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Highly *trans*-Stereoselective Synthesis of Bicyclic Isoxazolidines via Copper-Catalyzed Triple Cascade Catalysis

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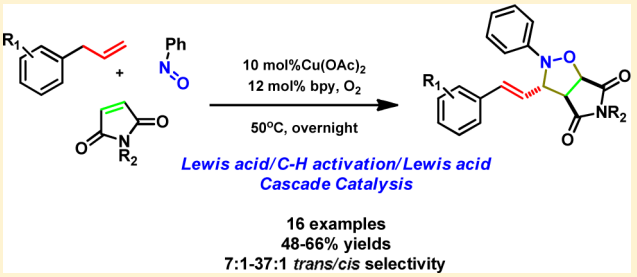
Supporting Information

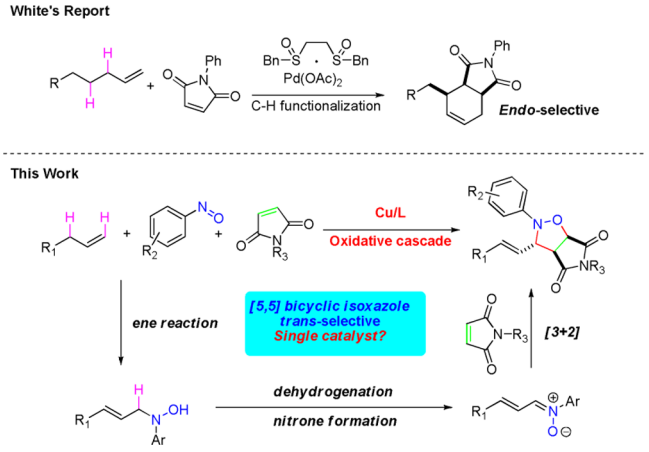
ABSTRACT: A triple cascade was developed using a simple copper catalyst to *trans*-selectively access bicyclic isoxazolidines in a one-pot synthesis. This strategy features the in situ generation of nitrones and subsequent trapping by [3 + 2] cycloaddition. In this method, copper serves three catalytic functions: as a Lewis acid for the ene reaction, as an organometallic for aerobic oxidation, and as a Lewis acid for an *endo*-selective [3 + 2] cycloaddition. The successful merging of aerobic oxidation and Lewis acid catalysis demonstrated efficient cascade synergy.



Cascade and synergistic catalysis has recently re-emerged as a powerful strategy for the rapid construction of sophisticated molecular architectures.[1] Much of the work in this field has concentrated on the nucleophilic reaction paradigm. Cascades involving redox catalytic cycles have been lacking, despite recent advances in transition-metal-catalyzed oxidative C−H activation[2] and aerobic oxidation reactions.[3] Cascades tethering these privileged functionalization methods, preferably using a simple catalyst, are highly desirable for the direct conversion of cheap industrial hydrocarbon feedstocks to molecules with rich functionalities. However, one-pot transformations involving hydrocarbons are challenging because strong oxidants are often required, which can lead to uncontrollable domino reaction pathways and catalyst quenching. One such example is the nitrones, a class of highly reactive functional groups that enable a number of chemical transformations.[4] Despite their versatile synthetic utilities, the use of nitrones requires a separate preparation step that typically involves the condensation of aldehydes and hydroxyamines.[5] The synthesis of nitrones via direct aerobic oxidation of more readily available olefins has not been successful. In this report, we describe a catalytic cascade involving double allylic C−H oxidation[6] leading to in situ nitrone formation[7] and a highly *endo*-selective [3 + 2] cycloaddition[8] using a simple, commercially available copper catalyst to access pharmacologically valuable [5,5] bicyclic isoxazolidines in one pot with high *trans*-diastereocontrol (Scheme 1). This novel method for in situ nitrone generation via aerobic oxidation may enable versatile applications tethered to this chemistry.

Bicyclic isoxazolidines are widely found in natural products, pharmaceutically valuable agents, and synthetic intermediates. A number of biologically desirable properties, such as antibacterial,[9] antiamnestic,[10] and antistress[11] activities, have been reported for molecules containing this bicyclic scaffold (Figure 1). In addition, via reductive cleavage of the N−O bond, isoxazolidines allow quick access to γ-amino alcohols, another important class of biologically relevant moieties.[12] We envisioned that a one-pot catalytic cascade involving aerobic oxidation and [3 + 2] cycloaddition would be an ideal way to access this class of important pharmacophores from simple olefins. This strategy necessitated straightforward conversion of an allyl group to the corresponding nitrone, which would be further trapped by a dipolarophile in situ to yield the desired bicyclic. Recently, Read de Alaniz, Jiao, and our group reported

Scheme 1. Double Allylic Oxidation [3 + 2] Strategy to Bicyclic Heterocycles



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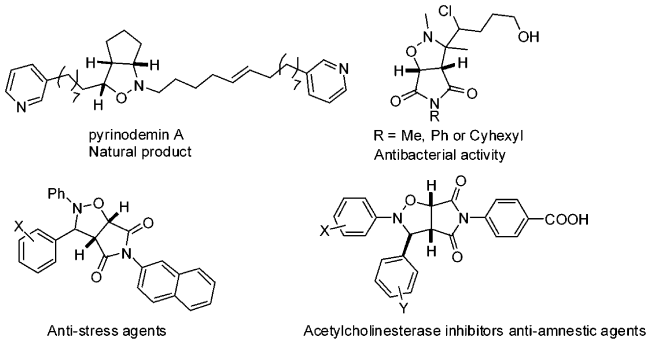


Figure 1. Natural products and biological agents containing bicyclic isoxazolidines.

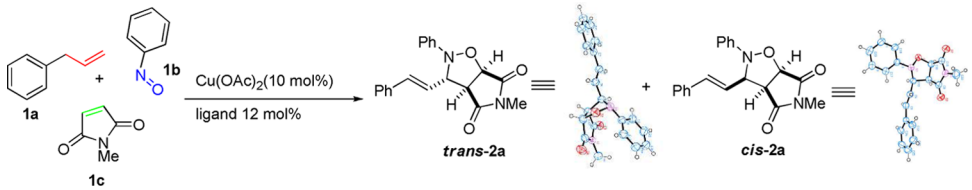
the aerobic dehydrogenation of hydroxyamines (to nitroso compounds) and hydrazines (to hydrazones) by either Pd or Cu catalysis.[13] Inspired by this development, we decided to investigate an ene reaction between allyl benzenes and nitrosobenzenes,[14] a key step for olefin oxidation. The corresponding hydroxyamines generated would be further dehydrogenated to afford transient nitrone species. Rapid [3 + 2] dipolar addition using maleimides would render the desired bicyclic isoxazolidines. This cascade combines transition-metal-catalyzed allylic oxidation and Lewis-acid-catalyzed cycloaddition reactions, a strategy that conceptually echoes White's allylic dehydrogenation–cycloaddition cascade.[6d]

We initially studied a reaction cascade involving allylbenzene, nitrosobenzene, and various electron-deficient olefins using transition metals. In agreement with our previous studies,[13c] most metals yielded messy mixtures, with the exception of copper. The reaction involving *N*-methylmaleimide led to the bicyclic isoxazolidine product in clean conversion using $Cu(OAc)_2$. Further optimization of the reaction conditions revealed the features described below (Table 1). First, copper proved to be the most efficient metal for this overall cascade. Second, catalyst turnover was only achieved in the presence of air or oxygen (Table 1, entries 1–3). Third, moderate *trans*-selectivity was observed in the absence of a ligand due to poor intrinsic *endo*/*exo* [3 + 2] cycloaddition. The direct oxidation of olefins using nitrosobenzenes under heating has been documented in the early literature.[15] Often, products with various oxidation stages were formed unselectively.[16] The reaction temperature and solvent were carefully examined, and the highest cascade conversion was observed at 50–60 °C in highly polar aprotic solvents. It has been reported that nitrosobenzenes are prone to self-dimerization to afford azoxybenzene in the presence of a transition metal.[17] Substrate ratios were studied in detail. Acceptable conversions were achieved when the amount of nitrosobenzene was increased to 2 equiv, and >80% yields were obtained with 4 equiv of PhNO. We tested various ligands in an effort to improve *trans*/*cis*-selectivity. The employment of nitrogen-based bidentate ligands significantly improved the *trans*-selectivity with somewhat compromised yields. Although the coupling constants for the *trans*- and *cis*-isomers were quite similar, the relative stereochemistries of both the *cis*- and *trans*-isomers of **2a** were unambiguously assigned based on their single-crystal X-ray diffractions.

The substrate scope was explored, and the results are summarized in Table 2. This protocol tolerated various electron-rich and electron-deficient substituents on the allylic aromatic rings, including heteroaromatics. For nonaromatic substrates, oxidation led to various products, and selective nitrone trapping was unsuccessful. Both alkyl and aryl maleimides smoothly underwent this aerobic oxidation–cycloaddition cascade. The N-alkylated maleimides led to higher *trans*/*cis*-selectivity than their arylated counterparts. The *trans*-selectivity for this transformation was uniformly high, and dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione scaffolds containing three continuous stereogenic centers were prepared in moderate to good yields. In general, the reaction rates were not affected by electronic and steric modulation of the substrates, and clean conversions were observed across the board. Other dipolarophiles were briefly examined. The yields involving maleic anhydrides and other ester-activated olefins were significantly lower.

Isoxazolidine **2a** could be opened reductively under Zn/AcOH conditions, yielding a γ-amino alcohol **3a** in 81% yield. Upon treatment with NBS, the two most reactive nucleophilic sites on **2a** (i.e., *p*-aniline and the double bond) were differentiated with complete selectivity. With 1 equiv of NBS,

Table 1. Reaction Condition Optimization for 2a[a]



entry	sol	oxd	L	*T*/°C	yield (*trans*/*cis*)[b]	entry	sol	oxd	L	*T*/°C	yield (*trans*/*cis*)[b]
1	MeCN	Ar		50	13% (2.4:1)	9	DMSO	O_2		50	38% (2.5:1)
2	MeCN	air		50	21% (3.2:1)	10	DMF	O_2		50	36% (2.3:1)
3	MeCN	O_2		50	28% (2.5:1)	11	NMP	O_2		50	39% (2.3:1)
4	MeCN	O_2		80	trace (–)	12	NMP	O_2		50	84% (2.5:1)
5	MeCN	O_2		50	36% (2.1:1)	13	NMP	O_2	1,10-phen	50	52% (16:1)
6	toluene	O_2		50	5% (–)	14	NMP	O_2	dzf[c]	50	60% (11:1)
7	DCM	O_2		50	9% (–)	15	NMP	O_2	bpy	50	69% (12:1)
8	DCE	O_2		50	9% (–)						

[a]Substrate ratio (**1a**/**1b**/**1c**) for entries 1–6 1:1:1; for entries 7–11 1:2:2; for entries 12–15 1.5:4:1. [b]Isolated yields. The *trans*/*cis* ratio was measured by crude NMR integration. [c]4,5-Diazafluorenone.

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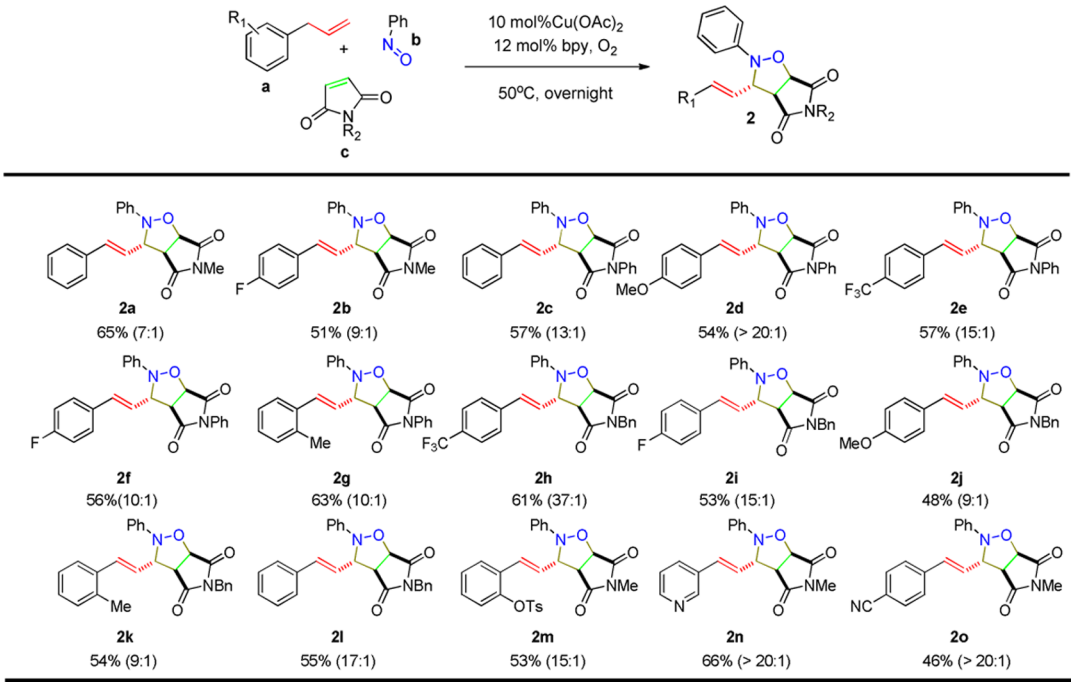
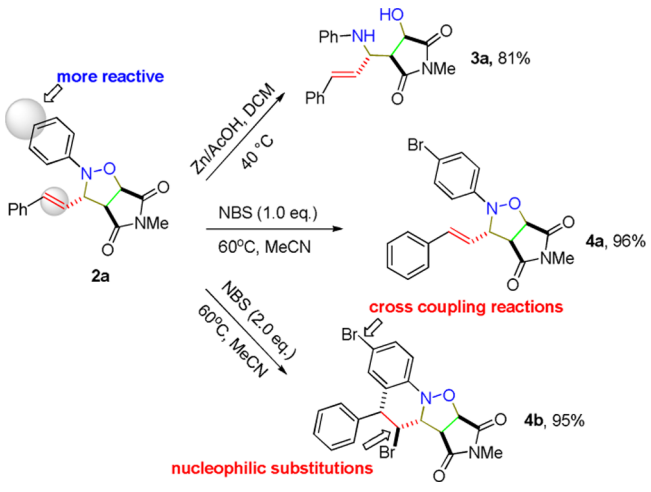
Table 2. Copper-Catalyzed Synthesis of Bicyclic Isoxazolidines[a]



[a]Isolated yield reflecting *trans* only; *trans*/*cis* ratio determined by crude NMR integration.

the *p*-position of the aniline was preferentially brominated at 60 °C in 96% yield. By increasing the amount of NBS to 2 equiv, a bromine onium-mediated electrophilic cyclization occurred following the initial aniline bromination. This led to a structurally sophisticated novel pentacyclic scaffold (**4b**) in 95% yield (Scheme 2). The presence of two chemically orthogonal bromine atoms (e.g., aryl bromide and alkyl bromide) opens the door to further versatile molecular manipulations.

Scheme 2. Derivatization of Bicyclic Isoxazolidines



This cascade was believed to proceed through the nitrone intermediate, as evidenced by the sequential experiments. Nitrone **5a** was obtained in 11% isolated yield when the reaction was conducted in the absence of maleimides (Scheme 3, eq a). The low yield was attributed to nitrone decomposition in the absence of a dipolarophile. Similar yields and *trans*-selectivities were observed when purified nitrone **5a** was subjected to a stand-alone [3 + 2] cycloaddition compared to the one-pot cascade. The much higher yields observed under cascade conditions indicated rapid nitrone trapping through sequential [3 + 2] dipolar cycloaddition, resulting in an efficient synergistic system. Nitrones generated in situ are best suited for a one-pot cascade without isolation. The first ene reaction is likely catalyzed by copper. Mixing allyl benzene and nitrosobenzene under Ar only resulted in nitrosobenzene dimerization as a major side reaction. Only trace amount of allylic oxidation was observed. On the other hand, the addition of $Cu(OAc)_2$ and bpy resulted in significantly less nitrosobenzene decomposition under otherwise identical conditions. These results indicated that copper is critical for controlling the oxidation pathways and that the subsequent cascade improved the overall chemoselectivity.

The proposed overall cascade mechanism is outlined in Scheme 4. Presumably, a nitroso-ene reaction catalyzed by copper generates the corresponding allylic hydroxylamine species.[18] The subsequent oxidation by another molecule of nitrone or by copper-catalyzed direct aerobic oxidation leads to the nitrone intermediate. The lack of catalyst turnover in the absence of air or oxygen suggests that aerobic oxidation might be the major pathway. Copper, which serves as a Lewis acid, catalyzes the final [3 + 2] cycloaddition. The high *trans*-selectivity is likely attributable to a square planar metal complex that involves *s-cis* copper maleimide.[19] The long styrenyl substituent of nitrone is oriented away from the dipolarophile (Scheme 4).

In summary, we have developed a simple copper system that catalyzes a cascade reaction to access pharmacologically attractive bicyclic isoxazolidines with high *trans*-diastereoselectivity. The experimental evidence supports a nitroso-ene/aerobic dehydrogenation cascade to generate a nitrone intermediate, followed by subsequent copper-catalyzed [3 + 2] cycloaddition. Copper's extended three-fold catalytic function includes acting as a tethering Lewis acid for the ene

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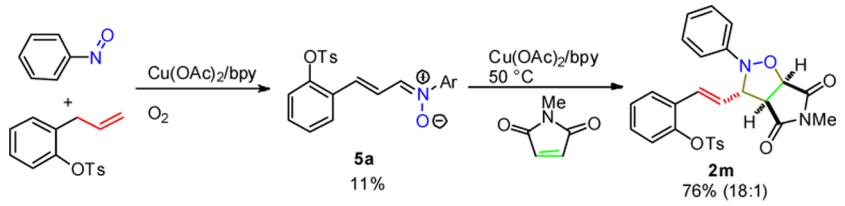
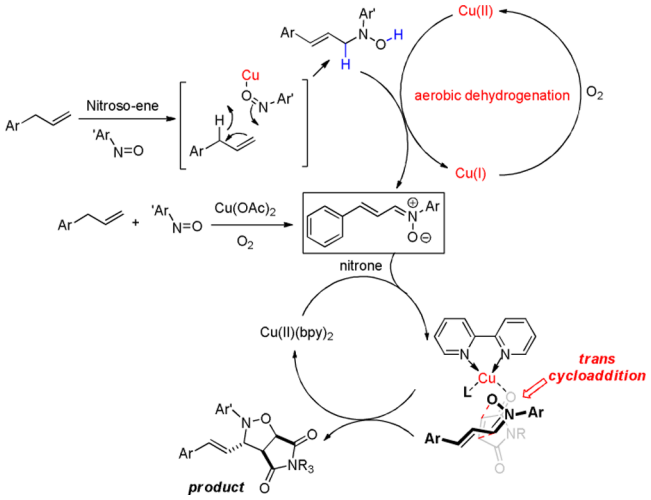
Scheme 3. Stepwise Execution of the Cascade



Scheme 4. Proposed Reaction Mechanism and Explanation for *trans*-Selective Cycloaddition



reaction, as an organometallic in the allylic dehydrogenation, and as a Lewis acid for the highly *trans*-selective [3 + 2] nitrone cycloaddition. These results represent a rare triple cascade catalysis involving both transition metal and Lewis acid catalysis.

EXPERIMENTAL SECTION

General Methods and Materials. All reactions were performed under an oxygen atmosphere (balloon) with dry solvents under anhydrous conditions. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. The chromatography solvents were technical grade and distilled prior to use. Flash chromatography was performed using 200−300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. The developed chromatogram was visualized by UV absorbance (254 nm). The ^{1}H NMR and ^{13}C NMR data were recorded on 400 MHz nuclear resonance spectrometers, unless otherwise specified. The chemical shifts (δ) in parts per million are reported relative to the residual signals of chloroform (^{1}H 7.26 ppm or ^{13}C 77.16 ppm). Multiplicities are described as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet), and coupling constants (J) are reported in hertz (Hz). ^{13}C NMR spectra were recorded with total proton decoupling. HRMS (ESI) analysis with a quadrupole time-of-flight (QqTOF) mass spectrometer yielded ion mass/charge (m/z) ratios in atomic mass units. IR spectra were measured as dry films (KBr) and are reported in terms of frequency (cm^{-1}) and intensity of absorption.

General Procedure for the Three-Component Reaction. $Cu(OAc)_2$ (9.1 mg, 0.05 mmol, 0.1 equiv) and bipyridine (9.4 mg, 0.06 mmol, 0.12 equiv) were weighed in a test tube, and NMP (3 mL) was added. The mixture was stirred under air until the copper salt completely dissolved (ca. 1 h). Allylbenzene (0.75 mmol, 1.5 equiv), nitrosobenzene (2 mmol, 4.0 equiv), and maleimide (0.5 mmol, 1.0 equiv) were sequentially added. The test tube was capped with a rubber septum, degassed, flushed with molecular oxygen three times, and stirred at 50 °C under an oxygen balloon overnight. The mixture was cooled to room temperature and diluted with water (10 mL) and ethyl acetate (10 mL). The organic layer was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined extract was washed with water (10 mL) and brine (10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether) to afford an analytically pure product.

*(3S,3aS,6aR)-5-Methyl-2-phenyl-3-((E)-styryl)dihydro-2H-pyrrolo-[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2a**):* ethyl acetate/petroleum ether = 1:5, 65% yield (0.109 g, dr = 7:1), yellow solid, mp 152−154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.19 (m, 7H), 7.02 (d, J = 8.0 Hz, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.77 (d, J = 16.0 Hz, 1H), 6.17 (dd, J = 16.0, 7.5 Hz, 1H), 5.06 (d, J = 7.5 Hz, 1H), 5.00 (d, J = 7.2 Hz, 1H), 3.68 (d, J = 7.2 Hz, 1H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.0, 173.9, 147.0, 135.7, 133.9, 128.9, 128.7, 128.3, 126.6, 124.8, 122.9, 115.7, 76.0, 68.2, 55.3, 25.0; HRMS (ESI) found 335.1367, calcd for $C_{20}H_{18}N_2O_3$ ([M + H]$^+$) 335.1396; IR (KBr) 1709, 1597, 1493, 1435, 1381, 1284, 1132, 1029, 968, 760, 737, 694, 625, 496.

*(3R,3aS,6aR)-5-Methyl-2-phenyl-3-((E)-styryl)dihydro-2H-pyrrolo-[3,4-d]isoxazole-4,6(5H,6aH)-dione (cis-**2a**):* ethyl acetate/petroleum ether = 1:4, yellow solid, mp 166−167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.26 (m, 7H), 7.23 (t, J = 4.4 Hz, 2H), 7.13 (t, J = 7.2 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.09 (dd, J = 15.9, 8.6 Hz, 1H), 5.06 (d, J = 7.5 Hz, 1H), 4.16 (t, J = 8.3 Hz, 1H), 3.79 (t, J = 7.8 Hz, 1H), 3.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 173.0, 146.9, 136.2, 136.0, 128.7, 128.6, 128.4, 126.8, 125.6, 121.8, 120.1, 76.0, 71.7, 53.4, 25.1; HRMS (ESI) found 335.1384, calcd for $C_{20}H_{18}N_2O_3$ ([M + H]$^+$) 335.1396; IR (KBr)1715, 1645, 1489, 1435, 1383, 1285, 1141, 1051, 968, 746, 694.

*(3S,3aS,6aR)-3-(4-Fluorostyryl)-5-methyl-2-phenyldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2b**):* ethyl acetate/petroleum ether = 1:5, 51% yield (0.090 g, dr = 9:1), brown solid, mp 154−156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (dd, J = 8.7, 5.4 Hz, 2H), 7.26−7.21 (m, 2H), 6.98 (ddd, J = 17.9, 11.2, 6.1 Hz, 5H), 6.73 (d, J = 16.0 Hz, 1H), 6.08 (dd, J = 16.0, 7.5 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 5.00 (d, J = 7.3 Hz, 1H), 3.67 (d, J = 7.3 Hz, 1H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 173.9, 147.0, 132.7, 128.9, 128.2, 128.2, 124.5, 122.9, 115.7, 115.7, 115.5, 76.1, 68.2, 55.2, 25.0; HRMS (ESI) found 353.1298, calcd for $C_{20}H_{17}FN_2O_3$ ([M + H]$^+$) 353.1301; IR (KBr) 1705, 1599, 1508, 1435, 1383, 1285, 1227, 1159, 1132, 1031, 970, 758, 694.

*(3S,3aS,6aR)-2,5-Diphenyl-3-((E)-styryl)dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2c**):* ethyl acetate/petroleum ether = 1:5, 57% yield (0.113 g, dr = 13:1), yellow solid, mp 116−117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (dq, J = 12.3, 7.5 Hz, 7H), 7.30−7.26 (m, 2H), 7.25 (d, J = 6.5 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 6.99 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 15.9 Hz, 1H), 6.81−6.71 (m, 2H), 6.27 (dd, J = 15.9, 6.8 Hz, 1H), 5.29 (d, J = 6.8 Hz, 1H), 5.13 (d, J = 7.5 Hz, 1H), 3.90−3.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 172.7, 147.9, 135.8, 133.4, 131.1, 129.3, 129.0, 128.9, 128.7, 128.3, 126.7, 126.2, 125.3, 123.0, 115.2, 68.5, 55.4; HRMS (ESI) found 397.1539, calcd for $C_{25}H_{20}N_2O_3$ ([M + H]$^+$) 397.1552; IR (KBr) 1721, 1717, 1595, 1495, 1385, 1196, 1030, 968, 758, 692, 623.

*(3S,3aS,6aR)-3-(4-Methoxystyryl)-2,5-diphenyldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2d**):* ethyl acetate/petroleum ether = 1:5, 54% yield (0.115 g, dr > 20:1), orange solid, mp 136−138 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (ddd, J = 13.7, 8.9,

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6.2 Hz, 5H), 7.29−7.22 (m, 2H), 7.15−7.08 (m, 2H), 6.99 (d, J = 7.4 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.82−6.72 (m, 3H), 6.12 (dd, J = 15.9, 6.9 Hz, 1H), 5.27 (d, J = 6.9 Hz, 1H), 5.12 (d, J = 7.5 Hz, 1H), 3.83 (dd, J = 7.5, 0.4 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 172.8, 159.8, 148.0, 132.9, 131.1, 129.3, 129.0, 128.9, 128.6, 127.9, 126.2, 123.0, 122.9, 115.2, 114.2, 68.6, 55.5, 55.3; HRMS (ESI) found 427.1650, calcd for $C_{26}H_{22}N_2O_4$ ([M + H]$^+$) 427.1658; IR (KBr) 3487, 3063, 1721, 1607, 1512, 1456, 1383, 1302, 1250, 1196, 1031, 692, 501.

(3S,3aS,6aR)-2,5-Diphenyl-3-((E)-4-(trifluoromethyl)styryl)-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2e**): ethyl acetate/petroleum ether = 1:5, 57% yield (0.133 g, dr = 15:1), pale yellow solid, mp 126−127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.40−7.31 (m, 3H), 7.26 (dd, J = 7.0, 1.6 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 15.9 Hz, 1H), 6.80−6.68 (m, 2H), 6.36 (dd, J = 15.9, 6.6 Hz, 1H), 5.32 (d, J = 6.6 Hz, 1H), 5.15 (d, J = 7.5 Hz, 1H), 3.94−3.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 172.6, 147.8, 139.3, 132.1, 131.0, 129.4, 129.1, 129.0, 128.0, 126.9, 126.2, 125.7, 125.7, 125.2, 123.2, 115.2, 68.3, 55.3; HRMS (ESI) found 465.1421, calcd for $C_{26}H_{19}F_3N_2O_3$ ([M + H]$^+$) 465.1426; IR (KBr) 1717, 1495, 1385, 1325, 1196, 1165, 1122, 1067, 1016, 758, 690, 617, 424.

(3S,3aS,6aR)-3-(4-Fluorostyryl)-2,5-diphenyldihydro-2H-pyrrolo-[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2f**): ethyl acetate/petroleum ether = 1:5, 56% yield (0.116 g, dr = 10:1), yellow solid, mp 174−176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (dd, J = 6.6, 5.1 Hz, 5H), 7.29 (t, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 7.03 (dd, J = 17.2, 8.4 Hz, 3H), 6.84 (d, J = 15.9 Hz, 1H), 6.80−6.73 (m, 2H), 6.20 (dd, J = 15.9, 6.8 Hz, 1H), 5.31 (d, J = 6.7 Hz, 1H), 5.15 (d, J = 7.5 Hz, 1H), 3.86 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 172.8, 163.9, 161.5, 147.9, 132.2, 131.9, 131.0, 129.3, 129.1, 129.0, 128.3, 128.2, 126.2, 124.9, 123.1, 115.78, 115.6, 115.1, 76.7, 68.4, 55.3; HRMS (ESI) found 415.1459, calcd for $C_{25}H_{19}FN_2O_3$ ([M + H]$^+$) 415.1458; IR (KBr) 1719, 1597, 1508, 1454, 1385, 1227, 1198, 970, 758, 692, 619.

(3S,3aS,6aR)-3-((E)-2-Methylstyryl)-2,5-diphenyldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2g**): ethyl acetate/petroleum ether = 1:5, 63% yield (0.130 g, dr = 10:1), pale yellow solid, mp 175−177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (q, J = 4.9 Hz, 4H), 7.30−7.26 (m, 2H), 7.18 (dt, J = 17.1, 7.3 Hz, 5H), 7.11−6.98 (m, 2H), 6.93−6.73 (m, 2H), 6.13 (dd, J = 15.8, 7.1 Hz, 1H), 5.31 (d, J = 7.1 Hz, 1H), 5.17 (d, J = 7.5 Hz, 1H), 3.89 (d, J = 7.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 172.9, 147.8, 135.8, 135.0, 131.7, 131.0, 130.4, 129.2, 129.1, 129.0, 128.2, 126.4, 126.2, 126.2, 125.8, 123.0, 115.4, 68.7, 55.3, 19.8; HRMS (ESI) found 411.1706, calcd for $C_{26}H_{22}N_2O_3$ ([M + H]$^+$) 411.1709; IR (KBr) 1716, 1647, 1597, 1491, 1383, 1263, 1196, 754, 691, 669, 651, 621.

(3S,3aS,6aR)-5-Benzyl-2-phenyl-3-((E)-4-(trifluoromethyl)styryl)-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2h**): ethyl acetate/petroleum ether = 1:5, 61% yield (0.146 g, dr = 37:1), brown solid, mp 61−62 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.30−7.24 (m, 5H), 7.21 (dd, J = 8.5, 7.5 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 16.0 Hz, 1H), 6.25 (dd, J = 16.0, 7.5 Hz, 1H), 5.03 (d, J = 7.5 Hz, 1H), 5.00 (d, J = 7.3 Hz, 1H), 4.49 (d, J = 1.7 Hz, 2H), 3.66 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5, 173.4, 146.8, 139.2, 134.8, 132.6, 128.9, 128.7, 128.6, 128.0, 127.6, 126.8, 125.6, 125.6, 125.6, 123.2, 115.8, 76.2, 68.3, 55.2, 42.8; HRMS (ESI) found 479.1574, calcd for $C_{27}H_{21}F_3N_2O_3$ ([M + H]$^+$) 479.1583; IR (KBr) 1715, 1489, 1396, 1325, 1169, 1123, 1067, 1016, 970, 758, 695, 669.

(3S,3aS,6aR)-5-Benzyl-3-(4-fluorostyryl)-2-phenyldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2i**): ethyl acetate/petroleum ether = 1:5, 53% yield (0.114 g, dr = 15:1), pale yellow solid, mp 104−105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.21 (m, 12H), 7.03 (d, J = 7.8 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 16.0, 7.7 Hz, 1H), 5.03 (dd, J = 7.4, 2.5 Hz, 2H), 4.52 (s, 2H), 3.69 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.6, 173.5, 163.9, 161.4, 146.8, 134.8, 132.8, 131.9, 131.9, 128.9, 128.7, 128.6, 128.2, 128.2, 128.0, 124.5, 123.0, 115.9, 115.7, 115.5, 76.2, 68.4, 55.3, 42.8; HRMS (ESI) found 429.1636, calcd for $C_{26}H_{21}FN_2O_3$ ([M + H]$^+$) 429.1614; IR (KBr) 1715, 1684, 1508, 1489, 1456, 1396, 1339, 1227, 1777, 1159, 756, 692, 669, 419.

(3S,3aS,6aR)-5-Benzyl-3-(4-methoxystyryl)-2-phenyldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2j**): ethyl acetate/petroleum ether = 1:5, 48% yield (0.106 g, dr = 9:1), orange oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.13 (m, 9H), 7.00 (d, J = 7.8 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 15.9 Hz, 1H), 6.00 (dd, J = 15.9, 7.7 Hz, 1H), 4.98 (t, J = 6.5 Hz, 2H), 4.49 (d, J = 1.8 Hz, 2H), 3.78 (s, 3H), 3.65 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 173.6, 159.8, 146.9, 134.9, 133.5, 128.8, 128.7, 128.6, 128.0, 127.9, 122.9, 122.5, 115.9, 114.1, 76.1, 68.6, 55.4, 55.3, 42.8; HRMS (ESI) found 441.1808, calcd for $C_{27}H_{24}N_2O_4$ ([M + H]$^+$) 441.1814; IR (KBr) 1717, 1684, 1559, 1541, 1508, 1396, 1339, 1250, 1175, 1030, 750, 690, 669, 419.

(3S,3aS,6aR)-5-Benzyl-3-(2-methylstyryl)-2-phenyldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2k**): ethyl acetate/petroleum ether = 1:5, 54% yield (0.115 g, dr = 9:1), brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.22 (m, 8H), 7.18−7.05 (m, 3H), 7.02 (d, J = 7.8 Hz, 2H), 6.97−6.86 (m, 2H), 5.98 (dd, J = 15.8, 7.9 Hz, 1H), 4.99 (t, J = 7.3 Hz, 2H), 4.54 (d, J = 4.5 Hz, 2H), 3.67 (d, J = 7.4 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7, 173.6, 146.8, 135.7, 135.1, 134.9, 132.5, 130.3, 128.8, 128.7, 128.5, 128.1, 128.0, 126.1, 126.0, 125.9, 123.0, 116.2, 75.9, 68.8, 55.2, 42.8, 19.7; HRMS (ESI) found 425.1859, calcd for $C_{27}H_{24}N_2O_3$ ([M + H]$^+$) 425.1865; IR (KBr) 1717, 1489, 1456, 1396, 1339, 1175, 1020, 968, 752, 692, 669, 419.

(3S,3aS,6aR)-5-Benzyl-2-phenyl-3-styryldihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2l**): ethyl acetate/petroleum ether = 1:5, 55% yield (0.113 g, dr = 17:1), yellow solid, mp 147−148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.20 (m, 13H), 7.03 (d, J = 7.8 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 16.0, 7.7 Hz, 1H), 5.03 (dd, J = 7.4, 2.5 Hz, 2H), 4.52 (s, 2H), 3.69 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7, 173.6, 146.8, 135.7, 134.8, 134.0, 128.8, 128.7, 128.6, 128.6, 128.3, 128.0, 126.6, 124.7, 123.0, 115.9, 76.0, 68.4, 55.3, 42.8; HRMS (ESI) found 411.1721, calcd for $C_{26}H_{22}N_2O_3$ ([M + H]$^+$) 411.1709; IR (KBr) 1715, 1645, 1634, 1489, 1395, 1339, 1175, 1020, 968, 752, 692, 669, 418.

(E)-2-(2-(5-Methyl-4,6-dioxo-2-phenylhexahydro-2H-pyrrolo[3,4-d]isoxazol-3-yl)vinyl)phenyl 4-Methylbenzenesulfon-ate (**2m**): ethyl acetate/petroleum ether = 1:4, 53% yield (0.134 g, dr = 15:1), pale yellow solid, mp 162−164 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 8.3 Hz, 2H), 7.38−7.28 (m, 3H), 7.28−7.14 (m, 5H), 7.07 (dd, J = 7.7, 1.6 Hz, 1H), 7.01−6.91 (m, 3H), 6.73 (d, J = 16.1 Hz, 1H), 6.08 (dd, J = 16.1, 7.1 Hz, 1H), 4.95 (t, J = 7.2 Hz, 2H), 3.59 (d, J = 7.3 Hz, 1H), 2.76 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 173.8, 147.0, 146.9, 145.5, 129.9, 129.7, 129.1, 128.9, 128.4, 127.6, 127.2, 126.9, 123.1, 122.9, 115.4, 76.1, 67.7, 54.8, 24.9, 21.6; HRMS (ESI) found 505.1429, calcd for $C_{27}H_{25}N_2O_6S$ ([M + H]$^+$) 505.1433; IR (KBr) 1790, 1707, 1597, 1489, 1456, 1435, 1375, 1285, 1194, 1180, 1163, 1082, 1034, 970, 880, 770, 719, 694, 669, 662, 561.

(3S,3aS,6aR)-5-Methyl-2-phenyl-3-((E)-2-(pyridin-3-yl)vinyl)-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**2n**): ethyl acetate/petroleum ether = 1:3, 66% yield (0.111 g, dr > 20:1), yellow solid, mp 153−154 °C; ^{1}H NMR (DMSO-*d*, 500 MHz) δ 7.52−7.37 (m, 3H), 7.35 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 7.1 Hz, 2H), 7.11 (d, J = 8.6 Hz, 1H), 6.55 (d, J = 1.0 Hz, 1H), 5.07 (d, J = 7.3 Hz, 1H), 4.64 (t, J = 11.1 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.28 (d, J = 11.0 Hz, 1H), 4.00 (d, J = 7.4 Hz, 1H), 2.93 (s, 3H); ^{13}C NMR (DMSO-*d*, 125 MHz) δ 174.7, 173.7, 149.1, 148.3, 146.9, 133.1, 130.4, 128.9, 127.3, 123.5, 123.1, 115.6, 75.9, 68.0, 55.0, 25.0; HRMS (ESI) found 336.1340, calcd for $C_{19}H_{17}N_3O_3$ ([M + H]$^+$) 336.1348; IR (KBr) 1869, 1843, 1825, 1717, 1705, 1558, 1541, 1506, 1435, 1418, 1339, 1287, 1134, 1026, 670, 419.

4-((E)-2-((3S,3aS,6aR)-5-Methyl-4,6-dioxo-2-phenylhexahydro-2H-pyrrolo[3,4-d]isoxazol-3-yl)vinyl)benzonitrile (**2o**): ethyl acetate/petroleum ether = 1:5, 46% yield (0.083 g, dr > 20:1), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (s, 1H), 7.52 (dd, J = 7.8, 1.5 Hz, 2H), 7.43−7.36 (m, 1H), 7.29−7.23 (m, 2H), 7.01 (dd, J = 8.7, 1.0

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Hz, 2H), 6.95 (dd, J = 10.6, 4.2 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 6.23 (dd, J = 16.0, 7.3 Hz, 1H), 5.07 (d, J = 7.2 Hz, 1H), 5.00 (d, J = 7.3 Hz, 1H), 3.67 (d, J = 7.2 Hz, 1H), 2.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 173.7, 146.9, 137.0, 131.7, 131.5, 130.7, 130.0, 129.5, 129.0, 127.7, 123.2, 118.4, 115.6, 113.0, 76.1, 67.9, 55.0, 25.1; HRMS (ESI) found 360.1342, calcd for $C_{21}H_{17}N_3O_3$ ([M + H]$^+$) 360.1343; IR (KBr) 1792, 1715, 1699, 1558, 1489, 1456, 1384, 1285, 1132, 1031, 970, 762, 689, 669.

*(E)-N-((E)-3-(2-(Tosyloxy)phenyl)allylidene)aniline oxide (**5a**):* ethyl acetate/petroleum ether = 1:1, yellow solid, mp 133−134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83−7.73 (m, 3H), 7.70 (d, J = 7.7 Hz, 3H), 7.50 (s, 4H), 7.35−7.27 (m, 4H), 7.15−7.00 (m, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.5, 147.4, 146.0, 136.0, 132.3, 131.8, 130.2, 130.2, 129.9, 129.2, 128.6, 127.6, 126.8, 123.4, 121.3, 120.6, 21.7; HRMS (ESI) found 394.1101, calcd for $C_{22}H_{19}NO_4S$ ([M + H]$^+$) 394.1113; IR (KBr) 1867, 1844, 1749, 1717, 1684, 1558, 1541, 1506, 1457, 1275, 1260, 764, 750, 669, 419.

*Derivatization of the Product (Synthesis of **3a**, **4a**, and **4b**). Synthesis of **3a**:* To a solution of **2a** (90 mg, 0.3 mmol) in DCM (7 mL) were added powdered Zn (294 mg, 4.5 mmol) and glacial acetic acid (1.0 mL). The reaction mixture was stirred vigorously at 40 °C for 24 h. The mixture was neutralized carefully with saturated aqueous $NaHCO_3$ solution and was extracted three times using DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash silica gel column chromatography (ethyl acetate/petroleum ether = 2:1) to give compound **3a**.

*(3R,4S)-3-Hydroxy-1-methyl-4-((S,E)-3-phenyl-1-(phenylamino)-allyl)pyrrolidine-2,5-dione (**3a**):* ethyl acetate/petroleum ether = 2:1, 81% yield (0.082 g), yellow solid, mp 188−189 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.27 (m, 4H), 7.23 (dt, J = 6.8, 3.1 Hz, 1H), 7.17 (t, J = 7.9 Hz, 2H), 6.73 (dd, J = 17.7, 7.8 Hz, 3H), 6.62 (d, J = 16.0 Hz, 1H), 6.28 (dd, J = 16.0, 6.3 Hz, 1H), 4.89 (s, 1H), 4.81 (d, J = 8.4 Hz, 1H), 4.56 (d, J = 8.4 Hz, 1H), 3.47 (br s, 1H), 3.39 (dd, J = 8.4, 3.0 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3, 175.8, 146.4, 136.4, 132.2, 129.3, 128.6, 127.8, 127.7, 126.5, 118.7, 114.6, 68.4, 55.1, 50.0, 24.7; HRMS (ESI) found 337.1538, calcd for $C_{20}H_{20}N_2O_3$ ([M + H]$^+$) 337.1552; IR (KBr) 1697, 1601, 1541, 1506, 1456, 1435, 1387, 1281, 1123, 970, 750, 692, 669, 419.

*Synthesis of **4a**:* To a solution of **2a** (90 mg, 0.3 mmol) in MeCN (1 mL) was added 1 equiv of NBS (53 mg, 0.3 mmol). The reaction mixture was stirred at 60 °C for 24 h. The mixture was quenched with saturated $NaHCO_3$ solution and was extracted three times using ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash silica gel column chromatography (petroleum ether/ethyl acetate = 5:1) to give compound **4a**.

*(3S,3aS,6aR)-2-(4-Bromophenyl)-5-methyl-3-((E)-styryl)dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione (**4a**):* ethyl acetate/petroleum ether = 1:5, 96% yield (0.118 g), yellow solid, mp 125−127 °C; ^{1}H NMR (MeOD, 400 MHz) δ 7.36 (d, J = 8.0 Hz, 4H), 7.30 (t, J = 7.3 Hz, 2H), 7.25 (d, J = 7.1 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 16.0, 7.8 Hz, 1H), 5.11 (dd, J = 14.9, 7.5 Hz, 2H), 3.83 (d, J = 7.2 Hz, 1H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 167.1, 146.3, 138.1, 134.3, 132.7, 132.3, 129.3, 128.2, 127.3, 125.6, 114.8, 110.6, 98.3, 67.9, 49.9, 39.5, 24.5; HRMS (ESI) found 411.0349, calcd for $C_{20}H_{17}BrN_2O_3$ ([M − H]$^-$) 411.0344; IR (KBr)1790, 1709, 1485, 1435, 1381, 1284, 1134, 1072, 1034, 1003, 968, 826, 694, 623, 501, 419.

*Synthesis of **4b**:* To a solution of **2a** (90 mg, 0.3 mmol) in MeCN (1 mL) was added 2 equiv of NBS (106 mg, 0.6 mmol). The reaction mixture was stirred at 60 °C for 24 h. The mixture was quenched with saturated $NaHCO_3$ solution and was extracted three times using ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash silica gel column chromatography (ethyl acetate/petroleum ether = 5:1) to give compound **4b**.

*(5R,6S,6aR,6bS,9aR)-3,6-Dibromo-8-methyl-5-phenyl-6,6a,8,9a-tetrahydropyrrolo[3′,4′:4,5]isoxazolo[2,3-a]quinoline-7,9(5H,6bH)-dione (**4b**):* ethyl acetate/petroleum ether = 1:5, 95% yield (0.140 g), yellow solid, mp 192−193 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.52−7.37 (m, 3H), 7.35 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 7.1 Hz, 2H), 7.11 (d, J = 8.6 Hz, 1H), 6.55 (d, J = 1.0 Hz, 1H), 5.07 (d, J = 7.3 Hz, 1H), 4.64 (t, J = 11.1 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.28 (d, J = 11.0 Hz, 1H), 4.00 (d, J = 7.4 Hz, 1H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.5, 175.4, 141.2, 139.7, 135.5, 131.9, 130.9, 129.6, 129.4, 128.2, 119.9, 76.3, 66.6, 54.7, 53.6, 52.2, 25.3; HRMS (ESI) could not be obtained for this particular compound under either positive or negative ionization; IR (KBr) 1715, 1705, 1684, 1558, 1541, 1506, 1472, 1456, 1435, 1339, 1281, 1136, 1040, 764, 750, 669, 419.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra of new compounds. X-ray data for compounds **2a**, *cis*-**2a**, **4b**, and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (b) Zhu, J. P. In *Multicomponent Reactions*, 1st ed.; Bienaymé, H., Ed.; Wiley-VCH: Weinheim, Germany, 2005. (c) Bruggink, A.; Schoevaart, B.; Kieboom, T. *Org. Process Res. Dev.* **2003**, *7*, 622.

(2) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (c) Patureau, F. W.; Wencel-Delord, F.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.

(3) (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (d) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

(4) (a) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1998. (b) Brown, R. C. *N-Oxides and Nitrones in Organic Chemistry of Aliphatic Compounds*; Oxford Clarendon Press: Oxford, 1994.

(5) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed.; Academic Press: San Diego, CA, 1989; Vol. 3, p 351.

(6) For recent reviews on allylic C−H oxidation reactions, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2944. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. For related examples, see: (c) Vermeulen, N. A.; Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 11323−11328. (d) Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892. (e) Qin, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 15893−15895. (f) Dong, S.; Qin, T.; Hamel, E.; Beutler, J. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2012**, *134*, 19782. (g) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*,

12584. (h) Young, A. J.; White, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6824.
(7) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.
(8) For examples on selective [3 + 2] dipolar cycloaddition of nitrones, see: (a) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411. (b) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (c) Desimoni, G.; Faita, G.; Mella, M.; Boiocchi, M. *Eur. J. Org. Chem.* **2005**, 1020. (d) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457. (e) Viton, F.; Bernardinelli, G.; Kuendig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968. (f) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353.
(9) Chakraborty, B.; Samanta, A.; Sharma, P. K.; Chhetri, M. S.; Kafley, S.; Banerjee, A.; Sinha, C. *J. Chem. Pharm. Res.* **2010**, *2*, 727.
(10) Agirbas, H.; Guner, S.; Budak, F.; Keceli, S.; Kandemirli, F.; Shvets, N.; Kovalishynd, V.; Dimoglo, A. *Bioorg. Med. Chem.* **2004**, *12*, 1629.
(11) Badru, R.; Anand, P.; Singh, B. *Eur. J. Med. Chem.* **2012**, *48*, 81.
(12) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.
(13) Recently, Read de Alaniz reported copper-catalyzed aerobic oxidation of hydroxyl amines to nitroso products and an ene tethered cascade: (a) Frazier, C. P.; Engelking, J. R.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2011**, *133*, 10430. (b) Frazier, C. P.; Bugarin, A.; Engelking, J. R.; Read de Alaniz, J. *Org. Lett.* **2012**, *14*, 3620. For copper-catalyzed dehydrogenation of hydrazines to hydrazones, see: (c) Gao, W.; He, Z.; Qian, Y.; Zhao, J.; Huang, Y. *Chem. Sci.* **2012**, *3*, 883. (d) Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6174−6177.
(14) (a) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131. (b) Leach, A. G.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 14820. (c) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5226.
(15) Kliegel, W. *Tetrahedron Lett.* **1969**, *10*, 2627.
(16) Knight, G. T.; Pepper, B. *Chem. Commun.* **1971**, 1507.
(17) Alper, H.; Vasapollo, G. *Tetrahedron Lett.* **1987**, *28*, 6411.
(18) (a) Baruah, J. B.; Samuelson, A. G. *Tetrahedron* **1991**, *47*, 9449. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.
(19) NOE studies by Corey et al. have shown that maleimides preferred to coordinate to Lewis acids in an *s-cis* manner to minimize stereoelectronic interaction. See: Corey, E. J.; Sarshar, S.; Lee, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 12089.