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Enabling the Cross-Coupling of Tertiary Organoboron Nucleophiles through Radical-Mediated Alkyl Transfer

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Supporting Information

ABSTRACT: The construction of quaternary centers is a common challenge in the synthesis of complex materials and natural products. Current cross-coupling strategies that can be generalized for setting these centers are sparse and, when known, are typically predicated on the use of reactive organometallic reagents. To address this shortcoming a new, photoredox-Ni dual catalytic strategy for the cross-coupling of tertiary organoboron reagents with aryl halides is reported. In addition to details on the cross-coupling scope and limitations, full screening efforts and mechanistic experiments are communicated.

The installation of quaternary centers has been a longstanding challenge, going back to the earliest days in the art of steroid synthesis. Woodward et al. succeeded in setting some of the first all-carbon stereocenters through cycloaddition chemistry over 60 years ago.[1] Although methods have evolved dramatically, there are still relatively few ways to install these centers reliably across a broad array of functionalized partners.[2] Among the most commonly employed methods, three predominate: (1) alkylation of 1,1-disubstituted allylic leaving groups,[3a] (2) conjugate addition to α,β-unsaturated carbonyls,[3b] and (3) alkylation of substituted enolate equivalents.[3c] In many cases, each of these subclasses can cleanly access the requisite quaternary center, but they are constrained by the requirement and natural reactivity pattern for a particular structural element (e.g., α,β-unsaturated carbonyls, allyl, or carbonyl systems). Most notably, none of these methods adequately addresses the synthesis of *arylated* quaternary centers.

In addition to these common approaches, a variety of niche metal-catalyzed reactions have also been developed for installing such centers between various nucleophile and electrophile combinations. Key contributions include Tsuji–Trost allylations,[4a] Heck couplings,[4b] Pauson–Khand cyclizations,[4c] redox relay arylations,[4d] and carbene C–H insertion reactions.[4e] These examples are by no means comprehensive, but they represent landmark catalytic approaches to the installation of challenging quaternary centers.

Although other metal-mediated catalytic reactions have enabled access to quaternary centers, there are, by contrast, vanishingly few examples of tertiary nucleophiles in classical cross-coupling chemistry. Seminal contributions from Biscoe[5a] and Glorius[5b] et al. highlighted the success of Grignard reagents with *N*-heterocyclic carbene-ligated nickel complexes. Unfortunately, these strongly basic nucleophiles are poorly tolerant of electrophilic and protic functional groups and are often accompanied by isomerization, generating byproducts when the temperature of these reactions is not carefully controlled. Beyond these seminal reports, there are additional isolated examples using Kumada[6] or Negishi[7] reagents, but they do not represent a unified strategy for tertiary cross-couplings. Particularly from a diversification perspective, approaches using these sensitive, pyrophoric reagents are wholly impractical when applied to a wide array of tertiary nucleophiles paired with an equally broad palette of aryl electrophiles. The clear absence of methods predicated on the use of bench-stable partners inspired the laboratory to explore tertiary organoboron nucleophiles more closely—especially given the recent surge in methods for their preparation.[8]

Studies were initiated using *tert*-butyltrifluoroborate **13** as the chosen nucleophile with 4′-bromoacetophenone as the aryl electrophile. Conditions (Figure 1A) successful in previous studies[9] proved completely ineffective for achieving the desired cross-coupling. For all bipyridyl ligands, only starting material or proto-dehalogenation products were observed. Furthermore, the alkyltrifluoroborate was often minimally consumed after 24 h. Given the lack of conversion under our initially developed conditions, we sought to understand in a more comprehensive manner the divergent reactivity of these tertiary radicals.

First, oxidation of the reagent was considered (Figure 1B). Notably, in previous work static quenching of alkyltrifluoroborates in the presence of a cationic photocatalysts was observed,[10] indicating the formation of a salt pre-complex that precedes a single-electron-transfer event. Because of the enhanced steric bulk of these tertiary precursors, it seemed prudent to confirm these reagents were indeed generating radical intermediates. Gratifyingly, both cyclic voltammetry analysis of the alkyltrifluoroborate ($E_{\text{red}}^{1/2}$ = +1.26 V vs SCE) and Giese-type trapping experiments[11] confirmed the viability of this oxidation, the latter affording the desired alkylated product **14** in 74% yield.

Next, attention was turned to the key bond-forming reductive elimination step in these couplings (Figure 1C). Here, the desired Ni^{III} intermediate was deemed to be accessible through the use of a preformed Ni^{II}(dtbbpy) oxidative addition complex **15** in the presence of alkyltrifluoroborate **13** and an appropriate oxidant.[12] Surprisingly, stoichiometric experiments exposing this complex to a variety of oxidant combinations in the presence of **13** failed to afford any of the desired coupling product, even under prolonged reaction times. The only products observed

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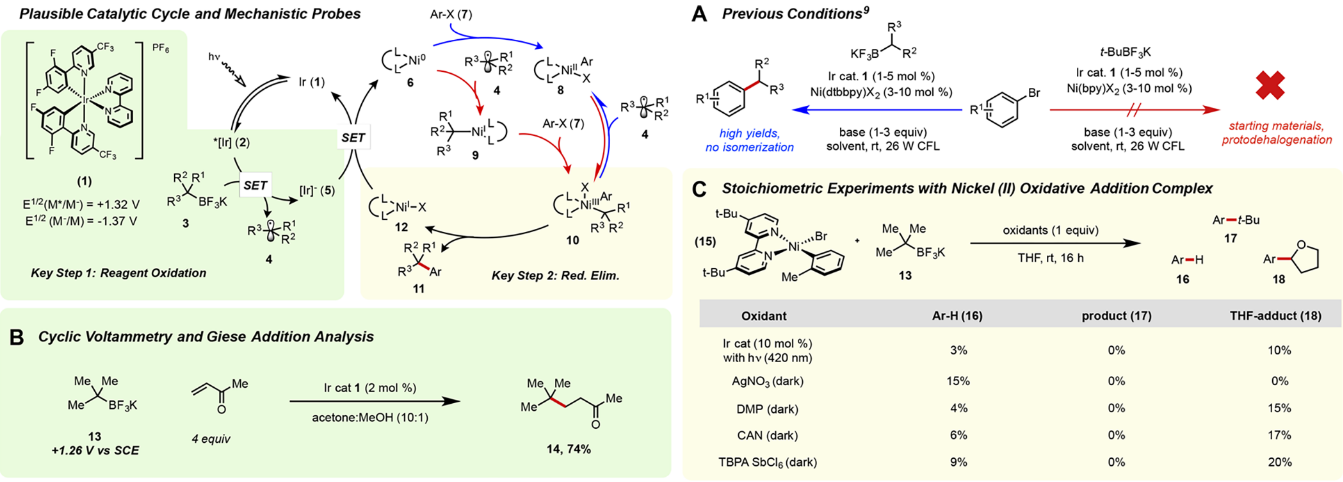


Oxidant	Ar-H (16)	product (17)	THF-adduct (18)
Ir cat (10 mol %) with hν (420 nm)	3%	0%	10%
$AgNO_3$ (dark)	15%	0%	0%
DMP (dark)	4%	0%	15%
CAN (dark)	6%	0%	17%
TBPA $SbCl_6$ (dark)	9%	0%	20%

Figure 1. Plausible catalytic cycle and key mechanistic experiments. (A) Previously developed conditions for alkyltrifluoroborate coupling. (B) Oxidation experiment and cyclic voltammetry analysis of **13**. (C) Stoichiometric experiments with Ni(II) oxidative addition complex **15**.

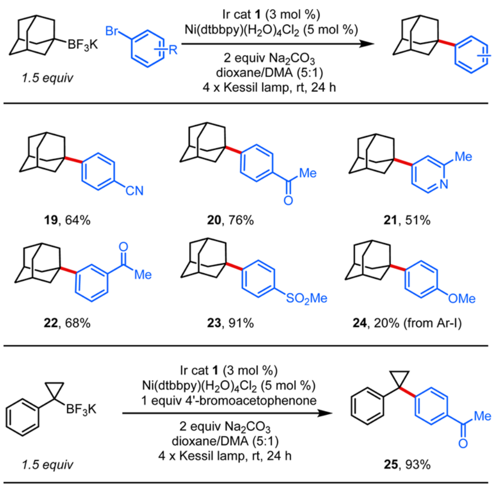


Figure 2. Constrained cyclic alkyltrifluoroborates in cross-coupling.

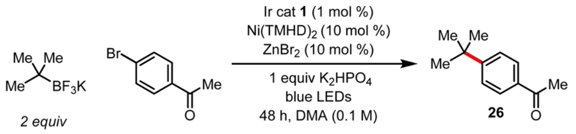
were THF adduct **18** (known to be generated under the reaction conditions through C−H abstraction[13] or halide abstraction pathways[14]) and protodehalogenation. Given these results, it appeared unlikely that the established bipyridyl ligand systems would be broadly applicable to their tertiary counterparts.

Although daunted by the failures here, we did achieve targeted success with adamantyltrifluoroborate and other constrained ring systems because of their unique structural properties. As a tied back (tetrahedral) radical possessing no sites for possible *β*-hydride elimination, slight modification of the previously developed conditions allowed access to an array of compounds (Figure 2). Electron-poor (**19**−**23**, **25**), electron-rich (**24**), and heteroaryl halides (**20**) all proved viable. Unfortunately, this rather niche reactivity was not unprecedented[7a,15] and by no means represented a general solution to tertiary radical coupling.

To identify a set of more robust general conditions, a screening effort was initiated to evaluate a wide variety of ligand classes that might be amenable to tertiary radical progenitors. Representative ligands from the Ni cross-coupling literature spanning phosphines,[16] pyridines,[17] terpyridines,[18] amino alcohols,[19] *N*-heterocyclic carbenes,[4] olefins,[20] and 1,3-diketones[21] were all introduced to both a Ni(0) and Ni(II) source in parallel. The reactions were then followed by UPLC to observe the desired coupling product (see Supporting Information (SI) for full details). Across all ligand classes, only diketonate-type species showed significant product formation. Interestingly, these ligands have seen use in mechanistically analogous reductive coupling chemistry reported by Gong et al.[21]

Further optimization of this ligand architecture identified a bulkier tetramethylheptanedione (TMHD) scaffold as suitable for promoting the desired coupling. Additional evaluation of bases showed that adding inorganic bases reduced protodehalogenation byproducts and increased yield. A solvent screen showed that DMA was essential for coupling success. Use of other polar, aprotic solvents such as DMF, DMSO, or NMP resulted in poorer conversions. $ZnBr_2$ and other Lewis acids were tested as additives to facilitate the coupling. Although these additives were deemed non-essential, rate studies show that they reduce the initial induction period observed for the coupling, particularly at larger reaction scales. Table 1 summarizes the effects of deviations from the optimized conditions. It should be

Table 1. Optimized Conditions for *tert*-Butyltrifluoroborate Cross-Coupling and Effects of Deviation from Standard Conditions



entry	deviation	% Ar-Br[a]	% Ar-H[a]	% product 26[a]
1	no change	<5	<5	>95
2	no light	>95	<5	<5
3	no PC	51	12	<5
4	no [Ni]	88	12	<5
5	no K_2HPO_4	15	36	36
6	no $ZnBr_2$	<5	9	81
7	$Ni(COD)_2$ (10%) $Zn(THMD)_2$ (20%)	27	9	57
8	$NiBr_2$ (10%) $Zn(THMD)_2$ (20%)	79	<5	8
9	CzIPN[b] instead of Ir cat. 1	<5	40	35

[a] HPLC yield with 4,4′-di-*tert*-butylbiphenyl as internal standard. [b] CzIPN = 2,4,5,6-tetra-9*H*-carbazol-9-yl-1,3-benzenedicarbonitrile.

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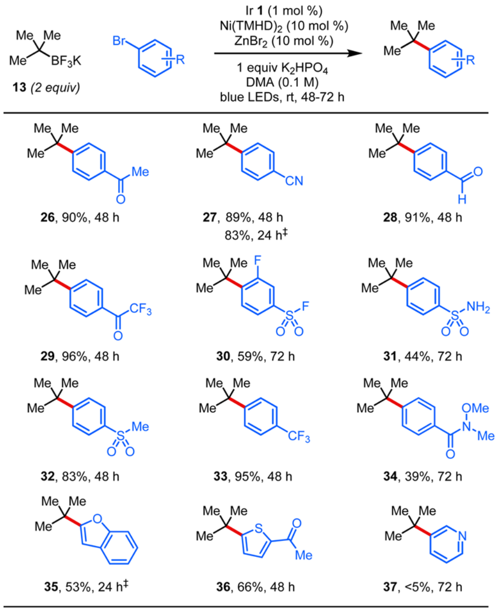

Figure 3. Aryl bromide scope in the cross-coupling of potassium *tert*-butyltrifluoroborate under the developed conditions. ‡Reactions irradiated with four H150 blue LED Kessil lamps.

noted that although reactions run in front of the low wattage LEDs were sluggish (48–72 h), increasing the light intensity through the use of blue aquarium lamps as in Figure 3, entries **27** and **35**, substantially reduced the reaction times (24 h).

With suitable conditions in hand, we evaluated this coupling across an array of aryl bromides (Figure 3). The use of numerous electron-poor aryl bromides resulted in moderate to excellent yields (**26**–**34**). Of note, a number of electrophilic functional groups that are intolerant of more reactive Kumada conditions could be employed to afford nitrile **27**, aldehyde **28**, sulfonyl fluoride **30**, Weinreb amide **34**, and ketones **26** and **36**. A bromo sulfonamide could also be engaged in the coupling to give **31**, demonstrating tolerance of some protic functional groups. Product **30** demonstrates electronic tolerance of *ortho*-substitution; attempts to use a more sterically demanding *o*-methyl-substituted bromide, however, resulted in trace conversion. A heteroaryl thiophene and benzofuran were acceptable partners to give **35** and **36**. Unfortunately, the more desirable *N*-heteroaryl bromides were ineffective under the coupling conditions (see **37**). At this time, we surmise that pyridine serves to ligate the metal center competitively, inhibiting the active catalyst. This is supported by doping experiments where adding 10 mol% of pyridine to the active catalyst mixture arrests conversion to desired product (see SI).

To evaluate the scope further, enone-derived alkyltrifluoroborate **38** was used to ease separation of reactions with incomplete conversion (Figure 4). Here, electron-poor systems worked well to give **39**–**44**. *Meta*-substitution was tolerated, giving **43** and **46** in moderate yields. Overall, the use of electron-neutral bromides resulted in poorer yields (**45**, **46**), and truly electron-rich systems such as 4-bromoanisole afforded trace product (**47**).

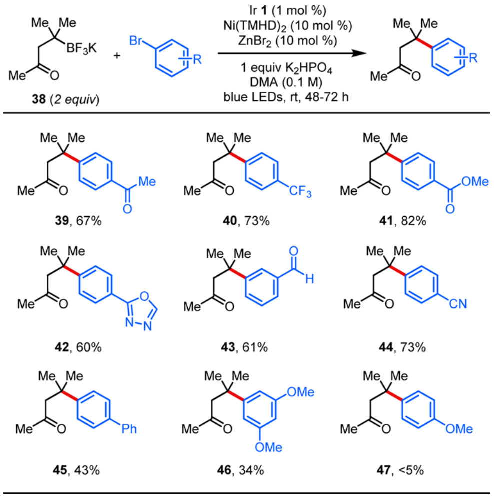

Figure 4. Further evaluation of aryl bromide scope with enone-derived alkyltrifluoroborate **38**.

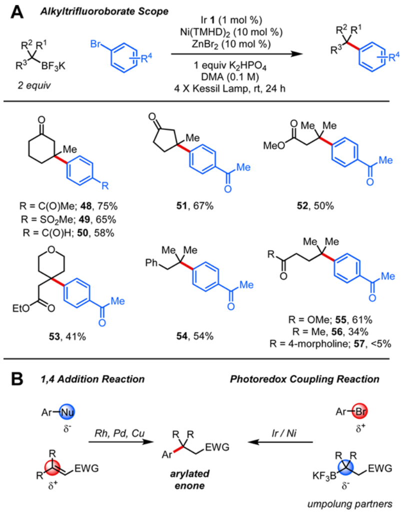

Figure 5. (A) Tertiary alkyltrifluoroborate scope with electron poor aryl bromides. (B) Comparison of enone- and enoate-derived trifluoroborate cross-coupling to metal-catalyzed 1,4-addition chemistry.

With this survey of electrophiles established, we next turned our attention to more complex tertiary alkyltrifluoroborate precursors, using electron-poor bromides as model electrophiles (Figure 5A). Cyclohexanone- and cyclopentanone-based ring systems could be coupled with an array of substituted aryl bromides (aldehydes, sulfones, ketones) to afford **48**–**51**. Notably, the products obtained from the coupling of these enone- and enoate-derived trifluoroborates are analogous to those accessed through 1,4-addition of aryl nucleophiles to *α*,*β*-unsaturated carbonyl systems.[22] As such, the coupling here represents an *umpolung* approach to these methods, where the carbon *β* to the carbonyl is rendered nucleophilic (Figure 5B). Considering the far greater number of commercially available aryl electrophiles relative to the corresponding aryl nucleophiles, this alternative approach has clear advantages for diversity-oriented synthesis. Other functionalized trifluoroborates could be employed to give quaternary centers in **52**–**56**. Here, ester-, ether-, and ketone-containing trifluoroborates all work well in the established protocol. Incorporating an amide in a nearby position shut down the reaction, returning only *β*-hydride elimination and reduction products (see **57**), suggesting that changes in the ligation around the nickel have drastic effects on the reaction profile for this tertiary cross-coupling. Importantly, the 1-adamantyl- and 1-phenylcyclopropyltrifluoroborates worked under these conditions as well.

In summary, the first general method for the cross-coupling of tertiary organotrifluoroborates is described. The development of this protocol hinged on the use of photoredox high-throughput screening technology to identify a new ligand architecture amenable to bulkier tertiary radical nucleophiles. Using the conditions identified therein, an array of functionalized, unactivated tertiary organoboron reagents were employed in transition metal-catalyzed cross-coupling for the first time.[23] These reactions generate quaternary centers, notoriously challenging to access, that are typically forged in cross-coupling through the use of highly reactive Kumada and Negishi partners. In contrast, these mild conditions tolerate a number of electrophilically sensitive functional groups such as aldehydes, ketones, esters, and amides.

At present, a few key limitations of this protocol remain, as the aryl bromide scope for this cross-coupling is currently limited to electron-poor and electron-neutral systems. From the standpoint of organoboron coupling, this limitation actually complements existing metal-free tertiary coupling work by Aggarwal et al., wherein tertiary alkyl pinacol boronates can be best coupled with electron-rich arene systems.[24] The current method also exhibits a notable absence of N-containing heteroaryl partners. In some ways, this failure of heteroaryl systems is mitigated by the successful implementation of tertiary alkyltrifluoroborates in Minisci processes,[25] but extension to other electrophilic sites on heteroaryl compounds would add significant value. Further refinement to the ligand scaffold and conditions will likely address these two limitations, as well as the *ortho*-substitution challenge; efforts in the laboratory toward this end are ongoing.

Given the growing suite of methods for the synthesis of tertiary organoboron compounds,[8] this photoredox cross-coupling is a timely addition, enabling tertiary organoboron reagents as partners in the installation of arylated quaternary centers. Although limitations remain, the ligand screening data and mechanistic interrogation will allow practitioners seeking to employ other tertiary radical feedstocks (carboxylic acids, halides, aldehydes, silicates, etc.) to channel these lessons into developing new tertiary alkyl cross-couplings of broad interest. Taken together, these findings introduce tertiary alkyl radicals to the photoredox cross-coupling portfolio.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b06288.

Experimental details and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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