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Note

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A cascade process for direct transforming aldehydes (RCHO) to nitriles (RCN) using inorganic reagents NH₂OH/Na₂CO₃/SO₂F₂ in DMSO

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ABSTRACT: A simple, mild and practical process for direct converting aldehydes to nitriles was developed feathering a wide substrate scope and great functional-groups tolerability (52 examples, over 90% yield in most cases) using inorganic reagents ($NH_2OH/Na_2CO_3/SO_2F_2$) in DMSO. This method allows transformations of readily-available, inexpensive and abundant aldehydes to highly valuable nitriles in a pot, atom and step-economical (PASE) manner without transition metals. This protocol will serve as a robust tool for the installation of cyano-moieties to complicated molecules.

The cyano group is a privileged functionality prevalent in numerous naturally occurring products and biologically active molecules.¹ The value of nitrile motifs has been extensionally serialized for the preparation of natural products, pharmaceuticals, agricultural chemicals, polymers and dyes as well as precursors for universal carboxylic acids, amines, amides, alcohols, ketones, aldehydes and heterocyclic compounds.² The Sandmeyer reaction and Rosenmund-von Braun reaction are the most frequently used conventional strategies for the construction of nitriles.³ On the other hand, the cyanide-halide exchange reactions for constructions of nitriles from metal cyanides or metalloid cyanides with organic halides, generally suffer from the usage of highly toxic reagents (e.g., NaCN, KCN, Zn(CN)₂ or CuCN).⁴ To accomplish nitriles synthesis with minimal effects of the above drawbacks, aldehydes have been employed as starting materials for assembly of nitriles due to their readily availability, low-cost, and environmentfriendliness,⁵⁻⁸ to generate nitriles *via* cleavage of coordinated cyanide anion,⁵ transoximation,⁶ or by using *N*-containing reagents' as nitrogen source. Besides, metal-catalyzed dehydration of aldoximes represents an additional option for the construction of nitriles with high efficiency,⁸ even though most of them encounter some limitations of high reaction temperature, and/or tedious operation procedure. Because of the great importance of nitrile moieties and the limitations of the available synthetic routes, the development of general, efficient, mild and reliable methods to synthesize nitriles continues to be of great significance and highly desirable as a challengeable target. In 2014, a new click chemistry, sulfonyl (VI) fluoride exchange (SuFEx), was introduced by professor Sharpless demonstrating that sulfuryl (VI) fluoride functional group could be utilized in a controllable and targeted manner for materials, medicinal and biological applications.⁹ And Sulfuryl fluoride (SO₂F₂), an inexpensive (about 1\$/kg), relatively inert gas (stable up to 400 °C when dry) was one of the key reagents for SuFEx click chemistry and versatile manipulations.¹⁰

One important goal in modern chemistry is to develop powerful, sustainable, and cost-effective methods from readily available, inexpensive and abundant starting materials in a pot, atom and step-economical (PASE) manner with the least requirements of isolation or purification of intermediates.¹¹ Another target for sustainable chemistry is to use no-toxic inorganic starting materials to achieve organic synthesis because the use of inorganic reagents has significant advantages over their organic counterparts, such as producing the lowest total organic carbon (TOC) in the waste, easy work-up and purification.¹²

a) Our previous work on one-pot converting alcohols to carbon-carbon triple bonds



Scheme 1. A proposed cascade process for direct converting aldehydes to nitriles.

Viewing on the high value of nitrile moieties, the easy availability of aldehydes, and the advantages of inorganic reagent such as inorganic base (K₂CO₃ or Na₂CO₃), NH₂OH and SO₂F₂ for organic synthesis, and our continuous efforts on utilization of SO₂F₂ for chemical transformations,^{10f-i} we proposed a one-pot process for direct converting aldehydes to nitriles (Scheme 1) through a cascade sequence following a similar mechanism for the alkyne synthesis.¹⁰ⁱ We envisioned (Scheme 1, b) that in polar solvent DMSO, aldehydes 1 would react with NH₂OH under the promotion of inorganic base (K_2CO_3) to provide aldoxime intermediates A after dehydration, subsequently the aldoxime will further react with SO_2F_2 to generate the corresponding sulfonyl ester **B**, with the assistant of the same base, the following beta-elimination of precursor sulfonyl ester B would generate the desired carbonnitrogen triple bonds of nitrile 2.

After screening a large variety of conditions (see supporting information for details), we were pleased to find that the proposed transformation (aldehydes to nitriles) was accomplished when Na₂CO₃ was used as base in DMSO under SO₂F₂ atmosphere (balloon) in up to nearly quantitative yields.

B Ph ό. 2w, 97% 2x, 98% **2y,** 96% 2z, 98%

(153 mg, 2.2 mmol), Na₂CO₃ (117 mg, 1.1 mmol) and DMSO (10 mL), r.t., 30-60 min; then Na₂CO₃ (1.06 g, 10 mmol) and SO₂F₂ (Toxic bv inhalation. **Operated** gas in fume hoods), r.t., 12 h. bIsolated yields. CHPLC yields. dAldoxime as starting material, Na₂CO₃ (1.27 g, 12 mmol) was used. ^eH₂NOH HCl (307 mg, 4.4 mmol), Na₂CO₃ (235 mg, 2.2 mmol), DMSO (10 mL); then Na₂CO₃ (2.12 g, 20 mmol). ${}^{t}H_{2}NOHHCl$ (208 mg, 3.0 mmol) and Na₂CO₃ (159 mg, 1.5 mmol) was used.

We subsequently evaluated the substrate scopes, functional group compatibility and limitation of the one-pot process as illustrated in Table 1. A large set of structurally and electronically diverse arylaldehydes were examined under the standard conditions and in most case, the corresponding nitriles were successfully furnished in excellent to quantitative yields (2a2af), regardless the substrates functionalized with prevalent electron-donating or electron-withdrawing groups of ether, phenyl, halogen, ester, amide, sulfonamide, nitro, and cyano on the aryl rings. Notably, the position of substituents on the aryl rings exhibited some influence on the efficiency. The ortho-position substituted aldehydes possessing steric hindrance accomplished the desired transformation in slightly lower yields than the para-position functionalized substrates (e.g. 2f compared to 2r). 2s, 2t and 2v were obtained in less than 90% yield attributing to the steric hindrance of orthosubstitutions as well. It has to be pointed out that because of their low boiling-points, the isolated yields of the high-volatile arylnitriles (2d, 2m, 2v, 2ag and 2ah) were lower than their HPLC yields. Delightingly, the synthesis of 4-cyanobenzoic acid (21) containing a base-sensitive functionality (carboxylic

acid) was also achieved in good yield (70%) when aldoxime intermediate was used as starting material for the SO₂F₂ medi-

ated dehydration process using 6.0 equivalent of Na₂CO₃ even though the one-pot transformation of para-carboxylic benzaldehyde (11) to the corresponding nitrile was not successful because the formation of aldoxime intermediate was not achieved under the developed condition. However, the developed system was not amenable to the preparation of aromatic nitriles functionalized with silyl ether moiety on the benzene ring which may be attributed to the high activity of silvl ether to react with fluoride anion to form the strong connection of Si-F bond. Excitingly, the double bond, triple bond and halides moieties, which are fragile in a lot of previous procedures for nitriles synthesis, remained intact during this transformation to provide the corresponding products in nearly quantitative yields (2d, 2e, 2f, 2q, 2r, 2u, 2w, 2x, 2y, and 2ac). The naturally occurring molecular 6-Bromoveratraldehyde (1y) was smoothly transformed to the desired nitrile 2y in 96% yield. Not surprisingly, the precursor for making Roflumilast 1z was also converted to the corresponding nitrile derivate 2z in guantitative yield using this expedient method. It is worth noting, polycyclic substrates (1aa-1ac) tolerated the cyanation system well and gave the final products in quantitative yields. Notably, molecules bearing two aldehyde groups on a single aryl ring or two different aryl rings were also successfully converted to their corresponding nitriles in nearly quantitative yields (2ad-2af). A grams-scale reaction was operated using 1k as model substrate, and the desired product 2k was generated in 99% yield, indicating the high possibility of application this method in big scale production of nitriles.

Giving the prevalence and wide utilization of heterocyclic molecular in industrial production and academic research, we turned our attention to transforming heterocyclic aldehydes to the corresponding nitriles. Not surprisingly, a broad of heterocyclic aldehydes bearing sulfur, nitrogen and oxygen atoms in aryl rings (2ag-2an) were smoothly converted to their nitriles in excellent to quantitative yields. It is worth noting, the aldehydes with nitrogen-containing aromatic rings suffering from low reactivity due to their electronically deficient property and strong Lewis basicity which were not compatible in many previous metal catalyzed nitriles synthesis, also provided their nitriles in quantitative yields (2ai, 2aj, 2ak, 2am and 2an) using this procedure.

To further examine the scope of this method, we expended this protocol to aliphatic allylic aldehydes (Table 2, 3a-3e). Excitingly, the allylic aldehydes (3a-3e) were smoothly converted to the corresponding nitriles (4a-4e) in good to excel-



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59 60 lent yields with complete retention of original *E*-configuration of the double bonds (**4b**, **4c**, **4d** and **4e**). Notably, by elevating the temperature to 50 °C, the conversion of regular aliphatic aldehydes (Table 2, **3f**, **3g** and **3i**) to the desire nitriles (**4f**, **4g** and **4i**) were accomplished in excellent yields. The propargylic aldehyde **3j** was transformed to nitrile **4j** in 84% yield at room temperature as well.

 Table 2. Scope of Converting Allylic, Aliphatic, and Propargylic Aldehydes to Nitriles



^aThe reactions were performed according to conditions in Table 1. ^bIsolated yields. ^cH₂NOH HCl (208 mg, 3.0 mmol), Na₂CO₃ (159 mg, 1.5 mmol) were used. ^d r.t., 12 h, then 50 °C, 5 h. ^er.t., 12 h, then 50 °C, 3 h. ^fHPLC yield.



Scheme 2. Application to Formal Synthesis Tarceva and Tazanolast

In order to demonstrate the applicability of this novel cyanation protocol in synthesis complicated molecules, aldehyde 7 (derived from commercially available aldehyde 5), was subjected to the standard reaction condition and provided the corresponding nitrile product 8, a key precursor for Tarceva, in 97% yield (Scheme 2a).¹³ In addition, starting from aldehyde 10, the formal synthesis tetrazole 9 for asthma medicine Tazanolast,¹⁴ was achieved in two steps with nearly quantitative yield by using this newly developed method (Scheme 2b).



Scheme 3. The intramolecular competition reaction between alkyl and aryl aldehyde moieties

To compare the reactivity between alkyl and aryl aldehyde moieties during the formation of nitriles through using this developed reaction system, an intramolecular competition reaction was conducted with 4'-(4-oxobutyl)-[1,1'-biphenyl]-4carbaldehyde (10) bearing both alkyl and aryl aldehyde functionalities as the substrate under the optimized conditions (Scheme 3). The results indicated that the reactivity of alkyl aldehyde was superior to aryl aldehyde to provide their corresponding nitrile counterparts in about 4:1 ratio generating cyanated products 11 and 12 in 68% and 17% yields respectively without formation of product 13.

CHO	(a)	1a	+ H ₂ NOH•HCI + DMSO	then Na ₂ CO ₃ , r.t. somin then Na ₂ CO ₃ , SO ₂ F ₂ r.t. 12 h standare condition	2 a 9%
1a	(b)		aldoxime I + DMSO	Na ₂ CO ₃ , SO ₂ F ₂	2a 9%
N	(c)	1a	+ H ₂ NOH•HCI + DMSO	Na ₂ CO ₃ , r.t. 30 min then Na ₂ CO ₃ , r.t. 12 h	2a 1%
BnO	(d)	1a	+ H ₂ NOH•HCI + DMSO	Na ₂ CO ₃ , r.t. 30 min then SO ₂ F ₂ , r.t. 12 h	2a 2%
aldoxime I	(e)	1a	+ H ₂ NOH+HCI + DMSO	Na ₂ CO ₃ , r.t. 30 min then SO ₂ F ₂ , r.t. 12 h then degass, Na ₂ CO ₃ r.t. 12 h	2a 2%
BnO 2a	(f)	1a	+ H ₂ NOH•HCI + DMSO-	Na ₂ CO ₃ , r.t. 30 min <u>then Na₂CO₃, r.t. 12 h</u> then SO ₂ F ₂ , r.t. 12 h	2a 8%

Figure 1. Control experiments for mechanism investigation

As illustrated in Figure 1, some control experiments were conducted to gain insight to the mechanism of this aldehydes cyanation process. Quantitative yield of 2a was achieved when the pure aldoxime I was served as starting material (Figure 1b) which was identically effective as the use of freshly in situ generated crude aldoxime I from the reaction of aldehyde with NH₂OH (Figure 1f). In addition, mixing the crude aldoxime I just with Na₂CO₃ without the presence of SO₂F₂, the desired nitrile was not generated (Figure 1c); mixing the crude aldoxime I just with SO_2F_2 without the additional 5.0 equivalent of Na₂CO₃, only a trace amount of nitrile was observed (Figure 1d); pre-mixing the crude aldoxime I with SO_2F_2 , then removing SO₂F₂ and adding additional 5.0 equivalent of Na₂CO₃, the nitrile was formed in negligible yield (Figure 1e); which indicating the generation and elimination of sulfonyl ester were crucial for this cyanation process.



Scheme 4. A plausible mechanism for converting aldehydes to carbon-nitrogen triple bonds

Based on the results of the control experiments, a plausible mechanism for this cyanation process was proposed in the Scheme 4. Firstly, aldehydes 1 reacted with H₂NOH in the polar solvent (DMSO) to generate aldoxime intermediate **A** through a nucleophilic addition and dehydration process. Then the corresponding sulfonyl ester **B** was formed from the reaction of aldoxime intermediate **A** with SO₂F₂ under the promotion of Na₂CO₃. Finally, the sulfonyl ester **B** underwent a base-promoted beta-elimination to generate the desired nitrile **2**.

In summary, we have developed a novel, mild, practical and robust method for the direct converting aldehydes into nitriles mediated by inorganic system of NH₂OH/SO₂F₂/Na₂CO₃ in a pot, atom and step-economical (PASE) manner. Moreover, the one-pot process was found to be applicable to the synthesis of key precursors for drugs Tarceva and Tazanolast in nearly

quantitative yields. In addition, more than fifty structurally diverse nitriles were synthesized with greater than 90% yields in most cases demonstrating the high efficiency, wide scope and functional-group compatibility of this new protocol.

EXPERIMENTAL SECTION

GENERAL INFORMATION

All reactions were carried out under an air atmosphere. Unless otherwise specified, NMR spectra were recorded in CDCl₃ or DMSO-d₆ on a 500 or 400 MHz (for ¹H), 471 MHz (for ¹⁹F{¹H, ¹³C}), 126 MHz (for ¹³C{¹H}) spectrometer. All chemical shifts were reported in ppm relative to TMS (¹H NMR, 0 ppm) as internal standards. The HPLC experiments were carried out on a Waters e2695 instrument (column: J&K, RP-C18, 5 μ m, 4.6 \times 150 mm), and the yields of the products were determined by using the corresponding pure compounds as the external standards. The coupling constants were reported in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Melting points were measured and uncorrected. MS experiments were performed on a TOF-Q ESI or CI/EI instrument. All reagents used in the reactions were all purchased from commercial sources and used without further purification.

General procedures for the cyanation of Aldehydes to Nitriles. Procedure A: Aldehyde (2.0 mmol, 1.0 eq.), H₂NOH HCl (153 mg, 2.2 mmol, or 208 mg, 3.0 mmol), Na₂CO₃ (117 mg, 1.1 mmol, or 159 mg, 1.5 mmol) and DMSO (10 mL, 0.2 M) were added into an oven-dried reaction tube (30 mL) equipped with a stirring bar, and the reaction mixture reacted at room temperature for 30-60 min. The reaction was monitored by TLC. After the aldehyde was completely consumed, another portion of the Na_2CO_3 (1.06 g, 10 mmol) was added and the reaction tube was covered with a plastic stopper before the SO₂F₂ gas was introduced into the stirring reaction mixture by slow bubbling through a SO₂F₂ balloon at the room temperature for an additional 12 h. After that, the reaction diluted with water and extracted with dichloromethane $(3 \times 20 \text{ mL})$. Then the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified through silica gel chromatography using a mixture of ethyl acetate and petroleum ether as eluent to afford the desired nitriles.

Procedure B: After reacting at room temperature for 12 h, then the reaction mixture was continued to stir at 50 °C for further 3 h or 5 h. The reaction was also monitored by TLC. After completion, the reaction diluted with water and extracted with dichloromethane (3×20 mL). Then the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified through silica gel chromatography using a mixture of ethyl acetate and petroleum ether as eluent to afford the desired nitriles.

524-(Benzyloxy)benzonitrile (2a).7f Following the Procedure A.53White solid, 400 mg, 1.92 mmol, 96% yield. M.p. 91-93 °C.54Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for55column chromatography.¹H NMR (500 MHz, DMSO-d₆) δ 567.77 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 7.3 Hz, 2H), 7.40 (t, J =577.1 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 8.9 Hz, 2H),58134.1, 128.9, 128.5, 127.6, 119.3, 115.7, 104.3, 70.4. ESI-MS59

HRMS calculated for $C_{14}H_{12}NO \ \left[M+H\right]^+$ 210.0913, found: 210.0916.

4-Methoxybenzonitrile (2b).^{7f} Following the Procedure A. White solid, 243 mg, 1.82 mmol, 91% yield. M.p. 54-56 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.57 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 162.9, 134.1, 119.3, 114.8, 104.0, 55.6.

[1,1'-Biphenyl]-4-carbonitrile (2c).^{7f} Following the Procedure A. White solid, 355 mg, 1.98 mmol, 99% yield. M.p. 83-85 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, J = 7.7 Hz, 2H), 7.69 (d, J = 7.3 Hz, 2H), 7.60 (d, J = 7.4 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 145.8, 139.3, 132.7, 129.2, 128.8, 127.8, 127.3, 119.0, 111.0.

4-Fluorobenzonitrile (2d).⁶ Following the Procedure A. Colorless oil, 184 mg, 1.52 mmol, 76% yield. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.69-7.67 (m, 2H), 7.17 (t, *J* = 8.3 Hz, 2H). ¹⁹F{¹H, ¹³C} NMR (471 MHz, CDCl₃) δ - 102.4 (s, 1F). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 165.2 (d, *J* = 256.1 Hz), 134.8 (d, *J* = 9.1 Hz), 118.1, 117.0 (d, *J* = 22.7 Hz), 108.7 (d, *J* = 3.6 Hz).

4-Chlorobenzonitrile (2e).^{7f} Following the Procedure A. White solid, 267 mg, 1.94 mmol, 97% yi eld. M.p. 87-89 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 139.7, 133.5, 129.8, 118.1, 110.9.

4-Bromobenzonitrile (2f).⁶ Following the Procedure A. White solid, 360 mg, 1.98 mmol, 99% yield. M.p. 108-110 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.63 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 133.5, 132.8, 128.1, 118.2, 111.4.

Methyl 4-cyanobenzoate (2g).^{7f} Following the Procedure A. White solid, 316 mg, 1.96 mmol, 98% yield. M.p. 63-65 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.13 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 3.96 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 165.5, 134.0, 132.3, 130.2, 118.1, 116.5, 52.8.

4-(Methylsulfo nyl)benzonitrile (2h).¹⁵ Following the Procedure A. White powder, 369 mg, 1.98 mmol, 99% yield. M.p. 142-143 °C. Petroleum ether / ethyl acetate = 2 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, DMSO-d₆) δ 8.15 (d, J = 8.0 Hz, 2H), 8.12 (d, J = 8.0 Hz, 2H), 3.32 (s, 3H). ¹³C{¹H} NMR (126 MHz, DMSO-d₆) δ 144.7, 133.5, 127.8, 117.6, 116.1, 42.9.

4'-Cyano-[1,1'-biphenyl]-4-yl dimethylcarbamate (2i). Following the Procedure A. White solid, 530 mg, 1.98 mmol, 99% yield. M.p. 147-149 °C. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, DMSO-d₆) δ 7.91 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 3.06 (s, 3H), 2.93 (s, 3H). ¹³C{¹H} NMR (126 MHz, DMSO-d₆) δ 153.8, 151.9, 143.9, 135.1, 132.9, 128.0, 127.5, 122.6, 118.9, 109.9, 36.3, 36.1. ESI-MS HRMS calculated for C₁₆H₁₅N₂O₂[M+H]⁺ 267.1128, found: 267.1125.

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104.7, 24.2.

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solid (727 mg, 88% yield). Then the synthesis of 4-Cyanobenzoic acid (21) followed a modified Procedure. The reaction was performed directly from the aldoxime intermediate in 2.0 mmol scale and Na₂CO₃ (1.27 g, 12 mmol) was used for the dehydration process under SO₂F₂ atmosphere at r.t. for 12 h. After completion of the reaction, the mixture was acidified with 1M HCl to adjust the pH value to 1.0. White solid, 206 mg, 1.40 mmol, 70% yield. M.p. 221-222 °C. Petroleum ether / ethyl acetate = 1 : 1 (v / v) as eluent for column chromatography. ¹H NMR (400 MHz, DMSO-d₆) δ 13.57 (br s, 1H), 8.07 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 8.3 Hz, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 166.9,

N-(4-cyanophenyl)acetamide (2j).¹⁶ Following the Procedure

A. White solid, 314 mg, 1.96 mmol, 98% yield. M.p. 201-203

^oC. Petroleum ether / ethyl acetate = 1 : 1 (v / v) as eluent for

column chromatography. ¹H NMR (500 MHz, DMSO-d₆) δ 10.35 (s, 1H), 7.76-7.73 (m, 4H), 2.09 (s, 3H). ¹³C{¹H} NMR

(126 MHz, DMSO-d₆) δ 169.2, 143.5, 133.3, 119.1, 116.9,

4-Nitrobenzonitrile (2k).⁶ Following the Procedure A. White

solid, 293 mg, 1.98 mmol, 99% yield. M.p. 145-147 °C. Petro-

leum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column

chromatography. ¹H NMR (500 MHz, DMSO-d₆) δ 8.38 (d, J

= 8.7 Hz, 2H), 8.18 (d, J = 8.9 Hz, 2H). ¹³C{¹H} NMR (126

4-Cyanobenzoic acid (21).^{10f} Aldoxime intermediate of 4-

formylbenzoic acid 11 was synthesized according to a known

procedure:¹⁷ 4-formylbenzoic acid (11, 751 mg, 5.0 mmol),

hydroxylamine hydrochloride (695 mg, 2.0 eq.), sodium ace-

tate (2.05 g, 5.0 eq.) and THF (20 mL) was added to a 50 mL

round reaction flask, and the reaction mixture was stirred at a

reflux temperature for 1 h, then washed with water, extracted

with EtOAc (3×10 mL). The combined organic layers were

washed with brine, dried over anhydrous Na₂SO₄, and concen-

trated to dryness to get its aldoxime intermediate as a white

MHz, DMSO-d₆) δ 149.9, 134.1, 124.3, 117.3, 117.2.

135.0, 132.1, 130.3, 118.2, 116.0. Benzonitrile (2m).^{7f} Following the Procedure A. Colorless oil, 132 mg, 1.28 mmol, 64% yield. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.62-7.57 (m, 3H), 7.44 (t, J = 7.5 Hz, 2H). ${}^{13}C{}^{1}H{}$ NMR (126 MHz, CDCl₃) δ 132.8, 132.0, 129.1, 118.8, 112.3.

3-Phenoxybenzonitrile (2n).^{7f} Following the Procedure A. Colorless oil, 371 mg, 1.90 mmol, 95% yield. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.38 (m, 3H), 7.35 (d, J = 7.6 Hz, 1H), 7.24-7.19 (m, 3H), 7.04 (d, J = 8.4 Hz,2H). ${}^{13}C{}^{1}H$ NMR (126 MHz, CDCl₃) δ 158.2, 155.6, 130.7, 130.2, 126.4, 124.7, 122.8, 121.1, 119.8, 118.3, 113.5.

Isophthalonitrile (20).¹⁸ Following the Procedure A. White solid, 251 mg, 1.96 mmol, 98% yield. M.p. 156-157 °C. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.96 (s, 1H), 7.91 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H). $^{13}C{^{1}H}$ NMR (126 MHz, CDCl₃) δ 136.1, 135.5, 130.5, 116.7, 114.2.

3-Nitrobenzonitrile (2p).¹⁹ Following the Procedure A. White solid, 284 mg, 1.92 mmol, 96% yield. M.p. 111-113 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.53 (s, 1H), 8.48 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.0$ Hz, 1H), 8.01 (d, J = 8.0 Hz,

1H), 7.76 (t, J = 8.1 Hz, 1H). ${}^{13}C{}^{1}H{}$ NMR (126 MHz, CDCl₃) δ 148.3, 137.7, 130.8, 127.7, 127.3, 116.6, 114.2.

3-Bromobenzonitrile (2q).²⁰ Following the Procedure A. White solid, 335 mg, 1.84 mmol, 92% yield. M.p. 35-37 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.78 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 136.2, 134.8, 130.8, 130.7, 123.0, 117.4, 114.3.

2-Bromobenzonitrile (2r).²⁰ Following the Procedure A. White solid, 331 mg, 1.82 mmol, 91% yield. M.p. 50-51 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.48-7.41 (m, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 134.4, 134.0, 133.3, 127.8, 125.4, 117.3, 116.0.

2-(Trifluoromethyl)benzonitrile (2s).²¹ Following the Procedure A. Light yellow oil, 301 mg, 1.76 mmol, 88% yield. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H). ¹⁹F{¹H, ¹³C} NMR (471 MHz, CDCl₃) -62.0 (s, 3F). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 134.8, 133.1, 132.8, 132.4, 126.8 (q, J = 4.5 Hz), 122.5 (q, J = 274 Hz), 115.6, 110.3.

5-Bromo-2-fluorobenzonitrile (2t).²² Following the Procedure A. White solid, 337 mg, 1.68 mmol, 84% yield. M.p. 75-77 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.76-7.71 (m, 2H), 7.14 (t, J = 8.5 Hz, 1H). ¹⁹F{¹H, ¹³C} NMR (471 MHz, CDCl₃) -108.2 (s, 1F). ¹³C{¹H} NMR (126 MHz, $CDCl_3$) δ 162.4 (d, J = 260.7 Hz), 138.2 (d, J = 8.2 Hz), 135.9, 118.4 (d, J = 20.8 Hz), 117.2 (d, J = 4.5 Hz), 112.6, 103.6 (d, J = 17.3 Hz).

3,4-Dichlorobenzonitrile (2u).¹⁹ Following the Procedure A. White solid, 337 mg, 1.96 mmol, 98% yield. M.p. 67-69 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 138.4, 134.2, 133.9, 131.6, 131.2, 116.9, 112.1.

2,6-Dimethylbenzonitrile (2v).²³ Following the Procedure A. Colorless oil, 147 mg, 1.12 mmol, 56% yield. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.34 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 2H), 2.52 (s, 6H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 142.2, 132.2, 127.4, 117.4, 113.4, 20.8.

Methyl (E)-3-(3-cyanophenyl)acrylate (2w).²⁴ Following the Procedure A. White solid, 363 mg, 1.94 mmol, 97% yield. M.p. 93-94 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.78 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.66-7.63 (m, 2H), 7.51 (t, J = 7.8 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 3.82 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 166.7, 142.2, 135.8, 133.3, 132.0, 131.4, 129.9, 120.7, 118.2, 113.5, 52.1.

3-(Phenylethynyl)benzonitrile (2x).²⁵ Following the Procedure A. Light yellow solid, 400 mg, 1.96 mmol, 98% yield. M.p. 67-69 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v)as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.81 (s, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.56-7.55 (m, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.39-7.38 (m, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 135.7, 135.0, 131.9, 131.5, 129.4, 129.1, 128.6, 125.1, 122.4, 118.2, 113.0, 91.9, 87.0.

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58 59 60 **2-Bromo-4,5-dimethoxybenzonitrile** (**2y**).¹⁸ Following the Procedure A. White solid, 466 mg, 1.92 mmol, 96% yield. M.p. 114-116 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ . 7.05 (s, 1H), 7.03 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 153.3, 148.6, 117.7, 117.6, 115.6, 115.3, 106.9, 56.6, 56.5.

3-(Cyclopropylmethoxy)-4-(difluoromethoxy)benzonitrile

(2z). Following the Procedure A. White solid, 469 mg, 1.96 mmol, 98% yield. M.p. 42-44 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.26-7.22 (m, 2H), 7.19 (s, 1H), 6.70 (t, *J* = 74.5 Hz, 1H), 3.89 (d, *J* = 7.0 Hz, 2H), 1.32-1.23 (m, 1H), 0.68 (d, *J* = 7.8 Hz, 2H), 0.38 (d, *J* = 4.7 Hz, 2H). ¹⁹F{¹H, ¹³C} NMR (471 MHz, CDCl₃) δ 150.9, 144.0 (t, *J* = 2.7 Hz), 125.7, 122.9, 118.2, 117.4, 115.6 (t, *J* = 262 Hz), 110.1, 74.4, 10.0, 3.4. ESI-MS HRMS calculated for C₁₂H₁₂F₂NO₂ [M+H]⁺ 240.0831, found: 240.0824.

24 1-Naphthonitrile (2aa).⁶ Following the Procedure A. Brown 25 solid, 303 mg, 1.98 mmol, 99% yield. M.p. 29-31 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column 26 chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.19 (d, J = 27 8.2 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.89-7.85 (m, 2H), 7.65 28 (t, J = 7.0 Hz, 1H), 7.59 (t, J = 7.1 Hz, 1H), 7.47 (t, J = 7.5 Hz, 29 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 133.2, 132.8, 132.5, 30 132.2, 128.6, 128.5, 127.5, 125.0, 124.9, 117.8, 110.0. 31

2-Naphthonitrile (**2ab**).⁶ Following the Procedure A. White solid, 300 mg, 1.96 mmol, 98% yield. M.p. 62-64 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.20 (s, 1H), 7.91-7.87 (m, 3H), 7.66-7.58 (m, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 134.8, 134.3, 132.3, 129.3, 129.1, 128.5, 128.2, 127.8, 126.4, 119.4, 109.5.

1-Bromo-2-naphthonitrile (2ac).²⁶ Following the Procedure A. White solid, 460 mg, 1.98 mmol, 99% yield. M.p. 88-90 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.29 (d, J = 8.1 Hz, 1H), 7.88-7.85 (m, 2H), 7.71-7.66 (m, 2H), 7.56 (d, J = 8.4 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 135.5, 131.8, 129.7, 129.1, 128.7, 128.6, 128.4, 127.5, 118.2, 113.6. Note: In the ¹³C{¹H} NMR spectrum of **2ab**, theoretically, there should be eleven peaks. Due to the compact overlaying, it is difficult to specify the overlaying peaks.

Tephthalonitrile (2ad).⁶ Following the Procedure A. White solid, 240 mg, 1.88 mmol, 94% yield. M.p. 212-214 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, DMSO-d₆) δ 8.07 (s, 4H). ¹³C{¹H} NMR (126 MHz, DMSO-d₆) δ 133.2, 117.5, 115.7.

[1,1'-Biphenyl]-4,4'-dicarbonitrile (2ae).²⁷ Following the Procedure A. White solid, 400 mg, 1.96 mmol, 98% yield. M.p. 237-239 °C. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, DMSO-d₆) δ 7.98-7.95 (m, 8H). ¹³C{¹H} NMR (126 MHz, DMSO-d₆) δ 142.7, 133.0, 128.1, 118.6, 111.3.

3-(4-Cyanophenoxy)benzonitrile (**2af**).²⁸ Following the Procedure A. White powder, 419 mg, 1.90 mmol, 95% yield. M.p. 96-98 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, DMSO-d₆) δ . 7.87 (d, *J* =8.5 Hz, 2H), 7.73-7.70 (m, 2H), 7.65 (t, *J* =8.1 Hz, 1H), 7.49 (d, *J* =8.1 Hz, 1H), 7.18 (d, *J* =8.6 Hz, 2H). ¹³C{¹H} NMR (126 MHz, DMSO-d₆) δ 160.0, 155.1, 134.8, 131.8, 128.9, 125.2, 123.5, 118.8, 118.6, 117.9, 113.1, 106.1.

Thiophene-2-carbonitrile (**2ag**).⁶ Following the Procedure A. Colorless oil, 164 mg, 1.50 mmol, 75% yield. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatog-raphy. ¹H NMR (500 MHz, CDCl₃) δ 7.64-7.63 (m, 1H), 7.61 (d, J = 4.7 Hz, 1H), 7.14-7.13 (m, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 137.5, 132.7, 127.7, 114.3, 109.8.

5-Nitrothiophene-2-carbonitrile (2**ah**).²⁹ Following the Procedure A. A little brown solid, 252 mg, 1.64 mmol, 82% yield. M.p. 38-40 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, J = 4.2 Hz, 1H), 7.58 (d, J = 4.1 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 155.7, 136.6, 127.7, 115.5, 112.1.

Picolinonitrile (2ai).^{4a} Following the Procedure A. A light yellow oil, 196 mg, 1.88 mmol, 94% yield. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatog-raphy. ¹H NMR (500 MHz, CDCl₃) δ 8.71 (d, J = 4.6 Hz, 1H), 7.85 (td, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.55-7.52 (m, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 151.2, 137.2, 134.0, 128.6, 127.1, 117.2.

Quinoline-2-carbonitrile (2aj).^{4a} Following the Procedure A. A little brown solid, 296 mg, 1.92 mmol, 96% yield. M.p. 88-90 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.29 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.88 (d, J =8.1 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.70-7.66 (m, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 148.3, 137.6, 133.7, 131.4, 130.1, 129.6, 128.8, 127.9, 123.4, 11 7.7.

1-Tosyl-1H-indole-3-carbonitrile (2ak).³⁰ Following the Procedure A. A little brown solid, 586 mg, 1.98 mmol, 99% yield. M.p. 154-156 °C. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.10 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 7.7 Hz, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 2.38 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 146.5, 134.2, 133.8, 133.3, 130.5, 128.5, 127.4, 126.7, 124.9, 120.4, 113.9, 113.6, 93.8, 21.8.

Benzofuran-2-carbonitrile (2al).³¹ Following the Procedure A. Yellow solid, 263 mg, 1.84 mmol, 92% yield. M.p. 30-32 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.46 (s, 1H), 7.37 (t, J = 7.0 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 155.8, 128.6, 127.4, 125.6, 124.7, 122.7, 118.6, 112.2, 112.0.

4-(Pyridin-2-yl)benzonitrile (2am).³² Following the Procedure A. White solid, 358 mg, 1.98 mmol, 99% yield. M.p. 95-97 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.71 (d, J = 4.1 Hz, 1H), 8.10 (d, J = 8.2 Hz, 2H), 7.80 (t, J = 7.8 Hz, 1H), 7.76-7.73 (m, 3H), 7.30 (t, J = 5.6 Hz, 1H).

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59 60 $^{13}C{^{1}H}$ NMR (126 MHz, CDCl₃) δ 155.3, 150.1, 143.6, 137.2, 132.6, 127.5, 123.4, 121.1, 118.9, 112.5.

Benzo[c][1,2,5]oxadiazole-4-carbonitrile (2an). Following the Procedure A. Light yellow powder, 287 mg, 1.98 mmol, 99% yield. M.p. 91-93 °C. Petroleum ether / ethyl acetate = 5 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 8.17 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 6.6 Hz, 1H), 7.58 (t, J = 8.1 Hz, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) & 148.6, 147.4, 139.3, 130.6, 122.2, 113.8, 102.3. ESI-MS HRMS calculated for C7H4N₃O [M+H]⁺ 146.0349, found: 146.0343.

13 4-Methyl-2-phenylpent-2-enenitrile (4a).³³ Following the Procedure A. A little yellow oil, 270 mg, 1,58 mmol, 79% 15 yield. Petroleum ether / ethyl acetate = 20 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.40 (m, 2H), 7.38-7.34 (m, 3H), 6.42 (d, J = 10.7 Hz, 1H), 2.83-2.75 (m, 1H), 1.06 (d, J = 6.5 Hz, 6H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 156.0, 132.6, 128.9, 128.8, 128.5, 19 119.7, 113.3, 28.6, 22.1.

(E)-3-(4-Methoxyphenyl)acrylonitrile (4b).^{7f} Following the Procedure A. Off-white solid, 279 mg, 1.76 mmol, 88% yield. M.p. 59-61 °C Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 16.6 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 5.71 (d, J = 16.6 Hz, 1H), 3.84 (s, 3H). ${}^{13}C{}^{1}H{}$ NMR (126 MHz, CDCl₃) δ 162.2, 150.2, 129.2, 126.5, 118.8, 114.6, 93.5, 55.6.

(E)-2-methyl-3-phenylacrylonitrile (4c).³¹ Following the Procedure A. A little yellow oil, 252 mg, 1.76 mmol, 88% yield. Petroleum ether / ethyl acetate = 20 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.42 (t, J = 7.0 Hz, 2H), 7.37 (t, J = 7.0 Hz, 1H), 7.33 (d, J =7.5 Hz, 2H), 7.21 (s, 1H), 2.15 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 144.4, 134.1, 129.4, 129.3, 128.7, 121.3, 109.7, 16.8.

35 (*E*)-dodec-2-enenitrile (4d).³⁴ Following the Procedure B, the 36 mixture was stirred at 50 °C for 5 h. Colorless oil, 325 mg, 37 1.82 mmol, 91% yield. Petroleum ether / ethyl acetate = 40:1(v / v) as eluent for column chromatography. ¹H NMR (500 38 MHz, CDCl₃) δ 6.70 (dt, J_1 = 16.3 Hz, J_2 = 7.0 Hz, 1H), 5.30 39 (d, J = 16.3 Hz, 1H), 2.20 (q, J = 7.0 Hz, 2H), 1.44-1.40 (m, J = 16.3 Hz, 10.1 Hz)40 2H), 1.29-1.25 (m, 12H), 0.86 (t, J = 7.0 Hz, 3H). ¹³C{¹H} 41 NMR (126 MHz, CDCl₃) δ 156.2, 117.6, 99.7, 33.3, 31.9, 29.5, 42 29.31, 29.27, 29.0, 27.7, 22.7, 14.1. 43

(2E,4E)-dodeca-2,4-dienenitrile (4e).³⁵ Following the Procedure A. A little yellow oil, 316 mg, 1.78 mmol, 89% yield. Petroleum ether / ethyl acetate = 40 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 6.98-6.93 (m, 1H), 6.13-6.12 (m, 2H), 5.22 (d, J = 16.0 Hz, 1H), 2.16-2.15 (m, 2H), 1.43-1.40 (m, 2H), 1.273-1.269 (m, 8H), 0.87 (t, J = 6.2 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 151.0, 146.2, 128.0, 118.5, 96.5, 33.0, 31.8, 29.2, 29.1, 28.6, 22.7, 14.1.

51 **3.7-Dimethyloct-6-enenitrile** (4f).^{7a} Following the Procedure 52 B, the mixture was stirred at 50 °C for 3 h. Colorless oil, 287 53 mg, 1.90 mmol, 95% yield. Petroleum ether / ethyl acetate = 54 40: 1 (v / v) as eluent for column chromatography. ¹H NMR 55 (500 MHz, CDCl₃) δ 5.06 (t, J = 6.6 Hz, 1H), 2.31 (dd, J₁ = 56 16.5 Hz, $J_2 = 5.3$ Hz, 1H), 2.22 (dd, $J_1 = 16.6$ Hz, $J_2 = 6.9$ Hz, 57 1H), 2.03-1.96 (m, 2H), 1.88-1.81 (m, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.48-1.41 (m, 1H), 1.36-1.31 (m, 1H), 1.06 (d, *J* = 6.7 58

Hz, 3H). ${}^{13}C{}^{1}H{}$ NMR (126 MHz, CDCl₂) δ 132.3, 123.5, 118.9, 35.9, 30.0, 25.7, 25.3, 24.5, 19.4, 17.7.

Dodecanenitrile (4g).³¹ Following the Procedure B, the mixture was stirred at 50 °C for 5 h. Colorless oil, 341 mg, 1.88 mmol, 94% yield. Petroleum ether / ethyl acetate = 40 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 2.31 (t, J = 7.0 Hz, 2H), 1.66-1.60 (m, 2H), 1.42-1.41 (m, 2H), 1.27-1.25 (m, 14H), 0.86 (t, J = 6.5 Hz, 3H). $^{13}C{^{1}H}$ NMR (126 MHz, CDCl₃) δ 119.9, 31.9, 29.6, 29.5, 29.3, 28.8, 28.7, 25.4, 22.7, 17.1, 14.1.Note: In the ${}^{13}C{}^{1}H$ NMR spectrum of 4g, theoretically, there should be twelve peaks. Due to the compact overlaying, it is difficult to specify the overlaying peaks.

2-Phenylacetonitrile (4h).²⁹ Following the Procedure A. Colorless oil, 162 mg, 1.38 mmol, 69% yield. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.39 (t, J = 7.3 Hz, 2H), 7.34-7.33 (m, 3H), 3.74 (s, 2H).¹³C{¹H} NMR (126 MHz, CDCl₃) δ 130.0, 129.2, 128.1, 128.0, 118.0, 23.6.

3-([1,1'-Biphenyl]-4-yl)propanenitrile (4i).³⁶ Following the Procedure B, the mixture was stirred at 50 °C for 3 h. White solid, 381 mg, 1.84 mmol, 92% yield. M.p. 96-98 °C. Petroleum ether / ethyl acetate = 10 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.60-7.58 (m, 4H), 7.46 (t, J = 7.3 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 3.01 (t, J = 7.4 Hz, 2H), 2.67 (t, J = 7.4 Hz, 2H). ${}^{13}C{}^{1}H$ NMR (126 MHz, CDCl₃) δ 140.7, 140.4, 137.2, 128.9, 128.8, 127.7, 127.5, 127.2, 119.3, 31.3, 19.4.

3-Phenylpropiolonitrile (4j).³⁷ Following the Procedure A. A clear solid, 213 mg, 1.68 mmol, 84% yield. M.p. 33-35 °C. Petroleum ether / ethyl acetate = 20 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.62 (d, J = 7.7 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H). ${}^{13}C{}^{1}H{}$ NMR (126 MHz, CDCl₃) δ 133.6, 132.0, 129.0, 117.7, 105.6, 83.1, 63.2.

Synthesis of 3,4-bis(2-methoxyethoxy)benzaldehyde (7). 3,4-bis(2-methoxy)benzaldehyde (7) was synthesized according to a modified procedure:⁶ Under N₂ atmosphere, 3,4-dihydroxybenzaldehyde 5 (2.0 g, 14.5 mmol), K₂CO₃ (8.0 g, 58 mmol) and DMF (13.2 mL, 1.1 M) were added to a 50 mL round bottom flask equipped with a stirring bar, then the mixture was subjected to stir at room temperature for 1 h before 1-bromo-2-methoxyethane 6 (4.84 g, 34.8 mmol) was introduced through the syringe. Then the reaction was allowed to react at 100 °C for an additional 5 h. After completion, the reaction diluted with water and extracted with dichloromethane $(3 \times 30 \text{ mL})$. Then the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified through silica gel chromatography using a mixture of ethyl acetate and petroleum ether (v/v = 1:3 to 1:2) as gradient eluent to afford the desired product as yellow oil (2.6 g, 71% yield).

Synthesis of 3,4-bis(2-methoxyethoxy)benzonitrile (8)⁶. Aldehyde 7 (2.0 mmol, 1.0 eq.), H₂NOHHCl (153 mg, 2.2 mmol), Na₂CO₃ (117 mg, 1.1 mmol) and DMSO (10 mL, 0.2 M) were added into an oven-dried reaction tube (30 mL) equipped with a stirring bar, and the reaction mixture reacted at room temperature for 30 min. The reaction was monitored by TLC. After the aldehyde 7 was completely consumed, another portion of the Na₂CO₃ (1.06 g, 10 mmol) was added and the reaction tube was covered with a plastic stopper before the SO2F2 gas was introduced into the stirring reaction mixture by slow bubbling through a SO₂F₂ balloon at the room temperature for an additional 12 h. After that, the reaction diluted with water and extracted with dichloromethane (3× 20 mL). Then the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified through silica gel chromatography using a mixture of ethyl acetate and petroleum ether (v/v =1:3) as eluent to afford the desired nitrile **8** as white gum, 487 mg, 1.94 mmol, 97% yield. M.p. 39-40 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 8.5 Hz, 1H), 7.13 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.18 (t, *J* = 4.2 Hz, 2H), 4.15 (t, *J* = 4.1 Hz, 2H), 3.79-3.77 (m, 4H), 3.44 (s, 6H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 153.0, 149.0, 126.9, 119.2, 117.2, 113.6, 104.3, 70.9, 70.8, 69.2, 68.7, 59.4, 59.3.

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58 59 60 Synthesis of 5-(3-nitrophenyl)-1H-tetrazole (9).³⁸ To a 30 mL reaction flask, 3-nitrobenzonitrile **20** (445 mg, 3 mmol), NaN₃ (293 mg, 4.5 mmol), NH₄Cl (209 mg, 3.9 mmol) and dry DMF (7.5 mL) were added and the mixture was allowed to stir at 120 °C for about 4 h until the TLC showed the full conversion of starting material. Then, the reaction mixture was pour into water and extracted with dichloromethane (3× 20 mL). Then the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated to dryness to afford the 5-(3-nitrophenyl)-1H-tetrazole **9** as white solid (566 mg) in quantitative yield. And the structure and purity of final product were identified by NMR. ¹H NMR (500 MHz, DMSO-d₆) δ 8.84 (s, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 7.91 (t, *J* = 8.1 Hz, 1H).

Procedure for gram-scale example (2k). Aldehvde 1k (3.0 g. 20 mmol), H₂NOHHCl (1.53 g, 22 mmol), Na₂CO₃ (1.17 g, 11 mmol) and DMSO (100 mL, 0.2 M) were added into an ovendried round reaction bottle (250 mL) equipped with a stirring bar, and the reaction mixture reacted at room temperature for 30 min. The reaction was monitored by TLC. After the aldehyde (1k) was completely consumed, another portion of the Na₂CO₃ (10.6 g, 100 mmol) was added and the reaction bottle was covered with a plastic stopper before the SO_2F_2 gas was introduced into the stirring reaction mixture by slow bubbling through a SO2F2 balloon at the room temperature for an additional 36 h. After that, the reaction diluted with water and extracted with dichloromethane (3×40 mL). Then the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. Evaporation of solvent under reduced pressure to give the target product 2k (2.94 g, 99% yield). And the structure and purity of final product were identified by NMR.

Intramolecular Competition Experiment: Following the modified procedure B in 1 mmol scale, the resulting mixture was stirred at 50 °C for 3 h. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatography to give the mixture of nitriles **11** and **12** as white solid, 212 mg. ¹H NMR (500 MHz, CDCl₃) δ 10.05 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 0.5H), 7.67 (d, *J* = 8.2 Hz, 0.5H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 0.5H), 7.31 (d, *J* = 8.1 Hz, 2.5H), 2.85 (t, *J* = 7.5 Hz, 2.5H), 2.37 (t, *J* = 7.0 Hz, 2.5H), 2.06-2.01 (m, 2.5H).

Note: The 4:1 ration was determined by the Proton NMR of products **11** and **12** mixture. And the compound **12** was isolated from the mixture by treating the mixture with NaBH₄ to reduce the aldehyde **11** to the benzyl alcohol **14**. Then the oxidation of benzyl alcohol **14** generated pure product **11**.

4-(4'-formyl-[1,1'-biphenyl]-4-yl)butanenitrile (11). White solid, 170 mg, 0.68 mmol, 68% yield. M.p. 61-63 °C. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 10.05 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.06-2.00 (m, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 191.9, 146.8, 140.4, 138.1, 135.3, 130.4, 129.2, 127.7, 127.6, 119.4, 34.1, 26.9, 16.5. ESI-MS HRMS calculated for C₁₇H₁₆NO [M+H]⁺250.1226, found: 250.1230.

4'-(3-cyanopropyl)-[1,1'-biphenyl]-4-carbonitrile (12). White solid, 42 mg, 0.17 mmol, 17% yield. M.p. 101-102 °C. Petroleum ether / ethyl acetate = 3 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2.0H), 2.85 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.0 Hz, 2H), 2.06-2.01 (m, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 145.4, 140.6, 137.6, 132.7, 129.4, 127.7, 127.6, 119.4, 119.0, 111.1, 34.2, 26.9, 16.6. ESI-MS HRMS calculated for C₁₇H₁₅N₂ [M+H]⁺247.1230, found: 247.1243.

4-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)butanenitrile

(14). White solid, 168 mg, 0.67 mmol, 99% yield. M.p. 123-125 °C. Petroleum ether / ethyl acetate = 2 : 1 (v / v) as eluent for column chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 4.73 (s, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.04-1.98 (m, 2H), 1.86 (s, 1H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 140.3, 140.1, 139.3, 139.0, 129.0, 127.6, 127.4, 127.2, 119.6, 65.1, 34.1, 27.0, 16.5. ESI-MS HRMS calculated for C₁₇H₁₇NNaO [M+Na]⁺274.1202, found: 274.1210.

Control experiments for mechanism investigation

General method: The yields were determined by HPLC using pure **2a** as the external standard ($t_R = 4.301 \text{ min}$, $\lambda_{max} = 248.8 \text{ nm}$, MeOH/H₂O = 80 : 20 (v / v)).

Experiment a: 4-Benzyloxybenzaldehyde (**1a**, 0.2 mmol), H₂NOH'HCl (0.22 mmol, 1.1 eq.), Na₂CO₃ (0.11 mmol, 0.55 eq.) and DMSO (1.0 mL, 0.2 M) were added into a 20 mL tube and reacted at room temperature for 30 min. Then another portion of Na₂CO₃ (1.0 mmol, 5.0 eq.) was added before SO_2F_2 was introduced by bubbling into the mixture *via* a balloon charged with needle, and the resulting mixture was allowed to stir at r.t. for 12 h.

Experiment b: Aldoxime (I, 0.2 mmol), Na₂CO₃ (1.0 mmol, 5.0 eq.) and DMSO (1.0 mL, 0.2 M) were added into a 20 mL tube before SO_2F_2 was introduced by bubbling into the mixture *via* a balloon charged with needle, and the resulting mixture was allowed to stir at r.t. for 12 h.

Experiment c: 4-Benzyloxybenzaldehyde (1a, 0.2 mmol), $H_2NOHHCl$ (0.22 mmol, 1.1 eq.), Na_2CO_3 (0.11 mmol, 0.55 eq.) and DMSO (1.0 mL, 0.2 M) were added into a 20 mL tube and reacted at room temperature for 30 min. Then another portion of Na_2CO_3 (1.0 mmol, 5.0 eq.) was added and the resulting mixture was allowed to stir at r.t. for 12 h.

Experiment d: 4-Benzyloxybenzaldehyde (**1a**, 0.2 mmol), H₂NOH⁺HCl (0.22 mmol, 1.1 eq.), Na₂CO₃ (0.11 mmol, 0.55 eq.) and DMSO (1.0 mL, 0.2 M) were added into a 20 mL tube and reacted at room temperature for 30 min. Then SO_2F_2 was introduced by bubbling into the mixture *via* a balloon

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59 60 charged with needle, and the resulting mixture was allowed to stir at r.t. for 12 h.

Experiment e: 4-Benzyloxybenzaldehyde (**1a**, 0.2 mmol), H₂NOHHCl (0.22 mmol, 1.1 eq.), Na₂CO₃ (0.11 mmol, 0.55 eq.) and DMSO (1.0 mL, 0.2 M) were added into a 20 mL tube and reacted at room temperature for 30 min. Then SO_2F_2 was introduced by bubbling into the mixture *via* a balloon charged with needle, and the resulting mixture was allowed to stir at r.t. for 12 h. The reaction mixture was degassed with gentle vacuum for about 3 minutes before the subsequent addition of Na₂CO₃ (1.0 mmol, 5.0 eq.) and the reaction mixture further stirred at r.t. for another 12 h.

Experiment f: 4-Benzyloxybenzaldehyde (**1a**, 0.2 mmol), H_2 NOHHCl (0.22 mmol, 1.1 eq.), Na_2CO_3 (0.11 mmol, 0.55 eq.) and DMSO (1.0 mL, 0.2 M) were added into a 20 mL tube and reacted at room temperature for 30 min. Then another portion of Na_2CO_3 (1.0 mmol, 5.0 eq.) was added and the stirring lasted for 12 h at r.t. SO_2F_2 was subsequently introduced by bubbling into the mixture *via* a balloon charged with needle, and the resulting mixture was allowed to stir at r.t. for another 12 h.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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