Asymmetric Selenomethoxylation of Olefins Involving a Chiral C_2 Symmetrical Electrophilic Organoselenium Reagent

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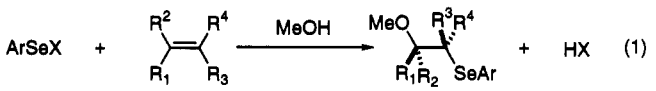
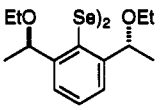
Summary: A new chiral C_2 symmetrical organoselenium reagent has been synthesized; this compound, in the presence of methanol, reacts with high facial selectivity with olefins to afford the *anti* selenomethoxylated adducts in very good yields.

The addition of electrophilic organoselenium reagents across double bonds represents a very useful reaction in organic synthesis.[1] Arylselenenyl halide derivatives (ArSeX) readily add with *anti* selectivity across double bonds to give the 1,2 adducts. Selenomethoxylated products are obtained when this reaction is carried out in the presence of methanol (eq 1).[2] In order to extend the usefulness of



this reaction, we sought to develop a chiral organoselenium reagent that would exhibit high diastereofacial selectivity.[3] In addition, the introduction of two contiguous chiral centers on a nonactivated achiral olefin in an *anti* pathway still represents a challenge. In order to increase our changes of achieving this goal, we undertook the synthesis of a reagent having C_2 symmetry. Numerous reports have shown that reagents having C_2 symmetry have proven to be efficient for asymmetric induction.[4] In this paper, we report the synthesis of bis[2,5-bis(1(*R*)-ethoxyethyl)]-phenyl diselenide (1) and its applications in the asymmetric selenomethoxylation of olefins.



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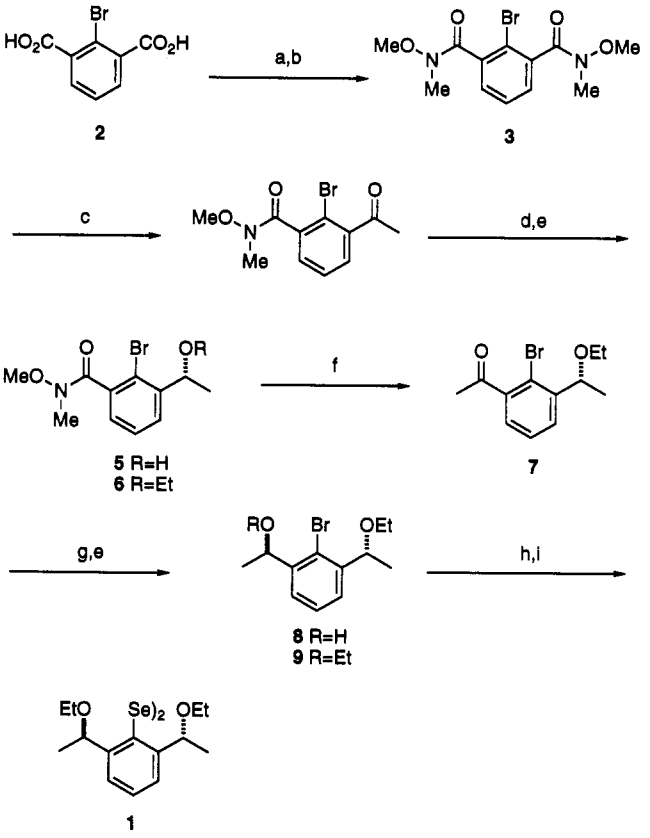
The synthesis of 1 is outlined in Scheme I. The readily available bromophthalic acid 2[5] was easily converted into its corresponding bis-*N,O*-(dimethylhydroxylamide) 3 in 79% overall yield. Treatment of 3 with 2.6 equiv of methylmagnesium bromide in THF at −78 °C followed by warming to room temperature gave after workup the methyl ketone derivative 4 in 83% yield. Attempts to convert 3 directly into its corresponding 1,3-diacetyl derivative by adding a larger excess of methylmagnesium bromide resulted in loss of the bromine atom. Therefore, we opted for the sequential route. The asymmetric reduction of the ketone 4 was achieved *via* the oxazaborolidine-catalyzed reduction (CBS) developed by Corey.[6] Thus, when 4 was reduced with 1 equiv of BH_3·THF in the presence of 0.3 equiv of (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole[7] (CBS

Scheme I[a]



[a] Reaction conditions: (a) $SOCl_2$, reflux, evaporation; (b) Me(OMe)-NH·HCl, Et_3N, CH_2Cl_2, 0 °C → room temperature, overnight (79%); (c) MeMgBr (2.6 equiv), THF, −78 °C → room temperature (83%); (d) (*S*)-CBS catalyst (0.3 equiv), BH_3·THF (1 equiv), −15 → 0 °C (72%); (e) NaH (1.8 equiv), DMF–THF, 0 °C → room temperature; EtI (5.4 equiv), room temperature (84%); (f) MeMgBr (3.0 equiv), THF, −78 → 0 °C (81%); (g) (*S*)-CBS catalyst (0.3 equiv), BH_3·THF (1 equiv), −15 → −5 °C (53%); (h) *t*-BuLi (2.3 equiv), THF, −78 → 0 °C; Se (1.1 equiv), 0 °C → room temperature; (i) EtOH, cat. NaOH, air; recrystallization from MeOH (76%).

(1) For excellent reviews on organoselenium chemistry, see: (a) *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: London, 1987. (b) *Selenium Reagents and Intermediates in Organic Synthesis*; Paulmier, C., Ed.; Pergamon Press: Oxford, 1986.

(2) Schmid, G. H.; Garratt, D. G. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed., Wiley: London, 1977; Supp. A, Part 2. (b) Garratt, D. G.; Kabo, A. *Can. J. Chem.* **1980**, *58*, 1030.

(3) Binaphthyl-based chiral organoselenium derivatives have already been reported but low asymmetric induction was observed from these compounds. (a) Tomoda, S.; Iwaoka, M. *Chem. Lett.* **1988**, 1895. (b) Tomoda, S.; Fujita, K.; Iwaoka, M. *J. Chem. Soc., Chem. Commun.* **1990**, 129.

(4) For a recent review on reagents with C_2 symmetry see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(5) Miyano, S.; Fukushima, H.; Inagawa, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3285.

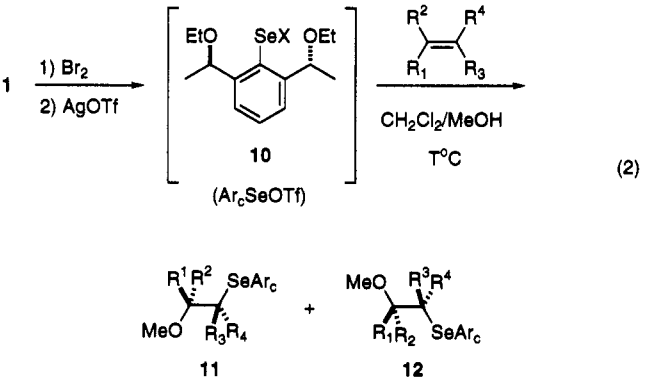
(6) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chew, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (e) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209.

(7) Prepared according to: Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner Jones, E. T.; Hoogstean, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

0022-3263/93/1958-3619$04.00/0

reagent) at −15 °C followed by warming to 0 °C, the desired alcohol **5** was obtained in 72% yield and in a 92:8 *R*:*S* ratio.[8] Treatment of **5** with NaH (60% in oil) in a 1:1 TMF–DMF mixture at 0 °C followed by addition of iodoethane at room temperature gave the ethyl ether derivative **6** in 84% yield. The methyl ketone **7** was obtained in 81% using the same protocol as for **4**. The CBS-catalyzed reduction of **7** was carried out as previously described to give the desired (*R*,*R*) alcohol **8** in 53% yield and with an enantiomeric purity >98%.[9] Treatment of **8** with NaH and iodoethane gave the (*R*,*R*) diethyl ether **9** in 88% yield. Lithiation of **9** with 2 equiv of *t*-BuLi in THF at −78 °C and then warming to 0 °C followed by the addition of elemental selenium gave after oxidation and crystallization from methanol the desired diselenide **1** as orange crystals (76% yield).[10]

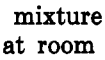
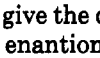
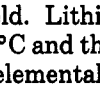
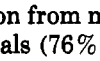
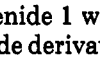
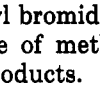
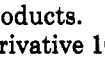
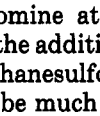
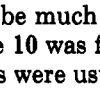
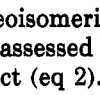
The diselenide **1** was easily converted into its electrophilic bromide derivative by treatment with bromine, but the selenenyl bromide reacted sluggishly with olefins in the presence of methanol and gave low yields of the addition products. However, the trifluoromethanesulfonate derivative **10**, generated by *in situ* by adding 1 equiv of bromine at −78 °C to **1** in dichloromethane followed by the addition of a methanolic solution of silver trifluoromethanesulfonate (1.4 equiv), turned out as expected to be much more reactive and suitable for our needs. Once **10** was formed, the olefins were added and the reactions were usually over in a matter of minutes.[11] The diastereoisomeric ratio of the resulting adducts **11** and **12** were assessed by NMR and HPLC analysis of the crude product (eq 2). As the results indicate (Table I),



(2)

the C_2 symmetrical electrophilic organoselenium reagent **10** can achieve facial selectivity up to 66:1 and afford the selenomethoxy adducts in very good yields. Low temperature was important for high selectivity, since in all cases studied, a higher facial selectivity was obtained at −100 °C. At higher temperature not only do the selectivities diminish but the yields also decrease. As expected, with 1,2-substituted olefins we obtained the *anti* adducts (entries 1–4, 7, 8, and 11) and attack by the methanol occurred at the benzylic position with the aromatic substrates (entries 1–10).[12] With vinylcyclohexane and 3,3-dimethyl-1-butene (entries 13 and 14), we obtained at −100 °C exclusively the *anti*-Markovnikov adducts,[12] i.e., attack of methanol at the less substituted carbon. At room temperature the facial selectivity was poor, and we also obtained a mixture of Markovnikov and *anti*-Markovnikov adducts. However, for 2,3,3-trimethyl-1-butene (entry 12) at −100 °C, we observed only the Markovnikov adduct, i.e., attack of methanol at the most substituted carbon.

Table I. Asymmetric Selenomethoxylation of Some Olefins

entry	olefins	*T* (°C)	ratio 11:12[a]	R_1	R_2	R_3	R_4	yield[b] (%)
1		25	3.4:1	H	Ph	Me	H	44
2		0	4.4:1	H	Ph	Me	H	76
3		−78	13:1	H	Ph	Me	H	82
4		−100	21:1	H	Ph	Me	H	81
5		−78	7.7:1	H	Ph	H	H	88
6		−100	21:1	H	Ph	H	H	89
7		−78	30:1	H	Ph	Ph	H	85
8		−78	3.4:1	H	Ph	H	Ph	74
9		−100	12:1	Me	Ph	H	H	72
10		−100	25:1	H	*p*-FPh	H	H	92
11		−78	3:1	H	Et	Et	H	91
12		−100	18:1	Me	*t*-Bu	H	H	61
13		−100	46:1	H	H	*t*-Bu	H	67
14		−100	66:1	H	H	c-C_6H_{11}	H	83

[a] Ratios were determined by ^{1}H-NMR and HPLC of the crude material. [b] Yield after purification by column chromatography on silica gel.

(8) Enantiomeric excess was determined by conversion of **5** into its Mosher ester ((*R*)-MTPA) and NMR and HPLC analysis of the resulting diastereoisomeric mixture.

(9) We also obtained some of the *R*,*S* diastereoisomer, which was easily separated by chromatography. The enantiomeric excess of **8** was assessed by HPLC analysis of the Mosher derivatives, and we observed a >100:1 *R*,*R*:*S*,*S* ratio.

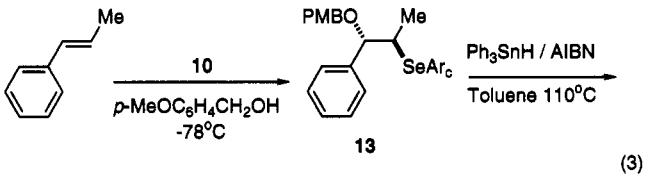
(10) The stereochemistry of **1** was confirmed by X-ray diffraction analysis. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(11) Typical procedure (entry 4, Table I): To an ether (2 mL) (dichloromethane for reactions at higher temperature) solution of **1** (30 mg, 0.05 mmol) at −78 °C was added a 1 M solution of bromine in CCl_4 (54 μL). The mixture turned brown immediately. After 15 min a MeOH solution (72 μL) of silver trifluoromethanesulfonate (500 mg/mL, 0.14 mmol) was added dropwise. The resulting colorless heterogeneous mixture of **10** was stirred at −78 °C for 30 min and then cooled to −100 °C, and β-methylstyrene (26 μL, 0.20 mmol) was added. After stirring for 1 h *s*-collidine was added (20 μL, 0.15 mmol) to neutralize the trifluoromethanesulfonic acid. The reaction mixture was diluted with ether, washed with a 7% solution of citric acid, dried ($MgSO_4$), and concentrated. The diastereoisomeric ratio was assessed by NMR and HPLC from the crude products, and then purification by flash column chromatography on silica gel gave the selenomethoxy adducts in 81% yield (36 mg) as a 21:1 mixture of diastereoisomers. Major diastereoisomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, *J* = 7.0 Hz, 6 H), 1.25 (d, *J* = 7.0 Hz, 3 H), 1.39 (d, *J* = 6.5 Hz, 6 H), 3.20–3.34 (m, 5 H), 3.32 (s, 3 H), 4.42 (d, *J* = 5.5 Hz, 1 H), 5.27 (q, *J* = 6.5 Hz, 2 H), 7.24–7.49 (m, 8 H). Minor diastereoisomer (distinct signals): 1.17 (t, *J* = 7.0 Hz, 6 H), 4.38 (d, *J* = 4.5 Hz, 1 H); HRMS calcd for $C_{24}H_{34}SeO_3$ 450.16724, found 450.16789. HPLC column D-DNB-Ph-Gly (Pirkel) 0.2% 2-propanol–hexane λ = 215 nM, t_R major 9.74 min, t_R minor 8.79 min, ratio 22:1.

(12) For leading references on the regiochemistry of addition of phenylselenyl halides to olefins, see: (a) Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, 4977. (b) Denis, J. N.; Vicens, J.; Krief, A. *Tetrahedron Lett.* **1979**, 2697. (c) Raucher, S. *Tetrahedron Lett.* **1977**, 3909. (d) Raucher, S. *J. Org. Chem.* **1977**, *42*, 2950. (e) Ho, P. T.; Kolt, R. J. *Can. J. Chem.* **1982**, *60*, 663. (f) Schmid, G. H.; Garratt, D. G. *Tetrahedron* **1978**, *34*, 2869.

cis-Stilbene and *trans*-3-hexene (entries 8 and 11) gave the poorest selectivity. Overall, the selenomethoxylation of olefins with **10** occurred with very high facial selectivity.

To date, we have only established the absolute stereochemistry of the adducts resulting from the asymmetric selenoetherification of *trans*-β-methylstyrene. For practical purposes, we used *p*-methoxybenzyl alcohol instead of methanol in order to give, after reduction, a less volatile ether derivative that would facilitate purification and characterization. Thus, when the *trans*-β-methylstyrene was added to a −78 °C solution in **10** in dichloromethane containing *p*-methoxybenzyl alcohol (PMBOH) the adduct **13** was obtained in 71% yield as a 11:1 diastereoisomeric mixture after chromatography.[13] Removal of the chiral organoselenium moiety with triphenyltin hydride in the presence of a catalytic amount of AIBN in refluxing toluene[14] occured smoothly and gave after chromatography the PMB ether derivative **14** in 78% yield (eq 3). The



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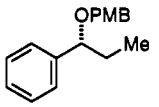

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ratio of enantiomers found was 11:1 *R*:*S*[15] and was assessed by HPLC with a chiral column and by comparison with authentic material.[16]

In summary, the addition of the C_2 symmetrical electrophilic organoselenium reagent **10** to olefins, in the presence of methanol, occured with very high facial selectivity. The results reported herein represent, to the best of our knowledge, the most efficient asymmetric *anti* addition to nonactivated achiral olefins. Further synthetic applications of this new chiral reagent including selenomediated cyclizations and studies toward the understanding of the mechanism of asymmetric induction are currently in progress.

Acknowledgment. We thank Dr. Neil Moss for his assistance in the preparation of this manuscript, Serge Valois for the HPLC analysis, Professor André Michel (Université de Sherbrooke) for the X-ray of **1**, and the National Sciences and Engineering Research Council of Canada (NSERC) for undergraduate research awards to J.B. and J.B. We are also grateful to Dr. Yvan Guindon for his support and encouragement for this work.

Supplementary Material Available: Procedures, compound characterization data, and an ORTEP of **1** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) In this particular case, the diastereoisomeric ratio in the crude material was 6:1, and after purification over a silica gel column, the mixture was enriched to 11:1. A detailed study with various alcohols and other nucleophiles is in progress.

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

(15) Although the absolute stereochemistry of the adduct **13** has been assessed, this is not sufficient for drawing conclusions about the absolute stereochemistry of the other adducts. Work along this line is in progress and will be reported in due course.

(16) The pure (*R*)-(+)-1-phenyl-1-propanol was purchased from Fluka and was converted to the corresponding PMB ether.