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A Photochemical Strategy for the Synthesis of Caprolactams via Dearomative Ring Expansion of Nitroarenes

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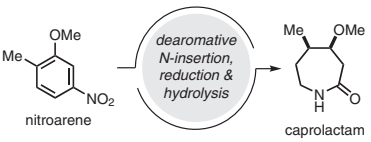
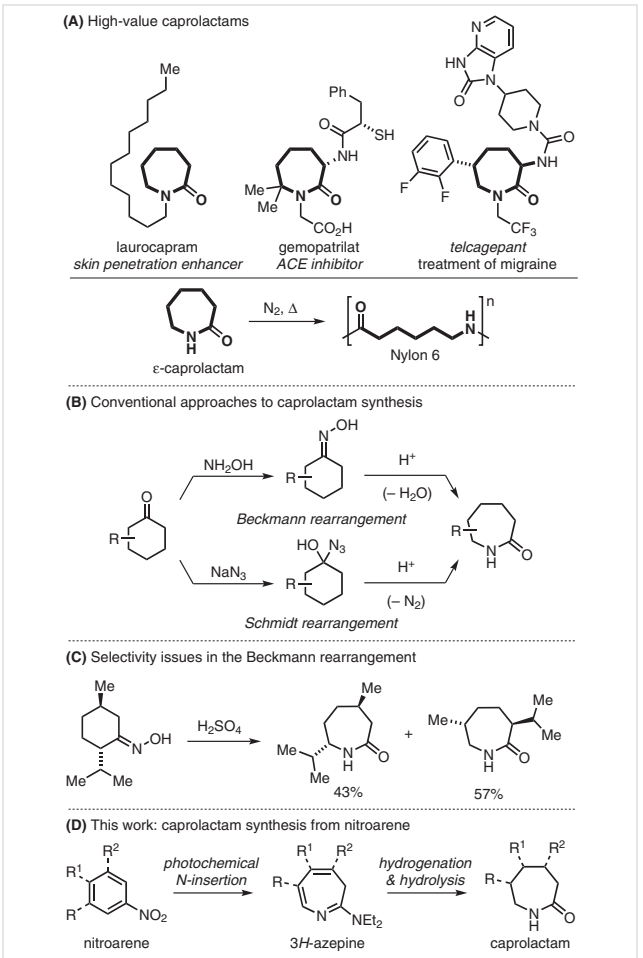
Abstract This paper outlines a novel strategy for the preparation of seven-membered-ring lactams from simple nitroarenes. The approach is based on a photochemical dearomative ring expansion starting with the conversion of the nitro group into a singlet nitrene. This process is mediated by blue light, occurs at room temperature and overall enables the insertion of the nitro *N*-atom into the benzenoid framework. This step transforms the aromatic starting material into a seven-membered ring azepine that, following hydrogenation and hydrolysis, is converted into the desired caprolactams in just three steps.

Key words singlet nitrene, photoexcited nitroarenes, ring expansion, azepines, hydrogenation, caprolactams, *N*-insertion

The seven-membered ring caprolactams are significant saturated heterocycles with strong applications in the production of high-value products like pharmaceuticals and organic materials.[1,2] These species are found in the structure of many natural products and commercial medicines, and are also valuable building blocks for the synthesis of novel amino acids and alkaloids.[3,4] Their wide array of industrial applications is further illustrated by the global demand for ε-caprolactam (>5 million tons per year), a crucial synthon used in polymer chemistry to make Nylon 6 filaments, fibers and plastics[5] (Scheme 1A).

Traditionally, caprolactams have been mostly prepared from readily available cyclohexanones by Beckmann or Schmidt rearrangement (Scheme 1B).[6,7] The Beckmann rearrangement requires converting the ketone functionality into an oxime, followed by acid-catalyzed ring expansion (generally H_2SO_4). In the Schmidt rearrangement, a nucleophilic azide reagent reacts with the ketone to promote, upon acidic treatment, a following migration to the desired caprolactam. Despite their synthetic utility, both methods present several drawbacks such as the use of somewhat harsh reaction conditions as well as highly energetic re-





Scheme 1 (A) Caprolactams and their relevance. (B) Common strategies for the preparation of caprolactams use cyclohexanones via Beckmann or Schmidt rearrangement. (C) Regioselectivity issues in Beckmann rearrangement of unsymmetrical cyclohexanones. (D) This work assembles caprolactams from nitroarenes in three steps.

agents. Furthermore, a lack of regioselectivity in the ring-expansion step is often observed when unsymmetrical cyclohexanones are used (Scheme 1C).[8]

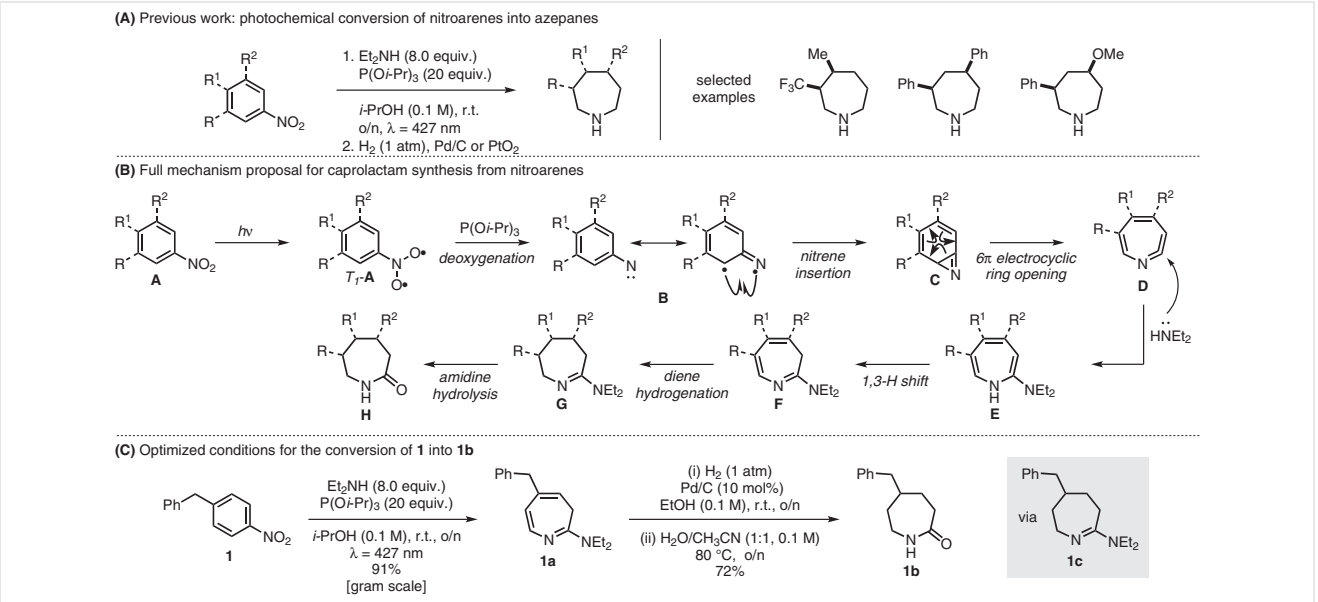
Other approaches to caprolactam synthesis are based on condensation[9] and cycloaddition[10] chemistry. For example, Zuo and co-workers[11] recently developed a novel two-step sequence to access various mono- or disubstituted lactams via a photoinduced C–C bond cleavage of cyclopentanones, followed by a formal [5+2] ring expansion. Branco[12] and Parvathaneni[13] and co-workers also reported the ring opening of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to access *N*-alkylated derivatives.

Overall, despite the many methods and approaches available, accessing polysubstituted caprolactams, especially in high diastereoselectivity, remains an outstanding synthetic challenge. In this paper, we describe the development of an alternative process that streamlines access to these species using nitroarenes as the starting materials (Scheme 1D). This enables the use of readily available and easy-to-functionalize aromatic substrates that are quickly converted into highly complex saturated seven-membered ring heterocycles.

Our group has recently demonstrated the synthesis of polysubstituted azepanes by photochemical dearomative ring expansion of nitroarenes (Scheme 2A).[14] This method uses blue light to photoexcite the nitroarenes in the presence of a P(III) reagent and a nucleophilic secondary amine. Under these conditions, the nitro group is converted into a singlet nitrene that undergoes a *N*-insertion to form 3*H*-azepine intermediates. In our initial work, a global hydrogenolysis was used to produce the desired azepanes in just two steps. One of the key retrosynthetic advantages of this process is that the substitution pattern of the starting nitroarene (*ortho*, *meta*, *para*) is fully translated into the one of the azepane.

We recently wondered if this photochemical approach could be modified to enable the synthesis of caprolactams. For this to be possible, however, it would be necessary to identify conditions whereby the 3*H*-azepines would be partially hydrogenated to the corresponding saturated amidines before hydrolysis to the desired caprolactams would take place (Scheme 2A). The detailed mechanistic interplay for caprolactam synthesis is outlined in Scheme 2B. The photoexcitation of nitroarenes **A** occurs under visible light irradiation (e.g., blue light) and their electrophilic[15] triplet state T_1-**A** is trapped by the electron-rich P(O*i*-Pr)$_3$. This stepwise [3+1]-like radical cycloaddition results in deoxygenation to eventually deliver the singlet nitrene **B**. At this point, intramolecular cyclization from the iminyl radical-type resonance form generates the azirine **C**.[16] A 6π-electrocyclic ring opening then leads to the seven-membered ring ketimine **D**.[17] This intermediate is strain-activated and is trapped by Et$_2$NH to then give 1*H*-azepine **E**.[18] Since this species has antiaromatic character, it immediately isomerizes to the thermodynamically stable 3*H*-azepine **F**.[19] At this point, the identification of reaction conditions able to selectively hydrogenate the diene component would give amidine **G**, that upon hydrolysis ought to afford the desired caprolactams **H**.

Based on our previous results, we used a set of optimized conditions to perform the initial ring expansion of the nitroarene to the 3*H*-azepine. Thus, treatment of *p*-ben-

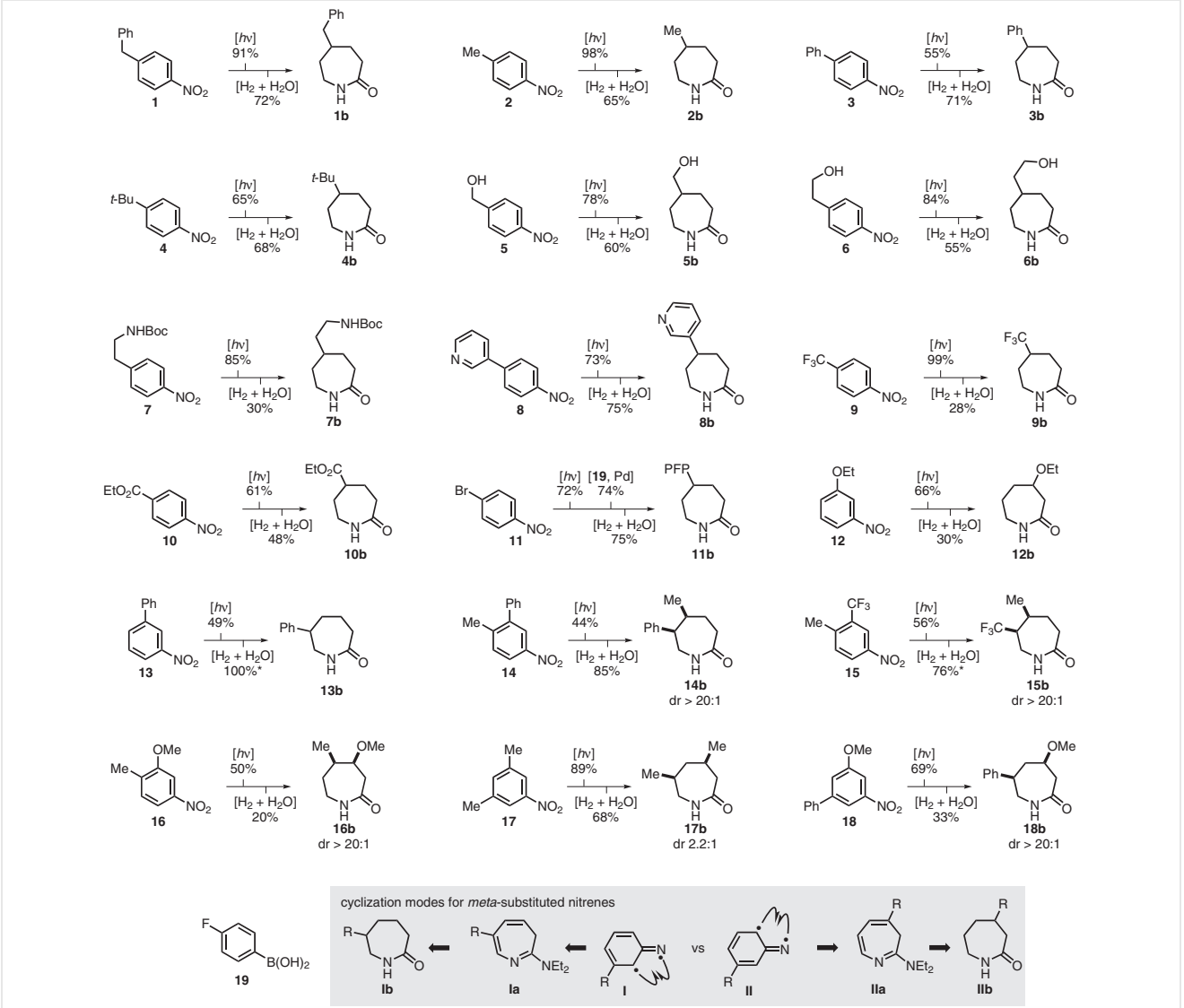


Scheme 2 (A) Previous work uses photoexcited nitroarenes for the synthesis of azepanes. (B) Proposed mechanistic steps for the conversion of nitroarenes **A** into caprolactams **H** via 3*H*-azepines **F**. (C) Optimized reaction conditions for the conversion of nitroarene **1** into caprolactam **1b** via **1a** and **1c**.

zylnitrobenzene (**1**) with Et_2NH (8.0 equiv.) and $P(Oi\text{-}Pr)_3$ (20 equiv.) in *i*-PrOH at room temperature under blue light irradiation (λ = 427 nm) gave **1a** in high yield, where the benzyl group is correctly located at the C5 position of the seven-membered heterocycle. This derivative can be conveniently obtained on a multiple gram scale from a single batch reaction.

Our work progressed onto evaluating conditions for the diene hydrogenation (for further details, see Supporting Information). Pleasingly, full conversion of **1a** into amidine **1c** could be realized using Pd/C (10 mol%) under an atmosphere of H_2 (balloon) at room temperature. A simple filtration (over Celite) and evaporation led to clean **1c** without the need of further purification. Finally, amidine hydrolysis was realized upon heating **1c** in a mixture of H_2O/CH_3CN (1:1, 0.1 M) at 80 °C. Under these conditions, caprolactam **1b** was obtained in overall 72% yield from **1a** (Scheme 2C).

With these optimized conditions in hand, we explored the scope of the process. We started by evaluating several *para*-substituted nitroarenes **1**–**11** that gave the corresponding C5-substituted caprolactams **1b**–**11b** in generally good yields (Scheme 3). The reaction demonstrated a tolerance of many commonly encountered functional groups like hydrogen-atom-transfer-labile[20] benzylic positions (**1b**, **2b**, **5b**, **6b**, **7b**), free alcohol (**5b** and **6b**), protected amine (**7b**) and pyridine (**8b**). We examined substrates containing electron-withdrawing groups (**9** and **10**), that provided **9b** and **10b** in moderate yields. *p*-Bromonitrobenzene (**11**) un-



Scheme 3 Scope of the process. PFP = *p*-FC_6H_4. Yields of caprolactams were determined by NMR analysis using 1,3-dinitrobenzene as the internal standard, on 0.1 mmol scale. * Isolated yield on 0.3 mmol scale.

derwent efficient ring expansion but the following diene hydrogenation could not be achieved, resulting in almost complete dehalogenation. Nonetheless, we demonstrated the utility of the resulting C5-bromo-3*H*-azepine in Suzuki–Miyaura cross-coupling with boronic acid **19**. This provided the C5-arylated derivative that was successfully hydrogenated and hydrolyzed to caprolactam **11b**.

meta-Substituted nitrobenzenes (**12**, **13**) were evaluated next to access C4- or C6-substituted caprolactams (**12b**, **13b**). In these cases, there are two possible modes of cyclization available to the singlet nitrene: the box in Scheme 3 describes the cyclization of mode **I** versus **II**, leading to azepines **Ia** and **IIa** and caprolactams **Ib** and **IIb**, respectively.[16] As we have previously determined, the ring expansion of *m*-phenylnitrobenzene (**13**) is fully selective (azirine formation via mode **I**) leading to the C6-arylated caprolactam **13b**. In contrast, the reactivity of *m*-OEt **12** took place selectively via mode **II**, providing the C4 derivative **12b** in high selectivity and moderate yield.

Introducing multiple substituents across the caprolactam core is challenging by the previously discussed methods, but can be simplified by our approach which requires *para*,*meta*-disubstituted or *meta*,*meta*-disubstituted nitroarenes. Indeed, we were able to apply our strategy to obtain complex polysubstituted derivatives with substituents at either C4,C5 or C5,C6 or C4,C6 (**14b**–**18b**). Hence, starting materials **14** and **15** were used to access **14b** and **15b**, crucially with high *syn* diastereoselectivity. Furthermore, the ability of a *m*-OMe group to control the nitrene ring insertion (mode **II**, box in Scheme 3) allowed us to selectively convert the unsymmetrical nitroarene **16** into *syn*-**16b**. The symmetrical 3,5-disubstituted nitroarene **17** was used to prepare the corresponding C4,C6-disubstituted caprolactam **17b** in moderate yield and low diastereocontrol. Finally, the unsymmetrical 3,5-disubstituted nitroarene **18** bearing a *m*-OMe group controlling the nitrene ring insertion (mode **II**, box in Scheme 3) led to caprolactam **18b**, also with high *syn* diastereoselectivity.

In conclusion, we have presented a streamlined approach for the preparation of complex caprolactams from simple nitroarenes. By employing a dearomative retrosynthetic strategy that translates the nitroarene substitution pattern across to the caprolactam core, polysubstituted derivatives can be obtained with high diastereoselectivity in just three steps.

All required fine chemicals were used directly without purification unless stated otherwise. All air- and moisture-sensitive reactions were carried out under nitrogen atmosphere using standard Schlenk manifold techniques. All solvents were bought from Acros as 99.8% purity and degassed by N_2 bubbling. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance Neo 600 MHz, Varian VNMRS 600 MHz, Bruker NanoBay Avance III HD 500 MHz or Varian VNMRS 400 MHz spectrometer. ^{1}H, ^{13}C and ^{19}F NMR spectra were acquired at various field strengths as indicated and were referenced to the residual peak solvent (for ^{1}H and ^{13}C) or by the instrument internally after locking and shimming to the deuterated solvent (for ^{19}F). ^{1}H NMR coupling constants (*J*) are reported in hertz (Hz) and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, etc.), coupling constant(s), integration. Melting points were measured on a Büchi B-540 melting point apparatus (heating rate: 5.0 °C/min). High-resolution mass spectra were obtained using a JEOL JMS-700, Fissions VG Trio 2000 quadrupole, Thermo Scientific LTQ Orbitrap XL or Finnigan MAT 95 mass spectrometer. Spectra were obtained using electron impact ionization (EI) or positive electrospray (ESI) techniques. Analytical TLC: aluminum-backed plates precoated (0.25 mm) with Merck silica gel 60 F254. Compounds were visualized by exposure to UV light or by dipping the plates in ninhydrin and permanganate ($KMnO_4$) stain followed by heating. Flash column chromatography was performed using Merck silica gel 60 (40–63 μm). All mixed solvent eluents are reported as v/v solutions. The LEDs used were Kessil PR160 427 nm and 390 nm. All the reactions were conducted in CEM 9-mL glass microwave tubes.

Ring Expansion of Nitroarenes 1–18; General Procedure 1 (GP1)

A dry tube equipped with a stirring bar was charged with the nitroarene (0.1 mmol, 1.0 equiv.), if solid. The tube was capped with a Supelco aluminum crimp seal with septum (PTFE/butyl), evacuated and refilled with N_2 (3 ×). The nitroarene (0.1 mmol, 1.0 equiv.) if liquid, Et_2NH (82 μL, 0.8 mmol, 8.0 equiv.), degassed P(O*i*-Pr)$_3$ (490 μL, 2.0 mmol, 20 equiv.) and anhydrous *i*-PrOH (1.0 mL, 0.1 M) were added. Blue LEDs (Kessil PR160 427 nm, intensity 100%) and a fan were switched on, and the mixture was stirred under irradiation at room temperature for 16 h. The solvent was evaporated and an excess of HCl (3 M in CPME) was added until formation of a precipitate. The residue was purified by column chromatography on silica gel to give the desired 3*H*-azepin-2-amine product **1a**, **S2a**–**S18a** (see Supporting Information).

Lactam Formation; General Procedure 2 (GP2)

A dry tube equipped with a stirring bar was charged with the 3*H*-azepin-2-amine (0.1 mmol, 1.0 equiv.) and Pd/C (10 wt %, 11 mg, 0.01 mmol, 10 mol%). The tube was capped with a Supelco aluminum crimp seal with septum (PTFE/butyl), evacuated and refilled with N_2 (3 ×). Anhydrous EtOH (1 mL, 0.1 M) was added and H_2 (balloon) was bubbled into the reaction mixture for 1 min. The reaction was stirred under an atmosphere of H_2 (1 atm) at room temperature for 16 h. The mixture was filtered through a Celite pad, and evaporated to give the tetrahydro-2*H*-azepin-7-amine intermediate. Then, a dry tube equipped with a stirring bar was charged with the crude amidine (0.1 mmol, 1.0 equiv.). The tube was capped with a Supelco aluminum crimp seal with septum (PTFE/butyl), evacuated and refilled with N_2 (3 ×). H_2O (0.5 mL) and CH_3CN (0.5 mL) were added, and the reaction was stirred at 80 °C for 16 h. The mixture was cooled to room temperature. 1,3-Dinitrobenzene (16.8 mg, 0.1 mmol, 1.0 equiv.) was added and the solution was stirred for 1 min. An aliquot (0.2 mL) of the solution was placed in an NMR tube, diluted with $CDCl_3$ (0.5 mL) and analyzed by ^{1}H NMR spectroscopy to determine the NMR yield. The residue was evaporated and purified by column chromatography on silica gel to give the desired lactam product **1b**–**18b**.

5-Benzylazepan-2-one (1b)

Following GP2, **1a** (26 mg, 0.1 mmol) gave **1b** (72% NMR yield) (8 mg, 40% isolated yield, 0.1 mmol scale) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.5 Hz, 2 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.13 (d, *J* = 7.4 Hz, 2 H), 6.30 (br s, 1 H), 3.24–3.13 (m, 2 H), 2.56 (qd, *J* = 13.5, 6.8 Hz, 2 H), 2.50–2.38 (m, 2 H), 1.89–1.77 (m, 3 H), 1.32 (m, 1 H), 1.25 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.7, 140.1, 129.3, 128.5, 126.2, 43.9, 43.8, 41.8, 35.8, 35.4, 29.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}ONNa$: 226.1202; found: 226.1197.

Data in accordance with the literature.[21]

5-Methylazepan-2-one (2b)

Following GP2, **S2a** (53 mg, 0.3 mmol) gave **2b** (0.1 mmol scale, 65% NMR yield) (17 mg, 45% isolated yield, 0.3 mmol scale) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.13 (br s, 1 H), 3.28–3.14 (m, 2 H), 2.46 (dd, *J* = 9.2, 3.5 Hz, 2 H), 1.84–1.78 (m, 2 H), 1.72–1.64 (m, 1 H), 1.32–1.25 (m, 1 H), 1.25–1.18 (m, 1 H), 0.97 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.8, 41.9, 38.0, 36.9, 35.5, 31.3, 23.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_{13}ONNa$: 150.0889; found: 150.0887.

Data in accordance with the literature.[21]

5-Phenylazepan-2-one (3b)

Following GP2, **S3a** (24 mg, 0.1 mmol) gave **3b** (71% NMR yield) (11 mg, 57% isolated yield, 0.1 mmol scale) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.5 Hz, 2 H), 7.22 (t, *J* = 7.4 Hz, 1 H), 7.17 (d, *J* = 7.4 Hz, 2 H), 6.39 (br s, 1 H), 3.40 (br t, *J* = 12.6 Hz, 1 H), 3.31–3.27 (m, 1 H), 2.77 (tt, *J* = 12.3, 2.8 Hz, 1 H), 2.68–2.52 (m, 2 H), 2.01 (br dt, *J* = 13.1, 4.0 Hz, 2 H), 1.80 (q, *J* = 13.3 Hz, 1 H), 1.73 (q, *J* = 12.9 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.5, 146.5, 128.8, 126.8, 126.7, 49.0, 42.3, 37.5, 36.1, 30.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{15}ONNa$: 212.1046; found: 212.1041.

Data in accordance with the literature.[21]

5-(*tert*-Butyl)azepan-2-one (4b)

Following GP2, **S4a** (22 mg, 0.1 mmol) gave **4b** (68% NMR yield) (7 mg, 44% isolated yield, 0.1 mmol scale) as a white solid; mp 139–146 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.10 (br s, 1 H), 3.30–3.18 (m, 2 H), 2.54–2.36 (m, 2 H), 2.04–1.91 (m, 2 H), 1.30–1.18 (m, 3 H), 0.88 (s, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 179.0, 52.5, 42.5, 35.9, 33.4, 30.9, 27.7, 24.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{19}ONNa$: 192.1359; found: 192.1360.

Data in accordance with the literature.[21]

5-(Hydroxymethyl)azepan-2-one (5b)

Following GP2, **S5a** (58 mg, 0.3 mmol) gave **5b** (0.1 mmol scale, 60% NMR yield) (25 mg, 58% isolated yield, 0.3 mmol scale) as a colorless oil.

R_f = 0.40 (Et_2O/MeOH, 8:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.00 (br s, 1 H), 3.35–3.46 (m, 2 H), 3.32–3.22 (m, 2 H), 2.57–2.44 (m, 2 H), 2.01–1.88 (m, 2 H), 1.81–1.72 (m, 1 H), 1.66 (br s, 1 H), 1.37–1.22 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.3, 67.6, 44.5, 41.6, 35.0, 32.5, 25.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_{13}O_2NNa$: 166.0838; found: 166.0838.

This compound is known in the literature but spectroscopic data were not provided.[22]

5-(2-Hydroxyethyl)azepan-2-one (6b)

Following GP2, **S6a** (62 mg, 0.3 mmol) gave **6b** (0.1 mmol scale, 55% NMR yield) (19 mg, 40% isolated yield, 0.3 mmol scale) as a white solid; mp 89–91 °C.

R_f = 0.40 (Et_2O/MeOH, 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.91 (br s, 1 H), 3.72 (t, *J* = 6.5 Hz, 2 H), 3.31–3.17 (m, 2 H), 2.48 (dd, *J* = 8.7, 3.5 Hz, 2 H), 1.93–1.85 (m, 2 H), 1.82–1.73 (m, 1 H), 1.60–1.52 (m, 3 H), 1.36–1.28 (m, 1 H), 1.28–1.24 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.6, 60.4, 41.9, 39.8, 38.2, 36.1, 35.3, 29.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{15}O_2NNa$: 180.0995; found: 180.0996.

***tert*-Butyl (2-(7-Oxoazepan-4-yl)ethyl)carbamate (7b)**

Following GP2, **S7a** (93 mg, 0.3 mmol) gave **7b** (0.1 mmol scale, 30% NMR yield) (17 mg, 22% isolated yield, 0.3 mmol scale) as a colorless oil.

R_f = 0.40 (Et_2O/MeOH, 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.94 (br s, 1 H), 4.48 (br s, 1 H), 3.25–3.20 (m, 2 H), 3.19–3.13 (m, 2 H), 2.53–2.39 (m, 2 H), 1.93–1.81 (m, 2 H), 1.66–1.54 (m, 1 H), 1.50–1.39 (m, 13 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.3, 156.0, 41.7, 39.1, 38.2, 37.4, 35.7, 35.2, 30.3, 29.2, 28.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{24}O_3N_2Na$: 279.1679; found: 279.1679.

5-(Pyridin-3-yl)azepan-2-one (8b)

Following GP2, **S8a** (72 mg, 0.3 mmol) gave **8b** (0.1 mmol scale, 75% NMR yield) (41 mg, 71% isolated yield, 0.3 mmol scale) as a white solid; mp 106–110 °C.

R_f = 0.60 (Et_2O/MeOH, 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.48 (br s, 2 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.30–7.27 (m, 1 H), 6.22 (br s, 1 H), 3.47–3.37 (m, 1 H), 3.37–3.27 (m, 1 H), 2.82 (tt, *J* = 11.9, 3.0 Hz, 1 H), 2.70–2.54 (m, 2 H), 2.09–1.91 (m, 2 H), 1.88–1.65 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.0, 148.6, 148.1, 134.3, 125.7, 123.9, 46.3, 42.1, 37.3, 35.8, 30.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{15}N_2O$: 191.1179; found: 191.1180.

5-(Trifluoromethyl)azepan-2-one (9b)

Following GP2 but stirring the reaction for 24 h, **S9a** (23 mg, 0.1 mmol) gave **9b** (28% NMR yield) (2 mg, 12% isolated yield, 0.1 mmol scale) as a colorless oil.

R_f = 0.55 (Et_2O/MeOH, 97:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.03 (br s, 1 H), 3.34 (dt, *J* = 13.6, 6.1 Hz, 1 H), 3.27 (ddd, *J* = 15.4, 11.2, 4.1 Hz, 1 H), 2.62 (dd, *J* = 14.4, 7.7 Hz, 1 H), 2.48 (t, *J* = 13.3 Hz, 1 H), 2.35–2.21 (m, 1 H), 2.19–2.10 (m, 2 H), 1.69–1.53 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.1, 126.9 (q, *J* = 279.5 Hz), 45.8 (q, *J* = 26.0 Hz), 40.4, 34.0, 28.7, 21.7.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.51 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_{10}ONF_3Na$: 204.0607; found: 204.0609.

Ethyl 7-Oxoazepane-4-carboxylate (10b)

Following GP2, **S10a** (24 mg, 0.1 mmol) gave **10b** (48% NMR yield) (6 mg, 30% isolated yield, 0.1 mmol scale) as a colorless oil.

R_f = 0.70 (Et_2O/MeOH, 95:5).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.30 (br s, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.38–3.28 (m, 1 H), 3.25–3.21 (m, 1 H), 2.63–2.52 (m, 2 H), 2.44 (ddd, *J* = 14.1, 11.9, 1.5 Hz, 1 H), 2.13–2.00 (m, 2 H), 1.89–1.76 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.0, 174.4, 60.8, 46.3, 40.8, 34.5, 32.0, 25.3, 14.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{15}O_3NNa$: 208.0944; found: 208.0939.

This compound is known in the literature but spectroscopic data were not provided.[23]

5-(4-Fluorophenyl)azepan-2-one (11b)

Following GP2, **S11b** (26 mg, 0.1 mmol) gave **11b** (75% NMR yield) (15 mg, 72% isolated yield, 0.1 mmol scale) as a colorless oil.

R_f = 0.40 (Et_2O/MeOH, 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.13 (dd, *J* = 8.2, 5.5 Hz, 2 H), 6.99 (t, *J* = 8.6 Hz, 2 H), 6.08 (br s, 1 H), 3.43–3.35 (m, 1 H), 3.33–3.25 (m, 1 H), 2.76 (t, *J* = 11.8 Hz, 1 H), 2.66–2.53 (m, 2 H), 2.02–1.96 (m, 2 H), 1.79–1.72 (m, 1 H), 1.72–1.65 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.2, 128.2, 128.1, 115.6, 115.5, 48.2, 42.2, 37.8, 35.9, 30.8.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –116.46 to –116.58 (m).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}ONFNa$: 230.0952; found: 230.0945.

4-Ethoxyazepan-2-one (12b)

Following GP2, **S12a′** (21 mg, 0.1 mmol) gave **12b** (30% NMR yield) (4 mg, 25% isolated yield, 0.1 mmol scale) as a white solid; mp 59–60 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.99 (br s, 1 H), 3.64 (dd, *J* = 9.0, 7.1 Hz, 1 H), 3.54 (t, *J* = 7.8 Hz, 1 H), 3.52–3.42 (m, 1 H), 3.30–3.15 (m, 2 H), 2.77 (dd, *J* = 13.5, 9.2 Hz, 1 H), 2.69 (d, *J* = 13.4 Hz, 1 H), 2.04–1.94 (m, 1 H), 1.93–1.79 (m, 2 H), 1.62–1.53 (m, 1 H), 1.19 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.6, 72.8, 64.3, 42.7, 42.1, 36.6, 26.3, 15.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{15}NO_2Na$: 180.0995; found: 180.0990.

Data in accordance with the literature.[24]

6-Phenylazepan-2-one (13b)

Following GP2, **S13a** (72 mg, 0.3 mmol) gave **13b** (60 mg, 100% isolated yield, 0.3 mmol scale) as a white solid; mp 150–151 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (td, *J* = 7.3, 1.3 Hz, 2 H), 7.22 (tt, *J* = 7.5, 1.3 Hz, 1 H), 7.15 (d, *J* = 7.1 Hz, 2 H), 6.60 (br s, 1 H), 3.50 (ddd, *J* = 14.8, 10.1, 4.8 Hz, 1 H), 3.21 (ddt, *J* = 14.8, 7.6, 1.8 Hz, 1 H), 2.72 (ddt, *J* = 11.9, 10.1, 2.5 Hz, 1 H), 2.65–2.46 (m, 2 H), 2.24–2.09 (m, 1 H), 2.05–1.95 (m, 1 H), 1.87–1.65 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.8, 144.6, 128.8, 126.8, 126.8, 48.7, 47.0, 38.6, 36.6, 23.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{15}NONa$: 212.1051; found: 212.1055.

Data in accordance with the literature.[25]

syn-5-Methyl-6-phenylazepan-2-one (14b)

Following GP2, **S14a** (76 mg, 0.3 mmol) gave **14b** (0.1 mmol scale, 85% NMR yield) (50 mg, 81% isolated yield, 0.3 mmol scale) as a colorless oil; dr >20:1.

R_f = 0.60 (Et_2O/MeOH, 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.5 Hz, 2 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 7.12 (d, *J* = 7.3 Hz, 2 H), 5.85 (br s, 1 H), 3.60 (dt, *J* = 14.4, 7.2 Hz, 1 H), 3.49–3.40 (m, 1 H), 2.95 (ddd, *J* = 6.9, 4.4, 1.6 Hz, 1 H), 2.70 (ddd, *J* = 14.3, 10.0, 1.8 Hz, 1 H), 2.49 (ddd, *J* = 14.1, 10.2, 1.5 Hz, 1 H), 2.24–2.15 (m, 1 H), 1.94–1.85 (m, 1 H), 1.85–1.77 (m, 1 H), 0.79 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.2, 128.9, 128.5, 126.8, 125.7, 49.2, 30.5, 29.9, 28.8, 22.8, 14.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}NONa$: 226.1202; found: 226.1203.

syn-5-Methyl-6-(trifluoromethyl)azepan-2-one (15b)

Following GP2, **S15a** (74 mg, 0.3 mmol) gave **15b** (45 mg, 76% isolated yield, 0.3 mmol scale) as a white solid; mp 80–82 °C; dr >20:1.

R_f = 0.60 (CH_2Cl_2/MeOH, 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.13 (br s, 1 H), 3.53 (ddd, *J* = 15.5, 8.1, 5.5 Hz, 1 H), 3.24 (dd, *J* = 15.5, 7.2 Hz, 1 H), 2.62 (ddd, *J* = 14.6, 9.5, 3.3 Hz, 1 H), 2.49–2.29 (m, 3 H), 1.81 (tt, *J* = 6.7, 3.5 Hz, 2 H), 1.19–1.06 (m, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 178.0, 126.9 (q, *J* = 281.8 Hz), 47.3 (q, *J* = 23.8 Hz), 37.8, 32.0, 29.8, 29.1, 15.5.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –65.70.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{12}NOF_3Na$: 218.0763; found: 218.0761.

syn-4-Methoxy-5-methylazepan-2-one (16b)

Following GP2, **S16a′** (62 mg, 0.3 mmol) gave **16b** (0.1 mmol scale, 20% NMR yield) (5 mg, 10% isolated yield, 0.3 mmol scale) as a white solid; mp 69–71 °C; dr >20:1.

R_f = 0.20 (Et_2O/MeOH, 97:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.86 (br s, 1 H), 3.44 (s, 3 H), 3.39 (dd, *J* = 7.6, 1.5 Hz, 1 H), 3.27–3.14 (m, 2 H), 3.00 (qd, *J* = 7.8, 1.5 Hz, 1 H), 2.61 (d, *J* = 14.1 Hz, 1 H), 1.85–1.73 (m, 1 H), 1.72–1.62 (m, 1 H), 1.57–1.50 (m, 1 H), 1.05 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.1, 77.4, 57.8, 41.7, 40.8, 39.2, 31.9, 19.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{15}NO_2Na$: 180.0995; found: 180.0994.

***syn*-4,6-Dimethylazepan-2-one (17b) and *anti*-4,6-Dimethylazepan-2-one (17b')**

Following GP2, **S17a** (57.6 mg, 0.3 mmol) gave **17b** and **17b'** (0.1 mmol scale, 68% NMR yield) (26 mg, 60% isolated yield, 0.3 mmol scale) as an inseparable mixture of diastereoisomers as a white solid; mp 85–86 °C; dr = 2.2:1.

^{1}H NMR (600 MHz, $CDCl_3$): δ (diastereoisomers) = 6.17 (br s, 0.7 H), 6.03 (br s, 0.3 H), 3.28–3.12 (m, 0.2 H), 3.08–2.98 (m, 1 H), 2.96–2.90 (m, 0.8 H), 2.48 (d, *J* = 12.6 Hz, 0.4 H), 2.43–2.32 (m, 1 H), 2.27 (d, *J* = 13.8 Hz, 0.8 H), 2.04 (br s, 0.5 H), 1.96–1.90 (m, 0.6 H), 1.90–1.78 (m, 1.6 H), 1.74–1.65 (m, 1 H), 1.62–1.51 (m, 0.8 H), 1.11–0.98 (m, 3 H), 0.93 (d, *J* = 6.9 Hz, 0.7 H), 0.89 (d, *J* = 6.8 Hz, 1.6 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (diastereoisomers) = 177.6, 177.3, 49.4, 48.6, 48.5, 45.6, 44.5, 43.4, 35.3, 30.3, 30.0, 25.5, 24.8, 21.1, 20.8, 18.1.

HRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{15}NO$: 141.1148; found: 141.1149.

Data in accordance with the literature.[26]

***syn*-4-Methoxy-6-phenylazepan-2-one (18b)**

Following GP2, **S18a** (81 mg, 0.3 mmol) gave **18b** (0.1 mmol scale, 33% NMR yield) (20 mg, 30% isolated yield, 0.3 mmol scale) as a colorless oil; dr >20:1.

R_f = 0.60 (CH_2Cl_2/MeOH, 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.5 Hz, 2 H), 7.24 (d, *J* = 7.3 Hz, 1 H), 7.18 (d, *J* = 7.3 Hz, 2 H), 6.01 (br s, 1 H), 3.55–3.50 (m, 1 H), 3.47 (tdd, *J* = 10.6, 3.1, 1.7 Hz, 1 H), 3.38 (s, 3 H), 3.21–3.14 (m, 1 H), 2.87–2.71 (m, 3 H), 2.49–2.40 (m, 1 H), 1.89 (td, *J* = 12.8, 11.0 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.6, 128.9, 128.8, 127.1, 126.6, 75.7, 56.5, 48.6, 45.3, 44.4, 42.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}NO_2Na$: 242.1152; found: 242.1152.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

(1) Llarrull, L. I.; Testero, S. A.; Fisher, J. F.; Mobashery, S. *Curr. Opin. Microbiol.* **2010**, *13*, 551.
(2) Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem.* **2016**, *14*, 10134.
(3) Saldívar-González, F. I.; Lenci, E.; Trabocchi, A.; Medina-Franco, J. L. *RSC Adv.* **2019**, *9*, 27105.
(4) Perry, C. M. *Am. J. Cardiovasc. Drugs* **2012**, *12*, 415.
(5) Kumar, R.; Shah, S.; Paramita Das, P.; Bhagavanbhai, G. G. K.; Al Fatesh, A.; Chowdhury, B. *Catal. Rev.: Sci. Eng.* **2019**, *61*, 516.
(6) Chandrasekhar, S. *Compr. Org. Synth.* **2014**, *7*, 770.
(7) Chenault, H. K. *Synthesis of Pyrrolidones and Caprolactams by Ring Modification or Multi-component Ring-Forming Reaction*, In *Handbook of Pyrrolidone and Caprolactam Based Materials, Vol. 1, Chap. 3*; Musa, O. M., Ed.; John Wiley & Sons Ltd: Weinheim, **2021**.
(8) Komatsu, N.; Simizu, S.; Sugita, T. *Synth. Commun.* **1992**, *22*, 277.
(9) Rasouli, M. A.; Mahdavi, M.; Rashidi Ranjbar, P.; Saeedi, M.; Shafiee, A.; Foroumadi, A. *Tetrahedron Lett.* **2012**, *53*, 7088.
(10) Alonso, D. A.; Falvello, L. R.; Mancheño, B.; Nájera, C.; Tomás, M. *J. Org. Chem.* **1996**, *61*, 5004.
(11) Chen, Y.; Du, J.; Zuo, Z. *Chem* **2020**, *6*, 266.
(12) Peixoto, D.; Malta, G.; Cruz, H.; Barroso, S.; Carvalho, A. L.; Ferreira, L. M.; Branco, P. S. *J. Org. Chem.* **2019**, *84*, 3793.
(13) Babu, G. V. S.; Bhaskaran, A.; Sridhar, B.; Rao, T. V.; Parvathaneni, S. P. *ChemistrySelect* **2021**, *6*, 5.
(14) Mykura, R.; Sánchez-Bento, R.; Matador, E.; Duong, V. K.; Varela, A.; Angelini, L.; Carbajo, R. J.; Llaveria, J.; Ruffoni, A.; Leonori, D. *Nat. Chem.* **2024**, in press DOI: 10.1038/s41557-023-01429-1.
(15) Testa, A. C. *J. Phys. Chem.* **1975**, *79*, 644.
(16) Gritsan, N. P.; Platz, M. S. *Chem. Rev.* **2006**, *106*, 3844.
(17) (a) DeGraff, B. A.; Gillespie, D. W.; Sundberg, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 7491. (b) Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* **1958**, *91*, 1.
(18) Chapman, O.; Roux, J.-P. *J. Am. Chem. Soc.* **1978**, *100*, 282.
(19) Satake, K.; Okuda, R.; Hashimoto, M.; Fujiwara, Y.; Watadani, I.; Okamoto, H.; Kimura, M.; Morosawa, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1154.
(20) Negele, S.; Wieser, K.; Severin, T. *J. Org. Chem.* **1998**, *63*, 1138.
(21) Lavinda, O.; Witt, C. H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202114183.
(22) Overberger, C. G.; Kozlowski, J. H.; Radlmann, E. *J. Polym. Sci., Part A-1: Polym. Chem.* **1972**, *10*, 2265.
(23) Chen, M.; Dong, G. *J. Am. Chem. Soc.* **2017**, *139*, 7757.
(24) Reimschuessel, H. K.; Sibilia, J. P. *J. Org. Chem.* **1969**, *34*, 959.
(25) Denmark, S. E.; Xie, M. *J. Org. Chem.* **2007**, *72*, 7050.
(26) Kitagawa, O.; Velde, D. V.; Dutta, D.; Morton, M.; Takusagawa, F.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 5169.