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PAPER

Enantioselective Synthesis of β-Amino Acid Derivatives via Nickel-Promoted Regioselective Carboxylation of Ynamides and Rhodium-Catalyzed Asymmetric Hydrogenation

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We succeeded in the development of a new method for enantioselective synthesis of α-substituted-β-amino acid derivatives. Thus, nickel(0)-promoted carboxylation of ynamide gave the α-substituted-β-aminoacrylate derivative in a highly regioselective manner. Then, rhodium-catalyzed asymmetric hydrogenation of the α-substituted β-aminoacrylate produced the corresponding α-substituted β-amino acid derivative as an optically active form.

Introduction

Optically active β-amino acid derivatives are found in various biologically active compounds, and some of them are used as important medical drugs such as an *anti*-diabetes agent **1**, antitumor agent **2**, immunostimulator **3**, and antibiotic **4** (Figure 1). Therefore, many methods for the synthesis of optically active β-amino acid derivatives have been developed.[1] Among them, transition metal-catalyzed asymmetric hydrogenation of β-aminoacrylates is expected to be one of the most promising and efficient methods for the synthesis of optically active β-amino acid derivatives.[2,3]

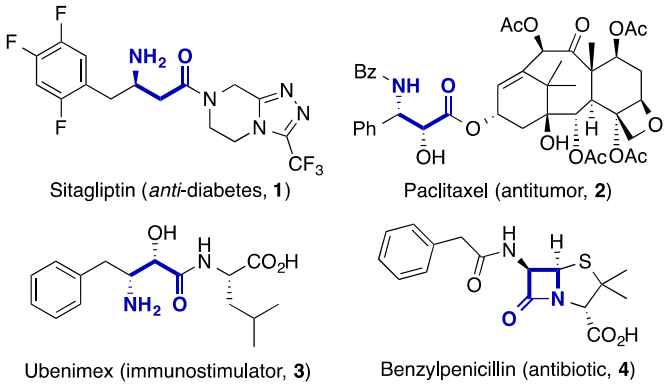
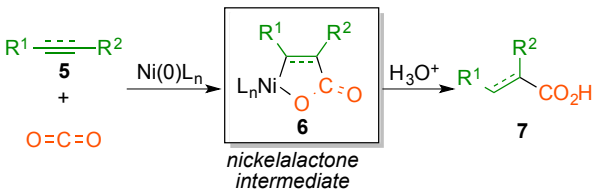


Figure 1. β-Amino acid derivatives in important medical drugs.

Carbon dioxide (CO_2) is a useful carbon source in organic synthesis because it is abundant, cheap and relatively non-toxic. Therefore, various methods for the incorporation of CO_2 into organic compounds have been developed.[4] Recently, transition metal-mediated carboxylation of organic compounds has attracted much attention due to its high level of efficiency.[5] A zero-valent nickel complex has been widely used for carboxylation of carbon-carbon multiple bonds (Scheme 1).[6] The reaction proceeds via a nickelalactone intermediate **6**, which is generated by oxidative cycloaddition of an unsaturated bond **5** and CO_2 to a nickel(0) complex, and hydrolysis of nickelalactone affords the corresponding carboxylic acid **7**. Thus, nickelalactone can be regarded as a useful intermediate for the synthesis of various carboxylic acids in synthetic organic chemistry. From the viewpoint of development of a new synthetic methodology using CO_2, a variety of synthetic applications of carboxylation via nickelalactone have recently been demonstrated using alkenes,[7] alkynes,[8] 1,3-dienes,[9] allenes,[10] and diynes[11] as well as enynes.[12]



Scheme 1. Synthesis of carboxylic acids **7** by carboxylation of carbon-carbon unsaturated compounds **5** via nickelalactone intermediate **6**.

In the context of our continuous efforts to utilize CO_2 as a C1 unit in synthetic organic chemistry,[13] we planned

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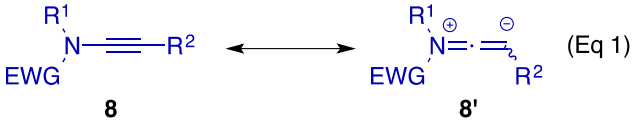
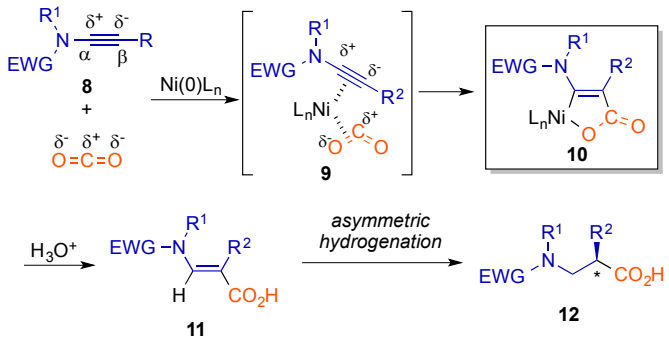
enantioselective synthesis of β-amino acid derivatives via the above nickel-mediated carboxylation of ynamide **8**,[14,15,16] which is recognized as a polarized alkyne due to the delocalization property of an unshared electron pair to the alkyne moiety depicted as **8'** (Eq 1).



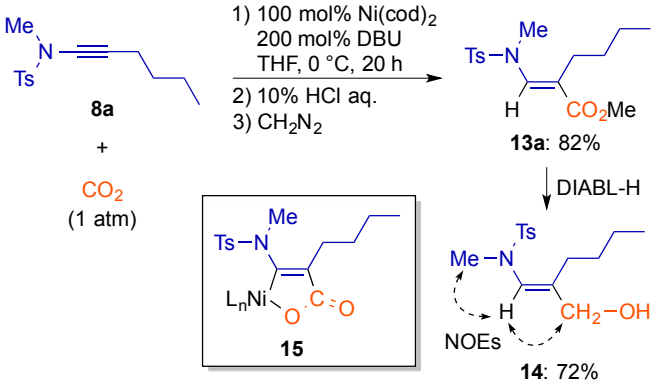
Thus, oxidative cycloaddition of ynamide **8** and CO_2 to the nickel (0) center would regioselectively proceed to give nickelalactone **10** via carbon-carbon bond formation between negatively charged β-carbon of **8** and positively charged sp-hybridized-carbon of CO_2 depicted as **9** (Scheme 2).[17] Hydrolysis of the nickelalactone **10** would produce α-substituted β-aminoacrylic acid **11**.[18] Subsequent catalytic asymmetric hydrogenation of **11** could give desired β-amino acid derivative **12** in an optically active form.



Scheme 2. Strategy for the enantioselective synthesis of β-amino acid derivatives via nickel-promoted carboxylation of ynamide and sequential asymmetric hydrogenation of α-substituted β-aminoacrylates

Results and Discussions

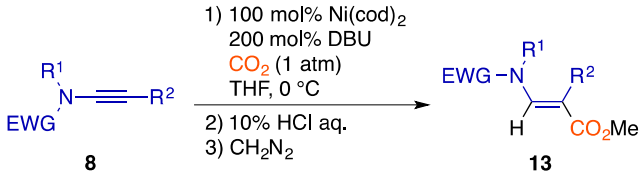
To examine the feasibility of the above strategy, carboxylation of tosylamide-derived ynamide **8a** was investigated (Scheme 3). Ynamide **8a** was reacted with an atmospheric pressure of CO_2 in the presence of a stoichiometric amount of $Ni(cod)_2$ complex and DBU as a ligand for 20 hours. Acidic work-up with HCl followed by methylation with CH_2N_2 gave the corresponding α-butyl-β-aminoacrylate derivative **13a** in 82% yield as a sole product. Structural elucidation of **13a** was conducted by an NOE experiment of the alcohol **14**, which was obtained by reduction of **13a** with DIBAL-H. The result strongly suggested that this reaction proceeded through the regioselective formation of nickelalactone **15** as shown in Scheme 2.

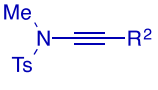
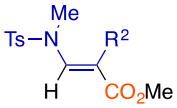
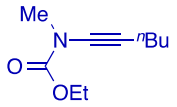
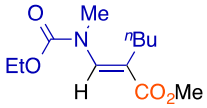
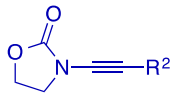
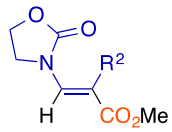


Scheme 3. Nickel(0)-promoted carboxylation of ynamide **8a**.

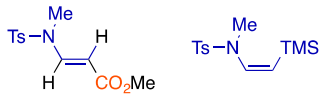
Encouraged by this result, nickel-promoted carboxylation of various ynamides was investigated (Table 1). At first, effects of substituents on the alkyne moiety were examined (runs 1-9). The reaction of ynamides having an oxygen functionality **8b**-**8e** with CO_2 gave the corresponding β-aminoacrylates **13b**-**13e** in good yields (runs 1-4). Although carboxylation of TMS group-substituted ynamide **8f** produced desired **13f** in a low yield, the reaction of **8g** proceeded to give **13g** in 73% yield as a single regio- and stereoisomer (runs 5 and 6). On the other hand, carboxylation of ynamides bearing an aromatic ring **8h**-**8j** produced the corresponding β-aminoacrylates **13h**-**13j** in good yields (runs 7-9). Next, effects of the protecting group of the nitrogen atom were investigated. Carboxylation of carbamate-derived ynamide **8k** smoothly proceeded to give the desired **13k** in 72% yield (run 10). Oxazolidinone-derived ynamides **8l** and **8m** were also applicable to the nickel-promoted carboxylation, and the desired compounds **13l** and **13m** were obtained in 75% and 90% yields, respectively (runs 11 and 12).

Table 1. Carboxylation of various ynamides.



run	ynamide (**8**)	product (**13**)
		
1[a]	**8b** (R^2 = CH_2OTBS)	**13b**: 78%
2[a]	**8c** (R^2 = CH_2CH_2OTBS)	**13c**: 73%
3[a]	**8d** (R^2 = CH_2CH_2OMOM)	**13d**: 78%
4	**8e** (R^2 = CO_2Me)	**13e**: 69%
5[b]	**8f** (R^2 = TMS)	**13f**: 11%
6	**8g** (R^2 = H)	**13g**: 70%
7	**8h** (R = C_6H_5)	**13h**: 74%
8	**8i** (R = 4-$MeOC_6H_4$)	**13i**: 65%
9	**8j** (R = 4-$MeO_2CC_6H_4$)	**13j**: 67%
10	 **8k**	 **13k**: 72%
		
11	**8l** (R^2 = ^{n}Bu)	**13l**: 75%
12	**8m** (R^2 = C_6H_5)	**13m**: 90%

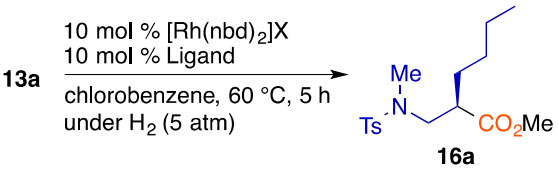
[a] Acidic work-up was conducted using saturated NH_4Cl aqueous solution instead of HCl. [b] In run 5, desilylation product **13f'** was also obtained in 16% yield along with the recovery of SM **8f** in 45% and **8f'** in 21%.



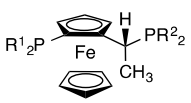
13f': 16% **8f'**: 21%

Next, we turned our attention to the asymmetric hydrogenation of α-substituted β-aminoacrylates. After a variety of chiral ligands and transition metal complexes were screened using **13a** as a substrate, a combination of a cationic rhodium(I) complex and ferrocene-based bisphoshine was found to be effective for asymmetric hydrogenation (Table 2). Thus, several Josiphos type and Walphos type ligands were investigated in the presence of $[Rh(nbd)_2]BF_4$ (10 mol%) in chlorobenzene at 60 °C under 5 atm of hydrogen gas (runs 1-8). As a result, hydrogenation of **13a** using SL-W008-1 gave the desired β-amino acid derivative **16a** in high yield and in a highly enantioselective manner (run 8). The catalyst loading can be reduced to 5 mol% without decreasing of the yield and ee (run 9), and $[Rh(cod)_2]BF_4$ can be also used instead of $[Rh(nbd)_2]BF_4$ although the yield of **16a** was slightly diminished (run 10). When the catalyst loading was decreased to 1 mol%, **16a** was obtained in low yield (run 11). It was found that the counter anion part of the rhodium complex affected the reactivity of the catalyst (runs 12 and 13), and the reaction using $[Rh(nbd)_2]SbF_6$ produced **16a** in quantitative yield and 89% ee nevertheless the catalyst loading was 1 mol% (run 13).

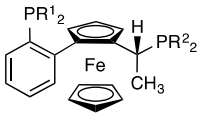
Table 2. Optimization of reaction conditions



run	X	Ligand	yield (%)	ee (%)
1	BF_4	SL-J001-1	80	16
2	BF_4	SL-J002-1	81	-23
3	BF_4	SL-J003-1	64	-49
4	BF_4	SL-J009-1	quant.	-66
5	BF_4	SL-W002-1	99	32
6	BF_4	SL-W003-1	85	8
7	BF_4	SL-W006-1	97	33
8	BF_4	SL-W008-1	95	88
9[a]	BF_4	SL-W008-1	91	89
10[b]	BF_4	SL-W008-1	88	89
11[c]	BF_4	SL-W008-1	27[d]	81
12[c]	PF_6	SL-W008-1	88	89
13[c]	SbF_6	SL-W008-1	quant	89



Josiphos



Walphos

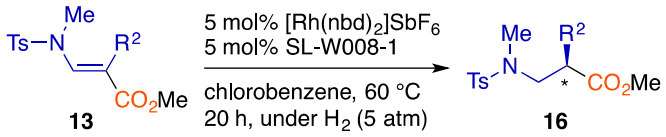
SL-J001-1: R^1 = Ph, R^2 = Cy
SL-J002-1: R^1 = Ph, R^2 = ^{t}Bu
SL-J003-1: R^1 = R^2 = Cy
SL-J009-1: R^1 = Cy, R^2 = ^{t}Bu

SL-W002-1: R^1 = R^2 = Ph
SL-W003-1: R^1 = Ph, R^2 = Cy
SL-W006-1: R^1 = Ph, R^2 = 3,5-$(CF_3)_2C_6H_3$
SL-W008-1: R^1 = Cy, R^2 = 3,5-$(CF_3)_2C_6H_3$

[a] Catalyst loading: 5 mol%. [b] 5 mol% of $[Rh(cod)_2]BF_4$ was used instead of $[Rh(nbd)_2]BF_4$. [c] Catalyst loading: 1 mol%, reaction time: 20 h. [d] Starting material was recovered in 69% yield.

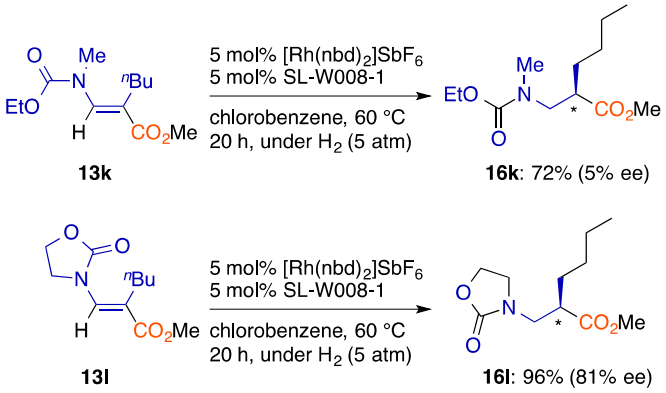
With optimal conditions in hand, asymmetric hydrogenation of various substrates was investigated (Scheme 4 and Table 3). In the asymmetric hydrogenation of enamide having a tosyl group on the nitrogen, various functional groups including an ether moiety, a silyl group as well as a substituted-aromatic ring in were tolerated in the reaction conditions, and the corresponding α-substituted-β-amino acid derivatives **16** were obtained in good yields and in good enantioselectivities (Table 3).

Table 3. Asymmetric hydrogenation of various α-substituted β-aminoacrylates.



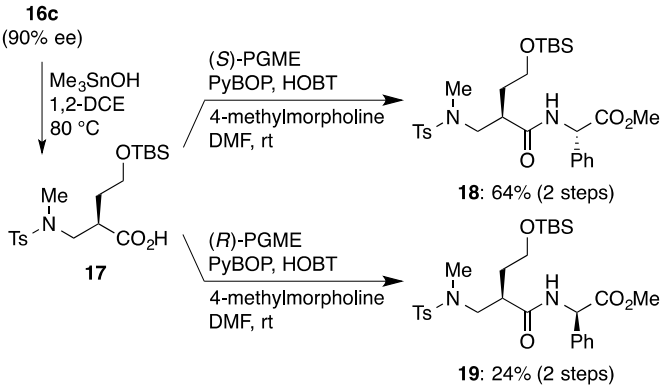
run	β-aminoacrylate (**13**)	product (**16**)
1	**13c** (R^2 = CH_2CH_2OTBS)	**16c**: 68%, 91% ee
2	**13f** (R^2 = TMS)	**16f**: 59%, 86% ee
3	**13h** (R^2 = C_6H_5)	**16h**: 81%, 91% ee
4	**13i** (R^2 = 4-$MeOC_6H_4$)	**16i**: 95%, 92% ee
5	**13j** (R^2 = 4-$MeO_2CC_6H_4$)	**16j**: 89%, 90% ee

In the case of enamide having carbamate moiety **13k**, the corresponding α-substituted-β-amino acid **16k** in 72% yield with very low enatioselectiviy (5% ee) although the reason was not clear. On the other hand, asymmetric hydrogenation of oxazolidinone-derived enamide **13l** produced **16l** in good yield with high enantioselectivity (Scheme 4).



Scheme 4. Asymmetirc hydrogenation of carbamated-derived enamide **13k** and oxazolidinone-derived enamide **13l**.

The absolute configuration of the C2-position of **16c** was determined by using Kusumi's PGME method (Scheme 5 and Figure 2).[19] Thus, after hydrolysis of **16c** by Me_3SnOH,[20] the carboxylic acid **17** was reacted with (*S*)- or (*R*)-phenylglycine methyl ester (PGME) to give the corresponding PGME amides **18** and **19**, respectively. The values of $\Delta\delta = \delta_{(S)\text{-PGME amide}}$**18** - $\delta_{(R)\text{-PGME amide}}$**19** in the 500 MHz ^{1}H NMR spectra were calculated as shown in Figure 2. These data were considered by applying Kusumi's PGME method, and the configuration at the C2 position of **16c** was determined to be *R*.[21]



Scheme 5. Transformation of **16c** into the corresponding PGME amide.

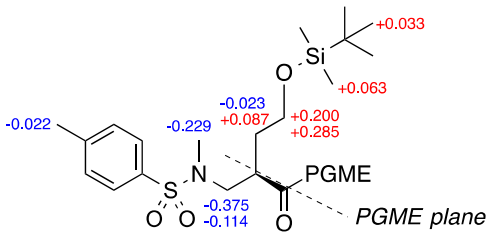


Figure 2. Determination of the absolute configuration of the C2 position of **16c**.

Conclusions

We succeeded in the development of a new method for enantioselective synthesis of α-substituted-β-amino acid derivatives. Nickel-promoted carboxylation of ynamide proceeded in a highly regio- and stereoselective manner to give the corresponding α-substituted β-aminoacrylate derivatives as a single regio- and stereoisomer. Subsequent rhodium-catalyzed asymmetric hydrogenation produced the α-substituted-β-amino acid derivatives in a highly enantioselective manner.

Experimental Section

Nickel-Promoted Carboxylation of Ynamides. Typical Procedure (Scheme 3): $Ni(cod)_2$ (99.0 mg, 0.360 mmol) was weighed into a flame-dried round bottom flask in a glove box (argon atmosphere). Then, the flask was taken out of the glove box, and THF (2.9 mL) and DBU (0.11 mL, 0.736 mmol) were added at 0 °C to the flask. After removal of argon gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO_2 gas using a balloon. To the resulting pale yellow suspension was slowly added a solution of ynamide **8a** (106.2 mg, 0.400 mmol) in THF (2.9 mL) over a period of 7 hours by a syringe pump at 0 °C. After addition of the solution of **8a**, the reaction mixture was stirred at the same temperature for 2 hours. To the mixture was added saturated 10% aqueous solution of HCl at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer

was washed with water, dried over Na_2SO_4, and concentrated. The residue was treated with diazomethane in Et_2O at 0 °C according to the standard procedure. After the mixture had been concentrated, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 8/1) to afford the carboxylated product **13a** (106.7 mg, 82%) as a colorless oil.

Methyl *E*-2-butyl-3-(*N*-methyl-*N*-tosylamino)propenoate (13a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (t, *J* = 7.0 Hz, 3H), 1.16-1.26 (m, 4H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 3.05 (s, 3H), 3.68 (s, 3H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.52 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.8, 21.5, 22.6, 25.8, 32.1, 35.7, 51.8, 119.6, 127.2, 127.2, 129.9, 129.9, 134.2, 137.1, 144.3, 168.5; IR (film, $CHCl_3$) 2956, 1708, 1629 cm^{-1}; EI-LRMS *m/z* 325 (M^+); EI-HRMS calcd for $C_{16}H_{23}NO_4S$ 325.1348, found 325.1348.

Methyl *E*-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(*N*-methyl-*N*-tosylamino)propenoate (13b). A crude product, which was obtained from Ni(cod)$_2$ (98.7 mg, 0.359 mmol), DBU (0.12 mL, 0.802 mmol), and **8b**[16c] (141.5 mg, 0.401 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **13b** (115.3 mg, 78%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.8 (s, 9H), 2.44 (s, 3H), 3.39 (s, 3H), 3.75 (s, 3H), 4.40 (s, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 8.09 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.3 (2C), 18.1, 21.6, 25.8 (3C), 34.2, 51.8, 55.5, 111.0, 127.3 (2C), 130.1 (2C), 134.4, 140.9, 144.7, 168.4; IR (film, $CHCl_3$) 1703, 1624 cm^{-1}; EI-LRMS *m/z* 412 [(M-H$^+$)]; EI-HRMS calcd for $C_{19}H_{30}NO_5SSi$ [(M-H)$^+$] 412.1619, found 412.1592.

Methyl *E*-2-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-(*N*-methyl-*N*-tosylamino)propenoate (13c). A crude product, which was obtained from Ni(cod)$_2$ (98.8 mg, 0.359 mmol), DBU (0.12 mL, 0.802 mmol), and **8c**[16c] (148.2 mg, 0.403 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **13c** (111.9 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.06 (s, 6H), 0.79 (s, 9H), 2.43 (s, 3H), 2.62 (t, *J* = 6.6 Hz, 2H), 3.27 (s, 3H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.74 (s, 3H), 7.33 (d, *J* = 10.5 Hz, 2H), 7.69 (d, *J* = 10.5 Hz, 2H), 7.94 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.7 (2C), 18.0, 21.3, 25.6 (3C), 28.8, 35.2, 51.6, 61.7, 111.2, 127.0 (2C), 129.7 (2C), 134.2, 138.5, 144.2, 168.5; IR (neat) 1706, 1633 cm^{-1}; EI-LRMS *m/z* 412 [(M-CH$_3$)$^+$], 370, 184, 91; EI-HRMS calcd for $C_{19}H_{30}NO_5SSi$ 412.16139, found 412.16024.

Methyl *E*-2-[2-(methoxymethoxy)ethyl]-3-(*N*-methyl-*N*-tosylamino)propenoate (13d). A crude product, which was obtained from Ni(cod)$_2$ (99.2 mg, 0.361 mmol), DBU (0.12 mL, 0.802 mmol), and **8d** (119.3 mg, 0.401 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **13d** (100.6 mg, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.70 (t, *J* = 6.6 Hz, 2H), 3.24 (s, 3H), 3.25 (s, 3H), 3.53 (t, *J* = 6.6 Hz, 2H), 3.75 (s, 3H), 4.49 (s, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz. 2H), 7.88 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.6, 26.4, 35.4, 52.0, 55.1, 66.3, 96.3, 112.5, 127.3 (2C), 130.0 (2C), 134.5, 138.9, 144.5, 168.6; IR (film, $CHCl_3$) 1706, 1633 cm^{-1}; EI-LRMS *m/z* 357 (M^+), 282; EI-HRMS calcd for $C_{16}H_{23}NO_6S$ 357.1246, found 357.1249.

Dimethyl (*N*-methyl-*N*-tosylamino)methylidenemalonate (13e). A crude product, which was obtained from Ni(cod)$_2$ (100.1 mg, 0.364 mmol), DBU (0.12 mL, 0.802 mmol), and **8e** (107.4 mg, 0.402 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **13e** (82.3 mg, 69%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.02 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.4, 32.6, 52.1, 52.3, 104.7, 127.1 (2C), 130.0 (2C), 133.7, 140.2, 145.1, 165.0, 166.1; IR (film, $CHCl_3$) 1724, 1619 cm^{-1}; EI-LRMS *m/z* 327 (M^+); EI-HRMS calcd for $C_{14}H_{17}NO_6S$ 327.0777, found 327.0774.

Methyl *Z*-3-(*N*-methyl-*N*-tosylamino)-2-trimethylsilylpropenoate (13f). A crude product, which was obtained from Ni(cod)$_2$ (99.8 mg, 0.363 mmol), DBU (0.12 mL, 0.802 mmol), and **8f**[16c] (83.7 mg, 0.400 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **13f** (14.0 mg, 11%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.25 (s, 9H), 2.44 (s, 3H), 2.92 (s, 3H), 3.72 (s, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.36 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 0.00 (3C), 21.3, 38.1, 51.4, 127.4 (2C), 128.0, 129.7 (2C), 133.2, 144.1, 148.8, 170.5; IR (film, $CHCl_3$) 1706, 1599 cm^{-1}; EI-LRMS *m/z* 341 (M^+); EI-HRMS calcd for $C_{15}H_{23}NO_4SSi$ 341.1117, found 341.1120.

Methyl *E*-3-(*N*-methyl-*N*-tosylamino)propenoate (13g). A crude product, which was obtained from Ni(cod)$_2$ (99.1 mg, 0.360 mmol), DBU (0.11 mL, 0.802 mmol), and **8g**[16c] (83.7 mg, 0.400 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 8/1) to give **13g** (75.4 mg, 70%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 2.95 (s, 3H), 3.72 (s, 3H), 5.03 (d, *J* = 14.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 8.15 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.6, 32.1, 51.4, 98.2, 127.1 (2C), 130.1 (2C), 134.4, 142.8, 144.8, 167.3; IR (film, $CHCl_3$) 1710, 1626 cm^{-1}; EI-LRMS *m/z* 269 (M^+); EI-HRMS calcd for $C_{12}H_{15}NO_4S$ 269.0722, found 269.0718.

Methyl *Z*-3-(*N*-methyl-*N*-tosylamino)-2-phenylpropenoate (13h). A crude product, which was obtained from Ni(cod)$_2$

(97.8 mg, 0.356 mmol), DBU (0.12 mL, 0.802 mmol), and **8h**[16c] (117.1 mg, 0.411 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 6/1) to give **13h** (90.8 mg, 74%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.47, (s, 3H), 3.73 (s, 3H), 7.02 (dd, *J* = 6.4, 1.6 Hz, 2H), 7.24-7.27 (m, 3H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 8.22 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.4, 34.8, 51.9, 113.6, 127.0 (2C), 127.5 (2C), 127.6, 129.9 (2C), 130.6 (2C), 133.7, 134.1, 138.2, 144.4, 168.1; IR (film, $CHCl_3$) 1706, 1617 cm^{-1}; EI-LRMS *m/z* 345 (M^+); EI-HRMS calcd for $C_{18}H_{19}NO_4S$ 345.1035, found 345.1048.

Methyl *Z*-3-(*N*-methyl-*N*-tosylamino)-2-(4-methoxyphenyl)propenoate (13i). A crude product, which was obtained from $Ni(cod)_2$ (98.6 mg, 0.359 mmol), DBU (0.12 mL, 0.802 mmol), and **8i**[16c] (125.8 mg, 0.399 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 6/1) to give **13i** (87.5 mg, 65%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.50 (s, 3H), 3.73 (s, 3H), 3.78 (s, 3H), 6.78 (d, *J* = 7.0 Hz, 2H), 6.93 (d, *J* = 7.0 Hz. 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.6, 35.0, 52.1, 55.2, 113.2 (2C), 113.8, 125.9, 127.2 (2C), 130.1 (2C), 131.9 (2C), 134.4, 138.3, 144.6, 159.1, 168.6; IR (film, $CHCl_3$) 1705, 1606, 1513 cm^{-1}; EI-LRMS *m/z* 375 (M^+); EI-HRMS calcd for $C_{19}H_{21}NO_5S$ 375.1140, found 375.1137.

Methyl *Z*-3-(*N*-methyl-*N*-tosylamino)-2-(4-methoxycarbonylphenyl)propenoate (13j). A crude product, which was obtained from $Ni(cod)_2$ (98.2 mg, 0.357 mmol), DBU (0.12 mL, 0.802 mmol), and **8j**[16c] (136.7 mg, 0.398 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 6/1) to give **13j** (95.8 mg, 67%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.47 (s, 3H), 3.73 (s, 3H), 3.90 (s, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 8.27 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.6, 35.2, 52.2 (2C), 112.5, 127.2 (2C), 128.9 (2C), 129.5, 130.2 (2C), 131.0 (2C), 134.1, 139.0, 139.1, 144.9, 166.6, 167.7; IR (film, $CHCl_3$) 1713 cm^{-1}; EI-LRMS *m/z* 403 (M^+); EI-HRMS calcd for $C_{20}H_{21}NO_6S$ 403.1090, found 403.1080.

Methyl 2-butyl-3-(*N*-ethoxycarbonyl-*N*-methylamino)propenoate (13k). A crude product, which was obtained from $Ni(cod)_2$ (99.8 mg, 0.363 mmol), DBU (0.12 mL, 0.802 mmol), and **8k** (75.3 mg, 0.411 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 6/1) to give **13k** (63.8 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.30-1.45 (s, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.24 (s, 3H), 3.73 (s, 3H), 4.24 (q, *J* = 7.0 Hz, 2H), 7.83 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.8, 14.5, 22.8, 26.2, 31.9, 35.3, 51.7, 62.9, 116.8, 138.7, 155.0, 169.2; IR (neat) 1704, 1634 cm^{-1}; EI-LRMS *m/z* 243 (M^+); EI-HRMS calcd for $C_{12}H_{21}NO_4$ 243.1471, found 243.1469.

Methyl *E*-2-butyl-3-(2-oxooxazolidin-3-yl)propenoate (13l). A crude product, which was obtained from $Ni(cod)_2$ (99.5 mg, 0.362 mmol), DBU (0.12 mL, 0.802 mmol), and **8l**[16c] (67.3 mg, 0.402 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **13l** (62.0 mg, 75%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.31-1.44 (m, 4H), 2.40 (t, *J* = 7.8 Hz, 2H), 3.74 (s, 3H), 4.12 (dd, *J* = 8.0, 8.0 Hz, 2H), 4.48 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.80 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.9, 22.7, 25.3, 33.3, 44.2, 51.8, 62.4, 113.7, 133.1, 156.1, 168.8; IR (film, $CHCl_3$) 1771, 1704 cm^{-1}; EI-LRMS m/z 227 (M^+); EI-HRMS calcd for $C_{11}H_{17}NO_4$ 227.1158, found 227.1156.

Methyl *E*-3-(2-oxooxazolidin-3-yl)-2-phenylpropenoate (13m). A crude product, which was obtained from $Ni(cod)_2$ (99.7 mg, 0.363 mmol), DBU (0.12 mL, 0.802 mmol), and **8m**[16c] (67.3 mg, 0.402 mmol) in THF (5.8 mL) was treated with CH_2N_2 in Et_2O at 0 °C. After the usual work-up, a crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **13m** (81.0 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.10 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.74 (s, 3H), 4.19 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.22-7.24 (m, 2H), 7.35-7.36 (m, 3H), 8.11 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 44.3, 52.4, 63.0, 114.2, 128.0 (2C), 128.4, 131.4 (2C), 133.6, 134.7, 156.2, 168.3; IR (film, $CHCl_3$) 1777, 1708 cm^{-1}; EI-LRMS *m/z* 247 (M^+); EI-HRMS calcd for $C_{13}H_{13}NO_4$ 247.0845, found 247.0848.

Rhodium-Catalyzed Asymmetric Hydrogenation. Typical Procedure (Table 2, run 13): $[Rh(nbd)_2]SbF_6$ (0.4 mg, 0.765 μmol) and SL W008-1 (0.7 mg, 0.743 μmol) were added to a flame-dried 10 mL test tube. The test tube was purged with H_2. Chlorobenzene (0.5 mL) was added to the test tube, and the resulting mixture stirred for 10 min under an atmosphere of H_2 (1 atm). To the mixture was added a solution of **13a** (24.3 mg, 0.075 mmol) in chlorobenzene (0.8 mL). The test tube was placed in an autoclave and pressurized under an H_2 atmosphere (5 atm). The reaction mixture was stirred at 60 °C for 20 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to afford **16a** (25.0 mg, quant) as a colorless oil. The enantiomeric excess was determined to be 89% by HPLC analysis with a DAICEL CHIRALPAK AS-H [eluent: hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, detector: UV (254 nm)]: t_R(major) = 23.2 min; t_R(minor) = 26.6 min.

Methyl (*R*)-2-Butyl-3-(*N*-methyl-*N*-tosylamino)propanoate (16a). $[\alpha]_D^{24}$ -14.5 (*c* 0.760, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.36-1.19 (m, 4H), 1.63-1.49 (m, 2H), 2.43 (s, 3H), 2.72 (s, 3 H), 2.72 (m, 1H), 3.16-3.08 (m, 2H), 3.69 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 21.5, 22.5, 29.1, 29.7, 36.0, 45.1, 51.8, 52.1, 127.5 (2C), 129.7 (2C), 134.2, 143.4, 174.8; IR (neat) 1736,

1598, 1344, 1164 cm^{-1}; EI-LRMS *m/z*172 [$(M\text{-}Ts)^+$], 198, 155, 91; EI-HRMS calcd for $C_9H_{18}NO_2$ 172.13375, found 172.13385.

Methyl (*R*)-2-(2-*tert*-butyldimethylsilyloxyethyl)-3-(*N*-methyl-*N*-tosylamino)propanoate (16c). A crude product, which was obtained from **13c** (26.9 mg, 0.063 mmol), $[Rh(nbd)_2]SbF_6$ (1.7 mg, 3.3 μmol), and SL W008-1 (3.0 mg, 3.2 μmol) in chlorobenzene (1.0 mL) at 60 °C for 5 h under H_2 (5 atm), was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **16c** (18.6 mg, 68%) as a colorless oil. The enantiomeric excess was determined to be 91% by HPLC analysis with a DAICEL CHIRALPAK AS-H [eluent: hexane/2-propanol = 98/2, flow rate: 0.5 mL/min, detector: UV (254 nm)]: t_R(major) = 14.7 min; t_R(minor) = 17.7 min. $[\alpha]_D^{21}$ -5.234 (*c* 0.564, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.90-1.76 (m, 2H), 2.43 (s, 3H), 3.71 (s, 3H), 2.89 (m, 1H), 3.11-3.20 (m, 2H), 3.59-3.66 (m, 2H), 3.68 (s, 3H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.5 (2C), 18.3, 21.5, 25.9 (3C), 32.5, 35.6, 41.5, 51.8, 52.0, 60.5, 127.5 (2C), 129.7 (2C), 134.2, 143.4, 174.4; IR (neat) 1738, 1599, 1346, 1164 cm^{-1}; EI-LRMS *m/z* 372 [$(M\text{-}^tBu)^+$], 198, 155, 91; EI-HRMS calcd for $C_{16}H_{26}NO_5SSi$ 372.13009, found 372.12979.

Methyl (*R*)-3-(*N*,4-dimethylphenylsulfonamido)-2-(trimethylsilyl)propanoate (16f). A crude product, which was obtained from **13f** (15.6 mg, 0.046 mmol), $[Rh(nbd)_2]SbF_6$ (1.2 mg, 2.3 μmol), and SL W008-1 (2.2 mg, 2.3 μmol) in chlorobenzene (1.0 mL) at 60 °C for 5 h under H_2 (5 atm), was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **16f** (9.3 mg, 59%) as a colorless oil. The enantiomeric excess was determined to be 86% by HPLC analysis with a DAICEL CHIRALPAK AS-H [eluent: hexane/2-propanol = 98/2, flow rate: 0.5 mL/min, detector: UV (254 nm)]: t_R(major) = 27.4 min; t_R(minor) = 23.0 min. $[\alpha]_D^{21}$ -10.529 (*c* 0.416, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 9H), 2.43 (s, 3H), 2.48 (dd, *J* = 9.0, 5.0 Hz, 1H), 2.72 (s, 3H), 3.28-3.36 (m, 2H), 3.65 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.72 (3C), 21.5, 35.9, 38.5, 48.5, 51.4, 127.4 (2C), 129.7 (2C), 134.4, 143.3, 174.5; IR (neat) 1716, 1598, 1343, 1162 cm^{-1}; EI-LRMS *m/z* 188 [$(M\text{-}Ts)^+$], 198, 155, 91, 84; EI-HRMS calcd for $C_8H_{18}NO_2Si$ 118.11068, found 118.11078.

Methyl (*R*)-3-(*N*-methyl-*N*-tosylamino)-2-phenylpropanoate (16h). A crude product, which was obtained from **13h** (18.4 mg, 0.053 mmol), $[Rh(nbd)_2]SbF_6$ (1.4 mg, 2.7 μmol), and SL W008-1 (2.5 mg, 2.7 μmol) in chlorobenzene (1.3 mL) at 60 °C for 20 h under H_2 (5 atm), was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **16h** (15.1 mg, 81%) as a colorless oil. The enantiomeric excess of **16h** was determined to be 91% by HPLC analysis with a DAICEL CHIRALPAK AS-H (eluent: hexane/2-propanol = 95/5, flow rate: 1.0 mL/min, detector: UV (254 nm)): t_R(major) = 28.2 min; t_R(minor) = 36.1 min. $[\alpha]_D^{22}$ +14.417 (*c* 0.508, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.68 (s, 3H), 3.28 (dd, *J* = 14.1, 6.4 Hz, 1H), 3.58 (dd, *J* = 14.1, 8.5 Hz, 1H), 3.69 (s, 3 H), 4.08 (dd, *J* = 8.5, 6.3 Hz, 1H), 7.28-7.35 (m, 7 H), 7.64 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 37.0, 51.9, 52.3, 53.6, 127.4 (2C), 127.9, 128.0 (2C), 128.9 (2C), 129.7 (2C), 134.2, 136.1, 143.5, 172.9; IR (neat) 1735, 1598, 1344, 1162 cm^{-1}; ESI-LRMS *m/z* 370 [$(M+Na)^+$]; ESI-HRMS calcd for $C_{18}H_{21}O_4NNaS$ 370.10835, found 370.10818.

Methyl (*R*)-2-(4-methoxyphenyl)-3-(*N*-methyl-*N*-tosylamino)propanoate (16i). A crude product, which was obtained from **13i** (29.0 mg, 0.077 mmol), $[Rh(nbd)_2]SbF_6$ (2.1 mg, 4.0 μmol), and SL W008-1 (3.8 mg, 4.0 μmol) in chlorobenzene (1.3 mL) at 60 °C for 5 h under H_2 (5 atm), was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **16i** (27.6 mg, 95%) as a colorless oil. The enantiomeric excess was determined to be 92% by HPLC analysis with a DAICEL CHIRALPAK AD-H [eluent: hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, detector: UV (254 nm)]: t_R(major) = 40.2 min; t_R(minor) = 50.8 min. $[\alpha]_D^{22}$ +10.014 (*c* 0.980, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.67 (s, 3H), 3.24 (dd, *J* = 13.8, 7.0 Hz, 1H), 3.55 (dd, *J* = 13.8, 8.5 Hz, 1H), 3.68 (s, 3H), 3.79 (s, 3H), 4.01 (dd, *J* = 8.5, 7.0 Hz, 1H), 6.84-6.87 (m, 2H), 7.21-7.36 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 37.0, 51.0, 52.2, 53.6, 55.2, 114.2 (2C), 127.4 (3C), 128.1, 129.1 (2C), 129.7, 134.2, 143.4, 159.2, 173.1; IR (neat) 1732, 1611, 1512, 1343, 1250, 1161 cm^{-1}; ESI-LRMS *m/z* 400 [$(M+Na)^+$]; ESI-HRMS calcd for $C_{19}H_{23}O_5NNaS$ 400.11891, found 400.11882.

Methyl (*R*)-2-(4-methoxycarbonylphenyl)-3-(*N*-methyl-*N*-tosylamino)propanoate (16j). A crude product, which was obtained from **13j** (45.4 mg, 0.113 mmol), $[Rh(nbd)_2]SbF_6$ (3.0 mg, 5.7 μmol), and SL W008-1 (5.4 mg, 5.7 μmol) in chlorobenzene (1.8 mL) at 60 °C for 5 h under H_2 (5 atm), was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give **16j** (40.8 mg, 89%) as a colorless oil. The enantiomeric excess was determined to be 90% by HPLC analysis with a DAICEL CHIRALPAK AS-H [eluent: hexane/2-propanol = 90/10, flow rate: 0.5 mL/min, detector: UV (254 nm)]: t_R(major) = 35.4 min; t_R(minor) = 40.8 min. $[\alpha]_D^{22}$ +7.124 (*c* 0.696, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.66 (s, 3H), 3.31 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.57 (dd, *J* = 14.5, 8.0 Hz, 1H), 3.69 (s, 3H), 3.91 (s, 3H), 4.13 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 37.1, 51.8, 52.2, 52.4, 53.3, 127.4 (2C), 128.2 (2C), 129.7 (2C), 129.8 (2C), 130.1, 134.0, 141.1, 143.6, 166.6, 172.3; IR (neat) 1725, 1612, 1283, 1162 cm^{-1}; EI-LRMS *m/z* 374 [$(M\text{-}OMe)^+$], 198, 155, 91; EI-HRMS calcd for $C_{19}H_{20}NO_5S$ 374.10622, found 374.10594.

Methyl (*R*)-2-butyl-3-(*N*-ethoxycarbonyl-*N*-methylamino)propanoate (16k). A crude product, which was obtained from **13k** (51.5 mg, 0.212 mmol), $[Rh(nbd)_2]SbF_6$ (5.6 mg, 10.7 μmol), and SL W008-1 (10.1 mg, 10.7 μmol) in chlorobenzene (3.0 mL) at 60 °C for 20 h under H_2 (5 atm), was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **16k** (37.5 mg, 72%) as a colorless oil. The enantiomeric excess was

determined to be 5% by HPLC analysis with DAICEL CHIRALCEL OJ-H + OD-H [eluent: hexane/2-propanol = 98/2, flow rate: 0.3 mL/min, detector: UV (210 nm)]: t_R(major) = 23.2 min; t_R(minor) = 22.3 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.22-1.31 (m, 4H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.36-1.46 (br, 1H), 1.52-1.61 (m, 1H), 2.63-2.77 (br, 1H), 2.86 (d, *J* = 10.9, 3H), 3.28-3.51 (m, 2H), 3.66 (s, 3H), 4.10 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.6, 22.5, 29.2, 29.7, 35.4, 44.8, 50.9, 51.7, 61.3, 156.4, 175.3; IR (neat) 1738, 1706 cm^{-1}; EI-LRMS *m/z* 245 (M^+), 116, 44; EI-HRMS calcd for $C_{12}H_{23}NO_4$ 245.16271, found 245.16244.

Methyl (*R*)-2-butyl-3-(2-oxooxazolidin-3-yl)propanoate (16l). A crude product, which was obtained from **13l** (43.3 mg, 0.191 mmol), $[Rh(nbd)_2]SbF_6$ (5.0 mg, 9.6 μmol), and SL W008-1 (9.0 mg, 9.6 μmol) in chlorobenzen (2.7 mL) at 60 °C for 20 h under H_2 (5 atm), was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **16l** (42.0 mg, 96%) as a colorless oil. The enantiomeric excess was determined to be 81% by HPLC analysis with DAICEL CHIRALCEL OJ-H + OD-H [eluent: hexane/2-propanol = 95/5, flow rate: 0.4 mL/min, detector: UV (210 nm)]: t_R(major) = 69.2 min; t_R(minor) = 75.2 min. $[\alpha]_D^{24}$ -1.860 (*c* 0.600, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.0 Hz, 3H), 1.21-1.34 (m, 4H), 1.42-1.51 (m, 1H), 1.55-1.56 (m, 1H), 2.69 (tt, *J* = 8.6, 4.0 Hz, 1H), 3.36-3.44 (m, 2H), 3.48-3.59 (m, 2H), 3.68 (s, 3H), 4.27 (tt, *J* = 8.6, 3.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.4, 29.1, 29.6, 44.4, 45.4, 46.3, 51.8, 61.8, 158.4, 174.9; IR (neat) 1736 cm^{-1}; EI-LRMS *m/z* 230 [$(M+H)^+$], 170, 100, 56; EI-HRMS calcd for $C_{11}H_{19}NO_4$ 229.13141, found 229.13117.

(*S*)-PGME amide 18. To a solution of **16c** (48.3 mg, 0.11 mmol) in 1,2-dichloroethane (2.8 mL), was added trimethyltinhydroxide (304.9 mg, 1.69 mmol). The mixture was stirred at 80 °C for 83 hours. After cooled to room temperature, the solvent was evaporated and the residue was taken up in AcOEt. The solution was washed with 0.01 M aqueous solution of $KHSO_4$, dried over Na_2SO_4, and concentrated to give **17**, which was used for the next reaction without purification. To a solution of the crude **17** in DMF (1.0 mL) were successively added (*S*)-PGME (25.6 mg, 0.13mmol), PyBOP (66.1 mg, 0.13 mmol), HOBT (17.2 mg, 0.13 mmol) and 4-methylmorpholine (40 μL, 0.37mmol) at 0 °C, and the mixture was stirred at room temperature for 23 hours. After the mixture was diluted with AcOEt, the organic layer was washed with 10% aqueous solution of HCl and saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 3/1) to give **18** (40.4 mg, 64% in 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.75 (dd, *J* = 12.0, 6.3 Hz, 2H), 2.41 (s, 3H), 2.53 (s, 3H), 2.87-2.94 (m, 2H), 3.27 (dd, *J* = 17.2, 9.7 Hz, 1H), 3.72 (s, 3H), 3.70-3.81 (m, 2H), 5.50 (d, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 6.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.32-7.41 (m, 5H), 7.63 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.4, 18.2, 21.4, 25.9, 33.1, 37.0, 43.1, 52.6, 52.7, 56.8, 60.3, 127.4, 127.5, 128.5, 128.9, 129.6, 134.0, 136.1, 143.4, 170.9, 173.2; IR (neat) 1748 cm^{-1}; EI-LRMS *m/z* 547 [$(M-CH_3)^+$], 505, 407, 198, 155, 91; EI-HRMS calcd for $C_{27}H_{39}N_2O_6SSi$ 547.2298, found 547.2294.

(*S*)-PGME amide 19. Similar to the synthesis of **18** from **16c**, (*R*)-PGME amide **19** (7.5 mg, 24% in 2 steps) was obtained from **16c** (23.5 mg, 0.05 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.66 (dq, *J* = 18.7, 4.7 Hz, 1H), 1.77 (dq, *J* = 18.7, 4.8 Hz, 1H), 2.43 (s, 3H), 2.76 (s, 3H), 2.89 (m, 1H), 3.01 (dd, *J* = 13.8, 8.3 Hz, 1H), 3.27 (dd, *J* = 13.8, 6.3 Hz, 1H), 3.44 (td, *J* = 9.9, 4.2 Hz, 1H), 3.59 (m, 1H), 3.73 (s, 3H), 5.54 (d, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.33-7.38 (m, 5H), 7.68 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.4, 18.2, 21.5, 25.9, 33.2, 36.7, 42.5, 52.4, 52.7, 56.7, 60.1, 127.3, 127.5, 128.6, 129.0, 129.7, 134.1, 136.4, 143.4, 170.9, 172.9; IR (neat) 1747 cm^{-1}; EI-LRMS *m/z* 547 [$(M-CH_3)^+$], 505, 407, 198, 155, 91; EI-HRMS calcd for $C_{27}H_{39}N_2O_6SSi$ 547.2298, found 547.2294.

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