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Improvement in the Palladium-Catalyzed Miyaura Borylation Reaction by Optimization of the Base: Scope and Mechanistic Study

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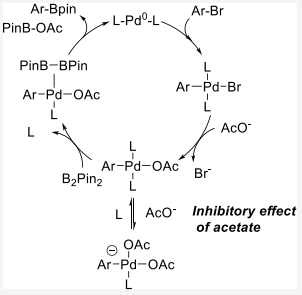
ABSTRACT: Aryl boronic acids and esters are important building blocks in API synthesis. The palladium-catalyzed Suzuki-Miyaura borylation is the most common method for their preparation. This paper describes an improvement of the current reaction conditions. By using lipophilic bases such as potassium 2-ethyl hexanoate, the borylation reaction could be achieved at 35 °C in less than 2 h with very low palladium loading (0.5 mol %). A preliminary mechanistic study shows a hitherto unrecognized inhibitory effect by the carboxylate anion on the catalytic cycle, whereas 2-ethyl hexanoate minimizes this inhibitory effect. This improved methodology enables borylation of a wide range of substrates under mild conditions.



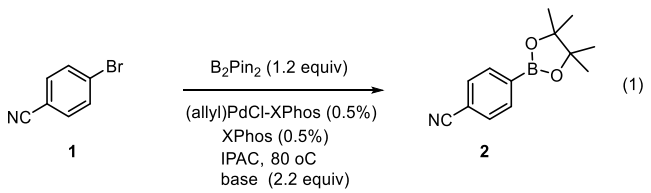
INTRODUCTION

Arylboronic acids and the corresponding esters are valuable reagents in organic synthesis and are often used in the synthesis of drug candidates.[1] They can be conveniently prepared by reaction of organomagnesium or -lithium compounds with trialkylborates; in addition, the transition-metal-catalyzed borylation of aryl halides using bis-(pinacolato)diborane, first described by Miyaura,[2] represents an invaluable tool in the synthesis of heavily functionalized molecules due to its much better functional group tolerance and its ability to be directly combined in a one-pot procedure with Suzuki coupling.[3] The palladium-catalyzed borylation using bis(pinacolato)diborane remains one of the most popular versions of the borylation reaction of unsaturated halides, in spite of the competition from other borylating agents[4] and other transition metals.[5]

In the Miyaura borylation reaction, a palladium-based catalyst or precatalyst (originally Pd(dppf)Cl_2) is treated with an aryl halide and the diboron reagent (typically 1.1−1.2 equiv) in the presence of a carboxylate salt, usually potassium acetate (generally 3 equiv). The resulting solution or suspension is generally heated to 80−100 °C in any of a very broad range of solvents. Such conditions may give rise to side reactions: indeed, we have sometimes experienced base- and heat-promoted epimerization of stereogenic centers during borylation reactions and have decided to embark on a systematic optimization aimed at running these couplings under milder conditions.

RESULTS AND DISCUSSION

Reaction Optimization. The base was selected as a key parameter as its role in these reactions has not been comprehensively explored and is not mechanistically understood. Although base-free versions of the borylation have been reported,[6] a carboxylate salt seems crucial for the reactivity of this system. A systematic base screen was performed using 4-bromobenzonitrile as model substrate (eq 1). Several organic



and inorganic bases were tested in our standard reaction conditions (Table 1 and Supporting Information). Isopropyl acetate (IPAc) is a process-friendly solvent and was selected based on our previous experience. (Xphos)(allyl)palladium chloride (formed in situ) was initially selected as a precatalyst based on the literature and previous screening.[7,8]

Under the above conditions, KOAc brought the reaction to full conversion and high yield in only 30 min at 80 °C (Table 1, entry 1). The final yield was calculated in all cases against an external or an internal standard. Amine bases such as 1,8-diazabicycloundec-7-ene (DBU) and Et_3N (entries 2−3) were inactive. Inorganic bases such as potassium phosphate and

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Table 1. Initial Base Screen

entry	base	temperature (°C)	time (h)	conversion (%)	yield (%)
1	KOAc	80	0.5	100	90
2	DBU	80	21	3	0
3	TEA	80	21	1	0
4	K_3PO_4	80	4.5	65	50
5	Cs_2CO_3	80	2	82	46
6	CF_3CO_2K	80	4.5	10	9
7	CCl_3CO_2K	80	4.5	2	2
8	$CHCl_2CO_2K$	80	4.5	15	15
9	CH_2ClCO_2K	80	21	65	62
10	$MeOCH_2CO_2K$	80	4.5	75	74
11	KSAc	80	21	1	0

cesium carbonate (entries 4−5) brought about some conversion, but impurities such as homocoupling and dehalogenation products were formed in significant amounts (Table S1). Clearly, carboxylate salts are preferred bases. The basicity of these carboxylates may play a key role: less basic salts led to very low conversion (entries 6−10). Thiocarboxylate is not effective at all for this borylation reaction even with prolonged reaction time (entry 11).

Based on this screening, acetate was fixed and a variety of counterions were tested (Table 2). A surprisingly strong effect

Table 2. Counterion Effect

entry	base	temperature (°C)	time (h)	conversion (%)	yield (%)
1	KOAc	80	0.5	100	90
2	NaOAc	80	21	63	53
3	AgOAc	80	0.5[a]	10	10
4	NH_4OAc	80	21	4	0
5	NMe_4OAc	80	0.5	100	90
6	NBu_4OAc	80	2	72	62
7	KOAc	55	8	99	96
8	NMe_4OAc	55	1	100	89
9	CsOAc	55	1	100	96
10	NMe_4OAc	35	45	91	50
11	CsOAc	35	20	59	34

[a]No further conversion was observed with more prolonged reaction time.

of the counterion was observed in this transformation. Compared to potassium acetate, sodium acetate (entry 2) gave much lower conversion, only 63% at 80 °C after 21 h. Both silver and ammonium acetate were ineffective (entries 3−4). Among two tetraalkylammonium salts tested, only tetramethylammonium gave better result than KOAc. All the best bases were tested at lower temperatures (55 and 35 °C) to test the limit of the system. At 55 °C, only CsOAc and Me_4NOAc provided full conversion in short reaction times (entry 8−9), and KOAc needed 8 h to reach full conversion (entry 7). 35 °C seemed to be the limit as the reaction was much slower, and more side products started to be observed (entry 10−11).

From this preliminary screen, one can glean some correlation of reactivity with solubility, although some outliers are noted. In order to better understand this correlation, more lipophilic carboxylates were investigated (Table 3). In most cases, they worked well at 80 °C with reaction times usually under 1 h. Lower reaction temperature (55 or 35 °C) were

Table 3. Screening Carboxylates with Increased Lipophilicity

entry	base	temperature (°C)	time (h)	conversion (%)	yield (%)
1	KOAc	55	8	99	96
2	K propionate	55	3.5	100	96
3	K propionate	35	23	99	92
4	K *n*-butyrate	35	20	82	79
5	K *n*-hexanoate	35	48	83	68
6	K *n*-octanoate	35	48	99	87
7	K isobutyrate	35	23	88	82
8	KOPiv	35	4	97	97
9	K 2-ethyl hexanoate	35	1.5	100	95

then tested to have a better comparison among different carboxylates. Switching from acetate to propionate improves significantly the reaction kinetics, 3.5 h instead of 8 h at 55 °C (entries 1−2). Moreover, propionate allowed lowering the reaction temperature to 35 °C, although much longer reaction time was observed (entry 3). Linearly increasing the carbon chain length of the carboxylate (propionate, butyrate, hexanoate, and octanoate) did not improve much further (entries 3−6). Significant improvement was noticed when steric hindrance was introduced (entries 7−9). Potassium pivalate showed a drastic reduction of reaction time, achieving full conversion at 35 °C in only 4 h. However, potassium 2-ethyl hexanoate (2-KEH) outperformed all other bases. In this case, the reaction reached full conversion after just 1.5 h at 35 °C (entry 9). Its sodium counterpart salt, however, was less effective, requiring higher temperatures and longer stirring times for completion (Table S2).

A mixed picture emerges from these two screens: the need for lipophilic carboxylates in conjunction with cations of intermediate hardness (Cs ~ NMe_4 >K > Na) seems evident.

A solvent screen was carried out to assess whether base solubility is the key parameter. Most common solvents give high yield and conversion with different reaction times by using highly active 2-KEH (Table 4). IPAc is still the best

Table 4. Solvent Screen with 2-KEH

entry	base	solvent	temperature (°C)	time (h)	conversion (%)	yield (%)
1	2-KEH	DMF	35	19	100	91
2	2-KEH	toluene	35	3	100	99
3	2-KEH	MeTHF	35	2.5	100	93
4	2-KEH	IPAC	35	1.5	100	95
5	2-KEH	methanol	55	0.5	100	96
6	2-KEH	heptane	80	1	90	87

solvent in our hands as the reaction is finished in 1.5 h (entry 4). Surprisingly, in dimethylformamide (DMF), where the reaction mixture is homogeneous, the reaction takes much longer time (19 h) to achieve full conversion (entry 1). Methanol and heptane are also compatible solvents, but higher temperature is needed for the reaction to proceed (entries 5−6). IPAc is also the optimal solvent when potassium acetate and cesium acetate were used as bases (Table S3). In parallel, we have also measured solubility of these bases (and corresponding KBr) in these solvents (Table S4), and we do not find any correlation between reaction kinetics with these

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solubilities. This result confirms that solubility of bases is not the only key parameter for the reaction kinetics.

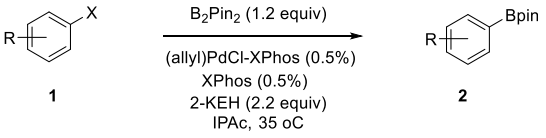
Several precatalysts were then tested for the reaction together with 2-KEH as a base (Table 5). The most active precatalyst was (Xphos)(allyl)PdCl, (entry 2), as described by Colacot et al.[8] Stock solutions of this catalyst can be prepared and used within hours without loss of activity. Alternatively, this precatalyst can be easily prepared and isolated as air-stable powder, which can be stored for a long time without special care. The corresponding Buchwald palladacycles[9] also gave satisfactory results but at lower rates (entries 1). $Pd(dba)_2$ and $Pd_2(dba)_3$ were comparatively slower and showed degradation over time (entries 3–4). Palladium acetate works well at 55 °C, but its activation is slow at 35 °C. We assume activation is provided by a small amount of B_2Pin_2.[10]

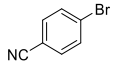
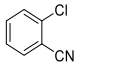
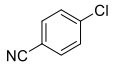
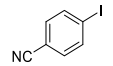
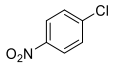
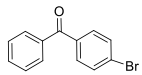
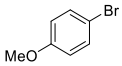
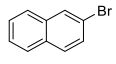
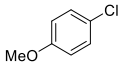
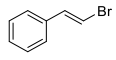
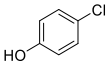
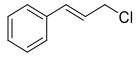
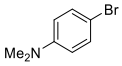
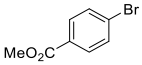
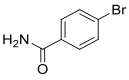
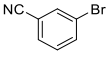
Table 5. Precatalyst Optimization

entry	pre-catalyst	ligand (equiv)	T (°C)	time (h)	conversion (%)	yield (%)
1	Xphos-Pd-G3	XPhos (1)	35	21	100	82
2	Xphos (allyl) PdCl	XPhos (1)	35	1.5	100	95
3	$Pd(dba)_2$	XPhos (2)	35	21	99	97
4	$Pd_2(dba)_3$	XPhos (2)	35	21	99	96
5	$Pd(OAc)_2$	XPhos (3)	35	21	100	93

Reaction Scope. With optimized conditions for the palladium-catalyzed borylation in hand, we investigated the reaction scope with respect to the aryl halide. As shown in Table 6, a wide range of substrates can be borylated under very mild conditions with excellent results, with most substrates requiring a temperature as low as 35 °C and 0.5 mol % Pd load

Table 6. Scope of Miyaura Borylation Using 2-KEH as Base in IPAC[11−13]



Entry[a]	Substrate	T (°C)	Time (h)	NMR yield (%)	Entry[a]	Substrate	T (°C)	Time (h)	NMR yield (%)
1[2]		35	1	100	15[2]		35	2	99
2[2]		45	5.5	99	16[11]		35 [d]	5	93
3[11]		35 [b]	21	93	17[2]		35	0.9	100
4		35	1.7	100	18[2]		35	13	98
5[11]		35	1.5	100	19[11]		35	2	100 (84) [e]
6[11]		35 [c]	21	98					
7[2]		80 [d]	16	27	20[7]		35	1	92
8[2]		35	2.5	100	21		35	2	99
9[2]		35	4	90	22[7]		35	16	83
10		35	24	75	23[13]		35	0.7	100
11[2]		35	1	93	24		80	24	0
12[2]		35	2	100	25		50 [f]	3.7	67
13		35	1.2	95	26[11]		35	6	90
14[12]		35	1	100	27[11]		35	0.5	73

[a]Reference to reported characterization. [b]1% Pd load was used. [c]Reaction run with 0.05% Pd load. [d]1.5% Pd load was used, with 2.2 equiv KOPiv. [e]Isolated yield in bracket (f) 1.5% Pd load was used.

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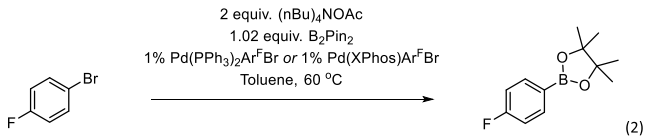
to achieve full conversion in a few hours. In all cases, the reactions were conducted on a gram scale. The reaction works with aryl iodides, bromides, and chlorides and can be applied to electron-rich and electron-poor aryl halides. Aryl iodides react more slowly than the bromides or chlorides, indeed chlorobenzene (entry 1) is borylated in just 1 h at 35 °C and iodobenzene (entry 2) requires more than 5 h at 45 °C to achieve full conversion. A similar trend holds for 4-halobenzonitriles (entries 15, 17 and 18). This trend may be offset by ring substituents. For example, 4-bromoanisole (entry 8) reacts more rapidly (2.5 h) than 4-chloroanisole (entry 9, 4 h). 4-Chlorophenol (entry 10) gave a moderate yield of 75% after 24 h. This reaction shows a significant slowdown upon progression, which was not seen with other substrates and may be related to the phenol functionality.

In general, p- or m-substitution allows for fast reaction. For example, *m*- and *p*-bromotoluene (entries 4 and 5) reach full conversion in less than 2 h, whereas *o*-bromotoluene (entry 3) needs 21 h and extra catalyst. The reaction with very hindered mesityl bromide (entry 7) gave poor results, requiring 80 °C and extra Pd to yield only 27% product (71% dehalogenation was detected) after 16 h. Similarly, *m*-bromobenzonitrile (entry 14), *p*-bromobenzonitrile (entry 15), and *p*-chlorobenzonitrile (entry 17) react quantitatively in less than 2 h. However, *o*-chlorobenzonitrile required 1.5 mol % catalyst to achieve full conversion in 5 h. In this case, potassium pivalate gave slightly better results (time, impurity profile) than 2-KEH. Alkenyl substrates can also be borylated (entry 22). Much faster reaction was seen with allyl systems, as illustrated by cinnamyl chloride (entry 23). Pyridines proved to be difficult substrates. Thus, 2-bromopyridine did not react at all even at 80 °C, whereas 3-chloropyridine required ca. 4 h at 50 °C with 1.5 mol % Pd to yield a moderate yield of product. In contrast, 2- and 3-bromothiophene (entries 26 and 27) react normally.

For less challenging substrates, further reduction of catalyst loading is possible. Thus, *p*-bromotoluene could be converted into the corresponding product in 21 h at 35 °C using only 0.05 mol % of (Xphos)(allyl)PdCl, which is one order of magnitude lower than that under the standard conditions used.

Although excellent results may be obtained using 2-KEH, some practical considerations about this base should be noted. This salt is very hygroscopic, which makes it difficult to weigh sub-gram amounts. The obvious remedy is to prepare a stock solution and dry it by azeotroping. This salt is fully soluble in neat IPAC and in most of the non-polar solvents just discussed. However, mixing 2-KEH and B_2Pin_2 may result in the formation of a gel at high concentrations, which can be difficult to stir. The viscosity of the slurry improves rapidly upon increasing the temperature, and mechanical stirring is usually effective at 35 °C. After 10−20% conversion, the solutions thin out noticeably.

Preliminary Mechanistic Information. The use of KEH clearly improved the Miyaura borylation reaction conditions. For a better understanding of this improvement, we have made some preliminary mechanistic observations that allow us to propose a more complete mechanism for the Miyaura borylation. 4-Bromo fluorobenzene was chosen as model substrate for analytical purposes (^{19}F NMR and GC analysis, eq 2).



(2)

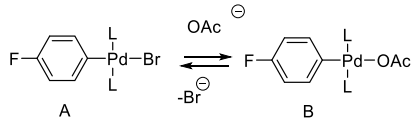
The reaction was studied in toluene using three different ligands, PPh_3, XPhos, and dppf (Miyaura's original ligand). $(n\text{Bu})_4$NOAc was chosen as a soluble base in this solvent to ensure homogeneity. Oxidative addition intermediate complexes, $Ar^FPd(PPh_3)_2Br$ $Ar^FPd(XPhos)Br$ and $Ar^FPd(dppf)Br$, were prepared and characterized and then used as catalysts (see Supporting Information).

Based on initial rate measurements, the reaction kinetics showed zero order in aryl bromide and first order in $(Bpin)_2$ with both PPh_3- and XPhos-based palladium catalysts (Figure S1). No saturation was seen with up to 6 equiv of $(Bpin)_2$. The apparent order of the reaction with respect to catalyst is around 1, although the relationship is not perfectly linear. These results confirmed that the borylation is rate-limiting.

Further studies showed that the reaction is inhibited by excess ligands when PPh_3 was used. There was a good inverse relationship between the observed reaction rate and [L]. For XPhos, the inhibition was essential nil, which is consistent with its bulkiness and high donicity. Given the inhibition by excess ligands, it was no surprise that dppf as a ligand afforded no coupling under the reaction conditions. This is in contrast with Miyaura's early work in which dppf was the preferred ligand (vide infra).

The initial reaction mechanism proposed by Miyaura requires the formation of B, where a transmetalation between B and $(Bpin)_2$ is the rate-limiting step. However, recent studies demonstrated that borylation without a base is feasible.[7] Moreover, density functional theory calculation suggested A could produce the borylated product via a base-assisted σ-bond metathesis.[14] To experimentally assess the key catalytic species (A or B, Scheme 1), we tested for inhibitory effect by either

Scheme 1. Plausible Intermediates in Borylation



soluble bromide or acetate (as tetrabutylammonium salts, Figure 1). Surprisingly, both additives inhibited the reaction. This effect was clearly seen also in the case of XPhos as the ligand.

These results suggest a previously unappreciated and very surprising inhibitory effect of acetate in the Miyaura borylation. Based on our experimental results, a new mechanism can be tentatively proposed (Scheme 2). After oxidative addition of Pd(0), intermediate A is formed. This species, in the presence of acetate, is in equilibrium with B. However, with large excesses of acetate, B yields the ate complex C where 2 acetate moieties are bound to palladium. Preliminary evidence for this complex was obtained by ^{31}P NMR, in which large excesses (200 equiv, to simulate catalytic conditions) of acetate versus B led to 2 new species and free PPh_3. In this equilibrium, only B is an active intermediate which can undergo the transmetalation, presumably via an associative precomplexation of the diboron species with concomitant displacement of a ligand moiety, as suggested by the ligand inhibition study. Both A and C are inactive toward borylation, which would explain the inhibitory effect of both bromide and acetate.

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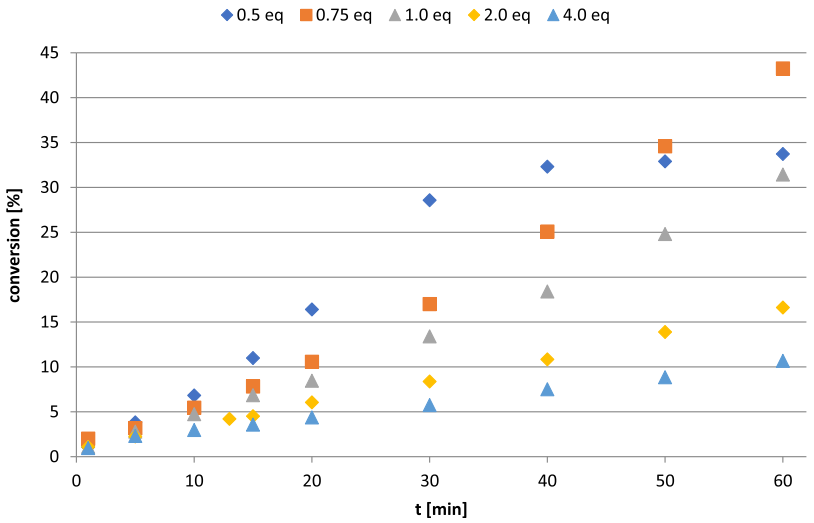
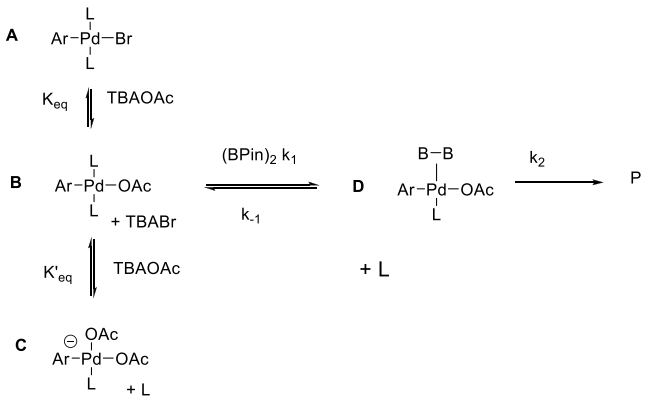


Figure 1. Effect of the amount of Bu_4NOAc (equiv w.r.t. substrate) on the rate of the reaction between B_2Pin_2 and 1-bromo-4-fluorobenzene catalyzed by $Pd(PPh_3)_2(p\text{-}C_6H_4F)Br$ in toluene at 60 °C.

Scheme 2. Proposed Mechanism for Different Inhibition Effects



Contrary to acetate, 2-ethyl hexanoate (or pivalate) provides not only an increased solubility but also, more importantly, an increased steric hindrance around palladium which may inhibit the formation of the corresponding unreactive ate-complex C. Indeed, the inhibitory effect in the presence of excess 2-KEH is minimal: almost identical initial rates were observed using 0.5, 1, or 2 equiv of 2-KEH (Figure 2).These results show that whereas Bu_4NOAc is an inhibitor of the borylation reaction, potassium ethyl hexanoate hardly inhibits. Note that KOAc inhibits much less as a result of its poorer solubility leading to a much lower concentration of −OAc compared to the ammonium salt.

A pre-coordination of the diboron species with the carbonyl oxygen atom of the acetate moiety in *D* could be postulated to be crucial, as carboxylates of reduced basicity are ineffective, but we prefer to be, at this preliminary stage, noncommittal about the exact structure of species *D*. The inactivity of the Miyaura ligand, dppf, deserves a special comment: when the borylation (eq. 2) was run with a monoxide of dppf as the ligand with $Pd_2(dba)_3$ as the Pd source, smooth conversion to a product was observed, whereas dppf required long activation period under the same conditions (Figure S6). Oxidation can also be triggered in situ by admixture of air to the borylation, under conditions of which a sigmoidal behavior, with slow activation, is seen in the kinetics. This is in agreement with our mechanistic proposal and suggests that under the original Miyaura conditions, the borylation only works because of ligand mono-oxidation resulted from the reduction of Pd(II)-precatalyst $Pd(ddpf)Cl_2$. The general observation of chelating

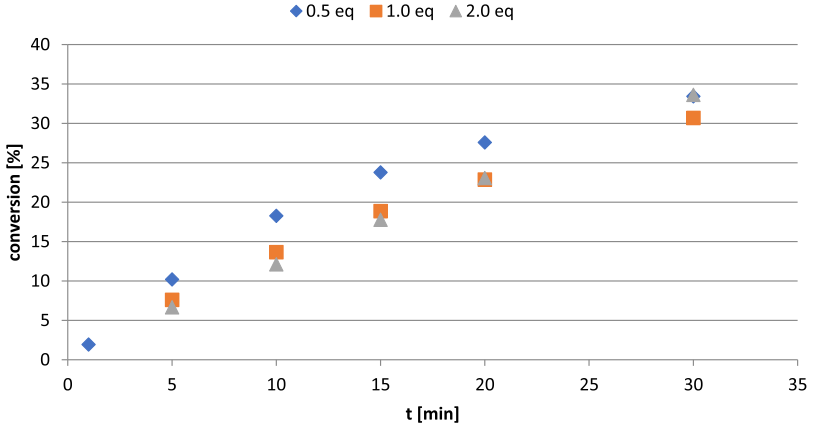


Figure 2. Effect of the amount of potassium ethyl-hexanoate (equiv w.r.t. substrate) on the rate of the reaction between B_2Pin_2 and 1-bromo-4-fluorobenzene catalyzed by $Pd(PPh_3)_2(p\text{-}C_6H_4F)Br$ in toluene at 60 °C.

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phosphines leading to active catalysts only through monooxidation is precedented in transition metal catalysis, and our data confirm this may be a broader phenomenon than so far appreciated.[15] We also speculate that the observed inhibitory effect of acetate bases and the need to employ bulky, highly soluble carboxylate salts for maximum efficiency might extend to other palladium-catalyzed reactions that require carboxylates as base, (e.g., C−H arylation), and that optimization of the base used may lead, in these cases also, to results of previously unacknowledged magnitude and mechanistic significance. A more complete kinetic analysis is being carried out, and the results will be published separately.

CONCLUSIONS

In conclusion, we have studied the base effect in the Miyaura borylation and have found a new base, potassium ethylhexanoate, which allows the reaction to be run under very mild conditions (usually 35 °C), thus avoiding potential side reactions. In addition, we have disclosed some new facets of the mechanism of the Miyaura borylation that were previously unappreciated.

General Procedure for the Pd-Catalyzed Borylation. Aryl halide (21.7 mmol), B_2Pin_2 (1.2 equiv), 2-KEH (2.2 equiv), and Xphos (0.005 equiv) are charged into the vessel and dissolved with IPAC (5.2 L/mol of ArX). Under an inert atmosphere (N_2), the mixture was heated up to 35 °C (oil bath), and then, (Xphos)(Allyl)PdCl (0.005 equiv) was added. The reaction was stirred until full conversion. Then, the organic phase was washed 3−4 times with aqueous $NaHCO_3$ 5% aq solution (5.2 L/mol each wash). Yields were obtained by NMR, using 1,4-dimethoxybenzene (anisole or maleic acid were used if NMR peaks superimposed) as external standard. NMR spectra were identical to those of authentic samples or those in the literature.

4-Nitrophenylboronic Acid Pinacol Ester. Following the general procedure, 12.5 g (79.3 mmol) of 4-chloronitrobenzene, 24.2 g of B_2Pin_2 (95.2 mmol, 1.2 equiv), 31.8 g of 2-KEH (174.5 mmol, 2.2 equiv), and 189 mg of XPhos (0.4 mmol, 0.005 equiv) were charged into a vessel equipped with mechanical stirring, followed by addition of 410 mL of IPAC (5.2 L/mol). Under an inert atmosphere (N_2), the mixture was heated up to 35 °C (jacketed reactor). Then, 261 mg of (Xphos) (Allyl)PdCl (0.005 equiv) was added to the mixture. The reaction was stirred until full conversion (2 h). Then, the mixture was cooled down to 20 °C, 1.3 g of *N*-acetylcysteine (7.9 mmol, 0.1 equiv) was added as aid to remove palladium, and three washes with 410 mL of a 5 w % $NaHCO_3$ aqueous solution were performed (>15 min stirring each time). The organic phase was distilled under reduced pressure (rotavapor) to remove volatiles. Then, 200 mL of heptane was added, and the resulting mixture was heated until a clear solution was obtained. This solution was slowly cooled to −5 °C over 2 h. The resulting suspension was filtered, and the solid was dried under vacuum to yield 84% (16.4 g) of product (NMR matches that of previous literature reports.[2] NMR analysis showed 1 mol % of residual 2-ethylhexanoate).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01758.

Extra screening data, detailed kinetic experiments, and NMR (PDF)

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Notes

The authors declare no competing financial interest.

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