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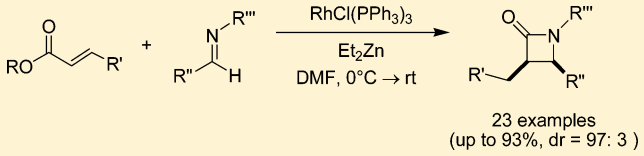
Diastereoselective Synthesis of *syn*-β-Lactams Using Rh-Catalyzed Reductive Mannich-Type Reaction of α,β-Unsaturated Esters

Motoyuki Isoda, Kazuyuki Sato, Masato Funakoshi, Keiko Omura, Atsushi Tarui, Masaaki Omote, and Akira Ando*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan

Supporting Information

ABSTRACT: The combination of Et_2Zn and $RhCl(PPh_3)_3$ led to the facile generation of a rhodium−hydride complex (Rh−H) that catalyzed the 1,4-reduction of α,β-unsaturated esters. The resulting rhodium enolate performed as a Reformatsky-type reagent and reacted with various imines to give *syn*-β-lactams in good to excellent yields with high diastereoselectivity.



β-Lactam (azetidin-2-one) skeletons can be found in a wide range of bioactive natural products and pharmaceutical compounds, such as antibiotics[1] and therapeutic agents for the treatment of dyslipidemia.[2] Following on from Sir Alexander Fleming's discovery of penicillin in 1928,[3] there have been numerous studies directed toward evaluating the biological properties of β-lactams. Furthermore, a wide variety of different approaches have been developed for the preparation of β-lactams.[4] For example, the intramolecular cyclization of β-amino acid derivatives and the Staudinger ketene cycloaddition reaction are both classical methods for the construction of β-lactams.[5] Several other methods have also been developed, including the metal-catalyzed carbonylation for aziridines,[6] the intramolecular C−H insertion reactions using diazo compounds,[7] and the Kinugasa reaction, which involves the reaction of a nitrone with a terminal alkyne.[8]

A wide variety of Mannich-type reactions have been reported to give β-amino esters and/or β-lactams via the reaction of a metal enolate with a copper,[9] cobalt,[10] or rhodium catalyst.[11] In contrast, there have been very few reports pertaining to the development of reductive Mannich-type reactions to give β-amino esters and/or β-lactams using R_3Si-H, $Li(Et_3BH)$, or hydrogen as a reductant.[10b,11a,12] We recently reported a reductive Reformatsky−Honda reaction with various electrophiles (e.g., acid derivatives, aldehydes, and ketones) to give the corresponding products in good to excellent yields.[13] Imines also reacted smoothly under these conditions to give the corresponding β-lactams as the major products, together with a small amount of the β-amino esters. It is noteworthy that this reaction afforded *syn*-β-lactams with good diastereoselectivity. In general, the formation of *syn*-β-lactams is particularly rare,[14] and there are no reports for synthesizing *syn*-β-lactams using the reductive Mannich reaction. Herein, we would like to report the *syn* selective synthesis of β-lactams via the reductive Mannich-type reaction of α,β-unsaturated esters with various imines.

In our previous paper,[13a] we reported that the reaction of methyl acrylate (**1a**) with imine **2Aa** gave the corresponding β-lactam **3Aa** in 70% yield and the β-amino ester **4Aa** in 12% yield with good *syn* selectivities (Scheme 1). Each diastereomer of **3Aa** could separate by column chromatography, and its stereochemistry was determined by NOE between the CH_3 and C_6H_5 groups on the azetidin-2-one ring and the coupling constant of protons on the C3 and C4 (*syn* form: J = 5.0−6.0 Hz, *anti* form: J = 2.0−3.0 Hz). In addition, **4Aa** was transformed into **3Aa**, and the stereochemistry was determined by the same manner. However, it was very difficult to separate the desired β-lactam **3Aa** and the corresponding amino ester **4Aa** from the reaction mixture because of using the excess amount of imine **2Aa**. This transformation was, therefore, selected as a model reaction by reducing the amount of imine **2Aa** from 2 equiv. to 1.2 equiv., and the reaction conditions were optimized. The results are summarized in Table 1. It seemed that the amino ester **4Aa** transformed to the β-lactam **3Aa** over time and reached the similar yield of a previous result by 72 h, as shown in entries 2−4. However, we thought the reaction time in entry 4 was too long to obtain **3Aa**, and we examined the solvents while fixing time for 24 h to improve the yield (Table 1, entries 6−10). Finally, we decided on entry 3 with optimal conditions.

With the optimum conditions in hand (Table 1, entry 3), we proceeded to examine the scope of the reaction by varying the nature of the substituent on the nitrogen of the imine, and the results are summarized in Table 2. Benzyl, phenyl, and *p*-methoxyphenyl (PMP) groups gave the corresponding β-lactams in moderate to good yields with high diastereoselectivities (Table 2, entries 1−3). In contrast, the use of alkyl and phosphonic groups failed to provide any of the desired products, although the phosphonic amide gave the *syn*-β-amino ester **4Fa** in low yield (Table 2, entries 4−6).

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Scheme 1. Previous Result

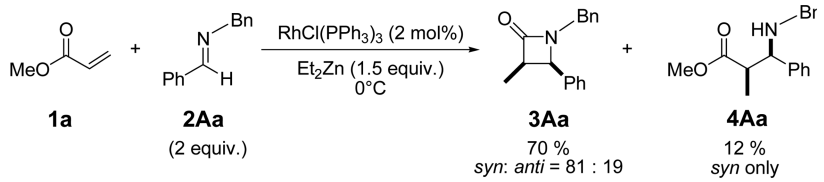
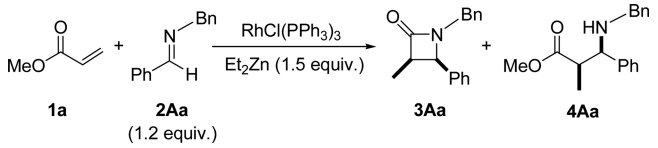


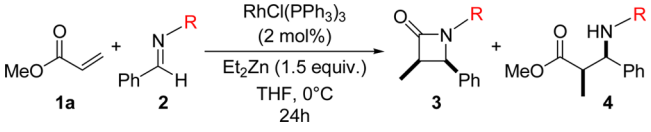
Table 1. Optimization of the Reaction Conditions



entry	$RhCl(PPh_3)_3$ (mol %)	solv.	time (h)	temp. (°C)	yield (%)[a] 3Aa [*syn*:*anti*][b]	yield (%)[a] 4Aa[c,d]
1	none	THF	5	0	0	0
2	2	THF	3	0	40 [77:23]	45
3	2	THF	24	0	64 [83:17]	22
4	2	THF	72	0	71 [83:17]	17
5	2	THF	24	rt	58 [78:22]	26
6	2	hexane	24	0	0	30
7	2	toluene	24	0	12 [75:25]	32
8	2	CH_2Cl_2	24	0	17 [100:0]	39
9	2	Et_2O	24	0	0	43
10	2	DME	24	0	34 [74:26]	33

[a]Isolated yield. [b]Diastereomeric ratio (*syn*:*anti*) after purification. [c]Only *syn* isomer was obtained. [d]The stereochemistry was determined by ^{1}H NMR after transforming into **3Aa**.

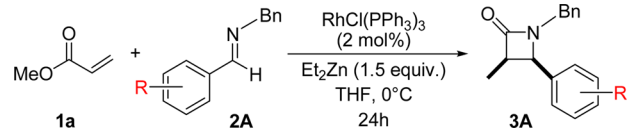
Table 2. Substituent Effect of Imines

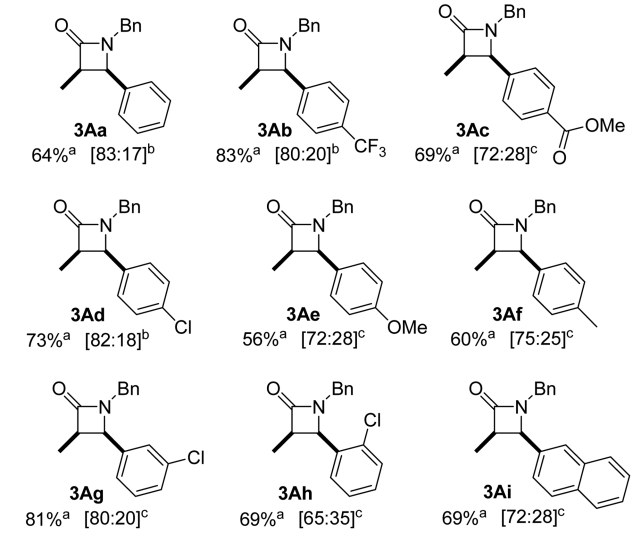


entry	imine		yield (%)[a] β-lactam (3)[b]		yield (%)[a] β-amino ester-(4)[c]	
1	Bn	**2Aa**	64 [83:17]	**3Aa**	22	**4Aa**
2	Ph	**2Ba**	53 [100:0]	**3Ba**	41	**4Ba**
3	PMP	**2Ca**	62 [100:0]	**3Ca**	21	**4Ca**
4	Me	**2Da**	nd	**3Da**	nd	**4Da**
5	*tert*-Bu	**2Ea**	nd	**3Ea**	nd	**4Ea**
6	$P(O)Ph_2$	**2Fa**	nd	**3Fa**	26	**4Fa**

[a]Isolated yield. [b]The individual diastereomers were isolated by column chromatography. [c]Only the *syn* isomer was obtained.

Table 3. Synthesis for *N*-Benzyl Substituted β-Lactams





[a]Isolated yield. [b]The individual diastereomers were isolated by column chromatography. [c]The diastereomeric ratio (*syn*:*anti*) was determined by ^{1}H NMR.

Various *N*-benzyl substituted imines **2A** were also investigated to further evaluate the scope of the reaction (Table 3). The presence of an electron-withdrawing or electron-donating group on the benzene ring did not give a significant influence in the yield and selectivity, and the desired products were obtained in good yields in all cases, together with small amounts of the corresponding *syn*-β-amino esters.

We found that the use of *N*-PMP imines **2C** in the Rh-catalyzed reaction in DMF resulted in the significant improvement of the *syn* stereoselectivity. Unfortunately, some of *N*-PMP imines did not react under the optimized reaction conditions because they were insoluble to THF. For this reason, several alternative solvents were examined, and it was found that changing the solvent to DMF led to significant improvements in the yield and selectivity of the reaction (Table 4). Having identified a suitable solvent for the *N*-PMP imines,

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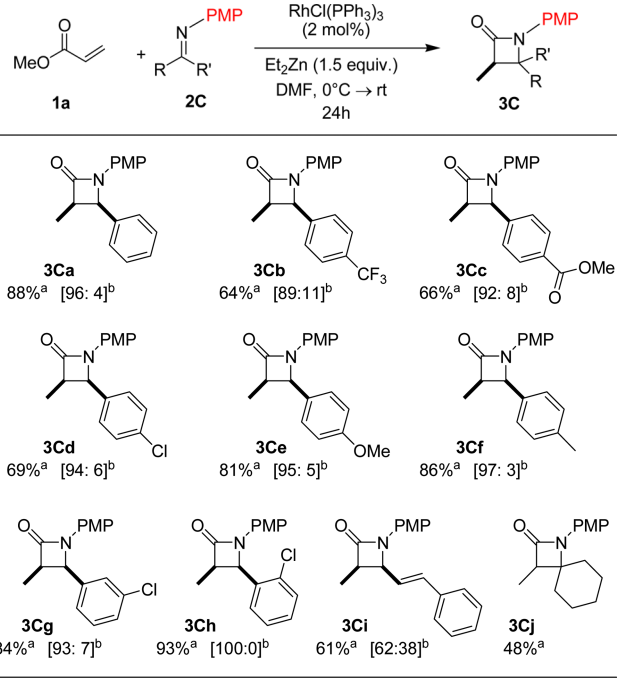
Table 4. Synthesis for *N*-*p*-Methoxyphenyl Substituted *β*-Lactams



[a]Isolated yield. [b]Diastereomeric ratio (*syn*:*anti*) after purification.

we proceeded to evaluate the scope of the reaction. The presence of an electron-withdrawing group on the benzene ring led to a slight decrease in the yield, although the products were isolated with high *syn* selectivity. Imines bearing an electron-donating group on their benzene ring gave the corresponding products in excellent yields with high *syn* selectivity, even when the substituent was positioned at the meta- or ortho-position. Notably, the imines derived from an aliphatic aldehyde and a ketone were also well tolerated and gave the corresponding *β*-lactams in moderate yields. The most interesting of these examples was the spiro-*β*-lactam **3Cj**, which was obtained in a one-pot reaction using ketimine.

It was envisaged that a rhodium−hydride complex (Rh−H) was involved in this reaction. We, therefore, considered a nucleophilic attack by rhodium enolate into imines at first.[15] However, an additional role of Zn species exists for several stages in this reaction, and the active species was zinc enolate because most of the reductive Mannich reactions without zinc species did not give the *β*-lactams, but the *β*-amino esters. With this in mind, we proposed a plausible mechanism for this reaction, which is shown in Figure 1.[13] The Rh catalyst would

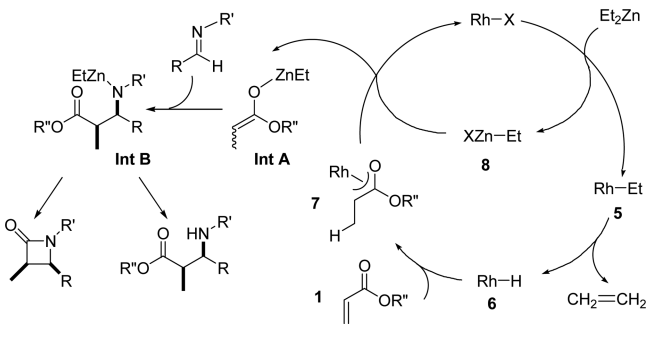


Figure 1. Plausible reaction mechanism.

react with Et_2Zn to give the Rh−H species **6** via the elimination of ethylene from the ethyl rhodium complex **5**. The 1,4-reduction of *α*,*β*-unsaturated ester **1** with **6** would give rhodium enolate **7**, which would undergo a transmetalation reaction with zinc species **8** to give the Reformatsky-type reagent **Int A**. **Int A** would then react with the imine substrate to give the corresponding *β*-lactam **3** and/or *β*-amino ester **4**. It seems reasonable to suggest that the *N*-zinc *β*-amino ester intermediate **Int B** would cyclize to give the *syn*-*β*-lactam via an intramolecular nucleophilic substitution reaction.

To develop a deeper understanding of the mechanism responsible for the high diastereoselectivity of the reaction, we investigated the reaction of *tert*-butyl acrylate (**1b**) with imine **2Ca** under the same conditions that gave the *syn*-*β*-amino ester **9** in 86% as the sole product. Several attempts were made to trap the **Int A** species formed during this reaction from *tert*-butyl acrylate with TMS−Cl, and it is noteworthy that this trapping procedure only resulted in the detection of the *E*-silyl enolate. Given that the configuration of the **Int A** species was identified as that of the *E*-enolate, it was speculated that the reaction was proceeding via a linear transition state (Figures 2 and 3).

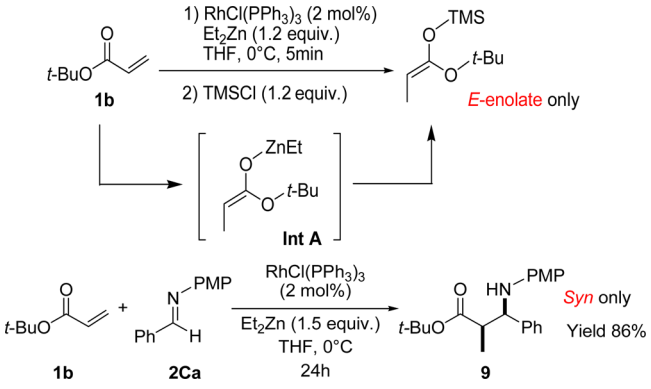


Figure 2. Reaction of **1b** and **2Ca** and the configuration of **Int A**.

To conclude this study, we also investigated the application of the optimized conditions to a series of *α*,*β*-unsaturated esters (Table 5). The presence of a substituent at the *β*-position of the *α*,*β*-unsaturated ester was found to have very little impact on the outcome of the reaction. Methyl crotonate (**1c**) gave the *β*-lactam **10** in low yield with reasonably high *syn* selectivity, whereas methyl cinnamate (**1d**) failed to provide any of the desired products. Notably, the *α*,*β*-unsaturated *γ*- and *δ*-lactones reacted smoothly to give the desired products (**12** and **13**), although the stereochemistry of these products was determined to be the *anti* configuration. It currently remains unclear as to why the *α*,*β*-unsaturated lactone substrates gave the corresponding *anti*-*β*-lactams exclusively.

In conclusion, we have developed a highly diastereoselective reductive Mannich-type reaction using a Rh catalyst with Et_2Zn. This reaction provided rapid access to *β*-lactams in good to excellent yields with excellent *syn* selectivity.

EXPERIMENTAL SECTION

General Information. NMR spectra were obtained from a solution in $CDCl_3$ using 400 MHz for ^1H, 100 MHz for ^{13}C, and 90 MHz for ^{19}F. Chemical shifts of ^1H NMR and ^{13}C NMR are reported in ppm from tetramethylsilane (TMS) as an internal standard. Chemical shifts of ^{19}F NMR are reported in ppm from ethyl

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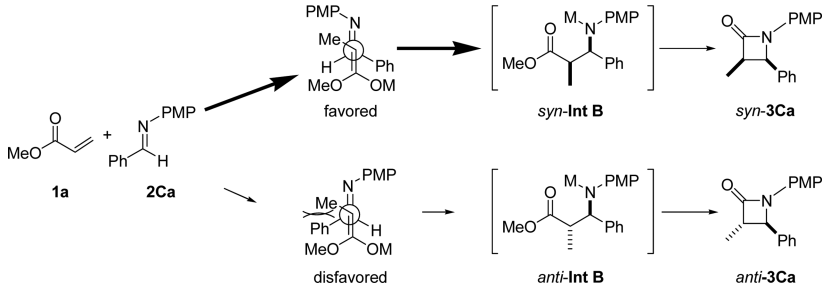
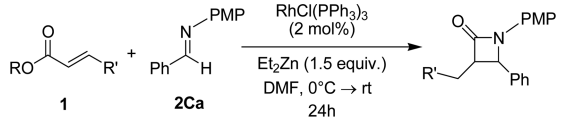
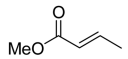
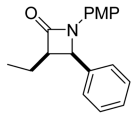
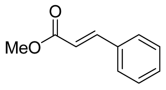
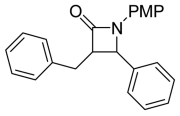
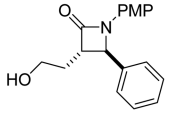
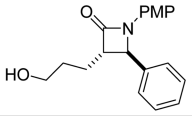


Figure 3. Tentative transition-state model.

Table 5. Steric Effect for β-Substituted α,β-Unsaturated Ester or Lactone



1 2Ca

entry	1		product		yield (%)
1		1c		10	34%[a] [100:0][b]
2		1d		11	nd
3		1e		12	28%[a] [0:100][b]
4		1f		13	11%[a] [0:100][b]

[a]Isolated yield. [b]Diastereomeric ratio (*syn*:*anti*) after purification.

trifluoroacetate (ETFA) as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qd = quartet doublet, br = broad, m = multiplet), coupling constants (Hz). High-resolution mass spectroscopy (HRMS) experiments were measured on a double-focusing mass spectrometer with an ionization mode of EI or positive FAB as indicated for each compound. Infrared (IR) spectra were recorded in KBr tablets or thin films on either KBr disks. Melting points were measured uncorrected.

MATERIALS

Tetrahydrofuran (THF) was purchased from Kanto Chemical Co. Inc. as "Dehydrated". All imines were prepared from corresponding aldehydes and amines. Methyl acrylate and *tert*-butyl acrylate were distilled just before use. Other commercially available reagents were used without further purification. All experiments were carried out under an argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

Method 1: Typical Procedure for Synthesis of *N*-Benzyl- or *N*-Phenyl-azetidin-2-one. Methyl acrylate (**1a**, 1 mmol) and (*E*)-*N*-benzylidene(phenyl)methanamine (**2Aa**, 1.2 mmol) were added to a solution of $RhCl(PPh_3)_3$ (2 mol %) in THF (2.5 mL) at 0 °C. Then, 1.0 M Et_2Zn in hexane (1.5 mmol, 1.5 mL) was gradually added to the mixture at 0 °C, and the mixture was stirred at the same temperature for 24 h. The mixture was quenched with sat. $NaHCO_3$ and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (AcOEt:hexane = 2:8). The diastereomers were obtained in 53% (132.7 mg; *syn*-**3Aa**) and 11% yield (26.9 mg; *anti*-**3Aa**), respectively. The stereochemistry of the products was determined by NOE between the CH_3 and C_6H_5 groups on the azetidin-2-one ring and the coupling constant between the protons of C3 and C4 (*syn* form: J = 5.0−6.0 Hz, *anti* form: J = 2.0−3.0 Hz).

Method 2: Typical Procedure for Synthesis of *N*-(*p*-Methoxyphenyl)-azetidin-2-one. Methyl acrylate (**1a**, 1 mmol) and (*E*)-*N*-benzylidene-4-methoxybenzenamine (**2Ca**, 1.2 mmol) were added to a solution of $RhCl(PPh_3)_3$ (2 mol %) in DMF (2.5 mL) at 0 °C. Then, 1.0 M Et_2Zn in hexane (1.5 mmol, 1.5 mL) was gradually added to the mixture at 0 °C, and the mixture was stirred at room temperature for 24 h. The mixture was quenched with sat. NH_4Cl and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (AcOEt:hexane = 2:8). The diastereomers were obtained in 84% (225.9 mg; *syn*-**3Ca**) and 4% yield (9.9 mg; *anti*-**3Ca**), respectively. The stereochemistry of the products was determined by NOE between the CH_3 and C_6H_5 groups on the azetidin-2-one ring and the coupling constant between the protons of C3 and C4 (*syn* form: J = 5.0−6.0 Hz, *anti* form: J = 2.0−3.0 Hz).

*1-Benzyl-3-methyl-4-phenylazetidin-2-one (**3Aa**).* The title product (**3Aa**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 53% (132.7 mg; *syn* form) and 11% yield (26.9 mg; *anti* form), respectively.

syn-**3Aa**: A colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, d, J = 7.2 Hz), 3.50 (1H, m), 3.90 (1H, d, J = 14.8 Hz), 4.59 (1H, d, J = 5.2 Hz), 4.90 (1H, d, J = 14.8 Hz), 7.14−7.18 (4H, m), 7.24−7.42 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.743, 44.37, 49.99, 57.95, 127.2, 127.6, 128.0, 128.4, 128.5, 128.7, 135.3, 135.6, 171.0; MS m/z: 251 (M^+); HRMS Calcd for $C_{17}H_{17}NO$: 251.131 (M^+), Found: 251.132; IR (neat) cm^{-1}: 3484, 1748.

anti-**3Aa**: A colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, d, J = 7.2 Hz), 3.07 (1H, m), 3.75 (1H, d, J = 15.0 Hz), 3.96 (1H, d, J = 1.6 Hz), 4.83 (1H, d, J = 15.0 Hz), 7.13−7.15 (2H, m), 7.23−7.39 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.91, 55.25, 62.03, 126.4, 127.5, 128.3, 128.3, 128.7, 128.8, 135.6, 137.6, 170.8; MS m/z: 251 (M^+); HRMS Calcd for $C_{17}H_{17}NO$: 251.131 (M^+), Found: 251.130; IR (neat) cm^{-1}: 3486, 1746.

*Methyl 3-(Benzylamino)-2-methyl-3-phenylpropanoate (**4Aa**).* The title product (**4Aa**) was purified by column chromatography (AcOEt:hexane = 1:9) and was obtained in 22% yield (62.9 mg).

syn-**4Aa**: A colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.18 (3H, d, J = 6.8 Hz), 1.84 (1H, br), 2.71−2.78 (1H, m), 3.48 (1H, d, J = 13.2 Hz), 3.51 (3H, s), 3.70 (1H, d, J = 13.2 Hz), 3.94 (1H, d, J = 6.0 Hz), 7.23−7.36 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.54, 46.64, 51.27, 51.44, 63.51, 126.8, 127.2, 127.5, 128.0, 128.18, 128.22, 140.3, 141.2, 175.2; MS (FAB$^+$) m/z: 284 $(M+H)^+$; HRMS Calcd for $C_{18}H_{22}NO_2$ ($C_{18}H_{21}NO_2$+H): 284.165, Found: 284.165; IR (neat) cm^{-1}: 3337, 1735.

*3-Methyl-1,4-diphenylazetidin-2-one (**3Ba**).* The title product (**3Ba**) was purified by column chromatography (AcOEt:hexane =

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2:8), and only the *syn* diastereomer was obtained in 53% yield (126.0 mg).

syn-**3Ba**: A colorless solid; mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, d, J = 8.0 Hz), 3.69 (1H, qd, J = 8.0, 5.6 Hz), 5.20 (1H, d, J = 5.6 Hz), 7.03−7.07 (1H, m), 7.23−7.28 (4H, m), 7.31−7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.777, 49.38, 58.47, 117.3, 123.9, 127.1, 128.3, 128.9, 129.2, 135.2, 137.9, 168.7; MS m/z: 237 (M^+); HRMS Calcd for $C_{16}H_{15}NO$: 237.115 (M^+), Found: 237.116; IR (KBr) cm^{-1}: 1743.

*Methyl 2-Methyl-3-phenyl-3-(phenylamino)propanoate (**4Ba**).* The title product (**4Ba**) was purified by column chromatography (AcOEt:hexane = 2:8), and only the *syn* diastereomer was obtained in 41% yield (110.7 mg).

syn-**4Ba**: A colorless solid; mp 97.5−98.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, d, J = 7.2 Hz), 2.96 (1H, qd, J = 7.2, 4.8 Hz), 3.62 (3H, s), 4.50 (1H, br), 4.72 (1H, br), 6.51−6.53 (2H, m), 6.62−6.66 (1H, m), 7.06−7.07 (2H, m), 7.21−7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.90, 46.15, 51.96, 59.72, 113.8, 117.8, 127.0, 127.5, 128.7, 129.2, 140.8, 147.2, 174.8; MS m/z: 269 (M^+); HRMS Calcd for $C_{17}H_{19}NO_2$: 269.142 (M^+), Found: 269.142; IR (KBr) cm^{-1}: 3418, 1743.

*1-(p-Methoxyphenyl)-3-methyl-4-phenylazetidin-2-one (**3Ca**).* The title product (**3Ca**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 84% (225.9 mg; *syn* form) and 4% yield (9.9 mg; *anti* form), respectively.

syn-**3Ca**: A colorless solid; mp 125.6−126.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, d, J = 7.2 Hz), 3.67 (1H, qd, J = 7.2, 5.6 Hz), 3.75 (3H, s), 5.16 (1H, d, J = 5.6 Hz), 6.80 (2H, m), 7.22−7.38 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.772, 55.41, 49.28, 58.43, 114.2, 118.2, 126.9, 127.9, 128.5, 131.3, 135.0, 155.8, 167.7; MS m/z: 267 (M^+); HRMS Calcd for $C_{17}H_{17}NO_2$: 267.126 (M^+), Found: 267.126; IR (KBr) cm^{-1}: 1730.

anti-**3Ca**: A colorless solid; mp 42.0−43.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (3H, d, J = 7.2 Hz), 3.11 (1H, qd, J = 7.2, 2.0 Hz), 3.74 (3H, s), 4.54 (1H, d, J = 2.0 Hz), 6.76−6.80 (2H, m), 7.21−7.25 (2H, m), 7.30−7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.07, 55.26, 55.37, 62.71, 114.1, 118.1, 125.7, 128.2, 128.9, 131.3, 137.9, 155.7, 167.5; MS m/z: 267 (M^+); HRMS Calcd for $C_{17}H_{17}NO_2$: 267.126 (M^+), Found: 267.126; IR (KBr) cm^{-1}: 1736.

*Methyl 3-(p-Methoxyphenylamino)-2-methyl-3-phenylpropanoate (**4Ca**).* The title product (**4Ca**) was purified by column chromatography (AcOEt:hexane = 2:8), and only the *syn* diastereomer was obtained in 6% yield (18.9 mg).

syn-**4Ca**: A colorless solid; mp 138.0−138.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (3H, d, J = 7.6 Hz), 1.59 (1H, br), 2.94 (1H, qd, J = 7.6, 4.8 Hz), 3.61 (3H, s), 3.68 (3H, s), 4.65 (1H, d, J = 4.8 Hz), 6.45−6.49 (2H, m), 6.65−6.69 (2H, m), 7.20−7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.89, 46.11, 51.75, 55.66, 60.49, 114.6, 114.9, 126.8, 127.1, 128.3, 140.8, 141.1, 152.0, 174.5; MS m/z: 299 (M^+); HRMS Calcd for $C_{18}H_{21}NO_3$: 299.152 (M^+), Found: 299.152; IR (KBr) cm^{-1}: 3382, 1712.

*1-Benzyl-3-methyl-4-(p-(trifluoromethyl)phenyl)azetidin-2-one (**3Ab**).* The title product (**3Ab**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 66% (211.1 mg; *syn* form) and 17% yield (54.3 mg; *anti* form), respectively.

syn-**3Ab**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, d, J = 7.2 Hz), 3.55 (1H, q, J = 7.2, 6.0 Hz), 3.92 (1H, d, J = 14.8 Hz), 4.63 (1H, d, J = 6.0 Hz), 4.90 (1H, d, J = 14.8 Hz), 7.15−7.17 (2H, m), 7.26−7.31 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.739, 44.81, 50.30, 57.68, 124.1 (q, J = 271.6 Hz), 125.7 (q, J = 3.4 Hz), 127.7, 128.0, 128.7, 129.0, 130.6 (q, J = 32.4 Hz), 135.5, 140.1, 170.8; ^{19}F NMR (90 MHz, $CDCl_3$) δ: 12.69 (3F, s); MS m/z: 319 (M^+); HRMS Calcd for $C_{18}H_{16}F_3NO$: 319.118 (M^+), Found: 319.118; IR (neat) cm^{-1}: 1755, 1325.

anti-**3Ab**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (3H, d, J = 8.0 Hz), 3.07 (1H, qd, J = 8.0, 2.0 Hz), 3.81 (1H, d, J = 14.4 Hz), 4.01 (1H, d, J = 2.0 Hz), 4.84 (1H, d, J = 14.4 Hz), 7.11−7.14 (2H, m), 7.27−7.35 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.94, 44.88, 55.77, 61.789, 124.2 (q, J = 271.1 Hz), 126.2 (q, J = 4.0 Hz), 127.0, 128.1, 128.7, 129.1, 131.0 (q, J = 32.5 Hz), 135.6, 142.4, 170.7; ^{19}F NMR (90 MHz, $CDCl_3$) δ: 12.62 (3F, s); MS m/z: 319 (M^+); HRMS Calcd for $C_{18}H_{16}F_3NO$: 319.118 (M^+), Found: 319.119; IR (neat) cm^{-1}: 1756, 1327.

*Methyl 4-(1-Benzyl-3-methyl-4-oxoazetidin-2-yl)benzoate (**3Ac**).* The title product (**3Ac**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 50% (154.7 mg; *syn* form) and 19% yield (58.8 mg; *anti* form), respectively.

syn-**3Ac**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, d, J = 8.0 Hz), 3.54 (1H, qd, J = 8.0, 5.2 Hz), 3.93 (1H, d, J = 15.2 Hz), 3.93 (3H, s), 4.63 (1H, d, J = 5.2 Hz), 4.90 (1H, d, J = 15.2 Hz), 7.14−7.17 (2H, m), 7.23−7.33 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.779, 44.90, 50.38, 52.24, 57.95, 127.5, 128.0, 128.8, 129.0, 130.1, 130.3, 135.6, 141.2, 166.9, 171.0; MS m/z: 309 (M^+); HRMS Calcd for $C_{19}H_{19}NO_3$: 309.136 (M^+), Found: 309.136; IR (KBr) cm^{-1}: 1741, 1714.

anti-**3Ac**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, d, J = 7.2 Hz), 3.06 (1H, m), 3.79 (1H, d, J = 15.2 Hz), 3.93 (3H, s), 4.00 (1H, d, J = 1.6 Hz), 4.83 (1H, d, J = 15.2 Hz), 7.11−7.13 (2H, m), 7.25−7.32 (6H, m), 8.02−8.04 (2H, m); ^{13}C NMR (100 MHz, CDCl3) δ: 12.94, 44.79, 52.25, 55.62, 61.92, 126.6, 128.0, 128.7, 129.0, 130.4, 130.5, 135.6, 143.3, 166.8, 170.8; MS m/z: 309 (M^+); HRMS Calcd for $C_{19}H_{19}NO_3$: 309.136 (M^+), Found: 309.136; IR (neat) cm^{-1}: 1754, 1724.

*1-Benzyl-4-(p-chlorophenyl)-3-methylazetidin-2-one (**3Ad**).* The title product (**3Ad**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 60% (142.9 mg; *syn* form) and 13% yield (37.1 mg; *anti* form), respectively.

syn-**3Ad**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, d, J = 8.0 Hz), 3.49 (1H, qd, J = 8.0, 5.6 Hz), 3.89 (1H, d, J = 14.8 Hz), 4.55 (1H, d, J = 5.6 Hz), 4.86 (1H, d, J = 14.8 Hz), 7.09−7.16 (4H, m), 7.25−7.36 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.787, 44.69, 50.21, 57.65, 128.0, 128.7, 128.8, 129.0, 129.1, 134.2, 134.3, 135.7, 171.1; MS m/z: 285 (M^+); HRMS Calcd for $C_{17}H_{16}ClNO$: 285.092 (M^+), Found: 285.091; IR (neat) cm^{-1}: 1753.

anti-**3Ad**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (3H, d, J = 7.2 Hz), 3.02 (1H, qd, J = 7.2, 2.4 Hz), 3.76 (1H, d, J = 15.2 Hz), 3.92 (1H, d, J = 2.4 Hz), 4.80 (1H, d, J = 15.2 Hz), 7.11−7.17 (4H, m), 7.26−7.34 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.89, 44.61, 55.53, 61.67, 127.9, 128.0, 128.6, 129.0, 129.3, 134.4, 135.7, 136.6, 170.9; MS m/z: 285 (M^+); HRMS Calcd for $C_{17}H_{16}ClNO$: 285.092 (M^+), Found: 285.092; IR (neat) cm^{-1}: 1754.

*1-Benzyl-4-(p-methoxyphenyl)-3-methylazetidin-2-one (**3Ae**).* The title product (**3Ae**) was purified by column chromatography (AcOEt:hexane = 2:8) and was obtained in 56% yield (*syn*:*anti* = 72:28) as a diastereomeric mixture.

Diastereomeric mixture-**3Ae**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (2.4H, d, J = 7.6 Hz), 1.33 (0.6H, d, J = 7.6 Hz), 3.06 (0.2H, qd, J = 7.6, 2.0 Hz), 3.45 (0.8H, qd, J = 7.6, 5.6 Hz), 3.72 (0.2H, d, J = 15.6 Hz), 3.14−3.82 (3H, m), 3.87 (0.8H, d, J = 15.6 Hz), 3.91 (0.2H, d, J = 2.0 Hz), 4.54 (0.8H, d, J = 5.6 Hz), 4.79 (0.2H, d, J = 15.6 Hz), 4.86 (0.8H, d, J = 15.6 Hz), 6.88−6.92 (2H, m), 7.07−7.17 (4H, m), 7.24−7.32 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.60, 12.73, 44.30, 44.34, 44.40, 49.99, 55.10, 55.23, 57.68, 61.76, 159.6, 159.9, 127.3, 127.7, 127.8, 128.47, 128.55, 128.58, 128.7, 129.6, 114.1, 114.4, 135.9, 136.0, 171.0, 171.3; MS m/z: 251 (M^+); HRMS Calcd for $C_{17}H_{17}NO$: 251.131 (M^+), Found: 251.132.

*1-Benzyl-3-methyl-4-p-tolylazetidin-2-one (**3Af**).* The title product (**3Af**) was purified by column chromatography (AcOEt:hexane = 2:8) and was obtained in 60% yield (*syn*:*anti* = 75:25) as a diastereomeric mixture.

Diastereomeric mixture-**3Af**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (2.4H, d, J = 7.6 Hz), 1.33 (0.6H, d, J = 7.6), 2.37(3H, s), 3.04 (0.2H, qd, J = 7.6, 4.0 Hz), 3.62 (0.8H, qd, J = 7.6, 5.2 Hz), 3.72 (0.2H, d, J = 14.8 Hz), 3.88 (0.8H, d, J = 14.8 Hz), 3.93 (0.2H, d, J = 4.0 Hz), 4.56 (0.8H, d, J = 5.2 Hz), 4.83 (0.2H, d, J = 14.8 Hz), 4.89 (0.8H, d, J = 14.8 Hz), 7.05−7.40 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.74, 12.90, 21.16, 44.33, 44.43, 50.09, 55.33, 58.02, 62.08, 126.6, 127.5, 127.77, 127.80, 128.6, 126.7, 128.9, 129.5, 129.8, 132.5, 134.9, 136.0,

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138.0, 138.4, 171.2, 171.4 ; MS *m/z*: 265 (M^+); HRMS Calcd for $C_{18}H_{19}NO$: 265.147 (M^+), Found: 265.146.

*1-Benzyl-4-(m-chlorophenyl)-3-methylazetidin-2-one (**3Ag**).* The title product (**3Ag**) was purified by column chromatography (AcOEt:hexane = 2:8) and was obtained in 81% yield (*syn*:*anti* = 80:20) as a diastereomeric mixture.

Diastereomeric mixture-**3Ag**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (2.55H, d, J = 7.2 Hz), 1.34 (0.45H, d, J = 7.2 Hz), 3.03 (0.15H, qd, J = 7.2, 2.0 Hz), 3.51 (0.85H, qd, J = 7.2, 6.0 Hz), 3.80 (0.15H, d, J = 14.4 Hz), 3.92 (0.85, d, J = 14.4 Hz), 3.92 (0.15H, d, J = 2.0 Hz), 4.55 (0.85H, d, J = 6.0 Hz), 4.80 (0.15H, d, J = 14.4 Hz), 4.86 (0.85H, d, J = 14.4 Hz) 7.05−7.20 (4H, m), 7.30−7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.757, 12.86, 44.69, 44.77, 50.30, 55.58, 57.68, 61.72, 124.7, 125.5, 126.8, 127.54, 127.9, 128.0, 128.5, 128.6, 128.7, 129.0, 130.1, 130.4, 135.0, 135.2, 135.6, 135.7, 138.1, 140.3, 170.8, 171.0; MS *m/z*: 285 (M^+); HRMS Calcd for $C_{17}H_{16}ClNO$: 285.092 (M^+), Found: 285.093.

*1-Benzyl-4-(o-chlorophenyl)-3-methylazetidin-2-one (**3Ah**).* The title product (**3Ah**) was purified by column chromatography (AcOEt:hexane = 2:8) and was obtained in 69% yield (*syn*:*anti* = 65:35) as a diastereomeric mixture.

Diastereomeric mixture-**3Ah**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (1H, d, J = 7.6 Hz), 1.43 (2H, d, J = 7.6 Hz), 3.00 (0.67H, qd, J = 7.6, 2.0 Hz), 3.62 (0.33H, qd, J = 7.6, 5.2 Hz), 3.90 (0.67H, d, J = 14.8), 4.02 (0.33H, d, J = 14.8 Hz), 4.50 (0.67H, d, J = 2.0 Hz), 4.88−4.96 (1.43H, m), 7.12−7.40 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.555, 13.38, 45.19, 45.36, 49.88, 55.20, 55.66, 58.66, 126.6, 127.0, 127.5, 127.9, 127.97, 128.03, 128.6, 128.7, 129.02, 129.05, 129.1, 129.2, 130.0, 130.1, 133.3, 133.4, 134.1, 135.7, 135.8, 136.2, 171.3, 171.6; MS *m/z*: 285 (M^+); HRMS Calcd for $C_{17}H_{16}ClNO$: 285.092 (M^+), Found: 285.092.

*1-Benzyl-3-methyl-4-(naphthalen-2-yl)azetidin-2-one (**3Ai**).* The title product (**3Ai**) was purified by column chromatography (AcOEt:hexane = 2:8) and was obtained in 69% (*syn*:*anti* = 72.28) as a diastereomeric mixture.

Diastereomeric mixture-**3Ai**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (2.4H, d, J = 7.2 Hz), 1.39 (0.6H, d, J = 7.2 Hz), 3.15 (0.2H, qd, J = 7.2, 2.4 Hz), 3.57 (0.8H, qd, J = 7.2, 5.6 Hz), 3.80 (0.2H, d, J = 14.8 Hz), 4.00 (0.8H, d, J = 14.8 Hz), 4.13 (0.2H, d, J = 2.4 Hz), 4.75 (0.8H, d, J = 5.6 Hz), 4.87 (0.2H, d, J = 14.8 Hz), 4.94 (0.8H, d, J = 14.8 Hz), 7.13−7.19 (2H, m), 7.25−7.36 (4H, m), 7.48−7.54 (2H, m), 7.63−7.67 (1H, m), 7.79−7.87 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.825, 12.99, 44.57, 44.73, 50.33, 55.39, 58.37, 62.43, 123.7, 125.1, 126.2, 126.4, 126.5, 126.64, 126.67, 126.73, 127.84, 127.90, 127.94, 127.97, 128.02, 128.57, 128.63, 128.7, 128.93, 128.94, 129.16, 133.29, 133.34, 133.41, 133.5, 135.4, 135.9, 136.0, 171.2, 171.4; MS *m/z*: 301 (M^+); HRMS Calcd for $C_{21}H_{19}NO$: 301.147 (M^+), Found: 301.147.

*1-(p-Methoxyphenyl)-3-methyl-4-(p-(trifluoromethyl)phenyl)-azetidin-2-one (**3Cb**).* The title product (**3Cb**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 57% (191.0 mg; *syn* form) and 7% yield (23.6 mg; *anti* form), respectively.

syn-**3Cb**: A colorless solid; mp 108.0−109.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, d, J = 7.6 Hz), 3.73 (1H, qd, J = 7.6, 6.0 Hz), 3.76 (3H, s), 5.21 (1H, d, J = 6.0 Hz), 6.80−6.83 (2H, m), 7.21−7.25 (2H, m), 7.36 (2H, d, J = 8.4 Hz), 7.63 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.867, 49.35, 55.40, 57.88, 114.3, 118.1, 123.8 (q, J = 270.2 Hz), 125.6 (q, J = 3.5 Hz), 127.2, 127.8, 130.3 (q, J = 32.4 Hz), 130.9, 139.4, 156.0, 167.1; ^{19}F NMR (90 MHz, $CDCl_3$) δ: 12.67 (3F, s); MS *m/z*: 335 (M^+); HRMS Calcd for $C_{18}H_{16}F_3NO_2$: 335.113 (M^+), Found: 335.114; IR (KBr) cm^{-1}: 1737, 1328.

anti-**3Cb**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (3H, d, J = 7.2 Hz), 3.10 (1H, qd, J = 7.2, 2.0 Hz), 3.75 (3H, s), 4.61 (1H, d, J = 2.0 Hz), 6.78−6.82 (2H, m), 7.18−7.22 (2H, m), 7.46 (2H, d, J = 8.4 Hz), 7.64 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.172, 55.55, 55.58, 62.23, 114.6, 118.4, 124.1 (q, J = 270.3 Hz), 126.4 (q, J = 4.1 Hz), 126.4, 130.9 (q, J = 32.8 Hz), 131.3, 142.4, 156.4, 167.4; ^{19}F NMR (90 MHz, $CDCl_3$) δ: 12.62 (3F, s); MS *m/z*: 335 (M^+); HRMS Calcd for $C_{18}H_{16}F_3NO_2$: 335.113 (M^+), Found: 335.114; IR (neat) cm^{-1}: 1769, 1331.

*Methyl 4-(1-(p-Methoxyphenyl)-3-methyl-4-oxoazetidin-2-yl)-benzoate (**3Cc**).* The title product (**3Cc**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 61% (197.6 mg; *syn* form) and 5% yield (16.3 mg; *anti* form), respectively.

syn-**3Cc**: A colorless solid; mp 124.0−125.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, d, J = 7.2 Hz), 3.72 (1H, qd, J = 7.2, 6.0 Hz), 3.75 (3H, s), 3.92 (3H, s), 5.21 (1H, d, J = 6.0 Hz), 6.78−6.82 (2H, m), 7.21−7.25 (2H, m), 7.31 (2H, d, J = 8.0 Hz), 8.04 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.801, 49.30, 52.14, 55.38, 58.02, 114.2, 118.1, 126.9, 129.8, 129.9, 130.9, 140.3, 155.8, 166.4, 167.2; MS *m/z*: 325 (M^+); HRMS Calcd for $C_{19}H_{19}NO_4$: 325.131 (M^+), Found: 325.131; IR (KBr) cm^{-1}: 1756, 1725.

anti-**3Cc**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (3H, d, J = 7.2 Hz), 3.11 (1H, qd, J = 7.2, 2.4 Hz), 3.74 (3H, s), 3.91 (3H, s), 4.60 (1H, d, J = 2.4 Hz), 6.76−6.80 (2H, m), 7.18−7.21 (2H, m), 7.40−7.43 (2H, m), 8.03−8.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.19, 52.27, 55.49, 55.54, 62.46, 114.5, 118.3, 126.0, 130.56, 130.63, 131.4, 143.4, 156.3, 166.7, 167.5; MS *m/z*: 325 (M^+); HRMS Calcd for $C_{19}H_{19}NO_4$: 325.131 (M^+), Found: 325.132; IR (neat) cm^{-1}: 1731.

*4-(p-Chlorophenyl)-1-(p-methoxyphenyl)-3-methylazetidin-2-one (**3Cd**).* The title product (**3Cd**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 65% (195.7 mg; *syn* form) and 4% yield (12.5 mg; *anti* form), respectively.

syn-**3Cd**: A colorless solid; mp 123.0−124.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, d, J = 8.0 Hz), 3.68 (1H, qd, J = 8.0, 5.2 Hz), 3.75 (3H, s), 5.13 (1H, d, J = 5.2 Hz), 6.78−6.82 (2H, m), 7.15−7.18 (2H, m), 7.21−7.25 (2H, m), 7.33−7.35 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.807, 49.27, 55.41, 57.83, 114.3, 118.2, 128.2, 128.8, 131.0, 133,7, 133.9, 155.9, 167.3; MS *m/z*: 301 (M^+); HRMS Calcd for $C_{17}H_{16}ClNO_2$: 301.087 (M^+), Found: 301.086; IR (neat) cm^{-1}: 1735.

anti-**3Cd**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (3H, d, J = 7.2 Hz), 3.08 (1H, qd, J = 7.2, 2.0 Hz), 3.74 (3H, s), 4.52 (1H, d, J = 2.0 Hz), 6.77−6.81 (2H, m), 7.18−7.21 (2H, m), 7.26−7.29 (2H, m), 7.33−7.36 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.10, 55.49, 55.53, 62.23, 114.5, 118.4, 127.4, 129.5, 131.4, 134.4, 136.8, 156.3, 167.7; MS *m/z*: 301 (M^+); HRMS Calcd for $C_{17}H_{16}ClNO_2$: 301.087 (M^+), Found: 301.086; IR (neat) cm^{-1}: 1732.

*1,4-Bis(p-methoxyphenyl)-3-methylazetidin-2-one (**3Ce**).* The title product (**3Ce**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 77% (228.8 mg; *syn* form) and 4% yield (12.0 mg; *anti* form), respectively.

syn-**3Ce**: A colorless solid; mp 123.0−124.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, d, J = 7.6 Hz), 3.63 (1H, qd, J = 7.6, 5.2 Hz), 3.75 (3H, s), 3.80 (3H, s), 5.11 (1H, d, J = 5.2 Hz), 6.77−6.81 (2H, m), 6.87−6.91 (2H, m), 7.13−7.16 (2H, m), 7.24−7.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.771, 49.26, 55.18, 55.36, 57.98, 1139, 114.1, 118.2, 126.7, 128.0, 131.2, 155.6, 159.2, 167.9; MS *m/z*: 297 (M^+); HRMS Calcd for $C_{18}H_{19}NO_3$: 297.136 (M^+), Found: 297.136; IR (KBr) cm^{-1}: 1730.

anti-**3Ce**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (3H, d, J = 7.2 Hz), 3.09 (1H, qd, J = 7.2, 2.4 Hz), 3.73 (3H, s), 3.80 (3H, s), 4.49 (1H, d, J = 2.4 Hz), 6.75−6.79 (2H, m), 6.88−6.91 (2H, m), 7.21−7.29 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.08, 55.39, 55.52, 62.61, 114.3, 114.7, 118.4, 127.4, 130.1, 131.7, 156.1, 159.9, 168.1; MS *m/z*: 297 (M^+); HRMS Calcd for $C_{18}H_{19}NO_3$: 297.136 (M^+), Found: 297.137; IR (neat) cm^{-1}: 1738.

*1-(p-Methoxyphenyl)-3-methyl-4-p-tolylazetidin-2-one (**3Cf**).* The title product (**3Cf**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 83% (234.7 mg; *syn* form) and 3% yield (7.3 mg; *anti* form), respectively.

syn-**3Cf**: A colorless solid; mp 115.0−119.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, d, J = 7.6 Hz), 2.34 (3H, s), 3.64 (1H, qd, J = 7.6, 5.6 Hz), 3.75 (3H, s), 5.12 (1H, d, J = 5.6 Hz), 6.77−6.81 (2H, m), 7.10 (2H, d, J = 7.6 Hz), 7.16 (2H, d, J = 7.6 Hz), 7.24−7.28 (2H,

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m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.80, 21.19, 49.32, 55.53, 58.42, 114.5, 118.5, 127.14, 129.5, 131.6, 132.2, 138.0, 156.1, 168.2; MS *m/z*: 281 (M^+); HRMS Calcd for $C_{18}H_{19}NO_2$: 281.142 (M^+), Found: 281.142; IR (KBr) cm^{-1}: 1732.

anti-**3Cf**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (3H, d, *J* = 7.2 Hz), 2.34 (3H, s), 3.09 (1H, qd, *J* = 7.2, 2.4 Hz), 3.73 (3H, s), 4.50 (1H, d, *J* = 2.4 Hz), 6.75−6.19 (2H, m), 7.18−7.26 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.25, 21.34, 55.56, 55.66, 62.97, 114.6, 118.6, 126.2, 130.1, 131.9, 135.4, 138.6, 156.3, 168.3; MS *m/z*: 281 (M^+); HRMS Calcd for $C_{18}H_{19}NO_2$: 281.142 (M^+), Found: 281.141; IR (neat) cm^{-1}: 1738.

*4-(m-Chlorophenyl)-1-(p-methoxyphenyl)-3-methylazetidin-2-one (**3Cg**)*. The title product (**3Cg**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 78% (235.7 mg; *syn* form) and 6% yield (17.7 mg; *anti* form), respectively.

syn-**3Cg**: A colorless solid; mp 123.0−124.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, d, *J* = 7.2 Hz), 3.68 (1H, qd, *J* = 7.2, 6.0 Hz), 3.76 (3H, s), 5.11 (1H, d, *J* = 6.0 Hz), 6.79−6.83 (2H, m), 7.09−7.12 (1H, m), 7.22−7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.701, 49.20, 55.29, 57.69, 114.2, 118.0, 124.9, 126.8, 128.1, 129.8, 130.8, 134.6, 137.2, 155.7, 167.2; MS *m/z*: 251 (M^+); HRMS Calcd for $C_{17}H_{17}NO$: 251.131 (M^+), Found: 251.132; IR (KBr) cm^{-1}: 1736.

anti-**3Cg**: A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (3H, d, *J* = 7.2 Hz), 3.10 (1H, qd, *J* = 7.2, 2.0 Hz), 3.75 (3H, s), 4.51 (1H, d, *J* = 2.0 Hz), 6.78−6.82 (2H, m), 7.20−7.34 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.12, 55.51, 55.54, 62.23, 114.6, 118.4, 124.1, 126.3, 128.8, 130.7, 131.4, 135.3, 140.5, 156.3, 167.5; MS *m/z*: 251 (M^+); HRMS Calcd for $C_{17}H_{17}NO$: 251.131 (M^+), Found: 251.132; IR (neat) cm^{-1}: 1732.

*4-(o-Chlorophenyl)-1-(p-methoxyphenyl)-3-methylazetidin-2-one (**3Ch**)*. The title product (**3Ch**) was purified by column chromatography (AcOEt:hexane = 2:8), and only the *syn* diastereomer was obtained in 93% yield (280.6 mg).

syn-**3Ch**: A colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, d, *J* = 7.6 Hz), 3.68 (1H, qd, *J* = 7.6, 5.6 Hz), 3.76 (3H, s), 5.12 (1H, d, *J* = 5.6 Hz), 6.79−6.83 (2H, m), 7.10−7.13 (1H, m), 7.22−7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.84, 49.45, 55.53, 57.97, 114.6, 118.4, 125.3, 127.3, 128.6, 130.2, 131.3, 135.0, 137.7, 156.3, 167.7; MS *m/z*: 251 (M^+); HRMS Calcd for $C_{17}H_{17}NO$: 251.131 (M^+), Found: 251.132; IR (neat) cm^{-1}: 1749.

*1-(p-Methoxyphenyl)-3-methyl-4-styrylazetidin-2-one (**3 Ci**)*. The title product (**3 Ci**) was purified by column chromatography (AcOEt:hexane = 2:8), and the diastereomers were obtained in 38% (110.9 mg; *syn* form) and 23% yield (68.0 mg; *anti* form), respectively.

syn-**3Ci**: A yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (3H, d, *J* = 8.0 Hz), 3.54−3.61 (1H, m), 3.76 (3H, s), 4.70−4.73 (1H, m), 6.24 (1H, dd, *J* = 16.0, 8.4 Hz), 6.75 (1H, d, *J* = 16 Hz), 6.81−6.85 (2H, m), 7.26−7.41 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.878, 49.18, 55.60, 57.49, 114.6, 118.4, 125.0, 126.8, 128.5, 128.9, 132.2, 135.5, 136.2, 156.3, 168.0; MS *m/z*: 293 (M^+); HRMS Calcd for $C_{19}H_{19}NO_2$: 293.142 (M^+), Found: 293.142; IR (neat) cm^{-1}: 1732.

anti-**3Ci**: A yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.44 (3H, d, *J* = 7.2 Hz), 3.12 (1H, qd, *J* = 7.2, 2.8 Hz), 3.76 (3H, s), 4.20 (1H, dd, *J* = 8.2, 2.8 Hz), 6.47 (1H, dd, *J* = 16.0, 8.2 Hz), 6.78 (1H, d, *J* = 16.0 Hz), 6.81−6.65 (2H, m), 7.25−7.40 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.82, 52.47, 55.59, 62.12, 114.6, 118.4, 126.8, 127.4, 128.5, 128.9, 132.3, 134.1, 136.1, 156.3, 137.6; MS *m/z*: 293 (M^+); HRMS Calcd for $C_{19}H_{19}NO_2$: 293.142 (M^+), Found: 293.142; IR (neat) cm^{-1}: 1732.

*1-(p-Methoxyphenyl)-3-methyl-1-azaspiro[3.5]nonan-2-one (**3Cj**)*. The title product (**3Cj**) was purified by column chromatography (AcOEt:hexane = 1:9) and obtained in 48% yield (124.5 mg).

A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14−1.45 (3H, m), 1.39 (3H, d, *J* = 7.2 Hz), 1.70−1.88 (4H, m), 1.95−1.99 (2H, m), 2.10 (1H, td, *J* = 12.7, 3.2 Hz), 2.96 (1H, q, *J* = 7.2 Hz), 3.78 (3H, s), 6.83−6.87 (2H, m), 7.38−7.43 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.22, 24.25, 24.47, 25.07, 30.33, 37.03, 53.914, 55.58, 64.93, 114.5, 121.8, 130.5, 156.8, 169.2; MS *m/z*: 259 (M^+); HRMS Calcd for $C_{16}H_{21}NO_2$: 259.157 (M^+), Found: 259.158; IR (neat) cm^{-1}: 1738.

*tert-Butyl 3-(p-Methoxyphenylamino)-2-methyl-3-phenylpropanoate (**9**)*. The title product (**9**) was purified by column chromatography (AcOEt:hexane = 2:8), and only the *syn* diastereomer was obtained in 86% yield (292.9 mg).

syn-**9**: A colorless solid; mp 103.5−104.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (3H, d, *J* = 6.8 Hz), 1.33 (9H, s), 2.83 (1H, qd, *J* = 6.8, 6.0 Hz), 3.68 (3H, s), 4.20 (1H, br), 4.59 (1H, d, *J* = 6.0 Hz), 6.44−6.48 (2H, m) 6.65−6.69 (2H, m), 7.19−7.339 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.08, 28.01, 47.14, 55.83, 60.90, 81.10, 114.9, 115.0, 126.9, 127.0, 128.2, 141.0, 141.3, 151.8, 173.3; MS *m/z*: 341 (M^+); HRMS Calcd for $C_{21}H_{27}NO_3$: 341.199 (M^+), Found: 341.200; IR (KBr) cm^{-1}: 3406, 1714.

*3-Ethyl-1-(p-methoxyphenyl)-4-phenylazetidin-2-one (**10**)*. The title product (**10**) was purified by column chromatography (AcOEt:hexane = 2:8), and only the *syn* diastereomer was obtained in 34% yield (95.7 mg)

syn-**10**: A colorless solid; mp 137.0−137.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, t, *J* = 7.6 Hz), 1.12−1.25 (1H, m), 1.46−1.57 (1H, m), 3.46 (1H, td, *J* = 8.0, 5.6 Hz), 3.74 (3H, s), 5.15 (1H, d, *J* = 5.6 Hz), 6.77−6.80 (2H, m), 7.22−7.27 (4H, m), 7.31−7.38 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.85, 18.96, 55.52, 56.36, 58.43, 114.46, 118.5, 127.4, 128.3, 128.8, 131.5, 135.4, 156.1, 167.8; MS *m/z*: 281 (M^+); HRMS Calcd for $C_{18}H_{19}NO_2$: 281.142 (M^+), Found: 281.142; IR (neat) cm^{-1}:1731.

*3-(2-Hydroxyethyl)-1-(p-methoxyphenyl)-4-phenylazetidin-2-one (**12**)*. The title product (**12**) was purified by column chromatography (AcOEt:hexane = 5:5), and only the *anti* diastereomer was obtained in 28% yield (83.3 mg).

anti-**12**: A colorless solid; mp 114.0−115.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12−2.17 (2H, m), 2.60 (1H, br), 3.16 (1H, td, *J* = 7.6, 2.4 Hz), 3.74 (3H, s), 3.82 (2H, br), 4.71 (1H, d, *J* = 2.4 Hz), 6.76−6.80 (2H, m), 7.20−7.24 (2H, m), 7.31−7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.87, 55.54, 59.06, 61.23, 61.37, 114.5, 118.6, 126.1, 128.7, 129.4, 131.3, 137.9, 156.4, 167.8; MS *m/z*: 297 (M^+); HRMS Calcd for $C_{18}H_{19}NO_3$: 297.136 (M^+), Found: 297.137; IR (KBr) cm^{-1}: 3354, 1735.

*3-(3-Hydroxypropyl)-1-(p-methoxyphenyl)-4-phenylazetidin-2-one (**13**)*. The title product (**13**) was purified by column chromatography (AcOEt:hexane = 5:5), and only the *anti* diastereomer was obtained in 11% yield (34.3 mg).

anti-**13**: A colorless solid; mp 124.0−124.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73−1.82 (2H, m), 1.89 (1H, br), 1.96−2.04 (2H, m), 3.11 (1H, td, *J* = 7.2, 2.8 Hz), 3.68−3.74 (2H, m), 3.74 (3H, s), 4.63 (1H, d, *J* = 2.8 Hz), 6.76−6.80 (2H, m), 7.20−7.2.4 (2H, m), 7.30−7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.41, 30.48, 55.52, 60.33, 61.57, 62.25, 114.5, 118.5, 126.1, 128.6, 129.4, 131.5, 138.2, 156.3, 167.7; MS *m/z*: 311 (M^+); HRMS Calcd for $C_{19}H_{21}NO_3$: 311.152 (M^+), Found: 311.152; IR (KBr) cm^{-1}: 3392, 1732.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01233.

^{1}H and ^{13}C NMR spectra for all *β*-lactams, **4Aa**, **4Ba**, **4Ca**, and **9** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aando@pharm.setsunan.ac.jp.

Notes

The authors declare no competing financial interest.

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