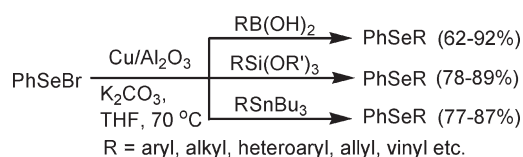# JOC Note

Al₂O₃-Supported Cu-Catalyzed Electrophilic Substitution by PhSeBr in Organoboranes, Organosilanes, and Organostannanes. A Protocol for the Synthesis of Unsymmetrical Diaryl and Alkyl Aryl Selenides

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Alumina-supported copper sulfate efficiently catalyzes electrophilic substitution in organoborane, organosilanes, and organostannanes by phenylselenium bromide providing a novel and efficient route to the synthesis of unsymmetrical diaryl and alkyl aryl selenides. A series of aryl, alkyl, and heteroaryl phenyl selenides were obtained in high yields. The catalyst is inexpensive, eco- and user-friendly, and recyclable. The mechanism involving Cu-assisted nucleophilic displacement of Br in PhSeBr by mild nucleophiles is described.
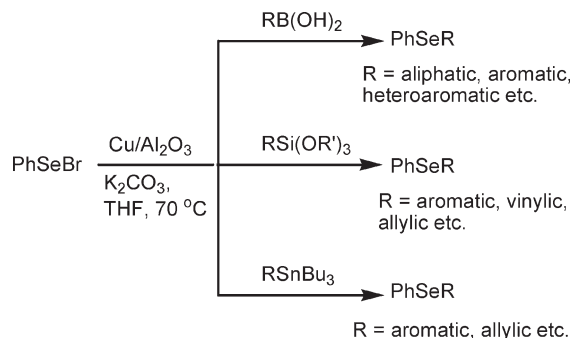
The phenylselenylation is a useful process in organic synthesis as selenium compounds are of much potential as anticancer and antioxidant agents.[1] The existing methods for the synthesis of aryl selenides are based on primarily two types of reactions. The most common one is the nucleophilic addition of ArSe⁻ to aryl halides[2] or aryl diazonium salts[3]

SCHEME 1. Cu-Catalyzed Carbon−Selenium Bond Formation

or aryl boronic acids under oxygen atmosphere (oxidative coupling)[4] in the presence of a transition metal catalyst. Another is the electrophilic substitution by ArSe⁺ (ArSeX, ArSeCN) in stronger nucleophiles such as aryl lithium, aryl Grignard reagent, or aryl mercurals.[5] However electrophilic substitution by ArSe⁺ in milder nucleophiles like aryl boronic acids, aryl siloxanes, and aryl stannanes is rare. Only one such reaction of phenylselenyl chloride and vinyl boronic acid/ester in the presence of ionic liquid has been reported by Kabalka et al.[6] Thus, we considered it interesting to investigate electrophilic substitution by PhSe⁺ in readily available milder nucleophilic reagents using a simple catalyst. This led us to report here a general reaction of phenylselenium bromide with aryl, alkyl, or heteroaryl boronic acids/siloxanes/stannanes using our recently developed heterogeneous alumina-supported copper(II) catalyst[7] (Scheme 1). This catalyst is very easy to prepare, inexpensive, and environmentally friendly.

To optimize the reaction conditions the coupling of phenylselenyl bromide with phenyl boronic acid/phenyl trimethoxysilane/phenyl tributylstannane using different solvents and base at varied temperatures in the presence of Cu/Al₂O₃ was studied. The best result was obtained by using 4 mol % of Cu/Al₂O₃ catalyst and K₂CO₃ in THF (Table 1, entries 5, 10, and 13). In the absence of catalyst (Table 1, entries 6, 11, and 14) the reaction did not proceed at all in the case of siloxane and stannane and occurred marginally (15%) with phenyl boronic acid. The reactions with either Al₂O₃ or

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TABLE 1. Optimization of Reaction Conditions[a]

PhSeBr + RZ $\xrightarrow{\text{Cu/Al}_2\text{O}_3 \ (4 \ \text{mol\%})}$ PhSeR

entry	RZ	solvent	base	temp (°C)	time (h)	yield (%)
1	PhB(OH)$_2$	DMF	K$_2$CO$_3$	120	16	70
2		DMSO	K$_2$CO$_3$	130	16	50
3		H$_2$O	K$_2$CO$_3$	100	16	0
4		toluene	K$_2$CO$_3$	110	16	20
5		THF	K$_2$CO$_3$	70	8	92
6		THF	K$_2$CO$_3$	70	18	15[b]
7		THF	Cs$_2$CO$_3$	70	16	84
8		THF	K$_3$PO$_4$	70	16	42
9		THF	NaOH	70	16	30
10	PhSi(OMe)$_3$	THF	K$_2$CO$_3$	70	9	88
11		THF	K$_2$CO$_3$	70	18	0[b]
12		DMF	K$_2$CO$_3$	120	16	55
13	PhSnBu$_3$	THF	K$_2$CO$_3$	70	8	86
14		THF	K$_2$CO$_3$	70	18	0[b]
15		DMF	K$_2$CO$_3$	120	16	48

[a]Reactions were carried out in the presence of 4 mol % of Cu/Al$_2$O$_3$ catalyst unless otherwise stated. [b]Reactions were carried out in the absence of Cu/Al$_2$O$_3$ catalyst.

CuSO$_4$ alone or a mixture of Al$_2$O$_3$ and CuSO$_4$ also provided the same results as observed in the absence of catalyst.

Thus in a typical experimental procedure, a mixture of phenylselenyl bromide and organo-boronic acid/siloxane/stannane was heated in THF at 70 °C in the presence of Cu/Al$_2$O$_3$ and K$_2$CO$_3$ for a period of time as required to complete the reaction (TLC) to provide the corresponding selenide. Standard workup followed by purification provided the product. The results were summarized in Tables 2−4. The phenylselenylation of organo-boronic acids was demonstrated in Table 2. A variety of substituted phenyl boronic acids participated in this reaction. Both electron-donating and electron-withdrawing groups in the phenyl ring of boronic acids are equally effective. The difluorophenyl boronic acid also provided the corresponding product without any difficulty. The naphthyl and heteroaryl such as furanyl, thiophenyl, and pyridinyl boronic acids are compatible with this reaction. These fluorophenyl and heteroaryl selenides may be of potential for biological activity.[1] The alkyl boronic acid also underwent reaction by this procedure. The phenylselenylation of aryl, vinyl, and allyl siloxanes and stannanes was achieved in high yields with the same catalyst (Tables 3 and 4).

In general the reactions are very clean and high yielding. A wide range of functionalized unsymmetrical diaryl, heteroaryl−aryl, and alkyl−aryl selenides were obtained by this procedure. This procedure is compatible with a variety of functionalities such as OMe, Cl, F, COMe, CN, etc. This protocol has enormous scope for an easy access to a library of organoselenides starting from any of the organo-boranes, silanes, and stannanes. The Cu/Al$_2$O$_3$ catalyst is very robust, nonair-sensitive, and user-friendly. No appreciable leaching of catalyst was detected as measured by ICP-MS (inductively coupled plasma mass spectrometry) (Cu content of the fresh catalyst: 0.517 mmol g^{-1}; and that after 7th cycle: 0.503 mmol g^{-1}) and the catalyst is recycled seven times without any appreciable loss of efficiency.

To investigate the mechanism of the reaction a series of experiments were conducted. The X-band EPR (electron paramagnetic resonance) spectrum of the fresh copper catalyst shows four well-defined hyperfine lines for solid sample

TABLE 2. Copper Catalyzed Phenylselenylation of Organyl Boronic Acids

ArSeBr + RB(OH)$_2$ $\xrightarrow[\substack{\text{K}_2\text{CO}_3, \text{ THF,} \\ 70 \ ^\circ\text{C}}]{\text{Cu/Al}_2\text{O}_3}$ ArSeR

entry	Ar	R	time (h)	yield (%)[a]	ref
1	Ph	phenyl	8	92	2i
2	Ph	4-methylphenyl (Me)	8	90	2a
3	Ph	3-methylphenyl (Me)	8.5	91	2a
4	Ph	3,5-dimethylphenyl (Me, Me)	9	90	8
5	Ph	4-methoxyphenyl (MeO)	8	89	2i
6	Ph	3-chlorophenyl (Cl)	9	85	3
7	Ph	4-acetylphenyl (MeOC)	10	88	2i
8	Ph	2-cyanophenyl (CN)	10	83	2e
9	Ph	difluorophenyl (F, F)	10	78	
10	Ph	naphthyl	9	81	2a
11	Ph	furanyl (O)	10	88	
12	Ph	thiophenyl (S)	9	84	2a
13	Ph	pyridinyl-phenyl (N)	10	80	
14	Ph	^{n}Bu	12	62	9
15	p-tolyl	phenyl	9	88	2a
16	p-tolyl	4-methoxyphenyl (MeO)	8.5	87	5b

[a]Isolated yield of pure product.

at 77 K resulting from the coupling of the unpaired electron with the nuclear spin of copper(II) (Figure 1). The g values of the fresh and used catalyst are $g_{\parallel}$ = 2.41367, 2.5408 and $g_{\perp}$ = 2.1406, indicating a tetragonally distorted octahedral

TABLE 3. Copper Catalyzed Phenylselenylation of Organo Silanes

$$\text{ArSeBr} \quad + \quad \text{RSi(OR')}_3 \xrightarrow[\substack{K_2CO_3, \text{ THF,} \\ 70\ ^\circ C}]{\text{Cu/Al}_2O_3} \text{ArSeR}$$

entry	Ar	R	R'	time (h)	yield (%)[a]	ref
1	Ph	(phenyl)	Me	9	88	2i
2	Ph	(Me-phenyl)	Et	9	86	2a
3	Ph	(MeO-phenyl)	Et	10	89	2i
4	Ph	(allyl)	Et	12	78	10
5	Ph	(butenyl)	Me	10	80	11
6	*p*-tolyl	(phenyl)	Me	9	87	2a

[a]Isolated yield of pure product.

TABLE 4. Copper Catalyzed Phenylselenylation of Organo Stannanes

$$\text{ArSeBr} \quad + \quad \text{RSnBu}_3 \xrightarrow[\substack{K_2CO_3, \text{ THF,} \\ 70\ ^\circ C}]{\text{Cu/Al}_2O_3} \text{ArSeR}$$

entry	Ar	R	time (h)	yield (%)[a]	ref
1	Ph	(phenyl)	8	86	2i
2	Ph	(Me-phenyl)	9.5	83	2a
3	Ph	(MeO-phenyl)	8	87	2i
4	Ph	(allyl)	10	77	11
5	*p*-tolyl	(allyl)	10	79	16

[a]Isolated yield of pure product.

FIGURE 1. The X-band EPR spectral pattern of Cu^{2+} in (a) fresh catalyst, (b) used catalyst, and (c) intermediate complex **2**.

SCHEME 2. Mechanistic Proposal

geometry for Cu(II).[12] The regenerated catalyst also shows a very similar axial EPR spectrum as observed in the freshly prepared catalyst. When the fresh catalyst was treated with phenylselenyl bromide in THF a dirty white complex **2** (Scheme 2) was obtained. The FTIR of this complex shows an additional band at $2800-3000$ cm^{-1} corresponding to the aromatic C−H stretching frequencies indicating the addition of PhSeBr with Cu(II) center (see the Supporting Information). These peaks disappeared in the FTIR spectrum of the used catalyst. The formation of this type of complex is also not unprecedented.[13] The EPR spectral pattern of this intermediate complex exhibited the *g* values as $g_3 = 2.055$, $g_2 = 2.124$, and $g_1 = 2.212$ which are indicative of an octahedral environment with a rhombic distortion at the metal center.

To check an alternative possibility of the reaction pathway we also treated the Cu catalyst with phenylboronic acid. The reaction residue did not show any change in FTIR and EPR spectra from those of fresh catalyst indicating no reaction. This clearly suggests that an interaction of substrate PhSeBr with the copper catalyst is the first step of the reaction to give an intermediate complex **2** giving rise to a rhombic distortion of the copper(II) coordination geometry. The UV-DRS (ultra violet diffuse electron spectrometry) experiments of the fresh and used catalyst show the band at > 750 nm while a

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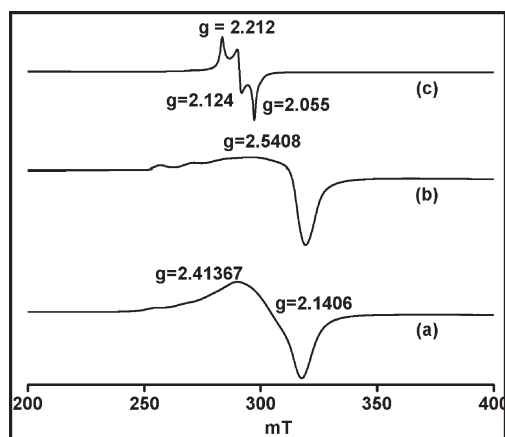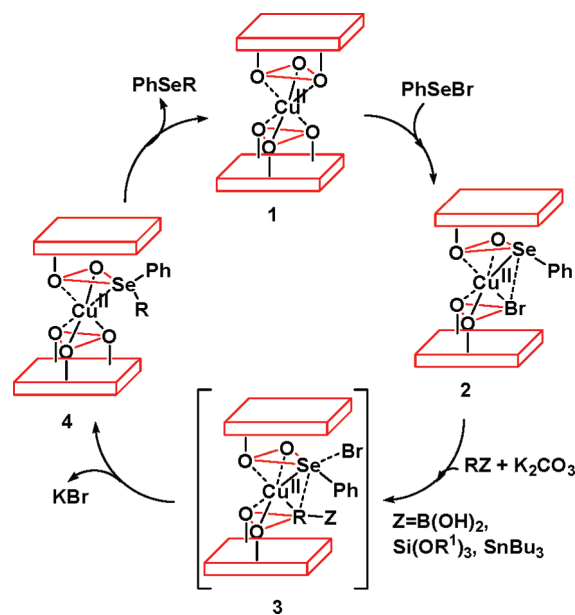
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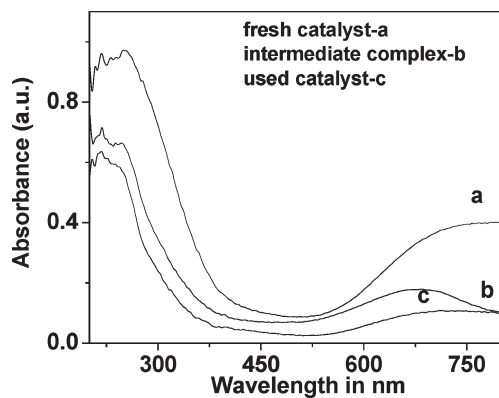
FIGURE 2. UV−vis−DR spectrum of (a) fresh catalyst, (b) intermediate complex **2**, and (c) used catalyst.

blue shift (680−700 nm) was observed for the intermediate complex (Figure 2).

This further supports the presence of octahedral geometry around Cu(II).[12b,14] Thus the formation of copper(II) selenide complex **2** as intermediate is proposed. Subsequent addition of RZ [Z = B(OH)$_2$, Si(OR^1)$_3$, SnBu$_3$] at **2** followed by aryl-selenium bond formation furnishes the intermediate **4** via a transient **3** where R interacts with the Se center being assisted by Cu(II) catalyst (Scheme 2). We speculate that a copper-assisted nucleophilic displacement[13,15] occurs at the selenium center of PhSeBr by the mild carbon nucleophiles (boronic acids, silanes, stannanes, etc.). The elimination of PhSeR from the coordination sphere of Cu(II) regenerates the catalyst, which initiates the next cycle.

In conclusion, we have developed a very efficient and general protocol for the synthesis of unsymmetrical aryl−aryl, alkyl−aryl, and heteroaryl−aryl selenides by the reaction of phenylselenyl bromide and any of the organo-boronic acids, siloxanes, and stannanes catalyzed by heterogeneous Cu(II)/Al$_2$O$_3$ catalyst. Such a wide scope demonstrated by a single strategy is noteworthy. The most significant feature of this protocol is the involvement of hitherto unexplored electrophilic substitution by PhSe$^+$ in milder carbon nucleophiles such as aryl boranes, silanes, and stannanes. The advantages of high yields, simplicity of operation, scaling up to multigram quantities, easy availability and recyclability of catalyst, and environmental acceptability with no

appreciable leaching of catalyst make this procedure more attractive for the synthesis of organoselenides.

Experimental Section

General Experimental Procedure for the Synthesis of Organo-selenides: Representative Procedure for Diphenyl Selenide by Phenylselenylation of Phenyl Boronic Acids (Table 2, Entry 1). To a solution of phenylselenyl bromide (236 mg, 1 mmol) and phenyl boronic acids (147 mg, 1.2 mmol) in THF (4 mL) was added K$_2$CO$_3$ (276 mg, 2 mmol) and Cu/Al$_2$O$_3$ catalyst (80 mg, 4 mol %) and the mixture was heated at 70 °C (oil bath) for 8 h. The reaction mixture was allowed to cool, extracted with Et$_2$O (3 × 20 mL), and washed with brine. The organic phase was dried (Na$_2$SO$_4$) and evaporated to leave the crude product, which was purified by column chromatography over silica gel (hexane) to provide pure diphenyl selenide as a colorless oil (215 mg, 92%). The spectroscopic data (¹H NMR and ¹³C NMR) of this product are in good agreement with those of an authentic sample.[2i] After workup the residual catalyst was washed with water (5 × 3 mL) followed by acetone (3 × 4 mL). The solid was then dried at 100 °C for 8 h for further use. The catalyst was recycled 7 times without any appreciable loss of activity (see the recyclability chart in the Supporting Information).

This procedure was followed for all the reactions listed in Table 2 and for phenylselenylation of organo-siloxanes (in the presence of 1 M THF solution of TBAF, 1.2 mL) and stannanes listed in Tables 3 and 4, respectively. Although the representative procedure is based on a 1 mmol scale reaction, it has been scaled up to 10 mmol with reproducible results. The compounds are of high purity as checked by ¹³C NMR.

The known compounds were identified by comparison of their spectra with those of authentic samples (see references in Tables 2−4). The unknown compounds were properly characterized by their spectroscopic data (IR, ¹H NMR, and ¹³C NMR) provided in the Supporting Information.

Supporting Information Available: Procedure for the preparation of intermediate complex **2** (Scheme 2), FTIR spectra of fresh catalyst, used catalyst, and intermediate complex **2** and catalyst recyclability chart, characterization data (IR, ¹H, and ¹³C NMR spectroscopic data, elemental analysis report) of the products in entries 9, 11, and 13 in Table 2, and copies of ¹H and ¹³C NMR spectra of all products listed in Tables 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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