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Synthesis of Nine-Membered Azlactones by Palladium-Catalyzed Ring-Expansion of γ-Methylidene-δ-valerolactones with Aziridines

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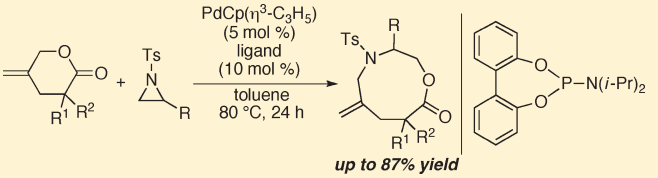
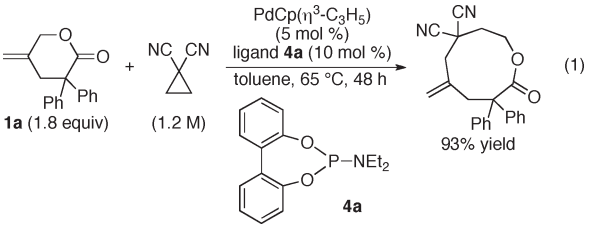
Supporting Information

ABSTRACT: A palladium-catalyzed formal [6 + 3] cyclization of γ-methylidene-δ-valerolactones with aziridines has been developed to produce 1,4-oxazonan-9-ones, a class of nine-membered azlactones that are not easily accessible by existing methods. The products thus obtained can also be further functionalized with ease.

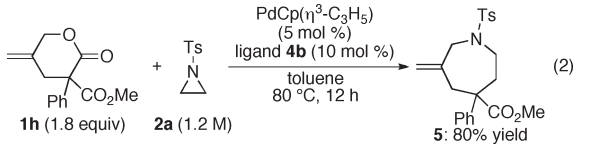


The development of a new synthetic method is one of the important objectives in organic chemistry, particularly for a class of compounds that are not easily accessible by existing methods. In this context, construction of cyclic compounds with medium ring sizes is usually more difficult than forming five- or six-membered rings.[1] In particular, 1,4-oxazonan-9-ones, nitrogen-containing nine-membered lactones, constitute a family of compounds that are difficult to prepare and of which only fewer than 10 compounds have been reported to date.[2] To provide a facile access to these nine-membered azlactones, here we describe a palladium-catalyzed ring expansion of γ-methylidene-δ-valerolactones[3,4] with aziridines.[5]

We recently reported that γ-methylidene-δ-valerolactone **1a** undergoes a ring-expansion reaction with 1,1-dicyanocyclopropane in the presence of a palladium/phosphoramidite catalyst to give the corresponding nine-membered lactone in high yield (eq 1).[3g] To develop a new synthetic method for 1,4-oxazonan-9-ones based on this previous result, we initially conducted a reaction of γ-methylidene-δ-valerolactone **1a** with *N*-tosylaziridine (**2a**) in the presence of 5 mol % of PdCp(η^3-C_3H_5) and 10 mol % of phosphoramidite ligand **4a**[6] in toluene at 65 °C. Under these conditions, desired 1,4-oxazonan-9-one **3aa** was obtained in 84% yield after 48 h of the reaction time (Table 1, entry 1). The use of *N*,*N*-diisopropyl phosphoramidite **4b**[7] as the ligand gave **3aa** in 86% yield (entry 2), and the reaction time could be shortened by conducting the reaction at 80 °C with retaining the high chemical yield (entry 3). In comparison, the use of triphenylphosphine as the ligand gave somewhat lower yield of 68% (entry 4) and only 6% yield was obtained by using electron-rich tricyclohexylphosphine (entry 5). A similar trend was observed for bisphosphine ligands: the use of binap gave moderate yield of **3aa** (46% yield; entry 6) and more electron-rich dppf resulted in only 3% yield (entry 7). The structure of **3aa** was confirmed by X-ray crystallographic analysis after recrystallization from 1,2-dichloroethane/pentane as shown in Figure 1.[8]



Under the conditions using phosphoramidite **4b**, several α,α-disubstituted γ-methylidene-δ-valerolactones (**1a**−**1f**) undergo formal [6 + 3] ring-expansion[9] with **2a** to give corresponding nine-membered azlactones **3** in high yield (78−87% yield; Table 2, entries 1−6), and α-monosubstituted γ-methylidene-δ-valerolactones can also be employed albeit with moderate efficiency (53% yield; entry 7). In contrast, as we recently reported,[3g] a reaction of γ-methylidene-δ-valerolactone **1h** having phenyl and methoxycarbonyl groups at the α-position results in the selective formation of azepane **5** in 80% yield through decarboxylative cyclization (eq 2).[10] In addition to the parent *N*-tosylaziridine, methyl- and benzyl-substituted *N*-tosylaziridines are also suitable reaction partners for the reaction of **1a**, regioselectively giving **3ab** and **3ac** as the major products, respectively (entries 8 and 9).



A proposed catalytic cycle for the ring-expansion reaction of lactone **1** with aziridine **2** is illustrated in Scheme 1. Thus, oxidative addition of the allyl ester moiety of **1** to palladium(0) gives π-allylpalladium carboxylate **A**. Successive nucleophilic attack of the carboxylate of **A** to **2** occurs at the sterically less hindered carbon atom to give intermediate **B**. This then undergoes a ring-closure

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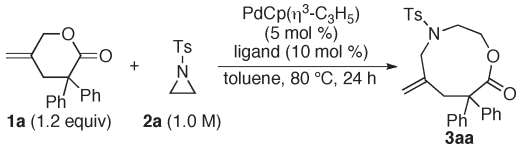
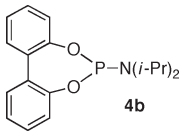
Table 1. Palladium-Catalyzed Ring-Expansion of γ-Methylidene-δ-valerolactone 1a with Aziridine 2a: Ligand Effect



entry	ligand	yield (%)[a]
1[b]	**4a**	84
2[b]	**4b**	86
3	**4b**	86 (84)[c]
4	PPh_3	68
5	PCy_3	6
6[d]	binap	46
7[d]	dppf	3

[a] Determined by ^1H NMR of the crude material against internal standard. [b] Reaction was conducted for 48 h at 65 °C. [c] Isolated yield in parentheses. [d] Ligand (5.5 mol %) was used.



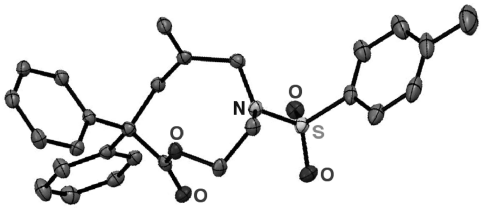
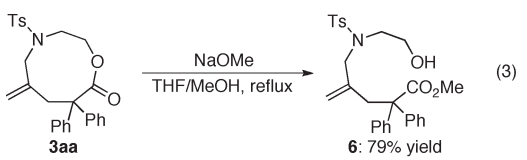


Figure 1. X-ray crystal structure of **3aa** (hydrogen atoms are omitted for clarity).

through a nucleophilic attack of the nitrogen atom to the π-allylpalladium moiety, leading to the formation of 1,4-oxazonan-9-one **3** along with regeneration of palladium(0).

Of course, the nine-membered heterocycles obtained in the present catalytic reactions can undergo ring-openings by alcoholysis if desired. For example, methanolysis of 1,4-oxazonan-9-one **3aa** gives acyclic δ-aminoacid derivative **6** in 79% yield (eq 3). In addition, a peripheral functionalization is also possible as shown in eq 4. Thus, the exomethylene moiety of **3aa** can be converted to a hydroxymethyl group by a hydroboration–oxidation sequence to give compound **7** in 78% yield.



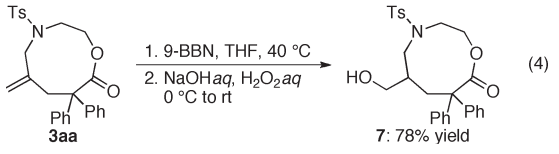
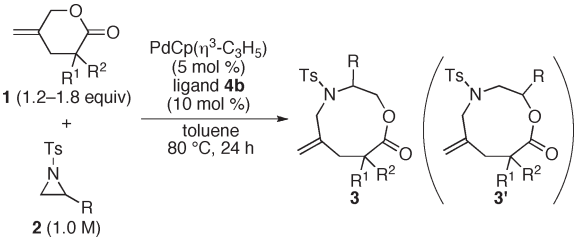


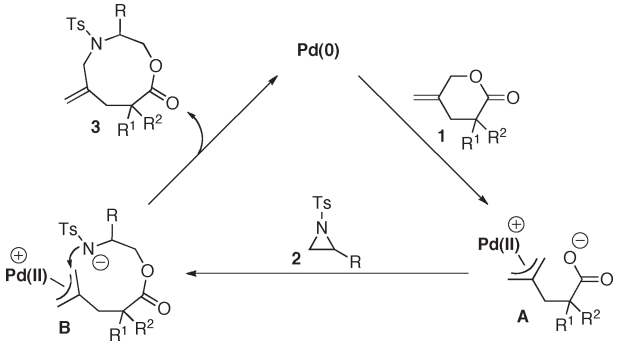
Table 2. Palladium-Catalyzed Ring-Expansion of γ-Methylidene-δ-valerolactones 1 with Aziridines 2



entry	**1** (R^1, R^2)	**2** (R)	product	yield (%)[a]
1	**1a** (Ph, Ph)	**2a** (H)	**3aa**	84
2	**1b** (4-ClC_6H_4, 4-ClC_6H_4)	**2a**	**3ba**	85
3	**1c** (Me, Me)	**2a**	**3ca**	87
4	**1d** (-$S(CH_2)_3S$-)	**2a**	**3da**	78
5	**1e** (Ph, Me)	**2a**	**3ea**	82
6[b]	**1f** (CH_2Ph, CO_2Me)	**2a**	**3fa**	80
7	**1g** (CH_2Ph, H)	**2a**	**3ga**	53
8	**1a**	**2b** (Me)	**3ab**/**3′ab** (92/8)	84[c]
9	**1a**	**2c** (CH_2Ph)	**3ac**/**3′ac** (97/3)	73[d]

[a] Isolated yield. [b] Reaction was conducted for 48 h at 70 °C. [c] Combined yield of **3ab** and **3′ab**. [d] Yield of **3ac**.

Scheme 1. Proposed Catalytic Cycle for the Palladium-Catalyzed Ring-Expansion of 1 with 2



In summary, we have developed a palladium-catalyzed formal [6 + 3] cyclization of γ-methylidene-δ-valerolactones with aziridines to produce 1,4-oxazonan-9-ones, a class of nine-membered heterocyclic compounds that are not easily accessible by existing methods, and the products thus obtained can be further functionalized with ease.

EXPERIMENTAL SECTION

General. All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen or in a glovebox under argon. Toluene and THF were purified by passing through neutral alumina columns under nitrogen. MeOH was distilled over Mg turnings under nitrogen. **1a**,[3g] **1f**,[3d] **1h**,[3a] **2a**,[11] **4a**,[3g] **4b**,[7] 2-(*tert*-butyldimethylsiloxy)methyl-2-propen-1-yl methanesulfonate,[12] α-*tert*-butoxycarbonyl-α-benzyl-γ-methylidene-δ-valerolactone,[3c] and $PdCp(\eta^3\text{-}C_3H_5)$[13] were synthesized following the literature procedures.

α,α-Bis(4-chlorophenyl)-γ-methylidene-δ-valerolactone (1b). Thionyl chloride (730 μL, 10.0 mmol) was added to a solution of

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bis(4-chlorophenyl)acetic acid (2.81 g, 10.0 mmol) in MeOH (20 mL) at 0 °C, and the mixture was stirred for 10 h at room temperature. After removal of the volatiles under vacuum, the residue was chromatographed on silica gel with EtOAc/hexane = 1/5→1/3 to afford methyl bis(4-chlorophenyl)acetate (CAS 5359−38−6) as a white solid (2.84 g, 9.62 mmol; 96% yield). ^{1}H NMR ($CDCl_3$): δ 7.30 (d, $^3J_{HH}$ = 8.1 Hz, 4H), 7.21 (d, $^3J_{HH}$ = 8.3 Hz, 4H), 4.96 (s, 1H), 3.75 (s, 3H).

A solution of methyl bis(4-chlorophenyl)acetate (2.84 g, 9.62 mmol) in THF (8 mL) was added to a suspension of NaH (404 mg, 10.1 mmol; 60 wt % in mineral oil) in THF (8 mL) at 0 °C. The mixture was stirred for 25 min at 0 °C and a solution of 2-(*tert*-butyldimethylsiloxy)methyl-2-propen-1-yl methanesulfonate (3.10 g, 11.1 mmol) in THF (15 mL) was added to it. The resulting mixture was stirred for 40 min at room temperature and for 20 h at 40 °C. After cooled to room temperature, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with saturated NaCl*aq*, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/hexane = 1/30→1/12 to afford methyl 4-((*tert*-butyldimethylsiloxy)methyl)-2,2-bis(4-chlorophenyl)-4-pentenoate as a colorless oil (4.19 g, 8.74 mmol; 91% yield). ^{1}H NMR ($CDCl_3$): δ 7.25 (d, $^3J_{HH}$ = 8.9 Hz, 4H), 7.21 (d, $^3J_{HH}$ = 8.6 Hz, 4H), 5.12 (q, J_{HH} = 1.7 Hz, 1H), 4.71 (s, 1H), 3.69 (s, 3H), 3.43 (s, 2H), 3.09 (s, 2H), 0.86 (s, 9H), −0.05 (s, 6H).

TBAF (9.60 mL, 9.60 mmol; 1.0 M solution in THF) was added to a solution of methyl 4-((*tert*-butyldimethylsiloxy)methyl)-2,2-bis-(4-chlorophenyl)-4-pentenoate (4.19 g, 8.74 mmol) in THF (25 mL) at −65 °C. The mixture was stirred for 5 h while gradually raising the temperature to 0 °C and the reaction was quenched with water. After extraction with Et_2O, the organic layer was washed with saturated NaCl*aq*, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/hexane = 1/7→1/4 to afford **1b** as a white solid (1.50 g, 4.50 mmol; 52% yield). ^{1}H NMR ($CDCl_3$): δ 7.32 (d, $^3J_{HH}$ = 8.9 Hz, 4H), 7.11 (d, $^3J_{HH}$ = 8.9 Hz, 4H), 5.05 (t, J_{HH} = 2.0 Hz, 1H), 4.96 (t, J_{HH} = 1.7 Hz, 1H), 4.60 (s, 2H), 3.34 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 172.6, 138.6, 137.1, 134.0, 129.4, 128.9, 111.5, 71.2, 55.6, 39.9; Anal. Calcd for $C_{18}H_{14}Cl_2O_2$: C, 64.88; H, 4.23. Found: C, 64.86; H, 4.10.

α,α-Dimethyl-γ-methylidene-δ-valerolactone (1c). *n*-BuLi (6.36 mL, 10.5 mmol; 1.65 M solution in hexane) was slowly added to a solution of diisopropylamine (1.48 mL, 10.6 mmol) in THF (12 mL) at −78 °C, and the mixture was stirred for 3 min at −78 °C and for 15 min at 0 °C. This was cooled to −78 °C, and methyl isobutyrate (1.15 mL, 10.0 mmol) was added dropwise. The resulting mixture was stirred for 1 h at −78 °C and for 1.5 h at −40 °C. This was cooled to −78 °C again, and a solution of 2-(*tert*-butyldimethylsiloxy)methyl-2-propen-1-yl methanesulfonate (3.09 g, 11.0 mmol) in THF (6 mL) was slowly added to it. The reaction mixture was stirred for 40 h while gradually raising the temperature to room temperature. The reaction was then quenched with water and extracted with Et_2O. The organic layer was washed with saturated NaCl*aq*, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/hexane = 1/20 to afford methyl 4-((*tert*-butyldimethylsiloxy)methyl)-2,2-dimethyl-4-pentenoate as a colorless oil (1.90 g, 6.64 mmol; 66% yield). ^{1}H NMR ($CDCl_3$): δ 5.17 (q, J_{HH} = 1.9 Hz, 1H), 4.82−4.79 (m, 1H), 3.97 (t, $^4J_{HH}$ = 1.6 Hz, 2H), 3.66 (s, 3H), 2.29 (s, 2H), 1.19 (s, 6H), 0.91 (s, 9H), 0.05 (s, 6H).

TBAF (7.30 mL, 7.30 mmol; 1.0 M solution in THF) was added to a solution of methyl 4-((*tert*-butyldimethylsiloxy)methyl)-2,2-dimethyl-4-pentenoate (1.90 g, 6.64 mmol) in THF (20 mL) at −60 °C. The mixture was stirred for 5 h while gradually raising the temperature to 0 °C and the reaction was quenched with water. After extraction with Et_2O, the organic layer was washed with saturated NaCl*aq*, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with Et_2O/pentane = 1/3 to afford **1c** as a pale yellow oil (356 mg, 2.54 mmol; 38% yield). ^{1}H NMR ($CDCl_3$): δ 5.07 (s, 1H), 4.99 (q, J_{HH} = 1.4 Hz, 1H), 4.83 (t, $^4J_{HH}$ = 1.7 Hz, 2H), 2.41 (s, 2H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 176.5, 137.6, 112.5, 73.1, 42.4, 39.5, 26.6; Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.89.

α,α-(1,5-Dithiapentylene)-γ-methylidene-δ-valerolactone (1d). This was synthesized from ethyl 1,3-dithiane-2-carboxylate, instead of methyl bis(4-chlorophenyl)acetate, following the procedure for **1b**. White solid. 19% overall yield. ^{1}H NMR ($CDCl_3$): δ 5.11 (s, 2H), 4.90 (s, 2H), 3.50 (t, J_{HH} = 13.6 Hz, 2H), 2.89 (s, 2H), 2.65 (dt, $^2J_{HH}$ = 13.6 Hz and $^3J_{HH}$ = 3.4 Hz, 2H), 2.20 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 1.84 (q, J_{HH} = 13.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 167.9, 134.1, 113.8, 72.0, 46.0, 41.4, 28.0, 24.4; Anal. Calcd for $C_9H_{12}O_2S_2$: C, 49.97; H, 5.59. Found: C, 49.87; H, 5.38.

α-Methyl-α-phenyl-γ-methylidene-δ-valerolactone (1e). Methyl 2-phenylpropanoate was prepared from 2-phenylpropanoic acid following the procedure for methyl bis(4-chlorophenyl)acetate, and this was converted to **1e**, following the procedure for **1c**. White solid. 53% overall yield. ^{1}H NMR ($CDCl_3$): δ 7.35 (t, $^3J_{HH}$ = 7.5 Hz, 2H), 7.31 (d, $^3J_{HH}$ = 6.8 Hz, 2H), 7.27 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.57 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 4.34 (dd, $^2J_{HH}$ = 14.3 Hz and $^4J_{HH}$ = 2.1 Hz, 1H), 3.28 (d, $^2J_{HH}$ = 17.0 Hz, 1H), 2.76 (dd, $^2J_{HH}$ = 17.0 Hz and $^4J_{HH}$ = 2.7 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 175.1, 140.5, 138.1, 129.2, 127.6, 125.5, 111.0, 71.0, 47.4, 38.5, 28.8; Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.07; H, 7.07.

α-Benzyl-γ-methylidene-δ-valerolactone (1g). Trifluoroacetic acid (3 mL) was slowly added to a solution of α-*tert*-butoxycarbonyl-α-benzyl-γ-methylidene-δ-valerolactone (607 mg, 2.01 mmol) in CH_2Cl_2 (3 mL) at room temperature and the mixture was stirred for 20 min. The volatiles were removed under vacuum and the residue was dissolved in DMF (6 mL). This solution was stirred for 1 h at 150 °C and cooled to room temperature. After dilution with water, this was extracted with Et_2O. The organic layer was washed with saturated NaCl*aq*, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/hexane = 1/6 to afford **1g** as a colorless oil (352 mg, 1.74 mmol; 87% yield). ^{1}H NMR ($CDCl_3$): δ 7.32 (t, $^3J_{HH}$ = 7.4 Hz, 2H), 7.24 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 7.21 (d, $^3J_{HH}$ = 6.9 Hz, 2H), 5.06 (s, 1H), 4.96 (s, 1H), 4.80 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 4.68 (d, $^2J_{HH}$ = 13.5 Hz, 1H), 3.36 (dd, $^2J_{HH}$ = 13.9 Hz and $^3J_{HH}$ = 4.4 Hz, 1H), 2.85 (dddd, $^3J_{HH}$ = 11.6, 9.5, 6.7, and 4.5 Hz, 1H), 2.68 (d, $^2J_{HH}$ = 13.9 Hz and $^3J_{HH}$ = 9.5 Hz, 1H), 2.63 (dd, $^2J_{HH}$ = 16.2 Hz and $^3J_{HH}$ = 6.7 Hz, 1H), 2.26 (ddq, $^2J_{HH}$ = 16.3 Hz, $^3J_{HH}$ = 11.7 Hz, and $^4J_{HH}$ = 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 174.1, 138.7, 138.1, 129.3, 128.7, 126.8, 112.5, 71.6, 41.3, 36.5, 31.2; Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.00; H, 7.06.

2-Methyl-1-tosylaziridine (2b) (CAS 25856−77−3). 2-Amino-1-propanol (1.17 mL, 15.0 mmol) was added dropwise to a solution of *p*-toluenesulfonyl chloride (6.01 g, 31.5 mmol) in pyridine (5.5 mL) at −10 °C, and the mixture was stirred for 18 h while gradually raising the temperature to 0 °C. The reaction was quenched with water and extracted with $CHCl_3$. The organic layer was washed with water and then with saturated NaCl*aq*. This was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in C_6H_6 (150 mL) and KOH (1.08 g, 16.4 mmol; 85 wt %) in water (5 mL) was added to it. The mixture was stirred for 30 min at room temperature and quenched with water. This was extracted with Et_2O and the organic layer was dried over $MgSO_4$ and filtered. A flake of *p*-tert-butylcatechol was added to the resulting solution and concentrated under vacuum. The residue was then redissolved in Et_2O and insolubles were filtered off. The solution thus obtained was concentrated under vacuum and the residue was washed with Et_2O/hexane and dried under vacuum to afford **2b** as a pale-orange solid (2.64 g, 12.5 mmol; 83% yield). ^{1}H NMR ($CDCl_3$): δ 7.81 (d, $^3J_{HH}$ = 7.5 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 7.5 Hz, 2H), 2.85−2.79 (m, 1H), 2.60 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 2.43 (s, 3H), 2.01

(d, $^3J_{HH}$ = 4.8 Hz, 1H), 1.24 (d, $^3J_{HH}$ = 5.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 144.5, 135.5, 129.8, 127.9, 36.0, 34.8, 21.7, 16.9.

General Procedure for Table 2. A mixture of PdCp(η^3-C_3H_5) (2.7 mg, 13 μmol), ligand **4b** (7.9 mg, 25 μmol), lactone **1** (0.30−0.45 mmol), and aziridine **2** (0.25 mmol) in toluene (0.25 mL) was stirred for 24 h at 80 °C. The reaction mixture was directly passed through a pad of silica gel with EtOAc and the solvent was removed under vacuum. The residue was purified by silica gel preparative TLC to afford compound **3**/**3′**.

Entry 1: 1.2 equiv of **1a** was used. White solid. **3aa**. 84% yield. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 7.37 (d, $^3J_{HH}$ = 8.1 Hz, 4H), 7.32−7.26 (m, 6H), 7.21 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 4.98 (s, 1H), 4.65 (s, 1H), 4.54 (t, $^3J_{HH}$ = 5.1 Hz, 2H), 3.66 (s, 2H), 3.38 (s, 2H), 3.29 (t, $^3J_{HH}$ = 5.1 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 173.7, 143.8, 143.2, 140.0, 135.5, 130.0, 128.5, 128.1, 127.5, 126.8, 121.4, 63.7, 61.4, 60.5, 48.1, 40.5, 21.7. Anal. Calcd for $C_{27}H_{27}NO_4S$: C, 70.26; H, 5.90. Found: C, 70.03; H, 6.13.

Entry 2: 1.8 equiv of **1b** was used. White solid. **3ba**. 85% yield. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.31 (d, $^3J_{HH}$ = 7.5 Hz, 2H), 7.29−7.23 (m, 8H), 4.98 (s, 1H), 4.56 (s, 1H), 4.53 (t, $^3J_{HH}$ = 5.4 Hz, 2H), 3.62 (s, 2H), 3.29 (s, 2H), 3.27 (t, $^3J_{HH}$ = 5.4 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 173.1, 143.9, 141.3, 139.6, 135.5, 133.0, 130.01, 129.96, 128.4, 127.5, 121.7, 64.0, 60.6, 60.5, 48.6, 40.9, 21.7. Anal. Calcd for $C_{27}H_{25}Cl_2NO_4S$: C, 61.13; H, 4.75. Found: C, 60.88; H, 4.48.

Entry 3: 1.5 equiv of **1c** was used. White solid. **3ca**. 87% yield. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.32 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 5.09 (s, 1H), 5.01 (s, 1H), 4.44 (t, $^3J_{HH}$ = 5.1 Hz, 2H), 3.53 (s, 2H), 3.17 (t, $^3J_{HH}$ = 5.1 Hz, 2H), 2.43 (s, 3H), 2.25 (s, 2H), 1.27 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 177.1, 143.8, 141.1, 135.3, 129.8, 127.6, 119.2, 63.2, 60.1, 49.6, 45.5, 42.6, 24.9, 21.6. Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87. Found: C, 60.34; H, 6.93.

Entry 4: 1.5 equiv of **1d** was used. Orange solid. **3da**. 78% yield. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 5.45 (s, 1H), 5.24 (s, 1H), 4.53 (t, $^3J_{HH}$ = 5.1 Hz, 2H), 3.58 (s, 2H), 3.27 (t, $^3J_{HH}$ = 5.4 Hz, 2H), 3.09 (ddd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 12.2 and 2.7 Hz, 2H), 2.79 (s, 2H), 2.76 (dt, $^2J_{HH}$ = 14.3 Hz and $^3J_{HH}$ = 4.1 Hz, 2H), 2.43 (s, 3H), 2.14−2.08 (m, 1H), 1.95−1.86 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 170.8, 144.0, 138.1, 135.3, 130.0, 127.6, 122.7, 65.3, 59.3, 56.6, 48.5, 43.5, 28.8, 24.8, 21.7. HRMS (ESI-TOF) calcd for $C_{18}H_{23}NO_4S_3Na$ ($M + Na^+$) 436.0681, found 436.0676.

Entry 5: 1.5 equiv of **1e** was used. Colorless viscous oil. **3ea**. 82% yield. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.37−7.32 (m, 4H), 7.31 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.28−7.24 (m, 1H), 5.15 (s, 1H), 5.09 (s, 1H), 4.73 (ddd, $^2J_{HH}$ = 10.9 Hz and $^3J_{HH}$ = 5.5 and 4.1 Hz, 1H), 4.17 (ddd, $^2J_{HH}$ = 10.9 Hz and $^3J_{HH}$ = 6.8 and 4.1 Hz, 1H), 3.68 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.59 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.32 (ddd, $^2J_{HH}$ = 14.9 Hz and $^3J_{HH}$ = 6.8 and 4.0 Hz, 1H), 3.23 (ddd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 5.4 and 4.1 Hz, 1H), 3.11 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 2.62 (d, $^2J_{HH}$ = 13.5 Hz, 1H), 2.43 (s, 3H), 1.55 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 175.6, 144.0, 143.8, 141.2, 135.6, 129.9, 128.5, 127.6, 126.9, 126.4, 120.6, 63.6, 59.9, 51.9, 48.8, 42.5, 26.9, 21.6. Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31. Found: C, 66.06; H, 6.22.

Entry 6: 1.8 equiv of **1f** was used and the reaction was conducted for 48 h at 70 °C. Colorless viscous oil. **3fa**. 80% yield. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.26 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 7.22 (t, $^3J_{HH}$ = 7.1 Hz, 1H), 7.13 (d, $^3J_{HH}$ = 6.8 Hz, 2H), 5.33 (s, 1H), 5.18 (td, J_{HH} = 10.5 Hz and $^3J_{HH}$ = 3.4 Hz, 1H), 5.08 (s, 1H), 3.94 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 3.90 (d, $^2J_{HH}$ = 11.6 Hz, 1H), 3.59 (s, 3H), 3.54 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.48 (dt, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 2.7 Hz, 1H), 3.11 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 3.09 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 3.03 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 2.88 (ddd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 10.2 and 4.0 Hz, 1H), 2.43 (s, 3H), 2.25 (d, $^2J_{HH}$ = 14.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 171.1, 170.7, 143.9, 139.6, 136.1, 135.3, 130.1, 130.0, 128.3, 127.6, 127.2, 121.6, 63.9, 60.7, 60.5, 52.0, 48.7, 42.3, 38.6, 21.6. Anal. Calcd for $C_{24}H_{27}NO_6S$: C, 63.00; H, 5.95. Found: C, 62.76; H, 6.18.

Entry 7: 1.8 equiv of **1g** was used. White solid. **3ga**. 53% yield. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.28 (t, $^3J_{HH}$ = 7.5 Hz, 2H), 7.22 (d, $^3J_{HH}$ = 6.8 Hz, 2H), 7.20 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 5.08 (s, 1H), 5.05 (s, 1H), 5.02 (td, J_{HH} = 10.9 Hz and $^3J_{HH}$ = 2.7 Hz, 1H), 4.04 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 3.88 (dd, $^2J_{HH}$ = 10.9 Hz and $^3J_{HH}$ = 2.7 Hz, 1H), 3.42 (dt, $^2J_{HH}$ = 14.3 Hz and $^3J_{HH}$ = 2.4 Hz, 1H), 3.16 (dd, $^2J_{HH}$ = 13.6 Hz and $^3J_{HH}$ = 8.1 Hz, 1H), 3.03 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 2.86−2.78 (m, 2H), 2.73 (dd, $^2J_{HH}$ = 13.6 Hz and $^3J_{HH}$ = 6.8 Hz, 1H), 2.53 (dd, $^2J_{HH}$ = 13.7 Hz and $^3J_{HH}$ = 4.8 Hz, 1H), 2.44 (s, 3H), 2.22 (ddd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 11.5 Hz, and $^4J_{HH}$ = 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 175.3, 143.9, 142.7, 139.5, 135.3, 129.9, 129.2, 128.6, 127.6, 126.5, 118.8, 63.6, 59.7, 50.0, 49.5, 37.2, 36.6, 21.7. Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31. Found: C, 66.06; H, 6.29.

Entry 8: 1.2 equiv of **1a** was used. Colorless viscous oil. **3ab**/**3′ab** = 92/8. 84% combined yield. The structures of regioisomers **3ab**/**3′ab** were distinguished by their ^{1}H NMR spectra, based on the fact that the protons on the carbons attached to the ester oxygen atoms are most downfield shifted among the protons on the sp^3-carbon atoms of these compounds: **3ab** shows a pair of ABX type signals at 4.68 ppm (1H) and 4.15 ppm (1H), and **3′ab** shows only one signal at 5.57−5.50 ppm (1H) as a multiplet. **3ab**: ^{1}H NMR ($CDCl_3$): δ 7.71 (d, $^3J_{HH}$ = 7.5 Hz, 2H), 7.38 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.28 (t, $^3J_{HH}$ = 7.5 Hz, 4H), 7.25 (d, $^3J_{HH}$ = 7.5 Hz, 4H), 7.21 (t, $^3J_{HH}$ = 7.5 Hz, 2H), 5.09 (s, 1H), 4.68 (dd, $^2J_{HH}$ = 10.9 Hz and $^3J_{HH}$ = 4.8 Hz, 1H), 4.57 (s, 1H), 4.15 (dd, $^2J_{HH}$ = 10.9 Hz and $^3J_{HH}$ = 6.8 Hz, 1H), 4.03−3.95 (m, 1H), 3.79 (d, $^2J_{HH}$ = 14.9 Hz, 1H), 3.74 (d, $^2J_{HH}$ = 14.9 Hz, 1H), 3.32 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 3.11 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 2.43 (s, 3H), 1.21 (d, $^3J_{HH}$ = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.7, 143.6, 143.3, 142.8, 140.8, 138.1, 129.7, 128.9, 128.1, 128.0, 127.9, 127.2, 126.72, 126.70, 121.3, 67.1, 61.1, 54.6, 53.8, 40.7, 21.6, 15.7. Anal. Calcd for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.15. Found: C, 70.72; H, 6.12. **3′ab**: ^{1}H NMR ($CDCl_3$): δ 7.73 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.41−7.38 (m, 2H), 7.34−7.31 (m, 4H), 7.28−7.18 (m, 4H), 7.15 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 5.57−5.50 (m, 1H), 4.92 (s, 1H), 4.38 (s, 1H), 4.22 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.73−3.66 (m, 2H), 3.46 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.05 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 2.59 (dd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 10.9 Hz, 1H), 2.44 (s, 3H), 1.28 (d, $^3J_{HH}$ = 6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.4, 144.0, 143.7, 142.2, 140.3, 135.8, 129.9, 129.1, 128.1, 127.6, 127.5, 126.8, 126.6, 120.0, 71.5, 61.3, 55.9, 41.5, 21.6, 17.3.

Entry 9: 1.2 equiv of **1a** was used. Colorless viscous oil. **3ac**/**3′ac** = 97/3. 73% yield of **3ac**. **3ac**: ^{1}H NMR ($CDCl_3$): δ 7.70 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.32 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.30−7.15 (m, 13H), 7.11 (d, $^3J_{HH}$ = 7.5 Hz, 2H), 5.12 (s, 1H), 4.74 (s, 1H), 4.59 (dd, $^2J_{HH}$ = 11.5 Hz and $^3J_{HH}$ = 4.0 Hz, 1H), 4.25 (dd, $^2J_{HH}$ = 10.2 Hz and $^3J_{HH}$ = 6.8 Hz, 1H), 4.10−4.04 (m, 1H), 3.82 (d, $^2J_{HH}$ = 15.0 Hz, 1H), 3.54 (d, $^2J_{HH}$ = 12.2 Hz, 1H), 3.19 (d, $^2J_{HH}$ = 13.6 Hz, 1H), 3.00 (dd, $^2J_{HH}$ = 13.6 Hz and $^3J_{HH}$ = 6.1 Hz, 1H), 2.94 (dd, $^2J_{HH}$ = 13.6 Hz and $^3J_{HH}$ = 9.6 Hz, 1H), 2.83 (d, $^2J_{HH}$ = 12.2 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 173.7, 143.7, 143.4, 142.6, 140.7, 137.8, 137.5, 129.8, 129.3, 128.8, 128.7, 128.2, 128.1, 127.8, 127.5, 126.9, 126.84, 126.76, 121.7, 64.5, 61.4, 59.6, 54.7, 40.5, 37.3, 21.7. Anal. Calcd for $C_{34}H_{33}NO_4S$: C, 74.02; H, 6.03. Found: C, 74.25; H, 6.33.

Procedure for eq 2. A mixture of PdCp(η^3-C_3H_5) (6.4 mg, 30 μmol), ligand **4b** (19.0 mg, 60.3 μmol), lactone **1h** (266 mg, 1.08 mmol), and aziridine **2a** (119 mg, 0.603 mmol) in toluene (0.50 mL) was stirred for 12 h at 80 °C. The reaction mixture was directly passed through a pad of silica gel with EtOAc and the solvent was removed under vacuum. The residue was purified by silica gel preparative TLC with EtOAc/hexane = 1/4 to afford compound **5** (CAS 1198581−69−9) as a pale-yellow solid (194 mg, 0.485 mmol; 80% yield). ^{1}H NMR ($CDCl_3$): δ 7.68 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.33−7.29 (m, 4H), 7.24 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 7.18 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 4.98

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(s, 1H), 4.95 (s, 1H), 4.39 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.74−3.69 (m, 1H), 3.61 (s, 3H), 3.44 (d, $^2J_{HH}$ = 14.4 Hz, 1H), 3.16 (d, $^2J_{HH}$ = 12.4 Hz, 1H), 3.02 (d, $^2J_{HH}$ = 12.4 Hz, 1H), 2.96 (dd, $^2J_{HH}$ = 13.8 Hz and $^3J_{HH}$ = 11.6 Hz, 1H), 2.49 (dd, $^2J_{HH}$ = 14.8 Hz and $^3J_{HH}$ = 4.8 Hz, 1H), 2.43 (s, 3H), 1.88 (ddd, $^2J_{HH}$ = 14.6 Hz and $^3J_{HH}$ = 11.6 and 2.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 175.0, 144.2, 143.4, 141.6, 136.0, 129.9, 128.8, 127.2, 127.1, 125.4, 117.2, 55.1, 55.0, 51.8, 45.1, 42.0, 39.3, 21.6.

Procedure for eq 3. MeOH (1.0 mL) and THF (1.0 mL) were added to **3aa** (55.4 mg, 0.120 mmol) and NaOMe (16.2 mg, 0.300 mmol) and the mixture was refluxed for 12 h. After cooled to room temperature, this was passed through a pad of silica gel with EtOAc and the solvent was removed under vacuum. The residue was purified by silica gel preparative TLC with EtOAc/hexane = 1/1 to afford compound **6** as a pale-yellow oil (47.0 mg, 95.2 μmol; 79% yield). ^{1}H NMR ($CDCl_3$): δ 7.54 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.32−7.23 (m, 12H), 4.96 (s, 1H), 4.90 (s, 1H), 3.69 (s, 3H), 3.62−3.56 (m, 2H), 3.18 (s, 2H), 3.04 (t, $^3J_{HH}$ = 5.2 Hz, 2H), 3.02 (s, 2H), 2.40 (s, 3H), 2.23 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 174.1, 143.6, 142.8, 140.9, 136.0, 129.7, 129.2, 128.0, 127.4, 127.0, 118.2, 61.2, 60.7, 56.3, 52.5, 50.8, 40.7, 21.6. Anal. Calcd for $C_{28}H_{31}NO_5S$: C, 68.13; H, 6.33. Found: C, 67.97; H, 6.43.

Procedure for eq 4. 9-BBN (480 μL, 0.240 mmol; 0.5 M solution in THF) was added dropwise to a suspension of **3aa** (55.4 mg, 0.120 mmol) in THF (0.20 mL), and the mixture was stirred for 1 h at room temperature and for 20 h at 40 °C. The reaction mixture was cooled to 0 °C and EtOH (95 μL) was added dropwise. The 3 M NaOH*aq* (195 μL, 0.585 mmol) and 30% H_2O_2*aq* (175 μL, 1.70 mmol) were successively added to it dropwise, and the resulting mixture was stirred for 30 min at 0 °C and for 2 h at room temperature. The reaction was quenched with water and extracted with Et_2O. The organic layer was washed with saturated NaCl*aq*, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/CH_2Cl_2 = 1/20→1/8 and the solid thus obtained was washed with pentane to afford compound **7** as a white solid (45.1 mg, 94.0 μmol; 78% yield). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.37 (d, $^3J_{HH}$ = 7.4 Hz, 2H), 7.34−7.20 (m, 10H), 4.63 (ddd, $^2J_{HH}$ = 10.6 Hz and $^3J_{HH}$ = 6.3 and 3.5 Hz, 1H), 4.56−4.50 (m, 1H), 3.40−3.25 (m, 5H), 3.11 (dd, $^2J_{HH}$ = 14.0 Hz and $^3J_{HH}$ = 9.4 Hz, 1H), 2.75 (dd, $^2J_{HH}$ = 15.0 Hz and $^3J_{HH}$ = 5.5 Hz, 1H), 2.44 (s, 3H), 2.31−2.25 (m, 2H), 1.41 (t, $^3J_{HH}$ = 4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 174.1, 144.0, 143.8, 141.9, 135.8, 130.0, 129.2, 128.21, 128.18, 127.5, 127.1, 126.9, 66.3, 64.5, 60.5, 57.2, 51.1, 41.0, 39.0, 21.7. HRMS (ESI-TOF) calcd for $C_{27}H_{29}NO_5SNa$ ($M + Na^+$) 502.1659, found 502.1656.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra of new compounds and X-ray data of **3aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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