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ASYMMETRIC MANNICH-TYPE ADDITION OF LITHIUM GLYCOLATES TO IMINES PRODUCING 3-HYDROXY-4-PHENYLAZETIDIN-2-ONES[#]

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Abstract – The external chiral ligand-controlled asymmetric Mannich-type reaction of a binary- or ternary-complexed lithium ester enolate of protected glycolates with benzaldehyde imines gave the corresponding 3-trialkylsilyl-oxy-4-phenylazetidin-2-ones, applicable as a synthetic intermediate of C13 side chain of taxan anticancer drugs, in moderate enantioselectivity.

INTRODUCTION

Azetidin-2-one is the central motif of biologically potent compounds as has been shown in β-lactam antibiotics and other pharmaceuticals.[2] The open chain analogues of β-lactams, β-amino acid derivatives, are also important and attractive units of artificial peptoides as well as pharmaceuticals.[3] We have been engaged in the asymmetric Mannich-type reaction of lithium ester enolates with imines producing β-lactams as well as β-amino acid derivatives. Four major methodologies have been proven to be useful in this approach (Figure 1). The three-component reagent of a lithium ester enolate complexed with an external chiral diether ligand (**1**) and a lithium amide gave the corresponding β-lactam with high enantioselectivity upon treatment with an imine, where 20 mol% of **1** catalyzes the reaction.[4] The binary reagent of a lithium ester enolate complexed with **1** or a chiral amino diether ligand (**2**) was also efficient for this purpose where 5 mol% of **2** catalyzes the addition-elimination reaction.[5] A chiral menthyl acetate was also convertible to the powerful lithium enolate by the aid of a lithium amide in the presence[6] or absence[7] of 5 mol% of **1** or **2** producing β-lactams or β-amino esters with high enantio- or diastereomeric ratio.[8-10]

[#] Dedicated to the memory of the late Professor Kenji Koga.

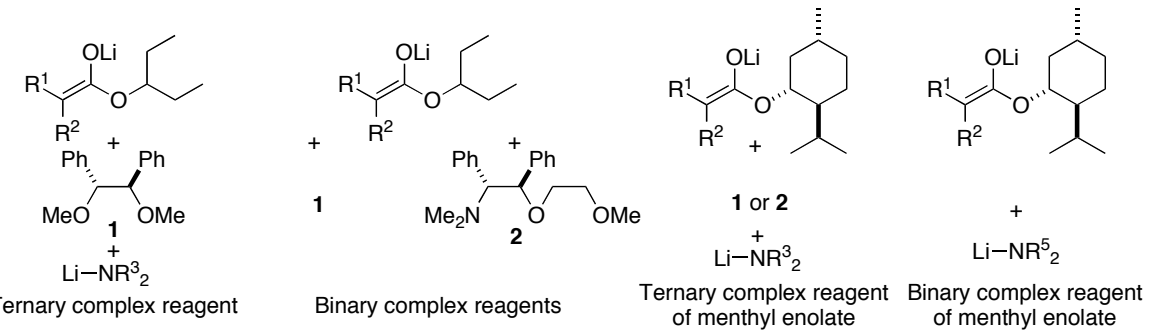


Figure 1. Four types of reagents of lithium enolates applicable in Mannich-type reaction

Extended application of these activated lithium enolate reagents to the short step asymmetric synthesis of biologically important β-lactams and β-amino carboxylic acid derivatives has been one of our current endeavors as has been shown in the short step asymmetric synthesis of a cholesterol absorption inhibitor Sch58053.[11] In this report we describe our approach to the asymmetric synthesis of 3-hydroxy-4-phenyl-azetidin-2-one, the synthetic intermediate of the essential C13 side chain of clinically evaluated anti-cancer drugs[12] paclitaxel and docetaxel (Figure 2).[13]

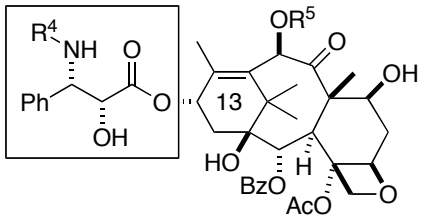
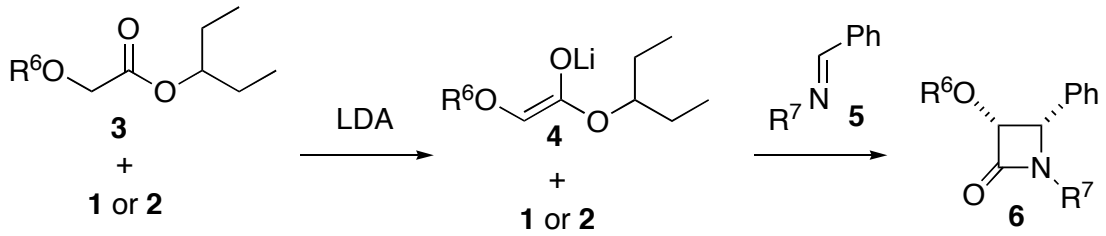


Figure 2. Taxan anticancer drugs

RESULTS AND DISCUSSION

The asymmetric Mannich-type reaction of protected glycolates (**3**) with benzaldehyde imines (**5**) was examined by the mediation of chiral ligands (**1**) and (**2**) in toluene (Scheme 1). The solution of a slightly excess equiv. of LDA was treated with a mixture of triisopropylsilyloxyacetate (**3a**: R^6 = *i*-Pr_3Si) (2.2 equv.) and **1** (3 equiv.) at –78°C for 0.5 h to form a binary complex reagent. To the mixture was added benzaldehyde 4-methoxyphenylimine (PMP-imie) (**5a**: R^7 = PMP) in toluene and the mixture was stirred at –40 °C for 2 h. Aqueous workup followed by purification by silica gel column chromatography gave β-lactam (**6a**) with 28% ee in 28% yield and recovered benzaldehyde (Table 1, run 1). The enantioselectivity was determined by a chiral stationary phase HPLC. The chiral amino diether (**2**) was much more effective to promote the reaction at –78 °C for 1 h giving *ent*-**6a** in 93% yield, though the ee was poorer 20% (run 2). TMS-imine (**5b**: R^7 = Me_3Si)[14] was a better substrate to give **6b** (R^7 = H) with 50% ee in 88% yield by the mediation of **1**, while the reaction with **2** gave *ent*-**6b** with 28% ee in 99% yield (entries 3, 4). *Tert*-butyldimethylsilyl ether (**3b**: R^6 = *t*-$BuMe_2Si$) was not a good source of a

nucleophile to give **6d** (R^7 = H) with 26% ee in 24% yield by **1**, *ent*-**6d** (R^7 = H) with 36% ee in 88% yield by **2**, and **6c** (R^7 = PMP) with 26% ee in 11% yield by **1** (runs 5-7). It is important to note that *cis*-**6** was the predominant product, although *trans*-**6d** was obtained as a minor product in 1% and 12% yields in the reaction of **3b** with **5b** (runs 6, 7). *Tert*-butyldiphenylsilyl ether (**3c**: R^6 = *t*-$BuPh_2Si$) was the best source of nucleophiles in the reaction with **5b** by the mediation of **1** to give **6e** (R^7 = H) with 65% ee in 73% yield, while other two ligands, (**2**) and sparteine, gave *ent*-**6e** (R^7 = H) with 11% and 13% ees (runs 8-10). The chiral ligands were recovered nearly quantitatively and reusable.



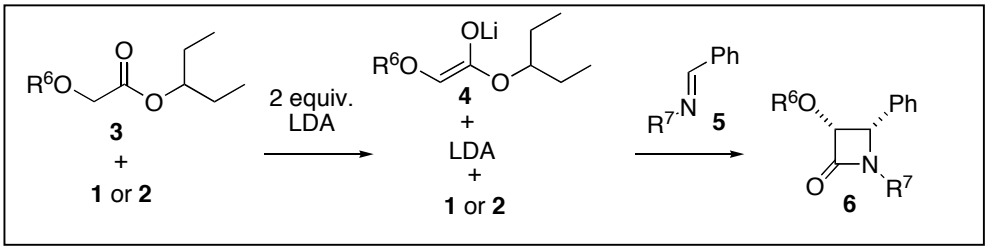
Scheme 1. Mannich addition reaction of binary complex reagent of lithium enolate

Table 1. Asymmetric Mannich-Type Reaction of Binary Reagents of Lithium Ester Enolate with Imine (**5**)

run	**3**	R^6	**5**	R^7	ligand	temp/°C	time/h	product	R^7	ee/ %	yield/%
1	**3a**	*i*-Pr_3Si	**5a**	4-$MeOC_6H_4$	**1**	–40	2	**6a**	4-$MeOC_6H_4$	28	28
2	**3a**	*i*-Pr_3Si	**5a**	4-$MeOC_6H_4$	**2**	–78	1	*ent*-**6a**	4-$MeOC_6H_4$	20	93
3	**3a**	*i*-Pr_3Si	**5b**	Me_3Si	**1**	–20	4	**6b**	H	50	88
4	**3a**	*i*-Pr_3Si	**5b**	Me_3Si	**2**	–40	2	*ent*-**6b**	H	28	99
5	**3b**	*t*-$BuMe_2Si$	**5a**	4-$MeOC_6H_4$	**1**	–20	1.5	**6c**	4-$MeOC_6H_4$	26	11
6	**3b**	*t*-$BuMe_2Si$	**5b**	Me_3Si	**1**	–20	4	**6d**	H	26	24/1[a)]
7	**3b**	*t*-$BuMe_2Si$	**5b**	Me_3Si	**2**	–40	2	*ent*-**6d**	H	36	88/12[a)]
8	**3c**	*t*-$BuPh_2Si$	**5b**	Me_3Si	**1**	–40	2.5	**6e**	H	65	73
9	**3c**	*t*-$BuPh_2Si$	**5b**	Me_3Si	**2**	–40	2	*ent*-**6e**	H	11	99
10	**3c**	*t*-$BuPh_2Si$	**5b**	Me_3Si	(-)-sparteine	–40	2	*ent*-**6e**	H	13	47

a) Yields of *cis*-**6**/*trans*-isomer.

The asymmetric reaction of ternary-complexed lithium ester enolate of **3** with **5** was then examined to improve the selectivity (Scheme 2). The ternary reagents containing **1** were more reactive than the binary reagent to promote the reaction at–78 °C lower than –40 °C (Table 2). The chiral diether (**1**) was more efficient than **2** to give **6** with better selectivity. Although the reactions of **3a** with **5a** were not promising (runs 1, 2), the reaction with **5b** gave **6b** with 64% ee in 88% yield (run 3). The reaction of **3b** with **5b** was also improved to give **6d** with 56% ee in 24% by the mediation of **1** and *ent*-**6d** with 45% ee in 77% by **2** (runs 5, 6). In these reactions of **3b** *trans*-isomer of **6d** was obtained in 6% and 13% yields, respectively. The reaction of **3c** with **5b** gave **6e** with 61% ee, while **2** and sparteine were also found to be the unsatisfactory ligands in these reactions of ternary complexed reagents (runs 7-9). The chiral ligands were recovered nearly quantitatively and reusable.



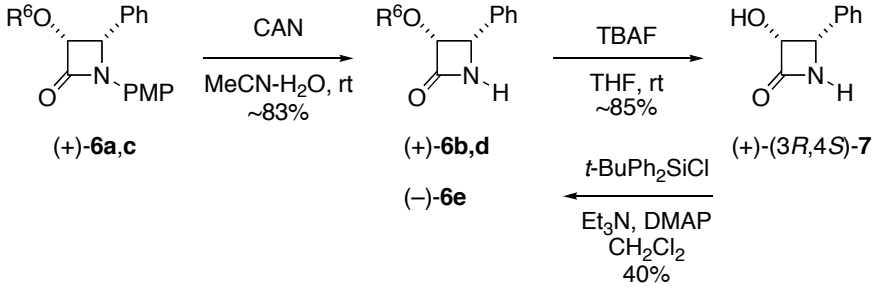
Scheme 2. Mannich addition reaction of ternary complex reagent of lithium enolate

Table 2. Asymmetric Mannich-Type Reaction of Ternary Reagents of Lithium Ester Enolate with Imine (**5**)

run	**3**	R^6	**5**	R^7	ligand	temp/°C	time/h	product	R^7	ee/ %	yield/%
1	**3a**	*i*-Pr_3Si	**5a**	4-$MeOC_6H_4$	**1**	–78	1.5	**6a**	4-$MeOC_6H_4$	31	42
2	**3a**	*i*-Pr_3Si	**5a**	4-$MeOC_6H_4$	**2**	–78	1	*ent*-**6a**	4-$MeOC_6H_4$	7	30
3	**3a**	*i*-Pr_3Si	**5b**	Me_3Si	**1**	–78	2	**6b**	H	64	88
4	**3a**	*i*-Pr_3Si	**5b**	Me_3Si	**2**	–78	2	*ent*-**6b**	H	18	58
5	**3b**	*t*-$BuMe_2Si$	**5b**	Me_3Si	**1**	–78	2	**6d**	H	56	24/6[a]
6	**3b**	*t*-$BuMe_2Si$	**5b**	Me_3Si	**2**	–78	2	*ent*-**6d**	H	45	77/13[a]
7	**3c**	*t*-$BuPh_2Si$	**5b**	Me_3Si	**1**	–78	2	**6e**	H	61	46
8	**3c**	*t*-$BuPh_2Si$	**5b**	Me_3Si	**2**	–78	2	**6e**	H	5	53
9	**3c**	*t*-$BuPh_2Si$	**5b**	Me_3Si	(-)-sparteine	–78	2	*ent*-**6e**	H	9	14

a) Yields of *cis*-**6**/*trans*-isomer.

The absolute configuration of (+)-**6** was determined unambiguously by converting to the (+)-(3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one (**7**)[15] with the established stereochemistry. Thus (+)-**6a**,**c** were treated with CAN in aqueous acetonitrile to afford (+)-**6b**,**d** in high yields, which were then treated with TBAF in THF to give (+)-(3*R*,4*S*)-**7** in high yields. Inversely, (+)-**7** was converted to (–)-**6e**. Thus, the absolute configurations of (+)-**6a**-**6d** and (–)-**6e** were correlated to (+)-(3*R*,4*S*)-**7**.



Scheme 3. Determination of the absolute configuration of **6**

CONCLUSION

The external chiral ligand–controlled asymmetric Mannich-type addition reaction of the ternary or binary complexed reagents of lithium enolates of protected glycolates with imines gave the corresponding 3-trialkylsilyloxy-4-phenylazetidin-2-ones with moderate ee, applicable as an substrate for the introduction of C13 side chain of taxan anticancer drugs. Further studies towards development of more efficient Mannich-type reaction are in progress by using menthyl acetate as a chiral enolate source in our laboratories.[16]

EXPERIMENTAL[17]

3-Pentyl glycolate (3: R^6 = H): Prepared as usual.[4] A mixture of glycolic acid (7.61 g, 0.10 mol), 3-pentanol (21.6 mL, 0.20 mol), and *p*-TsOH monohydrate (190 mg, 1.0 mmol) in 15 mL of benzene was stirred under reflux for 6 h, and then washed with satd. sodium bicarbonate and brine, and then concentrated. Distillation gave glycolate (73 °C/9.5 mmHg, 10.5 g, 72%) as a colorless oil. ^{1}H-NMR: 0.88 (6H, t, J=7.0 Hz), 1.4-1.8 (4H, m), 2.39 (1H, t, J=5.0 Hz, exchangeable with D_2O), 4.14 (2H, d, J=5.0 Hz), 4.88 (1H, quint, J=6.3 Hz). ^{13}C-NMR: 9.06 (q), 26.00 (t), 77.65 (d), 173.04 (s). IR (neat): 3430, 1740, 1210 cm^{-1}.

3-Pentyl triisopropylsilyloxyacetate (3a: R^6 = *i*-Pr_3Si): A mixture of glycolate (2.92 g, 20 mmol), triisopropylsilyl chloride (4.70 mL, 22 mmol), imidazole (1.63 g, 24 mmol), and *N*,*N*-dimethylaminopyridine (122 mg, 1.0 mmol) in 20 mL of methylene chloride was stirred at rt for 24 h. After dilution with 200 mL of ether, the whole was washed with satd. sodium bicarbonate, satd. ammonium chloride, and then brine. Concentration followed by distillation gave an acetate (132 °C/6.5 mmHg, 6.03 g, quant) as a colorless oil. ^{1}H-NMR: 0.88 (6H, t, J=7.5 Hz), 1.4-1.8 (4H, m), 2.0-2.3 (3H, m), 2.10 (18H, d, J=2.3 Hz), 1.4-1.8 (4H, m), 4.33 (2H, s), 4.85 (1H, quint, J=5.5 Hz). ^{13}C-NMR: 9.47 (q), 11.86 (d), 17.72 (q), 26.38 (t), 62.00 (t), 77.09 (d), 171.41 (s). IR (neat): 1750, 1720, 1155 cm^{-1}. MS *m*/*z*: 303 (M^++1). Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.43; H, 11.11.

3-Pentyl *tert*-butyldimethylsilyloxyacetate (3b: R^6 = *t*-$BuMe_2Si$): Prepared as a colorless oil (121-123 °C/14.5 mmHg) in 96% yield by the same procedure. ^{1}H-NMR: 0.16 (6H, s), 0.93 (6H, t, J=6.8 Hz), 0.96 (9H, s), 1.4-1.8 (4H, m), 4.26 (2H, s), 4.87 (1H, quint, J=6.3 Hz). ^{13}C-NMR: 5.75 (q), 9.31 (q), 18.12 (s), 25.47 (q), 26.26 (t), 61.51 (t), 76.86 (d), 171.27 (s). IR (neat): 1750, 1725, 1140 cm^{-1}. MS *m*/*z*: 261 (M^++1). Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 60.01; H, 10.56.

3-Pentyl *tert*-butyldiphenylsilyloxyacetate (3c: R^6 = *t*-$BuPh_2Si$): Prepared by using triethylamine and *N*,*N*-dimethylaminopyridine as bases in 70% yield as a colorless oil. ^{1}H-NMR: 0.16 (6H, t, J=7.3 Hz), 1.11 (9H, s), 1.4-1.6 (4H, m), 4.26 (2H, s), 7.3-7.4 (6H, m), 7.6-7.7 (4H, m). ^{13}C-NMR: 9.44 (q), 19.14 (s), 26.33 (t), 26.53 (q), 62.12 (t), 77.07, 127.64, 135.45 (each d), 129.72 (d), 132.81 (s), 171.00. IR (neat): 1740, 1200, 1100 cm^{-1}. MS *m*/*z*: 327 (M^+-*t*-Bu). Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.98; H, 8.13.

***cis*-(–)-(3*R*,4*S*)-3-*tert*-Butyldiphenylsilyloxy-4-phenylazetidin-2-one ((–)-6e: R^6 = *t*-$BuPh_2Si$, R^7 = H) (Table 1, run 8)**: To a mixture of lithium diisopropylamide, prepared from diisopropylamine (0.18 mL, 1.3 mmol) and *n*-butyllithium (1.59 M in hexane, 0.78 mL, 1.2 mmol), in 3 mL of toluene was added a mixture of TBDPS ether (**3c**: R^6 = *t*-$BuPh_2Si$) (434 mg, 1.1 mmol) and **1**[18] (355 mg, 1.5 mmol) in 3.5 mL of toluene at –20 °C. After the whole was stirred at –20 °C for 1 h, 3.5 mL of toluene solution of an imine (**5b**: R^7 = Me_3Si) (100 mg, 0.56 mmol) was added at –78 °C over 1 min. The whole was stirred at –40 °C

for 2.5 h and was quenched with satd. ammonium chloride, and was then extracted with ethyl acetate. The extracts were washed with brine and then dried over sodium sulfate. Concentration and silica gel column chromatography (ether/benzene=1/15) gave (–)-**6e** (164 mg, 73%) as a white solid of mp 127-130 °C and $[\alpha]^{25}_{D}$ –8.58 °(c 1.20, $CHCl_3$). 65% ee (HPLC, OD, *i*-PrOH/hexane=1/50, 1.0mL/min, (4*S*) 75 min, (4*R*) 88 min). ^{1}H-NMR: 0.78 (9H, s), 4.54 (1H, d, J=4.6 Hz), 4.97-4.98 (1H, m), 6.88 (1H, br s), 7.28-7.39 (13H, m), 7.60-7.67 (2H, m). ^{13}C-NMR: 18.83 (s), 26.13 (q), 59.35 (d), 79.62 (d), 127.46, 127.66, 128.10, 128.28, 135.53, 135.63 (each d), 128.01, 129.72, 129.79 (each d), 132.24, 132.53 (each s), 132.26 (s), 170.06. IR ($CHCl_3$): 1750 cm^{-1}. MS *m*/*z*: 401 (M^+). Anal. Calcd for $C_{25}H_{27}NO_2Si$: C, 74.77; H, 6.78; N, 3.49. Found: C, 74.55; H, 6.68; N, 3.56.

***cis*-(+)-(3*R*,4*S*)-4-Phenyl-3-triisopropylsilyloxyazetidin-2-one ((+)-6b: R^6 = *i*-Pr_3Si, R^7 = H) (Table 2, run 3)**: To LDA (2.1 mmol) in 5 mL of toluene was added a mixture of TIPS ether (**3a**: R^6 = *i*-Pr_3Si) (285 mg, 1.2 mmol) and **1** (446 mg, 1.8 mmol) at –20 °C and the whole was stirred at –20 °C for 1 h. A solution of an imine (**5b**: R^7 = Me_3Si) (84 mg, 0.47 mmol) in 1.5 mL of toluene was added at –70 °C and the whole was stirred at –78 °C for 2 h. The usual workup and column chromatography (ether/benzene=1/15) gave (+)-**6b** (132 mg, 88%) as white solid of mp 78-79 °C and $[\alpha]^{25}_{D}$ +32.2 °(c 1.04, $CHCl_3$). 64% ee (HPLC, AD, *i*-PrOH/hexane=1/100, 1.0 mL/min, (4*R*) 35 min, (4*S*) 56 min). ^{1}H-NMR: 0.77-1.38 (21H, m), 4.81 (1H, d, J=5.0 Hz), 5.18 (1H, dd, J=5.0, 2.5 Hz), 6.30 (1H, br s), 7.23-7.42 (5H, m). ^{13}C-NMR: 11.52, 17.24, 59.50, 79.53, 127.71, 127.78, 128.01, 136.30, 170.49. IR ($CHCl_3$): 1760 cm^{-1}. MS *m*/*z*: 319 (M^+). Anal. Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66; H, 9.15; N, 4.38. Found: C, 67.65; H, 9.16; N, 4.29.

***cis*-(–)-(3*S*,4*R*)-3-*tert*-Butyldimethylsilyloxy-4-phenylazetidin-2-one (*ent*-6d: R^6 = *t*-$BuMe_2Si$, R^7 = H) (Table 2, run 6)**: a colorless solid of mp 113-116 °C and $[\alpha]^{25}_{D}$ –31.1 °(c 0.95, $CHCl_3$). 45% ee (HPLC, AS, *i*-PrOH/hexane=1/20, 1.0 mL/min, (4*R*) 17 min, (4*S*) 38 min). ^{1}H-NMR: –0.16 (3H, s), 0.04 (3H, s), 0.63 (9H, s), 4.80 (1H, d, J=5.0 Hz), 5.06 (1H, dd, J=5.0, 2.5 Hz), 6.22 (1H, br s), 7.23-7.38 (5H, m). ^{13}C-NMR: –5.50, –5.01, 17.72, 25.18, 59.12, 79.56, 128.01, 128.03, 128.11, 136.30, 169.86. IR ($CHCl_3$): 3355, 1740 cm^{-1}. MS *m*/*z*: 277(M^+). Anal. Calcd for $C_{15}H_{23}NO_2Si$: C, 64.94; H, 8.36; N, 5.05. Found: C, 64.86; H, 8.33; N, 4.89.

***trans*-Isomer**: a colorless solid of mp 55-63 °C. 6% ee (HPLC, AS, *i*-PrOH/hexane =1/20, 1.0 mL/min, (4*R*) 16 min, (4*S*) 24 min). ^{1}H-NMR: 0.08 (6H, s), 0.91 (9H, s), 4.45-4.60 (2H, m), 6.33 (1H, br s), 7.20-7.42 (5H, m). ^{13}C-NMR: –4.92, -4.81, 18.08, 25.63, 62.21, 85.93, 125.62, 128.88, 128.39, 138.38, 169.09. IR ($CHCl_3$): 1755 cm^{-1}. MS *m*/*z*: 277(M^+). HRMS *m*/*z*: Calcd for $C_{15}H_{23}NO_2Si$ (M^+): 277.1498. Found: 277.1507.

Correlation of (+)-(3*R*,4*S*)-3-(*tert*-butyldimethylsilyloxy)-4-phenylazetidin-2-one ((+)-6d) to (+)-(3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one ((+)-7): A mixture of (+)-**6d** (Table 2, run 5, 56% ee, 36 mg,

0.13 mmol) and TBAF (1N THF solution, 0.39 mL, 0.39 mmol) was stirred at 0 °C for 2 h. Concentration and silica gel column chromatography (ethyl acetate/benzene=3/2) gave (+)-**7** (18 mg, 85%) as a colorless solid of mp 174-182°C and $[\alpha]^{20}_{D}$ +106.6 °(c 1.01, MeOH). ^{1}H-NMR: 2.0 (1H, br s), 4.93 (1H, d, J=5.0 Hz), 5.11 (1H, dd, J=5.0, 2.5 Hz), 6.25 (1H, br s), 7.17-7.63 (5H, m). IR ($CHCl_3$): 3360, 3200, 1715 cm^{-1}. Spectral data were identical with those reported.[15]

Correlation of (+)-(3*R*,4*S*)-4-phenyl-3-(triisopropylsilyloxy)azetidin-2-one (6b) to (+)-7: Prepared from (+)-**6b** (Table 1, run 3, 50% ee, 102 mg, 0.32 mmol) in 88% yield as a colorless solid of mp 174-181 °C and $[\alpha]^{20}_{D}$ +90.9 °(c 1.16, MeOH).

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