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

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
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$_2$OCH$_3$) (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]. 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[9] TentaGel®, was used and found to be supe rior to polystyrene as the solid-support. The loading was approximately 0.1 mmol/g.

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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

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 be 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.

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