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Selective and efficient synthesis of *trans*-arylvinylboronates and *trans*-hetarylvinylboronates using palladium catalyzed cross-coupling†

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Trans-arylvinylboronates derivatives are important synthesis blocks in natural products, pharmaceuticalsm and organic materials. There are only a few reaction conditions that could selectivly provided *trans*-arylvinylboronates by Heck coupling of pinacol vinylboronate and aryl halides. Here we report an efficient and versatile method with the palladium catalyzed cross-coupling between pinacol vinylboronate and various aryl or hetaryl bromides to get the corresponding trans-(het)arylvinylboronates in excellent yields and selectivitiy. 30 examples have been synthesized by this protocol which offers an alternative method to prepare these useful building blocks.

Introduction

Palladium-catalyzed cross-coupling reactions to construct carbon-carbon bonds and carbon-heteroatom bonds have attracted great attention since their extremely significance in synthetic organic chemistry. Using these reactions, a large number of complicated molecules closely related to human life have been successfully synthesized, including medicines, agricultural chemicals, high-tech polymer materials and natural products[1]. The Heck coupling reaction involves the palladium catalyzed coupling of alkenyl or aryl halides or triflates with olefins in the presence of a base to form conjugated arenes as products which result from the substitution of a hydrogen atom in the alkene coupling partner[2]. The Heck coupling reaction is of great importance and a valuable tool routinely employed in both academic research and industrial production. Richard Heck was thus awarded the 2010 Nobel Prize in Chemistry for the discovery and development of this reaction[3].

Aryl olefins and heteroaryl olefins are important structural motifs in bioactive derivatives[4] and organic materials[5] because of their conjugated rich electronic and linear characteristics[6]. The chemical structures of the representative bioactive derivatives containing arylvinyl or hetarylvinyl groups are shown in Figure 1. **1** (Piperlongumine) is a natural product which has shown selective anti-cancer activities by targeting the stress response to ROS (reactive oxygen species) in several representative cancer cells[4c] as well as anti-inflammatory properties[4f]. **2** (Axitinb), a small molecule tyrosine kinase inhibitor, has been approved for renal cell carcinoma (RCC) by the U.S. Food and Drug Administration[4d, 4g]. It contains a linear chain of vinyl pyridine which could potentially fit into the solvent-exposed side of the adenine binding pocket[4a]. **3** (CFI-400945), a selective Polo-like Kinase 4 inhibitor, has demonstrated efficacy *in vitro* and *in vivo* against breast and ovarian cancers and entered clinical trials[4e, 4h]. **4**, has an IC_{50} value of 1.1 nM for the inhibition of PKC and could block the production of IL-2 in both stimulated murine T cells and human whole blood[4b].

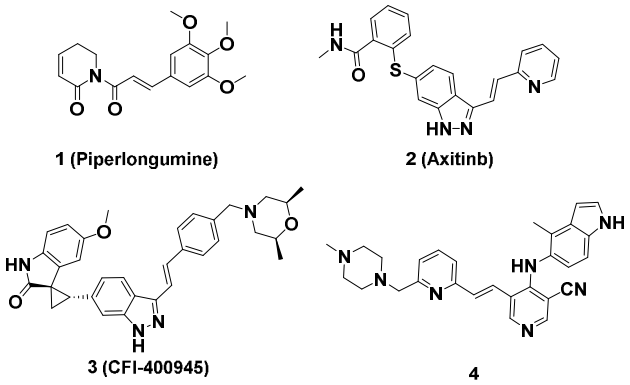

Figure 1 Chemical structures of representative bioactive derivatives containing arylvinyl or hetarylvinyl groups.

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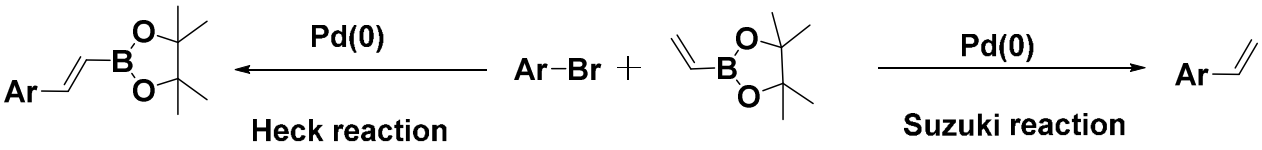


Scheme 1 The palladium catalyzed cross-coupling of arylbromides with pinacol vinylboronate in two alternative mechanisms.

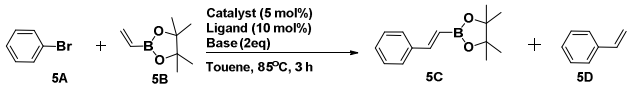
Organoboron reagents have been proved to be useful building blocks in organic chemistry and are widely applied in palladium catalyzed cross-coupling reactions for their stability, commercial availability and synthetic versatility[7]. Boronate moietys can be further transformed into other functional groups such as halides[8], ketones[9], amines[9b] and alkyl groups[10]. Most notably, trans-arylvinylboronates are important intermediates to construct arylvinyl derivatives via Suzuki cross-coupling reactions. There are mainly two distinctive methods for the synthesis of arylvinylboronates. 1) Arylvinylboronates can be accessed by direct hydroboration of arylethynylenes with pinacol borane by using various transition metal catalysts[11] and metal-free catalysts[12]. However, it often needs several steps to prepare terminal arylethynylenes which also lack inherent reactivity[13]. 2) Vinyl pinacol boronic esters can react with aryl halides to get alkenylboronates via the Heck coupling reaction[14]. The reaction of alkenylboronates with aryl halides could potentially provide either a Heck coupling product by the palladium (0) adds across the alkene or a Suzuki coupling product by the palladium (0) inserts into the C-B bond (Scheme 1). However, there is only a few conditions with limited scope of application that could selectively offer the Heck products[14a, 14c].

As a part of our ongoing research program on construction of (het)arylvinyl compound library for developing potential protein kinase inhibitors, we have found an efficient and versatile condition for the Heck coupling of pinacol vinylboronate with various (het)arylbromides in excellent yields and selectivity in this study.

Experimental

Initially, pinacol vinylboronate and bromobenzene were selected as model substrates for optimizing the reaction conditions. A range of bases, common palladium sources and ligands were tested respectively for their influence on the yield and selectivity between the Heck reaction versus the Suzuki reaction (Table 1). The reaction performed in the presence of $Pd(OAc)_2$ (5 mol%), Et_3N (2 *equiv.*) and various ligands (5 mol%) provided **5C** with yields of less than 50% (Table 1, entry 1-4) except $P(t\text{-}Bu)_3$ (Table 1, entry 5) as the ligand. PPh_3 (Table 1, entry 1) and PCy_3 (Table 1, entry 2) were shown to be in favour of Suzuki coupling, as **5D** was the major product in all attempts without regard to the palladium sources (Table 1, entry 1, 2, 10, 17 and 19). The reaction did not proceed in the presence of (±)-BINAP as ligand (Table 1, entry 3). Using phenanthroline as ligand offered good selectivity for the Heck product **5C** (Table 1, entry 4, 11, 18) but the yields were far from being satisfactory. It se-

Table 1 Optimization of the reaction conditions[a]



Entry	[Pd]	Ligand	Base	Yield (%, **5C**+**5D**)[b]
1	$Pd(OAc)_2$	PPh_3	Et_3N	12+61
2	$Pd(OAc)_2$	PCy_3	Et_3N	21+54
3	$Pd(OAc)_2$	(±)-BINAP	Et_3N	NA
4	$Pd(OAc)_2$	phenanthroline	Et_3N	49+7
5	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$	Et_3N	55+17
6	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$	DIPEA	68+14
7	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$	TMEDA	49+28
8	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$	AcOK	42+27
9	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$	Cs_2CO_3	55+8
10	$PdCl_2$	PPh_3	DIPEA	6+54
11	$PdCl_2$	phenanthroline	DIPEA	48+12
12	$PdCl_2$	$P(t\text{-}Bu)_3$	DIPEA	55+17
13	$Pd(PPh_3)_4$	/	DIPEA	17+68
14	$PdCl_2$(dppf)	/	DIPEA	7+83
15	$Pd(PPh3)_2Cl_2$	/	DIPEA	12+69
16	$Pd(P(t\text{-}Bu)_3)_2$	/	DIPEA	75+17
17	$Pd_2(dba)_3$	PPh_3	DIPEA	29+46
18	$Pd_2(dba)_3$	phenanthroline	DIPEA	50+13
19	$Pd_2(dba)_3$	PCy_3	DIPEA	37+54
20	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3$	DIPEA	81+11
21	$Pd_2(dba)_3$	$P(t\text{-}Bu)_3{\cdot}HBF_4$	DIPEA	75+9

[a] Reaction conditions: bromobenzene (0.5 mmol, 1.0 *equiv.*), pinacol vinylboronate (0.55 mmol, 1.1 *equiv.*), toluene (5.0 mL), 85°C, 3 h, under N_2 atmosphere. [b] Determined by the analysis of HPLC results.

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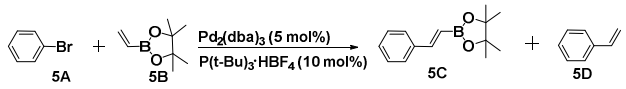


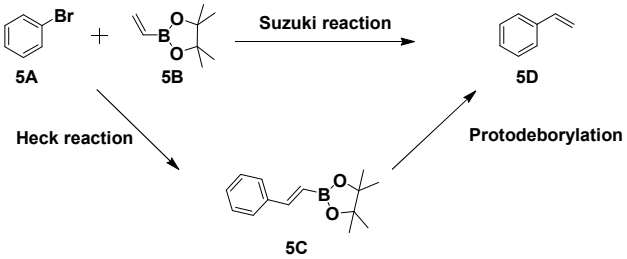
Entry	Solvent	Time (h)	Temp (^{o}C)	Yield (%, **5C**+**5D**)[b]
1	Toluene	3	75	62+13
2	Toluene	3	85	71+9
3	Toluene	3	95	83+10
4	Toluene	3	105	79+10
5	Toluene	3	115	69+14
6	Toluene	1	95	67+6
7	Toluene	6	95	58+8
8	Toluene	12	95	53+14
9	CH_3CN	3	95	54+11
10	Dioxane	3	95	68+13
11	DMF	3	95	63+11
12	DMA	3	95	61+16

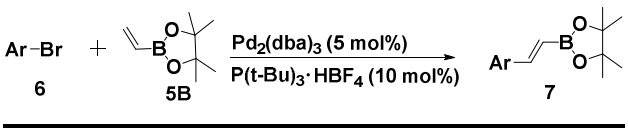
[a] Reaction conditions: bromobenzene (0.5 mmol, 1.0 *equiv.*), pinacol vinylboronate (0.55 mmol, 1.1 equiv.), DIPEA (1 mmol, 2.0 *equiv.*), slovent (5.0 mL), under N_2 atmosphere. [b] Determined by the analysis of HPLC results.

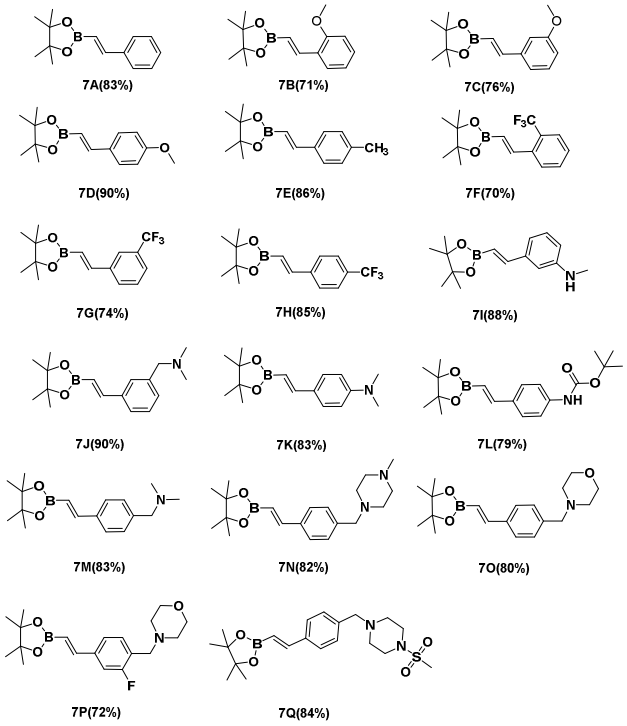
Table 2 Optimization of the reaction conditions[a].

emed that the ligand P(t-Bu)$_3$ tended to give the greatest yield than other ligands (Table 1, entry 5 versus 1-4). And next different bases were employed in the reaction in the presence of Pd(OAc)$_2$ (5 mol%) and P(t-Bu)$_3$ (10 mol%) to investigated their effects on the yields and selectivity (Table 1, entry 5-9). The addition of DIPEA (Table 1, entry 6) or Cs_2CO_3 (Table 1, entry 9) as bases offered greater yield and selectivity to **5C** compared with that addition of Et_3N, but more impurities were offered when Cs_2CO_3 was used. Subsequently, a variety of palladium sources and ligands were screened in the presence of DIPEA as base in the reaction. $PdCl_2$ showed similar reactivity and lower selectivity compared with Pd(OAc)$_2$ (Table 1, entry 10-12). It was also found that P(t-Bu)$_3$ tended to give greater

Scheme 2 Two possible ways for the formation of by-product **5D** in the optimised reaction.







[a] Reaction conditions: bromobenzene (2 mmol, 1.0 *equiv.*), pinacol vinylboronate (2.2 mmol, *1.1 equiv.*), toluene (8.0 mL), DIPEA (4 mmol, 2.0 *equiv.*), 95^{o}C, 3 h, under N_2 atmosphere. [b] Isolated yield after silica gel chromatography.

Table 3 Substrate scope for Heck coupling of pinacol vinylboronate with various arylbromides [a,b].

yield than other ligands (Table 1, entry 10-12). Palladium (0) catalysts such as Pd(PPh$_3$)$_4$ (Table 1, entry 13), PdCl$_2$(dppf) (Table 1, entry 14) and Pd(PPh$_3$)$_2$Cl$_2$ (Table 1, entry 15) gave more **5D** than Heck reaction product **5C**. While Pd(P(t-Bu)$_3$)$_2$ gave a higher yield and selectivity of **5C** (Table 1, entry 15) the air and moisture sensitivity made it inconvenient to be used. Pd$_2$(dba)$_3$ offered the best combination of yield and selectivity to **5C** especially in the presence of DIPEA as base and P(t-Bu)$_3$ (81%) or P(t-Bu)$_3$·HBF$_4$ (79%) as ligands (Table 1, entry 20-21).

As surmised from the results shown in Table 1, Pd$_2$(dba)$_3$ and P(t-Bu)$_3$ related ligands may be good combinations for this reaction

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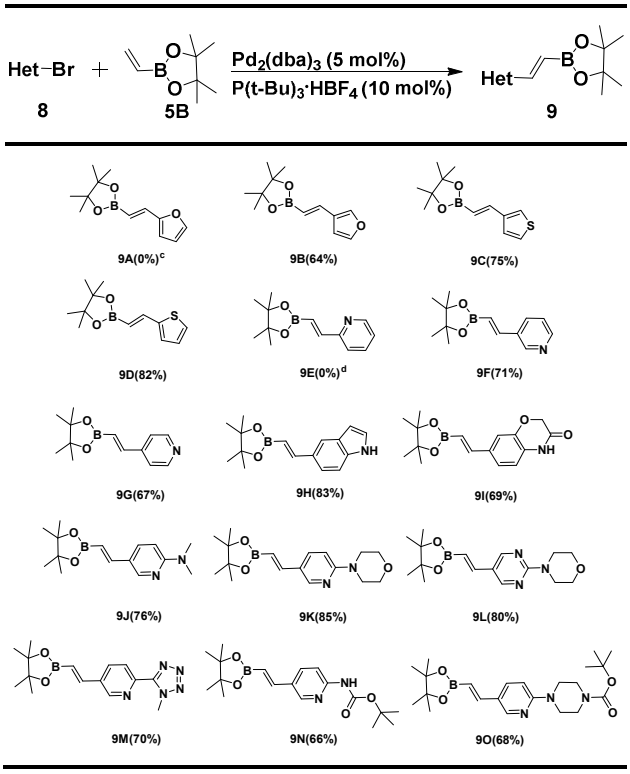

[a] Reaction conditions: bromobenzene (2 mmol, 1.0 *equiv.*), pinacol vinylboronate (2.2 mmol, 1.1 equiv.), toluene (8.0 mL), DIPEA (4 mmol, 2.0 equiv), 95°C, 3 h, under N_2 atmosphere. [b] Isolated yield after silica gel chromatography. [c] Messy reaction. [d] No reaction.

Table 4 Substrate scope for Heck coupling of pinacol vinylboronate with various hetarylbromides [a,b].

system that mainly provided the Heck reaction product **5C** in better yields. $P(t\text{-}Bu)_3$ and $P(t\text{-}Bu)_3{\cdot}HBF_4$ are usually used as bulky electron rich phosphines in palladium catalyzed reactions[15]. $P(t\text{-}Bu)_3$ is very air sensitive which requires strict air-exclusion while $P(t\text{-}Bu)_3{\cdot}HBF_4$ is an air and moisture stable HBF4-phosphonium salt form of $P(t\text{-}Bu)_3$ and allows easier manipulation. Hence, air and moisture stable catalyst $Pd_2(dba)_3$ and ligand $P(t\text{-}Bu)_3{\cdot}HBF_4$ in combination with DIPEA as base were selected as the catalytic system for further optimization to determine suitable temperature and solvent.

Reactions conducted at lower temperatures (Table 2, Entry 1-2) led to an evident decrease in yields, while a higher temperature resulted in decline in both yield and selectivity (Table 2, Entry 4-5). As mentioned above, it could be concluded that the Heck product **5C** may be kinetically dominated. When the reaction time extended from 1 h to 12 h, the yield of Heck product **5C** declined, but the yields of **5D** increased over time (Table 2, Entry 3, 6-8). Next, we investigated the influence of solvents on the reaction. The substrates could be efficiently transformed in a number of solvents. Although polar solvents such as DMF or MeCN are commonly used for Heck reaction, polar solvents decreased the yield of **5C** substantially (Table 9-12) and toluene turned out to be a much better solvent than other solvents in this reaction (Table 2, Entry 3).

After examined a range of Pd catalysts, ligands, bases, solvents and temperatures, the combination of 5 mol% of $Pd_2(dba)_3$, 10 mol% of $P(t\text{-}Bu)_3{\cdot}HBF_4$ and 2 *equiv.* of DIPEA in toluene at 95°C for 3 h under nitrogen emerged as the best reaction condition.

In the optimised reaction conditions, Suzuki reaction of **5A** with **5B** and protodeborylation of **5C** are two possible ways for the formation of by-product **5D** (Scheme 2). To verify whether Suzuki reaction could actually proceed in this condition, we treated **5C** with 1-bromo-4-methoxybenzene and obtained the Suzuki reaction product (*E*)-1-methoxy-4-styrylbenzene. Besides, Heck reaction product **5C** was re-treated to the optimized reaction condition to determine whether protodeborylation of **5C** occurred, and about 6% of **5C** was transformed into protodeborylation product in this condition after reacting 3 h. These results indicated that by-product **5D** might come from both Suzuki reaction and protodeborylation, which also explained that the yields of **5D** increased with the reaction time extended from 1 h to 12 h (Table 2, Entry 3, 6-8).

We next assessed the scope of this condition with various arylbromides. As shown in Table 3, a variety of monosubstituted bromo anisoles and bromo benzotrifluorides could be transformed to their corresponding Heck coupling products (**7B-7D**, **7F-7H**) in moderate to good yields, and the yield of an electron-riched substrate was slightly higher than an electron-defective substrate. *o*-Bromoanisoles and *o*-bromobenzotrifluorides resulted in significant decrease in yield (**7B**, **7F**), suggesting that hindrance would be detrimental to the reaction. 3-bromo-*N*-methylaniline and 1-(3-bromophenyl)-*N*,*N*-dimethylmethanamine were effective to offer target products (**7I**, **7J**). *p*-Bromoanilines and *p*-bromobenzylamines were employed to couple with pinacol vinylboronate to provide corresponding Heck coupling products (**7K**-**7Q**) also in respectable yields (72-84%).

After investigating the generality of this coupling reaction with respect to a series of substituted arylbromides, various hetaryl bromides were then studied to expand the scope of this method (Table 4). When 2-bromofuran was used as substrate, almost no corresponding Heck coupling product and Suzuki product were obtained, which may be ascribed to the instablity of 2-bromofuran under Pd catalyst and high temperature. However, 3-bromofuran could be effectively converted to the (*E*)-2-(furan-3-yl) vinylboronic

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acid pinacol ester (**9B**). Both 2-bromothiophene and 3-bromothiophene could react with pinacol vinylboronate to offer the respective Heck coupling products (**9C**, **9D**) in good yields and pyridine species could also be transformed to the target Heck products (**9F**-**9G**) except 2-bromopyridine (no reaction). We suspect that the electron density of C-Br bond in 2-bromopyridine is too low for palladium catalyst to initiate oxidative addition. 5-Bromoindole and 7-bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one were transformed to corresponding Heck coupling products also in satisfying yield (**9H**-**9I**). Then various 5-bromopyridines were used as substrates which all gave the desired products in good yields (**9J**-**9O**).

Conclusions

In conclusion, we have developed an effective method to prepare *tran*-(het)arylvinylboronates. Detailed studies have showed that the consistant of $Pd_2(dba)_3$ (5 mol%), P(t-Bu)$_3$·HBF_4 (10 mol%) and of DIPEA (2 *equiv*.) in toluene at 95°C for 3 h under nitrogen was the best condition in the reaction. The present work provides an easy manipulated and inexpensive protocol that is effective and selective to the synthesis of *trans*-vinyl boronates with wide substrate scope. We believe this work will greatly benefit the development of bioactive molecules and organic functional materials.

Experimental

General procedure for the Heck coupling of pinacol vinylboronate with (het)arylbromides

A mixture of vinylboronate pinacol ester (2.2 mmol, 1.1 *equiv.*), the corresponding aryl and hetaryl bromides (2.0 mmol, 1.0 *equiv.*), DIPEA (4.0 mmol, 2.0 *equiv.*), $Pd_2(dba)_3$ (0.1 mmol, 5 mol%) and P(t-Bu)$_3$·HBF_4 (0.2 mmol, 10 mol%) in dry toluene (8.0 mL) was stirred at 95°C for 3 h under N_2 atmosphere. Then the reaction mixture was evaporated under vacuum. H_2O (5 mL) was added to the residual mixture. The mixture was extracted with ethyl acetate (10 mL x 3), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was purified by silica gel chromatography using EtOAc/*n*-hexene as eluent to afford the products.

Acknowledgements

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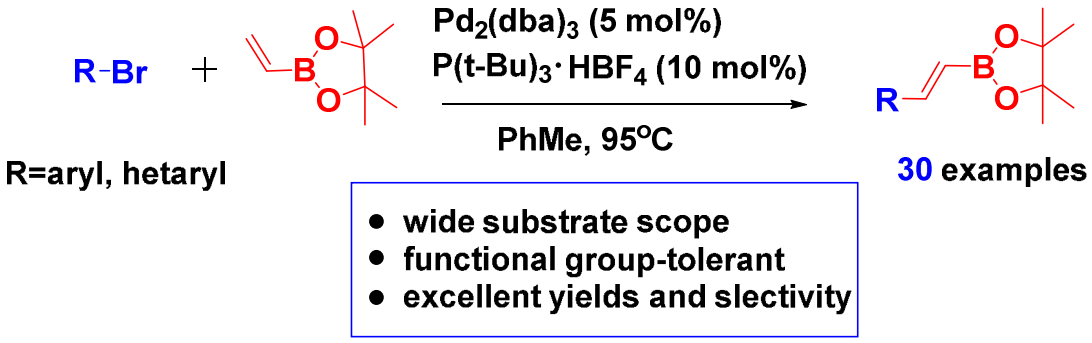
Table of contents entry

Selective and efficient synthesis of *trans*-arylvinylboronates and *trans*-hetarylvinylboronates using palladium catalyzed cross-coupling

Zhihao Liu, Wei Wei, Lu Xiong, Qiang Feng, Yaojie Shi, Ningyu Wang and Luoting Yu



An versatile method of palladium catalyzed cross-coupling between pinacol vinylboronate and (het)arylbromides to get trans-(het)arylvinylboronates in excellent yields and selectivity.