# 1,3-Dipolar cycloaddition on solid supports: nitrone approach towards isoxazolidines and isoxazolines and subsequent transformations†

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1,3-Dipolar cycloaddition reactions of nitrones with alkenes and alkynes are well-studied reactions in solution-phase organic chemistry. However, the number of studies concerned with their application in solid-phase organic synthesis is rather low compared to other 1,3-dipoles, *e.g.* azides or nitrile oxides. This tutorial review aims to summarise the main approaches towards the application of nitrones in 1,3-dipolar cycloaddition reactions on solid supports in addition to subsequent transformations with polymer-bound isoxazolidines and reactions using polymer-bound catalysts.

## 1 Introduction

Solid-phase synthesis has recently gained major interest among modern synthetic methods for the synthesis of libraries of biologically active compounds.[1] Inter- and intramolecular cycloaddition reactions play a key role in solution- and solid-phase chemistry for the straightforward construction of cyclic scaffolds. The [3+2] cycloaddition reaction of nitrones with alkenes is a powerful synthetic method that is applied for the synthesis of isoxazolidines **1**.[2,3] For example, cyclic five-membered nitrones have gained attention for the synthesis of pyrrolizidines, whereas the primary cycloadducts of acyclic nitrones offer a simple and efficient access to 1,3-amino alcohols by reductive cleavage of the N–O-bond.

A plethora of synthetic studies from Huisgen *et al.*[4] contributed to the importance of 1,3-dipolar cycloadditions in modern organic chemistry. In addition, the concept by Woodward and Hoffmann[5] of conservation of orbital symmetry and more recently contributions by Hu and Houk[6] are the foundation to understand the mechanisms and to predict the selectivities of 1,3-dipolar cycloaddition reactions.

Usually 1,3-dipolar cycloadditions of nitrones to alkenes in solution are performed under thermal conditions. Generally, 5-substituted isoxazolidines are obtained starting from mono-substituted and 1,1-disubstituted alkenes. The formation of 4-substituted products is observed only for strong electron-withdrawing groups. In cycloaddition reactions with 1,2-disubstituted alkenes more often mixtures of regioisomers are formed, but, depending upon the substitution pattern, the major isomer generally contains the less electron rich substituent in 4-position. Isoxazolines **2** (Scheme 1) are obtained from 1,3-dipolar cycloadditions of nitrones with alkynes. The regioselectivities are similar to alkenes, however, steric and electronic factors strongly affect the product ratio and the resulting isoxazolines are often thermally labile.

† Dedicated to Professor Steven Ley on the occasion of his 60th birthday.

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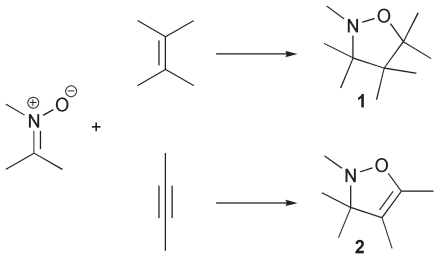

**Scheme 1** Reactions of nitrones with alkenes and alkynes.

In reactions of nitrones with alkenes a high degree of control of the regio- and stereochemistry is observed with a large variety of alkenes and generally up to three stereocentres are obtained in a stereospecific single reaction step.[2] Often diastereomeric pairs of *exo*- and *endo*-adducts are formed (Fig. 1).

In these reactions steric hindrance is of importance to control the approach of the alkenes towards the nitrones in intermolecular cycloadditions. Activation of the dipolarophiles by Lewis acids allowing stereoselective reactions at room temperature or below may be hampered due to simultaneous complexation and inactivation of the nitrone. Nevertheless, control of the relative and absolute stereochemistry can be achieved with chiral nitrones, but also by starting from alkenes employing chiral auxiliaries as well as by enantioselective catalysis using metal-catalysts or organocatalysts. Asymmetric 1,3-dipolar cycloaddition reactions carried out in solution phase were recently reviewed.[2,3]

In the last few years numerous publications concerning 1,3-dipolar cycloaddition reactions of nitrile oxides to alkenes and alkynes on solid supports have been published.[7,8] The first example of a 1,3-dipolar cycloaddition of a nitrile oxide to polymer-bound alkynes was published by Yedida and Leznoff in 1980.[9] Since then, reactions of nitrile oxides in solid-phase organic synthesis were found to give equal results or to exceed transformations carried out analogously in solution. However, only about ten publications are known for the successful application of 1,3-dipolar cycloadditions of nitrones with alkenes in solid-phase organic synthesis as well as for the solid-phase chemistry of immobilised isoxazolidines.

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*Frank Wierschem was born in 1974 in Rheinland-Pfalz, Germany. He studied chemistry and geography at the University of Mainz and received his Degree in 2000, with a research project on α,β-butenolides derived from iron-substituted (Z)-enals. He prepared his doctoral thesis at the University of Mainz and at the TU Berlin. In June 2004 he finished his PhD under the supervision of Professor K. Rück-Braun, dealing with the solid- and solution-phase synthesis of libraries of 2-oxo-1,4-piperazines.*

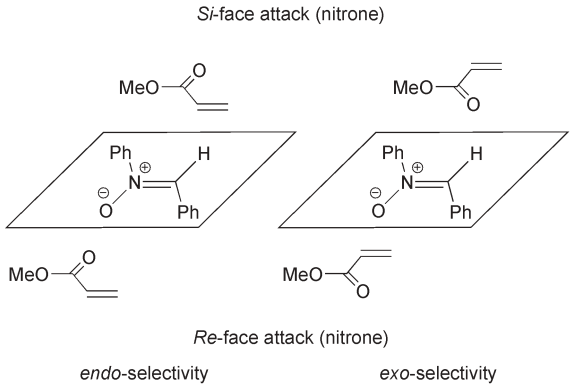



**Fig. 1** *Endo*/*exo*-selectivity in 1,3-dipolar cycloadditions.

For a number of reasons it is synthetically interesting to carry out 1,3-dipolar cycloadditions with nitrones on solid supports. The application of solid-phase modified procedures can result in an easier purification of the intermediates and isolation of the products. Due to steric hindrance caused by the support fewer side reactions were often observed in cycloadditions with nitrile oxides and other 1,3-dipoles in comparison to solution-phase studies.[7,8] Moreover, the typical advantages of solid-phase chemistry, including the application of reagents in large excess to shorten the reaction time, also include easier manipulations and handling. These advantages may open an access to thermally labile cycloadducts and their derivatives.

Difficulties associated with solid-phase synthesis are for example: the lower reactivity due to steric hindrance at the polymer interface, swelling of the resin, monitoring and characterisation of intermediates attached to the support. Solid-phase organic chemistry does require the compatibility of the polymer, the linker, the substrates and the reactions conditions including immobilisation and cleavage procedures as well as protecting group manipulations. The possibility of immobilising the nitrones and the dipolarophiles on solid supports for 1,3-dipolar cycloadditions has been investigated in the recent past. Furthermore, the application of supported versions of organic and of chiral metal-catalysts in 1,3-dipolar cycloadditions was examined. We describe herein the general synthetic concepts and present the achievements in 1,3-dipolar cycloadditions with nitrones in solid-phase organic synthesis.

## 2 Reactions of acyclic nitrones

As mentioned above, in reactions of nitrones with alkenes a pair of diastereomers (*endo* and *exo* isomers) is formed. The *endo* transition state is favoured by secondary π orbital interactions.[2,5] Hence the *endo*/*exo* selectivity is controlled by the structure of the substrates. Consequently for acyclic nitrones *Z*/*E*-isomerisation has to be taken into consideration. A lack of selectivity often can be caused by acid- or Lewis acid-catalyzed *Z*/*E*-isomerisation. On the other hand, a chelating group next to the C-atom of the nitrone double bond in the presence of a Lewis acid can lead to a higher selectivity, due to the favoured chelation and activation of the *Z*-nitrone.[2,10]

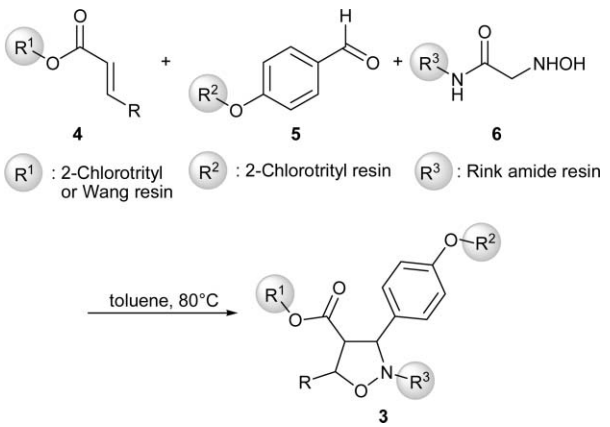
### 2.1 Alkene *vs.* nitrone immobilisation

A milestone towards the synthesis of substituted isoxazolidines on solid supports was presented by Jung and co-workers in 1998 based on the condensation of hydroxylamines with aldehydes and trapping of the resulting nitrones with various alkenes in an one-pot three-component cycloaddition reaction.[11] In these studies either substituted acrylic acids, aromatic hydroxyaldehydes or hydroxylamines were immobilised (Scheme 2). Five differently substituted isoxazolidines **3** were synthesised *via* alkene immobilisation on 2-chlorotrityl resin (1.3 mmol $g^{-1}$) **4** in toluene at 80 °C within 5 h reaction time by applying 10 equiv. of the nitrones prepared *in situ*. The heterocycles were isolated after acidic cleavage with TFA in 24–45% overall yield. Complete conversion of the starting material could not be achieved, neither by applying a large excess of nitrone (40 equiv.) nor by prolonged reaction times up to 18 h or by using the more stable Wang resin to avoid thermal cleavage of the acids from the resin at 80 °C.

In a second approach solid-supported aromatic hydroxyaldehydes were investigated. A library of 15 substituted isoxazolidines was synthesised starting from three aromatic hydroxyaldehydes immobilised on 2-chlorotrityl resin **5** (1.3 mmol $g^{-1}$), four commercially available hydroxylamines and nine alkenes. The products were obtained in 49–87% yield in toluene at 80 °C within 5 h by using an excess of the alkenes (10 equiv.), *e.g.* acrylic acid *tert*-butyl ester, cyclohexanone and vinylnaphthalene. No cycloadducts were obtained from tetra- and trisubstituted alkenes for steric reasons, as well as from strongly electron deficient or electron rich alkenes such as maleic acid anhydride or furan. In the case of cycloadducts derived from *N*-methylmaleimide, structure elucidation by means of NMR spectroscopy revealed an *endo*:*exo* ratio of 1:1 up to 3:1.

Due to the limitations in substitution pattern an additional approach furnishing isoxazolidines was investigated. α-Bromocarboxylic acids were coupled onto Rink amide resin (0.68 mmol $g^{-1}$) for the synthesis of polymer-bound *N*-substituted hydroxylamines **6** from hydroxylamine. This strategy proved to be superior to the methods above. The aldehyde component was varied and the resulting nitrones were reacted with alkenes yielding a diverse library of 30 differently substituted products after acidic cleavage from the resin with TFA. The immobilised nitrones were treated with 10 equiv. of the alkenes at 80 °C for 5 h or for 18 h in the case of styrenes. This route furnished the isoxazolidines in 31–95% yield. The synthesis of isoxazolidines derived from 3-bromoacetophenone was not possible. However, nitrones derived from ketones are known to be more unstable, *e.g.* towards hydrolysis. Reactions with strongly electron deficient or tri- and tetrasubstituted alkenes failed or resulted in low product yields.

Among the reaction pathways examined the nitrone immobilisation opened up a versatile route for screening a broad variety of commercial alkenes. The syntheses *via* immobilised alkenes proved to be less practicable due to the low yields of cycloadducts. In summary, the regio- and stereoselectivities were found to be similar to solution-phase studies.




**Scheme 2** One-pot three-component cycloaddition reaction.

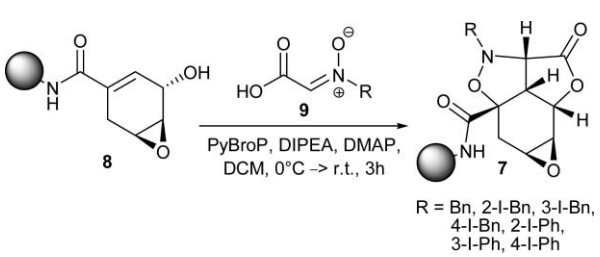
### 2.2 Intramolecular 1,3-dipolar cycloadditions

Schreiber and co-workers described the syntheses and preliminary evaluations of libraries of polycyclic molecules **7** on TentaGel S $NH_2$ resin (loading 0.27 meq. $g^{-1}$), a poly(ethylene glycol)polystyrene copolymer, with a photolabile linker.[12] The enantiopure compound **8** derived from shikimic acid, and linked to the solid support, was reacted with the nitrone carboxylic acids **9** (2 equiv.) in the presence of PyBroP, DIPEA and DMAP in DCM in 3 h to yield the tetracyclic immobilised isoxazolidines **7** in a tandem acylation/intramolecular cycloaddition reaction with complete stereo- and regioselectivity (Scheme 3). Due to the sensitive nature of the activated nitrone carboxylic acids, several coupling procedures were generally required.

A number of reactions were studied and optimised to generate a library of substantial size and diversity: Palladium-catalyzed coupling reactions at the isoxazolidine nitrogen substituents, lactone aminolyses and epoxide (thio)acidolysis as well as acylations of the liberated alcohol moieties with isocyanates, acids or acid chlorides.

### 2.3 Metal catalysis

First successful attempts to catalyse the cycloaddition of polymer-bound acyclic nitrones by Lewis acids were published by Kobayashi and Akiyama in 1998.[13] They investigated the catalytic activity of $Yb(OTf)_3$ in reactions of different polymer-bound acyclic nitrones **10** (Merrifield resin, loading 0.91 mmol $g^{-1}$), derived from a hydroxylamino resin *via* condensation of various aromatic and one aliphatic aldehyde. Several 2-enoyl-1,3-oxazolidin-2-ones, besides buten-2-one




**Scheme 3** Tandem acylation–intramolecular cycloaddition.

and acetylenedicarbonic acid methyl ester, were investigated as dipolarophiles.

Reactions of 2-enoyl-1,3-oxazolidin-2-ones **11** (5 equiv.) in toluene at room temperature proceeded smoothly in the presence of 20 mol% $Yb(OTf)_3$ in 20 h. Yields of 54–89% were achieved in the synthesis of $\Delta^2$-isoxazolines **12**, obtained by oxidative cleavage from the polymer with DDQ in DCM/$H_2O$ (Scheme 4). Nitrones derived from aromatic, heteroaromatic and aliphatic aldehydes gave the expected cycloadducts. As the stereocentre in 5-position is destroyed during this cleavage protocol, no *endo*:*exo* ratios for the initial cycloadducts could be determined.

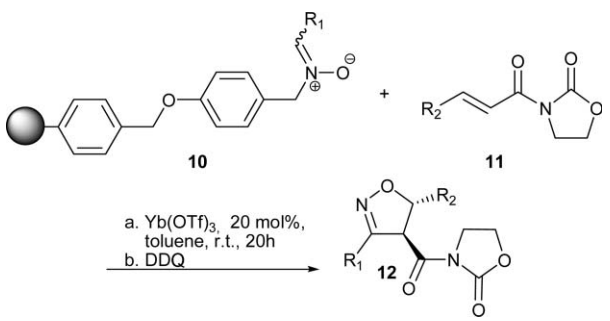
These data complement the studies by Jung and coworkers[11] discussed above with respect to the synthesis of immobilised acyclic nitrones from 4-hydroxybenzaldehydes grafted to a suitable polymer resin and additional alkenes being suitable for isoxazolidine synthesis on solid supports.

### 2.4 1,3-Dipolar cycloadditions promoted by high pressure

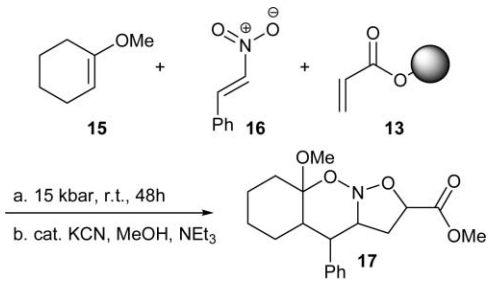
Multicomponent domino cycloaddition reactions under high pressure in solution and on solid supports were studied by Kuster and Scheeren.[14–16] Domino [4+2]/[3+2] cycloaddition reactions involve three building blocks: an enol ether, a nitroalkene and a third alkene. First a cyclic nitronate is formed in an inverse electron-demand Diels–Alder reaction. A subsequent 1,3-dipolar cycloaddition reaction of the former with an electron poor alkene then leads to a nitroso acetal. Only non-Lewis acid catalyzed domino cycloaddition reactions of this type can be carried out in a one-pot procedure. A Lewis acid hinders the subsequent [3+2] cycloaddition after formation of the nitronate, probably by inactivation of the dipole.

However, in solution-phase studies Kuster and Scheeren demonstrated that by using high pressure, a large excess of reagents, as well as long reaction times can be avoided.[16] In addition resin-bound acrylates[15] (**13**, Scheme 5) and immobilised nitroalkenes[14] (**14**, Scheme 6) were investigated by Kuster and Scheeren with comparable success. In the former case all reactions were carried out at a pressure of 15 kbar for 48 h at room temperature in a Teflon tube in DCM. The enol ether and the nitrostyrenes were applied in a twofold excess.

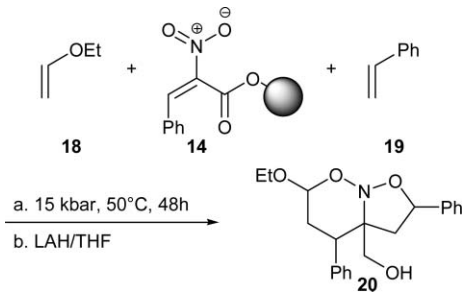
From six enol ethers **15**, two non-activated nitrostyrenes **16** and a resin-bound acrylate **13** (Wang resin, loading 1.22 mmol $g^{-1}$) a small library of nitroso acetals **17** was prepared and liberated from the solid phase by a cyanide-catalyzed transesterification reaction employing MeOH to obtain the




**Scheme 4** Lanthanide triflate-catalysed 1,3-dipolar cycloadditions.




**Scheme 5** Domino [4+2]/[3+2] cycloadditions – Part I.




**Scheme 6** Domino [4+2]/[3+2] cycloadditions – Part II.

cycloadducts as a mixture of diastereomers in 33–52% non optimised yield (**17**: 52%).

Immobilised nitroalkenes **14** are accessible by a microwave-assisted Knoevenagel condensation of resin-bound nitroacetic acid (Wang resin, loading 0.99 mmol $g^{-1}$) and aldehydes. Reactions were conducted in DCM with 4 equiv. of ethyl vinyl ether **18** and 5 equiv. of styrene **19** at a pressure of 15 kbar for 20 h at 50 °C. Starting from five aryl-, heteroaryl- and alkyl-substituted aldehydes five bicyclic nitroso acetals **20** were obtained after reductive cleavage with LAH in THF in 29–56% non optimised yield.

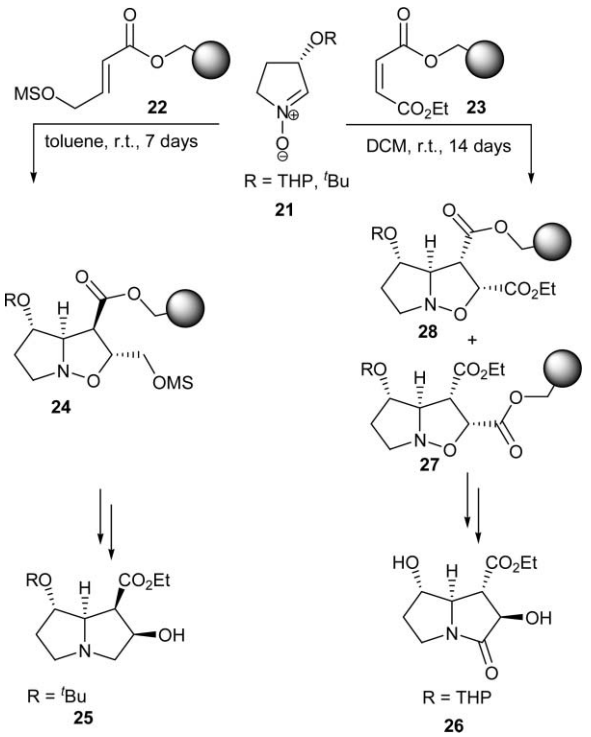
## 3 Application of cyclic nitrones

In recent years cyclic five-membered nitrones have been intensively investigated in the synthesis of pyrrolizidines, which are known to be of interest as inhibitors of glycosidases, besides indolizidines and azasugars.[17,18] These and other cyclic nitrones are of importance for the synthesis of diverse scaffolds from bicyclic isoxazolidines *via* reductive N–O-bond cleavage. Therefore, solid-phase strategies to produce libraries of compound classes of biological interest derived from isoxazolidine intermediates are highly appreciated.

### 3.1 Synthesis of pyrrolizidines *via* alkene immobilisation

Enantiopure cyclic five-membered 3-alkoxylated nitrones **21** derived from maleic acid were studied by Brandi and coworkers in solution as well as in reactions with resin-bound 4-mesyloxy crotonate **22** and monoethyl maleate **23** (Scheme 7). The aim was to prepare pyrrolizidine ring skeletons from the primary cycloadducts by reductive cleavage of the N–O-bond followed by intramolecular amide formation.[17,18] Starting from the crotonate **22** linked to Wang or Merrifield resin treatment with 4 equiv. of nitrone **21** at room




**Scheme 7** Pyrrolizidines derived from cyclic five-membered nitrones.

temperature for several days furnished compound **24** as a single cycloadduct by an attack *anti*(OR)–*endo*($CO_2R'$) to the alkoxy group vicinal to the nitrone functionality.[17] Because of the thermal instability of the cycloadduct heating was avoided. Pyrrolizidine **25** was obtained in a one-pot N–O-bond cleavage/ring closure/resin cleavage using $Pd(OAc)_2/H_2$ in DMF followed by esterification and neutralisation in 11% overall yield with respect to the resin loading. This isoxazolidine reductive ring opening proved to be troublesome. Several other methods for N–O-bond cleavage such as $Mo(CO)_6$ reduction or treatment with $SmI_2$ or $SnCl_2$ failed.

Cycloadditions with the resin-bound monoethyl maleate **23** occurred at room temperature in 14 days furnishing two regioisomers in *ca.* 1:1 ratio derived from an *anti*(OR)–*exo* transition state. The pyrrolizidine **26** was obtained in two batches. Treatment of the resin with $Mo(CO)_6$ in toluene–acetonitrile–water at reflux furnished product **26** from **27** in 22% yield. The lactam intermediate derived from **28** by treatment with $Mo(CO)_6$ was liberated from the resin applying TFA in DCM. Subsequent esterification afforded **26** in 18% yield.

### 3.2 Resin-linked dipolarophiles for nitrone protection

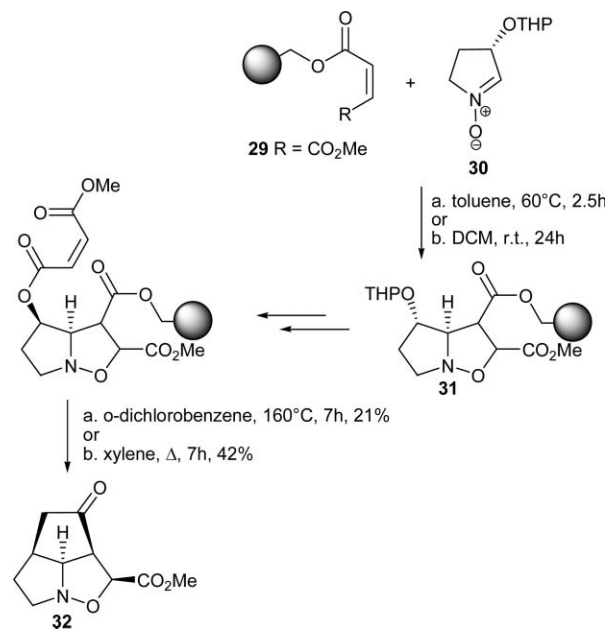
The maleate-based resin **29** was used by Brandi and co-workers as a polymer-bound reagent, besides other solid supported dipolarophiles, to investigate the temporary protection of the nitrone functionality of chiral five-membered 3-hydroxylated nitrones.[18] The nitrone functionality is highly reactive and protection has been achieved in solution by cycloaddition followed by cycloreversion. In an intramolecular route to pyrrolizidines in solution formation of a transient isoxazolidine was required to prevent racemisation of the stereocentre of the cyclic 3-hydroxylated five-membered nitrone **30** (Scheme 8).

Obviously, a solid supported dipolarophile being applied in this process would allow for an easier purification. Hence this concept was evaluated. In a multistage process first the cycloaddition of **30** to the resin-bound monomethyl maleate **29** (hydroxymethylpolystyrene, loading 0.68 mmol $g^{-1}$) furnished the transient isoxazolidine **31**. Secondly the deprotection of the hydroxyl group followed by Mitsunobu esterification with methyl maleate was carried out, and finally the domino cycloreversion/intramolecular cycloaddition reaction was performed to obtain the product **32** in 21% yield. The latter step was accomplished in refluxing *o*-dichlorobenzene at 160 °C for 7 h.

Since the temporary masking of nitrones is becoming increasingly popular for the application of nitrones in total synthesis of complex heterocyclic natural products[18] this concept developed by Brandi is awaiting useful future applications.

### 3.3 Synthesis of libraries of 2-oxo-1,4-piperazines *via* nitrone immobilisation

Another strategy towards the application of cyclic nitrones in solid supported syntheses of isoxazolidines and isoxazolines is starting from a polymer-supported nitrone.[19] The six-membered cyclic nitrone **33** was prepared by oxidation of the cyclic secondary amine precursor on a solid support (Wang resin, loading 0.4 up to 0.9 mmol $g^{-1}$). This oxidation can be carried out with 30% aqueous $H_2O_2$ (4.4 equiv.) and a catalytic amount of $Na_2WO_4 \cdot 2H_2O$ in methanol–THF at room temperature or by applying Davis reagent (2-benzsulfonyl-3-phenyloxaziridine, 4.4 equiv.) in chloroform. Nitrone **33** was found to be bench-stable for several months and was applied in thermal 1,3-dipolar cycloaddition reactions with twelve differently substituted alkenes (*e.g.* methylenecyclohexane,



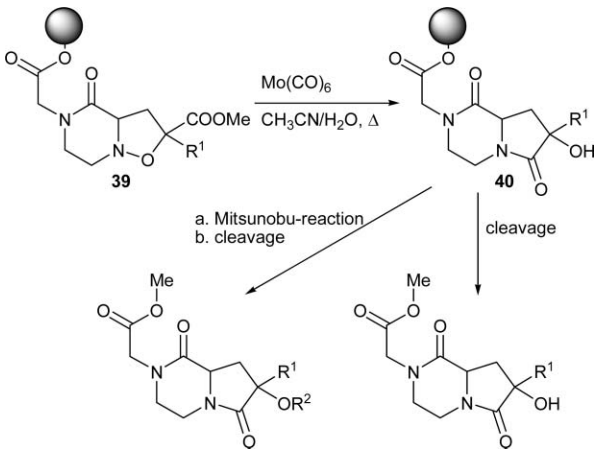

**Scheme 8** Nitrone protection using resin-bound dipolarophiles.

allylphenyl ether, *N*-methyl maleimide, acrylic acid methyl ester, 16–17 equiv.) yielding immobilised isoxazolidines **34** in 1–3 h reaction time at 65 °C in THF or dioxane (Scheme 9). The crude products **35** were obtained in >85% purity after basic cleavage (NaOMe in methanol–THF 1:4) from the resin and were isolated in 28–82% yield after purification by preparative RP-HPLC.

5-Substituted $\Delta^4$-isoxazolines **36** were obtained as the major products in purities ⩾90% from three monosubstituted alkynes (*e.g.* phenylacetylene, ⩾17 equiv.) within 1–2 h at 65 °C in THF. The cycloadducts were isolated after basic cleavage from the resins **37** (Scheme 9) in 23–54% total yield by purification by RP-HPLC. The large excess of the alkynes resulted in short reaction times and hence there was no evidence of thermal rearrangement or of decomposition of the cycloadducts as has been observed in solution-phase studies.[19] The selectivities determined for the alkene and alkyne 1,3-dipolar cycloadditions are essentially the same as in solution with a model nitrone of related structure.[19,20]

From the immobilised isoxazolidines **34**, 1,3-amino alcohols **38** are accessible by N–O-bond cleavage (Scheme 9). The immobilised isoxazolidines **39** derived from acrylic acids are well suited for functionalisation to furnish 7-aza-substituted indolizidine analogues **40** by reductive cleavage of the N–O-bond of the cycloadducts followed by intramolecular amidation (Scheme 10). By applying $Mo(CO)_6$ (5–14 equiv.) in wet acetonitrile at 85 °C for 5–29 h the immobilised 1,3-amino alcohols **38** (Scheme 9) and the lactam derivatives **40** (Scheme 10) were obtained in 50–99% purity after basic cleavage from the Wang resin and in 13–66% isolated yield by preparative RP-HPLC. Compared to solution-phase studies the products obtained *via* reductive N–O-bond cleavage on the solid support and isolated after a seven-, respectively, eight-step sequence, were generally of higher purity, and were isolated in higher yields, compared to those derived from solution-phase studies.

Small libraries of 2-oxo-1,4-piperazines **41** were obtained by non-optimised automated solid-phase synthesis in subsequent transformations of four polymer-supported 1,3-amino alcohols **38** by amine acylations with four carboxylic acids (Scheme 9), as well as by starting from the lactam derivatives **40** *via* Mitsunobu-reactions with four substituted phenols (Scheme 10).




**Scheme 10** Synthesis of 2-oxo-1,4-piperazine scaffolds.

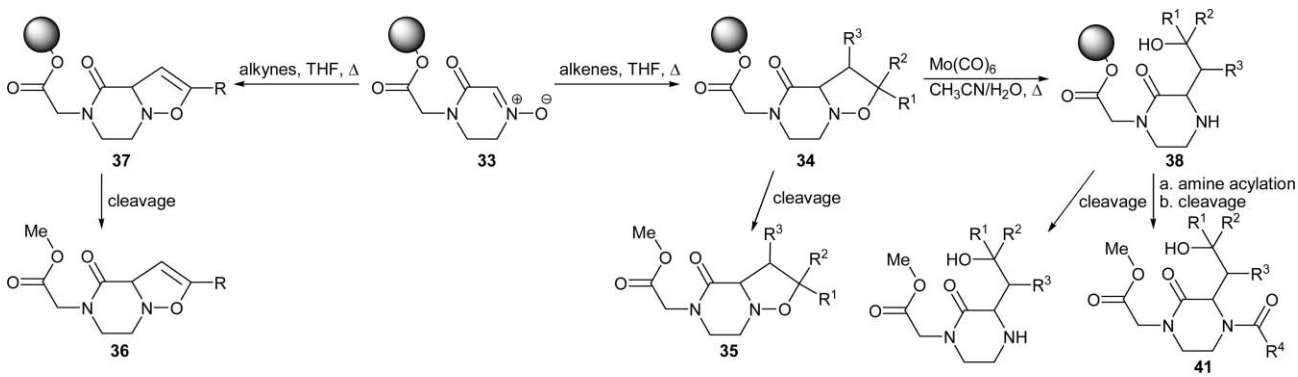
Finally, the first oxidative N–O-bond cleavage of an immobilised isoxazolidine **42** was recently presented.[19] MCPBA was investigated furnishing the polymer-bound second-generation aldo-nitrone **43** (Scheme 11) after acylation.

Subsequent [3+2] cycloaddition with phenylacetylene gave isoxazoline **44**, isolated in 9% yield by RP-HPLC after cleavage from the resin (ten-step reaction sequence). Protection of the hydroxyl functionality was necessary to circumvent the formation of a bicyclic hydroxylamine by an intramolecular addition of the hydroxyl group, derived from N–O-bond cleavage, to the nitrone double bond.

Further studies with other immobilised cyclic nitrones will demonstrate the versatility of this approach in solid-phase organic synthesis toward isoxazolidines and derivatives being accessible by N–O-bond cleavage.

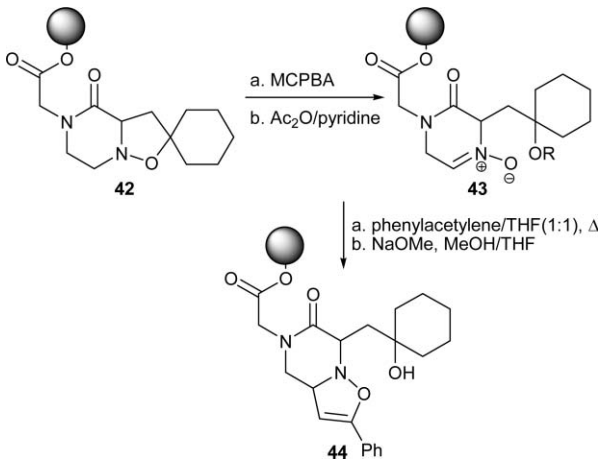
## 4 Supported auxiliaries and catalysts in asymmetric 1,3-dipolar cycloadditions

For asymmetric 1,3-dipolar cycloadditions in solid-phase organic synthesis two techniques are available. As mentioned above, the nitrone or the dipolarophile may be attached to a polymer and brought to reaction with a chiral catalyst. A more attractive alternative is given by the immobilisation of an auxiliary or a catalyst. Hence a simple work-up is sufficient to recycle expensive auxiliaries and catalysts.




**Scheme 9** Synthesis of libraries of 2-oxo-1,4-piperazines *via* nitrone immobilisation.

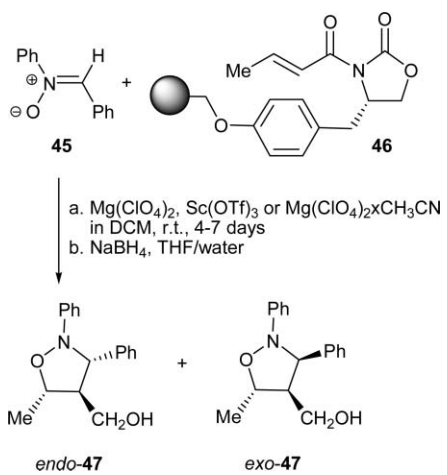



**Scheme 11** Oxidative N–O-bond cleavage.

### 4.1 Immobilised Evans' chiral auxiliary

A polymer-bound Evans' chiral auxiliary was investigated in 1,3-dipolar cycloadditions of diphenylnitrone **45** to *e.g.* a *N*-crotonyl derivative by Faita *et al*. in 2000.[21] Polymer-supported chiral auxiliaries offer the benefits of simple recovery and product separation. The precursor oxazolidin-2-one for immobilisation was derived from tyrosine and linked through the phenol residue to Merrifield resin (loading 0.97 mmol $g^{-1}$) and Wang resin (loading 0.86 mmol $g^{-1}$) prior to acylation with *trans*-crotonic anhydride to yield **46**. Cycloadditions with diphenylnitrone **45** (DPN) in DCM at room temperature were carried out in the presence of $Mg(ClO_4)_2$ and $Sc(OTf)_3$ as well as in the absence of any Lewis acid. The products **47** were cleaved from the oxazolidinone moiety on the resin by treatment with $NaBH_4$ (Scheme 12).

Compared to the solution-phase studies, significantly longer reaction times were required to complete the reaction under all conditions examined. However, lower yields were obtained on the solid-phase, probably due to decomposition of the nitrone, especially in the presence of Lewis acids. In DCM the selectivities were found to depend solely upon the resin used.[21]




**Scheme 12** Polymer-bound Evans' chiral auxiliary.

The cycloaddition reaction in solution gave an *exo*:*endo* ratio of 83:17 and an enantioselectivity of 84% ee for the *exo*-adduct and >99% ee for the *endo*-adduct. Merrifield resin almost equalised this selectivity and gave a ratio of 53:47 and Wang turned the selectivity to an *exo*:*endo* ratio of 31:69. The enantioselectivity of the *exo*-product was satisfactory in all cases examined (81–89% ee), while the results for the *endo*-product turned out to be poor (22–29% ee for Merrifield resin and 6–7% ee for Wang resin). It is assumed that under thermal conditions the *endo*-transition state with the two carbonyls in *s-trans* disposition offers a better differentiation of the *Si*- and *Re*-face of the nitrone than the *exo*-transition state consequently leading to a better enantiomeric excess.

In these 1,3-dipolar cycloadditions a strong catalytic effect of the Lewis acid was only observed upon treatment of the reactants in DCM with 1 M $Mg(ClO_4)_2$–acetonitrile solution. This resulted in an increased selectivity and reactivity.[22] The *endo*/*exo*- and enantioselectivity of the cycloaddition reactions were inverted in the presence of 50 mol% $Mg(ClO_4)_2$–acetonitrile solution with the *endo*-product being favoured with an *endo*:*exo* ratio up to 80:20 for Merrifield resin and 90:10 for Wang resin. The enantioselectivity ranged from 77 to 87% ee for both *endo*- and *exo*-product. Thus, for Wang resin, a higher sensitivity towards the salt concentrations and a higher level of selectivity was observed. The stereochemical outcome and the inversion of the enantioselectivity can be rationalised by the influence of the coordination of the Mg(II) cation to the 1,3-dicarbonyl moiety fixing the two carbonyl groups in a *s-cis* conformation.

Reactions with an Evans' auxiliary bound to a soluble polystyrene-based polymer instead of Merrifield resin were published in 2002 by the same group.[23] The selectivities were found to be more similar to those obtained in classical solution-phase studies with Evans' auxiliary and the products were obtained in higher overall yields compared to the auxiliaries grafted to insoluble polymers.

It can be concluded from the data reported that for the application of metal-catalysts in asymmetric 1,3-dipolar cycloadditions with an immobilised auxiliary the choice of the solvent and solvent additives is crucial. The dissolution of the Lewis acid as well as the swelling of the polymer, which affects the access of the Lewis acid to the reaction centres, has to be taken into consideration.

### 4.2 Immobilised metal-catalysts

In asymmetric 1,3-dipolar cycloaddition, in homogeneous solution-phase as well as on solid supports, reactions of 2-enoyloxazolidinones and of enol ethers with diphenylnitrone were introduced as test reactions for using catalytic amounts of chiral metal-catalysts.[2,24]

In solution-phase studies the cycloadducts are separated from the chiral ligands and the metals by aqueous work-up, by distillation or by chromatography.[2] Immobilisation does allow for easy separation from the products by simple filtration of the polymer-bound chiral ligands or by precipitation in the case of ligands grafted to soluble polymers or dendrimers. Hence this does allow recovering and reusing of the immobilised systems.[2,24] In the case of polymer-bound chiral

metal-catalysts often a decreased activity and selectivity is encountered compared to the solution-phase analogue. Seen especially during reuse, this may be attributed to leaching of the metals. For reaching a high catalytic activity dendrimers and soluble organic polymer resins proved to be superior compared to insoluble organic polymers. For the latter the swelling of the support is crucial to obtain access to the ligands for loading and during catalysis. Today silica supports of inert porous rigid structure are of interest to avoid swelling effects.[2,24]

The first 1,3-dipolar cycloaddition with polymer- and dendrimer-bound catalysts was published in 1996[25] when Seebach *et al*. reported the immobilisation of TADDOLs and the synthesis of $TiCl_2$–TADDOLate catalysts and others. The immobilisation was accomplished in three ways: *via* modification of Merrifield resin (TADDOL content 0.3 mmol $g^{-1}$), copolymerisation of TADDOLs containing styryl groups with styrene and divinylbenzene (TADDOL content 0.1–1.2 mmol $g^{-1}$) and by building cross-linked dendritic molecules with TADDOL centres located at the end of the branches. Titanation with $TiCl_2(OCHMe_2)_2$ or $Ti(OCHMe_2)_4$ lead to the $TiX_2$–TADDOLates, *e.g.* **48** and **49** (Fig. 2).

The cycloaddition between diphenylnitrone **45** (2 equiv.) and *trans*-3-crotonyl-1,3-oxazolidin-2-one **50** (R = Me) was carried out in toluene at room temperature for 24 h in the presence of 0.2 equiv. of the catalysts (Scheme 13, Table 1). The activity of the immobilised Lewis acids was slightly reduced in comparison to the activity of monomeric systems in solution-phase studies. With the dendrimeric catalysts, *e.g.* **49**, the yield varied in the range 45–75%, and the *exo*:*endo*-ratios (83:17 to 86:14) and the ee for the *exo*-product (40–48%) were quite similar to the results obtained in solution with monomeric Ti–TADDOLates, but yields were generally lower (Table 1, entry 6). The $TiCl_2$–TADDOLate **48a** derived from Merrifield resin (loading 0.3 mmol $g^{-1}$) gave poor results (37% yield, *exo*:*endo* = 76:24, and *rac*-*exo*-product). However, copolymerised catalysts (loading 0.3–1.2 mmol $g^{-1}$) lead to yields between 52 and 86% and gave satisfying stereoselectivities with *exo*:*endo* ratios between 76:24 and 92:8 and an ee for the *exo*-product of 32 up to 56% (Table 1, entry 5).

To improve the selectivities of dendritic catalysts, the TADDOL unit was embedded into a polystyrene network furnishing the monomer **51** (Fig. 3) to prepare the dendritically cross-linked catalysts **52a** (X = Cl) and **52b** (X = OTs). For complete conversion 50 mol% of the catalyst were required. As in solution-phase studies the configuration of the major enantiomer can be controlled by using either the $Cl_2Ti$–TADDOLate or the $(TsO)_2Ti$–TaDDOLate catalyst (Table 1, entries 7 and 8).[26,28]

In order to bypass the reduced catalytic activity due to swelling effects, the TADDOL ligands were also attached to highly porous silica gel (controlled-pore-glass, CPG).[27,28] CPG offers a constant accessibility of the immobilised catalyst independent of solvent, temperature and pressure due to its rigid pore structure. Before attaching different TADDOL ligands by grafting to a mercaptopropyl linker bound to the silica gel, the remaining SiOH-groups had to be turned hydrophobic. This is necessary, because these groups are acidic and bind water, which would destroy the water instable Ti–TADDOL complexes. This hydrophobisation turned out to have a positive effect in protecting the readily prepared catalyst from water, so that it even tolerated water washing routines. Additional TADDOL ligands were synthesised on CPG silica gel (controlled-pore-glass silica gel) from an immobilised tartaric ester and different aryl Grignard reagents.

The CPG-immobilised $Cl_2Ti$–TADDOLate **53a** and the $(TsO)_2Ti$–TADDOLate catalysts **53b** (loading: 0.3–0.4 mmol $g^{-1}$) were also tested in the 1,3-dipolar cycloaddition of diphenylnitrone (1.2 equiv.) to 3-crotonoyl-1,3-oxazolidin-2-one in toluene at room temperature for 48 h (Scheme 13). The results (Table 1, entries 9 and 10) were comparable to those obtained in solution-phase studies with monomeric catalysts when 0.5 equiv. of the CPG-immobilised catalysts were applied in the first run (Table 1). In all cases examined, recycling of the catalysts does require a hydrolysis followed by a reloading. A seasoning of the $Cl_2Ti$–TADDOL **53a** immobilised on hydrophobic CPG silica gel in these reactions was observed: after seven runs only 0.1 equiv. of the catalyst

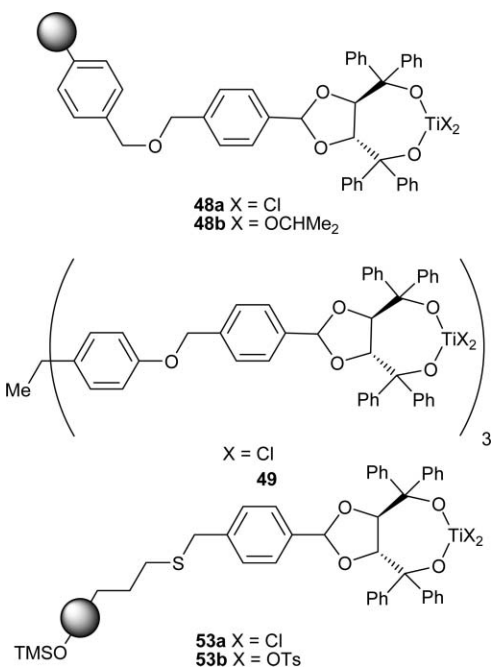
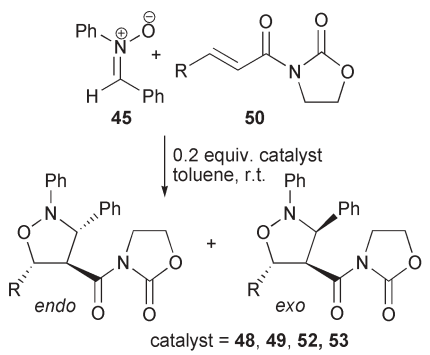



**Fig. 2** Immobilised $TiX_2$-TADDOLates.




**Scheme 13** Enantioselective 1,3-dipolar cycloadditions.

**Table 1** Comparison of immobilised TADDOLates (see Scheme 13)

| No. | Catalyst | Mol% | Conversion (%) | *Exo*:*endo* | ee (%) major product |
|---|---|---|---|---|---|
| 1 | $TiCl_2$–TADDOL (solution)[26] | 10 | 94 | 90:10 | 79 |
| 2 | $Ti(OTs)_2$–TADDOL (solution)[26] | 50 | 100 | >5:95 | 94 |
| 3 | $Yb(OTf)_3$[13] | 20 | 89[a] | —[b] | — |
| 4 | **48**[25] | 20 | 37[a] | 76:24 | — |
| 5 | copolymerised TADDOL[25] | 20 | 52–86[a] | 76:24–92:8 | 32–56 |
| 6 | dendrimeric TADDOL[25] | 20 | 45–75[a] | 83:17–86:14 | 40–48 |
| 7 | **52a**[26] | 50 | 93 | 82:18 | 75 |
| 8 | **52b**[26] | 50 | 72 | 12:88 | 86 |
| 9 | **53a**[28] | 50 | 100 | ~92:8 | ~70 |
| 10 | **53b**[27] | 50 | 91 | Up to 8.5:91.5 | Up to 85 |

[a] Yield. [b] Not determined.

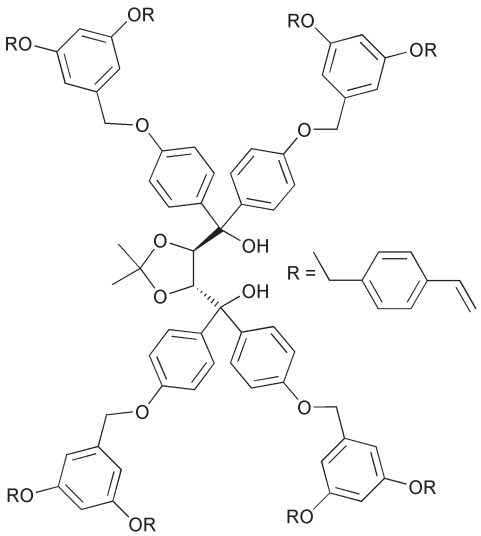



**Fig. 3** Cross-linker **51** for the preparation of **52**.

proved to be necessary in the next run to obtain identically good results as in the first run.

Already in 2000, Seebach and co-workers have reported the successful immobilisation of binaphthols on solid supports.[29] For 1,3-dipolar cycloaddition reactions the BINOL system *m*-**54** (Fig. 4) was obtained by a modification with vinylstyrene spacers in 3,3′-position.

Copolymerisation of the TIPS-protected BINOL cross-linker with styrene yielded polymer beads of 400 μm average size. After cleavage of the protecting groups the use of this immobilised ligand in enantioselective reactions was tested. With the catalyst p-**55**·AlMe derived from $AlMe_3$ (0.2 equiv, 0.14–0.39 mmol $g^{-1}$), the activation of diphenylnitrone **45** (1 equiv.) towards reactions with vinyl ethers **56** (5 equiv.) was performed in toluene at room temperature for 12 h as a test reaction (Scheme 14) to yield product **57**, and compared to the results of Jørgensen and co-workers for solution studies.[30]

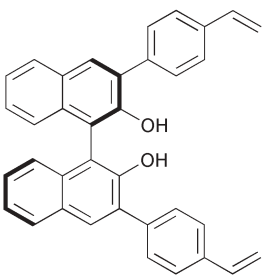
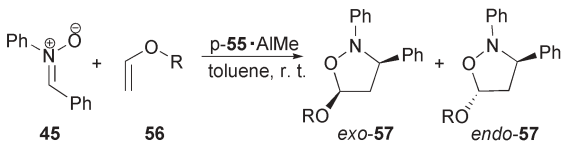



**Fig. 4** Cross-linker *m*-**54** for the preparation of *p*-**55**·AlMe.

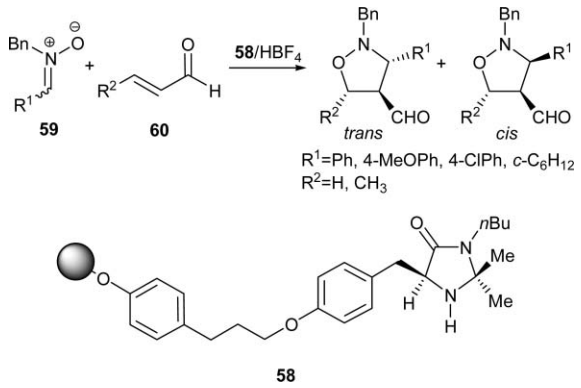
The *exo*:*endo* ratios and the enantioselectivities were determined as 93:7 and 97% ee (ethyl vinyl ether) and 95:5 and 95% ee (*tert*-butyl vinyl ether), respectively. These results coincide with the data obtained in homogeneous solution. The selectivities were found to be largely independent of the degree of loading of the supports. Unfortunately, the catalyst cannot be recycled or regenerated, neither by retreatment with $AlMe_3$ nor by hydrolysis and reloading.

### 4.3 Immobilised organocatalysts

Organocatalysts have the advantage of being bench-stable and they can be applied in wet solvents under aerobic conditions. The first immobilised organocatalyst **58** was reported by Celentano and co-workers in 2004.[31] Starting point were chiral imidazolidin-4-ones published by McMillan and co-workers to be efficient organocatalysts in solution in enantioselective Diels–Alder reactions as well as 1,3-dipolar cycloadditions of α,β-unsaturated aldehydes.[32] The binding to the polymer was achieved by the synthesis of an imidazolidin-4-one starting from tyrosine for grafting to polyethylene glycol *via* the phenol moiety (loading 0.192 meq $g^{-1}$). Different combinations of catalyst **58** (0.2 equiv.) and acids HX (0.2 equiv, X = Cl, $CF_3COO$, $ClO_4$, $BF_4$) were tested in the 1,3-dipolar cycloaddition of *N*-benzyl-*C*-phenylnitrone **59** ($R^1$ = Ph, 1 equiv.) with α,β-unsaturated aldehydes **60**, *e.g.* acrolein (4 equiv.), in wet nitromethane in the temperature range between −20 °C and room temperature (Scheme 15). The catalyst's efficiency depended strongly on the acid that was used to prepare the catalyst. The best results were obtained with $HBF_4$ at low temperatures ($R^1$ = Ph, $R^2$ = H, 0 to 24 °C: 73% yield, *trans*:*cis* = 86:14, ee(*trans*) = 44%).




**Scheme 14** Enantioselective Lewis acid-mediated nitrone activation.




**Scheme 15** Cycloaddition with an immobilised organocatalyst.

Generally, the stereoselectivities were comparable to those in solution, but the activity of the immobilised catalyst was considerably lower. After recycling, the selectivity of the catalyst is maintained, while the activity drops already after the first cycle. The organocatalyst **58** could not be recovered *in situ* by addition of the acid because the nitrone decomposed. The reduction of the activity is related to the decomposition of the catalytic centre that is not caused by the poly(ethylene glycol) matrix, but by the α,β-unsaturated aldehydes **60** applied in these cycloadditions.

So far, very few immobilised metal-catalysts and organocatalysts have been tested in 1,3-dipolar cycloadditions with nitrones. Most promising are the results obtained with ligands immobilised on controlled-pore-glass silica gel. It will be future work to find additional immobilised catalysts for highly selective 1,3-dipolar cycloadditions of acyclic and cyclic nitrones with various monosubstituted, 1,1-disubstituted and 1,2-disubstituted alkenes bearing electron rich and electron poor substituents.

## 5 Concluding remarks

In the past two decades in solution studies 1,3-dipolar cycloaddition reactions of nitrones have been increasingly applied in organic synthesis. The studies outlined in this tutorial review have demonstrated that solid-phase organic chemistry with nitrones can open a convenient access to libraries of biologically active heterocycles. Furthermore reactions of nitrones will remain to be of interest for scaffold design. Novel immobilised chiral catalysts and reactions of novel nitrones having additional functionalities will broaden the field of application for nitrones in solid-phase organic synthesis in the future.

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