Miyaura Borylation and One-Pot Two-Step Homocoupling of Aryl Chlorides and Bromides under Solvent-Free Conditions

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Abstract: Solvent-free protocols for Miyaura borylation and the one-pot, two-step homocoupling of aryl halides are reported for the first time. Bis(dibenzylideneacetone)palladium(0) $[Pd(dba)_2]$ is an optimal source of palladium for Miyaura borylation, while for one-pot two-step homocoupling palladium(II) acetate $[Pd(OAc)_2]$ gives highest yields. Aryl bromides are coupled most efficiently using the DPEphos ligand. Chlorides are coupled using XPhos. The developed protocols are robust, versatile and easily reproducible on a large scale.

Keywords: cross-coupling reactions; homocoupling; Miyaura borylation; palladium; solvent-free reactions

Arylboronic esters are widely used in organic synthesis in C-C, C-O, C-N, and C-S bond forming reactions.^[1] The most common method for the synthesis of arylboronic esters is the reaction of trialkyl borates with aryllithium or Grignard reagents. This method has obvious limitations due to the non-tolerance of a variety of functional groups towards lithium or magcompounds.^[2] organometallic nesium Recently, a series of catalytic methods for the preparation of arylboronates under mild conditions were developed.^[3] These include, in particular, palladium-catalyzed methods for the synthesis of pinacol and catechol borates from aryl iodides, bromides, chlorides and triflates (Scheme 1).^[4]

Arylboronate esters are widely used in the synthesis of biaryls *via* the Suzuki–Miyaura cross-coupling reaction.^[5] However, boronate esters are typically prepared and isolated prior to the cross-coupling step. It is of high interest to obtain boronate esters with little



Scheme 1. Miyaura reaction.

or no organic by-products for further use without isolation and purification. Utilization of a one-pot, twostep reaction protocol combining borylation and Suzuki–Miyaura steps to synthesize symmetrical biaryl compounds was documented only a few times (Scheme 2).

The first example of a one-pot, two-step approach for the synthesis of biaryls was reported in 2004.^[6] Aryl bromides, iodides, and triflates (14 examples) were homocoupled in DMSO using 4 mol% of a palladium catalyst in moderate to excellent yields (40-98%). In 2007, the triphenylphosphine-cyclopalladated ferrocenylimine complex was reported to catalyze the homocoupling of aryl bromides using 1 mol% of a palladium source.^[7] However, neither of these catalytic systems was able to promote the homocoupling of aryl chlorides. In 2007 the first example of borylation/coupling protocol for aryl chlorides was reported. However, the scope was limited to only four examples.^[8] Eventually, in 2009 the homocoupling of aryl chlorides using a cyclopalladated ferrocenylimine complex was reported to give moderate to high yields (14 examples, 31–98%).^[9]



Scheme 2. One-pot, two-step synthesis of biaryls.

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However, no examples of Miyaura borylation, or one-pot, two-step homocoupling of aryl halides under solvent-free conditions were reported to date. Obviously, it is of high importance to develop not only efficient, selective, and high yielding but also "green", environmentally friendly and safe protocols for organic reactions.^[10] The measure of "greenness" of a process is the E factor, introduced by Sheldon.^[11] It is defined as the ratio of weight of waste to weight of product. The E factor for most fine chemicals exceeds 100. The largest contributors to the magnitude of the E factor are organic solvents, many of which are ecologically harmful and require expensive regeneration. Thus, elimination of solvents from organic synthesis is of high importance. In the last two decades several approaches to eliminate solvents from organic synthesis were developed.^[12]

In continuation of our studies of palladium-catalyzed reactions under solvent-free conditions we tackled this problem.^[13] In this work we performed a systematic study of the Miyaura borylation and a onepot, two-step homocoupling of aryl halides using bis(pinacolato)diboron under solvent-free conditions. The use of an inert atmosphere, or highly pure reagents was avoided. We also focused on utilization of conventional and simple heating as activation tool to avoid the use of a microwave, ultrasonic irradiation, or ball mill equipment.

Initial screening of catalytic systems for the Miyaura borylation of phenyl bromide and B₂Pin₂ were performed using 1 mol% of palladium source [Pd], 1.2 equiv. of B₂Pin₂, 1.2 equiv. of anhydrous NaOAc at 110°C. Various palladium catalysts were tested: the well-defined expanded ring NHC complex (THP-Dipp)Pd(cinn)Cl recently developed in our group,^[14] catalytic systems the $Pd(dba)_2 - P(t Bu_{3} \cdot HBF_{4}$,^[15] Pd(OAc)₂/SPhos, Pd(dba)₂-XPhos, $Pd(dba)_2$ -t-BuXPhos, $Pd(dba)_2$ -RuPhos, Pd(dba)₂-DavePhos, Pd(dba)2-t-BuDavePhos,^[16] as well as the conventional palladium sources $Pd(PPh_3)_2Cl_2$, $Pd(dba)_2$ -dppf and $Pd(dba)_2$ -DPEPhos (Figure 1). Results of the catalytic tests are summarized in Table 1. We tested lower temperatures for the reaction for 2-bromoanisole (Table 2, Supporting Information). A decrease of temperature even to 90°C leads to a decrease in yield to only 3%. A decrease of the amount of a base to 1.0 equiv. led to unreproducible results.

The sterically demanding NHC complex (THP-Dipp)Pd(cinn)Cl exhibited no catalytic activity in the solvent-free borylation reaction (Table 1, entry 11). Monodentate phosphine ligands gave low to good yields (Table 1, entries 1–6). *t*-Butyl-substituted versions of phosphines exhibited low activity (Table 1, entries 4 and 9). The highest, nearly quantitative, yield was obtained with a bidentate ligand, DPEPhos (Table 1, entry 10).



Figure 1. Structure of ligands.

 Table 1. Screening of catalytic systems for Miyaura borylation of aryl bromides.^[a]

Br	+ B₂Pin₂ [Pd], L NaOAc, neat 110 °C	
Entry	Catalyst	Isolated yield [%]
1	Pd(PPh ₃) ₂ Cl ₂	74
2	$Pd(dba)_2$ - $P(t-Bu)_3$ · HBF_4	62
3	Pd(dba) ₂ -XPhos	82
4	$Pd(dba)_2$ -t-BuXPhos	21
5	Pd(dba) ₂ -SPhos	72
6	$Pd(dba)_2$ -RuPhos	73
7	Pd(dba) ₂ -dppf	75
8	Pd(dba) ₂ -DavePhos	86
9	Pd(dba) ₂ -t-BuDavePhos	11
10	Pd(dba) ₂ -DPEPhos	99
11	(THP-Dipp)Pd(cinn)Cl	0

^[a] Reaction conditions: bromobenzene (1.0 mmol), bis(pinacolato)diboron (1.05 mmol), NaOAc (1.2 mmol), neat, Pd source (0.01 mmol), phosphine (0.02 mmol) or Pd complex (0.01 mmol), 110°C, 12 h.

Optimization of the catalytic system for coupling of phenyl chloride with B_2Pin_2 revealed the following conditions: 1 mol% of Pd(dba)₂, 2 mol% of a ligand, 1.2 equiv. of B_2Pin_2 , 1.2 equiv. of anhydrous NaOAc at 110 °C.^[8a] Pd(dba)₂-DPEPhos exhibited no catalytic activity in the borylation of phenyl chloride (Table 2, entry 1). We tested a number of Buchwald's biaryl-

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Table 2. Screening of catalytic systems for Miyaura borylation of aryl chlorides.



Pd(dba)₂-SPhos

Table 3. Miyaura borylation of aryl bromides.^[a]

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phosphines.^[16] Utilization of SPhos and DavePhos led to low yields (Table 2, entries 3 and 4), while XPhos gave virtually quantitative yield (Table 2, entry 2).

The activity of the $Pd(dba)_2$ -DPEPhos catalytic system was tested on a variety of aryl bromides (Table 3).

The *meta-* and *para-*substituted aryl bromides gave nearly quantitative yields independently of the electronic properties of the substituents (Table 3, entries 1, 2, 5–7, 9, 10, 12, 13, 15 and 16). The *ortho-*substituted aryl bromides lead to somewhat lower yields (Table 3, entries 3, 4, 8 and 11). Non-quantitative yields in the cases of 4-fluorophenyl and 2,4-difluoro-



1 % Pd(dba)_{2,} 2 % DPEphos

NaOAc, 110 °C

^[a] *Reaction conditions:* aryl bromide (1.0 mmol), bis(pinacolato)diboron (1.05 mmol), NaOAc (1.2 mmol), neat, Pd(dba)₂ (0.01 mmol) DPEPhos (0.02 mmol), 110 °C, 12 h.

^[b] The NMR yield was calculated using ferrocene as an internal standard and is presented in brackets.

phenyl bromides can be attributed to losses during the isolation of the products due to their relatively high volatility (Table 3, entries 10 and 11). Moderate yields were obtained in the coupling of thienyl bromides (Table 3, entries 17 and 18). In addition, attempts to borylate nitrogen-containing heteroaryl bromides (3-bromoquinoline, 2- and 3-bromopyridines) failed under the described reaction conditions. For 3bromopyridine, starting materials were isolated, for 3bromoquinoline and 2-bromopyridine mixtures of unidentified products were obtained.

We found that the Pd(dba)₂-XPhos system is highly active in the Miyaura borylation of aryl chlorides (Table 4).The *ortho-*, *meta-*, and *para-*substitued substrates bearing acceptor as well as donor substituents are coupled in yields exceeding 95%.

Furthermore, we studied a one-pot, two-step Miyaura borylation/Suzuki coupling reaction sequence. The reaction conditions were optimized using a model homocoupling of 4-chlorotoluene (Table 5).

It is known that borylation and cross-coupling reactions are sensitive to the nature of the base used.^[9] Firstly, we optimized the base. In analogy to our previous results for Suzuki–Miyaura reactions under solvent-free conditions,^[13a] the use of mild bases leads to moderate yields (Table 5, entries 1 and 2), while strong bases give virtually quantitative yields (Table 5, entries 3 and 4). Sodium bases are less effective than potassium counterparts (Table 5, entries 3–6). Reduction of [Pd] loading from 1 mol% to 0.5 and 0.25 mol% led to significant loss in yields (Table 5, entries 7 and 8). It was found that substitution of

Table 5. Optimization of the reaction conditions for the Miyaura borylation/Suzuki coupling of 4-chlorotoluene.^[a]

Entry	Base	[Pd] [mol%]	Isolated yield [%]
1	K ₂ CO ₃	1	31
2	K ₃ PO ₄	1	13
3	KOH	1	94
4	t-BuOK	1	97
5	t-BuONa	1	85
6	NaOH	1	83
7	t-BuOK	0.5	88
8	t-BuOK	0.25	46
9	t-BuOK	1 ^[b]	99

[a] Reaction conditions: 4-chlorotoluene (2.05 mmol), bis(pi-nacolato)diboron (1 mmol), base (2.2 mmol), neat, Pd(dba)₂, XPhos (2 equiv. with respect to Pd), 110°C, 12 h.

^[b] Pd(OAc)₂ was used as the palladium source.

 $Pd(dba)_2$ with $Pd(OAc)_2$ as a palladium source leads to an increase of the yield (Table 5, entry 9). We tested lower temperatures for the reaction for 2-bromoanisole (Table 3, Supporting Information). The decrease of temperature leads to a significant decrease of the yield from 98% at 110 °C down to 1% at 50 °C. The decrease of the amount of a base to 2.0 equiv. led to unreproducible results.

For the homocoupling of aryl chlorides and bromides the optimized conditions were found to be: 1 mol% of Pd(OAc)₂, 2 mol% of XPhos, 2.2 equiv. of*t*-BuOK at 110°C (Table 6). In all cases, the yields of the products were good to excellent (81–99%). Inter-

Table 4. Miyaura borylation of aryl chlorides.^[a]



 [[]a] Reaction conditions: aryl chloride (1.0 mmol), bis(pinacolato)diboron (1.05 mmol), NaOAc (1.2 mmol), neat, Pd(dba)₂ (0.01 mmol), XPhos (0.02 mmol), 110 °C, 12 h.

 Table 6. One-pot two-step homocoupling of aryl chlorides and bromides.^[a]

 1 % Pd(OA)

Ar-Hal +
$$\begin{pmatrix} 0 \\ B-B \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 equiv. \\ \end{pmatrix} \begin{pmatrix} 1 & h^{1/6} Pd(OAC)_{2}, \\ 2 & k \\ Ligand \\ t-BuOK, 110 & C \\ 12 & h \\ \end{pmatrix} Ar-Ar$$



^[a] *Reaction conditions:* aryl halide (3.1 mmol), bis(pinacolato)diboron (1.5 mmol), base (3.3 mmol), neat, Pd(OAc)₂ (0.03 mmol), ligand (0.03 mmol of DPEPhos, 0.06 mmol of XPhos), 110 °C, 12 h.

- ^[b] Ligand = XPhos.
- [c] Ligand = DPEphos.

estingly, the obtained yields for phenyl bromide and 4-bromotoluene were rather low, 78% and 88%, respectively (Table 6, entries 6 and 7). Substitution of XPhos with DPEphos led to virtually quantitative yields of the homocoupling products. A variety of aryl bromides were efficiently coupled using the Pd(OAc)₂/DPEphos (1:2) system. The corresponding symmetrical biaryls were obtained in good to excellent yields (89–99%). It should be noted that the presence of *ortho*-substituents in the aryl halide has a significant impact on the yield of the homocoupling

product. In the case of di-*ortho*-substituted mesityl bromide, formation of the homocoupling product was not observed (Table 6, entry 10).

We performed the Miyaura borylation and one-pot, two-step Miyaura borylation/Suzuki coupling on a 50mmol scale. 4,4,5,5-Tetramethyl-2-*p*-tolyl-1,3,2-dioxaborolane and 4,4'-dimethyl-1,1'-biphenyl were obtained in high yields of 96% and 95%, respectively (Supporting information). Pure products were isolated from the reaction mixtures without the use of solvents by distillation under high vacuum. No preliminary isolation of the crude products was performed. The developed protocols meet the demands of "green" chemistry. Calculated E-factors are low: 1.91 and 3.88, respectively. for Miyaura borylation and one-pot, two-step homocoupling.

In conclusion, we have shown for the first time that aryl bromides and chlorides can be coupled with bis(pinacolato)diboron giving good to excellent yields of pinacol arylboronates under solvent-free conditions. Aryl halides can be homocoupled in a one-pot, two-step process under similar conditions giving symmetrical biaryls in high yields.

The optimal source of palladium for a solvent-free Miyaura borylation is $Pd(dba)_2$, while $Pd(OAc)_2$ performs better in the one-pot, two-step homocoupling. Reactions of aryl bromides are catalyzed more efficiently using DPEphos ligands. For aryl chlorides, XPhos is the ligand of choice.

The scope of coupling substrates is wide: acceptor, donor as well as sterically demanding aryl halides can be used. The developed protocols have a number of advantages: (i) no solvent is used, (ii) reactions are performed under aerobic conditions, (iii) low catalyst loadings, (iv) available bases, (v) activation of reactions by conventional heating (no milling, sonication, etc. needed), (vi) reaction protocols are easily scalable, and (vii) meet demands of "green" chemistry, exhibiting low E factors. Thus, we have developed versatile, robust, and highly active catalytic systems for Miyaura borylation and one-pot, two-step homocoupling of aryl halides under solvent-free conditions. We believe that our findings will lead to broader use of solvent-free protocols for coupling reactions in laboratory practice and in the development of "green" industrial technologies.

Experimental Section

General Procedure for Solvent-Free Miyaura Borylation

A screwcap vial equipped with magnetic stir bar was charged with 1 mmol of aryl halide, 1.2 mmol of B₂Pin₂, 0.01 mmol of palladium source, ligand and 2 mmol of anhydrous NaOAc. The vial was transferred to a preheated oil bath (110 °C). After 24 h, the reaction mixture was cooled, dissolved in CH₂Cl₂-H₂O mixture (1:1), the organic phase separated, the solvent evaporated under vacuum and the product isolated by flash chromatography on silica gel by elution with CH₂Cl₂.

General Procedure for Solvent-Free Homocoupling Reactions

A screwcap vial equipped with magnetic stir bar was charged with 3.1 mmol of aryl halide, 1.5 mmol of B_2Pin_2 , 0.03 mmol of palladium acetate, 0.06 mmol of ligand and 3.3 mmol of anhydrous potassium *tert*-butoxide. The vial was

transferred to a preheated oil bath (110 °C). After 12 h, reaction mixture was cooled, dissolved in $CH_2Cl_2-H_2O$ mixture (1:1), the organic phase separated, the solvent evaporated under vacuum and the product isolated by flash chromatography on silica gel by elution with hexane:ethyl acetate = 7:1.

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