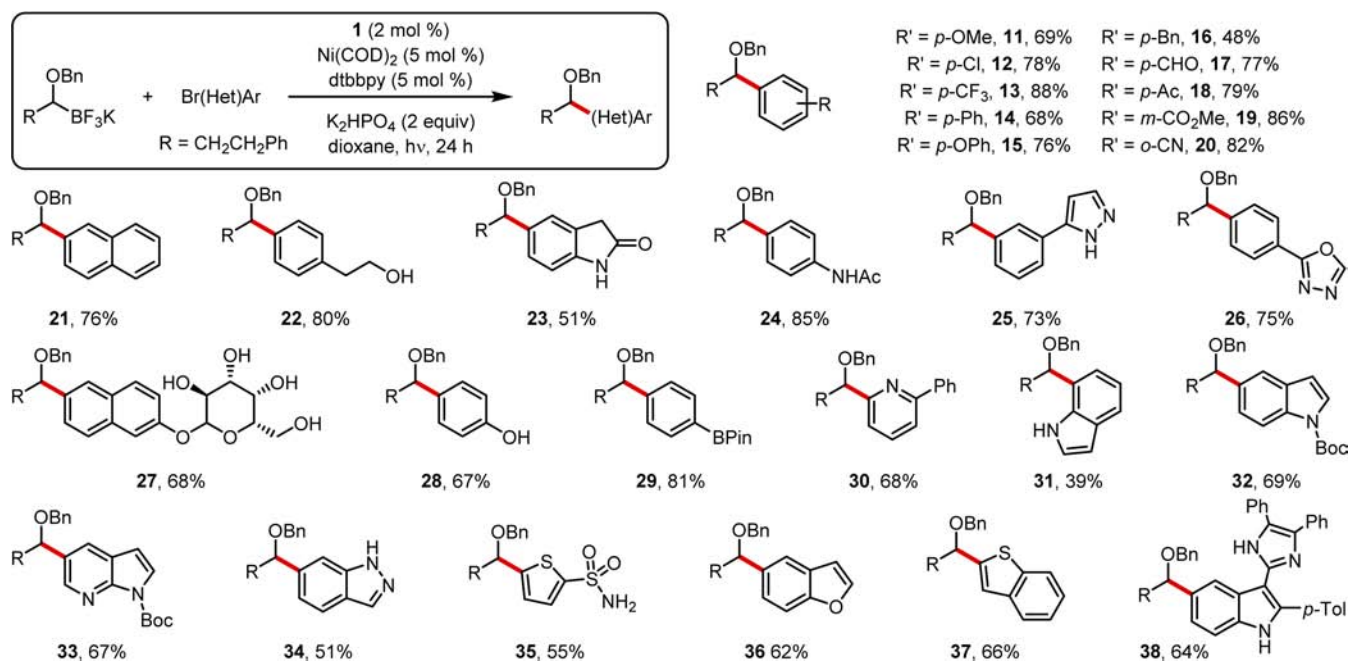
Both electron-poor and electron-rich aryl bromides provided products in good to excellent yields. Cross-coupling proceeded smoothly in the presence of ortho substituents (**20, 31**).

A tremendous variety of potentially reactive functional groups were also tolerated. Substrates bearing aldehydes (**17**), ketones (**18**), esters (**19**), ethers (**11, 15**), nitriles (**20**), and trifluoromethyl groups (**13**) generated products in good to excellent yields. Secondary amides, including acetanilide (**24**) and oxindole (**23**), were readily tolerated. Additional protic nitrogen substituents and heterocycles including sulfonamide (**35**), indole (**31, 38**), pyrazole (**25**), indazole (**34**), and imidazole (**38**) were cross-coupled readily. Other tolerated heterocycles include pyridine (**30**), azaindole (**33**), thiophene (**35**), benzofuran (**36**), and benzothiophene (**37**) systems. Consistent with previous observations, selective cross-coupling at the aryl bromide site occurred in the reaction of 4-chloro-1-bromobenzene. Furthermore, the pinacol ester of 4-bromophenylboronic acid smoothly afforded arylboronate product (**29**), thereby permitting potentially powerful sequential cross-coupling sequences with either nucleophilic or electrophilic partners.⁸

Most importantly, tolerance was observed for unprotected primary alcohols, secondary alcohols, and phenols. In this regard, an aryl bromide linked to a fully unprotected glycoside was cross-coupled in 68% yield to afford product **27**. In these examples, introduction of the benzylic alcohol in protected form would avoid any difficulties associated with selective downstream protection/deprotection in the context of target-oriented syntheses. Furthermore, the protecting group flexibility offered by these unified conditions permits strategic selection of the desired benzylic alcohol protecting group.

Although the presently reported method proved to be highly amenable to the coupling of electronically and sterically diverse substrates and also tolerant of a wide variety of functional groups, several limitations remain. Most notably, α -alkoxyalkyl and α -

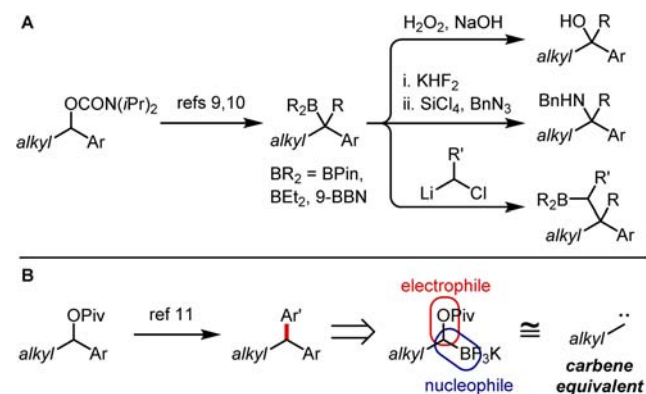
Scheme 2. Photoredox/Nickel Dual Catalytic Cross-Coupling of Benzyloxyalkyltrifluoroborates with Various (Hetero)aryl Bromides



acyloxyalkyltrifluoroborates derived from benzaldehyde tended to cross-couple in unsatisfactory yields. We surmise that this may be a consequence of the enhanced stability of the resultant radicals, which are resonance stabilized by both donation of the oxygen lone pair and delocalization throughout the aryl π -system. These radicals may be less likely to react with the Ni catalyst or may dissociate more readily from the Ni(III) species, potentially resulting in homocoupling and disruption of the catalytic cycle.^{5c} Furthermore, electron-rich aryl bromides coupled more effectively with α -benzyloxyalkyltrifluoroborates than α -acyloxyalkyltrifluoroborates, with the latter requiring extended reaction times to achieve moderate yields. Consistent with our previous studies, tertiary amines and nitro groups are not tolerated, and brominated five-membered N-heterocycles (pyrrole, pyrazole, imidazole, oxazole, etc.) were unreactive under the reported conditions.

An important advantage of the method reported herein is its ability to access synthetically valuable benzylic carbamates and pivalates directly in a convergent fashion and with excellent modularity with regard to the steric, electronic, and functional group demands of the requisite fragments. Aggarwal has demonstrated that secondary benzylic carbamates can be converted to tertiary organoboron compounds through a lithiation/ α -transfer sequence.⁹ These tertiary alkylboron compounds can be further functionalized to generate, for example, tertiary alcohols, tertiary amines, or quaternary carbon centers.¹⁰ Furthermore, Ni catalysts have been observed to engage secondary benzylic pivalates as electrophiles in cross-coupling reactions with arylboron reagents.¹¹ In view of this capability, it is possible to consider α -pivaloyloxyalkyltrifluoroborates as formal carbene equivalents because they can be selectively di-arylated by sequential reactions with an electrophilic partner and a nucleophilic partner (Scheme 3). From a strategic standpoint, this sequence would represent a conceptually novel approach to the synthesis of 1,1-diarylalkanes.

In summary, we have reported a general procedure for the protecting-group-independent cross-coupling of α -alkoxyalkyl-

Scheme 3. Elaboration of Reaction Products via (A) Lithiation/ α -Transfer of Benzylic Carbamates and (B) Ni-Catalyzed Cross-Coupling of Benzylic Pivalates

and α -acyloxyalkyltrifluoroborates with aryl and heteroaryl bromides. This method affords protected benzylic alcohol derivatives through a convergent pathway and typically in good to excellent yields with exceptional functional group tolerance. The reported protocol represents a significant advance in the cross-coupling of α -alkoxyalkyl anion synthons and enables the rapid synthesis of a ubiquitous class of compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00911.

Experimental procedures, compound characterization data, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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