Copper-Catalyzed Three-Component One-Pot Synthesis of Substituted 2-Aryl-1,3-benzoselenazoles

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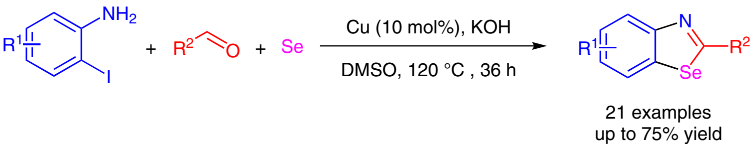

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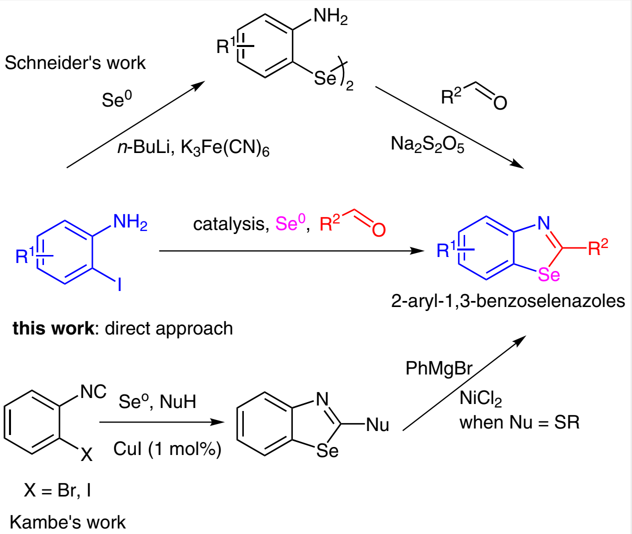
Abstract A simple copper-catalyzed, one-pot synthesis of 2-aryl-1,3-benzoselenazole derivatives was developed using inexpensive, readily available 2-iodoanilines, selenium powder, and aromatic aldehydes as the starting materials. The mild reaction conditions and simple procedure without ligands and other additives make this methodology an alternative for preparing these potential selenium-containing compounds very conveniently.

Key words multicomponent reactions, heterocycle, 2-aryl-1,3-benzoselenazoles

Selenium-containing compounds have attracted much attention as potential pharmaceuticals,[1–11] synthetic intermediates,[12–15] and catalysts[16,17] in organic synthesis during the last decades. Among them, 2-aryl-substituted benzoselenazoles are one of the important frameworks of selenium-containing heterocycles because of their pharmacologically and other applications.[18–21] However, there are limited reports on the preparation of this kind of compounds despite their potential importance. In 2007, Kambe and co-workers described the synthesis of 2-phenyl-1,3-benzoselenazoles by copper iodide catalyzed cross-coupling reaction and then with aryl Grignard reagent and nickel dichloride.[21] Very recently, Schneider reported the synthesis of substituted 2-aryl-1,3-benzoselenazoles from bis(2-aminophenyl)diselenides and arylaldehydes, using $Na_2S_2O_5$ as additive, where the starting material diselenide was prepared by the reaction of 2-iodoaniline with *n*-BuLi, and then, with elemental selenium and potassium ferrocyanide (Scheme 1).[18]

Multicomponent reactions (MCR) represent an attractive and powerful strategy in diversity-oriented synthesis of heterocycles.[22–27] Compared with the classical step-by-step reaction to give the target product, the multicomponent synthesis gather the formation of several bonds in one pot, without isolating the reaction intermediates, changing the reaction conditions or supplementing other reagents. Considering the potential importance of 2-aryl-substituted benzoselenazoles, herein we report a novel, efficient, and very simple one-pot strategy to achieve these compounds with easily available *ortho*-halo anilines, benzaldehydes, and selenium as starting materials catalyzed with copper.



Scheme 1 Methods for the synthesis of 2-aryl-1,3-benzoselenazoles

We initiated our study by examining the three-component cascade reaction using 2-iodoaniline, selenium powder, and benzaldehyde in the presence of copper chloride and potassium hydroxide at 120 °C in DMSO (Table 1, entry 2). Unfortunately, not any new compounds were observed except of Schiff base formed from benzaldehyde and 2-iodoaniline. Copper sulfate and copper bromide gave no products under the same reaction conditions. Keeping on

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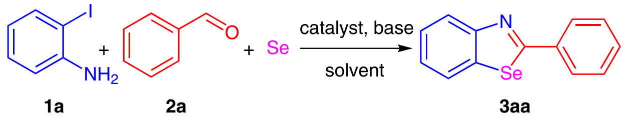
Table 1 Screening Catalysts and Reaction Conditions for the Catalytic Three-Component Reaction[a]



Entry	Catalyst	Solvent	Base	Yield of **3aa** (%)[b]
1	–	DMSO	KOH	–
2	$CuCl_2 \cdot 2H_2O$	DMSO	KOH	–
3	$CuCl_2 \cdot 2H_2O$[c]	DMSO	KOH	–
4	$CuSO_4 \cdot 5H_2O$	DMSO	KOH	–
5	$CuBr_2$	DMSO	KOH	–
6	CuI	DMSO	KOH	53
7	CuI[c]	DMSO	KOH	52
8	$Cu(OAc)_2$	DMSO	KOH	41
9	CuO	DMSO	KOH	59
10	Cu_2O	DMSO	KOH	36
11	Cu (powder)	DMSO	KOH	72
12	$Cu(OTf)_2$	DMSO	KOH	68
13	Cu (powder)	DMSO	K_2CO_3	27
14	Cu (powder)	DMSO	NaOH	61
15	Cu (powder)	DMF	KOH	67
16	Cu (powder)	toluene	KOH	–
17[d]	Cu (powder)	DMSO	KOH	65
18[e]	Cu (powder)	DMSO	KOH	61

[a] Reaction conditions: 2-iodoaniline (0.5 mmol), benzaldehyde (0.6 mmol), selenium powder (1.5 mmol), KOH (1.0 mmol), catalysts (0.05 mmol), 120 °C, 36 h, under insert gas atmosphere.
[b] Isolated yield.
[c] 1,10-Phenanthroline was added.
[d] At 100 °C.
[e] For 24 h.

screening we found that copper(I) iodide as the catalyst provide 53% yield of the product 2-phenyl-1,3-benzoselenazole. These result inspired us to devote more emotion to other copper resources, and the results are summarized in Table 1. Among the different copper catalysts tested, copper powder (Table 1, entry 11, 72% yield) gave the best result, which was superior to that of CuI, $Cu(OAc)_2$ (41%), CuO (59%), Cu_2O (36%), and $Cu(OTf)_2$ (68%). 1,10-Phenanthroline ligand was tested for acceleration of the reaction, but the results indicated no significant yields improvement (Table 1, entry 6 vs. 7). Base and solvent screening revealed that KOH was optimal and DMSO was the most suitable (Table 1, entries 13–16). Interesting, when the solvent changed to toluene (Table 1, entry 16), not any product was obtained. This result reminds us that the redox reaction may takes place as DMSO possesses oxidation. Reaction temperature and time were other factors to affect the reaction, a lower reaction temperature and shorter reaction time induced the decrease of the yields (Table 1, entries 17 and 18).

Further examination of this one-pot strategy's substrate scope under the optimized conditions revealed that the strategy was widely applicable (Scheme 2). Expanding the reaction to other 2-iodoanilines and aldehydes, different 2-aryl-1,3-benzoselenazoles were obtained with moderated to good yields. The yields of twelve products (**3aa**, **3ab**, **3ac**, **3ba**, **3ca**, **3da**, **3ah**, **3aj**, **3al**, **3an**, **3aq**, **3ar**) were more than 60%. It is also indicated that steric hindrance of the substituted groups affects the reaction effectively. The *para*- and *meta*-nitrobenzaldehyde reacted with aniline and selenium to provide good yields of **3ab** and **3ac** (71% and 75% yields, respectively), while no product was obtained from the reaction of *ortho*-nitrobenzaldehyde under the same conditions. The electronic effect is another important factor to affect the reaction. Substituted 2-iodoanilines and aldehydes containing electron-withdrawing groups, such as nitro and halogen, in aldehyde moiety seem favorable for the yields (Scheme 2, **3ab**, **3ac**, **3aj**, **3ai**, **3al**). On the contrary, electron-donating groups on the aldehyde moiety gave relatively lower yields (Scheme 2, **3ae**–**3ah**, **3ak**). Aromatic heterocyclic aldehydes, such as pyridinecarboxaldehydes **2n** and **2o**, 2-thienaldehyde (**2q**), and 1-methylindole-2-carboxaldehyde (**2r**) were also suitable for the one-pot, three-component reaction, which provide the corresponding products in moderate to good yield (44–75%, **3an**, **3ao**, **3aq**, **3ar**).

To investigate the reaction mechanism, we have explored the possible reaction pathway and intermediates (Scheme 3). First, 2-iodoaniline reacted with benzaldehyde in the presence of selenium powder only to produce Schiff base **4** in good yield without copper (Scheme 3,A). On the other hand, the reaction of 2-iodoaniline with selenium powder in presence of copper gave bis(2-aminophenyl)diselenide[28] (**5**) in good yield (82%, Scheme 3,B). The purified intermediate **5** reacted with benzaldehyde in DMSO to provide the target product **3aa** and intermediate **6** (Scheme 3,C), which proceeded well in the absence of catalyst. To further explore the detailed reaction process, GC–MS was used to detect the proposed intermediates for this reaction. The intermediate **5** and **6** were detected when the reaction proceeded for 6–12 hours (see the Supporting Information), which were converted into the target compound **3aa** in the absence of catalyst (Scheme 3,D, 72% yield) with the prolonged reaction time of 36 hours. Another control experiment (Scheme 3,E) was also carried out to investigate the role of the copper catalyst in the reaction D, and the result revealed that the copper has no effect on the reaction.

Based on our observations and previous literature,[18,28–31] a plausible mechanism is outlined in Scheme 4 with the generation of **3aa**[32] as the example.

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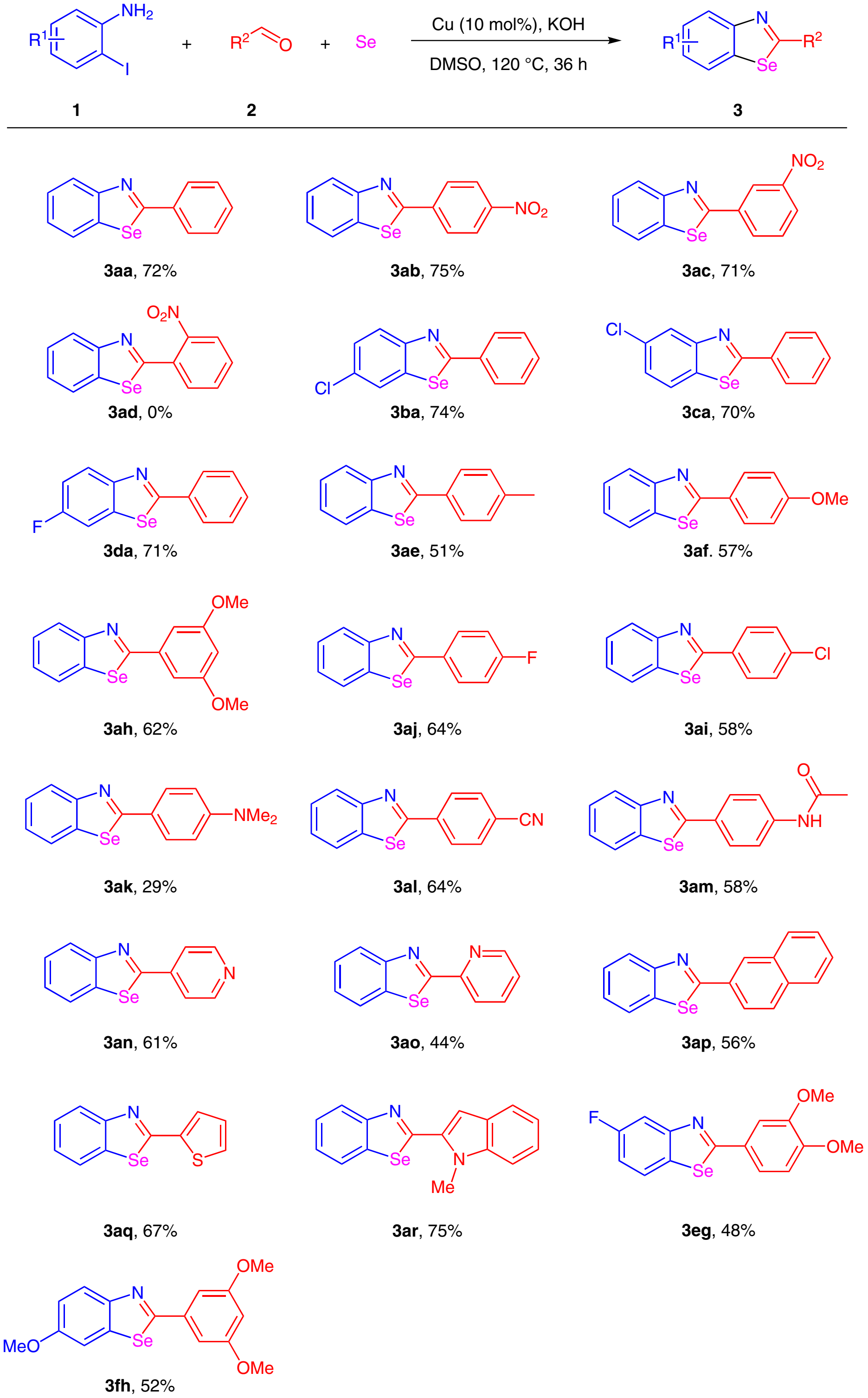

Scheme 2 Copper-catalyzed, three-component formation of 2-aryl-1,3-benzoselenazoles. Reaction was performed with 0.5 mmol of **1**, 0.6 mmol of **2**, 1.5 mmol of selenium powder, 1.0 mmol of KOH, and 0.05 mmol of Cu powder, in 1.5 mL of DMSO at 120 °C for 36 h. Isolated yields are reported.

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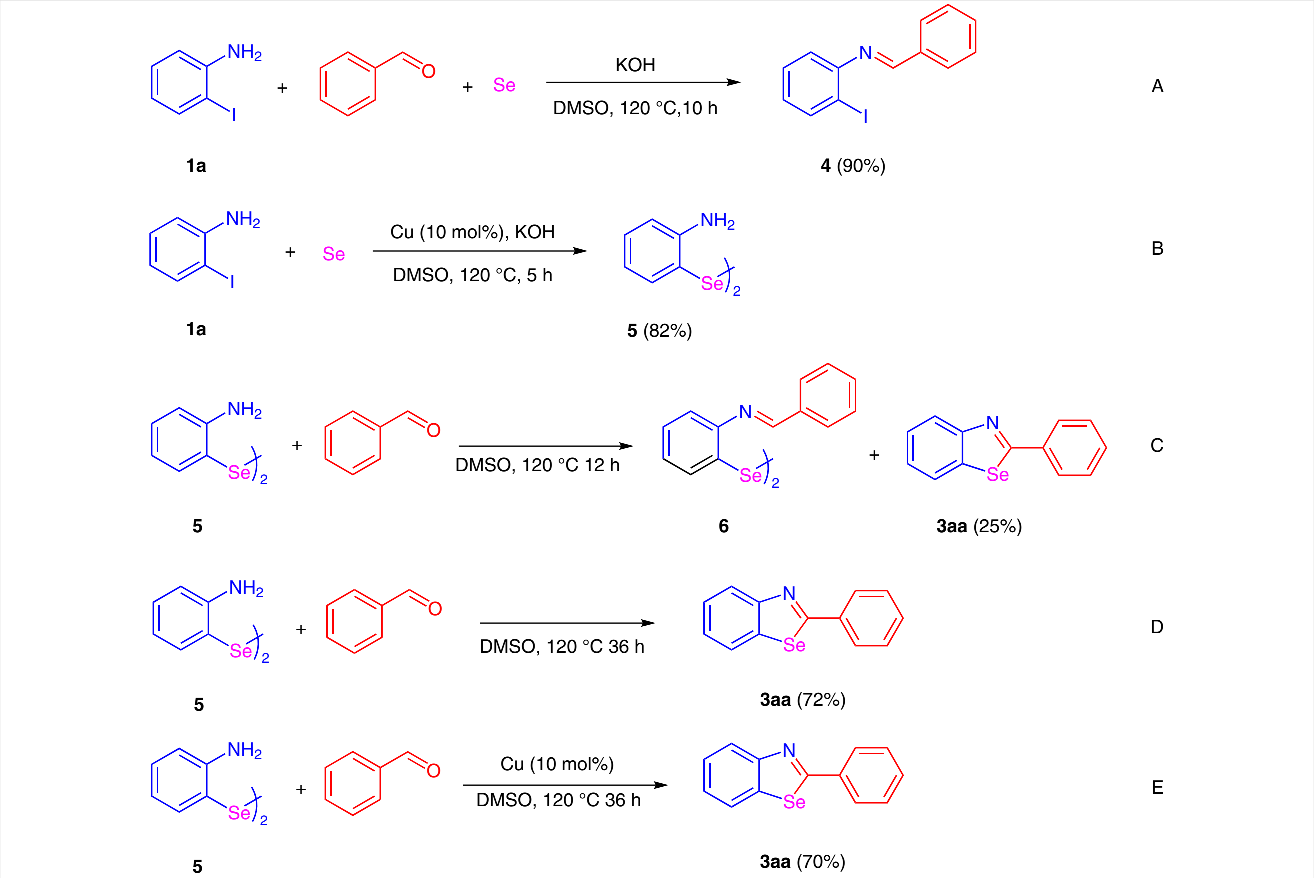

Scheme 3 Investigation of the reaction pathway

The reaction of 2-iodoaniline with selenium in the presence of copper powder produces bis(2-aminophenyl)diselenide (**5**), which reacts with the benzaldehyde to form the imine diselenide compound **6**. Finally, the homolytic cleavage of the imine diselenide **6** generates a radical which cyclize to provide the target product **3aa**. The generation pathway of other 2-aryl-1,3-benzoselenazole is similar to **3aa**.

In conclusion, we have developed a simple one-pot multicomponent strategy for the synthesis of 2-aryl-1,3-benzoselenazole derivatives using inexpensive, readily available 2-iodoanilines, selenium powder, and aromatic aldehydes as the starting materials. The mild reaction conditions, simple procedure without ligands and other additives, and good chemical yields make this methodology an alternative approach for preparing these potential selenium-containing compounds very conveniently.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378934.

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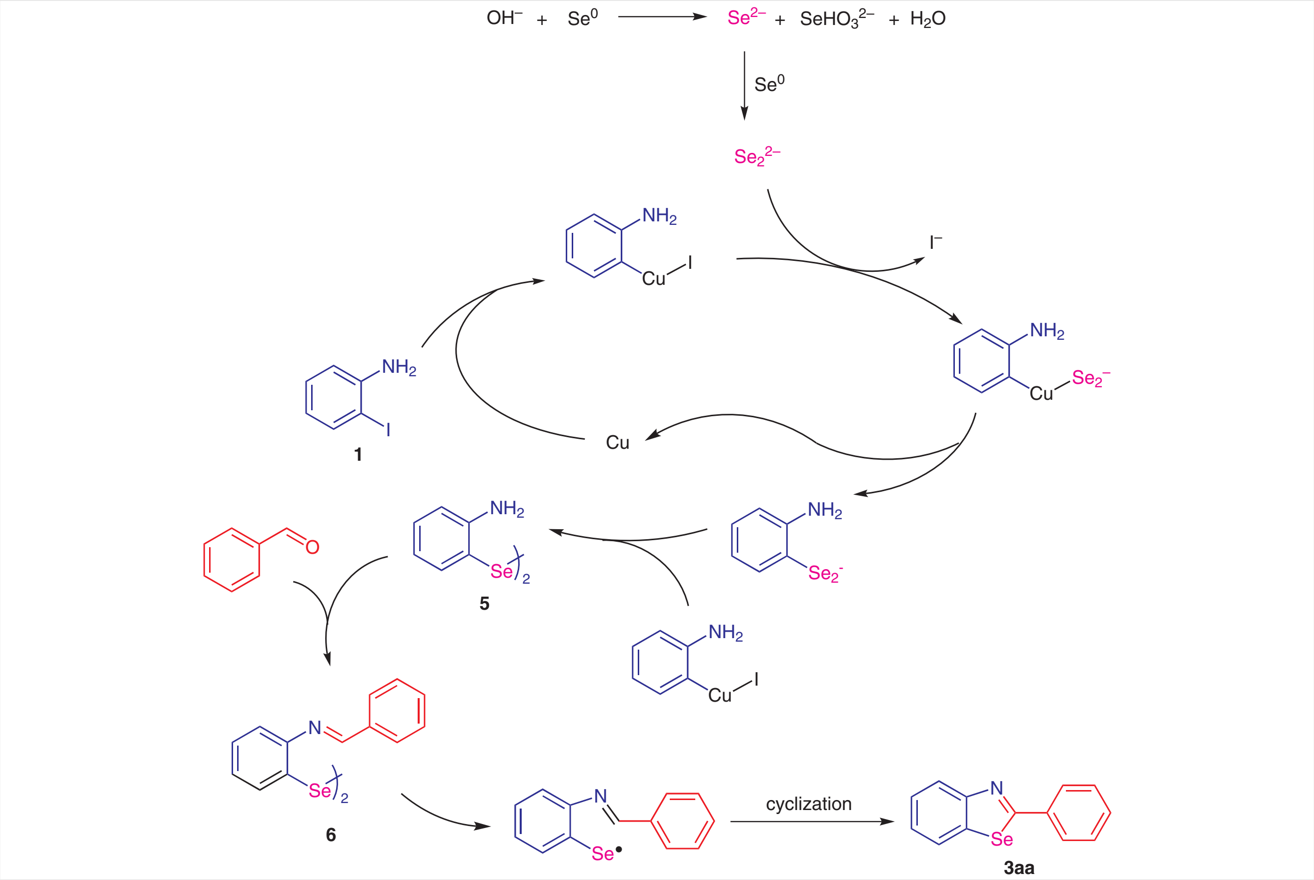

Scheme 4 Plausible reaction mechanism for the formation of 2-phenyl-1,3-benzoselenazole (**3aa**)

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(32) **Typical Procedure for the Synthesis of 2-Aryl-1,3-benzoselenazole 3aa**
To a solution of 2-iodoaniline (0.5 mmol) and benzaldehyde (0.6 mmol) in dry DMSO (1.5 mL), selenium powder (1.5 mmol), catalyst (0.05 mmol), and KOH (1.0 mmol) were added, the reaction mixture was stirred in a sealed tube under argon

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atmosphere at 120 °C for 36 h. After the reaction was finished, the mixture was cooled to r.t., diluted with sat. aq NH_4Cl (15 mL), and extracted with EtOAc (3 × 10 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding product **3aa**. White solid; mp 116.2–117.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 1 H), 8.06–7.98 (m, 2 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 7.50–7.46 (m, 4 H), 7.31 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.47, 155.85, 138.33, 136.20, 131.03, 129.06, 128.01, 126.39, 125.26, 124.86, 124.82. HRMS: *m/z* $[M + H]^+$ calcd for $C_{13}H_{10}NSe$: 259.9973; found: 259.9948.

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