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Single-Electron Transmetalation: Photoredox/Nickel Dual Catalytic Cross-Coupling of Secondary Alkyl β-Trifluoroboratoketones and -esters with Aryl Bromides

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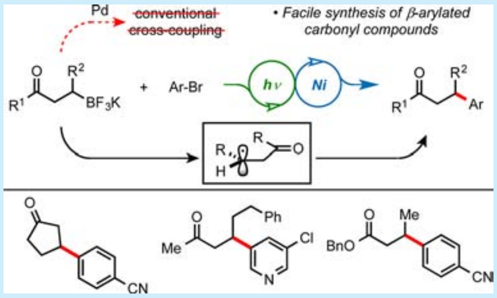
Ⓢ *Supporting Information*

ABSTRACT: The first cross-coupling of secondary alkyl β-trifluoroboratoketones and -esters has been achieved through application of photoredox/nickel dual catalysis. Although the related β-trifluoroboratoamides have been effectively cross-coupled via Pd-catalysis, the corresponding ketones and esters had proven recalcitrant prior to this report. Reactions occur under mild conditions, and a variety of functional groups and sterically and electronically diverse reaction partners are tolerated.



The application of secondary alkylboron reagents in cross-coupling represents a longstanding challenge in organic synthesis. Chiefly responsible for this methodological gap are the slow transmetalation rates associated with these sterically hindered, poorly nucleophilic organometallic reagents, thus limiting their utility in conventional Suzuki−Miyaura cross-coupling (Figure 1).[1] In an effort to enable the application of this subclass of reagents in transition-metal-catalyzed cross-coupling processes, our group has developed an alternative paradigm for the cross-coupling of alkylboron and alkylsilicon reagents that relies on the cooperative functions of a nickel cross-coupling catalyst and an Ir- or Ru-based photoredox catalyst.[2,3] Here, the organometallic reagent is activated by oxidative fragmentation to the corresponding alkyl radical. This transient intermediate is then readily intercepted by the nickel catalyst, which mediates C−C bond formation with an appropriate aryl halide partner. Exploitation of an odd-electron activation mode in this process provides reactivity trends complementary to that of conventional cross-coupling reactions, which typically rely on paradigms rooted in two-electron processes.

In an effort to expand the capabilities of this photoredox/nickel dual catalytic approach to cross-coupling, we identified β-trifluororboratoketones and -esters as a useful class of reagents for which no effective cross-coupling protocols currently exist. Although these organoboron compounds are easily accessed via borylation of the corresponding α,β-unsaturated carbonyl compounds,[4] a single, isolated example of the Suzuki coupling of a cyclopropyl ketone-derived pinacolboronate represents the entirety of their utilization in C−C bond-forming reactions.[5] Attempts within our own group to apply reaction conditions developed for use with related β-trifluoroboratoamides to the corresponding ketones were unsuccessful in affording any cross-coupled product.[6] A method for achieving the cross-coupling of these reagents would not only expand the utility of an underutilized class of easily prepared compounds but also complement existing Rh- and Cu-catalyzed methods for the synthesis of β-arylated ketones by offering an as-yet unrealized umpolung disconnection.[7] This disconnection is especially valuable upon consideration of the greater availability of aryl bromide building blocks relative to boronic acids and boronate esters.

Notably, organoboron reagents represent perhaps the only viable cross-coupling partners about which a general protocol for achievement of this particular union could be built. Secondary ketone homoenolates of zinc, magnesium, and lithium cannot be prepared because of rapid, intramolecular nucleophilic attack of the organometallic carbon into the carbonyl to afford the corresponding cyclopropanolates.[8] Although the resultant cyclopropanols can be engaged in ring-opening cross-coupling to generate β-arylated ketones, aldehydes, or esters, substituted cyclopropanols typically participate in C−C bond formation at the less sterically hindered carbon to generate products of primary alkyl arylation.[9] Furthermore, although secondary alkyltin homoenolates have been frequently prepared, only one successful example of their cross-coupling has been reported.[10] Indeed, the unique properties of organoboron compounds situate these reagents in a privileged position for realization of this transformation.

We began our studies with an investigation of the cross-coupling of secondary alkyltrifluoroborate **2a** with 4-bromobenzonitrile. Employing a catalytic system of photocatalyst **1**

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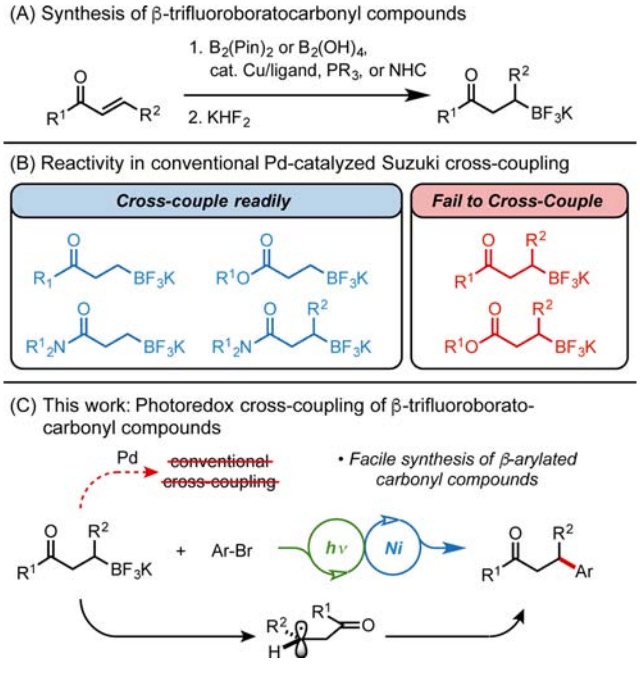
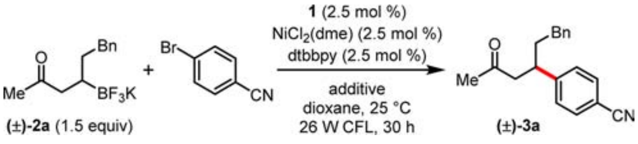


Figure 1. (A) Synthesis of *β*-trifluoroboratocarbonyl compounds from *α*,*β*-unsaturated ketones and esters. (B) *β*-Trifluoroboratocarbonyl compounds previously employed in cross-coupling reactions (left) and those utilized in this report (right). (C) Cross-coupling of *β*-trifluoroboratocarbonyl compounds via photoredox/nickel dual catalysis.

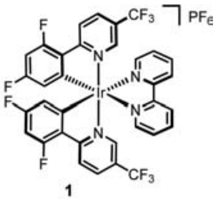
(2.5 mol %), $NiCl_2$·dme (2.5 mol %), and dtbbpy (2.5 mol %) in 1,4-dioxane led to the formation of product **3a** in 36% yield (Table 1, entry 1). Attempting to apply conditions previously optimized for structurally analogous unactivated secondary alkyltrifluoroborates,[2b] addition of 1.5 equiv of Cs_2CO_3 resulted in formation of product in an improved, yet still unsatisfactory, 49% yield (Table 1, entry 2). Exchanging Cs_2CO_3 for 2,6-lutidine, which had previously been demonstrated as an effective additive for these types of dual catalytic processes, was detrimental to the efficiency of the reactions. Unexpectedly, the combination of (super)stoichiometric Cs_2CO_3 and 2,6-lutidine proved more effective in promoting the desired reaction than each additive alone. Even more surprisingly, it was found that reduction of the concentration of these additives to 0.5 equiv each afforded the highest yield (83%) of *β*-arylated product (Table 1, entry 5).

Table 1. Effect of Additive Stoichiometry on Photoredox/Nickel Dual Catalytic Cross-Coupling of *β*-Trifluoroboratoketone 2



entry	equiv Cs_2CO_3	equiv 2,6-lutidine	yield (%)
1	0	0	36
2	1.5	0	49
3	0	1	29
4	1.5	1	60
5	**0.5**	**0.5**	**83**

reactions performed on 0.1 mmol scale, yield determined by crude HPLC analysis with 10 mol % di-*tert*-butylbiphenyl as an internal standard



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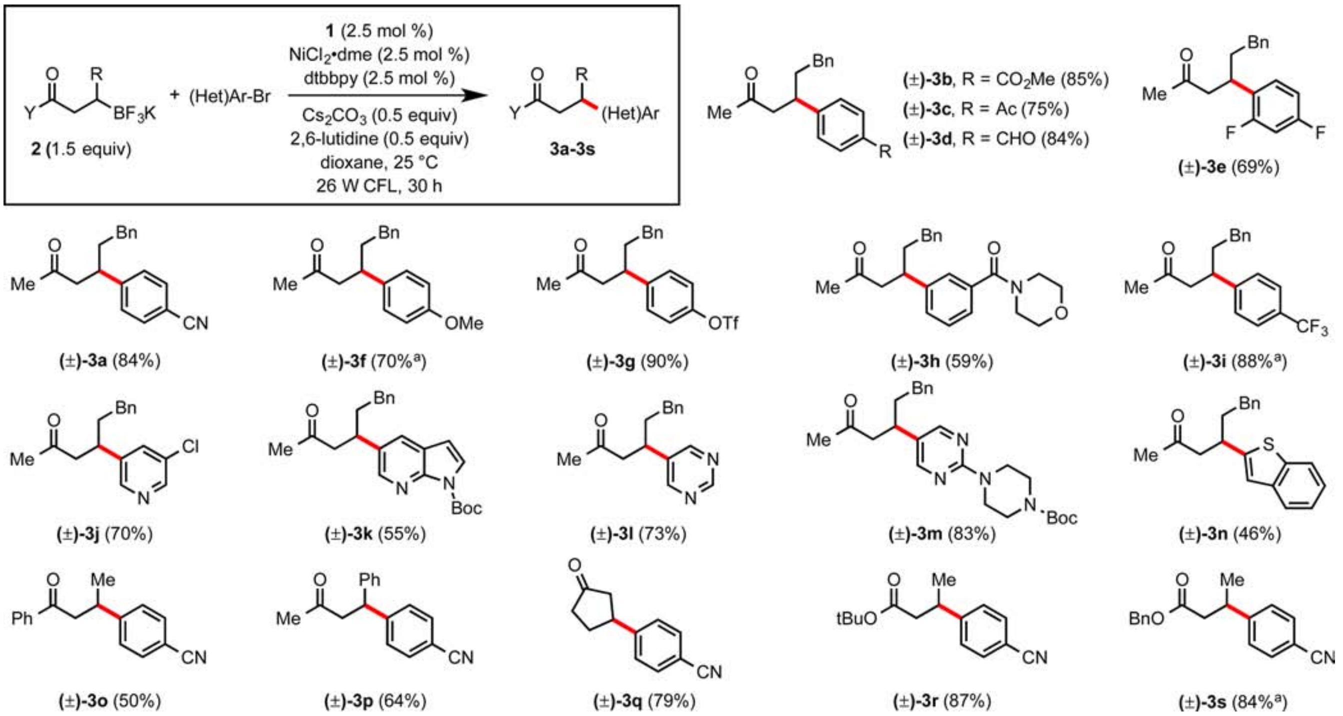
Presently, we are unable to explain the unique effects of this unusual combination of additives. We have previously proposed that the Lewis basic additives (2,6-lutidine, Cs_2CO_3, K_2HPO_4, and/or KF) employed in these cross-coupling reactions serve to sequester BF_3, the highly Lewis acidic byproduct of single-electron oxidative fragmentation of the alkyltrifluoroborate.[2b] Indeed, experiments have confirmed that reaction rates are reduced in the presence of exogenous BF_3·OEt_2. Furthermore, reactions of organobis(catecholato)silicates produce non-Lewis acidic byproducts and have been observed to proceed efficiently in the absence of exogenous Lewis base additives.[2d]

Although it is unclear how or why the combination of substoichiometric Cs_2CO_3 and 2,6-lutidine would be more effective than each additive alone in serving this role, we speculated that the observed effects may result from either (1) control of the keto−enol tautomerization rate of the *β*-trifluoroboratoketone/ester and/or the corresponding radical or (2) formation of a more highly active (soluble) salt form of the alkyltrifluoroborate. Regarding the keto−enol tautomerization, it has been documented that radical and radical ion intermediates can have drastically different acid/base properties relative to their closed-shell analogues.[11] Specifically, in this case the formation of the enol tautomer from the *β*-carbonyl radical would afford a much more highly stabilized enolic radical. DFT calculations (UB3LYP 6-311+G**) have indicated a strong thermodynamic preference for the enolic form of butenal when a radical resides on the *β*-carbon.[11d] However, it is unclear if the kinetics of enolization under the reported conditions are sufficiently fast as to outcompete the rate of radical capture at the Ni center. Alternatively, formation of the enol tautomer from the trifluoroborate precursor would drastically lower the oxidation potential of the C−B bond. The transient nature of these species and heterogeneity of the reaction mixture complicate any attempts to confirm or disprove the involvement of the enol tautomer during the cross-coupling, and it is unclear if formation of the species would be beneficial or detrimental to the process.

With regard to the hypothesized formation of a more highly active salt form, we have observed that although dioxane is the most effective reaction solvent, trifluoroborate **2** is almost entirely insoluble in this solvent at room temperature.[12] It is possible that combination of the potassium alkyltrifluoroborate with Cs_2CO_3 and 2,6-lutidine leads to formation of a trifluoroborate salt with greater solubility in dioxane and/or more favorable redox properties. However, notable in this context is the observation that employing the soluble tetrabutylammonium salt of **2a** nearly shuts down reactivity under identical conditions, eroding support for the more active salt argument.

We next examined the substrate scope of this cross-coupling reaction with regard to both the aryl bromide and alkyltrifluoroborate partner (Scheme 1). A variety of common functional groups were well tolerated. Although electron-poor aryl bromides generally performed best, electron-rich aryl bromides [4-bromoanisole, (±)-**3f**, 70%] could also be cross-coupled with extended reaction times (48 h). Electrophilic functional groups that may be prone to side reactions in the presence of more strongly nucleophilic organometallic reagents, including aldehydes [(±)-**3d**], ketones [(±)-**3c**], esters [(±)-**3b**], and nitriles [(±)-**3a**], were well tolerated. Heteroaryl bromides also proved to be able partners, including pyridine [(±)-**3j**], pyrimidines [(±)-**3l** and (±)-**3m**], azaindole [(±)-**3k**], and benzothiophene [(±)-**3n**]. The observed

Scheme 1. Photoredox/Nickel Dual Catalytic Cross-Coupling of β-Trifluoroboratocarbonyl Compounds: Substrate Scope[a]



[a] Reaction time 48 h.

tolerance of nitrogenous substrates bearing Lewis basic moieties is important for applications in the synthesis of therapeutically active compounds, where these types of motifs are prevalent. Also notable is the observed selectivity for reaction of the aryl bromide exclusively in the presence of (hetero)aryl chlorides [(±)-**3j**] and triflates [(±)-**3g**], thereby allowing the possibility of sequential functionalization with a second organometallic reagent.

A variety of β-trifluoroboratocarbonyl compounds were also found to be competent reaction partners. Importantly, both alkyl and aryl ketones were well tolerated, as was alkyl and aryl substitution in the β-position. Cyclic organoboron reagents were readily tolerated [(±)-**3q**] as well. Notably, methods previously developed for the cross-coupling of secondary β-trifluoroboratoamides in our laboratory proved ineffective for the cross-coupling of cyclic compounds, presumably because of the need for coordination of the amide carbonyl to the organopalladium intermediate to suppress undesired β-hydride elimination pathways and/or acceleration of the sluggish two-electron transmetalation. Secondary β-trifluoroboratoesters were also cross-coupled for the first time [(±)-**3r** and (±)-**3s**] in good yield.

The method reported here for the synthesis of β-arylated ketones and esters has numerous advantages over existing methods. Although some of the compounds synthesized in this report could be accessed via Rh- or Cu-catalyzed conjugate addition procedures, the photoredox/nickel dual catalytic cross-coupling displays comparable or greater functional group tolerance. Furthermore, the instability of many heteroarylmetallic reagents[13] would greatly reduce access to many of the compounds reported herein. Access to commercially available or easily prepared (hetero)aryl bromides makes this method more attractive for the systematic synthesis of a variety of β-(hetero)arylated ketones and esters from a common ketone or ester fragment. A C−H functionalization approach was reported by MacMillan and co-workers that provides access to β-(hetero)arylated ketones and aldehydes.[14] However, this method is only effective for electron-poor cyanoarenes and cannot be applied with sterically and/or electronically non-biased dialkyl ketones, again highlighting the complementary characteristics of the protocol reported herein among methods for the synthesis of this class of compounds.

Among the limitations of this method are sometimes modest yields, often resulting from sluggish conversion. We have previously suggested that long reaction times in these dual catalytic cross-coupling processes may be a result of poor light penetration into the reaction mixture, leading to inefficient excitation of the photocatalyst and effective reduction of the concentration of "active" photocatalyst.[15] This effect is likely to be exacerbated by the insolubility of the substrate, which both obscures the path of the light into the solution and introduces a mass-transfer limitation in oxidation of the trifluoroborate. The yields of many reactions can be improved by extension of reaction time, but this benefit comes at the expense of practicality.

Although a variety of useful functional groups are tolerated, nitro groups, primary and secondary amides, and primary, secondary, and tertiary amines have not been coupled successfully in our hands. Also, aryl bromides bearing *ortho* substitution typically coupled in very low yields. Furthermore, primary and tertiary alkyltrifluoroborates and β-trifluoroboratoamides are unreactive under the reported conditions. However, it should be noted that the poor reactivity of primary alkyl substrates and amides demonstrates the complementary nature of the reported method to previously reported Pd-catalyzed methods.[6a,16] Taken together, the Pd-catalyzed and newly reported dual catalytic process allows the cross-coupling of nearly any primary or secondary β-trifluoroboratoketone, -ester,

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or -amide, with the method reported herein filling the last remaining gaps in this series.

In summary, we have reported for the first time the cross-coupling of secondary *β*-trifluoroboratoketones and -esters with aryl bromides. Key to the realization of this particular bond disconnection was the application of photoredox/nickel dual catalysis wherein previously recalcitrant organoboron reagents are activated for cross-coupling via single electron oxidation and fragmentation to a secondary alkyl radical. The reported method exhibits tolerance of a variety of functional groups and heteroarenes and can be applied to structurally and electronically diverse *β*-trifluoroboratocarbonyl compounds. Reactions occur under mild conditions and in moderate to very good yields. The results disclosed herein not only offer an attractive method for the synthesis of secondary *β*-(hetero)arylated ketones and esters but also attest to the power of photoredox/nickel dual catalysis to realize previously challenging or impossible bond disconnections.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01357.

> 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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■ REFERENCES

(1) Leading references regarding unactivated secondary alkylboron cross-coupling: (a) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257. (b) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027. (c) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. *ACS Catal.* **2015**, *5*, 3680. (d) van den Hoogenband, A.; Lange, J. H. M.; Terpstra, J. W.; Koch, M.; Visser, G. M.; Visser, M.; Korstanje, T. J.; Jastrzebski, J. T. B. H. *Tetrahedron Lett.* **2008**, *49*, 4122.

(2) (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (b) Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195. (c) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896. (d) Jouffroy, M.; Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 475.

(3) Others have reported a similar dual catalytic system for the cross-coupling of alkylcarboxylates, alkylsilicates, and tertiary anilines with aryl/alkenyl halides: (a) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (b) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624. (c) Chu, L.; Lipshultz, J. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929. (d) Le, C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 11938. (e) Corcé, V.; Chamoreau, L. M.; Derat, E.; Goddard, J. P.; Ollivier, C.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 11414. (f) Lévêque, C.; Chenneberg, L.; Corcé, V.; Goddard, J. L.; Ollivier, C.; Fensterbank, L. *Org. Chem. Front.* **2016**, *3*, 462.

(4) (a) Molander, G. A.; McKee, S. A. *Org. Lett.* **2011**, *13*, 4684. (b) Lee, K.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253. (c) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5130.

(5) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375.

(6) (a) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108. (b) Molander, G. A.; Wisniewski, S. R.; Hosseini-Sarvari, M. *Adv. Synth. Catal.* **2013**, *355*, 3037.

(7) (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Tian, P.; Dong, H.; Lin, G. *ACS Catal.* **2012**, *2*, 95. (c) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039. (d) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (e) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.

(8) Cheng, K.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 2346.

(9) (a) Cheng, K.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 2298. (b) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83. (c) Parida, B. B.; Das, P. P.; Niocel, M.; Cha, J. K. *Org. Lett.* **2013**, *15*, 1780. (d) Rosa, D.; Orellana, A. *Org. Lett.* **2011**, *13*, 110. (e) Murali, R. V. N. S.; Rao, N. N.; Cha, J. K. *Org. Lett.* **2015**, *17*, 3854. (f) Nithiy, N.; Orellana, A. *Org. Lett.* **2014**, *16*, 5854. (g) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 6541. (h) Fujimura, T.; Aoki, S.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2809. (i) Rosa, D.; Orellana, A. *Chem. Commun.* **2013**, *49*, 5420.

(10) Li, L.; Wang, C.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607.

(11) (a) Dinnocenzo, J. P.; Banach, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 8646. (b) Zhang, X.; Yeh, S.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 4211. (c) Raczyńska, E. D.; Stępniewski, T. M.; Kolczyńska, K. *J. Mol. Model.* **2011**, *17*, 3229. (d) Huang, Y.; Srinivasadesikan, V.; Chen, W.; Lee, S. *Chem. Phys. Lett.* **2013**, *565*, 18.

(12) No detectable ^{11}B signal could be identified from the ^{11}B NMR of a suspension of **2a** in dioxane.

(13) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

(14) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593.

(15) Ryu, D.; Primer, D. N.; Tellis, J. C.; Molander, G. A. *Chem. - Eur. J.* **2016**, *22*, 120.

(16) Molander, G. A.; Wisniewski, S. R.; Hosseini-Sarvari, M. *Adv. Synth. Catal.* **2013**, *355*, 3037.