# Synthesis of Benzo[c]azepine-1,3(2*H*)-diones via C–H Alkylation/Cyclization with $\alpha$ , $\beta$ -Unsaturated Acyl Fluorides

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Dedicated to Professor Dr. Keiji Maruoka's 70th birthday.

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**Abstract:** Transition-metal-catalyzed directed C–H functionalization reactions are a powerful method to construct *N*-heterocycles. However, compared to the formation of five- and six-membered rings, that of seven-membered rings has been much less explored. Here, the synthesis of benzo[*c*]azepine-1,3(2*H*)-diones, which are benzene-fused seven-membered imides, from hydroxamates and  $\alpha$ , $\beta$ -unsaturated acyl fluorides via C–H activation using a Cp\*Rh(III) catalyst is described. Under mild reaction conditions, this reaction affords benzo[*c*]azepine-1,3(2*H*)-diones that bear a substituent at the 5-position.

#### Introduction

Nitrogen-containing heterocyclic structures are ubiquitous in organic compounds, and seven-membered N-heterocycles represent a common motif found in numerous biologically active compounds and drug molecules (Scheme 1a).<sup>[1,2]</sup> For example, benazepril is a nonsulfhydryl angiotensin-converting-enzyme (ACE) inhibitor prodrug used for the treatment of hypertension, [2a] while galantamine is an acetylcholinesterase (AchE) inhibitor used in Alzheimer's disease,<sup>[2b]</sup> and azelastine is a histamine-H<sub>1</sub>receptor antagonist for the treatment of allergic diseases.[2c] Moreover, seven-membered imides fused with a benzene ring constitute an interesting class of compounds (Scheme 1a, dashed box). Although the literature does not feature many examples of these compounds, they have been studied as selective-serotonin-5-HT<sub>1A</sub> agonists.<sup>[3]</sup> Given the success of other similar sevenmembered *N*-heterocycles as pharmaceuticals, sevenmembered imides would constitute an attractive chemical space to investigate, especially with regards to potential applications in medicinal chemistry. Therefore, we consider efficient synthetic

(a) Seven-membered N-heterocycles in biologically active compounds



(b) C–H functionalization for the synthesis of seven-membered imides Li and Zhao et al. (2022)



**Scheme 1.** Seven-membered *N*-heterocycles and their synthesis via directed C–H functionalization reactions.

routes to such seven-membered imide scaffolds to be of great importance.

Over the last few decades, transition-metal-catalyzed directed C-H functionalization reactions have attracted great attention as efficient synthetic transformations.<sup>[4]</sup> In particular, the construction of N-heterocyclic structures via the coupling of substrates that bear N-containing directing groups with unsaturated reactants has been extensively investigated.<sup>[5]</sup> However, compared to reactions that generate five- and six-membered rings, those that furnish seven-membered rings have been much less explored.<sup>[6-</sup> <sup>9]</sup> As a notable example of the synthesis of seven-membered imides, Li and Zhao have reported the coupling reactions of hydroxamates with 3-bromo-3,3-difluoropropene using a Cp\*Rh(III) catalyst to furnish benzo[c]azepine-1,3(2H)-diones (Scheme 1b).<sup>[8]</sup> On the other hand, we have recently reported the enantioselective synthesis of seven-membered lactams from benzylamines and  $\alpha,\beta$ -unsaturated acyl fluorides<sup>[10]</sup> via C-H activation using a Cp\*Rh(III) catalyst and a chiral Lewis base (Scheme 1c).<sup>[9]</sup> With this background in mind, we became interested in the synthesis of benzo[c]azepine-1,3(2H)-diones 3 from hydroxamates 1 and  $\alpha$ , $\beta$ -unsaturated acyl fluorides 2 via C-H activation, and herein, we report our findings (Scheme 1d). This synthetic route to 3 allows the introduction of a substituent at the 5-position, which expands the diversity of these easily accessible structures.

#### **Results and Discussion**

After the examination of various reaction conditions, we found that the reaction of hydroxamate 1a and acyl fluoride 2a proceeded in the presence of [Cp\*Rh(CH<sub>3</sub>CN)<sub>3</sub>][SbF<sub>6</sub>]<sub>2</sub> as a catalyst, (AcO)<sub>2</sub>SiMe<sub>2</sub> as a fluoride scavenger,<sup>[11]</sup> CsOPiv as a base, and MS13X in THF at 40 °C to afford the desired product (3aa) in high yield (Table 1, entry 1). The results of control experiments are summarized in Table 1 (entries 2-10). While omitting (AcO)<sub>2</sub>SiMe<sub>2</sub> significantly decreased the reactivity (entry 2), the reaction proceeded in moderate yield in the absence of CsOPiv (entry 3), probably because an acetate generated from (AcO)<sub>2</sub>SiMe<sub>2</sub> can also act as a base. The reactivity decreased moderately when MS13X was removed, or when the reaction was performed at room temperature (entries 4 and 5). While changing the solvent from THF to DCE had only a moderate effect (entry 6), the desired product was not obtained when using MeOH as the solvent (entry 7), probably due to the competitive solvolysis of 2a. Finally, we evaluated other related transition-metal catalysts, i.e., Cp\*Co(III), Cp\*Ir(III), and Ru(II), albeit that the desired product was not formed in any of these cases (entries 8-10).

We then examined the substrate scope under the optimized conditions (Scheme 2). Hydroxamates bearing various *para* or *meta* substituents furnished the corresponding products in 41–86% isolated yield (**3aa–3ha**). Substrates with an electron-withdrawing group generally exhibited attenuated reactivity (**3da–3fa, 3ha**) compared to substrates with an electron-donating group. The introduction of an *ortho*-methyl group to **1** also decreased the reactivity (**3ia;** 39%). We then investigated other  $\alpha$ , $\beta$ -unsaturated acyl fluorides **2**. In addition to simple linear and branched acyl

fluorides (**3ab** and **3ac**), benzyl-ether-substituted acyl fluoride provided the target product in satisfactory yield (**3ad**, 85%).

 Table 1. Optimized conditions for the C-H alkylation/cyclization of 1a and 2a

 and control experiments <sup>[a]</sup>



[a] Optimized standard reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol),  $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$  (0.005 mmol), (AcO)\_2SiMe<sub>2</sub> (0.15 mmol), CsOPiv (0.10 mmol), and MS13X (20 mg) in THF (0.2 mL) at 40 °C for 20 h. [b] Determined by <sup>1</sup>H NMR analysis of the crude mixture using dibenzyl ether as the internal standard. [c] Isolated yield at a 0.30 mmol (**1a**) scale. N.D. = not detected.

A plausible catalytic cycle is depicted in Figure 1. An active species with carboxylate anions (I) can be generated from  $[Cp*Rh(CH_3CN)_3]^{2+}$  and CsOPiv or  $(AcO)_2SiMe_2$ . The deprotonation and coordination of substrate 1 (II) followed by carboxylate-assisted C–H activation forms metallacycle III,<sup>[12]</sup> which further undergoes the coordination and insertion of 2 to furnish intermediate IV. After protonation to give V, intramolecular nucleophilic substitution between the hydroxamate moiety and acyl fluoride provide 3. The fluoride anion can be trapped by  $(AcO)_2SiMe_2$ , regenerating the active catalyst (I).



Scheme 2. Substrate scope.



Figure 1. Plausible catalytic cycle for the formation of benzo[c]azepine-1,3(2*H*)diones (3) from hydroxamates (1) and  $\alpha$ , $\beta$ -unsaturated acyl fluorides (2) via C– H activation.

#### Conclusion

In summary, we have demonstrated that the coupling reactions of hydroxamates (1) and  $\alpha$ , $\beta$ -unsaturated acyl fluorides (2) via Rh(III)-catalyzed C–H activation efficiently furnish benzo[*c*]azepine-1,3(2*H*)-diones (3) under mild reaction conditions (THF, 40 °C). Our findings can be expected to open new opportunities for the application of seven-membered imide

scaffolds in medicinal chemistry and the discovery of biologically active molecules.

#### Acknowledgements

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**Keywords:** C–H activation •  $\alpha$ , $\beta$ -unsaturated acyl fluoride • hydroxamate • imide • benzo[*c*]azepine-1,3(2*H*)-dione

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Rh(III)-catalyzed C–H alkylation/cyclization reactions of hydroxamates and  $\alpha$ , $\beta$ -unsaturated acyl fluorides are described. Optimized mild reaction conditions using a [Cp\*Rh(CH<sub>3</sub>CN)<sub>3</sub>][SbF<sub>6</sub>]<sub>2</sub> furnish benzo[*c*]azepine-1,3(2*H*)-diones bearing a substituent at the 5-positions.

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#### Supporting Information

## Synthesis of Benzo[c]azepine-1,3(2H)-diones via C–H Alkylation/Cyclization with $\alpha$ , $\beta$ -Unsaturated Acyl Fluorides

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#### 1. General

All non-aqueous reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted or in an argon-filled glove box. NMR spectra were recorded on JEOL JNM-ECS400 spectrometers operating at 391.78 MHz for <sup>1</sup>H NMR, 98.52 MHz for <sup>13</sup>C NMR and 368.59 Hz for <sup>19</sup>F NMR, JOEL JNM-ECX400 spectrometers operating at 395.88 MHz for <sup>1</sup>H NMR, 99.55 MHz for <sup>13</sup>C NMR and 372.48 MHz for <sup>19</sup>F NMR, JNM-ECA500 spectrometers operating at 500.16 MHz for <sup>1</sup>H NMR and 125.77 MHz for <sup>13</sup>C NMR, JOEL JNM-ECZ400 spectrometers operating at 399.78 MHz for <sup>1</sup>H NMR, 100.53 MHz for <sup>13</sup>C NMR and 368.61 MHz for <sup>19</sup>F NMR. Chemical shifts were reported in the scale relative to TMS (0.00 ppm for <sup>1</sup>H NMR in CDCl<sub>3</sub>), CHCl<sub>3</sub> (7.26 ppm for <sup>1</sup>H NMR in CDCl<sub>3</sub>), CDCl<sub>3</sub> (77.00 ppm for <sup>13</sup>C NMR in CDCl<sub>3</sub>) and PhCF<sub>3</sub> (–63.72 ppm for <sup>19</sup>F NMR) as an internal reference, respectively. ESI mass spectra were measured on Thermo Scientific Exactive spectrometer. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatography was performed with silica gel Kanto Silica gel 60 N (40-50 mesh), Yamazen YFLC AI-580 using Universal Column SiOH.

Materials: Tetrahydrofuran (THF) was purified by Glass Contour solvent purification system before use. Hydroxamates  $1^{[S1]}$  and acyl fluorides  $2^{[S2]}$  were synthesized according to the previously described methods. MS13X was preactivated by flame-drying under vacuum. All other reagents were commercially available and used as received unless otherwise noted. (AcO)<sub>2</sub>SiMe<sub>2</sub> was used after distillation with Kugelrohr.

#### 2. Experimental procedures



#### **General Procedure (GP1):**

In an argon-filled glovebox, a screw-cap test tube was charged with  $[Cp*Rh(CH_3CN)_3][SbF_6]_2$  (12.5 mg, 0.015 mmol, 5 mol %), CsOPiv (70.2 mg, 0.30 mmol, 1.0 equiv.), MS13X (60 mg), methyl hydroxamate **1** (0.30 mmol, 1.0 equiv.), and THF (0.6 mL). Then, acyl fluoride **2** (0.45 mmol, 1.5 equiv.) and (AcO)<sub>2</sub>SiMe<sub>2</sub> (0.45 mmol, 1.5 equiv.) were successively added. The test tube was capped, and then brought out of the glovebox. The reaction mixture was stirred for 20 h at 40 °C. The reaction mixture was filtered through a short pad of silica gel and eluted with AcOEt. After evaporation, the crude product was purified by silica gel column chromatography (hexane/EtOAc) to afford **3**. When removal of a carboxylic acid derived from an acyl fluoride was needed, the mixture was washed with NaHCO<sub>3</sub> aq. before or after silica gel column chromatography.

#### 2-methoxy-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3aa):



General Procedure GP1 using *N*-methoxybenzamide 1a (45.4 mg, 0.30 mmol) and (*E*)-5phenylpent-2-enoyl fluoride 2a (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1 to 4/1 to 2/1) afforded 3aa as a yellow amorphous (79.6 mg, 86%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 392 MHz)  $\delta$  8.21 (1H, d, *J* = 8.1, 1.3 Hz), 7.51 (1H, ddd, 7.5, 7.5, 1.5 Hz), 7.42 (1H, ddd, *J* = 7.6, 7.6, 1.3 Hz), 7.32-7.25 (2H, m), 7.23-7.12

(4H. m), 3.95 (3H, s), 3.16 (1H, dd, J = 17.1, 7.2 Hz), 3.10-2.98 (2H, m), 2.75-2.60 (2H, m), 2.07 (2H, q, J = 7.8 Hz). <sup>13</sup>C {<sup>1</sup>H} **NMR** (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.9, 164.0, 143.7, 140.4, 134.1, 133.1, 129.2, 128.5, 128.2, 127.5, 126.2, 63.4, 41.9, 38.6, 34.2, 33.4; one aromatic signal was missing probably due to overlapping. **HRMS** (ESI): m/z calculated for C<sub>19</sub>H<sub>19</sub>O<sub>3</sub>NNa<sup>+</sup> [M+Na]<sup>+</sup>: 332.1257, found: 332.1249. **Rf** 0.37 (hexane/EtOAc = 2/1).

#### 2-methoxy-7-methyl-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ba):



General Procedure GP1 using *N*-methoxy-4-methylbenzamide 1b (49.6 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride 2a (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1) afforded 3ba as a yellow amorphous (77.2 mg, 80%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 392 MHz)  $\delta$  8.13 (1H, d, *J* = 8.1 Hz), 7.31-7.26 (2H, m), 7.23-7.12 (4H, m), 6.93 (1H, s), 3.94 (3H, s), 3.16 (1H, dd, *J* = 16.4, 6.5

Hz), 3.02-2.92 (2H, m), 2.76-2.59 (2H, m), 2.40 (3H, s), 2.05 (2H, q, J = 7.8 Hz). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.9, 163.8, 144.1, 143.8, 140.5, 134.4, 129.0, 128.5, 128.3, 128.2, 126.3, 126.2, 63.4, 41.7, 38.8, 34.3, 33.5, 21.3. HRMS (ESI): m/z calculated for C<sub>20</sub>H<sub>21</sub>O<sub>3</sub>NNa<sup>+</sup> [M+Na]<sup>+</sup>: 346.1414, found: 346.1409. **Rf** 0.47

#### 2,7-dimethoxy-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ca):



**General Procedure GP1** using *N*,4-dimethoxybenzamide **1c** (54.4 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride **2a** (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1 to 4/1) afforded **3ca** as a yellow amorphous (84.9 mg, 83%). <sup>1</sup>**H NMR** (CDCl<sub>3</sub>, 392 MHz)  $\delta$  8.24 (1H, d, *J* = 9.1 Hz), 7.30-7.24 (2H, m), 7.22-7.12 (3H, m), 6.90 (1H, dd, *J* = 8.8, 2.5 Hz), 6.61 (1H, d, *J* = 2.7 Hz), 3.93 (3H, s), 3.86 (3H, s), 3.14 (1H, dd, *J* = 16.5, 6.6 Hz), 3.02-2.91 (2H, m),

2.76-2.60 (2H, m), 2.10-2.00 (2H, m). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.7, 163.2, 163.0, 146.2, 140.5, 137.0, 128.5, 128.2, 126.2, 121.2, 113.8, 112.5, 63.4, 55.5, 41.3, 39.0, 34.1, 33.4. HRMS (ESI): m/z calculated for C<sub>20</sub>H<sub>21</sub>O<sub>4</sub>NNa<sup>+</sup> [M+Na]<sup>+</sup>: 362.1363, found: 362.1358. **Rf** 0.32 (hexane/EtOAc = 2/1).

#### 7-chloro-2-methoxy-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3da):



General Procedure GP1 using 4-chloro-*N*-methoxybenzamide 1d (55.7 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride 2a (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1) afforded 3da as a yellow amorphous (63.8 mg, 62%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.17 (1H, d, J = 8.6 Hz), 7.38 (1H, dd, J = 8.6, 2.3 Hz), 7.32-7.25 (2H, m), 7.24-7.18 (1H, m), 7.17-

7.12 (3H, m), 3.94 (3H, s), 3.15 (1H, dd, J = 17.2, 7.2 Hz), 3.02-2.94 (2H, m), 2.78-2.60 (2H, m), 2.06 (2H, q, J = 7.7 Hz). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.5, 163.1, 145.5, 140.2, 139.5, 135.9, 128.7, 128.3, 128.2, 127.9, 127.7, 126.4, 63.6, 41.6, 38.5, 34.1, 33.4. HRMS (ESI): m/z calculated for C<sub>19</sub>H<sub>18</sub>O<sub>3</sub>NClNa<sup>+</sup>[M+Na]<sup>+</sup>: 366.0867, found: 366.0864. **Rf** 0.47 (hexane/EtOAc = 2/1).

#### 7-bromo-2-methoxy-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ea):



**General Procedure GP1** using 4-bromo-*N*-methoxybenzamide **1e** (69.0 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride **2a** (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1) afforded **3ea** as a yellow amorphous (68.3 mg, 59%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.08 (1H, d, *J* = 8.6 Hz), 7.55 (1H, dd, *J* = 8.6, 2.3 Hz), 7.32-7.25 (3H, m), 7.23-7.18 (1H, m), 7.17-7.12 (2H, m),

3.94 (3H, s), 3.15 (1H, dd, J = 16.8, 6.8 Hz), 3.02-2.92 (2H, m), 2.77-2.60 (2H, m), 2.05 (2H, q, J = 7.7 Hz). <sup>13</sup>C {<sup>1</sup>H} **NMR** (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.5, 163.3, 145.5, 140.1, 135.9, 131.1, 130.9, 128.7, 128.2, 128.2, 126.4, 63.6, 41.6, 38.4, 34.0, 33.4; one aromatic signal was missing probably due to overlapping. **HRMS** (ESI): m/z calculated for C<sub>19</sub>H<sub>18</sub>O<sub>3</sub>NBrNa<sup>+</sup> [M+Na]<sup>+</sup>:410.0362, found: 410.0360. **Rf** 0.43 (hexane/EtOAc = 2/1).

#### 2-methoxy-7-methyl-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione--carbon dioxide (3fa):



General Procedure GP1 using methyl 4-(methoxycarbamoyl)benzoate 1f (62.8 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride 2a (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1) afforded 3da as a yellow amorphous (55.7 mg, 51%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. before column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.25 (1H, d, *J* = 8.2 Hz), 8.03 (1H, dd, *J* = 8.4, 1.6 Hz), 7.84

(1H, d, J = 1.8 Hz), 7.31-7.25 (2H, m), 7.22-7.11 (3H, m), 3.96 (3H, s), 3.95 (3H, s), 3.20-3.06 (2H,m), 3.02 (1H, dd, J = 16.3, 1.8 Hz), 2.81-2.60 (2H, m), 2.14-2.03 (2H, m). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  167.7, 165.7, 163.4, 143.7, 140.2, 134.3, 133.8, 133.1, 129.2, 128.6, 128.2, 128.1, 126.3, 63.6, 52.6, 42.0, 38.5, 34.1, 33.5. HRMS (ESI): m/z calculated for C<sub>21</sub>H<sub>21</sub>O<sub>5</sub>NNa<sup>+</sup>[M+Na]<sup>+</sup>: 390.1312, found: 390.1306. **Rf** 0.50 (hexane/EtOAc = 2/1).

#### 2-methoxy-8-methyl-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ga):



General Procedure GP1 using *N*-methoxy-3-methylbenzamide 1g (49.6 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride 2a (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1 to 4/1) afforded 3ga as a yellow amorphous (82.8 mg, 85%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.01 (1H, s), 7.32-7.26 (3H, m), 7.21-7.15 (1H, m), 7.14-7.10 (2H, m), 7.04 (1H, d, *J* = 7.7 Hz), 3.94

(3H, s), 3.13 (1H, dd, J = 17.0, 7.0 Hz), 3.01-2.95 (2H, m), 2.73-2.58 (2H, m), 2.40 (3H, s), 2.04 (2H, q, J = 7.7 Hz). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  168.1, 164.2, 140.8, 140.6, 137.3, 134.4, 133.9, 129.0, 128.5, 128.2, 126.2, 63.4, 42.2, 38.3, 34.3, 33.5, 20.8; one aromatic signal was missing probably due to overlapping. HRMS (ESI): m/z calculated for C<sub>20</sub>H<sub>21</sub>O<sub>3</sub>NNa<sup>+</sup>[M+Na]<sup>+</sup>: 346.1414, found: 346.1407. **Rf** 0.52 (hexane/EtOAc = 2/1).

#### 2-methoxy-5-phenethyl-8-(trifluoromethyl)-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ha):



General Procedure GP1 using *N*-methoxy-3-(trifluoromethyl)benzamide 1h (65.7 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride 2a (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 19/1 to 10/1 to 5/1) afforded 3h as a colorless amorphous (40.6 mg, 41%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.49 (1H, brs), 7.74 (1H, dd, *J* = 8.3, 1.7 Hz), 7.32-725 (3H, m), 7.21-7.18 (1H, m), 7.16-7.10 (2H, m), 3.96 (3H, s), 3.19 (1H, dd, *J* = 16.6, 6.7 Hz), 3.14-

3.04 (1H, m), 3.01 (1H, dd, J = 16.5, 1.8 Hz), 2.80-2.59 (2H, m), 2.10-2.04 (2H, m). <sup>13</sup>C {<sup>1</sup>H, <sup>19</sup>F} NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  167.3, 162.8, 147.4, 140.0, 131.3, 130.3, 130.1, 129.5, 129.1, 128.7, 128.2, 126.4, 123.3, 63.6, 41.5, 38.5, 34.0, 33.3. <sup>19</sup>F NMR (CDCl<sub>3</sub>, 372 MHz) [C<sub>6</sub>H<sub>5</sub>CF<sub>3</sub> (-63.7 as an internal standard)]  $\delta$  -63.82 (s). HRMS (ESI): m/z calculated for C<sub>20</sub>H<sub>18</sub>O<sub>3</sub>NF<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 400.1131, found: 400.1121. **Rf** 0.44 (hexane/EtOAc = 2/1).

#### 2-methoxy-9-methyl-5-phenethyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ia):



General Procedure GP1 using *N*-methoxy-2-methylbenzamide 1i (49.6 mg, 0.30 mmol) and (*E*)-5-phenylpent-2-enoyl fluoride 2a (80.2 mg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 19/1 to 10/1 to 5/1) afforded 3ia as a colorless amorphous (37.6 mg, 39%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  7.46-7.16 (5H, m), 7.16-7.13 (2H, m), 7.00 (1H, d, *J* = 7.6 Hz), 3.97 (3H, s), 3.06-2.88 (3H, m), 2.67 (2H, t, *J* =

7.8 Hz), 2.45 (3H, s), 2.24-2.10 (1H, m), 2.06-1.94 (1H, m). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  169.5, 165.7, 141.6, 140.6, 131.3, 130.7, 130.6, 128.5, 128.3, 126.2, 123.5, 64.1, 45.1, 38.2, 33.7, 33.4, 21.3; one aromatic signal was missing probably due to overlapping. **HRMS** (ESI): m/z calculated for C<sub>20</sub>H<sub>21</sub>O<sub>3</sub>NNa<sup>+</sup> [M+Na]<sup>+</sup>: 346.1414, found: 346.1407. **Rf** 0.45 (hexane/EtOAc = 2/1).

#### 2-methoxy-5-pentyl-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ab):



General Procedure GP1 using *N*-methoxybenzamide 1a (45.4 mg, 0.30 mmol) and (*E*)-oct-2-enoyl fluoride 2b (72.1 µg, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 10/1 to 8/1) afforded **3ab** as a yellow amorphous (73.0 mg, 88%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.19 (1H, dd, *J* = 7.9, 1.1 Hz), 7.56-7.45 (1H, m), 7.40 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.19 (1H, d, *J* = 7.2 Hz), 3.95 (3H, s), 3.14 (1H, dd, *J* = 17.0, 7.0 Hz), 3.04-2.95 (2H, m), 1.75-1.68 (2H, m), 1.48-1.35 (1H, m), 1.35-1.20 (5H, m),

0.90-0.80 (3H, m). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  168.1, 164.1, 144.2, 134.0, 133.0, 129.1, 128.2, 127.3, 63.3, 42.1, 39.7, 32.7, 31.4, 27.3, 22.4, 13.8. HRMS (ESI): m/z calculated for C<sub>16</sub>H<sub>21</sub>NO<sub>3</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 298.1414, found: 298.1409. **Rf** 0.42 (hexane/EtOAc = 2/1).

#### 5-(cyclohexylmethyl)-2-methoxy-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ac):

In an argon-filled glovebox, a screw-cap test tube was charged with  $[Cp*Rh(CH_3CN)_3][SbF_6]_2$  (12.5 mg, 0.015 mmol, 5 mol %), CsOPiv (70.2 mg, 0.30 mmol, 1.0 equiv.), MS13X (60 mg), methyl *N*-methoxybenzamide **1a** (45.4 mg, 0.30 mmol, 1.0 equiv.), and THF (0.6 mL). Then, (*E*)-4-cyclohexylbut-2-enoyl fluoride **2c** (80.8 µg, 0.45 mmol) and (AcO)<sub>2</sub>SiMe<sub>2</sub> (0.45 mmol, 1.5 equiv.) were successively added. The test tube was capped, and then brought out of the glovebox. The reaction mixture was stirred for 20 h at



40 °C. The reaction mixture was filtered through a short pad of silica gel and eluted with AcOEt. After evaporation, the crude product was purified by silica gel column chromatography (hexane/EtOAc = 8/1 to 4/1 to 2/1). The residue was dissolved in a mixture of hexane and EtOAc (2:1) and washed with sat. NaHCO<sub>3</sub> aq. After evaporation, the residue was again purified by silica gel column chromatography (hexane/DCM/Et<sub>2</sub>O = 5:1:1) followed by gel permeation chromatography to afford **3ac** as a yellow amorphous (47.8 mg, 53%). <sup>1</sup>**H** NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.16 (1H, dd, *J* = 7.7, 1.4 Hz), 7.48 (1H, ddd, *J* = 7.5, 7.5, 1.4 Hz), 7.38 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.16 (1H, d, *J* = 7.7 Hz), 3.95 (3H, s), 3.20-3.07 (2H, m), 3.02-2.95 (1H, m), 1.81-1.56 (7H, m), 1.32-1.08 (4H, m), 0.98-0.81 (2H, m). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  168.2, 164.2, 144.5, 134.0, 133.1, 129.3, 127.9, 127.3, 63.3, 42.2,

40.5, 36.4, 34.8, 33.4, 33.1, 26.3, 25.9, 25.9. **HRMS** (ESI): m/z calculated for  $C_{18}H_{23}NO_3Na^+[M+Na]^+$ : 324.1570, found: 324.1567. **Rf** 0.47 (hexane/EtOAc = 2/1).

#### 5-(3-(benzyloxy)propyl)-2-methoxy-4,5-dihydro-1*H*-benzo[c]azepine-1,3(2*H*)-dione (3ad):



General Procedure GP1 using *N*-methoxybenzamide 1a (45.4 mg, 0.30 mmol) and (*E*)-6-(benzyloxy)hex-2-enoyl fluoride 2d (93.5  $\mu$ g, 0.45 mmol) and purification by silica gel column chromatography (hexane/EtOAc = 8/1 to 4/1 to 2/1) afforded 3ad as a yellow amorphous (89.7 mg, 85%). To remove the carboxylic acid, the mixture was washed with NaHCO<sub>3</sub> aq. before and after column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 396 MHz)  $\delta$  8.16 (1H, dd, *J* = 7.7, 1.4 Hz), 7.48 (1H, ddd, *J* = 7.5, 7.5, 1.4 Hz), 7.40 (1H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.35-7.25 (5H,

m), 7.16 (1H, dd, J = 7.5, 1.1 Hz), 4.45 (2H, s), 3.92 (3H, s), 3.44 (2H, t, J = 5.9 Hz), 3.14 (1H, dd, J = 17.0, 7.5 Hz), 3.05-2.97 (2H, m), 1.88-1.65 (3H, m), 1.65-1.50 (1H, m). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  168.0, 164.1, 143.8, 138.2, 134.1, 133.1, 129.3, 128.4, 128.3, 127.6, 127.6, 127.5, 73.0, 69.5, 63.4, 42.2, 39.5, 29.6, 27.9. HRMS (ESI): m/z calculated for C<sub>21</sub>H<sub>23</sub>NO<sub>4</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 376.1519, found: 376.1515. **Rf** 0.29 (hexane/EtOAc = 2/1).

#### 3. Reference

[S1] C. Zhou, J. Jiang, J. Wang, Org. Lett. 2019, 21, 4971-4975.

[S2] T. Kurihara, M. Kojima, T. Yoshino, S. Matsunaga, J. Am. Chem. Soc. 2022, 144, 7058-7065.

4. NMR spectra

### <sup>1</sup>H NMR spectrum of **3aa**



### <sup>13</sup>C NMR spectrum of **3aa**



### <sup>1</sup>H NMR spectrum of **3ba**



### <sup>13</sup>C NMR spectrum of **3ba**



### <sup>1</sup>H NMR spectrum of **3ca**



### <sup>13</sup>C NMR spectrum of **3ca**



### <sup>1</sup>H NMR spectrum of **3da**



### <sup>13</sup>C NMR spectrum of **3da**



### <sup>1</sup>H NMR spectrum of **3ea**



### <sup>13</sup>C NMR spectrum of **3ea**



### <sup>1</sup>H NMR spectrum of **3fa**



### <sup>13</sup>C NMR spectrum of **3fa**



### <sup>1</sup>H NMR spectrum of **3ga**



### <sup>13</sup>C NMR spectrum of **3ga**



### <sup>1</sup>H NMR spectrum of **3ha**



### <sup>13</sup>C NMR spectrum of **3ha**



### <sup>19</sup>F NMR spectrum of **3ha**



### <sup>1</sup>H NMR spectrum of **3ia**



### <sup>13</sup>C NMR spectrum of **3ia**



### <sup>1</sup>H NMR spectrum of **3ab**



### <sup>13</sup>C NMR spectrum of **3ab**



### <sup>1</sup>H NMR spectrum of **3ac**



### <sup>13</sup>C NMR spectrum of **3ac**



### <sup>1</sup>H NMR spectrum of **3ad**



### <sup>13</sup>C NMR spectrum of **3ad**

