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A new polymer-supported Evans-type chiral auxiliary derived from α-hydroxy-β-amino acid, phenylnorstatine: synthesis and application in solid-phase asymmetric alkylation reactions

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Abstract—Based on a new anchoring strategy, a polymer-supported chiral oxazolidinone was prepared starting from (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (phenylnorstatine, Pns) and Wang resin. Solid-phase asymmetric alkylation on this resin proceeded in high diastereoselectivity comparable to that of conventional solution-phase model experiments. This study suggests that anchoring through the 5-position of oxazolidinone is highly suited to achieving diastereoselective alkylation reactions on solid-support.

Recently, solid-phase organic synthesis has become a popular methodology for the preparation of organic molecules,[1] especially the preparation of compound libraries in the process of drug discovery.[2] It allows for a facile isolation of the desired compounds with easy elimination of by-products and excess reagents using a full- or semi-automatic process. Polymer-supported chiral auxiliaries are especially advantageous because they can be recovered by simple filtration and potentially recycled. Evans' oxazolidinone is one of the most versatile chiral auxiliaries for asymmetric acyl group-based transformation.[3] The attachment of Evans' oxazolidinone to solid-supports and its utility in asymmetric alkylation,[4] aldol condensation,[5] and Diels–Alder,[6] and 1,3-dipolar[7] cycloadditions have been reported using **1** (Fig. 1A). However, the application of **1** is limited, probably due to the difficulty of monitoring and optimizing the solid-phase reaction more than the corresponding solution-phase reactions. In addition, the solid-phase asymmetric alkylation on the resin **1** has not been accomplished in a high stereoselective manner (max 90% ee) and a marked undesired effect of the solid-supports on the yield and ee was reported.[4] One reason for these undesired results could be that the critical chiral discriminating unit, that is, the benzyl group at

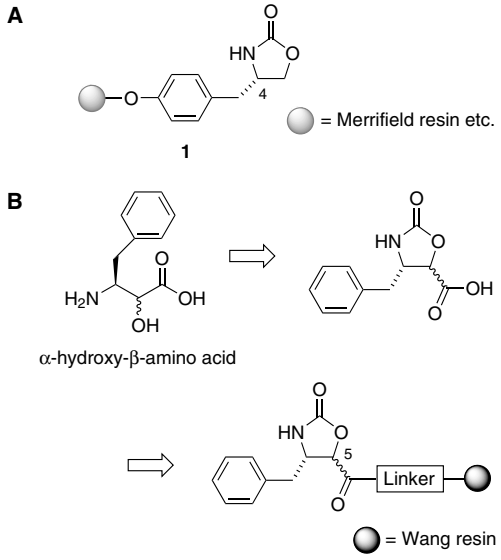

Figure 1. Polymer-supported Evans-type chiral auxiliaries. (A) Chiral auxiliary anchored at the 4-position.[4–7] (B) The new auxiliary derived from α-hydroxy-β-amino acid anchored at the 5-position.

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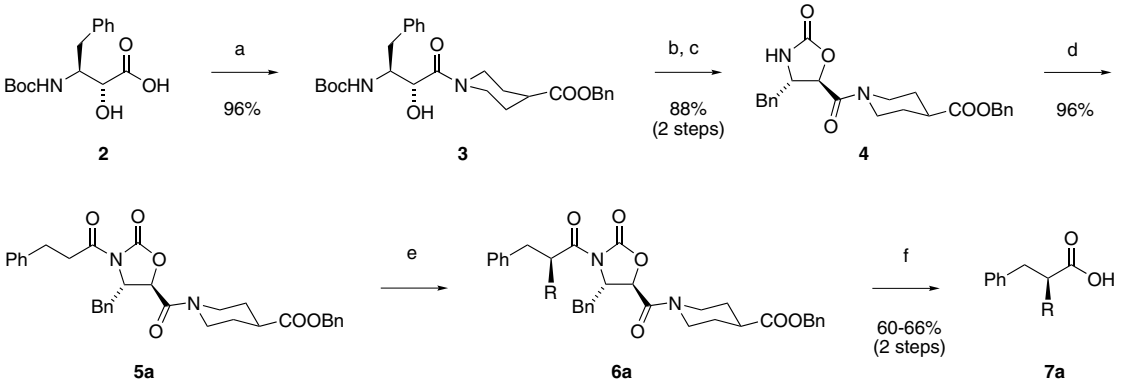
the 4-position of the oxazolidinone ring in **1**, was used to anchor the solid-support.

Hence, to create a new anchor liberating the benzyl group, we focused on the chiral α-hydroxy-β-amino acids, phenylnorstatine [Pns, (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid] and its (2*S*,3*S*)-stereoisomer, allophenylnorstatine (Apns), which are well-known units with the hydroxymethylcarbonyl (HMC) isostere necessary for inhibiting aspartyl proteases.[8] As shown in Figure 1B, these α-hydroxy-β-amino acids can be converted to the corresponding oxazolidinones with a carboxyl group at the 5-position of the ring for anchoring to the solid-support. Here, we describe the synthesis of a new polymer-supported Evans' chiral auxiliary derived from Pns and demonstrate that solid-phase asymmetric alkylation proceeds with high stereoselectivity parallel to that obtained with the model substrate under classical solution conditions.

In the design of new polymer-supported oxazolidinone, piperidine-4-carboxylic acid was used as a linker, which can connect the chiral auxiliary through a base-insensitive tertiary-amide bond. Wang resin[9] was used as the solid-support, since the ester bond between the linker and resin can be easily formed by standard condensation methods and cleaved by mild acids like TFA or methanolysis to monitor the reaction.

The synthesis of oxazolidinone derivative **4** is outlined below (Scheme 1). Boc—Pns—OH[10] **2** was coupled to benzyl piperidine-4-carboxylate·HCl by the EDC–HOBt method[11] to give **3**. Removal of the *N*-Boc group of **3** and subsequent reaction with 1,1′-carbonyldiimidazole (CDI)[12] gave the desired oxazolidinone **4** in good yields.[13] During this cyclization reaction, no epimerization at the 5-position, and no aziridine by-product formation[14] were observed. Oxazolidinone **4** was then *N*-3-phenylpropionylated and the resultant carboximide **5a** was subjected to a model alkylation study in the solution-phase.[15] As Table 1 shows, the new oxazolidinone derivative **4** could function as an efficient chiral auxiliary with suitable reactivity in terms of yield and stereoselectivity. In addition, no disruption of both the oxazolidinone ring and the benzyl ester was observed during the cleavage with LiOOH.[16] Similar results were also obtained in the use of other imides **5b** and **5c** with *N*-phenoxyacetyl and *N*-propionyl groups, respectively (Table 1).

In the case of *N*-acyloxazolidinone derived from Boc—Apns—OH, epimerization at the 5-position was observed during the base treatment, suggesting that the 5-position as well as the desired α-position of the acyl group were deprotonated by LDA, while deprotonation in the Pns-derived *N*-acyloxazolidinone was specific to the α-position. This was probably due to increased acidity at

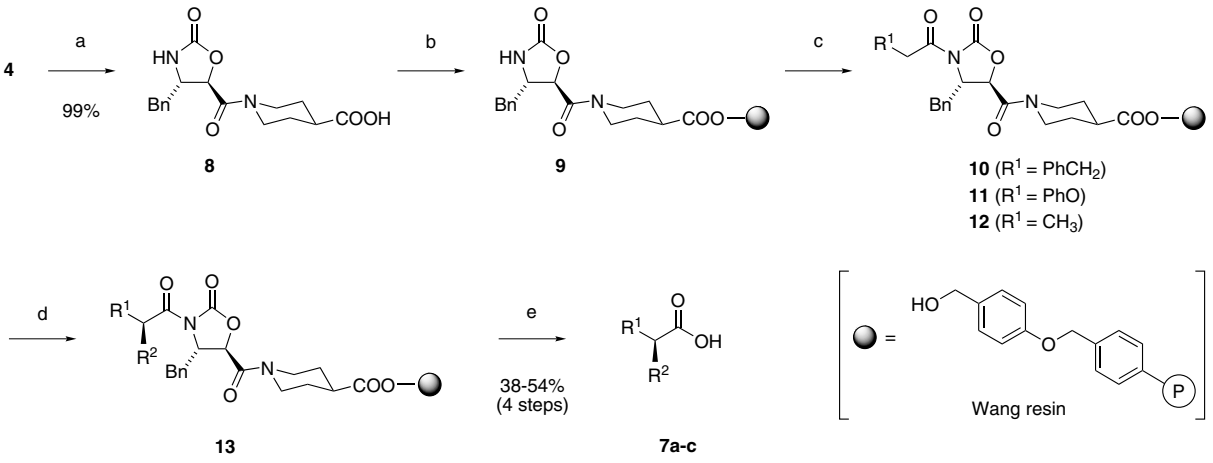


Scheme 1. Reagents and conditions: (a) benzyl piperidine-4-carboxylate·HCl, HOBt·H_2O, EDC·HCl, Et_3N, DMF, 0 °C to rt; (b) 4 M HCl/1,4-dioxane, 0 °C to rt; (c) Et_3N, CDI, THF, 0 °C to rt; (d) 3-phenylpropionic acid, ^{t}BuCOCl, Et_3N, LiCl, THF, −18 °C to rt; (e) LDA, RX, THF, −78 to 0 °C; (f) LiOH, 30% H_2O_2, THF–H_2O (3:1), 0 °C.

Table 1. Results of asymmetric alkylation

Entry	Imide	R^2X	Solid-phase		Solution-phase	
			Yield (%)[a]	Ee (%)[b]	Yield (%)[c]	Ee (%)[b]
1	**10/5a**	MeI	48	85	62	86
2	**10/5a**		54	96	66	96
3	**10/5a**		51	94	64	95
4	**10/5a**		47	92	60	90
5	**11/5b**		38	96	48	96
6	**12/5c**	BnBr	40	97	57	98

[a] Yield in four steps based on original loading of Wang resin (see Scheme 2).
[b] Determined by HPLC analysis after conversion to the corresponding (*S*)-phenylethyl amide derivatives.
[c] Yield in two steps starting from **5** (see Scheme 1).



Scheme 2. Reagents and conditions: (a) H_2, Pd/C, MeOH–H_2O (9:1), rt, overnight; (b) Wang resin, DIC, DMAP, DMF, rt, 3 h; (c) $R^1CH_2CO_2H$, 2-chloro-1-methylpyridinium iodide, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (d) LDA, R^2X, THF, 0 °C, 3.5 h; (e) LiOH, 30% H_2O_2, THF–H_2O (3:1), 0 °C, 1 h.

the 5-position of the Apns-derived oxazolidinone caused by steric repulsion between the benzyl and carboxamide groups in a *cis*-configuration.

Hence, for the solid-phase synthesis, Pns-derived oxazolidinone **4** was selected and its benzyl ester was removed by hydrogenolysis, and the resultant carboxylic acid **8** was attached to the Wang resin by the established method with 1,3-diisopropylcarbodiimide (DIC)[17] in the presence of a catalytic amount of DMAP (Scheme 2). Analysis of the loading rate by methanolysis of the resin **9** gave a complete recovery of the corresponding methyl ester, indicating that quantitative loading was achieved. It is pertinent to note that the previous reported auxiliary **1** on Wang resin having only 56% of loading might have potential side reactions by the residual free-hydroxyl group.[4] On the contrary, we were able to efficiently synthesize a new Wang resin-supported Evans-type chiral auxiliary **9** with a quantitative loading.

For the solid-phase asymmetric alkylation, to a well-swollen carboximide resin **10**–**12** in THF, derived from **9** by the mixed anhydride-LiCl N-acylation[18] or Mukaiyama reagent,[19] was added LDA (2 equiv) at 0 °C, followed by the addition of alkyl halide (10 equiv). After stirring for 3 h at the same temperature, the solid-phase reaction was quenched by adding saturated aqueous NH_4Cl. The resin was recovered by filtration and was subsequently washed with THF and MeOH to give **13**. LiOOH-mediated chemoselective hydrolysis of **13** gave the desired chiral α-alkylated carboxylic acids **7a**–**c**.[20] Since no disruption of the ester bond between the linker and resin was observed during these steps and methanolysis of recovered resin afforded the corresponding oxazolidinone methyl ester in high yield (94% yield Table 1, entry 2), it indicated that the polymer-supported auxiliary was stable to LiOOH treatment. Therefore, it is considered that the recovered resin **9** has a potential for reuse. Enantiomeric excess of the obtained acids was determined by HPLC analysis after derivatization to the corresponding (*S*)-phenylethyl amides by the EDC–HOBt method. As Table 1 shows, high stereoselectivity (85–97% ee) comparable to the solution-phase model experiments was obtained in this solid-phase system with a total yield of 38–54% (in four steps), calculated from the original loading of Wang resin. These results suggest that anchoring to the resin at the 5-position of the oxazolidinone ring is highly suitable for realizing reasonable enantiomeric ratios, probably achieving greater freedom from the polystyrene scaffold than the previous auxiliary involving the 4-position. It also suggests that the asymmetric alkylation reaction proceeded through the same chelation controlled model as reported in standard Evans-type oxazolidinone chemistry.[3a] These findings would resolve the concern raised by Burgess and Lim[4] in the solid-phase asymmetric alkylation using the polymer-supported Evans' chiral auxiliary, and our new polymer-supported oxazolidinone is applicable in the synthesis of a variety of chiral α-alkylated carboxylic acids.

In conclusion, we have developed a new polymer-supported Evans-type chiral auxiliary, anchored to the Wang resin through a carboxyl group at the 5-position of the oxazolidinone ring and a piperidine-4-carboxyl linker, and found it to be a useful tool for solid-phase asymmetric alkylation with no reduction in stereoselectivity. This convenient polymer-supported chiral auxiliary is applicable in the preparation of a library of chiral α-branched carboxylic acids such as 3-phenylpropionic acid derivatives having inhibitory activity against serine proteases.[21] Further studies of well-known asymmetric reactions in the use of the Evans' auxiliary, such as aldol condensation and cycloadditions, and the recycling of the resin are under investigation.

Acknowledgements

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13. Chemical data for benzyl *N*-[(4*S*)-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate (**4**): mp 91–93 °C; R_f 0.55 (*n*-hexane:AcOEt = 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 10H), 5.25 (br s, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 4.79 (d, 0.5H, J = 5.5 Hz), 4.78 (d, 0.5H, J = 5.5 Hz), 4.63–4.69 (m, 1H), 4.33–4.38 (m, 0.5H), 4.16–4.20 (m, 0.5H), 3.80–3.84 (m, 0.5H), 3.65–3.70 (m, 0.5H), 3.14–3.24 (m, 0.5H), 2.93–3.02 (m, 2H), 2.76–2.88 (m, 1.5H), 2.54–2.65 (m, 1H), 1.55–1.98 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.7, 173.4, 164.4, 164.3, 156.9, 135.8, 135.8, 135.7, 129.1, 129.0, 128.6, 128.3, 128.3, 128.1, 127.3, 76.8, 76.6, 66.5, 55.3, 44.8, 44.5, 42.0, 41.8, 41.0, 41.0, 40.9, 40.3, 28.4, 28.2, 27.5, 27.5; $[\alpha]_D^{27}$ −91.2 (c 1.281, $CHCl_3$); IR (KBr) 3452, 3036, 3007, 1771, 1730, 1653, 1456, 1387, 1313, 1271, 1238, 1209, 1173, 1038, 1011, 756, 737, 698, 667 cm^{-1}; HRMS (EI$^+$): m/z 422.1845 for [M$^+$] (calcd 422.1842 for $C_{24}H_{26}N_2O_5$); elemental analysis calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 67.99; H, 6.20; N, 6.55.
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