Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 665–669
Tetrahedron Letters

# Synthesis of diaryl selenides using the in situ reagent $SeCl_2$

Sanjio S. Zade,[a] Snigdha Panda,[a] Harkesh B. Singh[a,*] and Gotthelf Wolmershäuser[b,†]

[a]*Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400 076, India*
[b]*Fachbereich Chemie, Universität Kaiserslautern, Postfach 3049, Kaiserslautern 67653, Germany*

Received 14 September 2004; revised 19 November 2004; accepted 25 November 2004
Available online 10 December 2004

**Abstract**—Reactions of in situ prepared $SeCl_2$ with Grignard reagents (prepared from bromobenzene, *o*-tolyl bromide, 2,6-dimethyl-4-*tert*-butyl-1-bromobenzene, and 1-bromo-2-methylnaphthalene) and dilithiated benzamides (prepared from *N*-phenyl, *N*-cyclohexyl, and *N*-isopropyl benzamide) are described.


The preparation of divalent selenium compounds has attracted considerable efforts due to the fact that these compounds have widespread applications.[1] Diarylselenides with amino and amide groups, ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one) and its analogues, and selenium analogues of 2,3-dihydrobenzofuranol with Se(II) instead of oxygen are useful antioxidants.[2] The ligand chemistry of divalent selenium compounds is a well-developed branch of selenium chemistry.[3] Several chiral diorganoselenides have been utilized as ligands in chiral catalysis.[4]

The synthesis of diorganoselenides has been approached by various routes, which include; (i) the reaction of selenium dianions with aryl/alkyl halides, (ii) the reaction of aryl/alkyl metal selenolates with alkyl/aryl halides, (iii) the reaction of organometallic species (e.g., Grignard reagents, organolithiums) with selenium dications, (iv) reduction of diselenides by metals to monoselenides.[1] The selenium dianion can be produced easily by the treatment of elemental selenium with superhydride,[5] sodium borohydride,[6] sodium hydride[7] or directly by treating selenium with alkali metals in various solvents in the presence[8] or absence[9] of an electron carrier. Subsequent reaction of the selenium dianion with the alkyl/aryl halide affords the diorganoselenide. Using this route, dialkyl selenides can be obtained in excellent yield. However, this route is not suitable for unactivated or electron rich aryl halides as these reactions require elevated temperature (130–170 °C) with highly polar solvents (like HMPA, DMF, and NMP) and long reaction times (>24 h), and the reaction yields are unsatisfactory (<30%).[9] The alternative approach for the preparation of diaryl selenides and other Se(II) systems involves an electrophilic $Se^{2+}$ source such as selenium diethyldithiocarbamate [$Se(dtc)_2$].[10] However, the synthesis of $Se(dtc)_2$ is a multi-step process and requires the expensive precursor selenium dioxide.[11]

In view of the above we considered the use of $SeCl_2$ as a source of $Se^{2+}$ for preparing diaryl selenide and related systems, in particular, ebselen. The synthesis of $SeCl_2$ in pure and stable form has always been difficult. Whilst a number of attempts have been made to prepare pure $SeCl_2/SeBr_2$. In the preparation of the [1,4,2,3]-diselenadizolyl radical and its dimer, $SeCl_2$ was synthesized in situ by the disproportionation of $SeCl_4$ and Se.[12] Milne has synthesized $SeCl_2/SeBr_2$ in acetonitrile and studied their stability and composition in different solvents.[13] Bryce and Chesney reported $PhSO_2SeCl$ as a synthetic equivalent for $SeCl_2$ for the formation of C–Se and N–Se bonds.[14] Recently, Chivers and co-workers developed a novel reaction to prepare $SeCl_2$ in THF using Se powder and sulfuryl chloride as synthons.[15] The stability of $SeCl_2$ in various solvents has been investigated by $^{77}Se$ NMR. The prepared $SeCl_2$ was further characterized by Raman spectroscopy and by X-ray structures of its adducts with tetrahydrothiophene and tetramethylthiourea. The authors extended their studies by reacting $SeCl_2$ with bis(trimethylsilylamino)sulfane to

*Keywords*: Selenium dichloride; 2-Phenyl-1,2-benzisoselenazol-3(2*H*)-one; Lithiation; Diorganoselenide; Benzamide.
* Corresponding author. Tel.: +91 22 2576 7190; fax: +91 22 2572 3480; e-mail addresses: chhbsia@chem.iitb.ac.in; wolmersh@chemie.unk-kl.de
† Fax: +49 631 205 2187.

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.125

obtain cyclic compounds, which mimic the structures of $(SN)_x$ polymers.[16] They also studied the reaction of $SeCl_2$ with *t*-butylamine producing different interesting acyclic and cyclic compounds having selenium and nitrogen backbones.[17] However, the application of $SeCl_2$ for the preparation of organoselenium compounds has not been demonstrated. In this report, we have investigated the utility of $SeCl_2$ as a dicationic $Se^{2+}$ source for the preparation of several organoselenium compounds.

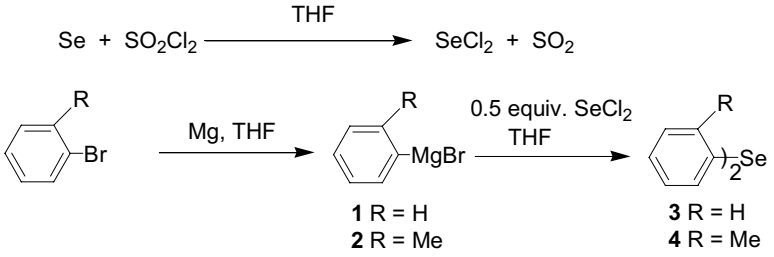
Selenium dichloride was conveniently generated in situ by the treatment of elemental selenium with $SO_2Cl_2$ in THF.[15] The reaction yields a clear brownish red solution, which was used for further reactions. The Grignard reagents **1** and **2** were prepared by stirring a THF solution of bromobenzene and *o*-tolyl bromide with Mg turnings for 6 and 4 h, respectively. On addition of the $SeCl_2$ solution at −78 °C, the turbid solutions changed to orange after which the reaction mixtures were allowed to warm to the room temperature. After usual work-up and purification,[18] the monoselenides **3** and **4** were obtained as yellow oil and a colorless solid in good yields (Scheme 1).[19]

The Grignard reagents **5**[20] and **8**[21] were prepared by reported methods. A similar procedure to that described above was followed to obtain the monoselenide **6**[22] (Scheme 2) and **9**[23] (Scheme 3).

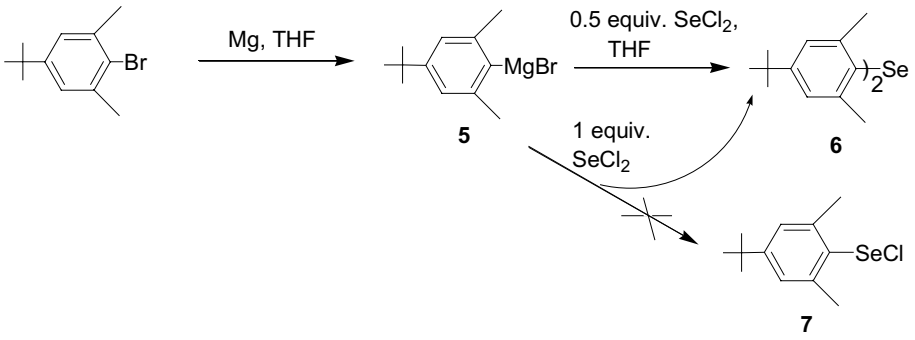
Interestingly, during crystallization of the crude product **9**, both yellow and red crystals were obtained, which were separated manually. Characterization of these two different colored compounds revealed that the yellow and red crystals were monoselenide **9**[23] and diselenide **10**,[21,23] respectively, in an 11:1 ratio. The formation of the diselenide may be due to oxidation of some Se to $Se_2^{2+}$ in addition to $Se^{2+}$.

Heteroatom directed aromatic lithiation is a key step in the synthesis of various heterocyclic ring systems and naturally occurring compounds.[24] Recently, this strategy has been found to be a promising approach for the synthesis of various organoselenium compounds.[25] The dilithiated species **15**–**17** were produced by treatment of benzamides **12**–**14** with 2 equiv of *n*-BuLi at 0 °C. Interestingly, in the reaction of dilithiated benzanilide with $SeCl_2$, only a cyclization reaction was observed affording ebselen **18** in 40% yield (Eq. 1, Scheme 4).[26] Although ebselen is a major GPx mimic, its synthesis has been a challenge[27] ever since it was first prepared in 1924.[28] In the earliest and most direct approach, 2,2′-diselenobis(benzoic acid) was converted to a selenenyl chloride benzoyl chloride, which was treated with aniline to give ebselen.[27c] The most expedient method was reported by Engman and Hallberg et al.[27d] and utilized a one-pot procedure in which benzanilide was *ortho*-lithiated and treated with selenium powder, followed by cuprous bromide-mediated oxidative ring closure. A free radical synthesis of ebselen has been achieved by intramolecular homolytic substitution with amidyl radicals.[27e,f] In contrast, the reaction of $SeCl_2$ with dilithium salt **16** afforded monoselenide **19** in moderate yield (Eq. 2, Scheme 3).[29] However, the treatment of $SeCl_2$ with dilithium salt **17** afforded only a black, sticky material, which decomposed to give an insoluble material on passing through a silica gel column.

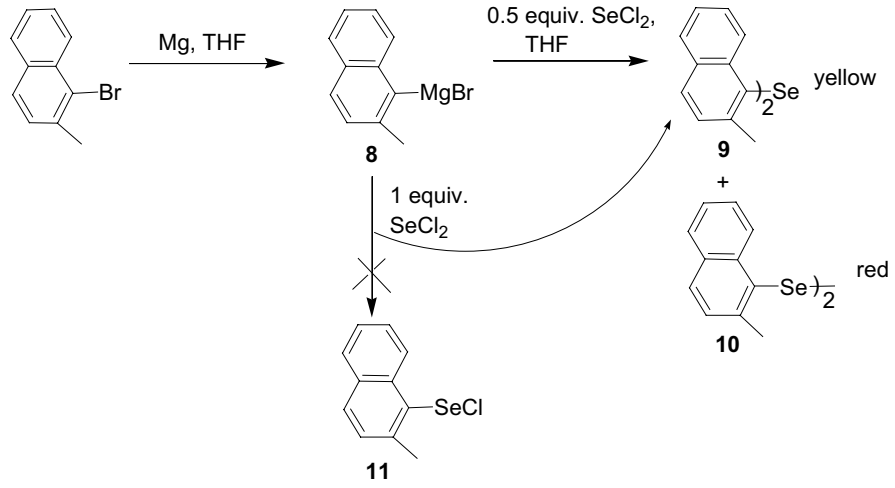
Organoselenenyl chlorides have potential applications in organic synthesis to manipulate unactivated carbon–



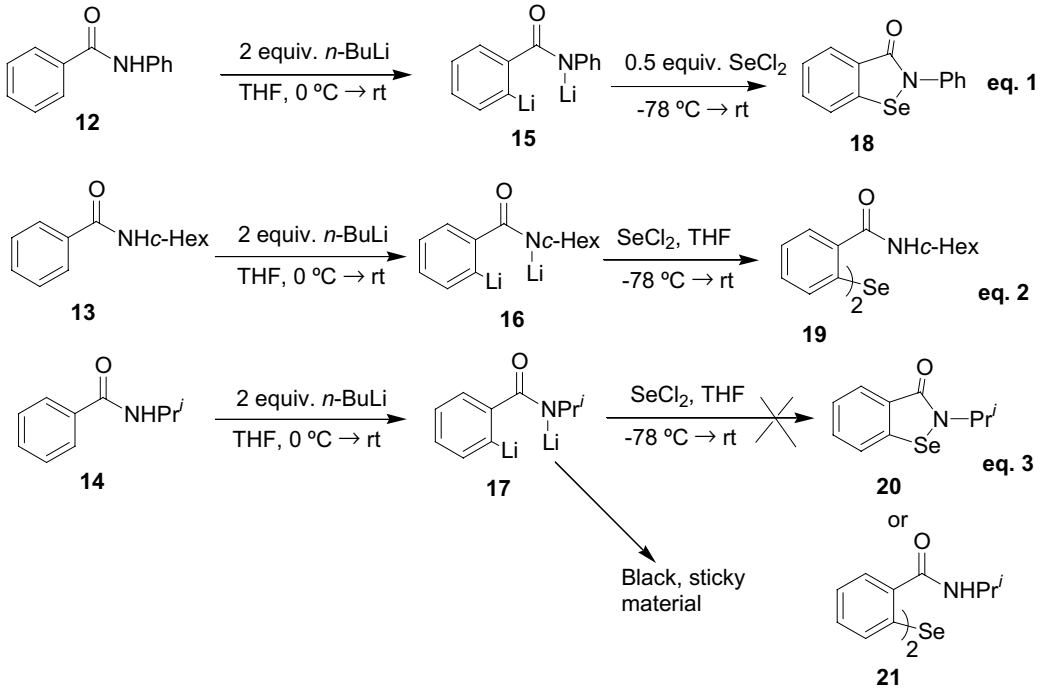

**Scheme 1.**




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

carbon double bonds as well as to prepare organoselenium compounds.[30] In this regard, the synthesis of arylselenenyl halides **7** and **11** was attempted. However, all attempts to prepare the aryl selenenyl chlorides by treatment of Grignard reagents/lithiated intermediates with 1 equiv of $SeCl_2$ were unsuccessful, in all cases the disubstituted products were obtained (Schemes 2 and 3).

The newly-synthesized compounds were characterized by $^{1}H$, $^{77}Se$ NMR and mass spectroscopy, and elemental analysis. In the case of **9**, the signal for the C-8 proton was shifted considerably downfield compared to the other aromatic protons. This is probably due to a 1,8-*peri* interaction. Compound **9** was additionally characterized by single crystal X-ray crystallography.[31]

In summary, the treatment of $SeCl_2$ with Grignard reagents (1:2) prepared from bromobenzene, *o*-tolyl bromide, 2,6-dimethyl-5-*t*-butyl-1-bromobenzene, and 1-bromo-2-methylnaphthalene afforded the corresponding monoselenides in very good yields. However, the 1:1 reactions did not afford the expected selenenyl halides. The reaction of $SeCl_2$ with dilithiated benzanilide afforded the cyclized product, ebselen in moderate yield. Furthermore, *N*-alkyl analogues of benzanilide did not afforded cyclized products, but gave the corresponding monoselenides instead.

## Acknowledgements

We are grateful to the Department of Science and Technology (DST), New Delhi for funding this work. Additional help from the Regional Sophisticated Instrumentation Center (RSIC), Indian Institute of Technology (IIT), Bombay, for 300 MHz NMR spectroscopy is gratefully acknowledged. S.S.Z. wishes to thank CSIR, New Delhi, for a fellowship.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.125.

## References and notes

1. (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1985; (b) *Chemistry of Organoselenium and Tellurium Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1987; (c) *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; (d) *Topics in Current Chemistry*; Wirth, T., Ed.; Springer: Heidelberg, 2000; Vol. 208.
2. (a) Engman, L.; Stern, D.; Pelcmanl, M.; Andersson, C.-M. *J. Org. Chem.* **1994**, *59*, 1973–1979; (b) Andersson, C.-M.; Hallberg, A.; Hoegberg, T. *Adv. Drug Res.* **1996**, *28*, 65–180; (c) Malmstrom, J.; Jonsson, M.; Cotgreave, I. A.; Hammarstrom, L.; Sjodin, M.; Engman, L. *J. Am. Chem. Soc.* **2001**, *123*, 3434–3440; (d) Mugesh, G.; Singh, H. B. *Chem. Soc. Rev.* **2000**, *29*, 347–357; (e) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125–2179.
3. (a) Gysling, H. J. *Coord. Chem. Rev.* **1982**, *42*, 133–244; (b) Hope, E. G.; Levason, W. *Coord. Chem. Rev.* **1993**, *122*, 109–170; (c) Levason, W.; Orchard, S. D.; Reid, G. *Coord. Chem. Rev.* **2002**, *225*, 159–199.
4. Hiroi, K. In *Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; 2000; Vol. 1, pp 67–79.
5. Gladysz, J.; Hornby, J. L.; Garbe, J. E. *J. Org. Chem.* **1978**, *43*, 1204–1208.
6. (a) Klayman, D. L.; Griffin, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197–199; (b) Kienitz, C. O.; Thöne, C.; Jones, P. G. *Inorg. Chem.* **1996**, *35*, 3990–3997.
7. Krief, A.; Derock, M. *Tetrahedron Lett.* **2002**, *43*, 3083–3086.
8. (a) Syper, L.; Mlochowski, J. *Tetrahedron* **1988**, *44*, 6119–6130; (b) Thompson, D. P.; Boudjouk, P. *J. Org. Chem.* **1988**, *53*, 2109–2112.
9. (a) Sandman, D. J.; Stark, J. C.; Foxman, B. M. *Organometallics* **1982**, *1*, 739–742; (b) Sandman, D. J.; Stark, J. C.; Acampora, L. A.; Gagne, P. *Organometallics* **1983**, *2*, 549–551.
10. (a) Bates, C. M.; Morley, C. P.; Hursthouse, M. B.; Malik, K. M. A. *J. Organomet. Chem.* **1995**, *489*, C60–C61; (b) Apte, S. D.; Singh, H. B.; Butcher, R. J. *J. Chem. Res. (S)* **2000**, 160–161; *J. Chem. Res. (M)* **2000**, 0559–0569; (c) Panda, A.; Menon, S. C.; Singh, H. B.; Butcher, R. J. *J. Organomet. Chem.* **2001**, *623*, 87–94.
11. Foss, O. *Inorg. Synth.* **1953**, *4*, 88–93.
12. (a) Cordes, A. W.; Glarum, S. H.; Haddon, R. C.; Hallford, R.; Hicks, R. G.; Kennepohl, D. K.; Oakley, R. T.; Palstra, T. T. M.; Scott, S. R. *J. Chem. Soc., Chem. Commun.* **1992**, 1265–1266; (b) Cordes, A. W.; Bryan, C. D.; Davis, W. M.; de Laat, R. H. S.; Glarum, H.; Goddard, J. D.; Haddon, R. C.; Hicks, R. G.; Kennepohl, D. K. *J. Am. Chem. Soc.* **1993**, *115*, 7232–7239.
13. Milne, J. *Polyhedron* **1985**, *4*, 65–68.
14. Bryce, M. R.; Chesney, A. *Chem. Commun.* **1995**, 195–196.
15. Maaninen, A.; Chivers, T.; Parvez, M.; Pietikäinen, J.; Laitinen, R. S. *Inorg. Chem.* **1999**, 4093–4097.
16. Konu, J.; Maaninen, A.; Paananen, K.; Ingman, P.; Laitinen, R. S.; Chivers, T.; Valkonen, J. *Inorg. Chem.* **2002**, *41*, 1430–1435.
17. (a) Maaninen, T.; Chivers, T.; Laitinen, R. S.; Schatte, G.; Nissinen, M. *Inorg. Chem.* **2000**, *39*, 5341–5347; (b) Maaninen, T.; Chivers, T.; Laitinen, R. S.; Wegelius, E. *Chem. Commun.* **2000**, 759–760.
18. Typical procedure: $SeCl_2$, prepared separately in a three-necked flask, was added via cannula to the solution of Grignard reagent at −78 °C in a dropwise manner. The mixture was allowed to warm to rt. The resulting solution was poured into water and extracted with dichloromethane. The organic layer was filtered through Celite, and dried ($Na_2SO_4$). Evaporation of the solvent afforded a gray-colored solid, which was purified by passing through a silica gel column (petroleum ether, 60–80) and recrystallized from petroleum ether (60–80) to give colorless crystals of the desired compound.
19. Yields: **3**: 82% and **4**: 74%. The mp of **4** and $^1$H NMR data for **3** and **4** match with reported values Taniguchi, M.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915–920.
20. Mugesh, G.; Panda, A.; Singh, H. B.; Punekar, N. S.; Butcher, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 839–850.
21. Mugesh, G.; Panda, A.; Kumar, S.; Apte, S. D.; Singh, H. B.; Butcher, R. J. *Organometallics* **2002**, *21*, 884–892.
22. Compound **6**: yield: 1.5 g (75%). Mp 97 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.26 (s, 18H), 2.28 (s, 12H), 7.01 (s, 4H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 24.02, 31.37, 34.29, 125.25, 129.64, 141.08, 150.27. $^{77}$Se NMR (300 MHz, $CDCl_3$): $\delta$ 231. GC–MS: *m/z* (%) 402 ($M^+$, 55), 387 (50), 242 (12), 225 (62), 186 (37), 158 (25), 145 (35), 131 (55), 119 (54), 105 (51), 91 (52), 77 (9), 57 (100). Anal. Calcd for $C_{24}H_{34}Se$: C, 71.85; H, 8.53. Found: C, 71.63; H, 9.07.
23. Yellow compound **9**: yield: 1.5 g (80%). Mp 108 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.36 (s, 6H), 7.24 (d, $J$ = 8.4 Hz, 2H), 7.36–7.46 (m, 4H), 7.68 (d, $J$ = 8.4 Hz, 2H), 7.74–7.80 (m, 2H), 8.56–8.66 (m, 2H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 24.47, 125.21, 126.74, 127.65, 128.37, 128.48, 129.00, 130.41, 132.68, 135.12, 140.54. $^{77}$Se NMR (300 MHz, $CDCl_3$): $\delta$ 202. GC–MS: *m/z* (%) 362 ($M^+$, 27), 282 (50), 267 (30), 220 (26), 141 (89), 115 (100), 89 (12), 69 (14). Anal. Calcd for $C_{22}H_{18}Se$: C, 73.14; H, 5.01. Found: C, 73.23; H, 5.32.
Red compound (diselenide) **10**:[20] yield: 0.15 g (7%). Mp 120–122 °C. Anal. Calcd for $C_{22}H_{18}Se_2$: C, 60.03; H, 4.11. Found: C, 60.23; H, 4.37. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.27 (s, 6H), 7.24 (d, $J$ = 8.8 Hz, 2H), 7.14–7.40 (m, 4H), 7.69 (dd, $J$ = 8.1, 8.3 Hz, 4H), 8.14 (d, $J$ = 8.4 Hz, 2H). $^{77}$Se NMR (300 MHz, $CDCl_3$): $\delta$ 355.
24. Schlosser, M. *Tetrahedron* **1994**, *50*, 5845–6128.
25. Mugesh, G.; Singh, H. B. *Acc. Chem. Res.* **2002**, *35*, 226–236.
26. Typical procedure for the reaction of dilithiated benzamides with $SeCl_2$: a stirred solution of benzamide (5 mmol) in 30 mL THF was treated dropwise with a 1.6 M hexane solution of *n*-BuLi (10 mmol) at 0 °C. The resulting solution was allowed to warm to rt and stirred for 2 h at this temperature. $SeCl_2$ (2.5 mmol) solution, prepared separately in a three-necked flask, was added to the dilithiated benzamide solution dropwise at −78 °C. The resulting

solution was then allowed to warm to rt. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was filtered through Celite, and dried over sodium sulfate. Evaporation of the solvent afforded a colorless solid, which was purified by silica gel column chromatography using dichloromethane as eluent.

27. (a) Weber, R.; Renson, M. *Bull. Soc. Chim. Fr.* **1976**, 1124–1126; (b) Lambert, C.; Welter, A.; Christiaens, L. E.; Dereu, N. *Synth. Commun.* **1991**, *21*, 85–98; (c) Christiaens, L. E.; Wirtz, P. Eur. Pat. Appl. EP 44453, 1982; *Chem. Abstr*. **1982**, *96*, 199699v; (d) Engman, L.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 2964–2965; (e) Fong, M. C.; Schiesser, C. H. *Tetrahedron Lett.* **1995**, *36*, 7329–7332; (f) Fong, M. C.; Schiesser, C. H. *J. Org. Chem.* **1997**, *62*, 3103–3108; (g) Jacquemin, P. V.; Christiaens, L. E.; Renson, M. J.; Evers, M. J.; Dereu, N. *Tetrahedron Lett.* **1992**, *33*, 3863–3866; (h) Kloc, K.; Mlochowski, J.; Osajda, M.; Syper, L.; Wojtowicz, H. *Tetrahedron Lett.* **2002**, *43*, 4071–4074.
28. Lesser, R.; Weiss, R. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1077–1082.
29. Monoselenide **19** was prepared using the typical procedure as a brown solid, which was purified by chromatography on silica gel (dichloromethane) to afford a white solid (60%). Mp 206–208. $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.00–1.46 (m, 12H), 1.58–1.74 (m, 4H), 1.84–1.96 (m, 4H), 3.82–3.96 (m, 2H), 6.32 (d, $J$ = 8.0 Hz, 2H), 7.20–7.40 (s, 6H), 7.64 (dd, $J$ = 7.2, 1.4 Hz, 2H). $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 24.98, 25.70, 32.98, 49.00, 127.85, 128.81, 131.28, 134.77, 137.66, 167.36. Anal. Calcd for $C_{26}H_{32}N_2O_2Se$: C, 64.60; H, 6.66; N, 5.79. Found: C, 64.10; H, 6.38; N, 6.05.
30. (a) Christov, V. C.; Ivanov, I. K. *Heterocycl. Commun.* **2003**, *9*, 629–634; (b) Osajda, M.; Mlochowski, J. *Synth. Commun.* **2003**, *33*, 1301–1307; (c) Kloc, K.; Osajda, M.; Mlochowski, J. *Chem. Lett.* **2001**, 826–827; (d) Potapov, V. A.; Amosova, S. V.; Petrov, B. V.; Starkova, A. A.; Malyushenko, R. N. *Sulfur Lett.* **1998**, *21*, 109–114; (e) Back, T. G.; Dyck, B. P.; Nan, S. *Tetrahedron* **1999**, *55*, 3191–3208.
31. For a detailed description see supporting information. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-250001. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].