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A Highly Selective Asymmetric Methoxyselenylation of Alkenes with a Chiral Ferrocenylselenium Reagent

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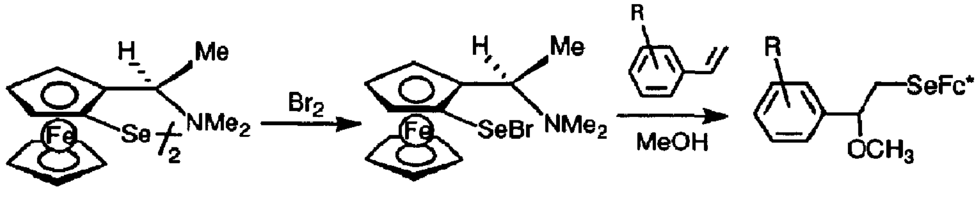
Abstract: Chiral diferrocenyl diselenide was easily converted into chiral ferrocenylselenyl bromide by treatment of bromine in CH_2Cl_2/CCl_4 at -78 °C. This chiral electrophilic selenium reagent reacted with alkenes in the presence of methanol with high facial selectivity to afford selenomethoxylated adducts in moderate yields.

We previously reported that a ferrocenyl-based chiral selenium reagent was effective and promising to achieve highly selective asymmetric organic syntheses. [1,2] In connection with our series of studies on the chiral ferrocenylselenium compounds in asymmetric organic synthesis, we would like to report here asymmetric methoxyselenylation of alkenes with this chiral selenium reagent. Tomoda et al.[3-6] and Deziel et al.[7] have already demonstrated that moderate to high asymmetric induction was observed in methoxyselenylation with chiral selenium electrophiles. However, it takes much multiple steps to prepare these chiral selenium reagents. On the other hand, the chiral ferrocenylselenium compound (1) is readily prepared from a commercially available chiral ferrocenylamine.

The chiral diferrocenyldiselenide (1) was converted into the ferrocenylselenyl bromide (2) by treatment with bromine in CH_2Cl_2 at -78 °C. The selenyl bromide reacted with styrene derivatives at room temperature for 20 h in the presence of methanol to give the β-methoxyselenium compound (3) as a single regioisomer (Markovnikov adduct; attack of methanol at the most substituted carbon) in a moderate yield. The diastereomer excess (de%) in the crude adduct was determined by ^1H NMR (400 MHz) integration of the



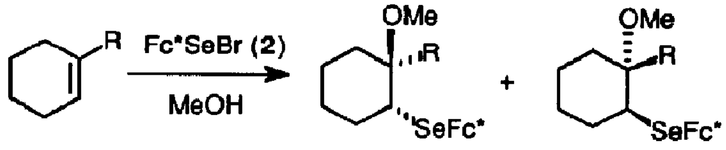
1

2 (Fc*SeBr)

3

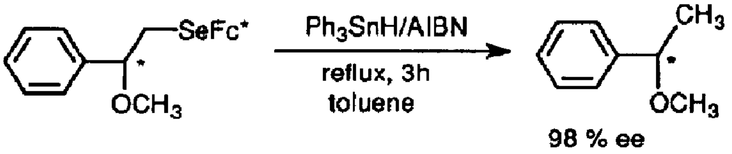
proton of the dimethylamino group and/or the methoxy group. Either the configuration of (R,S) or (S,R)-2 achieved a high facial selectivity (up to 97% de). The results of the reactions with the chiral electrophilic selenium reagent with alkenes were shown in Table 1. The diastereoselectivity in the reaction with styrene was very high compared with those attained by binaphthyl-[3] and C_2 symmetrical phenyl-based[7] chiral selenium compounds. Addition of a catalytic amount of Lewis acid (10 mol % to 2) increased a yield of the adduct, but addition of $BF_3.Et_2O$ and Et_2AlCl diminished the diastereoselectivity (entries 4-5). Addition of ZnI_2 effectively improved a yield maintaining a high diastereoselectivity (entries 6-7). Then we used a catalytic amount of ZnI_2 for the reactions with other alkenes.

With cyclohexene, we obtained the *trans* adduct, but the facial selectivity was poor (entries 12-13). When we tried to carry out the reaction at -78 °C, no reaction proceeded. On the other hand, with 1-substituted cyclohexenes, we achieved a higher selectivity than with cyclohexene; 1-methylcyclohexene and 1-phenylcyclohexene gave only Markovnikov adducts in 65 % and 88% de, respectively (entries 14-15). These results suggest that a sterically large group in an alkene is necessary to achieve a high facial selectivity.



4 R=H,Me,Ph **5a** **5b**

We confirmed the absolute configuration of the adducts from methoxyselenylation of styrene with either the (R,S)- or (S,R)-chiral ferrocenylselenium reagent. Reductive removal of the chiral organoselenium group of the diastereomeric mixture of the adduct (97% de) by Ph_3SnH in refluxing toluene gave 2-phenethylmethyl ether in 50-60 % yield. The enantiomer excess was determined by GLC analysis with a chiral capillary column (Astec, GT-A, 30 m) comparing with authentic samples. The (S) and (R) configurated methyl ether was formed in 98% ee from the (R,S)- and (S,R)-chiral ferrocenylselenium reagent, respectively. The enantiomer excess found was consistent with the diastereomer excess in the β-methoxyselenium compound.



Typical experimental procedure is as follows. To a CH_2Cl_2 solution (2.0 ml) of (S,R)-1 (0.380 g, 0.57 mmol)[7] at -78 °C was added CCl_4 (1.0 ml) solution of bromine (0.08 g, 0.50 mmol) slowly over a period of 10 min. After 15 min, styrene (0.125 g, 1.2 mmol) was added to the resulting solution at -78 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. Methanol (1.0 ml)

Table 1. Asymmetric Methoxyselenylation of Alkenes with a Chiral Ferrocenyl Bromide (2)[a]

Entry	Config. of 2	Alkene	Additive[b]	Yield(%)[c]	de(%)[d]
1	(R,S)	Styrene	none	21	97
2	(S,R)	Styrene	none	18	97
3[e]	(S,R)	Styrene	none	79	20
4	(R,S)	Styrene	$BF_3 \cdot Et_2O$	31	33
5	(R,S)	Styrene	Et_2AlCl	40	67
6	(R,S)	Styrene	ZnI_2	43	93
7	(S,R)	Styrene	ZnI_2	41	93
8	(R,S)	*o*-Methylstyrene	ZnI_2	14	90
9	(R,S)	*m*-Methylstyrene	ZnI_2	30	86
10	(R,S)	*p*-Methylstyrene	ZnI_2	19	83
11	(S,R)	*trans*-β-Methylstyrene	ZnI_2	20	98
12	(R,S)	Cyclohexene[f]	ZnI_2	48	19
13	(S,R)	Cyclohexene[f]	ZnI_2	45	22
14	(R,S)	1-Methylcyclohexene	ZnI_2	32	65
15	(R,S)	1-Phenylcyclohexene	ZnI_2	16	88

[a] (2) (1.0 mmol) (1; 0.56 mmol, Br_2; 0.50 mmol), alkene (1.0 mmol), methanol (1.0 ml); CH_2Cl_2-CCl_4 (2 ml-1 ml), rt, 20 h. [b] 10 mol % to (2). [c] Isolated yield. [d] Determined by ^{1}HNMR (400 MHz). [e] 1 (0.50 mmol), Br_2 (1.0 mmol). [f] 2.0 mmol of cyclohexene was used.

solution of ZnI_2 (0.035 g, 0.1 mmol) was added to the reaction solution and stirred at room temperature for 20 h. The mixture was treated with aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2 (20 ml X 2) and dried (K_2CO_3). Evaporation of the solvent left a dark brown residue which was subjected to preparative TLC (Al_2O_3; hexane/ethyl acetate=4/1). A mixture of diastereomers of the methoxyselenylation product was obtained as a yellow oil (0.20 g, 0.43 mmol, 43 % yield based on 2). The diastereomeric excess was determined by ^{1}H NMR (400 MHz). ^{1}H NMR (400 MHz) δ 1.33 (d, 3H, J=6.8 Hz, CH_3CH), 2.09 (s, 6H, $N(CH_3)_2$), 2.94 (dd, 1H, J=11.7, 8.6 Hz, one of CH_2Se), 3.07 (dd, 1H, J=11.7, 1.9 Hz, CH_2Se), 3.25 (s, 3H, OCH_3), 3.98 (q, 1H, J=6.8 Hz, CH_3CH), 4.0-4.2 (m, 9H, ferrocenyl H and $CHOCH_3$), 7.2-7.4 (m, 5H, phenyl). Minor diastereomer (distinct signals) δ 1.35 (d, J=6.8 Hz, CH_3CH), 2.12 (s, $N(CH_3)_2$), 3.21(s, OCH_3). Calcd for $C_{23}H_{29}NOFeSe$: C; 58.74; H, 6.22; N, 2.98. Found: C, 58.32; H, 6.27; N, 2.50.

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8. A slight excess of 1 to bromine was required to obtain a high diastereoselctivity; The use of just an equivalent amount of 1 somewhat decreased the diastereoselectivity (70-80 % de). When excess of bromine was used, the diastereoselectivity extremely diminished (Table 1, entry 3).

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