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Asymmetric Arene-Alkene Cyclizations Mediated by a Chiral Organoselenium Reagent

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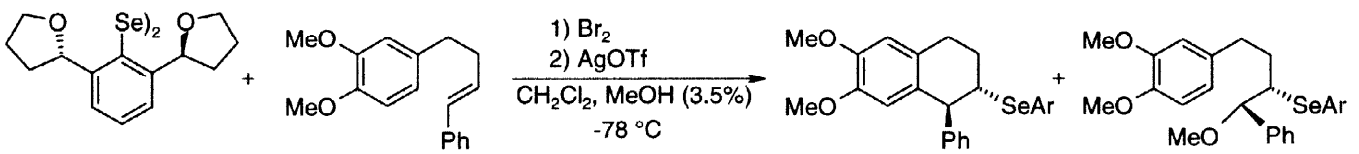
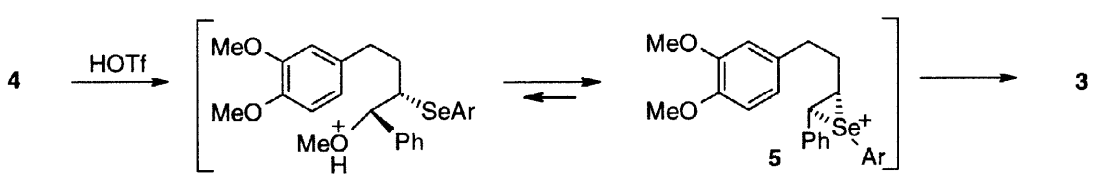
Abstract: Asymmetric arene-alkene cyclization reactions mediated by a chiral electrophilic organoselenium reagent afforded substituted carbocyclic derivatives with high diastereoselectivities. It was also found that β-methoxyselenides are good precursors of seleniranium ions when treated with strong acids. © 1998 Elsevier Science Ltd. All rights reserved.

Electrophilic addition of carbon-based nucleophiles to olefins is a process that is efficiently achieved with selenium-derived reagents [1]. This process is especially useful for the construction of carbocyclic systems in which the nucleophilic center is aromatic. In this communication we wish to report the first asymmetric variant to this reaction, which involves the chiral organoselenium reagent **1** [2a]. We first reacted the arene containing olefin **2** with the *in situ* generated trifluoromethanesulfonate salt of **1** under the optimum reaction conditions (i.e. in the presence of methanol) developed for the heteroatom-based ring-closure reactions [2b,c]. In this manner the desired cyclized product **3** was obtained with 98% diastereoisomeric excess and in a 1:1 ratio with the selenomethoxylated product **4**.



1 **2** **3** **4**

We had previously shown that the presence of a small amount of methanol is essential for high selectivity [2b]. As a consequence of this we observed that addition of methanol competed with the ring closure reaction to give **4**. When this reaction was repeated without methanol, the cyclized product **3** was obtained in low yield and with lower diastereoselectivity. After several trials we found that instead of quenching the reaction mixture at –78 °C with 2, 6-lutidine (to neutralize the trifluoromethanesulfonic acid), if we allowed the reaction to warm to 0 °C the selenomethoxylated intermediate **4** was smoothly transformed into the cyclized product **3**. Under



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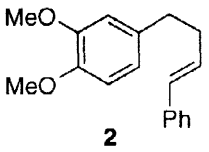
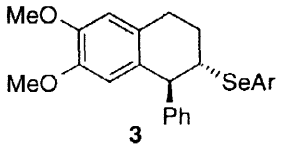
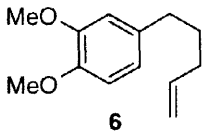
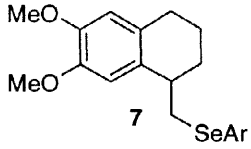
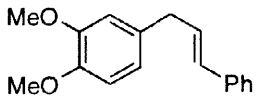
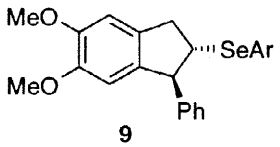
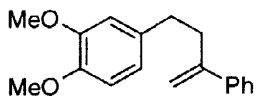
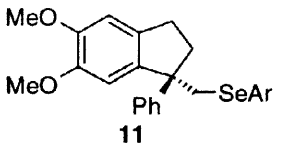
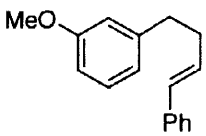
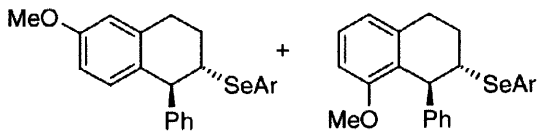
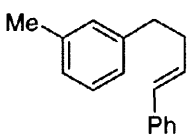
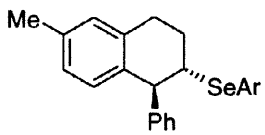
these conditions **3** was obtained from **2** in 70% yield with 98% de. The trifluoromethanesulfonic acid-assisted conversion of **4** to **3** may have proceeded *via* the stereospecific generation of the seleniranium ion intermediate **5** which was then irreversibly captured by the arene nucleophile. Cyclization of olefin **6** with **1** (Table 1) under the above reaction conditions afforded the desired cyclized product **7** in 76% yield, albeit with lower facial selectivity (i.e. 50% de).

Table 1. Asymmetric carbocyclization reactions with 1

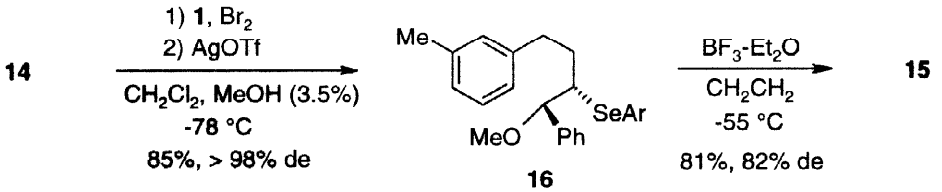
Olefin	Cyclized product[a]	de %[b]	Yield %[c]
 **2**	 **3**	98	70
 **6**	 **7**	50	76
 **8**	 **9**	95	62
 **10**	 **11**	86	64
 **12**	 **13a** **13b**	98, 96	68, 16
 **14**	 **15**	82	81

a) Absolute configuration of compounds **3**, **9**, **11**, **13**, and **15** was assigned according to previous results (see ref. 2a,b).
b) Diastereoisomeric excesses were assessed by HPLC and NMR analysis.
c) Yield of purified products, fully characterized by standard spectroscopic methods.

We next attempted to cyclize olefin **8** with **1** under the same reaction conditions (-78 °C → 0 °C) but none of the desired cyclized product was isolated. In this case the *in situ* generated

trifluoromethanesulfonic acid failed to induce the more demanding 5-*endo* mode of cyclization of the selenomethoxylated intermediate. After several attempts we found that it was best to isolate the crude selenomethoxylated product and treat it with a Lewis acid such as $BF_3{\cdot}Et_2O$ in dichloromethane at –55 °C. In this manner the desired indane derivative **9** was obtained in 62% yield from **8** with 95% de. Likewise, olefins **10**, **12** and **14** gave the corresponding cyclized products **11**, **13a,b** and **15** respectively in good yields and with excellent diastereoselectivities. Other Lewis acids such as TMSOTf and $Sc(OTf)_3$ were also found to promote the ring closure reaction but with lower yields and selectivities. The cyclization of olefin **10** deserves to be highlighted since it produced a quaternary carbon center in a stereospecific mode, a process not easily achieved [3]. The degree of selectivity observed for the asymmetric cyclizations depicted in Table 1 is consistent with what we obtained for the ring-closure reactions with heteroatom-based nucleophiles [2a,b]. When the double bond bears a large group, such as a phenyl, the facial selectivity is very high. On the other hand, olefins that are substituted with smaller groups (e.g. **6**) give lower selectivity. The assignment of the absolute configuration of the cyclized products in Table 1 was made by analogy with our previous results [2a,b].

The acid-catalyzed transformation of β-methoxyarylselenide derivatives into the corresponding cyclized products deserves some comments. The results obtained imply that treatment of the selenomethoxylated adducts with acids generates a transient seleniranium intermediate such as **5**. This is reminiscent of previous reports of β-hydroxyselenides as precursors of seleniranium ions upon treatment with strong acids [4, 5]. One of these reports clearly demonstrated that enantiomerically enriched seleniranium ions are prompt to epimerize (at the carbon centers) [5a]. We therefore monitored the facial selectivities of the two steps involved in the process; the selenomethoxylation and the acid-induced cyclization. We found that the asymmetric addition of



methanol to **14** giving **16** proceeded with high facial selectivity (>98% de) as expected. However when **16** was treated with $BF_3{\cdot}Et_2O$ in dichloromethane at –55 °C the cyclized product **15** was obtained in lower de (i.e. 82%). Clearly some epimerization occurred during the cyclization step. On the other hand the analogous substrate **12** gave the cyclized products **13** in much higher diastereoisomeric excess (>96%). In this case we also observed that the cyclization reaction rate was faster, a result not unexpected since the aryl moiety is more electron rich. We also observed that the temperature is critical in the BF_3-induced cyclization step as isomerization increased at temperatures higher than –55 °C. Attempts to achieve ring closure reaction with substrates having a non activated aryl ring (i.e. phenyl) failed to give any of the cyclized products.

In conclusion we have shown that the chiral trifluoromethanesulfonate salt of **1** efficiently mediates asymmetric carbon-carbon bond formation. We have also shown that β-methoxyarylselenides are good precursors of seleniranium ions when treated with strong acids.

General procedure. Step 1: To a solution of **1** (79.4 mg, 0.134 mmol) in CH_2Cl_2 (3 mL) cooled to –78 °C was added a 1 M solution of bromine in CCl_4 (141 μL, 0.141 mmol). After 5 min, a 2 M methanol solution of silver trifluoromethanesulfonate (141 μL, 0.282 mmol) was added. After 5

min the olefin (0.281 mmol, in 0.5 mL of CH_2Cl_2) was slowly introduced and the mixture was stirred at -78 °C for 30 min. Step 2: For the cyclization of olefins **2** and **6** the mixture was allowed to warm to 0 °C and stirred at this temperature for 30 min. The mixture was worked-up by adding *sym*-collidine (50 µL, 0.38 mmol) to neutralize the trifluoromethanesulfonic acid then diluted with ether and washed with a 1 M citric acid solution. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by silica gel flash chromatography to give the cyclized products in yield and diastereoisomeric purity as indicated in Table 1. For the cyclization of olefins **8**, **10**, **12** and **14** the reaction mixture was worked-up after step 1. The resulting crude products were dissolved in CH_2Cl_2 (2 mL) cooled to –78 °C and treated with $BF_3{\cdot}Et_2O$ (21.0 µL, 0.156 mmol). The mixture was stirred at –78 °C for 5 h and at –55 °C for 12 h then poured into a solution of $NaHCO_3$. The organic products were extracted with ether (2x) and the combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by silica gel flash chromatography to give the cyclized products.

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