Controlled reduction of nitriles by sodium hydride and zinc chloride

Derek Yiren Ong[a]
Shunsuke Chiba*[a]

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

Shunsuke@ntu.edu.sg

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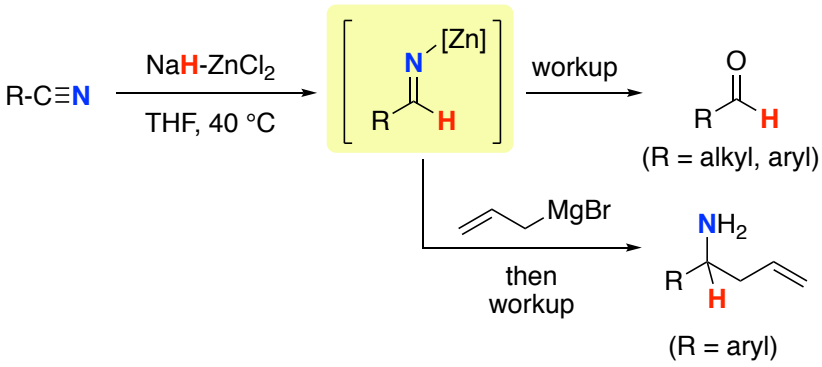

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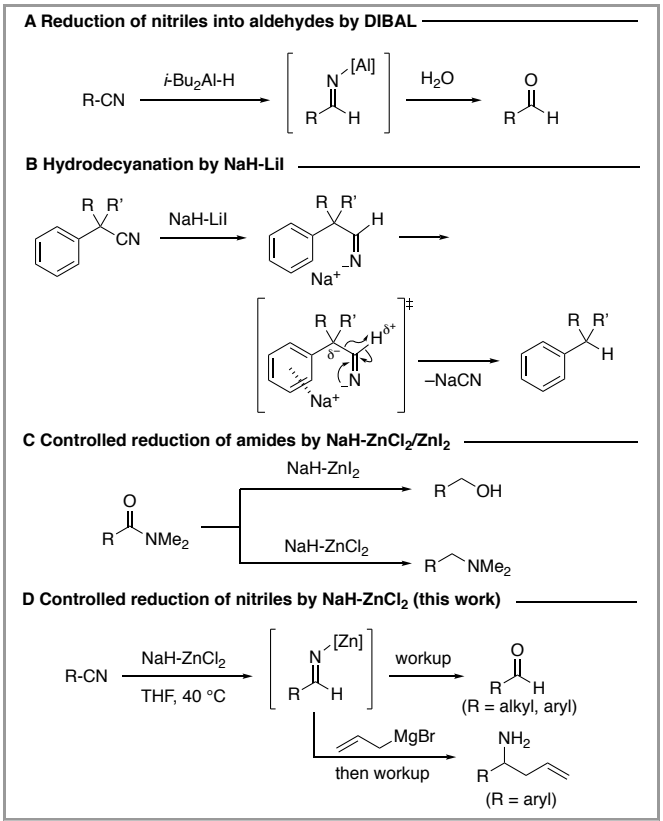
Abstract A new protocol for controlled reduction of nitriles to aldehydes was developed using combination of sodium hydride and zinc chloride. The iminyl zinc intermediates derived from aromatic nitriles could be further functionalized with allylmetal nucleophiles to afford homoallylamines. As the method allows for reduction of various aliphatic and aromatic nitriles with a concise procedure under milder reaction conditions and exhibits wide functional group compatibility, it is well suited for use in various opportunities in chemical synthesis.

Key words nitriles, aldehydes, sodium hydride, zinc chloride, reduction

Among organic polar π-electrophiles, nitriles (organic cyanides) possess versatile chemical reactivity for their functional group transformations. Especially, controlled mono-hydride reduction of nitriles is a synthetically valuable process, allowing for production of the corresponding aldehydes via hydrolysis of the aldimine intermediates. Diisopropylaluminum hydride (DIBAL)[1] is the most frequently used reagent for this purpose (Scheme 1A), despite certain disadvantage and drawback on its use such as cryogenic reaction conditions that are often needed to control the process and limitations on the functional group compatibility (*vide infra*).[2] While various alternative methods using hydride reagents based on aluminum[3-6] and borane[7] as well as transition metal-catalyzed hydrosilylation[8] have been developed, there is still demand for development of an operationally simple user-friendly protocol for controlled hydride reduction of nitriles to aldehydes.

Our group recently disclosed a simple and concise protocol to utilize sodium hydride (NaH) as an unprecedented hydride donor to the organic polar π-electrophiles in the presence of sodium or lithium iodide (NaI or LiI).[9,10] For example, hydrodecyanation of α-quaternary benzyl cyanides could be performed under NaH-LiI system (Scheme 1B).[10c,g] The process is triggered by hydride reduction of the cyano group by activated NaH to afford an iminyl sodium intermediate, that subsequently undergoes concerted C-C bond cleavage and 1,2-proton shift to deliver an alkane product with elimination of a cyanide ion. This reactivity is specific to benzyl cyanides and their aryl group plays a crucial role to form intramolecular cation-π interaction with the iminyl sodium intermediate to enable the following C-C bond cleavage event. Nonetheless, the NaH-NaI/LiI system could not be used for general hydride reduction of nitriles.

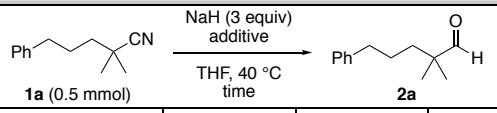


Scheme 1 Hydride reduction of polar π-electrophiles

On the other hand, we also found that NaH can serve as a hydride donor for generation of well-defined zinc hydrides by its counter ion metathesis with $ZnCl_2$ or ZnI_2.[11] The resulting zinc hydrides were found to perform controlled reduction of tertiary amides into the corresponding amines or alcohols, in which Lewis acidity of the Zn(II) center should be the key to mediate further decomposition of anionic carbinolamine intermediates via C-O or C-N bond cleavage (Scheme 1C). Based on these backgrounds, we wondered if the zinc hydrides derived from NaH and ZnX_2 could show reactivity toward the reduction of nitriles. This article describes controlled hydride reduction of nitriles to aldehydes by the NaH-$ZnCl_2$ system (Scheme 1D). The putative iminyl zinc intermediates derived from aromatic nitriles could be functionalized further with allylmetal nucleophiles to form homoallylamines . Reaction optimization, scope and limitation, and reactivity comparison of the NaH-$ZnCl_2$ system with DIBAL are discussed herein.

We embarked on our investigation for reduction of α-quaternary nitrile **1a** (Table 1). We observed that the reaction of **1a** with 3 equiv of NaH and 1.5 equiv of ZnI_2 proceeded rapidly to result in full conversion of **1a** within 2.5 h, providing aldehyde **2a** in 70% yield (entry 1). Change of the counter ions on the zinc(II) center from iodide to bromide (entry 2) and chloride (entry 3) improved the yield of **2a**. In place of NaH, LiH was also able to use as a hydride source with $ZnCl_2$, while the yield of aldehyde **2a** became slightly lower (entry 4). Reduction of the amount of $ZnCl_2$ to 1 equiv rendered the reaction time longer (entry 5), while further reduction to 0.5 equiv resulted in incomplete conversion of **1a** (entry 6). Use of sodium deuteride (NaD) with $ZnCl_2$ allowed for facile and efficient synthesis of deuterated aldehyde **2a-[D]** (Eq. 1).

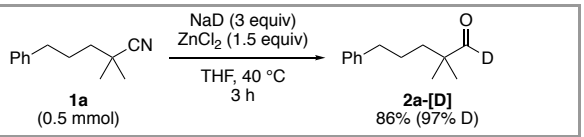
Table 1 Reaction optimization[a]



1a (0.5 mmol) **2a**

entry	Additive (equiv)	Time (h)	Conv. (%)	Yield of **2a** (%)
1	ZnI_2 (1.5)	2.5	>99	70
2	$ZnBr_2$ (1.5)	5	>99	88
3	$ZnCl_2$ (1.5)	3	>99	85
4[b]	$ZnCl_2$ (1.5)	3	>99	70
5	$ZnCl_2$ (1)	7	>99	91
6	$ZnCl_2$ (0.5)	24	83	74

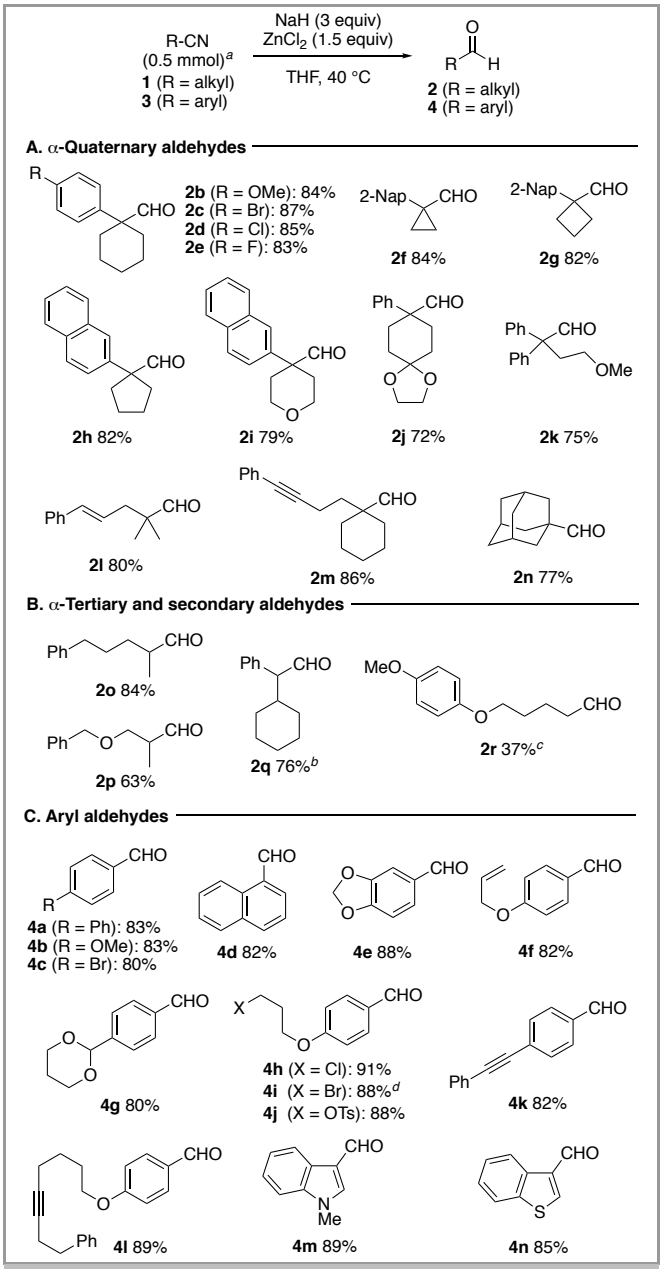
[a] The reactions were carried out using 0.5 mmol of **1a**. [b] LiH was used instead of NaH.



1a (0.5 mmol) **2a-[D]** 86% (97% D)

Equation 1 The reaction with NaD.

This protocol (Table 1, entry 3) was found applicable to reduction of both aliphatic nitriles **1** and aryl nitriles **3** to the corresponding aldehydes **2** and **4**, respectively, with wide functional group compatibility (Scheme 2). Sterically hindered α-quaternary nitriles **1b**-**1n** could be reduced into the corresponding aldehydes **2b**-**2n** in good yields (Scheme 1A). Especially, successful controlled reduction of α-quaternary benzyl cyanides **1b**-**1k** under the NaH-$ZnCl_2$ system could be complementary to their hydrodecyanation under the NaH-LiI system.[10c,g] As for reduction of aliphatic nitriles **1o**-**1r** having α-enolizable proton(s) (Scheme 1B), the reactions with α-tertiary nitriles **1o**-**1q** proceeded smoothly to afford α-tertiary aldehydes **2o**-**2q** in good yields, whereas synthesis of α-secondary aldehyde **2r** was not efficient. The present protocol also allowed for controlled reduction of various (hetero)aryl nitriles **3** efficiently to the corresponding aryl aldehydes (Scheme 2C).

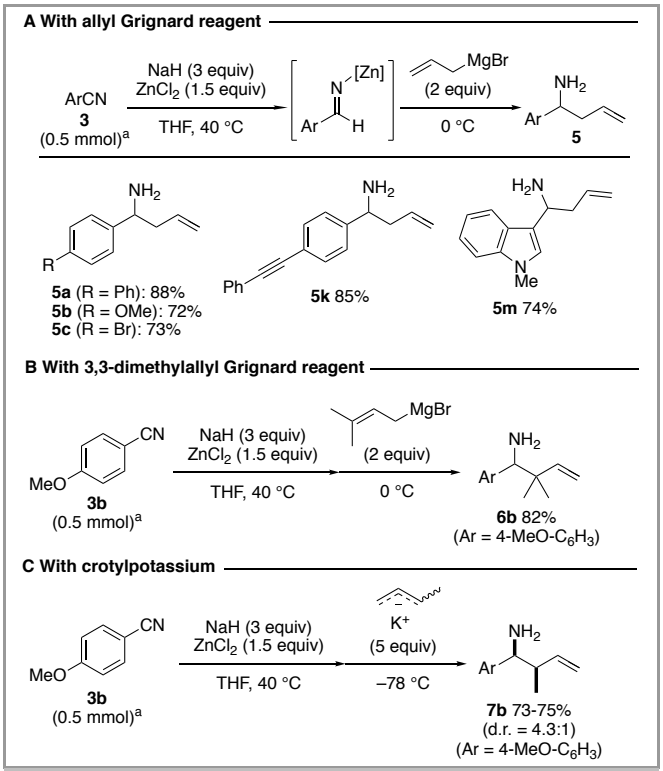


Scheme 2 Substrate scope. [a] The reactions were carried out using 0.5 mmol of nitriles. [b] The reaction were conducted using NaH (6 equiv) and $ZnCl_2$ (3 equiv). [c] The reaction was conducted at 60 °C. [d] 4-Propoxybenzaldehyde was formed in 4% yield via hydrodebromination.

Hydrodehalogenation was not observed in aryl halides (for **2c**-**2e**, **4c**) and alkyl (pseudo)halides (**4h**-**4j**) except for the case of alkyl bromide **4i**, forming a small amount of a hydrodebrominated product, 4-propoxybenzaldehyde (4% yield). The NaH-$ZnCl_2$ system could keep internal alkyne motifs,

which are often susceptible to aluminum hydrides such as DIBAL (i.e. hydroalumination),[12] entirely intact during the reduction process (for **2m**, **4k**, and **4l**). Lewis acidity of DIBAL has been utilized for several useful functional group interconversions. For example, DIBAL is known to mediate Claisen rearrangement of allyl phenyl ethers under milder reaction conditions.[13] On the other hand, reduction of 4-(allyloxy)benzonitrile under the NaH-$ZnCl_2$ system provided 4-(allyloxy)benzaldehyde (**4e**) as a sole product. Cleavage of benzylidene acetals of 1,2- and 1,3-glycoles to mono-Bn-protected diols could be mediated by DIBAL.[14] Such a transformation was not observed in the formation of **4g** bearing a benzylidene acetal moiety by the present method.

With assumption that iminyl zinc species is formed through mono hydride transfer to the cyano group under the present reaction conditions, we finally attempted functionalization of the resulting C=N bond by sequential addition of organometallic nucleophiles. We found that allylmagnesium bromide could be utilized for synthesis of homoallylic primary amines **5** starting from aromatic nitriles **3** (Scheme 2A). Interestingly, the reaction with 3,3-dimethylallylmagnesium bromide with the iminyl zinc intermediate derived from nitrile **3b** afforded branched homoallylamine **6b** as a sole product (Scheme 2B).[15] We also found that crotylpotassium prepared by the Schlosser's method from (*E*)-butene could react at –78 °C, affording branched homoallylamine **7b** with *syn*-diastereoselectivity regardless of the stereochemistry of crotylpotassium.[16,17] These observations suggested that the addition of allylmetal nucleophiles likely proceeds via an open transition-state model.[16d]



Scheme 3 Synthesis of homoallylamines. [a] The reactions were carried out using 0.5 mmol of nitriles.

In conclusion, we found that the NaH-$ZnCl_2$ system is capable in reducing a wide range of nitriles into aldehydes under well-controlled fashion. This reagent combination possesses several superior reactivity aspects to DIBAL for reduction of nitriles in terms of its operation and substituent compatibility, and therefore, it should be useful in various opportunities in chemical synthesis.

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All the experiments were carried out under a N_2 atmosphere with anhydrous THF, which was taken from a solvent purification system (PS-400-5, innovative technology Inc.). NaH (60% dispersion in mineral oil), $ZnCl_2$ were purchased from Sigma-Aldrich, Inc. Due to the moisture sensitivity of NaH and $ZnCl_2$, they were consistently handled under an argon atmosphere in a glovebox or with Schlenk techniques under a N_2 atmosphere. TLC analyses were performed on silica gel glass plates (Merck silica gel 60), and the spots were visualized with UV light (254 and 365 nm). Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Shimadzu GC-2010 was used for the GC analyses. High-resolution mass spectra were obtained with Q-Tof Premier LC HR mass spectrometer. ^{1}H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using TMS (for 1H, δ = 0.00) as internal standard]. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using $CDCl_3$ (for 13C, δ = 77.00) as internal standard]. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. The absorption data only for the key functional groups were recorded in the characterization of the respective substrates.

Reduction of nitriles to aldehydes; General procedure

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.750 mmol) in a 25 mL sealed tube was added a solution of nitrile **1** or **3** (0.500 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 40 °C. The reaction was quenched by following one of the two protocols described below:

Work-up protocol 1:

Upon full consumption of nitrile based on TLC or GC, Silica gel (2.0 g) was added to the reaction mixture and was diluted with hexane (10 mL) at 0°C. The resulting reaction mixture was stirred for 1 h at 24 °C. The mixture was then filtered through layers of cotton and sand and wash with ethyl acetate. The volatile materials were removed in vacuo from the resulting filtrate. The crude residue was purified by flash column chromatography to give the corresponding aldehyde **2** or **4**.

Work-up protocol 2:

Upon full consumption of amide based on TLC or GC, the reaction was quenched with pH 10 ammonium buffer at 0 °C and the organic materials were extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over $MgSO_4$. The volatile materials were removed in vacuo and the resulting crude residue was purified by flash column chromatography to give the corresponding aldehyde **2** or **4**.

2,2-dimethyl-5-phenylpentanal (2a)[10b]

Reaction time: 3 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; colorless oil; yield: 80.5 mg (0.423 mmol, 85%) from **1a** (93.6 mg, 0.500 mmol). The spectroscopic data for **2a** are identical to those reported in the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.20 – 7.15 (m, 3H), 2.60 (t, *J* = 7.1 Hz, 2H), 1.57 – 1.48 (m, 4H), 1.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 141.9, 128.33, 128.32, 125.8, 45.7, 36.7, 36.3, 26.1, 21.3.

Deuterated 2,2-dimethyl-5-phenylpentanal (2a-[D])[10b]

Sodium deuteride (NaD)[18] (37.5 mg, 1.50 mmol) was used instead of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol); Reaction time: 3 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; colorless oil; yield: 82.4 mg (0.431 mmol, 86%, 97% D incorporation) from **1a** (93.7 mg, 0.500 mmol). The spectroscopic data for **2a-D** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 0.03H of **2a**), 7.27 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.19 – 7.14 (m, 3H), 2.59 (t, *J* = 7.1 Hz, 2H), 1.59 – 1.46 (m, 4H), 1.03 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9 (t, *J* = 25.7 Hz), 141.9, 128.33, 128.32, 125.8, 45.5 (t, *J* = 3.1 Hz), 36.7, 36.3, 26.0, 21.2.

1-(4-methoxyphenyl)cyclohexane-1-carbaldehyde (2b)[19]

Reaction time: 4 h; work up protocol: 2; eluent system: 3% EtOAc/hexane; colorless oil; yield: 91.2 mg (0.418 mmol, 84%) from **1b** (107 mg, 0.499 mmol). The spectroscopic data for **2b** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 2.30 – 2.24 (m, 2H), 1.84 – 1.77 (m, 2H), 1.70 – 1.63 (m, 3H), 1.52 – 1.42 (m, 2H), 1.34 – 1.26 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 158.7, 131.5, 128.3, 114.2, 55.2, 53.6, 31.3, 25.6, 22.8.

1-(4-bromophenyl)cyclohexane-1-carbaldehyde (2c)[20]

Reaction time: 3 h; work up protocol: 1; eluent system: 2% EtOAc/hexane; white solid; yield: 116 mg (0.434 mmol, 87%) from **1c** (132 mg, 0.499 mmol). The spectroscopic data for **2c** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 2.28 – 2.24 (m, 2H), 1.85 – 1.78 (m, 2H), 1.69 – 1.56 (m, 3H), 1.52 – 1.42 (m, 2H), 1.37 – 1.26 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 138.8, 131.9, 128.9, 121.4, 54.1, 31.2, 25.5, 22.7.

1-(4-chlorophenyl)cyclohexane-1-carbaldehyde (2d)[20]

Reaction time: 3 h; work up protocol: 1; eluent system: 2% EtOAc/hexane; white solid; yield: 94.3 mg (0.423 mmol, 85%) from **1d** (110 mg, 0498 mmol). The spectroscopic data for **2d** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 2.29 – 2.26 (m, 2H), 1.85 – 1.78 (m, 2H), 1.67 – 1.63 (m, 3H), 1.53 – 1.44 (m, 2H), 1.35 – 1.31 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 138.2, 133.3, 129.0, 128.5, 54.0, 31.3, 25.5, 22.7.

1-(4-fluorophenyl)cyclohexane-1-carbaldehyde (2e)[20]

Reaction time: 3 h; work up protocol: 1; eluent system: 2% EtOAc/hexane; colorless oil; yield: 85.5 mg (0.415 mmol, 83%) from **1e** (101 mg, 0.499 mmol). The spectroscopic data for **2e** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.28 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.05 (dd, *J* = 8.7, 8.7 Hz, 2H), 2.31 – 2.27 (m, 2H), 1.84 – 1.77 (m, 2H), 1.68 – 1.59 (m, 3H), 1.52 – 1.43 (m, 2H), 1.35 – 1.26 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 161.9 (d, *J* = 246.7 Hz), 135.4, 128.7 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 21.2 Hz), 53.8, 31.4, 25.5, 22.7.
^{19}F NMR (376 MHz, $CDCl_3$): δ -115.3 – -115.4 (m).

1-(naphthalen-2-yl)cyclopropane-1-carbaldehyde (2f)

Reaction time: 4 h; work up protocol: 2; eluent system: 4% EtOAc/hexane; white solid; m.p.: 67.3 – 69.3 °C; yield: 82.3 mg (0.419 mmol, 84%) from **1f** (96.7 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.85 – 7.80 (m, 3H), 7.76 (s, 1H), 7.50 – 7.45 (m, 2H), 7.43 (dd, *J* = 8.5, 1.7 Hz, 1H), 1.66 – 1.63 (m, 2H), 1.52 – 1.49 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 135.0, 133.3, 132.8, 128.8, 128.3, 128.0, 127.71, 127.65, 126.3, 126.1, 37.6, 16.2.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}O$: 197.0966; Found: 197.0969.
IR (KBr): 2754 (formyl C-H), 1713 (C=O) cm^{-1}

1-(naphthalen-2-yl)cyclobutane-1-carbaldehyde (2g)

Reaction time: 3 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; colorless oil; yield: 85.9 mg (0.409 mmol, 82%) from **1g** (104 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.85 – 7.81 (m, 3H), 7.62 (s, 1H), 7.51 – 7.45 (m, 2H), 7.24 (dd, *J* = 8.4, 1.9 Hz, 1H), 2.85 – 2.79 (m, 2H), 2.55 – 2.48 (m, 2H), 2.12 – 1.92 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 138.2, 133.4, 132.3, 128.7, 127.72, 127.68, 126.4, 126.0, 125.2, 124.4, 57.7, 28.4, 15.9
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}O$: 211.1123; Found: 211.1122.
IR (KBr): 2704 (formyl C-H), 1714 (C=O) cm^{-1}

1-(naphthalen-2-yl)cyclopentane-1-carbaldehyde (2h)

Reaction time: 3 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; white solid; m.p.: 75.3 – 76.8 °C; yield: 91.5 mg (0.408 mmol, 82%) from **1h** (111 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.83 – 7.80 (m, 3H), 7.72 (s, 1H), 7.51 – 7.45 (m, 2H), 7.35 (dd, *J* = 8.6, 1.8 Hz, 1H), 2.65 – 2.59 (m, 2H), 2.04 – 1.97 (m, 2H), 1.84 – 1.76 (m, 2H), 1.74 – 1.67 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 137.7, 133.4, 132.4, 128.5, 127.9, 127.5, 126.33, 126.28, 126.1, 125.8, 63.8, 32.5, 24.3.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}O$: 225.1279; Found: 225.1276.
IR (KBr): 2716 (aldehyde C-H), 1715 (C=O) cm^{-1}

4-(naphthalen-2-yl)tetrahydro-2H-pyran-4-carbaldehyde (2i)

Reaction time: 3 h; work up protocol: 1; eluent system: 10% EtOAc/hexane; white solid; m.p.: 104.8 – 106.8 °C; yield: 94.8 mg (0.394 mmol, 79%) from **1i** (119 mg, 0.499 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.87 – 7.82 (m, 3H), 7.75 (s, 1H), 7.53 – 7.48 (m, 2H), 7.38 (dd, *J* = 8.7, 1.9 Hz, 1H), 3.95 (ddd, *J* = 11.8, 4.0, 4.0 Hz, 2H), 3.65 (ddd, *J* = 11.8, 11.8, 2.4 Hz, 2H), 2.52 – 2.49 (m, 2H), 2.24 – 2.16 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 135.8, 133.4, 132.6, 128.9, 128.0, 127.5, 126.53 (stacked), 126.2, 124.2, 64.9, 52.3, 31.2.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}O_2$: 241.1229; Found: 241.1230.
IR (KBr): 2698 (formyl C-H), 1728 (C=O), 1107 (C-O) cm^{-1}

8-phenyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (2j)[21]

Reaction time: 3 h; work up protocol: 2; eluent system: 15% EtOAc/hexane; white solid; yield: 88.3 mg (0.359 mmol, 72%) from **1j** (122 mg, 0.501 mmol). The spectroscopic data for **2j** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.37 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 3.97 – 3.91 (m, 4H), 2.38 – 2.35 (m, 2H), 2.18 – 2.11 (m, 2H), 1.77 – 1.65 (m, 4H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 138.3, 128.9, 127.4, 127.1, 108.1, 64.31, 64.28, 53.5, 31.5, 28.4.

4-methoxy-2,2-diphenylbutanal (2k)

Reaction time: 3 h; work up protocol: 1; eluent system: 4% EtOAc/hexane; colorless oil; yield: 94.8 mg (0.373 mmol, 75%) from **1k** (126 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.36 (dd, *J* = 7.2, 7.2 Hz, 4H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 4H), 3.22 (s, 3H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 140.0, 129.0, 128.6, 127.4, 69.1, 61.7, 58.6, 34.4.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{19}O_2$: 255.1385; Found: 255.1380.
IR (KBr): 2720 (aldehyde C-H), 1728 (C=O), 1115 (C-O), 1082 (C-O) cm^{-1}

(E)-2,2-dimethyl-5-phenylpent-4-enal (2l)[22]

Reaction time: 3 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; clear oil; yield: 75.4 mg (0.401 mmol, 80%) from **1l** (92.4

mg, 0.499 mmol). The spectroscopic data for **2l** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.29 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.42 (dt, *J* = 15.6, 1.2 Hz, 1H), 6.11 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.37 (dd, *J* = 7.6, 1.2 Hz, 2H), 1.11 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 137.1, 133.5, 128.5, 127.3, 126.1, 124.8, 46.3, 40.6, 21.4.

1-(4-phenylbut-3-yn-1-yl)cyclohexane-1-carbaldehyde (2m)

Reaction time: 3 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; pale yellow oil; yield: 97.1 mg (0.404 mmol, 81%) from **1m** (119 mg, 0.501 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.28 – 7.26 (m, 3H), 2.32 (t, *J* = 7.8 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.83 (t, *J* = 7.8 Hz, 2H), 1.63 – 1.52 (m, 3H), 1.42 – 1.29 (m, 5H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 131.4, 128.2, 127.7, 123.6, 89.5, 81.3, 49.3, 35.2, 30.7, 25.7, 22.3, 14.3.
HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{21}O$: 241.1592; Found: 241.1600.
IR (KBr): 2666 (formyl C-H), 2264 (C≡C), 1732 (C=O) cm^{-1}

(3r,5r,7r)-adamantane-1-carbaldehyde (2n)[23]

Reaction time: 1 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; white solid; yield: 63.1 mg (0.387 mmol, 77%) from **1n** (80.8 mg, 0.501 mmol). The spectroscopic data for **2n** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 2.08 – 2.07 (m, 3H), 1.80 – 1.68 (m, 12H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 44.8, 36.6, 35.9, 27.4.

2-methyl-5-phenylpentanal (2o)[10b]

Reaction time: 4 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; colorless oil; yield: 74.1 mg (0.420 mmol, 84%) from **1o** (86.5 mg, 0.499 mmol). The spectroscopic data for **2o** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.9 Hz, 1H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.20 – 7.16 (m, 3H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.40 – 2.31 (m, 1H), 1.80 – 1.61 (m, 3H), 1.45 – 1.36 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 141.9, 128.4, 125.9, 46.2, 35.8, 30.0, 28.7, 13.3.

3-(benzyloxy)-2-methylpropanal (2p)[24]

Reaction time: 2.5 h; work up protocol: 2; eluent system: 10% EtOAc/hexane; colorless oil; yield: 56.3 mg (0.316 mmol, 63%) from **1p** (87.8 mg, 0.501 mmol). The spectroscopic data for **2p** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1.4 Hz, 1H), 7.37 – 7.26 (m, 5H), 4.53 (s, 2H), 3.69 (dd, *J* = 9.4, 6.9 Hz, 1H), 3.64 (dd, *J* = 9.4, 5.4 Hz, 1H), 2.67 (qddd, *J* = 6.9, 6.9, 5.4, 1.4 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 137.9, 128.4, 127.7, 127.6, 73.3, 70.1, 46.8, 10.7.

2-cyclohexyl-2-phenylacetaldehyde (2q)[25]

Slightly modified procedure using NaH (120 mg, 3.00 mmol, 6 equiv) and $ZnCl_2$ (204 mg, 1.50 mmol, 3 equiv); Reaction time: 4 h; work up protocol: 2; eluent system: 2% EtOAc/hexane; colorless oil; yield: 78.9 mg (0.379 mmol, 76%) from **1q** (99.2 mg, 0.498 mmol). The spectroscopic data for **2o** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.5 Hz, 1H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 2H), 3.24 (dd, *J* = 9.6, 3.5 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.85 – 1.81 (m, 1H), 1.78 – 1.72 (m, 1H), 1.66 – 1.62 (m, 2H), 1.43 – 1.37 (m, 1H), 1.34 – 1.26 (m, 1H), 1.22 – 1.01 (m, 3H), 0.85 – 0.75 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 135.2, 129.3, 128.9, 127.4, 65.8, 38.2, 31.8, 30.2, 26.2, 26.1, 26.0.

5-(4-methoxyphenoxy)pentanal (2r)

Slightly modified procedure where the reaction was conducted at 60 °C; Reaction time: 4 h; work up protocol: 2; eluent system: 12% EtOAc/hexane; colorless oil; yield: 48.1 mg (0.231 mmol, 46%) from **1r** (103 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.5 Hz, 1H), 6.83 (s, 4H), 3.93 (t, *J* = 5.7 Hz, 2H), 3.77 (s, 3H), 2.53 (td, *J* = 6.9, 1.5 Hz, 2H), 1.85 – 1.79 (m, 4H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 153.8, 153.0, 115.4, 114.6, 68.0, 55.7, 43.5, 28.7, 18.8.
HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}O_3$: 209.1178; Found: 209.1171.
IR (KBr): 2723 (formyl C-H), 1722 (C=O), 1231 (C-O), 1180 (C-O) cm^{-1}

[1,1'-biphenyl]-4-carbaldehyde (4a) [CAS No.: 3218-36-8]

Reaction time: 3 h; work up protocol: 2; eluent system: 4% EtOAc/hexane; white solid; yield: 75.5 mg (0.414 mmol, 83%) from **3a** (89.7 mg, 0.5101mmol). The spectroscopic data for **4a** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.48 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 147.2, 139.7, 135.2, 130.3, 129.0, 128.5, 127.7, 127.4.

4-methoxybenzaldehyde (4b) [CAS No.: 123-11-5]

Reaction time: 3 h; work up protocol: 1; eluent system: 6% EtOAc/hexane; clear oil; yield: 56.9 mg (0.418 mmol, 83%) from **3b** (66.6 mg, 0.500 mmol). The spectroscopic data for **4b** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 164.6, 132.0, 129.9, 114.3, 55.6.

4-bromobenzaldehyde (4c) [CAS No.: 1122-91-4]

Reaction time: 0.5 h; work up protocol: 1; eluent system: 2% EtOAc/hexane; white solid; yield: 74.0 mg (0.400 mmol, 80%) from **3c** (90.8 mg, 0.499 mmol). The spectroscopic data for **4c** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 135.1, 132.4, 131.0, 129.8.

1-naphthaldehyde (4d) [CAS No.: 66-77-3]

Reaction time: 8 h; work up protocol: 1; eluent system: 2% EtOAc/hexane; pale yellow oil; yield: 64.0 mg (0.410 mmol, 82%) from **3d** (76.5 mg, 0.499 mmol). The spectroscopic data for **4d** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 9.25 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 7.0 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.70 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.65 – 7.58 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 136.6, 135.3, 133.7, 131.4, 130.5, 129.1, 128.5, 127.0, 124.863, 124.857.

Benzo[d][1,3]dioxole-5-carbaldehyde (4e) [CAS No.: 120-57-0]

Reaction time: 2 h; work up protocol: 1; eluent system: 10% EtOAc/hexane; white solid; yield: 66.3 mg (0.442 mmol, 88%) from **3e** (73.7 mg, 0.501 mmol). The spectroscopic data for **4e** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.42 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.34 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.08 (s, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 153.1, 148.7, 131.9, 128.6, 108.3, 106.9, 102.1.

4-(allyloxy)benzaldehyde (4f)[26]

Reaction time: 2.5 h; work up protocol: 1; eluent system: 6% EtOAc/hexane; colorless oil; yield: 62.8 mg (0.387 mmol, 81%) from **3f**

(75.8 mg, 0.476 mmol). The spectroscopic data for **4f** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.06 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.44 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.33 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.63 (dt, *J* = 5.3, 1.4 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 163.6, 132.2, 131.9, 130.0, 118.3, 115.0, 69.0.

4-(1,3-dioxan-2-yl)benzaldehyde (4g)[27]

Reaction time: 3 h; work up protocol: 1; eluent system: 20% EtOAc/hexane; white solid; yield: 80.1 mg (0.417 mmol, 83%) from **3g** (94.5 mg, 0.499 mmol). The spectroscopic data for **4g** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 5.56 (s, 1H), 4.29 (ddd, *J* = 12.1, 5.0, 1.3 Hz, 2H), 4.01 (ddd, *J* = 12.3, 12.1, 2.5 Hz, 2H), 2.24 (dtt, *J* = 13.5, 12.3, 5.0 Hz, 1H), 1.48 (dtt, *J* = 13.5, 2.5, 1.3 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 144.7, 136.6, 129.7, 126.8, 100.6, 67.4, 25.7.

4-(3-chloropropoxy)benzaldehyde (4h)[28]

Reaction time: 3 h; work up protocol: 1; eluent system: 10% EtOAc/hexane; colorless oil; yield: 90.8 mg (0.457 mmol, 91%) from **3h** (97.8 mg, 0.500 mmol). The spectroscopic data for **4h** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.21 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.28 (tt, *J* = 6.0, 6.0 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 163.7, 132.0, 130.1, 114.7, 64.6, 41.2, 32.0.

4-(3-bromopropoxy)benzaldehyde (4i)[29]

Reaction time: 3 h; work up protocol: 1; eluent system: 10% EtOAc/hexane; colorless oil; yield: 107 mg (0.442 mmol, 88%) from **3i** (120 mg, 0.502 mmol). The spectroscopic data for **4i** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.20 (t, *J* = 6.1 Hz, 2H), 3.61 (t, *J* = 6.1 Hz, 2H), 2.36 (tt, *J* = 6.1, 6.1 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 163.7, 132.0, 130.1, 114.8, 65.6, 32.0, 29.5.
4-Propoxybenzaldehyde[30] was formed in 4% yield based on ^{1}H NMR analysis of the crude material using 1,1,2,2-tetrachloroethane as the internal standard. The spectroscopic data were identical to those reported in the literature.

3-(4-formylphenoxy)propyl 4-methylbenzenesulfonate (4j)

Reaction time: 3 h; work up protocol: 1; eluent system: 40% EtOAc/hexane; white solid; m.p.: 115.0 – 116.5 °C; yield: 137 mg (0.439 mmol, 88%) from **3j** (155 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.25 (t, *J* = 5.9 Hz, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 2.37 (s, 3H), 2.16 (tt, *J* = 5.9, 5.9 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 163.4, 144.9, 132.7, 131.9, 130.1, 129.8, 127.8, 114.6, 66.6, 63.5, 28.7, 21.6.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{18}O_5S$: 335.0953; Found: 335.0950.
IR (KBr): 2735 (formyl C-H), 1694 (C=O). 1348 (S=O), 1267 (C-O), 1165 (C-O) cm^{-1}

4-(phenylethynyl)benzaldehyde (4k)[31]

Reaction time: 2 h; work up protocol: 1; eluent system: 2% EtOAc/hexane; white solid; yield: 83.9 mg (0.407 mmol, 82%) from **3k** (101 mg, 0.499 mmol). The spectroscopic data for **4k** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.57 – 7.55 (m, 2H), 7.38 – 7.37 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 135.4, 132.1, 131.8, 129.60, 129.56, 129.0, 128.5, 122.5, 93.4, 88.5.

4-((8-phenyloct-5-yn-1-yl)oxy)benzaldehyde (4l)

Reaction time: 3 h; work up protocol: 1; eluent system: 10% EtOAc/hexane; colorless oil; yield: 136 mg (0.444 mmol, 89%) from **3l** (152 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.28 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.22 – 7.18 (m, 3H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.04 (t, *J* = 6.3 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.44 (tt, *J* = 7.5, 2.3 Hz, 2H), 2.23 (tt, *J* = 6.9, 2.3 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.69 – 1.61 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 164.1, 140.9, 132.0, 129.8, 128.4, 128.3, 126.1, 114.7, 80.2, 80.1, 67.8, 35.5, 28.0, 25.3, 20.9, 18.4.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{23}O_2$: 307.1698; Found: 307.1693.
IR (KBr): 2737 (formyl C-H), 1694 (C=O), 1258 (C-O), 1159 (C-O) cm^{-1}

1-methyl-1H-indole-3-carbaldehyde (4m) [CAS No.: 19012-03-4]

Reaction time: 2 h; work up protocol: 1; eluent system: 40% EtOAc/hexane; pale brown solid; yield: 71.3 mg (0.448 mmol, 89%) from **3m** (78.2 mg, 0.501 mmol). The spectroscopic data for **4m** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.32 – 8.29 (m, 1H), 7.67 (s, 1H), 7.37 – 7.31 (m, 3H), 3.87 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 139.2, 137.9, 125.3, 124.0, 122.9, 122.0, 118.0, 109.8, 33.6.

benzo[b]thiophene-3-carbaldehyde (4n)[32]

Reaction time: 2.5 h; work up protocol: 1; eluent system: 3% EtOAc/hexane; pale yellow solid; yield: 68.7 mg (0.424 mmol, 85%) from **3n** (79.6 mg, 0.500 mmol). The spectroscopic data for **4n** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.68 (d, *J* = 7.7 Hz, 1H), 8.32 (s, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 7.7, 7.7 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 143.2, 140.5, 136.5, 135.2, 126.2, 126.1, 124.8, 122.4.

Synthesis of homoallylic amine using allyl Grignard reagents; General procedure

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.750 mmol) in a 25 mL sealed tube was added a solution of nitrile **3** (0.500 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 40 °C and monitored by GC or TLC until full consumption of **3**. Allylmagnesium bromide in diethyl ether (1.0 M; 1 mL. 1.00 mmol) was added to the reaction mixture and was stirred for 2 h at 0 °C. Silica gel (2.0 g) was added to the reaction mixture and was diluted with hexane (10 mL) at 0°C. The resulting reaction mixture was stirred for 1 h at 24 °C, and then triethylamine (3 mL) was added. The mixture was then filtered through layers of sand and cotton and wash with ethyl acetate. The volatile materials were removed *in vacuo* from the filtrate. The crude residue was purified by flash column chromatography to give the corresponding homoallylic amine **5** and **6**.

1-([1,1'-biphenyl]-4-yl)but-3-en-1-amine (5a)[33]

Reaction time: 3 h; eluent system: 50:50:1 = EtOAc:hexane:Et_3N; light yellow oil; yield: 92.0 mg (0.438 mmol, 88%) from **3a** (89.6 mg, 0.500 mmol). The spectroscopic data for **5a** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 4H), 7.45 – 7.40 (m, 4H), 7.33 (t, *J* = 6.9 Hz, 1H), 5.84 – 5.73 (m, 1H), 5.17 – 5.09 (m, 2H), 4.04 (dd, *J* = 7.9, 5.4 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.44 – 2.36 (m, 1H), 1.86 (brs, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 140.9, 139.9, 135.3, 128.7, 127.1(overlapped), 127.0, 126.7, 117.8, 55.1, 44.1.

1-(4-methoxyphenyl)but-3-en-1-amine (5b)[34]

Reaction time: 3 h; eluent system: 100:1 =EtOAc: Et_3N; pale yellow oil; yield: 63.8 mg (0.360 mmol, 89%) from **3b** (66.6 mg, 0.500 mmol). The spectroscopic data for **5b** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.79 – 5.70 (m, 1H), 5.13 – 5.06 (m, 2H), 3.95 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.80 (s, 3H), 2.47 – 2.40 (m, 1H), 2.38 – 2.30 (m, 1H), 1.72 (brs, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 137.9, 135.5, 127.3, 117.5, 113.7, 55.2, 54.7, 44.2.

1-(4-bromophenyl)but-3-en-1-amine (5c)[34]

Reaction time: 0.5 h; eluent system: 50:50:1 =EtOAc:Hexane: Et_3N; pale yellow oil; yield: 82.9 mg (0.367 mmol, 73%) from **3c** (91.1 mg, 0.501 mmol). The spectroscopic data for **5c** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 5.77 – 5.66 (m, 1H), 5.13 – 5.07 (m, 2H), 3.97 (dd, J = 7.8 Hz, 5.5 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.35 – 2.28 (m, 1H), 1.72 (brs, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 134.9, 131.4, 128.1, 120.6, 118.0, 54.8, 44.1.

1-(4-(phenylethynyl)phenyl)but-3-en-1-amine (5k)

Reaction time: 2 h; eluent system: 50:50:1 =EtOAc:Hexane:Et_3N; pale yellow oil; yield: 106 mg (0.427 mmol, 85%) from **3k** (102 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 4H), 7.37 – 7.31 (m, 5H), 5.79 – 5.68 (m, 1H), 5.14 – 5.08 (m, 2H), 4.01 (dd, *J* = 7.9, 5.4 Hz, 1H), 2.49 – 2.43 (m, 1H), 2.39 – 2.32 (m, 1H), 1.75 (brs, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 135.0, 131.7, 131.6, 128.3, 128.2, 126.4, 123.3, 121.8, 117.9, 89.3, 89.1, 55.2, 44.0.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{18}N$: 248.1439; Found: 248.1436.
IR (KBr): 3374 (amine N-H), 3076 (alkene C-H), 2214 (C≡C) cm^{-1}

1-(1-methyl-1H-indol-3-yl)but-3-en-1-amine (5m)

Reaction time: 2 h; eluent system: 100:1 =EtOAc:Et_3N; light yellow oil; yield: 74.4 mg (0.372 mmol, 74%) from **3m** (78.1 mg, 0.500 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.23 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.11 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.00 (s, 1H), 5.90 – 5.80 (m, 1H), 5.16 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 4.36 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.75 (s, 3H), 2.73 – 2.67 (m, 1H), 2.53 – 2.46 (m, 1H), 2.12 (brs, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.0, 126.4, 125.4, 121.6, 119.4, 119.2, 118.8, 117.4, 109.3, 48.0, 43.1, 32.7.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2$: 201.1392; Found: 201.1394.
IR (KBr): 3370 (amine N-H), 3073 (alkene C-H) cm^{-1}

1-(4-methoxyphenyl)-2,2-dimethylbut-3-en-1-amine (6b)

(3-Methylbut-2-en-1-yl)magnesium bromide (0.394 M in THF, 2.6 mL, 1.00 mmol) was used instead of allylmagnesium bromide; Reaction time: 3 h; eluent system: 50:50:1 = EtOAc:Hexane:Et_3N; colorless oil; yield: 84.3 mg (0.411 mmol, 82%) from **3b** (66.5 mg, 0.499 mmol).

The reaction with (3-methylbut-2-en-1-yl)magnesium bromide (0.394 M in THF, 2.6 mL, 1.00 mmol) at -78 °C; Reaction time: 3 h; yield: 80.9 mg (0.394 mmol, 79%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.86 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H), 5.03 (d, *J* = 17.5 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 1H), 1.72 (s, 2H), 0.97 (s, 3H), 0.93 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 145.9, 134.8, 129.3, 112.93, 112.86, 63.4, 55.2, 41.5, 25.5, 21.6.
HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{20}NO$: 206.1545; Found: 206.1547.
IR (KBr): 3381 (amine N-H), 3080 (alkene C-H), 1248 (C-O), 1177 (C-O) cm^{-1}

Synthesis of homoallylic amine **7b** using (*E*)-crotylpotassium

In a 25 mL sealed tube, a solution of tBuOK (287 mg, 2.56 mmol) in THF (1.3 mL) was added trans-2-butene (condensed from a gas lecture cylinder into a 5-mL graduated cylinder immersed in a dry ice/acetone bath, 0.5 mL) via cannula at -78 °C. *n*-BuLi (1.51 M in n-hexane, 1.65 mL, 2.49 mmol) was added dropwise over 50 min using a syringe pump at -78 °C. After the addition was complete, the resultant yellow mixture was allowed to warm to –55 °C and stirred at the same temperature for 25 min before re-cooling back to –78 °C for the reaction with the iminyl zinc species (below).

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.750 mmol) in a separate 25 mL sealed tube was added a solution of 4-methoxybenzonitrile (66.9 mg, 0.502 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 40 °C for 3 h. This resulting mixture was added directly into the solution of (*E*)-crotylpotassium (prepared above) at -78 °C and the mixture was stirred for 2 h at -78 °C. Silica gel (2.00 g) was added to the reaction mixture and was diluted with hexane (10 mL) at 0°C. The resulting reaction mixture was stirred for 1 h at 24 °C, and then triethylamine (3mL) was added. The mixture was then filtered through layers of cotton and sand and washed with ethyl acetate. The volatile materials were removed *in vacuo* from the filtrate. The crude residue was purified by flash column chromatography to give the corresponding amine **7**.

(1S,2R)-1-(4-methoxyphenyl)-2-methylbut-3-en-1-amine (7b)[35]

Eluent system: 100:1 =EtOAc:Et_3N; colorless oil; yield: 70.1 mg (0.367 mmol, 73%, with an estimated 81:19 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis)from **3b** (66.6 mg, 0.500 mmol). The spectroscopic data for **7b** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 0.19 X 2H), 7.19 (d, *J* = 8.6 Hz, 0.81 X 2H), 6.85 (d, *J* = 8.6 Hz, 0.19 X 2H + 0.81 X 2H), 5.78 – 5.62 (m, 0.19 X 1H + 0.81 X 1H), 5.18 – 5.09 (m, 0.19 X 2H), 5.01 (dd, *J* = 14.0, 3.1 Hz, 0.81 X 2H), 3.83 (d, *J* = 5.6 Hz, 0.81 X 1H), 3.80 (s, 0.19 X 3H + 0.81 X 3H), 3.59 (d, *J* = 8.5 Hz, 0.19 X 1H), 2.50 – 2.42 (m, 0.81 X 2H), 2.37 – 2.27 (m, 0.19 X 1H), 0.97 (d, *J* = 6.8 Hz, 0.81 X 3H), 0.80 (d, *J* = 6.8 Hz, 0.19 X 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 158.4, 141.9, 141.0, 136.6, 136.4, 128.2, 128.1, 115.7, 114.9, 113.6, 113.4, 60.0, 59.4, 55.21, 55.19, 46.5, 44.7, 17.7, 15.2.

Synthesis of homoallylic amine **7b** using (*Z*)-crotylpotassium

In a 25 mL sealed tube, a solution of tBuOK (287 mg, 2.56 mmol) in THF (1.3 mL) was added trans-2-butene (condensed from a gas lecture cylinder into a 5-mL graduated cylinder immersed in a dry ice/acetone bath, 0.5 mL) via cannula at -78 °C. *n*-BuLi (1.51 M in n-hexane, 1.65 mL, 2.49 mmol) was added dropwise over 50 min using a syringe pump at -78 °C. After the addition was complete, the resultant yellow mixture was allowed to warm to –55 °C (stirred for 25 min) and then further to -20 °C (stirred for 3 h for E/Z isomerization)[16d] before re-cooling back to –78 °C for the reaction with the iminyl zinc species under the same protocol described above.

(1S,2R)-1-(4-methoxyphenyl)-2-methylbut-3-en-1-amine (7b)[35]

Eluent system: 100:1 =EtOAc:Et_3N; colourless oil; yield: 71.7 mg (0.375 mmol, 75%, with an estimated 82:18 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis)) from **3b** (66.5 mg, 0.499 mmol). The spectroscopic data for **7b** are identical to those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 0.18 X 2H), 7.19 (d, *J* = 8.6 Hz, 0.82 X 2H), 6.85 (d, *J* = 8.6 Hz, 0.18 X 2H + 0.82 X 2H), 5.78 – 5.62 (m, 0.18 X 1H + 0.82 X 1H), 5.18 – 5.09 (m, 0.18 X 2H), 5.01 (dd, *J* = 14.0, 3.1 Hz, 0.82 X 2H), 3.83 (d, *J* = 5.6 Hz, 0.82 X 1H), 3.80 (s, 0.18 X 3H + 0.82 X 3H), 3.59 (d, *J* = 8.5 Hz, 0.18 X 1H), 2.50 – 2.42 (m, 0.82 X 2H), 2.37 – 2.27 (m, 0.18 X 1H), 0.97 (d, *J* = 6.8 Hz, 0.82 X 3H), 0.80 (d, *J* = 6.8 Hz, 0.18 X 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 158.4, 141.9, 141.0, 136.6, 136.4, 128.2, 128.1, 115.7, 114.9, 113.6, 113.4, 60.0, 59.4, 55.21, 55.19, 46.5, 44.7, 17.7, 15.2.

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Supporting Information

YES

Primary Data

NO

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Biosketches

	**Derek Yiren Ong** completed his undergraduate studies at Nanyang Technological University (NTU) Singapore in 2013. After working as an NMR technician at NTU for several years, he started his PhD work in the laboratory of Shunsuke Chiba in 2016. He is currently focussing on chemistry of main group metal hydrides for methodology development.
	**Shunsuke Chiba** earned his Ph.D. in 2006 under supervision of Prof. Koichi Narasaka at the University of Tokyo. In 2007, he embarked on his independent career as the faculty of Nanyang Technological University (NTU) Singapore, where he is currently Professor of Chemistry. His research group focuses on methodology development in the area of synthetic chemistry and catalysis.