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Chiral Selenium Electrophiles on Solid-Support

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Abstract: Organoselenium chemistry has developed rapidly and selenium-based methods are now very useful in synthetic chemistry. The selective introduction of various functionalities into complex molecules can be accomplished under very mild reaction conditions. This has led to versatile and new synthetic methods in organic chemistry. We have developed new and highly efficient selenium electrophiles and describe first attempts to use these reagents on polymer-support.

Keywords: Chirality · Organoselenium chemistry · Selenium · Stereoselective synthesis

Thomas Wirth, born in 1964, studied chemistry in Bonn (Germany) and stayed there to carry out his diploma work with Professor S. Blechert. He then moved along with his supervisor to the Technical University of Berlin, where he received his Ph.D. in 1992. After a postdoctoral stay with Professor K. Fuji at Kyoto University (Japan) as a JSPS fellow, he started his independent research in 1994 within the group of Professor B. Giese at the University of Basel (Switzerland), obtaining his habilitation on stereoselective oxidation reactions in 1999. In the fall of 1999 he was a guest lecturer at the University of Toronto (Canada) and in spring 2000 he was a visiting scientist at the Chuo University in Tokyo (Japan). In September 2000 he was appointed as a Professor of Organic Chemistry at Cardiff University (UK).

1. Introduction

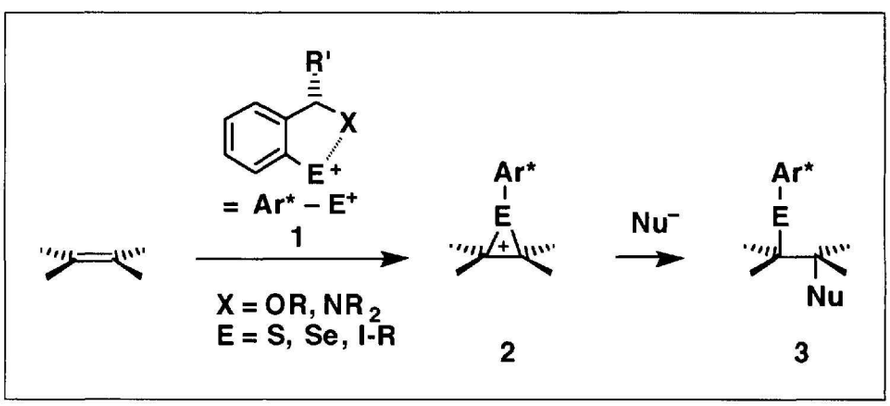
Good yields and stereochemically uniform compounds are two important demands for reactions to be useful in synthetic organic chemistry. Thus, many remarkable efforts have led to a vast amount of efficient and elegant stereochemical transformations. However, several compounds remain that are not readily obtained, for example, the products of stereoselective functionalization of unactivated or only weakly activated C,C double bonds. We have developed stereoselective addition reactions to such double bonds using chiral electrophilic reagents of type **1** (Scheme 1). Besides selenium electrophiles, which are discussed herein in more detail, we also have investigated sulfur electrophiles [1] and the electrophilic properties of hypervalent iodine compounds [2].

2. Results and Discussion

The development of chiral selenium electrophiles (E = Se) has established a very efficient tool for the highly stereoselective synthesis of various molecules [3]. Products of type **2** can be obtained in high stereoselectivities and employed in further transformations. Selenoxide eliminations, radical reactions or carbanionic chemistry are possible using the selenides **2** as precursor molecules.

Polymer-supported reagents have attracted growing interest because they can be applied to combinatorial chemistry and solid-phase synthesis [4]. Although polymers with selenium functionalities have been known for a long time [5], there is a strong interest in this kind of chemistry. Recently, selenium-based approaches for solid-phase chemistry have been reported from various research groups [6].

Herein we describe the development and the synthesis of first chiral selenium electrophiles on solid-support. The combination of selenenylation reactions with



Scheme 1. Addition of chiral electrophiles of type **1** to alkenes leading to addition products **3**.

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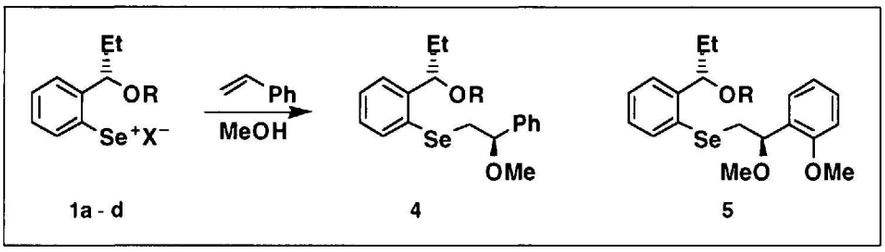


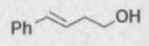
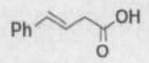
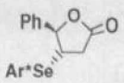
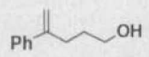
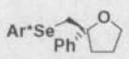
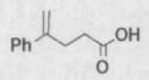
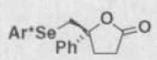
1a - d 4 5

Scheme 2. Methoxyselenenylation of styrene derivatives.

Table 1. Substituted selenium electrophiles in the methoxyselenenylation of styrene.

Entry	Electrophile	X^-	R	Yield **4**	d.r. **4** (*S,R*):(*S,S*)
1	**1a**	OTf^-	H	81%	17:1 (89% *de*) [7]
2	**1b**	OTf^-	CH_2OCH_3	93%	24:1 (92% *de*)
3	**1c**	OTf^-	$CH_2On\text{-}C_8H_{17}$	86%	14:1 (87% *de*)
4	**1d**	Br^-	H	20%	2.5:1 (43% *de*)

Table 2. Cyclization reactions with selenium electrophiles **1a** and **1b**.

Entry	Electrophile	Alkene	Product[a]	Yield	d.r. (Product)
1	**1a**			87%	11:1 (84% *de*)
	1b			88%	6:1 (71% *de*)
2	**1a**			41%	6:1 (72% *de*)
	1b			50%	5:1 (68% *de*)
3	**1a**			45%	11:1 (84% *de*)
	1b			92%	13:1 (86% *de*)
4	**1a**			58%	12:1 (85% *de*)
	1b			80%	11:1 (84% *de*)

[a] Major diastereomer is shown.

solid-phase synthesis might lead to further improvements in selenium-based chemistry.

The point of linkage from the polymer to the electrophile either *via* the chiral side chain or *via* the aromatic moiety has to be considered carefully, because the point of attachment might effect the stereoselectivity. To verify a possible connection from the polymer to the chiral side chain of the reagent we employed selenium electrophiles **1a–1d** (Scheme 2) with different side chains in the methoxyselenenylation of styrene as shown in Table 1. From earlier experiments [7] we know that a substituent on the oxygen atom influences the reaction and we were pleased to find that the MOM-protected reagent **1b** yields the addition product **4** sometimes with even higher selectivities than **1a**.

These first results encouraged us to use electrophile **1b** also in cyclizations and other addition reactions. The yields of the products were usually increased as shown in the addition of **1a** and **1b** to *ortho*-methoxystyrene leading to the addition products **5a** (R=H) (47% yield, 79% *de*) and **5b** (R=CH_2OCH_3) (83% yield, 89% *de*), respectively. In cyclization reactions almost similar selectivities have been obtained with **1a** and **1b**, but the yields again improved dramatically due to enhanced reactivity of electrophile **1b**. An interesting observation was made in the cyclization of 4-phenyl-3-buten-1-ol with **1b** (Table 2, entry 2), because the cyclization only proceeded in the presence of acetic acid. Applying the usual cyclization conditions using methanolic silver triflate solution, the acyclic methoxyselenenylated product was obtained in 84% yield (90% *de*).

For the first reagents on solid-support we therefore chose a linkage *via* the chiral side chain, which enabled us to use previously synthesized compounds as precursor molecules. For the generation of selenium electrophiles on solid-support, other precursors than the widely used diselenides have to be employed. First we tried to apply the known method of preparing the selenenylbromides from the corresponding selenomethyl ethers [6c][8] and synthesized the polymer-bound reagent **6** [9]. But exposure to bromine and subsequent refluxing in ethanol to transform the tetravalent selenium species to the divalent selenenylbromide led only to decomposition. We therefore introduced mixed acetals of type **7** as versatile precursor moieties for the generation of selenenyl bromides **8** under mild reaction conditions using bromine at 0 °C (Fig.). Such derivatives have been synthesized previously [10], but only been used for the synthesis of selenium-stabilized carbanions [11]. They can be prepared easily by MOM-protection of the selenols [10], but the introduction of the whole moiety in only one step is more straightforward. We therefore prepared the diselenide $MeOCH_2SeSeCH_2OMe$ which reacts with lithiated aryl derivatives under direct formation of the corresponding mixed acetals [12].

The reagent **8** has now been successfully used for the reaction with alkenes such as the unsaturated alcohol **9**. After radical cleavage of the carbon–selenium bond of product **10**, the tetrahydrofuran derivative **11** and the selenenylstannane **12** were obtained (Scheme 3). Furthermore, we could already establish reaction conditions for the regeneration of reagent **7** by treatment of **12** with CsF and MOM-Cl [13]. This is a quite interesting aspect, because the precursor **7** of the solid-supported reagent **7** can be very easily regenerated after the radical cleavage of the product molecule **11**.

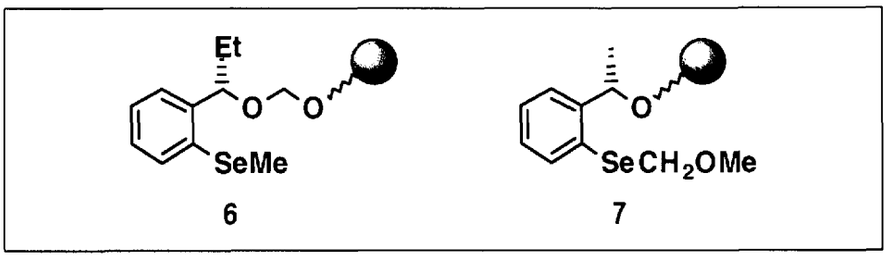
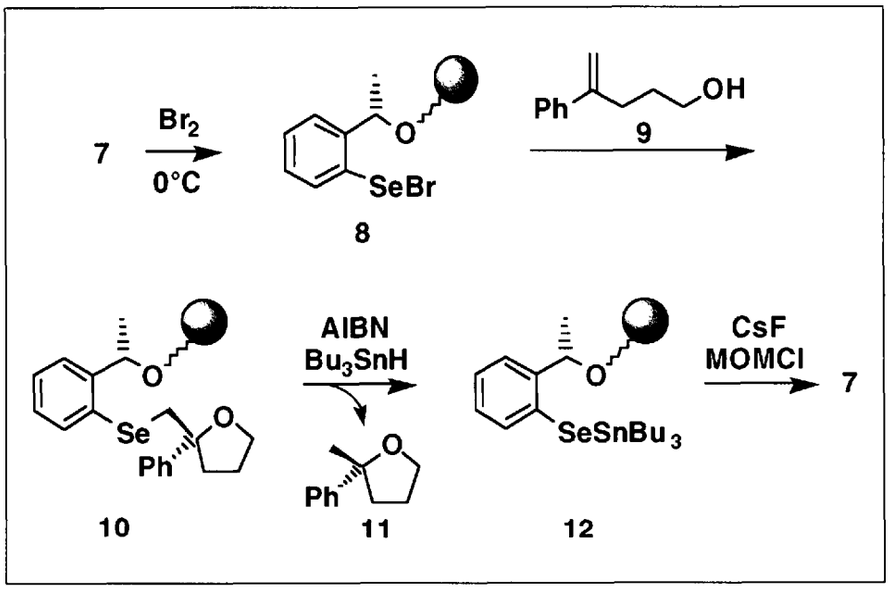


Fig. Polymer-bound precursors for chiral selenium electrophiles.



Scheme 3. Selenenylation of alkene **9** with reagent **8** and regeneration after radical cleavage of product **10**.

However, there are several points which need further improvement. We found that the enantiomeric excess of the cleavage product **11** is quite low (30%). It is known that the counterion of the selenium electrophile plays an important, but still not well understood role in the addition reactions. As it can also seen in Table 1, reagents of type **1** with bromide counterions (entry 4) usually give much lower selectivities in selenenylation reactions than with triflate counterion. The exchange of the selenenyl bromide **8** to the selenenyltriflate with silvertriflate yields, however, a reagent which is contaminated by colloidal silverbromide and which was found to be no longer reactive in subsequent reactions with alkenes. The use of other silver salts leading to selenium electrophiles with different counterions was not successful.

3. Summary

In conclusion, we have developed reactions with selenium electrophile **1b** which lead to the corresponding addition products in high yields and selectivities. One major requirement to achieve these high selectivities is the presence of the triflate counterion. The reagents on solid-support, however, only allowed the use of bromide as the counterion which resulted in low selectivities. The development of different polymer-supported selenium electrophiles is currently in progress.

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