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Asymmetric Synthesis of α-Branched Primary Amines on Solid Support via Novel Hydrazine Resins

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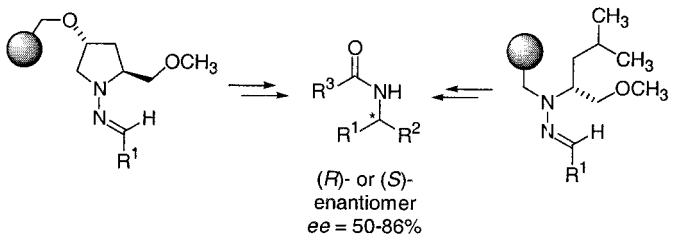
ABSTRACT



Two novel chiral hydrazine resins for asymmetric solid-phase synthesis have been developed. The enantiopure β-methoxyamino auxiliaries, derived from *trans*-4-hydroxy-(*S*)-proline and (*R*)-leucine, were attached to Merrifield resin and transformed into their corresponding hydrazines. Immobilization of various aldehydes, followed by 1,2-addition of organolithium reagents to the resulting enantiopure hydrazones and reductive cleavage from the solid support, furnished α-branched amines, which were isolated as their corresponding amides in good overall yields and enantiomeric excesses of up to 86%.

The synthesis of chiral, α-branched amines is of great importance in the preparation of compounds for therapeutical use, since a large number of primary amines show biological activity.[1] Moreover, the α-branched amine moiety is incorporated into many compounds such as amino acids or alkaloids encountered in medicinal chemistry.[2] Although the enantio- and diastereoselective synthesis of this class of compounds in liquid phase is well-known and has been extensively reviewed,[3] rather few efforts have been made to transform these methodologies to the solid phase. Especially, asymmetric syntheses on solid support have not been studied extensively.

Starting with the pioneering work of Kawana et al.,[4] the application of polymer-bound chiral auxiliaries has been focused thus far on the asymmetric α-alkylation of ketones[5] and amides,[6] the Ugi four-component condensation (4-CC),[7]and reactions with polymer-bound sulfoximines[8] and

† Synthesis of the SAMP-resin.

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oxazolidinones.[9] Such immobilized auxiliaries offer some advantages over their application in liquid phase, including the ease of workup, the easy recovery and potential recycling of the expensive reagents, and the isolation of reaction products by simple filtration. In addition, the microenvironment of the polymeric backbone could lead to an improved stereoselectivity for a given transformation.

To the best of our knowledge there have been only three reports of the enantioselective synthesis of α-branched amines employing a polymer-bound chiral catalyst or reagent, respectively. Soai et al.[10] described the enantioselective addition of dialkylzinc compounds to the C−N double bond of *N*-diphenylphosphinylimines, catalyzed by polystyrene-supported *N*,*N*-dialkylnorephedrins. The enantioselective allylation of *N*-(trimethylsilyl)benzaldehyde imines using a polymer-supported chiral allylboron reagent for the synthesis of homoallylamines has been reported by Itsuno et al.[11] The same group described the use of a chiral imine attached to a soluble polystyrene polymer, affording after oxidative degradation of the chiral auxiliary a homoallylic amine.[12]

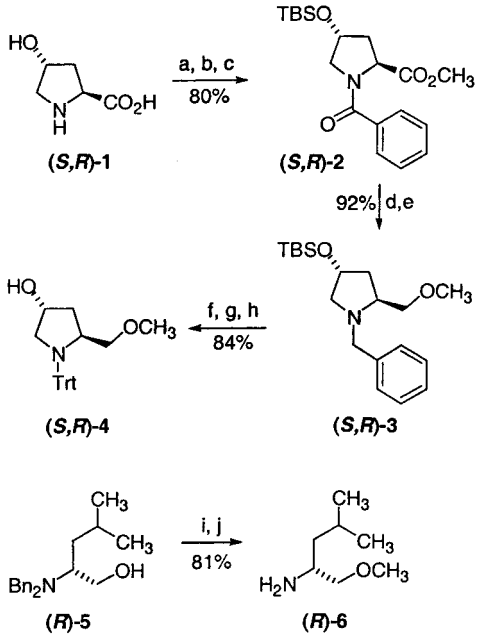
Although good to excellent enantiomeric excesses are obtained with these protocols, all methods are restricted to aromatic electrophiles which are not commercially available and therefore have to be synthesized in liquid phase. In addition, stoichiometric amounts of catalyst or boron reagent, respectively, are required and the latter two examples are limited to allylic nucleophiles.

We present here the first application of two novel chiral hydrazine resins in the asymmetric solid-phase synthesis of nonracemic α-branched primary amines, enabling the 1,2-addition of both aliphatic and aromatic nucleophiles to polymer-bound aliphatic and aromatic aldehyde hydrazones.

For the synthesis of the chiral hydrazine resins, the enantiopure β-methoxyamines (*S*,*R*)-**4** and (*R*)-**6** had to be attached to a polymeric support. The synthesis of these two chiral auxiliaries starts from readily available amino acid hydroxy proline [(*S*,*R*)-**1**] and *N*,*N*-dibenzylleucinol (*R*)-**5** (Scheme 1).

Esterification of hydroxy proline [(*S*,*R*)-**1**][13] and protection of both the amine and hydroxyl functionality led to the formation of (*S*,*R*)-**2**, which upon reduction with lithium aluminum hydride and subsequent methylation furnished the benzyl-protected amine (*S*,*R*)-**3**. After removal of the benzyl group, treatment with trityl bromide, and cleavage of the silyl

Scheme 1. Synthesis of Chiral Amines (*S*,*R*)-**4** and (*R*)-**6**[a]



[a] (a) $SOCl_2$, MeOH, 0 °C → rt; (b) BzCl, DMAP, NEt_3, CH_2Cl_2, 0 °C → rt; (c) TBSCl, imidazole, DMF; (d) $LiAlH_4$, THF, Δ; (e) NaH, MeI, THF, Δ; (f) H_2, Pd/C, 4 bar, EtOH, 60 °C; (g) Trt-Br, NEt_3, CH_2Cl_2, rt; (h) TBAF, THF, rt; (i) NaH, MeI, THF; Δ; (j) H_2, $Pd(OH)_2$/C, 4 bar, MeOH, rt.

ether, the enantiopure β-methoxyamine (*S*,*R*)-**4** was obtained in excellent yield (62% over eight steps) on a 30 g scale with only one chromatographic purification needed after the final step. Deprotonation of alcohol (*R*)-**5**[14] and methylation, followed by hydrogenolysis of the benzyl groups, furnished β-methoxyamine (*R*)-**6** in 81% yield.

The attachment of the chiral amines to Merrifield resin (**7**) was achieved via nucleophilic substitution of the chlorine by deprotonated alcohol (*S*,*R*)-**4**, followed by removal of the trityl group, yielding (*S*)-2-methoxymethylpyrrolidin (SMP)[15] analogue (*S*,*R*)-**8** (SMP-resin), while amine (*R*)-**6** was coupled through nucleophilic substitution by the amine moiety leading to (*R*)-methoxyleucinol (RML)-resin [(*R*)-**9**] (Scheme 2).

The immobilized secondary amines (*S*,*R*)-**8** and (*R*)-**9** were obtained in 66% and quantitative yield, respectively, judged by elemental analysis.

Nitrosation of these polymer-bound amines was conducted under standard conditions[16] with excess *tert*-butylnitrite in yields > 95% (elemental analysis). In the last step of the synthesis, nitrosamine resins (*S*,*R*)-**10** and (*R*)-**11** were treated with excess diisobutylaluminum hydride (DIBAL-H), affording hydrazine resins[17] (*S*,*R*)-**12** (SAMP-resin) and (*R*)-**13** (RAML-resin) in 93 and 81%, respectively. The loading

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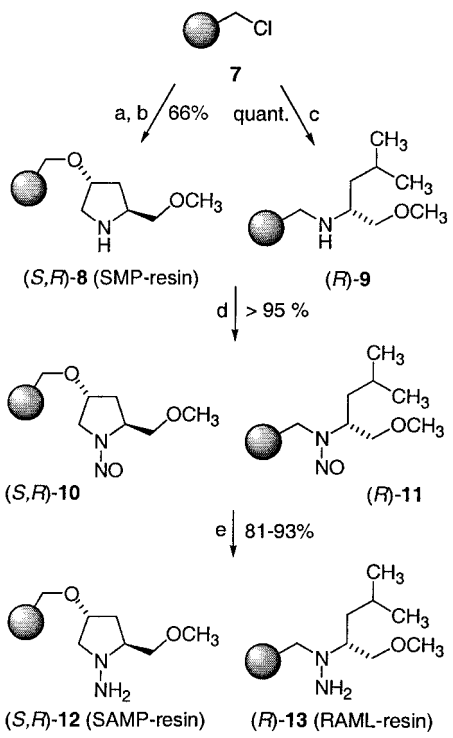
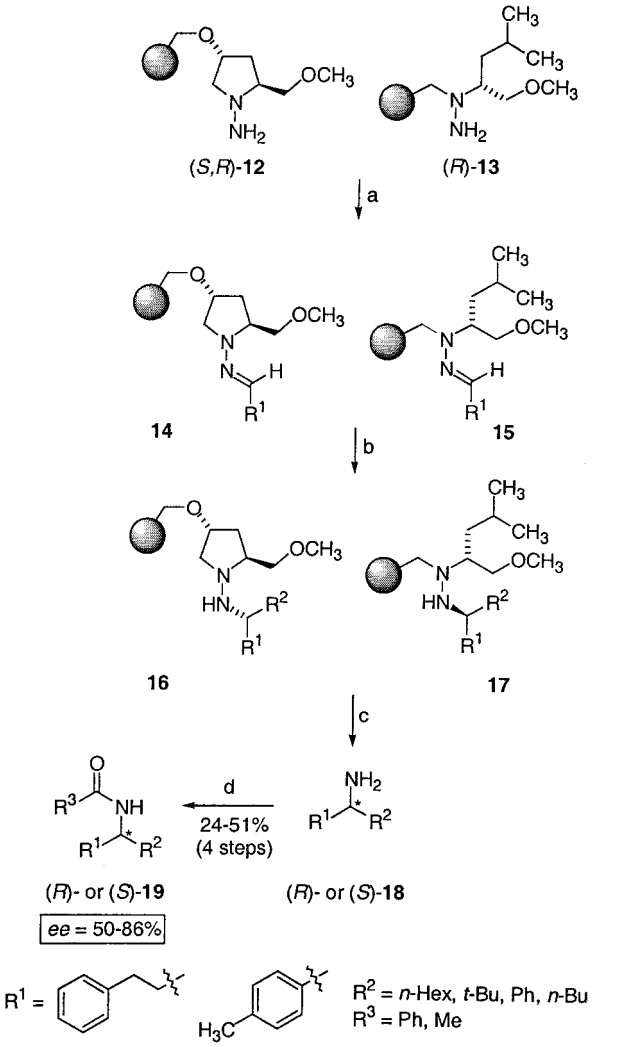
Scheme 2. Preparation of Chiral Hydrazine Resins (*S*,*R*)-**12** and (*R*)-**13**[a]



[a] (a) (*S*,*R*)-**4** (2.5 equiv), KH, DMF, 50 °C; (b) TFA/CH_2Cl_2 (1:10), then NEt_3; (c) (*R*)-**6** (4 equie), *n*-TBAI, DMF, 80 °C; (d) *t*-BuONO, THF, Δ; (e) DIBAL-H, THF, 50 °C.

Scheme 3. Formation of α-Branched Amides (*R*)- or (*S*)-**19**[a]



[a] (a) R^1CHO, THF, MS 4 Å, rt; (b) R^2Li, THF, −100 °C → rt, then H_2O; (c) BH_3·THF, THF, Δ, then HCl_{aq}, rt, then extraction; (d) R^3COCl, NEt_3, DMAP, CH_2Cl_2, 0 °C → rt.

of the linker resins was determined by condensation with nitrogen-containing aldehydes such as *p*-nitrobenzaldehyde and subsequent elemental analysis of the hydrazone resins, indicating a loading of 0.52 mmol·g^{-1} [(*S*,*R*)-**12**] and 0.54 mmol·g^{-1} [(*R*)-**13**], respectively.

With these linkers in hand, representing immobilized analogues of the SAMP[18] and (*R*)-methoxyleucinol[19] auxiliary, we were able to synthesize a series of enantiomerically enriched α-branched amines on solid support (Scheme 3).

First, coupling of resins (*S*,*R*)-**12** and (*R*)-**13** with excess aliphatic and aromatic aldehydes led to the formation of chiral resin-bound hydrazones **14** and **15**. Stereoselective addition of different carbon nucleophiles to the C−N double bond was achieved by treatment of the hydrazone resins with 7 (aliphatic nucleophile) or 10 (PhLi) equiv of organolithium reagent at −100 °C in THF. After warming to room temperature and subsequent hydrolysis, the hydrazine resins **16** and **17** were obtained with loadings ranging from 70 to 90% according to the nitrogen content determined by elemental analysis.

For the release of the α-branched primary amines via N−N bond cleavage, the trisubstituted hydrazines **16** and **17** were treated with excess borane−tetrahydrofuran complex (BH_3·THF) according to standard procedures developed in our group.[20] Hydrolysis with 3 M hydrochloric acid, followed by filtration and extraction procedures, furnished the enantiomerically enriched (*R*)- and (*S*)-amines **18** in yields of 30−70% on the basis of hydrazine resins (*S*,*R*)-**12** and (*R*)-**13** and initial purities of 50−70% (^{1}H NMR).

Further purification and determination of the enantiomeric excess was achieved by protection of the amine functionality as their corresponding amides. Thus, the reaction of crude amines with benzoyl chloride or acetyl chloride in the presence of triethylamine and catalytic amounts of DMAP furnished, after chromatography, (*R*)- and (*S*)-amides **19** in moderate to good enantiomeric excesses and yields (Table 1).

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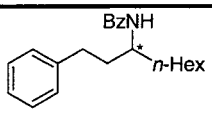
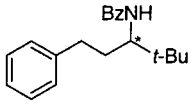
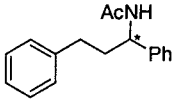
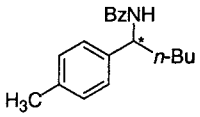
Table 1. Asymmetric Synthesis of Amides **19**

entry	product	resin	*ee*[a] [%]	Con-fig.[b]	yield[c] [%]
1	 **19a**	(*R*)-**13**	78	*S*	51
2		(*S*,*R*)-**12**	83	*R*	43
3	 **19b**	(*R*)-**13**	86	*R*	35
4		(*S*,*R*)-**12**	82	*S*	37
5	 **19c**	(*R*)-**13**	50	*R*	28
6		(*S*,*R*)-**12**	81	*S*	24
7	 **19d**	(*R*)-**13**	–	–	–
8		(*S*,*R*)-**12**	66	*R*	31

[a] The enantiomeric excess was determined by chiral HPLC. [b] Absolute configuration based on the assumption that linker (*S*,*R*)-**12** leads to the same enantiomer as the SAMP-auxiliary in liquid phase. [c] Each compound was characterized by ^{1}H NMR and mass spectroscopic analysis. The yields refer to the loading of resins (*S*,*R*)-**12** and (*R*)-**13**.

As shown in Table 1, both enantiomers of amides **19a**−**c** can be obtained by choosing either the SAMP-resin (*S*,*R*)-**12** or the RAML-resin (*R*)-**13**, respectively. For the addition of aliphatic nucleophiles to aliphatic aldehyde hydrazones (entries 1 and 3), the employment of the RAML-resin results in the formation of the desired products in good enantiomeric excesses (78, 86%) and yields (51, 35%). However, due to the lower reactivity of aromatic nucleophiles, the addition of phenyllithium to aliphatic 3-phenylpropanal aldehyde hydrazone (entry 5) furnished amide (*R*)-**19c** in lower enantiomeric excess (50%) and yield (28%). This drawback can be circumvented by the use of the SAMP-resin, which yields (*S*)-**19c** in good enantiomeric purity (ee = 81%). Also the addition of aliphatic organolithium reagents to an aliphatic hydrazone (entry 2 and 4) proceeds with good asymmetric inductions and chemical yields. Moreover, this linker enables the addition of *n*-butyllithium to an aromatic system (entry 8) in moderate enantioselectivity (ee = 66%).

The (*R*)-leucine resin obtained after N−N bond cleavage with BH_3·THF (Scheme 3) could be successfully recycled to the hydrazine linker (*R*)-**13** following the nitrosation/reduction protocol (Scheme 2). The so-generated hydrazine resin (loading 0.24 mmol·g^{-1}) was still suitable for aldehyde attachment. However, no further investigations in the asymmetric 1,2-addition were attempted.

In conclusion, two novel chiral hydrazine resins have been developed and successfully employed in the asymmetric synthesis of α-branched primary amines on solid support. The methodology enables the synthesis of the acyl-protected title compounds starting from readily available substrates in good yields (24−51% over four steps) and moderate to good enantiomeric excesses (50−86%). In addition, this protocol shows great flexibility regarding aliphatic and aromatic nucleophiles and hydrazones.

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Supporting Information Available: Experimental procedures and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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