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Asymmetric methoxyselenenylation of α,β-unsatured carbonyl derivatives

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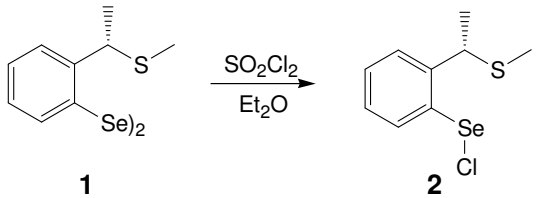
Abstract
In this communication we propose a convenient methodology to effect asymmetric methoxyselenenylation of α,β-unsatured carbonyl derivatives using as electrophilic reagents an optically pure sulfur containing selenenyl chloride.
Mechanistic aspects of the reaction were investigated and simple manipulation to prepare optically pure derivatives are reported.

Introduction

Organoselenium compounds are very useful reagents in organic synthesis and they have been extensively used in a wide range of reactions, varying from cationic, radical and anionic transformations, to rearrangements and eliminations.[1]
During the last decades the design of enantiomerically pure diselenides and their use as electrophilic reagents precursors has emerged as a practical and powerful tool for the stereoselective preparation of chiral molecules.[1-3] We reported the synthesis of a new class of enantiopure sulfur-containing diselenides and their synthetic applications to promote enantioselective selenium addition reactions to unsatured substrates.[4] Electrophilic reagents generated starting from diselenides **1** were successfully employed to prepare enantiomerically enriched alcohols,[5] ethers,[5] azides,[6] heterocycles[7] as well as for the kinetic resolution of allylic alcohols.[8] All the investigated reactions showed a very high facial selectivity, higher than those obtained with the corresponding nitrogen- or oxygen containing reagents. [3]
We demonstrated also that the facial selectivity is strongly correlated to the non bonding interaction established between the electrophilic selenium and the sulfur atom in compounds like **2**.[9] This latter is an air-stable solid that can be easily prepared starting from diselenide **1** by treatment with SO_2Cl_2 and crystallization from diethyl ether (Scheme 1) and that has been successfully used in a large series of asymmetric conversions.[5-8]



1 **2**

Scheme 1: Preparation of chiral electrophilic selenium reagent

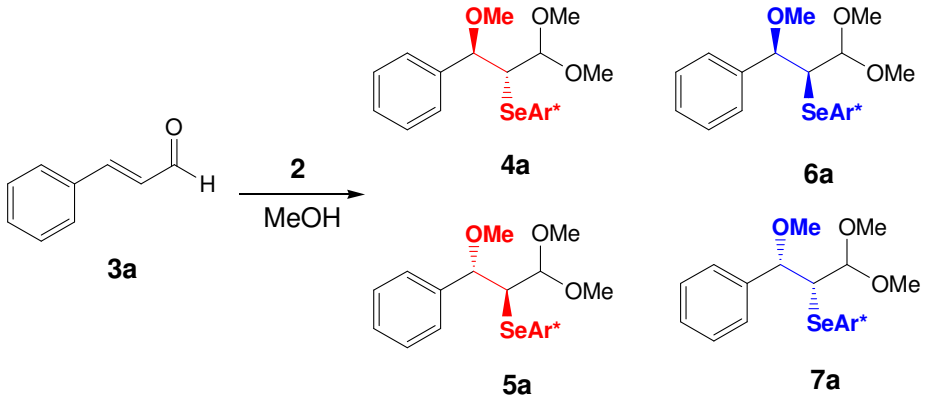
In this communication the first efficient asymmetric methoxyselenenylation reaction of α,β-unsatured carbonyl compounds is reported. Paulmier and coworkers already described a methodology for the methoxyselenenylation of α,β-unsatured aldehydes using PhSeCl in MeOH at -30°C.[10] The authors claim this process passing through a dimethylacetal intermediate, who undergoes electrophilic selenomethoxylation via seleniranium ion intermediate. This process however occurs with poor regio- and stereoselectivity and is strongly conditioned by the nature of the substrate.

Results and Discussion

In order to evaluate the best condition to effect the asymmetric methoxyselenenylation reaction of α,β-unsatured carbonyl compounds preliminary reactions were carried out starting from cinnamaldehyde **3a** using the Ar*SeCl **2** as electrophilic selenenylating reagent at different reaction conditions. The results are summarized in Table 1.

Every reaction leads to the formation of four enantiomerically pure diastereomers (**4a-7a**), one of which in much higher yield. From the reaction mixture only the major isomer **4a** can be purified by flash chromatography on silica gel. Unfortunately the mixture of the minor products could not be separated and the structures, as well as the ratios, were assigned by the NMR analysis of the crude.

Table 1: Preliminary experiments starting from cinnamaldehyde



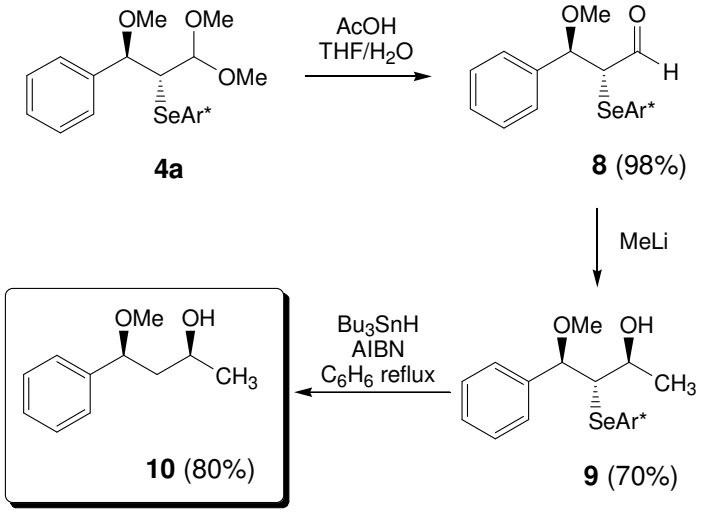
Entry	Additive	T°C	Time (days)	Overall yield %	Yield of 4 a %	Ratio 4a/5a	Anti/Syn
1	None	0	6	20	10	67/33	50/50
2	None	-30	6	30	20	80/20	75/25
3	None	-30	10	83	55	80/20	75/25
4	$MgSO_4$	0	6	34	26	90/10	90/10
5	$MgSO_4$	0	10	91	65	90/10	90/10

A "one pot" carbonyl protection as dimethylacetal and methoxyselenenylation occurred.[10] In a typical optimized procedure to 1 equiv. of aldehyde **3** 1 equiv. of Ar*SeCl **2**, dissolved in a CH_2Cl_2/MeOH mixture was added, and the reaction mixture was stirred in the conditions indicated in the table.

The reaction carried at 0°C (entry 1) is slow and affords the products **4a-7a** with very poor yields and selectivity. Morever several unidentified by-products were formed. Using lower temperature (-30°C) we observed an increase in yield as well as in diasteroselectivity. An unexpected increment on yield and selectivity was also observed at 0°C in the presence of 1 equivalent of $MgSO_4$.

In order to determine the absolute configurations of the addition products, the pure isomer **4a** was hydrolyzed by treatment with acetic acid in THF/H_2O giving the corresponding aldehyde **8** that was treated with MeLi to give as principal isomer the compound **9**. This latter subsequent to radicalic deselenation furnished the β-methoxyalcohol (+)-**10** (Scheme 3). The comparison of the

experimental optical rotation with the α-value reported in literature[8] allowed us to assign the *R* configuration at the benzylic carbon. In consideration that the methoxyselenenylation is a stereospecific *anti* addition reaction we could assign *R* configuration to selenium-binding carbon.



Scheme 2: Assignment of the absolute configuration of **4a**

This assessment has been also confirmed by evaluation of the coupling constants measured between ArSeC**H** and PhC**H** (9.1 Hz), very similar to that measured by Paulmier[10] in the analogous compound obtained with PhSeCl (8.7 Hz) (Figure 2).

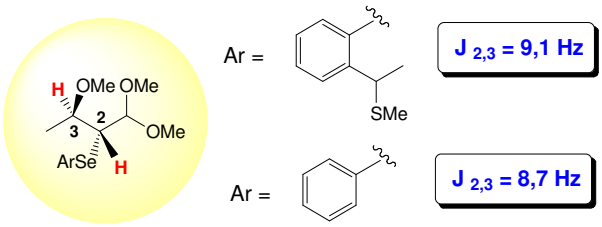


Figure 2: The vicinal J-coupling values confirm the absolute configuration

The experimental conditions reported in entry 5 were applied starting from acetals **11** and **12** (Figure 3) in order to evaluate the effect of different protection at the carbonyl function.

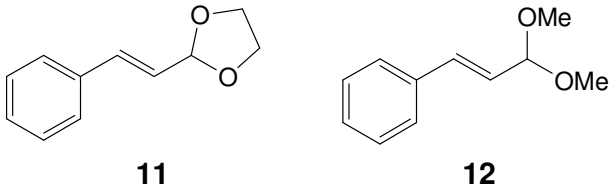
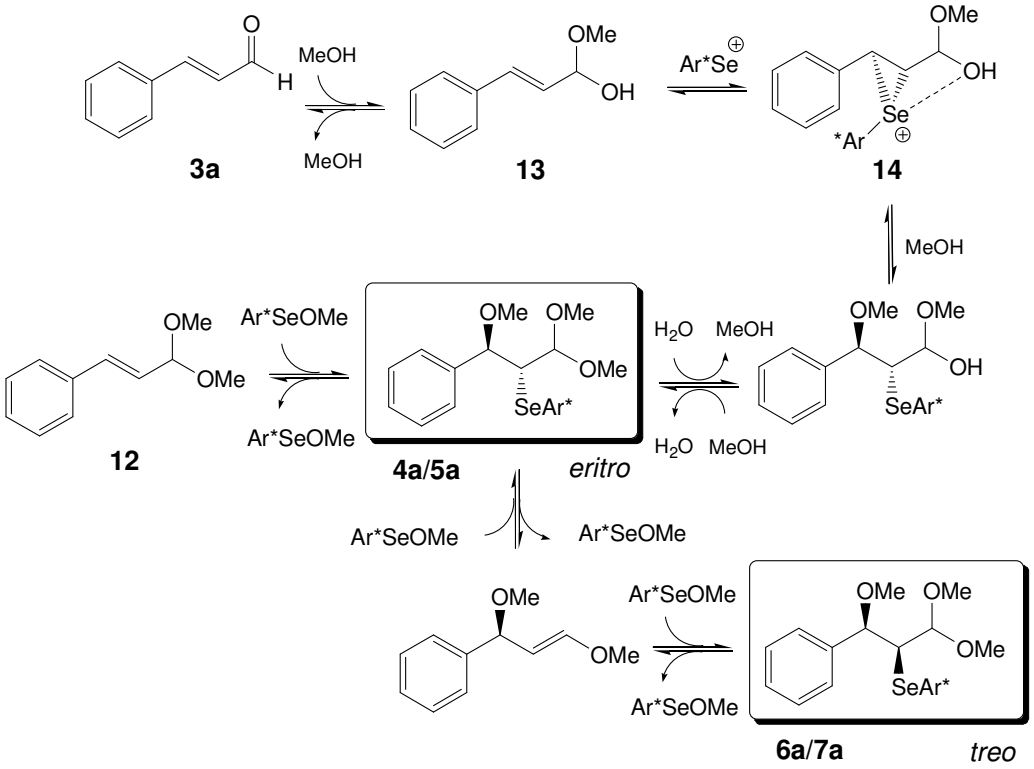


Figure 3: Acetals

1,3-dioxolane derivate **11** resulted unstable and the acetal converted completely in related dimethylacetal derivatives. Otherwise the dimethylacetal **12** compared with the unprotected **3** gives higher yields (overall yield: 62%; yield of **4a**: 49%) but lower diastereo- and enantioselectivity (**4/5**=79/21; *eritro/treo*=60/40). This clearly suggest that starting from the aldehyde the reaction involve an intermediate different from **12** and that in the "one-pot" reaction the formation of the dimethylacetal is not the first reaction step. We suppose this intermediate being the emiacetal **13** and that methoxyselenenylation occurs on it rather than on acetal. In this way the stereocontrol of the process may be improved by a stronger nonbonding interaction between seleniranium ion and hydroxy group in allylic position (**14**) (Scheme 3). We recently demonstrated that this coordination play an important role in governing the stereochemistry of electrophilic addition reactions during the kinetic resolution of allylic alcohols.[8]



3a **13** **14** **12** **4a/5a** **6a/7a**

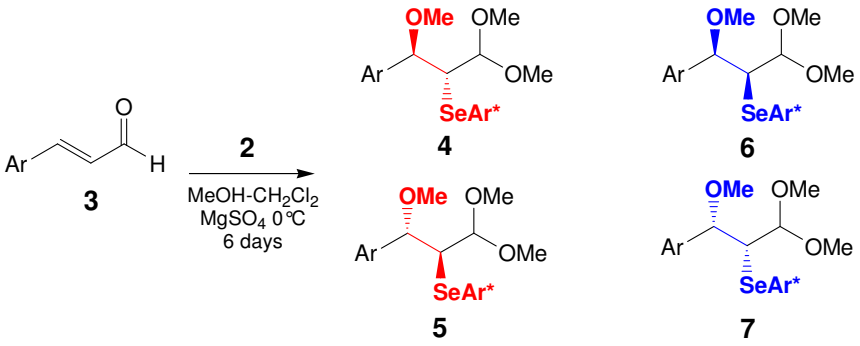
Scheme 3: Proposed mechanism

Then we performed the reaction in optimized conditions on some aromatic α,β-unsatured aldehydes (Table 2). Substrates **3b-3d** were prepared by Wittig reactions, while compound **3e** was prepared refluxing 2-naphthaldehyde, vinylacetate and $Ba(OH)_2$ in THF.[11]

With the exception of the reaction conduced starting from (*E*)-3-(4-nitrophenyl)acrylaldehyde **3d** each process showed moderate to good yield, good *anti/syn* ratios and good diastereomeric excesses between *anti* isomers. Moreover in each case the major isomer **4** can be recovered by chromatography on silica gel as a single diastereomer (de > 99%).

In addition we observed that increasing the reaction time the yields can be positively effected without modification of the diasteroisomeric ratios.

Table 2: Asymmetric methoxyselenenylation of **3a-e**



Entry	Substrate		Overall yield %	Yield of 4 a %	Ratio 4a/5a	Anti/Syn
1	Ar = C_6H_5	**3a**	34 (91)[a]	26 (65)[a]	90/10	90/10
2	Ar = *p*-Cl-C_6H_4	**3b**	82	39	90/10	80/20
3	Ar *p*-Me-C_6H_4	**3c**	66	45	85/15	86/14
4	Ar *p*-NO_2-C_6H_4	**3d**	-	-	-	-
5	Ar = 2-Naphthyl	**3e**	29 (67)[a]	18 (48)[a]	90/10	80/20

[a] Reaction time 10 days

Conclusion

In conclusion we reported the first methodology to effect asymmetric methoxyselenenylation of α,β-unsatured carbonyl derivatives using easily prepared chiral electrophilic selenenylating reagents. The proposed synthetic approach lead the formation of useful intermediates that can be manipulated in order to prepare other enantiomerically enriched derivatives.

Acknowledgments

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References

1. A. Krief, L. Hevesi *Organoselenium Chemistry,* Vol 1 Springer-Verlag: Berlin, **1988**; (b) A. Krief. in *Comprehensive Organometallic Chemistry;* B. M., Trost Ed.; Pergamon: Oxford, **1991**, 85; (c) "Organoselenium Chemistry: Modern Developments in Organic Synthesis": *Top. Curr. Chem.* Vol. 208; T. Wirth, Ed.; Springer: Berlin, **2000**; (d) *Organoselenium Chemistry - A Pratical Approach;* T. G. Back, Ed.; Oxford: New York **2000**. (e) T. Wirth *Angew. Chem. Int. Ed.* **2000**, *39*, 3742.
2. A. L. Braga, D. S. Ludtke, F. Vargas, R. C. Braga *Synlett* **2006**, *10*, 1453.
3. T. Wirth *Angew. Chem. Int. Ed.* **2000**, *39*, 3742.

4. M. Tiecco, L. Testaferri, L. Bagnoli, F. Marini, A. Temperini, C. Tomassini, C. Santi *Tetrahedron Lett.* **2000**, *41*, 3241.

5. M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini *Chem. Eur. J*. **2002**, *8*, 1118.

6. M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini *Angew. Chem. Int. Ed.* **2003**, *42*, 3131.

7. M. Tiecco, L. Testaferri, C. Santi *Eur. J. Org. Chem.* **1999**, 797-803; b) M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini *Tetrahedron: Asymmetry* **2000**, *11*, 4645-4650.

8. M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, R. Bonini, F. Marini, L. Bagnoli, A. Temperini *Org. Lett.* **2004**, *6*, 4751.

9. M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, S. Santoro, F. Marini, L. Bagnoli, A. Temperini, F. Costantino *Eur. J. Org. Chem.* **2006**, 4867.

10. J. F. Huot, F. Outurquin, C. Paulmier *Chem. Lett.*, **1991**, 1599.

11. P. K. Mahata, O. Barun, H. Ila, H. Junjappa *Synlett*, **2000**, *9*, 1345.