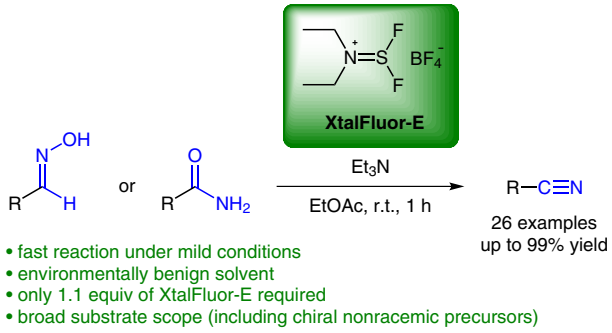
Synthesis M. Keita et al. Paper

Synthesis of Nitriles from Aldoximes and Primary Amides Using XtalFluor-E

Massaba Keita
Mathilde Vandamme
Jean-François Paquin*

CCVC, PROTEO, Canada Research Chair in Organic and Medicinal Chemistry, Département de Chimie, Université Laval, 1045 Avenue de la Médecine, Québec, QC, G1V 0A6, Canada
jean-francois.paquin@chm.ulaval.ca



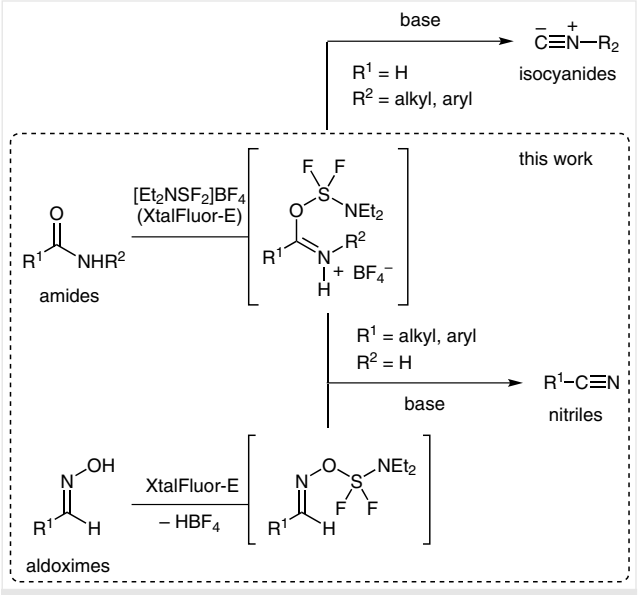
Received: 23.06.2015
Accepted after revision: 14.07.2015
Published online: 20.08.2015
DOI: 10.1055/s-0034-1378881; Art ID: ss-2015-m0394-op

Abstract The dehydration reaction of aldoximes and amides for the synthesis of nitriles using $[Et_2NSF_2]BF_4$ (XtalFluor-E) is described. Overall, the reaction proceeds rapidly (normally <1 h) at room temperature in an environmentally benign solvent (EtOAc) with only a slight excess of the dehydrating agent (1.1 equiv). A broad scope of nitriles can be prepared, including chiral nonracemic ones. In addition, in a number of cases, further purification of the nitrile after the workup was not required.

Key words nitriles, aldoximes, amides dehydration, XtalFluor-E

Nitriles are key building-blocks in organic synthesis.[1] In addition, a number of pharmaceuticals or natural products contain this functional group.[2,3] Due to their importance, numerous approaches have been published recently.[4] Nonetheless, the main synthetic route remains arguably the dehydration of a suitable precursor. To that effect, numerous protocols have been reported over the past years using either aldoximes[5] or primary amides[6] as starting materials. However, most of these suffer from one or multiple drawbacks including high temperature and/or the use of an excess of the dehydration reagent (>2 equiv). Finally, only a few methods are mild enough to allow the synthesis of chiral nonracemic nitriles.[7]

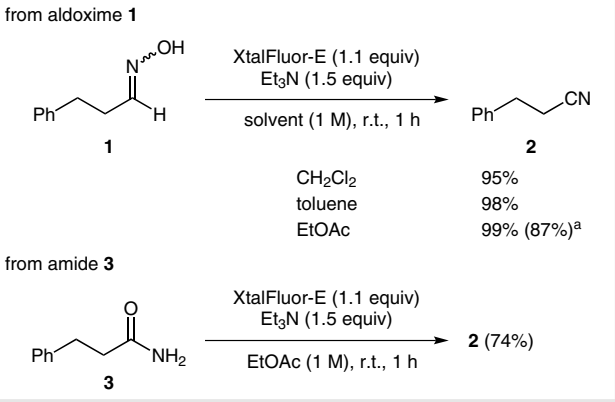
We have recently reported the use of diethylaminodifluorosulfinium tetrafluoroborate ($[Et_2NSF_2]BF_4$, XtalFluor-E),[8] a crystalline solid initially developed as a deoxofluorinating agent with enhanced thermal stability, for the synthesis of various isocyanides through the dehydration of formamides.[9] We envisioned that if primary amides or aldoximes were used as the starting substrate instead, upon activation with XtalFluor-E and in the presence of a base, nitriles would be obtained (Scheme 1). Herein, we report this transformation. Overall, the reaction proceeds rapidly at room temperature in an environmentally benign solvent with only a slight excess of the dehydrating agent. In a number of cases, further purification of the nitrile after the workup is not necessary. Finally, this method has a large scope, allowing the synthesis of aromatic, vinylic, aliphatic, and benzylic nitriles including chiral nonracemic ones and tolerates typical oxygen or nitrogen protecting groups.



Scheme 1 Activation of amides and aldoximes with XtalFluor-E for the synthesis of nitriles

The initial tests were performed using aldoxime **1**, derived from hydrocinnamaldehyde, using the conditions developed for the synthesis of isocyanides (Scheme 2).[9] Gratifyingly, performing the reaction at room temperature instead of –40 °C provided within one hour reaction time, the

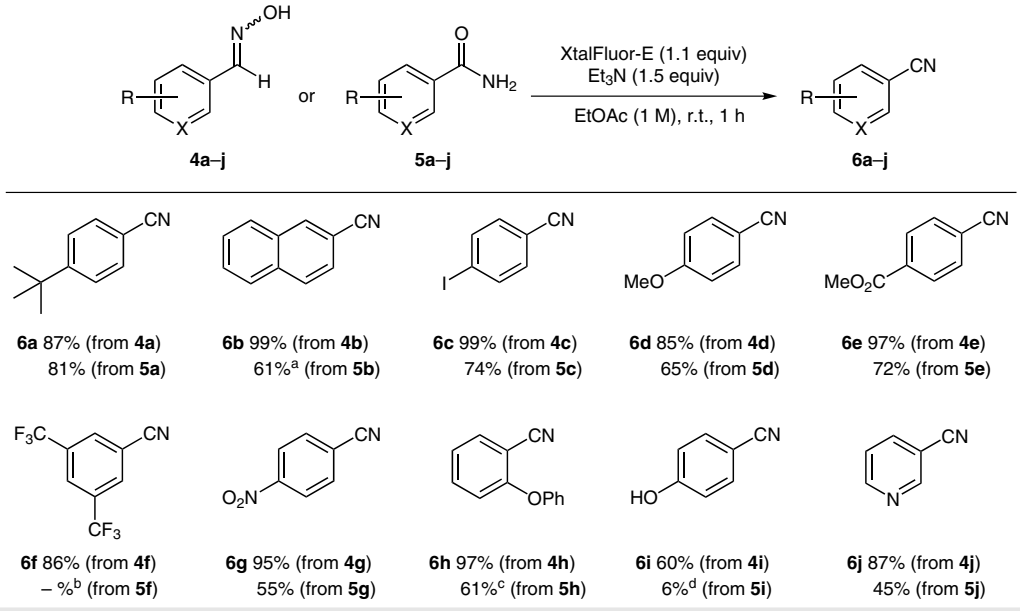
desired nitrile **2** in 95% yield. At this point, since CH_2Cl_2 has been identified as an undesirable solvent by various pharmaceutical solvent selection guides,[10] the use of alternative and potentially greener solvents was investigated. Both toluene and EtOAc furnished **2** in excellent yields (98% and 99%, respectively). Notably, the reaction could also be performed on a larger scale (6.7 mmol of **1**) with similar yield. With slightly better metrics,[10] EtOAc was chosen as the optimal solvent. The use of the corresponding primary amide, **3**, provided, under the same reaction conditions, the nitrile **2** in 74% yield (Scheme 2). A better yield of 90% could be obtained in CH_2Cl_2. Nonetheless, EtOAc was kept as the solvent for the rest of the studies.



Scheme 2 Initial results for the dehydration of **1** and **3** using XtalFluor-E. [a] Reaction was performed on 6.7 mmol scale (i.e., 1.0 g) of **1**.

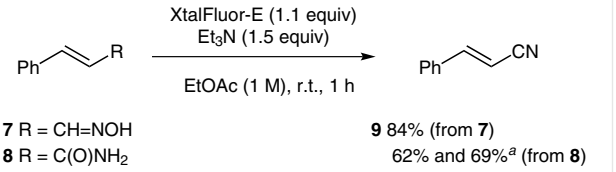
Nearly identical results being obtained from both starting materials, the scope of this reaction was studied in a comparative fashion to identify the strengths and weaknesses of each precursor (i.e., aldoximes vs primary amides) for the various classes of substrates.

First, the synthesis of aromatic nitriles was examined (Scheme 3). The reaction proceeded well with both aldoximes and primary amides, though the yields were always better for the former (6–42% higher). Higher nucleophilicity of the aldoxime oxygen (not conjugated with the aromatic ring) as opposed to the amide, which is conjugated with the aromatic ring, may account for the difference of reactivity in some cases. Overall, both electron-withdrawing and electron-donating groups were tolerated regardless of their position. Interestingly, a free phenol was tolerated and nitrile **6i** was obtained in 60% from the corresponding aldoxime. In this case, the reaction of the primary amide provided a complex mixture of products as shown by NMR analysis of the crude mixture. We hypothesized that the phenol competes with the less nucleophilic amide for the XtalFluor-E reagent, thus leading to undesirable products. In the case of the more nucleophilic aldoxime, this pathway does not compete. Finally, 3-cyanopyridine (**6j**), a heterocyclic nitrile, was obtained from both precursors, although more efficiently from the aldoxime (87% vs 45% from the amide). Practically, while most of the nitriles generated from primary amides required purification by flash chromatography, the majority of those generated from the aldoximes did not.



Scheme 3 Synthesis of aromatic nitriles **6** from aldoximes **4** or primary amides **5**. [a] The reaction was run in toluene for 4 h. [b] The yield could not be determined as the desired product co-eluted with an unidentified side-product. Overlaps in the NMR spectrum prevented the estimation of an NMR yield. [c] The reaction time was 5 h. [d] The crude ^{1}H NMR spectrum shows multiple unidentified products.

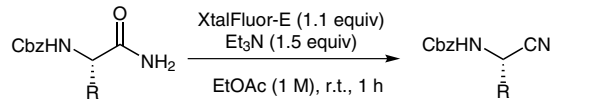
The synthesis of a vinyl nitrile, **9**, proceeded both from the aldoxime **7** or the primary amide **8**, but a higher yield was observed with the former (Scheme 4). Here again, the reaction could be performed on a larger scale (13.6 mmol of **8**) with a similar result.



Scheme 4 Synthesis of vinyl nitrile **9** from cinnamic acid derivatives **7** and **8**. [a] Reaction was performed on a 13.6 mmol scale (i.e, 2.0 g) of **8**.

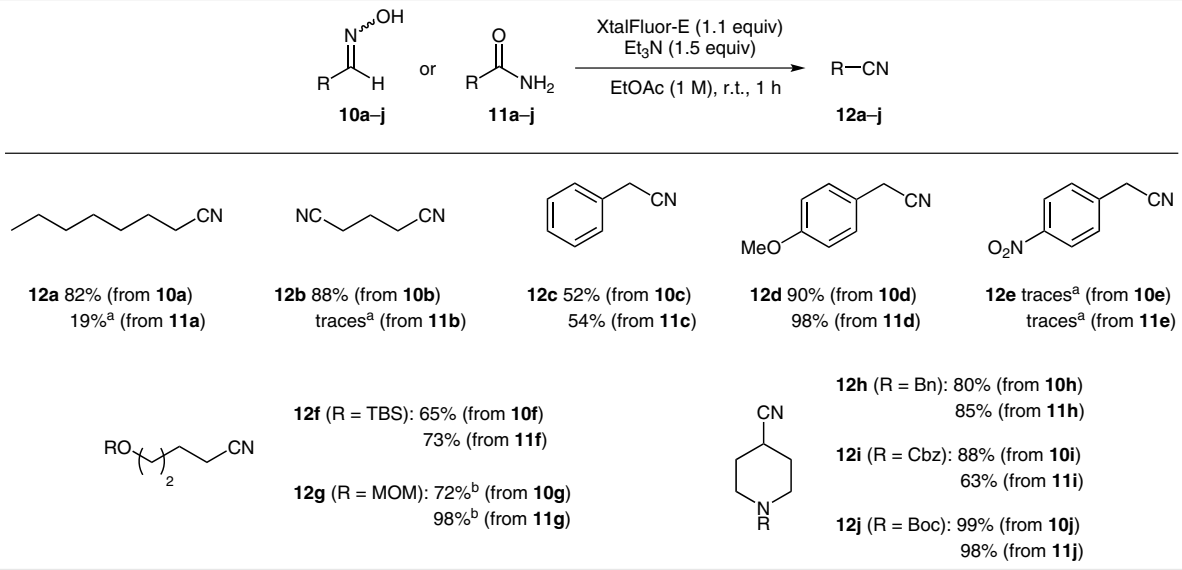
Our attention was then turned to the synthesis of aliphatic nitriles (Scheme 5). In this series, the difference of reactivity between both precursors is less obvious. For instance, the synthesis of caprylonitrile (**12a**) and glutaronitrile (**12b**) proceeded well from the aldoximes, but poorly from the amides. On the other hand, better yields were obtained from the amides for some nitriles (e.g., **12d**, **12f**, **12g**). Benzylic nitriles **12c**,**d** can be prepared from both precursors although in the case of the nitro-containing precursors, the crude NMR spectrum shows multiple nonidentified products. Acid-labile alcohol protecting groups such as TBS or MOM are well tolerated. Finally, a series of protected piperidines were tested and showed that benzyl, Cbz, and Boc protecting groups are all tolerated under those reaction conditions.

Considering the challenge that represents the synthesis of chiral nonracemic aliphatic nitriles,[7] we then investigated, whether or not, this methodology could be applied for their preparation. Initially, the use of aldoximes derived from L-valine or L-phenylalanine was considered. Unfortunately, under our conditions, none of them provided the desired nitriles and a complex mixture was obtained in both cases. Unexpectedly, but fortunately, the use of primary amides derived from L-valine (**13**) or L-phenylalanine (**14**) as the precursor allowed for the synthesis of the corresponding nitriles (Scheme 6).[11,12] In all cases, no erosion of the enantiomeric purity was observed by chiral HPLC analyses. The reaction was also possible with the threonine-derived amide **15**, although in this case the use of CH_2Cl_2 as the solvent was required to obtain the nitrile **18** in good yield. Interestingly, some of these nitriles have been used as synthetic precursors for various value-added products.[12,13]

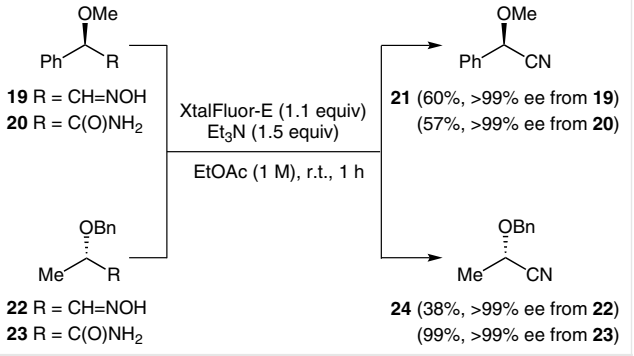


Scheme 6 Synthesis of chiral nonracemic nitriles from primary amides derived from protected amino acids. [a] Reaction was performed in CH_2Cl_2 for 2 h instead.

The synthesis of chiral nitriles was then extended to L-mandelic acid and L-lactic acid derivatives (Scheme 7). The desired nitriles **21**[14] and **24**[15–17] were obtained in moderate to excellent yields (38–99%) from both precursors. Again, in all cases, no erosion of the enantiomeric purity was observed by chiral HPLC analyses.



Scheme 5 Synthesis of aliphatic nitriles **12** from aldoximes **10** or primary amides **11**. [a] The crude ^{1}H NMR spectrum shows multiple unidentified products. [b] Crude yield.



Scheme 7 Synthesis of chiral nonracemic nitriles from L-mandelic acid and L-lactic acid derivatives

In conclusion, we have described the dehydration reaction of aldoximes and amides for the synthesis of nitriles using XtalFluor-E. The reaction normally proceeds within one hour at room temperature in EtOAc, an environmentally benign solvent, with only a slight excess of the dehydrating agent. In a number of cases, further purification of the nitrile after the workup is not necessary. Finally, this method has a large scope, allowing the synthesis of aromatic, vinylic, aliphatic, and benzylic nitriles including chiral nonracemic ones and tolerates standard oxygen or nitrogen protecting groups.

All reactions were carried out under an argon atmosphere with anhydrous solvents under anhydrous conditions. Unless otherwise noted, all commercial reagents were used without further purification. TLC analysis of reaction mixtures was visualized under UV (λ = 254 nm) or by staining with a $KMnO_4$ solution followed by heating. ^1H, ^{13}C and ^{19}F spectra were respectively recorded at 500, 125, and 470 MHz using $CDCl_3$ or DMSO-d_6 as the solvent at ambient temperature using TMS (^1H and ^{13}C NMR) or residual solvent (^1H and ^{13}C NMR) as the internal standards. Standard abbreviations are used to denote the multiplicities. Coupling constants *J* (Hz) were taken directly from the spectra and are not averaged. High-resolution mass spectra were obtained using electrospray ionization (ESI) on a time-of-flight (TOF) spectrometer. Melting points were obtained on a melting point apparatus with open capillary tubes and are uncorrected. IR spectra were measured on a FT-IR spectrometer. Optical rotation was recorded on a digital polarimeter with a sodium lamp at ambient temperature. Amides **5c**, **5d**, **5f**, **5g**, **5i**, **5j**, **8**, and **11d** were obtained from commercial sources and used as received.

Aldoximes; General Procedure

To a solution of the aldehyde in CH_2Cl_2 (0.2 M) was added hydroxylamine hydrochloride (2.0 equiv) and Et_3N (4.2 equiv) and the mixture was stirred at r.t. for 16 h. The reaction was quenched with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with aq 1 M HCl, dried ($MgSO_4$), and concentrated to give the crude aldoxime, which was purified by flash chromatography. The known aldoximes **1**,[18] **4a**,[5i] **4b**,[19] **4c**,[20] **4d**,[18] **4e**,[21] **4f**,[22] **4g**,[18] **4h**,[23] **4i**,[24] **4j**,[20] **7**,[25] **10a**,[25] **10b**,[26] **10c**,[18] **10d**,[27] **10e**,[27] **10f**,[28] **10j**,[5i] and **19**[29] were synthesized following the general procedure described above.

5-(Methoxymethoxy)pentanal Oxime (10g)

5-(Methoxymethoxy)pentanoate: To a mixture of methyl 5-hydroxypentanoate[30] (2.0 g, 15.1 mmol, 1.0 equiv) and *i*-Pr_2NEt (7.90 mL, 45.3 mmol, 3.0 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added chloromethyl methyl ether (3.4 mL, 45.3 mmol, 3 equiv). The reaction mixture was stirred at r.t. for 16 h, diluted with Et_2O, washed with H_2O, sat. aq NH_4Cl and brine, dried (Na_2SO_4), and concentrated to afford methyl 5-(methoxymethoxy)pentanoate as a yellow oil; yield: 2.46 g (92%).

IR (ATR, ZnSe): 2949, 1736, 1437, 1358 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.61 (s, 2 H), 3.67 (s, 3 H), 3.54 (t, *J* = 7.4 Hz, 2 H), 3.36 (s, 3 H), 2.36 (t, *J* = 7.4 Hz, 2 H), 1.76–1.69 (m, 2 H), 1.63–1.61 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.9, 96.4, 67.2, 55.1, 51.5, 33.7, 29.1, 21.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}N_2O$: 219.1492; found: 219.1493.

To a solution of methyl 5-(methoxymethoxy)pentanoate (1.0 g, 5.6 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at –78 °C was added dropwise DIBAL-H (8.4 mL, 1.5 equiv, 1 M in toluene). The resulting solution was stirred at –78 °C for 2 h. The reaction was quenched with MeOH (20 mL) and sat. aq Rochelle's salt solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. To a solution of the resulting crude product in CH_2Cl_2 (15 mL) was added hydroxylamine hydrochloride (778 mg, 11.2 mmol) and Et_3N (3.3 mL, 23.8 mmol). The mixture was stirred at r.t. for 16 h. The reaction was quenched with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with aq 1 M HCl, dried ($MgSO_4$), and concentrated to give the crude product. The residue was purified by silica gel chromatography, eluting with hexane–EtOAc (7:3), to give **10g** as a colorless oil; yield: 365 mg (40%); R_f = 0.15 (hexane–EtOAc, 7:3; SiO_2).

IR (ATR, ZnSe): 3351, 2933, 1441, 1387 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.88 (br s, 0.5 H), 8.45 (br s, 0.5 H), 7.42 (td, *J* = 6.1, 1.4 Hz, 0.5 H), 6.72 (td, *J* = 6.1, 1.2 Hz, 0.5 H), 4.61 (s, 2 H), 3.59–3.47 (m, 2 H), 3.49–3.01 (m, 3 H), 2.43 (m, 1 H), 2.24 (tdd, *J* = 7.3, 6.1, 1.2 Hz, 1 H), 1.74–1.52 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.4, 151.8, 96.4, 67.2, 55.1, 29.4, 29.2, 29.1, 24.6, 23.3, 22.8.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_7H_{15}NO_3Na$: 184.0944; found: 184.0878.

1-Benzylpiperidine-4-carbaldehyde Oxime (10h)

A solution of *tert*-butyl 4-[(hydroxyimino)methyl]piperidine-1-carboxylate[5i] (300 mg, 1.3 mmol, 1.0 equiv) in HCl–1,4-dioxane (10 mL, 4 M solution) was stirred at r.t. for 2 h and the solvent was evaporated. A mixture of the resulting crude amine hydrochloride, benzaldehyde (148 µL, 1.4 mmol, 1.1 equiv), Et_3N (454 µL, 3.2 mmol, 2.5 equiv), and $MgSO_4$ (313 mg, 2.0 equiv) in CH_2Cl_2 (15 mL) was stirred at r.t. for 16 h. The CH_2Cl_2 was evaporated and the residue was dissolved in MeOH (10 mL). $NaBH_4$ (49 mg, 1.3 mmol, 1.0 equiv) was then added and the mixture was stirred at r.t. for 1 h. The reaction was quenched with H_2O, the solvent was evaporated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give the crude product, which was purified by chromatography using hexane–EtOAc (1:1) as the eluent to give **10h** as a white solid; yield: 153 mg (54%); mp 85–88 °C; R_f = 0.1 (hexane–EtOAc, 1:1; SiO_2).

IR (ATR, ZnSe): 3061, 2920, 2818, 2767, 1496, 1449, 1395 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.13 (m, 6 H), 6.58 (d, *J* = 7.1 Hz, 0.5 H), 3.52 (s, 2 H), 2.99–2.84 (m, 2 H), 2.22 (m, 1 H), 2.10–2.01 (m, 2 H), 1.77–1.74 (m, 2 H), 1.69–1.56 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.0, 138.0, 129.3, 128.2, 127.1, 63.4, 53.0, 52.8, 36.7, 29.3, 28.67.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}N_2O$: 219.1445; found: 219.1431.

Benzyl 4-[(Hydroxyimino)methyl]piperidine-1-carboxylate (10i)

To a solution of benzyl 4-formylpiperidine-1-carboxylate[31] (850 mg, 3.4 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added hydroxylamine hydrochloride (474 mg, 6.8 mmol, 2.0 equiv) and Et_3N (2 mL, 14.5 mmol, 4.2 equiv). The mixture was stirred at r.t. for 16 h. The reaction was quenched with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with aq 1 M HCl, dried ($MgSO_4$), and concentrated to give the crude product. The residue was purified by chromatography using hexane–EtOAc (6:4) as the eluent to give **10i** as a colorless oil; yield: 851 mg (95%); R_f = 0.4 (hexane–EtOAc, 6:4; SiO_2).

IR (ATR, ZnSe): 3342, 2940, 2856, 1671, 1497, 1429, 1362 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (s, 0.5 H), 7.99 (s, 1 H), 7.59–7.26 (m, 5 H), 6.55 (d, *J* = 6.9 Hz, 0.5 H), 5.14 (s, 2 H), 4.29–4.01 (m, 2 H), 2.90 (br s, 2 H), 2.43 (m, 1 H), 1.80 (br s, 2 H), 1.49–1.47 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 128.0, 127.9, 67.2, 43.4, 36.6, 32.0, 29.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}N_2O_3$: 263.1343; found: 263.1323.

(*S*)-2-(Benzyloxy)propanal Oxime (22)

To a solution of ethyl (*S*)-2-(benzyloxy)propanoate[32] (700 mg, 3.4 mmol, 1.0 equiv) in Et_2O (10 mL) at –78 °C was added dropwise DIBAL-H (1 M in toluene) (4.0 mL, 1.2 equiv). The resulting solution was stirred at –78 °C for 2 h. The reaction was quenched with H_2O and the organic layer was washed with sat. aq $NaHCO_3$, brine and H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. To a solution of the crude product in CH_2Cl_2 (35 mL) was added hydroxylamine hydrochloride (467 mg, 6.7 mmol, 2.0 equiv) and pyridine (1.1 mL, 13.4 mmol, 4.0 equiv) and the mixture stirred at r.t. for 16 h. The reaction was quenched with aq 1 M HCl and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude product, which was purified by chromatography using hexane–EtOAc (6:4) as the eluent to give **22** as a colorless oil; yield: 275 mg (46% over 2 steps); R_f = 0.21 (hexane–EtOAc, 9:1; SiO_2).

IR (ATR, ZnSe): 3320, 2978, 2869, 1749, 1496, 1454, 1324 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.78 (s, 0.25 H), 9.61 (s, 0.75 H), 7.48 (d, *J* = 7.5 Hz, 0.75 H), 7.43–7.33 (m, 5 H), 6.95 (d, *J* = 6.1 Hz, 0.25 H), 4.92 (m, 0.25 H), 4.60 (dd, *J* = 45.2, 11.7 Hz, 0.5 H), 4.60 (dd, *J* = 62.5, 11.8 Hz, 1.5 H), 4.22 (dq, *J* = 7.4, 6.6 Hz, 0.75 H), 1.45 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.9, 152.9, 137.8, 137.8, 128.5, 128.0, 128.0, 128.0, 127.9, 72.2, 71.6, 70.8, 68.3, 19.5, 17.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{13}NO_2$: 180.1019; found: 180.1024.

Amides; General Procedure

A 0.2 M solution of the corresponding methyl ester in aq NH_4OH (28–30%) was stirred at r.t. for 16 h. The solvent was evaporated to afford the amide, which was, in some cases, purified by silica gel chromatography. The known amides **3**,[33] **5a**,[34] **5b**,[6c] **5h**,[35] **11a**,[36] **11b**,[37] **11c**,[36] **11e**,[38] **11h**,[4] **11i**,[39] **11j**,[39] **13**,[40] **14**,[41] **20**,[42] and **23**[43] were synthesized following the general procedure described above. Compound **5e** was synthesized following the literature.[44]

5-[(*tert*-Butyldimethylsilyl)oxy]pentanamide (11f)

Following the general procedure on a 3.2 mmol scale, **11f** was isolated after purification by silica gel chromatography (CH_2Cl_2–MeOH, 95:5) as a white solid; yield: 167 mg (23%); mp 39–41 °C; R_f = 0.38 (CH_2Cl_2–MeOH, 95:5; SiO_2).

IR (ATR, ZnSe): 3356, 3189, 2953, 2857, 1661, 1471, 1389 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.21 (s, 1 H), 6.68 (s, 1 H), 3.56 (t, *J* = 6.3 Hz, 2 H), 2.02 (t, *J* = 7.3 Hz, 2 H), 1.59–1.36 (m, 4 H), 0.85 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 174.6, 62.7, 35.2, 32.4, 26.3, 22.0, 18.4, –4.8.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{25}NO_2SiNa$: 254.1547; found: 254.1549.

5-(Methoxymethoxy)pentanamide (11g)

Following the general procedure on a 2.8 mmol scale, **11g** was isolated as a yellow oil, which was used without purification; yield: 442 mg (92%).

IR (ATR, ZnSe): 3335, 3206, 2935, 1660, 1404 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 22 (s, 1 H), 6.69 (s, 1 H), 4.53 (s, 2 H), 3.42 (t, *J* = 7.1 Hz, 2 H), 3.23 (s, 3 H), 2.04 (t, *J* = 7.1 Hz, 1 H), 1.54–1.46 (m, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 174.6, 96.0, 67.2, 54.9, 35.2, 29.3, 22.3.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_7H_{15}NO_3Na$: 184.0944; found: 184.0938.

Benzyl [(2*S*,3*R*)-1-Amino-3-methoxy-1-oxobutan-2-yl]carbamate (15)

Methyl (2S,3R)-2-{[(Benzyloxy)carbonyl]amino}-3-methoxybutanoate: To a solution of methyl (2*S*,3*R*)-2-amino-3-methoxybutanoate hydrochloride[45] (280 mg, 1.5 mmol, 1.0 equiv) in THF–H_2O (1:1, 10 mL) was added Na_2CO_3 (318 mg, 3.0 mmol, 2.0 equiv) and benzyl chloroformate (238 μL, 1.7 mmol, 1.1 equiv). The mixture was stirred at r.t. for 16 h. The reaction mixture was quenched with H_2O and extracted with EtOAc to give the crude product after evaporation of the solvent. The crude product was purified by chromatography using hexane–EtOAc (8:2) as the eluent to give methyl (2*S*,3*R*)-2-{[(benzyloxy)carbonyl]amino}-3-methoxybutanoate as a colorless oil; yield: 420 mg (99%); R_f = 0.2 (hexane–EtOAc, 8:2; SiO_2).

IR (ATR, ZnSe): 3432, 3031, 2950, 1720, 1511, 1436, 1317 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.31 (m, 5 H), 5.47 (d, *J* = 9.5 Hz, 1 H), 5.14 (d, *J* = 1.1 Hz, 1 H), 4.35 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.94 (qd, *J* = 6.3, 2.4 Hz, 1 H), 3.77 (s, 3 H), 3.28 (s, 3 H), 1.21 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4, 156.7, 136.3, 128.0, 128.1, 128.0, 127.6, 127.0, 67.0, 65.3, 58.5, 56.8, 52.5, 15.7.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{19}NO_5Na$: 304.1155; found: 304.1154.

Following the general procedure, from methyl (2*S*,3*R*)-2-{[(benzyloxy)carbonyl]amino}-3-methoxybutanoate on a 1.5 mmol scale, amide **15** was isolated as a white solid, which was used without purification; yield: 400 mg (99%); mp 154–155 °C.

IR (ATR, ZnSe): 3370, 3304, 3199, 2979, 2930, 2822, 1660, 1612, 1539, 1422, 1360 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.43–7.25 (m, 5 H), 7.13 (s, 1 H), 7.00 (d, *J* = 9.1 Hz, 1 H), 5.04 (d, *J* = 2.6 Hz, 2 H), 3.97 (dd, *J* = 9.1, 4.5 Hz, 1 H), 3.63 (m, 1 H), 3.21 (s, 3 H), 1.05 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.3, 156.6, 137.5, 128.8, 128.2, 128.0, 76.7, 65.9, 59.3, 56.7, 16.1.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}N_2O_4Na$: 289.1159; found: 289.1159.

Dehydration of Oximes and Amides to Nitriles; General Procedure

To a solution of the aldoxime or the amide (1.0 mmol) and Et_3N (1.5 mmol) in EtOAc (1 mL, 1 M) at r.t. was added XtalFluor-E[8] (1.1 mmol) portionwise over ca. 2 min. The resulting solution was stirred at r.t. for 1 h. The reaction mixture was quenched with sat. aq Na_2CO_3 and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated under vacuum to afford the crude nitrile, which was purified by flash chromatography, if required.

4-(*tert*-Butyl)benzonitrile (6a)

From aldoxime **4a**, nitrile **6a** was isolated as a colorless oil after purification by flash chromatography using hexane–EtOAc (1:1) as the eluent; yield: 139 mg (87%).

From amide **5a**, **6a** was isolated after purification through a pad of silica gel using CH_2Cl_2 as the eluent; yield: 99 mg (81%).

Spectral data for **6a** were identical to those previously reported.[46]

2-Naphthonitrile (6b)

From aldoxime **4b**, nitrile **6b** was isolated as a white solid without further purification; yield: 151 mg (99%).

From amide **5b**, **6b** was isolated after purification by flash chromatography using hexane–EtOAc (1:1) as the eluent; yield: 93 mg (61%).

Spectral data for **6b** were identical to those previously reported.[46]

4-Iodobenzonitrile (6c)

From aldoxime **4c**, nitrile **6c** was isolated as a yellow oil without further purification; yield: 227 mg (99%).

From amide **5c**, **6c** was isolated after purification by flash chromatography using hexane–EtOAc (9:1) as the eluent; yield: 170 mg (74%).

Spectral data for **6c** were identical to those previously reported.[46]

4-Methoxybenzonitrile (6d)

From aldoxime **4d**, nitrile **6d** was isolated as a yellow oil after purification by flash chromatography using hexane–EtOAc (8:2) as the eluent; yield: 113 mg (85%).

From amide **5d**, **6d** was also isolated after purification by flash chromatography using the same eluent; yield: 87 mg (65%).

Spectral data for **6d** were identical to those previously reported.[46]

Methyl 4-Cyanobenzoate (6e)

From aldoxime **4e**, nitrile **6e** was isolated as a brown solid without further purification; 157 mg (97%).

From amide **5e** (0.5 mmol scale), **6e** was also isolated without further purification; yield: 58 mg (72%).

Spectral data for **6e** were identical to those previously reported.[46]

3,5-Bis(trifluoromethyl)benzonitrile (6f)

From aldoxime **4f**, nitrile **6f** was isolated as a yellow oil without further purification; yield: 103 mg (86%).

Spectral data for **6f** were identical to those previously reported.[47]

4-Nitrobenzonitrile (6g)

From aldoxime **4g**, nitrile **6g** was isolated as a yellow solid without further purification; 140 mg (95%).

From amide **5g**, **6g** was isolated after purification by flash chromatography using hexane–EtOAc (9:1) as the eluent; yield: 81 mg (55%).

Spectral data for **6g** were identical to those previously reported.[47]

2-Phenoxybenzonitrile (6h)

From aldoxime **4h**, nitrile **6h** was isolated as a colorless oil after purification by flash chromatography using hexane–EtOAc (9:1) as the eluent; yield: 190 mg (97%).

From amide **5h**, **6h** was also isolated after purification by flash chromatography using the same eluent; yield: 118 mg (61%).

Spectral data for **6h** were identical to those previously reported.[48]

4-Hydroxybenzonitrile (6i)

From aldoxime **4i**, nitrile **6i** was isolated as a colorless oil after purification through a pad of silica gel using CH_2Cl_2 as the eluent; yield: 71 mg (60%).

Spectral data for **6i** were identical to those previously reported.[49]

3-Cyanopyridine (6j)

From aldoxime **4j**, nitrile **6j** was isolated as a pale yellow oil without further purification; yield: 91 mg (87%).

From amide **5j**, **6j** was isolated after purification by flash chromatography using hexane–EtOAc (8:2) as the eluent; yield: 47 mg (45%).

Spectral data for **6j** were identical to those previously reported.[47]

Cinnamonitrile (9)

From aldoxime **7**, nitrile **9** was isolated as a colorless oil after purification by flash chromatography using hexane–EtOAc (1:1) as the eluent; yield: 109 mg (84%).

From amide **8**, **9** was also isolated after purification by flash chromatography using the same eluent; yield: 80 mg (62%).

Spectral data for **9** were identical to those previously reported.[46]

3-Phenylpropanenitrile (2)

From aldoxime **1**, nitrile **2** was isolated as a colorless oil without further purification; yield: 130 mg (99%).

From amide **3**, **2** was isolated after purification by flash chromatography using hexane–EtOAc (9:1) as the eluent; yield: 97 mg (74%).

Spectral data for **2** were identical to those previously reported.[50]

Caprylonitrile (12a)

From aldoxime **10a**, nitrile **12a** was isolated as a yellow oil after purification through a pad of silica gel using CH_2Cl_2 as the eluent; yield: 102 mg (82%).

From amide **11a**, **12a** was isolated after purification by flash chromatography using hexane–EtOAc (95:5) as the eluent; yield: 24 mg (19%).

Spectral data for **12a** were identical to those previously reported.[51]

Glutaronitrile (12b)

From aldoxime **10b**, nitrile **12b** was isolated as a yellow oil after purification through a pad of silica gel using CH_2Cl_2 as the eluent; yield: 83 mg (88%).

Spectral data for **12b** were identical to those previously reported.[52]

2-Phenylacetonitrile (12c)

From aldoxime **10c**, nitrile **12c** was isolated as a yellow oil after purification through a pad of silica gel using CH_2Cl_2 as the eluent, yield: 61 mg (52%).

From amide **11c**, **12c** was isolated after purification by flash chromatography using hexane–EtOAc (9:1) as the eluent; yield: 63 mg (54%).

Spectral data for **12c** were identical to those previously reported.[53]

2-(4-Methoxyphenyl)acetonitrile (12d)

From aldoxime **10d**, nitrile **12d** was obtained as a yellow oil without further purification; yield: 133 mg (90%).

From amide **11d**, **12d** was also obtained without further purification; yield: 144 mg (98%).

Spectral data for **12d** were identical to those previously reported.[54]

5-[(*tert*-Butyldimethylsilyl)oxy]pentanenitrile (12f)

From aldoxime **10f**, nitrile **12f** was obtained as a yellow oil after purification through a pad of silica gel using CH_2Cl_2 as the eluent; yield: 138 mg (65%).

From amide **11f**, **12f** was also obtained after purification through a pad of silica gel using the same eluent; yield: 157 mg (73%).

Spectral data for **12f** were identical to those previously reported.[55]

5-(Methoxymethoxy)pentanenitrile (12g)

From aldoximes **10g**, nitrile **12g** was obtained as a colorless oil after purification through a pad of silica using CH_2Cl_2 as the eluent; yield: 94 mg (67%).

From amide **11g**, **12g** was also obtained after purification through a pad of silica gel using the same eluent; yield: 67 mg (44%).

IR (ATR, ZnSe): 2938, 2245, 1456, 1387 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.62 (s, 1 H), 3.57 (t, *J* = 5.8 Hz, 2 H), 3.36 (s, 3 H), 2.44 (t, *J* = 5.8 Hz, 2 H), 1.87–1.64 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 119.6, 96.4, 66.5, 55.2, 28.6, 22.6, 17.0.

HRMS-ESI: *m*/*z* $[M + H - H_2O]^+$ calcd for $C_7H_{12}NO$: 126.0913; found: 126.0905.

1-Benzylpiperidine-4-carbonitrile (12h)

From aldoxime **10h** (0.5 mmol scale), nitrile **12h** was isolated as colorless oil after purification by flash chromatography using hexane–EtOAc (1:1) as the eluent; yield: 75 mg (80%).

From amide **11h**, **10h** was also isolated after purification by flash chromatography using the same eluent; yield: 171 mg (85%).

Spectral data for **12h** were identical to those previously reported.[56]

Benzyl 4-Cyanopiperidine-1-carboxylate (12i)

From aldoxime **10i**, nitrile **12i** was obtained as a pale yellow oil after purification by flash chromatography using hexane–EtOAc (1:1) as the eluent; yield: 214 mg (88%).

From amide **11i**, **12i** was also obtained after purification by flash chromatography using the same eluent; yield: 154 mg (63%).

Spectral data for **12i** were identical to those previously reported.[5]

***tert*-Butyl 4-Cyanopiperidine-1-carboxylate (12j)**

From aldoxime **10j**, nitrile **12j** was obtained as a yellow oil without further purification; yield: 209 mg (99%).

From amide **11j**, **12j** was also obtained without further purification; yield: 206 mg (98%).

Spectral data for **12j** were identical to those previously reported.[6]

Benzyl (*S*)-(1-Cyano-2-methylpropyl)carbamate (16)

From amide **13**, nitrile **16** was obtained as a yellow oil after purification by flash chromatography using hexane–EtOAc (8:2) as the eluent; yield: 119 mg (51%).

HPLC: Daicel Chiralpak AD-H column; 20 °C, 254 nm, hexane–*i*-PrOH (95:5), 1 mL/min; t_R = 14.7 min; >99% ee.

Spectral data for **16** were identical to those previously reported.[7a]

Benzyl (*S*)-(1-Cyano-2-phenylethyl)carbamate (17)

Fom amide **14** (0.5 mmol scale), nitrile **17** was obtained as a pale yellow oil after purification by flash chromatography using hexane–EtOAc (8:2) as the eluent; yield: 98 mg (70%).

HPLC: Daicel Chiralpak AD-H column; 20 °C, 254 nm, hexane–*i*-PrOH (90:10), 0.8 mL/min; t_R = 13.7 min; >99% ee.

Spectral data for **17** were identical to those previously reported.[8a]

Benzyl [(1*R*,2*R*)-1-Cyano-2-methoxypropyl]carbamate (18)

From amide **15** (0.26 mmol scale), nitrile **18** was obtained as a pale yellow oil after purification through a pad of silica using CH_2Cl_2 as the eluent; yield: 40 mg (62%); $[\alpha]_D^{20}$ –22.5 (*c* 1.0, MeOH).

HPLC: Daicel Chiralpak AD-H column; 20 °C, 254 nm, hexane–*i*-PrOH (95:5), 1 mL/min; t_R = 22.3 min; >99% ee.

IR (ATR, ZnSe): 3316, 2937, 2877, 2251, 1707, 1511, 1454 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.30 (m, 5 H), 5.41 (d, *J* = 9.3 Hz, 1 H), 5.16 (s, 2 H), 4.63 (dd, *J* = 9.3, 2.8 Hz, 1 H), 3.71 (dd, *J* = 6.3, 2.8 Hz, 1 H), 3.44 (s, 3 H), 1.23 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.6, 135.5, 128.6, 128.5, 128.2, 117.7, 76.0, 67.8, 57.4, 47.1, 15.4.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{16}N_2O_3Na$: 271.1053; found: 271.1024.

(*R*)-2-Methoxy-2-phenylacetonitrile (21)

From aldoxime **19** (0.5 mmol scale), nitrile **21** was obtained as a pale yellow oil after purification through a pad of silica using CH_2Cl_2 as the eluent; yield: 44 mg (60%).

From amide **20**, **21** was also isolated after purification through a pad of silica gel using the same eluent; yield: 84 mg (57%).

HPLC: Daicel Chiralpak OJ-H column; 20 °C, 220 nm, hexane–*i*-PrOH (95:5), 1 mL/min; t_R = 11.2 min; >99% ee.

Spectral data for **21** were identical to those previously reported.[12a]

(*S*)-2-(Benzyloxy)propanenitrile (24)

From aldoxime **22** (0.7 mmol scale), nitrile **24** was obtained as a colorless oil after purification by flash chromatography using hexane–EtOAc (95:5) as the eluent; yield: 43 mg (38%).

From amide **23** (0.56 mmol scale), **24** was isolated without further purification; yield: 90 mg (99%).

HPLC: Daicel Chiralpak OJ-H column; 20 °C, 254 nm, hexane–*i*-PrOH (99:1), 1 mL/min; t_R = 16.6 min; >99% ee.

Spectral data for **24** were identical to those previously reported.[57]

Acknowledgment

This work was supported by the Canada Research Chair Program, the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, Fonds de recherche du Québec – Nature et technologies, OmegaChem, and the Université Laval.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378881.

References

(1) Selected reviews/books on the use of nitrile-containing molecules in organic synthesis, see: (a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) *Science of Synthesis: Three Carbon-Heteroatom Bonds: Nitriles, Isocyanides and Derivatives*; Vol. 19; Murahashi, S.-I., Ed.; Georg Thieme Verlag: Stuttgart, **2004**. (c) Ronald, M. R. *Nitriles*, In *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed.; Vol. 17; Othmer, K., Ed.; Wiley: Hoboken, **2006**, 227. (d) Otto, N.; Opatz, T. *Chem. Eur. J.* **2014**, *20*, 13064.

(2) Review: Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.

(3) Review: Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597.

(4) For other recent selected approaches to nitriles, see: (a) Laulhé, S.; Gori, S. S.; Nantz, M. H. *J. Org. Chem.* **2012**, *77*, 9334. (b) Tseng, K.-N. T.; Rizzi, A. M.; Szymczak, N. K. *J. Am. Chem. Soc.* **2013**, *135*, 16352. (c) Powell, K. J.; Han, L.-C.; Sharma, P.; Moses, J. E. *Org. Lett.* **2014**, *16*, 2158. (d) Nagase, Y.; Sugiyama, T.; Nomiyama, S.; Yonekura, K.; Tsuchimoto, T. *Adv. Synth. Catal.* **2014**, *356*, 347. (e) Cohen, D. T.; Buchwald, S. L. *Org. Lett.* **2015**, *17*, 202. (f) Lindsay-Scott, P. J.; Clarke, A.; Richardson, J. *Org. Lett.* **2015**, *17*, 476. (g) Wang, Y.-F.; Qiu, J.; Kong, D.; Gao, Y.; Lu, F.; Karmaker, P. G.; Chen, F.-X. *Org. Biomol. Chem.* **2015**, *13*, 365.

(5) For recent selected approaches to nitriles from aldoximes, see: (a) Cat. W-Sn hydroxide: Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 3922. (b) High temperature: Campbell, J. A.; McDougald, G.; McNab, H.; Rees, L. V. C.; Tyas, R. G. *Synthesis* **2007**, 3179. (c) [pmim]BF_4: Saha, D.; Saha, A.; Ranu, B. C. *Tetrahedron Lett.* **2009**, *50*, 6088. (d) BOP, DBU: Singh, M. K.; Lakshman, M. K. *J. Org. Chem.* **2009**, *74*, 3079. (e) Cat. $Cu(OAc)_2$, ultrasound: Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2010**, *51*, 4479. (f) Cat. propylphosphonic anhydride (T3P®): Augustine, J. K.; Kumar, R.; Bombrun, A.; Mandal, A. B. *Tetrahedron Lett.* **2011**, *52*, 1074. (g) Imidazole, Tf_2O: Kalkhambkar, R. G.; Bunge, S. D.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 5184. (h) Cat. Ph_3PO, $(COCl)_2$: Denton, R. M.; An, J.; Lindovska, P.; Lewis, W. *Tetrahedron* **2012**, *68*, 2899. (i) Cat. $Pd(en)(NO_3)_2$: Tambara, K.; Pantoş, G. D. *Org. Biomol. Chem.* **2013**, *11*, 2466. (j) Cat. cyclopropenone, $(COCl)_2$, DBU: Rai, A.; Yadav, L. D. S. *Eur. J. Org. Chem.* **2013**, 1889. (k) Cat. eosin Y, cat. DMF, CBr_4, hv: Yadav, A. K.; Srivastava, V. P.; Yadav, L. D. S. *RSC Adv.* **2014**, *4*, 4181. (l) Aldoxime dehydratase: Metzner, R.; Okazaki, S.; Asano, Y.; Gröger, H. *ChemCatChem* **2014**, *6*, 3105. (m) Ac_2O, K_2CO_3: Song, Y.; Shen, D.; Zhang, Q.; Chen, B.; Xu, G. *Tetrahedron Lett.* **2014**, *55*, 639. (n) Cat. $(3\text{-}FC_6H_4Se)_2/H_2O_2$: Yu, L.; Li, H.; Zhang, X.; Ye, J.; Liu, J.; Xu, Q.; Lautens, M. *Org. Lett.* **2014**, *16*, 1346. (o) $CBrCl_3$, Ph_3P: Al Jasem, Y.; Barkhad, M.; Al Khazali, M.; Butt, H. P.; El-Khwass, N. A.; Al Azani, M.; Al Hindawi, B.; Thiemann, T. *J. Chem. Res.* **2014**, 80. (p) DIAD, Ph_3P: Whiting, E.; Lanning, M. E.; Scheenstra, J. A.; Fletcher, S. *J. Org. Chem.* **2015**, *80*, 1229.

(6) For recent selected approaches to nitriles from primary amides, in addition to references 5b,j,k, see: (a) Cat. $PdCl_2$: Maffioli, S. I.; Marzorati, E.; Marazzi, A. *Org. Lett.* **2005**, *7*, 5237. (b) $EtOPOCl_2$, DBU: Kuo, C.-W.; Zhu, J.-L.; Wu, J.-D.; Chu, C.-M.; Yao, C.-F.; Shia, K.-S. *Chem. Commun.* **2007**, 301. (c) Ruthenium catalyst, 1,2-bis(dimethylsilyl)ethane: Hanada, S.; Motoyama, Y.; Nagashima, H. *Eur. J. Org. Chem.* **2008**, 4097. (d) Cat. TBAF, $PhSiH_3$: Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Org. Lett.* **2009**, *11*, 2461. (e) Cat. $[Et_3NH][HFe_3(CO)_{11}]$, $(EtO)_2MeSiH$: Zhou, S.; Addis, D.; Das, S.; Junge, K.; Beller, M. *Chem. Commun.* **2009**, 4883. (f) Supported vanadium catalyst: Sueoka, S.; Mitsudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2010**, 8243. (g) Cat. CuCl, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide: Enthaler, S.; Weidauer, M. *Catal. Lett.* **2011**, *141*, 1079. (h) Cat. $UO_2(NO_3)_2{\cdot}4H_2O$, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide: Enthaler, S. *Chem. Eur. J.* **2011**, 9316. (i) Cat. $FeCl_2{\cdot}4H_2O$, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide: Enthaler, S. *Eur. J. Org. Chem.* **2011**, 4760. (j) Cat. $Zn(OTf)_2$, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide: Enthaler, S.; Inoue, S. *Chem. Asian J.* **2012**, *7*, 169. (k) Silicotungstate catalyst: Itagaki, S.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *ChemCatChem* **2013**, *5*, 1725. (l) Cat. $In(OTf)_3$, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide: Mineno, T.; Shinada, M.; Watanabe, K.; Yoshimitsu, H.; Miyashita, H.; Kansui, H. *Int. J. Org. Chem.* **2014**, *4*, 1. (m) Cat. $PdCl_2(PPh_3)_2$, $Cu(OAc)_2$: Zhang, W.; Haskins, C. W.; Yang, Y.; Dai, M. *Org. Biomol. Chem.* **2014**, *12*, 9109.

(7) For selected examples of chiral nonracemic nitriles obtained from dehydration, see: (a) Claremon, D. A.; Phillips, B. T. *Tetrahedron Lett.* **1988**, *29*, 2155. (b) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1996**, *61*, 7398. (c) Maetz, P.; Rodriguez, M. *Tetrahedron Lett.* **1997**, *38*, 4221. (d) Bose, D. S.; Jayalakshmi, B. *Synthesis* **1999**, 64. (e) Bose, D. S.; Jayalakshmi, B. *J. Org. Chem.* **1999**, *64*, 1713. (f) Bose, D. S.; Sunder, K. S. *Synth. Commun.* **1999**, *29*, 4235. (g) Bose, D. S.; Jayalakshmi, B.; Goud, P. R. *Synthesis* **1999**, 1724. (h) Bose, D. S.; Kumar, K. K. *Synth. Commun.* **2000**, *30*, 3047. (i) Bose, D. S.; Narsaiah, A. V. *Synthesis* **2001**, 373. (j) Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3561. (k) Beaufort-Droal, V.; Pereira, E.; Théry, V.; Aitken, D. J. *Tetrahedron* **2006**, *62*, 11948. (l) Tka, N.; Kraïem, J.; Ben Hassine, B. *Synth. Commun.* **2013**, *43*, 735.

(8) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; Laflamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050. (b) L'Heureux, A.; Beaulieu, F.; Bennet, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401. (c) Mahé, O.; L'Heureux, A.; Couturier, M.; Bennett, C.; Clayton, S.; Tovell, D.; Beaulieu, F.; Paquin, J.-F. *J. Fluorine Chem.* **2013**, *153*, 57.

(9) Keita, M.; Vandamme, M.; Mahé, O.; Paquin, J.-F. *Tetrahedron Lett.* **2015**, *56*, 461.

(10) (a) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31. (b) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G.

G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. *Green Chem.* **2011**, *13*, 854. (c) Prat, D.; Pardigon, O.; Flemming, H.-W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; Hosek, P. *Org. Process Res. Dev.* **2013**, *17*, 1517.

(11) For other examples of the synthesis of **16** from **13**, see: (a) Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* **1997**, *38*, 2900. (b) Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3561. (c) Hoang, C. T.; Bouillère, F.; Johannesen, S.; Zulauf, A.; Panel, C.; Pouilhès, A.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Org. Chem.* **2009**, *74*, 4177.

(12) For other examples of the synthesis of **17** from **14**, see ref. 11c and: (a) Hoang, C. T.; Alezra, V.; Guillot, R.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 2521. (b) Sureshbabu, V. V.; Naik, S. A.; Hemanta, H. P.; Narendra, N.; Das, U.; Row, N. G. *J. Org. Chem.* **2009**, *74*, 5260. (c) Delacroix, S.; Bonnet, J.-P.; Courty, M.; Postel, D.; Van Nhien, A. N. *Carbohydr. Res.* **2013**, *381*, 12.

(13) Demko, Z. P.; Sharpless, B. K. *Org. Lett.* **2002**, *4*, 2525.

(14) For another exemple of the synthesis of **21** from **19**, see: Singh, B.; Gupta, P.; Chaubey, A.; Parshad, R.; Sharma, S.; Taneja, S. C. *Tetrahedron: Asymmetry* **2008**, *19*, 2579.

(15) For the synthesis of **24** via the dehydration of *tert*-butanesulfinyl imines, see: Tanuwidjaja, J.; Peltier, H. M.; Lewis, J. C.; Schenkel, L. B.; Ellman, J. A. *Synthesis* **2007**, 3385.

(16) For a chiral Brønsted acid mediated vinyl ether hydrocyanation enantio approach to **26**, see: Lu, C.; Su, X.; Floreancig, P. E. *J. Org. Chem.* **2013**, *78*, 9366.

(17) For examples of application of **24** in organic synthesis, see: (a) Charette, A. B.; Gagnon, A.; Janes, M.; Mellon, C. *Tetrahedron Lett.* **1998**, *39*, 5147. (b) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774.

(18) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011**, *13*, 2966.

(19) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096.

(20) Aakeroy, C. B.; Sinha, A. S.; Epa, K. N.; Chopade, P. D.; Smith, M. M.; Desper, J. *Cryst. Growth Des.* **2013**, *13*, 2687.

(21) Kim, K. D.; Yu, Y.; Jeong, H. J.; Jung, H. M.; Kim, K. L.; Kim, A. N.; Dagvajantsan, O.; Park, G. S.; Kim, S. C. *Bull. Korean Chem. Soc.* **2012**, *33*, 4275.

(22) Liu, A.; Wang, X.; Ou, X.; Huang, M.; Chen, C.; Liu, S.; Huang, L.; Liu, X.; Zhang, C.; Zheng, Y.; Ren, Y.; He, L.; Yao, J. *J. Agric. Food Chem.* **2008**, *56*, 6562.

(23) Yonekawa, M.; Koyama, Y.; Kuwata, S.; Takata, T. *Org. Lett.* **2012**, *14*, 1164.

(24) Hou, Y.; Lu, S.; Liu, G. *J. Org. Chem.* **2013**, *78*, 8386.

(25) Yu, J.; Cao, X.; Lu, M. *Tetrahedron Lett.* **2014**, *55*, 5751.

(26) Maurer, C.; Pittenauer, E.; Puchberger, M.; Allmaier, G.; Schubert, U. *ChemPlusChem* **2013**, *78*, 343.

(27) Castellano, S.; Kuck, D.; Viviano, M.; Yoo, J.; Lopez-Vallejo, F.; Conti, P.; Tamborini, L.; Pinto, A.; Medina-Franco, J. L.; Sbardella, G. *J. Med. Chem.* **2011**, *54*, 7663.

(28) Kozikowski, A. P.; Shum, P. W.; Basu, A.; Lazo, J. S. *J. Med. Chem.* **1991**, *34*, 2420.

(29) Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209.

(30) Hickmann, V.; Kondoh, A.; Gabor, B.; Alcazaro, M.; Fürstner, A. *J. Am. Chem. Soc.* **2011**, *133*, 13471.

(31) Boyer, N.; Gloanec, P.; De Nanteuil, G.; Jubault, P.; Quirion, J.-C. *Eur. J. Org. Chem.* **2008**, 4277.

(32) Yadav, J. S.; Mishra, A. K.; Dashavaram, S. S.; Kumar, S. G.; Das, S. *Tetrahedron Lett.* **2014**, *55*, 2921.

(33) Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Eur. J. Org. Chem.* **2004**, 4039.

(34) Li, X.-Q.; Wang, W.-K.; Han, Y.-X.; Zhang, C. *Adv. Synth. Catal.* **2010**, *352*, 2588.

(35) Lou, Z.; Yang, S.; Li, P.; Zhou, P.; Han, K. *Phys. Chem. Chem. Phys.* **2014**, *16*, 3749.

(36) Bonne, D.; Dekhane, M.; Zhu, J. *J. Am. Chem. Soc.* **2005**, *127*, 6926.

(37) Shirota, H.; Ushiyama, H. *J. Phys. Chem.* **2008**, *112*, 13542.

(38) Veisi, H.; Maleki, B.; Hamelian, M.; Ashrafi, S. *RSC Adv.* **2015**, *5*, 6365.

(39) Winkler, M.; Meischler, D.; Klempier, N. *Adv. Synth. Catal.* **2007**, *349*, 1475.

(40) Sawa, E.; Takahashi, M.; Kamishohara, M.; Tazunoki, T.; Kimura, K.; Arai, M.; Miyazaki, T.; Kataoka, S.; Nishitoba, T. *J. Med. Chem.* **1999**, *42*, 3289.

(41) Falorni, M.; Dettori, G.; Giacomelli, G. *Tetrahedron: Asymmetry* **1998**, *9*, 1419.

(42) Kimura, M.; Kuboki, A.; Sugai, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1059.

(43) Kametani, T.; Van Loc, C.; Higa, T.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2347.

(44) Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Chai, C. L. L.; Chen, A. *J. Org. Chem.* **2012**, *77*, 8007.

(45) Nobuharu, A.; Yukio, Y.; Jun'ichi, O.; Yuzo, I. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2369.

(46) Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. *Org. Lett.* **2010**, *12*, 2888.

(47) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Chem. Eur. J.* **2007**, *13*, 6249.

(48) Arundhathi, R.; Damodara, D.; Likhar, P. R.; Kantam, M. L.; Saravanan, P.; Magdaleno, T.; Kwon, S. H. *Adv. Synth. Catal.* **2011**, *353*, 1591.

(49) Yang, H.; Li, Y.; Jiang, M.; Wang, J.; Fu, H. *Chem. Eur. J.* **2011**, *17*, 5652.

(50) Mori, N.; Togo, H. *Synlett* **2005**, 1456.

(51) Cahiez, G.; Chaboche, C.; Duplais, C.; Giulliani, A.; Moyeux, A. *Adv. Synth. Catal.* **2008**, *350*, 1484.

(52) Choi, Y. M.; Kucharczyk, N.; Sofia, R. D. *J. Label. Compd. Radiopharm.* **1987**, *24*, 1.

(53) Nambo, M.; Yar, M.; Smith, J. D.; Crudden, C. M. *Org. Lett.* **2015**, *17*, 50.

(54) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(55) Vatèle, J.-M. *Synlett* **2014**, *25*, 1275.

(56) Honkanen, E.; Pippuri, A.; Kairisalo, P.; Nore, P.; Karppanen, H.; Paakkari, I. *J. Med. Chem.* **1983**, *26*, 1433.

(57) Cazes, B.; Julia, S. *Tetrahedron* **1979**, *35*, 2655.