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Copper-Mediated One-Pot Transformation of 2-*N*-Sulfonyl-aminoaryl Diselenides into Benzo[*b*][1,4]selenazines

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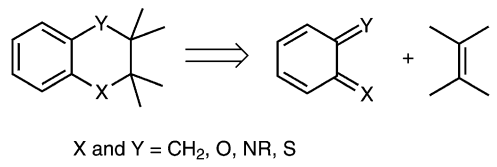
Abstract: A simple procedure for the one-pot transformation of 2-*N*-tosylamino diselenides into benzo[*b*][1,4]selenazines has been established. The data collected indicate that the six-membered heterocyclic ring is the result of a [4+2]cycloaddition reaction of a transient electron-poor *o*-iminoselenoquinone, acting as diene, with an electron-rich alkene, performing as dienophile. The key step of the synthesis is a 1,4-elimination at selenium of a selenolate ion, leading to the generation of the heterodiene, that requires catalytic amounts of copper(II) trifluoromethanesulfonate, for the activation of the selenium-selenium bond.

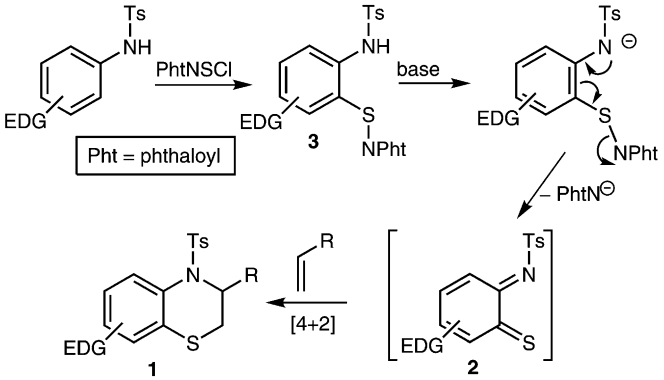
Keywords: copper; cycloaddition; Lewis acids; selenium; synthetic methods

Hetero Diels–Alder reactions are a powerful tool for the stereocontrolled construction of six-membered heterocycles. In this context, the preparation of benzo-fused derivatives is of particular interest since, synthetically, it is a challenge requiring that an aromatic moiety is transformed, transiently, in a dienic *o*-quinoid species[1] and, practically, it offers a straightforward opportunity for preparing a plethora of biologically relevant compounds (Scheme 1).[1,2]



Scheme 1. Hetero Diels–Alder approach to benzo-fused six-membered heterocycles.

In our continuous investigation on the chemistry[1g,3] and applications[4] of thioquinones, we demonstrated that benzo[*b*][1,4]thiazines of type **1** can be prepared by exploiting an inverse electron demand hetero Diels–Alder reaction of electron-rich alkenes with *o*-iminothioquinones **2** acting as electron-poor heterodienes as depicted in Scheme 2.[5]



Scheme 2. Hetero Diels–Alder approach to benzo[*b*]-[1,4]thiazines **1** *via* 1,4-elimination at sulfur mediated by generation of *o*-iminothioquinones **2**.

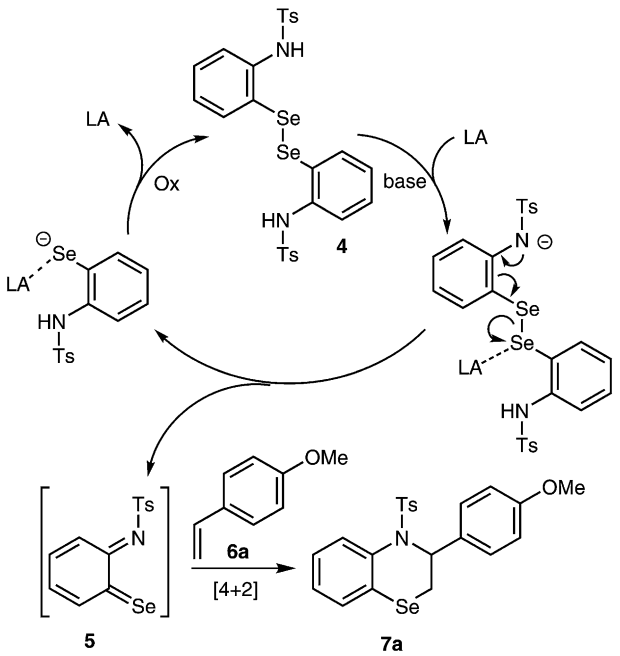
Such transient dienes are obtained, under very mild reaction condition, by base-promoted 1,4-elimination at sulfur in *N*-tosyl-2-thiophthalimides **3**, in turn, prepared by S_EAr of properly substituted *N*-tosylanilines with the phthalimidesulfenyl chloride (PhtNSCl, Pht = phthaloyl). The key steps of this procedure are: (i) the direct introduction, *via* S_EAr, of the sulfenic sulfur armed with a suitable leaving group (i.e., the phthalimide residue), and (ii) the deprotonation at nitrogen that promotes the 1,4-elimination at sulfur with generation of the *o*-iminothioquinone[5] (Scheme 2).

One of the drawbacks of the above procedure is the impossibility to apply it for the synthesis of the corresponding selenium derivatives. In fact, no examples of electrophilic selenyl reagents suitable for the introduction of a selenium atom armed with an efficient leaving group are reported in the literature,[6] thus preventing the possibility to obtain an *o*-iminoselenoquinone species *via* a 1,4-elimination at selenium, as depicted in Scheme 2.

Nevertheless, selenium is a highly important element in organic chemistry and several reviews describe its versatility in synthesis.[7] Moreover, it is an essential dietary component for many living systems, including humans. Recently, selenium-containing compounds are attracting increased attention for their ability to act as glutathione peroxidase (GPX) mimics, catalytic antioxidants and cancer-chemopreventive compounds.[8] Thus, we decided to study the possibility of generating *o*-iminoselenoquinones from easily available starting materials that are accessible circumventing the introduction of the selenium moiety *via* a S_EAr of a functionalized selenyl halide.

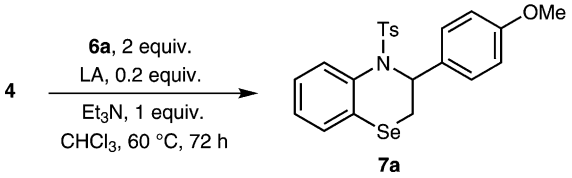
We reasoned that, possibly, an *o*-*N*-tosyl diselenide could serve as precursor of a selenoquinone. In fact, considering that in 1,4-elimination at chalcogens the leaving group ability can be approximated to the conjugated acid pK_a values, the elimination of a phenylselenolate ion could be even easier than that of the phthalimide anion.[9] Thus, we imagined that when reacting *o*-*N*-tosyl diselenide **4** with Et_3N the deprotonation at the ArNHTs residue, could be followed by a 1,4-elimination at selenium (of an arylselenolate ion) with generation of the *o*-iminoselenoquinones **5**. If this latter species was an electron-poor diene, carrying out the reaction in the presence of an electron-rich alkene, at the end of the process we could isolate the benzoselenazine **7** as depicted in Scheme 3.

N-Tosylated diselenide **4** was prepared from the corresponding 2-amino diselenide, in turn, obtained by reacting *o*-iodoaniline with powdered Se(0) in the presence of CuO nanoparticles as recently reported.[10] However, reacting **4** with 1 equivalent of Et_3N and 2 equivalents of styrene **6a**, as suitable trapping electron-rich dienophile, in $CHCl_3$ at 60 °C, i.e., under the reaction conditions that we found to be effective for the generation of *o*-imonothioquinones,[5] no reaction occurred and the starting diselenide **4** was recovered almost quantitatively after an acid work-up. Thus, although the pK_a values indicated that the selenolate ion should be a better leaving group than the phthalimide anion, the Se–Se bond in **4** was not broken under the reaction conditions tested. A possible solution, also strengthened by an inspection of the literature[11] reporting the activation of chalcogen-chalcogen bonds, was to use a Lewis acid, and in particular a copper salts, to promote the reaction. Indeed, after a fairly short investigation (see Table 1),



Scheme 3. Preparation of benzo[*b*][1,4]selenazines from *o*-*N*-tosyl diselenides *via* hetero Diels–Alder reaction of *o*-iminoselenoquinones.

Table 1. Effect of copper-based Lewis acids on the formation of benzo[*b*][1,4]selenazine **7a**.



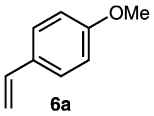
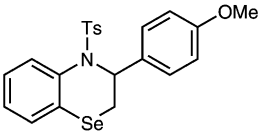
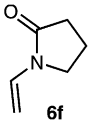
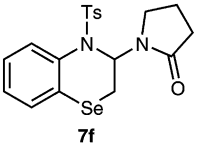
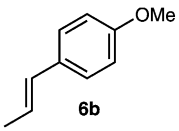
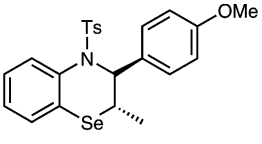
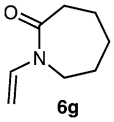
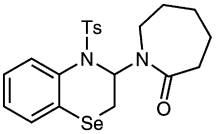
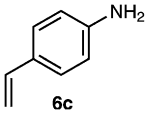
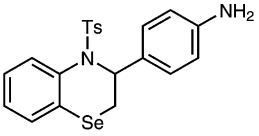
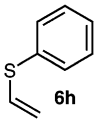
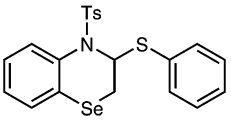
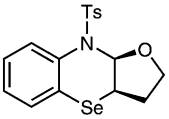
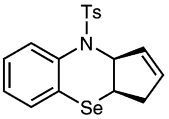
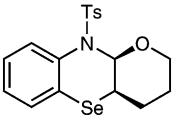
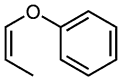
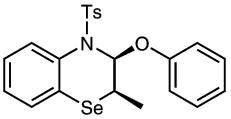
Entry	LA	Mol%	Yield [%][a]
1	–	–	–
2	CuO[b]	20	–
3	$Cu(acac)_2$	20	30
4	CuI	20	36
5	$Cu(OAc)_2$	20	63
6	$Cu(OTf)_2$	20	75

[a] Isolated yield after column chromatography.
[b] CuO nanoparticles.

we could verify that copper-based Lewis acids are able to promote the reaction,[12] and the best results were obtained using 20 mol% of copper(II) triflate, $Cu(OTf)_2$, that allows us to isolate the selenazine **7a** in 75% yield after column chromatographic purification.

This new approach for the generation of selenoquinones from diselenides foresees that one half of **4** is transformed into the heterodiene, while the second half behaves as a leaving group. Actually, as a crucial point for the success of this procedure, the yields of

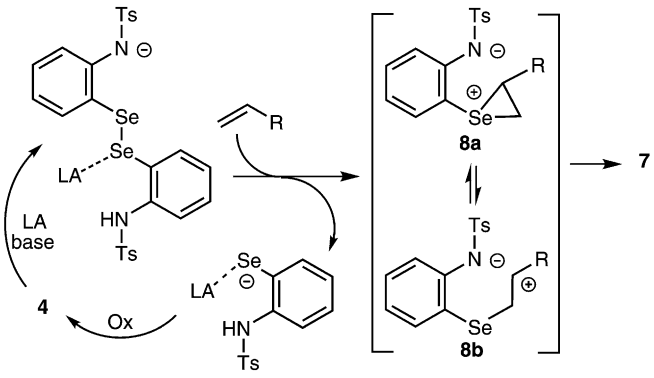
Table 2. Benzo[*b*][1,4]selenazines **7** prepared in this study.

Entry	Dienophile	Selenazine	t[a]	Yield[b]	Entry	Dienophile	Selenazine	t[a]	Yield[b]
1	 **6a**	 **7a**	72	75	6	 **6f**	 **7f**	48	75
2	 **6b**	 **7b**	48	58	7	 **6g**	 **7g**	48	79
3	 **6c**	 **7c**	72	55	8	 **6h**	 **7h**	72	-
4	 **6d**	 **7d**	48	60	9	 **6i**	 **7i**	60	43
5	 **6e**	 **7e**	48	59	10	 **6l**	 **7l**	48	60

[a] Reaction times (hours) for the complete consumption of diselenide **4** at 60 °C in $CHCl_3$.
[b] Isolated yields [%] after column chromatography.

selenazine **7a** reported in Table 1 have been calculated considering the consumption of both aminoselenyl units of diselenide **4**. This means that the selenolate ion, that has acted as leaving group, is not wasted during the process but, in turn, converted in the final derivative **7a**. The simplest rational for this hypothesis is that the selenolate ion is oxidized by molecular oxygen[11] to the starting diselenide **4** until its complete consumption. Indeed, when carrying out the reaction of **4** with **6a** in a deoxygenated solution and under a positive nitrogen atmosphere, after 72 h at 60 °C, the ^{1}H NMR spectra of the crude reaction mixture showed a large amount of unreacted diselenide **4** with a 78:22 ratio between diselenide **4** and selenazine **7a**. Compound **7a** was fully characterized and the structure solidly confirmed also taking in consideration the spectroscopic data of the corresponding thiazine.[5] The scope of the procedure was studied by reacting diselenide **4** with alkenes **6b–l** under the above optimized conditions. The results obtained are reported in Table 2.

The reaction was quite general and using the electron-rich alkenes[4,5] that were effective in the case of *o*-thioquinones and *o*-iminothioquinones, it affords acceptable to good yields of selenazines **7** isolated as single regioisomers with retention of the alkene geometry. In particular, the reaction proceeded reasonably well with EDG-substituted styrenes, vinyl ethers, *N*-vinylamides (entries 1–7, 10) and with cyclopentadiene (entry 9), while, surprisingly, it failed when using phenyl vinyl sulfide **6h** as potential dienophile (entry 8).[13] As expected, we verified that electron-poor or electron-neutral alkenes, like methyl vinyl ketone or cyclohexene respectively, do not afford any selenazine derivative. Actually, the mechanism depicted in Scheme 3, involving a hetero Diels–Alder cycloaddition as key step, is not the only one able to rationalize the formation of the selanazines **7**. For example, the possibility that the attack of the nucleophilic alkene to the LA-activated diselenide afforded an ionic intermediate, a classic episeleniranium ion[7] **8a** possibly in equilibrium with an open carbocation **8b** (*vide infra*), which evolves into selenazines **7** *via* an intramolecular ring closing, seems similarly feasible (Scheme 4). Conceivably, both mechanisms foresee the liberation of a selenolate ion, since its oxidation to diselenide **4** is mandatory to justify the isolation of selenazines **7** with yields higher than 50%.



Scheme 4. Lewis acids-mediated access to [1,4]selenazines *via* intramolecular cyclization.

Looking for indications on the more realistic mechanism, the possibility of using cyclopentadiene **6i** as dienophile (entry 9) is, in our opinion, worthy of mention. In fact, despite the low yield of derivative **7i**, the aptitude of 1,3-dienes to behave as electron-rich dienophiles is typical of those reactions involving quinone methides and the corresponding heterofunctionalized systems as dienes.[1]

In addition, the possibility of using styrene **6c** as a suitable reagent is another proof for the Diels–Alder mechanism, since the free amino moiety would probably strongly interact with any selenium electrophile preventing the formation of selenazine **7c**. Clearly, this is on the way to be conclusive in favour of a [4+2]-guided mechanism, and, on the other hand, we were unable to point out any retro Diels–Alder process from selenazines **7**.[14] However, the stereochemical features of this reaction are, in our opinion, a solid indication of the actual mechanism in action. In any case selenazines **7** were isolated as single regioisomers and, for entries 2, 4, 5, 9 and 10, with overall retention of the alkene geometry. The complete regioselectivity is typical but not exclusive of a cycloaddition path, thus, definitely, a single regioisomer is expected if the reaction occurs as depicted in Scheme 3,[4,5] but, reasonably, a complete regiocontrol could also be observed for the attack of the nucleophilic NTs group to the ionic intermediate **8** described in Scheme 4. The retention of the alkene geometry is much more supportive for a cycloaddition process. Retention of the alkene geometry has been reported, at very low temperature, for both *E*- and *Z*-alkenes in asymmetric cyclization reactions with diselenides[15] due to an *anti*-attack of an internal nucleophile to an episeleniranium ion intermediate. At the same time, an equilibrium between an episeleniranium ion and an open carbocation has already been described in the selenylation of enolethers, under reaction conditions milder than those required for this transformation,[16] indicating that, in our system, the possibility of an equilibrium between **8a** and the open cation **8b** must be seriously considered, above all when **8b** is a highly stabilized α-hetero-substituted carbocation (Table 2, entries 4, 5, 7 and 10). Moreover, it must be taken into consideration that the internal NTs nucleophile, linked to the selenium in the intermediate **8a**, appears sterically prevented to bring an *anti*-attack to one of the carbons of the episeleniranium ion.[17] In other words, the stereoelectronic characteristics of the ionic intermediate strongly support the presence of the open species **8b** that seems mandatory in order to achieve an intramolecular cyclization to selenazines **7** as depicted in Scheme 4. Thus, the overall retention of the alkene geometry makes such a mechanism poorly convincing.[18]

In conclusion, 2-*N*-sulfonylamino diselenides can be transformed in transient *o*-iminoselenoquinones *via* copper(II)-catalyzed activation of the Se–Se bond and base-mediated 1,4-elimination at the selenium of a selenolate anion. The selenolate ion, exploited as a leaving group, is oxidized by molecular oxygen to the starting diselenide which is completely transformed into the final selenazine The hitherto unknown 2-iminoselenoquinone can be efficiently trapped as electron-poor diene in an inverse electron demand hetero Diels–Alder reaction with several electron-rich alkenes to give, regio- and stereoselectively, benzo[*b*]-[1,4]selenazines, an interesting yet very poorly studied class of selenium-containing heterocycles. The scope and application of this new procedure as well as the validation of the proposed mechanism[18] are under investigation.

Experimental Section

Spectroscopic data for diselenide **4** and selenazines **7a–g**, **7i** and **7l** are reported in the Supporting Information. The following protocol, describing the synthesis of derivative **7a**, can be considered as the general procedure used for the preparation of all selenazines **7.**

3,4-Dihydro-3-(4-methoxyphenyl)-4-tosyl-2*H*-benzo[*b*][1,4]selenazine (7a)

In a reaction vial, to a solution of diselenide **4** (50 mg, 0.08 mmol) in dry $CHCl_3$, $Cu(OTf)_2$ (5 mg, 0.015 mmol), styrene **6a** (21 mg, 0.16 mmol) and Et_3N (8 mg, 0.08 mmol) were added in sequence and the mixture was heated at 60 °C until complete disappearance of diselenide **4** as monitored by TLC (72 h). Then, the crude reaction mixture was diluted with dichloromethane (20 mL), washed with saturated NH_4Cl (2×20 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. Silica gel column chromatographic purification (eluent dichloromethane:petrol = 3:1) allowed the isolation of derivative **7a** as a white solid; yield: 55 mg (75%); mp 50–51 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (dd, *J* = 8.0, 1.2 Hz, 1H) 7.47–7.43 (m, 2H), 7.34–7.30 (m, 2H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.20–7.15 (m, 3H), 7.04 (td, *J* = 7.6, 1,6 Hz, 1H), 6.81–6.77 (m, 2H), 5.74 (at, *J* = 6.6,

1H), 3.75 (s, 3H), 3.36 (dd, $J=12.2$, 6.6 Hz, 1H), 3.04 (dd, $J=12.2$, 6.6 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=158.9$, 143.5, 136.7, 135.5, 132.1, 131.3, 130.4, 129.3 (2C), 128.8, 127.8 (2C), 127.5 (2C), 126.8, 126.6, 113.9 (2C), 59.7, 55.2, 27.0, 21.6; MS: *m/z* (rel. abs. %) = 459 (M^{+}, 28), 304 (78), 224 (55), 223 (61), 134 (76), 91 (100); anal. calcd. for $C_{22}H_{21}NO_3SSe$: C 57.64, H 4.62, N 3.06; found: C 58.01, H 4.95, N 3.02.

Acknowledgements

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[14] Selenazines **7** are thermally stable under the reaction conditions required for their formation. In fact, no trace of selenazine **7f** was detected after heating selenazine **7a** and alkene **6f** for 72 h at 60 °C, in the presence of just Et_3N or also $Cu(OTf)_2$. As a matter of fact, a retro Diels–Alder process is the dominant fragmenta-

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