

# B-Alkyl $sp^3$ – $sp^2$ Suzuki–Miyaura Couplings under Mild Aqueous Micellar Conditions

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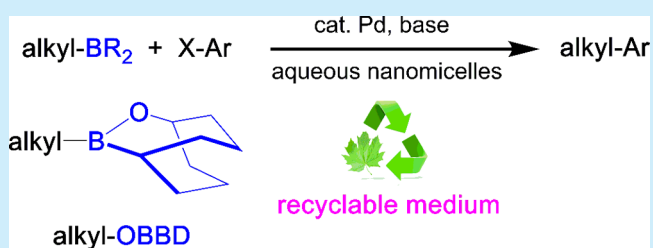
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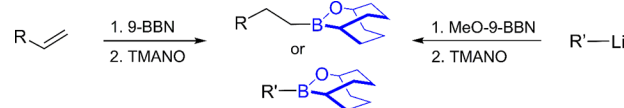
## Supporting Information

**ABSTRACT:** Use of B- $sp^3$ -alkyl reagents for Suzuki–Miyaura couplings under aqueous micellar catalysis conditions is reported. Studies as to substrate scope, use in a four-step one-pot sequence, and reaction medium recycling exemplify the synthetic utility of this technology. OBBD (B-alkyl-9-oxa-10-borabicyclo[3.3.2]decane) derivatives are easily made and utilized for couplings under mild conditions. Comparisons were also made between OBBD and 9-BBN (B-alkyl-9-borabicyclo[3.3.1]nonane) derivatives as reaction partners.



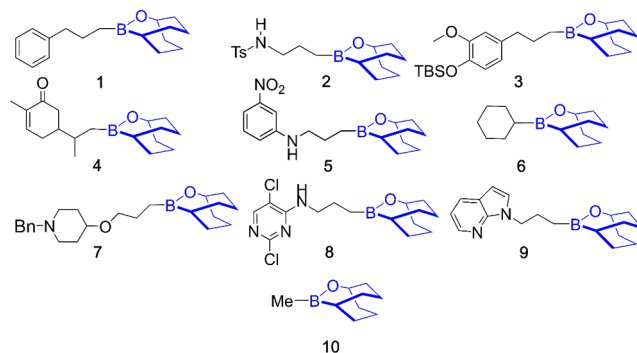
Suzuki–Miyaura cross-coupling reactions have been broadly applied to numerous C–C bond formations due, in part, to their ability to make connections that may be difficult by other means.<sup>1</sup> Couplings using 9-BBN derivatives are common,<sup>2</sup> however, notable variations including  $BF_3K^3$  and MeO-9-BBN<sup>2b</sup> reagents have found widespread use by broadening the scope and flexibility of this synthetic strategy. In the search for a boron species suitable for use in aqueous media, the OBBD (B-alkyl-9-oxa-10-borabicyclo[3.3.2]decane) framework, a derivative of 9-BBN, appeared to be one potentially attractive option. Practical applications associated with use of 9-BBN and other trialkylboranes are limited due to their sensitivity to air, as well as their pyrophoric nature and modest shelf life, leading to their typical formation and use *in situ*.<sup>4</sup> By contrast, OBBD reagents exhibit relatively good air stability and, therefore, are easily isolated and storable for future use. These reagents were developed primarily by Soderquist.<sup>5</sup> Several publications have since utilized these reagents in applications as diverse as reactions with allenes,<sup>6a</sup> installation of OBBDs onto a carbohydrate framework,<sup>6b</sup> and for attachment of an OBBD to a chromium complex,<sup>6c</sup> among others. Their potential for use as B- $sp^3$ -alkyl partners in Suzuki–Miyaura (SM) couplings, however, has not been explored outside of Soderquist's original reports with the exception of a methylation in a total synthesis<sup>6d</sup> and an example of coupling of a vinyl OBBD derivative to an aryl halide.<sup>6e</sup> Our group has focused mainly on  $sp^2$ – $sp^2$  SM reactions in aqueous surfactant media,<sup>7</sup> with TPGS-750-M being the preferred amphiphile; none to date forms  $sp^2$ – $sp^3$  bonds. These reagents have now been examined for their potential as coupling partners under micellar catalysis conditions. We have found that, in addition to their preparation being straightforward (Scheme 1), their reactivity is comparable to that of 9-BBN derivatives. However, their relatively greater

## Scheme 1. Preparation of OBBD Derivatives



stability and their isolable nature make them especially suitable for these highly valued C–C bond constructions using environmentally responsible reaction conditions, as described herein.

A library of OBBD derivatives was synthesized (Figure 1; see Supporting Information for details) with which the scope of the newly developed technology could be evaluated based on the



**Figure 1.** Representative OBBD derivatives prepared for cross-couplings in water.

Received: March 25, 2018

Published: May 8, 2018

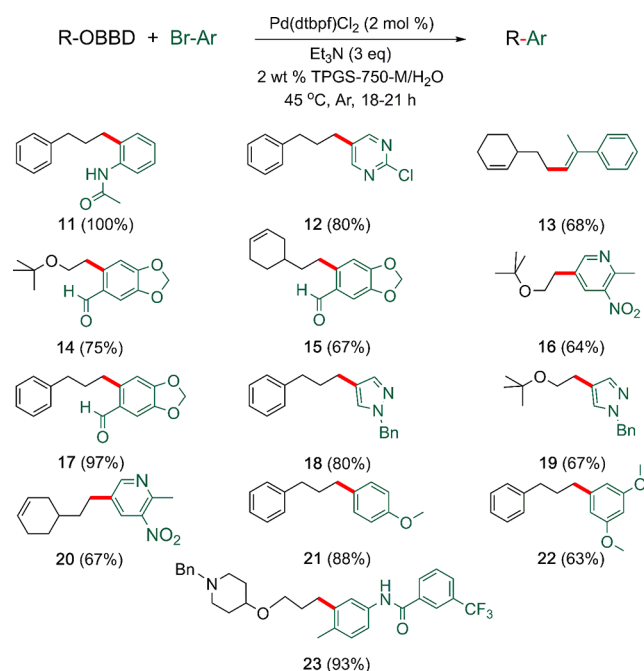
variety of resulting coupled products. Of note, was the facility with which the OBBD moiety could be installed notwithstanding the presence of other sensitive groups, including  $\alpha,\beta$ -unsaturated ketones, amines, *N*-heterocycles, aryl halides, and protecting groups. Both primary and secondary OBBDs were readily prepared. In agreement with previous reports,<sup>2b</sup> hydroboration was slowed by increasing degrees of substitution on the precursor alkene.

Although these reagents have been described as “air stable”,<sup>5a,e</sup> we found that they remain intact for 1–2 days when left open to air, after which significant deterioration does occur. However, their shelf life when stored under argon using refrigerated conditions was found to be good. For example, OBBD derivatives **1** and **3** have been stored by us for over one year with minimal degradation. The literature procedures by Soderquist involved distillation to purify OBBD-containing compounds.<sup>5c,f</sup> While this is suitable for lower molecular weight cases, it is not practical for high molecular weight or heat sensitive compounds. We found that upon completion of 9-BBN hydroboration/monooxidation, the solvent could instead be removed in vacuo and the crude OBBD product filtered through a short pad of silica gel to arrive at material useful for coupling reactions. Most of these compounds appeared to be stable to silica gel, although OBBD derivative **9** was found to rapidly decompose on SiO<sub>2</sub> at rt.

While “discovery conditions” involved use of (HandaPhos)-Pd<sup>7d</sup> as a catalyst at 1% loading, further reductions in the amount of catalyst resulted in decreased yields. Among several catalysts evaluated, Pd(dtbpf)Cl<sub>2</sub> was selected as the most suitable. Couplings were initially screened at the 2 mol % level to assess the substrate scope, the results from which are shown in Scheme 2.

Following this preliminary assessment suggesting broad substrate compatibility, we returned to catalyst screening and reaction optimization. Our investigation centered on the choice of ligand alternatives to that found in Pd(dtbpf)Cl<sub>2</sub>, such as SPhos, and Pd(dppf)Cl<sub>2</sub><sup>4a,Sb</sup> given its frequent use in 9-BBN-

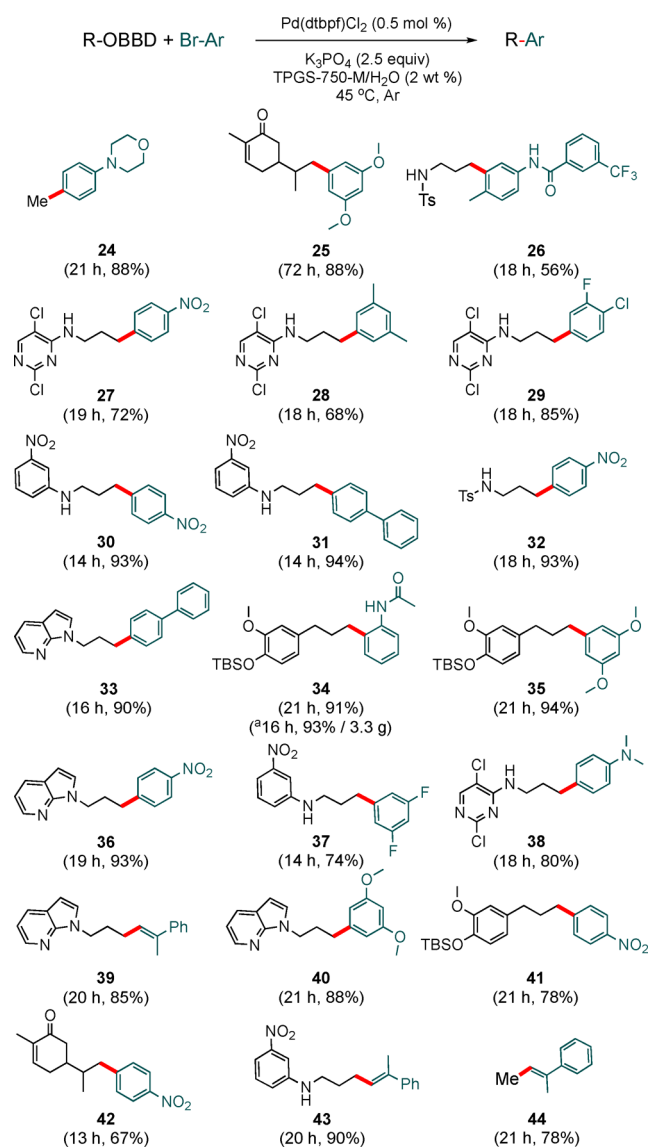
**Scheme 2. Preliminary Substrate Scope Using 2 mol % Pd**



based  $sp^2$ – $sp^3$  couplings. These trials revealed that Pd(dtbpf)Cl<sub>2</sub> is superior to Pd(dppf)Cl<sub>2</sub>, and (SPhos)<sub>2</sub>Pd. Indeed, using dtbpf as the supporting ligand, a model reaction could be run successfully at a catalyst loading as low as 0.25 mol % (i.e., 2500 ppm).

Initially, Et<sub>3</sub>N was used as a base for this model study, and while it helped to solubilize educts and leads to a much more uniform reaction appearance, better yields and shorter reaction times were noted by switching to K<sub>3</sub>PO<sub>4</sub> (Scheme 3). Although

**Scheme 3. Substrate Scope Using 0.5 mol % Pd**



<sup>a</sup>Et<sub>3</sub>N (3 equiv) as base.

traditional 9-BBN/OBBD couplings call for KOH or NaOH as the base,<sup>4a,Sb,c</sup> several byproducts were formed under these conditions. Reactions run at room temperature gave acceptable yields, although these required much longer reaction times. Attempts to use a 0.25 mol % catalyst loading, under ambient conditions, resulted in little-to-no conversion, especially in more challenging substrates. Therefore, further evaluation of substrate scope was conducted at 45 °C. Interestingly, reaction appearance seemed better at room temperature, producing “milky” reaction mixtures, while an increase to 45 °C led to

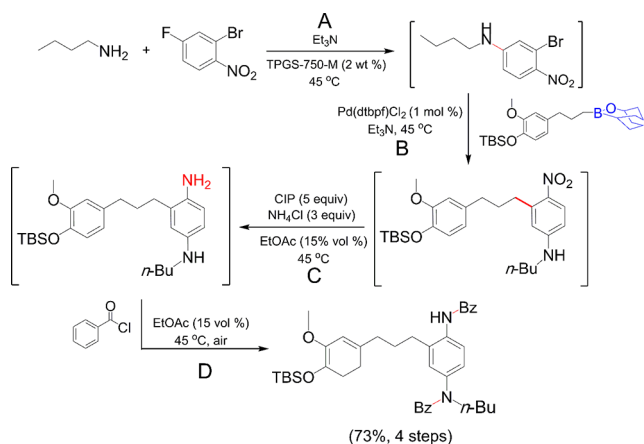
“oiling out”, despite improving the extent of conversion. Product isolation followed simple extraction of the aqueous mixtures with EtOAc.

While many substrate combinations proved viable at catalyst loadings of 0.25% Pd, those rich in nitrogen were more challenging and required an increase to 0.5 mol % Pd to go to completion (Scheme 3). In addition to slowing reactions, most substrates containing nitrogen were very challenging to purify by column chromatography, as the OBBD residue remained present, though column fractions appeared clean by TLC. Workup with hydrogen peroxide to remove boron-containing residues, prior to extraction, alleviated this issue.

As for limitations, OBBD-containing substrates bearing steric hindrance near the boronate led to significantly slower couplings. In addition, neither secondary OBBD nor 9-BBN derivatives were capable of coupling under these standard conditions; variations such as higher temperatures, catalyst loadings, or changes in base also had no effect.

To showcase the utility of OBBD reagents in the construction of a complex framework, a four-step one-pot sequence (A to D, Scheme 4) was conducted. The reaction

**Scheme 4. Tandem Four-Step One-Pot Sequence in Aqueous Media**



(A) (B) (C) (D)

involving an OBBD derivative was used in the second step (B), following an initial  $S_NAr$  reaction (A),<sup>8</sup> and was selected to illustrate that it can tolerate species in the pot that are unrelated to its couplings. The product from step B containing an aromatic nitro group was then reduced using our procedure based on carbonyl iron powder (CIP)<sup>9</sup> and then acylated to afford the final product in very good overall yield. An alternative sequence utilizing a more complex amine for the  $S_NAr$  was attempted, but resulted in very insoluble material. Moreover, the residual amines present hindered the subsequent OBBD coupling such that no conversion was seen.

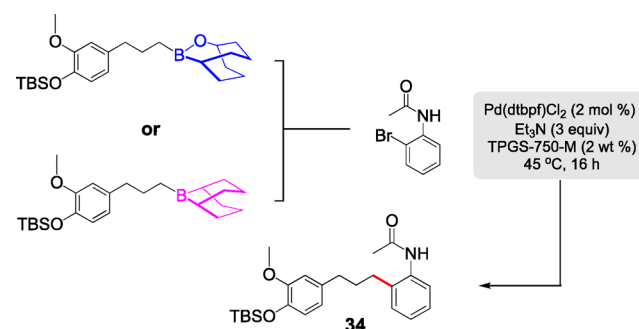
The effect of brief (1 h) exposure of OBBD and 9-BBN derivatives to air was tested (Table 1). When both were kept under an inert atmosphere before and during the reaction, they

**Table 1. Impact of Exposure of Reagent to Air for 1 h Prior to Use**

organoboron reagent	yield after 1 h exposure to air
9-BBN (1.1 equiv)	49%
OBBD (1.1 equiv)	92%

led to essentially equivalent yields (ca. 94%). However, while the OBBD derivative did not suffer from pre-exposure to air for an hour and gave a similar yield of coupling product (92%), the 9-BBN analog suffered significant degradation, resulting in a dramatic decrease in yield (49%; Scheme 5). Running both

**Scheme 5. 9-BBN vs OBBD Air Sensitivity Testing**



reactions fully open to air resulted in similar decreases in yields (Table 2). Even at 2 mol % Pd, the presence of oxygen is

**Table 2. Coupling Run Fully Open to Air**

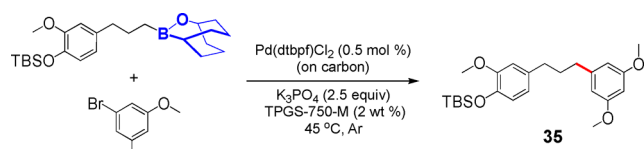
organoboron reagent	yield of reaction exposed to air
9-BBN (1.1 equiv)	50%
OBBD (1.1 equiv)	51%

extremely detrimental to reaction outcome, and this effect is of even greater consequence at lower catalyst loadings. Therefore, while the OBBD reagent is stable to air for short periods of time, both boron species require inert conditions for effective coupling. Such observations have important implications for use of these reagents, especially in industrial settings. That is, aside from their responsiveness to aqueous micellar catalysis conditions, tolerance of OBBDs to air allows for their ease of handling without concern over degradation or potential pyrophoric complications.

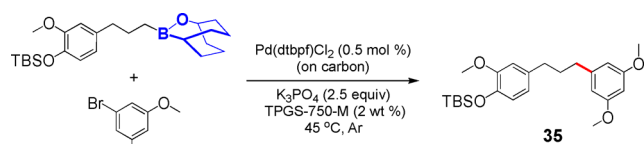
Examples in the literature of couplings with 9-BBN or OBBD are typically run in THF, dioxane, or mixtures with water, e.g., 20:1 THF/water. The reaction in Table 3 was found to proceed much faster in TPGS-750-M than in traditional solvent systems.

Reuse of an aqueous TPGS-750-M solution was practical for up to three recycles, after which the reaction medium becomes too viscous to stir and difficult to extract (Table 4). Efforts to recycle the catalyst as well were not successful, as extraction with EtOAc removes nearly all the Pd(dtbpf)Cl<sub>2</sub>, while use of Et<sub>2</sub>O or MTBE leaves enough for only partial conversion in a subsequent reaction.

In summary, both alkyl-9-BBN and the corresponding OBBD reagents have been studied in Suzuki–Miyaura reactions run in water under mild conditions. The latter derivatives were found to be particularly useful for  $sp^3$ – $sp^2$  couplings. Due to their relatively good air stability, non-pyrophoric nature, and ease of preparation, OBBD derivatives are attractive coupling partners in *B*-alkyl Suzuki–Miyaura

**Table 3. Comparison: Solvent vs Aqueous Surfactant as Reaction Medium after 6 h**


solvent/medium	isolated yield (%)
TPGS-750-M (2 wt % in water)	94
THF/H <sub>2</sub> O (20:1)	44
dioxane/H <sub>2</sub> O (20:1)	56

**Table 4. Recycling of TPGS-750-M and E Factor Calculations**


	reaction	first recycle	second recycle	third recycle
isolated yield (%)	81	85	86	88
E factor (organic solvent)	3.2	3.1	3.0	3.9
E factor (including aqueous)	7.8	5.1	3.0	6.0

couplings under aqueous micellar conditions, akin to our sp<sup>2</sup>–sp<sup>2</sup> SM couplings previously described.<sup>7</sup>

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00961.

Reaction optimization, details of control-experiments, analytical data of all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We warmly acknowledge Novartis and the NSF (GOALI SusChEM 1566212) for financial support.

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