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Solid Phase Asymmetric Benzylation Using 5,5-Dimethyl-2-Phenylamino-2-Oxazoline Chiral Auxiliary

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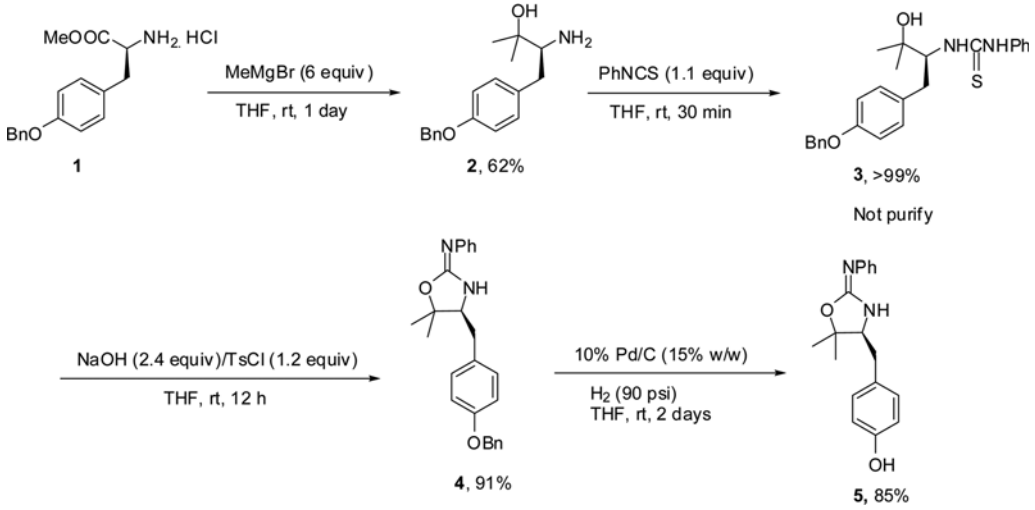
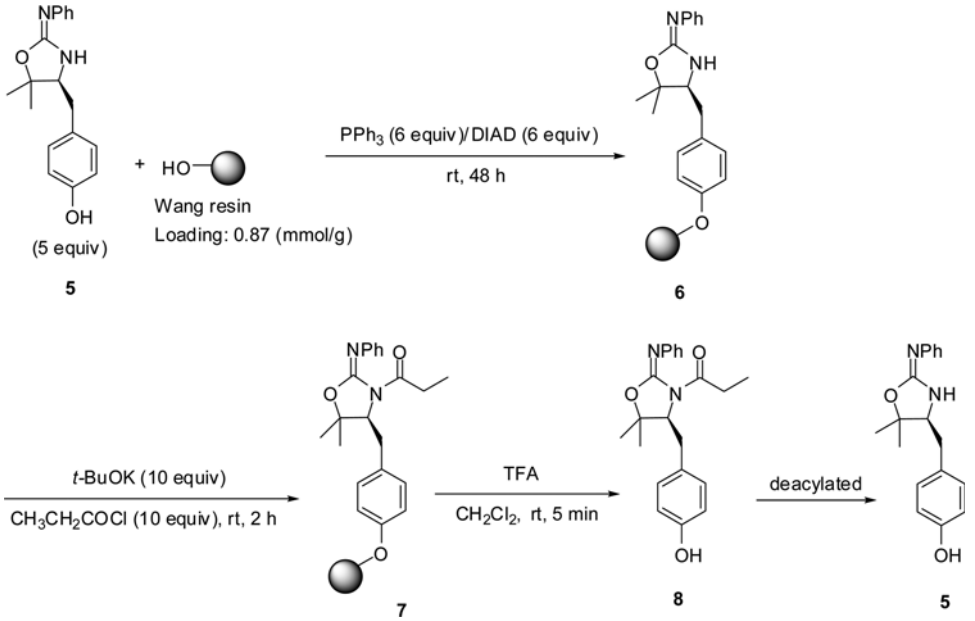
Solid phase synthesis has emerged as a versatile and powerful method in modern organic synthesis.[1] However, the application of solid-supported chiral auxiliaries is still relatively underdeveloped. Such solid-supported chiral auxiliaries offer some advantages as compared to their application in the 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.[2] In addition, the microenvironment of the polymeric backbone could lead to an improvement in the stereoselectivity for a given transformation.[2a,4a] 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.[3] As a part of our interest in solid-supported chiral auxiliaries,[4] 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 **5** was prepared from commercially available methyl ester hydrochloride **1** in 4 steps (Scheme 1). The 1,2-amino-alcohol **2** was synthesized according to the previous procedure by treatment with the methylmagnesium bromide.[3b] 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.[3] 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.

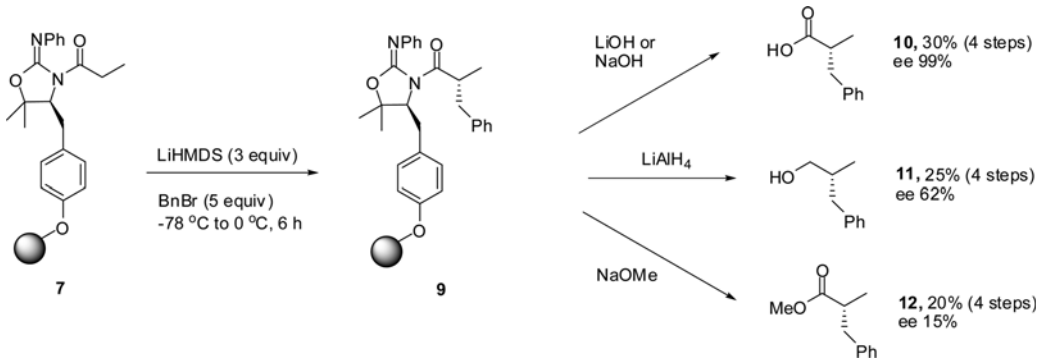
Next, the solid-supported 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary **6** was formed by the reaction of compound **5** and Wang resin under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) and triphenyl phosphine (Ph_3P). Acylation in the solid phase was carried out by deprotonation 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).[4] 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



Scheme 1. Synthesis of 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary.



Scheme 2. Synthesis of solid supported *N*-acylated 5,5-dimethyl-2-phenylamino-2-oxazoline chiral auxiliary.



Scheme 3. Asymmetric benzylation reaction on the solid phase and cleavage reactions.

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 °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 °C, reacted for 6 h and then quenched by adding saturated NH_4Cl. The resultant resin was separated from the reaction mixture by filtration, followed by washing with THF: H_2O (1:1 v/v), THF, DMF, CH_2Cl_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 ($LiAlH_4$) 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 (2*S*)-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. 3

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 NH_4Cl (aq.) and extracted with ethyl acetate (× 3 times). The combined organic extracts were washed with brine, dried with $MgSO_4$ 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{24}NO_2$ [M+H$^+$]: 286.1807, found: 286.1807.

Preparation of *N*-[(1*S*)-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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80-7.40 (14H, m), 6.19 (1H, b), 4.95 (2H, s), 4.70 (1H, b), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 157.6, 137.1, 135.8, 130.0, 128.6, 127.9, 127.5, 127.3, 125.5, 115.1, 76.6, 74.1, 70.1, 35.3, 28.6, 25.8; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_2S$ [M+H$^+$]: 421.1950, found: 421.1951.

Preparation of (4*S*)-4,5-Dihydro-5,5-dimethyl-4-[[4-(phenylmethoxy)phenyl]methyl]-*N*-phenyl-2-oxazolamine (4). To stirred 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 NH_4Cl (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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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, 115.2, 86.1, 70.2, 68.9, 36.7, 27.4, 21.8; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_2$ [M+H$^+$]: 387.2072, found: 387.2073.

Preparation of (4*S*)-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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{21}N_2O_2$ [M+H$^+$]: 297.1603, found: 297.1602.

Preparation of Solid Supported 5,5-Dimethyl-2-phenylamino-2-oxazoline 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, CH_2Cl_2, 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*-Acylated-5,5-dimethyl-2-phenylamino-2-oxazoline 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 NH_4Cl solution. The resultant resin **7** was separated from the reaction mixture by filtration, followed by washing with THF/H_2O (1:1 v/v), THF, DMF, CH_2Cl_2, 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**. ^{1}H NMR (300 MHz, $CDCl_3$) 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 NH_4Cl. The resultant resin was separated from the reaction mixture by filtration, followed by washing with THF:H_2O (1:1 v/v), THF, DMF, CH_2Cl_2, and MeOH (x5 times) sequentially, and then dried in vacuum.

Due to the unstable characteristic of *N*-acylated 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, $LiAlH_4$ 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): H_2O (5 mL) for 15 min. Then, $LiOH{\cdot}H_2O$ (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 30% (4 steps based on the original loading of Wang resin); R_f = 0.63 (*n*-hexane:EA = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (5H, m), 3.10 (1H, dd, *J* = 7, 13 Hz), 2.75 (1H, m), 2.67 (1H, dd, *J* = 7, 13 Hz), 1.16 (3H, d, *J* = 7 Hz); the enantiomer excess (ee) was determined by HPLC to be > 99% after conversion acid to ester with CH_2N_2.

Conversion of Acid 10 to Methyl Ester 12: Acid **10** was directly converted into ester **12** by treatment with CH_2N_2 previously prepared from Diazald. 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), Diazald (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 CH_2N_2 was evoked and transferred into flask 1 to react with acid **10** and formed the required ester **12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (5H, m), 3.65 (3H, s), 3.00 (1H, dd, *J* = 7, 13 Hz), 2.75-2.55 (2H, m), 1.16 (3H, d, *J* = 7 Hz); HPLC condition of ester derivative: chiral cell OD-H column, hexane/*i*-PrOH 10:1, flow rate 0.3 mL/min, detection at 254 nm, R_{T1} = 15.4 min and R_{T2} = 17.5 min; ee > 99%.

Preparation of (*R*)-2-Methyl-3-phenyl-1-propanol (11). Resin **9** (0.62 g, 0.54 mmol) was swollen in THF (30 mL) at 0 °C and then $LiAlH_4$ 1 M in THF (2.7 mL, 2.70 mmol) was added and reacted at 0 °C for 3 h and at rt for 6 h. The excess $LiAlH_4$ quenched with water (0.1 mL), aqueous sodium hydroxide 15% (0.1 mL), and water (0.3 mL) in sequence. The reaction mixture was filtered off and washed with methylene chloride. The filtrate was dried over magnesium sulfate and the solvent was evaporated. The crude product was purified by flash column chromatography to yield **11** as colorless oil. Yield 25% (4 steps based on the original loading of Wang resin); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (5H, m), 3.50 (2H, m), 2.73 (1H, dd, *J* = 7, 13 Hz), 2.45 (1H, dd, *J* = 7, 13 Hz), 1.95 (1H, m), 0.95 (3H, d, *J* = 7 Hz); the enantiomer excess 62% (determined by HPLC using chiral cell OD-H column; hexane/*i*-PrOH 10:1; flowrate 0.5 mL/min; detection at 254 nm; R_{T1} =10.3 min, R_{T2} = 11.8 min).

Preparation of (*R*)-2-Methyl-3-phenyl-propionic Acid Methyl Ester (12). Resin **9** (0.52 g, 0.45 mmol) was swollen in THF (30 mL) at 0 °C and then NaOMe 0.5 M in MeOH (9 mL, 4.50 mmol) was added and reacted at 0 °C for 3 h and at rt for 6 h. The reaction mixture was quenched by adding saturated NH_4Cl. The resin was filtered off and the filtrate was evaporated to remove THF and extracted with dichloromethane. The crude product was purified by flash column chromatography to yield **12** as colorless oil. Yield 20% (4 steps based on the original loading of Wang resin); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.00 (5H, m), 3.65 (3H, s), 3.00 (1H, dd, *J* = 6.2, 12.7 Hz), 2.75-2.55 (2H, m), 1.16 (3H, d, *J* = 7 Hz); the enantiomer excess 15% (determined by HPLC using chiral cell OD-H column, hexane/*i*-PrOH 10:1, flowrate 0.3 mL/min, detection at 254 nm, R_{T1} = 15.4 min, R_{T2} = 17.5 min).

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References and Notes

1. (a) Seneci, P. *Solid Phase and Combinatotial Technologies*; John Willey & Sons: New York, 2000. (b) Obrecht, D.; Villalgordo, J. M. In *Solid-Supported Combinatorial and Parallel Synthesis of Small Molacular-Weight Compound Libraries.* (c) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235.
2. (a) Gaertner, P.; Schuster, C.; Knollmueller, M. *Lett. Org. Chem.* **2004**, *1*, 249. (b) Burgess, K.; Lim, D. *Chem. Commun.* **1997**, 785. (c) Kotake, T.; Hayashi, Y.; Rajesh, S.; Mukai, Y.; Takiguchi, Y.; Kimuara, T.; Kiso, Y. *Tetrahedron* **2005**, *61*, 3819. (d) Purandare, A. V.; Natarajan, S. *Tetrahedron Lett*. **1997**, *38*, 8777. (e) Phoon, C. W.; Abell, C. *Tetrahedron Lett* **1998**, *39*, 2655. (f) Winker, J. D.; McCoull, W. *Tetrahedron Lett.* **1998**, *39*, 4935. (g) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313. (h) Chung, C. W. Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387.
3. (a) Lee, G.-J.; Kim, T. H.; Kim, J. N.; Lee, U. *Tetrahedron: Asymmetry* **2002**, *13*, 9. (b) Le, T. N.; Nguyen, Q. P. B.; Kim, J. N.; Kim, T. H. *Tetrahedron Lett*. **2007**, *48*, 7834.
4. (a) Nguyen, Q. P. B.; Kim, J. N.; Kim, T. H. *Tetrahedron Lett*. **2009**, *50*, 4015. (b) Nguyen, Q. P. B.; Kim, T. H. *Bull. Korean Chem. Soc*. **2009**, *30*, 2935.
5. The acylation of 5,5-dimethyl-2-phenylamino-2-oxazoline **4** with propionyl chloride and asymmetric benzylation 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, $LiAlH_4$, and NaOMe cleavage conditions in the solution phase.