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Sequential Ni-Catalyzed Borylation and Cross-Coupling of Aryl Halides via in Situ Prepared Neopentylglycolborane

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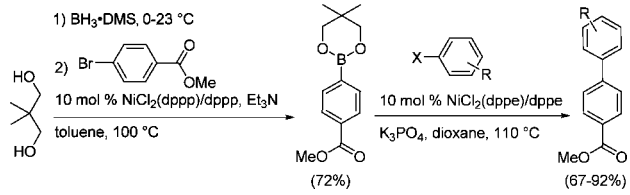
ABSTRACT



A procedure for $NiCl_2$(dppp)-catalyzed pinacolborylation and neopentylglycolborylation that utilizes in situ prepared inexpensive pinacolborane and neopentylglycolborane is reported. The scope of this reaction was demonstrated with a variety of aryl bromides and iodides. The resulting aryl neopentylglycolboronic esters undergo a $NiCl_2$(dppe)-catalyzed cross-coupling with aryl halides, resulting in an extremely efficient and cost-effective method for the synthesis of functional biaryls, dendritic building blocks, and other complex architectures.

Boronic acids are used as intermediates in the synthesis of biaryl and related architectures,[1] as building blocks for supramolecular polymers,[2] as precursors to liquid crystals,[3] as chemical sensors,[4] in total natural product synthesis,[5] as catalysts,[6] and in many other synthetic applications. The broad applicability of boronic acids in organic synthesis has encouraged pursuit of efficient methods for their synthesis. The traditional approach to arylboronic acids involves the formation of aryl Grignard and lithium reagents, followed by electrophillic trapping with trialkyl borates and subsequent hydrolysis. As it employs the least expensive reagents, this method is one of the few procedures that is used for large-scale applications. The sensitivity of this reaction to moisture and the incompatibility of Grignard and organolithium reagents with electrophillic functional groups are obstacles to its implementation. One solution to this problem is the "in situ" quench technique, wherein an alkyllithium reagent is added directly to a solution of aryl halide and trialkyl borate. Although this is an improvement, yields are still inadequate for many substrates including carboxylic esters.[7] An attractive alternative to direct boronic acid synthesis involves transition metal catalyzed installation of a cyclic boronate ester. The most well-known method utilizes Pd(0)[8] to catalyze the addition of tetraalkoxydiboron,[8a,9] pinacolborane (HBPin),[8b,10] or catecholborane[11] to an aryl iodide, bromide, or triflate. A one-pot Ir-catalyzed direct C−H

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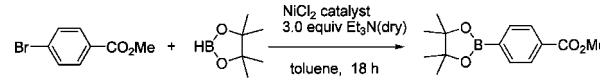
boration was developed to synthesize the relatively inaccessible 3,5-disubstiuted aryl boronic acids and aryltrifluoroborates from 1,3-disubstituted arenes.[12] Pd-catalyzed borations of aryl halides and direct Ir-catalyzed C−H borations are restrictively expensive due to the high cost of reagents and catalyst and the difficult synthesis of alkoxydiborons.[8]

Our laboratory has focused on the development of Ni-catalysts for Suzuki−Miyaura cross-coupling of aryl halides, tosylates, and mesylates.[13] The broad applicability of $NiCl_2$(dppe)[13b] for Suzuki−Miyaura cross-coupling and the need for large quantities of boronic acid derived biaryls[14] triggered the pursuit of a general method for Ni-catalyzed dialkoxyborations. Ni-catalyzed pinacolborylation has been reported once in the literature.[15] Therein, the Pd borylation was modified to use less expensive Ni and HBpin for the bis- and tris-borylation. For the purpose of multiborylation, 10% $NiCl_2$(dppp), 1.5 equiv of HBPin per halide, and 3.0 equiv of Et_3N were suitable.[15] Our investigation into Ni-catalyzed monoborations used these conditions as a starting point. Two significant modifications were incorporated at the onset of this study. To reduce the cost and eliminate a synthetic step, HBpin was prepared in situ by addition of BH_3•DMS to a toluene solution of pinacol and directly used in the boration via cannulation without purification. While the use of unpurified HBpin has been reported for hydroborations, prior distillation is standard for metal-catalyzed coupling. To ensure high conversion while using in situ formed HBpin, the starting equivalents of HBPin were increased from 1.5 to 2.0. Optimizations of the initial conditions were performed on electron-rich 4-bromoanisole and later on electron-deficient methyl 4-bromobenzoate (Table 1). The primary motivation for the two-substrate optimization is that limited protiodeboration was observed in electron-rich substrates, whereas extensive protiodeboration was initially observed in electron-deficient substrates.

In an initial screen with 4-bromoanisole, it was revealed that solvent choice is critical. Pinacolborylation proceeds in toluene but did not proceed in dioxane. This is unusual considering that Ni-catalyzed Suzuki−Miyaura cross-coupling proceeds in both dioxane and toluene.[13] Further, dioxane is an acceptable solvent for Pd-catalyzed Miyaura boration using HBpin.

In Pd-catalyzed coupling of dialkoxyboranes with aryl halides, Et_3N has been shown to be more efficient than Py, DBU, KOAc, or even Hünig's base. Due to the superiority of Et_3N in Pd-catalyzed reactions and the likely similar mechanism for Ni, Et_3N was used without investigating other bases. In order to develop the simplest procedure possible, the purity requirements for each reagent were investigated. It was found that the reaction was highly dependent on the quality of Et_3N. Use of as received Et_3N resulted in 66% conversion after 18 h. Et_3N distilled from CaH_2 raised conversion to 80%.

Table 1. Pinacolborylation of Methyl 4-Bromobenzoate



HBpin (equiv)	catalyst (equiv)	temp (°C)	convn (%)[a]	byproduct (%)[a]
2.0	$NiCl_2$(dppp) (0.1)	100	100	25
2.0	$NiCl_2$(dppp) (0.1)	80	0	0
2.0	$NiCl_2$(dppp) (0.1)	90	50	30
1.5	$NiCl_2$(dppp) (0.1)	100	80	35
2.0	$NiCl_2$(dppp) (0.05)	100	66	20
2.0	$NiCl_2$(dppe) (0.1)	100	90	10
2.0	$NiCl_2(PPh_3)_2$ (0.1)	100	70	15
2.0	$NiCl_2$(dppp)/dppp (0.1)	100	90	10

[a] Conversion and byproduct percentage determined via ^{1}H NMR.

After conditions for 4-bromoanisole were optimized, effort was focused on reduction of apparent protiodeboration in methyl 4-bromobenzoate (Table 1). Methyl 4-bromobenzoate was obtained with 100% conversion after 18 h at 100 °C. Decreased reaction temperature did not reduce the amount of protiodeboration but did have dramatic effects on conversion. Below 80 °C no measurable conversion was observed, and at 90 °C the reaction proceeded to only 50% conversion in 18 h. As protiodeboration did not appear to be temperature dependent, the potential for catalyst or borane loading levels dependence was assessed. Reducing the catalyst from 10.0 mol % or the equiv of HBpin from 2.0 decreased conversion and failed to reduce protiodeboration. Catalyst effects were investigated. As determined previously[15] for bis- and tris-borylations, the most effective catalyst for monoborylations is $NiCl_2$(dppp). This catalyst achieved 100% conversion of 4-carbonyl-methoxyphenyl-1-bromide in 18 h. $NiCl_2$(dppe) resulted in 90% conversion, while the conversion for $NiCl_2(PPh_3)_2$ was 70%. The $NiCl_2$(dppp) system can be modified to improve the product distribution. Introduction of an additional 1.0 equiv of dppp as a coligand reduced byproduct formation from 25% to 7%. It is unclear why dppp is superior to dppe or why increased dppp levels suppress protiodeboration. The role of ligand is under experimental and computational investigation.

Optimized Ni-catalyzed pinacolborylation was tested on an electron-deficient aryl bromide, two electron-rich aryl bromides, and an aryl iodide resulting in 60−80% yield (Table 2). More substrates were tested, but they proved to be difficult to isolate. However, analysis of the crude reaction mixture by NMR generally showed good to excellent conversion for aryl bromides and aryl iodides but very limited conversion for aryl chlorides. The high conversions hinted at a promising reaction, but the frequent difficulties in purification of the pinacol boronate esters, the incompatibility of the purifiable pinacol boronate esters with $NiCl_2$(dppe)

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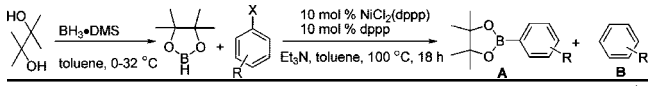
Table 2. Selected Ni-Catalyzed Pinacolborylations



entry	substrate	product A	% yield[a]	ratio A:B [b]
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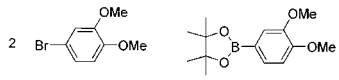
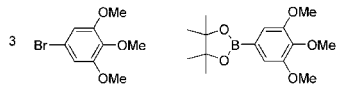
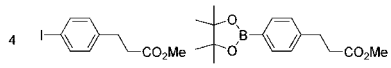
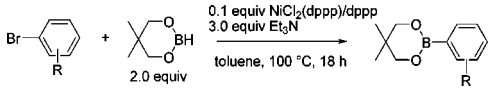
2			63 (96)	10:1
3			79 (100)	5:1
4			60 (100)[c]	5:1

[a] Isolated yield after column chromotography. ^{1}H NMR conversions shown in parenthesis. [b] Ratio based upon ^{1}H NMR. [c] Yield and conversion after 2 h.

cross-coupling, and the generally sluggish hydrolysis to the boronic acid instigated a search for alternatives to HBpin.

While HBpin has been used frequently as a somewhat less expensive and easier to prepare replacement to bis(pinacolato)diboron, only a few other dialkoxyboranes have been explored.[5,13] A screen of inexpensive diols revealed that while many diols are incompatible with in situ generation of dialkoxyborane, neopentylglycol ($0.02/g compared to $0.50/g for pinacol, Aldrich) is well-suited and has the added benefit of enforcing crystallinity. From ^{1}H NMR analysis (see Supporting Information), the reaction is believed to proceed via in situ formed neopentylglycolborane, a compound that to our knowledge has not been reported in the literature, despite frequent use of its diboron analogue.[16]

Table 3. Optimization of Neopentylglycolborylation



R-group	diol quality	catalyst	convn (%)[a]	byproduct (%)[a]
3,5-OMe	as received	$NiCl_2$(dppp)	80	nd
3,5-OMe	recrystallized	$NiCl_2$(dppp)/dppp	100	nd
3,5-OMe	recrystallized	$NiCl_2$(dppp)	39	nd
4-CO_2Me	recrystallized	$NiCl_2$(dppp)	92	17
4-CO_2Me	recrystallized	$NiCl_2$(dppp)/dppp	95+	9.5

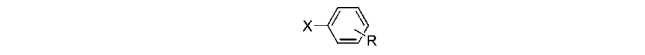
[a] Conversion and byproduct content determined by ^{1}H NMR.

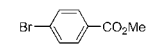
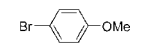
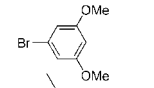
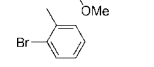
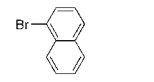
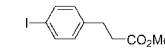
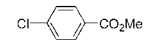
Because of the similarity of the pinacol and neopentylglycolborylations and good initial yields using previously optimized conditions, effort was not made to improve reaction conditions. However, due to the ease of neopentylglycol purification, the effect of the quality of neopentylgycol and the catalyst and coligand effects on conversion were assessed. Use of as-received neopentylglycol resulted in 80% conversion, while its recrystallization from CH_2Cl_2 prior to use resulted in 100% conversion. As decreased HBpin loading level reduces conversion, this demonstrates that a minor drawback of the in situ generation is that we need to make certain that sufficient dialkoxyborane is available.

Whereas $NiCl_2$(dppe) was only slightly less effective than $NiCl_2$(dppp) for pinacolborylations, it only showed 39% conversion for neopentylglycolborylation of an electron-rich bromide. As expected, addition of coligand dppp did not reduce the overall conversion of an electron-rich bromide. However, as in the case of pinacolborylations, addition of dppp during neopentylglycolborylation of an electron-poor substrate resulted in decreased protiodeboration (17% to 9.5%).

Using these optimized reaction conditions, neopentylglycolborylation was tested on a number of substrates (Table 4). This reaction works well with electron-deficient and

Table 4. Scope of Ni-Catalyzed Neopentylglycolborylation



entry	substrate	product A	% yield of A[a]	Ratio A:B[b]
1			72[c] (100)	9:1
2			78 (95)	1:0
3			67 (95)	6:1
4			nd (100)	nd
5			79 (100)	nd
6			72 (100)[d]	6.7:1
7			nd (16)	nd

[a] Yield after column chromotography. [b] Yield and product ratio based on ^{1}H NMR. [c] Yield after MeOH recrystalization. [d] Conversion and yield after 2 h.

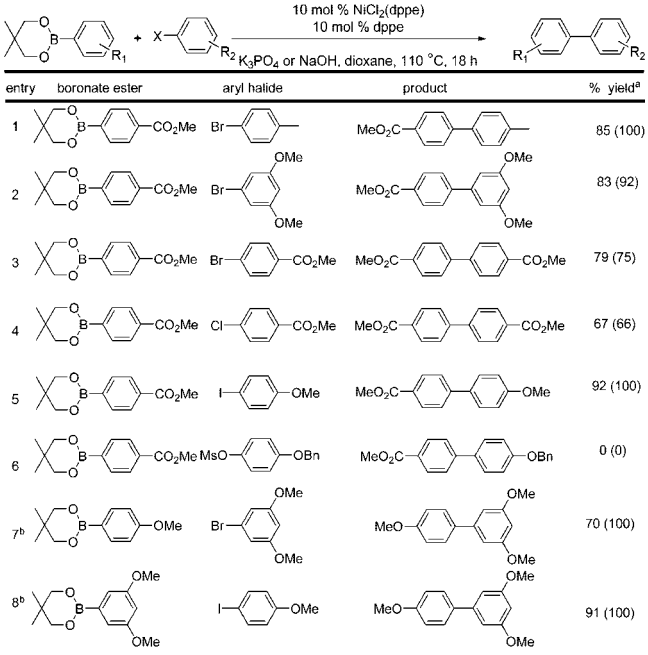
electron-rich aryl bromides as well as aryl iodides (67−79% yield). The ortho-substituted bromide was not recovered by column chromatography, despite complete consumption of starting material. The aryl chloride proceeded to only 16% conversion under these reaction conditions.

While the aryl pinacolborates produced via $NiCl_2$(dppp) catalysis were not useful in $NiCl_2$(dppe) cross-coupling,

(16) For example: (a) Kennedy, J. W. J.; Hall, D. G. *J. Organomet. Chem.* **2003**, *680*, 263. (b) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761.

$Ni(COD)_2/PPh_3$ or PCy_3 catalyzed cross-coupling of 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane with vinyl phosphates has been reported once in the literature.[17] Of the aryl neopentylglycolboronate esters that we derived via $NiCl_2$(dppp)/dppp coupling, most did not participate in $NiCl_2$(dppe) Suzuki−Miyaura coupling using previously established conditions.[13b] However, methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (Table 4, entry 1) proceeded with very good to excellent yield in direct cross-coupling with aryl bromides and iodides and good yield with aryl chlorides (Table 5). Lack of reactivity of electron-rich aryl neopentylglycolboronic esters was overcome by changing the base from K_3PO_4 to NaOH.

Table 5. Cross-Coupling of Aryl Neopentylglycolboronates



[a] Yield after chromatography, approximate ^{1}H NMR consumption of aryl halide in parenthesis. [b] NaOH required as base, all other reactions utilize K_3PO_4.

As exemplified by the synthesis of methyl 3′,5′-dimethoxybiphenyl-4-carboxylate (Table 5, entry 2), this technique has potential to greatly simplify the synthesis of biaryl dendritic building blocks. In this particular case it reduced the synthetic path from five to two steps.[14,18] Beyond the improvement of the synthesis of biaryls and related dendritic architectures, this technique provides rapid access to analogues of expensive but broadly useful boronic acids. For example, 4-methoxycarbonylphenyl-1-boronic acid is used for the preparation of enatiomeric α-aminoketones,[19] but it is very expensive ($31−54/g, Aldrich). Methods described in this paper achieve the pinacol- and neopentylboronate ester analogues in 80% and 72% yield, respectively, and at siginficantly lower cost. Pinacol boronate esters are compatible with Pd-catalyzed cross-coupling,[20] and the neopentylboronate ester is compatible with Ni-catalyzed cross-coupling and should proceed with Pd.[21] Also, the neopentylglycolboronate ester can be converted in high yield to the potassium trifluoroborate via KHF_2 (see Supporting Information) and allows entrance into cross-coupling with aryl halides.[22] All three species can be converted under appropriate hydrolytic, oxidative, or fluorophilic conditions to the boronic acid.[23]

In conclusion, $NiCl_2$(dppp)-catalyzed neopentylglycolborylation has been developed as a facile and inexpensive route to boronic acid substitutes, which can be immediately applied in $NiCl_2$(dppe)-catalyzed cross-coupling with aryl halides or converted to other useful intermediates.

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Supporting Information Available: Experimental procedures and spectral data for isolated prodcts. This material is available free of charge via the Internet at http://pubs.acs.org.

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