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COMMUNICATION

Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides†‡

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A protocol for the Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides that minimizes protodeboronation is described. A combination of catalytic amounts of Pd(OAc)$_2$ and SPhos in conjunction with CsF in isopropanol effectively affords a variety of coupled products. Surprisingly, a dramatic temperature dependence in product selectivity was observed.

Since the first report in 1979, the Suzuki-Miyaura coupling reaction has emerged as one of the most powerful C–C bond forming methodologies and is extensively utilized in the syntheses of natural products, pharmaceuticals, and materials.[1,2] Low catalyst loadings, flexibility of compatible functional groups, commercial availability of organoboron reagents, relative ease of product separation, and low toxicity of boron by-products have led its prominence in both academic and industrial research.[2d–f]

In recent years, significant progress has been made in the Suzuki-Miyaura coupling of heteroaryl boronic acids and aryl/heteroaryl halides. For example, Fu demonstrated the use of a Pd$_2$dba$_3$/PCy$_3$ catalytic system to couple *N*-heteroaryl boronic acids with aryl and *N*-heteroaryl chlorides in good to excellent yields.[3] Undoubtedly, the Buchwald group has made tremendous contributions to this field by designing sterically-hindered, electron-rich biarylmonodentate phosphine ligands such as SPhos and XPhos that, when combined with catalytic amounts of Pd(0), efficiently couple heteroaryl boronic acids with both aryl and heteroaryl chlorides.[4]

Despite these reports, the Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides is largely unexplored.[5,6] One of the challenges associated with heteroaryl boronic acids is their propensity to protodeboronate in the presence of base and polar protic solvents.[4a,7a,b] The instability of these boronic acids has led to the conventional approach of using excess amounts (>1.2 equiv.) of these transmetallating reagents while using the other electrophilic coupling partner as the limiting reagent. Furthermore, the protodeboronation is enhanced by the slow oxidative addition of vinyl chlorides leading to low yields of the desired coupling product. Molander has developed methods that utilize more stable potassium heteroaryltrifluoroborates in the coupling with the aryl/heteroaryl halides.[7b,c] However, these potassium trifluoroborate salts are themselves prepared from boronic acids in moderate to good yields.[7b]

Recently, we became interested in preparing vinyl indole **1a** *via* a Suzuki-Miyaura coupling (eqn (1)). Unfortunately, known protocols afforded either low yields or no desired product (**1a**). Specifically, when **1** and **a** were subjected to Fu's Pd$_2$dba$_3$/PCy$_3$ catalytic system,[3] complete protodeboronation to free indole (**1a′**) occurred exclusively. Some product was obtained (46% yield by ^{1}H NMR spectroscopy) utilizing Buchwald's conditions (*i.e.*, 2 mol% Pd(OAc)$_2$, 4 mol% SPhos, K$_3$PO$_4$, *n*-butanol, 100 °C).[4d] However, the remaining boronic acid **a** was completely protodeboronated. Alternatively, the more stable potassium trifluoroborate salt of boronic acid **1** was synthesized and subjected to Molander's conditions (*i.e.*, 2 mol% Pd(OAc)$_2$, 4 mol% RuPhos, 2 equiv. Na$_2$CO$_3$, EtOH, 85 °C).[7b] Unfortunately, a 1 : 1 mixture of coupling product **1a** and protodeboronated indole **1a′** was again obtained. Furthermore, attempts to isolate the coupling product **1a** proved futile as it co-elutes with **1a′** during chromatographic separation. As such, we began to evaluate an unconventional approach of using the heteroaryl boronic acid as the limiting reagent. Herein we describe an effective protocol for the Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides.

Using Buchwald's conditions as a guide, we evaluated whether a change in base, solvent, or temperature would result in higher product yields (eqn (1), Table 1). Initially, when K$_3$PO$_4$ and *n*-butanol were substituted for Cs$_2$CO$_3$ and toluene, a 1.1 : 1 mixture of product **1a** to protodeboronated **1a′** was obtained. Replacement of Cs$_2$CO$_3$ with CsF as the base led to a slight increase in the product ratio (*i.e.*, 1.9 : 1, entry 2). Although switching from toluene to *t*-butanol led to a decrease in selectivity (entry 3), the use of isopropanol as the solvent afforded a 3 : 1 ratio in favour of the desired **1a** (entry 4). Surprisingly, lowering the reaction from 110 °C to 100 °C resulted in an, albeit slight, increase in selectivity (entry 5). Further investigation revealed a dramatic temperature dependence (entries 4–9). Excellent selectivity of the coupling product over protodeboronated product was obtained when the reaction was run at 85 °C (entry 7). An increase or decrease of the reaction temperature by as little as 5 °C led to lower selectivities (entries 6 and 8).[8] Further optimization led to these reactions conditions: 2 mol% Pd(OAc)$_2$, 4 mol% SPhos, 1.4 equiv. CsF, isopropanol (0.2 M), 3–10 h.

With optimized conditions in hand, the coupling of other heteroaryl boronic acids and vinyl chlorides was explored. A particularly challenging heteroaryl boronic acid that is known for fast

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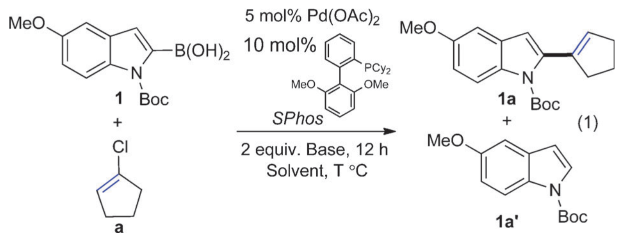
‡ Electronic supplementary information (ESI) available: characterization data and NMR spectra of characterized compounds. See DOI: 10.1039/c1cc15990a

Table 1 Various reaction parameters for the Suzuki-Miyaura coupling[a]



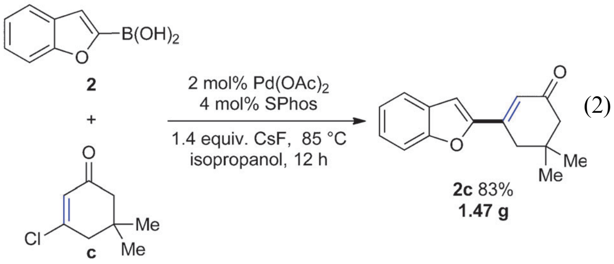
Entry	Base	Solvent	Temp. (°C)	Ratio[b] **1a** : **1a′**
1	Cs_2CO_3	Toluene	110	1.1 : 1
2	CsF	Toluene	110	1.9 : 1
3	CsF	^{t}Butanol	110	1.5 : 1
4	CsF	Isopropanol	110	3 : 1
5	CsF	Isopropanol	100	3.3 : 1
6	CsF	Isopropanol	90	10 : 1
7	**CsF**	**Isopropanol**	**85**	**16.7 : 1**
8	CsF	Isopropanol	80	11.1 : 1
9	CsF	Isopropanol	75	6.7 : 1

[a] Reaction conditions: **1** (1 equiv., 0.2 M), **a** (1.2 equiv.), 5 mol% $Pd(OAc)_2$, 10 mol% SPhos. [b] Ratio **1a** : **1a′** determined by ^1H NMR spectroscopy.

protodeboronation, *N*-Boc-indole-2-boronic acid,[4a,7b] was successfully coupled with both unactivated cyclic and acyclic vinyl chlorides to yield vinyl indoles in high yields (**1a**, **1b**, Table 2). Similarly, benzofuran-2-boronic acid and benzothiophene-2-boronic acid afforded the desired products (**2a**, **2b**, **2c**, **3c**). Notably boronic acid with *N*-heteroaromatics like pyrimidines, which can potentially bind [Pd] and kill its catalytic activity, worked efficiently in excellent yields (**4a**, **5a**, **5b**, **5d**). Additionally, both quinoline and isoquinoline boronic acids were also coupled in moderate to good yields (**6a**, **6e**, **7e**). The coupling with (*Z*)-2-chloro-2-butene afforded the vinyl heteroaryl compounds with retention of stereochemistry (**6e**, **7e**). Five-membered heteroaryl boronic acids were also demonstrated to couple effectively in good to excellent yields (**8d**, **9c**).

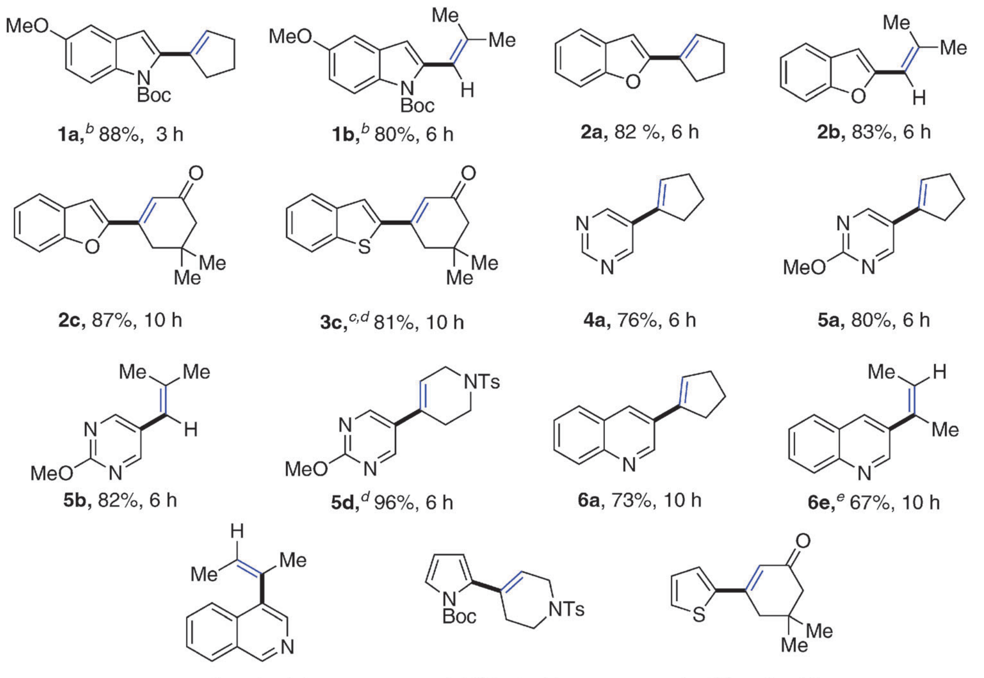
Gratifyingly, this coupling is scalable and was successfully applied to gram scale quantities of benzofuran-2-boronic acid and 3-chloro-5,5-dimethylcyclohex-2-en-1-one to afford the desired product (**2c**) in 83% yield (eqn (2)).

Gram Scale Reaction:



In conclusion, we have developed an efficient catalytic system to couple challenging heteroaryl boronic acids and vinyl chlorides. This coupling takes the advantage of using heteroaryl boronic acids as the limiting reagent. In addition, we found that the ratio of protodeboronation to coupled product was highly dependent on reaction temperature.

Table 2 Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides[a]



1a,[b] 88%, 3 h
1b,[b] 80%, 6 h
2a, 82 %, 6 h
2b, 83%, 6 h
2c, 87%, 10 h
3c,[c,d] 81%, 10 h
4a, 76%, 6 h
5a, 80%, 6 h
5b, 82%, 6 h
5d,[d] 96%, 6 h
6a, 73%, 10 h
6e,[e] 67%, 10 h
7e,[e] 51%, 10 h
8d,[d] 95%, 6 h
9c,[c,d] 77%, 10 h

[a] Reaction conditions: 1 equiv. heteroaryl boronic acid (0.2 M),1.2 equiv. vinyl chloride, 2 mol% $Pd(OAc)_2$, 4 mol% SPhos, Isopropanol, 85 °C. [b] Product was contaminated with very low amounts of protodeboronated indole **1a′** (see ESI‡). [c] 4 mol% $Pd(OAc)_2$/SPhos was used. [d] 1.1 equiv. of vinyl chloride was used. [e] Retention of stereochemistry was observed as determined by NOESY-1D spectroscopy.

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8 We currently do not know the reason for the dramatic temperature effect on product yields. We found, not surprisingly, that protodeboronation of **1** occurs within 30 min at 80 °C in the presence of only base. As such, the high yield of product **1a** at 85 °C does not seem to be due to a simple correlation between the rate of cross coupling and the rate of protodeboronation. We are investigating other possible reasons for the observed temperature effect.