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2,6-Bis[(2*S*)-tetrahydrofuran-2-yl]phenyl Diselenide: An Effective Reagent for Asymmetric Electrophilic Addition Reactions to Olefins

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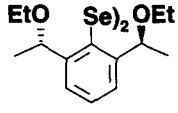
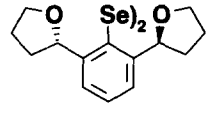
Abstract: The enantioselective synthesis of a new and extremely effective organoselenium reagent (**2**) is reported. This chiral reagent was found to react with alkenes with a very high degree of facial selectivity in selenomethoxylation and ring closure reactions. In some cases the diastereoselectivities were found to be as high as 98%. © 1997 Elsevier Science Ltd.

We recently reported the chiral C_2 symmetrical organoselenium reagent **1** and its enantiomer which mediate selenomethoxylation and ring closure reactions of alkenes with excellent facial differentiation.[1,2] We showed that **1** exerts high facial selectivity with alkenes substituted with a phenyl group or with bulky substituents such as *t*-butyl or cyclohexyl. On the other hand, when the double bond was substituted by smaller groups, the degree of facial selectivity was found to be much lower. As part of our efforts to develop a more effective reagent, we made a rigidified analog of **1**, the bis(tetrahydrofuranyl) based reagent **2**. This novel chiral organoselenium reagent turned out to exhibit a significantly improved asymmetric induction with olefins.

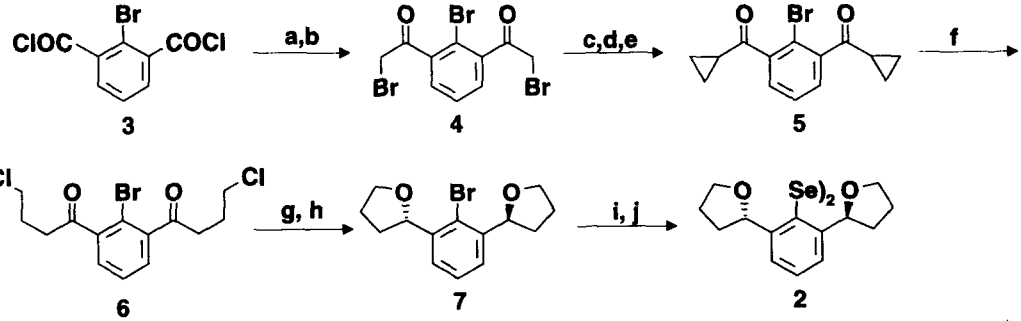


1



2

The synthesis of **2** is outlined in Scheme 1. Treatment of the bis(acylchloride) **3** with excess diazomethane in ether afforded a diazoketone intermediate which was then treated with HBr in acetic acid to



3 **4** **5**

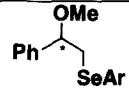
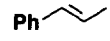
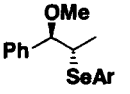
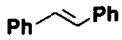
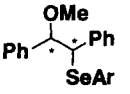
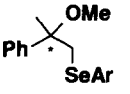
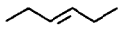
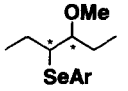
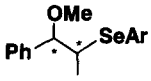
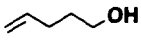
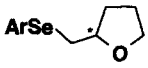
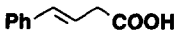
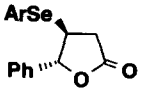
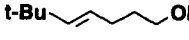
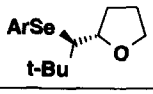
6 **7** **2**

Reagents and conditions: a) CH_2N_2, Et_2O, 79%; b) 30% HBr/HOAc, 94%; c) 1M LiHMDS/THF, -78 °C; d) $CH_2CHP(Ph_3)_3^+Br^-$; e) aqueous KOH, 84%; f) 4M HCl/dioxane, 96%; g) (-)-DIP-Cl, -25 °C; h) NaH, rt, 83%, >99% ee; i) Mg, Se ,THF reflux, 24h; j) cat NaOH, air, EtOH, 68%.

Scheme 1

give the bis(α-bromoketone) **4** in 74% yield from **3**. The bis(cyclopropane) intermediate **5** was prepared according to the protocol developed by Posner.[3] Thus, **4** was treated with 2.7 eq of lithium bis(trimethylsilyl)amide at -78 °C in THF followed by the addition of vinyltriphenylphosphonium bromide. The resulting cyclopropylphosphonium salt intermediate was then treated with aqueous KOH to give **5** in 84% yield after purification. Addition of anhydrous HCl in dioxane to **5** gave the bis(chlorobutanone) **6** in 96% yield. The enantioselective reduction of **6** was achieved with (-)-DIP chloride[4] in ether at -25 °C to give the corresponding *S, S* diol, which was treated without purification with sodium hydride in THF to afford the desired bis(tetrahydrofuranyl) derivative **7** in 83% yield and >99% ee.[5] The incorporation of the selenium

Table 1. Asymmetric Electrophilic Reactions with 1 and 2

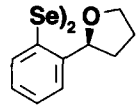
Entry[a]	Olefin	Product[b]	Ratio with 1[c] (yield)[d]	Ratio with 2[c] (yield)[d]
1			8 : 1 (88)	30 : 1 (73)
2			13 : 1 (82)	>100 : 1 (81)
3			30 : 1 (85)	>100 :1 (75)
4			18:1 (78)	18 : 1 (73)
5			3 : 1 (91)	8 : 1 (67)
6			1 : 1 (80)	2 : 1 (80)
7			2 : 1 (96)	10 : 1 (84)
8			13 : 1 (72)	>100 : 1 (62)
9			9 : 1 (89)	15 : 1 (61)

a. Entries 1 to 6: selenomethoxylation reactions. Entries 7 to 9 : ring closure reactions.
b. The absolute stereochemistry of the products of entries 2, 8 and 9 has previously been established.[1b, c]
c. Ratios assessed by HPLC (entries 2, 3 and 8) and NMR analysis.
d. Yield of purified products.

atom turned out to be more difficult than anticipated based on our previous experience with **1**. Treatment of **7** with *t*-butyllithium followed by addition of elemental selenium gave low yield of the desired product. After several unsuccessful attempts, we found that generation of the Grignard salt of **7** in the presence of elemental selenium in refluxing THF gave the best results. After work-up of the crude selenol and oxidation with air, the desired diselenide **2** was obtained in 68% yield.

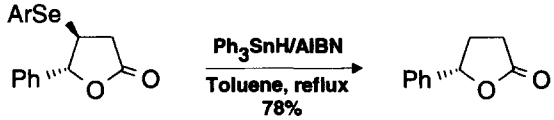
We next compared the degree of facial selectivity of the chiral reagents **1** and **2** in the selenomethoxylation and ring closure reactions. The electrophilic trifluoromethanesulfonate derivatives of **1** and **2** were generated *in situ* according to our published protocol and the reactions were carried out at -78 °C in dichloromethane in the presence of methanol (2.5% v/v).[1b,c] Results from Table 1 clearly show that the rigidified reagent **2** exhibits an overall superior degree of asymmetric induction compared with **1**. The *trans*-phenyl substituted olefins gave the highest selectivities with **2** and showed the most dramatic improvement (entries 1, 2, 3 and 8). We were also pleased to observed that olefins substituted with smaller groups gave better selectivities with **2** (entries 5 and 7). The α-methylstyrene (entry 4) showed no improvement while the *t*-butyl substituted olefin (entry 9) showed some improvement in facial selectivitiy with **2** compared to **1**. We can conclude from the above results that the rigidified reagent **2** exerts improved overall facial selectivitiy and is presently one of the most effective chiral organoselenium reagents reported to date.

In order to demonstrate that the C_2 symmetry is a key feature for high asymmetric induction, we prepared and compared the degree of facial selectivity of the monotetrahydrofuranyl analog **8** with **2** in some selenomethoxylation and ring closure reactions. Selenomethoxylation of olefins of entries 1 and 2 in Table 1 mediated with the trifluoromethanesulfonate salt of **8** gave a 8:1 and 6:1 selectivity respectively. Likewise, ring closure reaction of olefins from entries 7 and 8 in Table 1 mediated with **8** gave the cyclized products in a 2:1 and 5:1 diastereoisomeric ratio respectively. This overall dramatic decrease in the degree of facial selectivity highlights the essentially of the C_2 symmetry in order to achieve high facial differentiation.



8

The absolute stereochemistry of the nearly homogeneous lactone **9**, produced with **2** (Table 1, entry 8), was assessed by removal of the chiral organoselenium moiety and comparison of the optical rotation of the resulting lactone **10** with the literature value.[7, 1b] Thus, reduction[6] of **9** with triphenyltin hydride in the presence of a catalytic amount of AIBN in refluxing toluene afforded the lactone **10** with an $[\alpha]_D$ of -37.0, this value compares favorably with the reported value of $[\alpha]_D$= -35.5 for the *S* enantiomer.[7] This result shows that the nature of the facial selectivity of **2** is the same as of **1**.



9 **10**

In summary, we have synthesized a new and very effective chiral organoselenium reagent. The degree of facial selectivity of **2** with some olefins was found to be extremely high and gave some selenoadducts in ≥98% de. We have also shown that the element of C_2 symmetry is a key feature for high facial selectivity.

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References and Notes

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5. The enantiomeric purity of **7** was assessed by chiral HPLC analysis. The *R, R* diol was prepared from (+)-DIP-Cl.

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