Enantioselective synthesis on the solid phase

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Organic transformations on substrates which are immobilized on an insoluble, polymeric carrier have found broad application in compound collection synthesis. In contrast to other synthetic methodologies in solid-phase organic synthesis, reactions that afford non-racemic products are strikingly under-represented. Not only does the introduction of stereoinformation on immobilized, achiral starting materials provide enantioenriched products which can be of value for biological testing, but it also opens up new perspectives for accessible structures. This feature article gives an overview of successful enantioselective transformations on a solid support. Critical differences in the corresponding solution-phase protocols are highlighted, and applications to the generation of compound collections are particularly mentioned.

Introduction

The synthesis of compound collections has gained steadily increasing interest in both industry and academia.[1] Technological progress in biological and biochemical screening has enabled chemists and biologists to investigate a large number of substances and has consequently led to an increasing demand for new compounds.

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Preceded by the success of oligo-peptide and -nucleotide synthesis on polymeric carriers,[2] solid-phase organic synthesis, *i.e.* sequential molecular transformations on a substrate that is covalently bound to an insoluble support, has emerged as a powerful technique for the rapid and parallel synthesis of compound collections. The type of transformations carried out in solid-phase organic synthesis is mainly dictated by the desired target structures.

Initially, typically compound libraries were synthesized which contained hardly any stereocenter,[3] and asymmetric synthesis has been applied only occasionally in compound library development. Non-racemic structures in compound libraries resulted in the majority of the cases from the use of chiral building blocks derived from natural sources such as amino acids and sugars.

Torben Leßmann

Torben Leßmann was born in Hamburg, Germany, in 1976. He studied chemistry at the universities of Tübingen, Heidelberg and Padova, and received his diploma from the Ruprecht-Karls-Universität Heidelberg in 2002 with a thesis in the group of Professor G. Helmchen. He then joined the Department of Chemical Biology in the Max-Planck-Institute of Molecular Physiology in Dortmund, where he works as a PhD student in the group of Professor H. Waldmann.

Herbert Waldmann

Prof. Dr Waldmann studied chemistry at the University of Mainz and received his PhD in organic chemistry in 1985 under the guidance of Professor Kunz. After a postdoctoral appointment with Professor George Whitesides at Harvard University, Dr Waldmann completed his habilitation at the University of Mainz in 1991. In 1991 he was appointed as professor of organic chemistry at the University of Bonn, then in 1993 was appointed to full professor of organic chemistry at the University of Karlsruhe. In 1999 he was appointed as Director of the Max-Planck-Institute of Molecular Physiology, Dortmund, and Professor of Organic Chemistry at the University of Dortmund.
Dr Waldmann's research interests lie in protein domain and natural product structure with work on the syntheses of signal transduction modulators and the syntheses of natural product derived compound libraries, the development of solid phase synthesis methods-traceless linkers, and the synthesis and biological evaluation of lipidated peptides and proteins with work on Ras peptides and Ras proteins and the development of Ras activators and inhibitors of the Ras–Raf interaction.
Professor Waldmann has received many awards and honors, including the 2001 Otto Bayer Award and the 2003 Max Bergmann Medal; he is a Member of ''Deutsche Akademie der Naturforscher Leopoldina, Halle/Saale''.

Newer developments in library design that focus for instance on natural product guided[4a–c] and biology-oriented[4d] or diversity-oriented synthesis[5] try to access more complex structures. In such endeavours, control of the stereochemical course of a reaction needs to be guaranteed in order to minimize isomer formation. Therefore, asymmetric synthesis in particular employing enantioselective transformations is needed as an integral method of the library development effort.

The application of asymmetric transformations on immobilized substrates is challenged by the fact that minor products cannot be separated in the course of the synthesis. It is therefore evident that only such protocols for asymmetric transformations can be applied to solid-phase organic synthesis that provide high levels of asymmetric induction. Results from solution-phase chemistry give good indications as to which type of reaction can be taken into consideration, however, a transfer from solution to solid-phase chemistry is often not straightforward, and adequately adapted protocols (with respect to reaction times, temperature, catalyst loading *etc.*) are in urgent demand.

In this article, we review different synthetic approaches in which an enantioselective transformation is used to introduce chirality into a solid-phase bound, typically achiral starting material.

The applications of immobilized chiral catalysts and solid-phase bound chiral auxiliaries have been recently compiled elsewhere[6] and are beyond the scope of this feature article.

The material is presented according to different reaction classes, and both stoichiometric and catalytic ways of enantiodifferentiation are subsumed under the same paragraph.

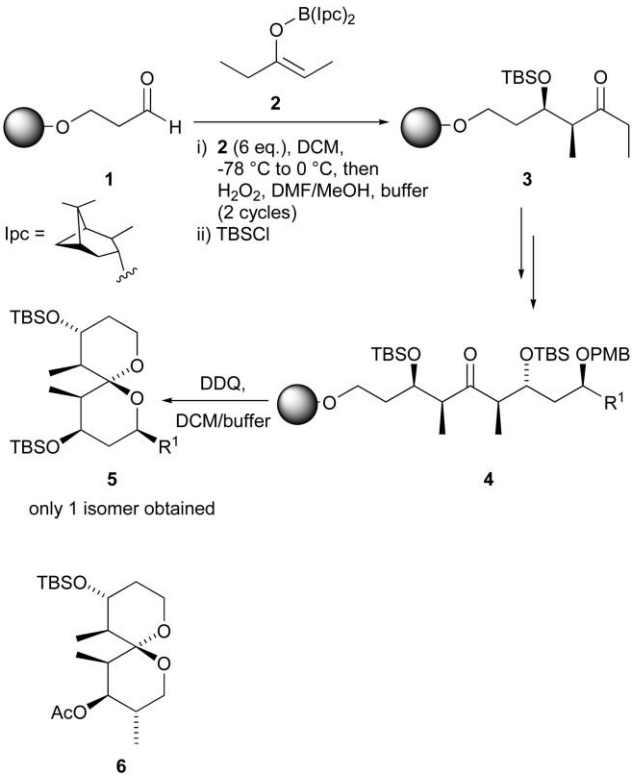
Where applicable, we additionally mention applications to the synthesis of compound collections and document results from biological screenings.

Enantioselective aldol reactions

Being one of the most enabling methods for the stereoselective construction of carbon–carbon bonds, the aldol reaction has become one of the standard transformations in organic synthesis. But although numerous protocols for enantioselective variations of the aldol reaction were developed in synthetic approaches towards complex molecules, only a few of them were applied to immobilized aldehydes or transferred to the synthesis of compound libraries.

The well-developed chemistry of boron enolates bearing chiral substituents at the boron atom[7] was developed to solid-phase applications by two groups:

In a study directed towards the biological exploration of a structural motif often found in natural products, Waldmann *et al.* used chiral boron enolates for the synthesis of a library of spiro[5.5]ketals.[8] Aldehyde **1** (Scheme 1) immobilized on a polystyrene resin with a Wang linker and the preformed *Z*-enolate **2** reacted to give the enantioenriched aldol adduct **3**. In contrast to reaction conditions in solution, two cycles with six equivalents of the chiral reagent **2** were necessary to achieve complete conversion of the aldehyde. Stereocontrolled formation of a boron-*E*-enolate on the solid phase was a prerequisite to control the course of a second, *anti*-selective aldol reaction with a set of aldehydes to build up the framework of protected



Scheme 1

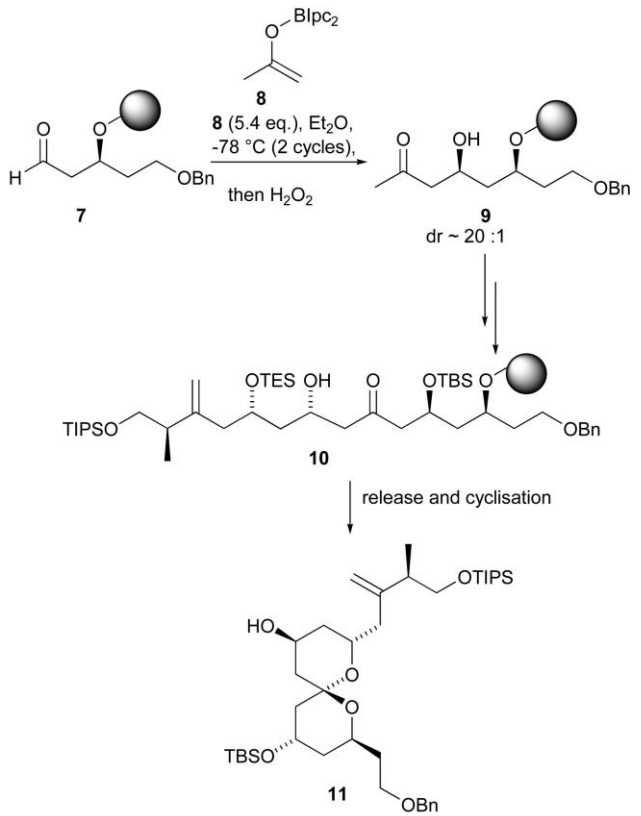
bis-β-hydroxyketones **4**. The final products **5** were obtained upon release from the carrier by oxidative cleavage of the *p*-alkoxybenzyl ether groups. Examination of the diastereomeric ratios showed that a *matched* case in the second aldol reaction led to exclusive formation of one isomer, whereas *mismatched* cases proceeded with lower stereoselectivity. Compound **6** from this collection was found to be an inhibitor of the phosphatases VHR and PTP1b with IC_{50} values of 6 and 39 μM respectively. In addition, compound **6** distorted the correct organization of the microtubulin network in a human breast carcinoma cell line.

Based on earlier studies,[9] Paterson *et al.* reported a similar synthesis of compound **11** (Scheme 2), a fragment of the natural product spongistatin:[10] the chiral boron-enolate **8** reacted with the solid phase bound aldehyde **7** (immobilized *via* a silyl linker) to yield **9** with a diastereomeric ratio of > 20 : 1. Also in this case, a second aldol reaction was performed after enolate formation on the methyl ketone of **9**. The protected polyol **10** could be converted into the final compound **11** by cleavage from the resin and *in situ* cyclisation.

Taken together, the high stereoselectivities obtained in solution could be reproduced on immobilized substrates. However, complete conversion of the aldol steps required two reaction cycles and an excess of the chiral reagents.

Aldehyde allylation and crotylation

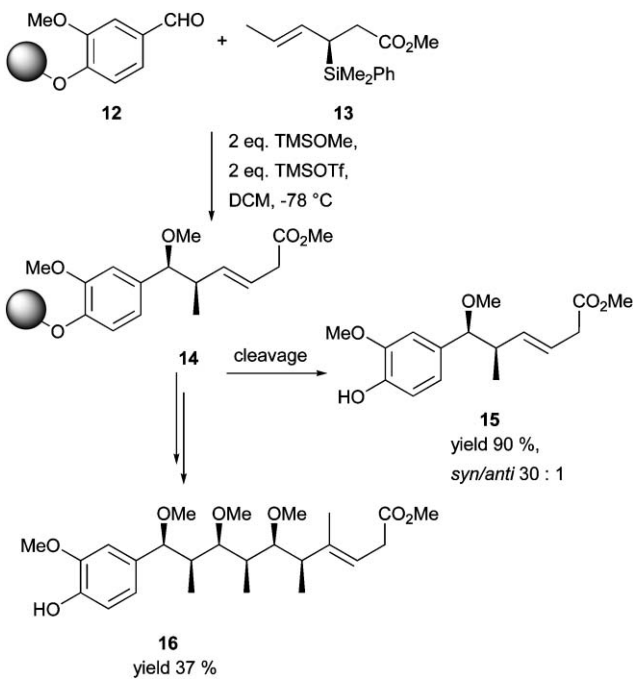
Successful asymmetric crotyl transfer to immobilized aldehydes was shown by Panek *et al.* (Scheme 3).[11] Crotylation of aldehyde **12** with chiral silane **13** gave rise to the expected *syn*-product **14** with a selectivity of 30 : 1 over the *anti*-product.



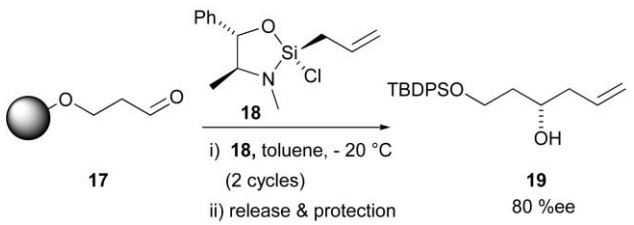
Scheme 2

Iterative application of this methodology was used to access polypropionate structures like **16**.

Tan *et al.* reported an asymmetric allylation of the aliphatic aldehyde **17** (Scheme 4) that was attached to the solid support



Scheme 3



Scheme 4

via a silyl linker.[12] In their study with the chiral allylchlorosilane **18** developed by Leighton *et al.*,[13] they could obtain an enantiomeric excess of 80% in the final compound **19**, which was in accordance with results observed in a parallel reaction in solution. But in contrast to the solution phase experiment, two reaction cycles were performed to drive the reaction to completion.

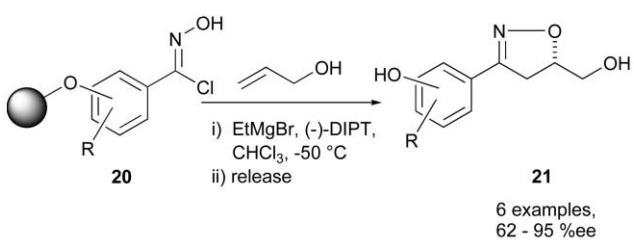
Cycloaddition reactions

Being important for the formation of both C–heteroatom-bonds and C–C-bonds with high stereoselectivity, cycloadditions were investigated in several solid-phase synthesis projects.

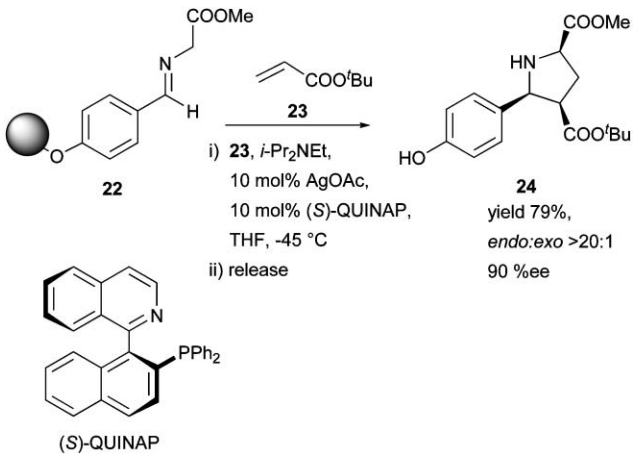
Jiang *et al.* reported the synthesis of a set of isoxazolines by applying an asymmetric 1,3-dipolar cycloaddition of nitrile oxides to allyl alcohol.[14] In their study, the use of four equivalents of (−)-diisopropyl tartrate ((−)-DIPT) as chiral auxiliary and EtMgBr as a base converted the resin-bound compounds **20** (Scheme 5) to the corresponding isoxazolines **21** in 50–70% yield and with up to 95% enantiomeric excess. The use of diethylzinc as reported for solution phase reactions[15] led to racemic products.

In a different approach, Schreiber *et al.* subjected an immobilized aromatic azomethine ylide (from **22**, Scheme 6) to a silver acetate/(*S*)-QUINAP-catalyzed [3 + 2] cycloaddition to *tert*-butyl acrylate **23**.[16] An overall yield of 79% and an enantiomeric excess of 90% in the favoured *endo*-isomer **24** proved the applicability of the method to library synthesis. Still, the catalyst loading had to be increased threefold (10 mol% instead of 3 mol% in solution) to obtain a system with activity similar to that in solution phase.

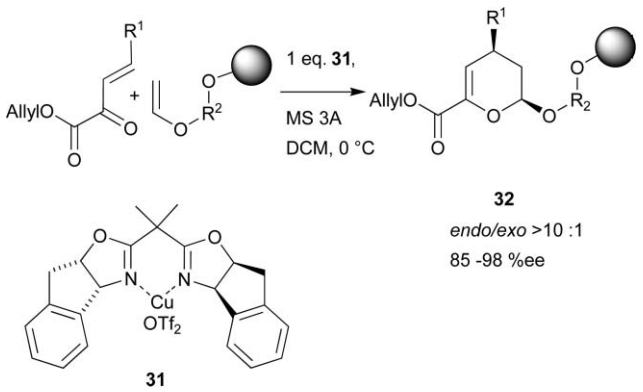
In the field of [4 + 2]-cycloadditions, Schreiber *et al.* succeeded in the synthesis of a 4320-member library *via* an enantioselective inverse-electron-demand hetero-Diels–Alder reaction.[17] Copper(II)-catalysts with C_2-symmetric bisoxazoline ligands were intensively studied for this reaction type in solution, leading to protocols in which the catalyst loading



Scheme 5



Scheme 6

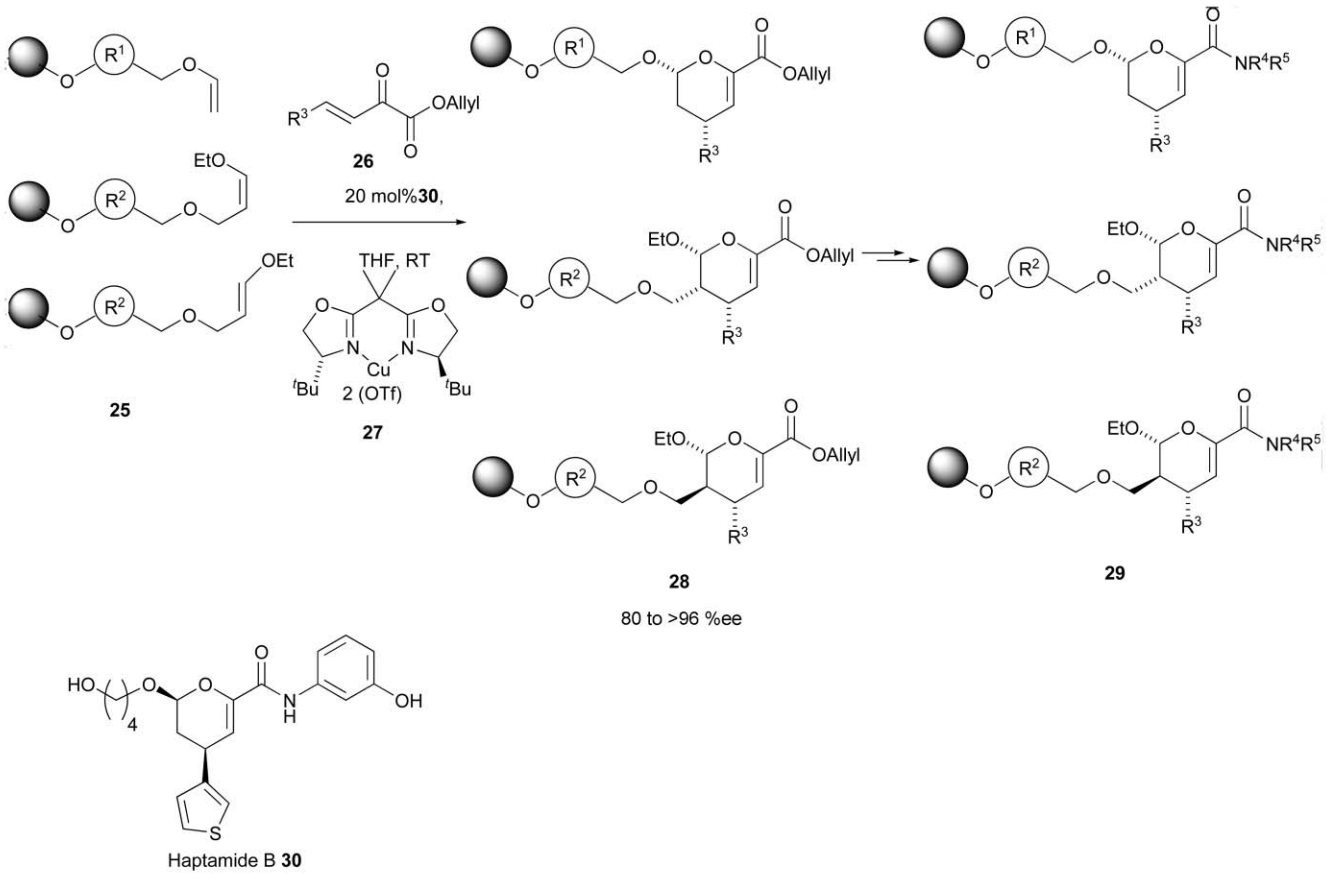


Scheme 8

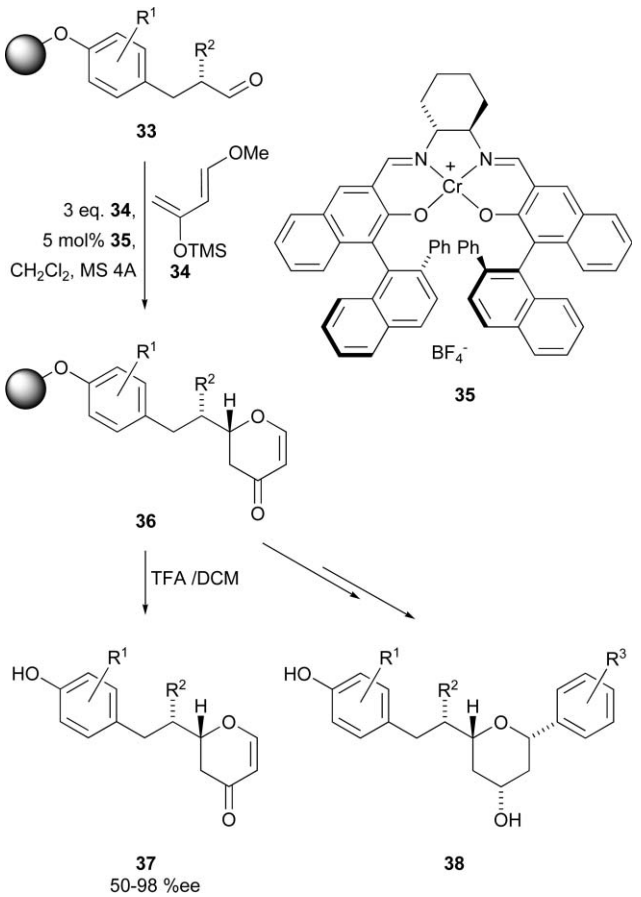
could be reduced to 2 mol%.[18] The transformation of a set of immobilized enol ethers **25** (Scheme 7) required 20 mol% of catalyst **27**[19] (which was used in both enantiomeric forms) for the enantioselective cycloaddition with 10 different heterodienes **26**. Compounds **28** were obtained with an enantiomeric excess varying from 80% to more than 96%. Cleavage of the allyl esters and subsequent coupling to a set of primary amines led to a collection of dihydropyran carboxamides **29**, which were released from the solid support in high purity ($\geqslant$ 95% in 72% of the analysed examples).

One of these compounds, called Haptamide B (**30**), was found to affect the activity of the transcription factor Hap3 *in vivo* with an IC_{50} value of 23.8 μM.[20]

The same methodology was used by Kurosu *et al.* who employed the related catalyst **31** and synthesised a set of 10 cycloadducts **32** (Scheme 8).[21] But despite the similarity of



Scheme 7

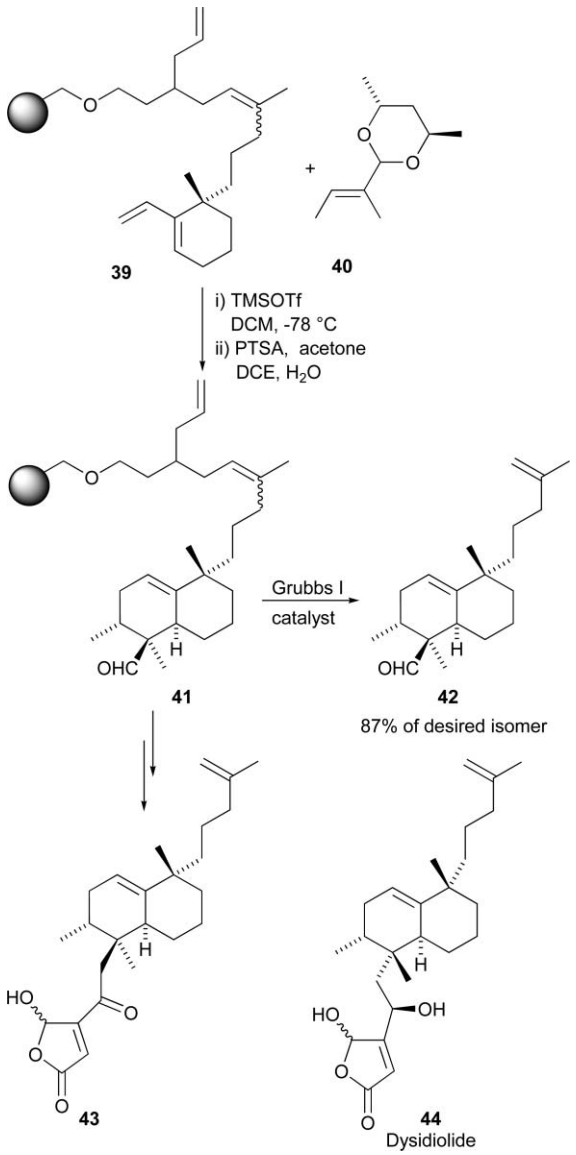


Scheme 9

catalyst, substrates and polymeric carrier to the previously described synthesis, here the authors used one equivalent of catalyst **31** to obtain the desired compounds.

Waldmann *et al.* employed an enantioselective oxa Diels–Alder reaction in order to generate a collection of 2,4,6-trisubstituted tetrahydropyrans, a scaffold that frequently occurs in natural products.[22] Resin-bound aldehydes **33** (Scheme 9) were treated with the Danishevsky diene **34** in the presence of 5 mol% of the chiral chromium catalyst **35**. The cycloadducts **36** could be released to furnish compounds **37** with > 98% enantiomeric excess in some cases. Alternatively, the polymer-bound compounds **36** were subjected to further transformations to yield the highly enantioenriched final products **38**. Interestingly, analogous reactions in solution resulted in a reversal of stereodirection when the second aryl substituent in **38** was introduced by means of a cuprate addition.

In a study to identify biologically active compounds derived from the natural phosphatase inhibitor Dysidiolide **44** (Scheme 10), Waldmann *et al.* reported the use of the chiral dienophile **40** to enhance the directing force of the resin-bound chiral diene **39**.[23] In the crucial Diels–Alder reaction to build up the bicyclic scaffold, diene **39** was treated with the tiglic aldehyde derived acetal **40** to yield compound **41**. The release of the cycloadduct by a ring closing metathesis reaction provided product **42** which displayed an *endo*/*exo* ratio of 91 : 1 and a selectivity of 95 : 5 in favour of the desired *endo*-isomer.

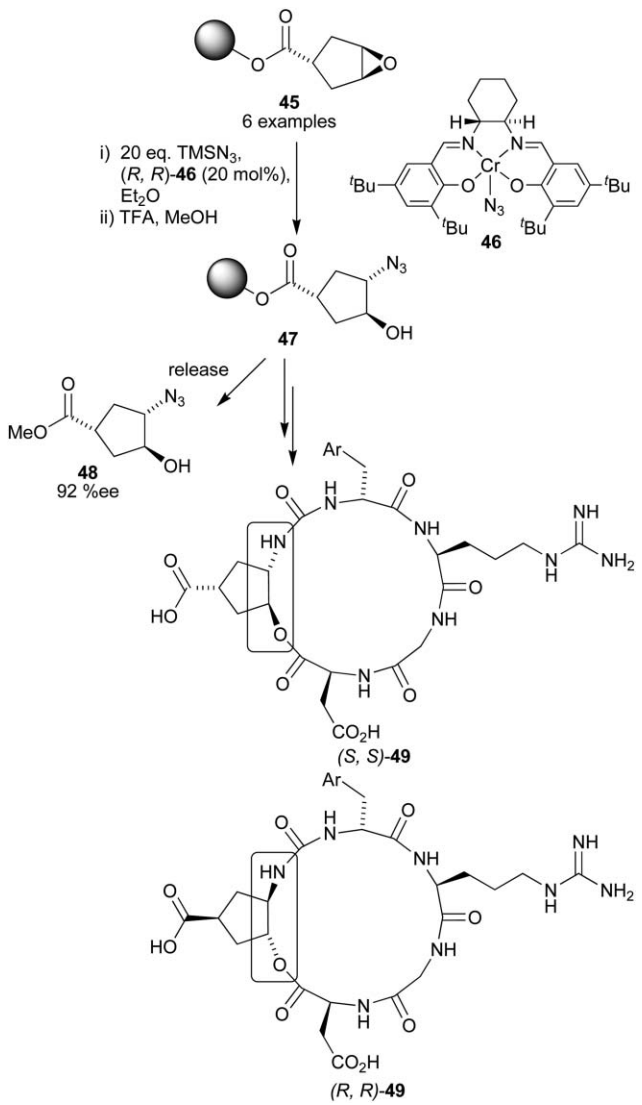


Scheme 10

Further reactions of the cycloadduct **41** led to products which could be released from the solid support by ring closing metathesis to furnish a total of eight analogues of the natural product Dysidiolide like **43**. Biological evaluation of this collection revealed inhibition of phosphatases and cytotoxic activity against different cancer cell lines, with compound **43** being the most potent inhibitor of the phosphatase Cdc25C with an IC_{50} value of 0.8 μM.

Epoxide openings

Jacobsen *et al.* used the chiral (*salen*)-chromium catalyst **46** to promote the ring opening of resin-bound *meso*-epoxides like **45** with $TMSN_3$ (Scheme 11) with 92% enantiomeric excess in the primary product **48**.[24] Further transformations led to a series of cyclic peptides that contained the Arg-Gly-Asp (RGD) sequence characteristic of integrin ligands. In an integrin binding assay, the diastereomeric compounds (*S*,*S*)-**49** and (*R*,*R*)-**49** inhibited the adhesion of integrin $\alpha_v\beta_3$ to osteopontin



Scheme 11

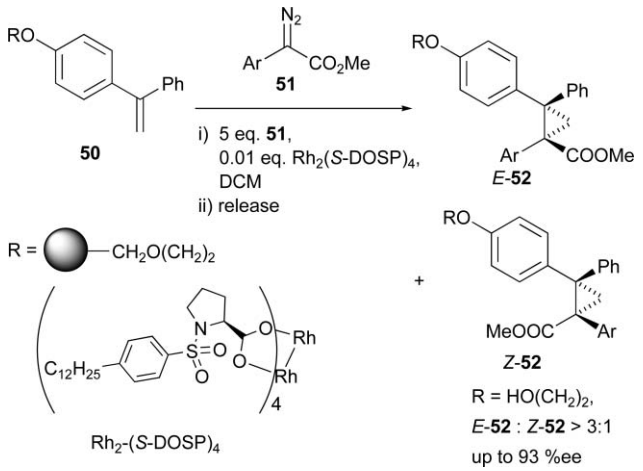
with IC_{50} values of 0.6 μM and 24 μM, respectively. This example nicely illustrates that targeting both enantiomers of an intermediate product independently may be necessary in order to explore the full and unbiased potential of the library members.

Cyclopropanations

Davies *et al.* reported an asymmetric catalytic cyclopropanation reaction of an immobilized 1,1-diarylethylene **50** (Scheme 12) with a set of seven different aryldiazoacetates **51**.[25] In this transformation, 1 mol% of the chiral catalyst Rh_2(*S*-DOSP)$_4$ was sufficient to achieve yields of more than 80% and to induce high diastereo- and enantioselectivity (*E*-**52** : *Z*-**52** > 3 : 1, up to 93% ee). Importantly, these results were consistent with solution phase studies.

Dihydroxylations

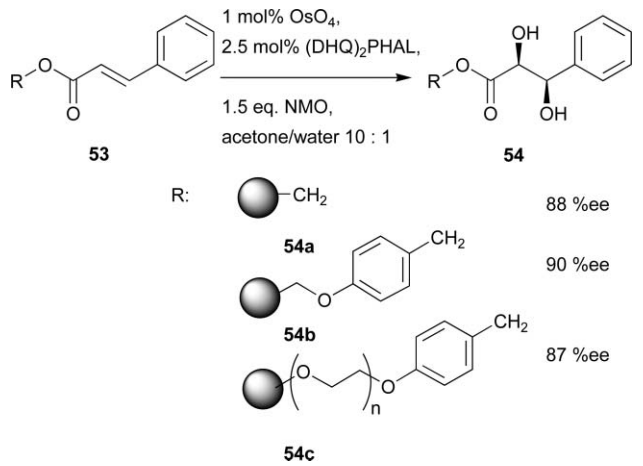
Asymmetric dihydroxylation of solid support-bound olefins was reported by Janda *et al.*[26] An investigation of the



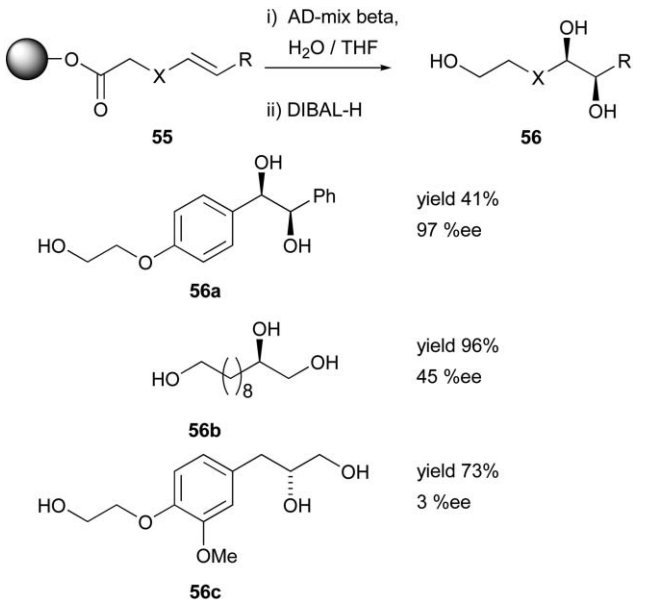
Scheme 12

asymmetric dihydroxylation of ethyl (*E*)-cinnamate **53** immobilized on different resin types demonstrated the influence of the immobilising material on the course of the reaction: when a *tert*-butanol/water mixture was used as solvent and $K_3Fe(CN)_6$ as reoxidizing agent, product **54** (Scheme 13) was only obtained in the case of the more hydrophilic TentaGel resin (**54c**), while polystyrene supports did not display any conversion. When the solvent was changed to acetone/water and *N*-methylmorpholine was used to regenerate the catalyst, the hydrophobic polystyrene resins (**54a**, **54b**) performed equally well. Remarkably, the reaction was also catalysed by a system which contained a $(DHQ)_2$PHAL-ligand bound to a soluble polymer with up to 99% ee.

This finding was complemented by a study by Berkessel *et al.* that focused more on the substrates which are bound to the solid support.[27] After investigating the asymmetric dihydroxylation of three different olefinic reactants **55** (Scheme 14), they concluded that only substrates that react with high enantioselectivity in solution are suited to the solid-phase variant of the reaction. A polymer-bound stilbene was dihydroxylated to yield compound **56a** with 97% ee (a similar substrate afforded 99% ee in a parallel solution experiment),



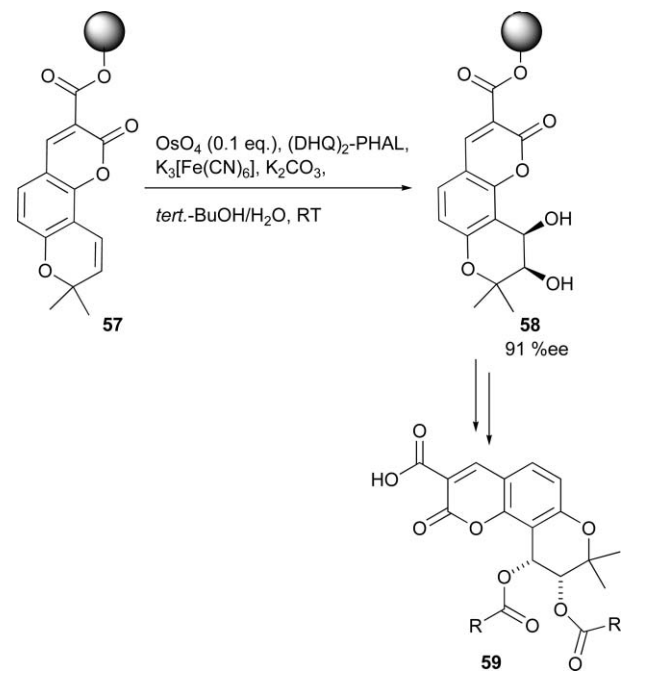
Scheme 13



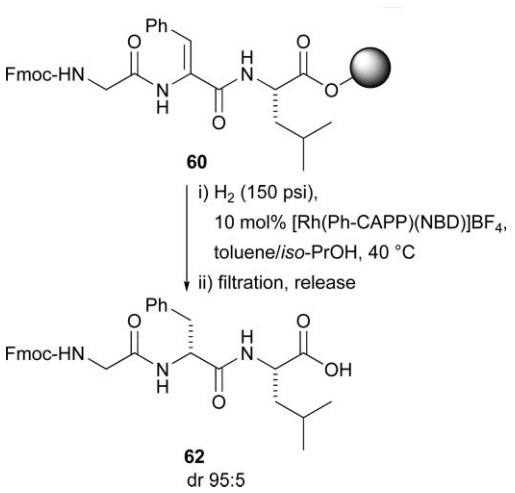
Scheme 14

while immobilized terminal alkenes yielded at most 45% ee (88% ee in solution) in the case of a linear aliphatic chain as substituent (**56b**).

Lee *et al.* developed a route to a collection of khellactones, a compound class currently under investigation as anti-HIV agents.[28] An immobilized coumarin derivative **57** (Scheme 15) was subjected to the Sharpless asymmetric dihydroxylation conditions. The resulting product **58** displayed an enantiomeric excess of 91% and could be further functionalized by esterification of the newly generated hydroxyl groups to the target compounds **59**.



Scheme 15

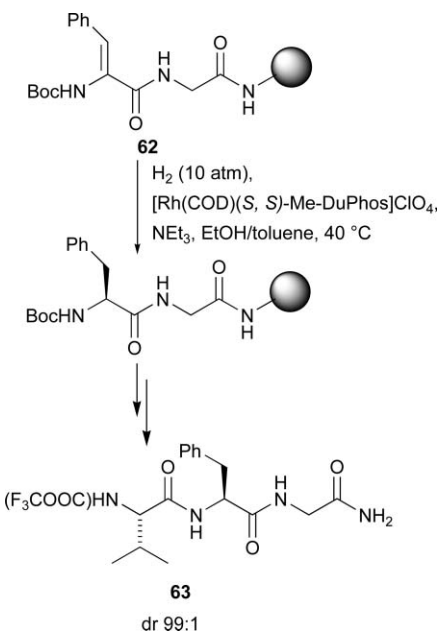


Scheme 16

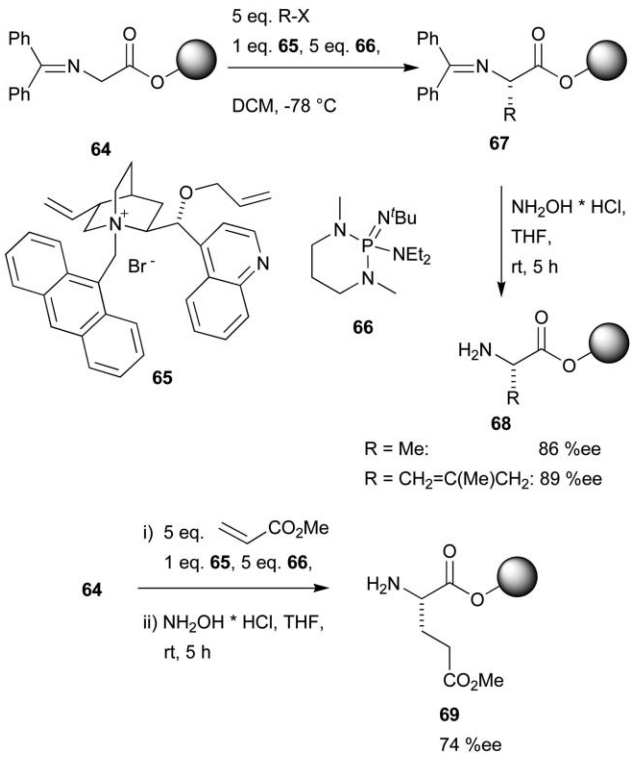
Hydrogenations

Although catalytic hydrogenations belong to the most important and industrially relevant asymmetric processes, their applications to solid phase synthesis are rare. In a pioneering study, Ojima *et al.* reported the asymmetric hydrogenation of a solid phase-bound dehydropeptide **60** (Scheme 16).[29] With 10 mol% of a chiral rhodium catalyst such as [Rh(Ph-CAPP)(NBD)]BF_4 at 150 psi hydrogen pressure, the diastereoselection went up to 95 : 5 in the product **62**, a result also found in solution-phase studies for this substrate.

In an extended study, Takahashi *et al.* hydrogenated a series of dehydroamino acids (Scheme 17).[30] A collection of dehydroarylalanines like **62** were generated by Heck-couplings on the Rink amide resin. In the presence of a Rh-Me-DuPHOS catalyst, hydrogenation proceeded with high selectivity in the



Scheme 17



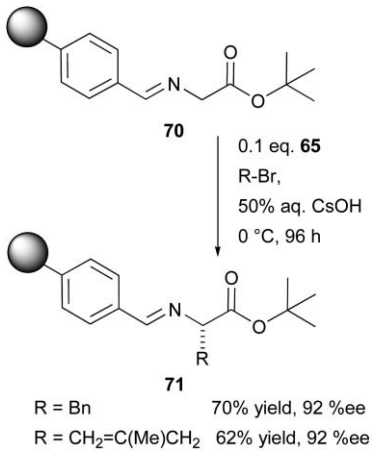
Scheme 18

released products **63** (> 94 : 4 in 20 out of 36 cases). Notably, the use of both enantiomers of the catalyst led to the same degree of induction even in the case of peptidic substrates with stereogenic carbon atoms, showing that this reaction proceeds under catalyst control. Still, although reaction times were extended to three days, more than 0.5 equivalents of the chiral catalyst were used for this transformation.

Alkylations

The enantioselective alkylation of immobilized glycine benzophenone imine **64** (Scheme 18) was investigated by O'Donnell *et al.*[31] In the presence of one equivalent of cinchonidine-derived catalyst **65**[32] and the strong Schwesinger base **66** a series of alkyl and benzyl halides reacted with almost quantitative conversion and selectivity of up to 89% ee to give the products **67**, which could be hydrolysed to give the immobilized amino acids **68**. This method was later expanded to the addition of Michael acceptors such as methyl acrylate (Scheme 18) to give compounds like **69** with 74% ee.[33]

As solution-phase reactions resulted in higher stereoselection, Park *et al.* assumed that the immobilization *via* the carboxyl group of the substrate was responsible for the diminished stereoselection.[34] In order to conserve the *tert*-butyl esters employed in solution phase experiments, they developed an imine linked substrate **70** (Scheme 19). A catalyst loading of 10 mol% and aqueous caesium hydroxide as a base were sufficient to obtain alkylated compounds **71** with selectivities of more than 90% ee for benzyl halides, demonstrating the influence of the anchoring point of the substrate on the stereoselection.



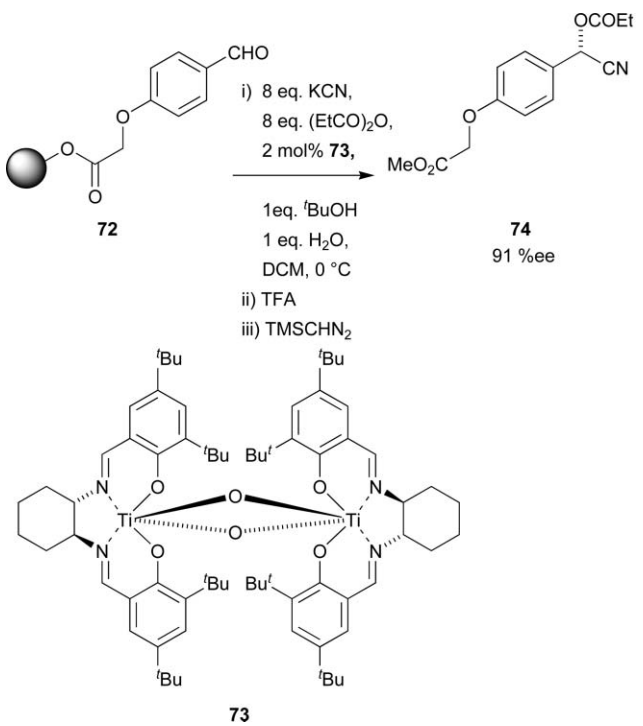
Scheme 19

Cyanohydrin synthesis

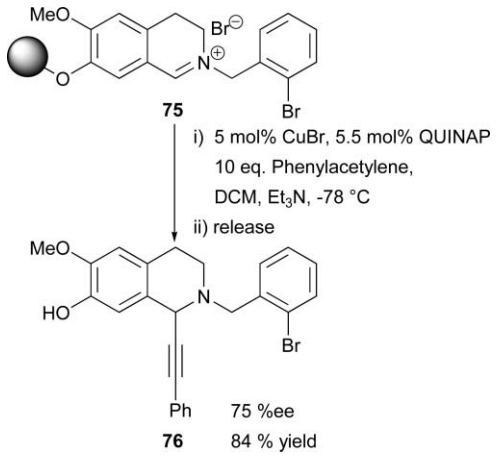
A bimetallic (*salen*)-titanium complex **73** (Scheme 20) was used by North *et al.* for the enantioselective synthesis of cyanohydrins.[35] Four electron-rich aromatic aldehydes like **72** were loaded on the solid support. A catalyst loading of 5 mol% was sufficient to induce selectivities of up to 91% ee in the reaction products **74** after release from the polymeric carrier. In this case, the transfer from solution to the solid phase required an increase in catalyst loading and temperature (0 °C instead of −90 °C to −40 °C).

Addition of acetylenes to iminium ions

In a study directed towards the development of a non-racemic variant of a previously accomplished compound collection



Scheme 20



Scheme 21

synthesis,[36] Schreiber *et al.* reported the enantioselective addition of alkynes to isoquinoline iminium ions catalysed by a copper–QUINAP system.[37] Alkylation of an immobilized dihydroisoquinoline led to compound **75** (Scheme 21), which was transformed into the reaction product **76** in the presence of 5 mol% of catalyst. When QUINAP (see Scheme 6) was used as a chiral ligand, 75% ee was obtained.

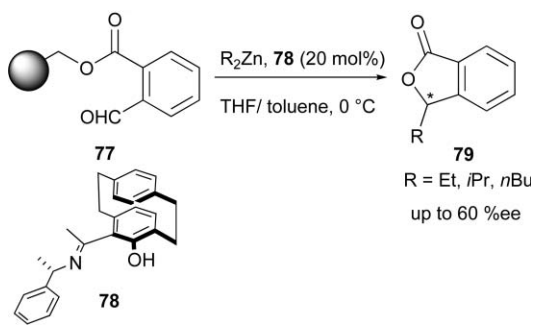
Addition of alkyl zinc reagents to aldehydes

In the course of a programme directed towards the synthesis of a collection of phthalides (benzoannelated butyrolactones), Bräse *et al.* reported the asymmetric addition of organozinc compounds to a solid phase-bound aldehyde **77** (Scheme 22).[38] Up to 60% enantiomeric excess was obtained in the released compounds **79** when the chiral [2.2]paracyclophane ligand **78** was used.

Conclusion

The examples discussed above demonstrate that enantioselective synthesis is possible on a solid support with high levels of stereoselection. Asymmetric induction on resin-bound substrates can be compared favourably with results obtained in solution-phase studies, usually after certain changes in the reaction protocol.

As different reaction types show a varying degree of sensitivity towards changes to their standard conditions, a general rule for the successful application of an asymmetric transformation to an immobilized substrate so far cannot be deduced. However, a few trends can be observed for a number of cases discussed here:



Scheme 22

In solid-phase organic synthesis, reagents are usually used in excess in order to drive the reaction to completion. Lower reaction rates, which might result from reduced accessibility and mobility of the substrates, can also be compensated in this way. Consequently, a higher consumption of precious chiral reagents frequently is the price to pay for the benefit of an enantioenriched compound collection.

Still, reactions on immobilized substrates proceed with lower velocity than in solution. But although the substrates may show a reduced reactivity, the degree of stereoselection usually does not exceed values obtained in solution.

Enantioselective catalysis has its own difficulties in solid-phase organic chemistry. The desired low catalyst loadings seem to contradict the use of excess reagent for rapid solid-phase transformations. And indeed, in some of the examples discussed above significantly higher catalyst loadings than in solution are needed in order to achieve the same degree of conversion and stereoinduction.

While a few enantioselective reaction types were successfully applied to the generation of compound collections, it is strikingly evident that the whole range of current asymmetric syntheses is not reflected by the presented examples. Interestingly, even reactions that have turned out to be highly reliable in terms of stereoselectivity in the solution phase synthesis of complex molecules, such as the Sharpless epoxidation, have found no application yet in the context of solid-phase organic synthesis.

With further improvement of such methods and their application to solid-phase synthesis and compound collection generation, combinatorial access to enantio- and diastereomerically pure sets of compounds with complex chiral scaffold architectures will be possible. This will enable the exploration of currently unaddressed regions of chemical space by means of compound collection synthesis, which is of major interest for the study of interactions of small molecules with biological systems.

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