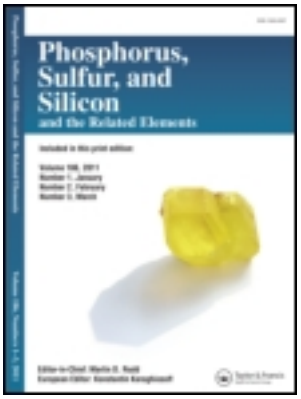

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of Enantiomerically Pure 1,2-Disubstituted 2-Selenoamines

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SYNTHESIS OF ENANTIOMERICALLY PURE 1,2-DISUBSTITUTED 2-SELENOAMINES

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Abstract *Optically pure phenylseleno-(S)-2-p-tolylsulfinylbenzylcarbanions react with (S)-N-2-p-tolylsulfinylimines derived from aliphatic and aromatic aldehydes in a highly stereoselective manner affording bis-sulfinylselenoamines, easily transformed into 1-phenyl, 2-aryl (or alkyl)-2-phenylseleno ethylamines by subsequent reactions, which were treatment reactions with t-BuLi and TFA.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Benzyl selenyl carbanion; double asymmetric induction; remote stereocontrol with sulfoxides; 1,2-selenoamines

INTRODUCTION

The biological and medical properties of organoselenium compounds are increasingly appreciated, mainly due to their antioxidant, antitumoral, and antimicrobial activities and their behavior as competitive inhibitors for target proteins.[1] In addition, enantiomerically pure 1,2-selenoamines are interesting structural subunits[2] that have been used as ligands in enantioselective reactions.[3] However, despite their importance, very few methods have been reported for synthesizing them in their enantiomerically pure form,[4,5] and they usually provide 1,2-selenoamines containing only one stereocenter bound to the carbon stereocenter bearing the nitrogen function. Therefore, the synthesis of these compounds with the selenium atom connected to the stereocenter[6] and with two stereocenters is still a challenging problem, and therefore we decided to investigate it, taking advantage of our experience in the field of organoselenium compounds.[7]

We have recently demonstrated that the *ortho*-sulfinyl group is highly efficient for controlling the stereoselectivity of the reactions of *ortho*-sulfinylbenzyl alkylcarbanions

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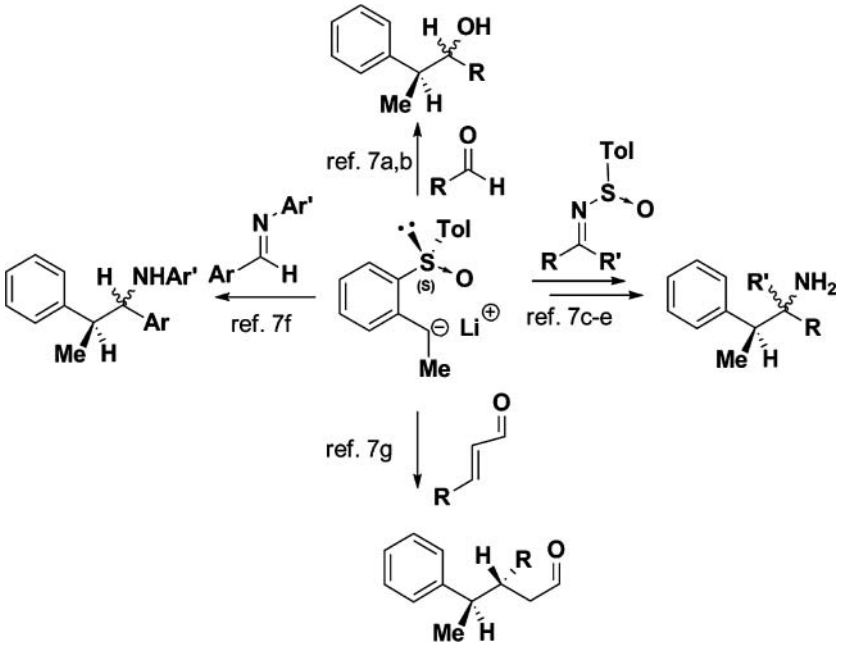
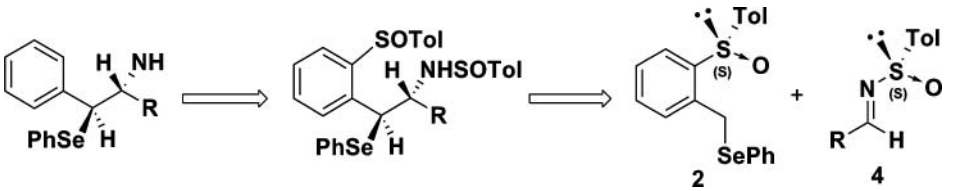


Scheme 1

with different electrophiles (Scheme 1).[8] This stereocontrol is also efficient for benzylcarbanions bearing different substituents at the benzylic positions (alkyl, OP,[9a] SMe,[9b–d] $^{+}SMe_2$,[9e] halogen,[9f,g] CN[9h]). In all these reactions, the configuration at the benzylic carbon atom was completely controlled by the chiral configuration of the chiral *ortho*-sulfinyl group.

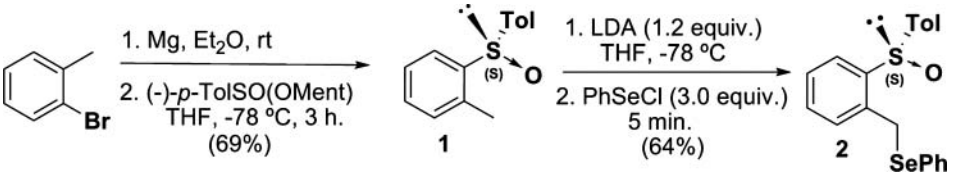
On the basis of these results, we decided to explore the behavior of the *ortho*-sulfinylbenzylselenylcarbanion derived from compound **2** (Scheme 2) in the reactions with activated imines **4** as a method for obtaining enantiomerically pure 1,2-selenoamines. Preliminary results obtained in this study will be reported in this article.



Scheme 2

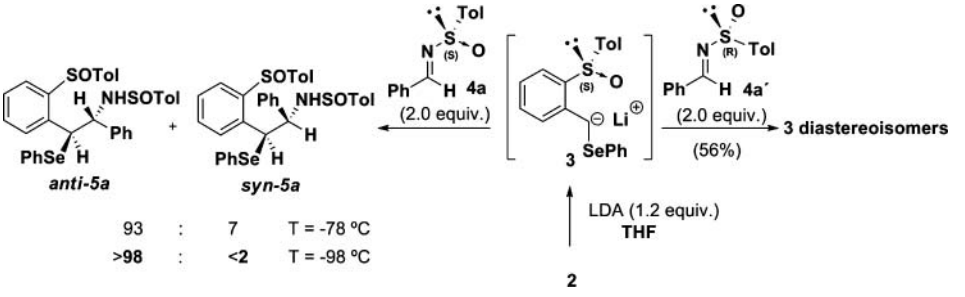
RESULTS AND DISCUSSION

The synthesis of the 2-*p*-tolylsulfinylbenzyl phenylselenide (**2**), precursor of the chiral benzylselenocarbanion **3** used as the nucleophile of these transformations, was performed starting from 2-bromotoluene according to the sequence indicated in Scheme 3.



Scheme 3

We first studied the reactions of (*S*)-**2** with both enantiomers of the *N*-sulfinylimine derived from benzaldehyde. We studied the generation of the α-selenocarbanion with different bases, but only LDA gave the desired results. When this base was added to a THF solution of (*S*)-**2**, cooled to -78°C, a strongly colored solution was immediately formed, indicating the formation of a highly conjugated benzylic carbanion. The addition of the (*R*)-*N*-sulfinylimine (**4a**′) evolved into a reaction mixture containing three compounds (presumably three of the four possible diastereoisomers, the configuration of which has not been established) with moderate yield (Scheme 4). Contrarily, the reaction of (*S*)-**2** with (*S*)-*N*-sulfinylimine **4a** only afforded a mixture of *anti*-**5a** and *syn*-**5a** with a diastereomeric ratio of 93:7. These results indicate that the matched pair in this double asymmetric synthesis is formed by reagents of the same configuration (*S*) at the sulfur atom. A complete control of the stereoselectivity was observed when the temperature was lowered to -98°C, indicating that the configuration at the benzylic carbon bound to the selenium function can be completely controlled by the sulfinyl group under proper conditions.

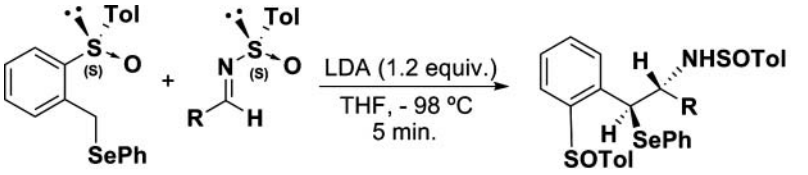


Scheme 4

We then studied the reactions of our (*S*)-selenylcarbanion with several (*S*)-*N*-sulfinylimines **4a**–**e**, derived from aromatic and aliphatic aldehydes. As we can see in Scheme 5, good isolated yields were obtained in all the studied cases. Diastereoisomeric excesses were always higher than 98% except for reactions with **4e** (R = *i*-Pr). The *anti* relationship of the obtained isomers **5** could be deduced from the high values of their vicinal coupling constants.

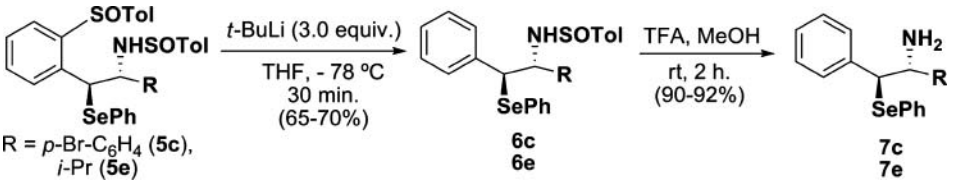
Removal of the chiral sulfinyl groups was performed in two steps from **5c** (R aromatic) and **5e** (R aliphatic, which had been previously separated from the minor diastereoisomer). *C*-Desulfinylation with *t*-BuLi followed by *N*-desulfinylation with TFA/MeOH provided the 1,2-selenoamines **7** in good yields (Scheme 6).

The stereochemical course that would account for the previosly indicated result would be similar to that proposed for explaining the behavior of the benzyl carbanions bearing a SMe group at the benzylic position.[8b]



2	**4a** (R=Ph)	*anti*-**5a** (69%, >98% de)
	4b (R=4-MeC_6H_4)	*anti*-**5b** (65%, >98% de)
	4c (R=4-BrC_6H_4)	*anti*-**5c** (71%, >98% de)
	4d (R=*n*-Bu)	*anti*-**5d** (69%, >98% de)
	4e (R=*i*-Pr)	*anti*-**5e** (51%, 88%de)

Scheme 5



Scheme 6

CONCLUSION

We have described a highly stereoselective reaction of (*S*)-γ-sulfinylbenzylselenyl carbanion with a variety (*S*)-*N*-*p*-toluenesulfinylimines. This reaction provides an efficient method for the preparation of optically pure *anti*-1,2-selenoamine derivatives. The sulfinyl group is capable of providing chemical and stereochemical stability to benzyl selenocarbanions.

EXPERIMENTAL

A solution of *n*-BuLi (3.05 mmol, 2.3 M in hexane) was added at 0°C to a THF solution (8 mL) of $i Pr_2NH$ (3.92 mmol). After 10 min stirring, the mixture was cooled to −98°C. A solution of the sulfoxide 1 (2.18 mmol) in THF (8 mL) was then added. After 10 min stirring, phenyselenyl chloride (6.54 mmol) was added at −98°C in THF (4 mL). When the reaction was completed (10 min), the mixture was hydrolyzed (saturated aqueous NH_4Cl), extracted with CH_2Cl_2 (3 × 40 mL) and dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by flash column chromatography (toluene/acetone 6:1) to afford the pure compound (64%). **2-[(*S*)-(*p*-Tolylsulfinyl)benzyl]phenylselenide** (**2**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, 1H, $J = 7.6$ Hz), 7.55–6.95 (m, 12H), 4.25 (AB system, 2H, $J = 12.6$ Hz), 2.37 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.52, 134.13, 130.99, 130.48, 129.98, 129.11, 128.40, 127.84, 129.06, 125.92, 125.76, 28.14, 21.35 ppm.

Typical Procedure: [1*R*,2*R*,*S*(S)]-*N*-{1-(4-bromophenyl)-2-(phenylselanyl)-2-[2-(S)-(*p*-tolylsulfinyl)phenyl]ethyl}*p*-toluenesulfinamide

A solution of *n*-BuLi (2.3 M in hexane, 0.54 mmol) was added over $i\text{Pr}_2\text{NH}$ (0.74 mmol, 1.8 equiv) in THF (2 mL) at 0°C. After 10 min stirring, the mixture was cooled to −98°C, and the solution of the nucleophile (0.38 mmol, 1 equiv) in THF (2 mL) was added. After 5 min stirring, *N*-sulfinylimine (0.76 mmol) was added at −98°C in THF (1 mL). When the reaction was completed (5–10 min), the mixture was hydrolyzed with saturated aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc 1:1). **[1*R*,2*R*,*S*(S)]-*N*-{1-(4-bromophenyl)-2-(phenylselanyl)-2-[2-(S)-(*p*-tolylsulfinyl)phenyl)ethyl}*p*-toluene-sulfinamide** (***anti*-5c**). Yield: 70%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.87 (d, 1H, $J = 7.2$ Hz), 7.64–6.83 (m, 15H), 6.76 (d, 3H, $J =$ 8.6 Hz) 6.57 (d, 2H, $J = 6.8$ Hz), 4.90 (d, 1H, $J = 10.6$ Hz), 4.75 (dd, 1H, $J = 10.6$ and 7.4 Hz), 5.03 (d, 1H, $J = 7.4$ Hz), 2.31 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.84, 140.69, 139.85, 135.09, 132.24, 130.81, 130.42, 130.10, 129.26, 128.70, 128.32, 127.85, 127.67, 127.33, 125.97, 125.44, 121.36, 61.76, 47.24, 21.49, 21.31 ppm.

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