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Communication

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Cross-coupling of primary amides to aryl- and heteroaryl-partners using *(DiMeIHept^{Cl})Pd* promoted by trialkylboranes or BCF.

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ABSTRACT: Boron-derived Lewis acids have been shown to effectively promote the coupling of amide nucleophiles to a wide variety of oxidative addition partners using Pd-NHC catalysts. Through a combination of NMR spectroscopy and control studies with and without oxygen and radical scavengers, we propose that boron-imidates form under the basic reaction conditions that aid coordination of nitrogen to Pd(II), which is rate limiting, and directly delivers the intermediate for reductive elimination.

The amide linkage forms the backbone of all peptides/proteins and is prevalent in the structure of numerous biologically important compounds, such as therapeutics.[1] Consequently, extensive effort has gone into the development of efficient and robust methods to form amide bonds.[2] Within this area of synthesis, Pd catalysis has been developed over the last 30 years to establish the bond between the carbonyl carbon and the nitrogen (i.e., carbonylative amine coupling)[3] or between the amide nitrogen and its substituents (i.e., cross-coupling of primary and secondary amides).[4]

Cross-coupling of (hetero)aryl oxidative addition partners with primary and secondary alkyl- and aryl-amines[5] is now well developed with catalysts capable of coupling together electronically and/or sterically challenged partners with mild base at low temperature.[6] Conversely, cross-coupling involving amide nucleophiles is less well developed as it poses new difficulties.[5] When considering nitrogen nucleophiles, the amide nitrogen is one of the least nucleophilic, which can be estimated by considering pKa values. Whereas an alkyl amine has a pKa of ~43 and an aniline ~30, an amide is ~23 (all values in DMSO). So when considering the general catalytic cycle for arylation of amines (Figure 1),[7] nitrogen (**4**) coordination to Pd of intermediate **3** (to create **5**) is dramatically reduced in this same order. Conversely, presuming for now

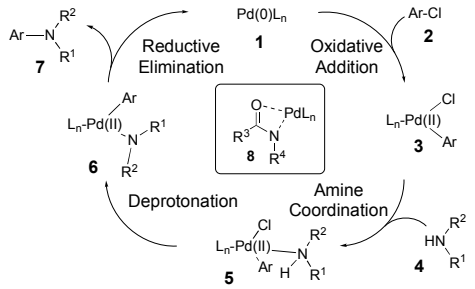


Figure 1. Catalytic cycle for Pd-catalyzed arylation of amines.

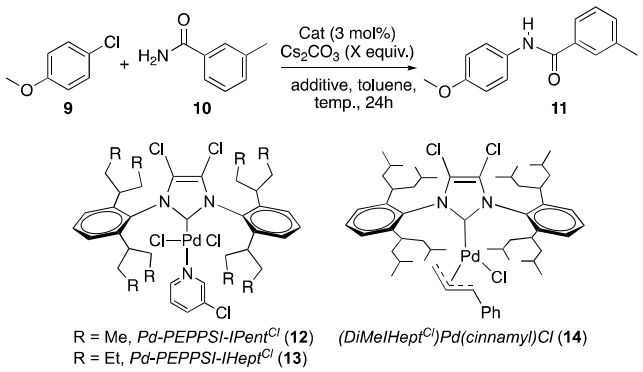
that amine coordination precedes deprotonation, the ease of proton removal to create the metal-amido intermediate (**6**) necessary for reductive elimination will improve in this same direction. However, assuming that the general cross-coupling mechanism in Figure 1 is operative in amide coupling, this ease of deprotonation can only be realized if the amide first coordinates. Herein we report the use of Lewis acids to ease the cross-coupling of amides to a selection of diverse partners using mild base (CO_3^{2-}) at moderate temperature (80-90 °C).

Based on experience we have had with couplings involving the 2-aminopyridine motif,[8] we recognized that a successful catalyst for amide coupling would have to resist κ^2 coordination (**8**, Figure 1) to Pd.[9] To this end, we examined three of our bulkiest N-heterocyclic carbene (NHC) ligands[10] and representative results are summarized in Table 1. As anticipated, the bulkiest catalyst (**14**) had the best initial results (entries 1-3). Inspired by earlier work by Hartwig,[11] we examined the impact of Lewis acids on this reaction. Trialkylboranes (entries 4 and 5) and $B(C_6F_5)$ (BCF, entry 6) all led to a clean conversion to the coupled product, while others (entries 7-9) were less effective. Catalyst **13**, inactive on its own (entry 2), now saw conversion of 55% with Et_3B (entry 10). A similar pattern of results was obtained when 2-chloropyridine was used as the oxidative addition partner (see Table S1 in the SI).

It is interesting to note that the results using Et_3B are in stark contrast to what Hartwig's group observed. Using bidentate phosphine ligands they reported that intermediate **6** required a heteroatom in the oxidative addition partner to complex the Lewis acid in order to lower the barrier for reductive elimination.[11] It should be noted that the intermediates Hartwig studied were not derived from amides, but diarylamines with an assumption, presumably, that the same trends would hold for amide nucleophiles; this appears not to be the case.

While methoxy groups can push electron density into the metal amido intermediate (e.g., **6**), presumably disfavoring

Table 1. Optimization of amide coupling using Pd-NHCs.



Entry	Base equiv.	Additive (20 mol %)	Temp. (°C)	Cat.	Conv.[a] (Yield)[b]
1	3	-	80	**12**	0
2	3	-	80	**13**	0
3	3	-	80	**14**	21
4	1.5	Et_3B	90	**14**	100 (86)
5	1.5	(secBu)$_3$B	90	**14**	100 (92)
6	1.5	$B(C_6F_5)_3$	90	**14**	100 (70)
7	1.5	$(MeO)_3B$	90	**14**	0
8	1.5	$ZnCl_2$	90	**14**	20
9	1.5	Et_2AlCl	90	**14**	26
10	1.5	Et_3B	90	**13**	55

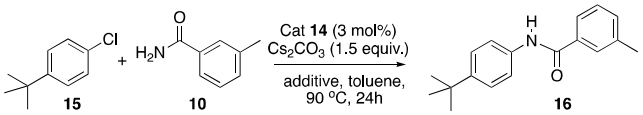
[a]Percent conversion is the conversion of **9** to **11** as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Percent yield is determined after purification on silica gel.

reductive elimination, it is also possible that coordination of the Lewis acid to oxygen could pull electron density out of **6**, actually driving reductive elimination. Replacing the methoxy group on **9** with a *tert*-butyl moiety (i.e., **15**) did not change the reaction outcome (Table 2).

The protocol using (secBu)$_3$B is easy to carry out operationally and shows good generality (Table 3). Base-sensitive nitrile (**29**), ketone (**18**, **30**) and ester (**31**) groups are well tolerated and the procedure works equally well for alkyl[12] or aryl amides. Of note, hinderance on the amide (**26**, **27**, **29**, **30**), oxidative addition partner (**32**-**34**), or both (**35**) is acceptable under the standard conditions. Temperatures up to 150 °C have been required to make such couplings work.[13]

On the surface, it is tempting to suggest that all three boron-derived Lewis acids used in this study promote the

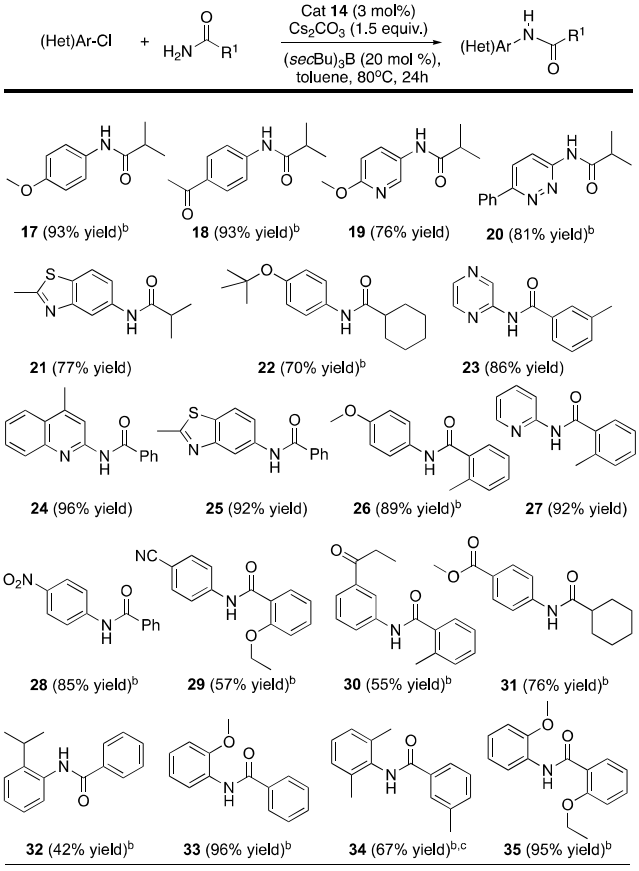
Table 2. Amide coupling to *tert*butyl-4-chlorobenzene (**15**).



Entry	Additive (20 mol%)	Conv.[a] (Yield)[b]
1	-	26
2	(secBu)$_3$B	100 (87)
3	$(C_6F_5)_3B$	100 (82)

[a]Percent conversion is the conversion of **15** to **16** as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Percent yield is determined after purification on silica gel.

Table 3. Scope of amide coupling using **14** and (secBu)$_3$B.[a]

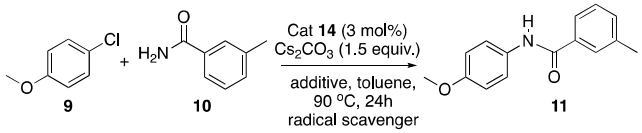


[a]Percent yield is determined after purification on silica gel. [b]Reaction run at 90°C. [c]Reaction run with 1 equiv. (secBu)$_3$B.

coupling by the same mechanism. However, a closer look will reveal three very different species. We have shown in alkyne hydrostannylation that while BCF[14] and Et_3B[15] gave products with identical regio- and stereoselectivity, the mechanisms could not be more unrelated. BCF is by far the most Lewis acidic of the three,[15] while the alkylboranes are prone to autoxidation leading to the formation of radicals under even the most careful attempts to exclude oxygen.[15,17] It is therefore possible that a redox shuttle might be operative with the alkylboranes. It has been shown recently by Buchwald and MacMillan that photoredox is effective for Ni-catalyzed amination.[18] To explore this possibility, we performed the coupling in the presence of radical scavengers (Table 4) and there do appear to be some differences between (secBu)$_3$B and Et_3B. With (secBu)$_3$B, there was a gradual decrease in conversion to product (entries 1-5), whereas Et_3B was less impacted (entries 6-10). That coupling went to 80% when one equivalent of TEMPO was used with Et_3B means that the scavenger is not just otherwise interfering in the (secBu)$_3$B runs. Substituting galvinoxyl for TEMPO produced similar results (entry 11).

Given the coupling is not fully suppressed when a scavenger is present with either alkylborane reagent suggests that a redox pathway is not operating with respect to this coupling. That said, it is known that alkylboranes react rapidly with the trace levels of oxygen that would be present in our reactions,[15] so there must be some impact of oxygen on these amide couplings. To examine this, reactions with both alkylboranes were set up in the glovebox using degassed (freeze-pump-thaw) solvents and glassware and syringes that had been first exten-

Table 4. Effect of radical scavengers TEMPO and galvinoxyl on amide coupling using **14** and Et_3B or $(sec Bu)_3B$.



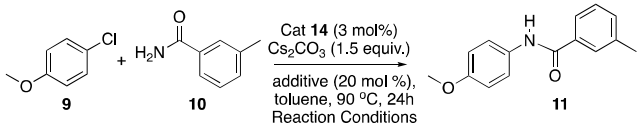
Entry	Additive (20 mol %)	Radical Scavenger (equiv.)	Conv.[a] (Yield)[b]
1	$(sec Bu)_3B$	-	100 (92)
2	$(sec Bu)_3B$	TEMPO (0.1)	94 (88)
2	$(sec Bu)_3B$	TEMPO (0.2)	75 (68)
3	$(sec Bu)_3B$	TEMPO (0.3)	65 (52)
4	$(sec Bu)_3B$	TEMPO (0.4)	55 (52)
5	$(sec Bu)_3B$	TEMPO (1.0)	27 (24)
6	Et_3B	-	100 (86)
7	Et_3B	TEMPO (0.1)	100 (88)
7	Et_3B	TEMPO (0.2)	100 (92)
8	Et_3B	TEMPO (0.3)	100 (92)
9	Et_3B	TEMPO (0.4)	100 (90)
10	Et_3B	TEMPO (1.0)	80 (71%)
11	Et_3B	galvinoxyl (1.0)	100 (97)

[a]Percent conversion is the conversion of **9** to **11** as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Percent yield is determined after purification on silica gel.

sively scrubbed free of oxygen for 7 days (Table 5, entry 4).[14]

The coupling proceeded well with the scrupulous removal of oxygen, supporting the hypothesis that radicals are not involved in this Pd-catalyzed process. Entries 2 and 3 are very instructive. $(sec Bu)_3B$ seems to be completely insensitive to oxygen, regardless of when it is introduced into the coupling

Table 5. Effect of oxygen on amide coupling using **14** and Et_3B or $(sec Bu)_3B$.



Entry/Additive	Reaction Conditions	Conv.
1a) Et_3B	Standard Schlenk technique	a) 100
1b) $(sec Bu)_3B$		b) 100
2a) Et_3B	Premix reagents using standard Schlenk technique, stir for 5 min., expose to air and heat for 24h	a) 100
2b) $(sec Bu)_3B$		b) 100
3a) Et_3B	Dissolve borane in toluene and stir open to air for 10 min., add all other reagents, heat for 24h	a) 0
3b) $(sec Bu)_3B$		b) 100
4a) Et_3B	Set up reaction in glove box with stringent removal of oxygen and degassed solvents, heat for 24h	a) 93
4b) $(sec Bu)_3B$		b) 78
5) Et_3B	Using std. Schlenk technique, Et_3B (1.0 equiv.) and **10** were stirred together for 1h, add base, **9** and **14** and heat for 24h	100

Percent conversion is the conversion of **9** to **11** as determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

set up. Conversely, Et_3B, which burns upon exposure to air, can tolerate oxygen when air is introduced *after* Et_3B first stirs with the other reaction components (entry 2a). When Et_3B was exposed to air *prior* to adding the rest of the reaction mixture (entry 3a), no turnover occurs at all. This would imply that something in the reaction mixture acts to 'protect' the Et_3B from the effects of oxygen. The same trend was observed when these couplings were performed using 2-chloropyridine as the oxidative addition partner (see Table S2 in the SI).

To explore possible interactions between the trialkylboranes and the amide, a series of NMR experiments were performed (see Figure 2 for Et_3B and Figures S1 and S2 in the SI for $(sec Bu)_3B$ and BCF). The ^{11}B resonance for trialkyl boranes (R_3B) typically comes around 85 PPM (panel d), while the borinate (R_2B-OR), boronate ($RB(OR)_2$), and borate species associated with autoxidation come at approximately 55, 35, and 20 PPM, respectively (panel f).[15] When the amide and boranes were mixed with careful exclusion of air, significant differences were seen in both the ^{11}B and ^{13}C NMR spectra. With Et_3B, the peak around 85 PPM in the ^{11}B spectra diminishes, and the peak at 55 PPM intensifies (panel e). At the same time the peak for the amide in the ^{13}C NMR spectrum (168.6 PPM) gives rise to three new signals, the most prominent of which is a broad peak at 169.5 PPM (panel b). After aqueous work up and extraction of this NMR sample, the single amide peak reemerges illustrating that nothing untoward has happened to **10** stemming from Et_3B (panel c). These data suggest that the amide is coordinated to Et_3B leading to the formation of a boron amidonium complex (**36**), which presumably under the basic conditions of the coupling would be deprotonated forming cesium boron amidate salt **37**. Keeping in mind the results where the reaction with Et_3B was initiated

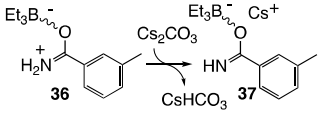
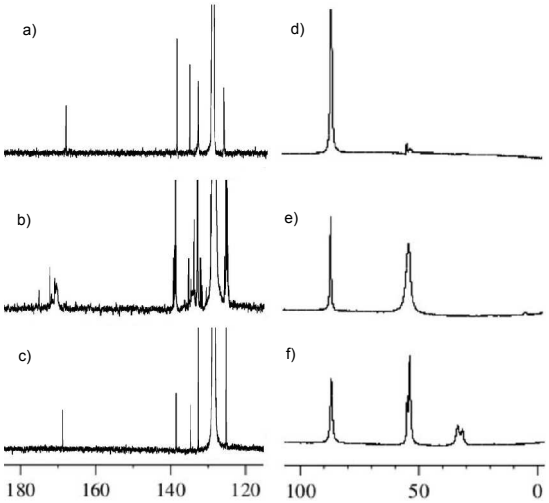


Figure 2. NMR spectra for Et_3B and amide **10**.



Spectra are all run in benzene D_6 at 75 °C. Panel a) ^{13}C NMR spectrum of amide **10**. Panel b) ^{13}C NMR spectrum of amide **10** plus Et_3B (1:1). Panel c) ^{13}C NMR spectrum of sample in b) following aqueous extraction. Panel d) ^{11}B NMR spectrum of Et_3B prepared with rigorous exclusion of air. Panel e) ^{11}B NMR spectrum amide **10** plus Et_3B. Panel f) ^{11}B NMR spectrum of Et_3B sample from panel a) after brief exposure to air.

and then exposed to air (Table 5, entry 2a), the species in panels b and e maybe be a stable boron amidate that resists autox-

idation. Based on negligible changes to both the ^{11}B and ^{13}C NMR spectra, it would appear that complexation with (*sec*-Bu)$_3$B is notably weaker than Et_3B (Fig. S1 in SI).

With other Pd-NHC catalysts we have shown that nitrogen coordination to Pd(II) is rate limiting for anilines,[19] and we believe that the same is the case here with more electron poor amide nucleophiles. Indeed, both oxidative addition and reductive elimination with bulky NHCs is spontaneous at room temperature.[6] This amide coupling progresses very smoothly in the absence of coordinating groups on either coupling partner, further shifting the focus away from reductive elimination[7] as the source of the acceleration of this coupling, at least with NHC ligands. It seems logical that the boron catalysts, under basic reaction conditions, form the boron-amidate complex, thereby heightening the amide's nucleophilicity. With Et_3B this appears to be rapid and complete, whereas (*sec*-Bu)$_3$B, with its additional steric bulk and lowered Lewis acidity, may only form weak complexes. In support of this, preforming the Et_3B-amidate complex (100 mol %) followed by the addition of the remaining reaction components led to full conversion (Table 5, entry 5). No one has reported successful amide coupling using NaO^{t}Bu, presumably because it is not strong enough to deprotonate the amide prior to binding to Pd(II) and the base out competes the amide for the metal. When we tried this coupling with NaO^{t}Bu alone there was no conversion; with 20% Et_3B, coupling proceeded fully to product because the amidate now preferentially coordinates to Pd.

We have also considered that in the case of BCF that something different could be happening, just as it did in our hydrostannylation work.[14] It is known that BCF can abstract anion ligands from Pd(II) to generate cationic Pd,[19] which would more readily coordinate the amide nucleophile. During the submission of this manuscript a very detailed mechanistic study by Becica and Dobereiner appeared asap reporting on the use of other Lewis acids to promote amide coupling, in their case using phosphine ligands.[21] Based on their data they also postulated that the Lewis acid may abstract the halide from the oxidative addition intermediate generating cationic Pd. While we do not believe that this would be likely with the trialkyboranes, this could support such the case with BCF, which is a potent anion abtractor.[15,19]

In summary, we have shown that (*sec*Bu)$_3$B, Et_3B, and BCF are all excellent promoters of Pd-catalyzed amide coupling. (*sec*Bu)$_3$B demonstrates broad-spectrum reactivity and was found to tolerate base-sensitive functional groups and steric congestion, which has proven difficult.[5,13] The reactions are simple to set up and require no careful exclusion of air. We propose that a boron-amidate complex forms under the basic reaction conditions that aids in transmetallation of the amide moiety to Pd(II) and drives coupling under mild conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. General Experimental details, details of synthesis, and characterization data (PDF).

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Author Contributions

The manuscript was written through contributions of all authors and all have given approval to the final version of the manuscript.

Notes

Some of the catalysts in this manuscript are commercially available and the Principal Author receives royalties from their sales.

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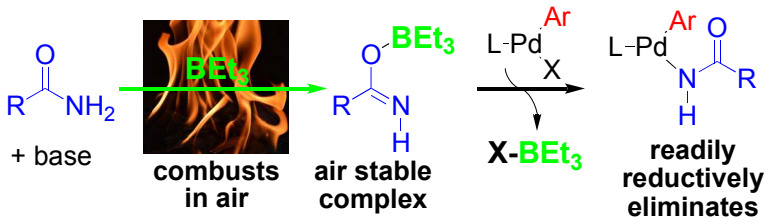

with borane >90% conversion, without borane no conversion