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Controlled Reduction of Nitriles by Sodium Hydride and Zinc Chloride

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Abstract A new protocol for the controlled reduction of nitriles to aldehydes was developed using a 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 the 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.

 $\ensuremath{\textit{Key words}}$ 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, the controlled monohydride 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 disadvantages and drawbacks in 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 aluminum³⁻⁶ and borane⁷ as well as transition-metal-catalyzed hydrosilylation⁸ have been developed, there is still demand for the development of an operationally simple user-friendly protocol for the 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 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 the 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 in forming intramolecular cation– π interactions with the iminyl sodium intermediate to enable the follow-



ing C–C bond cleavage event. Nonetheless, the NaH-Nal/LiI system could not be used for the general hydride reduction of nitriles.

On the other hand, we also found that NaH can serve as a hydride donor for the generation of well-defined zinc hydrides by its counterion metathesis with ZnCl₂ or ZnI₂.¹¹ The resulting zinc hydrides were found to perform controlled reduction of tertiary amides into the corresponding amines or alcohols, in which the 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 ZnX₂ could show reactivity toward the reduction of nitriles. This article describes controlled hydride reduction of nitriles to aldehydes by the NaH-ZnCl₂ 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-ZnCl₂ system with DIBAL are discussed herein.

We embarked on our investigation of the 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 ZnI₂ proceeded rapidly to result in full conversion of **1a** within 2.5 h, providing aldehyde **2a** in 70% yield (entry 1). Change of the counterions 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 be used as a hydride source with ZnCl₂, although the yield of aldehyde **2a** be-

Biographical Sketches



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 Ph.D. work in the laboratory of Shunsuke Chiba in 2016. He is currently focusing on the chemistry of main group metal hydrides for methodology development.

 Table 1
 Reaction Optimization^a

	Ph CN	NaH (3 equiv) additive		, L
	1a (0.5 mmol)	THF, 40 °C time	Ph' ~ X H 2a	
Entry	Additive (equiv)	Time (h)	Conv. (%)	Yield of 2a (%)
1	Znl 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 **1a** (0.5 mmol).

^b LiH was used instead of NaH.

came slightly lower (entry 4). Reduction of the amount of ZnCl₂ 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 ZnCl₂ allowed for facile and efficient synthesis of deuterated aldehyde **2a-[D]** (Equation 1).



Shunsuke Chiba earned his Ph.D. in 2006 under the 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.

This protocol (Table 1, entry 3) was found applicable to the reduction of both aliphatic nitriles **1** and aryl nitriles **3** to the aldehydes 2 and 4, respectively, with wide functional group compatibility (Scheme 2). Sterically hindered α-quaternary nitriles 1b-1n were reduced to give the corresponding aldehydes **2b-2n** in good yields (Scheme 2A). Especially, successful controlled reduction of α -quaternary benzyl cyanides **1b-1k** under the NaH-ZnCl₂ system could be complementary to their hydrodecyanation under the NaH-Lil system.^{10c,g} As for reduction of aliphatic nitriles **10**-**1r** having α -enolizable proton(s) (Scheme 2B), the reactions with α -tertiary nitriles **10–1g** proceeded smoothly to afford α -tertiary aldehydes **20–2q** in good yields, whereas synthesis of α -secondary aldehyde **2r** was not efficient. The present protocol also allowed for the controlled reduction of various (hetero)aryl nitriles 3 efficiently to the corresponding aryl aldehydes (Scheme 2C).

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, which formed a small amount of a hydrodebrominated product, 4-propoxybenzaldehyde (4% yield). The NaH-ZnCl₂ system maintained internal alkyne motifs, which are often susceptible to aluminum hydrides such as DIBAL (i.e. hydroalumination),¹² completely 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-ZnCl₂ system provided 4-(allyloxy)benzaldehyde (4f) as the sole product. Cleavage of benzylidene acetals of 1,2- and 1,3-glycols 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 the assumption that an iminyl zinc species is formed through monohydride 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 the synthesis of homoallylic primary amines 5 starting from aromatic nitriles 3 (Scheme 3A). Interestingly, the reaction with 3,3-dimethylallylmagnesium bromide with the iminyl zinc intermediate derived from nitrile 3b afforded branched homoallylamine **6b** as the sole product (Scheme 3B).¹⁵ We also found that crotylpotassium prepared by Schlosser's method from (E)-butene reacted at -78 °C to afford branched homoallylamine 7b with syn-diastereoselectivity regardless of the stereochemistry of the crotylpotassium (Scheme 3C).^{16,17} These observations suggested that the addition of allylmetal nucleophiles likely proceeds via an open transitionstate model.^{16d}

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Scheme 2 Substrate scope. ^a The reactions were carried out using nitrile (0.5 mmol). ^b The reaction was conducted using NaH (6 equiv) and ZnCl₂ (3 equiv). ^c The reaction was conducted at 60 °C. ^d 4-Propoxybenzaldehyde was formed in 4% yield via hydrodebromination.

In conclusion, we have found that the NaH-ZnCl₂ system is capable of reducing a wide range of nitriles into aldehydes in a well-controlled fashion. This reagent combination possesses several superior reactivity aspects to DIBAL for the reduction of nitriles in terms of its operation and substituent compatibility, and therefore, it should be useful in various opportunities in chemical synthesis.



Scheme 3 Synthesis of homoallylamines. ^a The reactions were carried out using nitrile (0.5 mmol).

All experiments were carried out under a N₂ atmosphere with anhyd THF, which was taken from a solvent purification system (PS-400-5, innovative technology Inc.). NaH (60% dispersion in mineral oil) and ZnCl₂ were purchased from Sigma-Aldrich, Inc. Due to the moisture sensitivity of NaH and ZnCl₂, they were consistently handled under an argon atmosphere in a glovebox or with Schlenk techniques under a N₂ 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 GC analyses. HRMS were obtained with Q-Tof Premier LC HR mass spectrometer. ¹H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 spectrometer in CDCl₃ [using TMS (for ¹H, δ = 0.00) as internal standard]. ¹³C 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 spectrophotometer. The absorption data only for the key functional groups were recorded in the characterization of the respective substrates.

Reduction of Nitriles 1 and 3 to Aldehydes 2 and 4; General Procedure

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and ZnCl₂ (102 mg, 0.750 mmol) in a 25-mL sealed tube was added a solution of nitrile 1 or 3 (0.500 mmol) in THF (2.5 mL). The mixture was sealed and stirred at 40 °C. The reaction was quenched by following one of the two protocols.

Workup protocol 1: Upon full consumption of the nitrile (TLC or GC monitoring), silica gel (2.0 g) was added to the mixture and it was diluted with hexane (10 mL) at 0 °C. The resulting mixture was stirred for 1 h at 24 °C. The mixture was then filtered through layers of cotton and sand and washed with EtOAc. 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.

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Workup protocol 2: Upon full consumption of amide (TLC or GC monitoring), the reaction was quenched with pH 10 ammonium buffer at 0 $^{\circ}$ C and the organic materials were extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried (MgSO₄). 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.42 (s, 1 H), 7.28 (dd, J = 7.3, 7.3 Hz, 2 H), 7.20–7.15 (m, 3 H), 2.60 (t, J = 7.1 Hz, 2 H), 1.57–1.48 (m, 4 H), 1.03 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.42 (s, 0.03 H of **2a**), 7.27 (dd, *J* = 7.4, 7.4 Hz, 2 H), 7.19–7.14 (m, 3 H), 2.59 (t, J = 7.1 Hz, 2 H), 1.59–1.46 (m, 4 H), 1.03 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.32 (s, 1 H), 7.23 (d, J = 8.9 Hz, 2 H), 6.90 (d, J = 8.9 Hz, 2 H), 3.80 (s, 3 H), 2.30-2.24 (m, 2 H), 1.84-1.77 (m, 2 H), 1.70–1.63 (m, 3 H), 1.52–1.42 (m, 2 H), 1.34–1.26 (m, 1 H).

¹³C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.35 (s, 1 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 7.19 (d, J = 8.7 Hz, 2 H), 2.28-2.24 (m, 2 H), 1.85-1.78 (m, 2 H), 1.69-1.56 (m, 3 H), 1.52-1.42 (m, 2 H), 1.37-1.26 (m, 1 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.35 (s, 1 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 2.29–2.26 (m, 2 H), 1.85–1.78 (m, 2 H), 1.67– 1.63 (m, 3 H), 1.53–1.44 (m, 2 H), 1.35–1.31 (m, 1 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.34 (s, 1 H), 7.28 (dd, J = 8.7, 5.4 Hz, 2 H), 7.05 (dd, J = 8.7, 8.7 Hz, 2 H), 2.31–2.27 (m, 2 H), 1.84–1.77 (m, 2 H), 1.68–1.59 (m, 3 H), 1.52–1.43 (m, 2 H), 1.35–1.26 (m, 1 H).

¹³C NMR (100 MHz, CDCl₃): 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. ¹⁹F NMR (376 MHz, CDCl₃): δ = -115.3 to -115.4 (m).

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

Reaction time: 4 h; workup protocol: 2; eluent system: 4% EtOAc/ hexane; white solid; yield: 82.3 mg (0.419 mmol, 84%) from 1f (96.7 mg, 0.500 mmol); mp 67.3–69.3 °C.

IR (KBr): 2754 (formyl C–H), 1713 cm⁻¹ (C=O).

¹H NMR (400 MHz, CDCl₃): δ = 9.35 (s, 1 H), 7.85–7.80 (m, 3 H), 7.76 (s, 1 H), 7.50–7.45 (m, 2 H), 7.43 (dd, *J* = 8.5, 1.7 Hz, 1 H), 1.66–1.63 (m, 2 H), 1.52–1.49 (m, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₄H₁₃O: 197.0966; found: 197.0969.

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

Reaction time: 3 h; workup protocol: 2; eluent system: 2% EtOAc/ hexane; colorless oil; yield: 85.9 mg (0.409 mmol, 82%) from **1g** (104 mg, 0.500 mmol).

IR (KBr): 2704 (formyl C–H), 1714 cm⁻¹ (C=O).

¹H NMR (400 MHz, CDCl₃): δ = 9.61 (s, 1 H), 7.85–7.81 (m, 3 H), 7.62 (s, 1 H), 7.51–7.45 (m, 2 H), 7.24 (dd, *J* = 8.4, 1.9 Hz, 1 H), 2.85–2.79 (m, 2 H), 2.55–2.48 (m, 2 H), 2.12–1.92 (m, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₅H₁₅O: 211.1123; found: 211.1122.

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

Reaction time: 3 h; workup protocol: 2; eluent system: 2% EtOAc/ hexane; white solid; yield: 91.5 mg (0.408 mmol, 82%) from **1h** (111 mg, 0.500 mmol); mp 75.3–76.8 °C.

IR (KBr): 2716 (aldehyde C–H), 1715 cm⁻¹ (C=O).

¹H NMR (400 MHz, CDCl₃): δ = 9.48 (s, 1 H), 7.83–7.80 (m, 3 H), 7.72 (s, 1 H), 7.51–7.45 (m, 2 H), 7.35 (dd, *J* = 8.6, 1.8 Hz, 1 H), 2.65–2.59 (m, 2 H), 2.04–1.97 (m, 2 H), 1.84–1.76 (m, 2 H), 1.74–1.67 (m, 2 H).

 ^{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 C₁₆H₁₇O: 225.1279; found: 225.1276.

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

Reaction time: 3 h; workup protocol: 1; eluent system: 10% EtOAc/ hexane; white solid; yield: 94.8 mg (0.394 mmol, 79%) from **1i** (119 mg, 0.499 mmol); mp 104.8–106.8 °C.

IR (KBr): 2698 (formyl C-H), 1728 (C=O), 1107 cm⁻¹ (C-O).

¹H NMR (400 MHz, CDCl₃): δ = 9.47 (s, 1 H), 7.87–7.82 (m, 3 H), 7.75 (s, 1 H), 7.53–7.48 (m, 2 H), 7.38 (dd, J = 8.7, 1.9 Hz, 1 H), 3.95 (ddd, J = 11.8, 4.0, 4.0 Hz, 2 H), 3.65 (ddd, J = 11.8, 11.8, 2.4 Hz, 2 H), 2.52–2.49 (m, 2 H), 2.24–2.16 (m, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₆H₁₇O₂: 241.1229; found: 241.1230.

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

Reaction time: 3 h; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.41 (s, 1 H), 7.37 (dd, J = 7.4, 7.4 Hz, 2 H), 7.32 (d, J = 7.5 Hz, 2 H), 7.27 (t, J = 7.4 Hz, 1 H), 3.97–3.91 (m, 4 H), 2.38–2.35 (m, 2 H), 2.18–2.11 (m, 2 H), 1.77–1.65 (m, 4 H).

 ^{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; workup protocol: 1; eluent system: 4% EtOAc/ hexane; colorless oil; yield: 94.8 mg (0.373 mmol, 75%) from **1k** (126 mg, 0.500 mmol).

IR (KBr): 2720 (aldehyde C–H), 1728 (C=O), 1115 (C–O), 1082 cm $^{-1}$ (C–O).

¹H NMR (400 MHz, CDCl₃): δ = 9.74 (s, 1 H), 7.36 (dd, *J* = 7.2, 7.2 Hz, 4 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.21 (d, *J* = 7.2 Hz, 4 H), 3.22 (s, 3 H), 3.16 (t, *J* = 7.0 Hz, 2 H), 2.60 (t, *J* = 7.0 Hz, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₇H₁₉O₂: 255.1385; found: 255.1380.

(E)-2,2-Dimethyl-5-phenylpent-4-enal (21)²²

Reaction time: 3 h; workup protocol: 2; eluent system: 2% EtOAc/ hexane; clear oil; yield: 75.4 mg (0.401 mmol, 80%) from **11** (92.4 mg, 0.499 mmol). The spectroscopic data for **21** are identical to those reported in the literature.

¹H NMR (400 MHz, CDCl₃): δ = 9.54 (s, 1 H), 7.33 (d, *J* = 7.3 Hz, 2 H), 7.29 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.21 (t, *J* = 7.3 Hz, 1 H), 6.42 (dt, *J* = 15.6, 1.2 Hz, 1 H), 6.11 (dt, *J* = 15.6, 7.6 Hz, 1 H), 2.37 (dd, *J* = 7.6, 1.2 Hz, 2 H), 1.11 (s, 6 H).

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 ^{13}C NMR (100 MHz, CDCl₃): 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; workup 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).

IR (KBr): 2666 (formyl C−H), 2264 (C≡C), 1732 cm⁻¹ (C=O).

¹H NMR (400 MHz, CDCl₃): δ = 9.53 (s, 1 H), 7.37 (d, J = 7.4 Hz, 2 H), 7.28–7.26 (m, 3 H), 2.32 (t, J = 7.8 Hz, 2 H), 1.93–1.89 (m, 2 H), 1.83 (t, J = 7.8 Hz, 2 H), 1.63–1.52 (m, 3 H), 1.42–1.29 (m, 5 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₇H₂₁O: 241.1592; found: 241.1600.

Adamantane-1-carbaldehyde (2n)²³

Reaction time: 1 h; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.32 (s, 1 H), 2.08–2.07 (m, 3 H), 1.80–1.68 (m, 12 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.0, 44.8, 36.6, 35.9, 27.4.

2-Methyl-5-phenylpentanal (20)^{10b}

Reaction time: 4 h; workup protocol: 2; eluent system: 2% EtOAc/ hexane; colorless oil; yield: 74.1 mg (0.420 mmol, 84%) from **10** (86.5 mg, 0.499 mmol). The spectroscopic data for **20** are identical to those reported in the literature.

¹H NMR (400 MHz, CDCl₃): δ = 9.60 (d, *J* = 1.9 Hz, 1 H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.20–7.16 (m, 3 H), 2.63 (t, *J* = 7.4 Hz, 2 H), 2.40–2.31 (m, 1 H), 1.80–1.61 (m, 3 H), 1.45–1.36 (m, 1 H), 1.09 (d, *J* = 7.0 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.73 (d, J = 1.4 Hz, 1 H), 7.37–7.26 (m, 5 H), 4.53 (s, 2 H), 3.69 (dd, J = 9.4, 6.9 Hz, 1 H), 3.64 (dd, J = 9.4, 5.4 Hz, 1 H), 2.67 (qddd, J = 6.9, 6.9, 5.4, 1.4 Hz, 1 H), 1.13 (d, J = 6.9 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): 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; workup 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 **2q** are identical to those reported in the literature.

¹H NMR (400 MHz, CDCl₃): δ = 9.70 (d, *J* = 3.5 Hz, 1 H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.28 (t, *J* = 7.3 Hz, 1 H), 7.18 (d, *J* = 7.3 Hz, 2 H), 3.24 (dd, *J* = 9.6, 3.5 Hz, 1 H), 2.15–2.06 (m, 1 H), 1.85–1.81 (m, 1 H), 1.78–1.72 (m, 1 H), 1.66–1.62 (m, 2 H), 1.43–1.37 (m, 1 H), 1.34–1.26 (m, 1 H), 1.22–1.01 (m, 3 H), 0.85–0.75 (m, 1 H).

 ^{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; workup protocol: 2; eluent system: 12% EtOAc/ hexane; colorless oil; yield: 48.1 mg (0.231 mmol, 46%) from **1r** (103 mg, 0.500 mmol).

IR (KBr): 2723 (formyl C-H), 1722 (C=O), 1231 (C-O), 1180 cm⁻¹ (C-O).

¹H NMR (400 MHz, CDCl₃): δ = 9.80 (t, J = 1.5 Hz, 1 H), 6.83 (s, 4 H), 3.93 (t, J = 5.7 Hz, 2 H), 3.77 (s, 3 H), 2.53 (td, J = 6.9, 1.5 Hz, 2 H), 1.85–1.79 (m, 4 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₇O₃: 209.1178; found: 209.1171.

Biphenyl-4-carbaldehyde (4a)

[CAS Reg. No. 3218-36-8]

Reaction time: 3 h; workup protocol: 2; eluent system: 4% EtOAc/ hexane; white solid; yield: 75.5 mg (0.414 mmol, 83%) from **3a** (89.7 mg, 0.5101 mmol). The spectroscopic data for **4a** are identical to those reported in the literature.

¹H NMR (400 MHz, $CDCI_3$): δ = 10.06 (s, 1 H), 7.95 (d, *J* = 8.3 Hz, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.64 (d, *J* = 7.2 Hz, 2 H), 7.48 (dd, *J* = 7.2, 7.2 Hz, 2 H), 7.42 (t, *J* = 7.2 Hz, 1 H).

 ^{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 Reg. No. 123-11-5]

Reaction time: 3 h; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.89 (s, 1 H), 7.84 (d, *J* = 8.7 Hz, 2 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 3.89 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 190.8, 164.6, 132.0, 129.9, 114.3, 55.6.

4-Bromobenzaldehyde (4c)

[CAS Reg. No. 1122-91-4]

Reaction time: 0.5 h; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.98 (s, 1 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 191.0, 135.1, 132.4, 131.0, 129.8.

1-Naphthaldehyde (4d)

[CAS Reg. No. 66-77-3]

Feature

Reaction time: 8 h; workup 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.

¹H NMR (400 MHz, $CDCI_3$): $\delta = 10.41$ (s, 1 H), 9.25 (d, J = 8.6 Hz, 1 H), 8.10 (d, J = 8.2 Hz, 1 H), 8.00 (d, J = 7.0 Hz, 1 H), 7.92 (d, J = 8.2 Hz, 1 H), 7.70 (dd, J = 7.7, 7.7 Hz, 1 H), 7.65–7.58 (m, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 Reg. No. 120-57-0]

Reaction time: 2 h; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.81 (s, 1 H), 7.42 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.34 (d, *J* = 1.5 Hz, 1 H), 6.93 (d, *J* = 7.9 Hz, 1 H), 6.08 (s, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.88 (s, 1 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 8.7 Hz, 2 H), 6.06 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1 H), 5.44 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.33 (dd, *J* = 10.5, 1.4 Hz, 1 H), 4.63 (dt, *J* = 5.3, 1.4 Hz, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 10.02 (s, 1 H), 7.89 (d, *J* = 8.2 Hz, 2 H), 7.66 (d, *J* = 8.2 Hz, 2 H), 5.56 (s, 1 H), 4.29 (ddd, *J* = 12.1, 5.0, 1.3 Hz, 2 H), 4.01 (ddd, *J* = 12.3, 12.1, 2.5 Hz, 2 H), 2.24 (dtt, *J* = 13.5, 12.3, 5.0 Hz, 1 H), 1.48 (dtt, *J* = 13.5, 2.5, 1.3 Hz, 1 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.89 (s, 1 H), 7.84 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 4.21 (t, *J* = 6.0 Hz, 2 H), 3.76 (t, *J* = 6.0 Hz, 2 H), 2.28 (tt, *J* = 6.0, 6.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 9.89 (s, 1 H), 7.84 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 4.20 (t, *J* = 6.1 Hz, 2 H), 3.61 (t, *J* = 6.1 Hz, 2 H), 2.36 (tt, *J* = 6.1, 6.1 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 190.7, 163.7, 132.0, 130.1, 114.8, 65.6, 32.0, 29.5.

4-Propoxybenzaldehyde³⁰ was formed in 4% yield based on ¹H 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; workup protocol: 1; eluent system: 40% EtOAc/ hexane; white solid; yield: 137 mg (0.439 mmol, 88%) from **3j** (155 mg, 0.500 mmol); mp 115.0–116.5 $^{\circ}$ C.

IR (KBr): 2735 (formyl C–H), 1694 (C=O), 1348 (S=O), 1267 (C–O), 1165 cm $^{-1}$ (C–O).

¹H NMR (400 MHz, CDCl₃): δ = 9.89 (s, 1 H), 7.81 (d, *J* = 8.7 Hz, 2 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.25 (t, *J* = 5.9 Hz, 2 H), 4.05 (t, *J* = 5.9 Hz, 2 H), 2.37 (s, 3 H), 2.16 (tt, *J* = 5.9, 5.9 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₁₉O₅S: 335.0953; found: 335.0950.

4-(Phenylethynyl)benzaldehyde (4k)³¹

Reaction time: 2 h; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 10.02 (s, 1 H), 7.86 (d, *J* = 8.2 Hz, 2 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.57–7.55 (m, 2 H), 7.38–7.37 (m, 3 H).

 ^{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 (41)

Reaction time: 3 h; workup protocol: 1; eluent system: 10% EtOAc/ hexane; colorless oil; yield: 136 mg (0.444 mmol, 89%) from **31** (152 mg, 0.500 mmol).

IR (KBr): 2737 (formyl C–H), 1694 (C=O), 1258 (C–O), 1159 cm⁻¹ (C–O).

¹H NMR (400 MHz, CDCl₃): δ = 9.88 (s, 1 H), 7.83 (d, J = 8.7 Hz, 2 H), 7.28 (dd, J = 7.4, 7.4 Hz, 2 H), 7.22–7.18 (m, 3 H), 6.98 (d, J = 8.7 Hz, 2 H), 4.04 (t, J = 6.3 Hz, 2 H), 2.80 (t, J = 7.5 Hz, 2 H), 2.44 (tt, J = 7.5, 2.3 Hz, 2 H), 2.23 (tt, J = 6.9, 2.3 Hz, 2 H), 1.91–1.84 (m, 2 H), 1.69–1.61 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃): 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 C₂₁H₂₃O₂: 307.1698; found: 307.1693.

1-Methyl-1H-indole-3-carbaldehyde (4m)

[CAS Reg. No. 19012-03-4]

Reaction time: 2 h; workup 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.

 ^1H NMR (400 MHz, CDCl₃): δ = 9.99 (s, 1 H), 8.32–8.29 (m, 1 H), 7.67 (s, 1 H), 7.37–7.31 (m, 3 H), 3.87 (s, 3 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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; workup 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.

¹H NMR (400 MHz, CDCl₃): δ = 10.15 (s, 1 H), 8.68 (d, J = 7.7 Hz, 1 H), 8.32 (s, 1 H), 7.89 (d, J = 7.7 Hz, 1 H), 7.52 (dd, J = 7.7 Hz, 1 H), 7.46 (dd, J = 7.7, 7.7 Hz, 1 H).

 ^{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 Amines 5 Using Allyl Grignard Reagents; General Procedure

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and ZnCl₂ (102 mg, 0.750 mmol) in a 25-mL sealed tube was added a solution of nitrile **3** (0.500 mmol) in THF (2.5 mL). The mixture was sealed and stirred at 40 °C and monitored by GC or TLC until full consumption of **3**. A 1.0 M soln of allylmagnesium bromide in Et₂O (1 mL, 1.00 mmol) was added to the mixture, which was stirred for 2 h at 0 °C. Silica gel (2.0 g) was added to the mixture was stirred for 1 h at 24 °C, and then Et₃N (3 mL) was added. The mixture was then filtered through layers of sand and cotton and washed with EtOAc. 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-(Biphenyl-4-yl)but-3-en-1-amine (5a)33

Reaction time: 3 h; eluent system: EtOAc/hexane/Et₃N 50:50:1; 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.

¹H NMR (400 MHz, $CDCl_3$): δ = 7.58 (m, 4 H), 7.45–7.40 (m, 4 H), 7.33 (t, *J* = 6.9 Hz, 1 H), 5.84–5.73 (m, 1 H), 5.17–5.09 (m, 2 H), 4.04 (dd, *J* = 7.9, 5.4 Hz, 1 H), 2.54–2.48 (m, 1 H), 2.44–2.36 (m, 1 H), 1.86 (brs, 2 H).

 ^{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: $EtOAc/Et_3N$ 100:1; pale yellow oil; yield: 63.8 mg (0.360 mmol, 72%) from **3b** (66.6 mg, 0.500 mmol). The spectroscopic data for **5b** are identical to those reported in the literature.

¹H NMR (400 MHz, CDCl₃): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 5.79–5.70 (m, 1 H), 5.13–5.06 (m, 2 H), 3.95 (dd, *J* = 7.8, 5.5 Hz, 1 H), 3.80 (s, 3 H), 2.47–2.40 (m, 1 H), 2.38–2.30 (m, 1 H), 1.72 (brs, 2 H).

 ^{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: EtOAc/hexane/Et₃N 50:50:1; 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.

¹H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.4 Hz, 2 H), 7.22 (d, J = 8.4 Hz, 2 H), 5.77-5.66 (m, 1 H), 5.13-5.07 (m, 2 H), 3.97 (dd, J = 7.8 Hz, 5.5 Hz, 1 H), 2.45-2.39 (m, 1 H), 2.35-2.28 (m, 1 H), 1.72 (brs, 2 H).

 ^{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: EtOAc/hexane/Et₃N 50:50:1; pale yellow oil; yield: 106 mg (0.427 mmol, 85%) from 3k (102 mg, 0.500 mmol).

IR (KBr): 3374 (amine N–H), 3076 (alkene C–H), 2214 cm⁻¹ (C≡C).

¹H NMR (400 MHz, CDCl₃): δ = 7.54–7.49 (m, 4 H), 7.37–7.31 (m, 5 H), 5.79–5.68 (m, 1 H), 5.14–5.08 (m, 2 H), 4.01 (dd, *J* = 7.9, 5.4 Hz, 1 H), 2.49–2.43 (m, 1 H), 2.39–2.32 (m, 1 H), 1.75 (brs, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₈H₁₈N: 248.1439; found: 248.1436.

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

Reaction time: 2 h; eluent system: EtOAc/Et₃N 100:1; light yellow oil; yield: 74.4 mg (0.372 mmol, 74%) from 3m (78.1 mg, 0.500 mmol).

IR (KBr): 3370 (amine N-H), 3073 cm⁻¹ (alkene C-H).

¹H NMR (400 MHz, CDCl₃): δ = 7.68 (d, *J* = 7.7 Hz, 1 H), 7.30 (d, *J* = 7.7 Hz, 1 H), 7.23 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.11 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.00 (s, 1 H), 5.90–5.80 (m, 1 H), 5.16 (d, *J* = 17.1 Hz, 1 H), 5.10 (d, *J* = 10.1 Hz, 1 H), 4.36 (dd, *J* = 7.9, 5.2 Hz, 1 H), 3.75 (s, 3 H), 2.73–2.67 (m, 1 H), 2.53–2.46 (m, 1 H), 2.12 (brs, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₇N₂: 201.1392; found: 201.1394.

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

A 0.394 M soln of (3-methylbut-2-enyl)magnesium bromide in THF (2.6 mL, 1.00 mmol) was used instead of allylmagnesium bromide; reaction time: 3 h; eluent system: EtOAc/hexane/Et₃N 50:50:1; colorless oil; yield: 84.3 mg (0.411 mmol, 82%) from **3b** (66.5 mg, 0.499 mmol).

Reaction with 0.394 M (3-methylbut-2-en-1-yl)magnesium bromide in THF (2.6 mL, 1.00 mmol) at -78 °C; reaction time: 3 h; yield: 80.9 mg (0.394 mmol, 79%).

IR (KBr): 3381 (amine N–H), 3080 (alkene C–H), 1248 (C–O), 1177 cm⁻¹ (C–O).

¹H NMR (400 MHz, CDCl₃): δ = 7.21 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 5.86 (dd, *J* = 17.5, 10.8 Hz, 1 H), 5.08 (d, *J* = 10.8 Hz, 1 H), 5.03 (d, *J* = 17.5 Hz, 1 H), 3.80 (s, 3 H), 3.71 (s, 1 H), 1.72 (s, 2 H), 0.97 (s, 3 H), 0.93 (s, 3 H).

 ^{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 C₁₃H₂₀NO: 206.1545; found: 206.1547.

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Synthesis of Homoallylic Amine 7b Using (E)-Crotylpotassium

In a 25-mL sealed tube, a solution of *t*-BuOK (287 mg, 2.56 mmol) in THF (1.3 mL) was added *trans*-but-2-ene (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. 1.5 M *n*-BuLi 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 ZnCl₂ (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 THF (2.5 mL). The mixture was sealed and stirred at 40 °C for 3 h. This resulting mixture was added directly to 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 mixture was stirred for 1 h at 24 °C, and then Et₃N (3 mL) was added. The mixture was then filtered through layers of cotton and sand and washed with EtOAc. 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: EtOAc/Et₃N 100:1; colorless oil; yield: 70.1 mg (0.367 mmol, 73%); diastereomeric mixture ~81:19 (based on ¹H NMR spectroscopy analysis) from **3b** (66.6 mg, 0.500 mmol). The spectroscopic data for **7b** are identical to those reported in the literature.

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (d, *J* = 8.6 Hz, 0.19 × 2 H), 7.19 (d, *J* = 8.6 Hz, 0.81 × 2 H), 6.85 (d, *J* = 8.6 Hz, 0.19 × 2 H + 0.81 × 2 H), 5.78–5.62 (m, 0.19 × 1 H + 0.81 × 1 H), 5.18–5.09 (m, 0.19 × 2 H), 5.01 (dd, *J* = 14.0, 3.1 Hz, 0.81 × 2 H), 3.83 (d, *J* = 5.6 Hz, 0.81 × 1 H), 3.80 (s, 0.19 × 3 H + 0.81 × 3 H), 3.59 (d, *J* = 8.5 Hz, 0.19 × 1 H), 2.50–2.42 (m, 0.81 × 2 H), 2.37–2.27 (m, 0.19 × 1 H), 0.97 (d, *J* = 6.8 Hz, 0.81 × 3 H), 0.80 (d, *J* = 6.8 Hz, 0.19 × 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): 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 *t*-BuOK (287 mg, 2.56 mmol) in THF (1.3 mL) was added *trans*-but-2-ene (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. 1.51 M *n*-BuLi 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: EtOAc/Et₃N 100:1; colorless oil; yield: 71.7 mg (0.375 mmol, 75%); diastereomeric mixture ~82:18 (based on ¹H NMR spectroscopy analysis) from **3b** (66.5 mg, 0.499 mmol). The spectroscopic data for **7b** are identical to those reported in the literature.

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (d, *J* = 8.6 Hz, 0.18 × 2 H), 7.19 (d, *J* = 8.6 Hz, 0.82 × 2 H), 6.85 (d, *J* = 8.6 Hz, 0.18 × 2 H + 0.82 × 2 H), 5.78–5.62 (m, 0.18 × 1 H + 0.82 × 1 H), 5.18–5.09 (m, 0.18 × 2 H), 5.01 (dd,

 $J = 14.0, 3.1 \text{ Hz}, 0.82 \times 2 \text{ H}), 3.83 \text{ (d, } J = 5.6 \text{ Hz}, 0.82 \times 1 \text{ H}), 3.80 \text{ (s, } 0.18 \times 3 \text{ H} + 0.82 \times 3 \text{ H}), 3.59 \text{ (d, } J = 8.5 \text{ Hz}, 0.18 \times 1 \text{ H}), 2.50-2.42 \text{ (m, } 0.82 \times 2 \text{ H}), 2.37-2.27 \text{ (m, } 0.18 \times 1 \text{ H}), 0.97 \text{ (d, } J = 6.8 \text{ Hz}, 0.82 \times 3 \text{ H}), 0.80 \text{ (d, } J = 6.8 \text{ Hz}, 0.18 \times 2 \text{ H}).$

 ^{13}C NMR (100 MHz, CDCl₃): 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

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690838.

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