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Synthesis of *anti* Tricyclic Morpholine Derivatives through Iodine(III)-Mediated Intramolecular Umpolung Cycloaddition of Olefins

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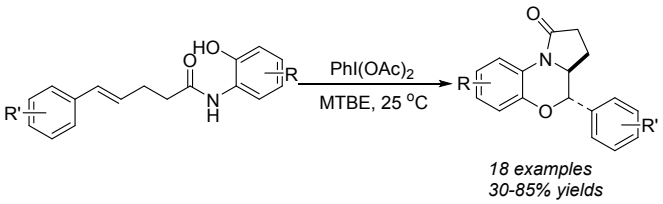


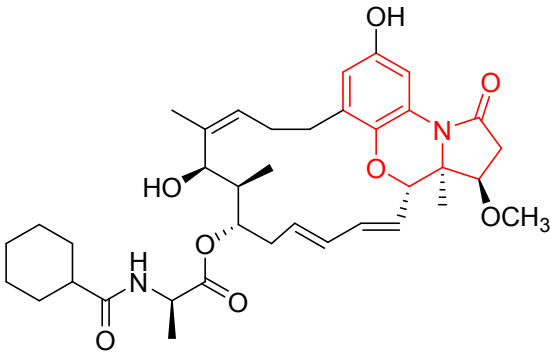
ABSTRACT

A (diacetoxyiodo)benzene-mediated intramolecular cycloaddition of olefins to construct tricyclic morpholines is presented. A series of substituted tricyclic morpholines were obtained in one-step simple operation under mild conditions, and the NMR studies were employed to see the interaction of reactants. The studies on stereochemistry showed that transformation of *Z*-alkene was inhibited, which is interpreted by DFT calculations on *Z*- and *E*-transition state models, and only *E*-alkene resulted in *anti* cycloaddition product, which is testified by a single-crystal X-ray diffraction analysis.

INTRODUCTION

Morpholine is the fundamental six-membered heterocycle and acts as an important motif in natural products, drugs, and advanced materials.[1] Particularly, polycyclic morpholine structures widely exist in pharmaceuticals and natural products,[2] such as ofloxacin, pazufloxacin, levofloxacin carboxylic acid, pollenopyrroside A, shensongine B, and acortatarin B.[3] Therefore, this versatile framework has been attracting much attention in the field of synthetic organic chemistry.[4] Benzoxazomycin with tricycle unit was assessed approximately in five

times more likely to possess drug activity than the former natural products (Figure 1).[5] Strategies that allow multiple transformations in one-pot process without excessive prefunctionalization of the substrates to afford substituted tricyclic morpholines as in benzoxazomycin are especially fascinating.



benzoxazomycin

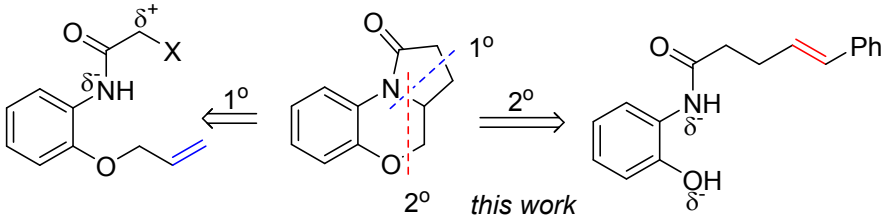
Figure 1. Biologically relevant tricyclic morpholine.

With regarding to development of the synthetic methodology, the acquisition of tricyclic morpholine derivatives in benzoxazomycin has been reported in one-pot process through intramolecular aminoalkylation of olefins (1°, Scheme 1). Li utilized BF_3-OEt_2 to promote 9-endo cyclization of various *N*-(hex-5-enyl)-2-iodoalkanamides through radical pathway[6] and Yang adopted a Pd-catalyzed intramolecular aminoalkylation of unactivated alkenes.[7] Both works showed that partially positive carbon and negative nitrogen were added reasonably to two ends of olefin, according to the polar principle of carbon-carbon double bond electrophilic addition.

Hypervalent iodine compounds possess reactivity similar to transition metals,[8] and they have been used successfully as effective umpolung reagents in the transformation of alkenes, such as cyanation[9] and aminocyanation.[10] Likewise, we envisioned that simultaneous addition of both nucleophilic hydroxyl and amino group of *ortho*-aminophenol to olefins is greatly feasible and expectable to form tricyclic mother structure in the presence of oxidant,[11] especially hypervalent iodine through umpolung aminoxylation process (2°, Scheme 1). For the synthesis of mother core 2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one, the report has been traced employing Dess-Martin periodinane (DMP) regent and staring from

N-phenylpent-4-enamide, where the *in situ* introduction of oxygen was speculated from water or oxidant.[12] In this work, from commercially available *ortho*-aminophenol to synthesize the tricycle morphine is performed in generally improved yields, presumably due to shortened reaction process.

Scheme 1. Two Approaches to Tricyclic Morpholine

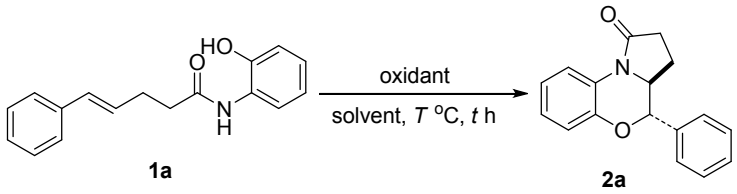


RESULTS AND DISCUSSION

Our investigations started with 0.25 mmol of (*E*)-*N*-(2-hydroxyphenyl)-5-phenylpent-4-enamide (**1a**) as the model substrate (Scheme 1), with the results collected in Table 1S in supporting information. When the reaction mixture of **1a** and DMP in DCM was stirred at 25 ℃ for 9 h, the desired cyclization product (**2a**) was obtained in 18% yield (entry 1). The structure of **2a** was confirmed convincingly through a single-crystal X-ray diffraction analysis and existed in a *anti*-configuration. When relative mild oxidizers such as trivalent (diacetoxyiodo)benzene (DIB) and PhIO were used as oxidants, **2a** was generated in 35% and 9% yields, respectively (entries 2 and 3). Likewise, several other commonly used hypervalent iodine regents such as IBA, PIFA, and ABX were utilized; however, no desired product was observed (entries 4-6). Subsequently, various solvents were screened under oxidation of best DIB. Both nonpolar and strongly polar solvents such as PhMe, MeCN, EtOAc, MeOH and acetone led to decrease of the yield of desired product to some extent (entries 7-11). It was worth to note that the yield of **2a** was generally elevated when various ethers with medium polarity were served as solvents one by one, and especially the best result was obtained in methyl *tert*-butyl ether (MTBE) with aliphatic group increased (entries 12-16). With a slight increase in the amount of DIB from 2.0 to 2.5 equivalents, the yield of **2a** increased and reached to

88% (entries 17-19). However, when the amount of DIB raised further to 2.8 equivalents, the yield of **2a** dropped to 77% (entry 20).

Furthermore, the temperature was investigated. Either slightly elevating or dropping the temperature from initial set temperature (25 °C) was executed and as a result dramatic reduction of yields occurred (entries 21 and 22), which suggests that the reaction was sensitive to temperature. The concentrations of reactants were then optimized, and as a result increase or decrease of concentration is detrimental to this reaction (entries 23 and 24). After gathering above conditions, the time was further optimized, and as a result neither prolonging nor shortening the reaction time is favorable to this transformation (entries 25 and 26). Therefore, the optimal reaction conditions were acquired as 2.5 equiv of DIB and 0.25 mmol of substrate in 2.0 mL of MTBE at 25 °C for 9 hours.



1a **2a**

Scheme 1. Condition optimization on transformation of model substrate **1a**.

With the optimal conditions in hand, we next investigated the scope of cycloaddition of substituted *ortho*-aminophenol and tethered *E*-olefin moieties, with results shown in Table 1. Compared with the level of activity of **2a** in 85% yield, electronic effects of substitutions on styryl were investigated, but it was found that they were unprominent. The neutral styryl substituted by electron-donating groups at the *para*-position, such as methyl and methoxy, gave corresponding products in good yields of 80% (**2b**) and 66% (**2c**), respectively. The styryl substituted with electron-withdrawing groups at the *para*-position all generated desired products in good yields (**2d**, **2e** and **2g**) and halo-substitution showed increasing reactivities with the electronegativity decreasing from F to Br. The substrate with strong electron-withdrawing trifluoromethyl group was able to work as well, albeit with a moderate yield (**2f**). It was worth to note that sterically chloroine-hindered substrates **1h** and **1i** were subjected to the cyclization of alkene, the reactions went smoothly

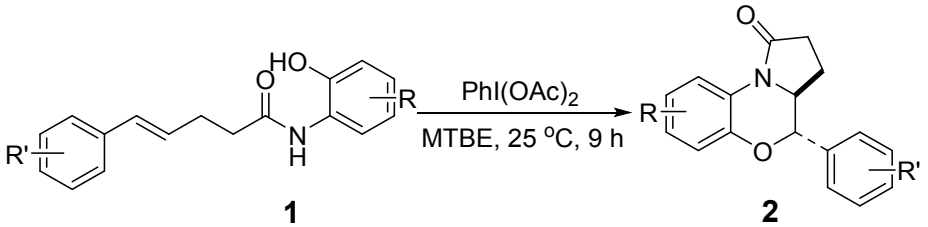
affording the corresponding products in 80% and 63% yields, respectively. Compared with *para*-chloro substitution (**2g**), *ortho*-chloro substitution (**2i**) showed the largest inhibition in reactivity and presented relatively less reactivity, while that of *meta*-chloro substitution (**2h**) was placed in the middle. Catalytic transformation of **1h** was attempted with 20% of iodobenzene as catalyst and 2.0 equiv of m-chloroperbenzoic acid as oxidant, the product **2h** was obtained in lower yield of 29%. Moreover, fused 2-naphthyl alkene was also applied to this cyclization successfully, resulting in good yield of 75% (**2j**). The benzoheterocyclic group such as benzotetrahydrofuran and indole moieties manifested good reactivity and gave rise to the desired products in 61% and 46% yields, respectively (**2k** and **2l**). Referred to Nicolaou's work[12], the cycloolefine substrate *N*-(2-hydroxyphenyl)cyclohex-3-enecarboxamide was subjected these conditions, however, no expected polycyclic product was obtained unfortunately.

The scope of *o*-aminophenols was next examined. Both electron-donating and electron-withdrawing groups were tolerated in these reactions. It was found that enlarging the bulkiness of *o*-aminophenols depressed the reactivity. Substitutions with methyl or halo (fluorine and bromine) groups on the aryl rings gave rise to corresponding products in moderate yields ranging from 30 to 52% (**2m-p**), and methyl and bromine atom led to lower yields than smallest fluorine atom. Here, halo-substitution effects demonstrated that stronger electron-withdrawing F resulted in better yield than bromo-substitution, which is converse to substitution effects on tethered styryl, and the position of fluorine affects the reactivity of cyclization (**2m** vs **2o**). Likewise, naphthyl substrate was also employed with the conditions, resulting in formation of corresponding polycyclic morpholine in 35% yield (**2q**). When terminal alkene was used as substrate, no desired product (**2r**) was detected in spite of starting material exhaustion, companied some uncertain side-products, which presumably attributes to its higher activity. The desired pyridinomorpholine (**2s**) was not acquired from lengthened carbon chain, which was probably due to relative instability of six-membered *N*-heterocycle and the misplacement of olefin in synergistic cyclization. Additionally, no reaction took place and was presumed resulting from rigid plane and

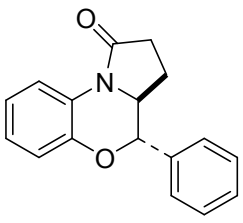
the lack of structure flexibility to forming two planes, which is essential to conjugation addition, when *N*-(2-hydroxyphenyl)-2-vinylbenzamide (**2t**) was utilized in intramolecular cyclization under optimal conditions. Fortunately, when the α-position of carbonyl group was substituted with two methyl groups, the flexibility of aliphatic carbon chain was maintained and the cyclization reaction provided 2,2-dimethylated **2u** in 35% yield.

In investigation of substrate scope, the large-scale synthesis and reaction selectivity need to be underlined. Considering potential application in industrial production, 1 mmol of (*E*)-*N*-(2-hydroxyphenyl)-5-phenylpent-4-enamide **(1a**) was subjected to the optimal conditions, a good yield of 61% was obtained yet (Table 1, footnote *b*). As a complementary, *Z*-olefin was expected to afford the *syn* products, and the starting material (*Z*)-*N*-(2-hydroxyphenyl)-5-phenylpent-4-enamide **(1a'**) with *Z*-olefin was attempted. As a result, no expectable *syn* product was obtained in the reaction, accompanied with uncertain side products monitored by thin layer chromatography, even if the starting material was converted in 93%, which implies a higher activation energy barrier in transformation of **1a'**.

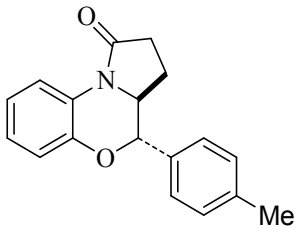
Table 1. Cyclization of Different Alkenes[a]



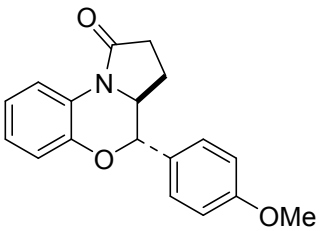
1 **2**



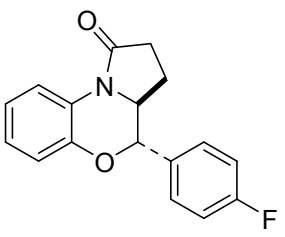
2a, 85% (61%)[b]



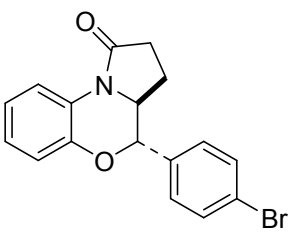
2b, 80%



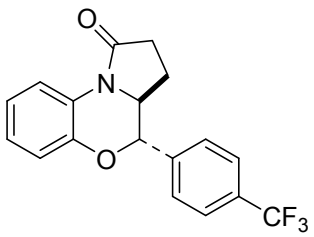
2c, 66%



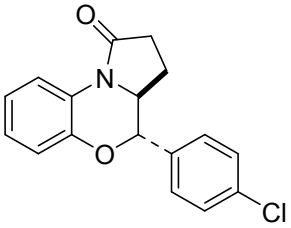
2d, 78%



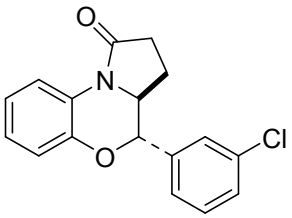
2e, 84%



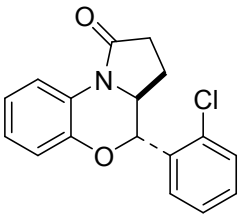
2f, 32%



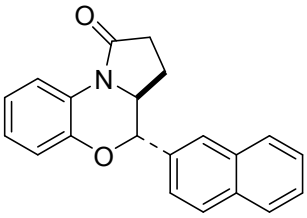
2g, 82%



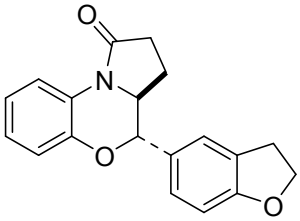
2h, 80%



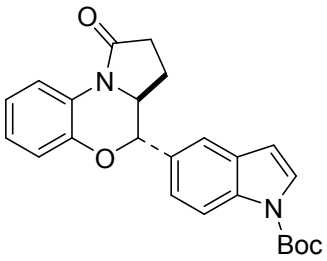
2i, 63%



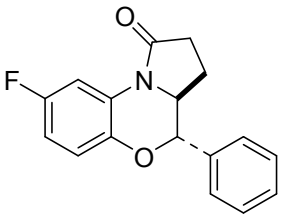
2j, 75%



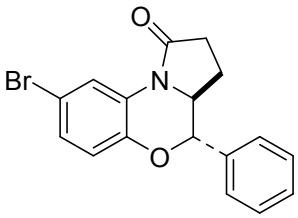
2k, 61%[c]



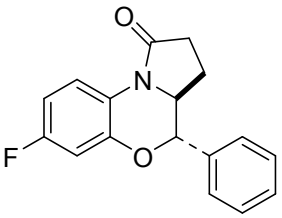
2l, 46%[c]



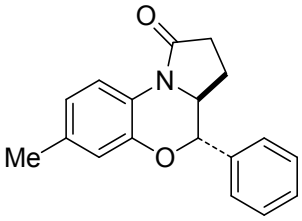
2m, 51%



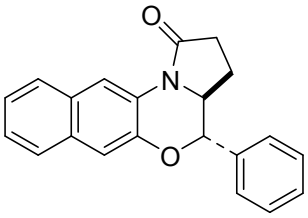
2n, 40%



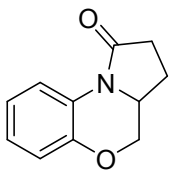
2o, 42%



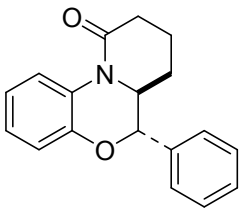
2p, 30%

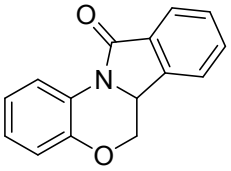


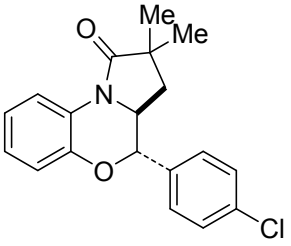
2q, 35%



2r, 0%







2s, 0%	**2t**, 0%	**2u**, 35%

[a] Conditions: **1** (0.25 mmol) and DIB (0.625 mmol) in MTBE (2 mL) at 25 ℃ (oil bath) for 9 h. Yield was isolated by silica gel column chromatography. [b] 1 mmol of synthetic scale. [c] At 30 ℃.

In order to glean an insight into the mechanism, ^{1}H NMR analysis was conducted to detect the interaction of electron-deficiency iodine(III) and *N*-(2-hydroxyphenyl)acetamide **3** simplified from model substrate. There exist six main active sites, i.e. basic amino, hydroxyl oxygen and their *ortho* or *para* aryl carbons (Figure 2). *N*-acyl anilines have been reported interacting with hypervalent iodine(V) at *ortho*- or *para*-aryl carbon, and the *para*-adduct was separated successfully by Nicolaou.[12] From ^{1}H NMR spectra, it was found that the signal peaks for OH and NH in **3** were clearly observed in six-deuterated DMSO (1), the peak shape of OH broadened, four aryl hydrogens were retained when mixing with DIB (2), and 30 minutes later, the signal peak of OH was gone (3). It could be concluded that the DIB attacked firstly with hydroxyl, once both of them were mixed.

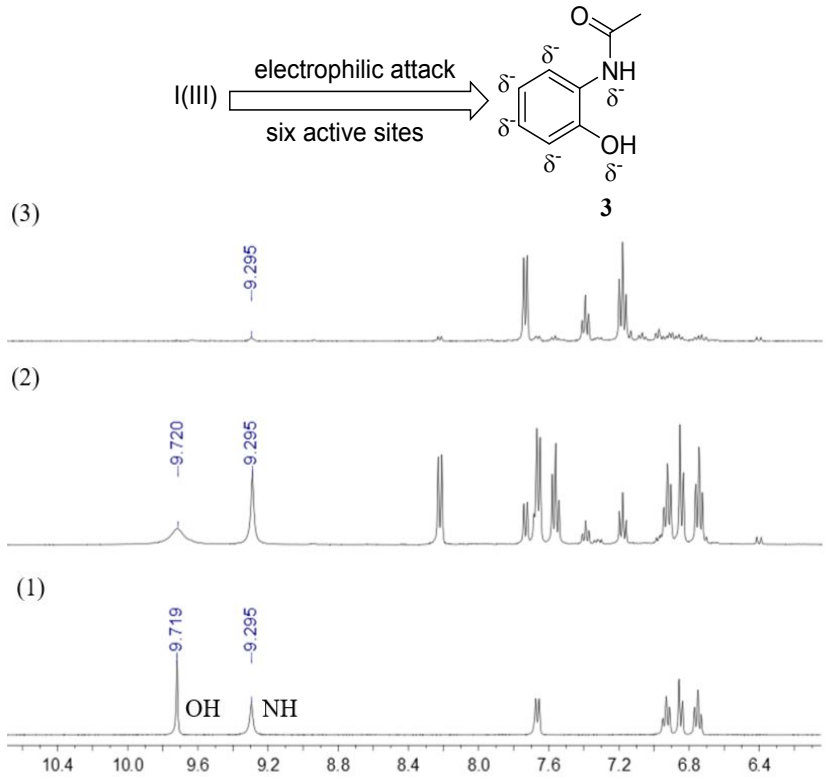


Figure 2. ^{1}H NMR analysis for mechanism insight. (1) Substrate **3**; (2) mixing **3** and DIB, no wait; (3) mixing **3** and DIB for 30 min.

A plausible mechanistic pathway for the reaction was proposed (Figure 3). Firstly, **1a** as an nucleophile attacks electron deficient iodine center of $PhI(OAc)_2$ to generate **4** with the release of one AcOH, following NMR demonstration. Through a reductive elimination of hypervalent iodine and split of iodobenzene, the intermediate of *o*-imidoquinone **5** is formed, similar to previous report, [5a,12,13] which undergoes intramolecular [4+2] cycloaddition with *E*-olefin between two conjugate planes like in ***E*-TS** to generate terminal product **2a**.

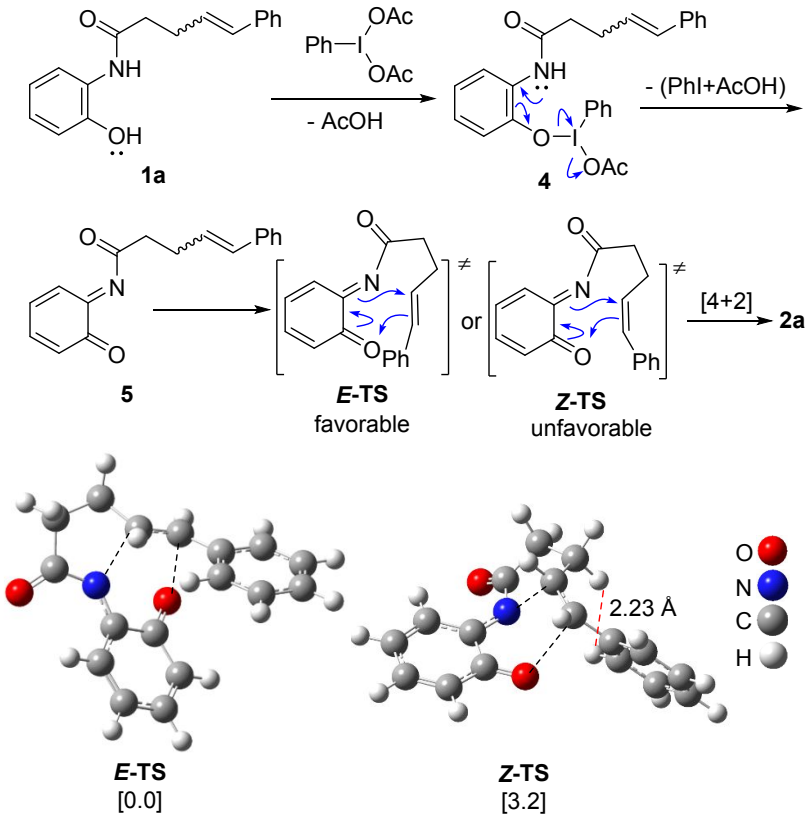


Figure 3. Plausible reaction mechanism.

As above shown, an attempt to use **1a'** with Z-olefin as substrate has been unsuccessful to furnish the *syn* product. In mechanistic pathway, similar to formation of **2a**, *Z*-olefin was assumed reasonably to proceed through a transition states ***Z*-TS** to reach to the *syn* diastereomer **2a'** (Figure 3). Therefore, both transition state ***E*-TS** and ***Z*-TS** were optimized for structure and energy comparison using the hybrid density functional method B3LYP with 6-31G basis sets, i.e. at the level of B3LYP/6-31G. The calculations showed that the *syn* transition state gives 3.2 kcal/mol higher energy at 25 ℃ than *anti* transition state, because of the strong repulsion between hydrogens

of methylene and benzene ring in ***Z*-TS**, where the distance of H···H is 2.23 Å, smaller than the sum of their Van der Waals radius. This delivers the rational interpretation of no cycloaddition product for *Z*-alkene and *anti* products totally in these transformations.

CONCLUSION

In summary, we have developed a metal-free oxidized intramolecular cyclization to synthesize substituted tricyclic morpholine derivatives under mild conditions through aminoxygenation of olefins, which provides an alternative tool for the synthesis of such polycycle compounds. In mechanistic insight, ^{1}H NMR analysis presented an initial interaction between phenolic hydroxyl group and hypervalent iodine, when electron rich phenolic hydroxyl group, amide and benzene ring were in coexistence. DFT calculation was employed to interpret the observed energetically and structurally favorable reaction pathway, i.e. active *E*-alkenes to *anti*-tricyclic morpholines. Further studies about the synthetic utility of this methodology and more mechanistic details are presently pursued in our laboratory.

EXPERIMENTAL SECTION

General Information. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on a Bruker DRX-400 spectrometer at 20~25 ℃. ^{1}H NMR spectra were reported in parts per million using tetramethylsilane TMS (δ = 0.00 ppm) as an internal standard. The data of ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants (*J*, Hz), and integration. ^{13}C NMR spectra were reported in parts per million using solvent $CDCl_3$ (δ = 77.2 ppm) as an internal standard, The data of ^{13}C NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), and coupling constants (*J*, Hz). High resolution mass spectra (HRMS) were obtained with a Q-TOF MS spectrometer. Reactions were monitored by TLC and column chromatography was performed using silica gel. Commercially available reagents were used without further purification unless otherwise specified. The calculations of *E*-TS and *Z*-TS were performed at the B3LYP/6-31G level using GASSIAN03 system of programs.

General Procedure for Synthesis of 1[14-17]

For starting materials: **1a-j, 1m-s,** or **1u**.

(i) 4-Pentenoic acid or 5-hexenoic acid (3 mmol), different substituted styrene (6 mmol) and Grubbs II catalyst (0.06 mmol, 51 mg) in CH_2Cl_2 (9 mL) at 45 °C (oil bath) for 12 h. Upon completion the reaction mixture was cooled to room temperature and solvent was removed under reduced pressure. The resulting residue was chromatographed to give corresponding carboxylic acid.

(ii) To a round-bottom flask was charged with prepared carboxylic acid (1 mmol), CH_2Cl_2 (5 mL), aminophenol (1.1 mmol, 120 mg), EDCI-HCl (1.2 mmol, 230 mg) and DMAP (1.3 mmol, 159 mg) successively. Then the mixture was stirred under conditions at room temperature for 12 h. Evaporation followed by column chromatography afforded compound **1a-j, 1m-s,** or **1u**.

For starting materials: **1k and 1l**

(i) To a stirred solution of 1-*H*-indole (5 mmol) and DMAP (0.05 mmol, 6.1 mg) in THF (40 mL) was added Boc_2O (5.5 mmol, 1.2 g) and mixture was stirred at room temperature for 2 h. Evaporation followed by column chromatography afforded *tert*-butyl 3-formyl-1H-indole-1-carboxylate with 90% yield.

(ii) *t*-BuOK (9.5 mmol, 1.07 g) was added to a suspension of $MePh_3PBr$ (9.5 mmol, 3.4 g) in THF (20 mL) at 0 °C for 30 min. The resulting mixture was allowed to warm to ambient temperature and stirred for additional 1 h. The solution was again cooled to 0 ºC, and a solution of compound *tert*-butyl 3-formyl-1H-indole-1-carboxylate (8.0 mmol, 1.96 g) in THF (3 mL) was added dropwise. The reaction was stirred at room temperature for 12 h, quenched with water and extracted with Et_2O (20 mL×3). The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to afford *tert*-butyl 3-vinyl-1H-indole-1-carboxylate with 80% yield.

(iii) The following steps are similar to **1a** to prepare **1k** and **1l**.

For starting materials: **1t**

To a round-bottom flask was added 2-vinylbenzoic acid (1 mmol, 148 mg),

CH_2Cl_2 (5 mL), 2-aminophenol (1.1 mmol, 120 mg), EDCI-HCl (1.2 mmol, 230 mg) and DMAP (1.3 mmol, 159 mg) successively. Then the mixture was stirred under conditions at room temperature for 12 h. Evaporation followed by column chromatography afforded compound **1t** with 75% yield.

General Procedure for Synthesis of 2

To a round-bottom flask was added **1a-j**, or **1m-u** (0.25 mmol), MTBE (2 mL) and DIB (0.625 mmol, 201 mg) successively. Then the resulting mixture was stirred under conditions at 25 ℃ (oil bath) for 9 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$. The organic phase was separated, and the aqueous layer was extracted with EtOAc (5 mL×3). The combined organic solution was dried with $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by a column chromatography to give the corresponding product **2a-j,** or **2m-u**.

To a round-bottom flask was added **1k** or **1l** (0.25 mmol), MTBE (2 mL) and DIB (0.625 mmol, 201 mg) successively. Then the resulting mixture was stirred under conditions at 30 ℃ (oil bath) for 9 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$. The organic phase was separated, and the aqueous layer was extracted with EtOAc (5 mL×3). The combined organic solution was dried with $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by a column chromatography to give the corresponding product **2k** or **2l**.

Procedure for Synthesis of 2a at the Scale of 1 mmol

To a round-bottom flask was added **1a** (1 mmol, 267 mg), MTBE (8 mL) and DIB (2.5 mmol, 805 mg) successively. Then the resulting mixture was stirred under conditions at 25 ºC for 9 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$. The organic phase was separated, and the aqueous layer was extracted with EtOAc (10 mL×3). The combined organic solution was dried with $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by a column chromatography to give the corresponding product **2a** in 61% yield (161.7 mg).

Procedure for Catalytic Synthesis of 2h

To a round-bottom flask was added **1h** (0.25 mmol, 75.5 mg), MTBE (2 mL), iodobenzene (0.05 mmol, 10 mg) and *m*-CPBA (0.5 mmol, 101 mg) successively.

Then the resulting mixture was stirred under conditions at 25 °C for 9 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$. The organic phase was separated, and the aqueous layer was extracted with EtOAc (5 mL×3). The combined organic solution was dried with $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by a column chromatography to give the corresponding product **2h** in 29% yield (22 mg).

^{1}H- and ^{13}C-NMR Analytical Data

*4-Phenyl-2,3,3a, 4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2a**)*: Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2a** as a white solid (56 mg, 85% yield), mp 163-168 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.4 Hz, 1H), 7.47-7.43 (m, 5H), 7.08-6.99 (m, 3H), 4.61 (d, *J* = 8.8 Hz, 1H), 3.96-3.90 (m, 1H), 2.58-2.44 (m, 2H), 1.92-1.85 (m, 1H), 1.79-1.70 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.0, 145.5, 135.9, 129.6, 129.1, 127.6, 125.1, 124.8, 121.9, 119.2, 117.2, 81.4, 59.5, 31.3, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}NO_2$, 266.1176; found, 266.1181.

*4-(p-Tolyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2b**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2b** as a white solid (55 mg, 80% yield), mp 164-167 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.0 Hz, 1H), 7.32-7.24 (m, 4H), 7.08-6.98 (m, 3H), 4.57 (d, *J* = 8.8 Hz, 1H), 3.97-3.90 (m, 1H), 2.63-2.44 (m, 2H), 2.40 (s, 3H), 1.94-1.86 (m, 1H), 1.77-1.66 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.1, 145.6, 139.5, 133.0, 129.8, 127.5, 125.1, 124.8, 121.8, 119.2, 117.2, 81.3, 59.4, 31.4, 22.0, 21.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}NO_2$, 280.1332; found, 280.1327.

*4-(4-Methoxyphenyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2 d][1,4]oxazin-1-one (**2c**)*: Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1, v/v) afforded **2c** as a white solid (48 mg, 66% yield), mp 182-186 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 9.6 Hz, 1H), 7.34 (d, *J* = 8.4, 2H), 7.07-6.96 (m, 5H), 4.55 (q, *J* = 4.0 Hz, 1H), 3.96-3.89 (m, 1H), 3.84 (s, 3H), 2.63-2.43 (m, 2H), 1.93-1.85 (m, 1H), 1.73-1.66 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.0, 160.6, 145.6, 128.9, 128.1, 125.1, 124.8, 121.8, 119.2, 117.2, 114.6, 81.1, 59.4, 55.6, 31.4, 22.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}NO_3$, 296.1281; found, 296.1293.

*4-(4-Fluorophenyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-o ne (**2d**)*: Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2d** as a white solid (55 mg, 78% yield), mp 165-168 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 7.6 Hz, 1H), 7.43-7.39 (m, 2H), 7.15 (t, *J* = 8.8 Hz, 2H), 7.09-7.00 (m, 3H), 4.60 (d, *J* = 8.8 Hz, 1H), 3.93-3.86 (m, 1H), 2.64-2.45 (m, 2H), 1.94-1.85 (m, 1H), 1.77-1.65 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.9, 163.5 (d, *J* = 247.0 Hz), 145.3, 131.9 (d, *J* = 9.0 Hz), 129.4 (d, *J* = 9.0 Hz), 124.9 (d, *J* = 17.0 Hz), 122.0, 119.2, 117.2, 116.2 (d, *J* = 21.0 Hz), 80.7, 59.5, 31.3, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}FNO_2$, 284.1083; found, 284.1090.

*4-(4-Bromophenyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-o ne (**2e**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2e** as a white solid (72 mg, 84% yield), mp 166-169 ℃;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.08-6.99 (m, 3H), 4.57 (d, *J* = 8.4 Hz, 1H), 3.89-3.83 (m, 1H), 2.63-2.45 (m, 2H), 1.93-1.85 (m, 1H), 1.77-1.68 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.9, 145.2, 135.0, 132.3, 129.2, 125.0, 124.9, 123.7, 122.0, 119.2, 117.2, 80.7, 59.4, 31.3, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}BrNO_2$, 344.0281; found, 344.0277.

*4-(4-(Trifluoromethyl)phenyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4] oxazin-1-one (**2f**)*: Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1, v/v) afforded **2f** as a white solid (26 mg, 32% yield), mp 167-170 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.10-7.01 (m, 3H), 4.68 (d, J = 8.8 Hz, 1H), 3.94-3.87 (m, 1H), 2.65-2.47 (m, 2H), 1.95-1.87 (m, 1H), 1.80-1.73 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.9, 145.1, 140.0, 132.0, 131.6, 127.9, 126.1 (q, *J* = 4.0 Hz), 124.8(d, *J* = 5.0 Hz), 122.2, 119.2, 117.2, 80.7, 59.5, 31.2, 29.9, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}F_3NO_2$, 334.1053; found, 334.1049.

*4-(4-Chlorophenyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2g**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2g** as a white solid (61 mg, 82% yield), mp 162-165 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.08-6.99 (m, 3H), 4.58 (d, *J* = 8.0 Hz, 1H), 3.91-3.83 (m, 1H), 2.64-2.45 (m, 2H), 1.93-1.85 (m, 1H), 1.77-1.68 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.9, 145.2, 135.5, 134.5, 129.4, 128.9, 125.0, 124.9, 122.0, 119.2, 117.2,

80.7, 59.4, 31.3, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}ClNO_2$, 300.0786 (^{35}Cl) and 302.0756 (^{37}Cl); found, 300.0788 and 302.0761.

*4-(3-Chlorophenyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2h**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2h** as a white solid (59 mg, 80% yield), mp 189-191 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 8.0 Hz, 1H), 7.44-7.29 (m, 4H), 7.09-7.00 (m, 3H), 4.58 (d, J = 8.0 Hz, 1H), 3.92-3.85 (m, 1H), 2.64-2.45 (m, 2H), 1.95-1.88 (m, 1H), 1.80-1.71 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.9, 145.2, 138.0, 135.2, 130.4, 129.7, 127.7, 125.7, 125.0, 124.9, 122.1, 119.2, 117.2, 80.7, 59.4, 31.2, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}ClNO_2$, 300.0786 (^{35}Cl) and 302.0756 (^{37}Cl); found, 300.0782 and 302.0761.

*4-(2-Chlorophenyl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2i**)*: Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2i** as a white solid (47 mg, 63% yield), mp 169-172 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 9.6 Hz, 1H), 7.51-7.45 (m, 2H), 7.42-7.34 (m, 2H), 7.08-6.99 (m, 3H), 5.29 (d, J = 8.8 Hz, 1H), 3.96 (q, J = 8.0 Hz, 1H), 2.63-2.46 (m, 2H), 2.05-1.87 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.1, 145.4, 134.0, 133.6, 130.4, 130.0, 129.1, 127.9, 125.1, 124.8, 122.0, 119.3, 117.2, 76.4, 60.0, 31.2, 20.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}ClNO_2$, 300.0786 (^{35}Cl) and 302.0756 (^{37}Cl); found, 300.0781 and 302.0760.

*4-(Naphthalen-2-yl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2j**):* Purification by column chromatography on silica gel (petroleum ether/ethyl

acetate = 6/1, v/v) afforded **2j** as a white solid (59 mg, 75% yield), mp 177-180 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 8.0 Hz, 1H), 7.95-7.88 (m, 4H), 7.56-7.50 (m, 3H), 7.11-7.01 (m, 3H), 4.77 (d, *J* = 8.0 Hz, 1H), 4.08-4.01 (m, 1H), 2.64-2.46 (m, 2H), 1.91-1.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.1, 145.6, 134.0, 133.4, 133.3, 129.2, 128.3, 128.0, 127.4, 127.0, 126.8, 125.1, 124.9, 124.5, 121.9, 119.3, 117.3, 81.6, 59.5, 31.4, 22.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{17}NO_2$, 316.1332; found, 316.1344.

*4-(2,3-Dihydrobenzofuran-5-yl)-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1, 4]oxazin-1-one (**2k**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1, v/v) afforded **2k** as a white solid (47 mg, 61% yield), mp 222-225 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.05-6.98 (m, 3H), 6.83 (d, *J* = 8.4 Hz, 1H), 4.62 (t, *J* = 8.8 Hz, 2H), 4.52 (d, *J* = 8.8Hz, 1H), 3.93 (q, *J* = 9.2 Hz, 1H), 3.25 (t, *J* = 8.8 Hz, 2H), 2.63-2.43 (m, 2H), 1.96-1.88 (m, 1H), 1.74-1.68 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.0, 161.3, 145.7, 128.2, 128.0, 125.1, 124.8, 124.2, 121.8, 119.2, 117.2, 109.7, 81.4, 71.7, 59.5, 31.4, 29.8, 22.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{17}NO_3$, 308.1281; found, 308.1281.

*tert-Butyl 5-(1-oxo-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-4-yl)-1H-indole-1-carboxylate (**2l**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1, v/v) afforded **2l** as a white solid (46 mg, 46% yield), mp 157-159 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 7.6 Hz, 1H), 8.23 (d, *J* = 8.0

Hz, 1H), 7.65 (d, *J* = 3.6 Hz, 1H), 7.62 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.08-6.99 (m, 3H), 6.60 (d, *J* = 3.6 Hz, 1H), 4.69 (d, *J* = 8.8 Hz, 1H), 3.99 (q, *J* = 9.2 Hz, 1H), 2.62-2.43 (m, 2H), 1.89-1.74 (m, 2H), 1.69 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 173.1, 149.7, 145.7, 135.9, 131.1, 130.3, 127.1, 125.1, 124.8, 123.5, 121.8, 120.2, 119.2, 117.2, 115.8, 107.4, 84.3, 81.7, 59.7, 31.8, 31.4, 29.9, 28.4, 22.8, 22.0, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}N_2O_4$, 405.1809; found, 405.1794.

*8-Fluoro-4-phenyl-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2m**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2m** as a white solid (36 mg, 51% yield), mp 146-148 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (dd, *J* = 2.8, 10.4 Hz, 1H), 7.47-7.40 (m, 5H), 6.96 (q, *J* = 5.2 Hz, 1H), 6.76 (td, *J* = 2.8, 8.0 Hz, 1H), 4.55 (d, *J* = 8.8 Hz, 1H), 3.95-3.89 (m, 1H), 2.63-2.45 (m, 2H), 1.92-1.85 (m, 1H), 1.79-1.68 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 173.2, 157.4 (d, *J* = 237.0 Hz), 141.7, 135.7, 129.4 (d, *J* = 49.0 Hz), 127.5, 125.3 (d, *J* = 11.0 Hz), 117.7 (d, *J* = 9.0 Hz), 111.2 (d, *J* =23.0 Hz) , 106.1 (d, *J* = 29.0 Hz), 81.2, 59.4, 31.3, 22.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}FNO_2$, 284.1082; found, 284.1086.

*8-Bromo-4-phenyl-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2n**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2n** as a white solid (34 mg, 40% yield), mp 182-185 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, *J* = 2.4 Hz, 1H), 7.47-7.39 (m, 5H), 7.15 (q, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.57 (d, *J* = 8.8 Hz, 1H), 3.94-3.87 (m, 1H), 2.63-2.45 (m, 2H), 1.94-1.86 (m, 1H), 1.80-1.68 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz,

$CDCl_3$): δ 173.1, 144.6, 135.5, 129.7, 129.2, 127.6, 127.5, 126.1, 121.7, 118.6, 114.0, 81.4, 59.3, 31.2, 22.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}BrNO_2$, 344.0281; found, 344.0267.

*7-Fluoro-4-phenyl-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2o**)*: Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2o** as a white solid (30 mg, 42% yield), mp 199-202 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (q, J = 6.0 Hz, 1H), 7.47-7.39 (m, 5H), 6.77-6.71 (m, 2H), 4.62 (d, J = 8.8 Hz, 1H), 3.92 (q, J = 8.8 Hz, 1H), 2.63-2.44 (m, 2H), 1.95-1.86 (m, 1H), 1.80-1.68 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.8, 159.4 (d, J = 242.0 Hz), 146.5 (d, J = 11.0 Hz), 135.5, 129.5 (d, J = 54.0 Hz), 127.5, 121.5 (d, J = 3.0 Hz), 120.2 (d, J = 9.0 Hz), 108.6 (d, J = 22.0 Hz), 104.6 (d, J = 25.0 Hz), 81.9, 59.2, 31.2, 21.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{14}FNO_2$, 284.1082; found, 284.1090.

*7-Methyl-4-phenyl-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2p**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2p** as a white solid (21 mg, 30% yield), mp 149-152 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.46-7.40 (m, 5H), 6.93-6.84 (m, 2H), 4.57 (d, J = 8.8 Hz, 1H), 3.92 (q, J = 8.8 Hz, 1H), 2.62-2.43 (m, 2H), 2.34 (s, 3H), 1.91-1.83 (m, 1H), 1.78-1.67 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.0, 143.4, 136.1, 131.4, 129.5, 129.1, 127.6, 125.5, 124.7, 119.4, 116.9, 81.4, 59.7, 31.4, 21.9, 21.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}NO_2$, 280.1332; found, 280.1321.

*4-Phenyl-2,3,3a,4-tetrahydro-1H-naphtho[2,3-b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2q**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2q** as a white solid (27 mg, 35% yield), mp 212-215 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.50-7.43 (m, 5H), 7.41 (s, 1H), 7.39-7.33 (m, 2H), 4.70 (d, *J* = 9.2 Hz, 1H), 4.08-4.02 (m, 1H), 2.68-2.50 (m, 2H),1.95-1.87 (m, 1H), 1.85-1.73 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.5, 145.0, 135.9, 131.0, 129.64, 129.56, 129.2, 128.0, 127.6, 126.5, 125.7, 125.5, 124.6, 116.6, 112.6, 81.6, 59.9, 31.4, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{17}NO_2$, 316.1332; found, 316.1322.

*4-(4-Chlorophenyl)-2,2-dimethyl-2,3,3a,4-tetrahydro-1H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-1-one (**2u**):* Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1, v/v) afforded **2u** as a white solid (28 mg, 35% yield), mp 162-165 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.08-7.00 (m, 3H), 4.55 (d, *J* = 8.8 Hz, 1H), 3.84-3.78 (m, 1H), 1.73 (q, *J* = 6.4 Hz, 1H), 1.60-1.55 (m, 1H), 1.26 (s, 3H), 1.19 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.6, 145.4, 135.5, 134.7, 129.4, 128.8, 125.1, 124.7, 122.1, 119.2, 117.2, 80.8, 56.3, 41.1, 37.7, 25.2, 24.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{18}ClNO_2$, 328.1099 (^{35}Cl) and 330.1069 (^{37}Cl); found, 328.1092 and 330.1068.

ASSOCIATED CONTENT

Supporting Information

Detailed optimization of reaction conditions, crystal structure and crystallographic data of **2a**, standard orientations and energies of ***E*-TS** and ***Z*-TS**, and ^{1}H- and ^{13}C

NMR Spectra. Supporting Information is available free of charge on the ACS Publications website at

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