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Synthesis of Diaryl Diselenides Having Chiral Pyrrolidine Rings with C_2 Symmetry. Their Application to the Asymmetric Methoxyselenenylation of *trans*-β-Methylstyrenes

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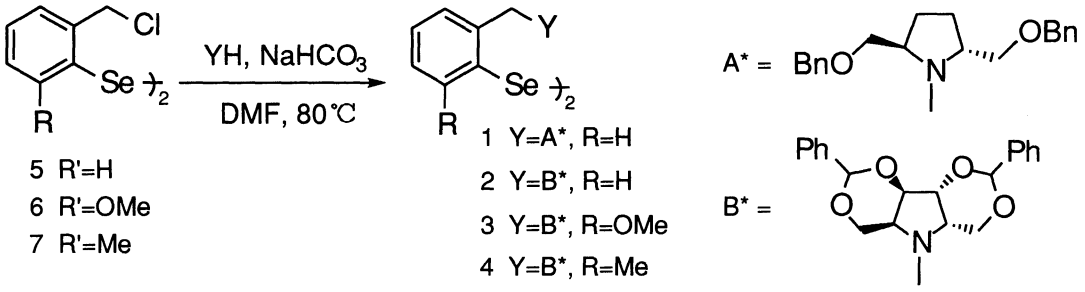
Optically active diaryl diselenides carrying C_2 symmetrical chiral pyrrolidines are synthesized by the condensation between 2,2'-diselenobis(benzyl chloride) derivatives and chiral pyrrolidines and are applied to methoxyselenenylation of *trans*-olefins. The observed diastereomeric excess (d.e.) is up to 60%.

Asymmetric synthesis based on organoselenium methodology has recently attracted considerable interest because of its versatile synthetic importance.[1, 2] However there have been no attempts to employ chiral organoselenium reagents as *asymmetric catalysts*. We have recently reported that diselenides having a *tertiary* amino group catalyze not only glutathione peroxidase catalytic cycle[3] but also the conversion of alkenes into oxygenated allylic compounds in the presence of sodium persulfate as an oxidizing agent.[4] Since plausible intermediates of the catalytic cycle (*e.g.* ArSeOH) possess strong Se···N non-bonded interaction between the selenium and the *tertiary* amino nitrogen,[3,5] it is expected that chiral modification of the amino group will be useful to cause asymmetric induction in oxyselenenylation of olefins. Herein we wish to report the first synthesis of this class of molecules (**1-4**) and their application to stoichiometric as well as catalytic asymmetric synthesis.

Chiral diaryl diselenides **1-4**[6] having chiral pyrrolidine rings with C_2 symmetry (A*[7] or B*[8]) at the *ortho*-position of the selenium have been selected as candidates of chiral selenium reagents, since effective interaction between the electrophilic selenium and the nitrogen of chiral pyrrolidine group were expected. Diselenides **1-4** were synthesized as shown in Scheme 1. The corresponding chloride (**5**, **6**, or **7**)[9] and the chiral pyrrolidine (A*H or B*H) were dissolved in *N*,*N*-dimethylformamide (DMF) and the solution was stirred



Scheme 1.

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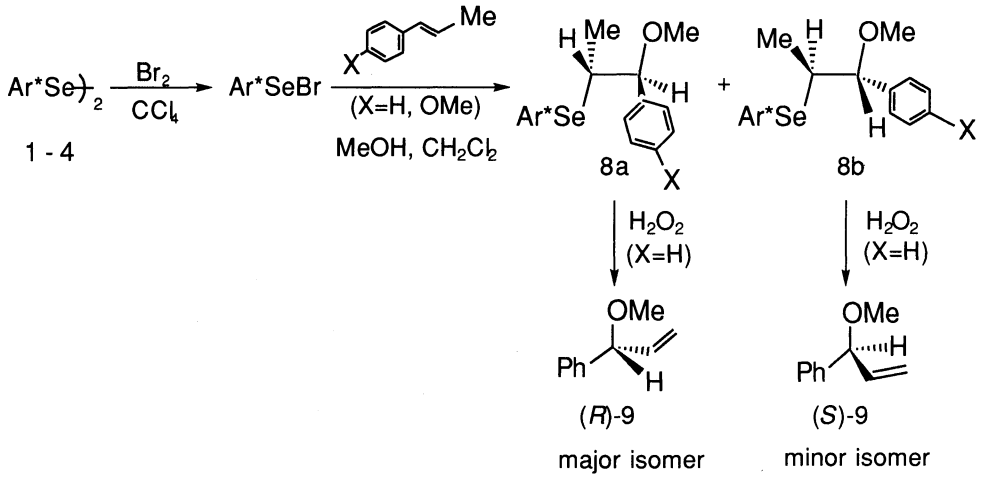
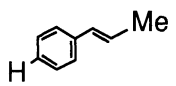
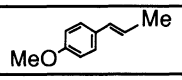
at 80 ℃ in the presence of a small amount of sodium hydrogen carbonate. Diselenides 1-4 were isolated in moderate yields (53%, 89%, 71%, and 48%, respectively).

The utility of diselenides **1-4** as chiral inducers was demonstrated by asymmetric methoxyselenenylation of *trans*-β-methylstyrene (X=H; (*E*)-phenylpropene) and *trans*-anethole (X=OMe; (*E*)-1-(4-methoxyphenyl)-propene) (Scheme 2). To a dichloromethane solution (2 ml) of a diaryl diselenide (0.5mmol) 0.1M tetrachloromethane solution of bromine (0.05ml) was added dropwise at room temperature under nitrogen atmosphere. After removal of the solvent *in vacuo*, the residual selenenyl bromide was dissolved in a mixture of methanol and dichloromethane (1:1) and to the solution was added an excess amount of olefin. The mixture was stirred for 12 hrs. The residual oil, obtained by the usual extractive workup with dichloromethane, was purified by gel permeation chromatography to give the corresponding methoxyselenenylation products (**8a** and **8b**) in



Scheme 2.

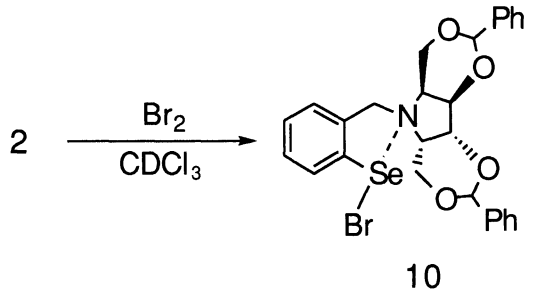
Table 1. Asymmetric Methoxyselenenylation of *trans*-β-Methylstyrenes using Diaryl Diselenides **1-4** Containing Chiral Pyrrolidine with C_2 Symmetry

Entry	Olefin	Ar*SeSeAr*	Condition	Yield/%[a]	d.e./%[b]
1		1	r.t.	90	8[c]
2		2	r.t.	84	28
3			-78℃→r.t.	85	52
4		3	r.t.	63	4
5			-78℃→r.t.	59	22
6		4	r.t.	64	30
7			-78℃→r.t.	71	53
8		2	-78℃→r.t.	74	60[d]

a) Isolated yield. b) Determined by integration of ^{1}H NMR absorptions due to -OCH_3 of methoxyselenenylation products **8** except for entry 1. c) Determined by integration of ^{1}H NMR absorptions due to -OCH_3 of deselenenylation product **9** by adding Eu(hfc)$_3$. d) It is assumed that the configuration of the major isomer is similar to that of Entries 2 and 3.

fairly good yield. The d.e.'s of **8** determined by integration of ^{1}H NMR absorptions are listed in Table 1. To determine the absolute stereochemistry, **8** (X=H) was oxidized with hydrogen peroxide to **9**, the stereochemistry of which was then determined according to the literature method.[2] The configuration of the major enantiomer of **9** was found to be *R* in all cases.

Diselenide **1** having a 2,5-disubstituted chiral pyrrolidine ring gave poor d.e. (8%de; Entry 1). When cyclic acetals were introduced in the pyrrolidine ring, the d.e. was slightly enhanced (28%de; Entry 2). When the reaction was started at -78 ℃, the d.e. was significantly enhanced (52%de; Entry 3), which was comparable with that attained with optically active selenobinaphthyl compounds[2,3]. We subsequently examined the effect of the substituent (R) at the *ortho*-position of the selenium, since it was expected that the approach of olefin might be significantly affected by R group. However the d.e.'s were not improved significantly (Entry4 through 7). On the other hand when *trans*-anethole (X=OMe) was employed as an olefin, the d.e. was increased up to 60% (Entry 8). The moderate asymmetric induction is probably due to the strong Se···N interaction between an electrophilic selenium and a *tertiary* nitrogen of chiral pyrrolidine ring during the process of the addition to the olefin. Indeed bromination of **2** (Scheme 3) gave **10**, the ^{77}Se NMR of which (1018.8ppm) appeared about 150 ppm downfield relative to benzeneselenenyl bromide (869.0ppm),[10] clearly suggesting the existence of strong intramolecular Se···N interaction.[11]



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Scheme 3.

Described finally is an application of the selenium reagents to the first *catalytic asymmetric conversion* of *trans*-β-methylstyrene into an optically active allylic ether **9** using **2** as a chiral selenium catalyst. The catalytic reaction was carried out according to the literature method[4] using copper (II) nitrate. The chemical yield of **9** with respect to **2** determined by gas chromatography was 241% and its optical yield was 32%ee, which was the same level of methoxyselenenylation of **2** at room temperature (Table1 Entry 2). We are now trying to enhance the ee as well as the catalytic efficiency of the asymmetric reaction.

References

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2) S. Tomoda, K. Fujita, and M. Iwaoka, *Phosphorus, Sulfur, and Silicon, and the Related Elements*, **67**, 125 (1992); S. Tomoda, K. Fujita, and M. Iwaoka, *J. Chem. Soc., Chem. Commun.*, **1990**, 129.

3) M. Iwaoka and S. Tomoda, *J. Am. Chem. Soc.*, **1994**, in press.

4) M. Iwaoka and S. Tomoda, *J. Chem. Soc., Chem. Commun.*, **1992**, 1165.

5) Se···N non-bonded interaction was crystallographically as well as NMR spectroscopically observed in diselenide having *tertiary* amino groups and its derivatives. M. Iwaoka and S. Tomoda, *Phosphorus, Sulfur, and Silicon, and the Related Elements*, **67**, 125 (1992).

6) **1**: pale yellow oil; $[\alpha]_D^{25}$ +30° (*c* 0.40, $CHCl_3$); IR (CH_2Cl_2) 2910, 2840, 1450, 1258, 1090, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ =7.67-6.60 (m, 28H, Ar*H*), 4.37 (s,8H, OCH_2Ph), 4.13 (d, *J*=13 Hz, 2H, CH_2N), 3.93 (d, *J*=13 Hz, 2H, CH_2N), 3.67-3.33 (m, 8H, BnOCH_2), 3.33-2.90 (m, 4H, NC*H*), 2.23-1.48 (m, 8H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ =73.2, 72.1, 61.2, 54.5, 27.5; ^{77}Se NMR ($CDCl_3$) δ =418.4; MS m/z 480 (M^+/2); Found: m/z 480.1411. Calcd for $C_{27}H_{30}NO_2Se$: M, 480.1439. **2**: yellow powder; mp 125-127 ℃; $[\alpha]_D^{25}$ +141° (*c* 0.714, $CHCl_3$); IR (KBr) 2900, 2850, 1385, 1115, 980, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ =7.90-6.95 (m, 28H, Ar*H*), 5.49 (s, 4H, C*H*Ph), 4.73 (d, J=15 Hz, 2H, CH_2N), 4.37 (d,J=2.0 Hz, 4H, OC*H*C*H*O), 4.21 (d, J=13 Hz, 4H, OCH_2), 4.06 (d, J=15 Hz, 2H, CH_2N), 3.92 (d, J=12 Hz, 4H, OCH_2), 3.50 (s, 4H, NC*H*); ^{13}C NMR ($CDCl_3$) δ =99.9, 79.5, 66.7, 59.1, 56.0; ^{77}Se-NMR ($CDCl_3$) δ =414.5; MS m/z 508 (M^+/2), 105 (base); Found: C, 63.90; H, 5.16; N, 2.76%, Calcd for $C_{54}H_{52}O_8N_2Se_2$: C, 63.93; H, 5.43; N, 2.77%. **3**: yellow powder; mp 111-113 ℃; $[\alpha]_D^{25}$ +295° (*c* 0.418, $CHCl_3$); IR (KBr) 2830, 1630, 1455, 1260, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ =7.58-6.65 (m, 28H, Ar*H*), 5.41 (s, 4H, C*H*Ph), 4.65 (d, J=16 Hz, 2H, CH_2N), 4.30 (s, 4H, OC*H*C*H*O), 3.93 (d, J=13 Hz, 4H, OCH_2), 3.77 (d, J=13 Hz, 4H, OCH_2), 3.67 (s, 6H, OCH_3), 3.50 (d, J=16 Hz, 2H, CH_2N), 3.33 (s, 4H, NC*H*); ^{13}C NMR ($CDCl_3$) δ =99.5, 79.4, 66.7, 58.2, 56.0, 54.1; ^{77}Se NMR ($CDCl_3$) δ =355.8; MS m/z 538 (M^+/2), 105 (base). **4**: yellow powder; mp 121-123 ℃; $[\alpha]_D^{25}$ +215° (*c* 0.20, $CHCl_3$); IR (KBr) 2900, 2840, 1488, 1100, 1015cm^{-1}; ^1H NMR ($CDCl_3$) δ =7.59-7.02 (m, 28H, Ar*H*), 5.39 (s, 4H, C*H*Ph), 4.66 (d, J=17 Hz, 2H, CH_2N), 4.30 (d, J=1.7 Hz, 4H, OC*H*C*H*O), 3.87 (d, J=13 Hz, 4H, OCH_2), 3.75 (d, J=12 Hz, 4H, OCH_2), 3.99-3.30 (m, 2H, CH_2N), 3.31 (s, 4H, NC*H*), 2.40 (s, 6H, ArCH_3); ^{13}C NMR ($CDCl_3$) δ =99.6, 79.4, 66.8, 58.1, 53.9, 23.9; ^{77}Se NMR ($CDCl_3$) δ =365.2; MS m/z 522 (M^+/2), 105 (base); Found: C, 64.49; H, 5.41; N, 2.69%. Calcd for $C_{56}H_{56}O_8N_2Se_2$: C, 64.27; H, 5.49; N, 2.79%.

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8) Tony K. M. Shing, *Tetrahedron*, **44**, 7261 (1988).

9) 2,2'-Diselenobis (benzyl chloride) **5** was prepared according to the literature methods.[5] **6** (R=OMe) was prepared from 3-methoxy-2-nitrobenzoic acid by five simple steps (21% overall yield) and **7** (R=Me) was prepared from 2-amino-3-methyl benzoic acid by four simple steps (8% overall yield). Details will be described elsewhere.

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11) Strong Se···N interaction usually shifts the ^{77}Se NMR signal toward downfield with respect to the corresponding phenylseleno compound.[5]

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