ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

Synthesis of Benzodioxepinones and Benzoxazepinones via Tandem Oxidation and Iodolactonization of 2-*O*/*N*-tethered Alkenyl Benzaldehyde Mediated by CuI/TBHP

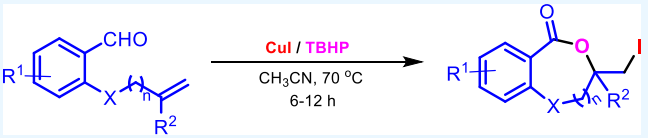
Archana Chutia, Pallav Jyoti Arandhara, Bipin Kumar Behera, Ankita Pradhan, and Anil K. Saikia*

Cite This: *ACS Omega* 2024, 9, 14217−14232

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An efficient methodology for the synthesis of halogenated benzodioxepinones and benzoxazecinones has been developed via tandem oxidation and iodolactonization reaction of 2-*O*/*N*-tethered alkenyl benzaldehydes mediated by CuI and tertiarybutylhydro-peroxide in acetonitrile at 70 °C in moderate to good yields. The reaction involves initial oxidation of aldehyde to acid followed by iodolactonization. Terminal propargyl ether resulted in a mixture of mono- and diiodido-3-methylene-1,4-dioxepin-5-ones. The post-synthetic modification of the reaction products leads to the formation of corresponding thiocyanate, azide, thioether, and triazole derivatives.



INTRODUCTION

Lactones are important structural motifs in organic chemistry and found in many biologically active molecules and natural products.[1] For example, octalactin A,[2] an eight-membered lactone, has cytotoxic activity against melanoma and colon tumor cells; (+)-penicillide and (+)-purpactin A are natural products isolated from *Penicillium simplicissimum*, which have inhibitory activity against acyl-CoA-cholestrol acyltransferase (Figure 1).[3] Seven-membered lactones such as 2,3-dihydro-5*H*-

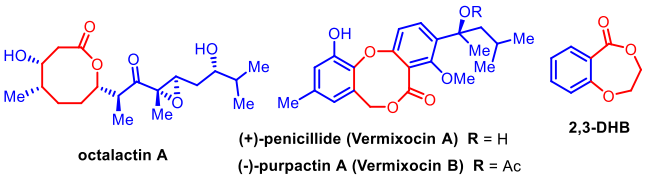
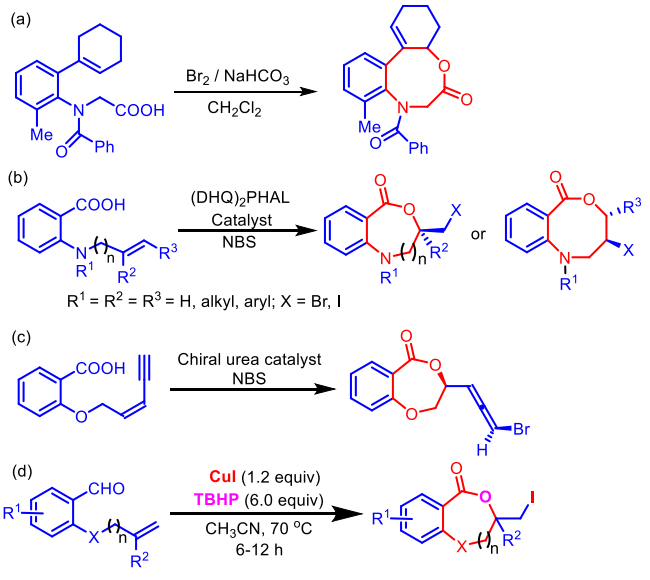


Figure 1. Biologically active lactones.

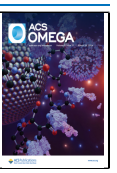
1,4-benzodioxepin-5-ones (2,3-DHB) are the starting material for the synthesis of polyester (Figure 1).[4] Therefore, several methods have been developed for the synthesis of lactones via classical ring closure of alcohols and acids.[5] The classical methods require either activation of acid or alcohol functionality to achieve good yield, chemoselectivity, and to avoid side products. In contrast, transition metal-catalyzed intramolecular ketone hydroacylation reactions,[6] allylic oxidation/lactonization,[7] and *N*-heterocyclic carbene catalyzed oxidative lactonization[8] have also been used.

Synthesis of medium-ring lactones is challenging as the cyclization suffers from low reactivity due to transannular strain and high degree of conformational flexibility.[9] Recently, alkene halolactonization of unsaturated acids has received special attention in preparing medium-ring lactones (Scheme 1).[10] Gataullin reported the synthesis of benzoxazocinones via

Scheme 1. Halolactonization of Alkenes



Received: December 11, 2023
Revised: February 21, 2024
Accepted: February 26, 2024
Published: March 12, 2024



halolactonization of N-acyl-N-(2-cyclohex-1-en-1-yl-6-methylphenyl) (Scheme 1a).[10a] Xiang has reported the catalytic asymmetric halocyclization procedure for the synthesis of benzoxazepinones and benzoxazecinones using $(DHQ)_2PHAL$ as the catalyst (Scheme 1b).[10b] Although halolactonization of intramolecular bifunctional alkenes and acids is reported in the literature (Scheme 1c),[11] halolactonization of intramolecular bifunctional alkenes and aldehydes is not reported so far. In this article, we have disclosed a new methodology for the synthesis of benzodioxepinones and benzoxazepinones via tandem oxidation and iodolactonization of 2-*O*/*N*-tethered alkenyl benzaldehydes mediated by the CuI/TBHP system for the first time (Scheme 1d).

RESULTS AND DISCUSSION

In our study, compound **1a** was considered as standard starting material and treated with 5.0 equiv of tertiarybutylhydroperoxide (TBHP) and 1.0 equiv of CuI in acetonitrile at room temperature for 6 h. To our dismay, no product was observed from the reaction (Table 1, entry 1). However, when the reaction was performed at 80 °C compound **2a** was obtained in 67% yield (Table 1, entry 6). While decreasing the temperature from 80 to 70 and 60 °C, it provided 69 and 61% yields, respectively (Table 1, entries 7−8). Subsequent increase in TBHP to 6.0 equiv and CuI to 1.2 equiv at 70 °C resulted in 75% yield (Table 1, entry 9). Mixed solvents like acetonitrile and water gave 73% yield (Table 1, entry 10). Increasing the amount of CuI to 1.5 equiv resulted in same yield of the corresponding product (Table 1, entry 11). Other variants like oxidants H_2O_2, $K_2S_2O_8$,and molecular oxygen (Table 1, entries 13−15); halogen sources like I_2, NIS, NaI, $CuCl_2$, CuBr could not provide better yields (Table 1, entries 16−21). Solvents such as DCM, DCE, 1,4-dioxane, and toluene were proved to be inefficient for this transformation (Table 1, entries 2−5). Therefore, 6.0 equiv of TBHP and 1.2 equiv of CuI in CH_3CN at 70 °C for 6 h are the optimal conditions for the reaction.

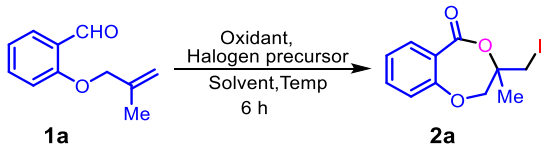
With this optimal condition in hand, the scope of the reaction was investigated with a variety of substrates as depicted in Scheme 2. It was observed from Scheme 2 that both substituted and unsubstituted allyl/homoallyl ethers work well to provide the seven-membered iodolactones **2a−2p** and eight-membered lactones **2q−2s** in moderate to good yields. Similarly, electron-withdraing and electron-donating groups in the aromatic ring are also compatible under the reaction conditions. However, the yield of the eight-membered iodolactones **2q−2s** is lower than the seven-membered rings. The methodology is applicable to the synthesis of benzoxazepinones **2t−2y** and benzooxazocinone **2z**. The reaction is also compatible with the substrate without a heteroatom (X = $-CH_2-$) giving 3-(iodomethyl)-4,5-dihydrobenzo[c]oxepin-1(3*H*)-one **2a′a** in 68% yield. However, the reaction with internal alkene **1b′** resulted in the formation of benzodioxinone **2b′b** in 10% yield (Scheme 3).

The scope of the reaction was extended to propargyl ethers. The reaction with terminal propargyl ether resulted in a mixture of mono- and di-iodosubstituted products (Scheme 4), whereas silyl substituted propargyl ether gave single diiodide product **4a** in 38% yield. The structure of all the compounds was determined by ^1H, $^{13}C\{1H\}$ NMR, IR spectroscopy, high-resolution mass spectrometry (HRMS), and finally by X-ray crystallographic analysis of the compounds **2a**, **4a**, and **4a′**.

A comparison of the present reaction conditions for the conversion of carboxylic acid to lactone with an earlier reaction was carried out considering acid **C**, as shown in Table 2. It was observed that although time required for conversion is decreased from 5 to 2.5 h in the present system, the yield decreased from 63 to 43%. In the case of a source of halogen in both cases 1.2 equiv was used. The major advantage of the earlier reaction was the usage of a catalytic amount of the reagent, which yielded a chiral product with 32% ee. On the other hand, present reaction conditions provided more reactive iodo derivatives for further transformations.

In order to establish the reaction pathway some control experiments were undertaken (Scheme 5). The compound **1a** was subjected to react with TEMPO (3.0 equiv) and BHT (3.0 equiv) under standard reaction conditions (Scheme 5a). The product **2a** was obtained in 21% with TEMPO and trace amount in the case of BHT. The intermediate 2,2,6,6-tetramethylpiperidin-1-yl 2-((2- methylallyl)oxy)benzoate **5** was detected by the HRMS experiment. This indicates that the reaction proceeds via

Table 1. Optimization of the Reaction[a]



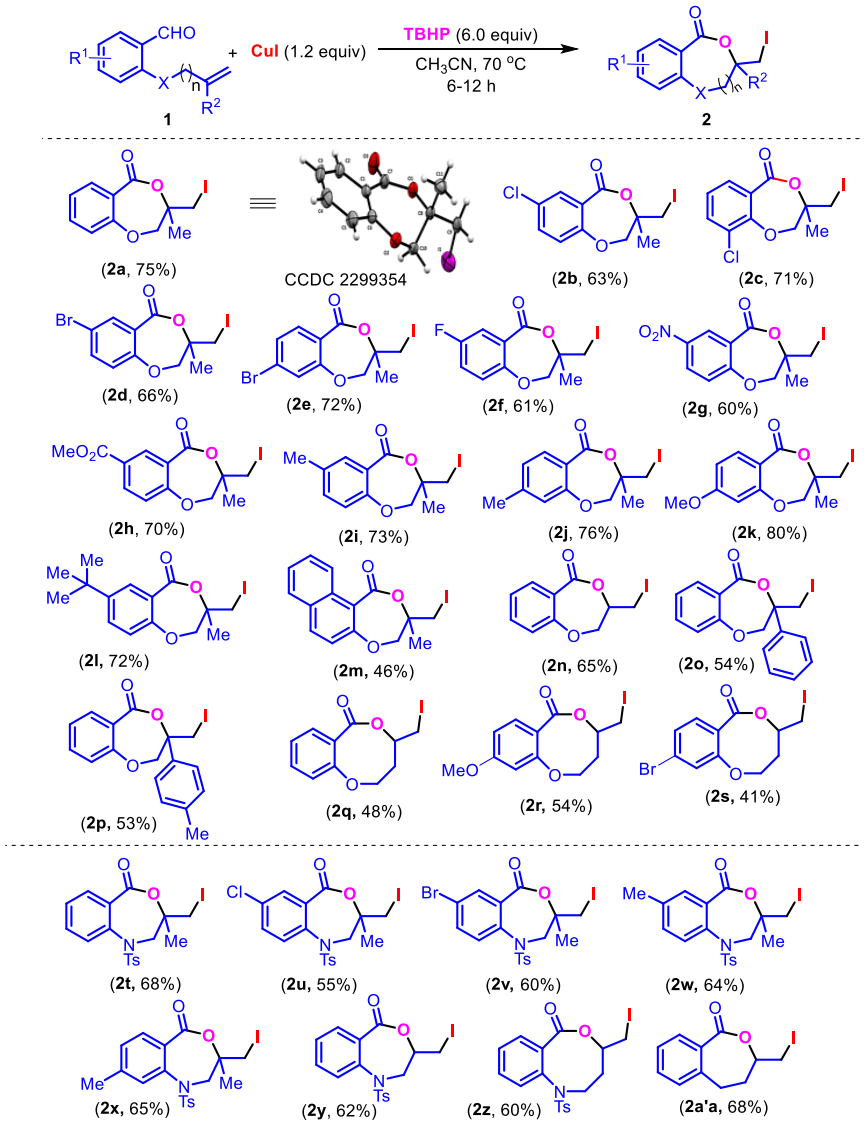
1a **2a**

entry	oxidant (equiv)	halogen precursor (equiv)	solvent	temp. (°C)	yield[b] (%)
1	TBHP (5.0)	CuI (1.0)	CH_3CN	rt	[c]
2	TBHP (5.0)	CuI (1.0)	DCM	40	55
3	TBHP (5.0)	CuI (1.0)	DCE	80	[c]
4	TBHP (5.0)	CuI (1.0)	1,4-dioxane	100	35
5	TBHP (5.0)	CuI (1.0)	toluene	110	[c]
6	TBHP (5.0)	CuI (1.0)	CH_3CN	80	67
7	TBHP (5.0)	CuI (1.0)	CH_3CN	70	69
8	TBHP (6.0)	CuI (1.2)	CH_3CN	60	61
9	**TBHP (6.0)**	**CuI (1.2)**	**CH_3CN**	**70**	**75**
10	TBHP (6.0)	CuI (1.5)	CH_3CN:H_2O (3:1)	70	73
11	TBHP (8.0)	CuI (1.5)	CH_3CN	70	75
12	H_2O_2 (3.0)	CuI (1.2)	CH_3CN	70	70
13	$K_2S_2O_8$ (3.0)	CuI (1.2)	CH_3CN	70	[c]
14	O_2	CuI (1.2)	CH_3CN	70	[c]
15	TBHP (6.0)	NIS (2.0)	CH_3CN	70	[c]
16	TBHP (6.0)	NaI (2.0)	CH_3CN	70	35
17	TBHP (6.0)	KI (2.0)	CH_3CN	70	45
18	TBHP (6.0)	I_2 (2.0)	CH_3CN	70	50
19	TBHP (6.0)	$CuCl_2$ (1.2)	CH_3CN	70	[c]
20	TBHP (6.0)	CuBr (1.2)	CH_3CN	70	[c]
21				70	[c]

[a]Reaction conditions: **1a** (0.57 mmol, 1.0 equiv), oxidant, halogen precursor, solvent 4.0 mL, N_2 atmosphere, 6 h. [b]Isolated yield. [c]No reaction.

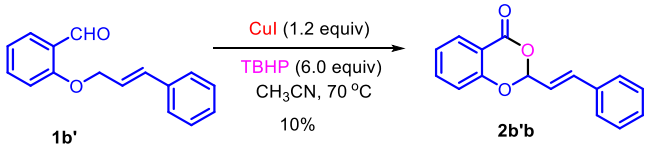
https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

Scheme 2. Synthesis of 3-Iodomethyl-1,4-dioxepin-5-one and 3-Iodomethyl-1,4-oxazepin-5-one Derivatives[a]



[a]Reaction conditions: 1(0.57 mmol, 1.0 equiv), CH_3CN 4.0 mL, N_2 atmosphere.

Scheme 3. Reaction with Internal Alkene



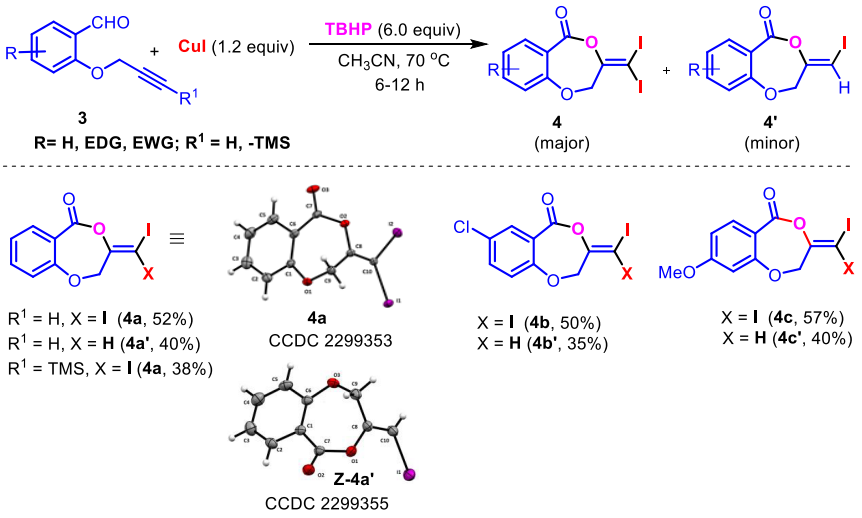
a radical mechanism and aldehyde is oxidized to acid in situ. On the other hand, the reaction with corresponding benzoic acid **5a** with CuI in the absence of TBHP resulted in **2a** with 45% yield, indicating the formation of benzoic acid as reaction intermediate (Scheme 5b). Interestingly, the yield of the reaction decreased by 30% (Scheme 5b). However, the reaction of **1a** with TBHP in the absence of CuI resulted in the formation of carboxylic acid in trace amount (Scheme 5c). Therefore, CuI is important in converting aldehyde to corresponding carboxylic acid.

From the above experiments and literature evidence,[12] a plausible mechanism is proposed (Scheme 6). Reaction of CuI and TBHP generates *tert*-butoxide and *tert*-butylhydroperoxide radicals of which *tert*-butoxide radical abstracts hydrogen from aldehyde to form radical intermediate **A**. The intermediate **A** then reacts with *tert*-butylhydroperoxide radical to form peroxy ester **B**, which after hydrolysis gives acid **C**. Again, the reaction between CuI and ^{t}BuOOH produced reactive species ^{t}BuOI, which reacts with olefin to form intermediate **E** via **D**. The nucleophilic attack of carboxylate ion on iodonium ion forms the final compound **2**. It is evident from the mechanism that TBHP is involved in oxidizing Cu(I) to Cu(II) and back to Cu(I); transforming CuI to ^{t}BuOI for the iodolactonization reaction. Therefore, an excess amount of TBHP is required for this reaction.

The applicability of the synthesized iodolactone was demonstrated by converting the iodofunctionality to its thiocyanate **6** and azide **7** by reacting with ammonium thiocyanate and sodium azide, respectively (Scheme 7). The azide can conveniently be converted into its triazole derivative **8** with the reaction of phenylacetylene in 89% yield. The iodofunctionality can also be converted to its thioether **9** by reacting with thiophenol in 51% yield (Scheme 7).

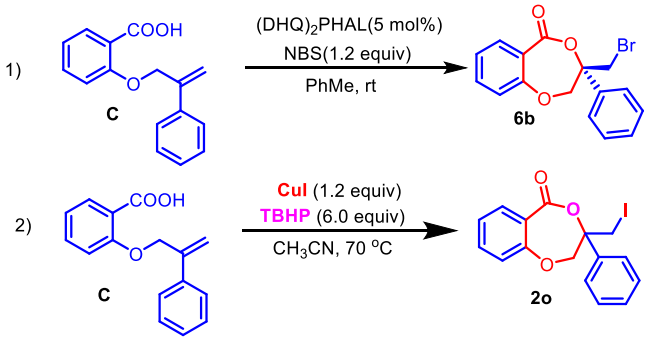
https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

Scheme 4. Synthesis of 3-(Diiodomethylene)-1,4-dioxepin-5-one and 3-(Iodomethylene)-1,4-dioxepin-5-one Derivatives[a]



[a]Reaction conditions: 1(0.63 mmol, 1.0 equiv), CH_3CN 4.0 mL, N_2 atmosphere.

Table 2. Comparison of Present Reaction Conditions with the Reported Reaction



entry	catalyst/oxidant (equiv)	halogen source (equiv)	time (h)	yield (%)
1	$(DHQ)_2PHAL$ (0.05)	NBS (1.2)	5	63
2	TBHP (6.0)	CuI (1.2)	2.5	43

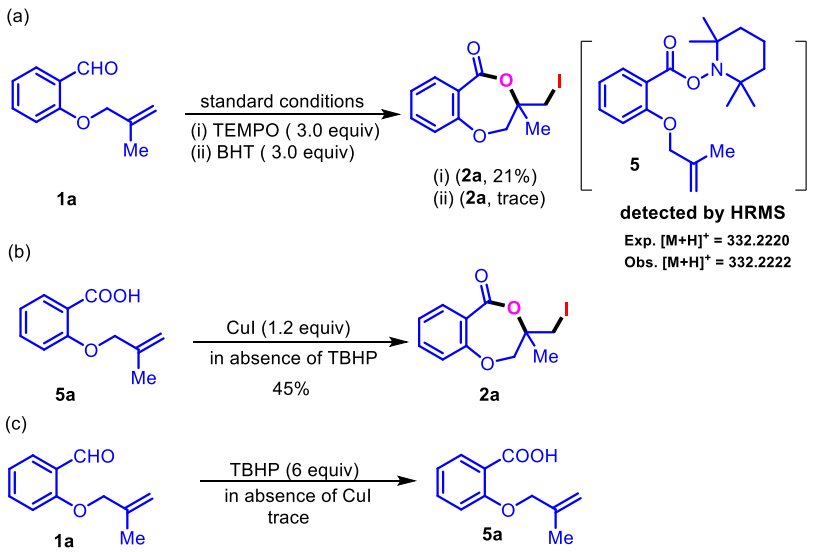
In order to check the scalability of the reaction a gram-scale synthesis of the product **2a** was carried out from starting compound **1a** (1.00g) under standard reaction conditions. This resulted product **2a** in 61% yield (1.10 g) (Scheme 8).

In conclusion, we have demonstrated an efficient methodology for the synthesis of benzodioxepinones and benzoxazepinones via tandem oxidation and iodolactonization of 2-*O*/*N*-tethered alkenyl benzaldehyde mediated by CuI/TBHP in moderate to good yields. The reaction is compatible with a variety of functional groups. The synthetic utility of the methodology is extended to the synthesis of its azide, thiocyanide, and thioether. The azide can also be converted to its 1,2,3-triazole derivative.

EXPERIMENTAL SECTION

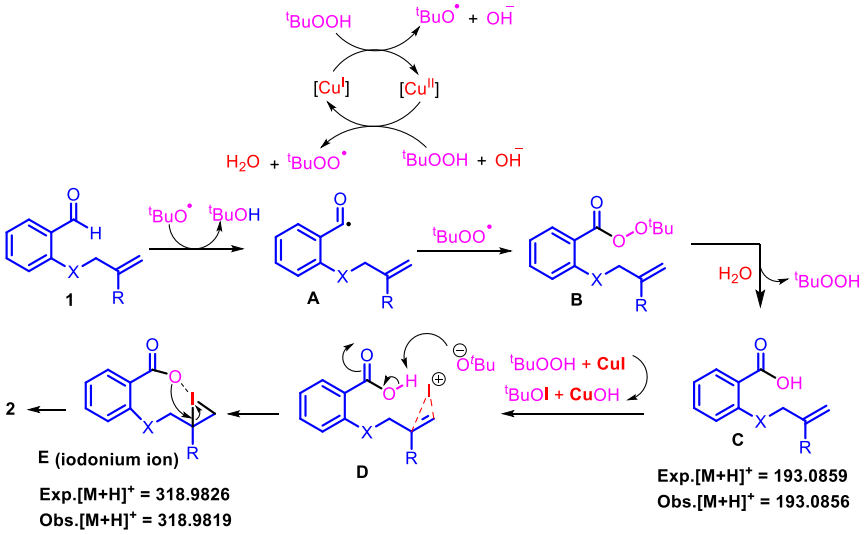
General Information. All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60−120 mesh size) was used for column chromatography. Reactions were monitored by thin-layer

Scheme 5. Controlled Experiments

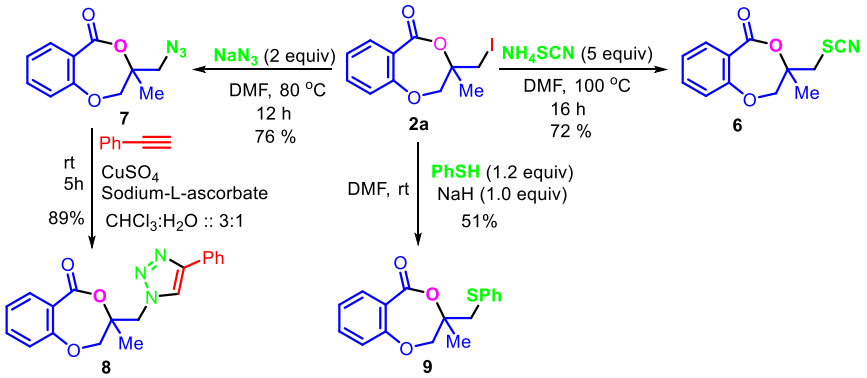


https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

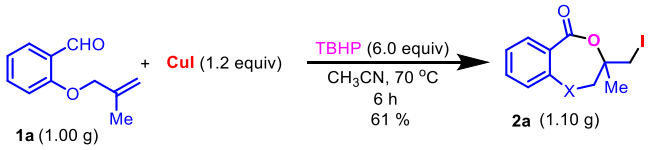
Scheme 6. Plausible Mechanism



Scheme 7. Post-Synthetic Applications

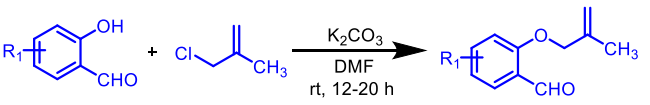


Scheme 8. Gram-Scale Synthesis



chromatography (TLC) on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infrared spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (500 and 400 MHz) or $^{13}C\{^1H\}$ (100 and 125 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin−spin coupling constants (J) are given in Hertz. HRMS spectra were recorded using Q-TOF mass spectrometer.

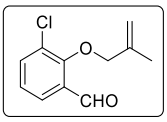
The starting material 2-((2-methylallyl)oxy)benzaldehyde derivatives (**1a**−**1b**, **1d**−**1f**, **1i**−**1k**, **1n**−**1q**), *N*-(2-formylphenyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide derivative (**1y**), **1a′**, **1b′**, and 2-(prop-2-yn-1-yloxy)benzaldehyde derivatives (**3a**, **3b**, and **3c**) were prepared by following the previous work literature.[13] The substrates **1a′**[14] **1b′**[15] were prepared from the literature procedure. The spectroscopic data of the above compounds are in good agreement with the literature one. The experimental procedure and the characterization data of the remaining starting material 2-((2-methylallyl)oxy)-benzaldehyde derivatives (**1c**, **1g**, **1h**, **1l**, **1m**, **1r**, and **1s**), *N*-(2-formylphenyl)-4-methyl-*N*-(2-methylallyl)-benzenesulfonamide derivatives (**1t**−**1x** and **1z**) and 2-((3-(trimethylsilyl)prop-2-yn-1-yl)oxy)benzaldehyde are given as follows:



General Experimental Procedure for the Synthesis of 1c, 1g, 1h, 1l, and 1m. To a suspension of K_2CO_3 (7.38 mmol, 3 equiv) in DMF under the N_2 atmosphere was added substituted 2-hydroxybenzaldehyde (2.46 mmol, 1.0 equiv) and 3-chloro-2-methylprop-1-ene (3.69 mmol, 1.5 equiv). The reaction mixture was then allowed to stir at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction (12−20 h), the combined organic layer was washed with brine and ice water and further extracted with ethyl acetate (3 × 15 mL) followed by drying over anhydrous Na_2SO_4. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **1**.

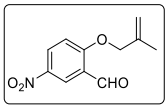
https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

*3-Chloro-2-((2-methylallyl)oxy)benzaldehyde (**1c**).*



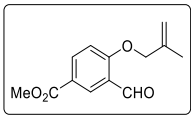
Yellow liquid; R_f (hexane/EtOAc, 9:1) 0.55; yield 403 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1 H), 7.69 (dd, J = 8.0, 2.0 Hz, 1 H), 7.57 (dd, J = 8.0, 1.6 Hz, 1 H), 7.12 (t, J = 8.0 Hz, 1 H), 5.09 (s, 1 H), 4.99 (s, 1 H), 4.45 (s, 2 H), 1.87 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.1, 158.1, 140.1, 136.4, 131.3, 129.0, 126.9, 125.2, 114.5, 79.6, 19.8. IR (KBr, neat) 3081, 2862, 1690, 1586, 1443, 1379, 1243, 1136, 956, 908, 785, 728, 620 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}ClO_2$ $(M + H)^+$ 211.0520, found 211.0520.

*2-((2-Methylallyl)oxy)-5-nitrobenzaldehyde (**1g**).*



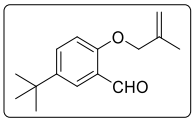
Brown solid; R_f (hexane/EtOAc, 4:1) 0.55; mp 73−75 °C; yield 163 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1 H), 8.65 (d, J = 3.2 Hz, 1 H), 8.37 (dd, J = 9.2, 3.2 Hz, 1 H), 7.11 (d, J = 9.2 Hz, 1 H), 5.13 (s, 1 H), 5.09 (s, 1 H), 4.69 (s, 2 H), 1.86 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 187.6, 165.0, 141.8, 138.9, 130.7, 124.9, 124.7, 114.6, 113.6, 73.3, 19.4. IR (KBr, neat) 2958, 2919, 1691, 1608, 1522, 1488, 1344, 1272, 1078, 997, 823, 749, 664 cm^{-1}; anal. calcd. for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 60.39; H, 5.19; N, 6.25.

*Methyl-3-formyl-4-((2-methylallyl)oxy)benzoate (**1h**).*



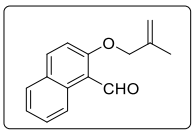
White solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 49−51 °C; yield 351 mg, 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1 H), 8.40 (d, J = 2.4 Hz, 1 H), 8.12 (dd, J = 8.8, 2.4 Hz, 1 H), 6.96 (d, J = 8.8 Hz, 1 H), 5.07 (s, 1 H), 5.00 (s, 1 H), 4.55 (s, 2 H), 3.83 (s, 3 H), 1.80 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.7, 166.0, 164.0, 139.4, 137.0, 130.5, 124.7, 123.0, 113.8, 112.8, 72.5, 52.2, 19.4. IR (KBr, neat) 2955, 2923, 1722, 1688, 1607, 1437, 1265, 1126, 1000, 766, 654 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{15}O_4$ $(M + H)^+$ 235.0965, found 235.0977.

*5-(tert-Butyl)-2-((2-methylallyl)oxy)benzaldehyde (**1l**).*

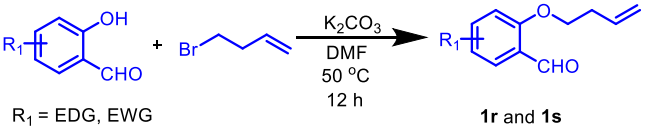


Pale yellow liquid; R_f (hexane/EtOAc, 9:1) 0.55; yield 434 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1 H), 7.86 (d, J = 2.8 Hz, 1 H), 7.55 (dd, J = 8.4, 2.4 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 1 H), 5.11 (s, 1 H), 5.02 (s, 1 H), 4.52 (s, 2 H), 1.84 (s, 3 H), 1.30 (s, 9 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.2, 159.4, 143.9, 140.5, 133.3, 125.0, 124.6, 113.3, 112.8, 72.4, 34.4, 31.5, 19.6; IR (KBr, neat) 2962, 2866, 1684, 1608, 1494, 1264, 1188, 1010, 818, 646 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{21}O_2$ $(M + H)^+$ 233.1536, found 233.1534.

*2-((2-Methylallyl)oxy)-1-naphthaldehyde (**1m**).*

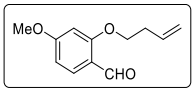


Brown solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 72−74 °C; yield 367 mg, 66%; ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR δ 10.99 (s, 1 H), 9.31 (d, J = 9 Hz, 1 H), 8.04 (d, J = 9.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.64 (t, J = 7.0 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.27 (d, J = 9.0 Hz, 1 H), 5.18 (s, 1 H), 5.09 (s, 1 H), 4.70 (s, 2 H), 1.91 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.2, 163.5, 140.2, 137.6, 131.8, 130.0, 128.8, 128.4, 125.2, 125.0, 117.2, 114.0, 113.8, 73.2, 19.6; IR (KBr, neat) 2955, 2918, 1670, 1591, 1511, 1436, 1242, 1155, 1022, 811, 753, 710 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{15}O_2$ $(M + H)^+$ 227.1067, found 227.1066.



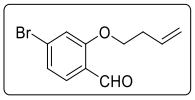
General Experimental Procedure for the Synthesis of 1r and 1s. To a suspension of K_2CO_3 (7.38 mmol, 3 equiv) in DMF under the N_2 atmosphere was added substituted 2-hydroxybenzaldehyde (2.46 mmol, 1.0 equiv) and 4-bromobut-1-ene (3.69 mmol, 1.5 equiv). The reaction mixture was then allowed to stir at 50 °C and the progress of the reaction was monitored by TLC analysis. After completion of the reaction (12 h), the combined organic layer was washed with brine and ice water and further extracted with ethyl acetate (3 × 15 mL) followed by drying over anhydrous Na_2SO_4. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **1r** and **1s**.

*2-(But-3-en-1-yloxy)-4-methoxybenzaldehyde (**1r**).*



White liquid; R_f (hexane/EtOAc, 9:1) 0.50; yield 233 mg, 46%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1 H), 7.79 (d, J = 8.5 Hz, 1 H), 6.52 (dd, J = 9.0, 2.5 Hz, 1 H), 6.41 (d, J = 2.5 Hz, 1 H), 5.92−5.84 (m, 1 H), 5.19−5.15 (m, 1 H), 5.11 (d, J = 10.0 Hz, 1 H), 4.08 (t, J = 6.5 Hz, 2 H), 3.84 (s, 3 H), 2.60−2.56 (m, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 188.5, 166.3, 163.3, 134.1, 130.4, 119.4, 117.8, 106.2, 98.8, 67.9, 55.8, 33.6; IR (KBr, neat) 2928, 2845, 1674, 1596, 1443, 1257, 1198, 1112, 1028, 815, 549, 406 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}O_3$ $(M + H)^+$ 207.1016, found 207.1022.

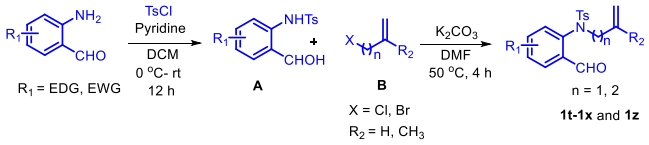
*4-Bromo-2-(but-3-en-1-yloxy)benzaldehyde (**1s**).*



White solid; R_f (hexane/EtOAc, 9:1) 0.55; mp 70−72 °C; yield 358 mg, 57%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (d, J = 4.0 Hz, 1 H), 7.61 (q, J = 6.0 Hz 1 H), 7.12−7.08 (m, 2 H), 5.89−5.80 (m, 1 H), 5.18−5.09 (m, 2 H), 4.09−4.05 (m, 2 H), 2.58−2.54 (m, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 188.8, 161.5, 133.7, 130.5, 129.5, 124.3, 123.9, 117.9, 116.3, 68.2, 33.5; IR (KBr, neat) 2926, 2867, 1684, 1585, 1381, 1236, 1020, 915,

https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

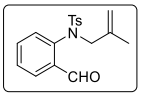
840, 808 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}BrO_2$ $(M + H)^+$ 255.0015, found 255.0020.



General Experimental Procedure for the Synthesis of 1t−1x and 1z. To a suspension of substituted 2-aminobenzaldehyde (4.13 mmol, 1.0 equiv) and p-TsCl (4.54 mmol, 1.1 equiv) in DCM under the N_2 atmosphere was added pyridine (9.09 mmol, 2.2 equiv) dropwise at 0 °C. The reaction mixture was then allowed to stir at 0 °C for 5 min, which was then allowed to stir at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (12 h), the combined organic layer was washed with brine and further extracted with DCM (3 × 15 mL) followed by drying over anhydrous Na_2SO_4. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired *N*-(2-formylphenyl)-4-methylbenzenesulfonamide derivative **A**.

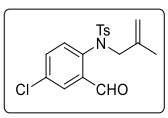
To a suspension of K_2CO_3 (3.27 mmol, 3 equiv) in DMF under the N_2 atmosphere was added *N*-(2-formylphenyl)-4-methylbenzenesulfonamide derivative **A** (1.09 mmol, 1.0 equiv) and **B** (1.64 mmol, 1.5 equiv). Then, the reaction mixture was allowed to stir at 50 °C, and the reaction time was monitored by TLC. After completion of the reaction (4 h), the combined organic layer was washed with brine and ice water and further extracted with ethyl acetate (3 × 15 mL) followed by drying over anhydrous Na_2SO_4. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **1t−1x and 1z**.

*N-(2-Formylphenyl)-4-methyl-N-(2-methylallyl)-benzenesulfonamide (**1t**).*



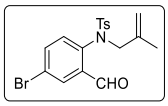
Yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 120−122 °C; yield 326 mg, 91%; ^1H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1 H), 8.00 (dd, J = 7.0, 2.5 Hz, 1 H), 7.45−7.41 (m, 4 H), 7.28 (s, 1 H), 7.26 (d, J = Hz, 1 H), 6.69 (d, J = 7.5 Hz, 1 H), 4.75 (s, 1 H), 4.62 (s, 1 H), 4.46 (s, 1 H), 3.80 (s, 1 H), 2.44 (s, 3 H), 1.75 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.1, 144.5, 141.4, 139.0, 136.3, 134.1, 133.9, 129.9, 128.7, 128.6, 128.3, 127.5, 117.2, 57.8, 21.8, 20.6; IR (KBr, neat) 2917, 1691, 1597, 1348, 1163, 1089, 819, 661, 575 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{20}NO_3S$ $(M + H)^+$ 330.1158, found 330.1155.

*N-(4-Chloro-2-formylphenyl)-4-methyl-N-(2-methylallyl)-benzenesulfonamide (**1u**).*



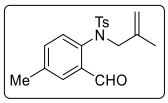
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 105−107 °C; yield 298 mg, 75%; ^1H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1 H), 7.90 (d, J = 2.8 Hz, 1 H), 7.40−7.33 (m, 3 H), 7.26 (s, 1 H), 7.24 (d, J = 4.0 Hz, 1 H), 6.57 (d, J = 8.4 Hz, 1 H), 4.73 (s, 1 H), 4.59 (s, 1 H), 4.43 (s, 1 H), 3.69 (s, 1 H), 2.40 (s, 3 H), 1.68 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 188.6, 144.8, 139.6, 138.6, 137.3, 134.8, 133.8, 133.5, 130.0, 128.7, 128.5, 128.2, 117.5, 57.5, 21.8, 20.5; IR (KBr, neat) 2955, 2919, 1694, 1593, 1474, 1348, 1161, 1090, 1025, 862, 725, 666, 583, 553, 493 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}ClNO_3S$ $(M + H)^+$ 364.0769, found 364.0785.

*N-(4-Bromo-2-formylphenyl)-4-methyl-N-(2-methylallyl)-benzenesulfonamide (**1v**).*



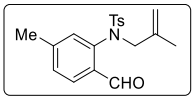
Brown solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 91−93 °C; yield 342 mg, 77%; ^1H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1 H), 8.08 (d, J = 2.5 Hz, 1 H), 7.52 (dd, J = 8.5, 2.5 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 6.53 (d, J = 8.5 Hz, 1 H), 4.76 (s, 1 H), 4.62 (s, 1 H), 4.46 (s, 1 H), 3.71 (s, 1 H), 2.43 (s, 3 H), 1.71 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 188.5, 144.8, 140.1, 138.5, 137.5, 136.7, 133.5, 131.5, 130.0, 128.9, 128.2, 122.7, 117.5, 57.5, 21.8, 20.5; IR (KBr, neat) 2958, 2922, 1692, 1596, 1474, 1349, 1162, 1091, 860, 723, 664, 581, 551, 419 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}BrNO_3S$ $(M + H)^+$ 408.0264, found 408.0284.

*N-(2-Formyl-4-methylphenyl)-4-methyl-N-(2-methylallyl)-benzenesulfonamide (**1w**).* Red solid; R_f (hexane/EtOAc, 4:1)



0.50; mp 102−104 °C; yield 187 mg, 50%; ^1H NMR (500 MHz, $CDCl_3$) δ 10.40 (s, 1 H), 7.78 (s, 1 H), 7.44 (d, J = 8.5 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 4.74 (s, 1 H), 4.61 (s, 1 H), 4.43 (s, 1 H), 3.75 (s, 1 H), 2.43 (s, 3 H), 2.37 (s, 3 H), 1.73 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.4, 144.4, 139.1, 138.9, 138.7, 135.8, 134.8, 134.2, 129.8, 128.9, 128.3, 127.3, 117.0, 57.8, 21.8, 21.2, 20.6; IR (KBr, neat) 2923, 2866, 1692, 1492, 1346, 1163, 864, 682, 658, 589, cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1315, found 344.1320.

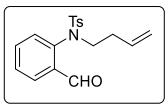
*N-(2-Formyl-5-methylphenyl)-4-methyl-N-(2-methylallyl)-benzenesulfonamide (**1x**).* White solid; R_f (hexane/EtOAc,



4:1) 0.50; mp 100−102 °C; yield 206 mg, 55%; ^1H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 8.5 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 1 H), 6.47 (s, 1 H), 4.75 (s, 1 H), 4.62 (s, 1 H), 4.41 (s, 1 H), 3.77 (s, 1 H), 2.44 (s, 3 H), 2.26 (s, 3 H), 1.74 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.0, 145.2, 144.4, 141.5, 139.1, 134.2, 133.8, 129.7, 129.5, 128.6, 128.3, 128.2, 116.9, 58.0, 21.8, 21.8, 20.6; IR (KBr, neat) 2955, 2917, 1689, 1604, 1345, 1162, 1090, 816, 687, 657, 577, 545 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ $(M + H)^+$ 344.1315, found 344.1320.

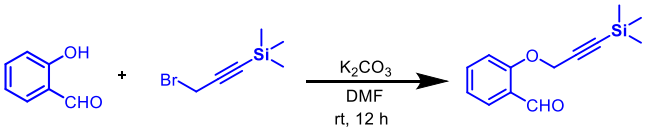
*N-(But-3-en-1-yl)-N-(2-formylphenyl)-4-methylbenzenesulfonamide (**1z**).* White solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 118−120 °C; yield 233 mg, 65%; ^1H NMR (500 MHz, $CDCl_3$) δ 10.43 (s, 1 H), 8.01 (dd, J = 7.0, 2.0 Hz, 1 H), 7.48−7.44 (m, 3 H), 7.43 (s, 1 H), 7.27 (d, J = 8.0 Hz, 2 H), 6.69 (d, J =

https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232



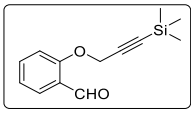
7.0 Hz, 1 H), 5.73−5.67 (m, 1 H), 5.03 (d, J = 10.0 Hz, 1 H), 4.97 (d, J = 17.0 Hz, 1 H), 4.04 (s, 1 H), 3.33 (s, 1 H), 2.43 (s, 3 H), 2.21 (q, J = 7.0 Hz, 2 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.4, 144.4, 141.6, 136.5, 134.4, 134.2, 134.2, 129.8, 128.8, 128.7, 128.2, 127.3, 118.0, 50.6, 32.8, 21.8; IR (KBr, neat) 2924, 2867, 1692, 1595, 1346, 1162, 1061, 719, 661, 574 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{20}NO_3S$ $(M + H)^+$330.1158, found 330.1155.

General Experimental Procedure for the Synthesis of 3d.



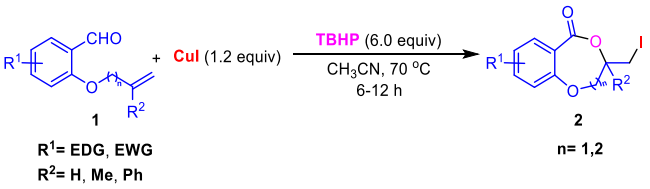
To a suspension of K_2CO_3 (4.92 mmol, 2 equiv) in DMF under the N_2 atmosphere was added 2-hydroxybenzaldehyde (2.46 mmol, 1.0 equiv) and (3-bromoprop-1-yn-1-yl)trimethylsilane (4.92 mmol, 2 equiv). The reaction mixture was then allowed to stir at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction (12 h), the combined organic layer was washed with brine and ice water and further extracted with ethyl acetate (3 × 15 mL) followed by drying over anhydrous Na_2SO_4. The organic phase was concentrated in a rotary evaporator to give the crude product, which was then subjected to column chromatography over silica gel to provide the desired product **3d**.

*2-((3-(Trimethylsilyl)prop-2-yn-1-yl)oxy)benzaldehyde (**3d**).* White liquid; R_f (hexane/EtOAc, 9:1) 0.55; yield 143 mg,



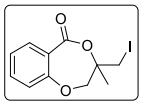
25%; ^1H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1 H), 7.85 (d, J = 6.0 Hz, 1 H), 7.55 (t, J = 8.5 Hz, 1 H), 7.11 (d, J = 8.5 Hz, 1 H), 7.07 (t, J = 7.5 Hz, 1 H), 4.80 (s, 2 H), 0.16 (s, 9 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 189.9, 160.3, 135.8, 128.6, 125.8, 121.8, 113.8, 99.3, 94.2, 57.7, −0.2; IR (KBr, neat) 2960, 2864, 2180, 1688, 1595, 1481, 1459, 1250, 1216, 1029, 837, 755, 638 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{17}O_2Si$ $(M + H)^+$ 233.0992, found 233.1014.

General Experimental Procedure for the Synthesis of 2a−2s, 2b′b.



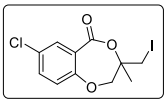
To a stirred solution of **1** (0.57 mmol, 1.0 equiv) and CuI (0.68 mmol, 1.2 equiv) in CH_3CN (4 mL) was added 70% aq. solution of TBHP (3.42 mmol, 6.0 equiv,) dropwise at room temperature. Then, the reaction mixture was allowed to stir at 70 °C, and the reaction time was monitored by TLC. After completion of the reaction (6−12 h), the reaction mixture was brought to room temperature. The solvent was removed under vacuo in a rotary evaporator and extracted with ethyl acetate (3 × 15 mL) and washed with aqueous solution of $Na_2S_2O_3$, NH_4Cl, and saturated brine solution. The combined organic extracts were dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **2a−2s**.

*3-(Iodomethyl)-3-methyl-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one (**2a**).*



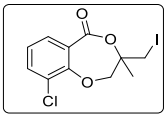
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 85−87 °C; yield 136 mg, 75%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.0 Hz, 1 H), 7.51−7.46 (m, 1 H), 7.10−7.03 (m, 2 H), 4.53 (d, J = 13.6 Hz, 1 H), 4.38 (d, J = 13.6 Hz, 1 H), 3.42 (d, J = 10.8 Hz, 1 H), 3.36 (d, J = 10.8 Hz, 1 H), 1.62 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 157.5, 136.1, 135.3, 122.3, 120.0, 116.5, 80.3, 75.1, 23.2, 8.1; IR (KBr, neat) 2969, 1738, 1696, 1480, 1277, 1261, 1118, 753, cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}IO_3$ $(M + H)^+$ 318.9826, found 318.982.

*7-Chloro-3-(iodomethyl)-3-methyl-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**2b**).*



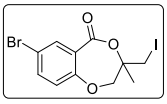
White solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 82−84 °C; yield 127 mg, 63%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 2.5 Hz, 1 H), 7.42 (dd, J = 9.0, 2.5 Hz, 1 H), 7.00 (d, J = 8.5 Hz, 1 H), 4.52 (d, J = 13.5 Hz, 1 H), 4.38 (d, J = 14 Hz, 1 H), 3.40 (d, J = 11.0 Hz, 1 H), 3.36 (d, J = 10.5 Hz, 1 H), 1.61 (s, 3 H).; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.03, 156.06, 135.34, 134.99, 127.67, 121.74, 117.69, 80.59, 75.41, 23.13, 7.74; IR (KBr, neat) 2955, 2911, 1696, 1477, 1389, 1276, 1134, 824, 723 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}ClIO_3$ $(M + H)^+$ 352.9436, found 352.9432

*9-Chloro-3-(iodomethyl)-3-methyl-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**2c**).*



Brown solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 128−130 °C; yield 143 mg, 71%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.5, 2.0 Hz, 1 H), 7.59 (dd, J = 8.0, 2.0 Hz, 1 H), 7.02 (t, J = 8.0 Hz, 1 H), 4.61 (d, J = 13.5 Hz, 1 H), 4.51 (d, J = 14 Hz, 1 H), 3.42 (d, J = 11.0 Hz, 1 H), 3.38 (d, J = 11.0 Hz, 1 H), 1.63 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.3, 153.1, 135.7, 134.7, 124.8, 122.3, 118.5, 80.4, 76.0, 23.1, 8.1; IR (KBr, neat) 2922, 1698, 1465, 1282, 1184, 1080, 748 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}ClIO_3$ $(M + H)^+$ 352.9436, found 352.9440.

*7-Bromo-3-(iodomethyl)-3-methyl-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**2d**).*

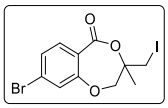


Brown solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 105−107 °C; yield 149 mg, 66%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 2.8 Hz, 1 H), 7.56 (dd, J = 8.8, 2.4 Hz, 1 H), 6.95 (d, J = 8.8 Hz, 1

https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

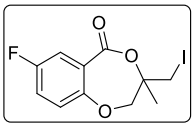
H), 4.53 (d, J = 13.6 Hz, 1 H), 4.38 (d, J = 14 Hz, 1 H), 3.41 (d, J = 10.8 Hz, 1 H), 3.36 (d, J = 10.4 Hz, 1 H), 1.62 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.90, 156.53, 138.11, 137.94, 122.00, 118.12, 114.68, 80.52, 75.40, 23.10, 7.77; IR (KBr, neat) 2958, 2924, 1695, 1474, 1386, 1275, 1135, 823, 764 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}BrIO_3$ $(M + H)^+$ 396.8931, found 396.8928.

*8-Bromo-3-(iodomethyl)-3-methyl-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**2e**).*



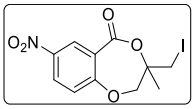
White solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 107−109 °C; yield 163 mg, 72%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 1 H), 7.27−7.26 (m, 1 H), 7.22 (dd, J = 8.8, 2.0 Hz, 1 H), 4.54 (d, J = 14 Hz, 1 H), 4.39 (d, J = 13.6 Hz, 1 H), 3.41 (d, J = 10.8 Hz, 1 H), 3.37 (d, J = 10.8 Hz, 1 H), 1.62 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.54, 157.65, 137.31, 129.75, 125.93, 123.02, 115.58, 80.30, 75.39, 23.11, 7.71; IR (KBr, neat) 2924, 1696, 1593, 1410, 1277, 1105, 864, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}BrIO_3$ $(M + H)^+$ 396.8931, found 396.8934.

*7-Fluoro-3-(iodomethyl)-3-methyl-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**2f**).*



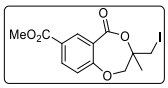
Red solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 117−119 °C; yield 117 mg, 61%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89−7.86 (m, 1 H), 7.24−7.19 (m, 1 H), 7.04−7.01 (m, 1 H), 4.51 (dd, J = 14.0, 2.0 Hz, 1H), 4.36 (d, J = 13.5 Hz, 1 H), 3.42 (d, J = 10.5 Hz, 1 H), 3.37 (d, J = 10.5 Hz, 1 H), 1.62 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.0, 164.0, 157.5 (d, J = 240.4 Hz), 153.9, 153.8, 123.3, 123.1, 121.8, 121.8, 120.80.(d, J = 25.25 Hz), 117.5, 117.4, 80.8, 75.4, 23.2, 7.9; ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ 40.41 (s, -F); IR (KBr, neat) 2980, 2927, 1695, 1488, 1411, 1275, 1167, 827, 751 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}FIO_3$ $(M + H)^+$ 336.9731, found 336.9736.

*3-(Iodomethyl)-3-methyl-7-nitro-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**2g**).*



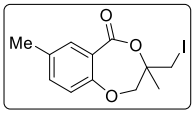
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 142−144 °C; yield 124 mg, 60%; ^1H NMR (500 MHz, $CDCl_3$) δ 9.13 (d, J = 3.0 Hz, 1 H), 8.32 (dd, J = 9.5, 3.0 Hz, 1 H), 7.20 (d, J = 9.0 Hz, 1 H), 4.66 (d, J = 13.5 Hz, 1 H), 4.53 (d, J = 14.0 Hz, 1 H), 3.41 (d, J = 10.5 Hz, 1 H), 3.39 (d, J = 11.0 Hz, 1 H), 1.66 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.0, 161.4, 142.8, 132.8, 129.7, 121.6, 121.6, 117.0, 80.5, 76.1, 23.0, 7.2; IR (KBr, neat) 2958, 2919, 1702, 1524, 1337, 1276, 1132, 841, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}INO_5$ $(M + H)^+$ 363.9676, found 363.9674.

*Methyl-3-(iodomethyl)-3-methyl-5-oxo-2,3-dihydro-5H-benzo[e][1,4]dioxepine-7-carboxylate (**2h**).*



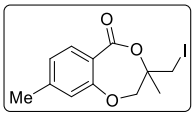
White solid; R_f (hexane/EtOAc, 3:1) 0.50; mp 166−168 °C; yield 150 mg, 70%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 2.5 Hz, 1 H), 8.12 (dd, J = 8.5, 2.0 Hz, 1 H), 7.10 (d, J = 8.5 Hz, 1 H), 4.59 (d, J = 14.0 Hz, 1 H), 4.46 (d, J = 14.0 Hz, 1 H), 3.91 (s, 3 H), 3.41 (d, J = 11.0, 1 H), 3.37 (d, J = 10.5, 1 H), 1.63 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 13C NMR δ 165.8, 164.3, 160.4, 138.6, 135.9, 124.7, 120.5, 116.3, 80.2, 75.5, 52.4, 23.1, 7.6; IR (KBr, neat) 2955, 2922, 1686, 1611, 1409, 1259, 1112, 852, 761 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{14}IO_5$ $(M + H)^+$ 376.9880, found 376.9884.

*3-(Iodomethyl)-3,7-dimethyl-2,3-dihydro-5H-benzo[e]-[1,4]dioxepin-5-one (**2i**).*



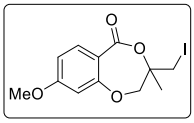
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 89−91 °C; yield 138 mg, 73%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.29 (dd, J = 8.4, 2.4 Hz, 1 H), 6.94 (d, J = 8.4 Hz, 1 H), 4.50 (d, J = 13.6 Hz, 1 H), 4.34 (d, J = 13.6 Hz, 1 H), 3.42 (d, J = 10.8, 1 H), 3.36 (d, J = 10.4, 1 H), 2.31 (s, 3 H), 1.61 (s, 3 H).; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.4, 155.4, 136.4, 135.5, 131.7, 119.8, 115.9, 80.3, 75.0, 23.2, 20.4, 8.2. IR (KBr, neat) 2966, 2919, 1694, 1617, 1494, 1398, 1286, 1137, 822, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}IO_3$ $(M + H)^+$ 332.9982, found 332.9980.

*3-(Iodomethyl)-3,8-dimethyl-2,3-dihydro-5H-benzo[e]-[1,4]dioxepin-5-one (**2j**).*



White solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 138−140 °C; yield 144 mg, 76%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1 H), 6.89 (d, J = 8.0, 2 H)6.85 (s, 1 H), 4.51 (d, J = 13.6 Hz, 1 H), 4.35 (d, J = 13.6 Hz, 1 H), 3.42 (d, J = 10.4, 1 H), 3.35 (d, J = 10.8, 1 H), 2.35 (s, 3 H), 1.61 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.3, 157.4, 146.7, 136.0, 123.7, 120.0, 113.7, 80.1, 75.0, 23.2, 21.4, 8.1; IR (KBr, neat) 2922, 1692, 1619, 1412, 1283, 1136, 1093, 963, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}IO_3$ $(M + H)^+$ 332.9982, found 332.9991.

*3-(Iodomethyl)-8-methoxy-3-methyl-2,3-dihydro-5H-benzo[e][1,4]dioxepin-5-one (**2k**).*

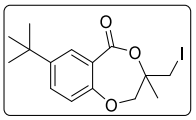


Gray solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 108−110 °C; yield 159 mg, 80%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, J = 9.5, 3.5 Hz, 1 H), 6.65 (m, 1 H), 6.48 (t, J = 2.5 Hz, 1 H), 4.52 (d, J = 13.5 Hz, 1 H), 4.35 (d, J = 13.5 Hz, 1 H), 3.84 (s, 3 H), 3.42 (d, J = 10.5, 1 H), 3.36 (d, J = 10.5, 1 H), 1.61 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.3, 164.9, 159.4, 137.9, 110.8, 109.2, 102.9, 79.8, 75.1, 55.9, 23.2, 8.0; IR (KBr, neat) 2960,

https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

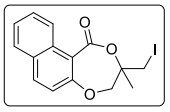
2924, 1687, 1612, 1419, 1231, 1120, 1027, 841, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}IO_4$ $(M + H)^+$ 348.9931, found 348.9941.

*7-(tert-Butyl)-3-(iodomethyl)-3-methyl-2,3-dihydro-5H-benzo[e][1,4]dioxepin-5-one (**2l**).*



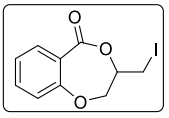
Brown gummy; R_f (hexane/EtOAc, 4:1) 0.55; yield 153 mg, 72%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 2.4 Hz, 1 H), 7.53 (dd, J = 8.8, 2.8 Hz, 1 H), 6.99 (d, J = 8.4 Hz, 1 H), 4.51 (d, J = 13.6 Hz, 1 H), 4.35 (d, J = 13.6 Hz, 1 H), 3.43 (d, J = 10.8, 1 H), 3.37 (d, J = 10.4, 1 H), 1.62 (s, 3 H), 1.31 (s, 9 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.7, 155.4, 145.2, 133.1, 132.2, 119.7, 115.6, 80.4, 75.0, 34.6, 31.5, 23.3, 8.1; IR (KBr, neat) 2961, 2873, 1696, 1611, 1494, 1400, 1294, 1251, 1144, 832, 766 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{20}IO_3$ $(M + H)^+$ 375.0452, found 375.0464.

*3-(Iodomethyl)-3-methyl-3,4-dihydro-1H-naphtho[2,1-e][1,4]dioxepin-1-one (**2m**).*



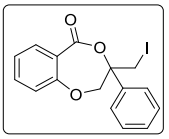
Brown gummy; R_f (hexane/EtOAc, 4:1) 0.55; yield 96 mg, 46%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 8.8 Hz, 1 H), 7.89 (d, J = 8.8 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.58 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.15 (d, J = 8.8 Hz, 1 H), 4.63 (d, J = 13.2 Hz, 1 H), 4.55 (d, J = 13.6 Hz, 1 H), 3.48 (d, J = 10.8 Hz, 1 H), 3.41 (d, J = 10.8 Hz, 1 H), 1.64 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.2, 156.5, 135.1, 132.8, 130.1, 128.8, 128.5, 125.9, 125.4, 119.8, 113.2, 81.4, 75.6, 23.7, 8.9; IR (KBr, neat) 2919, 2851, 1710, 1472, 1343, 1275, 1236, 827, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{14}IO_3$ $(M + H)^+$ 368.9982, found 368.9982.

*3-(Iodomethyl)-2,3-dihydro-5H-benzo[e][1,4]dioxepin-5-one (**2n**).*



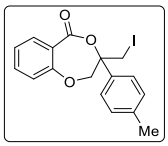
Brown Solid; R_f (hexane/EtOAc, 4:1) 0.55; mp 90−92 °C; yield 113 mg, 65%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94−7.89 (m, 1 H), 7.52−7.48 (m, 1 H), 7.16−7.12 (m, 1 H), 7.05−7.01 (m, 1 H), 4.65−4.62 (m, 1 H), 4.59−4.54 (m, 1 H), 4.48−4.41 (m, 1 H), 3.41−3.36 (m, 1 H), 3.33−3.29 (m, 1 H), $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.0, 155.5, 135.3, 134.0, 123.3, 121.1, 119.4, 75.7, 74.3, −0.3; IR (KBr, neat) 2928, 1716, 1603, 1480, 1444, 1293, 1217, 1115, 751, 443 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}IO_3$ $(M + H)^+$ 304.9669, found 304.9667.

*3-(Iodomethyl)-3-phenyl-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one (**2o**).*



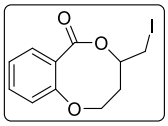
Black solid; R_f (hexane/EtOAc, 4:1) 0.55; mp 90−92 °C; yield 117 mg, 54%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.5 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 2 H), 7.33−7.27 (m, 4 H), 6.95 (t, J = 7.5 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 1 H), 4.92 (d, J = 14.0 Hz, 1 H), 4.79 (d, J = 14.0 Hz, 1 H), 3.60 (d, J = 11.0 Hz, 1 H), 3.56 (d, J = 11.0 Hz, 1 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.0, 156.5, 137.1, 135.5, 135.1, 128.9, 126.0, 121.9, 119.7, 116.8, 82.2, 76.0, 12.2; IR (KBr, neat) 2969, 1735, 1277, 750, 454 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{14}IO_3$ $(M + H)^+$ 380.9982, found 380.9980.

*3-(Iodomethyl)-3-(p-tolyl)-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one (**2p**).*



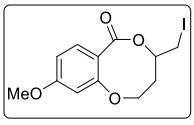
White solid; R_f (hexane/EtOAc, 4:1) 0.55; mp 80−82 °C; yield 119 mg, 53%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1 H), 7.35−7.27 (m, 3 H), 7.11 (d, J = 8.0 Hz, 2 H), 6.96 (t, J = 7.6 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 4.89 (d, J = 13.6 Hz, 1 H), 4.77 (d, J = 14.0 Hz, 1 H), 3.58 (d, J = 11.2 Hz, 1 H), 3.53 (d, J = 11.2 Hz, 1 H), 2.28 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.0, 156.5, 138.8, 135.5, 135.1, 134.1, 129.6, 125.9, 121.8, 119.8, 116.8, 82.2, 76.0, 21.3, 12.5; IR (KBr, neat) 2955, 2919, 1700, 1290, 1119, 751, 458 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{16}IO_3$ $(M + H)^+$ 395.0139, found 395.0136.

*4-(Iodomethyl)-3,4-dihydro-2H,6H-benzo[b][1,5]dioxocin-6-one (**2q**).*



White gummy; R_f (hexane/EtOAc, 4:1) 0.55; yield 87 mg, 48%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.5, 1.5 Hz, 1 H), 7.42−7.39 (m, 1 H), 7.05 (t, J = 7.5 Hz, 1 H), 6.95 (d, J = 8.5 Hz, 1 H), 4.53−4.48 (m, 1 H), 4.38−4.28 (m, 2 H), 3.37−3.29 (m, 2 H), 2.47−2.40 (m, 1 H), 2.02−1.95 (m, 1 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.9, 157.3, 133.6, 133.3, 122.2, 119.9, 116.8, 75.6, 65.6, 36.7, 5.5; IR (KBr, neat) 2957, 2923, 1709, 1603, 1485, 1441, 1289, 1122, 1089, 1054, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}IO_3$ $(M + H)^+$ 318.9826, found 318.9838.

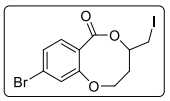
*4-(Iodomethyl)-9-methoxy-3,4-dihydro-2H,6H-benzo[b]-[1,5]dioxocin-6-one (**2r**).*



White gummy; R_f (hexane/EtOAc, 4:1) 0.50; yield 105 mg, 53%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 9.5 Hz, 1 H), 6.63−6.60 (m, 1 H), 6.42 (s, 1 H), 4.52−4.50 (m, 1 H), 4.38−4.35 (m, 1 H), 4.29−4.24 (m, 1 H), 3.81 (s, 3 H), 3.38−3.28 (m, 2 H), 2.46−2.42 (m, 1 H), 1.96−1.90 (m, 1 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.7, 162.9, 158.3, 134.4, 108.7, 107.9, 102.4, 64.6, 54.8, 35.5, 4.5; IR (KBr, neat) 2960, 2917, 1707, 1613, 1258, 1010, 1161, 789, cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{14}IO_4$ $(M + H)^+$ 348.9931, found 348.9931.

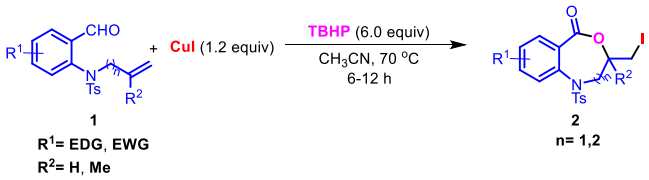
https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

*9-Bromo-4-(iodomethyl)-3,4-dihydro-2H,6H-benzo[b]-[1,5]dioxocin-6-one (**2s**).*



White gummy; R_f (hexane/EtOAc, 4:1) 0.55; yield 93 mg, 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 1 H), 7.19−7.15 (m, 2 H), 4.51−4.44 (m, 1 H), 4.41−4.36 (m, 1 H), 4.32−4.25 (m, 1 H), 3.41−3.28 (m, 2 H), 2.50−2.41(m, 1 H), 2.00−1.92 (m, 1 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.0, 157.7, 134.6, 127.5, 125.5, 122.8, 115.5, 75.7, 65.7, 36.5, 5.0; IR (KBr, neat) 2955, 2917, 1713, 1592, 1405, 1365, 1272, 1131, 1044, 932 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}BrIO_3$ (M + H)$^+$ 396.8931, found 396.8931.

General Experimental Procedure for the Synthesis of 2t−2z.

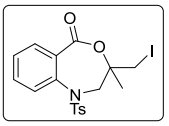


1
R^1= EDG, EWG
R^2= H, Me

2
n= 1,2

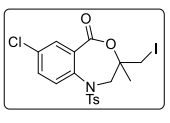
To a stirred solution of **1** (0.30 mmol, 1.0 equiv) and CuI (0.36 mmol, 1.2 equiv) in CH_3CN (4 mL) was added 70% aq. solution of TBHP (1.8 mmol, 6.0 equiv) dropwise at room temperature. Then, the reaction mixture was allowed to stir at 70 °C, and the reaction time was monitored by TLC. After completion of the reaction, the reaction mixture was brought to room temperature. The solvent was removed under vacuo in a rotary evaporator, extracted with ethyl acetate, and washed with aqueous solution of $Na_2S_2O_3$, NH_4Cl, and saturated brine solution. The combined organic extracts were dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **2t−2z**.

*3-(Iodomethyl)-3-methyl-1-tosyl-2,3-dihydrobenzo[e]-[1,4]oxazepin-5(1H)-one (**2t**).*



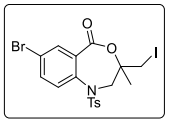
Brown solid; R_f (hexane/EtOAc, 3:1) 0.50; mp 153−155 °C; yield 96 mg, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.61 (m, 3 H), 7.52−7.47 (m, 3 H), 7.26 (t, J = 7.6 Hz, 2 H), 4.35 (d, J = 14.8 Hz, 1 H), 4.16 (d, J = 14.8 Hz, 1 H), 3.20 (d, J = 10.8 Hz, 1 H), 3.08 (d, J = 10.8 Hz, 1 H), 2.43 (s, 3 H), 1.37 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.8, 144.8, 136.0, 135.5, 134.3, 131.9, 131.8, 131.5, 130.1, 129.9, 127.7, 78.5, 57.4, 27.6, 21.9, 13.9; IR (KBr, neat) 2955, 2922, 1727, 1595, 1455, 1348, 1291, 1161, 1085, 712, 660, 575, 545 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}INO_4S$ (M + H)$^+$ 472.0074, found 472.0076.

*7-Chloro-3-(iodomethyl)-3-methyl-1-tosyl-2,3-dihydrobenzo[e][1,4]oxazepin-5(1H)-one (**2u**).*



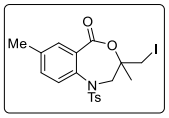
Pale yellow solid; R_f (hexane/EtOAc, 3:1) 0.50; mp 135−137 °C; yield 83 mg, 55%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 2.5 Hz, 1 H), 7.62−7.55 (m, 2 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.26 (t, J = 3.5 Hz 2 H), 4.36 (d, J = 14.5 Hz, 1 H), 4.11 (d, J = 14.5 Hz, 1 H), 3.22 (d, J = 11.0 Hz, 1 H), 3.12 (d, J = 11.0 Hz, 1 H), 2.42 (s, 3 H), 1.38 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.4, 145.0, 136.0, 135.2, 134.5, 134.3, 133.1, 132.8, 131.6, 130.2, 127.7, 78.8, 57.4, 27.6, 21.9, 13.7; IR (KBr, neat) 2956, 2922, 1725, 1596, 1478, 1350, 1161, 1087, 707, 660, 589, 546 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}ClINO_4S$ (M + H)$^+$ 505.9684, found 505.9689.

*7-Bromo-3-(iodomethyl)-3-methyl-1-tosyl-2,3-dihydrobenzo[e][1,4]oxazepin-5(1H)-one (**2v**).*



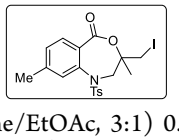
Brown solid; R_f (Hexane/EtOAc, 3:1) 0.50; mp 153−155 °C; yield 99 mg, 60%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 2.5 Hz, 1H), 7.75 (dd, J = 8.5, 2.5 Hz, 1 H), 7.47 (t, J = 9.0 Hz, 3 H), 7.24 (d, J = 8.0 Hz, 2 H), 4.35 (d, J = 14.5 Hz, 1 H), 4.09 (d, J = 14.5 Hz, 1 H), 3.21 (d, J = 11.0 Hz, 1 H), 3.11 (d, J = 11.0 Hz, 1 H), 2.41 (s, 3 H), 1.37 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.3, 145.0, 137.3, 135.1, 135.0, 134.5, 133.2, 132.9, 130.2, 127.7, 123.7, 78.8, 57.3, 27.6, 21.9, 13.7; IR (KBr, neat) 2956, 2917, 1729, 1456, 1401, 1352, 1162, 1085, 737, 663, 647, 588 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}BrINO_4S$ (M + H)$^+$ 549.9179, found 549.9180.

*3-(Iodomethyl)-3,7-dimethyl-1-tosyl-2,3-dihydrobenzo[e]-[1,4]oxazepin-5(1H)-one (**2w**).*



Brown solid; R_f (hexane/EtOAc, 3:1) 0.50; mp 140−142 °C; yield 93 mg, 64%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.43 (s, 1 H), 7.45 (m, 4 H), 7.22 (d, J = 8.0 Hz, 2 H), 4.31 (d, J = 14.5 Hz, 1 H), 4.12 (d, J = 14.5 Hz, 1 H), 3.17 (d, J = 11.0 Hz, 1 H), 3.07 (d, J = 11.0 Hz, 1 H), 2.40 (s, 6 H), 1.34 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.0, 144.6, 140.4, 135.5, 135.1, 133.2, 132.0, 131.7, 131.4, 130.1, 127.7, 78.5, 57.3, 27.7, 21.9, 21.2, 14.0; IR (KBr, neat) 2924, 1725, 1493, 1349, 1161, 1089, 814, 713, 662, 598, 547 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}INO_4S$ (M + H)$^+$ 486.0230, found 486.0234.

*3-(Iodomethyl)-3,8-dimethyl-1-tosyl-2,3-dihydrobenzo[e]-[1,4]oxazepin-5(1H)-one (**2x**).*

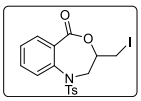


White solid; R_f (hexane/EtOAc, 3:1) 0.50; mp 133−135 °C; yield 95 mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 2 H), 7.42 (s, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.23 (d, J = 8.0 Hz, 2 H), 4.30 (d, J = 14.8 Hz, 1 H), 4.13 (d, J = 14.4 Hz, 1 H), 3.16 (d, J = 11.2 Hz, 1 H), 3.06 (d, J = 11.2 Hz, 1 H), 2.46 (s, 3 H), 2.41 (s, 3 H), 1.34 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.9, 145.6, 144.7, 135.9, 135.5, 132.1, 131.7, 130.7, 130.1, 128.9, 127.7, 78.4, 57.4, 27.7, 21.9, 21.9, 14.0; IR (KBr, neat) 2917, 1728, 1374, 1349, 1162,

https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

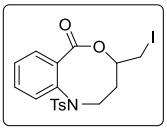
1090, 800, 707, 661, 577 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}INO_4S$ $(M + H)^+$ 486.0230, found 486.0256.

*3-(Iodomethyl)-1-tosyl-2,3-dihydrobenzo[e][1,4]-oxazepin-5(1H)-one (**2y**).*



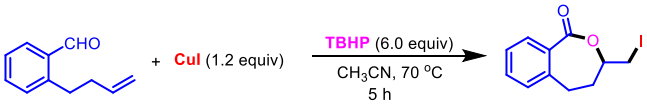
Pale yellow solid; R_f (hexane/EtOAc,3:1) 0.50; mp 163−165 °C; yield 102 mg, 62%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.61 (m, 3 H), 7.51−7.48 (m, 1 H), 7.41 (d, J = 8.0 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H), 4.31 (q, J = 11.5 Hz, 1 H), 4.10−4.06 (m, 1 H), 3.94 (dd, J = 13.5, 3.5 Hz, 1 H), 3.27 (d, J = 5.5 Hz, 2 H), 2.41 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.5, 144.8, 135.0, 134.9, 134.2, 132.5, 131.7, 130.2, 129.8, 127.6, 75.3, 55.1, 21.9, 0.5; IR (KBr, neat) 2958, 2928, 1738, 1595, 1455, 1351, 1296, 1161, 1115, 926, 750, 663, 580, 545 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{17}INO_4S$ $(M + H)^+$ 547.9917, found 547.9917.

*4-(Iodomethyl)-1-tosyl-1,2,3,4-tetrahydro-6H-benzo[c][1,5]oxazocin-6-one (**2z**).*



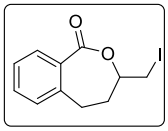
White solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 163−165 °C; yield 85 mg, 60%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63−7.61 (m, 1 H), 7.57 (d, J = 8.0 Hz, 2 H), 7.48−7.46 (m, 2 H), 7.27 (s, 1 H), 7.25 (s, 1 H), 7.01−6.99 (m, 1 H), 4.39−4.35 (m, 1 H), 4.30−4.25 (m, 1 H), 3.32−3.29 (m, 1 H), 3.20−3.13 (m, 2 H), 2.41 (s, 3 H), 2.34−2.25 (m, 1 H), 1.98−1.94 (m, 1 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.8, 144.2, 138.1, 136.8, 134.2, 133.3, 130.6, 130.1, 130.0, 129.9, 127.7, 79.3, 49.7, 35.7, 21.8, 8.4.; IR (KBr, neat) 2956, 2923, 1727, 1596, 1344, 1287, 1241, 1158, 1091, 818, 684, 569 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}INO_4S$ $(M + H)^+$ 472.0074, found 472.0076.

Experimental Procedure for the Synthesis of 2a′a.



To a stirred solution of **1** (0.63 mmol, 1.0 equiv) and CuI (0.76 mmol, 1.2 equiv) in CH_3CN (4 mL) was added 70% aq solution of TBHP (3.78 mmol, 6.0 equiv, 70% aq solution) dropwise at room temperature. Then, the reaction mixture was allowed to stir at 70 °C, and the reaction time was monitored by TLC. After completion of the reaction (5 h), the reaction mixture was brought to room temperature and CH_3CN was evaporated in a rotary evaporator. Then, the reaction mixture was extracted with ethyl acetate (3 × 15 mL) and washed with saturated $Na_2S_2O_3$, NH_4Cl, and brine solution. The combined organic extracts were dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **2a′a** in 68% yield.

*3-(Iodomethyl)-4,5-dihydrobenzo[c]oxepin-1(3H)-one (**2a′a**).*

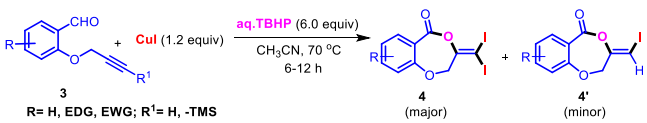


White solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 86−88 °C; yield 129 mg, 68%; 1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.2, 1.2 Hz, 1 H), 7.51−7.47 (m, 1 H), 7.40−7.36 (m, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 4.16−4.09 (m, 1 H), 3.39 (dd, J = 10.4, 6.0 Hz, 1 H), 3.33 (dd, J = 10.4, 6.0 Hz, 1 H), 3.06−2.98 (m, 1 H), 2.83−2.77 (m, 1 H), 2.31−2.22 (m, 1 H), 2.16−2.08 (m, 1 H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 137.9, 133.1, 131.4, 130.5, 129.0, 127.8, 77.5, 34.2, 29.8, 5.5; IR (KBr, neat) 2953, 2924, 1719, 1453, 1293, 1257, 1085, 756, 705, 593 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}IO_2$ $(M + H)^+$ 302.9876, found 302.9891.

*(E)-2-Styryl-4H-benzo[d][1,3]dioxin-4-one (**2b′b**).*

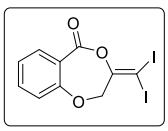
White solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 82−84 °C; yield 14 mg, 10%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 1 H), 7.60 (t, J = 7.0 Hz, 1 H), 7.48 (d, J = 7.0 Hz, 2 H), 7.38 (t, J = 7.0 Hz, 2 H), 7.35 (d, J = 7.0 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.10 (d, J = 8.5 Hz, 1 H), 7.04 (d, J = 16.0 Hz, 1 H), 6.42 (dd, J = 16.0, 5.0 Hz, 1 H), 6.19 (d, J = 5.5 Hz, 1 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.1, 158.3, 137.1, 136.6, 135.1, 130.5, 129.4, 129.0, 127.4, 123.8, 121.2, 117.1, 114.9, 100.4; IR (KBr, neat) 2920, 1743, 1613, 1469, 1301, 1236, 954, 759, 691, 588 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{13}O_3$ $(M + H)^+$ 253.0859, found 253.0879.

General Experimental Procedure for the Synthesis of 4a−4c and 4a′−4c′.



To a stirred solution of 2-(prop-2-yn-1-yloxy)benzaldehyde derivative (0.63 mmol, 1.0 equiv) and CuI (0.76 mmol, 1.2 equiv) in CH_3CN (4 mL) was added 70% aq solution of TBHP (3.78 mmol, 6.0 equiv) dropwise at room temperature. Then, the reaction mixture was allowed to stir at 70 °C, and the reaction time was monitored by TLC. After completion of the reaction (6−12 h), the reaction mixture was brought to room temperature. The solvent was removed under vacuo in a rotary evaporator, extracted with ethyl acetate (3 × 15 mL), and washed with $Na_2S_2O_3$, NH_4Cl, and saturated brine solution. The combined organic extract was dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **4** and **4′**.

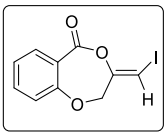
*3-(Diiodomethylene)-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one (**4a**).*



https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

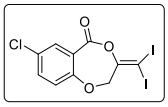
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.55; mp 153−155 °C; yield 140 mg, 52%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.0, 2.0 Hz, 1 H), 7.56−7.53 (m, 1 H), 7.20−7.16 (m, 1 H), 7.09 (dd, J = 8.0, 1.0 Hz, 1 H), 5.06 (s, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.4, 156.8, 150.4, 135.7, 134.1, 123.8, 121.1, 118.5, 71.2, 11.3; IR (KBr, neat) 3745, 2955, 2922, 1735, 1601, 1477, 1274, 1033, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_7I_2O_3$ (M + H)$^+$ 428.8479, found 428.8470.

*(Z)-3-(Iodomethylene)-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one (**4a′**).*



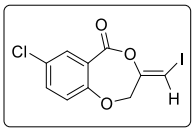
Brown solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 104−106 °C; yield 76 mg, 40%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97−7.94 (m, 1 H), 7.53−7.49 (m, 1 H), 7.16−7.13 (m, 1 H), 7.03 (d, J = 8.0 Hz, 1 H), 6.14 (s, 1 H), 4.83 (s, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.2, 156.7, 152.1, 135.5, 134.2, 123.4, 120.9, 118.5, 71.1, 70.3; IR (KBr, neat) 3081, 2960, 2922, 1736, 1635, 1604, 1478, 1281, 1226, 1116, 1037, 753 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_8IO_3$ (M + H)$^+$ 302.9513, found 302.9509.

*7-Chloro-3-(diiodomethylene)-2,3-dihydro-5H-benzo[e]-[1,4]dioxepin-5-one (**4b**).*



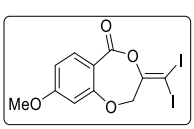
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.55; mp 208−210 °C; yield 146 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.04 (d, J = 8.8 Hz, 1 H), 5.05 (s, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.2, 155.3, 149.9, 135.7, 133.2, 129.1, 122.7, 119.6, 71.3, 12.5; IR (KBr, neat) 3745, 2960, 2919, 1714, 1606, 1471, 1397, 1266, 1164, 1130, 1024, 763, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_6ClI_2O_3$ (M + H)$^+$ 462.8089, found 462.8086.

*(Z)-7-Chloro-3-(iodomethylene)-2,3-dihydro-5H-benzo[e]-[1,4]dioxepin-5-one (**4b′**).*



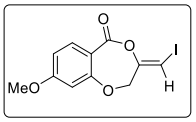
Brown gummy; R_f (hexane/EtOAc, 4:1) 0.50; yield 74 mg, 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 2.8 Hz, 1 H), 7.47 (dd, J = 8.8, 2.4 Hz, 1 H), 7.04 (d, J = 8.8 Hz, 1 H), 6.51 (s, 1 H), 5.01 (s, 2 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.3, 155.4, 148.9, 135.5, 133.3, 128.9, 122.8, 120.2, 72.2, 71.6; IR (KBr, neat) 3073, 2955, 2920, 1729, 1633, 1602, 1474, 1398, 1269, 1222, 1130, 1026, 826 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_7ClIO_3$ (M + H)$^+$ 336.9123, found 336.9120.

*3-(Diiodomethylene)-8-methoxy-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**4c**).*



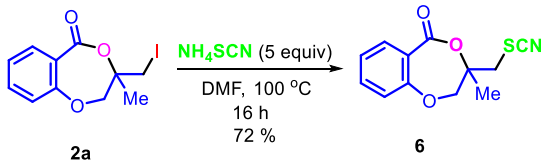
White solid; R_f (hexane/EtOAc, 3:1) 0.55; mp 148−150 °C; yield 164 mg, 57%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1 H), 6.70 (dd, J = 9.0, 2.5 Hz, 1 H), 6.51 (d, J = 2.5 Hz, 1 H), 5.04 (s, 2 H), 3.85 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.6, 162.8, 159.1, 150.5, 136.4, 111.3, 109.5, 104.0, 70.3, 56.0, 10.6; IR (KBr, neat) 2955, 2914, 1724, 1609, 1450, 1208, 1115, 1030 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_9I_2O_4$ (M + H)$^+$ 458.8585, found 458.8583.

*(Z)-3-(Iodomethylene)-8-methoxy-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**4c′**).*



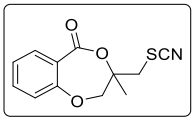
Pale yellow solid; R_f (hexane/EtOAc, 3:1) 0.50; mp 135−137 °C; yield 84 mg, 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 1 H), 6.68 (dd, J = 8.8, 2.4 Hz, 1 H), 6.46 (d, J = 2.4 Hz, 1 H), 6.10 (s, 1 H), 4.79 (s, 2 H), 3.83 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.5, 163.4, 159.1, 152.1, 136.6, 110.9, 109.8, 103.9, 70.3, 68.8, 55.9; IR (KBr, neat) 3739, 3007, 1716, 1609, 1275, 1261, 1225, 750 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{10}IO_4$ (M + H)$^+$ 332.9618, found 332.961.

Experimental Procedure for the Synthesis of 6.



3-(Iodomethyl)-3-methyl-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one **2a** (0.31 mmol, 1.0 equiv) and NH_4SCN (1.55 mmol, 5.0 equiv) in DMF (4 mL) under the N_2 atmosphere was allowed to stir at 80 °C in an oil bath and the reaction time was monitored by TLC. After completion of the reaction (16 h), the reaction mixture was brought to room temperature, diluted with ethyl acetate, and saturated brine solution. The organic phase was extracted with ice water (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **6**.

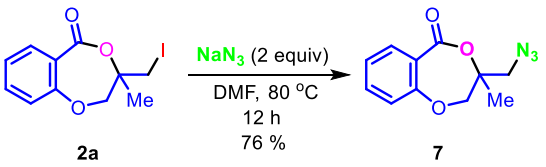
*3-Methyl-3-(thiocyanatomethyl)-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**6**).*



Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 109−111 °C; yield 56 mg, 72%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, J = 8.0, 2.0 Hz, 1 H), 7.52−7.49 (m, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.06 (d, J = 8.0 Hz, 1 H), 4.52 (d, J = 13.5 Hz, 1 H), 4.40 (d, J = 13.5 Hz, 1 H), 3.33 (q, J = 14 Hz, 2 H), 1.61 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.8, 157.1, 136.1, 135.6, 122.7, 120.1, 116.5, 112.1, 81.4, 74.4, 40.6, 21.8; IR (KBr, neat) 2955, 2919, 1695, 1481, 1447, 1280, 1118, 751 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{12}NO_3S$ (M + H)$^+$ 250.0532, found 250.0525.

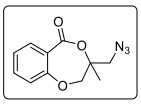
https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

Experimental Procedure for the Synthesis of 7.



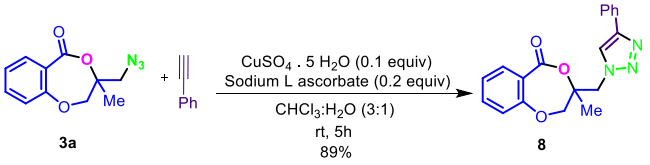
3-(Iodomethyl)-3-methyl-2,3-dihydro-5*H*-benzo[e][1,4]-dioxepin-5-one **2a** (0.31 mmol, 1.0 equiv) and NaN_3 (0.62 mmol, 2.0 equiv) in DMF (4 mL) under the N_2 atmosphere was allowed to stir at 80 °C in an oil bath and the reaction time was monitored by TLC. After completion of the reaction (12 h), the reaction mixture was brought to room temperature, diluted with ethyl acetate, and saturated brine solution. The organic phase was extracted with ice water (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **7.**

*3-(Azidomethyl)-3-methyl-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one (**7**).*



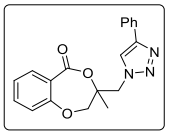
Pale yellow solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 53−55 °C; yield 55 mg, 76%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.0, 1.5 Hz, 1 H), 7.50−7.47 (m, 1 H), 7.08 (t, J = 8.0 Hz, 1 H), 7.04 (d, J = 8.0 Hz, 1 H), 4.35 (q, J = 14.0 Hz, 2 H), 3.60 (d, J = 13.0 Hz, 1 H), 3.40 (d, J = 12.5 Hz, 1 H), 1.46 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.4, 157.5, 136.1, 135.3, 122.3, 120.0, 116.7, 81.5, 74.1, 56.4, 20.4; IR (KBr, neat) 2925, 2108, 1696, 1606, 1482, 1443, 1292, 1119, 1069, 945, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}N_3O_3$ $(M + H)^+$ 234.0873, found 234.0872.

Experimental Procedure for the Synthesis of 8.



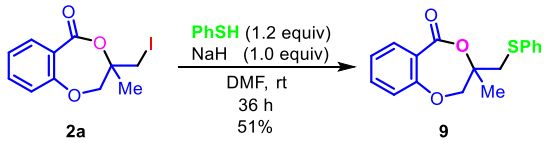
To a stirred solution of 3-(azidomethyl)-3-methyl-2,3-dihydro-5H-benzo[e][1,4]dioxepin-5-one (0.43 mmol, 1.0 equiv), CuSO4 $0.5H_2O$ (0.043 mmol, 0.1 equiv), and sodium L ascorbate (0.086 mmol, 0.2 equiv) in $CHCl_3/H_2O$ (3:1) (15 mL) was added phenylacetylene (0.43 mmol, 1.0 equiv) dropwise at 0 °C. Then, the reaction mixture was allowed to stir at room temperature. After completion of the reaction, the reaction mixture was diluted with DCM and saturated brine solution. The combined organic extracts were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **8.**

*3-Methyl-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3-dihydro-5H-benzo[e][1,4]-dioxepin-5-one (**8**).*



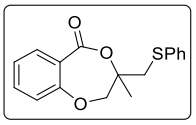
White solid; R_f (hexane/EtOAc, 3:2) 0.50; mp 165−167 °C; yield 89 mg, 89%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.0, 1.5 Hz, 1 H), 8.10 (s, 1 H), 7.84 (d, J = 8.0 Hz, 2 H), 7.50−7.47 (m, 1 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.35−7.31 (m, 1 H), 7.08 (t, J = 7.0 Hz, 1 H), 7.04 (d, J = 8.0 Hz, 1 H), 4.70 (s, 2 H), 4.57 (d, J = 14.0 Hz, 1 H), 4.02 (d, J = 14.0 Hz, 1 H), 1.47 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.2, 157.5, 148.5, 135.9, 135.5, 130.4, 129.1, 128.6, 126.0, 122.5, 121.5, 120.1, 116.4, 81.3, 74.2, 56.4, 20.1; IR (KBr, neat) 2956, 2918, 1694, 1606, 1481, 1290, 1120, 752, 694, cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{18}N_3O_3$ $(M + H)^+$ 336.1343, found 336.1366.

Experimental Procedure for the Synthesis of 9.



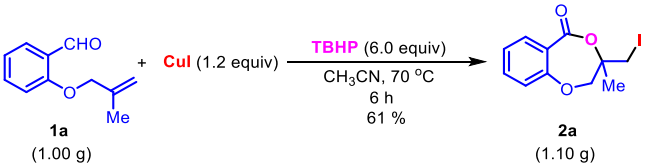
To a stirred solution of NaH (0.31 mmol, 1.0 equiv) in DMF (4 mL) under the N_2 atmosphere, thiophenol (0.37 mmol, 1.2 equiv) was added dropwise at 0 °C, and the resulting mixture was allowed to stir for 30 min at room temperature. Then, the substrate 3-(iodomethyl)-3-methyl-2,3-dihydro-5*H*-benzo[*e*]-[1,4]dioxepin-5-one **2a** (0.31 mmol, 1.0 equiv) in DMF was added dropwise to the reaction mixture. The progress of the reaction was monitored by TLC. After completion of the reaction (36 h), the reaction mixture was brought to room temperature, diluted with ethyl acetate, and saturated brine solution. The organic phase was extracted with ice water (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **9.**

*3-Methyl-3-((phenylthio)methyl)-2,3-dihydro-5H-benzo-[e][1,4]dioxepin-5-one (**9**).*



Yellow liquid; R_f (hexane/EtOAc, 4:1) 0.50; yield 47 mg, 51%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (dd, J = 8.5, 2.0 Hz, 1 H), 7.52−7.48 (m, 1 H), 7.46 (d, J = 7.0 Hz, 2 H), 7.34 (t, J = 7.0 Hz, 2 H), 7.28 (d, J = 7.0 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 7.50 (d, J = 8.5 Hz, 1 H), 4.50 (d, J = 14.0 Hz, 1 H), 4.39 (d, J = 13.5 Hz, 1 H), 3.34 (d, J = 2.0 Hz, 2 H), 1.54 (s, 3 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.6, 157.4, 135.9, 135.9, 135.0, 130.7, 129.3, 127.2, 122.0, 119.9, 116.7, 83.0, 74.6, 41.7, 22.0; IR (KBr, neat) 2919, 1694, 1605, 1481, 1292, 1119, 750, 691 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{20}NO_3S$ $(M + NH_4)^+$ 318.1158, found 318.1169.

Experimental Procedure for Gram-Scale Synthesis of Compound 2a.



To a stirred solution of 2-((2-methylallyl)oxy)benzaldehyde (5.68 mmol, 1.0 equiv) and CuI (6.82 mmol, 1.2 equiv) in CH_3CN (15 mL) was added 70% aq solution of TBHP (34.08

https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232

mmol, 6.0 equiv,) dropwise at room temperature. Then, the reaction mixture was allowed to stir at 70 °C, and the reaction time was monitored by TLC. After completion of the reaction (6 h), the reaction mixture was brought to room temperature, extracted with ethyl acetate (3 × 10 mL), and washed with $Na_2S_2O_3$, NH_4Cl, and saturated brine solution. The combined organic extract was dried over Na_2SO_4 and concentrated in a rotary evaporator. The crude was subjected to column chromatography over silica gel to give the corresponding product **2a** in 61% yield (1.10 g).

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c09878.

Control experimental procedure and copies of ^1H, $^{13}C\{^1H\}$, and ^{19}F NMR spectra of all new compounds; X-ray crystallographic data of compound **2a** and **4a** (PDF)

Accession Codes

CCDC 2299354, 2299353, and 2299355 contain the supplementary crystallographic data for this paper.

■ AUTHOR INFORMATION

Corresponding Author

Anil K. Saikia − *Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India;* orcid.org/0000-0002-3721-8156; Email: asaikia@iitg.ac.in

Authors

Archana Chutia − *Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India;* orcid.org/0000-0002-9884-998X

Pallav Jyoti Arandhara − *Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India;* orcid.org/0000-0002-3428-8386

Bipin Kumar Behera − *Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India*

Ankita Pradhan − *Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c09878

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.C. gratefully acknowledges the Ministry of Education (MoE) for a Prime Ministers Research Fellowship (PMRF). The authors are grateful to the DST-FIST program (Grant No. SR/FST/CS-II/2017/23C) for providing analytical facility.

■ REFERENCES

(1) (a) Schulz, S.; Hötling, S. The use of the lactone motif in chemical communication. *Nat. Prod. Rep.* **2015**, *32*, 1042−1066. (b) Shiina, I. Total synthesis of natural 8-and 9-membered lactones: recent advancements in medium-sized ring formation. *Chem. Rev.* **2007**, *107*, 239−273. (c) Sartori, S. K.; Diaz, M. A. N.; Munoz, G. D. Lactones: Classification, synthesis, biological activities, and industrial applications. *Tetrahedron* **2021**, *84*, 132001.

(2) Buszek, K. R.; Sato, N.; Jeong, Y. Total Synthesis of Octalactin A and B. *J. Am. Chem. Soc.* **1994**, *116*, 5511−5512.

(3) (a) Komai, S.; Hosoe, T.; Nozawa, T. I. K.; Fukushima, T. Y. K.; Kawai, K. New penicillide derivatives isolated from *Penicillium simplicissimu*. *J. Nat. Med.* **2006**, *60*, 185−190. (b) Nishida, H.; Tomoda, H.; Cao, J.; Okuda, S.; Omura, S. Urpactins, New Inhibitors of Acyl-CoA: Cholesterol Acyltransferase Produced by *Penicillium purpurogenum*. *J. Antibiot.* **1991**, *44*, 144−151.

(4) (a) Lizundia, E.; Makwana, V. A.; Larrañaga, A.; José Luis Vilas, J. L.; Shaver, M. P. Thermal, structural and degradation properties of an aromatic−aliphatic polyester built through ringopening polymerization. *Polym. Chem.* **2017**, *8*, 3530−3538. (b) MacDonald, J. P.; Shaver, M. P. An aromatic/aliphatic polyester prepared *via* ring-opening polymerisation and its remarkably selective and cyclable depolymerisation to monomer. *Polym. Chem.* **2016**, *7*, 553−559.

(5) (a) Parenty, A.; Moreau, X.; Campagne, J.-M. Macrolactonizations in the Total Synthesis of Natural Products. *Chem. Rev.* **2006**, *106*, 911−939.

(6) (a) Phan, D. H. T.; Kim, B.; Dong, V. M. Phthalides by Rhodium-Catalyzed Ketone Hydroacylation. *J. Am. Chem. Soc.* **2009**, *131*, 15608−15609. (b) Shen, Z.; Khan, H. A.; Dong, V. M. Rh-Catalyzed Carbonyl Hydroacylation: An Enantioselective Approach to Lactones. *J. Am. Chem. Soc.* **2008**, *130*, 2916−2917. (c) Ye, Z.; Lv, G.; Wang, W.; Zhang, M.; Cheng, J. Rhodium-Catalyzed Cascade Reaction: Aryl Addition/Intramolecular Esterification to Access 3-Aryl and 3-Alkenyl Phthalides. *Angew. Chem., Int. Ed.* **2010**, *49*, 3671−3674. (d) Ye, Z.; Qian, P.; Lv, G.; Luo, F.; Cheng, J. Palladium-Catalyzed Cascade Aryl Addition/Intramolecular Lactonization of Phthalaldehyde To Access 3-Aryl- and Alkenylphthalides. *J. Org. Chem.* **2010**, *75*, 6043−6045.

(7) (a) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. Macrolactonization *via* Hydrocarbon Oxidation. *J. Am. Chem. Soc.* **2006**, *128*, 9032−9033. (b) Velasco-Rubio, Á.; Varela, J. A.; Saá, C. Pd-Catalyzed allylic C-H activation to seven-membered N, O-heterocycles. *Chem. Commun.* **2021**, *57*, 10915−10918.

(8) Rose, C. A.; Zeitler, K. Efficient Catalytic, Oxidative Lactonization for the Synthesis of Benzodioxepinones Using Thiazolium-Derived Carbene Catalysts. *Org. Lett.* **2010**, *12*, 4552−4555.

(9) (a) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. Ring-Closure Reactions. 7. Kinetics and Activation Parameters of Lactone Formation in the Range of 3-to 23-Membered Rings. *J. Am. Chem. Soc.* **1977**, *99*, 2591−2597. (b) Illuminati, G.; Mandolini, L. Ring closure reactions of bifunctional chain molecules. *Acc. Chem. Res.* **1981**, *14*, 95−102.

(10) (a) Gataullin, R. R. Halolactonization of N-Acyl-N-(2-cyclohex-1-en-1-yl-6-methylphenyl) glycines: Towards Production of 4,1-Benzoxazoheterocycles. *Synthesis* **2023**, *55*, 2053−2060. (b) Jiang, X.; Xu, X.; Xu, W.; Yu, P.; Yeung, Y.-Y. Catalytic Enantioselective Halocyclizations to Access Benzoxazepinones and Benzoxazecinones. *Org. Lett.* **2021**, *23*, 6316−6320. (c) Verma, A.; Jana, S.; Prasad, C. D.; Yadav, A.; Kumar, S. Organoselenium and DMAP co-catalysis: regioselective synthesis of medium-sized halolactones and bromooxepanes from unactivated alkenes *Chem. Commun.* **2016**, *52*, 4179−4182. (d) Payne, J. L.; Deng, Z.; Flach, A. L.; Johnston, J. N. Enantioselective iodolactonization to prepare 3-lactone rings using hypervalent iodine. *Chem. Sci.* **2022**, *13*, 7318−7324.

(11) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. Enantioselective Bromolactonization of Conjugated (*Z*)-Enynes. *J. Am. Chem. Soc.* **2010**, *132*, 3664−3665.

(12) (a) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quid, S. Kharasch and Metalloporphyrin Catalysis in the Functionalization of Alkanes, Alkenes, and Alkylbenzenes by t-BuOOH. Free Radical Mechanisms, Solvent Effect, and Relationship with the Gif Reaction. *J. Am. Chem. Soc.* **1995**, *117*, 226−232. (b) Zhu, Y.; Yan, H.; Lu, L.; Liu, D.; Rong, G.; Mao, J. Copper-Catalyzed Methyl Esterification Reactions *via* C−C Bond Cleavage. *J. Org. Chem.* **2013**, *78*, 9898−9905. (c) Singh, J. B.; Mishra, K.; Gupta, T.; Singh, R. M. TBHP-promoted oxidative cyclization of o-alkynylquinoline aldehydes:

Metal/additive-free domino synthesis of pyrano[4,3-b]quinolin-1-ones. *Tetrahedron Lett.* **2018**, *59*, 1019−1022.
(13) (a) Martín-Acosta, P.; Feresin, G.; Tapia, A.; Estévez-Braun, A. Microwave-assisted organocatalytic intramolecular Knoevenagel/Hetero Diels−Alder reaction with O-(arylpropynyloxy)-salicylaldehydes: Synthesis of polycyclic embelin derivatives. *J. Org. Chem.* **2016**, *81*, 9738−9756. (b) Zhang, X.; Sivaguru, P.; Zanoni, G.; Han, X.; Tong, M.; Bi, X. Catalytic asymmetric C (sp3)−H carbene insertion approach to access enantioenriched 3-fluoroalkyl 2, 3-dihydrobenzofurans. *ACS Catalysis.* **2021**, *11*, 14293−14301. (c) Piel, I.; Steinmetz, M.; Hirano, K.; Froehlich, R.; Grimme, S.; Glorius, F. Highly Asymmetric NHC-Catalyzed Hydroacylation of Unactivated Alkenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983−4987. (d) Rohlmann, R.; Daniliuc, C. G.; Mancheño, O. G. Highly enantioselective synthesis of chiral 7-ring O- and N-heterocycles by a one-pot nitro-Michael−cyclization tandem reaction. *Chem. Comm.* **2013**, *49*, 11665−11667. (e) Sharma, A.; Gogoi, P. A cascade process for the synthesis of ortho-formyl allyl aryl ethers and 2 H-chromen-2-ol derivatives from arynes *via* trapping of o-quinone methide with an activated alkene. *Org. Biomol. Chem.* **2019**, *17*, 333−346. (f) Martínez-Gualda, A. M.; Domingo-Legarda, P.; Rigotti, T.; Díaz-Tendero, S.; Fraile, A.; Alemán, J. Asymmetric [2+ 2] photocycloaddition *via* charge transfer complex for the synthesis of tricyclic chiral ethers. *Chem. Commun.* **2021**, *57*, 3046−3049. (g) Dreis, A. M.; Douglas, C. J. Catalytic carbon−carbon σ bond activation: an intramolecular carbo-acylation reaction with acylquinolines. *J. Am. Chem. Soc.* **2009**, *131*, 412−413. (h) Sanguinetti, M.; Sanfilippo, S.; Castagnolo, D.; Sanglard, D.; Posteraro, B.; Donzellini, G.; Botta, M. Novel macrocyclic amidinoureas: Potent non-azole antifungals active against wild-type and resistant Candida species. *ACS Med. Chem. Lett.* **2013**, *4*, 852−857. (i) Hu, H.; Chen, X.; Sun, K.; Wang, J.; Liu, Y.; Liu, H.; Zhao, Y. Silver-catalyzed radical cascade cyclization toward 1, 5-/1, 3-dicarbonyl heterocycles: an atom-/step-economical strategy leading to chromenopyridines and isoxazole-/pyrazole-containing chroman-4-ones. *Org. Lett.* **2018**, *20*, 6157−6160. (j) Xuyu, Z.; Aijun, Z.; Qingqing, Z.; Qing'an, L.; Jun, X. Visible Light-Induced 4-Chromanones Synthesis: Radical Cascade Cyclization of α-Oxocarboxylic Acids with o-(Allyloxy) arylaldehydes Promoted by Phenyliodine (III) Diacetate. *Chin. J. Org. Chem.* **2022**, *42*, 2488.
(14) Wu, N.; Li, R.; Cui, F.; Pan, Y. Application of Dehydroabietic Acid in Palladium-Catalysed Enyne Cycloisomerisation. *Adv. Synth. Catal.* **2017**, *359*, 2442−2447.
(15) Miege, F.; Meyer, C.; Cossy, J. Rhodium-Catalyzed Cycloisomerization Involving Cyclopropenes: Efficient Stereoselective Synthesis of Medium-Sized Heterocyclic Scaffolds. *Angew. Chem., Int. Ed.* **2011**, *50*, 5932−5937.

NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, this paper was published ASAP on March 12, 2024 with the structures misplaced. The corrected version was reposted on March 13, 2024.

https://doi.org/10.1021/acsomega.3c09878
ACS Omega 2024, 9, 14217−14232