$CsOH{\cdot}H_2O$ Promoted Areneselenenylation of Aryl Bromides and Iodides[#]

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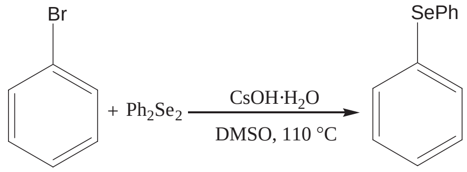
We report a transition metal-free synthetic protocol for the cross-coupling reaction of aryl bromides and aryl iodides and diphenyl diselenide (Ph_2Se_2) using $CsOH{\cdot}H_2O$ as a base in DMSO at 110 °C. Using this protocol, we show that a variety of diaryl selenides can be synthesized in moderate to good yields.

The construction of an aryl–heteroatom bond is an important study[1] and preparation of diaryl selenides continues to be an area of great interest because of their potential as anticancer and antioxidant agents.[2] They are also key intermediates in the synthesis of a plethora of biologically and pharmaceutically important selenium compounds such as selenonium salts, selenoxides, selenimines, and selenide dihalides.[3] In recognition of their importance, various synthetic methods for the formation of diaryl selenides have been reported in literature.[4] However, these synthetic approaches have many significant limitations, such as the availability of the corresponding organometallic compounds, harsh reaction conditions such as the use of polar and toxic solvents such as HMPA and high reaction temperatures.[5] Even though these reported methods are very efficient and provide good conversion for the synthesis of diaryl selenides, these synthetic methodologies require the use of transition-metal complexes, suffer from long reaction times, and have a relatively narrow application scope for substrates. Furthermore, the use of transition-metal complexes leads to the generation of hazardous waste, which has a number of environmental health problems associated with it.[6] Thus, development of improved synthetic methods for the synthesis of diaryl selenides still remains an active ongoing research area. $CsOH{\cdot}H_2O$ has received increasing interest over the last few years, and many publications have reported its powerful basicity offering a new reagent for the formation of a variety of carbon–heteroatom and carbon–carbon bond forming reactions.[7] Recently, we have reported that $CsOH{\cdot}H_2O$ can be used as an excellent reagent in the aryl–nitrogen and aryl–sulfur bonds involving transition metal-free syntheses.[7d,e] This prompted us to investigate the aryl–selenium bond forming reaction with $CsOH{\cdot}H_2O$ and we wish to present our findings in this paper.

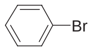
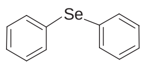
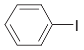
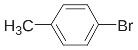
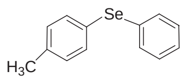
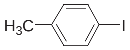
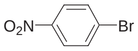
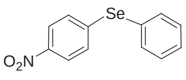
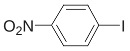
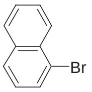
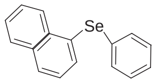
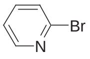
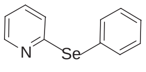
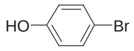
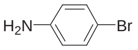
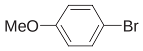
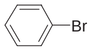
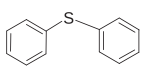
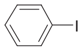
Herein, we present our preliminary findings in the development of the transition metal-free coupling of various structurally divergent aryl halides and Ph_2Se_2 using $CsOH{\cdot}H_2O$ as an efficient base. To the best of our knowledge, the direct cross coupling of aryl halides with Ph_2Se_2 to form diaryl selenides using $CsOH{\cdot}H_2O$ has not been reported to date. At first, we evaluated the feasibility of the direct cross coupling of bromobenzene and Ph_2Se_2 using $CsOH{\cdot}H_2O$ (Scheme 1).[8] Both coupling partners were taken (bromobenzene-1.0 mmol and Ph_2Se_2-1.5 mmol), along with 2 mmol of $CsOH{\cdot}H_2O$ in 3 mL of DMSO in a sealed tube. Then, it was placed in an oil bath pre-heated to 110 °C and held at this temperature for 10 min.

To our satisfaction, the addition product was obtained in 64% yield after purification of the crude product using silica-gel flash chromatography (Table 1, Entry 1). We carried out the same reaction with KO^tBu and DMSO as the solvent; the



Scheme 1.

Table 1. $CsOH{\cdot}H_2O$-Promoted Arylselenenylation of Aryl Bromides and Iodides

Entry	Aryl halide	Reactant	Product	Time /min	Yield /%[a)]
1		A		10	64
2		A		10	68
3		A		15	52
4		A		10	55
5		A		10	72
6		A		5	82
7		A		10	78
8		A		20	47
9		A	—	30	0
10		A	—	30	0
11		A	—	30	0
12		B		10	67
13		B		5	70

a) Isolated yield. A = Ph_2Se_2, B = Ph_2S_2.

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reaction progress was very slow (5–7% of yield) and in other solvents such as THF, NMP with KO^{t}Bu, which did not furnish the expected product under the above experimental conditions, demonstrated the efficacy of our reagent in the arylselenenylation.

Encouraged by these results, we carried out the reaction under different conditions and the results were quite satisfactory. At ambient temperatures the cross coupling between bromobenzene and Ph_2Se_2 did not proceed, even after stirring the reaction for several days. As a control experiment, the same reaction mixture was heated in the absence of the base at 110 °C. No cross-coupled product was formed, even after heating the coupling fragments for a longer period of time. Thus, base plays a vital role in this reaction. The optimum yields of the product were obtained with a ratio of aryl halide to Ph_2Se_2 of 1:1.5. Among the solvents used were DMSO–THF, NMP, THF, and DMSO and all were found to be good media for this transformation. It seems that DMSO is a much better solvent in terms of yields than all of the other tested solvents. With the absence of DMSO, no product could be isolated from the crude reaction mixture.

Having found the optimum reaction conditions, we carried out the reactions of Ph_2Se_2 with bromobenzene. We then investigated the direct cross-coupling reactions of a wide range of substituted aryl halides, having both electron withdrawing and electron donating substituents Ph_2Se_2. The results from this study are shown in Table 1. It is clear from Table 1 that most substrates underwent direct cross-coupling reactions to afford the corresponding selenides in moderate to good yields. Reaction times are also very short (5–20 min) for most of the substrates. However, the areneselenenylation of aryl halides containing electron-donating substituents required a longer reaction time. The electron-withdrawing group containing ($-NO_2$) aryl halides reacted faster when compared to electron-donating groups like the $-CH_3$ counter part (see Entries 3–6, Table 1). For Entries 3 and 4, the product is formed in a 1:1 ratio of regioisomers (*meta*:*para*). The iodo aryl analogues when compared to bromo aryl analogues gave good yields on reacting with diphenyl diselenides (see Table 1). Heterocyclic aryl halide, like 2-bromopyridine (Entry 8), reacted slowly to form the corresponding product exclusively in *ortho*-position with a low yield of 47% on reacting with Ph_2Se_2. However, aryl halides that contain *p*-hydroxy, *p*-amino, and *p*-methoxy substituents do not undergo adduct formation at all under our experimental conditions (Entries 9–11).[9] We evaluated the feasibility of the direct cross coupling of bromo/iodobenzenes with diphenyl disulfide (Ph_2S_2) also as described in the general procedure, (see Entries 12 and 13, Table 1) and the results are satisfactory. However, this type of coupling reaction does not seem to work well with aryl chlorides and fluorides. We have also evaluated the feasibility of this reaction with chlorobenzene and Ph_2Se_2, which did not furnish the desired product even after 1 h. Also, with *o*-bromotoluene as an example, *m*-substituted product is exclusively formed with Ph_2Se_2. In the case of alkylhalide such as benzyl bromide, the corresponding coupled product is formed in 5 min at 70 °C with a yield of 82%. The mechanism of this facile arylselenenylation is not clear at present and investigation is under way.

In conclusion, we have demonstrated that the coupling of aryl halides with Ph_2Se_2 to give the corresponding aryl selenides can be promoted with $CsOH \cdot H_2O$. The reaction conditions are compatible with functional groups in the substrates as well with some limitations. Since the seleno group could be subjected to diverse transformations, there is a possibility that this reaction may be developed into a synthetically useful process, although further work is needed to expand the scope of the reaction in large scale applications.

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8 A mixture of aryl halide (1 mmol), Ph_2Se_2/Ph_2S_2 (1.5 mmol), and $CsOH \cdot H_2O$ (2 mmol) in DMSO (3 mL) was taken in a sealed tube placed in preheated oil bath at the given temperature (Table 1) and then held at that temperature for the given time. Then, the reaction mixture was cooled to rt, poured into water containing crushed ice, and stirred for 5 min. Saturated aqueous NH_4Cl solution was added to this mixture, and the organic portion was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with a saturated NH_4Cl solution and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel to furnish the product. All isolated compounds were fully characterized by comparing their spectral data (^{1}H NMR and mass spectra) to authentic compounds.[4c]