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Chiral auxiliaries in polymer-supported organic synthesis

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Abstract—The use of chiral auxiliaries in polymer-supported organic synthesis is reviewed. In many of the examples presented, not only does the auxiliary serve as an element for inducing asymmetry into the synthesis, but it also functions as the linker for attaching the synthesis substrate to the polymer support.
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Contents

1. Introduction

The use of polymers in various formats in what is known as polymer-supported synthesis (PSS) has emerged as a versatile and powerful technique in organic synthesis.[1] This process involves the temporary attachment of synthesis substrates to a polymer carrier and thus reduces product purification and isolation to simple filtration and washing operations. Since the polymers used in PSS are usually unfunctionalized and inert to the many reaction conditions used in organic synthesis, a readily cleavable linker moiety is used to attach the synthesis substrate to the polymer.[2] Many of these linker groups are analogues of common protecting groups that are used in multi-step solution-phase syntheses.[3] As are the majority of such standard protecting groups, most linker groups used in PSS are achiral. However, chiral molecules have also been examined as linker groups in such a way that they act as chiral auxiliaries[4] in asym-

metric PSS.[5] This review summarizes the literature describing the use of such chiral linkers and other chiral auxiliaries in PSS. The examples presented herein are organized according to the functional group of the auxiliary that is used to attach the synthesis substrate. This review does not cover the use of polymer-bound chiral ligands that are used in conjunction with metals and metalloids in asymmetric catalysis since this subject has already been extensively reviewed elsewhere.[6] Furthermore, chiral organic catalysts[7] attached to polymer supports have been recently reviewed,[8] and hence are not covered here.

In the field of PSS, the use of insoluble polymers is most common in what is known as solid-phase organic synthesis and most of the chiral auxiliary applications presented in this review are used in this context. However, soluble polymers are also frequently used as synthesis supports[9] and chiral auxiliaries used in this context are also presented. Additionally, the use of fluorous technologies for phase separations in organic synthesis is conceptually related to PSS and is becoming more widespread.[10] Therefore, an example in the use of

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a chiral auxiliary/linker in conjunction with this technology is included here. This review covers the literature through to the end of September, 2003.

2. Alcohol and carbohydrate-based auxiliaries

In 1972, Kawana et al. reported the first example of a polymer-supported chiral auxiliary in asymmetric synthesis.[11] In this work, both D- and L-1,2-O-cyclohexylidene-α-xylofuranose were used as chiral auxiliaries in the asymmetric synthesis of α-hydroxy acids (Scheme 1). The auxiliary was attached to polystyrene by a trityl linker via its primary hydroxyl group. The thus formed polymer-bound secondary alcohol **1** was esterified with both benzoylformic acid and pyruvic acid to form esters **2**, which were subsequently subjected to a Grignard reaction. The thus formed products were cleaved from the polymer by saponification to afford the desired chiral α-hydroxy acids **3** in yields ranging from 18% to 84%, with ee's of between 36% and 65%. The authors also reported that the recovered polymer could be used repeatedly with essentially no decrease in both the observed yield and enantioselectivity.
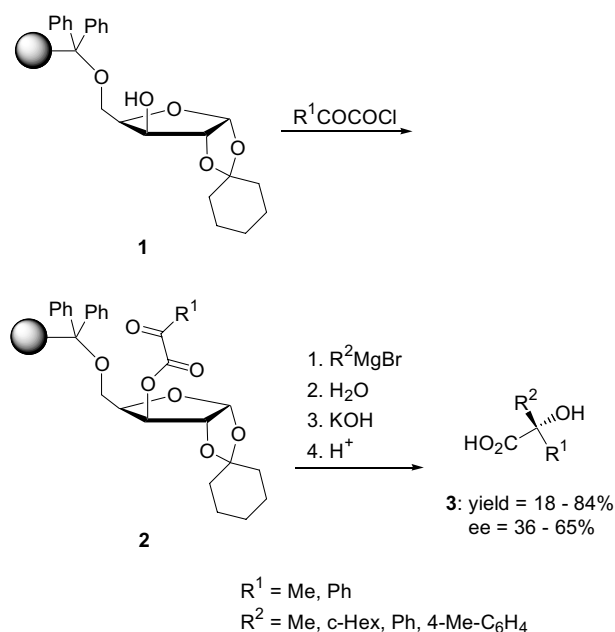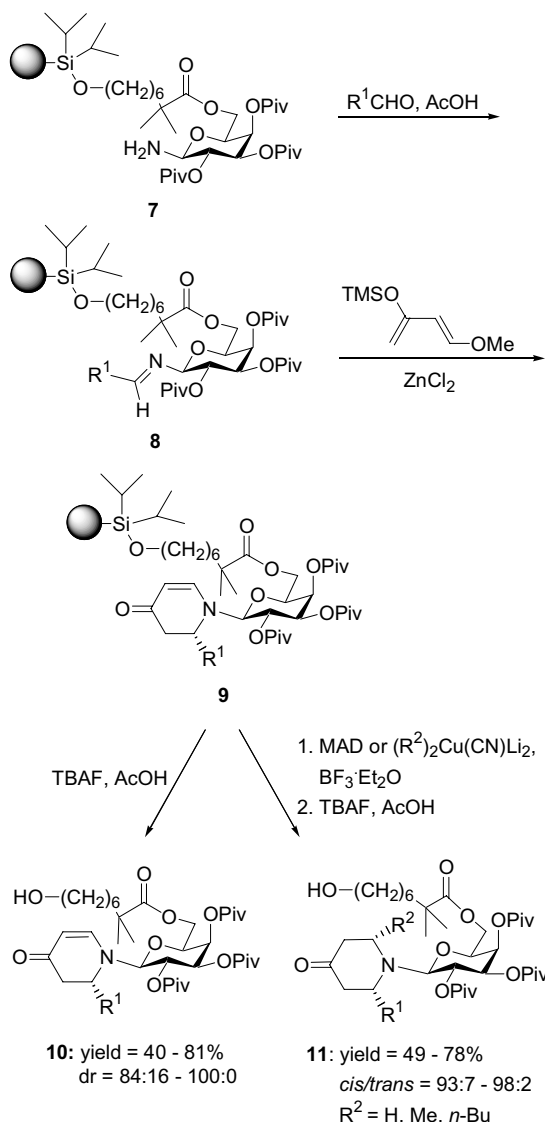

Scheme 1.

In an application of a different chiral carbohydrate-based auxiliary, Kunz and co-workers have recently reported the solid-phase adaptation of the Ugi four-component condensation reaction.[12] Chiral O-pivaloylated galactosylazide was attached to Wang resin through a tetramethyl azelaic acid spacer and reduced to serve as an equivalent of 'asymmetric ammonia' (Scheme 2). It was found that the use of a shorter, amide-based linker led to sluggish reactions. The azide functional group was reduced to the corresponding amine group without anomerization by treatment with propane-1,3-dithiol and base to afford **4**. A one-pot condensation of
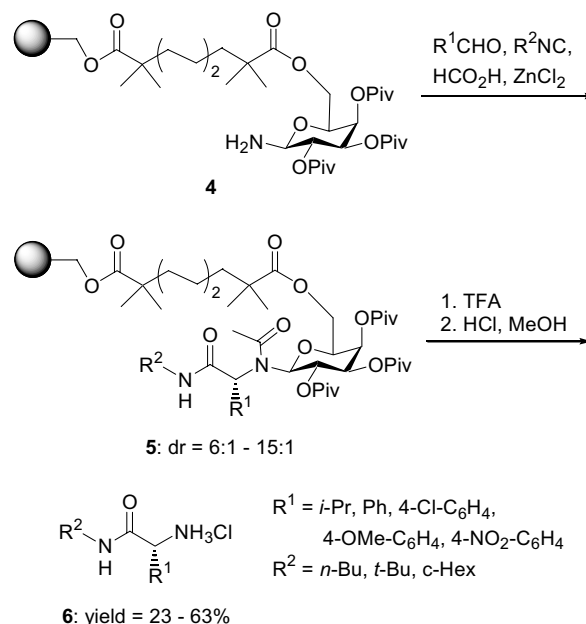
Scheme 2.

the resin-bound amine **4** with an aldehyde, formic acid, and an isonitrile (5 equiv of each) in the presence of zinc chloride at low temperature afforded the desired immobilized amino acid derivatives **5**. The diastereomeric ratios of the thus formed products **5** were determined to range from 6:1 to 15:1 by acid cleavage of the spacer-auxiliary-amino acid conjugate from the resin followed by HPLC analysis. This conjugate was treated with acidic methanol to afford the desired amino acid derivatives **6**. The generality of this method was established by using five different aldehydes and three different isonitriles to afford products **6** in 23–63% yield.
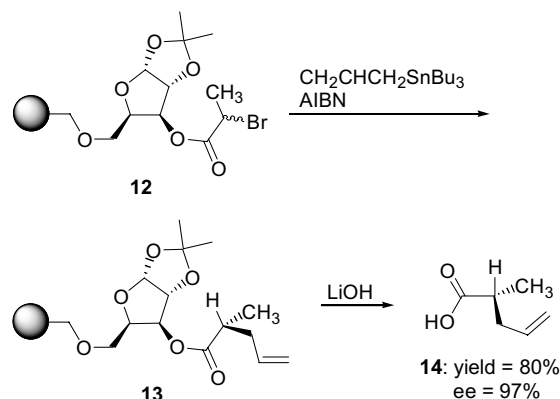
More recently, Kunz and co-workers have used the same galactosyl amine in domino Mannich–Michael condensation reactions for the asymmetric synthesis of structurally diverse chiral piperidine derivatives.[13] The spacer used in this study was a hydroxy acid instead of the diacid used previously. This allowed for the attachment of the auxiliary to the polymer using a silyl ether linkage (Scheme 3). Reduction of the immobilized azide was accomplished as before and the resulting amine **7** condensed with an aldehyde in the presence of acetic acid to obtain the polymer-bound imine **8**. Alkyl and aryl aldehydes (17 total) were used in this step. Imines **8** were then treated with electron-rich Danishefsky's diene in the presence of zinc chloride to afford the corresponding resin-bound didehydropiperidinones **9**, via a domino Mannich–Michael condensation reaction. As before, the linker-auxiliary-product conjugates were cleaved from the resin in order to determine the diastereomeric ratios of the products. The thus synthesized 2-substituted N-galactosyl-5,6-dehydropiperidin-4-ones **10** were obtained in 40–81% yield (purity generally >90%) with diastereomeric ratios that ranged from 80:20 to 100:0. It is noteworthy that the condensation reactions carried out to form **8** occurred without the anomerization that was observed in the analogous solution-phase reaction.

Scheme 3.

Scheme 4.

afforded acid **14**, in good yield (80%) with excellent ee (97%). It should be noted that attempts to use Lewis acids resulted in cleavage of the sugar auxiliary from the polymer at the benzyl ether site.

Enholm and Cottone also reported on the first example of an asymmetric radical cyclization on a soluble polymer support.[15] In this case, a (+)-isosorbide chiral auxiliary was used as the stereocontrol element with the norbornyl succinimide-derived polymer **15**, prepared by ring opening metathesis polymerization, acting as the polymer support (Scheme 5). An *ortho*-substituted cinnamic acid was attached to the auxiliary as an ester to prepare the 6-heptenyl radical cyclization substrate **16**. A variety of cyclization conditions were assayed and it was found that treatment of **16** with tributyltin hydride in the presence of triethylborane and zinc chloride afforded the best results for the formation of **17**. This initiator–Lewis acid combination produced the desired product **18** in 80% yield with greater than 99% ee after saponification to remove it from the polymer.

Additionally, the polymer-bound enaminones **9** were subjected to conjugate addition reactions by treating with both methylaluminum bis[2,6-di-*tert*-butyl-4-methyl-phenoxide] (MAD) and cyano-modified Gilman reagents in the presence of boron trifluoride etherate. Following cleavage from the polymer, the thus formed 2,6-disubstituted piperidinones **11** were obtained in 49–78% yield with *cis/trans* ratios ranging from 93:7 to 98:2.
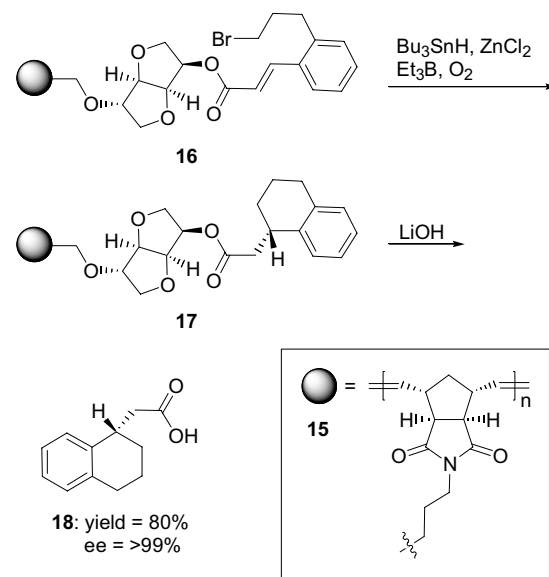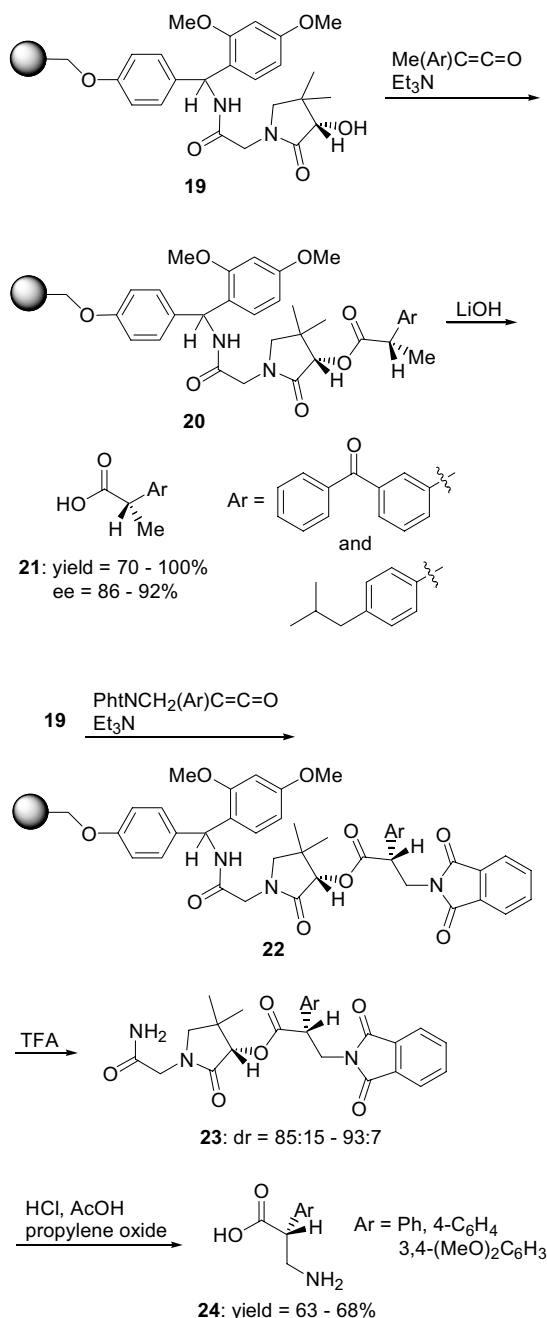
Enholm et al. have also used polymer-supported carbohydrate-based auxiliaries to induce asymmetry. Their first report described radical allylation reactions on a soluble polystyrene support.[14] An enantiopure D-xylose derivative was attached to soluble, non-cross-linked polystyrene via its primary hydroxyl group (Scheme 4). The secondary alcohol group of the auxiliary was subsequently esterified with bromoacetic acid to afford the allylation substrate **12**. Treatment of this bromoester with allyltributyltin in the presence of AIBN under thermal initiation conditions afforded allylated **13**. Subsequent product cleavage with lithium hydroxide

Scheme 5.

Calmes and co-workers have reported using a panto-lactone-based auxiliary in stereoselective reactions with prochiral ketenes.[16] In their first report, polymer-bound alcohol **19** was reacted with two different aryl ketenes to afford esters **20** (Scheme 6).[16a] The thus formed chiral propionic acids **21** were then cleaved from the resin by lithium hydroxide in high yield with high ee.
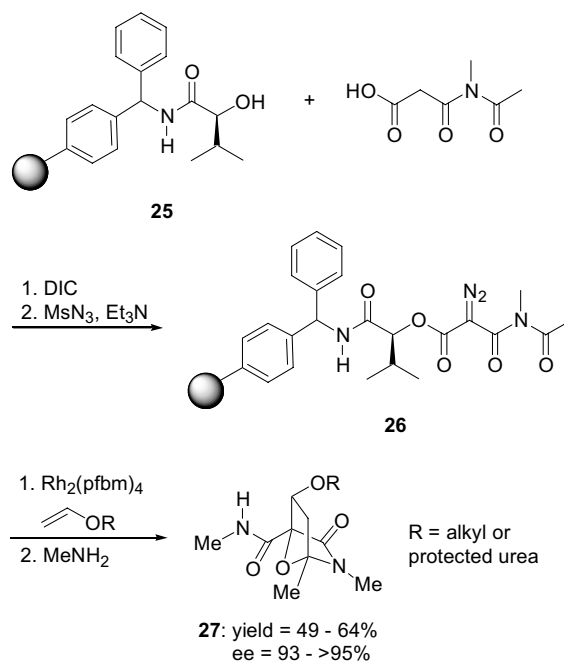
then cleaved so that the diastereomeric ratios of the products **23** could be determined. Finally, the auxiliary was cleaved to afford the desired β²-homoarylglycines **24** in 63–68% yield.

Diastereoselective 1,3-dipolar cycloaddition of isomünchnones with vinyl ethers on solid support has been reported by Savinov and Austin.[17] The chiral auxiliary α-hydroxyvaline was attached to benzhydryl amine resin to afford **25**, which was then acylated and diazotized to produce diazoimide **26** (Scheme 7). This was then subjected to Rh(II)-catalyzed nitrogen extrusion and treated with a variety of vinyl ethers. Cleavage of the thus formed cyclization products was achieved by treatment with methylamine in methanol and afforded bicyclic products **27** in 49–64% yield with ee's ranging from 93% to greater than 95%.

Scheme 6.

Scheme 7.

3. Amine and hydrazine auxiliaries

The same authors have also reported using the polymer-supported chiral auxiliary **19** to prepare β²-homoaryl-glycines **24** (Scheme 6).[16b] In this work, protected amine containing ketenes were used to prepare esters **22** in a manner analogous to the previous synthesis of **20**. The benzhydryl amide bond at the Rink linker group was

In another early report, Lenzoff and co-workers demonstrated the first use of a polymer-supported chiral amine auxiliary.[18] The potassium salt of (*S*)-2-phthal-amido-1-propanol was reacted with Merrifield resin, followed by treatment with sodium iodide and tribu-tyltin hydride to remove any residual benzyl chloride groups, and finally hydrazinolysis to deprotect the chiral amine to produce **28** (Scheme 8). Treatment of the auxiliary with cyclohexanone afforded the polymer-bound imine **29**, which was deprotonated with LDA. Alkylation of the thus formed metalloenamine with methyl and propyl iodide afforded the α-substituted imines **30** that were cleaved with acid to afford the 2-alkylated cyclohexanones **31** in 80% yield with ee's of
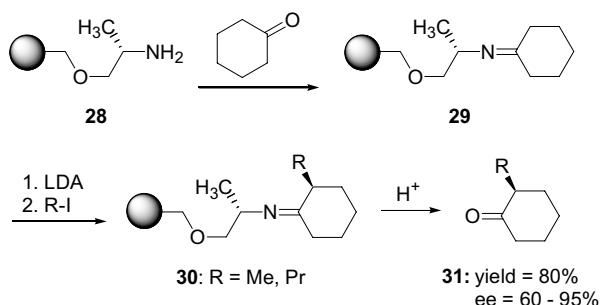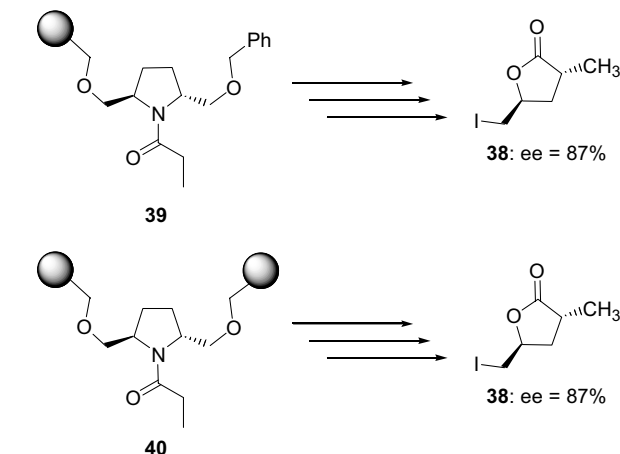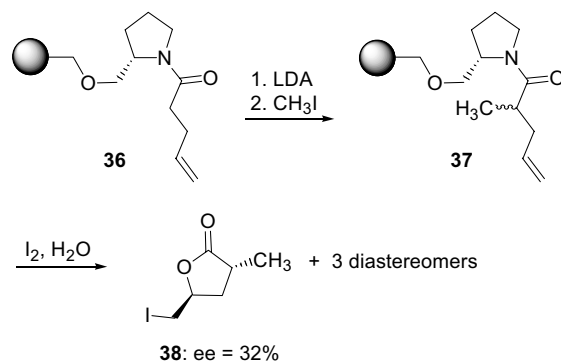
Scheme 8.

95% and 60%, respectively. It was noted that the recovered chiral auxiliary could be reused with only slight loss of capacity but with no decrease in stereoselectivity.

Fréchet et al. have also studied the asymmetric polymer-supported alkylation of cyclohexanone.[19] In their report, chiral immobilized phenethylamine **32** was used as the auxiliary (Scheme 9). This allowed for the chiral moiety to be attached directly to the polymer backbone, rather than through an intermediate ether linkage. Using this auxiliary, the imine **33** was formed and alkylated in a manner similar to that used by Lenzoff et al., to produce **34**. The product cyclohexanone **35** was then cleaved from the polymer and isolated in 75% yield and 61% ee.
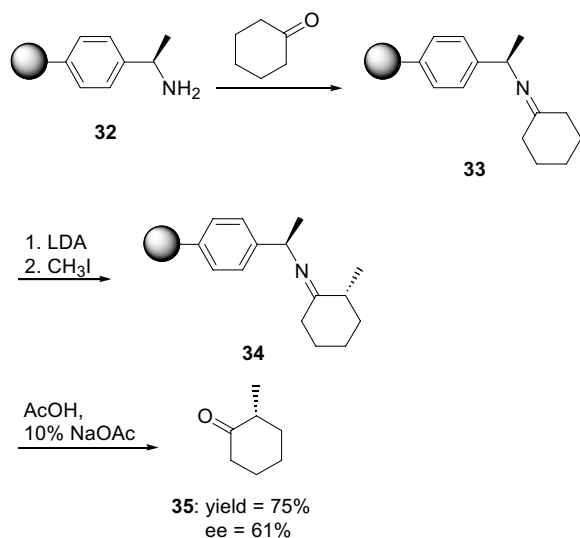
Scheme 9.

Asymmetric solid-phase iodolactonization has been reported by Schore and co-workers.[20] Prolinol was used as the chiral auxiliary to attach the cyclization substrate via acylation of the ring nitrogen, as in **36** (Scheme 10).[20a] Alkylation of this amide, to afford **37**, was followed by iodocyclization to yield the desired lactones **38**, which were released from the polymer during the cyclization step. A mixture of the four possible α-substituted γ-butyrolactones **38** was obtained in 33% overall yield. In these reactions *trans* selectivity was favored, with the
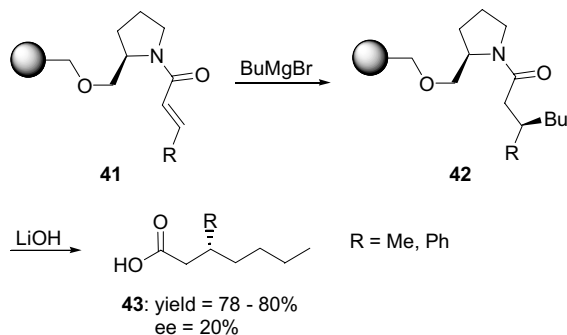

Scheme 10.

ratio of *trans/cis* 94:6 observed in the product mixture, with the major product **38** (shown) being obtained with 32% ee. The authors also demonstrated the reusability of the polymeric chiral auxiliary.

More recently, the same authors have reported using the related pseudo-C_2-symmetric **39** and C_2-symmetric **40** auxiliaries in the same reaction (Scheme 10).[20b,c] Using an identical alkylation–iodolactonization sequence, product **38** was obtained with exclusively *trans* selectivity and 87% ee in both instances.
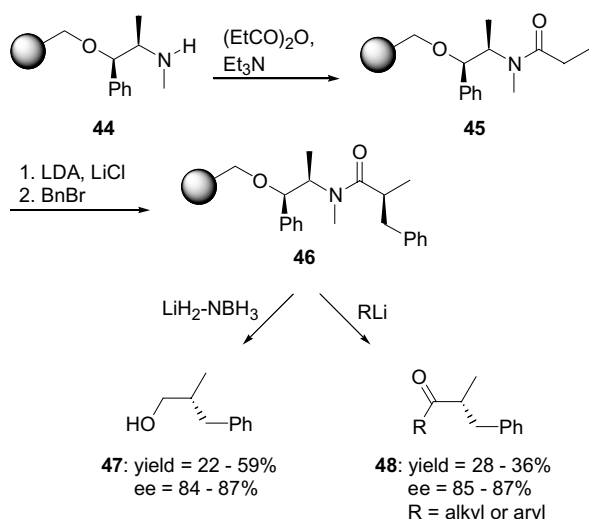
Huang et al. have used polymer-supported prolinol as an auxiliary in asymmetric Michael addition reactions.[21] The ring nitrogen of the supported prolinol was acylated to afford the *N*-enoylprolinols **41** (Scheme 11). These
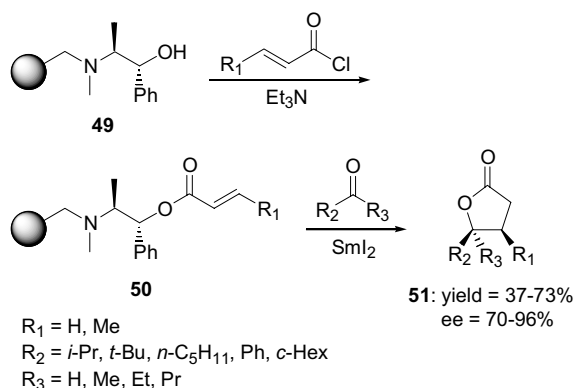

Scheme 11.

were then subjected to Grignard addition with butyl-magnesium bromide to afford **42**, followed by treatment with base to yield the desired acids **43**. (S)-3-Phenyl-heptanoic acid and (S)-3-methylheptanoic acid were obtained in 80% and 78% yield, respectively, and both with 20% ee. While the enantioselectivities of these reactions were low, the authors reported that they are in fact higher than what is observed in analogous solution-phase reactions.

Procter and co-workers have used polymer-supported pseudoephedrine as a chiral auxiliary in solid-phase enolate alkylation reactions.[22] Pseudoephedrine was immobilized onto the resin via its hydroxyl group, as in **44**, leaving the secondary amine group free for acylation (Scheme 12). Treatment of **44** with propionic anhydride in the presence of triethylamine afforded the alkylation substrate **45**. This was deprotonated with LDA and alkylated with benzyl bromide (shown) or iodobutane to afford **46**. Primary alcohols **47** were obtained via reduction of **46** with lithium amidotrihydroborate in 22–59% yield and 84–87% ee. Ketones **48** were obtained by treatment of **46** with both alkyl and aryl organolithiums in 28–36% yield and 85–87% ee. Heteroaromatic ketones were prepared with high ee's by treatment with 2-lith-iothiophene and 2-lithio-5-methylfuran.
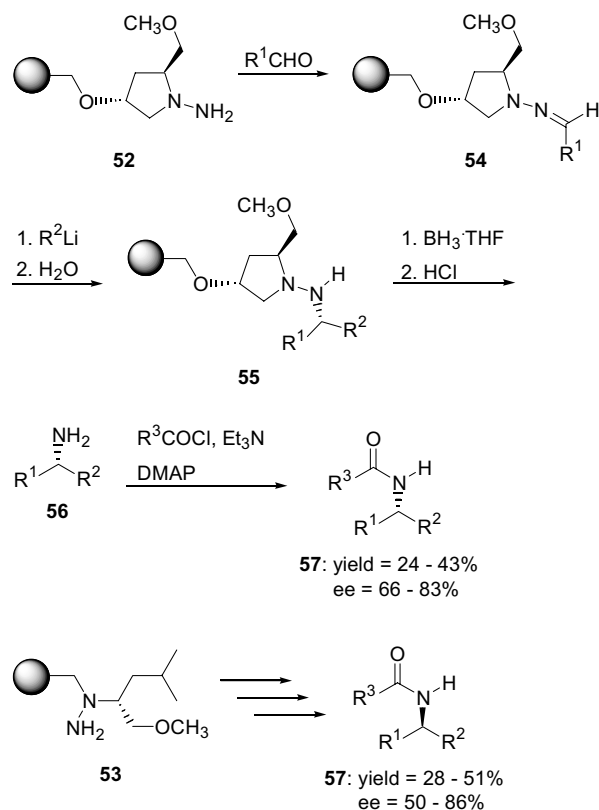

Scheme 13.

Enders et al. have reported the asymmetric synthesis of α-primary amines using polymer-supported hydrazine auxiliaries.[24] Two enantiopure β-methoxyamino auxiliaries derived from *trans*-hydroxy-(S)-proline and (R)-leucine, were attached to polystyrene resin and then transformed to hydrazines **52** and **53**, respectively (Scheme 14). The hydrazine auxiliaries were first cou-

Scheme 12.

Procter and co-workers have also reported the asymmetric synthesis of γ-butyrolactones using polymer-supported ephedrine as a chiral linker.[23] In this report, the auxiliary was immobilized through the nitrogen center rather than via the oxygen atom. The ephedrine resin **49** was treated with acryloyl chloride or crotonyl chloride to afford the corresponding esters **50** (Scheme 13). These were added to carbonyl compounds followed by SmI₂ at low temperatures to afford γ-butyrolactones **51**, in what are referred to as 'catch-release' reactions. A range of aldehydes and ketones were used and the products **51** isolated in 37–73% yield and 70–96% ee. The authors note that the release of the substrate from the auxiliary during the cyclization should allow for **49** to be directly recycled.
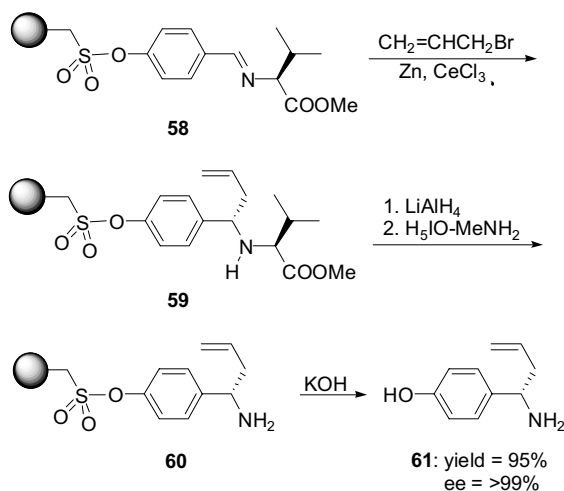

Scheme 14.

pled to excess aliphatic and aromatic aldehydes to afford hydrazones **54**. Subsequent nucleophilic addition reactions to these hydrazones with organolithium reagents gave hydrazines **55**. The products were cleaved from the polymers by reductive cleavage with borane to afford the desired α-branched primary amines **56** in 24–51% yield. In order to determine the ee's of the amines **56**, they were acylated with acetyl and benzoyl chloride to form the amides **57**. The observed ee's ranged between 50% and 86%. The two auxiliaries afforded comparable chemical yields and enantioselectivities.

Itsuno et al. have reported the asymmetric allylation of polymer-bound chiral imines.[25] In this case, the chiral auxiliary did not serve as the linker between the resin and synthesis substrate (Scheme 15). The polymer-bound imine **58** was treated with zinc, cerium trichloride, and allyl bromide to afford the desired allylated product **59**. The chiral auxiliary was then detached by reduction of **59** with lithium aluminum hydride followed by treatment with hydroiodic acid and methylamine to afford the corresponding amine **60**. Finally, treatment with base afforded the desired homoallylamine **61** in 95% yield with ee >99%.

Scheme 15.

4. Oxazolidinone auxiliaries

Evans' oxazolidinones are amongst the most efficient and widely used chiral auxiliaries in traditional solution-phase asymmetric synthesis. They are easily synthesized from readily available starting materials and afford high enantioselectivities in a broad range of reactions that involve enolate intermediates. Therefore there has been much interest in immobilizing them onto polymer supports as linker groups so that they can easily be recovered and reused. The first such report was published by Allin and Shuttleworth.[26] They reported that the chiral auxiliary derived from (S)-serine could be efficiently attached to polystyrene resin (Scheme 16). Acylation of the auxiliary by treatment with propionic anhydride
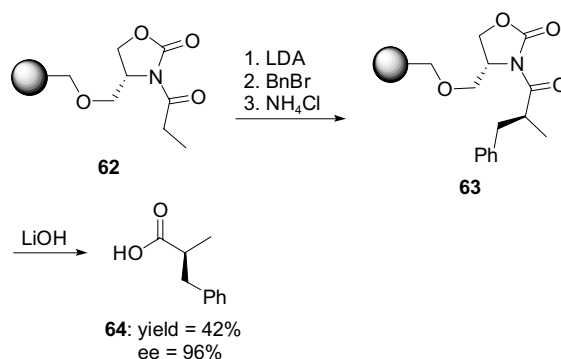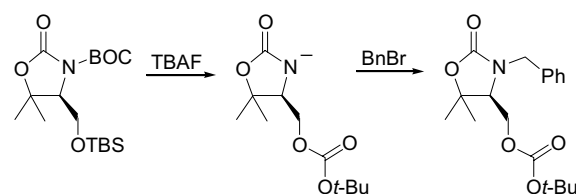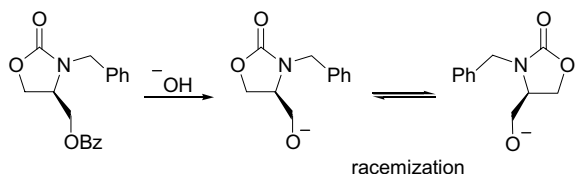

Scheme 16.

under basic conditions afforded the desired amide **62**. Alkylation of this was accomplished by deprotonation using LDA and subsequent addition of benzyl bromide to afford **63**. It was reported that basic hydrolysis of this alkylation product afforded the α-benzylated acid **64** in 42% yield with 96% ee.

These findings by Allin and Shuttleworth have been disputed by Davies and co-workers.[27] They report that both exocyclic and endocyclic rearrangements occur when serine derived oxazolidinones are coupled to resins (Scheme 17). These rearrangements may lead to the incorrect attachment of the oxazolidinone to resin and racemization of the originally enantiopure auxiliary.

Scheme 17.

In the original report, the hydroxyl group of the auxiliary was deprotected using TBAF prior to its immobilization on the resin. When this reaction was performed on a model system, the thus formed alkoxide readily underwent intramolecular attack at the N-Boc carbonyl center, resulting in migration of the protecting group to afford an O-Boc-oxazolidinone (Scheme 17, exocyclic rearrangement). Hence, the nitrogen anion underwent alkylation. For this reason, Davies et al. propose that in the report by Allin and Shuttleworth, the oxazolidinone was actually attached to the resin through the nitrogen atom, rather than as desired through the oxygen atom.

Moreover, they cite the report by Katsumura et al. that the alkoxide ion of the serine-derived oxazolidinone undergoes 5-*endo*-cyclic rearrangement via intramolecular attack at the oxazolidinone carbonyl center (Scheme 17, endocyclic rearrangement).[28] As a result, racemic *N*-benzyl-oxazolidinone is obtained and thus it is not possible to obtain an enantiopure enolate alkylation product, as previously reported by Allin and Shuttleworth.
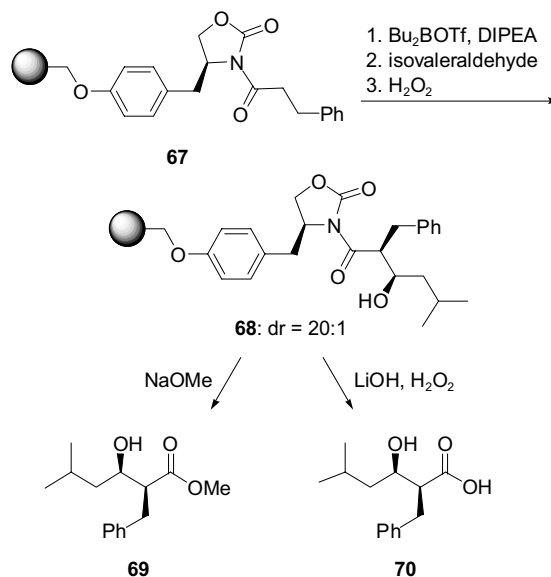
Burgess et al. have reported results of attaching a tyrosine derived oxazolidinone auxiliary to a variety of polymer supports, with and without another intermediate linker group.[29] This auxiliary was attached through its phenolic hydroxyl group to polystyrene, polystyrene with the Wang linker and Tentagel (Scheme 18). The auxiliary was acylated with propionic anhydride prior to attachment to the polymer to form **65**. The substrate was deprotonated with LDA and then treated with benzyl bromide. Reductive cleavage with lithium borohydride afforded the desired α-benzylated alcohol **66**. The authors state that by comparison of ee's and reaction times, polystyrene with the Wang linker is the preferred support because it afforded reasonably high ee and good yield even after extended reaction times. Furthermore, these authors comment that based on well known solution-phase chemistry, they anticipate that their tyrosine-based auxiliary would afford higher ees compared to the previously mentioned serine-based auxiliary and that they find it 'surprising' that the opposite was observed (96% ee reported with the serine-based auxiliary and 55% ee observed with the tyrosine-based auxiliary).

Scheme 19.

their product by comparison to a sample prepared independently.

Phoon and Abell have reported aldol and conjugate addition reactions also using the polymer-bound tyrosine-based oxazolidinone **65**.[31] The chiral auxiliary was synthesized and attached to the resin as before.[29] After enolization with triethylamine in the presence of dibutylboron triflate, benzylaldehyde was added to afford the polymer-bound aldol adduct **71** (Scheme 20). The α-
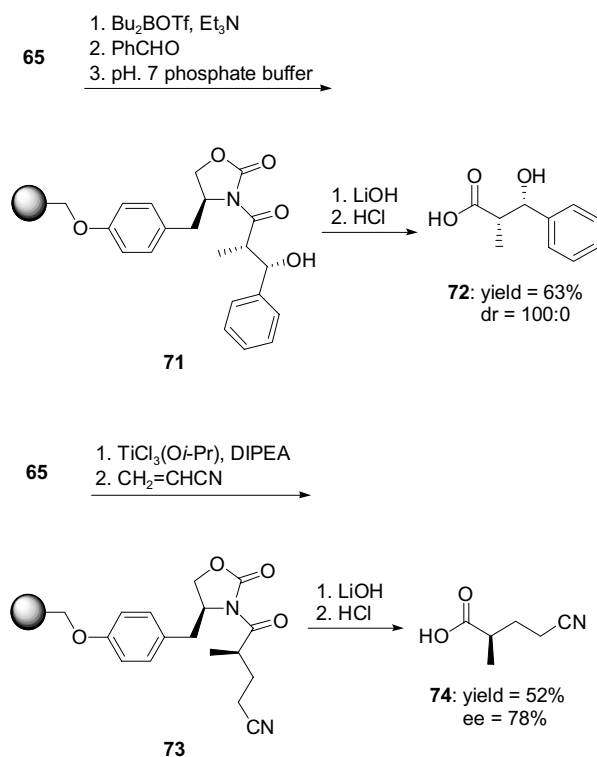

Scheme 18.

The asymmetric synthesis of α-substituted β-hydroxy acid derivatives using the tyrosine-based auxiliary has been reported by Purandare and Natarajan.[30] The polymer-bound oxazolidinone was acylated with hydrocinnamoyl chloride to afford **67** (Scheme 19). This was enolized using Hunig's base and dibutylboron triflate, and then finally treated with isovaleraldehyde to furnish the polymer-bound aldol product **68**. The cleaved product could be isolated as the methyl ester **69** when sodium methoxide was used in the detachment step. Alternatively, the acid **70** was obtained via lithium hydroxide/hydrogen peroxide cleavage. The authors report that essentially only one diastereomer (20:1) was formed and they confirmed the *syn* stereochemistry of
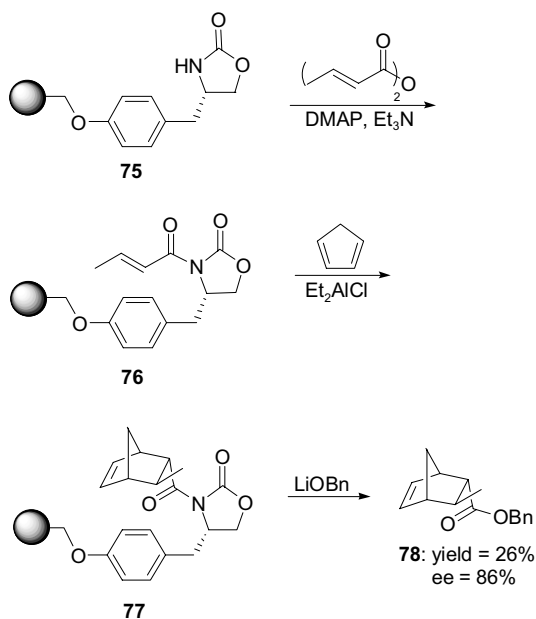

Scheme 20.

substituted β-hydroxy acid product was detached from the polymer by treatment with lithium hydroxide in 63% yield to afford **72** as a single diastereomer.

Additionally, *N*-propionyl resin **65** was enolized by Hunig's base under titanium-mediated conditions, and was subsequently treated with acrylonitrile. The 1,4-conjugate addition adduct **73** was cleaved from the resin by treatment with lithium hydroxide. The product, α-methylated 3-cyanobutyric acid **74** was obtained in 52% yield with 78% ee.

An asymmetric solid-phase Diels–Alder reaction using the tyrosine-based oxazolidinone auxiliary has been reported by Winkler and McCoull.[32] As opposed to the previous examples, these authors prepared the oxazolidinone on the polymer by first attaching protected tyrosine through its phenolic hydroxyl group to polystyrene resin and then elaborated it into the auxiliary structure **75**. This was acylated by treating it with in situ generated *trans*-crotonic anhydride to afford **76**, which was then treated with diethylaluminum chloride (Et₂AlCl) and cyclopentadiene to afford the Diels–Alder cycloaddition adduct **77** (Scheme 21). The product **78** was cleaved from resin using lithium benzyloxide in 26% yield with 86% ee. These results are in good agreement with those observed in the analogous solution-phase reaction. Additionally, the authors report that the use of the Wang linker to attach the auxiliary to the polystyrene resin did not allow for any desired product to be isolated. They speculate that this is due to the incompatibility of the linker to the Lewis acid catalyst.

Scheme 21.

Faita et al. have reported the use of the tyrosine-based oxazolidinone auxiliary in asymmetric 1,3-dipolar cycloaddition reactions involving mesitonitrile oxide and diphenylnitrone.[33] The *N*-acylated oxazolidinone **76** was treated with 1,3-dipolar reagents to give the corre-

sponding polymer-bound cycloadducts (Scheme 22). The reaction of **76** with mesitonitrile oxide afforded isomeric cycloadducts **79** and **80**. The products **81** and **82** were subsequently released from the polymer by reduction with sodium borohydride. Reaction of **76** with diphenylnitrone afforded isomeric cycloadducts **83** and **84**. Product release was achieved as before to yield **85** and **86**. Generally, the reactions with diphenylnitrone were sluggish and afforded low yields of the desired products and the presence of a catalyst such as magnesium perchlorate strongly influenced the reactivity and changed the stereoselectivity of the nitrone cycloadditions.[33b] The authors also noted that the polymer-supported auxiliary gave slightly lower yields and enantioselectivities than did the analogous solution-phase reactions and that upon more than one reuse, the
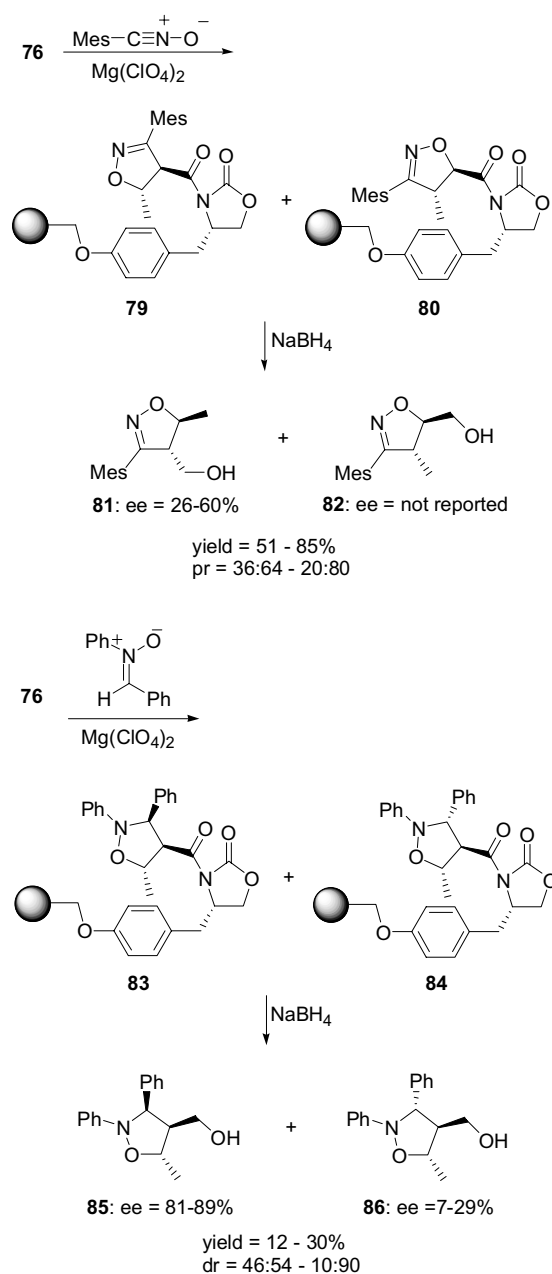
Scheme 22.

enantioselectivity afforded by the auxiliary was reduced still further. They have also reported using a soluble polymer to support the oxazolidinone and was used in the nitrone cycloaddition reactions.[33c] This soluble polymer allowed for higher loading, easier characterization of the reaction intermediates, and more desirable interactions between the metal cations and the coordinating substrates as compared to the previous solid-phase reactions.

Fluorous synthetic methodologies are similar to polymer-supported synthesis techniques in that the physical properties of the fluorine containing synthesis carrier are used to selectively manipulate it in order to simplify product purification.[10] In this regard, a fluorous version of an oxazolidinone chiral auxiliary has been reported by Hein and Hultin and used in asymmetric aldol reactions.[34] Fluorous oxazolidinones **87** and **88** were prepared from (*S*)-phenylalanine (Scheme 23). The *syn*-*N*-propionyl fluorous oxazolidinone **89** was converted to its titanium enolate and then reacted with several aldehydes. After hydrolysis, the *syn*-hydroxy acids **90** were isolated in 74–94% yield with >99% ee.
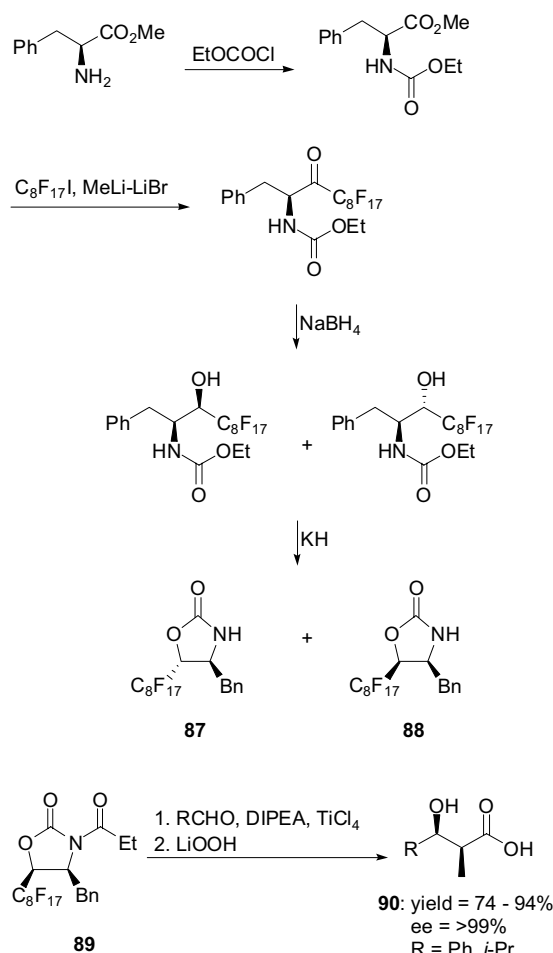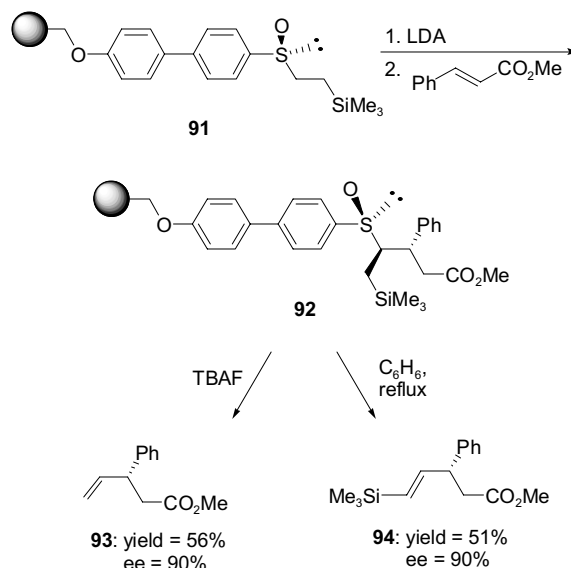
Scheme 23.

The use of the fluorous auxiliary enabled the reactions to occur under normal solution-phase conditions and

allowed for the products to be readily separated by fluorous solid-phase extraction (FSPE). FSPE was accomplished by dissolving the crude products in *n*-propanol, and this solution was then applied to a column charged with perfluoroalkyl-modified silica gel. All undesirable organic and inorganic impurities were removed by washing with a fluorophobic solvent mixture. Finally, the fluorous product was eluted using either THF or acetone.

## 5. Sulfoxide, sulfinamide, and sulfoximine auxiliaries

The use of a polymer-bound chiral sulfoxide auxiliary in asymmetric conjugate addition reactions has been reported by Toru and co-workers.[35] The chiral sulfoxide linker was attached to the polymer by reacting 4′-hydroxybiphenyl β-silylethyl sulfoxide with polystyrene to afford **91** (Scheme 24). This was deprotonated and subsequently added to methyl cinnamate to yield **92**. Two separate cleavage reactions were performed to afford alkene products. Treatment of **92** with TBAF furnished optically active methyl 3-phenylpent-4-enoate **93** in 56% yield with 90% ee. Simple heating of the polymer **92** in benzene liberated optically active methyl 3-phenyl-5-trimethylsilylpent-4-enoate **94** in 51% yield with 90% ee. The authors report that the biphenyl spacer used afforded higher enantioselectivity than the analogous phenyl spacer. It should be noted that the chirality of sulfoxide moiety is destroyed upon product cleavage and thus, it is not possible to directly recycle this auxiliary.
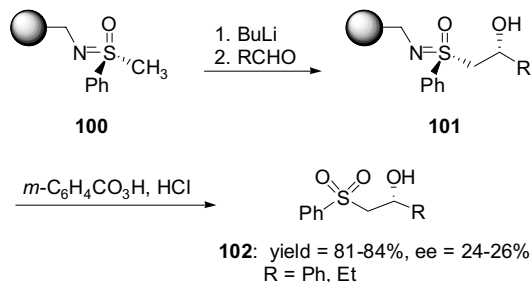
Scheme 24.

Ellman and co-workers have reported the asymmetric synthesis of α-alkylated amines using a polymer-supported enantiopure sulfinamide.[36] The sulfinamide resin **95** was treated with various aldehydes in the presence of Ti(OEt)$_4$, followed by the addition of ethylmagnesium bromide to afford the resin-supported products **96** with

diastereomeric ratios of up to 97:3 (Scheme 25). Cleavage of the products was accomplished by the treatment of **96** with HCl in CH$_2$Cl$_2$ and *n*-butanol to afford the α-ethylated amines **97** in 90–95% yield. This methodology was applied in the asymmetric synthesis of pavine **98** and isopavine **99** alkaloids in 86:14 enantiomeric ratios and in 45% and 47% yields, respectively. As in the previous example, the chirality of the auxiliary is destroyed during the product cleavage process.

95

96: dr = 88:12 - 97:3

97: yield = 90 - 95%
R = *i*-Pr, Ph, Bn,
4-MeO-C$_6$H$_4$

98: yield = 45%

99: yield = 47%
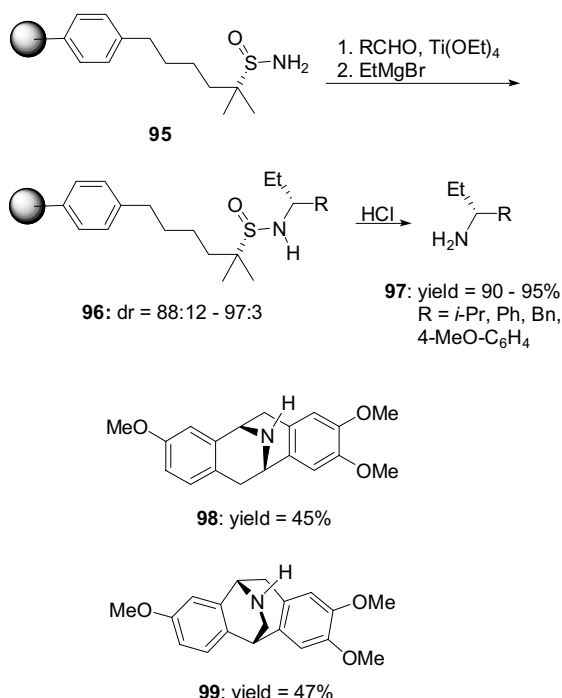
Scheme 25.

Hachtel and Gais have reported the use of polymer-supported enantiopure sulfoximines in the asymmetric synthesis of sulfones.[37] The sulfoximine **100** was deprotonated and then treated with either benzaldehyde or propanal to afford the corresponding β-hydroxysulfoximine resins **101** (Scheme 26). Oxidative cleavage of the desired sulfoxide products **102** was accomplished by treatment with *m*-CPBA and HCl in 81% and 84% yield, and 26% and 24% ee, respectively. In this example, the chiral sulfoximine was converted to a sulfone group in the oxidative cleavage of the product.

100   **101**

**102**: yield = 81-84%, ee = 24-26%
R = Ph, Et

Scheme 26.

6. Miscellaneous

The use of a polymer-supported oxazoline in the asymmetric synthesis of an α-alkylated ester has been reported by McManus and co-workers.[38] The chiral reagent **103** was deprotonated and the subsequent addition of benzyl chloride afforded the α-alkylated adduct **104** (Scheme 27). The α-benzylated ethyl ester **105** was then released from resin by acid-catalyzed hydrolysis. This afforded the desired product in 43–48% yield and 56% ee. The authors commented that the low chemical yields were due to slow and incomplete hydrolysis.

103   **104**

105: yield = 43 - 48%
ee = 56%
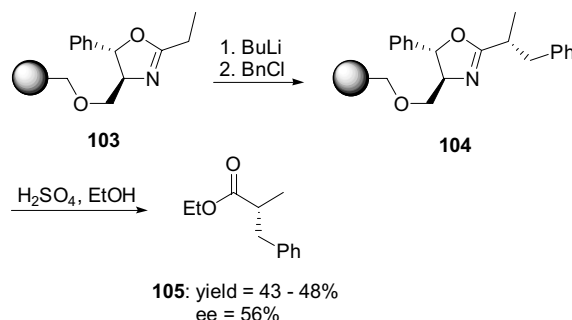
Scheme 27.

Asymmetric radical addition to a polymer-supported oxime ether has been reported by Naito and co-workers.[39] In this case, Oppolzer's camphorsultam acted as a chiral auxiliary but not as a linker, in **106** (Scheme 28). An ethyl radical was generated using triethylborane. Following treatment with TFA, the ethylated α-amino acid derivative **107**, still containing the auxiliary and the linker, was cleaved from resin in 74% yield with greater than 95% ee. The chemical yield was lower (67%) when diethylzinc was used as the radical initiator. The authors have also examined other radical precursors, such as isopropyl iodide and cyclohexyl iodide. However, the

106

107: yield = 74%
ee = >95%
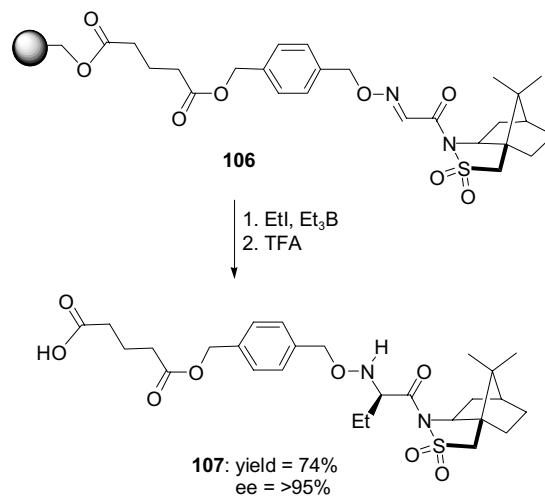
Scheme 28.

ethyl radical afforded the best results in terms of both chemical yield and enantioselectivity.

7. Conclusions

After some initial successful reports, the use of polymer-supported chiral auxiliaries was a relatively dormant area of research. However, along with the recent resurgence of interest in polymer-supported organic synthesis in general, the use of auxiliaries in such asymmetric synthesis has now increased over the past few years. Already, the immobilization of a wide range of auxiliaries onto polymer supports has been reported. In most such cases, the auxiliary is used both to induce asymmetry into the reaction, and also to link the synthesis substrate to the polymer carrier. Generally, when direct comparisons have been made, the results of the polymer-supported reactions mirror those of the analogous solution-phase experiments. In a few reported cases, the polymer-supported auxiliaries actually afforded higher enantioselectivity than their soluble counterparts.

Most of the examples presented here used commercially available polystyrene resins as the polymer support. Given the recent and continuing research into the development of new polymers that provide improved physical and chemical properties,[40] it can be expected that polymer-supported auxiliaries will become ever more useful in asymmetric synthesis. For example, polystyrene resins that contain novel cross-linkers[41,42] or polar grafts[43,44] have been reported that broaden the range of solvents with which they are compatible. Furthermore, in addition to polystyrene polymers, polyethers,[45,46] polyamines,[47] and polysaccharides[48] have all been recently examined as supports that may have beneficial properties. Therefore, as the polymer supports are improved and become more compatible with the necessary solvents, they may offer better solvation of the coordination complexes and/or transition states required for high enantioselectivity and thus lead to reactions with increased selectivity.

Acknowledgements

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