Solid phase synthesis has emerged as a versatile and powerful method in modern organic synthesis. However, the application of solid-supported chiral auxiliaries is still relatively underdeveloped. Such solid-supported chiral auxiliaries offer some advantages as compared to their application in the solution phase, including a simple filtration procedure for the isolation of the desired compounds or the recovery of the expensive chiral auxiliaries, and their possible extension to a continuous flow system. In addition, the microenvironment of the polymeric backbone could lead to an improvement in the stereoselectivity for a given transformation. Recently, we have investigated 2-phenylamino-2-oxazolines as effective chiral auxiliaries for asymmetric alkylation, which provided some beneficial effects for the removal problem as well as stereoselectivity. As a part of our interest in solid-supported chiral auxiliaries, we herein wish to introduce 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary in solid phase as a good leaving group in the final cleavage step. Asymmetric benzylation as a model alkylation reaction using this chiral auxiliary with different cleavage conditions for the parallel synthesis of several kinds of chiral products will be discussed.

First, 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary was prepared from commercially available methyl ester hydrochloride in 4 steps (Scheme 1). The 1,2-aminoalcohol 2 was synthesized according to the previous procedure by treatment with the methylmagnesium bromide. The reaction of aminoalcohol 2 with phenyl isothiocyanate afforded the thiourea 3 in excellent yield, and the cyclization of the thiourea to the 2-phenylamino-2-oxazolines by a one-pot reaction using p-toluenesulfonyl chloride and sodium hydroxide gave the chiral auxiliary 4 in 91% yield. Finally, the desired chiral auxiliary 5 was formed after removing the O-protecting benzyl group of 4. With the free hydroxy group, chiral auxiliary 5 was conveniently linked to resin to carry out the asymmetric synthesis in the solid phase.

Next, the solid-supported 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary was formed by the reaction of compound 5 and Wang resin under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (Ph3P). Acylation in the solid phase was carried out by deprotonation of resin 6 with excess potassium tert-butoxide (10 equiv), followed by treatment with excess propionyl chloride (10 equiv) to afford resin 7 (Scheme 2). The monitoring of the reaction progress in the solid phase may be achievable by using the conventional TLC of compound 8 after the cleavage of the acylated resin 7 with trifluoroacetic acid (TFA). However, we failed to monitor the acylated compound 8. The treatment of resin 7 with TFA for 5 min at room temperature provided the mixture of...
compound 5 and 8 which was then easily deacylated to form the compound 5 because this chiral auxiliary as expected was a very good leaving group.

The asymmetric benzylation using the solid-supported 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary 7 was examined (Scheme 3). For the solid phase asymmetric alkylation reaction, resin 7 was swollen in THF and cooled to \(-78^\circ C\), followed by the dropwise addition of 1 M LiHMDS (3 equiv). After continuously stirring for 3 h at the same temperature, benzyl bromide (5 equiv) was added. The reaction mixture was warmed up to 0 \(^\circ C\), reacted for 6 h and then quenched by adding saturated \(\text{NH}_4\)Cl. The resultant resin was separated from the reaction mixture by filtration, followed by washing with THF: \(\text{H}_2\text{O}\) (1:1 v/v), THF, DMF, \(\text{CH}_2\text{Cl}_2\), and MeOH sequentially, and then dried in vacuum.

Upon the removal of chiral auxiliary, chiral acid 10, alcohol 11 and ester 12 were obtained from the treatment of resin 9 with sodium hydroxide (NaOH), lithium aluminum hydride (LiAlH₄) and sodium methoxide (NaOMe), respectively (Scheme 3). Although performing very well in the solution phase, \(^{4,5}\) the 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary unexpectedly caused some different racemization levels upon different cleavage conditions in the solid phase (Scheme 3). The chiral ester 12 and alcohol 11 were obtained in very low enantiomeric excess (ee), at only 15 and 62% ee, respectively. Fortunately, the chiral acid 10 could be obtained in excellent stereoselectivity, with ee > 99%. Therefore, the removal conditions played an important role in the optical purity of the chiral products in the solid phase synthesis due to their compatibility with the polymeric backbone of the chiral auxiliary.

In summary, we developed a new solid supported 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary. Asymmetric benzylation reaction in the solid phase proceeded with good yield and excellent stereoselectivity. Treatment of the benzylated product with NaOH released highly optical pure carboxylic acid.

**Experimental Section**

**Preparation of (2S)-2-Amino-1,1-dimethyl-3-[4-(phenylmethoxy)phenyl]-1-propanol (2).** The amino methyl ester 1 (1 g, 3.11 mmol) was suspended in freshly distilled THF (200 mL) at room temperature under Ar atmosphere.
M methyl magnesium bromide solution in ether (6.22 mL, 18.66 mmol) was added dropwise and the reaction mixture was left to stir at room temperature for 24 h. After that, the reaction was cautiously quenched with saturated NH₄Cl (aq.) and extracted with ethyl acetate (>3 times). The combined organic extracts were washed with brine, dried with MgSO₄ and then evaporated. The crude product was purified by flash column chromatography to yield the pure amino alcohol 2. Yield 62%; White solid; mp 80 °C; ¹H NMR (300 MHz, CDCl₃) δ 6.50-7.50 (9H, m), 7.58 (2H, br), 5.02 (2H, s), 5.00 (1H, s), 3.01 (1H, m), 2.82 (1H, dd, J = 9, 15 Hz), 2.49 (1H, dd, J = 9, 15 Hz), 1.22 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 157.6, 137.2, 132.1, 130.0, 128.6, 128.0, 127.5, 115.2, 71.4, 70.2, 61.6, 38.2, 27.3, 23.9; HRMS (ESI) calcd for C₁₈H₂₃NO₃: [M+H⁺]: 286.1472, found: 286.1470.

Preparation of N-[(1S)-2-Hydroxy-2-methyl-1-[(4-(phenylmethoxy)phenyl)methyl]propyl]-N-phenylthiourea (3). To the stirred solution of compound 2 (1.2 g, 4.20 mmol) in THF (300 mL) under Ar at room temperature, a solution of phenyl isothiocyanate (0.46 mL, 3.82 mmol) was added dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and then concentrated. The crude product was purified by column chromatography to give the requisite product 3. Yield > 99%; colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 6.80-7.40 (14H, m), 6.19 (1H, br), 4.95 (2H, s), 4.70 (1H, br), 3.00 (1H, dd, J = 3, 15 Hz), 2.53 (1H, t, J = 15 Hz), 2.22 (1H, t, J = 15 Hz), 1.19 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 181.5, 157.1, 137.6, 135.8, 130.0, 128.6, 127.9, 127.5, 127.3, 125.5, 115.1, 76.4, 74.1, 70.1, 35.3, 28.6, 25.8; HRMS (ESI) calcd for C₂₉H₂₇NO₅S [M+H⁺]: 421.1950, found: 421.1951.

Preparation of (4S)-4,5-Dihydro-5,5-dimethyl-4-[(4-(phenylmethoxy)phenyl)methyl]-N-phenyl-2-oxazolamine (4). To stir a solution of thiourea (3) (0.8 g, 1.90 mmol) in THF (200 mL) under Ar, a solution of NaOH (0.18 g, 4.57 mmol) in water (10 mL) was added, followed by the addition of a solution of p-toluenesulfonyl chloride (0.44 g, 2.28 mmol) in THF (30 mL) dropwise with a syringe. The reaction mixture was stirred at room temperature for 12 h, quenched with saturated NH₄Cl (aq.), and then extracted with ether. The crude product was purified by flash column chromatography to yield the pure compound 4. Yield 91%; beige solid; mp 155 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.0-7.90 (14H, m), 5.23 (2H, s), 5.35 (1H, br) 3.86 (1H, m), 2.87 (2H, d, J = 15 Hz), 1.55 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 157.7, 154.4, 143.2, 137.2, 130.9, 130.1, 128.8, 128.6, 128.0, 127.5, 122.1, 120.7, 112.5, 86.1, 70.2, 68.9, 36.7, 27.4, 21.8; HRMS (ESI) calcd for C₂₉H₂₇NO₅: [M+H⁺]: 387.2072, found: 387.2073.

Preparation of (4S)-4,5-Dihydro-5,5-dimethyl-4-[(4-hydroxyphenyl)methyl]-N-phenyl-2-oxazolamine (5). To a solution of compound 4 (1.35 g, 2.85 mmol) in glacial acetic acid (50 mL), 10% palladium on charcoal (2 g, 15% w/w) was added. The mixture was hydrogenated at 95 psi of hydrogen pressure at room temperature for two days. After that, the catalyst was filtered off and washed with methylene chloride, and the filtrate was concentrated in vacuum. The crude product was purified by flash column chromatography to give the pure compound 5. Yield 85%; white solid; mp 190 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.76 (2H, br), 6.70-7.50 (9H, m), 3.91 (1H, t, J = 6 Hz), 2.82 (1H, dd, J = 6, 15 Hz), 2.67 (1H, dd, J = 6, 15 Hz), 1.46 (3H, s), 1.40 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 130.0, 128.8, 127.9, 122.7, 122.4, 116.0, 65.6, 36.4, 27.3, 21.8; HRMS (ESI) calcd for C₁₉H₁₈N₂O₂: [M+H⁺]: 297.1603, found: 297.1602.

Preparation of Solid Supported 5,5-Dimethyl-2-phenylamino-2-oxazole Chiral Auxiliary (6). Wang resin (0.37 g, loading capacity 0.87 mmol/g) was swollen in dichloromethane (20 mL) for 2 min at room temperature under Ar. Chiral auxiliary 5 (0.48 g, 1.62 mmol) and triphenylphosphine (0.51 g, 1.94 mmol) were dissolved in dichloromethane (10 mL) and added to the swollen resin. DIAD (0.38 mL, 1.94 mmol) was diluted in dichloromethane (2 mL) and added dropwise to the resin. The reaction mixture was shaken at RT for 2 days. After that, the resultant resin was separated from the reaction mixture by filtration, followed by washing with THF, DMF, CH₂Cl₂, and MeOH (5 times) sequentially and then dried in vacuum to obtain the required resin bound chiral auxiliary 6. The yield of loading was 80% (determined by the increase in mass of resin after attaching).

Preparation of Solid Supported N-Acetylated-5,5-dimethyl-2-phenylamino-2-oxazole Chiral Auxiliary (7). Resin 6 (0.36 g, 0.31 mmol) was swollen in THF (10 mL) under an argon atmosphere at 0 °C. Then, a 1 M solution of t-BuOK in THF (3.13 mL, 3.1 mmol) was added dropwise, followed by the addition of acyl chloride (0.27 mL, 3.1 mmol). The reaction mixture was stirred for 2 h at RT and quenched by adding saturated NH₄Cl solution. The resultant resin 7 was separated from the reaction mixture by filtration, followed by washing with THF/H₂O (1:1 v/v), THF, DMF, CH₂Cl₂, and MeOH (x5 times) sequentially and then dried in vacuum.

To Monitor the Reaction: Resin 7 (0.2 g) was shaken in a 1:1 v/v mixture of dichloromethane (10 mL) and trifluoroacetic acid (10 mL) for 5 min. Then, the reaction mixture was filtered and washed with dichloromethane and methanol. The filtrate was concentrated in vacuum to obtain the crude product, which was purified by flash column chromatography to yield the pure compound 8. ¹H NMR (300 MHz, CDCl₃) δ 6.70-7.30 (9H, m), 5.50 (1H, br), 4.55 (1H, q, J = 4 Hz), 3.15 (2H, m), 2.92 (2H, dd, J = 4, 12 Hz), 1.35 (6H, s), 1.16 (3H, t, J = 4 Hz). However, compound 8 was unstable due to the presence of the free hydroxyl group.

Preparation of Benzylated Resin (9). Under Ar atmosphere, resin 7 (0.38 g, 0.33 mmol) was swollen in THF (15 mL) and cooled to −78 °C, followed by the dropwise addition of 1 M LiHMDS (0.99 mL, 0.99 mmol). After continuously stirring for 2 h at the same temperature, benzyl bromide (0.2 mL, 1.65 mmol) was added and reacted at −78 °C for 2 h and 0 °C for 4 h. Then the reaction mixture was quenched by adding saturated NH₄Cl. The resultant resin was separated from the reaction mixture by filtration, followed by washing with THF/H₂O (1:1 v/v), THF, DMF, CH₂Cl₂, and MeOH (x5 times) sequentially, and then dried in vacuum.
Due to the unstable characteristic of N-acetylated 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary 8 in the presence of free hydroxyl group, this reaction could not be monitored by TFA cleavage. The benzylated resin 9 was cleaved directly by the reactions with LiOH or NaOH, LiAlH₄ and NaOMe to obtain the final chiral products 10, 11, and 12 respectively.

Preparation of (R)-2-Methyl-3-phenylpropanoic Acid (10). Using LiOH: Resin 9 (0.38 g, 0.33 mmol) was swollen in excess THF (15 mL): H₂O (5 mL) for 15 min. Then, LiOH·H₂O (0.14 g, 3.30 mmol) was added. The reaction mixture was shaken at room temperature for 2 days. The deacylated resin was filtered off and the filtrate was acidified to pH 2 with HCl and extracted with ethyl acetate. The crude product was purified by flash column chromatography to yield compound 10 as colorless oil. Yield: 24% (4 steps based on the original loading of Wang resin).

Using NaOH/dioxane: Resin 9 (0.38 g, 0.33 mmol) was swollen in excess NaOH 2 N (15 mL): dioxane (15 mL). After 4 h at 100 °C, the deacylated resin was filtered off and the filtrate was acidified to pH 2 with HCl and extracted with ethyl acetate. The crude product was purified by flash column chromatography to yield compound 10 as colorless oil. Yield: 20% (4 steps based on the original loading of Wang resin).

Conversion of Acid 10 to Methyl Ester 12: Acid 10 was directly converted into ester 12 by treatment with CH₃N₂ previously prepared from Diazaid. In a 25 mL flask (flask 1), acid 10 (20 mg) was dissolved in diethyl ether (2 mL) and cooled to 0 °C. In another 2-neck flask (flask 2), Diazaid (1 g) was suspended in (5 mL) ethanol. The solution of NaOH (0.2 g) in water (3 mL) was prepared and added dropwise into flask 2. During the addition of NaOH solution, the CH₃N₂ was evoked and transferred into flask 1 to react with acid 10 and formed the required ester 12. ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.00 (5H, m), 3.65 (3H, s), 3.00 (1H, d, J = 7 Hz); the enantiomer excess (ee) was determined by HPLC to be > 99% after conversion acid to ester with CH₂Cl₂.

References and Notes

5. The acylation of 5,5-dimethyl-2-phenylamino-2-oxazoline 4 with propionyl chloride and asymmetric benzylaton in the solution phase gave an excellent diastereoselectivity (> 99% d.e.). Several chiral products such as acid, alcohol and ester were easily obtained in high yields and excellent enantiomeric excess values (ee 98, 96, and 97, respectively). No racemization was occurred in the NaOH, LiAlH₄, and NaOMe cleavage conditions in the solution phase.