JOC The Journal of Organic Chemistry

Article

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# Synthesis of γ-Lactams by Mild, *o*-Benzoquinone-Induced Oxidation of Pyrrolidines Containing Oxidation-Sensitive Functional Groups

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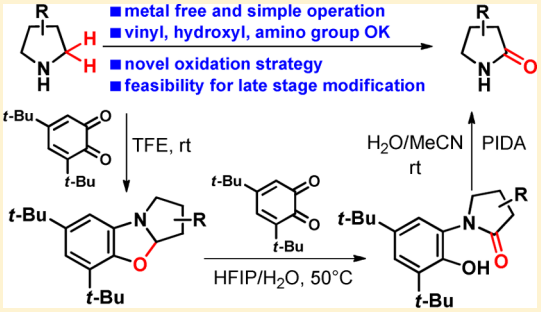
Supporting Information

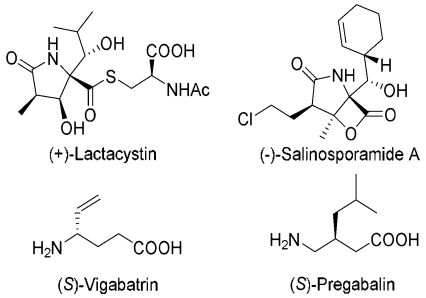
**ABSTRACT:** The late-stage oxidation of substituted pyrrolidines offers good flexibility for the construction of γ-lactam libraries, and especially in recent years the methods for functionalization of pyrrolidine have been available. We reported a new strategy for oxidation of pyrrolidines to γ-lactams: reaction of pyrrolidine with an *o*-benzoquinone gives an *N*,*O*-acetal by direct oxidation of the α-C−H bond of the pyrrolidine ring, and then the *N*,*O*-acetal is further oxidized by the *o*-benzoquinone to the γ-lactam. Because the first oxidation occurs selectively at the α-C−H of the pyrrolidine ring, oxidation-sensitive functional groups (allyl-, vinyl-, hydroxyl-, and amino groups) on pyrrolidine ring are unaffected. The synthetic utility of this novel method was demonstrated by the facile syntheses of (*S*)-vigabatrin and two analogues.




## INTRODUCTION

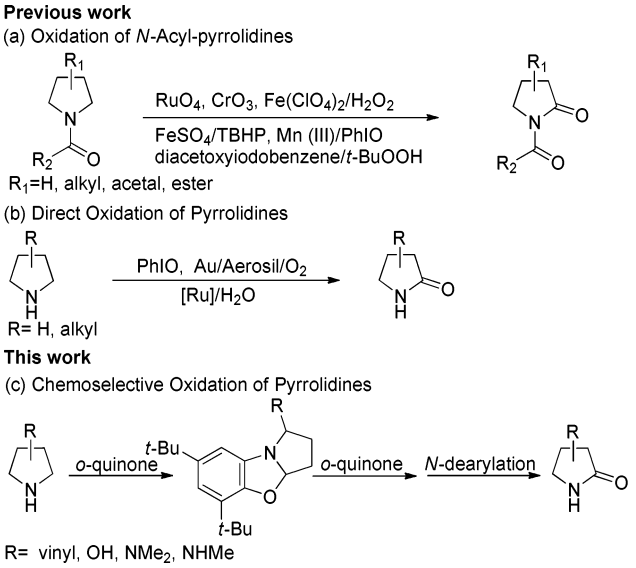
The γ-lactam is a heterocyclic moiety that is widespread in bioactive natural products,[1] such as lactacystin[1a,b] and salinosporamide A.[1c] In addition, γ-lactams are synthetic precursors of therapeutic analogues of γ-aminobutyric acid, a major inhibitory neurotransmitter in the central nervous system of mammals.[2] Some γ-aminobutyric acid analogues, such as vigabatrin[2c] and pregabalin,[2d] have been commercialized as antiepileptic agents (Chart 1).

**Chart 1. γ-Lactam Natural Products and γ-Aminobutyric Acid Drugs**




Various methods have been developed for γ-lactam synthesis.[3] Among them, late-stage oxidation of substituted pyrrolidines offers good flexibility for the construction of γ-lactam libraries, especially in recent years the methods for functionalization of pyrrolidine have been available.[4] However, the chemoselective oxidation of α-C−H of pyrrolidine ring is difficult to achieve. In some of the literatures, the NH of the pyrrolidine was protected prior to oxidation by, for example, $RuO_4$,[5] $CrO_3$,[6] Mn(III)/PhIO,[7] $Fe(ClO_4)_2/H_2O_2$,[8] or $FeSO_4$/*t*-butyl hydroperoxide,[9] diacetoxyiodobenzene/*t*-butyl hydroperoxide[10] and subsequently deprotected to afford the corresponding γ-lactam (Scheme 1a). There are a few reports of direct conversion of unprotected pyrrolidines to γ-lactams by oxidation with iodosobenzene,[11a] [Au]/$O_2$,[11b] or [Ru]/$H_2O$

**Scheme 1. Oxidative Transformations of Pyrrolidines to γ-Lactams**




**Received:** October 22, 2016
**Published:** December 2, 2016





DOI: 10.1021/acs.joc.6b02562
J. Org. Chem. 2017, 82, 532−540

(Scheme 1b).[11c,d] Also the current oxidations of protected or unprotected pyrrolidines lack chemoselectivities, oxidations only work with unsubstituted, alkyl, acetal, or ester-substituted heterocyclic amines, and oxidation-sensitive functional groups (alkenes and hydroxy and amino groups) are not tolerated.

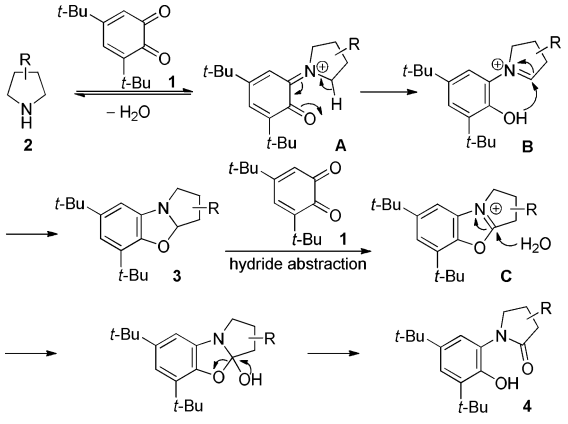
Quinones, which are important organic oxidizing reagents and redox shuttles, have broad applications in both industry and the research laboratory.[12] Quinones with high reduction potentials (DDQ and chloranil) often mediate hydride abstractions from benzylic or allylic positions.[13] Quinones with low reduction potentials (such as *o*-quinone cofactors in copper amine oxidases (CAOs)) mediate oxidations of primary amines to aldehydes by molecular oxygen.[14] Secondary amines often inhibit *o*-quinone cofactors because of the formation of irreversible covalent adducts following the transamination mechanism.[15] Recently, *o*-quinone catalyzed dehydrogenations of secondary amines have been achieved by Stahl et al. through the addition−elimination mechanism.[16] We recently found that the redox-neutral oxidation[17] of pyrrolidine by 3,5-di-*tert*-butyl-*o*-benzoquinone in 2,2,2-trifluoroethanol (TFE) transiently generated a *N*,*O*-acetal and the afterword nucleophilic ring-opening of the *N*,*O*-acetal could afford 2-functionalized or 2,5-difunctionalized pyrrolidines.[18] During the course of our work, we found that treatment of pyrrolidine with an excess of the quinone results in the formation of small amounts of *N*-aryl-pyrrolidin-2-ones. In this work, we investigate this phenomenon and report a new strategy for oxidation of pyrrolidines to γ-lactams (Scheme 1c): specifically, reaction of pyrrolidine with an *o*-benzoquinone under mild reaction condition initially gives an *N*,*O*-acetal by direct oxidation of the α-C−H bond of the pyrrolidine ring, and then the *N*,*O*-acetal is further oxidized by the *o*-benzoquinone to the γ-lactam.[19] Because the first oxidation occurs selectively at the α-C−H of the pyrrolidine ring, other oxidation-sensitive functional groups on the pyrrolidine ring are unaffected.

## RESULTS AND DISCUSSION

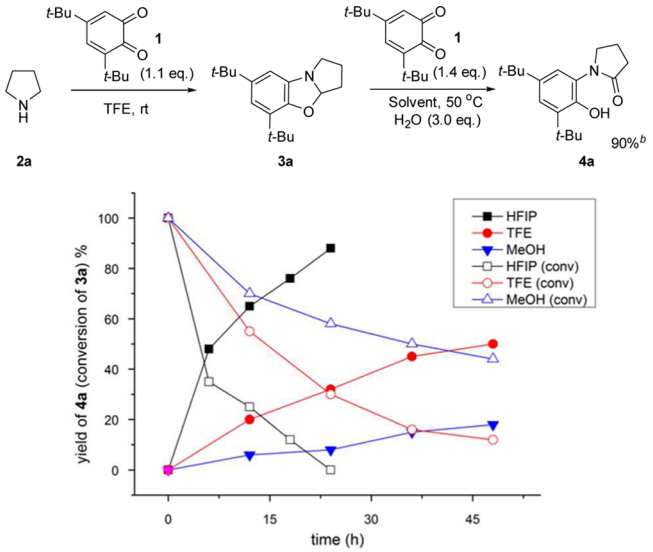
First, we investigated how pyrrolidine was oxidized to *N*-aryl-pyrrolidin-2-one by *o*-benzoquinone in fluorinated alcohol. The first step of this process, the reaction of 3,5-di-*tert*-butyl-*o*-benzoquinone (**1**) with 2-substituted pyrrolidine **2** (Scheme 2), is similar to the reaction of *o*-quinone cofactors in copper amine oxidases.[14] Specifically, the condensation of the pyrrolidine with the quinone gives iminium intermediate **A**. Tautomerization to iminium intermediate **B** (by means of intramolecular 1,5-proton abstraction) and subsequent cyclization afford *N*,*O*-acetal **3**. The quinone then acts as a hydride abstractor to oxidize **3** to aromatic iminium intermediate **C**,[12] which is attacked by water to provide *N*-aryl-pyrrolidin-2-one **4**. Fluorinated alcohol could stabilize the positive charged iminium species toward intramolecular cyclization or intermolecular nucleophilic addition.[20]

Initially, the oxidative reaction was carried out by treatment of pyrrolidine (**2a**) with 2.5 equiv of 3,5-di-*tert*-butyl-*o*-benzoquinone (**1**) in TFE, but the reaction took rather long time and the yield of *N*-aryl-pyrrolidin-2-one **4a** was moderate. We found that the reaction of **2a** and **1** in TFE at room temperature finished within 0.5 h and gave quantitative yield of *N*,*O*-acetal **3a**, but the further oxidation of **3a** in TFE took more than 48 h. Then we screened other solvents, including $CH_3OH$ and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), in the hydride abstraction of *N*,*O*-acetal **3a** (Scheme 3). The results showed that the combination of HFIP (even high polarity and high ionizing power than TFE) with 3 equiv of water delivered the highest reaction rate and highest yield. But the relatively low pH of HFIP hindered the formation of iminium intermediate **A** and slowed the formation of *N*,*O*-acetal **3a**. To circumvent this problem, we separated the process into two steps that were conducted in one pot (Scheme 3). First, pyrrolidine **2a** was allowed to react with 1.1 equiv of quinone **1** in TFE at room temperature for 0.5 h to generate *N*,*O*-acetal **3a**, which was not isolated. Then the TFE was removed by rotary evaporation, and the residue was dissolved in HFIP containing 3 equiv of water. To the resulting solution was added 1.4 equiv of the quinone **1**, and the reaction mixture was stirred at 50 °C for 24 h. This procedure afforded *N*-aryl-pyrrolidin-2-one **4a** in 90% yield.

**Scheme 2. Mechanism of the Oxidation of Substituted Pyrrolidines by *o*-Benzoquinone**




**Scheme 3. One-Pot, Two-Step Synthesis of *N*-Aryl-2-pyrrolidinone 4a[a]**




[a]Reaction conditions: pyrrolidine **2a** (0.2 mmol) and quinone **1** (0.22 mmol) in TFE (10 mL) were stirred at room temperature for 0.5 h; then TFE was removed, the residue was dissolved in the solvent tested (10 mL), quinone **1** (0.28 mmol) and $H_2O$ (0.6 mmol) were added, and the mixture was stirred at 50 °C. [b]The yield was based on **2a**.

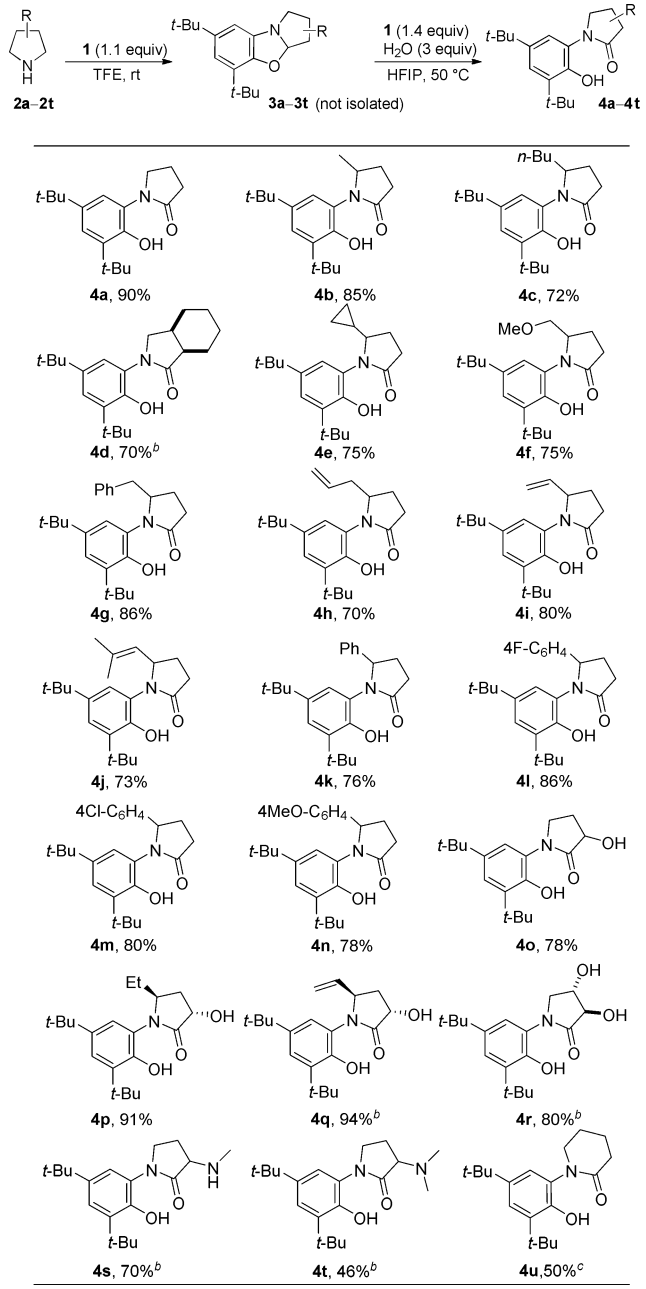


DOI: 10.1021/acs.joc.6b02562
J. Org. Chem. 2017, 82, 532−540

Under these one-pot, two-step conditions, the reactions of pyrrolidines with alkyl, methoxymethyl, benzyl, allyl, vinyl, aryl, and cyclopropyl substituents (**2b**−**n**) readily gave the corresponding *N*-aryl-pyrrolidin-2-ones (**4b**−**4n**, Scheme 4). Notably, substrates with a free hydroxyl group or a vicinal diol moiety (**2o**−**2r**) were tolerated, affording **4o**−**4r** in 78−94% yields. The first-step oxidation of **2o** occurred selectively at the C-2 position.[21] According to literature, tautomerization of iminium intermediate **A** to iminium intermediate **B** through the abstraction of the $\alpha$-H of pyrrolidine is the rate-determining step, this regioselectivity may have resulted from the higher acidity of the C-2 hydrogen due to the nearby 3-hydroxyl group.[22] In the reaction of amino-substituted pyrrolidine **2s**, the intermediate *N*,*O*-acetal underwent a side elimination reaction in HFIP, giving aryl substituted pyrrole as the major product.[23] Therefore, for this substrate, we conducted the second step in TFE. Also tetrachloro-*o*-benzoquinone, which is a stronger hydride abstractor delivered higher yield than **1**. Under the optimized condition, desired product **4s** was obtained in 70% yield. Under the same conditions, **4t** was obtained in 46% yield. Piperidine also reacted but with a much lower reaction rate, the desired product **4u** was obtained with 50% yield (70% conv.) after 72 h.[24] A large-scale reaction of **2i** (5 mmol) provided the product in 83% yield, a result that shows the potential synthetic utility of this method.

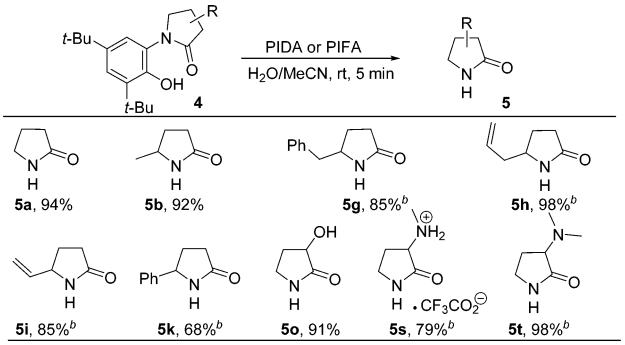
Treating *N*-aryl-2-pyrrolidones **4** with phenyliodinediacetate (PIDA) or phenyliodine bis(trifluoroacetate (PIFA) in a mixture of $H_2O$ and MeCN for 5 min removed the aryl moieties[25] to afford substituted $\gamma$-lactams **5** in good to excellent chemical yields (Scheme 5).

**Scheme 4. Substrate Scope in the Synthesis of *N*-Aryl-2-pyrrolidones 4**[a]




[a]Reaction conditions: Pyrrolidine **2** (0.2 mmol) and quinone **1** (0.22 mmol) in TFE (10 mL) were stirred at room temperature; then TFE was removed, the residue was dissolved in HFIP (10 mL), quinone **1** (0.28 mmol) and $H_2O$ (0.6 mmol) were added, and the mixture was stirred at 50 °C. [b]Tetrachloro-*o*-benzoquinone and TFE were used in the second step. [c]Piperidine (0.2 mmol) and quinone (0.5 mmol) was heated in solvent (10 mL, TFE:$H_2O$ = 9:1)

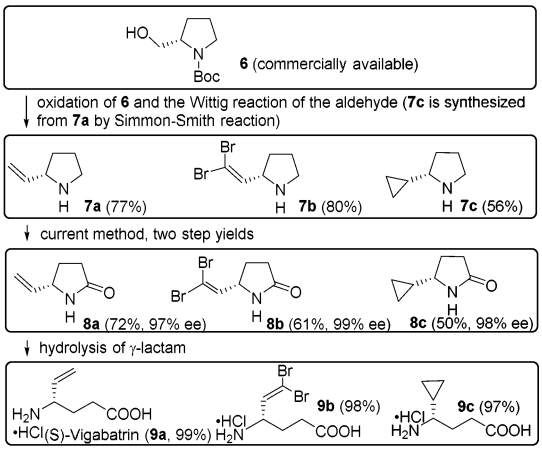
**Scheme 5. Removal of the Aryl Moiety from 4**[a]




[a]Reaction conditions: **4** (0.2 mmol) and PIDA (0.22 mmol) in 20 mL of 1:2 (v/v) $H_2O$/MeCN. [b]PIFA was used.

The synthetic utility of this method was further demonstrated by the synthesis of chiral $\gamma$-aminobutyric acid (*S*)-vigabatrin and two analogues (Scheme 6).[26] Oxidation, Wittig reaction of commercially available *N*-Boc-L-prolinol (**6**, optical

**Scheme 6. Synthesis of (*S*)-Vigabatrin and Two Analogues**






DOI: 10.1021/acs.joc.6b02562
J. Org. Chem. 2017, 82, 532−540

purity ee: 99%) gave (*S*)-2-vinyl pyrrolidine **7a**, which was readily transformed to corresponding γ-lactam **8a** by the method described herein. No loss of enantiomeric purity was observed. Hydrolysis of **8a** led to (*S*)-vigabatrin (**9a**). Our late-stage oxidation strategy was also applicable to the synthesis of optical active vigabatrin analogues **9b** and **9c**.

## CONCLUSION

In summary, by means of a strategy involving direct oxidation of the α-C−H of pyrrolidines with an *o*-benzoquinone, we realized the chemoselective oxidation of pyrrolidines with alkene, hydroxyl, and amino substituents to the corresponding γ-lactams. Following the late-stage functionalization and oxidation strategy, we synthesized chiral γ-aminobutyric acid drug (*S*)-vigabatrin and its two analogues. The mildness and operational simplicity of this novel method make it an excellent tool for late-stage oxidation of substituted pyrrolidines to γ-lactams.

## EXPERIMENTAL SECTION

**General Information.** Unless specially indicated, all reactions were carried out in aerial atmosphere. All reagents were used without any further purification. Flash column chromatographies were performed on silica gel (200−300 mesh). $^1$H, $^{13}$C spectra were measured on a NMR instrument (400 MHz for $^1$H NMR; 100 MHz for $^{13}$C NMR). Chemical shifts of $^1$H NMR spectra were recorded relative to internal standard or residual solvent resonance (TMS δ 0.00; $CDCl_3$ δ 7.26; $D_2O$ δ 4.79; $CD_3OD$ δ 3.31). The following abbreviations were used to express the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. Chemical shifts of $^{13}$C NMR spectra were recorded relative to solvent resonance ($CDCl_3$ δ 77.0). HPLC analysis was conducted using Shimadzu LC−20AT with a UV detector SPD−20A and chiral column of CHIRALPAK AD−H (25 cm × 0.46 cm), CHIRALCEL OD−H (25 cm × 0.46 cm). Optical rotations were determined at indicated temperature and solvents. High-resolution mass spectral analyses were performed on a high resolution ESI-FTICR mass spectrometer.

**Preparation and Characterization of Substrates.** Substrates (**2e**, **2l**, **2m**) were synthesized according to the previously reported method.[18]

*2-Cyclopropylpyrrolidine Hydrochloride (**2e**).* Cyclopropyl magnesium bromide (0.5 M in THF) was used and the title compound was obtained in 90% yield as a viscous colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 0.8H), 9.35 (s, 0.5H), 3.69−3.40 (m, 1H), 3.37−3.23 (m, 1H), 2.93−2.86 (m, 1H), 2.28−2.07 (m, 2H), 2.06−1.81 (m, 2H), 1.28−1.25 (m, 1H), 0.82−0.58 (m, 3H), 0.36 (dt, J = 9.4, 4.6 Hz, 1H);$^{13}$C NMR (100 MHz, $CDCl_3$) δ 66.2, 44.4, 30.2, 23.8, 12.2, 4.9, 4.4; HRMS (ESI) calculated for $[C_7H_{14}N]^+$ 112.1121, found 112.1122.

*2-(4-Fluorophenyl)pyrrolidine Hydrochloride (**2l**).* 4-Fluorophenylmagnesium bromide (2.0 M in $Et_2O$) was used, the title compound was obtained in 75% yield as a viscous yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.69 (s, 1H), 7.56 (dd, J = 8.5, 5.1 Hz, 2H), 7.05 (dd, J = 8.8 Hz, 8.5 Hz 2H), 4.56 (brs, 1H), 3.47 (brs, 1H), 3.24 (brs, 1H), 2.41−2.37(m, 1H), 2.24−2.18 (m, 2H), 2.14−2.01 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.18 (d, J = 249.4 Hz), 130.6 (d, J = 8.5 Hz), 129.1 (d, J = 3.2 Hz), 116.1 (d, J = 21.7 Hz), 63.0, 44.8, 31.4, 23.5.

*2-(4-Chlorophenyl)pyrrolidine Hydrochloride (**2m**).* Following the synthetic procedure of **2i**, 4-chlorophenylmagnesium bromide (1.0 M in $Et_2O$) was used, the title compound was obtained in 53% yield as a viscous yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 10.20 (brs, 0.9H), 9.41 (brs, 0.9H), 7.48 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 4.41 (brs, 1H), 3.38 (brs, 1H), 3.17 (brs, 1H), 2.35 (brs, 1H), 2.16 (brs, 2H), 2.03 (brs, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.2, 132.3, 129.5, 129.1, 62.6, 44.7, 31.5, 23.4.

*2-(2-Methylprop-1-en-1-yl)pyrrolidine Trifluoroacetate (**2j**).* To the solution of isopropyl triphenylphosphonium iodide (1.7 g, 4 mmol) in THF (40 mL) was added *t*-BuOK (449 mg, 4 mmol) at room temperature under argon. The reaction was stirred at room temperature for 2 h. Then *tert*-butyl-2-formylpyrrolidine-1-carboxylate[27] (398 mg, 2 mmol) in THF (10 mL) was added dropwisely. When completed, the reaction was quenched with saturated $NH_4Cl$, extracted with EtOAc (3X), dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/PE = 1:9). The product was then dissolved in a solution of TFA (2 mL) and DCM (18 mL) and was stirred at room temperature. Upon completion, the reaction mixture was concentrated to afford the title compound **2j** (324 mg, 73% yield) as a colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.70 (brs, 1H), 8.82 (brs, 1H), 5.27 (d, J = 9.3 Hz, 1H), 4.43−4.12 (m, 1H), 3.66−3.09 (m, 2H), 2.70 (brs, 1H), 2.24−2.03 (m, 2H), 2.05−1.92 (m, 1H), 1.74 (s, 3H), 1.71 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.3, 119.0, 57.8, 44.5, 31.6, 25.7, 23.9, 18.3. HRMS (ESI) calculated for $[C_8H_{15}N + H]^+$ 126.1277, found 126.1274.

**Preparation and Characterization of *N*-Aryl-2-pyrrolidones.** *1-(3,5-Di-tert-butyl-2-hydroxyphenyl)pyrrolidin-2-one (**4a**).* To a solution of pyrrolidine (14 mg, 16 μL, 0.2 mmol) in TFE (10 mL) was added 3,5-di-*tert*-butyl-*o*-benziquinone **1** (48 mg, 0.22 mmol) at room temperature. It should be noted that when use pyrrolidine hydrochloride or trifluoroacetate instead of pyrrolidine, $K_2CO_3$ (2 equiv) should be added to free the pyrrolidine from its salt (the exact amount of pyrrolidine in its salt should be determined by $^1$H NMR). After the reaction was completed in 0.5 h, TFE was evaporated and the residue was dissolved in HFIP (10 mL). Then compound **1** (62 mg, 0.28 mmol) and $H_2O$ (11 mg (11 μL), 0.6 mmol) were added in the above solution and the reaction mixture was heated at 50 °C for 24 h. HFIP was evaporated and the residue was dissolved in DCM (40 mL). The organic layer was washed with brine, dried with $MgSO_4$ and was concentrated and purified by column chromatography on silica gel using EtOAc/PE = 1:9 to give **4a** (52 mg, 90% yield) as a light yellow solid. mp = 213-215 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.25 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 3.98 (t, J = 7.0 Hz, 2H), 2.68 (t, J = 8.0 Hz, 2H), 2.43−2.13 (m, 2H), 1.44 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.8, 147.1, 142.4, 140.3, 128.1, 122.4, 116.4, 51.5, 35.5, 34.5, 32.2, 31.5, 29.9, 19.6; IR(neat) 3061, 2962, 1662, 1482, 1445, 1223,1199 $cm^{-1}$; HRMS (MALDI) calculated for $[C_{18}H_{27}NO_2 + Na]^+$ 312.1934, found 312.1938.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-methylpyrrolidin-2-one (**4b**).* Following the synthetic procedure of **4a**, 2-methylpyrrolidine was used and the title compound was obtained in 85% yield as a light yellow solid; mp = 177−179 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.24 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 2.3 Hz, 1H), 4.52−4.33 (m, 1H), 2.85−2.58 (m, 2H), 2.53−2.39 (m, 1H), 2.00−1.81 (m, 1H), 1.44 (s, 9H), 1.29 (s, 9H), 1.18 (d, J = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.7, 148.4, 142.4, 140.2, 126.3, 122.4, 117.8, 57.3, 35.4, 34.4, 31.6, 31.2, 29.9, 27.7, 20.1; IR(neat) 3469, 2953, 1669, 1440, 1306 $cm^{-1}$; HRMS (MALDI) calculated for $[C_{19}H_{29}NO_2 + Na]^+$ 326.2091, found 326.2095.

*5-Butyl-1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyrrolidin-2-one (**4c**).* Following the synthetic procedure of **4a**, 2-butylpyrrolidine hydrochloride[18] and $K_2CO_3$ (55 mg, 0.4 mmol) were used and the title compound was obtained in 72% yield as a light yellow solid; mp = 82−85 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.24 (d, J = 2.2 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 4.38−4.31 (m, 1H), 2.99−2.56 (m, 2H), 2.51−2.34 (m, 1H), 1.98−1.88 (m, 1H), 1.64−1.59 (m, 2H), 1.43 (s, 9H), 1.36−1.12 (m, 4H), 1.28 (s, 9H), 0.79 (t, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.8, 148.3, 142.3, 140.2, 126.4, 122.4, 117.9, 61.4, 35.4, 34.4, 32.8, 31.6, 31.2, 29.9, 26.3, 25.0, 22.3, 13.9; IR(neat) 3109, 2956, 2869,1674, 1586, 1445, 1228 $cm^{-1}$; HRMS (MALDI) calculated for $[C_{22}H_{35}NO_2 + Na]^+$ 368.2560, found 368.2566.

*cis-2-(3,5-Di-tert-butyl-2-hydroxyphenyl)octahydro-1H-isoindol-1-one (**4d**).* Following the synthetic procedure of **4t**, octahydro-1*H*-isoindole was used and the title compound was obtained in 70% yield as a colorless liquid;$^1$H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.25 (d, J = 2.4 Hz, 2H), 6.90 (d, J = 2.3 Hz, 1H), 4.07 (dd, J = 9.6, 5.6 Hz, 1H), 3.38 (dd, J = 9.7, 2.1 Hz, 1H), 2.86−2.74 (m, 1H), 2.59−2.46



DOI: 10.1021/acs.joc.6b02562
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(m, 1H), 2.15 (dd, $J$ = 13.9, 4.1 Hz, 1H), 1.86−1.74 (m, 1H), 1.72−1.52 (m, 4H), 1.44 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 176.9, 147.2, 142.2, 140.3, 128.6, 122.2, 116.1, 55.2, 42.9, 35.5, 34.4, 33.8, 31.6, 29.9, 27.6, 23.5, 22.7. HRMS (ESI) calculated for $[C_{22}H_{33}NO_2 + H]^+$ 344.2584, found 344.2588.

*5-Cyclopropyl-1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyrrolidin-2-one (**4e**).* Following the synthetic procedure of **4a**, 2-cyclopropylpyrrolidine hydrochloride (**2e**) and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 75% yield as a light yellow solid; mp = 153−154 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (d, $J$ = 2.2 Hz, 1H), 7.11 (s, 0.9H), 6.92 (d, $J$ = 2.3 Hz, 1H), 3.64 (td, $J$ = 8.1, 5.5 Hz, 1H), 2.89−2.56 (m, 2H), 2.46−2.37 (m, 1H), 2.16−1.97 (m, 1H), 1.43 (s, 9H), 1.28 (s, 9H), 0.87−0.85 (m, 1H), 0.41−0.33 (m, 2H), 0.14−0.05 (m, 1H), 0.02−0.00 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 175.2, 148.3, 141.5, 139.2, 126.2, 122.2, 118.9, 66.4, 35.0, 34.4, 34.0, 31.2, 30.6, 29.5, 25.4, 14.8, 4.8; IR(neat) 3469, 2957, 1673, 1442, 1323 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{21}H_{31}NO_2 + Na]^+$ 352.2247, found 352.2246.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-(methoxymethyl)-pyrrolidin-2-one (**4f**).* Following the synthetic procedure of **4a**, 2-(methoxymethyl)pyrrolidine was used and the title compound was obtained in 75% yield as a light yellow liquid; mp = 163−165 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.27 (d, $J$ = 2.0 Hz, 1H), 6.91 (s, 0.8H), 6.90 (d, $J$ = 2.0 Hz, 1H), 4.12 (brs, 1H), 3.37−3.28 (m, 5H), 2.84−2.66 (m, 1H), 2.42−2.50 (m, 1H), 2.41−2.22 (m, 1H), 2.29−2.06 (m, 1H), 1.42 (s, 9H), 1.28 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.2, 149.6, 142.4, 138.3, 124.5, 123.8, 120.5, 72.2, 61.7, 59.1, 35.3, 34.4, 31.6, 31.2, 29.7, 22.2; IR(neat) 3392, 2952, 1681, 1448, 1220 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{20}H_{31}NO_3 + Na]^+$ 356.2196, found 356.2198.

*5-Benzyl-1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyrrolidin-2-one (**4g**).* Following the synthetic procedure of **4a**, 2-benzylpyrrolidine[18] was used and the title compound was obtained in 86% yield as a light yellow solid; mp = 130−133 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (s, 0.9H), 7.31−7.24 (m, 3H), 7.23−7.17 (m, 1H), 7.11−7.06 (m, 2H), 7.03 (d, $J$ = 2.3 Hz, 1H), 4.68−4.53 (m, 1H), 2.93 (dd, $J$ = 13.6, 3.8 Hz, 1H), 2.67−2.53 (m, 2H), 2.51−2.41 (m, 1H), 2.31−2.19 (m, 1H), 2.18−1.93 (m, 1H), 1.46 (s, 9H), 1.32 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.8, 148.4, 142.5, 140.5, 136.4, 129.3, 128.6, 126.7, 126.3, 122.6, 117.6, 62.7, 39.4, 35.4, 34.4, 31.6, 30.9, 29.8, 24.2; IR (neat) 3141, 2960, 1671, 1587, 1482, 1233, 761, 699 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{25}H_{33}NO_2 + Na]^+$ 402.2404, found 402.2405.

*5-Allyl-1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyrrolidin-2-one (**4h**).* Following the synthetic procedure of **4a**, 2-allylpyrrolidine hydrochloride[18] and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 70% yield as a light yellow solid; mp = 136−138 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (s, 0.9H), 7.25 (d, $J$ = 2.2 Hz, 1H), 6.93 (d, $J$ = 2.2 Hz, 1H), 5.89−5.50 (m, 1H), 5.08 (dd, $J$ = 10 Hz, 1.2 Hz 1H), 5.03 (dd, $J$ = 9 Hz, 1.2 Hz, 1H), 4.58−4.27 (m, 1H), 2.75−2.57 (m, 2H), 2.45−2.34 (m, 1H), 2.33−2.24 (m, 1H), 2.23−2.13 (m, 1H), 2.07−1.96 (m, 1H), 1.43 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.8, 148.4, 142.5, 140.3, 132.1, 126.1, 122.6, 119.1, 117.8, 60.9, 37.5, 35.4, 34.4, 31.5, 31.1, 29.8, 23.9; IR(neat) 3262, 3077, 2967, 1611, 1604, 1479, 1308 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{21}H_{31}NO_2 + Na]^+$ 352.2247, found 352.2250.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-vinylpyrrolidin-2-one (**4i**).* Following the synthetic procedure of **4a**, 2-vinylpyrrolidine hydrochloride[18] and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 80% yield as a light yellow solid; mp = 130−132 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (s, 1H), 7.21 (d, $J$ = 2.1 Hz, 1H), 6.89 (d, $J$ = 2.2 Hz, 1H), 5.89−5.53 (m, 1H), 5.25 (d, $J$ = 17.1 Hz, 1H), 5.13 (d, $J$ = 10.2 Hz, 1H), 4.86−4.79 (m, 1H), 2.67 (t, $J$ = 7.8 Hz, 2H), 2.55−2.41 (m, 1H), 2.14−1.91 (m, 1H), 1.43 (s, 9H), 1.26 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.9, 147.7, 141.9, 140.0, 137.0, 126.7, 122.2, 118.2, 118.0, 64.7, 35.4, 34.4, 31.4, 31.0, 29.8, 27.1; IR (neat) 3076, 2958, 1655, 1483, 1298 cm$^{-1}$; HRMS (ESI) calculated for $[C_{20}H_{29}NO_2 + H]^+$ 316.2271, found 316.2274.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-(isobutenyl)pyrrolidin-2-one (**4j**).* Following the synthetic procedure of **4a**, 2-(isobutenyl)-pyrrolidine trifluoroacetate (**2j**) and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 73% yield as a light yellow solid; mp = 146−148 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (s, 1H), 7.20 (d, $J$ = 2.2 Hz, 1H), 6.82 (d, $J$ = 2.3 Hz, 1H), 5.09−4.95 (m, 2H), 2.67−2.63 (dd, $J$ = 9.0, 6.6 Hz, 2H), 2.48−2.36 (m, 1H), 2.01−1.84 (m, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.43 (s, 9H), 1.24 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.8, 147.7, 141.8, 139.7, 135.8, 126.8, 124.5, 122.1, 118.1, 60.2, 35.4, 34.3, 31.5, 31.4, 30.0, 27.7, 25.6, 18.1; IR (neat) 3105, 2955, 1688, 1585, 1483, 1297 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{22}H_{33}NO_2 + H]^+$ 344.2584, found 344.2588.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-phenylpyrrolidin-2-one (**4k**).* Following the synthetic procedure of **4a**, 2-phenylpyrrolidine was used and the title compound was obtained in 76% yield as a light yellow solid; mp = 52−54 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (s, 1H), 7.30−7.15 (m, 5H), 7.07 (d, $J$ = 2.3 Hz, 1H), 6.73 (d, $J$ = 2.3 Hz, 1H), 5.51−5.24 (m, 1H), 2.79−2.70 (m, 3H), 2.31−2.01 (m, 1H), 1.40 (s, 9H), 1.09 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.3, 147.7, 142.0, 140.6, 140.0, 128.7, 127.8, 126.9, 126.0, 122.0, 117.8, 66.3, 35.3, 34.2, 31.3, 30.7, 29.8; IR (neat) 3679, 2959, 1674, 1279, 758, 698 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{24}H_{31}NO_2 + Na]^+$ 388.2247, found 388.2248.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-(4-fluorophenyl)-pyrrolidin-2-one (**4l**).* Following the synthetic procedure of **4a**, 2-(4-fluorophenyl)pyrrolidine hydrochloride (**2l**) and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 86% yield as a light yellow solid; mp = 158−160 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (s, 0.9H), 7.2−7.12 (m, 2H), 7.08 (s, 1H), 6.98−6.87 (m, 2H), 6.72 (s, 1H), 5.40 (t, $J$ = 6.6 Hz, 1H), 3.01−.60 (m, 3H), 2.28−2.01 (m, 1H), 1.40 (s, 9H), 1.11 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.2, 162.2 (d, $J$ = 246.5 Hz), 147.8, 142.1, 140.0, 136.3, 127.8 (d, $J$ = 8.2 Hz), 126.7, 122.1, 117.7, 115.6 (d, $J$ = 21.6 Hz), 65.5, 35.3, 34.2, 31.3, 31.2, 30.7, 29.7; IR (neat) 3124, 2968, 1661, 1605, 1442, 1511, 1229, 839 cm$^{-1}$ ; HRMS (ESI) calculated for $[C_{24}H_{30}FNO_2 + H]^+$ 384.2333, found 384.2337.

*5-(4-Chlorophenyl)-1-(3,5-di-tert-butyl-2-hydroxyphenyl)-pyrrolidin-2-one (**4m**).* Following the synthetic procedure of **4a**, 2-(4-chlorophenyl)pyrrolidine hydrochloride (**2m**) and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 80% yield as a light yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (brs, 0.9H), 7.21 (d, $J$ = 8.5 Hz, 2H), 7.12 (d, $J$ = 8.5 Hz, 2H), 7.09 (d, $J$ = 2.2 Hz, 1H), 6.72 (d, $J$ = 2.3 Hz, 1H), 5.40 (t, $J$ = 7.0 Hz, 1H), 2.87−2.53 (m, 3H), 2.16−1.92 (m, 1H), 1.40 (s, 9H), 1.11 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.2, 147.8, 142.2, 140.2, 139.2, 133.6, 128.9, 127.4, 126.7, 122.3, 117.6, 65.5, 35.3, 34.2, 31.3, 31.2, 30.6, 29.7; IR (neat) 3426, 3158, 2957, 1659, 1484, 1441, 1389, 817 cm$^{-1}$; HRMS (ESI) calculated for $[C_{24}H_{30}ClNO_2 + H]^+$ 400.2038, found 400.2042.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-(4-methoxyphenyl)-pyrrolidin-2-one (**4n**).* Following the synthetic procedure of **4a**, 2-(4-methoxyphenyl)pyrrolidine trifluoroacetate[28] and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 78% yield as a viscous light yellow liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 (s, 0.9H), 7.16−7.05 (m, 3H), 6.84−6.57 (m, 3H), 5.41−5.28 (m, 1H), 3.73 (s, 3H), 2.80−2.62 (m, 3H), 2.19−1.99 (m, 1H), 1.39 (s, 9H), 1.11 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.2, 159.1, 147.8, 141.9, 139.9, 132.6, 127.3, 126.9, 122.0, 117.9, 114.1, 65.7, 55.2, 35.3, 34.2, 31.3, 30.8, 29.8; IR (neat) 3421, 2957, 1651, 1586, 1540, 1390, 1247, 1150, 868 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{25}H_{33}NO_3 + Na]^+$:418.2353, found 418.2358.

**Regioselectivity in the *N,O*-Acetal Formation of Pyrrolidin-3-ol (2o).** *5,7-Di-tert-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazol-3-ol (**3o**).* To a solution of pyrrolidin-3-ol (**2o**, 17 mg, 0.2 mmol) in TFE (10 mL) was added 3,5-di-*tert*-butyl-1,2-benzoquinone (48 mg, 0.22 mmol) at room temperature. After 0.5 h, TFE was evaporated, the residue was purified by chromatography using EtOAc/PE (1:9) to give **3o** (52 mg, 90% yield). The configuration of **3o** was determined by 2D COSY and 2D NOESY. $^1$H NMR (400 MHz, $CDCl_3$ diastereoisomers (*cis*/*trans* = 11:9)) $\delta$ 6.80 (d, $J$ = 1.8 Hz,



DOI: 10.1021/acs.joc.6b02562
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0.45H), 6.78 (d, $J$ = 1.8 Hz, 0.54H), 6.72 (d, $J$ = 1.8 Hz, 0.44H), 6.68 (d, $J$ = 1.8 Hz, 0.51H), 5.87−5.79 (m, 0.55H), 5.67−5.60 (m, 0.46H), 4.46−4.44 (m, 0.45H), 4.4−4.36 (m, 0.55H), 3.70−3.59 (m, 0.48H), 3.51−3.47 (m, 0.61H), 3.23−3.16 (m, 1H), 2.09−1.72 (m, 3H), 1.37 (s, 5H), 1.33 (s, 4H), 1.28 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$ diastereoisomers (*cis*/*trans* = 11:9)) $\delta$ 147.3, 147.0, 144.5, 143.9, 141.5, 141.0, 130.7, 130.5, 116.8, 116.2, 109.5, 108.5, 106.7, 101.5, 71.4, 54.7, 53.0, 34.6, 34.0, 33.99, 31.7, 31.7, 31.5, 31.4, 29.5, 29.4.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-3-hydroxypyrrolidin-2-one (**4o**).* Following the synthetic procedure of **4a**, 3-hydroxypyrrolidine was used, the title compound was obtained in 78% yield as a colorless solid. The regioselectivity of the reaction was determined by $^1$H−$^1$H-COSY NMR experiment. mp = 236−239 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.81 (s, 1H), 7.28 (d, $J$ = 2.2 Hz, 1H), 6.93 (d, $J$ = 2.3 Hz, 1H), 4.60 (t, $J$ = 8.7 Hz, 1H), 4.10−3.91 (m, 1H), 3.88−3.71 (m, 1H), 3.25 (s, 1H), 2.66 (dt, $J$ = 12.8, 6.5 Hz, 1H), 2.36−2.19 (m, 1H), 1.44 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.2, 147.1, 142.7, 140.4, 127.5, 123.0, 116.4, 70.2, 47.0, 35.5, 34.4, 31.5, 29.8, 29.2; IR (neat) 3392, 2967, 1664, 1443, 1247, 1110 cm$^{-1}$; HRMS (ESI) calculated for $[C_{18}H_{27}NO_3 + Na]^+$ 328.1883, found 328.1885.

*(3R,5R)-1-(3,5-di-tert-butyl-2-hydroxyphenyl)-5-ethyl-3-hydroxy-pyrrolidin-2-one (**4p**).* Following the synthetic procedure of 4a, (3*R*,5*R*)-5-ethylpyrrolidin-3-ol hydrochloride[29] and $K_2CO_3$ (55 mg, 0.4 mmol) were used and the title compound was obtained in 91% yield as a light yellow oil; $[\alpha]_D^{24}$ = −145.6 ($c$ = 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.27 (d, $J$ = 2.2 Hz, 1H), 6.97 (d, $J$ = 2.3 Hz, 1H), 6.95 (s, 1H), 4.65 (dd, $J$ = 7.6, 6.1 Hz, 1H), 4.43−4.27 (m, 1H), 3.39 (brs, 0.7H), 2.49−2.23 (m, 2H), 1.66−1.51 (m, 1H), 1.45−1.39 (m, 1H), 1.43 (s, 9H), 1.29 (s, 9H), 0.80 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.1, 148.2, 142.7, 139.7, 125.3, 123.2, 118.8, 70.01, 60.3, 35.3, 34.4, 32.8, 31.5, 29.8, 26.0, 8.9; IR (neat) 3421, 2959, 1658, 1446, 1363, 1225, 1103, 1027 cm$^{-1}$; HRMS (ESI) calculated for $[C_{20}H_{31}NO_3 + H]^+$ 334.2377, found 334.2382.

*(3R,5S)-1-(3,5-di-tert-butyl-2-hydroxyphenyl)-3-hydroxy-5-vinyl-pyrrolidin-2-one (**4q**).* Following the synthetic procedure of **4a**, (3*R*,5*R*)-5-vinylpyrrolidin-3-ol hydrochloride[29] and $K_2CO_3$ (55 mg, 0.4 mmol) were used and the title compound was obtained in 94% yield as a light yellow solid; mp = 53−54 °C; $[\alpha]_D^{24}$ = −41.6 ($c$ = 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.26 (s, 1H), 7.13 (s, 1H), 6.99 (d, $J$ = 1.9 Hz, 1H), 5.75 (ddd, $J$ = 17.3, 10.2, 7.4 Hz, 1H), 5.19 (d, $J$ = 17.1 Hz, 1H), 5.13 (d, $J$ = 10.3 Hz, 1H), 4.77 (td, $J$ = 7.5, 2.7 Hz, 1H), 4.66 (t, $J$ = 7.6 Hz, 1H), 4.10 (s, 1H), 2.47 (dt, $J$ = 15.4, 7.8 Hz, 1H), 2.43−2.33 (m, 1H), 1.42 (s, 9H), 1.26 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.3, 147.6, 142.6, 140.0, 136.3, 126.1, 123.0, 118.5, 117.9, 69.5, 62.0, 35.7, 35.4, 34.4, 31.4, 29.8; IR (neat) 3421, 2957, 1665, 1482, 1442, 1362, 1200, 1107, 927 cm$^{-1}$; HRMS (ESI) calculated for $[C_{20}H_{29}NO_3 + H]^+$ 332.2220, found 332.2225.

*trans-1-(3,5-di-tert-butyl-2-hydroxyphenyl)-3,4-dihydroxypyrrolidin-2-one (**4r**).* Following the synthetic procedure of **4t**, *trans*-3,4-dihydroxypyrrolidine was used, the title compound was obtained in 80% yield as a yellow solid. mp = 204.5−206.0 °C; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.28 (s, 1H), 7.01 (s, 1H), 4.41−4.29 (m, 2H), 3.80 (t, $J$ = 8.3 Hz, 1H), 3.69−3.58 (m, 1H), 1.41 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 173.9, 148.0, 142.3, 138.6, 126.4, 122.8, 119.3, 76.1, 72.5, 53.2, 34.9, 33.9, 30.5, 28.8; HRMS (MALDI) calculated for $[C_{18}H_{27}NO_4 + Na]^+$ 344.1832, found 344.1835.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-3-(methylamino)-pyrrolidin-2-one (**4s**).* Following the same procedure for **4t**, 3-(methylamino)pyrrolidine trifluoroacetate and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 70% yield as a light yellow solid and **4s′** was obtained in 6% yield as a light yellow solid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.27 (d, $J$ = 2.1 Hz 1H), 6.94 (d, $J$ = 2.1 Hz, 1H), 4.08−3.92 (m, 1H), 3.84−3.75 (m, 1H), 3.70−3.60 (m, 1H), 2.53 (s, 3H), 2.53−2.47 (m, 1H), 2.24−2.01 (m, 1H), 1.44 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.0, 147.2, 142.5, 140.2, 127.71, 122.74, 116.5, 60.8, 48.0, 35.5, 34.5, 33.8, 31.5, 29.8, 27.0; IR (neat) 3298, 3064, 1698, 1483, 1285 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{19}H_{30}N_2O_2 + H]^+$ 319.2380, found 319.2385.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl) pyrrole (**4s′**).* $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34 (d, $J$ = 2.2 Hz, 1H), 7.10 (d, $J$ = 2.3 Hz, 1H), 6.89−6.77 (m, 2H), 6.49−6.35 (m, 2H), 5.21 (s, 1H), 1.43 (s, 9H), 1.30 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 145.0, 142.3, 136.3, 127.9, 123.6, 122.1, 121.5, 110.4, 35.3, 34.4, 31.5, 29.5; IR(neat) 3511, 3458, 2959, 1598, 1488, 1416, 1392, 1234 cm$^{-1}$.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-3-(dimethylamino)-pyrrolidin-2-one (**4t**).* The synthetic procedure was same as **4a**, except that 3-(*N*,*N*-dimethylamino)pyrrolidine was consumed after 1 h in the first step. In the second step, 1,2,3,4-tetrachloro-*o*-benzoquinone (0.28 mmol, 69 mg) and $H_2O$ (11 μL, 0.6 mmol) were added and the reaction was heated at 50 °C until the consumption of the *N*,*O*-acetal. Next TFE was evaporated and the residue was dissolved in DCM (40 mL). The crude reaction mixture was washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure, the crude product was purified by column chromatography on silica gel using EtOAc/PE = 1:6 to afford **4t** (46% yield) and **4s′** (26% yield).

**4t**: colorless solid; mp = 131−133 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (s, 0.9H), 7.26 (brs, 1H), 6.92 (brs, 1H), 4.13−3.90 (m, 1H), 3.87−3.66 (m, 2H), 2.50 (s, 6H), 2.39−2.20 (m, 2H), 1.44 (s, 9H), 1.28 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.9, 147.1, 142.5, 140.4, 128.0, 122.6, 116.2, 65.7, 47.7, 41.5, 35.5, 34.41, 31.5, 29.8, 21.4; IR (neat) 3728, 2924, 2854, 1699, 1481, 1389, 1360, 1201 cm$^{-1}$; HRMS (MALDI) calculated for $[C_{20}H_{32}N_2O_2 + Na]^+$ 355.2356, found 355.2358.

*1-(3,5-Di-tert-butyl-2-hydroxyphenyl)piperidin-2-one (**4u**).* A solution of piperidine (0.2 mmol, 17 mg) and 3,5-di-*tert*-butyl-*o*-benzoquinone (0.5 mmol, 110 mg) in the mixed solvent of TFE (9 mL) and $H_2O$ (1 mL) was heated at 80 °C and the reaction was monitored by TLC. After 72 h, TFE was evaporated and the residue was dissolved in DCM (40 mL), the crude reaction mixture was washed with brine and dried with $MgSO_4$ and concentrated. The crude product was further purified by chromatography using EtOAc/PE = (1:4) to give the title compound **4u** (30 mg) in 50% yield as yellow solid; mp = 181−183 °C $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.01 (s, 1H), 6.90 (s, 1H), 3.74 (s, 2H), 2.64 (s, 2H), 1.95 (s, 4H), 1.43 (s, 9H), 1.27 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5, 147.6, 142.9, 139.8, 132.6, 122.8, 118.9, 52.3, 35.4, 34.5, 32.5, 31.5, 29.9, 23.4, 20.8; HRMS (ESI) calculated for $[C_{19}H_{29}NO_2 + Na]^+$ 326.2091, found 326.2095.

***N*-Dearylation of *N*-Aryl-2-Pyrrolidones.**[25] *2-Pyrrrolidinone (**5a**).*[11c] To the solution of **4a** (58 mg, 0.2 mmol) in the mixed solvent of $H_2O$ and MeCN (20 mL, $H_2O$/MeCN = 1/2 (v:v)) was added PIDA (71 mg, 0.22 mmol) at room temperature. Upon completion, MeCN was evaporated. Saturated $NaHCO_3$ (2 mL) was added to the reaction mixture. The resulted reaction mixture was extracted with mixed solvent of $CHCl_3$ and 2-propanol ($CHCl_3$/2-propanol (v:v = 3:1)) three times. The combined organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (MeOH/EtOAc = 1:9) to afford **5a** (16 mg, 94% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.91 (brs, 1H), 3.41 (t, $J$ = 6.9 Hz, 2H), 2.31 (t, $J$ = 8.1 Hz, 2H), 2.21−2.01 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 179.3, 42.2, 30.0, 20.7.

*5-Methyl-2-pyrrolidinone (**5b**).*[11c] Following the same procedure for **5a**, the title compound was obtained in 92% yield as a colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.43 (brs, 1H), 4.06−3.61 (m, 1H), 2.43−2.32 (m, 2H), 2.3−2.23 (m, 1H), 1.77−1.50 (m, 1H), 1.23 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.6, 50.2, 30.6, 29.0, 22.1.

*5-Benzyl-2-pyrrolidinone (**5g**).*[30] To the solution of **4g** (76 mg, 0.2 mmol) in the mixed solvent of $H_2O$ and MeCN (20 mL, $H_2O$/MeCN = 1/4 (v:v)) was added PIFA (95 mg, 0.22 mmol). Upon completion, MeCN was evaporated. Saturated $NaHCO_3$ (2 mL) was added to the reaction mixture. The resulted reaction mixture was then extracted with the mixed solvent of $CHCl_3$ and 2-propanol ($CHCl_3$/2-propanol (v:v = 3:1)) three times. The combined organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (MeOH/EtOAc = 1:9) to give the title compound (30 mg) in 85% yield as a colorless solid; mp = 57−58 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.29 (m, 2H), 7.28−7.24 (m, 1H), 7.2−


DOI: 10.1021/acs.joc.6b02562
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7.15 (m, 2H), 6.05 (s, 1H), 4.07−3.81 (m, 1H), 2.84 (dd, $J$ = 13.4, 5.6 Hz, 1H), 2.73 (dd, $J$ = 13.4, 8.0 Hz, 1H), 2.36−2.29 (m, 2H), 2.29−2.20 (m, 1H), 1.93−1.76 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.1, 137.5, 129.1, 128.8, 126.9, 55.8, 43.0, 30.1, 26.9.

*5-Allyl-2-pyrrolidinone (**5h**).*[31] Following the same procedure for **5g**, the title compound was obtained in 98% yield as a colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.03 (s, 0.8H), 5.92−5.57 (m, 1H), 5.14 (d, $J$ = 4.4 Hz, 1H), 5.10 (s, 1H), 3.83−3.66 (m, 1H), 2.51−2.36 (m, 2H), 2.33−2.16 (m, 3H), 1.95−1.67 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 179.0 133.45, 118.5, 54.1, 40.8, 30.3, 26.4.

*5-Vinyl-2-pyrrolidinone (**5i**).*[32] To a solution of **4i** (63 mg, 0.2 mmol) in the mixed solvent $H_2O$ and $CH_3CN$ (20 mL, $H_2O/CH_3CN$ = 1:4 (v:v)) was added $K_2CO_3$ (28 mg, 0.2 mmol). Then PIFA (95 mg, 0.22 mmol) was added at room temperature. Upon completion, MeCN was evaporated. Saturated $NaHCO_3$ (2 mL) was added to the reaction mixture. The aqueous layer was extracted with the mixed solvent of $CHCl_3$ and 2-propanol ($CHCl_3$/2-propanol (v:v = 3:1)) three times. The combined organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/EtOAc = 1:9) to give the title compound in 85% yield as a viscous colorless solid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.21 (brs, 1H), 5.81 (ddd, $J$ = 17.0, 10.2, 6.8 Hz, 1H), 5.23 (d, $J$ = 17.0 Hz, 1H), 5.13 (d, $J$ = 10.2 Hz, 1H), 4.24−4.01 (m, 1H), 2.45−2.26 (m, 3H), 2.05−1.73 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.7, 138.6, 115.6, 56.7, 29.9, 27.9.

*5-Phenyl-2-pyrrolidinone (**5k**).*[33] Following the same procedure for **5i**, the title compound was obtained in 68% yield as a colorless solid; mp = 103−104 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.34 (m, 2H), 7.33−7.25 (m, 3H), 6.31 (brs, 0.9H), 4.76 (t, $J$ = 7.1 Hz, 1H), 2.67−2.52 (m, 1H), 2.51−2.37 (m, 2H), 2.05−1.92 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.6, 142.5, 128.9, 128.0, 125.7, 58.1, 31.4, 30.3.

*3-Hydroxy-2-pyrrolidinone (**5o**).*[34] The synthetic procedure was same as **5a** except that after MeCN in the reaction mixture was evaporated, the aqueous layer was washed with hexane for three times. Water in the aqueous phase was evaporated to give the title compound in 91% yield as a colorless solid with excellent purity; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.21 (brs, 0.9H), 4.72 (s, 1H), 4.36 (t, $J$ = 8.4 Hz, 1H), 3.42 (t, $J$ = 9.3 Hz, 1H), 3.37−3.24 (m, 1H), 2.60−2.44 (m, 1H), 2.21−1.97 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 179.0, 69.0, 38.8, 29.9.

*3-(Methylamino)pyrrolidin-2-one Trifluoroacetate (**5s**).* Following the same procedure for **5g**, except that after MeCN in the reaction mixture was evaporated, the aqueous layer was washed with hexane for three times. Water in the aqueous phase was evaporated to give the title compound with excellent purity in 79% yield as a light brown solid; $^1$H NMR (400 MHz, $D_2O$) $\delta$ 4.11 (t, $J$ = 9.5 Hz, 1H), 3.54−3.29 (m, 2H), 2.77 (s, 3H), 2.65−2.58 (m, 1H), 2.22−2.10 (m, 1H); $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 172.2, 57.6, 39.2, 30.8, 23.8; HRMS (ESI) calculated for $[C_5H_{10}N_2O + H]^+$ 115.0866, found 115.0870.

*3-(Dimethylamino)-2-pyrrolidinone (**5t**).* Following the same procedure for **5g**, the title compound was obtained in 98% yield as a light brown solid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.88 (brs, 0.9H), 3.43 (t, $J$ = 8.8 Hz, 1H), 3.39−3.25 (m, 2H), 2.39 (s, 6H), 2.26−2.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.9, 64.3, 41.4, 39.2, 21.4. HRMS (ESI) calculated for $[C_6H_{12}N_2O + H]^+$ 129.1022 , found 129.1021.

**Synthesis of *S*-Vigabatrin and Its Analogues.** *(S)-2-Vinylpyrrolidine Trifluoroacetate (**7a**).* To a solution of methyltriphenylphosphonium iodide (1.6 g, 4 mmol) in $Et_2O$ (40 mL) was added *t*-BuOK (449 mg, 4 mmol) at room temperature under argon. After stirred 2 h at room temperature, Boc-(*S*)-pyrrolidine-2-carbaldehyde **6a**[27] (398 mg, 2 mmol) in $Et_2O$ (10 mL) was added dropwisely. Upon completion, the reaction was quenched by saturated $NH_4Cl$. The reaction mixture was extracted with EtOAc three times. The combined organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc = 1:1). Then the residue was dissolved in the solution of TFA and DCM (20 mL, TFA:DCM = 1:9 (v:v)) and stirred at room temperature. When completed, evaporation of the solvent gave **7a** (373 mg, 96% yield) as a colorless oil, which spectroscopic data was identical with compound **2i**; $[\alpha]_D^{24}$ = −3.0 ($c$ = 0.28, MeOH/$H_2O$ = 1:1).

*(S)-1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-vinyl-2-pyrrolidinone (**10a**).* Following the same procedure for **4i**, the title compound was obtained in 82% yield as a light yellow solid, which spectroscopic data was identical with compound **4i**; $[\alpha]_D^{24}$ = −204.0 ($c$ = 0.20, $CHCl_3$).

*(S)-5-Vinyl-2-pyrrolidinone (**8a**).*[32] Following the same procedure for **5i**, the title compound was obtained in 88% yield as a colorless solid, which spectroscopic data was identical with compound **5i**; optical purity ee: 97%; HPLC condition: Chiralpak AD-H column (25 cm × 0.46 cm ID), hexane/2-propanol = 96:4, 0.8 mL/min, 227 nm UV detector, $t_R$ = 21.37 min (major) and $t_R$ = 25.51 min (minor). $[\alpha]_D^{24}$ = +34.1 ($c$ = 0.34, $CHCl_3$).

*(S)-4-Amino-5-hexenoic acid Hydrochloride (**9a**).*[32] A solution of (*S*)-5-vinyl-2-pyrrolidinone **8a** (22 mg, 0.2 mmol) in 1 M HCl (10 mL) was heated to reflux. When completed, the aqueous phase was washed with EtOAc and concentrated to give the title compound **9a** (33 mg) in 99% yield as a colorless solid; $[\alpha]_D^{24}$ = −12.0 ($c$ = 0.6, MeOH); $^1$H NMR (400 MHz, $D_2O$) $\delta$ 5.79 (ddd, $J$ = 17.2, 10.4, 8.4 Hz, 1H), 5.48−5.0 (m, 2H), 3.86−3.80 (m, 1H), 2.72−2.37 (m, 2H), 2.29−2.02 (m, 1H), 2.01−1.83 (m, 1H); $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 176.9, 132.3, 121.7, 53.4, 29.7, 27.0.

*(S)-1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-5-(2,2-dibromovinyl)-2-pyrrolidinne(**10b**).* Following the synthetic procedure of **4a**, (*S*)-2-(2,2-dibromovinyl)pyrrolidine trifluoroacetate (**7b**)[27] and $K_2CO_3$ (55 mg, 0.4 mmol) were used, the title compound was obtained in 81% yield as a light yellow solid; mp = 184−185 °C ; $[\alpha]_D^{24}$ = −67.7 ($c$ = 0.57, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (s, 1H), 7.25 (brs, 1H), 6.82 (brs, 1H), 6.31 (d, $J$ = 8.1 Hz, 1H), 5.14−5.08 (m, 1H), 2.85−2.64 (m, 2H), 2.64−2.46 (m, 1H), 2.28−1.77 (m, 1H), 1.44 (s, 9H), 1.30 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.5, 147.5, 142.6, 140.3, 137.4, 126.3, 122.7, 117.3, 92.7, 63.7, 35.5, 34.5, 31.6, 31.1, 29.9, 25.6; HRMS (ESI) calculated for $[C_{20}H_{27}Br_2NO_2 + H]^+$, 472.0481, found 472.0483.

*(S)-5-(2,2-Dibromovinyl)-2-pyrrolidinone (**8b**).* Following the synthetic procedure of **5a**, the title compound was obtained in 75% yield as a colorless solid; mp = 122−124 °C; optical purity ee: 99%; HPLC condition: Chiralpak AD-H column (25 cm × 0.46 cm ID), hexane/2-propanol = 96:4, 0.8 mL/min, 227 nm UV detector, $t_R$ = 24.40 min (minor) and $t_R$ = 29.27 min (major); $[\alpha]_D^{24}$ = +8.5 ($c$ = 0.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.46 (d, $J$ = 8.1 Hz, 1H), 6.23 (brs, 1H), 4.61−4.21 (m, 1H), 2.56−2.41 (m, 1H), 2.42−2.32 (m, 2H), 1.96−1.86 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.8, 138.6, 92.3, 56.1, 29.6, 26.9.

*(S)-4-Amino-6,6-dibromo-5-hexenoic acid Hydrochloride (**9b**).* Following the same procedure for **9a**, the title compound was obtained in 98% yield as a colorless solid; $[\alpha]_D^{24}$ = +10.9 ($c$ = 0.44, MeOH); $^1$H NMR (400 MHz, $D_2O$) $\delta$ 6.53 (d, $J$ = 9.8 Hz, 1H), 4.15 (td, $J$ = 10.0, 4.7 Hz, 1H), 2.69−2.37 (m, 2H), 2.11 (dd, $J$ = 13.5, 5.0 Hz, 1H), 1.96 (ddd, $J$ = 13.7, 10.2, 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 176.7, 132.5, 97.5, 52.7, 29.5, 26.9; HRMS (ESI) calculated for $[C_6H_9Br_2NO_2 + H]^+$:285.9073, found285.9067.

*(S)-2-Cyclopropylpyrrolidine Trifluoroacetate (**7c**).* To the solution of methyltriphenylphosphonium iodide (1.6 g, 4 mmol) in $Et_2O$ (40 mL) was added *t*-BuOK (449 mg, 4 mmol) at room temperature under argon. After stirred at room temperature for 2 h, Boc-(*S*)-pyrrolidine-2-carbaldehyde **6a**[27] (398 mg, 2 mmol) in $Et_2O$ (10 mL) was added dropwisely. Upon completion, the reaction was quenched with saturated $NH_4Cl$ solution. The reaction mixture was extracted with EtOAc three times. The combined organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc = 1:6) to give the Boc protected (*S*)-2-vinylpyrrolidine (383 mg, 97%). Then to the solution of $CH_2I_2$ (1.3 g (0.4 mL), 5 mmol) in DCM was added $Et_2Zn$ (1.0 M in hexane, 2.5 mL, 2.5 mmol) at 20 °C. After stirred 30 min at 20 °C, Boc protected (*S*)-2-vinylpyrrolidine (383 mg, 1.94 mmol) was added. Upon completion, the reaction was quenched by the addition of saturated $NH_4Cl$ solution. The reaction mixture was extracted with EtOAc three times. The combined organic phase was dried with


DOI: 10.1021/acs.joc.6b02562
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$MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in the mixed solvent of TFA and DCM (20 mL, TFA:DCM = 1:9 (v:v)) and stirred at room temperature. When completed, the solvent was removed under reduced pressure. The residue was purified by chromatography (DCM/MeOH = 8:1) to give the title compound in 77% yield, which spectroscopic data was identical with compound **2e**; $[\alpha]_D^{24}$ = +6.9 ($c$ = 0.14, MeOH/$H_2O$ = 2:1).

*(S)-5-Cyclopropyl-1-(3,5-di-tert-butyl-2-hydroxyphenyl)-2-pyrrolidinone (**10c**).* Following the same procedure for **4e**, the title compound was obtained in 74% yield as a light yellow solid, which spectroscopic data was identical with compound **4e**; $[\alpha]_D^{24}$ = −186.3 ($c$ = 0.58, $CHCl_3$).

*(S)-5-Cyclopropyl-2-pyrrolidinone (**8c**).* Following the same procedure for **5g**, the title compound was obtained in 68% yield as a colorless solid; optical purity ee: 98%; HPLC condition: Chiralpak AD-H column (25 cm × 0.46 cm ID), hexane/2-propanol = 96:4, 0.8 mL/min, 227 nm UV detector, $t_R$ = 20.93 min (major) and $t_R$ = 26.92 min (minor); $[\alpha]_D^{24}$ = +44 ($c$ = 0.20, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.35 (brs, 0.9H), 3.14−2.87 (m, 1H), 2.50−2.22 (m, 3H), 2.01−1.84 (m, 1H), 1.08−0.75 (m, 1H), 0.70−0.44 (m, 2H), 0.39−0.12 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.4, 57.7, 28.6, 25.6, 14.5, 1.1, 0.0; HRMS (ESI) calculated for $[C_7H_{11}NO + Na]^+$ 148.0733, found 148.0734.

*(S)-4-Amino-4-cyclopropylbutanoic acid Hydrochloride (**9c**).* Following the same procedure for **9a**, the title compound was obtained in 97% yield as a colorless solid; $[\alpha]_D^{24}$ = −97.2 ($c$ = 0.33, MeOH); $^1$H NMR (400 MHz, $D_2O$) $\delta$ 3.11−2.43 (m, 3H), 2.30−1.94 (m, 2H), 1.04−0.86 (m, 1H), 0.74 (dt, $J$ = 8.4, 4.7 Hz, 1H), 0.63 (dd, $J$ = 12.6, 8.5 Hz, 1H), 0.45−0.29 (m, 2H); $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 174.9, 54.5, 27.7, 26.0, 10.5, 1.9, 0.0; HRMS (ESI) calculated for $[C_7H_{13}NO_2 + H]^+$ 144.1019, found 144.1020.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02562.

Copies of NMR and HPLC spectra (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was financially supported by the NSFC (21072098, 21372119, 21121002), and Tianjin Natural Science Foundation (14JCYBJC20200). We thank Prof. Guang-Xin Liang at Nankai University for helpful discussions.

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DOI: 10.1021/acs.joc.6b02562
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DOI: 10.1021/acs.joc.6b02562
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