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In situ formation and reaction of 2-pyridylboronic esters

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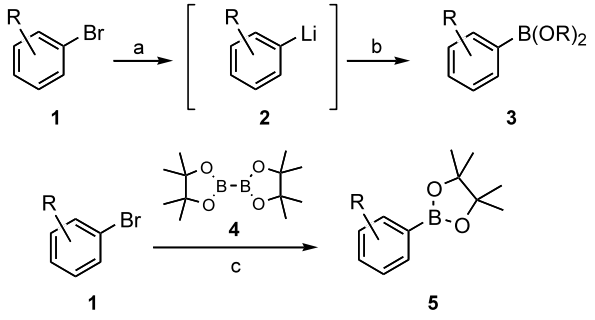
Abstract—2-Pyridylboronic esters were generated by cross-coupling 2-bromopyridines with bis(pinacolato)diboron in the presence of a base and palladium catalyst. The boronic esters reacted in situ with unreacted 2-bromopyridines to afford high yields of 2,2′-bipyridines as homocoupled products. Depending upon the reaction conditions, varying amounts of protodeboronated products were also observed. An attempted cross-coupling between two different 2-bromopyridines produced a nearly statistical mixture of homo- and cross-coupled products.

1. Introduction

Arylboronic acids and esters are required reagents in the Suzuki cross-coupling reaction.[1] The traditional procedure for making an arylboronic ester (**3**) involves reacting an aryllithium (**2**) or aryl Grignard with a borate ester (Scheme 1).[2] If desired, the newly formed boronic ester can be hydrolyzed to the corresponding boronic acid.[3] A more recently developed procedure for preparing boronic esters, specifically pinacol esters (**5**), involves a palladium-catalyzed coupling of an aryl halide with bis(pinacolato)diboron (**4**).[4]

While many syntheses of arylboronic acids and esters have been reported in the literature, relatively few heterocyclic examples have been noted. This is especially true for pyridylboronic acids. Very recently, syntheses for 3- and 4-pyridylboronic acids and esters have been published.[5] Both these classes of compounds can be formed and isolated in high yield and efficiently undergo Suzuki couplings.



Scheme 1. *Regents and conditions*: (a) *n*-BuLi; (b) $B(OR)_3$, then H_2O; (c) Pd catalyst, base.

In contrast, the 2-pyridylboronic acids and their derivatives remain virtually unknown. Isolated reports have noted difficulties in synthesizing these compounds.[4a,6] To our knowledge, only Ogawa and co-workers have successfully prepared and reported characterization data for a 2-pyridylboronic acid derivative, dimethyl 2-pyridylboronate.[7] This compound was not purified, and the only characterization data listed was a ^1H NMR spectrum. The crude boronic ester coupled to an arylhalide in modest yield in a Suzuki reaction.

Given the scarcity of information on 2-pyridylboronic esters and the relative lack of efficient methods for their synthesis, we sought to investigate the preparation of these compounds. Boronic esters of this type may then be more available for use in Suzuki couplings in applications ranging from pharmaceuticals to transition metal ligand synthesis.[5a,7]

2. Results and discussion

Our initial work on this project followed the procedures outlined by Ogawa. Unfortunately, in our hands these reactions proved to be troublesome. 2-Lithiopyridine (**7**) was formed by lithium–halogen exchange on 2-bromopyridine (**6**) with *n*-butyllithium (Scheme 2). All attempts to quench anion **7** with trimethyl borate failed to afford useful amounts of the desired 2-pyridylboronic ester product (**8**). 2-Pyridyllithium (**7**) could be

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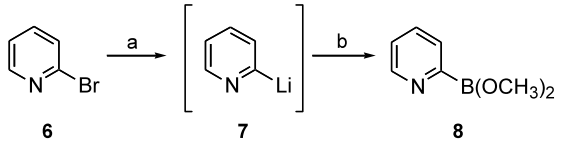
reacted with aldehyde electrophiles to give good yields of alcohols after aqueous work-up. Therefore, the problem in making borate esters of type **8** appears to be either reaction of the anion with the trialkyl borate or isolation of the product. This is consistent with other reports in the literature.[4a,6]

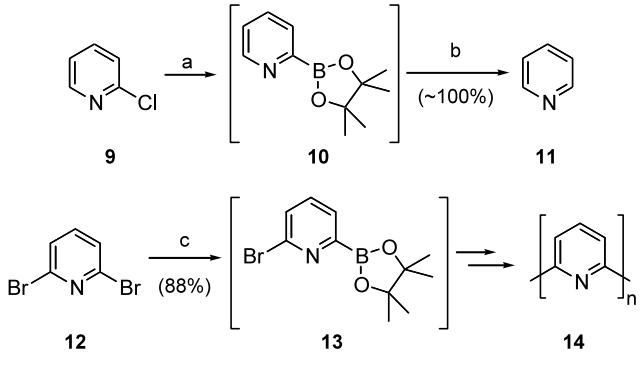
Since we were unable to prepare 2-pyridylboronic esters through standard metalation–quench protocols, we chose to investigate Miyaura's bis(pinacolato)diboron chemistry (Scheme 1).[4] This approach is mild, direct, and generally gives excellent yields of arylboronic esters with a variety of functionality.

The literature held two reports that were directly related to our planned work. One reference was not encouraging. Miyaura noted that 2-chloropyridine (**9**) reacts with diboron **4** in the presence of KOAc and a palladium catalyst in DMSO to quantitatively afford pyridine (**11**) (Scheme 3).[4a] This product presumably arises from in situ protodeboronation of the desired boronic ester **10**. A second publication was more supportive. Masuda and co-workers successfully formed an uncharacterized poly(pyridine) (**14**) in 88% yield by reacting 2,6-dibromopyridine (**12**) with diboron **4** in the presence of NaOH and a palladium catalyst in DMF.[8] This polymeric product forms by homocoupling of dibromide **12** and likely procedes through a 2-pyridylboronic ester intermediate (**13**).

Our first attempts to make 2-pyridylboronic esters used reaction conditions similar to those outlined by Miyaura.[4] Under these conditions 2-bromopyridine (**15**) and bis(pinacolato)diboron (**4**) reacted to give 78% bipyridine (**16**) and 17% pyridine (**11**) with 5% recovered bromopyridine (**15**) in 24 h by GC analysis with an internal standard of biphenyl (Scheme 4).[9,10]



Scheme 2. *Reagents and conditions*: (a) *n*-BuLi, THF, −78°C; (b) $B(OCH_3)_3$, then CH_3OH.



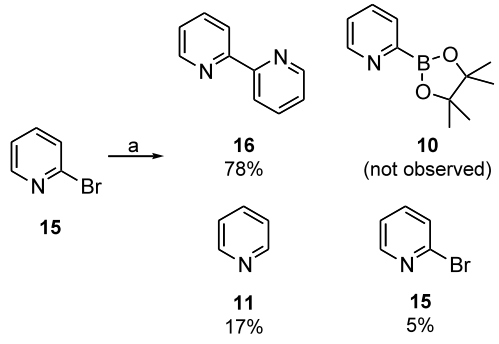
Scheme 3. *Reagents and conditions*: (a) **4**, $PdCl_2$(dppf), KOAc, DMSO, 80°C; (b) protodeboronation; (c) **4**, $PdCl_2$(dppf), NaOH, DMF, 100°C.

The high yield of bipyridine (**16**), a homocoupling product, is in agreement with Masuda's observations.[8] Likewise, the formation of pyridine (**11**) by protodeboronation is consistent with Miyaura's findings.[4a] Unfortunately, the pinacol ester of 2-pyridylboronic acid (**10**) was not observed by GC–MS or ^1H NMR. Both raising the reaction temperature to 100°C and using K_3PO_4 in place of KOAc increased the rate of the reaction without significantly changing the yield or relative ratio of the products.

The same reaction was repeated with 20 equivalents of the diboron reagent (**4**) in the hope of increasing the chances of observing boronic ester **10** and minimizing the formation of the homocoupling product (**16**). While this change did effectively prevent homocoupling, only pyridine was observed in the reaction by GC. Presumably, boronic ester **10** is not very stable under the reaction conditions and undergoes protodeboronation if no other reaction pathway is available.

A number of solvents were investigated for this reaction, and DMF was found to be the best with regard to reaction time and maximizing the yield of homocoupled product relative to protodeboronation (**16**:**11**) (Table 1). The presence of small amounts of water did not have a major impact on the amount of protodeboronation (entries 1–3), but running the reaction in a protic solvent such as 2-propanol (entry 7) resulted in more protodeboronation than homocoupling. Large amounts of pinacol were also observed when 2-propanol was used as the solvent. Pinacol likely arises from transesterification of diboron ester **4**. Toluene (entry 5) and THF (entry 8) were very poor solvents for the coupling. In both cases the pinacol ester of phenylboronic acid and 2-phenylpyridine were observed by GC–MS. These compounds probably form by migration of a phenyl group off palladium-bound triphenylphosphine.[11] These side products were less prevalent in the other solvents.

Protodeboronation is a known issue for heteroarylboronic acids, specifically when the boron is on a carbon adjacent to a heteroatom.[4a,13] The protodeboronation of 2-pyridylboronic acid (**20**) may be related to the facile decarboxylation of pyridine-2-



Scheme 4. *Reagents and conditions*: (a) **4**, $PdCl_2(PPh_3)_2$, KOAc, DMSO, 80°C.

Table 1. Homocouplings[a] of 2-bromopyridine (**12**) (Scheme 3)[12]

Entry	Solvent[a]	Reaction time (h)	GC yield (%)[b]			Ratio **16**:**11**
			16	**11**	**15**[c]	
1	DMF	6	88	12	0	7.3:1
2	DMF[d]	5	78	18	4	4.3:1
3	DMF[e]	6	88	12	0	7.3:1
4	DMSO	3	75	25	0	3.0:1
5	$PhCH_3$	66	41	18	41	2.3:1
6	CH_3CN	60	84	13	3	6.5:1
7	2-PrOH	3	30	70	0	0.4:1
8	THF	72	54	24	22	2.3:1

[a] All solvents were HPLC or ACS reagent grade and used without purification unless otherwise noted.
[b] GC yields are normalized to 100% total yield. The average, unnormalized GC yield for all table entries is 100.2 ($\sigma = 6.6$).
[c] Recovered starting material.
[d] 5% H_2O.
[e] Distilled from CaH_2.

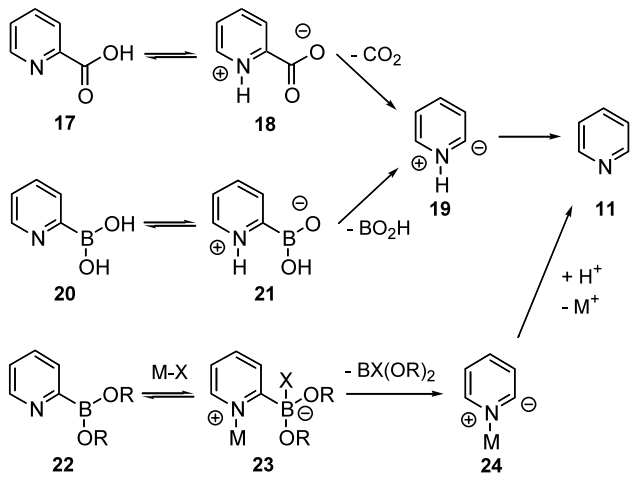
carboxylic acid (**17**).[14] Both processes likely proceed through the same pyridininum ylide intermediate (**19**) (Scheme 5). While it was hoped that 2-pyridylboronic esters would be more resistant to protodeboronation than the corresponding acids, the esters still seem prone to decomposition. It is possible that the esters coordinate to Lewis acids and bases present in solution. The resulting zwitterion (**23**) could decompose to afford pyridine through an ylide intermediate (**24**). The possibility of decomposition occurring after transmetalation to a 2-pyridylpalladium(II) species cannot be excluded. Despite their apparent instability, the 2-pyridylboronic esters do form readily and can be reacted in situ in high yield.

The homocoupling of 2-bromo-5-methylpyridine (**25**) in DMF gave essentially the same results as the homocoupling of 2-bromopyridine (Scheme 6). The ratio of homocoupled product (**26**) to protodeboronation (**27**) was 8.1:1.0. No boronic ester intermediates (**28**) were observed by GC–MS or ^1H NMR.

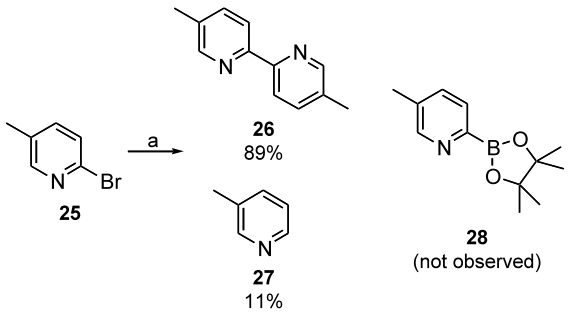
One cross-coupling was attempted between 2-bromopyridine (**15**) and 2-bromo-5-methylpyridine (**25**) (Scheme 7). The experimental product distribution observed by GC was found to be 1.2:1.9:1.0 **16**:**29**:**26**.[15] This experimental ratio is very similar to a statistical mixture of homo- and cross-coupled products with a theoretical value of 1:2:1 **16**:**29**:**26**. Although this cross-coupling reaction to form an unsymmetrical bipyridine is not as efficient as some Negishi[6,16] and Stille[5,17] approaches, the simplicity of this one-step Suzuki procedure may more than compensate for its lower yield. To realize the potential of this method, a suitable protocol for separating the products would need to be developed.

3. Conclusion

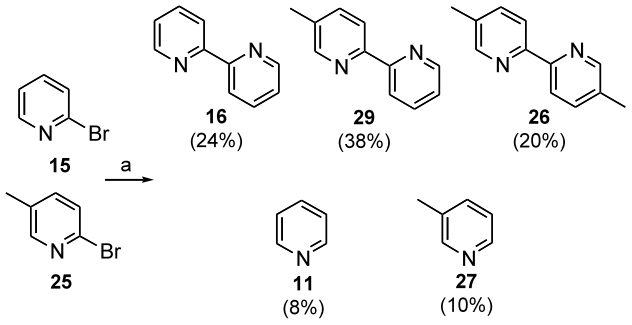
In summary, we have successfully formed and reacted 2-pyridylboronic esters to afford homo- and cross-coupled 2,2′-bipyridine products in high yields. This is the first systematic study of this elusive type of boronic ester. While 2-pyridylboronic esters do not seem sufficiently stable to be isolated under our reaction conditions, their solution lifetime is sufficient for them to be trapped in situ. If 2-pyridylboronic esters are not immediately reacted, they decompose through protodeboronation. Investigations are continuing on boronic esters of other five- and six-membered nitrogen heterocycles to determine their stability and feasibility of isolation.



Scheme 5.



Scheme 6. *Reagents and conditions*: (a) **4**, $PdCl_2(PPh_3)_2$, K_3PO_4, DMF, 100°C.



Scheme 7. *Reagents and conditions*: (a) **4**, $PdCl_2(PPh_3)_2$, K_3PO_4, DMF, 100°C.

Acknowledgements

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12. *General procedure*: Diboron **4** (330 mg, 1.3 mmol), 2-bromopyridine (95 μL, 1.0 mmol), $K_3PO_4 \cdot H_2O$ (450 mg, 2.1 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and biphenyl (50 mg) were dissolved in solvent (10 mL) in a 20 mL scintillation vial equipped with a stir bar. No precautions were taken to exclude atmospheric oxygen. The vial was sealed and heated to 100°C. The reaction was periodically monitored by GC to determine extent of reaction relative to the size of the biphenyl internal standard peak.
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