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Selective copper-promoted cross-coupling reaction of anilines and alkylboranes

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ABSTRACT

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Keywords: Chan-Lam Copper Boranes Phenylethylamine reported. Alkylboranes, synthesized by hydroboration of styrenes, are effectively coupled with anilines, which comprises a facile method for the synthesis of highly functionalized phenethylaniline derivatives. This is the first time that alkylboranes are used in C–N copper-promoted cross-coupling reactions. © 2011 Elsevier Ltd. All rights reserved.

Extension of the Chan-Lam N-alkylation of anilines by using alkylboranes as organoboron partners is

Aromatic amines are ubiquitous compounds used in pharmaceuticals, crop-protection chemicals, and material science.¹ Hence, the development of new methods for their synthesis is still an active area of research.

Transition metal-catalyzed cross-coupling reactions are well established for C–N bond formation.² In the last decade, Buchwald and Hartwig have pioneered palladium-catalyzed cross-coupling reactions of amines with aryl halides, triflates, and tosylates.³

Copper-promoted or catalyzed carbon–nitrogen bond forming reactions are a useful complement to palladium chemistry, due to the high stability, low toxicity, and low cost of the copper reagents. Among these, the coupling with boronic acids has emerged as a powerful synthetic method since the initial reports by Chan, Lam, and Evans.⁴ This methodology, as compared to classical Ullmann reaction or Pd-catalyzed transformations has several advantages: use of very mild reaction conditions, weak base, and that reactions can be performed in the presence of air. The scope of the reaction has been extended to NH containing nucleophiles such as amines, amides, imides, ureas, hydrazines, carbamates, and different classes of aromatic heterocycles (imidazole, pyrazole, indole, and others). Catalytic versions of several of these processes have also been reported.⁵

Although tremendous progress has been made in recent years in the development of effective methods for copper-mediated cross-couplings of aryl and alkenyl organoboron compounds,⁶ comparable success has not yet been achieved for alkyl organoboron reagents. Alkyl boronic acids rarely act as effective reagents because of their low reactivity toward transmetallation with Cu salts,

* Corresponding author. E-mail address: jacobo.cruces@galchimia.com (J. Cruces). with the exception of cyclopropylboron derivatives due to the significant sp²-character of the carbon atoms.⁷ Cyclopropyl boronic acid has been successfully coupled with a range of different NH containing substrates (most of them being compounds with increased NH acidity like amides and indoles).⁸

Even so, we have recently developed a simple copper-promoted N-monoalkylation of anilines which relies on the use of alkylboronic acids as the alkylating partner.⁹ During the last decade, efforts have been expended toward further development of the most important component of the process, the organoboron itself. Several types of organoboron reagents have been employed in Chan-Lam coupling, such as boronic acids, boronate esters, organotrifluoroborates, boroxines, and aryltriolborates.¹⁰ Our interest in copper-promoted cross-coupling reactions prompted us to consider the possibility of further expanding the toolbox of boron reagents by using alkylboranes. Despite the fact that they have been extensively employed in the Suzuki reaction¹¹ there are no examples where alkylboranes are involved in C-N crosscoupling bond forming reactions. We realized that if they could act as an effective partner in Chan-Lam coupling reactions, Nalkylation of anilines could be carried out by the use of alkylboranes, which can be synthesized in a highly regioselective manner by means of the hydroboration of the corresponding olefin.¹²

In this Letter, we describe the results of our effort aimed at exploring and developing a novel copper-promoted reaction based on the use of alkylboranes as organoboron partner. We focused on the synthesis of phenethylanilines, as these are interesting targets due to their biological properties but difficult to prepare by direct alkylation.¹³

In previous work we found that optimal reaction conditions for the coupling between anilines and alkyl boronic acids were the use of $Cu(OAc)_2$ as the copper source and pyridine as the base in reflux-



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Scheme 1. Preparation of phenethylamine 3a from aniline 1a and styrene 2a.

ing dioxane, in air-opened reaction flask.⁹ Under these conditions, full conversion is achieved in several hours, affording only monoalkylated anilines. We decided to apply the same reaction conditions to the coupling of alkylboranes.

Alkylboranes are not air-stable and so they are usually difficult to isolate, purify and handle.¹⁴ Thus, they were prepared in situ via hydroboration of appropriate styrenes and used without isolation or purification. Our research was started by exploring the reaction of 4-*tert*-butylaniline (**1a**) with 4-*tert*-butoxy styrene (**2a**) (Scheme 1, Table 1). We used 9-BBN at the beginning as the boron source, and hydroboration of styrene **2a** proceeded smoothly at room temperature. The coupling reaction was performed under conditions similar to those previously reported: 2.5 equiv of Cu(OAc)₂ and 3 equiv of pyridine in dioxane. No reaction took place at rt, even when 4 equiv of alkyl BBN reagent were used, but it proceeded to completion after 4 h at reflux, (Table 1, entries 1 and 2). Nevertheless, purification was quite tedious due to the presence of byproducts from BBN, and yield of pure product was only moderate.

The reaction was regioselective, furnishing the product with the nitrogen attached to terminal carbon of the styrene, arising from addition of boron to the less hindered carbon of the olefin. Besides that, although dialkylated compounds can be formed under forced reaction conditions (large excess of reagents and long reaction times), only monoalkylated product was detected.

This result, although not useful from a synthetic point of view, demonstrated that alkyl boranes were viable reagents in copperpromoted C–N cross-coupling reactions. We decided to use BH_3 ·THF complex for the preparation of the alkylborane reagent. Unlike BBN, when olefins are reacted with BH_3 the outcome is the formation of a trialkylborane (R_3B).¹⁵

When the coupling was carried out with trialkylboranes reactions were quite clean, and full conversion was achieved within 3 h. Furthermore, pure samples were obtained after flash chromatography purification.

Table 1

Screening of alkylboranes for the coupling between 4-t-butylaniline and 4-t-butoxystyrene^a

Entry	Borane	Equiv	Yield ^b (%)
1 ^c	R-BBN	4	0
2	R-BBN	4	35
3	R ₃ B	0.4	47
4	R ₃ B	0.8	73
5	R ₃ B	1.1	86
6 ^c	R ₃ B	1.1	26
7 ^d	R ₃ B	1.1	0

^a Reagents and conditions: a mixture of borane, 1 mmol of 4-*t*-butylaniline (**1a**), 2.5 mmol of $Cu(OAc)_2$ and 3 mmol of pyridine in dioxane (15 mL) was reacted at reflux.

^b Isolated yields.

^c Reaction was run at rt.

^d Alkylborane was not preformed.

We tested the minimal amount of alkylborane that was needed to achieve full conversion. It was found that aniline was consumed to furnish coupling product using as low as 0.4 equiv of trialkylborane (Table 1, entry 3). A twofold raise in yield was achieved by using 1.1 equiv of trialkylborane (Table 1, entry 5), whereas larger excess of boron reagent did not result in any yield improvement. As in other Chan–Lam reactions, the use of some excess of boron reagent is necessary to avoid competitive side reactions, so we decided to use 1.1 equiv of trialkylborane in next experiments.¹⁶

Trialkylboranes proved to be more reactive than analogous alkyl BBN reagents or alkyl boronic acids. While the latter reacted only at high temperature, moderate conversion was observed when trialkyl borane was allowed to react at rt (Table 1, entry 6).

Several control experiments were carried out to confirm that copper was promoting the cross-coupling between trialkylborane and aniline. Coupling product was not formed in the absence of Cu(OAc)₂, although aniline was totally consumed to furnish the corresponding azobenzene. No product was detected when all

Table 2Aniline and styrene electronic properties influence^a



^a Typical procedure: 1 mmol of aniline (1), 1.1 mmol of trialkylborane, 2.5 mmol of $Cu(OAc)_2$ and 3 mmol of pyridine in dioxane (15 mL) were refluxed until aniline was consumed or for a maximum time of 16 h.

^b Isolated yields.

^c A 5% of dialkylated compound was detected by LC-MS.

 $^{\rm d}\,$ A 7% of dialkylated compound was detected by LC-MS.

the reagents, aniline, copper reagent, styrene, BH₃·THF and pyridine were mixed together and refluxed (Table 1, entry 7). As it should be expected, it is necessary to prepare the alkylborane before its addition to the reaction mixture. The order of addition of reagents was important to optimize conversions: slightly higher yields were obtained when aniline and copper were incubated at rt for an induction period (10–15 min) before the addition of the alkylborane.

With the optimal reaction conditions in hand, a broader study was undertaken. As seen in the previous work, electronic properties of substrates could dramatically influence the reaction outcome; thus we decided to test the reaction over three anilines (4-*tert*-butyl-, 4-methoxy- and 4-chloroaniline) against alkylboranes derived from three different styrenes (4-*tert*-butoxy, 4methyl and 3,4-dichloro styrene) ranging both partners from electron rich to electron poor. This exploratory study provided the results displayed in Table 2.

Using the standard protocol, moderate to excellent yields were obtained for all combinations, except in the reaction of 4-chloroaniline with dichlorostyrene, where full conversion was not achieved even after extending reaction time to 16 h. It was noticed that there is a relationship between the electronic properties of anilines and their reaction rate: reactions are faster for electron rich anilines (completed in 1-2 h), and slower for electron poor ones, which require for longer reaction times (up to 6 h). However, the yield is similar for electron rich and neutral anilines, and slightly lower for electron deficient substrates.

In some cases, yield was lower with *p*-anisidine due to the formation of some dialkylated product. It is likely that yields could be increased by adjusting the general reaction conditions to each type of substrate.

To study the scope and limitations of our conditions, we further evaluated the cross-coupling of different trialkylboranes with anilines (Table 3).

The reaction tolerates a variety of functional groups in both aniline and styrene fragments, including ester, ketones, alkylether, thioether, and halides (chlorine and bromine). Chemoselective coupling of bromoderivatives (entries 7, 10, 16, and 19) is particularly interesting for several reasons. First, it reveals that the N coupling process is favorable over possible C Suzuki or Ullmann type reactions. Second, this selectivity allows further functionalization of the product, since the product still bears a bromine atom which is helpful for additional modifications.

Table 3

Scope and limitations of copper-promoted alkylation of anilines with trialkylboranes^a



^a Typical procedure: 1 mmol of aniline (1), 1.1 mmol of trialkylborane, 2.5 mmol of Cu(OAc)₂ and 3 mmol of pyridine in dioxane (15 mL) were allowed to react at reflux for 1–6 h.

^b Isolated yield.

It is noteworthy that the reaction can be applied to substrates containing a thioether moiety (entry 12) that proved problematic in other cross-coupling reactions. Aniline bearing carbonyl groups were also transformed to the desired products, in moderate yields for acetyl moiety (entry 13), and low yields for methyl ester (entry 1), although in the last example it can be caused by the location of the methoxycarbonyl group in ortho position to the amino group.

To summarize, we have developed conditions for a copper-promoted cross-coupling of anilines with trialkylboranes. This new transformation expands the utility of copper-promoted coupling reaction to a new type of reagents, not reported before, and complements the use of boronic acid derivatives in the Chan–Lam coupling methodology. The fact that alkyl borane reagents are easily synthesized in a highly regioselective manner by means of the hydroboration of the corresponding styrenes makes cross-coupling chemistry using these reagents highly attractive. Efforts to expand the utility of this reaction for the formal amination of alkenes are ongoing in our laboratory.

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Supplementary data

Supplementary data (experimental procedures, analytical instrumentation and data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.144.

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- 16. General procedure for the preparation of *N*-alkylboranes **3**: A dioxane solution of trialkylborane was prepared via hydroboration of styrene with BH₃:THF complex (0.4 equiv) in dioxane at rt for 3 h. In a separate vessel, copper(II) acetate (454 mg, 2.5 mmol) was added to a solution of aniline (1.0 mmol) and pyridine (238 mg, 3 mmol) in dioxane (15 mL). The mixture was stirred for 15 min, and the trialkylborane solution in dioxane (1.1 mmol) was added. The reaction mixture was refluxed until aniline was totally consumed (TLC analysis, 3–4 h). The reaction mixture was allowed to reach rt, poured into NH₄Cl (60 mL, saturated aqueous solution), and extracted with CH₂Cl₂ (60 mL). The organic layer was dried over Na₂SO₄ (anhydrous), filtered, and concentrated. The crude residue was purified by flash chromatography on SiO₂ (0–50% EtOAc/hexanes) to afford the *N*-alkylaniline as colorless oil.