Synthesis of Optically Acitve γ-Lactams by Palladium Catalyzed Asymmetric Dicarbonylation Reaction of N-Arylsufonyl Homoallylic Amines

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SYNTHESIS OF OPTICALLY ACTIVE *γ*-LACTAMS BY PALLADIUM CATALYZED ASYMMETRIC DICARBONYLATION REACTION OF *N*-ARYLSUFONYL HOMOALLYLIC AMINES

Ryosuke Takahashi, Nga Hang Thi Phan, Takuya Suga, Takahiro Soeta, and Yutaka Ukaji*

Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa, Ishikawa 920-1192, Japan. E-mail: ukaji@staff.kanazawa-u.ac.jp

Abstract – Optically active *γ*-lactams were prepared by asymmetric dicarbonylation reaction of *N*-arylsulfonyl homoallylic amines catalyzed by palladium in the presence of copper(I) triflate. By the use of benzyl-substituted bioxazoline ligand, the corresponding *γ*-lactams were obtained with enantioselectivities of up to 67% ee.

INTRODUCTION

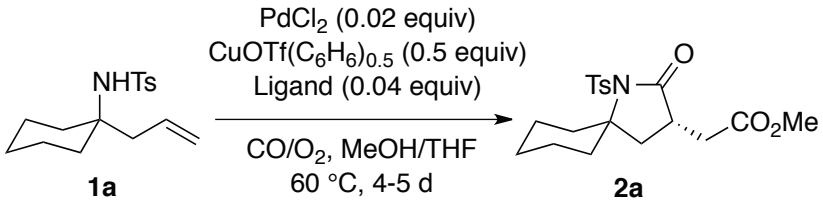
The *γ*-lactams are widespread among biologically active natural and non-natural products and have therefore been used as a privileged structural subunit for the design of several pharmaceutical agents. In addition, they also serve as important intermediates for the synthesis of nitrogen-containing molecules.[1] Among many synthetic approaches developed for *γ*-lactams, those using the transition-metal catalysts are of high value since they generally allow efficient and selective production of functionalized *γ*-lactams under mild reaction conditions.[2] Chemoselective formation of *γ*-lactams via intramolecular C-H amidation of 1,4,2-dioxazol-5-ones is a straightforward way to furnish *γ*-lactams.[3] Transition-metal catalyzed cyclocarbonylation of amine derivatives with CO via C-H bond activation is an attractive method to directly introduce a carbonyl group.[4] Furthermore, aminocarbonylation to a carbon-carbon double bond is a promising alternative.[5] Until recently, the development of enantioselective intramolecular aminocarbonylation has remained limited.[3b,5d,e] Previously, as part of our program aimed at the development of palladium-catalyzed carbonylation reactions, we discovered asymmetric bis(alkoxycarbonylation) of homoallylic alcohols via cyclocarbonylation/alkoxycarbonylation to produce

the corresponding optically active γ-lactones.[6] In this paper, we will describe synthesis of γ-lactams by asymmetric dicarbonylation of *N*-arylsulfonyl homoallylic amine derivatives catalyzed by palladium in the presence of a copper salt.

RESULTS AND DISCUSSION

Based on our previous study on dicarbonylation of homoallylic amine derivatives, *N*-tosyl homoallylic amine **1a** possessing a cyclohexane skeleton was chosen as the substrate.[7] Thus, **1a** was treated with a 0.02 equiv. of $PdCl_2$ and a 0.5 equiv. of $CuOTf(C_6H_6)_{0.5}$ under normal pressure of CO and O_2 (ca. 1/1, v/v) using (4*S*,4'*S*)-4,4'-dibenzyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (**L1**) as a chiral ligand in MeOH/THF at 60 °C.[8] To our delight, the desired doubly carbonyl-incorporated γ-lactam **2a** was obtained in 53% yield.[9] The optical purity of **2a** was determined to be 67% ee by HPLC analysis (Table 1, Entry 1). The effect of substituents at the 4- and 4'-positions in the bioxazoline ligands was investigated. Dicarbonylation using aliphatic substituted ligands **L2** and **L3** gave disappointing results (Entries 2 and 3).

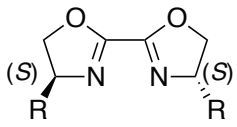
Table 1. Asymmetric dicarbonylation reaction of **1a** using various ligands



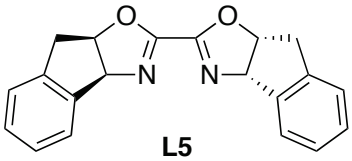
1a **2a**

Entry	Ligand	Yield/%	ee/%[a]
1	**L1**	53	67
2	**L2**	31	2
3	**L3**	41	34
4	**L4**[b]	62	–49
5	**L5**	30	60
6	**L6**	51	47
7	**L7**[b]	57	–53
8	**L8**	47	30
9	**L9**	44	–9

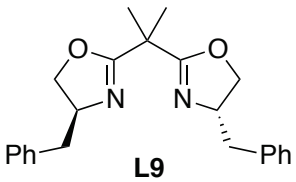
[a]Enantioselectivities were determined by HPLC analysis (Daicel CHIRALCEL OJ-H). [b](*R*,*R*)-Ligand was used.



L1: R = CH_2Ph
L2: R = *i*-Pr
L3: R = *i*-Bu
L4: R = Ph
L6: R = CH_2(1-Nap)
L7: R = CH_2(2-Nap)
L8: R = CH_2OH



L5



L9

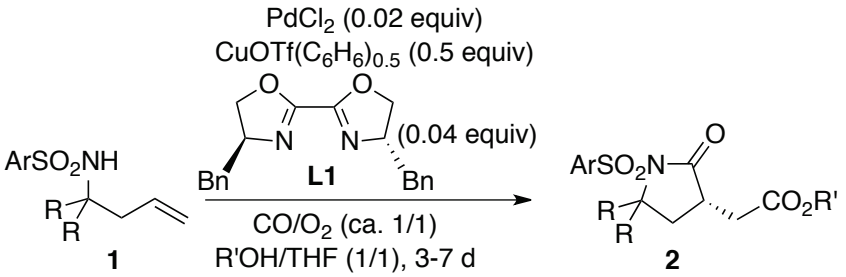
The phenyl-substituted bioxazoline ligand **L4** was effective (Entry 4). The aromatic fused ligand **L5** induced relatively good enantiodifferentiation (Entry 5). In the case of naphtyl-substituted benzyl-type ligands **L6** and **L7**, the *γ*-lactam **2a** was obtained with moderate enatioselectivities (Entries 6 and 7). The bioxazoline ligand **L8** with hydroxy groups was examined, but the enantioselectivity was not improved (Entry 8). The use of the bis(oxazoline) ligand **L9** was unpromising, giving the product with poor enantioselectivity (Entry 9). Overall, among all tested ligands, benzyl-substituted bioxazoline **L1** appeared to be the most effective ligand for the intra- and intermolecular dicarbonylation reaction of *N*-tosyl homoallylic amine **1a**.

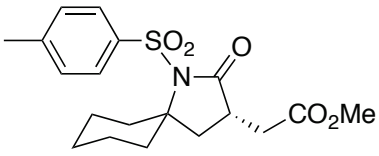
Next, the asymmetric dicarbonylation reactions using other solvents and various substrates were investigated as shown in Table 2. When the asymmetric dicarbonylation reactions of **1a** in EtOH and *i*-PrOH with THF instead of MeOH were examined, the corresponding ethyl ester **2aE** and isopropyl ester **2aP** were obtained with lower enantioselectivities, respectively. Therefore, all the following reactions were examined in MeOH/THF.

The asymmetric dicarbonylation reactions of several *N*-arylsulfonyl homoallylic amines by the use of $PdCl_2$ and $CuOTf(C_6H_6)_{0.5}$ under CO and O_2 (ca. 1/1, v/v) were carried out. *N*-(4-Methoxyphenyl)sulfonyl homoallylic amine **1b** was applicable to this reaction, giving the product **2b** with 51% ee. *γ*-Lactam formation of sterically demanding *N*-(2,4,6-triisopropylphenyl)sulfonyl homoallylic amine **1c** proceeded rather cleanly to produce the product **2c** in 85% yield with 50% ee. Reactions of electron-withdrawing *p*-bromo and *p*-nitrosubstituted *N*-arylsulfonyl substrates **1d** and **1e** gave the corresponding *γ*-lactams **2d** and **2e** with 25% ee and 46% ee, respectively. In the case of *N*-*α*-naphthylsulfonyl and *N*-*β*-naphthylsulfonyl substituted homoallylic amines **1f** and **1g**, the corresponding *γ*-lactams **2f** and **2g** were obtained with enantioselectivities of 42% ee and 51% ee, respectively. After all, most of *N*-arylsulfonyl homoallylic amine derivatives afforded the corresponding *γ*-lactams with about 50% ee.

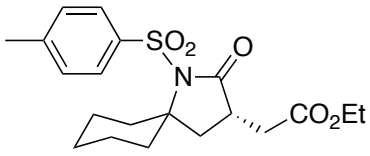
Finally, the asymmetric dicarbonylation reactions of several *N*-tosyl homoallylic amines with substituents other than cyclohexane backbone were carried out. Dicarbonylation reactions of the substrates possessing cyclopentane and cycloheptane ring moieties **1h** and **1i** were sluggish and the *γ*-lactams **2h** and **2i** were obtained in poor yields. Unfortunately, simple non-substituted *N*-tosyl 3-butenylamine was not applicable to the reaction and the desired product was not obtained (not shown). The dicarbonylation reaction of the dimethyl-substituted homoallylic amine derivative **1j** afforded the corresponding *γ*-lactam **2j** in 55% ee. In the case of diphenyl-substituted substrate **1k**, intra- and intermolecular dicarbonylation proceeded to give the corresponding *γ*-lactam **2k** in 68% yield with 52% ee.

Table 2. Asymmetric dicarbonylation reaction of *N*-arylsulfonyl homoallylic amines **1**[a,b]

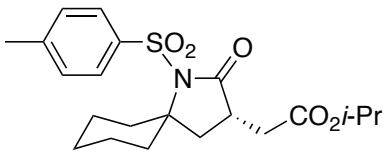




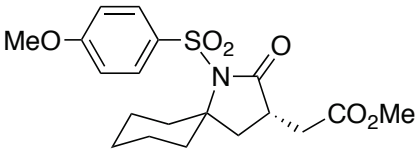
2a; 53%, 67% ee



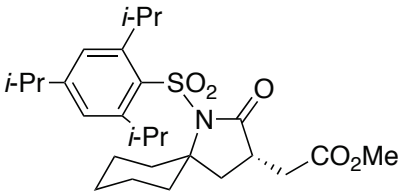
2aE; 48%, 38% ee



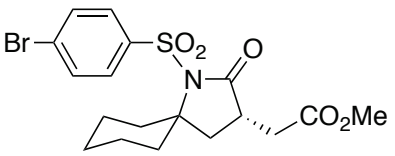
2aP; 69%, 40% ee



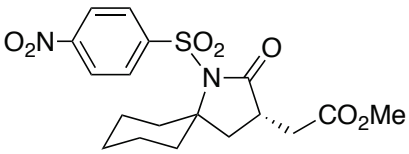
2b; 47%, 51% ee



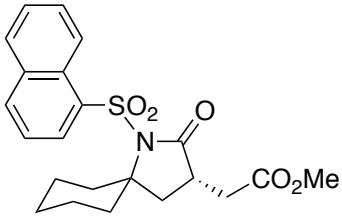
2c; 85%, 50% ee



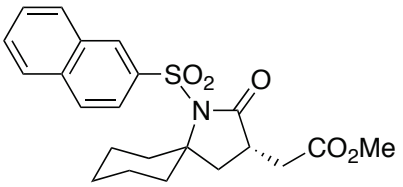
2d; 51%, 25% ee



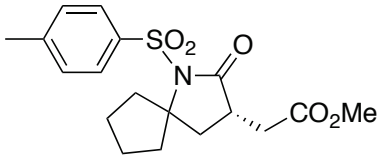
2e; 50%, 46% ee



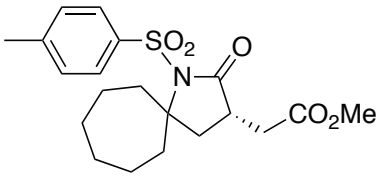
2f; 36%, 42% ee



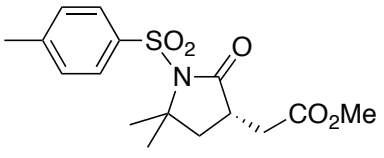
2g; 45%, 51% ee



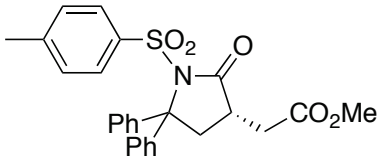
2h; 17%, 38% ee



2i; 15%, 65% ee



2j; 39%, 55% ee



2k; 68%, 52% ee

[a]Reaction times were shown in Experimental section. [b]Enantioselectivities were determined by HPLC analysis.

The absolute configuration of **2a** was determined to be *S* by X-ray crystallographic analysis of a single crystal (CCDC-1889364): the Flack parameter was 0.017(4). The absolute configurations of other products were tentatively determined to be *S* as well.

Because of the coincidence in the absolute configuration between **2a** and the product of dicarbonylation reaction from 1-allylcyclohexanol using ligand **L1** previously reported,[6a] we propose that the mechanism of the present reaction is identical to that of the dicarbonylation of homoallylic alcohols, which has been proved to include the *syn*-insertion of an alkene moiety to a Pd-carbonyl bond.[6b] In both reactions, the stereochemical outcomes can be explained by the similar models T_1 and T_2 (Figure 1).[6a] That is, steric hindrance between a benzyl group in **L1** and the substituent R in the *N*-tosyl homoallylic amines in **1** would disfavor the transition state T_2, and the second carbonyl insertion from T_1 proceeds in *syn*-fashion to furnish (*S*)-*γ*-lactam mainly.

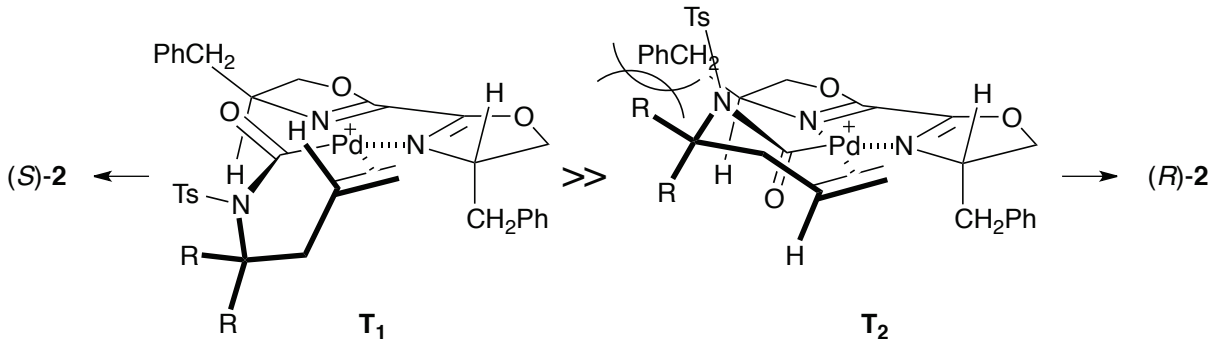


Figure 1. Proposed stereochemical models for dicarbonylation

In conclusion, we have developed a palladium-catalyzed asymmetric dicarbonylation reaction of *N*-arylsulfonyl homoallylic amines to form the optically active (methoxycalbonyl)methyl group-substituted *γ*-lactams with enantioselectivities of up to 67% ee. This represents a new synthetic method for the rapid construction of optically active *γ*-lactams, which are important scaffolds for biologically relevant molecules.

EXPERIMENTAL

^{1}H NMR spectroscopy was performed in $CDCl_3$ using a JEOL ECS 400 NMR (400 MHz) spectrometer. Chemical shifts (δ) were determined relative to TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR spectroscopy was performed in $CDCl_3$ on a JEOL ECS 400 NMR (100 MHz) spectrometer and chemical shifts (δ) were determined relative to $CDCl_3$ (δ = 77.0 ppm) as an internal standard. IR spectra were acquired on a JASCO FT/IR-230 spectrometer. Melting points were determined on a micro-melting apparatus (As One) and were uncorrected. The MS spectra were recorded with JEOL JMS-T100TD and Bruker micrOTOF II mass spectrometers. Merck silica gel 60 PF254 (Art. 7749), Cica silica gel 60N

spherical neutral (37563-84), and JAIGL-SIL (s-043-15) were used for thin-layer chromatography (TLC), flash column chromatography, and recycle HPLC, respectively.

Representative Procedure for the Asymmetric Dicarbonylation Reaction of 1a (Table 2): Under an Ar atmosphere, $PdCl_2$ (1.1 mg, 0.006 mmol), $CuOTf(C_6H_6)_{0.5}$ (37.8 mg, 0.15 mmol), benzyl-substituted bioxazoline ligand **L1** (3.8 mg, 0.012 mmol) were placed in a flask. Next, a solution of *N*-(1-allylcyclohexyl)-4-methylbenzenesulfonamide (**1a**) (92.8 mg, 0.3 mmol) in MeOH (3 mL) and THF (3 mL) were added. The Ar atmosphere was replaced with CO/O_2 (ca. 1/1, v/v) and the reaction mixture was stirred for 5 d at 60 °C. A saturated aq solution of $NaHCO_3$ was added to the reaction mixture at rt, and the insoluble substance was filtered off through Celite. After the filtrate was extracted three times with AcOEt, the combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was separated by preparative TLC on silicagel (hexane/AcOEt = 2/1) to give *γ*-lactam **2a** (60.4 mg, 53%).

(*S*)-Methyl 2-(2-oxo-1-tosyl-1-azaspiro[4.5]decan-3-yl)acetate (2a)[7]: Reaction time was 5 d. A solid. Mp 141−142 °C. $[\alpha]_D^{25}$ −1 (*c* 0.6, $CHCl_3$). The ee was determined to be 67% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 10/1, 0.75 mL/min, 220 nm, major 35 min, minor 77 min). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.24−1.49 (m, 4H), 1.66−1.85 (m, 5H), 2.33 (dd, *J* = 16.9, 8.7 Hz, 1H), 2.42 (s, 3H), 2.44−2.51 (m, 1H), 2.67 (dd, *J* = 12.4, 9.2 Hz, 1H), 2.80 (dd, *J* = 16.9, 4.1 Hz, 1H), 2.85−2.91 (m, 2H), 3.65 (s, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.6, 22.8, 24.1, 24.5, 33.5, 34.3, 36.6, 36.8, 37.8, 51.9, 69.7, 128.5, 129.2, 136.6, 144.6, 171.7, 174.7. IR (KBr): 2938, 2867, 1722, 1596, 1442, 1363, 1343, 1260, 1215, 1161, 1089, 1066, 998, 882, 826, 683, 657 cm^{-1}. Enantiomerically pure **2a** was obtained by recrystallization procedure: First recrystallization of **2a** (ca 40% ee) from EtOH gave the solid **2a** with lower optical purity. Condensation of the filtrate furnished **2a** with higher optical purity (87% ee). The recrystallization of the latter gave the solid and the filtrate. The filtrate was condensed and recrystallized again. Then almost optically pure **2a** (99.7% ee) was recovered from its filtrate. Finally recrystallization of the sample from EtOH afforded the single crystal. Crystal data: $C_{19}H_{25}NO_5S$, M_r = 379.46, monoclinic, $P2_1$, a = 10.0472(3), b = 15.6733(5), c = 11.8531(3) Å, β = 96.148(1). V = 1855.81(9) $Å^3$, Z = 4, D_{calcd} = 1.358 g cm^{-3}, R = 0.0413 (R_w = 0.1380) for 6784 reflections, Flack parameter = 0.017(4). Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as deposition number CCDC-1889364. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

In a similar manner, other *γ*-lactams **2aE**, **2aP**, and **2b**−**2k** were prepared from the corresponding *N*-arylsulfonyl homoallylic amines **1a**−**1k**.

Ethyl 2-(2-oxo-1-tosyl-1-azaspiro[4.5]decan-3-yl)acetate (2aE): Reaction time was 5 d. A solid. Mp 116–117 °C. $[\alpha]_D^{25}$ –2 (*c* 1.3, $CHCl_3$). The ee was determined to be 38% by HPLC (Daicel CHIRALPAK

IB, hexane/EtOH = 20/1, 0.5 mL/min, 220 nm, major 49 min, minor 51 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.3 Hz, 3H), 1.23–1.52 (m, 4H), 1.23–1.52 (m, 5H), 2.32 (dd, J = 16.5, 8.7 Hz, 1H), 2.42 (s, 3H), 2.42–2.53 (m, 1H), 2.67 (dd, J = 12.9, 6.9 Hz, 1H), 2.77–2.94 (m, 3H), 4.10 (q, J = 7.3 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.6, 22.8, 24.1, 24.5, 33.5, 34.5, 36.6, 36.8, 37.8, 60.8, 69.7, 128.5, 129.2, 136.7, 144.5, 171.2, 174.7. IR (KBr): 2980, 2938, 2969, 1947, 1716, 1595, 1455, 1382, 1364, 1345, 1305, 1262, 1215, 1152, 1066, 1029, 983, 884, 825, 682, 656 cm^{-1}. HRMS (DART) *m*/*z*: Calcd for $C_{20}H_{28}NO_5S$ $[M+H]^+$: 394.1688, Found: 394.1688.

Isopropyl 2-(2-oxo-1-tosyl-1-azaspiro[4.5]decan-3-yl)acetate (2aP): Reaction time was 3 d. An oil. $[\alpha]_D^{25}$ −4 (*c* 0.3, $CHCl_3$). The ee was determined to be 40% by HPLC (Daicel CHIRALPAK IB, hexane/EtOH = 20/1, 0.2 mL/min, 230 nm, major 95 min, minor 98 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, J = 6.4 Hz, 6H), 1.22–1.50 (m, 4H), 1.62–1.88 (m, 5H), 2.29 (dd, J = 17.0, 9.2 Hz, 1H), 2.42 (s, 3H), 2.41–2.52 (m, 1H), 2.66 (dd, J = 12.4, 9.2 Hz, 1H), 2.75 (dd, J = 17.0, 3.7 Hz, 1H), 2.79–2.93 (m, 2H), 4.93–5.02 (m, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 21.69, 21.73, 22.9, 24.1, 24.5, 33.5, 34.8, 36.6, 36.8, 37.9, 68.3, 69.7, 128.6, 129.2, 136.7, 144.5, 170.7, 174.7. IR (KBr): 2934, 2867, 1721, 1597, 1496, 1452, 1364, 1343, 1298, 1225, 1157, 1109, 1075, 1011, 957, 906, 812, 769, 684, 658 cm^{-1}. HRMS (DART) *m*/*z*: Calcd for $C_{21}H_{30}NO_5S$ $[M+H]^+$: 408.1845, Found: 408.1851.

Methyl 2-(1-((4-methoxyphenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (2b): Reaction time was 4 d. A solid. Mp 151–152 °C. $[\alpha]_D^{25}$ +1 (*c* 0.4, EtOH). The ee was determined to be 51% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.75 mL/min, 240 nm, major 26 min, minor 66 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.48 (m, 4H), 1.66–1.84 (m, 5H), 2.33 (dd, J = 16.9, 8.2 Hz, 1H), 2.42–2.52 (m, 1H), 2.66 (dd, J = 12.4, 10.1 Hz, 1H), 2.77–2.92 (m, 3H), 3.64 (s, 3H), 3.86 (s, 3H), 6.96 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.0, 24.5, 33.4, 34.3, 36.6, 36.7, 37.8, 51.9, 55.6, 69.6, 113.7, 130.8, 131.1, 163.5, 171.7, 174.6. IR (KBr): 2988, 2946, 2861, 1721, 1595, 1498, 1453, 1367, 1344, 1330, 1261, 1162, 1072, 1021, 838, 730, 662 cm^{-1}. HRMS (DART) *m*/*z*: Calcd for $C_{19}H_{26}NO_6S$ $[M+H]^+$: 396.1481, Found: 396.1474.

Methyl 2-(2-oxo-1-((2,4,6-triisopropylphenyl)sulfonyl)-1-azaspiro[4.5]decan-3-yl)acetate (2c): Reaction time was 4 d. An oil. $[\alpha]_D^{25}$ −6 (*c* 1.3, EtOH). The ee was determined to be 50% by HPLC (Daicel CHIRALCEL OJ-H, hexane/*i*-PrOH = 50/1, 0.5 mL/min, 240 nm, major 25 min, minor 27 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12–1.48 (m, 24H), 1.54–1.88 (m, 4H), 2,14–2.24 (m, 1H), 2.40–2.50 (m, 1H), 2.58–2.90 (m, 3H), 3.57 (s, 3H), 4.10–4.20 (m, 3H), 7.07 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 23.3, 23.4, 24.1, 24.2, 24.4, 24.5, 24.7, 28.7, 33.3, 34.0, 34.7, 36.5, 36.8, 37.5, 51.8, 60.3, 71.0, 123.7, 128.2, 133.6, 151.2, 153.4, 171.7, 175.1. IR (KBr): 2955, 2868, 2359, 1730, 1601, 1462, 1362,

1327, 1151, 1060, 988, 881, 658 cm^{-1}. HRMS (DART) *m/z*: Calcd for $C_{27}H_{42}NO_5S$ $[M+H]^+$: 492.2784, Found: 492.2797.

Methyl 2-(1-((4-bromophenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (2d): Reaction time was 4 d. A solid. Mp 122–123 °C. $[\alpha]_D^{25}$ −2 (*c* 0.5, $CHCl_3$). The ee was determined to be ee was determined to be 25% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 1.0 mL/min, 230 nm, major 13 min, minor 25 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.57 (m, 4H), 1.66–1.94 (m, 5H), 2.34 (dd, *J* = 17.4, 8.7 Hz, 1H), 2.38－2.50 (m, 1H), 2.67 (dd, *J* = 12.8, 9.6 Hz, 1H), 2.78 (dd, *J* = 17.4, 4.1 Hz, 1H), 2.82–2.93 (m, 2H), 3.65 (s, 3H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.0, 24.5, 33.6, 34.1, 36.4, 36.7, 37.7, 51.9, 70.0, 128.8, 130.0, 131.9, 138.5, 171.5, 174.8. IR (KBr): 2944, 2867, 1727, 1574, 1443, 1366, 1347, 1300, 1160, 1068, 1011, 970, 823, 763, 702 cm^{-1}. HRMS (DART) *m/z*: Calcd for $C_{18}H_{23}BrNO_5S$ $[M+H]^+$: 444.0480, Found: 444.0477.

Methyl 2-(1-((4-nitrophenyl)sulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (2e): Reaction time was 4 d. A solid. Mp 176–179 °C. $[\alpha]_D^{25}$ −1 (*c* 0.4, $CHCl_3$). The ee was determined to be 46% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 254 nm, major 85 min, minor 116 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.48 (m, 4H), 1.58–1.84 (m, 5H), 2.22–2.42 (m, 2H), 2.58–2.84 (m, 3H), 3.57 (s, 3H), 8.18 (d, *J* = 7.8 Hz, 2H), 8.28 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.0, 24.4, 33.8, 33.9, 36.3, 36.6, 37.6, 52.0, 70.4, 123.9, 129.9, 144.9, 150.4, 171.4, 175.1. IR (KBr): 2928, 2859, 1730, 1607, 1530, 1439, 1357, 1296, 1228, 1178, 1151, 1085, 1009, 852, 742, 687 cm^{-1}. HRMS (DART) *m/z*: Calcd for $C_{18}H_{23}N_2O_7S$ $[M+H]^+$: 411.1226, Found: 411.1232.

Methyl 2-(1-(naphthalen-1-ylsulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (2f): Reaction time was 4 d. A solid. Mp 151−152 °C. $[\alpha]_D^{25}$ −3 (*c* 0.3, $CHCl_3$). The ee was determined to be 42% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 230 nm, minor 37 min, major 41 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.62 (m, 4H), 1.68–2.06 (m, 5H), 2.31 (dd, *J* = 17.4, 8.7 Hz, 1H), 2.60–2.74 (m, 3H), 2.83–2.92 (m, 1H), 2.96–3.05 (m, 1H), 3.58 (s, 3H), 7.54–7.68 (m, 3H), 7.93 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.80 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 24.2, 24.6, 33.9, 34.1, 36.2, 36.8, 37.9, 123.8, 124.1, 126.7, 128.1, 128.3, 128.4, 129.1, 131.8, 133.9, 135.2, 171.6, 175.0. IR (KBr): 2929, 2862, 1724, 1594, 1507, 1436, 1335, 1305, 1198, 1158, 1061, 1011, 907, 802, 769, 685 cm^{-1}. HRMS (DART) *m/z*: Calcd for $C_{22}H_{26}NO_5S$ $[M+H]^+$: 416.1532, Found: 416.1530.

Methyl 2-(1-(naphthalen-2-ylsulfonyl)-2-oxo-1-azaspiro[4.5]decan-3-yl)acetate (2g): Reaction time was 3 d. A solid. Mp 148−150 °C. $[\alpha]_D^{25}$ +3 (*c* 0.6, $CHCl_3$). The ee was determined to be 51% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, 230 nm, major 38 min, minor 46 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.56 (m, 4H), 1.68–1.96 (m, 5H), 2.32 (dd, *J* = 16.9, 8.7 Hz, 1H), 2.56–2.62 (m, 1H), 2.67–2.75 (m, 1H), 2.77 (dd, *J* = 16.9, 4.1 Hz, 1H), 2.85–3.02 (m, 2H), 3.61 (s, 3H), 7.62–

7.68 (m, 2H), 7.93–8.06 (m, 4H), 8.66 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.1, 24.5, 33.6, 34.1, 36.5, 36.7, 37.8, 51.8, 69.8, 122.8, 127.4, 127.8, 128.8, 129.2, 129.6, 130.6, 131.7, 135.1, 136.4, 171.6, 174.7. IR (KBr): 2926, 2862, 1734, 1593, 1441, 1342, 1301, 1171, 1150, 1071, 996, 907, 816, 749, 657 cm^{-1}. HRMS (DART) *m*/*z*: Calcd for $C_{22}H_{26}NO_5S$ $[M+H]^+$: 416.1532, Found: 416.1532.

(*S*)-Methyl 2-(2-oxo-1-tosyl-1-azaspiro[4.4]nonan-3-yl)acetate (2h): Reaction time was 4 d. A solid. Mp 110 °C. $[\alpha]_D^{25}$ −6 (*c* 0.2, EtOH). The ee was determined to be 38% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, major 30 min, minor 58 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59−1.71 (m, 5H), 1.90−2.01 (m, 3H), 2.31 (ddd, *J* = 17.2, 8.7, 2.8 Hz, 1H), 2.37 (dd, *J* = 12.4, 8.7 Hz, 1H), 2.43 (s, 3H), 2.81 (dd, *J* = 17.2, 4.0 Hz, 1H) 2.86−2.93 (m, 2H), 3.65 (s, 3H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.8, 24.1, 33.8, 36.4, 37.4, 38.5, 42.8, 51.8, 73.3, 128.4, 129.3, 136.4, 144.7, 171.7, 174.6. IR (KBr): 2938, 1727, 1595, 1457, 1350, 1313, 1156, 1086, 1041, 815, 668 cm^{-1}. HRMS (ESI) *m*/*z*: Calcd for $C_{18}H_{23}NO_5SNa$ $[M+Na]^+$: 388.1189. Found: 388.1199.

(*S*)-Methyl 2-(2-oxo-1-tosyl-1-azaspiro[4.6]undecan-3-yl)acetate (2i): Reaction time was 5 d. A solid. Mp 160 °C. $[\alpha]_D^{25}$ −3 (*c* 0.1, EtOH). The ee was determined to be 65% by HPLC (Daicel CHIRALCEL OJ-H, hexane/EtOH = 4/1, 0.5 mL/min, major 38 min, minor 43 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35−1.84 (m, 10H), 1.99 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.31 (dd, *J* = 16.9, 8.7 Hz, 1H), 2.43 (s, 3H), 2.48−2.56 (m, 1H), 2.55 (dd, *J* = 12.8, 8.7 Hz, 1H), 2.81 (dd, *J* = 16.9, 3.7 Hz, 1H), 2.87−2.95 (m, 2H), 3.65 (s, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.6, 23.5, 27.0, 27.4, 34.2, 36.7, 38.3, 38.5, 39.7, 51.9, 72.8, 128.6, 129.2, 136.7, 144.6, 171.8, 174.3. IR (KBr): 2932, 1720, 1596, 1440, 1353, 1160, 1046, 824, 739, 707, 655 cm^{-1}. HRMS (ESI) *m*/*z*: Calcd for $C_{20}H_{27}NO_5SNa$ $[M+Na]^+$: 416.1502, Found: 416.1489.

(*S*)-Methyl 2-(5,5-dimethyl-2-oxo-1-tosylpyrrolidin-3-yl)acetate (2j): Reaction time was 7 d. A solid. Mp 140 °C. $[\alpha]_D^{25}$ +1 (*c* 0.3, EtOH). The ee was determined to be 55% by HPLC (Daicel CHIRALCEL OJ-H, hexane/*i*-PrOH = 20/1, 0.5 mL/min, 230 nm, major 108 min, minor 136 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57−1.64 (m, 1H), 1.59 (s, 3H), 1.67 (s, 3H), 2.19 (dd, *J* = 12.4, 8.7 Hz, 1H), 2.26 (dd, *J* = 16.9, 8.7 Hz, 1H), 2.36 (s, 3H), 2.75 (dd, *J* = 16.9, 4.1 Hz, 1H), 2.83−2.92 (m, 1H), 3.57 (s, 3H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 26.9, 29.5, 34.1, 37.1, 42.5, 51.9, 65.0, 128.6, 129.3, 136.4, 144.7, 171.7, 174.2. IR (KBr): 2923, 1731, 1598, 1446, 1342, 1290, 1159, 1091, 1038, 811, 673 cm^{-1}. HRMS (ESI) *m*/*z*: Calcd for $C_{16}H_{21}NO_5SNa$ $[M+Na]^+$: 362.1033. Found: 362.1022.

(*S*)-Methyl 2-(2-oxo-5,5-diphenyl-1-tosylpyrrolidin-3-yl)acetate (2k): Reaction time was 5 d. A solid. Mp 101−103 °C. $[\alpha]_D^{25}$ –13 (*c* 0.7, $CHCl_3$). The ee was determined to be 52% by HPLC (Daicel CHIRALPAK IB, hexane/*i*-PrOH = 20/1, 0.5 mL/min, 230 nm, major 46 min, minor 43 min). ^{1}H NMR

(400 MHz, $CDCl_3$): δ 2.22−2.32 (m, 1H), 2.29 (s, 3H), 2.49 (dd, J = 17.4, 7.3 Hz, 1H), 2.63−2.82 (m, 3H), 3.52 (s, 3H), 7.01 (d, J = 8.2 Hz, 2H), 7.05−7.39 (m, 10H), 7.56 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 33.2, 37.0, 46.5, 51.8, 75.5, 125.2, 127.68, 127.74, 127.8, 128.09, 128.13, 128.3, 128.5, 128.7, 128.9, 129.6, 136.0, 141.0, 141.2, 144.6, 171.3, 174.4. IR (KBr): 2979, 1723, 1658, 1599, 1435, 1325, 1154, 1093, 989, 816, 666 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{25}NO_5SNa$ $[M+Na]^+$: 486.1351, Found: 486.1367.

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8. Examination of reaction conditions on asymmetric dicarbonylation reaction using other palladium and/or copper salts was shown in Table S1 in Supporting Information.
9. By the analysis of ^{1}H NMR of the crude products, a corresponding dimethyl succinate derivative derived from bis(methoxycarbonylation) reaction toward the terminal alkene moiety in **1a** was observed in ca 15% yield. Spectral data of the succinate was listed in Supporting Information.