Tetrahedron
journal homepage: www.elsevier.com

Oxidative Synthesis of Benzo[1,4]oxazines from α-Branched Primary Amines and *ortho*-Benzoquinones

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

ABSTRACT

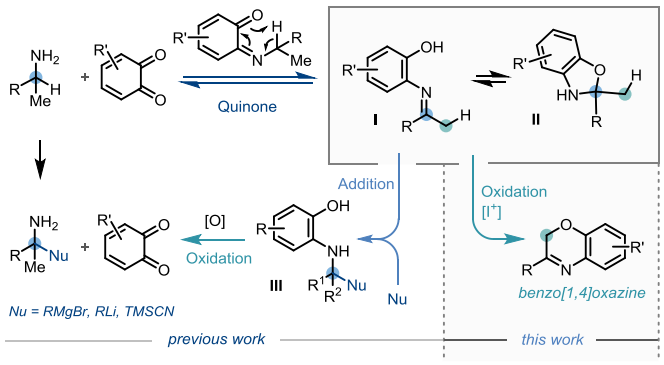
The efficient oxidative construction of benzo[1,4]oxazines from simple α-branched amines and *ortho*-benzoquinones is reported. The procedure pivots on a triethylamine and iodine mediated oxidative ring closure from the ketimine intermediate formed upon their condensation. This reaction was shown to tolerate a variety of α-branched benzylamines and downstream derivatization to substituted benzomorpholine structures was also demonstrated.

1. Introduction

The use of *ortho*-benzoquinone reagents for the efficient oxidation of amines leads back to pioneering work from McCoy and Day,[1] and Corey.[2] These studies revealed that treatment of a primary amine with *ortho*-benzoquinones afforded the corresponding aldehyde/ketone *via* a mechanism that involved an initial condensation to afford the Schiff base, a subsequent [1,5]-H-shift, and a final hydrolysis of the resulting imine. These investigations also confirmed that the imine intermediates (Scheme 1, I) are in equilibrium with their corresponding ring-closed hemiaminal forms (Scheme 1, II). More recent investigations from the groups of Klinman and Mure,[3] and Sayre[4] amongst others[5] have established that this type of mechanism is also at play in copper amine oxidases,[6] facilitating the biocatalytic conversion of primary amines to aldehydes utilizing a quinone co-factor.

These biocatalytic studies have launched recent interest in synthetic bio-inspired amine manipulation using *ortho*-quinones,[7] with notable contributions from Stahl,[8] Kobayashi,[9] Largeron and Fleury[10] (for amine oxidation), Qu,[11] Clift[12] (for amine functionalization), and Lumb[13] (for heterocycle synthesis).

Scheme 1: Previous work on the functionalization of primary amines with *ortho*-benzoquinones and the current application to oxidative benzo[1,4]oxazine synthesis.



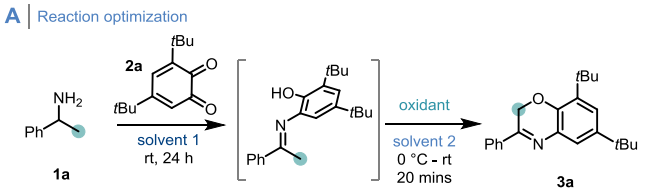
Very recently, our group disclosed the application of the ketimine intermediates for carbon-carbon bond formation in a three-step, one-pot protocol for the α-functionalization of primary amines. The ketimine intermediates would engage with nucleophiles (Scheme 1, I) such as organometallic reagents and cyanide, and also in photoredox reverse polarity catalysis, enabling union with electrophiles *via* an intermediary nucleophilic α-amino radical.[14] In a continuation of our work, and aligned to Lumb's elegant report on the manipulation of similar quinone intermediates into a diverse portfolio of heterocycles, we were intrigued to explore the performance of the ketimines intermediates in subsequent ring forming reactions, and herein we wish to report our findings.

2. Results and Discussion

During some preliminary studies leading up to our amine-to-amine C-H functionalization protocol,[14] we noted that in instances where the nucleophilic addition step was somewhat inefficient (for various reasons), low yields of benzo[1,4]oxazine products were obtained from the reaction mixture. This product – presumably arising from base-mediated iodine oxidation of the ketimine intermediate – constitutes a formal α-oxidation / β-C–H functionalization of the amine substrate rather than just α-oxidation / functionalization as was expected. As benzo[1,4]oxazines have been shown to possess interesting biologically activity for potential use in cancer therapeutics,[15] we recognized that establishing a mild and simple protocol to access them could be of interest to future discovery and development programmes.

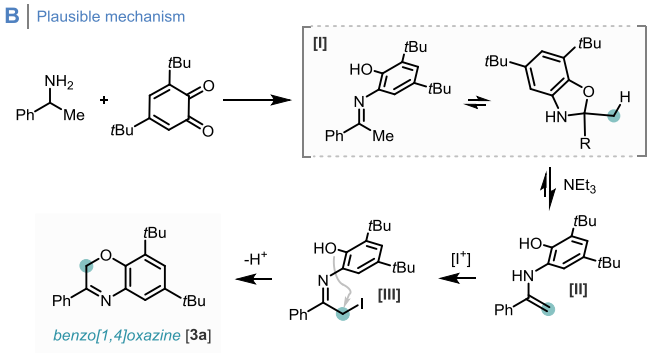
Pleasingly when conducting the transformation using 1-phenylethan-1-amine (**1a**) and 3,5-di-*tert*-butyl-*o*-benzoquinone (**2a**) without the organometallic addition step, efficient heterocycle formation (**3a**) resulted (81%, Scheme 2A, entry 1). In attempts to increase yield and probe the reaction mechanism different oxidation conditions were studied (entries 2-6). When we exchanged the oxidation system for H_5IO_6, no formation of **3a** was observed (entry 2), and acetophenone – arising from hydrolysis of the ketimine intermediate – was isolated in almost quantitiatve yield from the reaction mixture.

Scheme 2: (A) Optimization of the synthesis of benzo[1,4]oxazine from primary amines. (B) Plausible reaction mechanism.



entry	solvent 1	oxidant	solvent 2	3a[a]
1	PhMe	I_2 (1.1 eq) / NaOH (5 eq)	MeCN:H_2O (1:2)	81
2	PhMe	H_5IO_6 (1.1 eq)	MeCN:H_2O (1.5:1)	-[b]
3	MeCN	$PhI(OAc)_2$ (2 eq)	MeCN:H_2O (1.5:1)	-
4	**MeCN**	**I_2 (2 eq) / NEt_3 (3 eq)**	**MeCN**	**89**
5	MeCN	NIS (1.2 eq)	MeCN	-
6	MeCN	NIS (1.2 eq) / NaOH (5 eq)	MeCN:H_2O (1:2)	33

General reaction conditions: step (i) 1-phenylethan-1-amine (**1a**, 1 mmol), 3,5-di-*tert*-butyl-*o*-benzoquinone (**2a**, 1 mmol), solvent 1 (0.1 M). step (ii) oxidant (x eq), solvent 2 (0.1 M), 0 °C - rt, 20 mins. *a* : isolated yield after silica gel colum chromatography. *b* : acetophenone observed as a byproduct in quantitative yield.

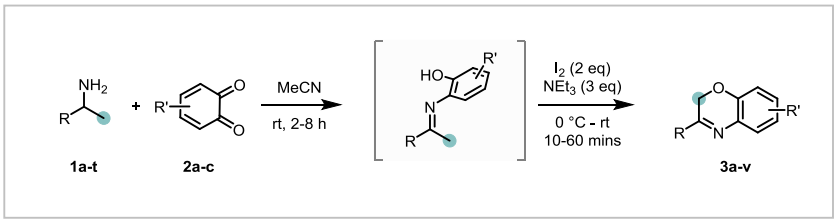


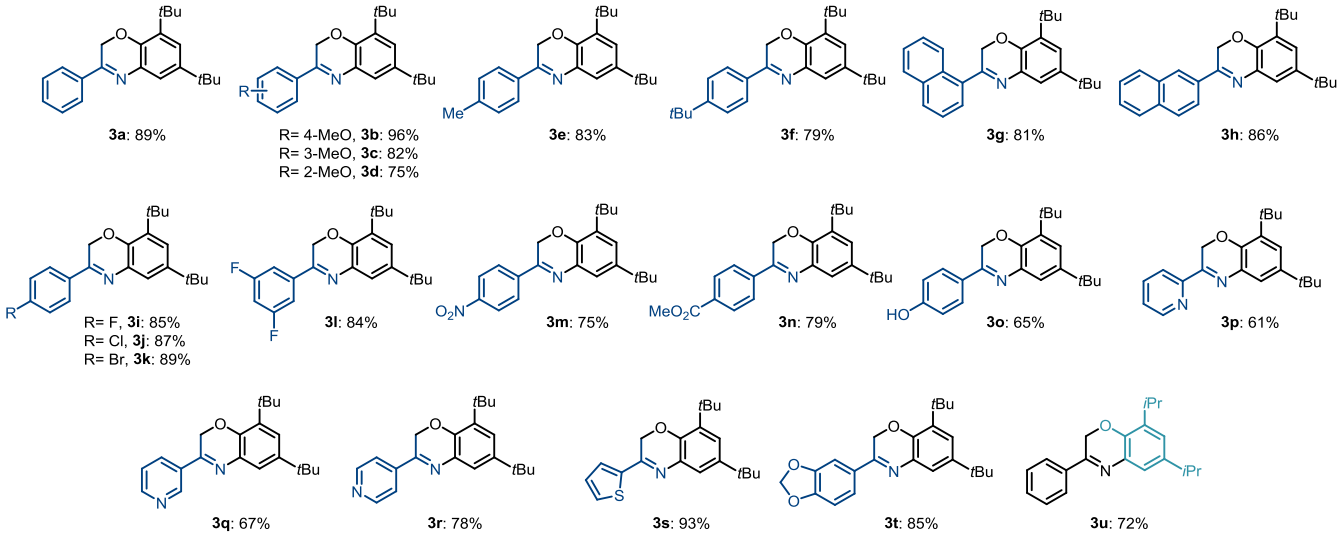
Furthermore, $PhI(OAc)_2$ also gave no formation of the **3a** (entry 3).[16] Preliminary investigations suggested a solvent switch to acetonitrile would still permit ketimine formation and would create a more streamlined process. Using this solvent and with iodine as the oxidant and switching to triethylamine as the base we were delighted to find that the benzo[1,4]oxazine **3a** was formed in 89% yield (entry 4). Further experiments demonstrated that using NIS as the oxidant with no added base was ineffective, however, on addition of base, reactivity was restored (entries 5-6).

As there is a need for an electrophilic iodine oxidant *plus* a base for efficient formation of benzo[1,4]oxazine **3a**, a plausible mechanistic pathway arises (Scheme 2B). We suggest that – aligned to previous reports – condensation of our primary amine with the *ortho*-benzoquinone delivers the ketimine/hemiaminal equilibrating pair [I]. Added Brønsted base then promotes ketimine / enamine tautomerization and in the presence of iodine, the enamine nucleophile reacts to afford the α-imino-alkyl iodide [III]. Subsequent base-promoted intramolecular ring closure from the pendant phenol delivers the benzo[1,4]-oxazine.

With optimal conditions in hand we proceeded to explore the scope of this transformation (Scheme 3). Gratifyingly substitution across the aromatic ring of the phenylethanamine was tolerated as *ortho*-, *meta*-, and *para*-methoxyarenes delivered the heterocyclic product in excellent yields (**3b-d**). Following this, substrates possessing alkyl substituents and naphthyl derivatives were submitted to the reaction conditions and pleasingly formed products in excellent efficiency (**3e-h**). Halogen (**3i-k**), nitro (**3m**), ester (**3n**) and even phenolic (**3o**) substituents were also compatible with the transformation and the respective products were obtained in good to excellent yields. Furthermore heteroaromatic ethyl amine substrates were studied; 2-, 3-, and 4-pyridyl systems performed effectively, as did one containing a thiophene structure (**3s**); in all cases the desired benzo[1,4]-oxazine product was obtained with excellent efficiency.

Scheme 3: Scope of the oxidative synthesis of benzo[1,4]oxazines

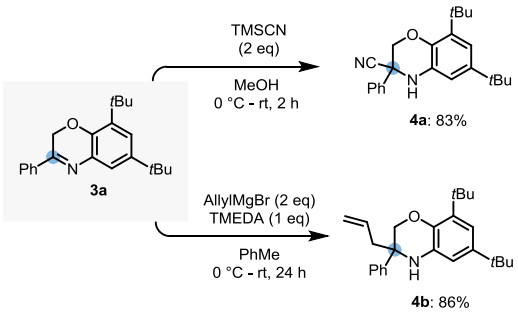




On varying the quinone coupling partner, we were pleased to see that *iso*-propyl variant (**3u**) proceeded well under the reaction conditions. Unfortunately neither substrates bearing further functionalization on the β-position of the primary amine nor unsubstituted *ortho*-benzoquinones were tolerated in this methodology.

We then looked to demonstrate that the benzo[1,4]oxazine products could be transformed into substituted benzomorpholine structures. In order to explore this we subjected benzo[1,4]oxazine **3a** to nucleophilic allylation and cyanation conditions. Satisfyingly, these efforts delivered α-allyl (**4a**) and α-cyano (**4b**) benzomorpholine derivatives in excellent yields (Scheme 4).

Scheme 4: Synthesis of benzomorpholines from the benzo[1,4]oxazine product **3a**.



Conclusion

In conclusion we have disclosed a new one-pot synthesis of substituted benzo[1,4]-oxazines from α-branched amines and *ortho*-quinones. This transformation proceeds *via* the well-precedented quinone oxidative rearrangement upon initial condensation, followed by an electrophilic iodine/base mediated ring closure to create the oxazine heterocycle. The transformation was applicable to a wide range of α-branched benzylamine derivatives and their respective benzo[1,4]-oxazines products were afforded in excellent yields.

Acknowledgement. D.V. acknowledge funding from the European Union's Horizon 2020 research and innovation framework programme under the Marie Skłodowska-Curie grant agreement No 703789. J.A.L. thanks the Leverhulme Trust (RPG-2017-069) for a research fellowship.

Conflict of interest: The authors declare no conflict of interest

3. Experimental

General information:

All reagents were purchased from commercial sources and used without further purification. Unless otherwise noted, all the reactions were performed under argon atmosphere. All reactions were monitored by thin-layer chromatography (TLC) using Merck Kieselgel 60 F254 fluorescent treated silica. Visualization was accomplished under UV light (λ_{max}= 254 nm) and by staining with potassium permanganate staining dip. Chromatographic purification was performed on VWR 60 silica gel 40-63 μm using HPLC grade solvents that were used as supplied. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 400 or 500 MHz in deuterated solvents at 25 ºC. Proton chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) with the solvent resonance as internal standard: $CDCl_3$, δ = 7.26 ppm; CD_3OD, δ = 3.31 ppm. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the solvent resonance as internal standard: $CDCl_3$, δ = 77.16 ppm; CD_3OD, δ = 49.00 ppm. High-resolution mass spectra (HRMS) were recorded on Bruker Daltonics MicroTOF mass spectrometer equipped with an ESI source. Infrared spectra (IR) were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film on a diamond ATR module and reported a selected maximum absorbances.

General procedure for the synthesis of benzo[1,4]oxazines:

To a stirred solution of *ortho*-benzoquinone (0.825 mmol, 1.0 equiv) in acetonitrile (4.0 mL), was added dropwise a solution of primary amine (0.825 mmol, 1.0 equiv) in acetonitrile (4.25 mL) over 5 min under an argon atmosphere. The deep green coloured solution was stirred at room temperature for 2-8 h. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to 0 ˚C. To this, triethylamine (0.34 mL, 2.48 mmol, 3 equiv) and iodine granules (0.419 g, 1.65 mmol, 2 eq), were added. The resulting mixture was stirred vigorously for 10-60 minutes under argon atmosphere. Upon completion, the reaction mixture was diluted with water and extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with aqueous saturated sodium thiosulfate (1 x 10 mL) and brine (2 x 10 mL), respectively, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with pentane:EtOAc (95:5-80:20 v:v) to afford the desired benzo[1,4]oxazine product.

Data for the benzo[1,4]oxazine products:

6,8-di-tert-butyl-3-phenyl-2H-benzo[b][1,4]oxazine **(3a**).

Yellow amorphous solid (236 mg, 0.734 mmol, 89%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 3961, 2905, 1601, 1479, 14478. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 – 7.89 (m, 2H), 7.50 – 7.46 (m, 3H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 4.99 (s, 2H), 1.42 (s, 9H), 1.36 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.5, 144.3, 142.7, 136.9, 135.9, 134.4, 131.0, 128.9, 126.6, 123.2, 122.8, 62.1, 34.8, 34.7, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{22}H_{28}NO$ [$(M+H)^+$]: 322.2165, found: 322.2167.

6,8-di-tert-butyl-3-(4-methoxyphenyl)-2H-benzo[b][1,4]oxazine **(3b).**

Off-white solid (223 mg, 0.634 mmol, 96%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2968, 1734, 1606, 1560, 1515, 1502, 1462, 1422. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 4.94 (s, 2H), 3.87 (s, 3H), 1.41 (s, 9H), 1.35 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.0, 158.0, 144.2, 142.7, 136.8, 134.6, 128.6, 128.3, 122.7, 122.5, 114.3, 61.9, 55.6, 34.8, 34.6, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{23}H_{30}NO_2$ [$(M+H)^+$]: 352.2271, found: 352.2271.

6,8-di-tert-butyl-3-(3-methoxyphenyl)-2H-benzo[b][1,4]oxazine **(3c)**.

Yellow oil (190 mg, 0.541 mmol, 82%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1582, 1462. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.57 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.43 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.04 (ddd, *J* = 8.0, 2.7, 1.2 Hz, 1H), 4.96 (s, 2H), 3.90 (s, 3H), 1.42 (s, 9H), 1.36 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.1, 158.3, 144.3, 142.8, 137.3, 136.9, 134.4, 129.8, 123.3, 122.8, 119.1, 117.5, 111.2, 62.1, 55.6, 34.8, 34.6, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{23}H_{30}NO_2$ [$(M+H)^+$]: 352.2271, found: 352.2266.

***6,8-di-tert-butyl-3-(2-methoxyphenyl)-2H-benzo[b][1,4]oxazine* (3d).**

Pale yellow soild (175 mg, 0.498 mmol, 75%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2959, 1601, 1488, 1463, 1437, 1411. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.84 (s, 2H), 3.88 (s, 3H), 1.40 (s, 9H), 1.33 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.7, 158.5, 144.1, 143.4, 136.9, 134.8, 131.8, 129.6, 126.9, 122.8, 122.5, 121.4, 111.1, 64.5, 55.6, 34.8, 34.7, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{23}H_{30}NO_2$ [$(M+H)^+$]: 352.2271, found: 352.2272.

***6,8-di-tert-butyl-3-(p-tolyl)-2H-benzo[b][1,4]oxazine* (3e)**.

Yellow oil (206 mg, 0.614 mmol, 83%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2980, 2969, 1601, 1641, 1478, 1461. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.84 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 2.4 Hz, 1H), 4.96 (s, 2H), 2.42 (s, 3H), 1.42 (s, 9H), 1.36 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.5, 144.2, 142.8, 141.4, 136.8, 134.5, 133.2, 129.6, 126.6, 122.9, 122.7, 62.0, 34.8, 34.6, 31.7, 29.9, 21.7. **HRMS** (ESI) Calcd for $C_{23}H_{30}NO$ [$(M+H)^+$]: 336.2322, found: 336.2317.

***6,8-di-tert-butyl-3-(4-(tert-butyl)phenyl)-2H-benzo[b][1,4]oxazine* (3f)**.

Pale yellow solid (168 mg, 0.445 mmol, 79%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2926, 2905, 2970, 1607, 1557, 1478, 1410. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 4.97 (s, 2H), 1.42 (s, 9H), 1.37 (s, 9H), 1.36 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.5, 154.5, 144.2, 142.8, 136.8, 134.6, 133.2, 126.4, 125.8, 122.9, 122.7, 62.0, 35.1, 34.8, 34.6, 31.7, 31.3, 29.9. **HRMS** (ESI) Calcd for $C_{26}H_{36}NO$ [$(M+H)^+$]: 378.2791, found: 378.2792.

***6,8-di-tert-butyl-3-(naphthalen-1-yl)-2H-benzo[b][1,4]oxazine* (3g).**

Yellow oil (176 mg, 0.474 mmol, 81%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2962, 2904, 1591, 1509, 1479, 1462, 1410. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.50 – 8.39 (m, 1H), 7.98 – 7.87 (m, 2H), 7.66 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.61 – 7.52 (m, 3H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 4.95 (s, 2H), 1.45 (s, 9H), 1.37 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.5, 144.5, 142.8, 137.2, 135.0, 134.5, 134.2, 130.7, 130.6, 128.8, 127.3, 126.5, 126.3, 125.7, 125.2, 123.5, 122.9, 64.9, 34.9, 34.7, 31.7, 30.0. **HRMS** (ESI) Calcd for $C_{26}H_{30}NO$ [$(M+H)^+$]: 372.2322, found: 372.2328.

***6,8-di-tert-butyl-3-(naphthalen-2-yl)-2H-benzo[b][1,4]oxazine* (3h)**

Yellow solid (186 mg, 0.501 mmol, 86%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 1699, 14622. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 – 8.20 (m, 2H), 7.96 – 7.84 (m, 3H), 7.59 – 7.50 (m, 2H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 5.12 (s, 2H), 1.44 (s, 9H), 1.37 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.2, 144.4, 142.8, 136.9, 134.7, 134.6, 133.3, 133.1, 129.0, 128.8, 128.0, 127.6, 126.9, 126.8, 123.6, 123.3, 122.9, 62.0, 34.8, 34.7, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{26}H_{30}NO$ [$(M+H)^+$]: 372.2322, found: 372.2322.

***6,8-di-tert-butyl-3-(4-fluorophenyl)-2H-benzo[b][1,4]oxazine* (3i).**

Yellow solid (207 mg, 0.610 mmol, 85%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1601, 1510, 1475. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97 – 7.92 (m, 2H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.19 – 7.13 (m, 2H), 4.95 (s, 2H), 1.42 (s, 9H), 1.35 (s, 9H). **^{19}F NMR** (377 MHz, $CDCl_3$): δ -109.0. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.6 (d, $J_{C\text{-}F}$ = 252.7 Hz), 157.3, 144.4, 142.6, 136.9, 134.3, 132.2 (d, $J_{C\text{-}F}$ = 3.3 Hz), 128.7 (d, $J_{C\text{-}F}$ = 8.7 Hz), 123.3, 122.8, 116.0 (d, $J_{C\text{-}F}$ = 22.1 Hz), 61.9, 34.8, 34.6, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{22}H_{27}FNO$ [$(M+H)^+$]: 340.2071, found: 340.2057.

***6,8-di-tert-butyl-3-(4-chlorophenyl)-2H-benzo[b][1,4]oxazine* (3j)**

Yellow oil (199 mg, 0.559 mmol, 87%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1594, 1475. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 – 7.85 (m, 2H), 7.48 – 7.42 (m, 2H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 4.95 (s, 2H), 1.41 (s, 9H), 1.35 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.1, 144.5, 142.6, 137.1, 137.0, 134.3 (2xC), 129.2, 127.9, 123.5, 122.8, 61.8, 34.8, 34.7, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{22}H_{27}{}^{35}ClNO$ [$(M+H)^+$]: 356.1776, found: 356.1777.

***3-(4-bromophenyl)-6,8-di-tert-butyl-2H-benzo[b][1,4]oxazine* (3k)**

Yellow oil (178 mg, 0.445 mmol, 89%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1734, 1589, 1477. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.84 – 7.77 (m, 2H), 7.64 – 7.57 (m, 2H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 4.94 (s, 2H), 1.40 (s, 9H), 1.34 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2, 144.5, 142.6, 137.0, 134.7, 134.3, 132.1, 128.1, 125.6, 123.5, 122.8, 61.7, 34.8, 34.6, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{22}H_{27}{}^{79}BrNO$ [$(M+H)^+$]: 400.1271, found: 400.1269.

***6,8-di-tert-butyl-3-(3,5-difluorophenyl)-2H-benzo[b][1,4]oxazine* (3l)**

Pale yellow solid (190 mg, 0.532 mmol, 84%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1622, 1592, 1461. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 – 7.42 (m, 2H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.92 (tt, *J* = 8.6, 2.3 Hz, 1H), 4.91 (s, 2H), 1.40 (s, 9H), 1.35 (s, 9H). **^{19}F NMR** (377 MHz, $CDCl_3$): δ -108.7. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.4 (dd, $J_{C\text{-}F}$ = 250.1, 12.3 Hz), 155.7 (t, $J_{C\text{-}F}$ = 3.2 Hz), 144.7, 142.7, 139.1 (t, $J_{C\text{-}F}$ = 9.3 Hz),137.1, 134.0, 124.1, 123.1, 109.5 (dd, $J_{C\text{-}F}$ = 19.1, 7.4 Hz), 106.2 (t, $J_{C\text{-}F}$ = 25.6 Hz), 61.8, 34.8, 34.7, 31.6, 29.9. **HRMS** (ESI) Calcd for $C_{22}H_{26}F_2NO$ [$(M+H)^+$]: 358.1977, found: 358.1975.

***6,8-di-tert-butyl-3-(4-nitrophenyl)-2H-benzo[b][1,4]oxazine* (3m)**

Yellow solid (167 mg, 0.456 mmol, 75%). FT-IR (thin film) ν_{max} (cm^{-1}): 2980, 1598, 1523, 1478. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 5.01 (s, 2H), 1.41 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8, 149.1, 144.8, 142.6, 141.3, 137.2, 134.2, 127.4, 124.5, 124.1, 123.3, 61.8, 34.8, 34.7, 31.6, 29.9. HRMS (ESI) Calcd for $C_{22}H_{27}N_2O_3$ [$(M+H)^+$]: 367.2016, found: 367.2016.

***methyl 4-(6,8-di-tert-butyl-2H-benzo[b][1,4]oxazin-3-yl)benzoate* (3n)**

Pale yellow solid (168 mg, 0.443 mmol, 79%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1726, 1612, 1462. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 – 8.10 (m, 2H), 8.04 – 7.96 (m, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 5.00 (s, 2H), 3.95 (s, 3H), 1.41 (s, 9H), 1.35 (s, 9H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.7, 157.3, 144.5, 142.7, 139.7, 137.0, 134.4, 132.0, 130.1, 126.5, 123.9, 123.1, 61.9, 52.5, 34.8, 34.7, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{24}H_{30}NO_3$ [$(M+H)^+$]: 380.2220, found: 380.2219.

***4-(6,8-di-tert-butyl-2H-benzo[b][1,4]oxazin-3-yl)phenol* (3o)**

Yellow oil, (159 mg, 0.471 mmol, 65%). **FT-IR** (thin film) ν_{max} (cm^{-1}):2981, 2889, 1671, 1595, 1514, 1462. **^{1}H NMR** (400 MHz, $CDCl_3$ and CD_3OD): δ 7.08 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.64 (s, 2H), 1.40 (s, 9H), 1.11 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$ and CD_3OD): δ 166.9, 158.3, 145.6, 142.7, 139.0, 132.1, 130.4, 128.4, 119.5, 117.2, 113.6, 68.2, 35.6, 35.1, 31.6, 30.2. **HRMS** (ESI) Calcd for $C_{22}H_{28}NO_2$ [$(M+H)^+$]: 338.2115, found: 338.2116.

***6,8-di-tert-butyl-3-(pyridin-2-yl)-2H-benzo[b][1,4]oxazine* (3p)**

Yellow solid, (161 mg, 0.499 mmol, 61%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2956, 2868, 1586, 1566, 1479, 1466, 1437, 1409.. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.64 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 8.36 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.81 (td, *J* = 7.8, 1.8 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 5.24 (s, 2H), 1.41 (s, 9H), 1.35 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.2, 154.0, 149.0, 144.1, 143.5, 137.2, 136.6, 134.3, 125.0, 123.9, 122.9, 121.3, 61.5, 34.8, 34.6, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{21}H_{27}N_2O$ [$(M+H)^+$]: 323.2118, found: 323.2115.

***6,8-di-tert-butyl-3-(pyridin-3-yl)-2H-benzo[b][1,4]oxazine* (3q)**

Brown oil, (175 mg, 0.543 mmol, 67%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2980, 2970, 1588, 1476, 1416. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.07 (d, *J* = 2.3 Hz, 1H), 8.69 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.31 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.41 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 4.98 (s, 2H), 1.41 (s, 9H), 1.35 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.0, 151.6, 147.9, 144.6, 142.6, 137.1, 134.2, 133.9, 131.5, 123.8, 123.7, 122.9, 61.6, 34.8, 34.6, 31.6, 29.9. **HRMS** (ESI) Calcd for $C_{21}H_{27}N_2O$ [$(M+H)^+$]: 323.2118, found: 323.2117.

***6,8-di-tert-butyl-3-(pyridin-4-yl)-2H-benzo[b][1,4]oxazine* (3r)**

Yellow powder, (205 mg, 0.636 mmol, 78%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1462. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.79 – 8.70 (m, 2H), 7.81 – 7.71 (m, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.26 – 7.25 (m, 1H), 4.96 (s, 2H), 1.40 (s, 9H), 1.34 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.1, 150.7, 144.7, 142.8, 142.6, 137.2, 134.1, 124.5, 123.3, 120.3, 61.6, 34.8, 34.6, 31.6, 29.9. **HRMS** (ESI) Calcd for $C_{21}H_{27}N_2O$ [$(M+H)^+$]: 323.2118, found: 323.2117.

***6,8-di-tert-butyl-3-(thiophen-2-yl)-2H-benzo[b][1,4]oxazine* (3s)**

Yellow solid, (67 mg, 0.205 mmol, 93%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2980, 2970, 2904, 1665, 1597, 1562, 1477, 1461, 1429, 1409. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.42 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.91 (s, 2H), 1.41 (s, 9H), 1.34 (s, 9H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.5, 144.4, 142.9, 141.9, 136.9, 134.4, 130.4, 128.0, 127.9, 123.0, 122.5, 62.1, 34.8, 34.7, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{20}H_{26}NOS$ [$(M+H)^+$]: 328.1730, found: 328.1730.

***3-(benzo[d][1,3]dioxol-5-yl)-6,8-di-tert-butyl-2H-benzo[b][1,4]oxazine* (3t)**

Yellow solid, (188 mg, 0.514 mmol, 85%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1474. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 1.7 Hz, 1H), 7.33 (td, *J* = 3.7, 1.8 Hz, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 2H), 4.91 (s, 2H), 1.41 (s, 9H), 1.35 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.6, 150.2, 148.6, 144.3, 142.7, 136.8, 134.4, 130.5, 122.8, 122.6, 121.4, 108.2, 106.7, 101.7, 62.0, 34.8, 34.6, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{23}H_{28}NO_3$ [$(M+H)^+$]: 366.2064, found: 366.2060.

***6,8-diisopropyl-3-phenyl-2H-benzo[b][1,4]oxazine* (3u)**

Yellow oil, (99 mg, 0.337 mmol, 72%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 2981, 2889, 1462. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 – 7.87 (m, 2H), 7.50 – 7.45 (m, 3H), 7.19 (d, *J* = 2.2 Hz, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 5.02 (s, 2H), 3.29 – 3.22 (m, 1H), 2.92 – 2.85 (m, 1H), 1.26 (dd, *J* = 6.9, 6.1 Hz, 12H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.6, 142.6, 141.6, 135.9, 135.4, 133.8, 131.0, 128.9, 126.6, 124.2, 122.8, 62.9, 33.8, 27.3, 24.3, 22.8. **HRMS** (ESI) Calcd for $C_{20}H_{24}NO$ [$(M+H)^+$]: 294.1852, found: 294.1852.

Data for the benzomorpholine products

***6,8-di-tert-butyl-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-3-carbonitrile* (4a)**

To an oven-dried rbf under argon atmosphere, was charged **3a** (75 mg, 0.23 mmol). To the flask was added anhydrous MeOH (2.4 mL), and the reaction mixture cooled to 0 °C and was added TMSCN (58 µL, 0.47 mmol) over a 10 minute period. After this time the reaction mixture was allowed to return to room temperature and stir for 2 hours. After this time, the reaction mixture was concentrated *in vacuo* and purified *via* silica gel column chromatography (EtOAc:Pentane, 2:98 v:v) to give a pale yellow oil, (67 mg, 0.193 mmol, 83%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 3332, 2962, 2225, 1598, 1451, 1437. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.64 (m, 2H), 7.56 – 7.42 (m, 3H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 4.44 (dd, *J* = 10.8, 2.5 Hz, 1H), 4.30 (s, 1H), 3.97 (d, *J* = 11.0 Hz, 1H), 1.41 (s, 9H), 1.30 (s, 9H**). ^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.4, 139.2, 138.2, 135.1, 130.0, 129.8, 129.4, 126.3, 119.3, 116.0, 111.7, 72.4, 56.2, 35.2, 34.6, 31.7, 29.9. **HRMS** (ESI) Calcd for $C_{23}H_{29}N_2O$ [$(M+H)^+$]: 349.2274, found: 349.2278.

***3-allyl-6,8-di-tert-butyl-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazine* (4b)**

To an oven-dried rbf under argon atmosphere, was charged **3a** (80 mg, 0.25 mmol). To the vessel was charged anhydrous toluene (2.5 mL). To the reaction mixture was cooled to 0 °C, and was added TMEDA (35 µL, 0.25 mmol), and allyl magnesium bromide (1M in Et_2O, 0.5 mL, 0.5 mmol). The reaction mixture was stirred at 0 °C for 30 minutes, before returning to room temperature and stirring overnight. The reaction mixture was again cooled to 0 °C, and quenched with NH_4Cl (sat., 1.5 mL) dropwise and the aqueous mixture extracted with MeCN (3 x 20 mL). The combined organic layers were washed with aqueous saturated sodium thiosulfate (1 x 10 mL) and brine (2 x 10 mL), respectively, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified *via*

silica gel column chromatography (5% EtOAc in Pentane) to give a yellow oil, (78 mg, 0.215 mmol, 86%). **FT-IR** (thin film) ν_{max} (cm^{-1}): 3305, 2955, 2868, 1638, 1595, 1492, 1436. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 – 7.47 (m, 2H), 7.41 – 7.34 (m, 2H), 7.30 – 7.24 (m, 1H), 6.74 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 5.57 (dddd, *J* = 18.1, 10.7, 8.9, 5.7 Hz, 1H), 5.16 – 5.03 (m, 2H), 4.12 (q, *J* = 10.5 Hz, 3H, NH and OCH_2), 2.85 (ddt, *J* = 13.8, 5.8, 1.3 Hz, 1H), 2.67 (ddt, *J* = 13.8, 9.0, 0.9 Hz, 1H), 1.36 (s, 9H), 1.32 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.5, 142.6, 139.7, 137.3, 132.8, 132.2, 128.6, 127.2, 126.4, 119.6, 113.4, 111.3, 72.7, 55.7, 41.0, 35.0, 34.5, 31.8, 29.9. **HRMS** (ESI) Calcd for $C_{25}H_{34}NO$ [$(M+H)^+$]: 364.2635, found: 364.2635.

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16. Other non-iodine based oxidants were also ineffective in this method.

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