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ARTICLE TYPE

# A Metal-Free Tandem Ring-opening/Ring-closing Strategy for the Heterocyclic conversion of Benzoxazin-4-ones to Oxazolines

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**A facile metal-free tandem ring-opening/ring-closing strategy was developed for the synthesis of oxazolines in good to excellent reaction yields under mild reaction conditions. This reaction essentially describes a novel tool for the heterocyclic conversion of benzoxazin-4-ones to 2,5-disubstituted oxazolines directly in one-pot.**

## Introduction

In recent years a momentous attention has been focused on the development of new synthetic methodologies aiming at the synthesis of novel heterocyclic compounds such as oxazolines, thiazolines, and imidazoline since these scaffolds play a pivotal role in a variety of biological activities[1] and they are also widely used in materials science, bioorganic chemistry, and organometallic chemistry.[2,3] In particular the Leupyrrin,[4] an antifungal, Bistratamide,[5] an anticancer and Mycobactin T,[6] a high affinity $Fe^{3+}$-chelating natural products possess an active oxazoline structural motif for their notable biological activities (Figure 1).

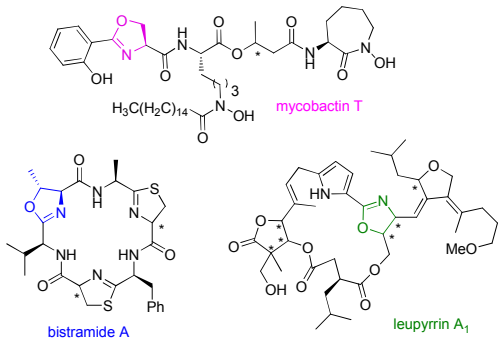
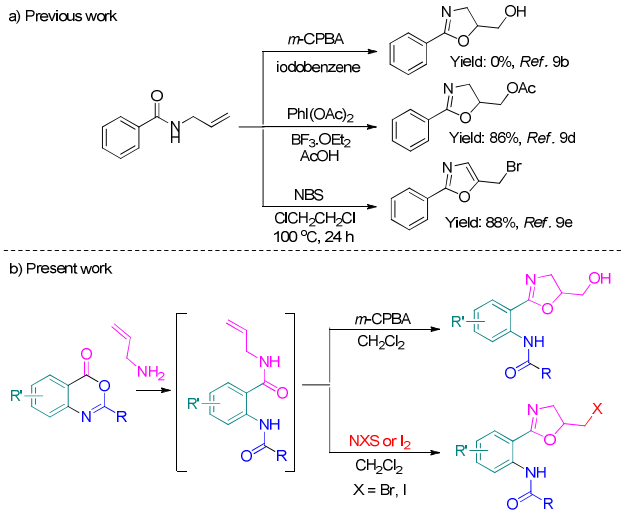



**Figure 1**. Examples of oxazoline containing natural products.

Developing new synthetic methodologies towards the construction of *N*-heterocycles[7] always remained fascinating areas for organic chemists due to their high importance in the biological studies. In particular, the oxazoline ring could be constructed either by dehydration of amido alcohol or condensation of a nitrile with an amino alcohol.[8] Conversely, in the recent times several new synthetic methodologies emerged towards the synthesis of oxazolines.[9] Remarkably, the conversion of *N*-allylbenzamides to 2,5-disubstituted oxazoline by an $\alpha$-exo mode cyclization process stands out (Scheme 1). Some esoteric reagents, metal or metal-free catalysts are reported for this transformation. Most prominent amongst them are: Moran *et. al.*[9b] reported iodoarene-catalyzed synthesis of oxazolines that involves cyclization of unsaturated amides using selectfluor as the oxidant, while Harned *et. al.*[9d] reported iodine(III) promoted synthesis of oxazoline acetates from *N*-allylamides in the presence of Lewis acids at elevated temperatures. Though the former protocol offered an interesting strategy however was limited in its reagent scope. When *m*-CPBA or oxone were used as the oxidants along with iodoarene precatalysts the reaction failed to afford either the resultant oxazoline or the corresponding epoxide.[9b] Likewise, synthesis of halo oxazoline derivatives in the presence NBS or NIS required elevated temperatures.[9e] Due to these limitations,[9b,9d-e] there still remains scope to expand the synthetic horizon of accessing oxazoline scaffolds under mild and at ambient temperatures.



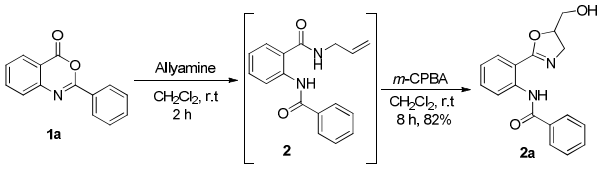

**Scheme 1**. Synthesis of 2,5-disubstituted oxazolines.

## Results and discussion

In continuation of our interest in the development of novel synthetic methodologies towards construction of heterocyclic scaffolds,[10] next we planned to synthesize oxazoline heterocycles. We were particularly interested in developing a conceptually new strategy wherein a tandem ring-opening/ring-closing reaction set maybe invoked to realize oxazolines from benzoxazin-4-ones that essentially involves a heterocyclic conversion as the strategic tool. The results are disclosed in this paper.

At the outset, we presumed that benzoxazin-4-one **1a**[11] on nucleophilic ring-opening reaction with allylamine would lead to the corresponding *N*-allylbenzamide intermediate **2** *in situ* which can ring-close to form the oxazoline **2a** in presence of an appropriate oxidant *via* an oxidative cyclization (Scheme 2).

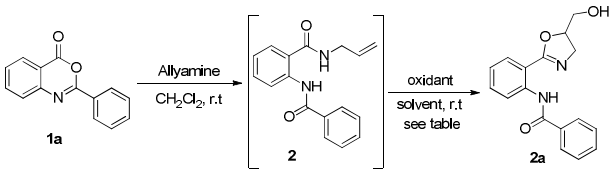
**Scheme 2.** Synthesis of oxazolines[a]




[a] Reaction conditions: **1a** (0.44 mmol, 1.0 equiv.), allylamine (0.89 mmol, 2.0 equiv.), *m*-CPBA (0.89 mmol, 2.0 equiv.), solvent (3 mL).

Checking on this hypothesis, we chose **1a** as the test substrate and subjected to tandem ring-opening/ring-closing protocol. As per the plan, the first reaction set *i.e.* ring-opening of **1a** proceeded smoothly with allylamine and the next ring-closing reaction was equally facile with *m*-CPBA as an oxidant in dichloromethane solvent at 27 $^oC$ affording the desired 2,5-substituted oxazoline **2a** in good yield (82%, entry 1, Table 1).

**Table 1.** Screening of reaction conditions[a]




| Entry | Oxidant | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| **1** | ***m*-CPBA** | **$CH_2Cl_2$** | **10** | **82 (2a)** |
| 2 | Oxone | $CH_2Cl_2$ | 4 | 44 (**2a**) |
| 3 | Oxone | $CH_2Cl_2$ | 6 | 0[c] |
| 4 | TBHP (5M) | $CH_2Cl_2$ | 12 | 66 (**2**) |
| 5 | TBHP (aq.) | $CH_2Cl_2$ | 12 | 60 (**2**) |
| 6 | CHP | $CH_2Cl_2$ | 12 | 64 (**2**) |

[a]Reaction conditions: oxidant (2 equiv.), solvent (3 mL). [b]Yields of isolated compounds in the parenthesis. [c]decomposition of reaction mixture.

Delighted at accomplishing a single step conversion, next we screened commercially available oxidants such as oxone, TBHP and CHP in place of *m*-CPBA which facilitated the second-stage operation during the conversion of **1a** to **2a** (Table 1). Excepting oxone (entry 2, Table1), with TBHP and CHP the reaction did not yield the expected product **2a** but rather stopped at the *N*-allylamide stage **2** (Scheme 1 and entries 4, 5 and 6 in Table 1). However with oxone, **2a** was obtained in 44% yield or no product depending on the reaction time (entries 2 and 3, Table 1). Optimum product (82%) was obtained when *m*-CPBA was the oxidant (entry 1, Table 1). Incidentally, it may be recalled that both *m*-CPBA and oxone oxidants failed[9b] to give the desired products when the starting material was *N*-allylbenzamide.

Next, the other parameters like optimal oxidant (*m*-CPBA) amount and the best solvent system for the maximum conversion were explored (Table 2). It was found that the use of 2.5 equiv of *m*-CPBA in dichloromethane solvent gave the best result of **2a** (90% yield). Varying the amount of *m*-CPBA to 1.0, 1.5 and 2.0 equiv. resulted in varying yields (40%, 65% and 82% respectively). Optimum yields were obtained in $CH_2Cl_2$ as the solvent (entry 4, Table 2) and hence it was selected as the solvent of choice for all further investigations. Increasing the reaction temperature or time-line has deleterious effect on the product profile.

**Table 2.** Optimization of reaction conditions[a]

| Entry | Oxidant | Equiv. | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| **1** | *m*-CPBA | 1.0 | $CH_2Cl_2$ | 40 |
| 2 | *m*-CPBA | 1.5 | $CH_2Cl_2$ | 65 |
| 3 | *m*-CPBA | 2.0 | $CH_2Cl_2$ | 82 |
| **4** | ***m*-CPBA** | **2.5** | **$CH_2Cl_2$** | **90** |
| 5 | *m*-CPBA | 2.5 | $CHCl_3$ | 66 |
| 6 | *m*-CPBA | 2.5 | $CH_3CN$ | 48 |
| 7 | *m*-CPBA | 2.5 | DCE | 72 |

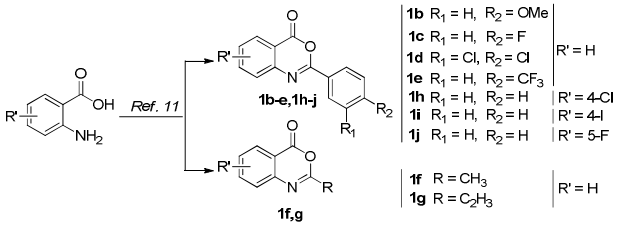
[a]Reaction conditions: **1a** (1.0 equiv.), allylamine (2.0 equiv.), solvent (3 mL), [b]Yields of isolated compound **2a**. DCE = 1,2-dichloroethane

Subsequent to optimization of the oxidant equivalents, we then turned our attention to the quantities of allylamine used wherein initially 2 equivalents were employed to affect the transformation of benzoxazinone to allyl amide **2**. To rationalise its quantity, we undertook some control experiments. Firstly, in order to facilitate this transformation we planned a sequential investigation of the allylamine equiv. required in combination with an external base (For eg. $Et_3N$). The results revealed that with 1.0 and 2.0 equiv. of allylamine in absence of $Et_3N$ 55% and 95% conversion of **1a** to **2** respectively has occured followed by the next conversion of **2** to **2a** with 2.5 equiv. of *m*-CPBA to result in 40% and 90% yields respectively. Surprisingly, when the same experiment was conducted with 1.0 equiv. of allylamine in presence of 1.0 equiv. of $Et_3N$, a 100% conversion from **1a** to **2** was found but no further *m*-CPBA oxidation was observed suggesting that excess equiv. of allylamine (2.0) plays a dual role as an internal base and as a nucleophile.

After optimizing the reactions, we studied the substrate scope of this protocol. In order to do so, several benzoxazin-4-ones (**1b-**

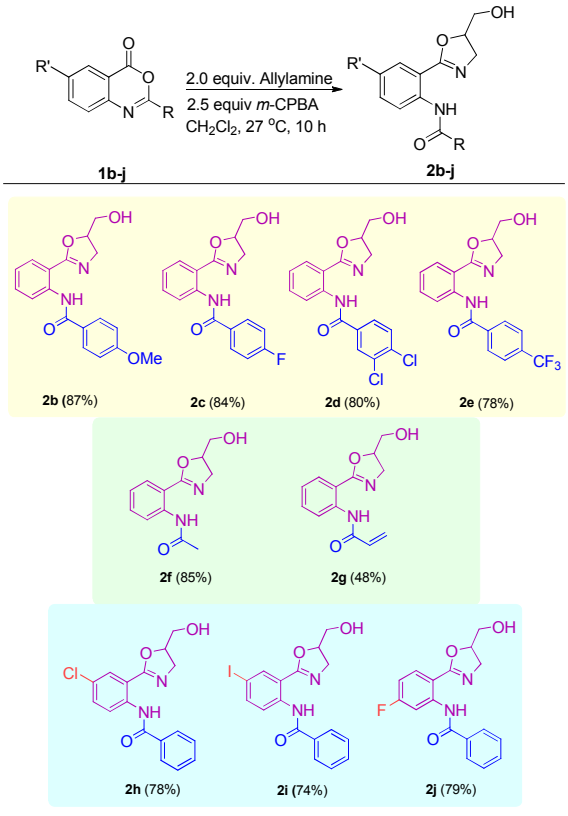
**j,** Scheme 3) were prepared from the corresponding amino acids and acid chlorides as per the literature procedure.[11]

**Scheme 3**. Synthesis of benzoxazin-4-ones




Subsequently, the thus prepared benzoxazin-4-ones **1b-j** were subjected to the facile heterocyclic conversion to afford the corresponding oxazoline derivatives **2b-j** in good to excellent yields (61-90%) under the optimized reaction conditions (Scheme 4). All the products are well characterized by their spectral analysis.[12] Presence of various substituent groups on either aryl moieties (as shown in Scheme 3) showed no significant effect on interconversion process excepting **1g**. Thus several substituent groups, including methyl, substituted aryls (4-methoxy **2b**, 4-fluoro **2c**, 3,4-dichloro **2d**, 4-trifluoromethyl **2e**, methyl **2f**) groups well tolerated the reaction conditions. Interestingly, the halo-substituted substrates **1h-j** also underwent this transformation to afford **2h-j** (74-79%).

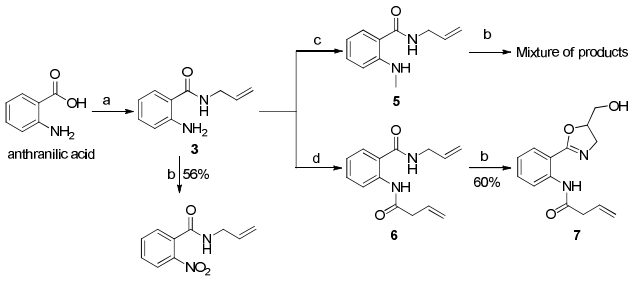
**Scheme 4**. Scope of cyclization of different benzoxazin-4-ones under metal free conditions[a]




[a]Yields of the isolated compounds in the parenthesis.

After showcasing the substrate scope of this protocol, we wanted to investigate the role of the ortho amide group in this unique oxidative-heterocyclic conversion.[13] Hence we prepared a set of compounds, starting from anthranilic acid, to conduct some control experiments (Scheme 5). Thus, compound **3**[14] was prepared by the coupling of antharanilic acid with allylamine according to the literature procedure.[15] Compound **3** itself on reaction with *m*-CPBA resulted in the nitro compound **4**[9d] (56%) rather than the target oxazoline product. Next, compound **3** on treatment with MeI under $K_2CO_3$ conditions provided the *N*-alkylated product **5**[16] (70%) which on subsequent *m*-CPBA oxidation resulted in a mixture of products rather than the expected oxazoline product. In the next experiment, compound **3** was *N*-acylated[15] with but-3-enoic acid to afford the diamide **6** (78%) which on *m*-CPBA oxidation under optimized conditions furnished the corresponding oxazoline **7**[12] (60%). These experiments conclusively prove that the presence of ortho amidic moiety plays an important role in the *m*-CPBA oxidation, unlike literature reports where unsubsituted aryl amides failed to yield the oxazoline derivatives.[9b]

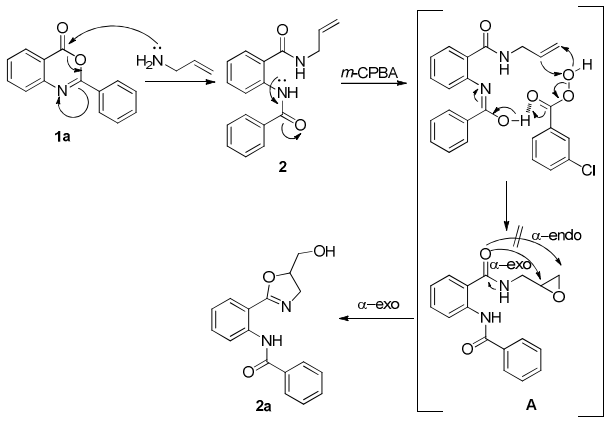
**Scheme 5.** Some control experiments[a]




[a]Reaction conditions: a) allylamine, EDCI, DMAP, $CH_2Cl_2$, 0 °C to rt, 12 h, 72%; b) *m*-CPBA, $CH_3Cl$, rt, 8 h; c) MeI, $K_2CO_3$, $CH_3CN$, reflux, 8 h, 70%; d) but-3-enoic acid, EDCI, DMAP, $CH_2Cl_2$, 0 °C to rt, 12 h, 78%.

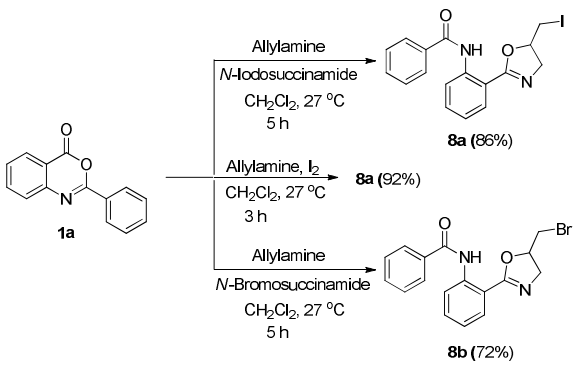
On the basis of these results, a plausible mechanism is proposed (Scheme 6). Firstly, the regioselective addition of amine nucleophile on benzoxazinone **1a** affords a ring-opened intermediate **2** which on tautomerization of ortho amidic group facilitates the H-bonding with C=O of *m*-CPBA increasing the electrophilic character of *m*-CPBA on electron rich olefin to result in the corresponding epoxide intermediate **A** followed by the cyclization of epoxy amide to oxazoline derivative.

**Scheme 6**: Plausible mechanism




Following our efforts towards one-pot (nucleophilic ring opening of benzoxazin-4-one followed by intramolecular oxidative cyclization) synthesis of heterocyclic scaffold, oxazolines; we were intrigued to know if such a methodology could be extrapolated to access the halo oxazoline derivative which is considered a privileged structure. Interestingly, NBS promoted synthesis of oxazolines was previously reported[9e] via oxidative cyclization of *N*-allylbenzamides albeit at elevated temperatures. However, herein when NBS/NIS and molecular $I_2$ were tried under the optimized reaction conditions with **1a** as the starting material, the corresponding bromo/iodo oxazoline derivatives were obtained at ambient temperatures in good to high yields (Scheme 7). The conversion of **1a** to the iodo oxazoline **8a** in one-pot under molecular $I_2$ promoted cyclization is perhaps the most promising reaction for its subsequent exploitation. This reaction follows the same mechanistic pathway as reported in literature.[9e]

**Scheme 7**. Synthesis of halo derived oxazolines using NIS/NBS/$I_2$[a]




[a]Reaction conditions: **1a** (1.0 equiv.), allylamine (2.0 equiv.), NIS/NBS/$I_2$ (2.0 equiv.), solvent (3 mL). [b]Yields of the isolated compounds in the parenthesis.

## Conclusion

In conclusion, a facile one-pot heterocyclic conversion of benzoxazin-4-ones to oxazolines involving a tandem ring-opening and ring-closing strategy in the presence of allylamine and *m*-CPBA was successfully demonstrated under metal-free conditions. More importantly, the one-pot conversion of benzoxazinone to the iodo oxazoline derivative under allylamine/molecular $I_2$ promoted cyclization is notable. Likewise, NIS or NBS under similar conditions gave the corresponding halo oxazoline derivatives.[12] Application of this strategy towards accessing a library of compounds is underway.

## Experimental section

Unless otherwise noted, commercial chemicals were used without any further purification. Solvents were dried and distilled prior to use by the usual methods. The starting materials (**1a-j**) were prepared according to reported method.[11] Melting points are uncorrected. $^1$H NMR spectra were recorded at 300, 400 and 500 MHz in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}$C NMR was recorded at 75, 100 and 125 MHz in $CDCl_3$ unless otherwise stated with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.4 ppm). Mass spectrometry (m/z) was performed in ESI mode. High-resolution mass spectra for all the new compounds were collected on Micromass Q-Tof instrument (ESI). Infrared (IR) spectra *v*max are reported in $cm^{-1}$.

### General procedure for the Synthesis of *N*-(2-(5-(Hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)benzamide, 2a

Allylamine (0.067 mL, 0.89 mmol, 2 equiv) and 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1a** (0.1 g, 0.44 mmol, 1 equiv.) was dissolved in $CH_2Cl_2$ (3 mL) and the mixture was stirred for 1 h at room temperature under nitrogen. Then, aqueous *m*-CPBA (0.192 g, 1.12 mmol) was added by portion to the reaction mixture and allowed to stir for another 8 h at same temperature. Then, 30% aq. KOH solution (3 mL) was added and the mixture was extracted with $CH_2Cl_2$ (2 x 5 mL). The organic layers were combined and dried with anhydrous $Na_2SO_4$, filtered and concentrated under *vacuum*. The residue was purified by flash chromatography (2.4:7.6 EtOAc/petroleum ether) to provide **2a** as a white solid (0.11 g, 90%); mp 159-161 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm) 12.92 (1H, s), 8.97 (1H, d, *J* = 8.5 Hz), 8.08 (2H, dt, *J* = 7.0, 1.5 Hz), 7.92 (1H, dd, *J* = 7.7, 1.5 Hz), 7.57-7.47 (4H, m), 7.12 (1H, td, *J* = 7.7, 1.0 Hz), 4.86-4.79 (1H, m), 4.25 (1H, dd, *J* = 14.4, 9.9 Hz), 4.03 (1H, dd, *J* = 14.6, 7.6 Hz), 3.93 (1H, ddd, *J* = 12.2, 5.3, 3.3 Hz), 3.76 (1H, dt, *J* = 11.7, 5.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 166.1, 164.2, 140.3, 135.3, 132.8, 131.7, 129.2, 128.6, 127.7, 122.4, 120.0, 113.3, 78.7, 64.0, 56.1; IR(neat) 3478, 2930, 2866, 1664, 1642, 1624, 1588, 1546, 1446, 1354, 1304, 1256, 1058, 757, 712 $cm^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{17}H_{17}N_2O_3$ 297.1233, found 297.1230.

### *N*-(2-(5-(Hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)-4-methoxybenzamide, 2b

This compound was prepared according to the representative procedure for **2a** using allylamine and 2-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **1b** giving **2b** as a white solid (0.12 g, 87%); mp 163-166 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.80 (1H, s), 8.94 (1H, d, *J* = 8.4 Hz), 8.04 (2H, dt, *J* = 8.9, 1.9

Hz), 7.90 (1H, dd, *J* = 7.9, 1.5 Hz), 7.51 (1H, td, *J* = 8.6, 1.5 Hz), 7.08 (1H, td, *J* = 8.5, 0.9 Hz), 6.98 (2H, dt, *J* = 8.9, 2.8 Hz), 4.86-4.78 (1H, m), 4.25 (1H, dd, *J* = 14.5, 9.9 Hz), 4.03 (1H, dd, *J* = 14.5, 7.5 Hz), 3.92 (1H, dd, *J* = 12.2, 3.1 Hz), 3.88 (3H, s), 3.75 (1H, dd, *J* = 12.3, 5.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.7, 164.2, 162.4, 140.5, 132.8, 129.5, 129.2, 127.6, 122.1, 119.9, 113.8, 113.1, 78.6, 64.2, 56.1, 55.4; IR(neat) 3438, 2928, 1637, 1614, 1512, 1445, 1329, 1258, 1177, 1026, 841, 757, 680 cm$^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{18}H_{19}N_2O_4$ 327.1339, found 327.1341.

**4-Fluoro-*N*-(2-(5-(hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)benzamide, 2c**

This compound was prepared according to the representative procedure for **2a** using allylamine and 2-(4-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **1c** giving **2c** as white solid (0.10 g, 84%); mp 139-142 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm) 12.90 (1H, s), 8.92 (1H, dd, *J* = 8.5, 1.0 Hz), 8.12-8.06 (2H, m), 7.93 (1H, dd, *J* = 7.9, 1.5 Hz), 7.53 (1H, td, *J* = 8.6, 1.5 Hz), 7.20-7.09 (3H, m), 4.87-4.80 (1H, m), 4.25 (1H, dd, *J* = 14.4, 9.9 Hz), 4.04 (1H, dd, *J* = 14.4, 7.6 Hz), 3.94 (1H, dd, *J* = 12.3, 3.0 Hz), 3.76 (1H, dd, *J* = 12.3, 5.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 165.0, 164.3, 163.9, 140.2, 132.9, 130.0, 129.3, 122.5 119.9, 115.7, 115.5, 113.3, 78.7, 63.9, 56.0; IR(neat) 3428, 3250, 2923, 2853, 1666, 1623, 1547, 1448, 1326, 1298, 1231, 1162, 1053, 886, 847, 750, 670 cm$^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{17}H_{16}N_2O_3F$ 315.1139, found 315.1141.

**3,4-Dichloro-*N*-(2-(5-(hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)benzamide, 2d**

This compound was prepared according to the representative procedure for **2a** using allylamine and 2-(3,4-dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **1d** giving **2d** as a white solid (0.088 g, 80%); mp 165-168 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 13.03 (1H, s), 8.88 (1H, dd, *J* = 8.5, 0.9 Hz), 8.19 (1H, d, *J* = 2.0 Hz), 7.91 (2H, td, *J* = 9.4, 1.5 Hz), 7.58 (1H, d, *J* = 8.3 Hz), 7.53 (1H, td, *J* = 8.9, 1.7 Hz), 7.13 (1H, td, *J* = 8.4, 1.1 Hz), 4.89-4.80 (1H, m), 4.27 (1H, dd, *J* = 14.5, 9.9 Hz), 4.06 (1H, dd, *J* = 14.6, 7.7 Hz), 3.96 (1H, dd, *J* = 12.3, 3.1 Hz), 3.77 (1H, dd, *J* = 12.3, 5.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 164.4, 163.7 139.8, 136.0, 135.0, 133.0, 132.9, 130.6, 130.0, 129.3, 126.9, 122.8, 119.9, 113.3, 78.8, 63.9, 55.9; IR(neat) 3419, 2924, 2861, 1663, 1629, 1589, 1550, 1450, 1321, 1257, 1112, 1058, 1031, 891, 832, 750, 676 cm$^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{17}H_{15}N_2O_3Cl_2$ 365.0454, found 365.0464.

***N*-(2-(5-(hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)-4-(trifluoromethyl)benzamide, 2e**

This compound was prepared according to the representative procedure for **2a** using allylamine and 2-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one **1e** giving **2e** as yellow solid (0.093 g, 78%); mp 146-148 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm) 13.07 (1H, s), 8.93 (1H, dd, *J* = 8.3, 0.7 Hz), 8.18 (1H, d, *J* = 8.0 Hz), 7.93(1H, dd, *J* = 7.9, 1.5 Hz), 7.76 (2H, d, *J* = 8.2 Hz), 7.54 (1H, td, *J* = 8.6, 1.5 Hz), 7.14 (1H, td, *J* = 7.9, 1.0 Hz), 4.87-4.80 (1H, m), 4.25 (1H, dd, *J* = 14.4, 9.9 Hz), 4.04 (1H, dd, *J* = 14.6, 7.7 Hz), 3.95 (1H, dd, *J* = 12.3, 3.2 Hz), 3.77 (1H, dd, *J* = 12.3, 5.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 164.7, 164.3, 139.8, 138.5, 133.1, 132.9, 132.6, 129.0, 128.1, 125.6, 122.8, 120.0, 113.4, 78.8, 63.9, 56.0; IR(neat) 3426, 2924, 2853, 1657, 1630, 1582, 1552, 1453, 1341, 1254, 1167, 1112, 1061, 997, 971, 856, 761, 693 cm$^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{18}H_{16}O_3N_2F_3$ 365.1107, found 365.1117.

***N*-(2-(5-(Hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)acetamide, 2f**

This compound was prepared according to the representative procedure for **2a** using allylamine and 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1f** giving **2f** as a yellow solid (0.118 g, 85%); mp 116-119 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm) 12.08 (1H, s), 8.70 (1H, d, *J* = 8.3 Hz), 7.87 (1H,dd, *J* = 7.9, 1.5 Hz), 7.45 (1H, td, *J* = 8.6, 1.5 Hz), 7.06 (1H, td, *J* = 8.0, 1.0 Hz), 4.82-4.75 (1H, m), 4.19 (1H, dd, *J* = 14.6, 10.0 Hz), 3.94 (2H, *J* = 14.6, 7.6Hz), 3.73 (1H, dd, *J* = 12.3, 5.4 Hz), 2.21 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.4, 163.9, 140.0, 132.6, 129.1, 122.1, 119.7, 112.6, 78.5, 63.9, 56.1, 25.4; IR(neat) 3393, 2927, 1637, 1535, 1448, 1367, 1305, 1250, 1061, 769, 676 cm$^{-1}$; HRMS m/z calc'd for $[M+H]^+$ $C_{12}H_{15}N_2O_3$ 235.1077, found 235.1075.

***N*-(2-(5-(Hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)acrylamide, 2g**

This compound was prepared according to the representative procedure for **2a** using allylamine and 2-vinyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1g** giving **2g** as yellow solid (0.066 g, 48%); mp 138.7 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm) 12.37 (1H, s), 8.83 (1H, dd, *J* = 8.3, 0.7 Hz), 7.89 (1H, dd, *J* = 7.9, 1.6 Hz), 7.49 (2H, td, *J* = 8.6, 1.5 Hz), 7.09 (1H, td, *J* = 8.2, 1.0 Hz), 6.42 (1H, dd, *J* = 17.0, 1.2 Hz), 6.31 (1H, dd, *J* = 17.0, 10.2 Hz), 5.76 (1H, dd, *J* = 10.2, 1.2 Hz), 4.83-4.77 (1H, m), 4.20 (1H, dd, *J* = 14.6, 10.0 Hz), 3.95 (2H, dd, *J* = 14.6, 7.6 Hz), 3.74 (1H, dd, *J* = 12.3, 5.4 Hz); $^{13}$C NMR (100MHz, $CDCl_3$) δ (ppm) 164.4, 164.0, 139.9, 132.7, 129.2, 126.8, 122.4, 119.9, 113.0, 78.6, 63.9, 58.1; IR(neat) 3450, 2922, 2852, 1637, 1462, 1219, 768 cm$^{-1}$; HRMS m/z calcd for $[M+Na]^+$ $C_{13}H_{14}N_2O_3Na^+$ 269.0896, found 269.0893.

***N*-(4-Chloro-2-(5-(hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)benzamide, 2h**

This compound was prepared according to the representative procedure for **2a** using allylamine and 6-chloro-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1h** giving **2h** as a white solid (0.098 g, 78%); mp 176-178 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.84 (1H, s), 8.93 (1H, d, *J* = 9.0 Hz), 8.04 (2H, dd, *J* = 8.1, 1.2 Hz), 7.88 (1H, d, *J* = 2.5 Hz), 7.58-7.43 (4H, m), 4.88-4.79 (1H, m), 4.26 (1H, dd, *J* = 14.7, 10.0 Hz), 4.06 (1H, dd, *J* = 14.7, 7.8 Hz), 3.95 (1H, dd, *J* = 12.3, 3.1 Hz), 3.76 (1H, dd, *J* = 12.3, 5.2 Hz); $^{13}$C NMR (100MHz, $CDCl_3$) δ (ppm) 166.1, 163.3, 138.8, 134.8, 132.5, 131.9, 128.9, 128.6, 127.7, 127.4, 121.4, 114.6, 79.0, 63.8, 56.1; IR(neat) 3443, 2924, 2853, 1638, 1614, 1528, 1307, 1232, 1106, 1054, 826, 704 cm$^{-1}$; HRMS m/z calcd for $[M+Na]^+$ $C_{17}H_{15}ClN_2O_3Na^+$ 353.0663, found 353.0657.

***N*-(2-(5-(hydroxymethyl)-4,5-dihydrooxazol-2-yl)-4-iodophenyl)benzamide, 2i**

This compound was prepared according to the representative procedure for **2a** using allylamine and 6-iodo-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1i** giving **2i** as a yellow solid (0.88 g, 74%); mp 135-138 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm) 12.86 (1H, s), 8.76 (1H, d, *J* = 9.0 Hz), 8.23 (1H, d, *J* = 2.1 Hz) 8.05 (2H, dt, *J* = 7.0, 1.5 Hz), 7.80 (1H, dd, *J* = 9.0, 2.1 Hz), 7.58- 7.46 (3H, m), 4.86-4.80 (1H, m), 4.26 (1H, dd, *J* = 14.6, 9.9 Hz), 4.06 (1H, dd, *J* = 14.6, 7.7 Hz), 3.95 (1H, d, *J* = 11.9 Hz), 3.76 (1H, dt, *J* = 12.2, 4.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 166.1, 164.2, 140.2, 135.2, 132.8, 131.7, 129.2, 128.6, 127.7, 122.4, 120.0, 113.3, 78.7, 64.0, 56.1; IR(neat) 3438, 2923, 2853, 1668, 1621, 1570, 1521, 1310, 1229, 1058, 775, 700, 567 cm$^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{17}H_{16}IN_2O_3^+$ 423.0200, found 423.0217.

***N*-(5-Fluoro-2-(5-(hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)benzamide, 2j**

This compound was prepared according to the representative procedure for **2a** using allylamine and 7-fluoro-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1j** giving **2j** as a white solid (0.099 g, 79%); mp 158-161 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) 13.07 (1H, s), 8.78 (1H, dd, *J* = 12.1, 2.5 Hz), 8.07 (2H, dd, *J* = 8.0, 1.1 Hz), 7.91 (1H, dd, *J* = 8.8, 6.4 Hz), 7.58 -7.47 (2H, m), 6.81 (1H, td, *J* = 7.5, 2.5 Hz), 4.86-4.79 (1H, m), 4.25 (1H, dd, *J* = 14.5, 9.9 Hz), 3.99 (1H, dd, *J* = 14.5, 7.7 Hz), 3.76 (1H, dd, *J* = 12.2, 5.3 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.3, 163.8, 163.7, 142.2, 134.8, 131.9, 131.1, 128.6, 127.7, 109.4, 107.3, 78.7, 63.9, 56.0; IR(neat) 3499, 3440, 2923, 2853, 1666, 1643, 1539, 1429, 1297, 1270, 1161, 1099, 1055, 979, 873, 712, 668 cm$^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{17}H_{16}O_3N_2F$ 315.11395, found 315.11442.

***N*-Allyl-2-(but-3-enamido)benzamide, 6**

To a solution of *N*-allyl-2-aminobenzamide **3** (0.2 g, 1.13 mmol) in $CH_2Cl_2$ (5 mL) at 0 $^{o}$C were successively added DMAP (0.07 g, 0.57 mmol), but-3-enoic acid (0.09 g, 1.13 mmol) and EDCI (0.30 g, 1.59 mmol) portion wise. After 12 h, the reaction mixture was hydrolyzed with water and extracted with $CH_2Cl_2$. The combined organic extracts were successively washed with a 1 M aqueous solution of hydrochloric acid, a saturated aqueous solution of $NaHCO_3$, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1.5:8.5 EtOAc/petroleum ether) to provide **6** as a white solid (0.21 g, 78%); mp 123-125 $^{o}$C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ (ppm) 11.03 (1H, br.s), 8.58 (1H, dd, *J* = 8.8, 1.0 Hz), 7.49-7.44 (2H, m), 7.07 (1H, td, *J* = 7.7, 1.0 Hz), 6.33 (1H, m), 6.09-6.00 (1H, m), 5.98-5.89 (1H, m), 5.32-5.26 (3H, m), 5.23 (1H, dq, *J* = 10.2, 1.3 Hz), 4.06 (2H, tt, *J* = 5.6, 1.5 Hz), 3.20 (2H, dt, *J* = 7.1, 1.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.8, 168.7, 139.4, 133.5, 132.6, 130.7, 126.3, 122.8, 121.7, 120.4, 119.7, 117.1, 43.3, 42.3; HRMS m/z calcd for $[M+Na]^+$ $C_{14}H_{16}N_2O_2Na$ 267.1104, found 267.1095.

***N*-(2-(5-(Hydroxymethyl)-4,5-dihydrooxazol-2-yl)phenyl)but-3-enamide, 7**

To a solution of *N*-allyl-2-(but-3-enamido)benzamide **6** (0.1 g, 0.40 mmol) in $CH_3Cl$ (5 mL) at 0 $^{o}$C was added aqueous *m*-CPBA (0.21 g, 1.22 mmol) by portion and allowed to stir at room temperature. After complete consumption of 7 (after 8h, monitored by tlc) 30% aq. KOH solution (3 mL) was added and the mixture was extracted with $CH_2Cl_2$ (2 x 5 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$, filtered and concentrated under *vacuum*. The residue was purified by column chromatography (2:8 EtOAc/petroleum ether) to provide **7** as a white solid (0.06 g, 60%); mp 116-118 $^{o}$C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ (ppm) 12.13 (1H, br.s), 8.72 (1H, d, *J* = 8.5 Hz), 7.87 (1H, dd, *J* = 7.9, 1.5 Hz), 7.49-7.43 (1H, m), 7.07 (1H, t, *J* = 7.6 Hz), 6.10-5.98 (1H, m), 5.30-5.23 (2H, m), 4.82-4.75 (1H, m), 4.18 (1H, dd, *J* = 14.8, 10.0 Hz), 3.95 (1H, dd, *J* = 14.6, 7.6 Hz), 3.91 (1H, dd, *J* = 12.2, 3.2 Hz), 3.74 (1H, dd, *J* = 12.2, 5.4 Hz), 3.22 (2H, d, *J* = 7.9 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 170.2, 163.8, 139.9, 132.6, 131.0, 129.1, 122.3 119.8, 119.2, 112.9, 78.6, 64.0, 56.1, 43.6; HRMS m/z calcd for $[M+H]^+$ $C_{14}H_{17}N_2O_3$ 261.1233, found 261.1225.

***N*-(2-(5-(Bromomethyl)-4,5-dihydrooxazol-2-yl)phenyl)benzamide, 8b**

Allylamine (0.067 mL, 0.89 mmol, 2 equiv) and 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1a** (0.1 g, 0.44 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (3 mL) and the mixture was stirred for 2 h at room temperature under $N_2$. Then, NBS (0.19 g, 1.07 mmol, 2.5 equiv) was added to the reaction mixture and allowed to stir for another 4 h at same temperature. After completion of reaction the reaction mixture was diluted with $CH_2Cl_2$ (3 mL) and quenched with saturated aqueous $Na_2SO_3$. The aqueous phase was extracted with $CH_2Cl_2$ (2 x 5 mL), and the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, concentrated and purified by column chromatography (1.4:8.6 EtOAc/petroleum ether) to provide **8b** as a yellow solid (0.1 g, 72%); mp 105-108 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.80 (1H, s), 8.97 (1H, dd, *J* = 8.4, 1.1 Hz), 8.10-8.05 (2H, m), 7.91 (1H, dd, *J* = 7.8, 1.5 Hz), 7.58-7.47 (4H, m), 7.13 (1H, td, *J* = 8.0, 1.1 Hz), 4.98-4.90 (1H, m), 4.34 (1H, dd, *J* = 15.0, 9.6 Hz), 4.09 (1H, dd, *J* = 15.0, 6.6 Hz), 3.59 (1H, dd, *J* = 10.7, 4.7 Hz), 3.54 (1H, dd, *J* = 10.7, 6.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.1, 164.0, 140.2, 135.2, 133.0, 131.7, 129.3, 128.6, 127.7, 122.5, 120.0, 113.1, 76.5, 59.0, 33.2; IR (neat) 3456, 3010, 2925, 2865, 1665, 1622, 1585, 1444, 1307, 1233, 1053, 757, 703, 679, 648 cm$^{-1}$; HRMS m/z calcd for $[M+H]^+$ $C_{17}$ $H_{16}N_2O_2Br$ 359.0389, found 359.0392.

***N*-(2-(5-(Iodomethyl)-4,5-dihydrooxazol-2-yl)phenyl)benzamide, 8a**

a). This compound was prepared according to the representative procedure for **8b** using allylamine (0.067 mL, 0.89 mmol, 2 equiv) and 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1a** (0.1 g, 0.44 mmol, 1 equiv) and NIS (0.23 g, 1.02 mmol, 2.5 equiv) giving **8a** as a pale yellow solid (0.14 g, 86 %).

b). The compound **8a** was prepared in another way according to the representative procedure for **8b** using allylamine (0.067 mL, 0.89 mmol, 2 equiv) and 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one **1a** (0.1 g, 0.44 mmol, 1 equiv) and $I_2$ (0.27 g, 2.5 equiv) giving **8a** as a white solid (0.15 g, 92%); mp 106-109 $^{o}$C; $^{1}$H NMR (500MHz, $CDCl_3$) δ (ppm) 12.80 (1H, s), 8.97 (1H, dd, *J* = 8.5, 1.0 Hz), 8.10-8.05 (2H, m), 7.91 (1H, dd, *J* = 7.9, 1.6 Hz), 7.58-7.47 (4H, m), 7.13 (1H, td, *J* = 8.3, 1.2 Hz), 4.85-4.77 (1H, m), 4.33 (1H, dd, *J* = 14.9, 9.4 Hz), 3.97 (1H, dd, *J* = 14.9, 6.7 Hz), 3.41 (1H, dd, *J* = 10.3, 4.5 Hz), 3.34 (1H, dd, *J* = 10.3, 7.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) 166.0, 163.9, 140.3, 135.2, 132.9, 131.6, 129.3, 128.6, 127.7, 122.4, 120.0, 113.2, 76.8, 60.5, 7.1; IR(neat) 3458, 2923, 2854, 1665, 1630, 1583, 1444, 1306, 1233, 1052, 879, 702, 678, 536 cm$^{-1}$; HRMS m/z calcd $C_{17}H_{16}O_2N_2I$ 407.0251, found 407.02465.

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(12) See *Supplementary Information* for spectra.

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## GRAPHICAL ABSTRACT

**A Metal-Free Tandem Ring-opening/Ring-closing Strategy for the Heterocyclic conversion of Benzoxazin-4-ones to Oxazolines**

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