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Rhodium-Catalyzed Asymmetric Cycloisomerization of 1,6-Ene-ynamides

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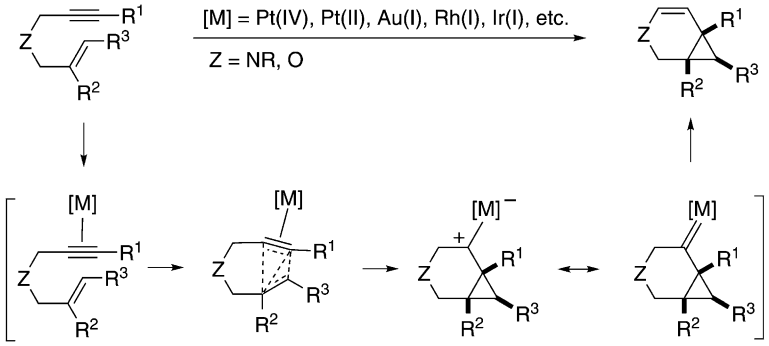
Abstract: The rhodium-catalyzed asymmetric cycloisomerization of heteroatom-bridged 1,6-ene-ynamides proceeded to give high yields of functionalized 3-aza- and oxabicyclo[4.1.0]heptene derivatives with high enantioselectivity, which was achieved by use of a rhodium/chiral diene catalyst. The 1,6-ene-ynamides substituted with 2-oxazolidinone and 2-azetidinone moieties at the alkyne terminus were found to display high reactivity towards the rhodium/chiral diene catalyst, where the chelate coordination of the alkyne moiety and the carbonyl oxygen of the ene-ynamides might be responsible for the high catalytic activity.

Keywords: asymmetric synthesis; chiral diene; cycloisomerization; ene-ynamides; rhodium

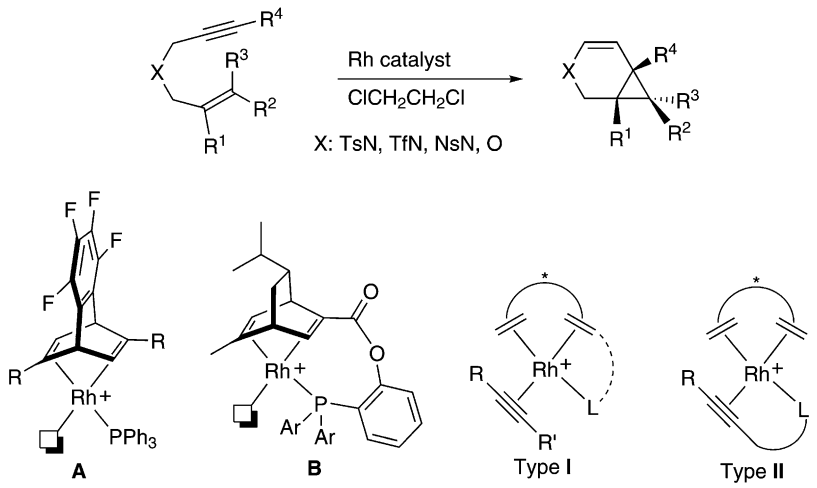
Introduction

Since the initial development of the cycloisomerization of 1,n-enynes through palladium catalysis by Trost and co-workers,[1] the transition metal-catalyzed cycloisomerization has been one of the most powerful methods for the preparation of complicated cyclic compounds in a single step.[2] Considerable efforts have also been made to achieve the enantioselective cycloisomerization and this has been realized in the last decade.[3] Of several cycloisomerization reactions leading to cyclic compounds, a useful method for the synthesis of bicyclo[4.1.0]heptene derivatives is the cycloisomerization of heteroatom-bridged 1,6-enynes, where it is proposed that a 6-*endo* cyclization *via* the electrophilic activation of an alkyne moiety by π-acidic metals, such as Pt,[4] Au,[5] Rh,[6] and Ir,[7,8] forms a metal carbenoid or a metal-stabilized cationic species, and the following 1,2-hydrogen shift gives a bicyclic compound (Scheme 1).

An asymmetric variant of this type of reaction is valuable[3] because the chiral bicyclic compounds containing heteroatoms have potential biological activities.[9] In 2005, Shibata and co-workers reported the first asymmetric cycloisomerization of nitrogen-bridged 1,6-enynes catalyzed by an iridium/bisphosphine complex under CO.[10] Fensterbank and co-workers reported that iridium complexes with chiral



Scheme 1. Cycloisomerization of heteroatom-bridged 1,6-enynes.



Scheme 2. Rhodium-catalyzed asymmetric cycloisomerization of 1,6-enynes.

counterions effectively catalyzed the same type of the reaction.[11] Chiral bisphosphine/NHC- and monophosphine/cyclometalated NHC-platinum complexes have been developed by Marinetti and co-workers.[12] Michelet and co-workers reported that the asymmetric cycloisomerization with high enantioselectivity is catalyzed by chiral gold/bisphosphine complexes.[13] The gold-catalyzed asymmetric cycloisomerization has also been applied to the synthesis of antidepressive drug candidates by Elitzin[14] and Fürstner,[15] independently.[16] In this context, we recently reported that rhodium(I) complexes coordinated with a chiral diene and a phosphorus moiety are good catalysts for the asymmetric cycloisomerization of nitrogen- and oxygen-bridged 1,6-enynes (Scheme 2),[17] where the active cationic rhodium species such as **A** and **B** were generated. Thus, the designed cationic rhodium(I) catalysts have a stereochemically controlled single vacant site for the electrophilic activation of the alkyne moiety, which is created by the ligand coordination (Type **I**).[18] We next focused on an alternative concept for the formation of such rhodium species, which involves the use of a chelate coordination of the alkyne moiety and a functional group on the ene-yne compound (Type **II**).[19] Here we report the asymmetric cycloisomerization of nitrogen- and oxygen-bridged 1,6-ene-ynamides[20] bearing an amide moiety at the alkyne terminus to give bicyclo[4.1.0]heptene derivatives with high enantioselectivity, which was realized by use of a rhodium/chiral diene catalyst.

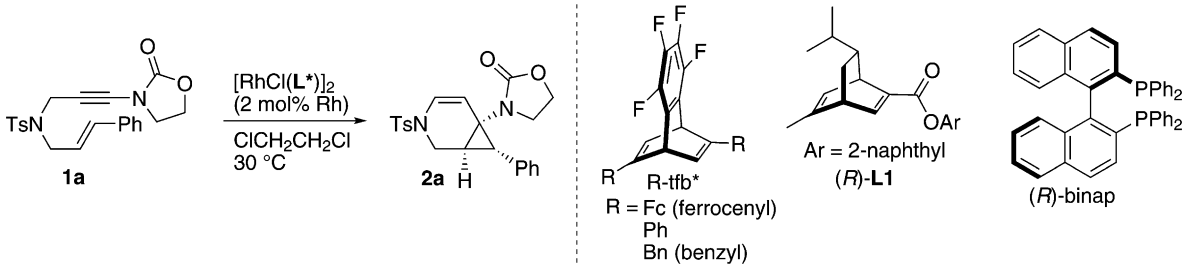
Results and Discussion

Based on the concept described in Scheme 2, we prepared a nitrogen-bridged 1,6-ene-ynamide substituted with 2-oxazolidinone at the alkyne terminus, and it was found that the cycloisomerization of this ene-ynamide took place in the presence of a rhodium/chiral diene[21] catalyst (Table 1). Thus, the reaction of ene-ynamide **1a** in the presence of {RhCl[(*S*,*S*)-Fc-tfb*]}$_2$[22] (Fc = ferrocenyl, tfb = tetrafluorobenzobarrelene;[23] 2 mol% of Rh) in 1,2-dichloroethane at 30 °C for 18 h gave 95% yield of the cycloisomerization product **2a**, whose *ee* was 97% (entry 1). In the present reaction, the addition of NaBAr$^F_4$ [Ar^F = 3,5-bis-(trifluoromethyl)phenyl], which is essential for the formation of the cationic rhodium species in our previous studies,[17] was not required: both reactions with and without NaBAr$^F_4$ gave the same yield (75%) of **2a** for 3 h (entries 2 and 3). Of several chiral diene ligands (Fc-, Ph-, Bn-tfb*, and **L1**,[21f] entries 1, 4–6) and a bisphosphine ligand [(*R*)-binap; entry 7], Fc-tfb* was found to be the best ligand displaying high catalytic activity and enantioselectivity.

It is likely that the chelate coordination of the alkyne moiety and carbonyl oxygen of the ene-ynamides is essential for the high catalytic activity. Thus, the reaction of 1,6-enyne **3** substituted with a methyl group at the alkyne terminus did not take place at all under the same reaction conditions (Scheme 3). The 1,6-enyne **3** was a good substrate giving the corresponding cycloisomerization product in high yield with high enantioselectivity by use of the Type **I** catalyst (Scheme 2) in our previous studies.[17] The reaction of oxygen-bridged ene-ynamide **4** bearing a tosylamide group also did not proceed, despite the fact that oxygen-bridged 1,6-ene-ynamides substituted with 2-oxazolidinone at the alkyne terminus are good substrates to give high yields of the cycloisomerization products (*vide infra*).

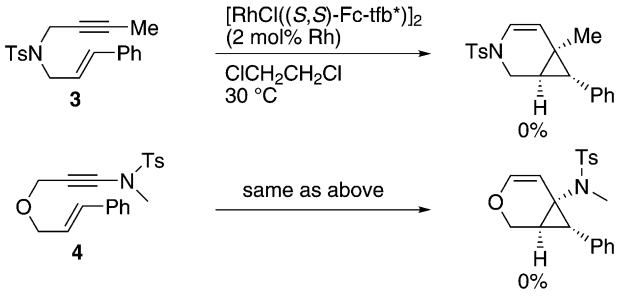
The relative and absolute configuration of **2a** obtained with (*S*,*S*)-Fc-tfb* was determined to be (1*S*,6*R*,7*S*) by X-ray crystallographic analysis (Figure 1).[24]

Table 1. Rhodium-catalyzed asymmetric cycloisomerization of 1,6-ene-ynamide **1a**.[a]



Entry	Ligand	Time [h]	Yield [%][b]	ee [%][c]
1	(*S*,*S*)-Fc-tfb*	18	95[d]	97
2	(*S*,*S*)-Fc-tfb*	3	75	–[e]
3[f]	(*S*,*S*)-Fc-tfb*	3	75	–[e]
4	(*R*,*R*)-Ph-tfb*	18	92[d]	96
5	(*R*,*R*)-Bn-tfb*	18	36	66
6	(*R*)-**L1**	18	83	85
7	(*R*)-binap	18	7	90

[a] *Reaction conditions:* **1a** (0.10 mmol), $[RhCl(\mathbf{L}^*)]_2$ (2 mol% of Rh) in 1,2-dichloroethane (0.5 mL) at 30 °C for 18 h.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis with a chiral stationary phase column: Chiralpak IA.
[d] Isolated yield.
[e] Not determined.
[f] Performed with $NaBAr^F_4$ (4 mol%).



Scheme 3. Reactivity of 1,6-enynes.

Scheme 4 summarizes the results obtained for the cycloisomerization of several ene-ynamides. Asymmetric cycloisomerization can be applied to the ene-ynamides bearing not only *p*-toluenesulfonyl (Ts: **1a**) on the nitrogen atom, but also 2-nitrobenzenesulfonyl (*o*-Ns: **1b**), *tert*-butoxycarbonyl (Boc: **1c**), and benzyloxycarbonyl (Cbz: **1d**) to give the corresponding bicyclic compounds **2a**–**2d** in high yields, the enantioselectivity ranging between 93 and 97% *ee*. The reaction of ene-ynamides substituted with 2-methoxyphenyl (**1e**) and propyl (**1f**) on the alkene moiety (R^2) and phenyl (**1g**) on R^1 proceeded to give the corresponding bicyclic compounds **2e**–**2g** in high yields with 82, 65, and 90% *ee*, respectively. The reaction of ene-ynamide **1h** derived from 2-azetidinone gave the corresponding bicyclic compound **2h** in 92% with 85% *ee*. The same type of reaction was observed for oxygen-bridged ene-ynamides **1i**–**1m** to give the corresponding oxabicyclic compounds **2i**–**2m** with 85–95% *ee*.

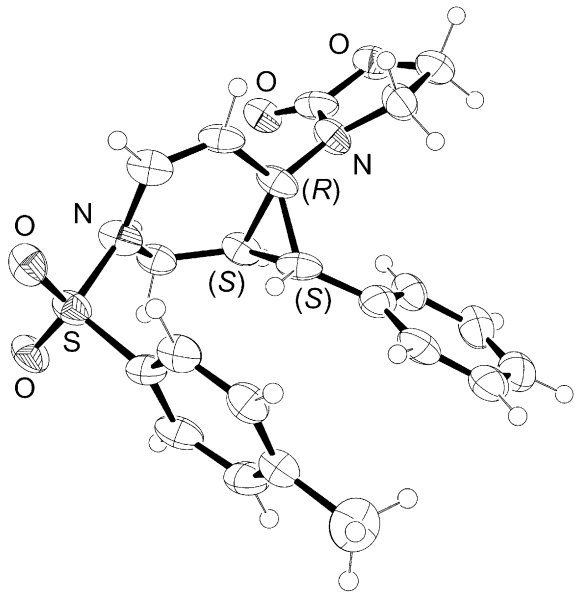
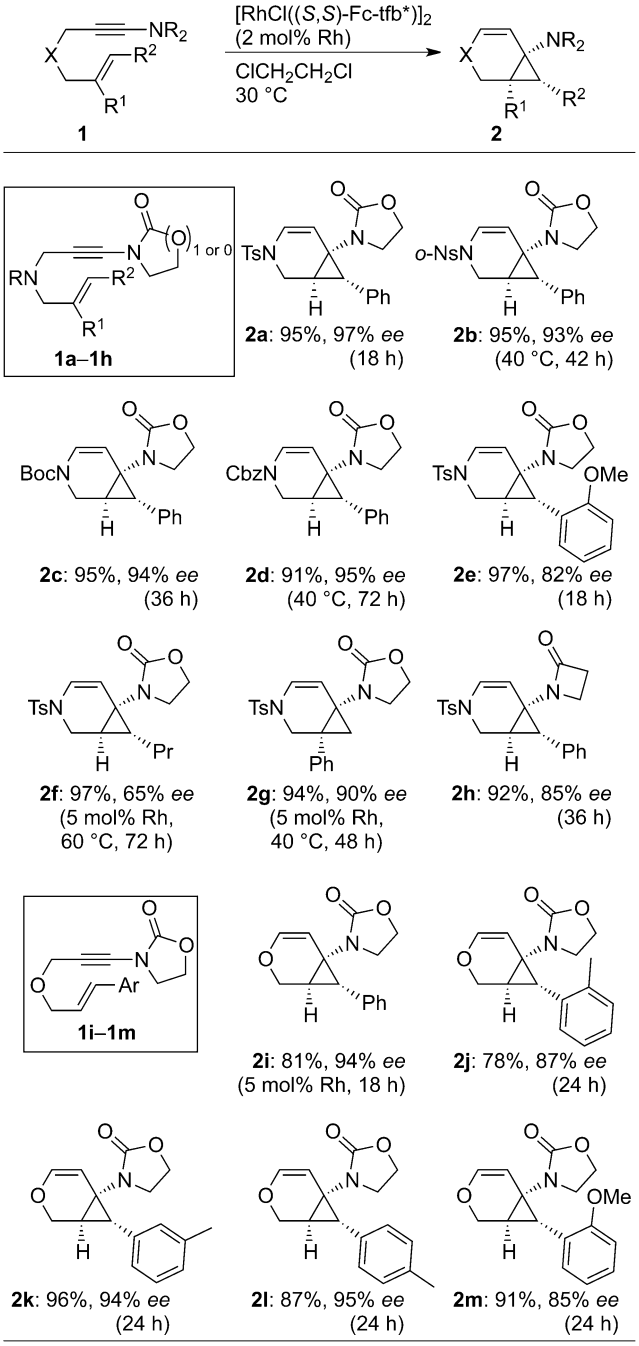
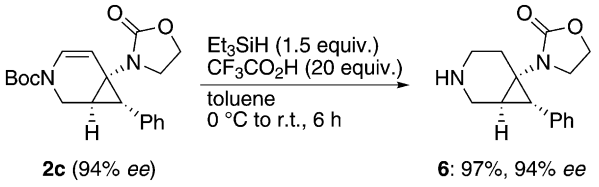


Figure 1. ORTEP illustration of **2a** (a solvent molecule is omitted for clarity).

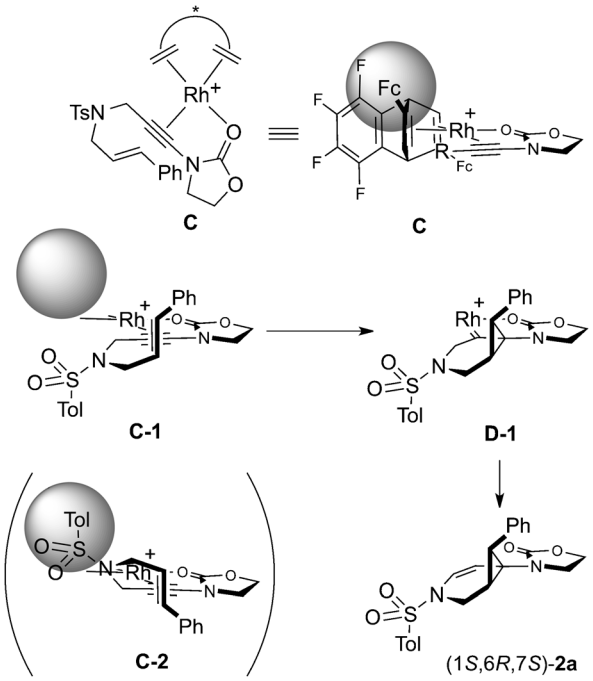
The cycloisomerization product **2c** obtained here with 94% *ee* was readily converted into a 3-azabicyclo[4.1.0]heptane derivative, which is one of the basic structures displaying biological activity[9] (Scheme 5). Thus, treatment of **2c** with triethylsilane



Scheme 4. Rhodium-catalyzed asymmetric cycloisomerization of 1,6-ene-ynamides **1**. *Reaction conditions:* **1** (0.20 mmol), [RhCl((*S*,*S*)-Fc-tfb*)]$_2$ (2 mol% of Rh) in 1,2-dichloroethane (1.0 mL) at 30 °C. The yields are isolated yields and the *ee*s were determined by chiral HPLC analysis.



Scheme 5. Transformation of **2c**.



Scheme 6. Proposed stereochemical model.

and trifluoroacetic acid gave bicyclic amine **6** in 97% yield without loss of its enantiomeric purity (94% *ee*), where the reduction of the alkene moiety and removal of the Boc group on nitrogen were carried out at once.

Provided that the present rhodium-catalyzed cycloisomerization proceeds *via* a rhodium carbenoid as previously proposed for the platinum-catalyzed reaction,[2,4a,25] the enantioselectivity observed in the present catalytic system can be rationalized by using a stereochemical model as shown in Scheme 6. The proposed cationic rhodium species **C** is coordinated with an alkyne moiety and a carbonyl oxygen of ene-ynamide **1a**. The favorable conformation of the coordinated ene-ynamide is illustrated as a **C-1** structure, where an *N*-tosyl group is placed at a less shielded site avoiding the steric repulsion (**C-2**) between the *N*-tosyl group and a ferrocenyl group of the ligand (*S*,*S*)-Fc-tfb*. The 6-*endo-dig* cyclization from **C-1** gives the rhodium-carbenoid **D-1**, which leads to (1*S*,6*R*,7*S*)-**2a**.

Conclusions

In conclusion, we have developed a rhodium-catalyzed asymmetric cycloisomerization of heteroatom-bridged 1,6-ene-ynamides giving high yields of functionalized 3-aza- and oxabicyclo[4.1.0]heptene derivatives with high enantioselectivity, which was achieved by use of a rhodium/chiral diene catalyst. The 1,6-ene-ynamides substituted with 2-oxazolidinone and 2-

azetidinone at the alkyne terminus were found to display high reactivity toward the rhodium/chiral diene catalyst, where the chelate coordination of the alkyne moiety and the carbonyl oxygen of the ene-ynamides might be responsible for the high catalytic activity.

Experimental Section

General and Materials

All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen. NMR spectra were recorded on a JEOL JNM LA-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C) or a JEOL JNM ECA-600 spectrometer (600 MHz for ^{1}H, 150 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) referenced to the residual peaks of $CDCl_3$ ($\delta=7.26$), CD_2Cl_2 ($\delta=5.33$), DMSO-d_6 ($\delta=2.49$), and CD_3OD ($\delta=3.31$) for ^{1}H NMR and $CDCl_3$ ($\delta=77.00$), CD_2Cl_2 ($\delta=53.84$), DMSO-d_6 ($\delta=39.50$), and CD_3OD ($\delta=49.00$) for ^{13}C NMR. Optical rotations were measured on a JASCO P-2200 polarimeter. Flash column chromatography was performed with silica gel 60 N (spherical, neutral) (Cica-Reagent). Alumina (activated 200) for column chromatography was purchased from Nacalai Tesque. 1,2-Dichloroethane was distilled over CaH_2. Rhodium complexes, $[RhCl((R,R)\text{-Bn-tfb*})]_2$,[22] $[RhCl((R,R)\text{-Ph-tfb*})]_2$,[22] $[RhCl((S,S)\text{-Fc-tfb*})]_2$,[22] $[RhCl((R)\text{-}\mathbf{L1})]_2$,[21f] and $[RhCl((R)\text{-binap})]_2$,[26] were prepared according to the reported procedures.

Preparation of 1,6-Ene-ynamides

A typical procedure for **1a** is shown below. The other 1,6-ene-ynamides are described in the Supporting Information.

N-Cinnamyl-4-methyl-*N*-[3-(2-oxooxazolidin-3-yl)-prop-2-yn-1-yl]benzenesulfonamide (1a)

To a mixture of $CuCl_2$ (807 mg, 6.0 mmol), Na_2CO_3 (6.36 g, 60 mmol), 2-oxazolidinone (6.53 g, 75 mmol), and pyridine (4.85 mL, 60 mmol) in toluene (50 mL) was added *N*-cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide[27] (4.88 g, 15 mmol) in toluene (100 mL) at 70 °C over 4 h under O_2 (1 atm).[28] After completion of the addition, the mixture was stirred at 70 °C for 1 h. The mixture was filtered through a pad of celite and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel with hexane/$CHCl_3$/ethyl acetate (3:2:1) to give **1a**; yield: 4.03 g (9.8 mmol, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=2.43$ (s, 3H), 3.61–3.66 (m, 2H), 4.00 (d, $J=6.9$ Hz, 2H), 4.27 (s, 2H), 4.33–4.38 (m, 2H), 6.06 (dt, $J=15.9$, 6.9 Hz, 1H), 6.64 (d, $J=15.9$ Hz, 1H), 7.22–7.36 (m, 7H), 7.78 (d, $J=8.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=21.5$, 36.4, 46.4, 48.8, 62.9, 64.7, 75.5, 122.7, 126.5, 127.7, 128.0, 128.5, 129.6, 135.0, 136.1, 136.2, 143.4, 155.8; HR-MS (ESI): $m/z=433.1193$, calcd. for $C_{22}H_{22}N_2NaO_4S$ $(M+Na)^+$: 433.1192.

General Procedure for Asymmetric Cycloisomerization of 1,6-Ene-ynamides

A mixture of $\{RhCl[(S,S)\text{-Fc-tfb*}]\}_2$ (2.9 mg, 4.0 μmol of Rh), 1,6-ene-ynamides **1** (0.20 mmol) in 1,2-dichloroethane (1.0 mL) was stirred at 30 °C under N_2. The mixture was passed through a short column of alumina with ethyl acetate as eluent. After removal of the solvent, the residue was subjected to preparative TLC on silica gel with hexane/ethyl acetate to give **2**.

3-{(1*S*,6*R*,7*S*)-7-Phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2a): The *ee* was measured by HPLC (Chiralpak IA column, hexane/$CHCl_3$/2-propanol = 12:4:1, flow 0.7 mL min^{-1}, 254 nm): $t_1=9.7$ min (major), $t_2=18.9$ min (minor); $[\alpha]_D^{20}$: −95 (*c* 1.00, $CHCl_3$) for 97% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=2.17$ (d, $J=6.8$ Hz, 1H), 2.45 (s, 3H), 2.50 (td, $J=8.8$, 4.1 Hz, 1H), 2.87 (dd, $J=6.8$, 2.0 Hz, 1H), 3.24 (dd, $J=11.5$, 2.0 Hz, 1H), 3.40 (q, $J=8.8$ Hz, 1H), 3.76 (q, $J=8.8$ Hz, 1H), 4.09 (td, $J=8.8$, 4.1 Hz, 1H), 4.14 (d, $J=11.5$ Hz, 1H), 5.42 (d, $J=8.2$ Hz, 1H), 6.48 (d, $J=8.2$ Hz, 1H), 6.98 (d, $J=6.8$ Hz, 2H), 7.19–7.29 (m, 3H), 7.34 (d, $J=8.1$ Hz, 2H), 7.68 (d, $J=8.1$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=21.5$, 31.8, 36.6, 38.2, 39.7, 42.7, 61.9, 109.6, 122.5, 126.9, 127.0, 127.2, 128.3, 130.0, 134.5, 134.7, 144.2, 158.1; HR-MS (ESI): $m/z=433.1198$, calcd. for $C_{22}H_{22}N_2NaO_4S$ $(M+Na)^+$: 433.1192.

3-{(1*S*,6*R*,7*S*)-3-[(2-Nitrophenyl)sulfonyl]-7-phenyl-3-azabicyclo[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2b): The *ee* was measured by HPLC (Chiralpak IA column, hexane/$CHCl_3$/2-propanol = 12:4:1, flow 0.50 mL min^{-1}): 254 nm, $t_1=24.5$ min (major), $t_2=44.5$ min (minor); $[\alpha]_D^{20}$: +31 (*c* 0.51, $CHCl_3$) for 93% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (600 MHz, CD_2Cl_2): $\delta=2.32$ (d, $J=6.8$ Hz, 1H), 2.57 (td, $J=8.8$, 4.1 Hz, 1H), 2.90 (d, $J=6.8$, 2.4 Hz, 1H), 3.43 (q, $J=8.8$ Hz, 1H), 3.49 (dd, $J=12.2$, 2.4 Hz, 1H), 3.79 (q, $J=8.8$ Hz, 1H), 4.10 (td, $J=8.8$, 4.1 Hz, 1H), 4.21 (d, $J=12.2$ Hz, 1H), 5.61 (d, $J=8.2$ Hz, 1H), 6.51 (d, $J=8.2$ Hz, 1H), 7.05 (d, $J=7.5$ Hz, 2H), 7.20–7.32 (m, 3H), 7.69 (dd, $J=7.5$, 2.1 Hz, 1H), 7.73–7.82 (m, 2H), 8.01 (dd, $J=7.5$, 2.0 Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta=32.2$, 37.5, 38.5, 40.7, 43.2, 62.5, 111.4, 122.1, 124.8, 127.4, 127.8, 128.7, 131.17, 131.20, 132.6, 134.9, 135.1, 148.4, 158.5; HR-MS (ESI): $m/z=464.0883$, calcd. for $C_{21}H_{19}N_3NaO_6S$ $(M+Na)^+$: 464.0887.

(1*S*,6*R*,7*S*)-*tert*-Butyl 6-(2-oxooxazolidin-3-yl)-7-phenyl-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate (2c): The *ee* was measured by HPLC (Chiralpak IA column, hexane/$CHCl_3$/2-propanol = 12:4:1, flow 0.7 mL min^{-1}, 254 nm): $t_1=6.5$ min (major), $t_2=8.0$ min (minor); $[\alpha]_D^{20}$: +34 (*c* 1.00, $CHCl_3$) for 94% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (600 MHz, DMSO-d_6, 60 °C): $\delta=1.47$ (s, 9H), 2.40 (d, $J=6.8$ Hz, 1H), 2.70–2.80 (m, 2H), 3.32 (br s, 1H), 3.57 (q, $J=8.8$ Hz, 1H), 3.85 (q, $J=8.8$ Hz, 1H), 4.09 (td, $J=8.8$, 6.1 Hz, 1H), 4.17 (d, $J=12.2$ Hz, 1H), 5.44 (d, $J=8.1$ Hz, 1H), 6.57 (d, $J=8.1$ Hz, 1H), 7.19 (d, $J=7.5$ Hz, 2H), 7.22 (t, $J=7.5$ Hz, 1H), 7.29 (t, $J=7.5$ Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, 60 °C): $\delta=28.9$, 30.3, 38.1, 38.9, 39.5, 43.9, 62.7, 81.7, 108.8, 124.0, 127.3, 128.5, 128.9, 136.6, 153.2, 158.3. HR-MS (ESI): $m/z=379.1629$, calcd. for $C_{20}H_{24}N_2NaO_4$ $(M+Na)^+$: 379.1628.

(1*S*,6*R*,7*S*)-Benzyl 6-(2-oxooxazolidin-3-yl)-7-phenyl-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate (2d): The *ee* was measured by HPLC (Chiralpak IA column, hexane/$CHCl_3$/2-propanol = 12:4:1, flow 0.5 mL min^{-1}, 254 nm): $t_1=$

12.7 min (major), t_2 = 15.7 min (minor); $[\alpha]_D^{20}$: +35 (*c* 1.03, $CHCl_3$) for 95% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (600 MHz, DMSO-d_6, 60 °C): δ = 2.43 (d, *J* = 7.5 Hz, 1H), 2.73 (td, *J* = 8.9, 6.1 Hz, 1H), 2.81 (br s, 1H), 3.41 (br s, 1H), 3.57 (q, *J* = 8.9 Hz, 1H), 3.85 (q, *J* = 8.9 Hz, 1H), 4.09 (td, *J* = 8.9, 6.1 Hz, 1H), 4.26 (d, *J* = 12.9 Hz, 1H), 5.19 (d, *J* = 12.2 Hz, 1H), 5.21 (d, *J* = 12.2 Hz, 1H), 5.54 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 7.17–7.24 (m, 3H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 6.8 Hz, 1H), 7.36–7.44 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6, 60 °C): δ = 29.1, 36.9, 38.0, 38.2, 42.7, 61.6, 66.9, 109.0, 122.3, 126.1, 127.3, 127.4, 127.70, 127.74, 128.2, 135.3, 136.0, 153.0, 157.1; HR-MS (ESI): *m/z* = 413.1462, calcd. for $C_{23}H_{22}N_2NaO_4$ $(M+Na)^+$: 413.1472.

3-{(1*S*,6*R*,7*S*)-7-(2-Methoxyphenyl)-3-tosyl-3-azabicyclo-[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2e): The *ee* was measured by HPLC (Chiralpak IA column, hexane/$CHCl_3$/2-propanol = 12:4:1, flow 0.5 mL min^{-1}, 254 nm): t_1 = 13.6 min (major), t_2 = 15.6 min (minor); $[\alpha]_D^{20}$: −115 (*c* 1.01, $CHCl_3$) for 82% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 2.54 (td, *J* = 8.9, 4.1 Hz, 1H), 2.71 (d, *J* = 7.5 Hz, 1H), 2.90 (dd, *J* = 7.5, 2.4 Hz, 1H), 3.21 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.42 (q, *J* = 8.9 Hz, 1H), 3.66 (q, *J* = 8.9 Hz, 1H), 3.81 (s, 3H), 4.05 (td, *J* = 8.9, 4.1 Hz, 1H), 4.11 (d, *J* = 10.9 Hz, 1H), 5.41 (d, *J* = 8.9 Hz, 1H), 6.50 (d, *J* = 8.9 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.84–6.89 (m, 2H), 7.17–7.23 (m, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.4, 30.0, 30.5, 37.5, 39.9, 42.2, 55.3, 61.8, 109.3, 109.9, 120.1, 122.2, 123.0, 126.4, 127.0, 128.0, 129.8, 134.4, 144.0, 158.1, 158.6; HR-MS (ESI): *m/z* = 463.1297, calcd. for $C_{23}H_{24}N_2NaO_5S$ $(M+Na)^+$: 463.1298.

3-{(1*S*,6*R*,7*R*)-7-Propyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2f): The *ee* was measured by HPLC (Chiralpak AD-H column, hexane/2-propanol = 4:1, flow 0.7 mL min^{-1}, 254 nm): t_1 = 21.0 min (minor), t_2 = 22.3 min (major); $[\alpha]_D^{20}$: +74 (*c* 1.01, $CHCl_3$) for 65% *ee* (1*S*,6*R*,7*R*). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.5 Hz, 3H), 0.82–0.89 (m, 1H), 0.91–1.11 (m, 1H), 1.20–1.31 (m, 2H), 1.61–1.70 (m, 2H), 2.42 (s, 3H), 3.12 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.51 (q, *J* = 8.1 Hz, 1H), 3.57 (q, *J* = 8.1 Hz, 1H), 3.97 (d, *J* = 11.5 Hz, 1H), 4.22–4.33 (m, 2H), 5.38 (d, *J* = 8.1 Hz, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 21.6, 22.2, 30.1, 32.1, 33.7, 35.2, 40.0, 44.4, 62.0, 110.9, 122.1, 127.0, 130.0, 134.9, 144.1, 158.4; HR-MS (ESI): *m/z* = 399.1350, calcd. for $C_{19}H_{24}N_2NaO_4S$ $(M+Na)^+$: 399.1349.

3-{(1*R*,6*S*)-1-Phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2g): The *ee* was measured by HPLC (Chiralpak IB + IA column, hexane/$CHCl_3$/EtOH = 30:10:1, flow 0.5 mL min^{-1}, 254 nm): t_1 = 37.1 min (major), t_2 = 42.1 min (minor); $[\alpha]_D^{20}$: −113 (*c* 1.03, $CHCl_3$) for 90% *ee* (1*R*,6*S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.55 (d, *J* = 6.1 Hz, 1H), 1.92 (d, *J* = 6.1 Hz, 1H), 2.47 (s, 3H), 3.13 (q, *J* = 8.9 Hz, 1H), 3.21 (q, *J* = 8.9 Hz, 1H), 3.37 (d, *J* = 11.5 Hz, 1H), 3.86–3.96 (m, 2H), 3.97 (d, *J* = 11.5 Hz, 1H), 5.47 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 7.25–7.40 (m, 7H), 7.64 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.5, 22.7, 38.4, 41.6, 44.7, 47.0, 61.7, 113.2, 123.2, 127.0, 127.9, 128.6, 128.8, 130.0, 134.7, 135.8, 144.2, 158.0; HR-MS (ESI): *m/z* = 433.1191, calcd. for $C_{22}H_{22}N_2NaO_4S$ $(M+Na)^+$: 433.1192.

1-{(1*S*,6*R*,7*S*)-7-Phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-en-6-yl}azetidin-2-one (2h): The *ee* was measured by HPLC (Chiralpak IA column, hexane/$CHCl_3$/2-propanol = 12:4:1, flow 0.7 mL min^{-1}, 254 nm): t_1 = 7.6 min (major), t_2 = 13.1 min (minor); $[\alpha]_D^{20}$: −48 (*c* 1.03, $CHCl_3$) for 85% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.10 (d, *J* = 6.8 Hz, 1H), 2.17 (td, *J* = 5.8, 2.7 Hz, 1H), 2.44 (s, 3H), 2.52 (ddd, *J* = 15.0, 5.8, 2.7 Hz, 1H), 2.65 (ddd, *J* = 15.0, 5.8, 2.7 Hz, 1H), 3.00 (td, *J* = 5.8, 2.7 Hz, 1H), 3.05 (dd, *J* = 6.8, 2.7 Hz, 1H), 3.21 (dd, *J* = 11.6, 2.7 Hz, 1H), 4.09 (d, *J* = 11.6 Hz, 1H), 5.43 (d, *J* = 8.2 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 6.8 Hz, 2H), 7.18–7.28 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.5, 30.1, 36.3, 37.2, 37.5, 38.0, 39.6, 110.4, 121.6, 126.8, 127.0, 127.4, 128.3, 130.0, 134.4, 134.7, 144.2, 168.1; HR-MS (ESI): *m/z* = 417.1241, calcd. for $C_{22}H_{22}N_2NaO_3S$ $(M+Na)^+$: 417.1243.

3-{(1*R*,6*R*,7*S*)-7-Phenyl-3-oxabicyclo[4.1.0]hept-4-en-6-yl}-oxazolidin-2-one (2i): The *ee* was measured by HPLC (Chiralcel OD-H column, hexane/2-propanol = 4:1, flow 0.5 mL min^{-1}, 254 nm): t_1 = 18.3 min (minor), t_2 = 19.4 min (major); $[\alpha]_D^{20}$: −8 (*c* 1.03, $CHCl_3$) for 84% *ee* (1*R*,6*R*,7*S*); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.57–2.62 (m, 1H), 2.61 (d, *J* = 6.8 Hz, 1H), 2.81 (d, *J* = 6.8 Hz, 1H), 3.46 (q, *J* = 8.8 Hz, 1H), 3.81 (q, *J* = 8.8 Hz, 1H), 4.07 (d, *J* = 10.9 Hz, 1H), 4.12 (td, *J* = 8.8, 4.1 Hz, 1H), 4.31 (d, *J* = 10.9 Hz, 1H), 5.33 (d, *J* = 6.1 Hz, 1H), 6.27 (d, *J* = 6.1 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 30.7, 36.6, 37.1, 42.8, 60.8, 61.9, 104.5, 126.8, 127.3, 128.3, 135.4, 142.3, 158.2; HR-MS (ESI): *m/z* = 280.0943, calcd. for $C_{15}H_{15}NNaO_3$ $(M+Na)^+$: 280.0944.

3-{(1*R*,6*R*,7*S*)-7-(*o*-Tolyl)-3-oxabicyclo[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2j): The *ee* was measured by HPLC (Chiralpak AD-H column, hexane/2-propanol = 4:1, flow 0.5 mL min^{-1}, 254 nm): t_1 = 15.2 min (major), t_2 = 16.9 min (minor); $[\alpha]_D^{20}$: +95 (*c* 1.00, $CHCl_3$) for 87% *ee* (1*R*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 2.55 (td, *J* = 8.9, 4.5 Hz, 1H), 2.63 (d, *J* = 7.2 Hz, 1H), 2.90 (d, *J* = 7.2 Hz, 1H), 3.44 (q, *J* = 8.9 Hz, 1H), 3.69 (q, *J* = 8.9 Hz, 1H), 4.06 (td, *J* = 8.9, 4.5 Hz, 1H), 4.10 (d, *J* = 10.6 Hz, 1H), 4.30 (d, *J* = 10.6 Hz, 1H), 5.39 (d, *J* = 6.1 Hz, 1H), 6.29 (d, *J* = 6.1 Hz, 1H), 6.95 (d, *J* = 6.1 Hz, 1H), 7.09–7.19 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.1, 29.3, 34.1, 36.6, 42.1, 61.0, 61.7, 104.7, 125.2, 125.8, 126.8, 129.8, 133.2, 138.0, 142.2, 158.3; HR-MS (ESI): *m/z* = 294.1101, calcd. for $C_{16}H_{17}NNaO_3$ $(M+Na)^+$: 294.1101.

3-{(1*R*,6*R*,7*S*)-7-(*m*-Tolyl)-3-oxabicyclo[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2k): The *ee* was measured by HPLC (Chiralpak AD-H column, hexane/2-propanol = 4:1, flow 0.5 mL min^{-1}, 254 nm): t_1 = 16.4 min (major), t_2 = 20.4 min (minor)]; $[\alpha]_D^{20}$: −8 (*c* 1.02, $CHCl_3$) for 94% *ee* (1*R*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.32 (s, 3H), 2.57 (d, *J* = 6.8 Hz, 1H), 2.63 (td, *J* = 8.8, 4.1 Hz, 1H), 2.79 (dd, *J* = 6.8, 1.4 Hz, 1H), 3.44 (q, *J* = 8.8 Hz, 1H), 3.80 (q, *J* = 8.8 Hz, 1H), 4.06 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.13 (td, *J* = 8.8, 4.1 Hz, 1H), 4.29 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.32 (dd, *J* = 6.1, 1.4 Hz, 1H), 6.26 (d, *J* = 6.1 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.3, 30.7, 36.5, 36.9, 42.8, 60.8, 61.9, 104.6, 124.1, 127.5, 128.2, 128.3, 135.3, 137.9,

142.1, 158.2; HR-MS (ESI): $m/z = 294.1101$, calcd. for $C_{16}H_{17}NNaO_3$ $(M+Na)^+$: 294.1101.

3-{(1*R*,6*R*,7*S*)-7-(*p*-Tolyl)-3-oxabicyclo[4.1.0]hept-4-en-6-yl}oxazolidin-2-one (2l): The *ee* was measured by HPLC (Chiralcel OD-H column × 2, hexane/2-propanol = 4:1, flow 0.6 mL min^{-1}, 254 nm): $t_1 = 28.3$ min (minor), $t_2 = 30.0$ min (major); $[\alpha]_D^{20}$: +1 (*c* 1.01, $CHCl_3$) for 95% *ee* (1*R*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H), 2.57 (d, $J = 6.8$ Hz, 1H), 2.65 (td, $J = 8.8$, 4.1 Hz, 1H), 2.76 (d, $J = 6.8$ Hz, 1H), 3.35 (q, $J = 8.8$ Hz, 1H), 3.83 (q, $J = 8.8$ Hz, 1H), 4.06 (dd, $J = 10.2$, 2.0 Hz, 1H), 4.12 (td, $J = 8.8$, 4.1 Hz, 1H), 4.30 (dd, $J = 10.2$, 1.4 Hz, 1H), 5.33 (dd, $J = 6.1$, 1.4 Hz, 1H), 6.26 (d, $J = 6.1$ Hz, 1H), 7.05 (d, $J = 8.2$ Hz, 2H), 7.10 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 21.0$, 30.6, 36.3, 36.8, 42.8, 60.8, 61.9, 104.6, 127.2, 129.0, 132.2, 136.4, 142.1, 158.2; HR-MS (ESI): $m/z = 294.1103$, calcd. for $C_{16}H_{17}NNaO_3$ $(M+Na)^+$: 294.1101.

3-{(1*R*,6*R*,7*S*)-7-(2-Methoxyphenyl)-3-oxabicyclo[4.1.0]-hept-4-en-6-yl}oxazolidin-2-one (2m): The *ee* was measured by HPLC (Chiralpak AD-H column × 2, hexane/2-propanol = 4/1, flow 0.5 mL min^{-1}, 254 nm): $t_1 = 45.3$ min (major), $t_2 = 46.7$ min (minor)]; $[\alpha]_D^{20}$: +61 (*c* 1.00, $CHCl_3$) for 85% *ee* (1*R*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.62$ (td, $J = 8.9$, 4.1 Hz, 1H), 2.83 (d, $J = 7.5$ Hz, 1H), 2.90 (d, $J = 7.5$ Hz, 1H), 3.47 (q, $J = 8.9$ Hz, 1H), 3.72 (q, $J = 8.9$ Hz, 1H), 3.86 (s, 3H), 4.06–4.12 (m, 2H), 4.28 (dd, $J = 10.2$, 1.4 Hz, 1H), 5.35 (d, $J = 6.1$ Hz, 1H), 6.27 (d, $J = 6.1$ Hz, 1H), 6.86 (d, $J = 8.1$ Hz, 1H), 6.89 (dd, $J = 8.1$, 7.5 Hz, 1H), 6.94 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.21 (ddd, $J = 8.1$, 7.5, 1.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 29.6$, 30.6, 36.7, 42.5, 55.6, 61.2, 62.0, 104.8, 110.1, 120.4, 123.9, 126.6, 127.9, 142.1, 158.4, 158.9; HR-MS (ESI): $m/z = 310.1050$, calcd. for $C_{16}H_{17}NNaO_4$ $(M+Na)^+$: 310.1050.

3-{(1*S*,6*R*,7*S*)-7-Phenyl-3-azabicyclo[4.1.0]heptan-6-yl}oxazolidin-2-one (6)

To a solution of **2c** (35.7 mg, 0.10 mmol, 94% *ee*) in toluene (0.5 mL) were added triethylsilane (24 μL, 0.15 mmol) and trifluoroacetic acid (0.15 mL, 2.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 6 h. The mixture was concentrated on a rotary evaporator and the residue was dissolved in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, aqueous NaF, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was dried under vacuum to give analytically pure **6**; yield: 25.0 mg (0.097 mmol). The *ee* of **6** was determined by HPLC analysis of 3-(7-phenyl-3-tosyl-3-azabicyclo[4.1.0]heptan-6-yl)oxazolidin-2-one (**s13**) derived from **6**. $[\alpha]_D^{20}$: +88 (*c* 1.24, $CHCl_3$) for 94% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 1.93$ (dt, $J = 14.2$, 5.7 Hz, 1H), 2.15–2.25 (m, 2H), 2.31 (d, $J = 7.0$ Hz, 1H), 2.65–2.80 (m, 3H), 3.06 (d, $J = 13.3$ Hz, 1H), 3.41 (dd, $J = 13.3$, 5.7 Hz, 1H), 3.48 (q, $J = 8.8$ Hz, 1H), 3.82 (q, $J = 8.8$ Hz, 1H), 4.11 (td, $J = 8.8$, 4.9 Hz, 1H), 7.15–7.30 (m, 3H), 7.28 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 24.3$, 29.1, 34.7, 40.8, 42.4, 44.0, 44.2, 63.7, 127.4, 128.4, 129.2, 138.3, 160.8. HR-MS (ESI): $m/z = 281.1260$, calcd. for $C_{15}H_{18}N_2NaO_2$ $(M+Na)^+$: 281.1260.

3-{(1*S*,6*R*,7*S*)-7-Phenyl-3-tosyl-3-azabicyclo[4.1.0]-heptan-6-yl}oxazolidin-2-one (s13)

This compound was prepared from **6** and tosyl chloride in the presence of triethylamine. The *ee* was measured by HPLC (Chiralpak IA column, hexane/$CHCl_3$/2-propanol = 15/5/1, flow 0.7 mL min^{-1}, 254 nm): $t_1 = 8.8$ min (major), $t_2 = 17.5$ min (minor); $[\alpha]_D^{20}$: +42 (*c* 0.90, $CHCl_3$) for 94% *ee* (1*S*,6*R*,7*S*). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.00$ (ddd, $J = 14.3$, 4.8, 2.0 Hz, 1H), 2.26–2.37 (m, 3H), 2.41–2.50 (m, 2H), 2.45 (s, 3H), 3.03 (dd, $J = 11.6$, 3.4 Hz, 1H), 3.28 (q, $J = 8.9$ Hz, 1H), 3.57–3.66 (m, 1H), 3.74 (q, $J = 8.9$ Hz, 1H), 3.92 (d, $J = 11.6$ Hz, 1H), 4.07 (td, $J = 8.9$, 3.0 Hz, 1H), 7.13 (d, $J = 6.8$ Hz, 2H), 7.20–7.24 (m, 1H), 7.25–7.30 (m, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.63 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 21.5$, 24.8, 29.8, 32.8, 38.4, 42.6, 43.4, 43.9, 62.1, 126.7, 127.2, 127.5, 128.3, 129.8, 133.1, 135.8, 143.8, 158.6; HR-MS (ESI): $m/z = 435.1344$, calcd. for $C_{22}H_{24}N_2NaO_4S$ $(M+Na)^+$: 435.1349.

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