Nickel- and Palladium- Catalyzed Cross-Coupling Reactions of Organostibines with Organoboronic Acids

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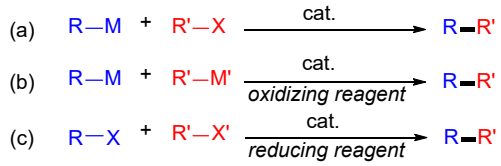
Abstract: A strategy for the formation of antimony−carbon bond was developed by nickel-catalyzed cross-coupling of halostibines. This method has been applied to the synthesis of various triaryl- and diarylalkylstibines from the corresponding cyclic and acyclic halostibines. This protocol showed a wide substrate scope (72 examples) and was compatible to a wide range of functional groups such as aldehyde, ketone, alkene, alkyne, haloarenes (F, Cl, Br, I), and heteroarenes. A successful synthesis of arylated stibine **3a** in a scale of 34.77 g demonstrates high synthetic potential of this transformation. The formed stibines (R_3Sb) were then used for the palladium-catalyzed carbon−carbon bond forming reaction with aryl boronic acids [$R-B(OH)_2$], giving biaryls with high selectivity, even the structures of two organomoieties (R and R') are very similar. Plausible catalytic pathways were proposed based on control experiments.

Introduction

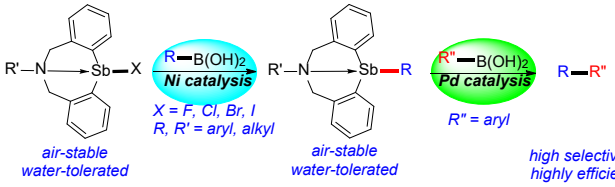
Cross-coupling reactions between carbon nucleophiles and carbon electrophiles have been widely used in organic synthesis as a reliable method for carbon−carbon (C−C) bond formation (Scheme 1a).[1] Among various organometallic reagents including Li,[2] Mg,[3] Zn,[4] Sn,[5] Ge,[6] Si,[7] or B[8] that have been employed as the carbon nucleophiles, organoboron, -silicon, and -tin compounds are stable in air, easy to handle and compatible to various functional groups. Especially, organoboron reagents are widely employed since they are commercially available and show very high performance as the cross-coupling partner. Recently, much attention has been paid to the oxidative cross-coupling of organometallic reagents and reductive cross-coupling of organohalides (Scheme 1b and 1c).[9, 10] In these reactions, however, high selectivity of cross-coupling against homo-coupling is difficult to achieve. Actually, the successful



Scheme 1. Cross-coupling reactions

examples are only limited to the cases in which the structures of two organomoieties (R and R') are largely different and it is still difficult to control the selectivity by the nature of metals (M and M') or halogens (X and X'). This is a big issue to be solved from a synthetic viewpoint.

It is known that organotellurides undergo oxidative addition to Pd(0) more readily than the corresponding organoiodides[11] and react preferentially with organoborates.[12] Therefore we became interested in the chemical behaviors of organostibines in the cross-coupling reactions since Sb is located between Sn and Te with a medium electronegativity (2.05) between these elements, 1.96 and 2.10, respectively. Although pioneering studies on the C−C bond formation by cross-coupling reactions of trivalent stibines were already reported by the Kurita's group[13a−c] and the Chaplin's group[13d], such chemistry is not well exploited yet (vide infra).[14−20] After detailed studies, we found that organostibines with 5,6,7,12-tetrahydro-dibenzo[*c,f*][*1,5*]azastibocines structure are promising coupling partners with enhanced reactivity due to the special N-Sb coordination bond,[13b] and disclose herein the detailed results (Scheme 2). Chlorostibines react with organoboronic acids to give aryl or alkyl organostibines with high selectivity by the use of $Ni(OAc)_2$. Furthermore, the obtained arylstibines further react with arylboronic acids to give biaryls selectively in the presence of $PdCl_2$. The organostibines are stable to handle in air. The present reactions are compatible to various functional groups and easy to scale up.

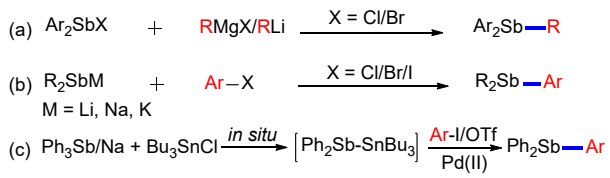


- **Catalysis**: Ni-catalyzed Sb-C bond formation and Pd-catalyzed C-C bond formation
- **Application**: Compatible to various functional groups, large scalable synthesis

Scheme 2. Cross-coupling reactions of organoantimony compounds

At the beginning of the study aiming at the use of stibines (R_3Sb) as the synthetic coupling partners, we realized that convenient and versatile synthetic methods of triarylstibines are not available. Scheme 3 summarizes the hitherto known

synthetic methods of triorganostibines.[21] All of these reactions need highly reactive and moisture/oxygen sensitive reagents and/or conditions, which limits severely the compatibility to functional groups. Therefore, we started our research by establishing a convenient and versatile synthetic method of triorganostibines. The second step of the third procedure in Scheme 3c is the Pd-catalyzed cross-coupling between a nucleophilic Sb-reagent and electrophilic aryls such as aryl halides and tosylates.[21g, h] Being inspired by this reaction, we attempted to achieve cross-coupling by electronically reverse combination, i.e., electrophilic Sb-compounds (Ar_2SbX) and nucleophilic carbon nucleophiles ($RB(OH)_2$), both of which are readily available and easy to handle.



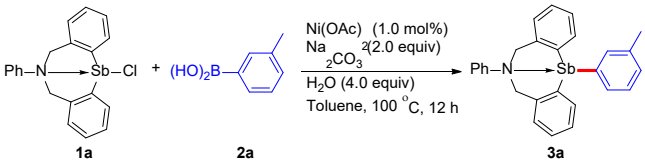
Scheme 3. Synthesis of trivalent antimony compounds

Results and Discussion

We chose chlorostibine **1a** and *meta*-tolylboronic acid **2a** as the coupling partners to form an antimony−carbon (Sb−C) bond and optimized the reaction conditions (Table 1, and Table S1−2, See the Supporting Information (SI) for full experimental details). To our delight, the attempted cross-coupling proceeded efficiently at 100 °C to give the desired arylated stibine **3a** in 96% yield by the use of $Ni(OAc)_2$ as the catalyst in the presence of Na_2CO_3 and 4.0 equivalent of water in toluene (Table 1, entry 1). Addition of phosphine ligands did not improve the efficiency (entries 2−8). Na_2CO_3 was essential (entry 10) and the yield decreased in the absence of water (entry 11). Other Ni, Pd and Cu salts also catalyzed this reaction, albeit less efficiently (entries 12−18).

With the optimal conditions in hand, the substrate scope of this reaction was examined (Scheme 4). Scheme 4a lists the results obtained using various arylboronic acids. Aryl boronic acids with either an electron-rich or electron-deficient substituent afforded the cross-coupling products in good to excellent yields. It is noteworthy that this reaction is compatible towards a wide range of functional groups including fluoride (**3m**, **3s**, **3w**), trifluoromethyl (**3o**, **3p**, **3q**, **3r**), chloride (**3k**, **3t**), bromide (**3n**, **3u**, **3v**), iodide (**3l**), aldehyde (**3x**), ketone (**3y**, **3z**), alkenyl (**3ab**), alkynyl (**3ac**), silyl (**3ae**), siloxy (**3af)** and ester (**3aa**) groups on the aromatic ring. The functionized stibines **3ag** and **3ah** were afforded in acceptable 57% and 61% yields, respectively. *Ortho*-substituted aryl boronic acids also reacted with **1a** to give the products **3b**, **3q**, **3t**, **3v** in moderate to good yields (53−85%) under the same conditions, indicating that steric effect is not significant in this reaction. Arylboronic acids with a fused aromatic ring could couple with chlorostibine **1a** smoothly to provide the desired products **3al**, **3am** and **3an** in 89%, 64% and 58% yields, respectively. As a derivative of steroid natural product a stibine analogue of an estrone **3aj** was successfully obtained in 86% yield.[8b] Various heteroaryl- and vinylboronic acids can also couple with **1a** smoothly to provide the corresponding stibines as shown in Scheme 4b. It is noteworthy that the alkyl boronic acids also reacted with **1a** to give the corresponding alkylstibines **5a−d**, which were isolated as stable solids in moderate to good yields (Scheme 4c). We continued to examine this cross-coupling reaction using various chlorostibines **1** and the results are shown in Scheme 5. Chlorostibines bearing a variety of substituents on the nitrogen efficiently coupled with arylboronic acids to give **6a−6k** in good to excellent yields. Stiboles **6m−q** were obtained in excellent yields. This reaction also applied successfully to the synthesis of acyclic triarylstibines, giving rise to **6r−6u** in high yields.

Table 1. Optimization of reaction conditions of Ni-catalyzed cross-coupling of chlorostibine **1a** with arylboronic acid **2a**[a]

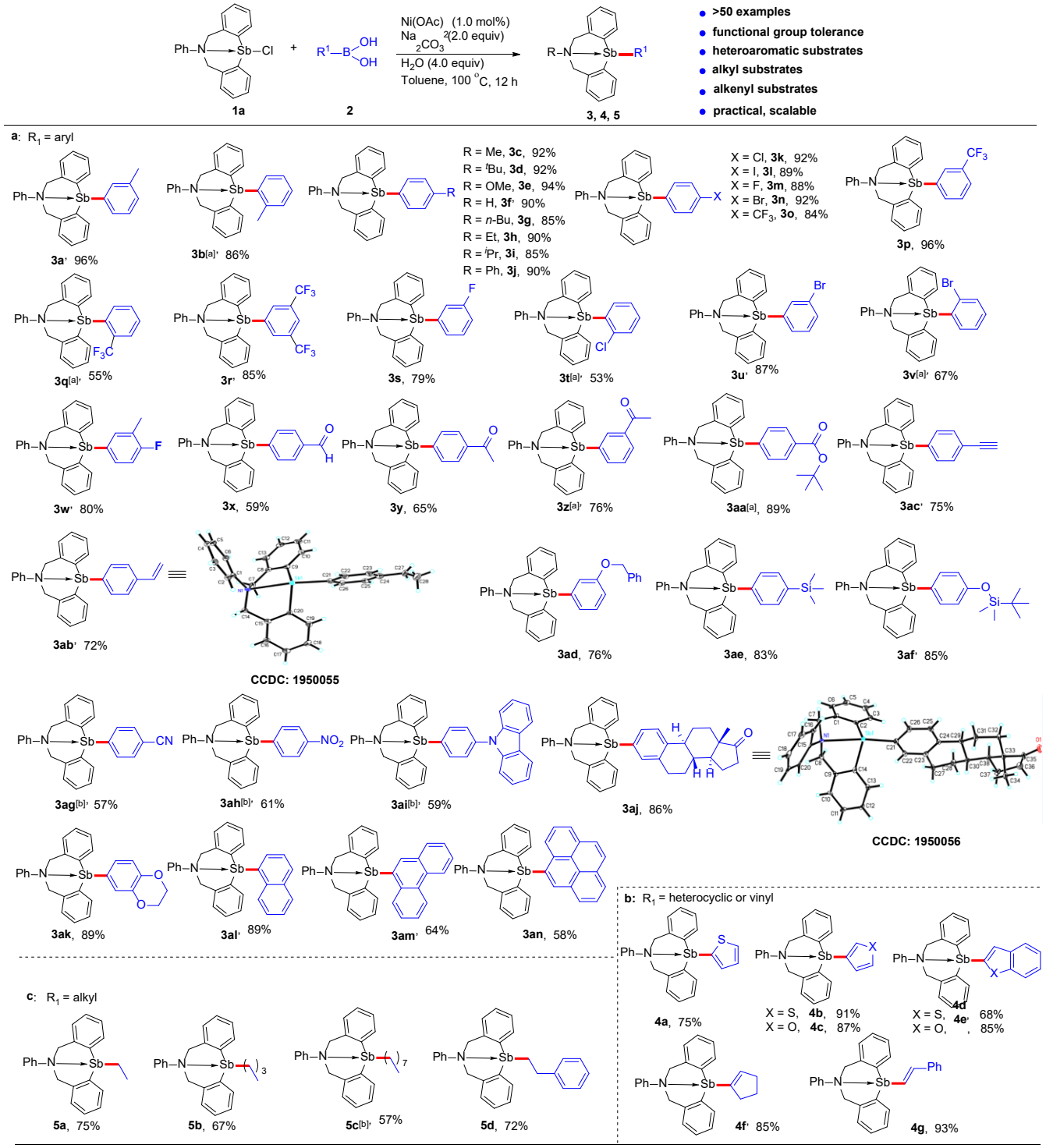


1a 2a 3a

Entry	Deviation from standard conditions	3a (%)
1	**none**	**96**
2	PPh_3 (2.0 mol%) as ligand	31
3	PCy_3 (2.0 mol%) as ligand	47
4	$^tBu_3P$ (2.0 mol%) as ligand	37
5	dppf (2.0 mol%) as ligand	34
6	Xantphos (2.0 mol%) as ligand	79
7	Brettphos (2.0 mol%) as ligand	69
8	BINAP (2.0 mol%) as ligand	38
9	Without $Ni(OAc)_2$	0
10	Without Na_2CO_3	0
11	Without H_2O	27
12	$Ni(PPh_3)_2Cl_2$ instead of $Ni(OAc)_2$	10
13	$Ni(PCy_3)_2Cl_2$ instead of $Ni(OAc)_2$	15
14	$Ni(acac)_2$ instead of $Ni(OAc)_2$	57
15	$Ni(OTf)_2$ instead of $Ni(OAc)_2$	53
16	$Ni(COD)_2$ instead of $Ni(OAc)_2$	48
17	$Pd(OAc)_2$ instead of $Ni(OAc)_2$	35
18	$Cu(OAc)_2$ instead of $Ni(OAc)_2$	43

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.11 mmol), Na_2CO_3 (0.20 mmol, 2.0 equiv), metal salt (0.001 mmol, 1.0 mol%), ligand (0.002 mmol, 2.0 mol%), H_2O (0.40 mmol, 4.0 equiv), toluene (1.0 mL) at 100 °C for 12 h, Isolated yield.

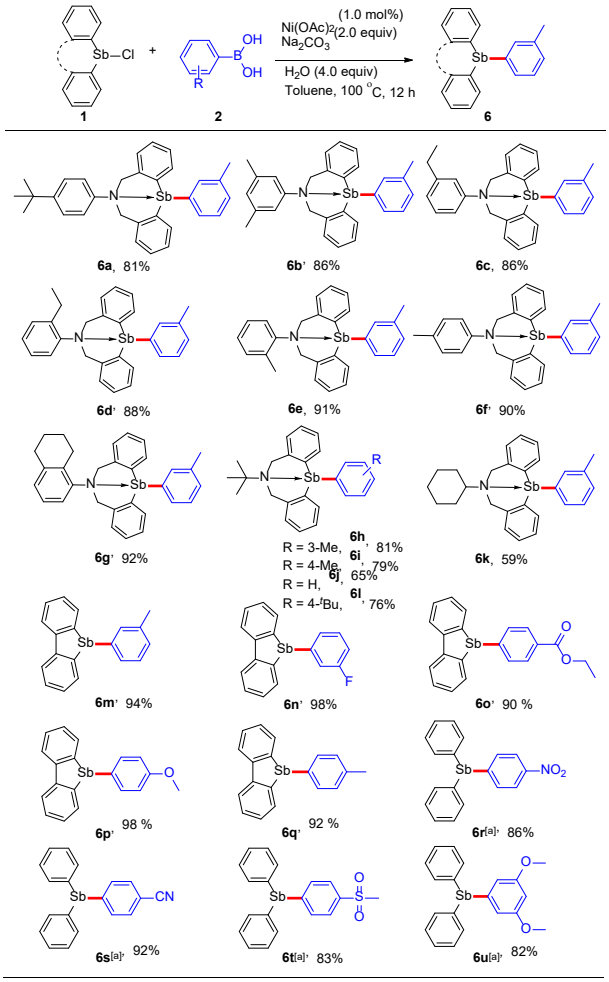
We then examined the reactivity of halostibines. In addition to the chlorostibines, all fluorostibine (**1m**), bromostibine (**1l**) and iodostibine (**1k**) reacted with boronic acids **2** to give the corresponding cross-coupling products as shown in Scheme 6. It is interesting that the relative reactivity decreases in the order of Cl > Br > I > F (see also Figure 1), which was different from general reactivities of organohalides (F < Cl < Br < I),[22] and longer reaction time was required to complete the reaction in the cases of Br and I (16 h and 20 h, respectively) in comparison to Cl (12 h). The reaction of the fluorostibine was much slower and required 24 h using a larger amount of $Ni(OAc)_2$ (10 mol%) and the yields were slightly lower than in the cases of other halostibines. All combinations of halostibines with aryl-, heteroaryl- and alkylboronic acids provided the corresponding products in good to excellent yields (Scheme 6). Arylboronic acids having an electron-donating group tend to give relatively higher yields than those possessing an electron-withdrawing group.



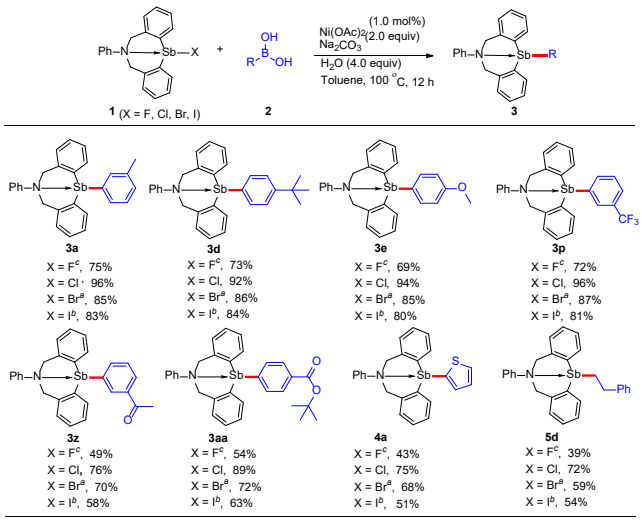
Scheme 4. Arylation, alkylation, and vinylation of chlorostibine **1a** with Boronic Acids **2**. Reaction conditions: **1a** (0.20 mmol), **2** (0.22 mmol), Na_2CO_3 (0.40 mmol, 2.0 equiv), $Ni(OAc)_2$ (0.002 mmol, 1.0 mol%), H_2O (0.80 mmol, 4.0 equiv), toluene (2.0 mL) at 100 °C for 12 h, isolated yield. [a] 20 h. [b] Boronic acids (0.30 mmol), $Ni(OAc)_2$ (0.01 mmol, 5.0 mol%), 24 h.

Aiming at synthetic application of the present protocols, a large scale production was carried out and 34.77 g of **3a** was obtained in 96% yield as shown in Scheme 7, demonstrating the high potential of this procedure as a practical synthetic process.

Oxidative cross-coupling reactions between two different organometallic reagents have emerged as useful methods for C−C bond formation.[9, 23] Recently, Chaplin's group reported Pd-catalyzed oxidative cross-coupling of triarylstibines with aryl trifluoroborate salts.[13d] We then attempted an oxidative cross-coupling of organostibines with aryl boronic acids which has never been reported yet. We performed the reaction of *Sb*-aryl dibenzo-1,5-azastibocines **3a** with phenylboronic acid **2f** in the

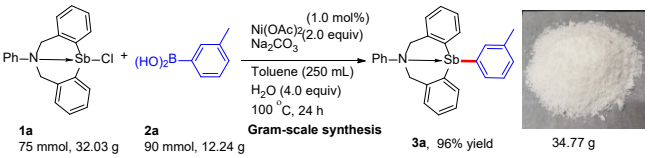


Scheme 5. Scope of chlorostibines. Reaction conditions: **1a** or **1n** or Ph_2SbCl (0.20 mmol), **2a** (0.22 mmol), Na_2CO_3 (0.40 mmol, 2.0 equiv), $Ni(OAc)_2$ (0.002 mmol, 1.0 mol%), H_2O (0.80 mmol, 4.0 equiv), toluene (2.0 mL) at 100 °C for 12 h, isolated yield. [a] Without H_2O.



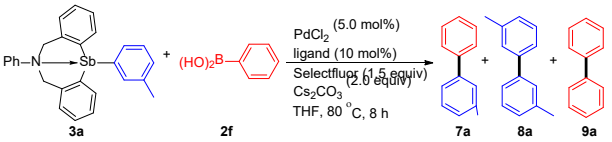
Scheme 6. Reaction of fluorostibine (**1m**), bromostibine (**1l**) and iodostibine (**1k**). Reaction conditions: **1a** (0.20 mmol), boronic acid **2** (0.22 mmol), Na_2CO_3 (0.40 mmol, 2.0 equiv), $Ni(OAc)_2$ (0.002 mmol, 1.0 mol%), H_2O (0.80 mmol, 4.0 equiv), toluene (2.0 mL) at 100 °C for 12 h, isolated yield. [a] 16 h. [b] 20 h. [c] Boronic acid (0.30 mmol) and $Ni(OAc)_2$ (0.02 mmol, 10 mol%), 24 h.

presence of a commercially available and inexpensive oxidant, Selectfluor, which was frequently employed in oxidative cross-coupling reactions.[24]



Scheme 7. Gram-scale experiment. Reaction conditions: **1a** (75 mmol), **2a** (90 mmol), Na_2CO_3 (150 mmol, 2.0 equiv), $Ni(OAc)_2$ (0.75 mmol, 1.0 mol%), H_2O (300 mmol, 4.0 equiv), toluene (250 mL) at 100 °C for 24 h, isolated yield.

Table 2. Optimization of reaction conditions of oxidative cross-coupling of *N*-phenyl Sb-aryl-1,5-azastibocines **3a** with Phenylboronic acid 2f.[a]

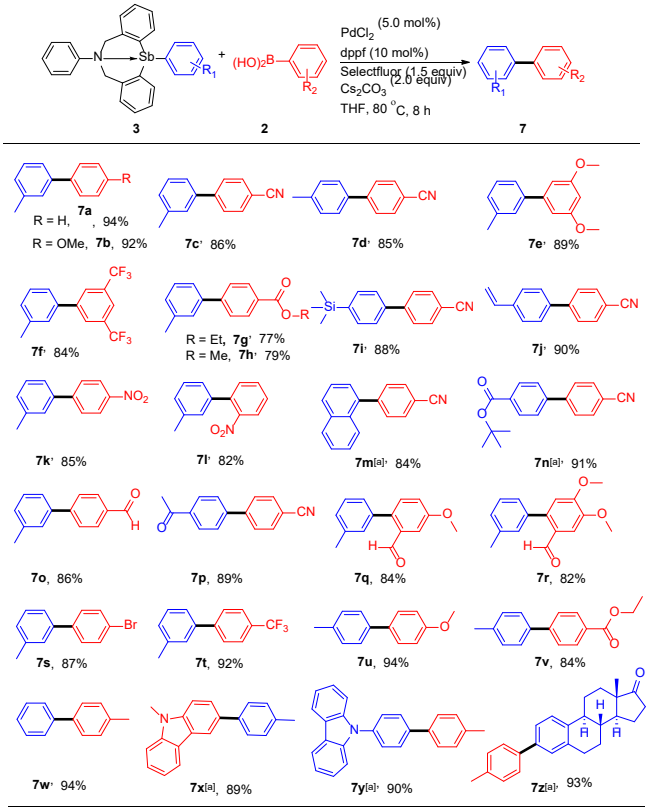


Entry	Deviation from standard conditions	Yield(%)[b] 7a	8a	9a
1	none	96	<1	<1
2	dppf (5 mol %)	45	2	<1
3	without dppf	5	<1	<1
4	PPh_3 instead of dppf	19	3	5
5	PCy_3 instead of dppf	15	4	3
6	BINAP instead of dppf	20	2	7
7	$Pd(OAc)_2$ instead of $PdCl_2$	47	13	3
8	$Pd(acac)_2$ instead of $PdCl_2$	23	2	5
9	$Pd(CH_3CN)_2Cl_2$ instead of $PdCl_2$	27	5	12
10	$Pd(dba)_2$ instead of $PdCl_2$	21	8	<1
11	$Pd(PPh_3)_4$ instead of $PdCl_2$	16	<1	36
12	^{t}BuOK instead of Cs_2CO_3	63	6	2
13	^{t}BuONa instead of Cs_2CO_3	56	8	<1
14	CH_3ONa instead of Cs_2CO_3	44	5	3
15	$K_2S_2O_8$ instead of Selectfluor	14	5	30
16	$PhI(OAc)_2$ instead of Selectfluor	2	<1	16
17	without $PdCl_2$	0	0	0
18	without Selectfluor	2	<1	<1
19	without Cs_2CO_3	10	11	<1

[a] Reaction conditions: **3a** (0.1 mmol), **2f** (0.1 mmol), $PdCl_2$ (0.005 mmol, 5 mol%), dppf (0.01 mmol, 10 mol%), Selectfluor (0.15 mmol, 1.5 equiv), Cs_2CO_3 (0.2 mmol, 2.0 equiv), THF (1.0 mL) at 80 °C for 8 h. [b] GC yields using *n*-dodecane as an internal standard.

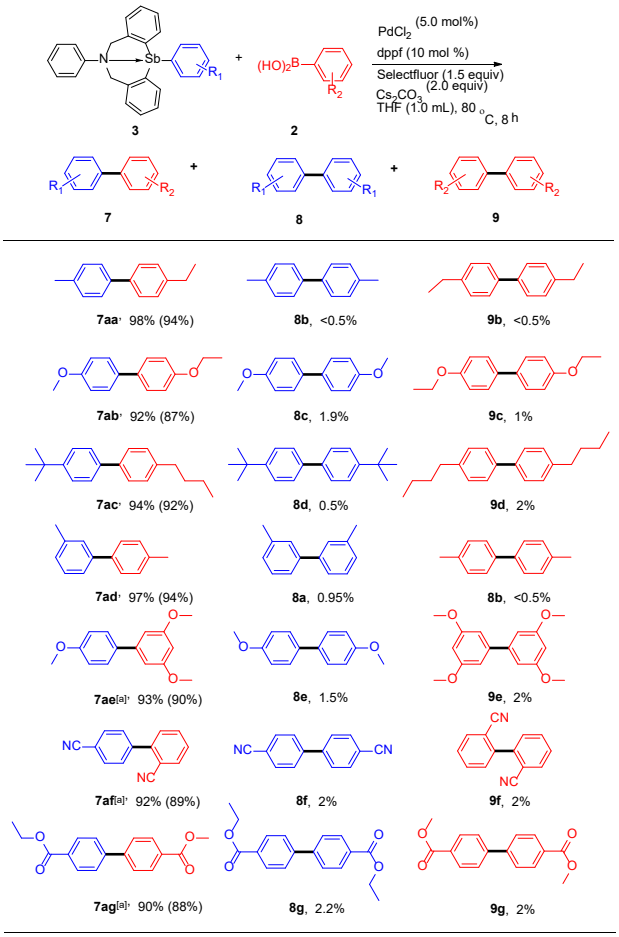
Table 2 shows the selected examples of the reactions conducted using various ligands, catalysts, bases and oxidants (see SI, Table S3−9). After systematic screening of these factors, the combination of $PdCl_2$/dppf/Selectfluor/Cs_2CO_3 was found to give the best result as shown in entry 1 in Table 4, where the desired cross-coupling product **7a** was formed in 96% yield. When the amount of dppf was reduced to 5.0 mol%, the yield of **7a** was decreased to 45%, and the cross-coupling products were formed in only 5% yield in the absence of dppf (entries 2, 3). PPh_3, PCy_3 and BINAP can not effectively promote the reaction (entries 4−6). Other Pd(II) complexes (entries 7−9) and

Pd(0) complexes (entries 10, 11) gave the cross-coupling product **7a** in moderate yields along with, in some cases, considerable amount of the homo-coupling product **8a** from **3a**. Sodium and potassium alkoxides also worked as the base to give the **7a** in moderate yields (entries 12−14). Cross-coupling products were formed in poor yields when $K_2S_2O_8$ or $PhI(OAc)_2$ was employed as the oxidant (entries 15, 16). When one of the reagents $PdCl_2$, dppf, Selectfluor, Cs_2CO_3 was absent, the present reaction did not proceed efficiently (entries 3, 17−19).



Scheme 8. Pd-catalyzed cross-coupling of stibines **3** with aryl boronic Acids **2**. Reaction conditions: stibine **3** (0.2 mmol), aryl boronic acid **2** (0.2 mmol), $PdCl_2$ (0.01 mmol, 5.0 mol%), dppf (0.02 mmol, 10 mol%), Selectfluor (0.30 mmol, 1.5 equiv), Cs_2CO_3 (0.4 mmol, 2.0 equiv), THF (2.0 mL), at 80 °C for 8 h, isolated yield. [a] Aryl boronic acid (0.24 mmol), at 100 °C for 12 h.

Under the optimized conditions as shown in entry 1 of Table 2, the reaction was carried out using a variety of aryl boronic acids. Aryl boronic acids with electron-withdrawing substituents or electron-donating substituents coupled with various *Sb*-aryl dibenzo-1,5-azastibocines, and the corresponding products were formed in good to excellent yields (Scheme 8). *Para*- and *ortho*-nitrophenylboronic acids underwent the cross-coupling with **3a** to provide **7k** and **7l** in 85% and 82% yields, respectively. Cross-coupling product **7s** bearing a bromide substituent was afforded in 87% yield. Ketones and nitriles were tolerated in this coupling. We then chose different *Sb*-aryl dibenzo-1,5-azastibocines as coupling partners to react with *para*-cyanophenylboronic acid **2ag**. It was found that diverse functional groups such as trimethylsiyl, vinyl and *tert*-butoxycarbonyl groups were compatible with the reaction conditions. Stibines with complex structures, such as **3ai**, **3aj** and **3ao**, could also smoothly couple with 4-methyl phenylboronic acid to generate the corresponding biaryls **7y**, **7z** and **7x** in excellent yields. The cross-coupling of alkyl-Sb(III) with aryl boronic acids could not occur, but the cross-coupling of alkenyl-Sb(III) provides **12a** in 26% yield (see SI, Scheme S11-12), further optimization is still under investigation in our lab.

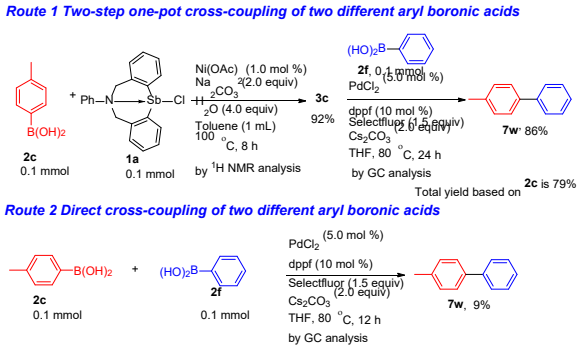


Scheme 9. High selective synthesis of biaryls with similar or same substituents. Reaction conditions: stibine **3** (0.2 mmol), aryl boronic acids **2** (0.2 mmol), $PdCl_2$ (0.01 mmol, 5.0 mol%), dppf (0.02 mmol, 10 mol%), Selectfluor (0.30 mmol, 1.5 equiv), Cs_2CO_3 (0.4 mmol, 2.0 equiv) and THF (2.0 mL) at 80 °C for 8 h, GC yield using *n*-dodecane as an internal standard, isolated yield is listed in the parentheses. [a] Aryl boronic acid (0.24 mmol), at 100 °C for 16 h.

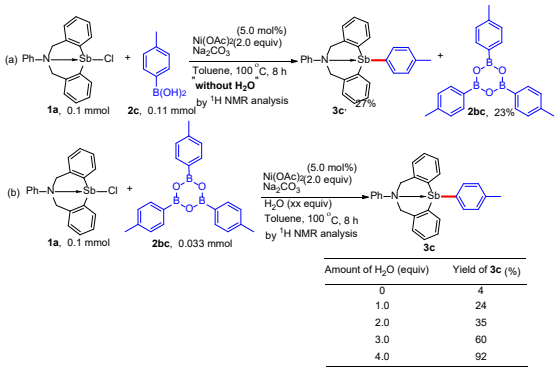
Selectivity of cross-coupling over homo-coupling is a key factor in the practical application of oxidative cross-coupling reactions.[9] We examined the generality of the selectivity of the present procedure (Scheme 9). When triarylstibine **3c** having a 4-methylphenyl group was allowed to react with 4-ethylphenylboronic acid **2c**, the cross-coupling product **7aa** was obtained in 98% yield. Likewise, biaryls **7ab**,[23c] **7ac** and **7ag** carrying a similar substituent on the *para*-position of each aromatic ring were obtained selectively in 92%, 94% and 90% yields, respectively. Furthermore, the present oxidative cross-coupling between two similar aryls having the same substituent at different positions proceeded efficiently, giving rise to the desired biaryls **7ad**−**af** in >92% yields. These results indicated that stibines are promising reagents for selective oxidative cross-coupling with boronic acids.

The oxidative cross-coupling with boronic acids mentioned above could be carried out by employing a stibine intermediate without isolation which was *in-situ* generated from a different boronic acid. For example, chlorostibine **1a** was firstly allowed to

react with phenylboronic acid **2f** under the conditions shown in *Route 1* of Scheme 10, and then toluene was removed under reduced pressure. Into the resulting mixture containing **3c** (92% by ^{1}H NMR analysis) were added 4-methylphenylboronic acid **2c**, $PdCl_2$, dppf, Selectfluor, Cs_2CO_3 and THF. After stirring for 24 h, **7w** was found to be formed in 86% GC yield, and the total yield based on **2c** was 79%. A direct reaction of *para*-tolylboronic acid **2c** with phenylboronic acid **2f** gave the cross-coupling product **7w** in 9% yield under the same condition. These results demonstrate the usefulness of this one-pot biaryls synthesis via halostibines.



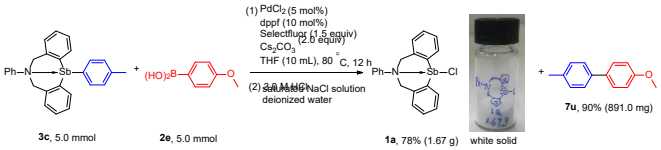
Scheme 10. One-pot synthesis of a biaryl from two boronic acids via a stibine intermediate.



Amount of H_2O (equiv)	Yield of **3c** (%)
0	4
1.0	24
2.0	35
3.0	60
4.0	92

Scheme 11. Investigation on the role of H_2O

As shown in Table 1, addition of H_2O to the cross-coupling reaction of chlorostibine **1a** with *meta*-tolylboronic acid **2a** improved the yield of arylated stibine **3a**. In order to reveal the role of H_2O, we investigated the reaction of **1a** using *para*-tolylboronic acid **2c** and the corresponding boroxine **2bc** as the coupling partner (Scheme 11). In the absence of H_2O, reaction of *p*-tolylboronic acid **2c** with chlorostibine **1a** afforded the cross-coupling product **3c** in 27% yield along with dehydrated trimer, boroxine **2bc**, in 23% yield. Although boroxine **2bc** reacted with chlorostibine **1a** to give **3c** only in 4% yield, the yield of **3c** gradually increased with the addition of H_2O up to 92% in the presence of 4.0 equivalents of H_2O. These results demonstrated that H_2O may accelerate the transmetalation by inhibiting conversion of a boronic acid to the corresponding trimer, which maybe not effective for the cross-coupling reaction.



Scheme 12. Recovery of stibine **1a**.

5,6,7,12-Tetrahydrodibenz[*c,f*][*1,5*]azabismocines has been recovered from the reaction system by Tanaka et al.[29] Therefore, we turn our attention to the reuse of halostibines. A recovery experiment was performed under standard conditions in a 5.0 mmol scale and 78% of chlorostibine **1a** was recycled (Scheme 12, see SI).

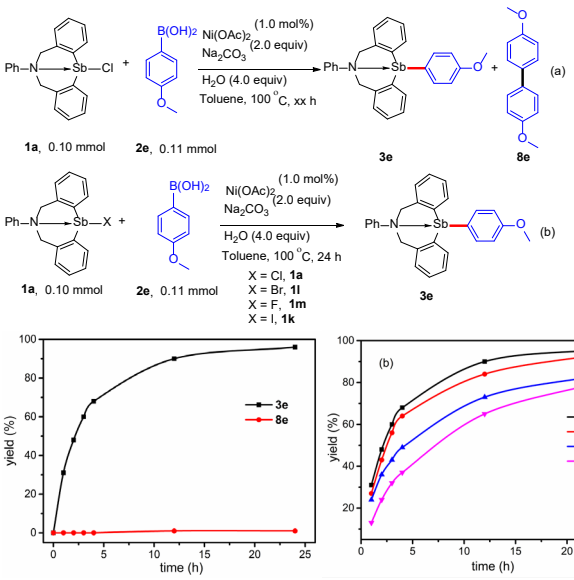


Figure 1. (a) Time course plots of cross-coupling reaction of *para*-methoxyphenylboronic acid **2e** with chlorostibine **1a**. Reaction conditions: **1a** (0.10 mmol), **2e** (0.11 mmol), $Ni(OAc)_2$ (0.001 mmol), Na_2CO_3 (0.20 mmol), H_2O (0.40 mmol), toluene (1.0 mL), monitoring at 100 °C for 0−24 h. All yields were ^{1}H NMR yields using mesitylene as an internal standard. (b) Comparison of the relative reactivity of fluorostibine **1m**, chorostibine **1a**, bromostibine **1l** and iodostibine **1k**. Reaction conditions: halostibine **1** (0.10 mmol), **2e** (0.11 mmol), $Ni(OAc)_2$ (0.001 mmol), Na_2CO_3 (0.20 mmol), H_2O (0.40 mmol), toluene (1.0 mL), monitoring at 100 °C for 1−24 h. All yields were ^{1}H NMR yields using mesitylene as an internal standard.

Figure 1 shows the time course plots of the cross-coupling of (4-methoxyphenyl)boronic acid **2e** with various halostibines (see SI, Table S10). As shown in Figure 1a, the reaction between chlorostibine **1a** and **2e** proceeded rapidly in the first five hours, after that, the yield of the cross-coupling product **3e** gradually increased up to 96% in 24 hours with only a trace amount of homo-coupling product **8e**. In order to compare the reactivity of halostibines, the similar time course plots of experiments using **1l**, **1m** and **1k** were shown in Figure 1b. These results indicated that the reactivity as well as the yields of the desired product **3e** decreased in the order of Sb−Cl > Sb−Br > Sb−I > Sb−F, but the difference is not very large. It is interesting that chlorostibine reacted fastest to give the highest yield.

We roughly performed kinetic studies of the reaction of **1a** with **2e** and the results are shown in Figure 2, in which the yield

of the arylated product **3e** at the early stage of the reaction (20 min and 40 min) was plotted. These results showed that the rate of reaction depends on the amount of *para*-methoxyphenyl boronic acid **2e**, but it is independent of the amount of chlorostibine **1a**. This is in accordance with the results of Figure 1b in which the reactivity of halostibines did not vary largely depending on the halides. These results implied that transmetalation of boronic acids with an active Ni intermediate is the rate-determining step in this cross-coupling reaction.

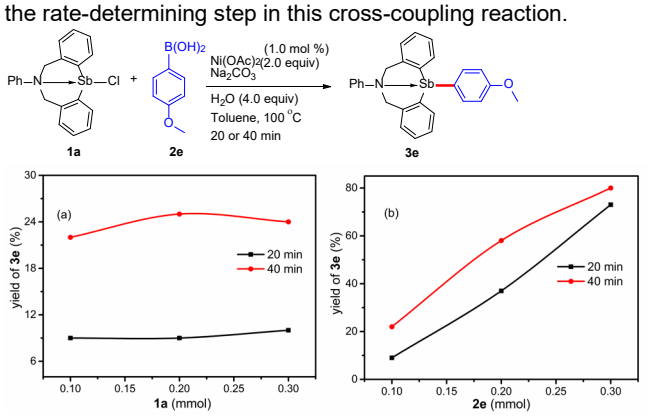
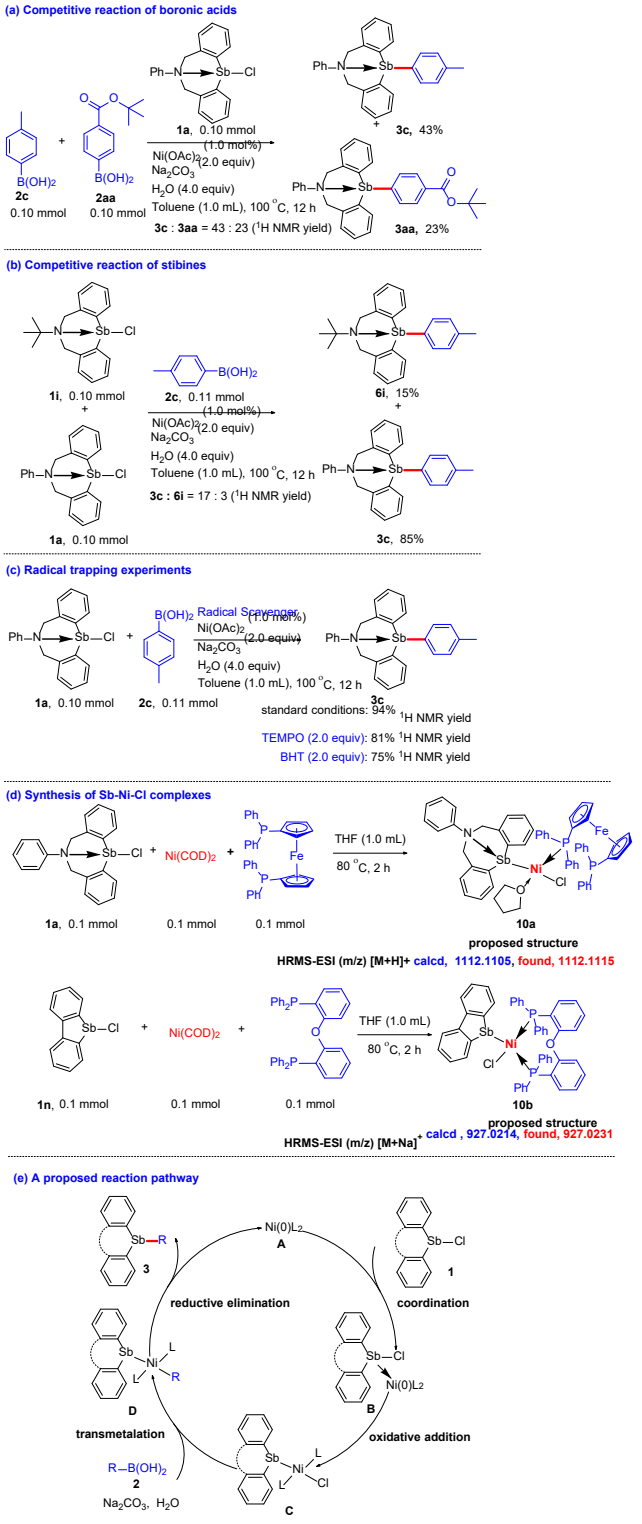


Figure 2. (a) The effect of the concentration of chlorostibine **1a** on the rate of the cross-coupling reaction of chlorostibine **1a** with *para*-methoxyphenylboronic acid **2e**. Reaction conditions: **1a** (0.10 or 0.20 or 0.30 mmol), **2e** (0.10 mmol), $Ni(OAc)_2$ (0.001 mmol), Na_2CO_3 (0.20 mmol), H_2O (0.40 mmol), toluene (1.0 mL), at 100 °C for 20 min or 40 min. All yields were ^1H NMR yields using mesitylene as an internal standard. (b) The effect of the amount of *para*-methoxyphenylboronic acid **2e** on the cross-coupling reaction of chlorostibine **1a** with *para*-methoxy phenylboronic acid **2e**. Reaction conditions: **2e** (0.10 or 0.20 or 0.30 mmol), **1a** (0.10 mmol), $Ni(OAc)_2$ (0.001 mmol), Na_2CO_3 (0.20 mmol), H_2O (0.40 mmol), toluene (1.0 mL), at 100 °C for 20 min or 40 min. All yields were ^1H NMR yield using mesitylene as an internal standard.

We next carried out some control experiments to reveal the electronic effect on the reaction and the reaction mechanisms (Scheme 13). Competitive reaction using two aryl boronic acids (**2c** and **2aa**) showed that the boronic acid having an electron-donating group reacted preferentially (Scheme 13a). On the other hand, the chlorostibine bearing an electron-withdrawing group on the nitrogen reacted preferentially (Scheme 13b). The addition of 2.0 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxyl- toluene (BHT) did not suppress the reaction, giving **3a** in 81% and 75% yields, respectively (Scheme 13c). These results suggested that the reaction does not involve a radical intermediate. Antimony ligands have proven to be effective donors to metal centers under certain conditions.[25] Reid's group reported the first example of a Ni(II) halide stibine complex.[26] In 2014, Gabbaï's group published several intriguing Ni(II) complex stabilized with tripodal antimony-phosphorus ligands.[27] There are several reports of nickel-antimony dimeric structures formed by the reaction of Ph_2SbCl or $PhSbCl_2$ with Ni(0) species.[28] Being inspired by these pioneering works, we attempt to synthesize Sb-Ni complexes intermediate. Chlorostibines **1a** and **1n** could be



Scheme 13. Control experiments and mechanism of the nickel-catalyzed cross-coupling of chlorostibines with boronic acids.

oxidatively added to $Ni(COD)_2$ in the presence of THF and phosphine ligands, giving rise to the possible nickel species. However, all attempts for the synthesis of these single crystals were failed. Then we analyzed these species by high resolution mass spectrometry (HRMS), and the possible structures **10a**

and **10b** were shown in Scheme 13d. It indicates the oxidative addition of chlorostibine with Ni(0) species is possible.[28] On the basis of these previous reports[25–28] and the above experimental results, we propose a possible catalytic cycle for this nickel-catalyzed cross-coupling reaction (Scheme 13e). The reaction begins with the coordination of Ni(0)L_2 (**A**) to a chlorostibine to form **B**, followed by oxidative addition to give **C**. Subsequent transmetalation with boronic acids occurs, as a rate-determining step, providing Ni-intermediate **D** which undergoes reductive elimination to give **3** and regenerates the active nickel(0) species **A**.

Then, our attention was turned to mechanistic study on the oxidative cross-coupling of arylated stibines with aryl boronic acids. The Pd-catalyzed cross-coupling reaction of *Sb*-aryl sstibine **3c** with aryl boronic acid **2e** was monitored by GC and the results are summarized in Figure 3. The yield of the desired biaryl **7u** increases rapidly at 80 °C in the first 1 hour and gradually in the next 3 hour reaches to 96% yield along with the formation of only small amounts of homo-coupling by-products **8b** and **8e** in 0.5% and 1.5% yields, respectively (see SI, Table S13). Figure 3 seems to show a quite short induction period.

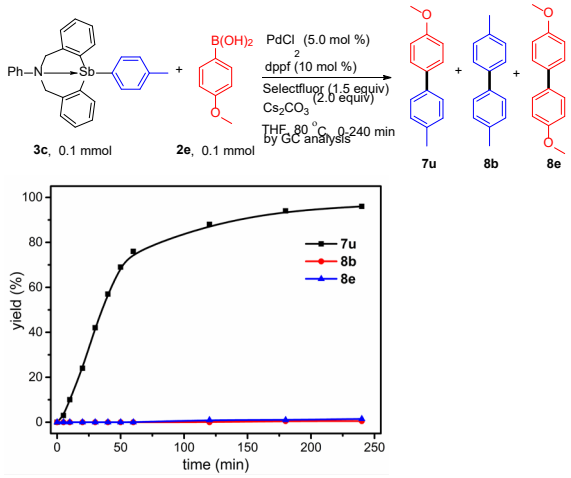


Figure 3. Time course plots of reaction of stibine **3c** with (4-methoxy phenyl)boronic acid **2e**. Reaction conditions: **3c** (0.10 mmol), **2e** (0.10 mmol), $PdCl_2$ (0.005 mmol), dppf (0.01 mmol), Selectfluor (0.15 mmol), Cs_2CO_3 (0.20 mmol) and THF (1.0 mL) at 80 °C for 0−4 h (240 min), GC yields using *n*-dodecane as an internal standard.

In order to explore the relation between the reaction rate and substrate concentrations, the reactions were run using different amounts of the substrates and quenched at early stages of the reaction (10, 20, or 30 min). The results were plotted in Figure 4, which showed that the yield of a biaryl **7u** remains unchanged under different concentrations of **3c** (Figure 4a). In contrast, the yield of **7u** apparently increased when larger amounts of **2e** were employed, albeit not obeying first order kinetics, indicating that transmetalation by aryl boronic acids might not be a rapid step in the catalytic cycle. Detailed kinetic experiments show that the cross-coupling is 2/3 order in aryl boronic acids (see SI, Table S15-16, Figure S12-13).

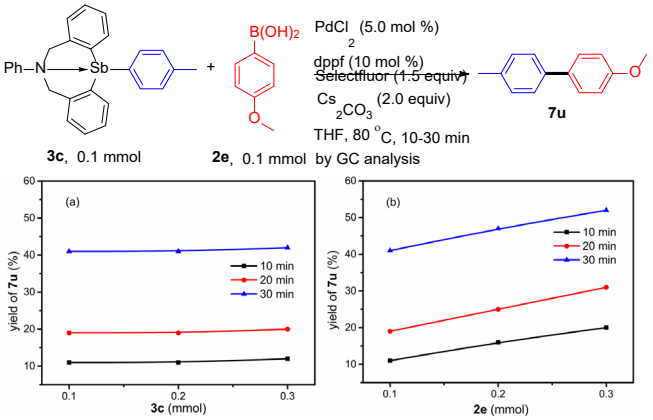


Figure 4. (a) The effect of the concentration of stibine **3c** on the rate of the reaction with (4-methoxyphenyl)boronic acid **2e**. Reaction conditions: **3c** (0.10, 0.20, or 0.30 mmol), **2e** (0.10 mmol), $PdCl_2$ (0.005 mmol), dppf (0.01 mmol), Selectfluor (0.15 mmol), Cs_2CO_3 (0.20 mmol) and THF (1.0 mL) at 80 °C for 10 min or 20 min or 30 min, GC yields using *n*-dodecane as an internal standard. (b) The effect of the concentration of (4-methoxyphenyl)boronic acid **2e** on the rate of the reaction with stibine **3c**. Reaction conditions: **2e** (0.10, 0.20, or 0.30 mmol), **3c** (0.10 mmol), $PdCl_2$ (0.005 mmol), dppf (0.01 mmol), Selectfluor (0.15 mmol), Cs_2CO_3 (0.20 mmol) and THF (1.0 mL) at 80 °C for 10 min or 20 min or 30 min, GC yield using *n*-dodecane as an internal standard.

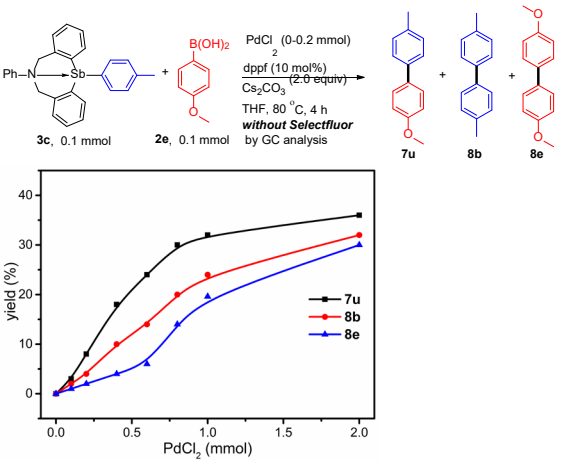
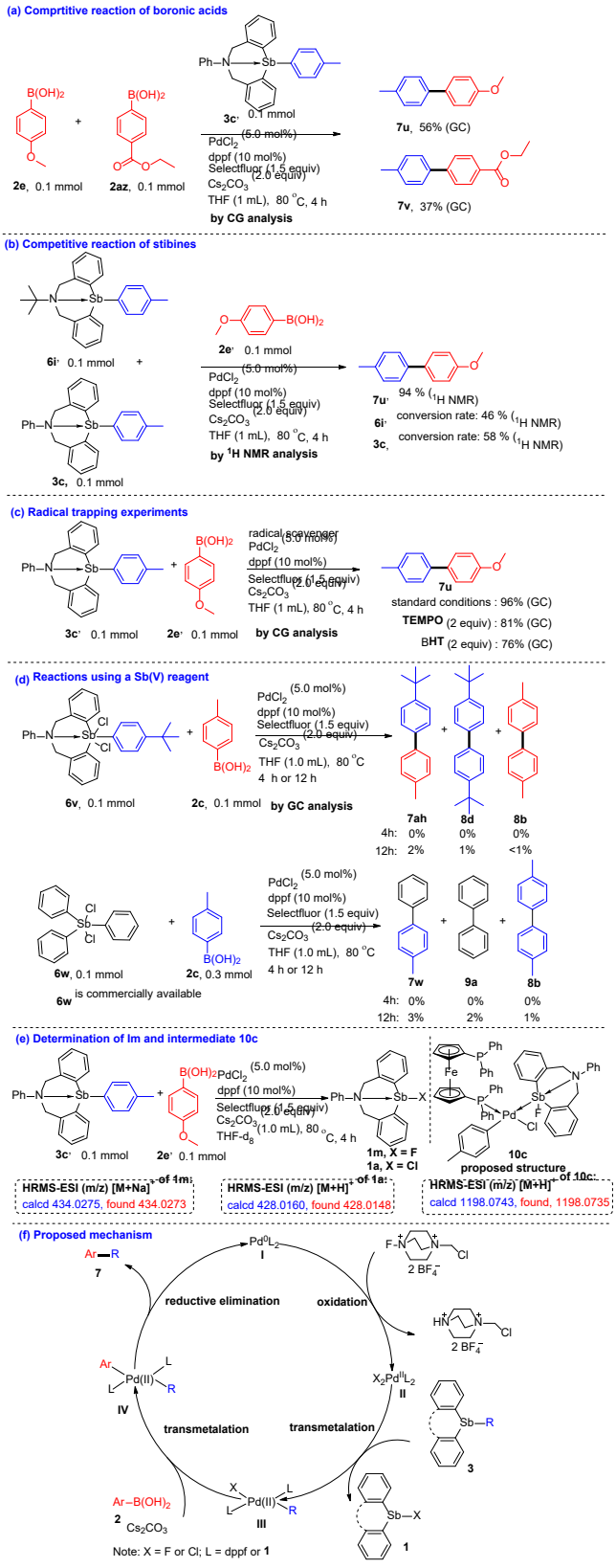


Figure 5. Pd-promoted oxidative cross-coupling reaction of (4-methoxyphenyl)boronic acid **2e** with stibine **3c** in the absence of Selectfluor. Reaction conditions: **3c** (0.10 mmol), **2e** (0.10 mmol), $PdCl_2$ (0−2.0 mmol), dppf (0.01 mmol), Cs_2CO_3 (0.20 mmol), THF (1.0 mL) at 80 °C for 4 h, GC yield using *n*-dodecane as an internal standard.

When the reaction of (4-methoxyphenyl)boronic acid **2e** with stibine **3c** was examined using different amounts of $PdCl_2$ in the absence of Selectfluor, not only cross-coupling but also homo-coupling took place competitively, giving a mixture of three biaryls (**7u**, **8b** and **8e**, Figure 5, see SI, Table S17). When 2.0 equivalent of $PdCl_2$ were employed, a mixture of **7u**, **8b** and **8e** was obtained in 96% total yield with a nearly 1: 1: 1 ratio. These results indicated that Pd(II) promotes coupling reaction of **2e** with **3c**, but Selectfluor is essential to perform the oxidative cross-coupling of stibines with aryl boronic acids with high selectivity.



Scheme 14. Control experiments and mechanism of the Pd-catalyzed oxidative cross-coupling of *sb*-aryl stibines with aryl boronic acids

Competitive reaction of two aryl boronic acids having a *para*-substituent (**2e** vs. **2az**) showed that the substituent on the aromatic ring exerted a small electronic effect on the present oxidative cross-coupling in a fashion that the reaction proceeded faster with electron-rich boronic acid (Scheme 14a). On the other hand, the substituent on the nitrogen atom of stibines (**6i** vs. **3c**) showed little effect on the reaction rate (Scheme 14b). Stoichiometric reactions (see SI, Tables S18-19, Figures S19-20) indicate that the rate of transmetallation of stibines with $PdCl_2$ is faster than that of aryl boronic acids at the first step of transmetalation, while at the second step of transmetallation, the rate of transmetallation of aryl boronic acids with ArPdX is faster than that of stibines. This palladium-catalyzed oxidative cross-coupling was not inhibited by the addition of TEMPO and BHT, suggesting that this cross-coupling does not involve a radical intermediate (Scheme 14c). In order to test whether stibines(v) serve as the reactive coupling agents, we chose **6v** and **6w** as the coupling partners to react with **2c** under standard conditions (Scheme 14d).[20] When the reactions were carried out for 4 hours, neither the cross-coupling products nor the homo-coupling products were detected, but when reaction time was extended to 12 h, very low yields of the coupling products were determined by GC analysis. This result demonstrated that a stibine(v) was not an intermediate. In addition, the signals observed by ^{19}F NMR, ^{31}P NMR, and HRMS during the reaction (0.5-3 h) can be attributed to the formation of possible intermediates **1m**/**1a** and **10c** (proposed structure based on HRMS, the synthesis of the single crystal of **10c** was failed) (Scheme 14e, and Figure S21-22 in SI), indicating Selectfluor, dppf and stibine exhibit a possible cooperative interaction with Pd, which may improve the selectivity of this coupling. With these experimental results in hand, we propose a possible catalytic cycle for this palladium-catalyzed oxidative cross-coupling reaction in which Pd(0) was oxidized to Pd(II) by Selectfluor (Scheme 14f).[24a] The reaction might start with the reaction of Pd(II) species **II** with stibines **3** to give the intermediate **III**, which then transmetalates with aryl boronic acids **2** to form diaryl Pd(II) intermediate **IV**. Reductive elimination of intermediate **IV** affords the desired cross-coupling product **8** along with Pd(0) species (**I**), which is then oxidized by Selectfluor to generate Pd(II) to restart the catalytic reaction. Based on these results and reviewer 2's comments, both the transmetallation to intermediate **IV** from Pd(II) intermediate **III** and the reductive elimination of intermediate **IV** to **7** may proceed at similar rates under the present conditions and both processes would contribute to the rate-determining steps.

Conclusion

We developed a general method for the synthesis of various stibines from halostibines. The formed stibines are successfully employed to carry out the Pd-catalyzed oxidative cross-coupling with boronic acids in the presence of Selectfluor as the oxidizing reagent. These two reactions developed in this study tolerated various functional groups such as aldehyde, ketone, nitro, cyano and heteroarene groups. All stibines prepared and used here are air/moisture-stable. It was also demonstrated that successive Ni- and Pd-catalyzed processes were carried conveniently in one flask without the isolation of the stibine intermediates. Based on the control experiments, plausible catalytic pathways were proposed. Consequently, the present Ni-catalyzed reaction provides triorganostibines as synthetic intermediates carrying various functional groups. The

combination of this reaction with the Pd-catalyzed cross-coupling will constitute a novel, useful and practical route to functionalized arenes by the use of widely available boronic acids.

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Keywords: nickel catalysis • palladium catalysis • Sb−C bond formation • oxidative cross-coupling • biaryl synthesis

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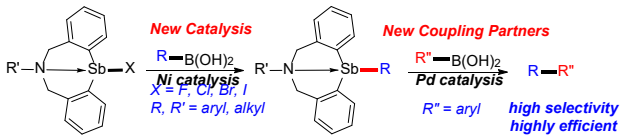

A general strategy for the formation of antimony-carbon bond was developed via the nickel-catalyzed cross-coupling of halostibines with aryl- or alkyl-boronic acids. The obtained stibines can be used as useful cross-coupling partners for further transformation towards boronic acids. The present study revealed chemical behaviors of stibines which reacts with aryl boronic acids to create Sb−C and C−C bonds.