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RESEARCH ON UNIQUE MASKED *ortho*-BENZOQUINONE, MONOHEMIAMINAL: SYNTHESIS AND REACTIONS

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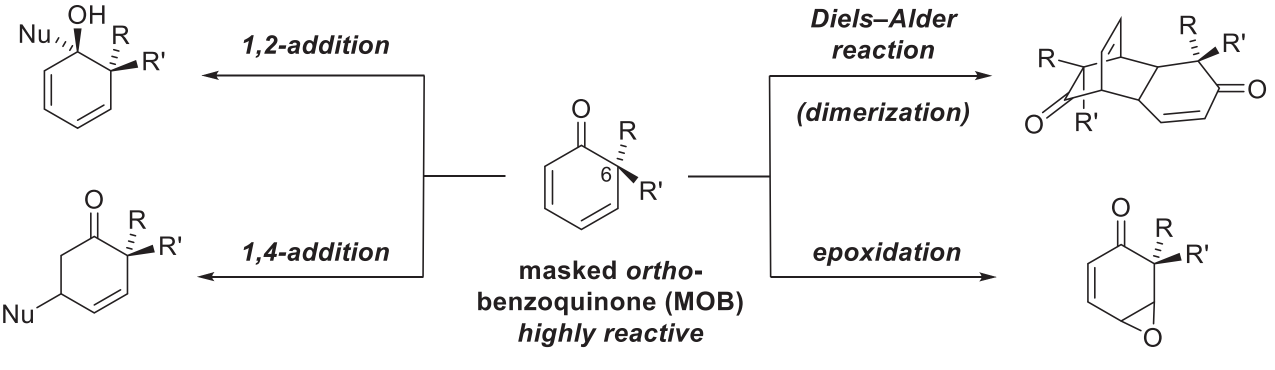
Abstract – Synthesis of *ortho*-benzoquinone monohemiaminals via the oxidative dearomatization/*O*-cyclization cascades of phenols bearing an *ortho* substituent derived from an amino alcohol with PIDA is described. The cascade reactions of substrates bearing a chiral substituent were found to proceed in a stereoselective manner. The Diels–Alder reactions of the *ortho*-benzoquinone monohemiaminals proceed in a highly stereoselective manner. The oxidative dearomatization/*O*-cyclization cascade affording the *ortho*-benzoquinone monohemiaminal had never been reported; hence, there is still ample scope for further investigation.

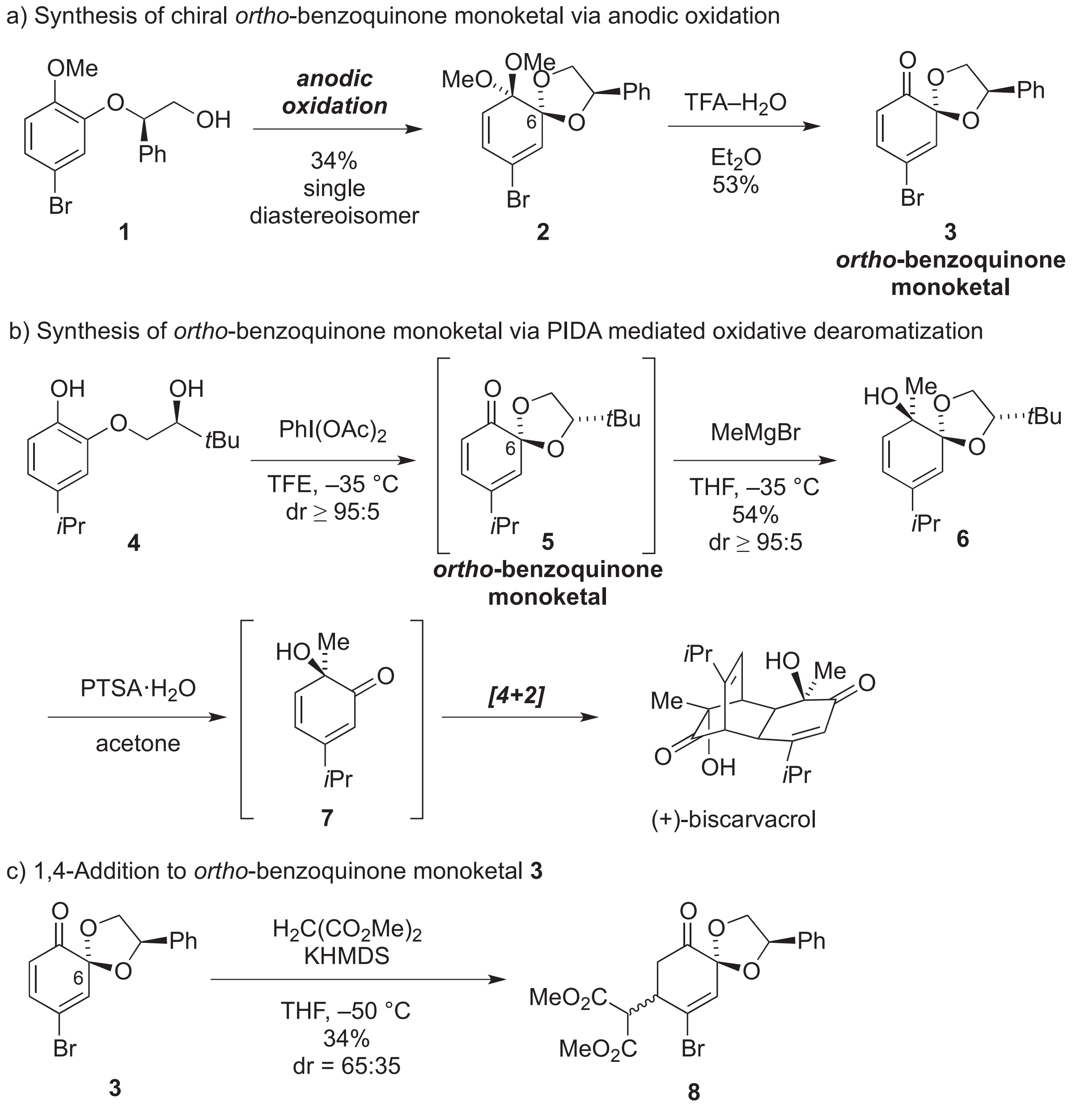
INTRODUCTION

Masked *ortho*-benzoquinones (MOBs) are 2,4-cyclohexadienones which are chiefly formed by the oxidative dearomatization of phenols.[1] MOBs can undergo a variety of reactions, including 1,2- and 1,4-additions, Diels–Alder reactions, and epoxidations among others (Scheme 1). [1]



Scheme 1. Synthetically useful transformations of masked *ortho*-benzoquinones (MOBs)

Hence, MOBs are useful synthetic intermediates and have been utilized in natural product synthesis.[2] However, reports of the preparation and reactions of chiral MOBs have been limited despite their promise in enantioselective total syntheses of natural products.[3] Indeed, to the best of our knowledge, only a few examples of chiral MOBs have been reported.[4,5]


a) Synthesis of chiral *ortho*-benzoquinone monoketal via anodic oxidation

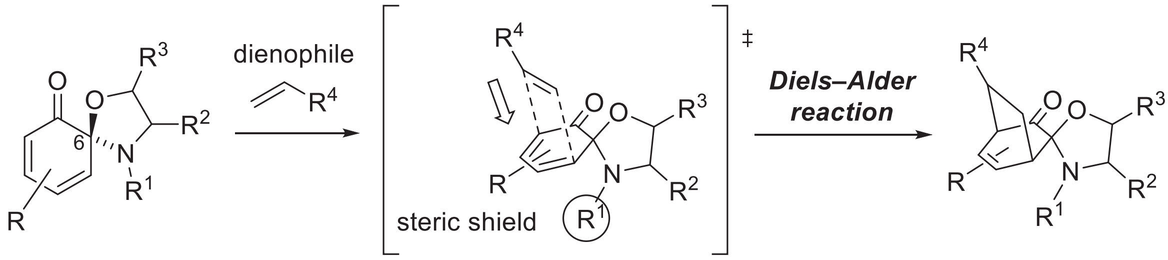
b) Synthesis of *ortho*-benzoquinone monoketal via PIDA mediated oxidative dearomatization

c) 1,4-Addition to *ortho*-benzoquinone monoketal **3**

Scheme 2. Stereoselective synthesis and reactions of chiral MOBs

Quideau and co-workers reported the first stereoselective synthesis of a chiral *ortho*-benzoquinone monoketal (compound **3**, Scheme 2a), which is an important class of MOBs, by the stereoselective anodic oxidation of **1**, which contains a chiral side-chain, and subsequent hydrolysis of the resultant **2** (Scheme

2a).[4a] The overall yield of **3** from **1** was low; however, the authors subsequently reported the oxidative dearomatization of **4** using phenyliodine(III) diacetate ($PhI(OAc)_2$, PIDA), which induced to afford **5** with high yield and stereoselectivity (Scheme 2b).[4b] They also reported the stereoselective reaction of **5** and Grignard reagent to afford **6**, which was then converted to **7** by hydrolysis to accomplish the total synthesis of (+)-biscarvacrol via a [4+2] cycloaddition (Scheme 2b). However, the stereoselectivity of the Michael reaction of chiral **3** with dimethyl malonate was low, due to the asymmetric induction caused by the chiral ketal moiety (Scheme 2c).[4a]



9

10

Scheme 3. Presumed stereoselective Diels–Alder reaction of *ortho*-benzoquinone monohemiaminal

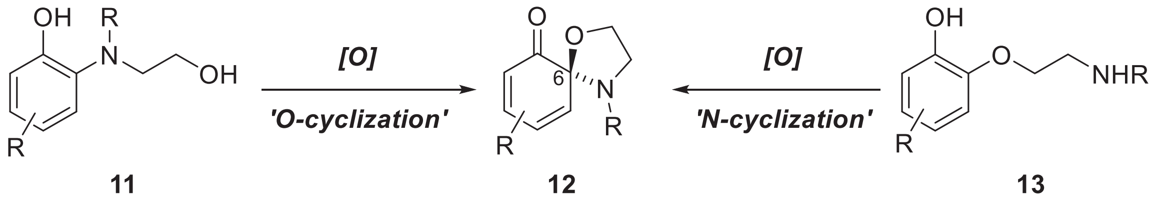
We envisioned that *ortho*-benzoquinone monohemiaminal **9** (Scheme 3) would be a useful synthetic intermediate for stereoselective reactions, because the substituent of the nitrogen atom would sterically hinder reaction at one side of the diene in **9**; e.g., the Diels–Alder reaction of **9** with alkenes would stereoselectively afford **10**. Moreover, the hemiaminal moiety of the product **10** is a masked carbonyl group, which could be hydrolyzed to afford chiral compounds in the overall transformations starting from chiral **9**.

2,4-Cyclohexadienones containing a five-membered spiro-ring, e.g., spiro-isooxazolins,[6] dioxolanes,[4b,4d,5] spiro-tetrahydrofurans,[7] spiro-lactones,[8] spiro-lactams,[9] spiro-amides,[10] spiro-cyclopentanes,[11] and spiro-oxindoles[12] among others, have been prepared by the oxidative dearomatization of phenols. However, to the best of our knowledge, only one example of the formation of a cyclic hemiaminal by the oxidative dearomatization of the corresponding phenol derivative has been reported.[13] Hence, we decided to undertake a feasibility study of the formation of an *ortho*-benzoquinone monohemiaminal by the oxidative dearomatization of a simple achiral compound.

RESULTS AND DISCUSSION

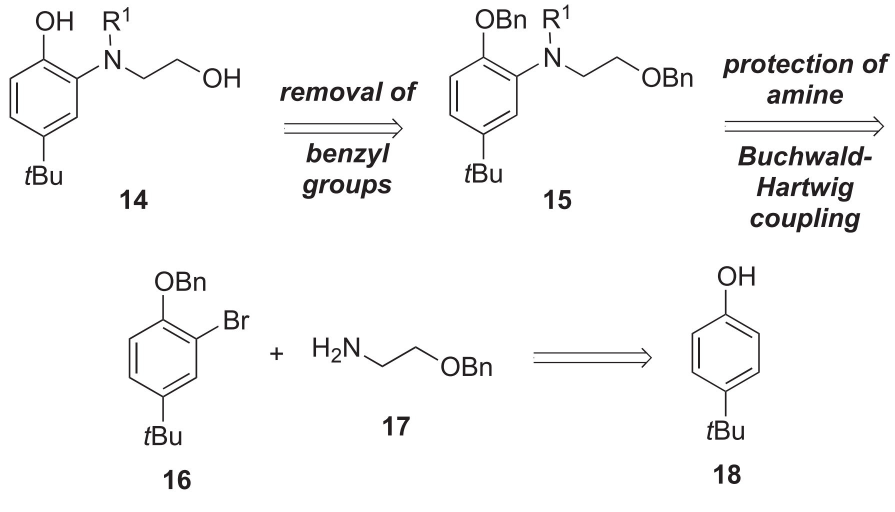
As shown in Scheme 4, two methods for synthesizing *ortho*-benzoquinone monohemiaminal **12** are possible; *O*-cyclization of **11** to form the spiro-ring by the reaction of the hydroxy group, and

N-cyclization of **13** to form the spiro-ring by the reaction of the protected-amine group. We were interested in the two methods and first examined *O*-cyclization of **11**, and herein we report the results of this study.



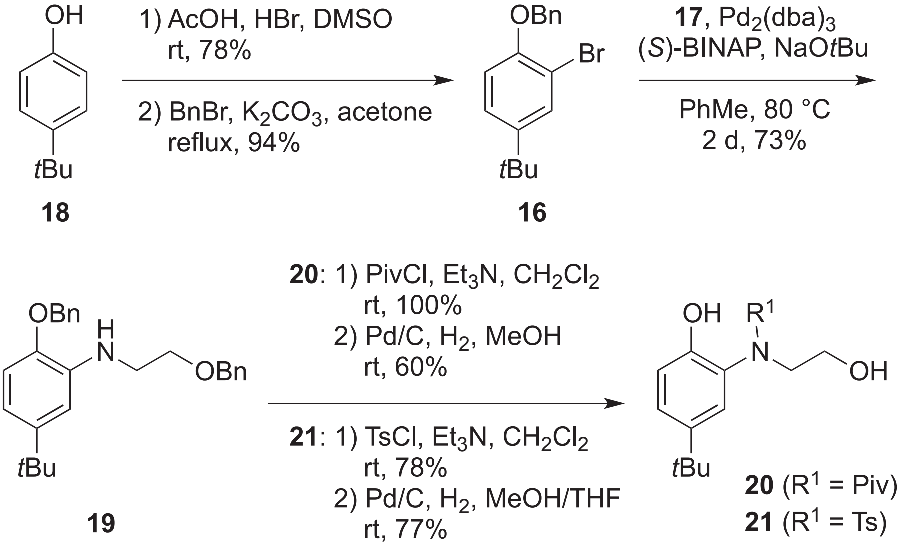
Scheme 4. Two methods for synthesizing *ortho*-benzoquinone monohemiaminals

Generally, MOBs dimerize easily by [4+2] cycloaddition owing to their high reactivity.[1] However, the dimerization of MOBs prepared by the oxidative dearomatization of phenols bearing a bulky or electron-donating substituent at the *para* position is known to be inhibited.[4b,14] Hence, in order to investigate the oxidative dearomatization/*O*-cyclization cascade, we introduced a *tert*-butyl group at the *para* position of the phenols to avoid the dimerization of the *ortho*-benzoquinone monohemiaminal products. Additionally, the amine in the substrates was protected as a bulky amide to prevent undesired side-reactions under the oxidative reaction conditions and to provide effective steric hindrance of one side of the diene moiety of the products for the subsequent stereoselective reactions.



Scheme 5. Plan for preparing achiral substrate for oxidative dearomatization/*O*-cyclization cascade

We planned to prepare the simple achiral compound **14** as shown in Scheme 5 to investigate the oxidative dearomatization/*O*-cyclization cascade. Compound **14** was expected to be prepared by debenzylation of **15**, which would be obtained via protection of the amino group of the product obtained by the Buchwald–Hartwig coupling[15] of **16** and **17**, which in turn would be prepared from commercially available **18**. Hence, the preparation of **14** was commenced with the bromination of **18**.



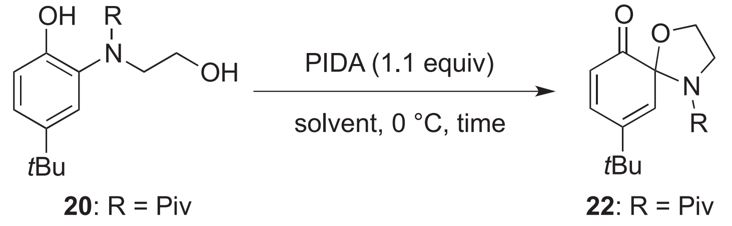
Scheme 6. Preparation of achiral substrates **20** and **21** for oxidative dearomatization/*O*-cyclization

The *ortho*-selective bromination[16] of **18** and subsequent benzylation afforded **16** (Scheme 6). The Buchwald–Hartwig coupling of **16** with **17**[17] afforded **19**, which then underwent *N*-protection with a pivaloyl and tosyl group and removal of the benzyl groups to afford **20** and **21**, respectively.

The results of the oxidative dearomatization/*O*-cyclization cascades of **20** and **21** are summarized in Table 1. The reaction of pivalamide **20** with PIDA in CH_2Cl_2 at 0 ºC afforded **22** in 44% yield (entry 1) while the yield of **23** from the corresponding reaction with tosylamide **21** was 31% (entry 2). Use of 2,2,2-trifluoroethanol (TFE)[18] as the solvent accelerated the reactions producing **22** and **23**, and their yields were improved to 95% (entry 3) and 99% (entry 4), respectively.

The reactions shown in Table 1 revealed that the oxidative dearomatization/*O*-cyclization cascade of **20** and **21** afforded the *ortho*-benzoquinone monohemiaminals **22** and **23** in high yield. Hence, we next investigated their reactivity (Table 4). The reactions of **22** and **23** with *n*-butyl vinyl ether gave no products even at 90 ºC and both compounds gradually decomposed, indicating that their Diels–Alder reactions with an electron-rich alkene would require harsh reaction conditions (entries 1 and 2). On the other hand, the reactions of **22** and **23** with an electron-deficient alkene, methyl vinyl ketone, afforded **24** (entry 3) and **25a** (entry 4) as single products, respectively. The reaction of **23** with *N*-phenylmaleimide also stereoselectively afforded **25b** (entry 5). The yield was excellent in the cases of entries 3-5 and their structural analysis by NOE studies revealed that their reactions stereoselectively took place at the sterically less-hindered side of **22** and **23** as depicted in Scheme 3.

Table 1. Oxidative dearomatization/*O*-cyclization cascade of **20** and **21**



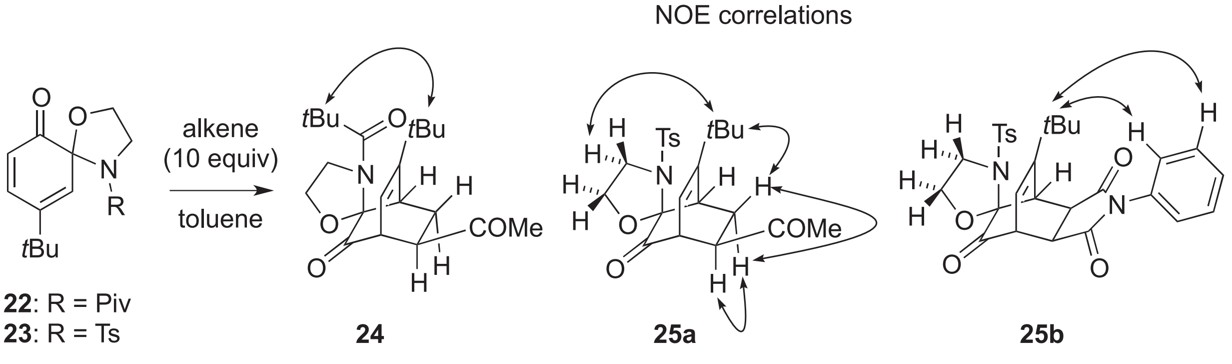
20: R = Piv
21: R = Ts

22: R = Piv
23: R = Ts

entry	substrate	solvent	time (min)	yield (%)^a
1	**20**	CH_2Cl_2	30	44 (**22**)
2	**21**	CH_2Cl_2	30	31 (**23**)
3	**20**	TFE	15	95 (**22**)
4	**21**	TFE	15	99 (**23**)

^{a}Isolated yield.

Table 2. Diels–Alder reactions of **22** and **23**, and NOE correlations observed in the NOESY spectra of **24**, **25a**, and **25b**



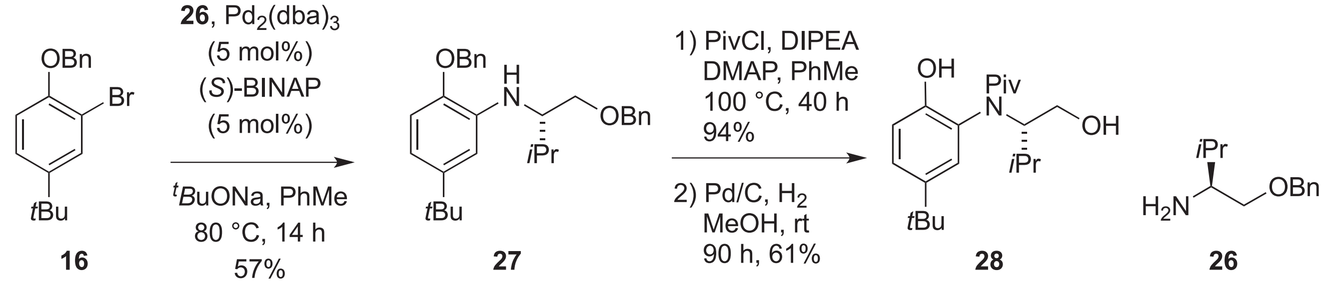
22: R = Piv
23: R = Ts

24 **25a** **25b**

entry	substrate	alkene	temp (°C)	time (h)	yield (%)^a
1^b	**22**	*n*-butyl vinyl ether	90	13	NR
2^b	**23**	*n*-butyl vinyl ether	90	13	NR
3^b	**22**	methyl vinyl ketone	130	48	81 (**24**)^c
4	**23**	methyl vinyl ketone	100	13	95 (**25a**)^c
5	**23**	*N*-phenylmaleimide	100	13	97 (**25b**)^c

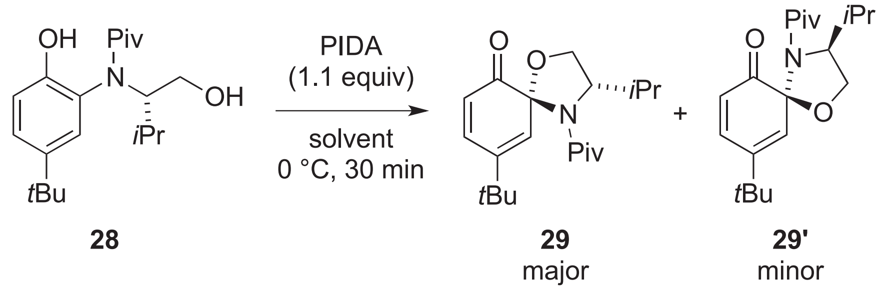
^{a}Isolated yield. ^{b}Reaction in a sealed tube. ^{c}Single isomer.

Next, cascade reactions of phenols bearing a chiral substituent were pursued. To examine the relationship between the stereoselectivity of the *O*-cyclization and structure of the chiral substituent, we prepared a substrate possessing a substituent with a chiral carbon center bearing a protected amino group (**28**).



Scheme 7. Preparation of **28**

Table 3. Oxidative dearomatization/*O*-cyclization cascade of **28**



entry	solvent	yield (%)[a]	dr (**29**:**29'**)[b]
1	TFE	57	4:1
2	TFE/CH_2Cl_2	42	3:1

[a]Isolated yield. [b]Determined by ^1H NMR analysis.

To prepare the substrate possessing a substituent with a chiral carbon center bearing amino group, we selected L-valinol as the substituent for the substrate (Scheme 7). The Buchwald–Hartwig coupling of **16** with L-valinol derivative **26**[17] afforded **27** in 57% yield. The reaction of **27** with pivaloyl chloride did not proceed at room temperature, probably due to the steric hindrance of the adjacent isopropyl group. However, reaction at 100 °C in toluene successfully afforded the product in 94% yield, which was converted to **28** by hydrogenolysis of the benzyl group. Unfortunately, all the attempted reactions of **27** with alkyl and aryl sulfonyl chlorides failed to afford the corresponding sulfonamides. Hence, compound **28** was used for the oxidative dearomatization/*O*-cyclization cascade.

The reaction of **28** with PIDA was carried out under the optimized conditions in Table 1 (Table 3). The *ortho*-benzoquinone monohemiaminal **29** was obtained in 57% yield as an inseparable mixture of diastereomers with a ratio of 4:1 (entry 1). The configuration of **29** was elucidated based on the NOE correlations observed in the NOESY spectrum of **29** (Figure 1). Both the yield and stereoselectivity decreased when a mixed solvent (TFE/CH_2Cl_2 = 1:1) was used (entry 2).

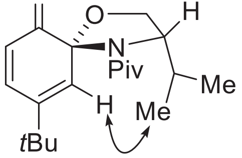
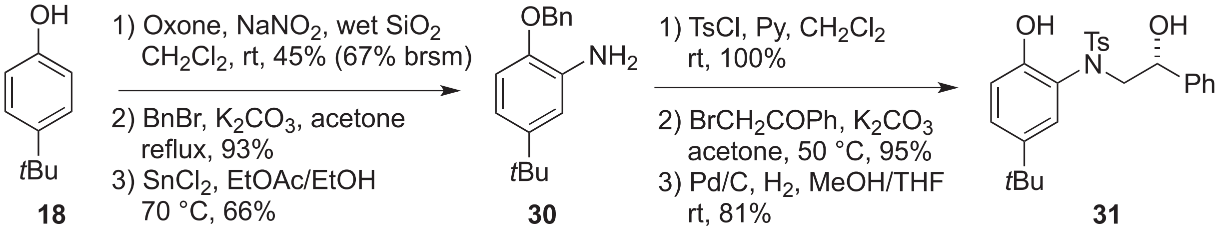
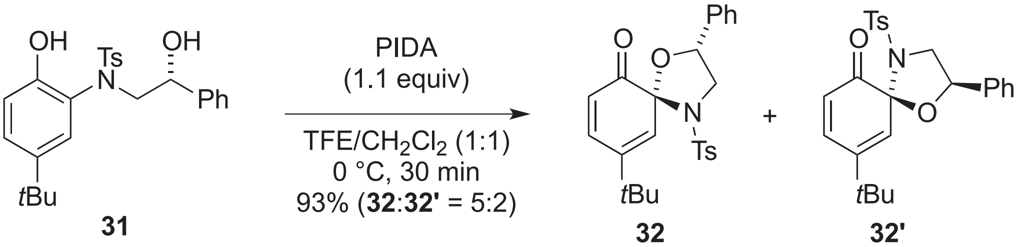


Figure 1. NOE correlation observed in the NOESY spectra of **29**



Scheme 8. Preparation of **31**



Scheme 9. Stereoselective oxidative dearomatization/*O*-cyclization cascade of **31**

We next prepared **31**, which possessed a substituent with a chiral carbon center bearing hydroxy group in order to investigate the selectivity in the oxidative dearomatization/*O*-cyclization cascade (Scheme 8). The preparation of **31** was commenced with the nitration[19] of commercially available **18**, followed by formation of the benzyl ether and reduction of the nitro group to afford **30**. Subsequent formation of the tosyl amide, *N*-alkylation with phenacyl bromide, and de-benzylation with concomitant reduction of the ketone under the catalytic hydrogenation conditions afforded **31**.

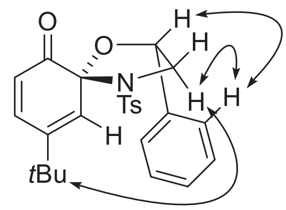
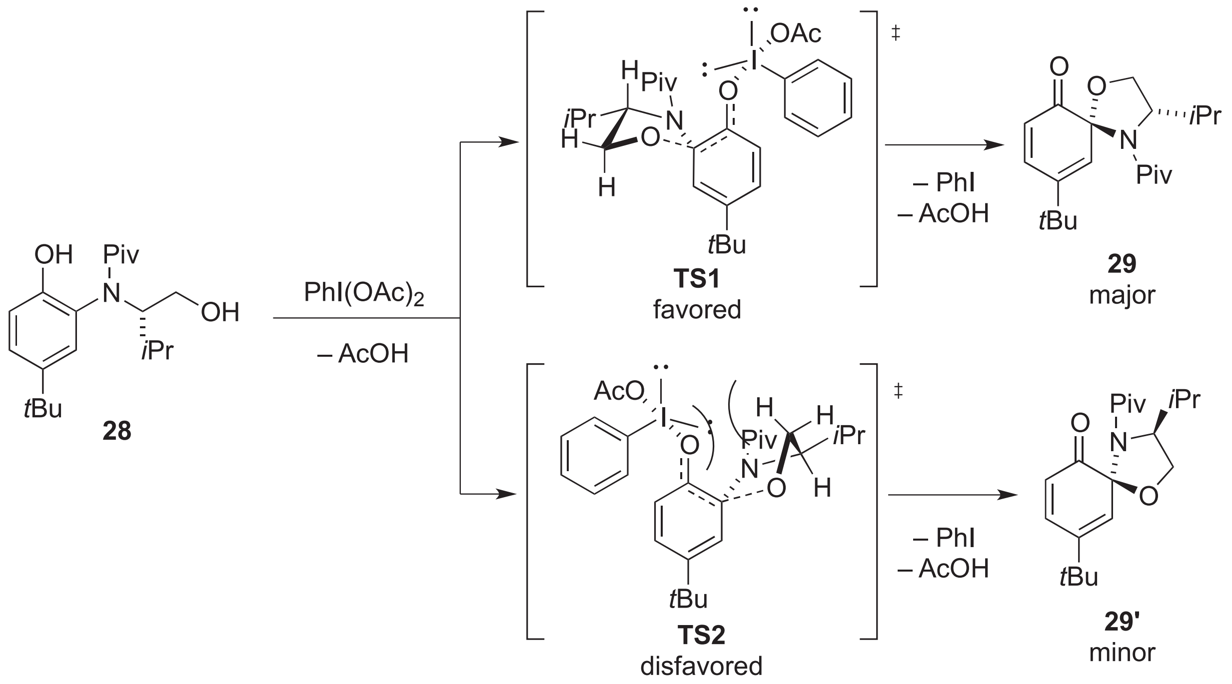


Figure 2. NOE correlations observed in the NOESY spectra of **32**

Because the solubility of **31** in TFE was low, the reaction of **31** with PIDA was carried out in the mixed solvent (TFE/CH$_2$Cl$_2$ = 1:1) (Scheme 9). The reaction proceeded smoothly to afford **32** and **32’** in 93% yield as an inseparable mixture with a ratio of 5:2, with **32** being the major product. The configuration of **37** was elucidated based on the NOE correlations observed in the NOESY spectrum of **32** (Figure 2).



Scheme 10. Proposed rationale for the stereoselective formation of **29**

Treatment of the mixture of products with PPTS in acetone at reflux temperature did not cause isomerization. Therefore, the oxidative dearomatization/*O*-cyclization cascades are kinetically controlled reactions. The stereoselectivity observed in the *O*-cyclization of **28** could be explained by transition-state models in Scheme 10. Based on molecular modeling, the energetically favorable transition states of the reaction of **28** could be **TS1** and **TS2**, which are envelope-forms with an equatorial isopropyl group. However, **TS2**, which leads to the formation of **29’**, would be unfavorable because of the steric strain between the pseudoaxial hydrogen atom of the methylene group and the oxygen lone pair of the phenol. Hence, **TS1** would be energetically more favorable, so that **29** was preferentially formed. The stereoselectivity observed in the reaction of **31** could be also explained by the same transition-state models as **TS1** and **TS2** in Scheme 10.

In summary, we found that oxidative dearomatization/*O*-cyclization cascades of phenols bearing an *ortho* substituent derived from an amino alcohol with PIDA afforded the corresponding *ortho*-benzoquinone monohemiaminals for the first time. The cascade reactions of substrates bearing a chiral substituent were found to proceed in a stereoselective manner. Because the oxidative dearomatization/*O*-cyclization cascade affording the *ortho*-benzoquinone monohemiaminal had never been reported, there is still ample scope for further investigation. Accordingly, further related studies are now underway, and the results will be reported in due course.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-400 spectrometer or a JEOL ECZ500R or a JEOL ECX500 spectrometer. Chemical shifts are reported in ppm with the residual solvent resonance as internal standard ($CDCl_3$ ^{1}H, $\delta = 7.26$ ppm, ^{13}C, $\delta = 77.0$ ppm; $(CD_3)_2SO$ ^{1}H, $\delta = 2.50$ ppm, ^{13}C, $\delta = 39.52$ ppm.) The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; sep, septet; br, broad. IR spectra were recorded on a JASCO FT/IR-8300 using an attenuated total reflectance (ATR). Melting points (mp) are uncorrected, recorded on a Yanaco micro melting point apparatus. Mass spectra analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and phosphomolybdic acid, basic potassium permanganate, *p*-anisaldehyde, or ninhydrin and heat as developing agents. Kanto Chemical Silica Gel 60N (spherical, neutral, 63-210 μm or 40-50 μm partial size) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). TLC R_fs of purified compounds were included. In general, reactions were carried out in dry solvents under an argon atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. THF and Et_2O were distilled from sodium/benzophenone ketyl, and CH_2Cl_2, benzene, and hexane from calcium hydride. DMSO were distilled from calcium hydride under reduced pressure. Toluene and EtOH were distilled from sodium. MeOH was distilled from magnesium and I_2. All reagents were purchased from Aldrich, TCI, Merck, or Kanto Chemical Co. Ltd.

2-Bromo-4-*tert*-butylphenol (16A). To a stirred solution of 4-*tert*-butylphenol **18** (5.00 g, 33.3 mmol) in AcOH (67 mL) and 48% aq. HBr (110 mL) was added DMSO (33 mL) dropwise.[16] After stirring at room temperature for 3 h, the reaction mixture was quenched with 5 M aqueous NaOH solution (150 mL) and saturated aqueous $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with Et_2O (200 mL × 3), and the combined organic layer was washed with brine (300 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 30/1) to afford **16A** (5.97 g, 78%) as a colorless oil. Spectroscopic analyses of **16A** were in agreement with previous literature report[20]: $R_f = 0.50$ (hexane/EtOAc = 4/1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 2.3, 8.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 5.35 (br s, 1H, -OH), 1.28 (s, 9H) ppm.

1-Benzyloxy-2-bromo-4-*tert*-butylbenzene (16). To a stirred solution of **16A** (5.31 g, 23.2 mmol) in acetone (33 mL) were added K_2CO_3 (6.41 g, 46.4 mmol) and benzyl bromide (3.3 mL, 27.8 mmol). After stirring at reflux for 3 h, the reaction mixture was quenched with 5 M aqueous HCl solution (30 mL). The aqueous layer was extracted with Et_2O (20 mL × 3), and the combined organic layer was washed with brine (50 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1) to afford **16** (6.92 g, 94%) as a colorless oil: $R_f = 0.68$ (hexane/EtOAc = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 2.3 Hz, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.22 (dd, J = 2.3, 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.13 (s, 2H), 1.28 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 145.5, 136.9, 130.6, 128.7, 128.0, 127.1, 125.3, 113.6, 112.2, 71.0, 34.3, 31.5 ppm; IR (ATR) ν_{max}: 2960, 2904, 1740, 1599, 1499, 1228, 1079, 880, 604, 582 cm^{-1}; HRMS (ESI) [$M+Na^+$] calcd for $C_{17}H_{19}OBrNa$: 341.0511, found 341.0506.

2-Benzyloxy-*N*-2-benzyloxyethyl-5-*tert*-butylaniline (19). To a stirred solution of **16** (2.30 g, 7.20 mmol) in toluene (45 mL) were added 2-phenylmethoxyethanamine **17**[17] (1.24 g, 8.19 mmol), sodium *tert*-butoxide (2.09 g, 21.7 mmol), $Pd_2(dba)_3$ (336 mg, 0.367 mmol), and (*S*)-BINAP (547 mg, 0.879 mmol). After stirring at 80 °C for 19 h, the reaction mixture was cooled to room temperature and then diluted with Et_2O (20 mL). The mixture was filtered through a Celite pad and the residue was washed with Et_2O for several times. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 30/1) to afford **19** (2.06 g, 73%) as a white solid: $R_f = 0.50$ (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 10H), 6.79-6.68 (m, 3H), 5.06 (s, 2H), 4.55 (s, 2H), 3.74 (t, J = 5.5 Hz, 2H), 3.40 (t, J = 5.5 Hz, 2H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 144.4, 138.3, 137.8, 137.5, 128.6, 128.5, 127.9, 127.7, 127.6, 113.2, 110.7, 108.3, 73.1, 70.6, 68.8, 43.7, 34.4, 31.7 ppm; IR (ATR) ν_{max}: 3386, 3063, 2966, 2859, 1604, 1451, 1391, 1213, 1035, 695, 650 cm^{-1}; HRMS (ESI) [$M+H^+$] calcd for $C_{26}H_{32}NO_2$: 390.2428, found 390.2419; mp 56.7 °C.

(*N*-2-Benzyloxy-5-*tert*-butylphenyl-*N*-2-benzyloxyethyl)pivalamide (20A). To a stirred solution of **19** (1.02 g, 2.63 mmol) in CH_2Cl_2 (25 mL) were added pivaloyl chloride (0.35 mL, 2.84 mmol) and triethylamine (0.50 mL, 3.59 mmol). The reaction mixture was stirred at room temperature for 2 h, and then, the mixture was quenched with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 20/1 to 6/1) to afford **20A** (1.24 g, 100%) as a white solid: $R_f = 0.50$ (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.43-7.23 (m, 12H), 7.09 (d, J = 8.7 Hz, 1H), 5.11 (d, J = 6.9 Hz, 2H), 4.38 (s, 2H), 4.21-4.14 (m, 1H), 3.61-3.53 (m, 1H), 3.50-3.43 (m, 1H), 3.14-3.05 (m, 1H), 1.19 (s, 9H), 0.90 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 152.5, 143.4, 138.6, 136.8, 132.1, 129.5, 128.7, 128.4, 128.0, 127.7, 127.5, 126.9, 125.7, 111.9, 73.0, 69.9, 67.8, 51.1, 40.9, 34.0, 31.4, 29.0 ppm; IR (ATR) ν_{max}: 2957, 2863, 1623, 1342, 1204, 1025, 744, 721, 541 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{31}H_{39}O_3NNa$: 496.2822, found 496.2811; mp 38.8 °C.

(*N*-5-*tert*-Butyl-2-hydroxyphenyl-*N*-2-hydroxyethyl)pivalamide (20). To a stirred solution of **20A** (1.24 g, 2.63 mmol) in MeOH (25 mL) was added palladium on activated carbon (250 mg, 20 wt%). The suspension was sparged with H_2 via a balloon and subsequently stirred under hydrogen atmosphere at room temperature for 2 days. Then, the reaction mixture was sparged with argon to remove excess hydrogen, diluted with EtOAc (20 mL), filtered through a Celite pad and the residue was washed with EtOAc for several times. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1) to afford **20** (462 mg, 60%) as a white solid: $R_f = 0.30$ (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.19 (dd, J = 2.3, 8.2 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 3.72 (br s, 1H), 3.53 (br s, 2H), 3.20 (br s, 1H), 1.23 (s, 9H), 0.92 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.5, 151.2, 143.4, 130.2, 127.1, 117.4, 59.8, 54.8, 41.3, 34.1, 31.5, 28.9 ppm; IR (ATR) ν_{max}: 3170, 2962, 2871, 1583, 1422, 1291, 1207, 823, 722 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{17}H_{27}O_3NNa$: 316.1883, found 316.1876; mp 155.4 °C.

***N*-2-Benzyloxy-5-*tert*-butylphenyl-*N*-2-benzyloxyethyl-4-methylbenzenesulfonamide (21A).** To a stirred solution of **19** (1.01 g, 2.59 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (0.5 mL, 3.59 mmol) and *p*-toluenesulfonyl chloride (555 mg, 2.91 mmol). The reaction mixture was stirred at room temperature for 17 h, and then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 20/1 to 10/1) to afford **21A** (1.09 g, 78%) as a white solid: $R_f = 0.50$ (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.49 (d, J = 8.2 Hz, 2H), 7.35-7.13 (m, 13H), 7.01 (d, J = 6.4 Hz, 1H), 7.00 (s, 1H), 4.89 (br s, 2H), 4.32 (s, 2H), 3.74 (br s, 2H), 3.45 (s, 2H), 2.29 (s, 3H), 1.15 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 143.8, 142.8, 138.2, 137.6, 136.7, 130.5, 129.1, 128.4, 127.7, 127.7, 127.6, 126.8, 126.3, 112.3, 73.2, 69.9, 69.0, 49.7, 34.1, 31.4, 21.6 ppm; IR (ATR) ν_{max}: 3057, 2959, 2855, 1598, 1341, 1146, 972, 732, 660, 543 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{33}H_{37}O_4NNaS$: 566.2336, found 566.2335; mp 85.2 °C.

***N*-5-*tert*-Butyl-2-hydroxyphenyl-*N*-2-hydroxyethyl-4-methylbenzenesulfonamide (21).** To a stirred solution of **21A** (1.09 g, 2.01 mmol) in MeOH (16 mL) and THF (4.0 mL) was added palladium on activated carbon (219 mg, 20 wt%). The suspension was sparged with hydrogen via a balloon and subsequently stirred under hydrogen atmosphere at room temperature for 2 days. Then, the reaction mixture was sparged with argon to remove excess hydrogen, diluted with EtOAc (10 mL), filtered through a Celite pad and the residue was washed with EtOAc for several times. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 6/1) to afford **21** (560 mg, 77%) as a white solid: R_f = 0.30 (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.16 (dd, J = 2.3, 8.2 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 3.53 (t, J = 6.4 Hz, 2H), 3.38 (t, J = 6.4 Hz, 2H), 2.39 (s, 3H), 1.10 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 144.1, 143.7, 135.2, 129.7, 128.1, 127.4, 125.1, 125.0, 117.2, 60.0, 54.2, 34.0, 31.2, 21.7 ppm; IR (ATR) ν_{max}: 3491, 3178, 2952, 2865, 1598, 1325, 1106, 813, 724, 534 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{19}H_{25}O_4NNaS$: 386.1397, found 386.1392; mp 120.9 °C.

(*R*)-9-*tert*-Butyl-4-pivaloyl-1-oxa-4-azaspiro[4.5]deca-7,9-dien-6-one (22) (Table 1, entry 3). To a stirred solution of **20** (20.8 mg, 0.0710 mmol) in TFE (1.7 mL) was added PIDA (25.8 mg, 0.0801 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 15 min. Then, the mixture was quenched with saturated aqueous $NaHCO_3$ solution (1.0 mL) and saturated aqueous $Na_2S_2O_3$ solution (1.0 mL), and the aqueous layer was extracted with CH_2Cl_2 (3.0 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 to 5/1) to afford a yellow solid. It was further purified by PTLC (hexane/EtOAc = 2/1) to afford **22** (19.6 mg, 95%) as a pale yellow solid: R_f = 0.30 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (dd, J = 2.3, 10.1 Hz, 1H), 6.13 (d, J = 10.1 Hz, 1H), 5.72 (d, J = 2.3 Hz, 1H), 4.48-4.41 (m, 1H), 4.22-4.12 (m, 2H), 3.83-3.75 (m, 1H), 1.25 (s, 9H), 1.15 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 175.7, 145.5, 140.3, 127.6, 125.4, 87.1, 66.4, 46.6, 38.5, 34.3, 28.6, 27.0 ppm; IR (ATR) ν_{max}: 2962, 1678, 1618, 1363, 1136, 824 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{17}H_{25}O_3NNa$: 314.1727, found 314.1726; mp 72.7 °C.

9-*tert*-Butyl-4-tosyl-1-oxa-4-azaspiro[4.5]deca-7,9-dien-6-one (23) (Table 1, entry 4). To a stirred solution of **21** (26.6 mg, 0.0732 mmol) in TFE (1.83 mL) was added PIDA (28.5 mg, 0.0885 mmol) at

0 °C and the reaction mixture was stirred at 0 °C for 15 min. Then, the mixture was quenched with saturated aqueous $NaHCO_3$ solution (1.0 mL) and saturated aqueous $Na_2S_2O_3$ solution (1.0 mL), and the aqueous layer was extracted with CH_2Cl_2 (3.0 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 to 5/1) to afford a yellow solid. It was further purified by PTLC (hexane/EtOAc = 2/1) to afford **23** (26.3 mg, 99%) as a pale yellow solid: $R_f = 0.50$ (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.07 (dd, J = 2.3, 10.5 Hz, 1H), 6.06 (d, J = 10.5 Hz, 1H), 5.75 (d, J = 2.3 Hz, 1H), 4.45-4.40 (m, 1H), 4.18-4.14 (m, 1H), 3.87-3.82 (m, 1H), 3.67-3.61 (m, 1H), 2.43 (s, 3H), 1.58 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 146.4, 143.8, 141.1, 137.2, 129.6, 127.8, 127.5, 124.7, 86.0, 65.8, 46.8, 34.5, 28.2, 21.6 ppm; IR (ATR) ν_{max}: 2954, 1682, 1151, 994, 825, 547 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{19}H_{23}O_4NNaS$: 384.124, found 384.124; mp 104.9 °C.

(1*R,2*R**,4*R**,8*R**)-8-Acetyl-6-*tert*-butyl-3'-pivaloylspiro[bicyclo[2.2.2]octane-2,2'-oxazolidin]-5-en-3-one (24).** To a stirred solution of **22** (22.2 mg, 0.0762 mmol) in toluene (0.76 mL) was added methyl vinyl ketone (0.062 mL, 0.761 mmol) and the reaction mixture was stirred at 130 °C in a sealed tube for 48 h. After the reaction was complete, the mixture was cooled to room temperature and the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1 to 2/1) to afford **24** as a white solid (22.2 mg, 81%): $R_f = 0.13$ (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, J = 2.3, 6.4 Hz, 1H), 4.18-4.08 (m, 3H), 3.68 (dd, J = 1.8, 6.4 Hz, 1H), 3.59-3.49 (m, 1H), 3.00 (ddd, J = 1.8, 5.5, 9.6 Hz, 1H), 2.97 (dd, J = 2.3, 5.5 Hz, 1H), 2.17 (s, 3H), 2.16-2.11 (m, 1H), 1.76 (ddd, J = 2.8, 5.5, 12.8 Hz, 1H), 1.20 (s, 9H), 1.01 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 202.9, 174.7, 149.7, 118.4, 88.9, 66.2, 50.0, 49.8, 46.5, 42.5, 38.7, 34.6, 28.4, 28.0, 27.5, 23.8 ppm; IR (ATR) ν_{max}: 2959, 2892, 1740, 1703, 1640, 1475, 1361, 1140, 785 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{21}H_{31}O_4NNa$: 384.2145, found 384.2147; mp 185.2 °C.

(1*R,2*R**,4*R**,8*R**)-8-Acetyl-6-*tert*-butyl-3'-tosylspiro[bicyclo[2.2.2]octane-2,2'-oxazolidin]-5-en-3-one (25a).** To a stirred solution of **23** (30.2 mg, 0.0836 mmol) in toluene (0.84 mL) was added methyl vinyl ketone (0.070 mL, 0.859 mmol) and the reaction mixture was stirred at 100 °C with a reflux condenser for 13 h. After the reaction was complete, the mixture was cooled to room temperature and the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1) to afford **25a** as a white solid (34.3 mg, 95%): $R_f = 0.51$ (hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 5.90 (dd, J = 2.3, 6.4 Hz, 1H), 3.94-3.88 (m, 1H), 3.72 (dd, J = 2.3, 6.4 Hz, 1H), 3.64-3.59 (m, 1H), 3.59-3.53 (m, 1H), 3.52-3.43 (m, 1H), 3.07 (dd, J = 2.3, 5.5 Hz, 1H), 2.96 (ddd, J = 2.3, 4.6, 9.2 Hz, 1H), 2.42 (s, 3H), 2.19 (s, 3H), 2.07-1.99 (m, 1H), 1.96-1.89 (m, 1H), 1.17 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 204.2, 152.8, 144.0, 135.5, 129.6, 128.8, 116.2, 92.0, 65.1, 50.7, 50.0, 46.4, 43.9, 35.1, 28.3, 28.2, 22.1, 21.7 ppm; IR (ATR) ν_{max}: 2966, 2892, 1748, 1708, 1466, 1360, 1158, 1002, 815, 586 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{23}H_{29}O_5NNaS$: 454.1659, found 454.1659; mp 150.3 °C.

(2*R,3a'*R**,4'*R**,7'*R**,7a'*S**)-5'-*tert*-Butyl-2'-phenyl-3-tosyl-3a',4',7',7a'-tetrahydro-1'H-spiro[oxazolidine-2,9'-[4,7]ethanoisoindole]-1',3',8'(2'H)-trione (25b).** To a stirred solution of **23** (31.3 mg, 0.0866 mmol) in toluene (0.90 mL) was added *N*-phenylmaleimide (0.139 g, 0.804 mmol) and the reaction mixture was stirred at 100 °C with a reflux condenser for 13 h. After the reaction was completed, the mixture was cooled to room temperature and the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1) to afford **25b** as a white solid (45.0 mg, 97%): R_f = 0.46 (hexane/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.49-7.44 (m, 2H), 7.42-7.37 (m, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.24-7.20 (m, 2H), 6.27 (dd, J = 2.3, 6.4 Hz, 1H), 4.05-3.96 (m, 2H), 3.77-3.69 (m, 1H), 3.65-3.62 (m, 1H), 3.61-3.48 (m, 3H), 3.35 (dd, J = 3.2, 8.7 Hz, 1H), 2.44 (s, 3H), 1.16 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 176.0, 174.6, 150.5, 144.3, 135.1, 131.5, 129.6, 129.2, 128.8, 128.7, 126.1, 119.5, 90.6, 65.5, 47.8, 46.4, 46.3, 43.6, 39.5, 34.4, 28.9, 21.5 ppm; IR (ATR) ν_{max}: 2959, 2885, 1755, 1715, 1380, 1347, 1160, 1048, 813, 669, 579 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{29}H_{30}O_6N_2NaS$: 557.1717, found 557.1717; mp 307.9 °C.

(*S*)-2-Benzyloxy-*N*-1-benzyloxy-3-methylbutan-2-yl-5-*tert*-butylaniline (27). To a stirred solution of **16** (2.95 g, 9.24 mmol) in toluene (15 mL) were added (*S*)-1-benzyloxy-3-methylbutan-2-amine **26**[17] (1.95 g, 10.1 mmol) in toluene (15 mL), sodium *tert*-butoxide (2.67 g, 27.8 mmol), $Pd_2(dba)_3$ (421 mg, 0.460 mmol), and (*S*)-BINAP (692 mg, 1.11 mmol). After stirring at 90 °C for 14 h, the reaction mixture was cooled to room temperature and then diluted with Et_2O (20 mL). The solution was filtered through a Celite pad and the residue was washed with Et_2O for several times. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 200/1) to afford **27** (2.28 g, 57%) as a yellow oil: R_f = 0.60 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43-7.25 (m, 10H), 6.79 (d, J = 8.7 Hz, 1H), 6.64 (d, J = 2.3 Hz, 1H), 6.49 (dd, J = 2.3, 8.7 Hz, 1H), 5.07 (s, 2H), 4.50-4.42 (m, 3H), 3.52 (dd, J = 4.6, 10.0 Hz, 1H), 3.49 (dd, J = 4.6, 10.0 Hz, 1H), 3.42-3.36 (m, 1H), 2.01-1.93 (m, 1H), 1.21 (s, 9H), 0.94 (d, J = 5.5 Hz, 3H), 0.92 (d, J = 5.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 144.3, 138.6, 138.0, 137.8, 128.7, 128.5, 127.9, 127.7, 127.6, 127.4, 112.5, 111.1, 108.5, 73.5, 70.8, 70.5, 58.2, 34.5, 31.8, 29.9, 19.8, 18.4 ppm; IR (ATR) ν_{max}: 3432, 3032, 2956, 2866, 1593, 1453, 1208, 1101, 732, 647 cm^{-1}; HRMS (ESI) [M+H$^+$] calcd for $C_{29}H_{38}O_2N$: 432.2897, found 432.2895; $[\alpha]_D^{23}$ –29.7 (*c* 0.58, $CHCl_3$).

((*S*)-*N*-1-Benzyloxy-3-methylbutan-2-yl-*N*-2-benzyloxy-5-*tert*-butylphenyl)pivalamide (28A). To a stirred solution of **27** (692 mg, 1.60 mmol) in toluene (5.3 mL) were added DIPEA (1.4 mL, 8.04 mmol), DMAP (196 mg, 1.60 mmol) and pivaloyl chloride (0.96 mL, 7.80 mmol). After stirring at 100 °C for 40 h, the reaction mixture was cooled to room temperature and then quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (10 mL × 3), and the combined organic layer was washed with saturated aqueous NH_4Cl solution (30 mL × 1) and brine (30 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 20/1) to afford product **28A** (773 mg, 94%) as a yellow oil: $R_f = 0.60$ (hexane/EtOAc = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of two rotamers) δ 7.44-7.27 (m, 6H), 7.25-7.16 (m, 5H), 7.05-6.94 (m, 1H), 6.85-6.78 (m, 1H), 5.08-4.93 (m, 2H), 4.31-3.49 (m, 5H), 2.42-2.18 (m, 1H), 1.26 (s, 6H), 1.26 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.00 (s, 9H), 0.91(d, J = 6.9 Hz, 1H), 0.84 (d, J = 6.9 Hz, 2H) ppms; ^{13}C NMR (125 MHz, DMSO-d_6, mixture of two rotamers) δ 178.5, 177.8, 154.2, 153.4, 142.9, 142.7, 139.0, 138.9, 137.2 (2), 129.9, 129.0, 128.9, 128.6, 128.5 (2), 128.4, 128.2, 128.1, 127.8, 127.6, 127.5 (2), 126.2, 125.8, 112.6, 112.4, 79.7 (2), 72.3, 72.0, 71.2 (2), 70.2, 69.8, 41.7, 41.4, 34.2, 34.1, 31.6 (2), 29.6 (2), 29.4 (2), 29.2 (2), 22.7, 21.0, 20.6, 20.1 ppm; IR (ATR) ν_{max}: 2959, 2869, 1630, 1454, 1287, 1025, 732, 663, 543 cm^{-1}; HRMS (ESI) $[M+H^+]$ calcd for $C_{34}H_{46}O_3N$: 516.3472, found 516.3483; $[\alpha]_D^{26}$ +0.4 (c1.04, $CHCl_3$).

((*S*)-*N*-5-*tert*-Butyl-2-hydroxyphenyl-*N*-1-hydroxy-3-methylbutan-2-yl)pivalamide (28). To a stirred solution of **28A** (621 mg, 1.20 mmol) in MeOH (4.0 mL) was added palladium on activated carbon (124 mg, 20 wt%). The suspension was sparged with hydrogen via a balloon and subsequently stirred under hydrogen atmosphere at room temperature for 2 days. Then, the reaction mixture was sparged with argon to remove excess hydrogen, diluted with EtOAc (10 mL), filtered through a Celite pad and the residue was washed with EtOAc for several times. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (hexane/EtOAc = 20/1 to 10/1) to afford **28** (247 mg, 61%) as a yellow oil: $R_f = 0.13$ (hexane/EtOAc = 4/1); ^{1}H NMR (500 MHz, DMSO-d_6, observed as a 3:2 mixture of two rotamers) δ 7.27 (dd, J = 2.3, 8.7 Hz, 0.4 H), 7.22-7.19 (m, 1.2 H), 7.04 (d, J = 2.3 Hz, 0.4 H), 6.83 (d, J = 8.7 Hz, 0.4 H), 6.78-6.76 (m, 0.6 H), 4.62-4.56 (m, 0.4 H), 3.99 (t, J = 10.1 Hz, 0.6 H), 3.69-3.61 (m, 1H), 3.03 (t, J = 10.5 Hz, 0.4 H), 2.86 (dt, J = 4.1, 9.6 Hz, 0.6 H), 2.43-2.32 (m, 0.6 H), 1.65-1.56 (m, 0.4 H), 1.23 (s, 9H), 1.06-1.02 (m, 3H), 0.92 (s, 3.6 H), 0.91 (s, 5.4 H), 0.84-0.81 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, observed as a mixture of two rotamers) for the major rotamer: δ 182.6, 154.0, 142.3, 129.3, 127.2, 124.4, 117.8, 63.5, 61.0, 42.0, 34.0, 31.4, 29.0, 27.5, 21.5, 19.5 ppm; for the minor rotamer: δ 180.1, 151.0, 141.0, 128.3, 126.6, 131.8, 117.4, 75.3, 61.0, 41.5, 34.1, 31.5, 29.5, 28.9, 21.7, 21.4 ppm; IR (ATR) ν_{max}: 3380, 2959, 2871, 1604, 1287, 1191, 1013, 720, 583 cm^{-1}; HRMS (ESI) $[M+Na^+]$ calcd for $C_{20}H_{33}O_3NNa$: 358.2353, found 358.2352; $[\alpha]_D^{26}$ –63.4 (c 0.62, $CHCl_3$).

(3*S*,5*R*)- and (3*S*,5*S*)-9-*tert*-Butyl-3-isopropyl-4-pivaloyl-1-oxa-4-azaspiro[4.5]deca-7,9-dien-6-one (29 and 29') (Table 3, entry 1). To a stirred solution of **28** (27.0 mg, 0.0805 mmol) in TFE (2.0 mL) was added PIDA (30.5 mg, 0.0947 mmol) and the reaction mixture was stirred at 0 °C for 30 min. Then, the mixture was quenched with saturated aqueous $NaHCO_3$ solution (1.0 mL) and saturated aqueous $Na_2S_2O_3$ solution (1.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3.0 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1) to afford a mixture of two diastereomers (**29** and **29'**) as a yellow oil (15.4 mg, 57%, **29**:**29'** = 4:1, determined by ^{1}H NMR analysis): R_f = 0.70 (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$, 4:1 mixture of diastereomers) δ 7.05 (dd, J = 2.3, 10.5 Hz, 0.8 H), 7.00 (dd, J = 2.3, 10.5 Hz, 0.2 H), 6.15 (d, J = 10.5 Hz, 0.2 H), 6.10 (d, J = 10.5 Hz, 0.8 H), 5.91 (d, J = 2.3 Hz, 0.8 H), 5.79 (s, 0.2 H), 4.39 (dd, J = 6.4, 8.2 Hz, 0.8 H), 4.27-4.24 (m, 0.8 H), 4.23-4.10 (m, 0.6 H), 3.95 (d, J = 8.7 Hz, 0.8 H), 2.39-2.31 (m, 0.2 H), 2.29-2.20 (m, 0.8 H), 1.27 (s, 7.2 H), 1.24 (s, 1.8 H), 1.17 (s, 7.2 H), 1.13 (s, 1.8 H), 1.05 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) for the major isomer 32: δ 195.8, 177.8, 145.1, 140.1, 128.0, 125.7, 88.5, 65.8, 61.8, 40.0, 34.3, 31.7, 28.6, 28.2, 20.2, 17.4 ppm; IR (ATR) ν_{max}: 2961, 2873, 1751, 1608, 1364, 1115, 816, 733, 560 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{20}H_{31}O_3NNa$: 356.2196, found 356.2193.

4-*tert*-Butyl-2-nitrophenol (30A). To a stirred solution of 4-*tert*-butylphenol **18** (2.89 g, 19.2 mmol) in CH_2Cl_2 (64 mL) was added SiO_2 (1.93 g), H_2O (1.9 mL), Oxone® (5.90 g, 9.60 mmol) and $NaNO_2$ (1.33 g, 19.3 mmol).[19] After stirred for 30 min at room temperature, the reaction mixture was diluted with CH_2Cl_2 (20 mL), filtered through a Celite pad and the residue was washed with CH_2Cl_2 for several times. The combined filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/EtOAc = 50/1 to 20/1) to afford **30A** (1.67 g, 45%) as a white solid. 4-*tert*-butylphenol **18** was also recovered (975 mg, 34% recovered). Spectroscopic analyses of **30A** were in agreement with previous literature report.[21]

1-Benzyloxy-4-*tert*-butyl-2-nitrobenzene (30B). To a stirred solution of **30A** (1.67 g, 8.57 mmol) in acetone (30 mL) were added K_2CO_3 (2.37 g, 17.2 mmol) and benzyl bromide (1.0 mL, 8.59 mmol). The reaction mixture was stirred at reflux temperature for 2 days and then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (10 mL × 3), and the combined organic layer was washed with brine (30 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 20/1) to afford **30B** (2.26 g, 93%) as a pale yellow solid: R_f = 0.50 (hexane/EtOAc = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 1.8 Hz, 1H), 7.51 (dd, J = 1.8, 8.7 Hz, 1H), 7.47-7.31 (m, 5H), 7.04 (d, J = 8.7 Hz, 1H), 5.22 (s, 2H), 1.31 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 144.2, 139.9, 135.9, 131.2, 128.8, 128.2, 127.0, 122.6, 115.0, 71.3, 34.4, 31.3 ppm; IR (ATR) ν_{max}: 2960, 2868, 1619, 1521, 1478, 1254, 1015, 842, 736, 692 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{17}H_{19}O_3NNa$: 308.1257, found 308.125; mp 48.7 °C.

2-Benzyloxy-5-*tert*-butylaniline (30). To a stirred solution of **30B** (3.14 g, 11.0 mmol) in EtOAc (18 mL) and EtOH (18 mL) was added $SnCl_2$ (5.23 g, 27.6 mmol) and the reaction mixture was stirred at room temperature for 5 h. Then, the mixture was warmed up to 70 °C and stirred at 70 °C for 20 h. After the reaction was complete, the mixture was cooled to 0 °C and quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (30 mL × 3), and the combined organic layer was washed with brine (100 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 30/1) to afford **30** (1.84 g, 66%) as a yellow solid: R_f = 0.50 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 2.8 Hz, 1H), 7.51 (dd, J = 2.8, 8.7 Hz, 1H), 7.47-7.30 (m, 5H), 7.04 (d, J = 8.7 Hz, 1H), 5.22 (s, 2H), 1.32 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 144.3, 139.8, 136.0, 131.2, 128.8, 128.2, 127.0, 122.6, 115.0, 71.3, 34.4, 31.3 ppm; IR (ATR) ν_{max}: 2960, 2868, 1619, 1462, 1348, 1264, 1015, 823, 735, 692 cm^{-1}; HRMS (ESI) [M+H$^+$] calcd for $C_{17}H_{22}ON$: 256.1696, found 256.169; mp 47.3 °C.

***N*-2-Benzyloxy-5-*tert*-butylphenyl-4-methylbenzenesulfonamide (31A).** To a stirred solution of **30** (981 mg, 3.84 mmol) in CH_2Cl_2 (20 mL) were added pyridine (1.9 mL, 23.0 mmol) and *p*-toluenesulfonyl chloride (872 mg, 4.57 mmol) and the reaction mixture was stirred at room temperature for 2.5 h. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3), and the combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 50/1 to 10/1) to afford **31A** (1.57 g, 100%) as a white solid: R_f = 0.25 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 2.5 Hz, 1H), 7.50 (dd, J = 2.5 Hz, 8.7 Hz, 1H), 7.47-7.31 (m, 7H), 7.04 (d, J = 8.7 Hz, 1H), 5.22 (s, 2H), 2.50 (s, 3H), 1.31 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 146.9, 144.3, 141.8, 139.8, 136.0, 131.2, 130.3, 128.8, 128.2, 127.1, 127.1, 122.6, 115.0, 71.3, 34.4, 31.3, 21.9 ppm; IR (ATR) ν_{max}: 3256, 3213, 2949, 2865, 1598, 1330, 1164, 1090, 809, 695, 680, 543 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{24}H_{27}O_3NNaS$: 432.1604, found 432.1608; mp 88.6 °C.

***N*-2-Benzyloxy-5-*tert*-butylphenyl-4-methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (31B).** To a stirred solution of **31A** (1.56 g, 3.82 mmol) in acetone (20 mL) were added K_2CO_3 (797 mg, 5.77 mmol) and phenacyl bromide (798 mg, 4.01 mmol) and the reaction mixture was stirred at room temperature for 30 min. Then, the mixture was warmed up to 50 °C and stirred at 50 °C for 1 h. After the reaction was complete, the mixture was cooled to room temperature and quenched with H_2O (20 mL). The aqueous layer was extracted with EtOAc (30 mL × 3), and the combined organic layer was washed with brine (100 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 9/1) to afford **31B** (1.92 g, 95%) as a white solid: R_f = 0.25 (hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 1.4, 8.2 Hz, 2H), 7.60-7.52 (m, 3H), 7.44-7.30 (m, 5H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.22-7.17 (m, 3H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.09 (s, 2H), 4.80 (s, 2H), 2.36 (s, 3H), 1.17 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 153.0, 143.8, 143.1, 137.3, 136.7, 135.5, 133.4, 131.5, 129.2, 128.7, 128.5, 128.3, 127.9, 127.1, 126.4, 126.3, 112.2, 70.2, 56.2, 34.1, 31.3, 21.7 ppm; IR (ATR) ν_{max}: 2961, 2868, 1702, 1605, 1328, 1217, 1153, 985, 744, 543 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{32}H_{33}O_4NNaS$: 550.2023, found 550.2012; mp 136.4 °C.

(*R)-*N*-5-*tert*-Butyl-2-hydroxyphenyl-*N*-2-hydroxy-2-phenylethyl-4-methylbenzenesulfonamide (31).** To a stirred solution of **31B** (252 mg, 0.477 mmol) in MeOH (4.8 mL) and THF (2.4 mL) was added palladium on activated carbon (25.0 mg, 10 wt%). The suspension was sparged with hydrogen via a balloon and subsequently stirred under hydrogen at room temperature for 20 h. Then, the reaction mixture was sparged with argon to remove excess hydrogen, diluted with EtOAc (5.0 mL), filtered through a Celite pad and the residue was washed with EtOAc for several times. The combined filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/EtOAc = 10/1) to afford **31** (170 mg, 81%) as a white solid: R$_f$ = 0.30 (hexane/EtOAc = 2/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (br s, 1H, -OH), 7.50-7.20 (m, 9H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.58 (s, 1H), 5.56 (br s, 1H, -OH), 4.60 (br s, 1H), 3.74-3.53 (m, 2H), 2.37 (s, 3H), 1.09 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 143.7, 140.6, 136.1, 129.7, 128.8, 128.4, 128.1, 127.5, 126.2, 124.7, 117.2, 74.4, 70.9, 61.1, 59.0, 34.0, 31.3, 21.7 ppm; IR (ATR) ν_{max}: 3556, 3265, 2951, 2860, 1597, 1506, 1345, 1160, 1047, 812, 556 cm^{-1}; HRMS (ESI) [M+Na$^+$] calcd for $C_{25}H_{29}O_4NNaS$: 462.171, found 462.1703; mp 143.7 °C.

(2*R,5*S**)- and (2*R**,5*R**)-9-*tert*-Butyl-2-phenyl-4-tosyl-1-oxa-4-azaspiro[4.5]deca-7,9-dien-6-one (32 and 32’).** To a stirred solution of **31** (114 mg, 0.258 mmol) in TFE (3.2 mL) and CH_2Cl_2 (3.2 mL) was added $PhI(OAc)_2$ (93.7 mg, 0.291 mmol) and the reaction mixture was stirred at 0 °C for 30 min. Then, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (3.0 mL) and saturated aqueous $Na_2S_2O_3$ solution (3.0 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10/1) to afford an inseparable mixture of two diastereomers **32** and **32’** (106 mg, 93%, **32**:**32’** = 5:2, determined by ^{1}H NMR analysis) as a yellow solid: R$_f$ = 0.60 (hexane/EtOAc = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) for **32**: δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.36-7.27 (m, 7H), 7.09 (dd, *J* = 2.3, 10.1 Hz, 1H), 6.12 (d, *J* = 10.1 Hz, 1H), 5.83 (d, *J* = 1.8 Hz, 1H), 5.71 (dd, *J* = 6.4, 8.7 Hz, 1H), 4.14 (dd, *J* = 6.4, 8.2 Hz, 1H), 3.42 (dd, *J* = 8.2, 8.7 Hz, 1H), 2.44 (s, 3H), 1.17 (s, 9H) ppm; for **32’**: δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.43-7.39 (m, 2H), 7.35-7.27 (m, 5H), 7.12 (dd, *J* = 2.3, 10.5 Hz, 1H), 6.09 (d, *J* = 10.5 Hz, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 5.34 (dd, *J* = 5.5, 9.6 Hz, 1H), 4.06 (dd, *J* = 5.5, 8.2 Hz, 1H), 3.71 (dd, *J* = 8.2, 9.6 Hz, 1H), 2.43 (s, 3H), 1.18 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) for

32: δ 197.2, 146.6, 143.9, 141.1, 137.2, 136.7, 129.7, 129.0, 128.8, 127.8, 127.5, 126.9, 124.8, 127.8, 127.5, 126.9, 124.8, 86.7, 78.5, 77.3, 53.3, 34.6, 28.2 ppm; for **32'**: δ 196.6, 145.2, 144.0, 141.8, 136.5, 136.4, 129.6, 129.1, 129.1, 128.7, 127.6, 127.4, 124.7, 86.0, 80.4, 54.9, 34.5, 28.2, 21.7 ppm; IR (ATR) ν_{max}: 2964, 2872, 1686, 1649, 1597, 1466, 1346, 1156, 1009, 699 cm^{-1}; HRMS (ESI) [$M+Na^+$] calcd for $C_{25}H_{27}O_4NNaS$: 460.1553, found 460.1551.

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