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New Chiral Auxiliaries for Highly Stereoselective Asymmetric Methoxyselenenylations

Thomas G. Back* and Ziad Moussa

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

tgback@ucalgary.ca

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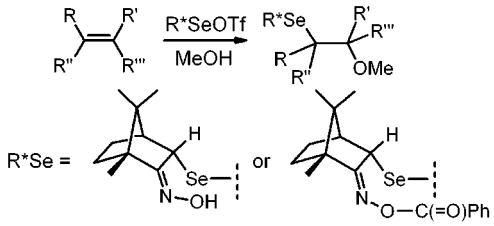
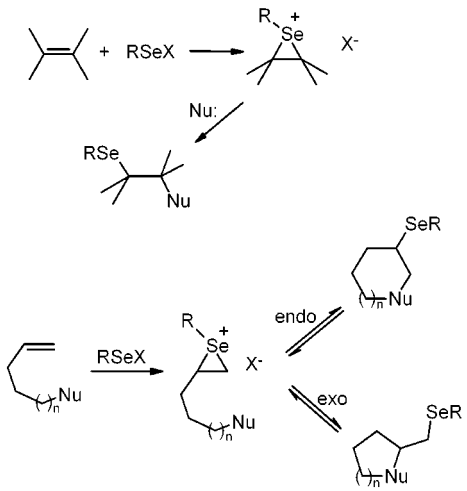
ABSTRACT



Replacement of the 2-keto group of readily available di(*endo*-3-camphoryl) diselenide with oxime or *O*-benzoyloxime substituents, followed by conversion into the corresponding selenenyl triflates, produced highly effective chiral selenium electrophiles for the asymmetric oxyselenenylation of alkenes in the presence of methanol.

Organoselenium chemistry has many proven applications in modern organic synthesis.[1] The development of asymmetric variations of selenium-mediated transformations has the potential to further increase their usefulness, and several strategies have been designed for this purpose in the past few years.[2] Among such reactions, the 1,2-additions of selenium electrophiles to alkenes in the presence of nucleophiles have attracted particularly keen interest.[3] These processes typically proceed with Markovnikov regiochemistry and via *anti* addition of the selenium moiety and the nucleophile because of the intermediacy of bridged seleniranium ions (Scheme 1). Cyclizations occur when the nucleophile is tethered to the alkene (Scheme 1). Furthermore, asymmetric variations of these reactions require the control of facial selectivity, which can, in principle, be achieved by attaching a chiral auxiliary group to the selenium atom of the electrophilic reagent. This leads to the diaste-

Scheme 1



(1) (a) *Organoselenium Chemistry − A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999. (b) *Topics in Current Chemistry: Organoselenium Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, 2000; Vol. 208.

(2) For a recent review, see: Wirth, T. *Tetrahedron* **1999**, *55*, 1−28.

(3) For reviews of electrophilic selenium reactions, see: (a) Beaulieu, P. L.; Déziel, R. In ref 1, Chapter 3. (b) Back T. G. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987; Chapter 1. (c) Back, T. G. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Ed.; Wiley: Chichester, 1987; Vol. 2, Chapter 3. (d) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986; Chapters 7 and 8. (e) Schmid, G. H.; Garratt, D. G. In *The Chemistry of Double-bonded Functional Groups. Supplement A, Part 2*; Patai S., Ed.; Wiley: New York, 1977; Chapter 9.

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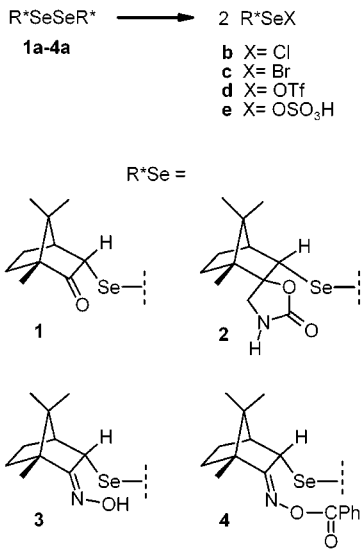
reoselective formation of initial 1,2-adducts, with enantioselective formation of final products after deselenization of the former.

We recently showed that diselenide **1a** can be conveniently prepared in one pot from camphor, via its enolate, and elemental selenium.[4] Moreover, **1a** can be easily converted into electrophiles, such as the corresponding selenenyl halides (**1b**,**c** X = Cl, Br) and triflate (**1d**; X = OTf) (Scheme 2),

Scheme 2

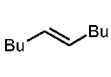
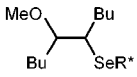
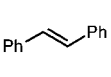
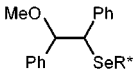
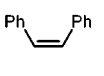
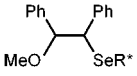
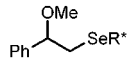
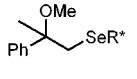
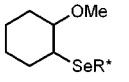
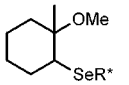
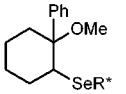


which can in turn be employed in diastereoselective 1,2-additions and cyclizations.[5] The keto group of the camphor moiety of **1a** also provides the opportunity for further structural modifications of the auxiliary to improve the facial selectivity of such reactions. Thus, while the selenenyl triflate **1d** proved to be the most stereoselective of several camphorseleno reagents studied for asymmetric oxyselenenylations[5a,b] (where the nucleophile is an alcohol or water), the corresponding spiro-oxazolidinone **2b** was more effective in cyclizations.[5a,c] Subsequently, the selenenyl sulfate **1e** was independently studied[6] but afforded generally lower diastereoselectivity than the triflate **1d**.

The principal drawback to the use of our[5] and other[6,7] existing chiral selenium electrophiles for oxyselenenylations and related processes is that the stereoselectivity is highly variable and dependent upon the substitution pattern of the substrate and the conditions of the reaction. Thus, there is a need for new reagents capable of delivering more consistent results. We now report the preparation of two new camphor-based diselenides, **3a** and **4a**, containing oxime and *O*-benzoyloxime substituents at C-2 instead of the original keto group and their conversion into the corresponding triflates **3d** and **4d**, respectively. These modifications, especially in the case of **3d**, have resulted in a dramatic improvement in the diastereomeric ratios obtained in the methoxyselenenylation of a series of variously substituted olefins.

Thus, the readily available diselenide **1a**[4] was converted into the novel oxime **3a** with hydroxylamine hydrochloride in refluxing pyridine. Acylation of **3a** with benzoyl chloride in pyridine at room temperature in the presence of catalytic DMAP afforded **4a**. The geometry of the oxime moiety of **4a** was determined to be *Z* by X-ray crystallography and is similarly inferred to be Z in **3a**. Diselenides **3a** and **4a** were converted into the corresponding selenenyl bromides **3c** and **4c**, respectively, with bromine in dichloromethane and then into the corresponding selenenyl triflates **3d** and **4d** with methanolic silver triflate. Methoxyselenenylation of a series of alkenes was performed with the resulting selenenyl triflates at −78 °C. The results are given in Table 1.[8] The products

Table 1. [a]Methoxyselenenylations of Alkenes with **3d** and **4d**

			isolated yield (%) (d.r.)[b]	
entry	substrate	product	with **3d**	with **4d**
1			73 (92:8)[c]	60 (94:6)[c]
2			68 (>98:2)[c,e]	70 (90:10)[d]
3			78 (90:10)[c]	30 (77:23)[d]
4			52 (94:6)[c]	[f]
5			[f]	92 (82:18)[d]
6			56 (88:12)[d]	50 (62:38)[d]
7			81 (>98:2)[c,e]	71 (>95:5)[c,e]
8			72 (90:10)[c]	80 (95:5)[c]

(a) All reactions were performed in dichloromethane/methanol at -78°C. (b) d.r. = diastereomeric ratio. (c) Measured by ^{77}Se-NMR integration. (d) Measured by ^{1}H-NMR integration. (e) The minor diastereomer was not detected; ratio is based on estimated minimum detection threshhold. (f)The products could not be separated from impurities that precluded an unambiguous determination of yield and d.r.

were isolated by flash chromatography as unseparated mixtures of diastereomers, and the diastereomeric ratios (dr) were measured by integration of either their ^{1}H or ^{77}Se NMR

(4) Back, T. G.; Dyck, B. P.; Parvez, M. *J. Org. Chem.* **1995**, *60*, 703−710.

(5) For asymmetric electrophilic reactions of **1b**−**1d** and **2b**−**2d**, see: (a) Back, T. G.; Dyck, B. P.; Nan, S. *Tetrahedron* **1999**, *55*, 3191−3208. (b) Back, T. G.; Nan, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3123−3124. (c) Back, T. G.; Dyck, B. P. *J. Chem. Soc., Chem. Commun.* **1996**, 2567−2568.

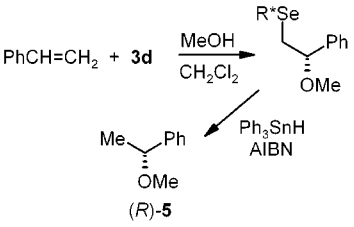
(6) (a) Tiecco, M.; Testaferri, L.; Santi, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Tetrahedron Lett.* **1998**, *39*, 2809. (b) Tiecco, M.; Testaferri, L.; Marini, F.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron Asymmetry.* **1999**, *10*, 747−757.

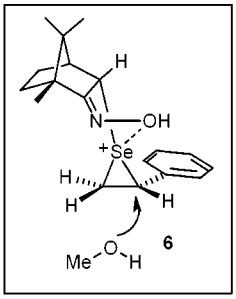
signals. The products were further characterized by IR and ^{13}C NMR spectroscopy, as well as by low- and high-resolution mass spectrometry.

Table 1 shows that the electrophilic addition can be performed with monosubstituted, *gem*-, *cis*-, or *trans*-disubstituted, or trisubstituted alkenes. In general, selenenyl triflate **3d** afforded superior or comparable yields and diastereoselectivities than did the benzoylated analogue **4d**. The differences between the dr's achieved with the two reagents are especially striking in entries 3 and 6, where *cis*-disubstituted alkenes were substrates. This is especially relevant because *cis*-disubstituted alkenes often afford particularly poor stereoselectivity in asymmetric oxyselenenylations.[9] Moreover, it has been demonstrated that the stereoselectivities of these processes are often improved when a substituent capable of coordination with the selenium atom is present in the chiral auxiliary.[2,7a,10] Thus, the superior performance of the free oxime **3d** may be the result of coordination of the oxime hydroxyl group with the selenium center during the addition to the alkene.[11]

Finally, the adduct obtained in entry 4 with **3d** was treated with triphenyltin hydride and AIBN to obtain the corresponding deselenized product **5** (Scheme 3).[12] A comparison

Scheme 3





of **5** with an authentic sample of the (*R*)-enantiomer[13] by GC on a chiral column (Cyclodex B) revealed that the enantiomeric ratio of the deselenized product was 98:2 in favor of the (*R*)-enantiomer. This confirmed the high dr shown in entry 4 of Table 1 and was consistent with the intermediacy of the seleniranium ion stereoisomer **6** (Scheme 3), which allows the placement of the bulky styrene phenyl group into the least congested quadrant around the alkene double bond in the preceding transition state.

In summary, the new chiral selenenyl triflate **3d**, and to a lesser extent the related **4d**, can be used in highly diastereoselective methoxyselenenylations. The success of **3d** with *cis*-alkenes is particularly noteworthy. Further experiments to improve the diastereoselectivity of these and related processes and to gain additional insight into the mechanism are in progress.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support.

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(7) For a review of asymmetric oxyselenenylations, see: (a) Fujita, K. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU, Tokyo, 1997; Vol. 16, pp 101−117. For examples of other chiral auxiliaries used in oxyselenenylations, see: (b) Déziel, R.; Malenfant, E.; Thibault, C.; Fréchette, S.; Gravel, M. *Tetrahedron Lett.* **1997**, *38*, 4753−4756. (c) Déziel, R.; Goulet, S.; Grenier, L.; Bordeleau, J.; Bernier, J. *J. Org. Chem.* **1993**, *58*, 3619−3621. (d) Fukuzawa, S.; Takahashi, K.; Kato, H.; Yamazaki, H. *J. Org. Chem.* **1997**, *62*, 7711−7716. (e) Fujita, K.; Murata, K.; Iwaoka, M.; Tomoda, S. *Tetrahedron* **1997**, *53*, 2029−2048. (f) Fujita, K.; Murata, K.; Iwaoka, M.; Tomoda, S. *Tetrahedron Lett.* **1995**, *36*, 5219−5222. (g) Tomoda, S.; Fujita, K.; Iwaoka, M. *J. Chem. Soc., Chem. Commun.* **1990**, 129−130. (h) Fujita, K.; Iwaoka, M.; Tomoda, S. *Chem. Lett.* **1992**, 1123−1124. (i) Tomoda, S.; Iwaoka, M. *Chem. Lett.* **1988**, 1895−1898. (j) Santi, C.; Fragale, G.; Wirth, T. *Tetrahedron Asymmetry.* **1998**, *9*, 3625−3628. (k) Fragale, G.; Neuburger, M.; Wirth, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1867−1868. (l) Wirth, T.; Fragale, G. *Chem. Eur. J.* **1997**, *3*, 1894−1902. (m) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1726−1728. (n) Wirth, T.; Fragale, G.; Spichty, M. *J. Am. Chem. Soc.* **1998**, *120*, 3376−3381. (o) Wirth, T.; Häuptli, S.; Leuenberger, M. *Tetrahedron: Asymmetry* **1998**, *9*, 547−550.

(8) **Typical procedure** (Table 1, entry 1): Diselenide **3a** (0.18 mmol) in dry CH_2Cl_2 was treated with Br_2 (0.18 mmol) at −40 °C, followed by the addition of AgOTf (0.53 mmol) in methanol. The mixture was cooled to −78 °C, *trans*-5-decene (0. 94 mmol) was added, and the reaction was quenched with an aqueous $NaHCO_3$ solution after 1 h. The product was isolated as a pale yellow oil by flash chromatography over silica gel (elution with 10% ethyl acetate−hexanes) to afford 111 mg (73%, based on **3a**): IR (neat) 3375, 1649, 1376, 1091, 938 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) major diastereomer, δ 3.78 (d, J = 4.3 Hz, 1 H), 3.57−3.46 (m, 1 H), 3.40 (s, 3 H), 3.38−3.32 (m, 1 H), 2.08−2.00 (m, 1 H), 1.91−1.52 (m, 6 H), 1.45−1.20 (m, 10 H), 0.98 (s, 6 H), 0.96−0.85 (m, 6 H), 0.81 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.2, 127.6, 85.4, 58.1, 52.5, 50.2, 48.4, 47.6, 39.6, 31.8, 31.7, 31.3, 30.5, 28.3, 24.1, 22.9, 22.7, 19.1, 18.9, 14.1, 11.8; ^{77}Se NMR ($CDCl_3$) major diastereomer, δ 292.7 (relative to Me_2Se = 0 ppm); minor diastereomer, δ 394.0; mass spectrum, *m/z* (relative intensity) 417 (3, M^+), 399 (8), 228 (10), 148 (54), 106 (67), 69 (100), 41 (80). Exact mass calcd for $C_{21}H_{39}NO_2Se$: 417.2146. Found: 417.2124.

(9) It has been pointed out (see refs 7a and 7i) that the stereochemistry of oxyselenenylations of symmetrically *cis*-disubstituted alkenes is fixed in the second step, where ring opening of the seleniranium intermediate occurs, rather than in the initial addition of the electrophile to the alkene. This is in contrast to unsymmetrical or *trans*-disubstituted alkenes, where the stereochemistry is set in the first step and may account for the poorer diastereoselectivities generally observed with *cis*-alkenes. The reason for the particular effectiveness of **3d** with *cis*-alkenes is not known.

(10) For a theoretical analysis of some asymmetric oxyselenenylations where an Se-coordinating substituent is present in the chiral auxiliary, see: Wang, X.; Houk, K. N.; Spichty, M.; Wirth, T. *J. Am. Chem. Soc.* **1999**, *121*, 8567−8576.

(11) (a) Coordination via the oxime nitrogen is less likely because it would require isomerization to the more crowded *E*-oxime in order to render the nitrogen atom's nonbonding electrons accessible to the selenium atom. Moreover, coordination through nitrogen instead of through the oxime oxygen would involve a more strained four- instead of five-membered ring. (b) The ^{77}Se NMR spectra of diselenides **3a** and **4a** are very similar to that of **1a** (δ 377.3, 375.3, and 375.2 ppm relative to dimethyl selenide, respectively), suggesting that coordination effects are not significant in the parent diselenides **3a** and **4a**. However, the X-ray structure of **4a** reveals relatively short interatomic distances of 2.95 and 2.97 Å between the oxime O and Se atoms of the two camphorseleno moieties. Thus, O−Se coordination should be possible in species where the selenium atom assumes a more strongly positive character.

(12) Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438−4447.

(13) Authentic (*R*)-**5** was obtained from (*R*)-1-phenylethanol by treatment with NaH and iodomethane.