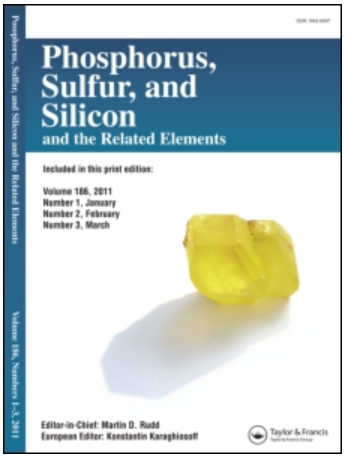

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SYNTHESIS OF INDOLES, 3,1-BENZOXAZINES, AND QUINOLINES FROM 2-ALKENYLANILIDES AND ACTIVE SELENIUMS

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The reaction of diphenyl diselenide with [bis(trifluoroacetoxy)iodo]benzene followed by the addition of 2-allylphenol gave 2-phenylselenomethyl-2,3-dihydro-benzofuran in 82% yield. The reaction of phenylselenenyl chloride with* N-*tosyl-2-isopropenylanilide followed by the addition of* m-*CPBA afforded N-tosyl-3-methylindole in 68% yield. Interestingly, the reaction of diphenyl diselenide with [bis(trifluoroacetoxy)iodo]benzene followed by the addition of 2-isopropenylaniline gave 4-methyl-4-phenylselenomethyl-2-trifluoromethyl-3,1-benzooxazine in 65% yield.

Keywords 3,1-Benzooxazine; [bis(trifluoroacetoxy)iodo]benzene; diphenyl diselenide; indole; quinoline

INTRODUCTION

Phenylselenenyl chloride (**1**) is a useful reagent for the synthesis of cyclic ethers or amines.[1] Phenylseleno derivative of 2,3-dihydro-benzofuran was prepared by the reaction of **1** with 2-allylphenol, which is classified as a cyclofunctionalization process.[2] Recently, Browne et al. reported the synthesis of butenolide from diphenyl diselenide (**2**) catalyzed intramolecular cyclization.[3] Indoles are very important compounds because of their synthetic and pharmacological utility. One of the most useful methods for the synthesis of indoles and quinoines is the intramolecular cyclization of alkenylanilides and alkynylanilides with active halogens because of commercial availability of starting alkenylanilines.[4–6] We have also reported the synthesis of *N*-tosylindoles (**3**) and 3,1-benzoxazine (**4**) from 2-alkenylanilides (**5**) and DMTST.[7] However, to our knowledge, there is no report on the synthesis of indoles **3** by intramolecular selenoamination using **1** or diphenyl diselenide **2**. We report in this article the synthesis of *N*-tosylindoles **3**, and 3,1-benzoxazines **4** from activated phenylselenenyl compounds with 2-alkenylanilides **5**.

RESULTS AND DISCUSSION

We first tried the reaction of diphenyl diselenide **2** with 2-allylphenol followed by the addition of [bis(trifluoroacetoxy)iodo]benzene (**6**). When allylphenol was added to a

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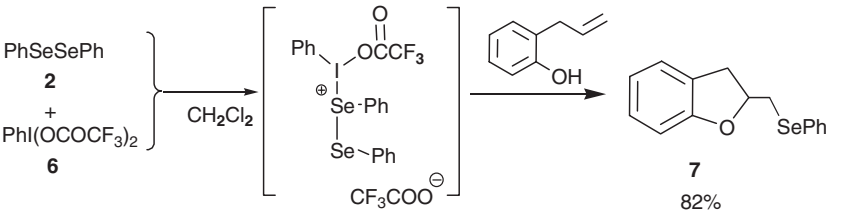
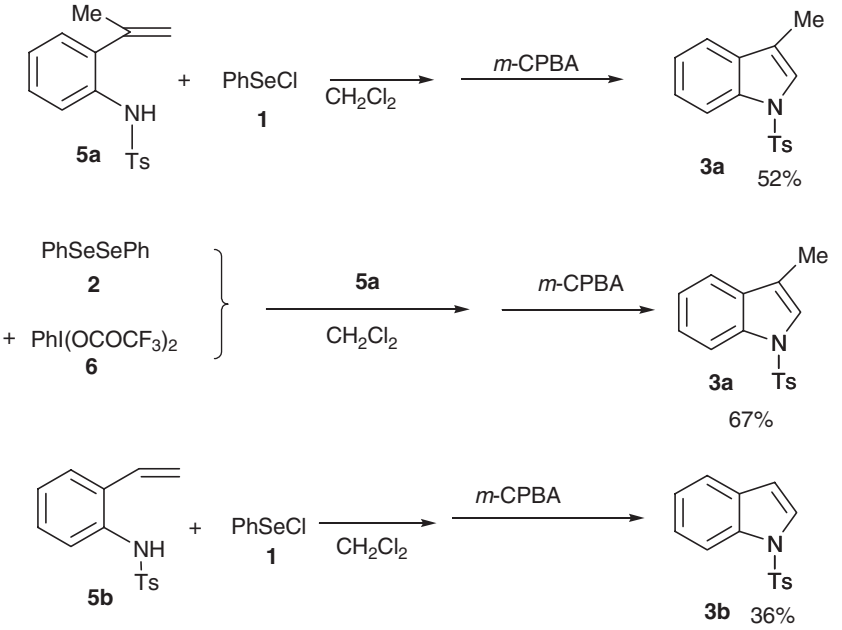
mixture of diselenide **2** and iodobenzene **6** in dichloromethane at rt, 2-phenylselenomethyl-2,3-dihydrobenzofuran **7** was obtained in 82% yield (Scheme 1). The result was quite similar to the reaction by using phenylselenenyl chloride as an active selenation reagent.[2]



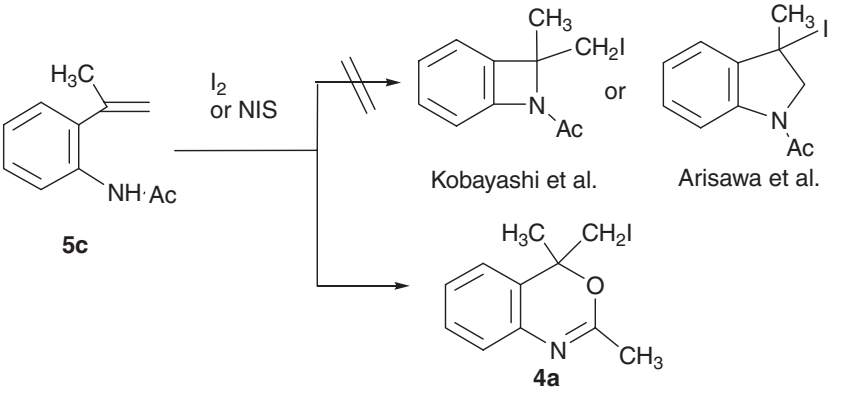
Scheme 1

Since this method proved to be a good procedure for intramolecular cyclization using diselenide **2**, we applied it to the synthesis of indole **3** via intramolecular aminocyclization of 2-isopropenylanilides **5**, which were easily synthesized from 2-alkenylnitrobenzenes.[4] When 2-isopropenyl-*N*-tosylanilide (**5a**) was treated with selenenyl chloride **1** at rt for 6 h followed by the addition of *m*-chloroperoxybenzoic acid (*m*-CPBA), 3-methyl-*N*-tosylindole (**3a**) was obtained in 52% yield. Similarly, the reaction of **5a** with diselenide **2** and **6** at rt for 6 h followed by oxidation gave **3a** in 67% yield (Scheme 2). The reaction of 2-vinyl-*N*-tosylanilide (**5b**) with selenenyl chloride followed by oxidation also gave *N*-tosylindole (**3b**), while the yield was 36%. Thus, the synthesis of indoles from 2-alkenylanilides was achieved by selenoamination.



Scheme 2

The reaction of 2-isopropenylacetanilide (**5c**) with active halogens has already been reported by Kobayashi et al.[4] and Arisawa et al.,[5] respectively. Although they claimed the different structures for the reaction products, we have found that the correct structure was 2,4-dimethyl-4-iodomethyl-3,1-benzoxazine (**4a**), whose structure was determined by X-ray crystallographic analysis (Scheme 3).[7]



Scheme 3

These results prompted us to investigate the reaction of active selenium compounds with 2-isopropenylacetanilide **5c** as to whether a similar reaction would occur. We investigated the reaction of **1** with acetanilide **5c**. Treatment of phenylselenenyl chloride **1** with acetanilide **5c** followed by the addition of aq. Na_2CO_3 gave 2,4-dimethyl-4-phenylselenomethyl-3,1-benzoxazine (**4b**) in 84% yield. Diphenyl diselenide **2** also reacted with acetanilide **5c** to give **4b** in 93% yield. Interestingly, the reaction of diselenide **2** with 2-isopropenylaniline (**8**) followed by the addition of [bis(trifluoroacetoxy)iodo]benzene **6** afforded 4-methyl-4-phenylselenomethyl-2-trifluoromethyl-3,1-benzoxazine (**4c**) in 70% yield, suggesting that [bis(trifluoroacetoxy)iodo]benzene **6** not only activates diphenyl diselenide but also acts as an acylating reagent (Scheme 4).

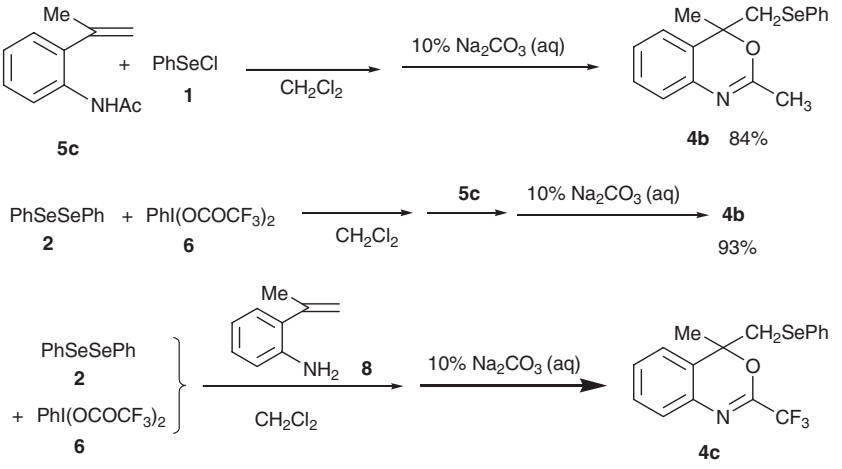
These results clearly show that activated intermediate (**a**) was attacked by acyl oxygen at the benzyl position, which is more cationic than the β-position, to afford the less strained six-membered heterocycle, 3,1-benzoxazine **4** (Scheme 5).

Since intramolecular cyclization that used active halogens or active sulfur and 2-aminochalcones has been proven to be a good procedure for the synthesis of quinolines,[8] we finally investigated the reaction of 2-aminochalchone (**10**) with active selenium reagents. When 2-aminochalchone **10** was treated with 1 at rt followed by the addition of aq. Na_2CO_3, 2-phenylquinoline (**11**) was obtained in almost quantitative yield (Scheme 6).

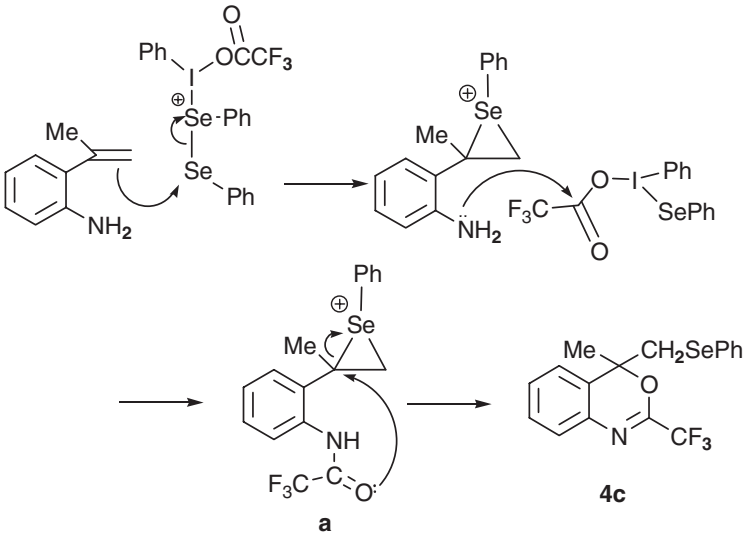
In conclusion, we have developed a simple method for the synthesis of indoles, 3,1-benzoxazines, and quinolines, using phenylselenenyl chloride or diphenyl diselenide as double-bond activating reagents.

EXPERIMENTAL

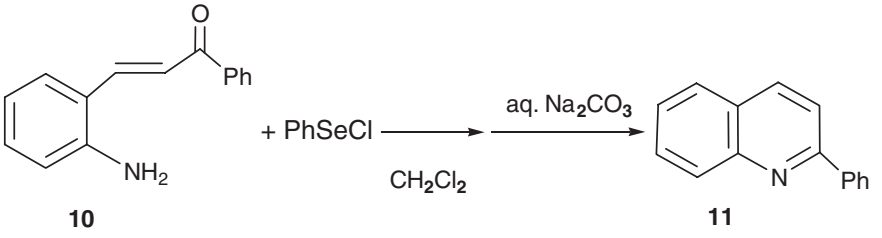
Flash chromatography was carried out by Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography (TLC) was carried out on commercially available coated plates (Merck silica Kieselgel $60F_{254}$). All solvents were distilled before use, and no



Scheme 4



Scheme 5



Scheme 6

further treatment was carried out. NMR spectra were measured on a Varian Innova-400 (400 MHz for 1H, 100 MHz for 13C). The melting points were uncorrected. Phenylselenenyl chloride, diphenyl diselenide, bis(trifluroacetoxy)iodobenzene, 2-allylphenol, and 2-isopropenylaniline are commercially available. 2-Alkenylanilides were synthesized by the reported procedure.[4]

Reaction of 2-Allylphenol with Phenylselenenyl Chloride 1

To a solution of phenylselenenyl chloride **1** (211 mg, 1.1 mmol) in dichloromethane (5 mL), a solution of 2-allylphenol (134 mg, 1.0 mmol) in dichloromethane (5 mL) was added dropwise at rt. After stirring for 2 h, aq. Na_2CO_3 (5%, 5 mL) was added to the reaction mixture and separated. The dichloromethane layer was dried over magnesium sulfate, filtered, and evaporated to give 2-phenylselenomethyl-2,3-dihydrobenzofuran (**7**) (237 mg, 0.82 mmol). Colorless oil: The spectral data was identical with the reported value.[2] ^{1}H NMR ($CDCl_3$) δ = 2.97–3.14 (m, 2H, CHH and PhSeCHH), 3.30–3.40 (m, 2H, CHH and PhSeCHH), 4.93 (br m, 1H, CH), 6.74 (d, 1H, J = 8.0 Hz, Ar), 6.83 (dd, 1H, J = 7.2 Hz, 8.0 Hz, Ar), 7.05–7.16 (m, 2H, Ar), 7.25 (br s, 3H, PhSe), 7.55 (br s, 2H, PhSe).

Reaction of 2-Isopropenyl-*N*-*p*-tosylanilide 5a with Phenylselenenyl Chloride 1

To a solution of chloride **1** (211 mg, 1.1 mmol) in dichloromethane (10 mL), a solution of 2-isopropenyl-*N*-*p*-tosylanilide **5a** (287 mg, 1.0 mmol) in dichloromethane (5 mL) was added at rt. After stirring for 8 h, *m*-CPBA (190 g, 1.1 mmol) in dichloromethane (10 mL) was added to the reaction mixture. After stirring for 5 h, the reaction mixture was washed with 10% of aq. sodium carbonate (10 mL) and separated. The water layer was extracted with dichloromethane (5 mL × 2), and the combined extract was dried over sodium sulfate, filtered, and evaporated to give a pale yellow solid, which was chromatographed over silica gel by elution with hexane/dichloromethane (1:1) to afford colorless plates of 3-methyl-*N*-tosylindole **3a** (148 mg, 0.52 mmol). Mp 112–114°C. (lit.[9] mp 114–115°C.) ^{1}H NMR ($CDCl_3$) δ = 2.22 (s, 3H, CH_3), 2.29 (s, 3H, TsMe), 7.16 (d, 2H, J = 8.0 Hz, Ts), 7.20 (t, 1H, J = 8.4 Hz, Ar), 7.30 (t, 1H, J = 8.0 Hz, Ar), 7.43 (d, 1H, J = 8.0 Hz, Ar), 7.73 (d, 2H, J = 8.0 Hz, Ts), 7.98 (d, 1H, J = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 9.91 (Me), 21.74 (TsMe), 113.89 (Ar), 118.83 (Ar), 119.61 (Ar), 123.20 (Ar), 123.29 (Ar), 124.79 (Ar), 126.95 (Ts), 130.00 (Ts), 132.02 (Ar), 135.49 (Ar), 135.64 (Ts), 144.88 (Ts).

Reaction of 2-Isopropenyl-*N*-*p*-tosylanilide 5a with Diphenyl Diselenide and [Bis(trifluoroacetoxy)iodo]benzene

To a solution of diselenide **2** (187 mg, 0.60 mmol) and [bis(trifluoroacetoxy)iodo] benzene **6** (516 mg, 1.2 mmol) in dichloromethane (15 mL), 2-isopropenyl-N-tosylanilide **5a** (287 mg, 1.0 mmol) in dichloromethane (5 mL) was added at rt. After stirring for 9 h, *m*-CPBA (182 mg, 1.0 mmol) in dichloromethane (10 mL) was added to this solution. After stirring for 5 h, the mixture was poured into aq sodium carbonate (10%), and separated. The water layer was extracted with dichloromethane (5 mL × 2), and the combined extract was dried over sodium sulfate, filtered, and evaporated to give a yellow oil, which was

chromatographed over silica gel by elution with dichloromethane/hexane (1:3) to give 3-methyl-*N*-tosylindole (191 mg, 0.67 mmol).

Reaction of 2-Isopropenylacetanilide 5c with Phenylselenenyl Chloride 1

To a solution of phenylselenenyl chloride **1** (211 mg, 1.1 mmol) in dichloromethane (5 mL), a solution of 2-isopropenylacetanilide **5c** (175 mg, 1.0 mmol) in dichloromethane (5 mL) was added at rt. After stirring for 5 h, the reaction mixture was washed with 10% of aq. sodium carbonate (10 mL) and separated. The water layer was extracted with dichloromethane (5 mL × 2), and the combined extract was dried over sodium sulfate, filtered, and evaporated to give pale yellow solid, which was chromatographed over silica gel by elution with hexane/dichloromethane (1:1) to afford colorless plates of 2,4-dimethyl-4-phenylselenomethyl-3,1-benzoxazine (**4b)** (277 mg, 0.84 mmol). Colorless oil. ^{1}H NMR ($CDCl_3$) $\delta = 1.78$ (s, 3H, Me), 1.92 (s, 3H, Me), 3.24 (d, 1H, $J = 13.2$ Hz, C$\underline{H}$H), 3.46 (d, 1H, $J = 13.2$ Hz, C$\underline{H}$H), 7.00–7.43 (m, 9H, Ar). ^{13}C NMR ($CDCl_3$) $\delta = 21.45$ (Me), 27.28 (Me), 40.62 (CH_2), 123.27, 124.20, 126.66, 127.27, 127.80, 129.17, 129.21, 130.47, 133.09, 137.90 (Ar), 160.30 (C = N). HRMS: Found; 331.0475. Calcd for $C_{17}H_{17}O^{80}Se(M^+)$; 331.0475.

Reaction of 2-Isopropenylacetanilide 5c with Diphenyl Diselenide 2 and [Bis(trifluoroacetoxy)iodo]benzene 6

To a solution of diphenyl diselenide **2** (187 mg, 0.6 mmol) and iodobenzene **6** (516 mg, 1.2 mmol) in dichloromethane (15 mL), a solution of 2-isopropenylacetanilide **5c** (175 mg, 1.0 mmol) in dichloromethane (5 mL) was added at rt. After stirring for 8 h, the reaction mixture was washed with 10% of aq. sodium carbonate (10 mL) and separated. The water layer was extracted with dichloromethane (5 mL × 2), and the combined extract was dried over sodium sulfate, filtered, and evaporated to give a colorless solid, which was chromatographed over silica gel by elution with hexane/dichloromethane (1:1) to afford benzoxazine **4b** (307 mg, 0.93 mmol). Colorless oil.

Reaction of 2-Isopropenylaniline 8 with Diphenyl Diselenide 2 and [Bis(trifluoroacetoxy)iodo]benzene 6

To a solution of diselenide **2** (187 mg, 0.60 mmol) and iodobenzene **6** (516 mg, 1.2 mmol) in dichloromethane (15 mL), a solution of 2-isopropenylaniline **8** (133 mg, 1.0 mmol) in dichloromethane (5 mL) was added at rt. After stirring for 8 h, the reaction mixture was washed with 10% of aq. sodium carbonate (10 mL) and separated. The water layer was extracted with dichloromethane (5 mL × 2), and the combined extract was dried over sodium sulfate, filtered, and evaporated to give colorless solid, which was chromatographed over silica gel by elution with hexane/dichloromethane (1:1) to afford 2-trifluoromethyl-4-phenylselenomethyl-4-methyl-3,1-benzoxazine (**4c**) (268 mg, 0.70 mmol). Colorless oil. ^{1}H NMR ($CDCl_3$) $\delta = 1.84$ (s, 3H, Me), 3.30 (d, 1H, $J = 13.2$ Hz, C$\underline{H}$H), 3.51 (d, 1H, $J = 13.2$ Hz, C$\underline{H}$H), 7.10 (d, 1H, $J = 8.0$ Hz, Ar), 7.12–7.46 (m, 8H, Ar). ^{13}C NMR ($CDCl_3$) $\delta = 28$ (Me), 40.5 (CH_2), 83.5, 117 (q, $J_{C\text{-}F} =$ Hz, CF_3), 124.02, 126.51, 127.62, 128.55,

129.18, 129.31, 129.65, 130.10, 133.52, 135.94 (Ar), 147.63 (C = N). HRMS: Found; 385.0175. Calcd for $C_{15}H_{10}F_3NO^{80}Se$ (M^+); 385.0193.

Reaction of 2-Aminochalchone 10 with Phenylselenenyl Chloride 1

To a solution of chloride **1** (211 mg, 1.1 mmol) in dichloromethane (10 mL), a solution of 2-aminochalchone **10** (223 mg, 1.0 mmol) in dichloromethane (5 mL) was added at rt. After stirring for 8 h, the reaction mixture was washed with 10% of aq. sodium carbonate (10 mL) and separated. The water layer was extracted with dichloromethane (5 mL × 2), and the combined extract was dried over magnesium sulfate, filtered, and evaporated to give a colorless solid, which was chromatographed over silica gel by elution with hexane/dichloromethane (1:1) to afford colorless crystals of 2-phenylquinoline (**11**) (207 mg, 0.96 mmol). Mp 83–84°C. Spectral data of **11** was identical with the commercially available sample (mp 84–85°C).

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