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Preparation of O-Protected Cyanohydrins by Aerobic Oxidation of α-Substituted Malononitriles in the Presence of Diarylphosphine Oxides

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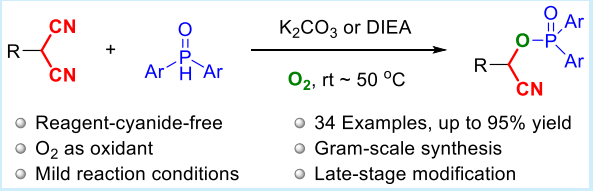
Supporting Information

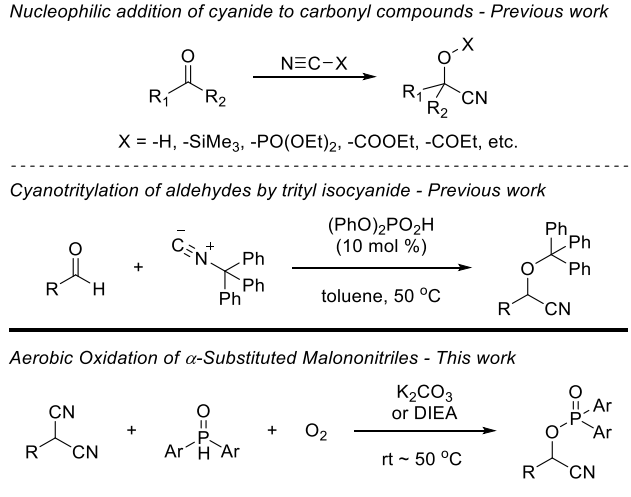
ABSTRACT: A mild, reagent-cyanide-free, and efficient synthesis of *O*-phosphinoyl-protected cyanohydrins from readily available α-substituted malononitriles was realized using diarylphosphine oxides in the presence of O_2. Mechanistic studies indicated that in addition to the initial aerobic oxidation of the malononitrile derivative notable features of this process include the formation of a tetrahedral intermediate and a subsequent intramolecular rearrangement. The phosphinoyl-protecting group can be removed by alcoholysis or by reduction with DIBAL-H.



Cyanohydrins or O-protected cyanohydrins are important synthons because nitrile- and alcohol-containing molecules can be easily converted into a diverse range of 1,2-difunctional compounds, such as α-hydroxy aldehydes, α-hydroxy acids, and β-hydroxy amines.[1] Recently, it has been reported that highly functionalized compounds can be prepared from cyanohydrins,[2] and *O*-acetyl cyanohydrins can also act as a derivatizable directing group for Pd-catalyzed regioselective olefination reactions.[3] Cyanohydrins are also present in a number of natural products,[4] and these compounds show high insecticidal,[5] antiviral,[6] and anticancer activities.[7] Numerous strategies for accessing cyanohydrins or the more stable O-protected derivatives generally rely on highly toxic cyanide sources such as HCN, metal cyanides, and TMSCN.[1a,d,4e,8] Until recently, only Ruijter and Orru had documented a Brønsted-acid-catalyzed cyanide-free method, and they utilized trityl isocyanide as a pseudocyanide source to prepare *O*-trityl cyanohydrin (Scheme 1).[9]

Based on our previous work on environmentally benign methods for the α-hydroxylation of β-ketoesters,[10] we hypothesized that O_2 could be used to generate a C−O bond at the α-position of a nitrile group. Based on this assumption, malononitrile derivatives, which contain two nitrile groups, attracted our attention.[11] Although α-position derivatization reactions of malononitriles have become common,[12] a method for α-C−O bond formation via the oxidation of malononitrile, yielding the corresponding cyanohydrin or its derivative, has not been reported. In 2016, the Hayashi group reported an oxidative amidation of α-substituted malononitriles with amines, but both nitrile groups were lost in the reaction.[13] During the aerobic process, the oxidation state of the carbon atom in the α-position of malononitrile was increased from −1 to +2; however, the required oxidation state of the α-carbon in cyanohydrin is 0.[14] We speculate that reducing agents, especially those containing nonmetallic elements at lower oxidation states, may reduce the

Scheme 1. Synthetic Strategies toward Cyanohydrins or Their O-Protected Derivatives



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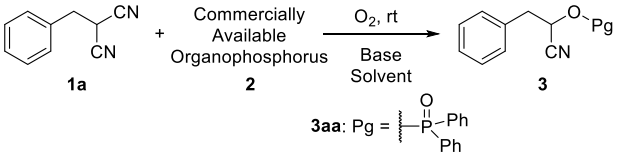
oxidation state of acyl cyanide from +2 to 0, facilitating the formation of cyanohydrin or its O-protected derivative.

Based on this hypothesis, we explored some commercially available organophosphorus reagents as reductants in the proposed aerobic preparation of cyanohydrin derivatives from α-benzyl malononitrile (**1a**, Table 1). To our delight, the treatment of **1a** and diphenylphosphine oxide (**2a**) with O_2 in the presence of K_2CO_3 gave *O*-phosphinoyl-protected cyanohydrin **3aa** in 54% yield. Encouraged by this result, we further optimized the reaction conditions. Screening inorganic and organic bases in different solvents at room temperature demonstrated that the mixture of MeCN and K_2CO_3 gave the highest reaction yield (Table 1, entry 9). A diminished yield was obtained when the reaction was carried out at a lower temperature (Table 1, entry 15), while a modestly reduced yield was achieved at a higher temperature (Table 1, entry 14).

With the optimized reaction conditions in hand (Conditions A), we turned our attention to the scope of the reaction with respect to the α-substituted malononitrile substrates. As shown in Table 2, the scope of substrates with different substituents on the benzyl ring (**1b**–**1k**, **1v**) was investigated first. Electron-donating or electron-withdrawing groups at the *ortho*, *meta*, or *para* positions slightly affected the reactivity, giving desired products **3ba**–**3ka** in moderate to good yields. Sterically hindered substrates, such as mesityl- or naphthalene-containing compounds **1v** or **1u**, afforded *O*-diphenylphosphinoyl cyanohydrins **3va** and **3ua** in 85% and 75% yields, respectively.

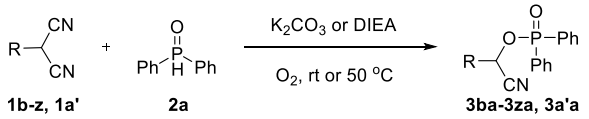
Table 1. Optimization of Organophosphorus and Reaction Conditions[a]



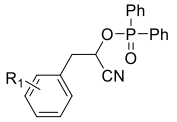
entry	organophosphorus	base	solvent	time (h)	yield (%)[b]
1	$P(Ph)_3$	K_2CO_3	THF	24	-[c]
2	$(EtO)_2P(O)H$	K_2CO_3	THF	24	-[c]
3	$P(OEt)_3$	K_2CO_3	THF	24	-[c]
4	$Ph_2P(O)H$ **2a**	K_2CO_3	THF	12	**3aa**, 54%
5	**2a**	DIEA	THF	24	**3aa**, 56%
6	**2a**	DMAP	THF	24	**3aa**, 49%
7	**2a**	LiOH	THF	4	-[c]
8	**2a**	Cs_2CO_3	THF	8	**3aa**, 19%
9	**2a**	K_2CO_3	MeCN	6	**3aa**, 67%
10	**2a**	K_2CO_3	DMF	20	**3aa**, 59%
11	**2a**	K_2CO_3	MeOH	7	-[c]
12	**2a**	K_2CO_3	DCM	24	**3aa**, 44%
13	**2a**	K_2CO_3	toluene	24	NR[d]
14[e]	**2a**	K_2CO_3	MeCN	3	**3aa**, 50%
15[f]	**2a**	K_2CO_3	MeCN	24	NR[g]
16[h]	**2a**	K_2CO_3	MeCN	24	**3aa**, 54%

[a]Reaction conditions: **1a** (1.25 mmol), organophosphorus (2.0 equiv), and base (2.0 equiv) in solvent (5 mL) were stirred under a constant flow (bubbling) of O_2 at room temperature. NR = No reaction. [b]Isolated yield based on **1a**. [c]Complex reaction mixture with **1a** consumed. [d]55% of **1a** was recovered. [e]Reaction was performed at 50 °C. [f]Reaction was performed at −10 °C. [g]72% of **1a** was recovered. [h]0.5 equiv of K_2CO_3 was used. DIEA = *N*,*N*-diisopropylethylamine, DMAP = dimethylaminopyridine.

Table 2. Oxidation of α-Substituted Malononitriles in the Presence of Diphenylphosphine Oxide 2a[a,b]

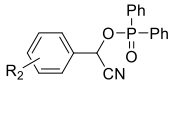


α-benzyl malononitriles



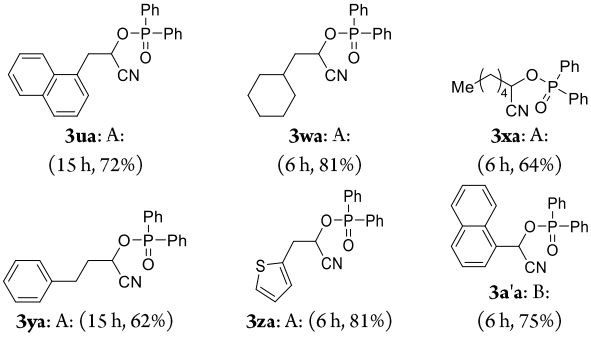
3ba: A: R_1 = 2-Cl, (6 h, 51%)
3ca: A: R_1 = 2-Me, (6 h, 43%)
3da: A: R_1 = 3-Cl, (20 h, 40%)
3ea: A: R_1 = 3-Br, (6 h, 50%)
3fa: A: R_1 = 3-OMe, (15 h, 44%)
3ga: A: R_1 = 3-Me, (6 h, 67%)
3ha: A: R_1 = 3-CF_3, (12 h, 32%)
3ia: A: R_1 = 4-Me, (5 h, 61%)
3ja: A: R_1 = 4-*t*Bu, (15 h, 73%)
3ka: A: R_1 = 4-Cl, (12 h, 54%)
3va: A: R_1 = 2,4,6-tri-Me, (5.5 h, 85%)

α-phenyl malononitriles



3la: B: R_2 = H, (6 h, 54%)
3ma: B: R_2 = 2-Me, (5 h, 95%)
3na: B: R_2 = 2-F, (50 h, **NR**)
3oa: B: R_2 = 2-OMe, (8 h, 77%)
3pa: B: R_2 = 3-OMe, (8 h, 50%)
3qa: B: R_2 = 4-F, (8 h, 59%)
3ra: B: R_2 = 4-Me, (6 h, 54%)
3sa: B: R_2 = 4-OMe, (6 h, 41%)
3ta: B: R_2 = 4-Cl, (6 h, 50%)

other α-substituted malononitriles



[a]Reaction conditions: **1a**–**z**, **1a**′ (1.25 mmol), and $Ph_2P(O)H$ (2.0 equiv) in MeCN (5 mL) were stirred under a constant flow (bubbling) of O_2. Conditions A: K_2CO_3 (2.0 equiv), room temperature. Conditions B: DIEA (2.0 equiv), 50 °C. [b]Isolated yield.

Next, our intent was to apply this oxidative process to more challenging α-phenyl malononitriles **2l**–**2t**, as the previous conditions were not effective for the synthesis of these cyanohydrins. The choice of the appropriate base was crucial, and **3la** was formed in 54% yield once the base was switched from K_2CO_3 to DIEA (Conditions B). The following examinations showed that substrates **2m** and **2o**, bearing electron-donating substituents at the *ortho* position, were well tolerated, while **2n**, with electron-withdrawing substituents, was not suitable for the reaction. However, aromatic malononitriles with substituents with different electronic demands at the *meta* or *para* positions showed similar reactivities and gave corresponding products **3pa**–**3ta** in 41% to 59% yields. To our delight, α-naphthol substrate **2a**′ with greater steric hindrance afforded corresponding cyanohydrin derivative **3a**′**a** in 76% yield. In addition, the

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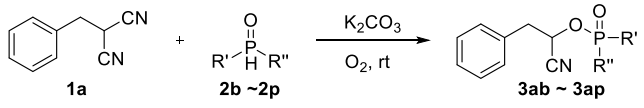
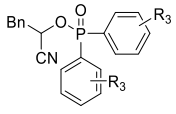
incorporation of heteroarene and alkane moieties is tolerated, and **2w**–**2z** underwent the transformation to produce **3wa**–**3za** in up to 81% yield.

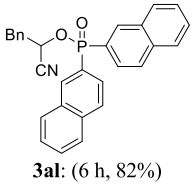
Having established the scope of α-substituted malononitriles **1**, we next screened the scope of diarylphosphine oxides **2b**–**2m** and other organophosphorus compounds **2n**–**2p** (Scheme 2). Only diarylphosphine oxides with an electron-withdrawing

Scheme 2. Oxidation of α-Benzyl Malononitrile 1a in the Presence of Diarylphosphine Oxide 2[a,b]

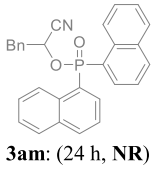




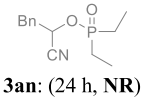
3ab: R_3 = 4-OMe, (3.5 h, 20%)
3ac: R_3 = 4-F, (4 h, 70%)
3ad: R_3 = 4-Br, (4 h, 60%)
3ae: R_3 = 4-N(CH_3)$_2$, (6 h, **NR**)
3af: R_3 = 4-Ph, (48 h, 55%)
3ag: R_3 = 3-Me, (6.5 h, 44%)
3ah: R_3 = 3-F, (6 h, 24%)
3ai: R_3 = 3-Cl, (10 h, 48%)
3aj: R_3 = 2-Me, (24 h, **NR**)
3ak: R_3 = 2-OMe, (6 h, **NR**)



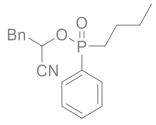
3al: (6 h, 82%)



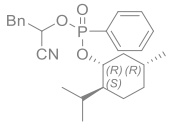
3am: (24 h, **NR**)



3an: (24 h, **NR**)



3ao: (24 h, **NR**)



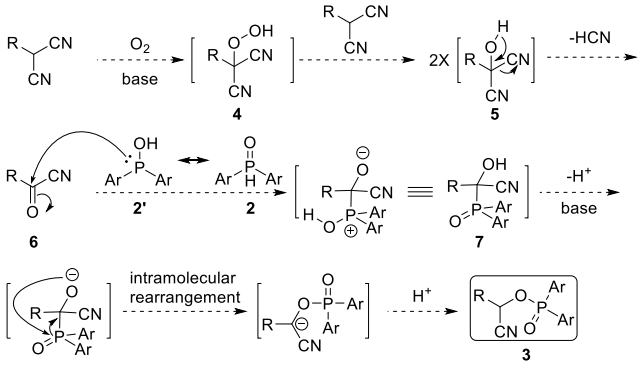
3ap: (24 h, **NR**)

[a]Reaction conditions: **1a** (1.25 mmol), **2b**–**p** (2.0 equiv), and K_2CO_3 (2.0 equiv) in MeCN (5 mL) were stirred under a constant flow (bubbling) of O_2 at room temperature. [b]Isolated yield based on **1a**.

group at the *para* position (**2c**, **2d**, **2f**) or limited group at the *meta* position (**2g**, **2i**) were tolerated in the reaction and gave moderate to good yields. Similarly, compared with unreactive di-α-naphthylphosphine oxide (**2m**), β-naphthyl derivative **2l** gave the desired product in high yield. Unfortunately, **2n**–**2p** were not suitable for the reaction, probably due to inhibition of the p–π conjugation between the phosphorus atom and the benzene ring, which may be critical for the nucleophilicity of the organophosphorus reagent (see Supporting Information for details).

Based on literature reports and our previous work on the α-hydroxylation of β-keto esters, a plausible mechanism for the process is proposed as shown in Scheme 3.[10a−c,13a] Initially, radical insertion of O_2 into an α-C–H bond of malononitrile **1** under basic conditions affords α-hydroperoxide **4**, which can be reduced by another equivalent of **1** to form two equivalents of α-hydroxy malononitrile **5**. Consequently, acyl cyanide intermediate **6** is produced by the elimination of HCN from **5** in the presence of base. For diarylphosphine oxide **2** to tautomerize to the P–OH form (**2′**), the in situ formation of a quaternary carbon center must be accomplished through the nucleophilic addition of phosphinous acid **2′** to acyl cyanide **6**. Finally, an intramolecular exchange through a four-centered

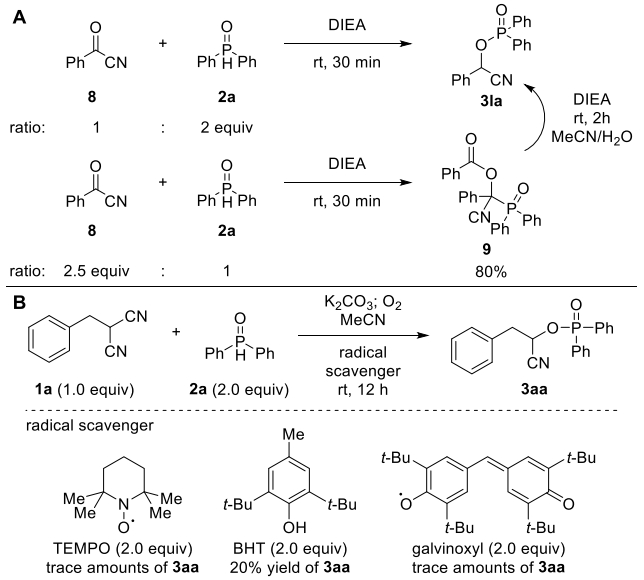
Scheme 3. Proposed Reaction Mechanism



P–C–O–H system results in the formation of the *O*-phosphinoyl cyanohydrin.

Experiments were then carried out to clarify and evaluate the proposed reaction mechanism. First, commercially available benzoyl cyanide **8** was subjected to the standard conditions, and corresponding product **3la** was obtained in 98% yield after 30 min (Scheme 4A). Strikingly, when the amount of benzoyl

Scheme 4. Mechanism Studies



cyanide **8** was increased to 2.5 equiv, benzoyl-protected compound **9** was isolated in 80% yield, and this compound could be readily converted to **3la** under basic conditions in the presence of stoichiometric water. Second, two peaks with a mass-to-charge ratio (m/z) of 348.11 were detected in the LC/MS spectrum (see the Supporting Information). One of the peaks was presumed to be the intermediate **7** (R = Bn). Although the intermediates were not isolated, the proposed mechanism can suitably explain the experimental results. Finally, a series of control experiments were also designed to probe the oxidation process, and the decreased yield of **3aa** in the presence of radical scavenger implied that a radical species might be involved (Scheme 4B).

A multigram-scale reaction of **1a** with **2a** afforded product **3aa** (6.9 g, 20 mmol) in 70% yield, highlighting the good reliability of the bubbling process. To demonstrate the synthetic utility of this transformation, we further elaborated

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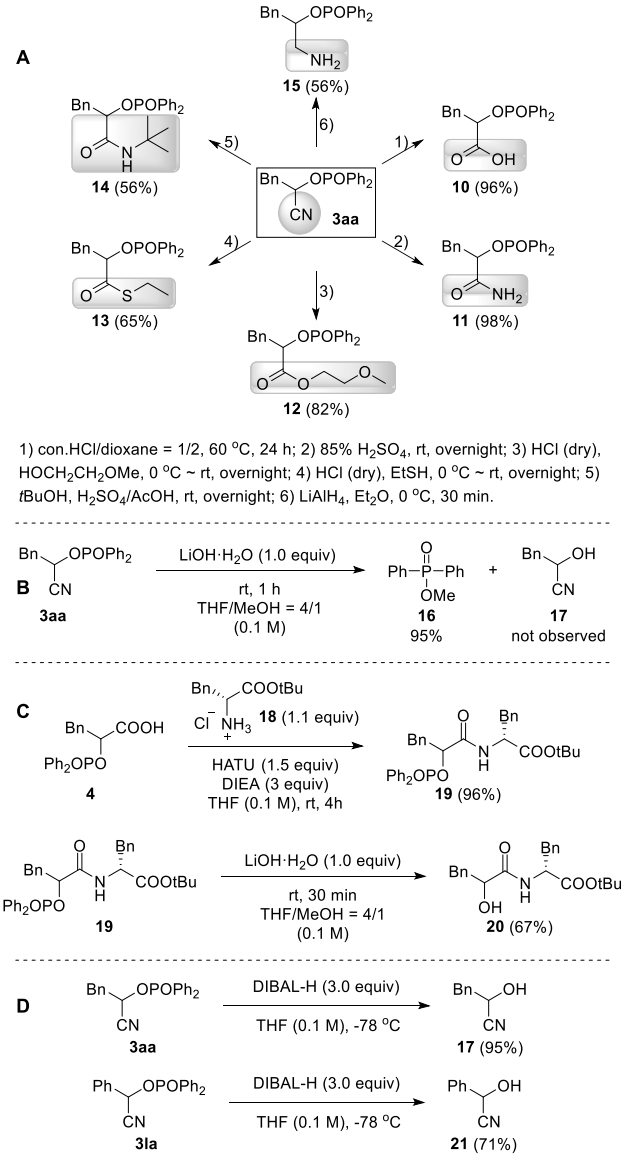
product **3aa** (Scheme 5A). The nitrile group could be selectively hydrolyzed in the presence of hydrochloric acid or sulfuric acid, producing carboxylic acid **10** or amide **11** in excellent yields. Pinner reactions between **3aa** and an alcohol or a thiol to yield ester **12** or thioether **13** were successfully conducted. In addition, **3aa** reacted well with a tertiary alcohol in a Ritter reaction, resulting in the formation of *N*-*tert*-alkylamide **14** in 56% yield. In addition, **3aa** was readily reduced to afford primary amine **15** in 56% yield upon exposure to $LiAlH_4$, and the phosphinoyl group was not affected by this reaction.

Scheme 5. Elaboration of Product 3aa and Deprotection of the *O*-Phosphinoyl Cyanohydrins



Finally, we focused on developing an efficient method to cleave the diphenylphosphinoyl group. The base-catalyzed alcoholysis of **3aa** in THF/methanol afforded methyl diphenylphosphinate **16** in high yield, but the expected cyanohydrin **17** was not detected (Scheme 5B). We speculated that base-accelerated elimination of HCN led to the failure of the alcoholysis. With respect to the alcoholysis strategy, carboxyl-protected amino acid **18** was initially coupled with nitrile derivatization product **10**, and deprotection of the diphenylphosphinoyl group was performed with LiOH in a THF/MeOH solution to give compound **20** in a total yield of 64% from **3aa** (Scheme 5C).[15] To our delight, we also established a straightforward method of accessing the free hydroxyl group by breaking the P−O bond. The partial reduction of a nitrile group with diisobutylaluminum hydride (DIBAL-H) at a low temperature (~40 °C) affords an aldehyde. However, the treatment of **3aa** or **3la** with excess DIBAL-H at −78 °C resulted in the formation of cyanohydrins **17** and **21** in high yields with the nitrile functionality intact (Scheme 5D).

In conclusion, we have developed an aerobic redox strategy for the synthesis of *O*-phosphinoyl cyanohydrins under mild reaction conditions using α-substituted malononitriles as the nitrile source and diarylphosphine oxides as the reducing agents. Importantly, this approach is different from conventional cyanohydrin syntheses. Mechanistic studies supported that the mild process involves a radical oxidation, the generation of a quaternary carbon center, and an intramolecular rearrangement. Finally, the phosphinoyl substituent is demonstrated to be a convenient protecting group. Given the utility of O-protected cyanohydrins, we anticipate that this approach will facilitate the construction of this important and challenging moiety in synthetic applications. Further studies on an asymmetric catalyst system are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00569.

Experimental details, analytical data, and ^{1}H, ^{13}C, and ^{31}P NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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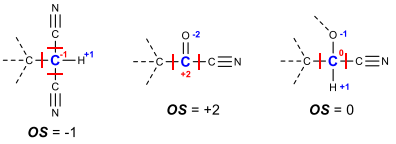
■ REFERENCES

(1) For representative reviews, see: (a) Chen, F. X.; Feng, X. M. *Synlett* **2005**, *2005*, 892−899. (b) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555−1564. (c) Brunel, J. M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752−2778. (d) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146−5226. (e) Bracco, P.;

DOI: 10.1021/acs.orglett.9b00569
Org. Lett. XXXX, XXX, XXX−XXX

Busch, H.; von Langermann, J.; Hanefeld, U. *Org. Biomol. Chem.* **2016**, *14*, 6375−6389.
(2) (a) Rad, N.; Makosza, M. *Eur. J. Org. Chem.* **2018**, *2018*, 376−380. (b) Yoneyama, H.; Numata, M.; Uemura, K.; Usami, Y.; Harusawa, S. *J. Org. Chem.* **2017**, *82*, 5538−5556. (c) Yoneda, N.; Fujii, Y.; Matsumoto, A.; Asano, K.; Matsubara, S. *Nat. Commun.* **2017**, DOI: 10.1038/s41467-017-01099-x. (d) Du, S. T.; Sun, Z.; Liu, W.; Liao, W. W. *Org. Lett.* **2017**, *19*, 6598−6601. (e) Turnbull, B. W. H.; Oliver, S.; Evans, P. A. *J. Am. Chem. Soc.* **2015**, *137*, 15374−15377.
(3) Liang, Q.-J.; Jiang, B.; Xu, Y.-H.; Loh, T.-P. *J. Org. Chem.* **2018**, *83*, 8265−8271.
(4) (a) Chang, H. K.; Shin, M. S.; Yang, H. Y.; Lee, J. W.; Kim, Y. S.; Lee, M. H.; Kim, J.; Kim, K. H.; Kim, C. J. *Biol. Pharm. Bull.* **2006**, *29*, 1597−1602. (b) Cioni, J. P.; Doroghazi, J. R.; Ju, K. S.; Yu, X. M.; Evans, B. S.; Lee, J.; Metcalf, W. W. *J. Nat. Prod.* **2014**, *77*, 243−249. (c) Mitchell, B. L.; Bhandari, R. K.; Bebarta, V. S.; Rockwood, G. A.; Boss, G. R.; Logue, B. A. *Toxicol. Lett.* **2013**, *222*, 83−89. (d) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597−606. (e) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649−3682.
(5) (a) Peterson, C. J.; Tsao, R.; Coats, J. R. *Pest Manage. Sci.* **2000**, *56*, 615−617. (b) Park, D. S.; Coats, J. R. *J. Pestic. Sci.* **2005**, *30*, 99−102.
(6) Zhai, Y. Y.; Zhao, X. S.; Cui, Z. J.; Wang, M.; Wang, Y. X.; Li, L. F.; Sun, Q.; Yang, X.; Zeng, D. B.; Liu, Y.; Sun, Y. N.; Lou, Z. Y.; Shang, L. Q.; Yin, Z. *J. Med. Chem.* **2015**, *58*, 9414−9420.
(7) (a) Chang, J.; Zhang, Y. *Process Biochem.* **2012**, *47*, 195−200. (b) Ramalho, R. T.; Aydos, R. D.; Schettert, I.; de Assis, P. V.; Cassino, P. C. *Acta. Cir. Bras.* **2013**, *28*, 728−732.
(8) Kurono, N.; Ohkuma, T. *ACS Catal.* **2016**, *6*, 989−1023.
(9) Cioc, R. C.; Schuckman, P.; Preschel, H. D.; Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Org. Lett.* **2016**, *18*, 3562−3565.
(10) (a) Wang, Y. K.; Zheng, Z. H.; Lian, M. M.; Yin, H.; Zhao, J. N.; Meng, Q. W.; Gao, Z. X. *Green Chem.* **2016**, *18*, 5493−5499. (b) Lian, M. M.; Li, Z.; Cai, Y. C.; Meng, Q. W.; Gao, Z. X. *Chem. - Asian J.* **2012**, *7*, 2019−2023. (c) Wang, Y. K.; Yin, H.; Tang, X. F.; Wu, Y. F.; Meng, Q. W.; Gao, Z. X. *J. Org. Chem.* **2016**, *81*, 7042−7050. (d) Bryliakov, K. P. *Chem. Rev.* **2017**, *117*, 11406−11459.
(11) α-Substituted malononitriles are readily prepared from obtainable malononitrile or by dehydration of malonodiamide derivatives, without using toxic HCN or metal cyanides. For representative reviews and preparations on malononitriles, see: (a) Freeman, F. *Chem. Rev.* **1969**, *69*, 591−624. (b) Fatiadi, A. J. *Synthesis* **1978**, *1978*, 165−204. (c) Freeman, F. *Synthesis* **1981**, *1981*, 925−954. (d) Suzuki, H.; Kobayashi, T.; Osuka, A. *Chem. Lett.* **1983**, *12*, 589−590. (e) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932−933. (f) Uno, M.; Seto, K.; Masuda, M.; Ueda, W.; Takahashi, S. *Tetrahedron Lett.* **1985**, *26*, 1553−1556.
(12) For selected examples, see: (a) Adamson, N. J.; Wilbur, K. C. E.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 2761−2764. (b) Jang, D. O.; Kim, D. D.; Pyun, D. K.; Beak, P. *Org. Lett.* **2003**, *5*, 4155−4157. (c) Ohwada, T.; Kojima, D.; Kiwada, T.; Futaki, S.; Sugiura, Y.; Yamaguchi, K.; Nishi, Y.; Kobayashili, Y. *Chem. - Eur. J.* **2004**, *10*, 617−626. (d) Kitson, P. J.; Parenty, A. D. C.; Richmond, C. J.; Long, D. L.; Cronin, L. *Chem. Commun.* **2009**, 4067−4069. (e) Dickmeiss, G.; Jensen, K. L.; Worgull, D.; Franke, P. T.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1580−1583. (f) Muresan, N. M.; Willkomm, J.; Mersch, D.; Vaynzof, Y.; Reisner, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 12749−12753. (g) Turner, T. C.; Shibayama, K.; Boger, D. L. *Org. Lett.* **2013**, *15*, 1100−1103. (h) Chang, S.; Hur, S.; Britton, R. *Chem. - Eur. J.* **2015**, *21*, 16646−16653. (i) Huang, X.; Wu, S. Z.; Wu, W. T.; Li, P. B.; Fu, C. L.; Ma, S. M. *Nat. Commun.* **2016**, DOI: 10.1038/ncomms12382. (j) Chen, X. Y.; Li, S.; Liu, Q.; Kumar, M.; Peuronen, A.; Rissanen, K.; Enders, D. *Chem. - Eur. J.* **2018**, *24*, 9735−9738.
(13) (a) Li, J.; Lear, M. J.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 9060−9064. (b) Forster, S.; Tverskoy, O.; Helmchen, G. *Synlett* **2008**, *2008*, 2803−2806.
(14) The oxidation state (OS) of an atom is the charge of this atom after ionic approximation of its heteronuclear bonds. See IUPAC. *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book"); Blackwell Scientific Publications: Oxford, 1997. http://goldbook.iupac.org. DOI: 10.1351/goldbook.O04365.



(15) Compound **20** has the structural feature of the Aeruginosin family. For review, see: Ersmark, K.; Del Valle, J. R.; Hanessian, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 1202−1223.

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