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Gold(I)-Catalyzed Synthesis of Optically Active 1,4-Oxazepan-7-ones

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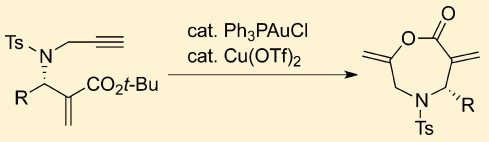
Supporting Information

ABSTRACT: Optically active seven-membered lactones, dimethyleneoxazepanones, were readily prepared in good yields from chiral *β*-(*N*-propargylic)-amino-*α*-methylene carboxylic acid *tert*-butyl esters in the presence of catalytic amounts of Ph_3PAuCl and $Cu(OTf)_2$. A smooth 7-exo-dig cyclization was observed.



1,4-Oxazepane, a seven-membered heterocyclic compound, is a structural motif often observed in natural and biologically active compounds such as holstine,[1] apohemeanthamine,[2] batrachotoxin,[3] and calvine.[4] These oxaaza-heterocyclic compounds are also recognized as one-carbon homologues of morpholines, a structural feature observed among many biologically active compounds.[5] Thus, the development of methods for the efficient synthesis of these compounds has been of interest in organic synthesis.

We have recently developed a facile method for the synthesis of enantiomerically enriched aza-Morita−Baylis−Hillman (aza-MBH) adducts, which are regarded as useful synthetic building blocks.[6] For example, we have employed the chiral *N*-allylic and *N*-propargylic *β*-amino-*α*-methylene esters for the synthesis of various heterocyclic compounds via the RCM reaction,[7] the Pauson-Khand reaction,[8] and the domino radical cyclization reaction.[9] A 1,6-enyne motif in the *N*-propargylic aza-MBH adducts prompted us to explore their potential as substrates in Au(I)-catalyzed reactions. Transition-metal-catalyzed cycloisomerization, a reaction characteristic of 1,6-enyne compounds, has been extensively studied.[10] Carbo- and heterocyclic compounds are prepared in a one-step reaction from 1,6-enynes in the presence of catalytic amounts of an Au(I) complex.[11] Echavarren and co-workers have extensively investigated the scope of this reaction and proposed reaction mechanisms.[12] If an ester motif is strategically located relative to an enyne moiety, the activation of the alkyne moiety can initiate an attack on the ester to yield the lactone. While this strategy can be used to effectively generate five- and six-membered heterocyclic compounds, its utility in the production of seven-membered lactones remains low, resulting in moderate yields.[13] Interestingly, our *N*-propargylic aza-MBH products retain a *tert*-butyl carboxylic ester functionality at the other terminus,[14] appropriately oriented for the synthesis of oxazepanes. Here we report a facile synthesis of chiral seven-membered heterocyclic lactones, i.e., oxazepanones, from *N*-propargyl-*β*-amino-*α*-methylene esters.

First, we examined the transformation of compound **1a** in the presence of Ph_3PAuCl and $AgSbF_6$ (Table 1). No reaction was observed in the absence of silver cocatalyst (Table 1, entry 1). Addition of both JohnPhosAuCl and $AgSbF_6$ gave compound **2a** in low yield (Table 1, entry 2). When the reaction was catalyzed by Ph_3PAuCl in the presence of $AgSbF_6$, the yield of **2a** increased to 40% (Table 1, entry 3). Use of $AgNTf_2$ instead of $AgSbF_6$ enhanced the yield to 62%, while $AgBF_4$ did not promote the reaction (Table 1, entries 4 and 5). Only a moderate yield of **2a** was observed on elevating the reaction temperature in the presence of Ag(I) salt as cocatalyst (Table 1, entry 6). When Ag(I) salts were replaced by $Cu(OTf)_2$,[15] known as an effective cocatalyst in some Au(I)-catalyzed reactions, the yield of **2a** was improved to 70% under 1,2-dichloroethane reflux conditions, although the reaction at room temperature failed the formation of **2a** (Table 1, entries 7−9). Use of toluene instead of 1,2-dichloroethane afforded **2a** in comparable yield (Table 1, entry 10). We next examined the influence of the amount of gold catalyst. When the load of Ph_3PAuCl was reduced to 1 mol %, the yield of **2a** was dependent on the amount of $Cu(OTf)_2$. Compound **2a** was obtained in 80% yield when 6 mol % of $Cu(OTf)_2$ was used (Table 1, entries 11 and 12). HPLC analysis using CHIRALPAK ID revealed that the optical purity of **2a** was 94% ee, which was similar to that of the starting material **1a**. Thus, no significant racemization at chiral carbon occurred during the reaction. The presence of gold(I) catalyst was required to effectively promote the formation of **2a**. For example, the use of catalytic amounts of CuCl and $CuCl_2$ in the absence of Ph_3PAuCl did not promote the transformation; instead, the substrate **1a** was recovered completely (Table 1, entries 13 and 14). The presence of catalytic amounts of $Cu(OTf)_2$, on the other hand, consumed **1a** and *N*-propargyltosylamide was isolated in 18% yield (Table 1, entry 15). This decomposition of **1a** might be caused by the hidden Brønsted acid catalyst generated from $Cu(OTf)_2$.[16] However, treatment of **1a** with catalytic amounts of TfOH resulted in the formation of a complex mixture. Under these conditions, AgOTf was less effective in comparison with $Cu(OTf)_2$, and compound **2a** was isolated in moderate to poor yields (Table 1, entries 16 and 17).

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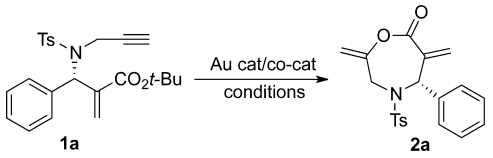
Table 1. Optimization of the Conditions for 7-Exo Cyclization



1a 2a

entry	Au cat. (amt (mol %))	cocat. (amt (mol %))	solvent	temp	yield of **2a** (%)[a]
1	Ph_3PAuCl (7)	none	CH_2Cl_2	room temp	nr[b]
2	[(JohnPhos)AuCl] (10)	$AgSbF_6$ (15)	CH_2Cl_2	room temp	4
3	Ph_3PAuCl (10)	$AgSbF_6$ (15)	CH_2Cl_2	room temp	40
4	Ph_3PAuCl (6)	$AgNTf_2$ (9)	CH_2Cl_2	room temp	62
5	Ph_3PAuCl (10)	$AgBF_4$ (30)	CH_2Cl_2	room temp	14
6	Ph_3PAuCl (6)	$AgNTf_2$ (9)	CH_2Cl_2	reflux	50
7	Ph_3PAuCl (6)	$Cu(OTf)_2$ (18)	CH_2Cl_2	room temp	nr[b]
8	Ph_3PAuCl (6)	$Cu(OTf)_2$ (18)	CH_2Cl_2	reflux	13
9	Ph_3PAuCl (6)	$Cu(OTf)_2$ (18)	$ClCH_2CH_2Cl$	reflux	70
10	Ph_3PAuCl (6)	$Cu(OTf)_2$ (18)	toluene	reflux	62
11	Ph_3PAuCl (1)	$Cu(OTf)_2$ (15)	$ClCH_2CH_2Cl$	reflux	60
12	Ph_3PAuCl (1)	$Cu(OTf)_2$ (6)	$ClCH_2CH_2Cl$	reflux	80
13	none	$CuCl_2$ (8)	$ClCH_2CH_2Cl$	reflux	nr[b]
14	none	CuCl (8)	$ClCH_2CH_2Cl$	reflux	nr[b]
15	none	$Cu(OTf)_2$ (8)	$ClCH_2CH_2Cl$	reflux	0[c]
16	Ph_3PAuCl (1)	AgOTf (6)	$ClCH_2CH_2Cl$	reflux	49
17	Ph_3PAuCl (1)	AgOTf (12)	$ClCH_2CH_2Cl$	reflux	14

[a]Isolated yield. [b]Recovery of starting material. [c]Compound **1a** was consumed. *N*-Propargyltosylamide was isolated in 18% yield instead.

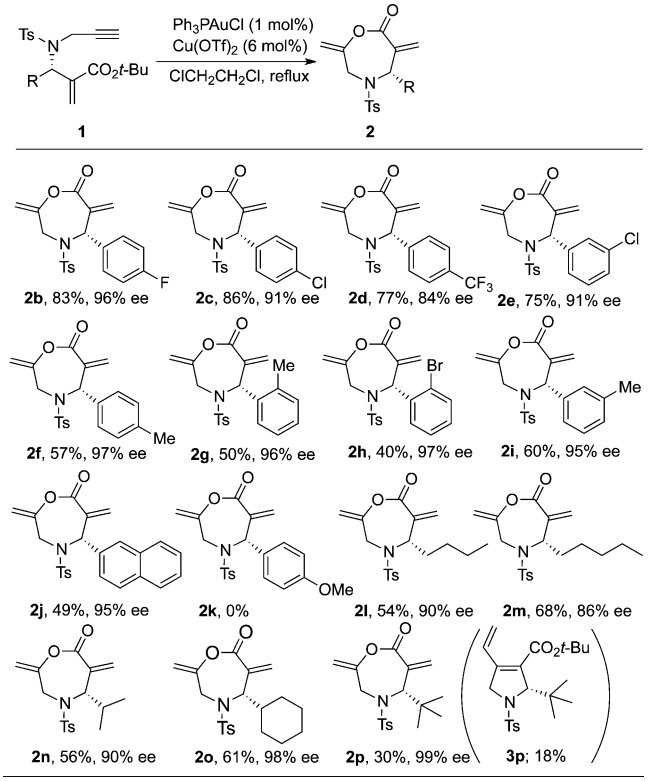
With the optimized reaction conditions in hand, we examined the 7-exo-dig cyclization reaction of various *N*-propargylic aza-MBH products **1b−p**. The results are summarized in Table 2. Oxazepanones **2b−p** were prepared in moderate to good yields. For example, 4-fluoro-, 4-chloro-, and 4-CF_3-substituted aromatic derivatives of **1** gave the corresponding oxazepanones **2b−d** in good yields, respectively. Enantiomeric excesses of the cyclic products were close to those of the starting materials, indicating no loss in optical purity during the reaction. The reaction of **1** containing other aromatic substituents progressed smoothly, but the yields of **2e−j** were moderate. The reaction of **1k**, which had a *p*-methoxyphenyl substituent, underwent decomposition, giving *N*-tosylpropargylamine in 32% yield instead of the corresponding cyclic product **2k**. Compounds **1** containing aliphatic substituents at the R group led to the formation of corresponding compounds **2l−o** in moderate yields. The enantiomeric excesses of these compounds were almost at the same level as those of the starting materials, and the reaction progressed without the loss of optical purity. Conversion of *tert*-butyl derivative **1p** provided the expected **2p** in 30% yield along with the formation of dihydropyrrole **3p** in 18% yield.

The internal alkyne derivative **1q** underwent a similar reaction to produce the corresponding **2q** as a single isomer, although the reaction progressed sluggishly and the yield was only 12% (Scheme 1). Note that NOESY spectrum of **2q** revealed cross peaks between the vinylic H and the NCH_2 group, indicating the selective formation of (*Z*)-**2q**. *α*-Methyl precursor **1r** underwent a smooth cyclization reaction, giving the corresponding oxazepane **2r** in 76% yield.

Oxazepanone **2a** underwent the cleavage of the lactone bond to give ketone **4** in 68% yield by treatment with 1.0 equiv of NaOMe. Acid-catalyzed hydrolysis of oxazepanone **2a** also provided **4** in 56% yield (Scheme 2).

The hydrogenation reaction of **2a** gave the saturated oxazepine **5** in 67% yield (Scheme 3). Compound **5** contained two diastereomers whose ratio was almost 1:1. The two diastereomers **5a,b** were separated by a recycle GPC apparatus, and their configuration was determined by NOE experiments;

Table 2. Preparation of Chiral Oxazepanones 2a−p[a,b]



[a]Isolated yield. [b]The enantiomeric excess was determined by chiral HPLC analyses.

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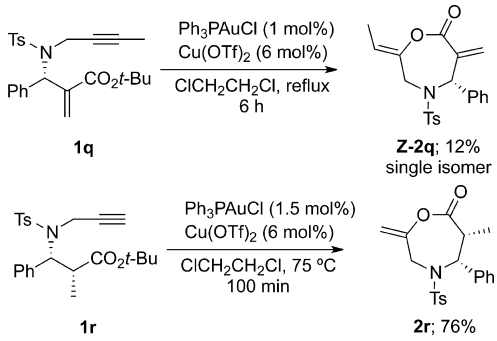
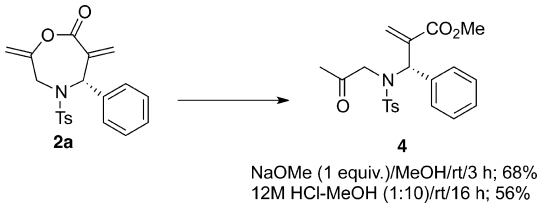
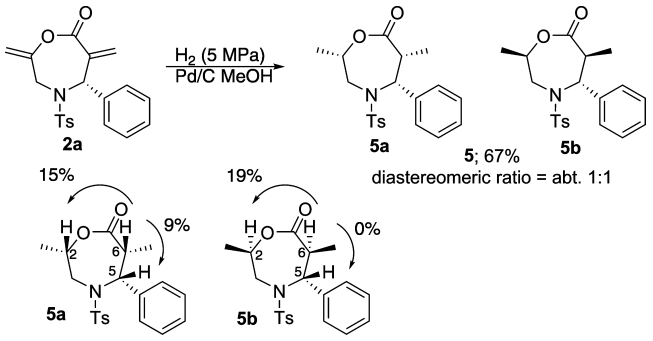
Scheme 1



Scheme 2



Scheme 3

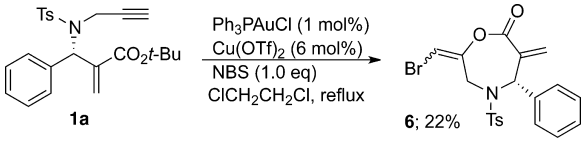


strong signal enhancements for H2 (15%) and H5 (9%) were observed when H6 in **5a** was irradiated, while signal enhancement was observed for only H2 (19%) when H6 in **5b** was irradiated. These results clearly indicated that **5a** has an all-*cis* configuration but that **5b** has a 2,6-*cis*-5,6-*trans* configuration. It is surprising that the steric bias expected by the phenyl group at C5 position provided no effects on the stereocontrol during the hydrogenation reaction at the C6 position. Note that very high 2,6-*cis* selectivity was observed in the hydrogenation.

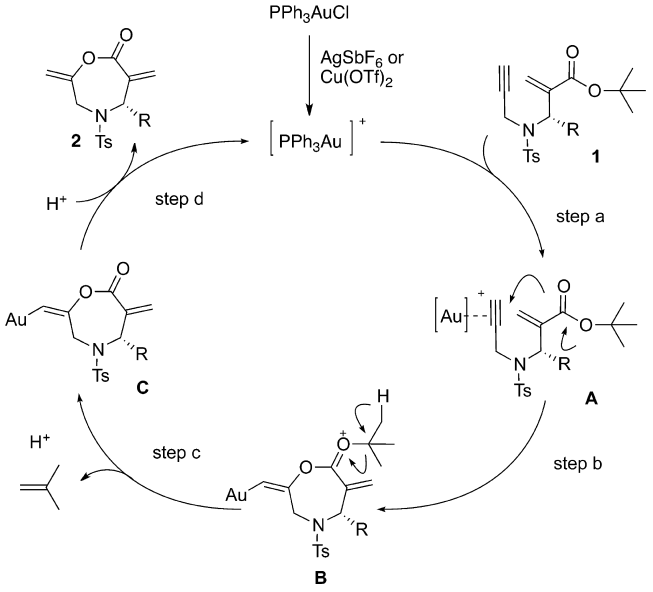
The reaction in the presence of NBS gave the oxazepanone **6**, with a bromine atom introduced at the vinyl ether moiety of the molecule (Scheme 4). When the same reaction was conducted in the absence of the gold catalyst, the starting material **1a** was recovered in 79% yield.

We postulate that Scheme 5 depicts the mechanism for the Au(I)-catalyzed formation of oxazepanones. At first, the active

Scheme 4



Scheme 5



reagent Ph_3PAuX (X = OTf, SbF_6) is generated from Ph_3PAuCl in the presence of the cocatalyst $AgSbF_6$ or $Cu(OTf)_2$. Lafollée and Gandon have reported that the presence of $Cu(OTf)_2$ gradually generates the active $[PPh_3Au^I]^+$ and that this process slowly reaches equilibrium.[15] This slow conversion of PPh_3AuCl provides a preferable generation of the active catalyst in a high-temperature reaction. The active Au(I) catalyst attacks the terminal alkyne unit in compound **1** to generate active intermediate **A**, wherein an internal 7-exo-dig cyclization by the oxygen in the ester gives intermediate **B**.[14] Subsequent elimination of isobutene or *tert*-butyl cation generates intermediate **C**, which is protonated to give product **2** and regenerates active Au(I) catalyst.

In conclusion, we have developed a new route for the preparation of 1,4-oxazepan-7-ones **2** in one step from optically active alkynyl esters **1** using catalytic amounts of Ph_3PAuCl and $Cu(OTf)_2$. The conversion is efficient, and oxazepanones are prepared in moderate to good yields. Oxazepanones **2** contain two exo methylenes that are poised for further synthetic modifications and are also regarded to be efficient precursors in the synthesis of optically active calvine[4] and the nitrogen analogue of the floresolide B structural motif.[17]

EXPERIMENTAL SECTION

Preparation of Compound 1a. Under a nitrogen atmosphere, **1a** (405.3 mg, 1,05 mmol) was added to a mixture of K_2CO_3 (1.46 g, 10.5 mmol) and propargyl bromide (0.32 mL, 4.2 mmol) in dry DMF (2 mL), and the resulting mixture was strirred at room temperature for 24 h. The reaction mixture was diluted with water (10 mL), and the resulting mixture was extracted with ether (3 × 10 mL). The organic layer was combined, washed with brine (1 × 20 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude residue was purified through flash chromatography (silica gel, hexane/EtOAc 10/1 then 5/1, v/v) to give **1a** in 83% yield (371.0 mg, 0.8725 mmol): white solid, mp 57.7−58.5 °C; $[\alpha]_D$ = +86.1° (*c* 0.97, $CHCl_3$). The enantiomeric purity was determined as 99% ee by HPLC analysis (230 nm, 30 °C): t_R 15.6 min (major); t_R 16.7 min (minor) [DAICEL CHIRALPAK IC (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 82/18, 1,0 mL/min]. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.20−7.15 (m, 3H), 6.99 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.35 (d, *J* = 1.6 Hz, 1H), 6.05 (d, *J* = 1.7 Hz, 1H), 5.83 (d, *J* = 1.8 Hz,

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1H), 4.00 (dd, J = 18.4, 2.5 Hz, 1H), 3.82 (dd, J = 18.4, 2.5 Hz, 1H), 2.39 (s, 3H), 1.92 (t, J = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0, 143.6, 140.3, 137.4, 136.7, 129.5 (2C), 128.8 (2C), 128.6 (2C), 128.2, 127.7 (2C), 126.8, 81.4, 79.1, 72.4, 62.2, 34.9, 27.7 (3C), 21.6. HRMS (ESI-TOF): calcd for $C_{24}H_{28}NO_4S$ 426.1739 [M + H^+], found 426.1738.

Preparation of (*S*)-2,6-dimethylene-5-phenyl-4-tosyl-1,4-oxazepan-7-one (2a). Under a nitrogen atmosphere, a mixture of **1a** (84.1 mg, 0.198 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 100 min. After it was cooled, the reaction mixture was concentrated by a rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 then 3/1 v/v), giving **2a** in 80% yield (58.5 mg, 0.158 mmol): white solid; mp 153−154 °C; $[\alpha]_D$ = −37.9° (c 1.48, $CHCl_3$). The enantiomeric purity was determined as 94% ee by HPLC analysis (230 nm, 40 °C): t_R 12.1 min (minor); t_R 13.0 min (major) [CHIRALPAK ID (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 70/30, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.3 Hz, 2H), 7.37−7.31 (m, 5H), 6.24 (s, 1H), 6.07 (s, 1H), 5.50 (s, 1H), 4.89 (s, 1H), 4.64 (s, 1H), 4.26 (d, J = 14.9 Hz, 1H), 3.80 (d, J = 15.0 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.3, 149.4, 144.4, 138.6, 136.2, 135.9, 131.4, 130.0 (2C), 128.8(2C), 128.4, 127.8 (2C), 127.4 (2C), 106.8, 60.3, 46.3, 21.7. HRMS (ESI-TOF): calcd for $C_{20}H_{19}NNaO_4S$ 392.0933 [M + Na^+], found 392.0939.

Preparation of (*S*)-5-(4-Fluorophenyl)-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2b). Under a nitrogen atmosphere, a mixture of **1b** (88.0 mg, 0.199 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 75 min. After it was cooled, the reaction mixture was concentrated by a rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 8/1 then 3/1 v/v), giving **2b** in 82% yield (63.0 mg, 0.163 mmol): white solid; mp 129−130 °C; $[\alpha]_D$ = −46.0° (c 0.85, $CHCl_3$). The enantiomeric purity was determined as 96% ee by HPLC analysis (230 nm, 30 °C): t_R 21.2 min (minor); t_R 23.0 min (major) [CHIRALPAK AD (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 0.50 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.1 Hz, 2H), 7.38 (dd, J = 8.4, 5.4 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.04 (t, J = 8.5 Hz, 2H), 6.23 (s, 1H), 6.02 (s, 1H), 5.47 (s, 1H), 4.89 (s, 1H), 4.67 (s, 1H), 4.23 (d, J = 14.9 Hz, 1H), 3.81 (d, J = 14.9 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0, 162.7 (d, J = 247.0 Hz), 149.3, 144.6, 138.6, 136.0, 131.8 (d, J = 3.2 Hz), 131.6, 130.1 (2C), 129.7 (d, J = 8.2 Hz, 2C), 127.4 (2C), 115.8 (d, J = 8.2 Hz. 2C), 106.7, 59.8, 46.3, 21.7. HRMS (ESI-TOF): calcd for $C_{20}H_{18}FNNaO_4S$ 410.0838 [M + Na^+], found 410.0831.

Preparation of (*S*)-5-(4-Chlorophenyl)-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2c). Under a nitrogen atmosphere, a mixture of **1c** (92.7 mg, 0.202 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 70 min. After it was cooled, the reaction mixture was concentrated by a rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 then 3/1 v/v), giving **2c** in 86% yield (69.3 mg, 0.172 mmol): colorless oil; $[\alpha]_D$ = −31.5° (c 1.43, $CHCl_3$). The enantiomeric purity as 91% ee was determined by HPLC analysis (230 nm, 30 °C): t_R 56.1 min (minor); t_R 61.2 min (major) [CHIRALPAK AD (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 0.20 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 6H), 6.26 (s, 1H), 6.01 (s, 1H), 5.48 (s, 1H), 4.89 (s, 1H), 4.66 (s, 1H), 4.22 (d, J = 14.9 Hz, 1H), 3.81 (d, J = 14.9 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.8, 149.1, 144.6, 138.2, 136.0, 134.6, 134.5, 131.9, 130.1 (2C), 129.2 (2C), 129.0 (2C), 127.4 (2C), 106.8, 59.9, 46.4, 21.7. HRMS (ESI-TOF): calcd for $C_{20}H_{19}{}^{35}ClNO_4S$ 404.0723 [M + H^+], found 404.0719; calcd for $C_{20}H_{19}{}^{37}ClNO_4S$ 406.0694 [M + H^+], found 406.0692.

Preparation of (*S*)-2,6-Dimethylene-4-tosyl-5-(4-(trifluoromethyl)phenyl)-1,4-oxazepan-7-one (2d). Under a nitrogen atmosphere, a mixture of **1d** (88.5 mg, 0.179 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 45 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 7/1 then 3/1 v/v), giving **2d** in 77% yield (60.5 mg, 0.138 mmol): colorless oil; $[\alpha]_D$ = −31.2° (c 2.02, $CHCl_3$). The enantiomeric purity was determined as 84% ee by HPLC analysis (230 nm, 30 °C): t_R 10.0 min (minor); t_R 11.4 min (major) [CHIRALPAK AD (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 0.80 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 6.30 (s, 1H), 6.06 (s, 1H), 5.51 (s, 1H), 4.88 (s, 1H), 4.65 (s, 1H), 4.22 (d, J = 14.8 Hz, 1H), 3.85 (d, J = 14.8 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.6, 149.1, 144.8, 140.4, 137.8, 135.9, 132.4, 130.8 (d, J = 32.8 Hz), 130.2 (2C), 128.2 (2C), 127.5 (2C), 125.8 (d, J = 3.5 Hz, 2C), 123.9 (d, J = 272.1 Hz), 106.8, 60.2, 46.6, 21.6. HRMS (ESI-TOF): calcd for $C_{21}H_{18}F_3NNaO_4S$ 460.0806 [M + Na^+], found 460.0801.

Preparation of (*S*)-5-(3-Chlorophenyl)-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2e). Under a nitrogen atmosphere, a mixture of **1e** (91.7 mg, 0.200 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 30 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 then 3/1 v/v), giving **2e** in 75% yield (60.8 mg, 0.151 mmol): colorless oil; $[\alpha]_D$ = −35.0° (c 1.05, $CHCl_3$). The enantiomeric purity was determined as 91% ee by HPLC analysis (230 nm, 30 °C): t_R 9.7 min (minor); t_R 11.6 min (major) [CHIRALPAK AD (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 0.50 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.5 Hz, 3H), 7.28 (d, J = 14.3 Hz, 3H), 6.28 (s, 1H), 6.01 (s, 1H), 5.50 (s, 1H), 4.91 (s, 1H), 4.68 (s, 1H), 4.25 (d, J = 14.9 Hz, 1H), 3.84 (d, J = 14.9 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.7, 149.1, 144.6, 138.3, 137.9, 135.9, 134.8, 132.2, 130.1 (2C), 128.7, 127.9, 127.4, 127.4 (2C), 126.0, 106.9, 60.0, 46.5, 21.7. HRMS (ESI-TOF): calcd for $C_{20}H_{19}{}^{35}ClNO_4S$ 404.0723 [M + H^+], found 404.0747; calcd for $C_{20}H_{19}{}^{37}ClNO_4S$ 406.0694 [M + H^+], found 406.0706.

Preparation of (*S*)-2,6-Dimethylene-5-(*p*-tolyl)-4-tosyl-1,4-oxazepan-7-one (2f). Under a nitrogen atmosphere, a mixture of **1f** (86.6 mg, 0.198 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 30 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 then 3/1 v/v), giving **2f** in 57% yield (43.3 mg, 0.113 mmol): colorless oil; $[\alpha]_D$ = −33.2° (c 1.39, $CHCl_3$). The enantiomeric purity was determined as 97% ee by HPLC analysis (230 nm, 30 °C: t_R 15.7 min (minor); t_R 16.9 min (major) [YMC Chiral Amylose-C (0.46 cm × 250 mm) (from YMC Co., Ltd.) hexane/*i*-PrOH, 90/10, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.21 (s, 1H), 6.03 (s, 1H), 5.48 (s, 1H), 4.90 (s, 1H), 4.66 (s, 1H), 4.26 (d, J = 15.0 Hz, 1H), 3.77 (d, J = 15.0 Hz, 1H), 2.45 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.5, 149.5, 144.3, 139.0, 138.3, 136.3, 132.8, 130.9, 130.0 (2C), 129.5 (2C), 127.8 (2C), 127.4 (2C), 106.7, 60.1, 46.2, 21.7, 21.1. HRMS (ESI-TOF): calcd for $C_{21}H_{21}NNaO_4S$ 406.1089 [M + Na^+], found 406.1088.

Preparation of (*S*)-2,6-Dimethylene-5-(*o*-tolyl)-4-tosyl-1,4-oxazepan-7-one (2g). Under a nitrogen atmosphere, a mixture of **1g** (88.1 mg, 0.201 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated

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at reflux temperature for 35 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 then 3/1 v/v), giving **2g** in 50% yield (38.5 mg, 0.100 mmol): colorless oil; $[\alpha]_D$ = −18.2° (*c* 1.28, $CHCl_3$). The enantiomeric purity was determined as 96% ee by HPLC analysis (230 nm, 30 °C): t_R 42.3 min (minor); t_R 45.0 min (major) [DAICEL CHIRALPAK ID (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 0.50 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.32−7.18 (m, 5H), 7.09 (t, *J* = 6.8 Hz, 1H), 6.20 (s, 1H), 6.09 (s, 1H), 5.28 (s, 1H), 4.97 (s, 1H), 4.70 (s, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 3.89 (d, *J* = 16.1 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4, 150.2, 144.3, 140.2, 137.7, 136.1, 134.6, 131.3, 129.9 (2C), 129.5, 128.7, 128.6, 127.5 (2C), 125.9, 105.1, 58.5, 46.6, 21.7, 19.9. HRMS (ESI-TOF): calcd for $C_{21}H_{21}NNaO_4S$ 406.1089 [M + Na^+], found 406.1096.

Preparation of (*S*)-5-(2-Bromophenyl)-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2h). Under a nitrogen atmosphere, a mixture of **1h** (100.5 mg, 0.200 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 45 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 then 2/1 v/v), giving **2h** in 40% yield (35.5 mg, 0.079 mmol): colorless oil; $[\alpha]_D$ = −30.9° (*c* 1.18, $CHCl_3$). The enantiomeric purity was determined as 97% ee by HPLC analysis (230 nm, 30 °C): t_R 30.0 min (minor); t_R 32.4 min (major) [DAICEL CHIRALPAK ID (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 4H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.08 (s, 1H), 6.00 (s, 1H), 5.24 (s, 1H), 4.98 (s, 1H), 4.80 (s, 1H), 4.39 (q, *J* = 15.8 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 1164.7, 150.6, 144.4, 138.4, 136.3, 135.4, 133.6, 130.1, 129.9 (2C), 129.3, 127.9, 127.6 (2C), 124.1, 102.8, 77.1, 61.8, 47.4, 21.6. HRMS (ESI-TOF): calcd for $C_{20}H_{19}{}^{79}BrNO_4S$ 448.0218 [M + H^+], found 448.0193; calcd for $C_{20}H_{19}{}^{81}BrNO_4S$ 450.0198 [M + H^+], found 450.0203.

Preparation of (*S*)-2,6-Dimethylene-5-(*m*-tolyl)-4-tosyl-1,4-oxazepan-7-one (2i). Under a nitrogen atmosphere, a mixture of **1i** (87.1 mg, 0.198 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 45 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 then 3/1 v/v), giving **2i** in 60% yield (45.1 mg, 0.118 mmol): pale yellow oil; $[\alpha]_D$ = −41.5° (*c* 1.50, $CHCl_3$). The enantiomeric purity was determined as 95% ee by HPLC analysis (230 nm, 30 °C): t_R 8.8 min (minor); t_R 10.2 min (major) [DAICEL CHIRALPAK AD (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.21 (q, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 2H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.22 (s, 1H), 6.02 (s, 1H), 5.49 (s, 1H), 4.90 (s, 1H), 4.65 (s, 1H), 4.28 (d, *J* = 15.0 Hz, 1H), 3.80 (d, *J* = 15.0 Hz, 1H), 2.45 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4, 149.6, 144.3, 138.8, 138.6, 136.4, 135.8, 131.3, 130.0 (2C), 129.2, 128.6, 128.6, 127.5 (2C), 124.9, 106.7, 60.4, 46.3, 21.7, 21.5. HRMS (ESI-TOF): calcd for $C_{21}H_{21}NNaO_4S$ 406.1089 [M + Na^+], found 406.1094.

Preparation of (*S*)-2,6-Dimethylene-5-(naphthalen-2-yl)-4-tosyl-1,4-oxazepan-7-one (2j). Under a nitrogen atmosphere, a mixture of **1j** (88.9 mg, 0.187 mmol), Ph_3PAuCl (0.9 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 1.9 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 15 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 8/1 then 5/1 v/v), giving **2j** in 49% yield (38.0 mg, 0.091 mmol): pale yellow oil; $[\alpha]_D$ = −31.9° (*c* 1.27, $CHCl_3$). The enantiomeric purity was determined as 95% ee by HPLC analysis (230 nm, 30 °C): t_R 13.9 min (minor); t_R 15.6 min (major) [DAICEL CHIRALPAK AD (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86−7.82 (m, 2H), 7.78−7.73 (m, 4H), 7.55−7.49 (m, 3H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.33 (s, 1H), 6.23 (s, 1H), 5.58 (s, 1H), 4.90 (s, 1H), 4.62 (s, 1H), 4.32 (d, *J* = 15.0 Hz, 1H), 3.80 (d, *J* = 15.0 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.2, 149.5, 144.5, 138.6, 136.3, 133.3, 133.1, 133.0, 131.7, 130.1 (2C), 128.8, 128.2, 127.7, 127.5 (2C), 127.4, 126.8, 126.6, 125.3, 106.9, 60.5, 46.5, 21.7. HRMS (ESI-TOF): calcd for $C_{24}H_{21}NNaO_4S$ 442.1089 [M + Na^+], found 442.1094.

Preparation of (*S*)-5-Butyl-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2l). Under a nitrogen atmosphere, a mixture of **1l** (81.0 mg, 0.200 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 5 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 8/1 then 6/1 v/v), giving **2l** in 56% yield (38.7 mg, 0.111 mmol): colorless oil; $[\alpha]_D$ = −3.47° (*c* 1.27, $CHCl_3$). The enantiomeric purity was determined as 91% ee by HPLC analysis (230 nm, 30 °C): t_R 33.8 min (minor); t_R 35.4 min (major) [DAICEL CHIRALPAK ID (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 85/15, 0.50 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.88 (s, 1H), 5.41 (s, 1H), 4.99 (d, *J* = 1.4 Hz, 1H), 4.90 (s, 1H), 4.71−4.61 (m, 1H), 4.29 (d, *J* = 15.1 Hz, 1H), 3.90 (d, *J* = 15.1 Hz, 1H), 2.43 (s, 3H), 1.85−1.76 (m, 1H), 1.68 (dt, *J* = 12.6, 6.3 Hz, 1H), 1.34−1.26 (m, 4H), 0.88 (dd, *J* = 9.0, 4.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 150.6, 144.1, 141.3, 136.6, 129.9 (2C), 128.4, 127.4 (2C), 106.5, 57.7, 45.5, 32.3, 28.1, 22.2, 21.7, 13.9. HRMS (ESI-TOF): calcd for $C_{18}H_{23}NNaO_4S$ 372.1246 [M + Na^+], found 372.1254.

Preparation of (*S*)-2,6-Dimethylene-5-pentyl-4-tosyl-1,4-oxazepan-7-one (2m). Under a nitrogen atmosphere, a mixture of **1m** (83.9 mg, 0.200 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 50 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 8/1 then 5/1 v/v), giving **2m** in 68% yield (49.4 mg, 0.136 mmol): white solid; mp 82−83 °C; $[\alpha]_D$ = −11.1° (*c* 1.65, $CHCl_3$). The enantiomeric purity was determined as 86% ee by HPLC analysis (230 nm, 30 °C): t_R 11.1 min (major); t_R 12.1 min (minor) [YMC Chiral Cellulose-C (0.46 cm × 250 mm) (from YMC Co., Ltd.) hexane/*i*-PrOH, 80/20, 0.50 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 5.88 (s, 1H), 5.42 (s, 1H), 4.99 (s, 1H), 4.90 (s, 1H), 4.65 (t, *J* = 7.7 Hz, 1H), 4.29 (d, *J* = 15.1 Hz, 1H), 3.89 (d, *J* = 15.1 Hz, 1H), 2.42 (s, 3H), 1.79 (dt, *J* = 18.7, 7.0 Hz, 1H), 1.70−1.62 (m, 1H), 1.27 (d, *J* = 3.5 Hz, 6H), 0.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 150.6, 144.1, 141.3, 136.6, 129.9 (2C), 128.3, 127.4 (2C), 106.5, 57.7, 45.5, 32.6, 31.3, 25.6, 22.5, 21.6, 14.0. HRMS (ESI-TOF): calcd for $C_{19}H_{25}NNaO_4S$, 386.1402 [M + Na^+], found 386.1395.

Preparation of (*S*)-5-Isopropyl-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2n). Under a nitrogen atmosphere, a mixture of **1n** (78.1 mg, 0.200 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 60 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 8/1 then 5/1 v/v), giving **2n** in 56% yield (37.7 mg, 0.112 mmol): colorless oil; $[\alpha]_D$ = −34.8° (*c* 1.24, $CHCl_3$). The enantiomeric purity was determined as 90% ee by HPLC analysis (230 nm, 30 °C): t_R 17.8 min (major); t_R 20.4 min (minor) [DAICEL CHIRALPAK IC (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 0.80 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.88 (s, 1H), 5.40 (s, 1H), 4.95 (s, 1H),

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4.80 (s, 1H), 4.18 (d, J = 14.9 Hz, 1H), 4.09 (d, J = 11.2 Hz, 1H), 3.87 (d, J = 14.9 Hz, 1H), 2.42 (s, 3H), 2.08−1.90 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.8, 151.0, 144.1, 139.3, 136.7, 130.4, 129.8 (2C), 127.8 (2C), 106.7, 65.3, 45.5, 28.9, 21.5, 19.8, 19.5. HRMS (ESI-TOF): calcd for $C_{17}H_{21}NNaO_4S$ 358.1089 [M + Na^+], found 358.1097.

Preparation of (*S*)-5-Cyclohexyl-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2o). Under a nitrogen atmosphere, a mixture of **1o** (86.0 mg, 0.199 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), and $Cu(OTf)_2$ (4.0 mg, 0.011 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 120 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 8/1 then 6/1 v/v), giving **2o** in 61% yield (45.6 mg, 0.122 mmol): colorless oil; $[\alpha]_D$ = −24.4° (c 1.52, $CHCl_3$). The enantiomeric purity was determined as 98% ee by HPLC analysis (230 nm, 30 °C): t_R 20.1 min (major); t_R 21.2 min (minor) [DAICEL CHIRALPAK ID (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 0.80 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.86 (s, 1H), 5.38 (s, 1H), 4.95 (s, 1H), 4.77 (s, 1H), 4.20−4.14 (m, 2H), 3.84 (d, J = 15.0 Hz, 1H), 2.42 (s, 3H), 1.88−1.61 (m, 6H), 1.22−1.09 (m, 3H), 0.93 (dd, J = 22.6, 10.8 Hz, 1H), 0.81 (dd, J = 17.1, 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.8, 150.8, 143.9, 138.9, 136.6, 130.4, 129.7 (2C), 127.6 (2C), 106.7, 63.9, 45.5, 37.4, 30.3, 29.6, 26.0, 25.7, 25.7, 21.5. HRMS (ESI-TOF): calcd for $C_{20}H_{25}NNaO_4S$ 398.1402 [M + Na^+], found 398.1397.

Preparation of (*S*)-5-(*tert*-Butyl)-2,6-dimethylene-4-tosyl-1,4-oxazepan-7-one (2p). Under a nitrogen atmosphere, a mixture of **1p** (94.3 mg, 0.233 mmol), Ph_3PAuCl (1.1 mg, 0.0022 mmol), and $Cu(OTf)_2$ (4.8 mg, 0.013 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2.4 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 40 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 12/1 then 5/1 v/v), giving **2p** in 30% yield (24.6 mg, 0.0705 mmol) along with **3p** in 18% yield (17.1 mg, 0.0422 mmol). Compound **2p**: colorless oil; $[\alpha]_D$ = +11.5° (c 0.82, $CHCl_3$). The enantiomeric purity was determined as 99% ee by HPLC analysis (230 nm, 30 °C): t_R 23.6 min (major); t_R 26.3 min (minor) [DAICEL CHIRALPAK AD (0.46 cm × 250 mm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80/20, 0.30 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 5.79 (s, 1H), 5.44 (s, 1H), 4.84 (s, 1H), 4.49 (d, J = 1.7 Hz, 1H), 4.46 (d, J = 16.0 Hz, 1H), 4.42 (s, 1H), 4.08 (d, J = 16.0 Hz, 1H), 2.42 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.3, 150.8, 144.1, 138.6, 136.8, 130.4, 129.7 (2C), 128.1 (2C), 108.07, 67.87, 47.11, 36.7, 28.6 (3C), 21.6. HRMS (ESI-TOF): calcd for $C_{18}H_{23}NNaO_4S$ 372.1246 [M + Na^+], found 372.1242. Compound **3p**: colorless oil; $[\alpha]_D$ = +16.4° (c 0.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 6.91 (dd, J = 17.9, 10.9 Hz, 1H), 5.32 (d, J = 10.9 Hz, 1H), 5.23 (d, J = 17.8 Hz, 1H), 4.56 (d, J = 2.6 Hz, 1H), 4.37 (d, J = 17.4 Hz, 1H), 4.21 (dd, J = 17.4, 2.7 Hz, 1H), 2.37 (s, 3H), 1.42 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.9, 144.6, 143.6, 134.0, 130.5, 129.5 (2C), 128.3, 127.7 (2C), 121.1, 81.5, 56.2, 38.7, 30.7, 28.0 (3C), 26.9 (3C), 21.6. HRMS (ESI-TOF): calcd for $C_{22}H_{31}NNaO_4S$ 428.1866 [M + Na^+], found 428.1872.

Preparation of (*S*)-6-Methylene-5-phenyl-2-(*Z*)-propylidene-4-tosyl-1,4-oxazepan-7-one (2q). Under a nitrogen atmosphere, a mixture of **1q** (147.3 mg, 0.33 mmol), Ph_3PAuCl (1.7 mg, 0.0034 mmol), and $Cu(OTf)_2$ (7.1 mg, 0.020 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 3 mL) in a 30 mL round-bottom flask was heated at reflux temperature for 6 h. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 5/1 v/v), giving (*Z*)-**2q** in 15% yield as a single isomer (15.0 mg, 0.039 mmol): colorless oil; $[\alpha]_D$ = −35.1° (c 0.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.3 Hz, 2H), 7.38−7.26 (m, 7H), 6.28 (d, J = 1.2 Hz, 1H), 6.06 (s, 1H), 5.47 (d, J = 1.4 Hz, 1H), 4.90 (qd, J = 6.7, 1.0 Hz, 1H), 4.16 (ddd, J = 14.5, 2.7, 1.4 Hz, 1H), 3.74 (d, J = 14.5 Hz, 1H), 2.44 (s, 3H), 1.42 (dd, J = 6.9, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.7, 144.3, 142.0, 138.6, 136.6, 136.4, 131.3, 130.0 (2C), 128.7 (2C), 128.3, 127.5 (2C), 127.4 (2C), 118.2, 60.2, 47.1, 21.7, 10.5. HRMS (ESI-TOF): calcd for $C_{21}H_{22}NO_4S$ 384.12670 [M + H^+], found 384.1272.

Preparation of (5*R*,6*R*)-6-Methyl-2-methylene-5-phenyl-4-tosyl-1,4-oxazepan-7-one (2r). Under a nitrogen atmosphere, a mixture of **1r** (82.7 mg, 0.194 mmol), Ph_3PAuCl (1.4 mg, 0.0028 mmol), and $Cu(OTf)_2$ (4.4 mg, 0.0121 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2 mL) in a 30 mL round-bottom flask was heated at 75 °C temperature for 100 min. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 15/1 then 7/1 v/v), giving **2r** in 76% yield (54.4 mg, 0.147 mmol): colorless semisolid; $[\alpha]_D$ = +29.9° (c 1.48, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 8.2 Hz, 2H), 7.27−7.06 (m, 7H), 5.02 (s, 1H), 5.01 (s, 1 H), 4.99 (d, J = 3.8 Hz, 1 H), 4.53 (d, J = 15.2 Hz, 1H), 3.56 (d, J = 15.3 Hz, 1H), 3.21 (qd, J = 7.0, 3.1 Hz, 1H), 2.32 (s, 3H), 1.16 (d, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 151.6, 144.1, 136.8, 134.6, 129.9 (2C), 129.0 (2C), 128.7, 128.5 (2C), 127.5 (2C), 107.9, 60.9, 45.6, 43.1, 21.6, 16.5. HRMS (ESI-TOF): calcd for $C_{20}H_{21}NNaO_4S$ 394.1089 [M + Na^+], found 394.1089.

Basic Hydrolysis of Compound 2a. Under a nitrogen atmosphere, a solution of **2a** (56.8 mg, 0.154 mmol) and NaOMe (8.1 mg, 0.15 mmol) in MeOH (1.5 mL) was stirred at room temperature for 3 h. The solution was diluted with aqueous NH_4Cl (10 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The organic layer was combined, washed with brine (1 × 20 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude residue was purified through flash chromatography (silica gel, hexane/EtOAc 10/1 then 3/1, v/v) to give **4** in 68% yield (41.6 mg, 0.104 mmol): white solid, mp 133−134 °C; $[\alpha]_D$ = +139.0° (c 0.74, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 7.2 Hz, 2H), 7.35−7.19 (m, 5H), 7.08 (s, 2H), 6.31 (s, 1H), 6.11 (s, 1H), 5.68 (s, 1H), 3.97 (dd, J = 37.8, 18.2 Hz, 2H), 3.60 (s, 3H), 2.44 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 203.6, 166.2, 143.8, 138.5, 136.5, 136.4, 129.5 (2C), 128.7 (2C), 128.6 (2C), 128.4, 128.1 (2C), 127.8, 61.7, 54.3, 52.1, 26.6, 21.7. HRMS (ESI-TOF): calcd for $C_{21}H_{23}NNaO_5S$ 424.1195 [M + Na^+], found 424.1197.

Acidic Hydrolysis of Compound 2a. Under a nitrogen atmosphere, a solution of **2a** (36.5 mg, 0.099 mmol) in MeOH/12 M HCl (10/1, 10 mL) in a 30 mL round-bottom flask was stirred at room temperature for 16 h. The solution was diluted with water (10 mL,) and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was combined, washed with water (1 × 20 mL) and brine (1 × 20 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude residue was purified through flash chromatography (silica gel, hexane/EtOAc 2/1, v/v) to give **4** in 56% yield (22.2 mg, 0.055 mmol).

Hydrogenation Reaction of 2a. A mixture of **2a** (51.1 mg, 13.8 mmol) and Pd/C (29.7 mg) in MeOH (2 mL) was charged in a pressure bottle (90 mL) and stirred vigorously under 5 MPa of hydrogen atmosphere for 24 h at room temperature. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give **5** in 67% yield (34.3 mg, 0.092 mmol). The product contained two diastereomers which were separated by a recycle GPC apparatus.

5a: colorless oil; $[\alpha]_D$ = −18.1° (c 0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50−7.16 (m, 9H), 5.20 (d, J = 2.9 Hz, 1H), 4.69 (dt, J = 14.2, 6.6 Hz, 1H), 3.88 (d, J = 15.9 Hz, 1H), 3.33 (qd, J = 7.0, 3.2 Hz, 1H), 3.20 (dd, J = 15.0, 8.8 Hz, 1H), 2.39 (s, 3H), 1.37 (d, J = 6.5 Hz, 3H), 1.24 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 143.9, 136.8, 134.7, 129.9 (2C), 128.9 (2C), 128.6, 128.5 (2C), 127.1 (2C), 77.4, 75.9, 60.8, 49.6, 44.2, 21.6, 19.6, 16.4. HRMS (ESI-TOF): calcd for $C_{20}H_{23}NNaO_4S$ 396.1246 [M + Na^+], found 396.1237.

5b: colorless oil; $[\alpha]_D$ = +4.08° (c 0.64, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69−7.26 (m, 9H), 5.18 (d, J = 8.3 Hz, 1H), 4.51 (hept, J = 6.3 Hz, 1H), 3.54 (dt, J = 14.0, 6.7 Hz, 1H), 3.46 (dd, J = 13.5, 10.8 Hz, 1H), 3.20 (dd, J = 13.9, 4.5 Hz, 1H), 2.42 (s, 3H), 1.29

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(d, J = 6.6 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.6, 144.1, 136.5, 136.2, 129.8 (2C), 129.4 (2C), 128.6, 127.6 (2C), 127.3 (2C), 69.4, 60.6, 48.1, 41.6, 21.7, 19.0, 16.7. HRMS (ESI-TOF): calcd for $C_{20}H_{23}NNaO_4S$ 396.1246 [M + Na^+], found 396.1246.

Preparation of Compound 6. Under a nitrogen atmosphere, a mixture of **1a** (83.0 mg, 0.195 mmol), Ph_3PAuCl (1.0 mg, 0.002 mmol), $Cu(OTf)_2$ (4.0 mg, 0.011 mmol), and NBS (35.0 mg, 0.197 mmol) in 1,2-dichloroethane (dried over CaH_2 and distilled, 2.0 mL) in a 30 mL round-bottom flask was heated at reflux until the disappearance of **1a**. After it was cooled, the reaction mixture was concentrated by rotary evaporator and then purified through flash chromatography (silica gel, hexane/EtOAc 8/1 then 5/1 v/v), giving **6** in 22% yield (18.9 mg, 0.0423 mmol): white semisolid; $[\alpha]_D$ = + 47.5° (c 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.3 Hz, 2H), 7.42−7.32 (m, 7H), 6.26 (d, J = 1.7 Hz, 1H), 6.20 (d, J = 1.4 Hz, 1H), 6.11 (s, 1H), 5.51 (d, J = 1.7 Hz, 1H), 4.20 (dd, J = 34.6, 15.6 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.6, 145.9, 144.5, 138.5, 136.2, 135.4, 131.5, 130.1 (2C), 129.1 (2C), 128.7, 128.2 (2C), 127.5 (2C), 102.4, 60.2, 43.6, 21.7. HRMS (ESI-TOF): calcd for $C_{20}H_{18}{}^{79}BrNNaO_4S$ 470.0038 [M + Na^+], found 470.0044; calcd for $C_{20}H_{18}{}^{81}BrNNaO_4S$ 472.0017 [M + 2 + Na^+], found 472.0034.

■ ASSOCIATED CONTENT

Supporting Information

Figures and a CIF file giving ^{1}H and ^{13}C NMR spectra for compounds **1a**, **2**, **3p**, **4**, **5**, and **6**, an ORTEP drawing and crystallographic data for **2a**, and chiral HPLC data for **1a** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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