ChemPubSoc Europe

DOI: 10.1002/ejoc.201700689

EurJOC European Journal of Organic Chemistry

Full Paper

Mechanochemical Oxidation

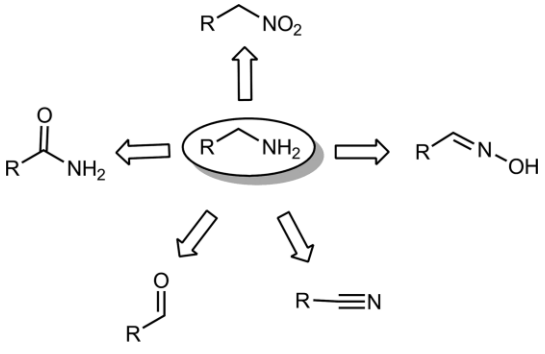
A Mechanochemical-Assisted Oxidation of Amines to Carbonyl Compounds and Nitriles

Silvia Gaspa,[a] Andrea Porcheddu,[b] Antonio Valentoni,[a] Sebastiano Garroni,[c,d] Stefano Enzo,[a] and Lidia De Luca*[a]

Abstract: A mild, efficient, metal- and solvent-free oxidation of primary amines to aldehydes, ketones, and nitriles under ball-milling conditions is presented. This method has proved to be compatible with various functional groups and only requires easily accessible starting materials. Simple purification of the reaction mixtures by short-column chromatography afforded pure aldehydes, ketones, and nitriles as products.

Introduction

The oxidation of amines is a potent tool for the production of a broad range of available synthetic intermediates, such as imines, amides, oximes, nitro compounds, nitriles, aldehydes, and ketones (Scheme 1).[1]



Scheme 1. Oxidation of amines.

The conventional route to aldehydes and ketones involves the oxidation of primary and secondary alcohols,[2] but a challenging alternative is the synthesis of carbonyl compounds from readily available and abundant precursors like amines. The existing methodologies, despite their efficiency, suffer from the required use of stoichiometric amounts of toxic metal-containing reagents, such as $KMnO_4$,[3] argentic picolinate,[4] $ZnCr_2O_7$ trihydrate,[5] and nicotinium dichromate,[6] or palladium-,[7] copper-,[8] and ruthenium-based[9] catalysts, and toxic solvents.

In addition, these methodologies are sometimes affected by poor yields, overoxidation of the carbonyl products to carboxylic acids, or the formation of imines as side-products. For the above-mentioned reasons, new procedures, run under neat and metal-free conditions, would be particularly desirable and attractive, especially to avoid toxic metal contamination of the final products and the use of toxic and volatile organic solvents.

Nitriles are used as versatile intermediates in organic synthesis, as they can be readily converted into carboxylic acids, esters, and amides. Different methodologies have been developed for their synthesis,[10] and, of these, the preparation of nitriles from amines appears to be the most direct and suitable. However, the selective oxidation of primary amines to nitriles presents many difficulties due to the fact that amines are subject to a variety of oxidative processes that yield an array of products.[11] Ruthenium-[12] and copper-catalyzed[13] oxidations of amines to nitriles have recently been reported, but, despite their large substrate scope, they suffer from low selectivity, the use of toxic solvents, and drastic reaction conditions. Other interesting metal-free procedures have been reported, but, even if they have a large substrate scope and are high-yielding, they demand the use of large excesses of oxidants and bases, which makes them impractical for large-scale synthesis.[14]

In this context, ball-milling synthesis has attracted significant interest in the scientific community due to its advantages over traditional solution-based methods.[15] The major benefit of this technology is that it is solvent-free and minimizes traditional workup procedures.[16] Higher yields and selectivity, fewer by-products, and minimum purification requirements are additional benefits of this procedure.[17] For these reasons we have decided to investigate a new approach to the oxidation of amines under ball-milling conditions.[18]

[a] *Dipartimento di Chimica e Farmacia, Università degli Studi di Sassari, via Vienna 2, 07100 Sassari, Italy*
E-mail: ldeluca@uniss.it
https://www.dcf.uniss.it/it
[b] *Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Monserrato, Italy*
[c] *International Research Centre in Critical Raw Materials-ICCRAM, University of Burgos, Plaza Misael Banuelos s/n, 09001 Burgos, Spain*
[d] *Advanced Materials, Nuclear Technology and Applied Bio/Nanotechnology, Consolidated Research Unit UIC-154, University of Burgos, Hospital del Rey s/n, 09001 Burgos, Spain*

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201700689.

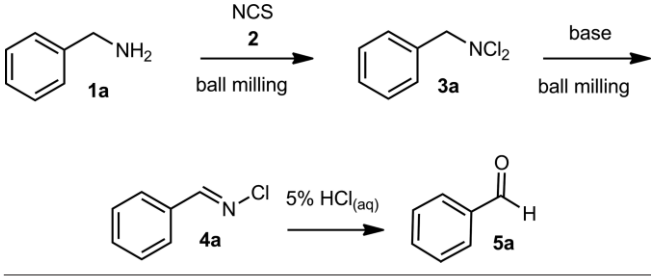
Results and Discussion

Oxidation of Primary Benzylamine to Carbonyl Compounds

As part of our on-going efforts to design new synthetic methodologies for the preparation of aldehydes and ketones,[19] we have developed a highly useful procedure for converting primary amines into aldehydes and ketones under ball-milling and solvent-free conditions at room temperature. To the best of our knowledge, this is the first example of an oxidative transformation of amines to carbonyl compounds by a mechanochemical-assisted procedure.

We started our investigation by mixing benzylamine (**1a**, 1.5 mmol) with *N*-chlorosuccinimide[20] [NCS (**2**), 3 mmol] at room temperature for 10 min (Table 1), sealing the two reagents in a zirconia jar (50 mL) containing two balls (d = 11.2 mm) of the same material. The corresponding dichloroamine **3a** was quantitatively formed. Then triethylamine (4.5 mmol) was added, and the mixture was subjected to mechanical treatment at room temperature for a further 10 min. Upon completion of the ball-milling process and subsequent hydrolysis carried out with 5 % $HCl_{(aq)}$, benzaldehyde (**5a**) was obtained in 66 % yield (Table 1, Entry 1). To find the optimum reaction conditions, the quantity of triethylamine was decreased to 3.0 mmol (Table 1, Entry 2) and 2.25 mmol (Table 1, Entry 3), and the desired aldehyde **5a** was obtained in yields of 70 and 82 %, respectively. Different bases were also screened: Pyridine (3.0 mmol; Table 1, Entry 4) gave the product **5a** in 40 % yield, whereas $NaOH_{aq}$ (2 mL, 1.5 M, 3 mmol; Table 1, Entry 5), K_2CO_3 (4.5 mmol; Table 1, Entry 6), and MgO (4.5 mmol; Table 1, Entry 7) did not furnish benzaldehyde (**5a**), but the dichloroamine **3a** was recovered.

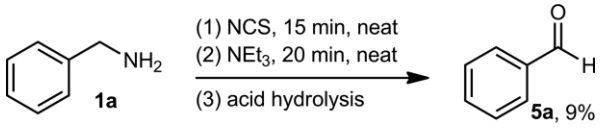
Table 1. Screening of reaction conditions.



Entry	Base	Amount of base [mmol]	Yield[a] [%]
1	NEt_3	4.5	66
2	NEt_3	3.0	70
3	NEt_3	2.25	82
4	pyridine	3.0	40
5	$NaOH_{aq}$	3.0	–
6	K_2CO_3	4.5	–
7	MgO	4.5	–

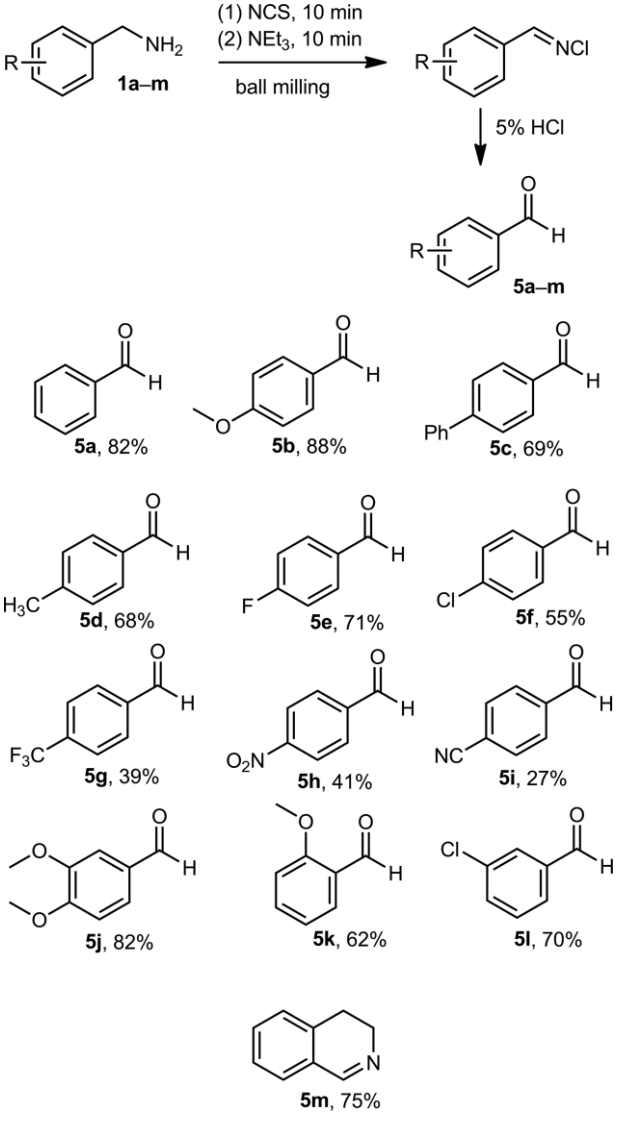
[a] Yield refers to the isolated product.

Experiments to compare the reaction under neat conditions and ball milling were carried out, which revealed the ball-milling process to give a better performance. Thus, the reaction was performed with benzylamine (**1a**, 1.5 mmol; Scheme 2) in the presence of *N*-chlorosuccinimide (**2**, 3 mmol; Scheme 2) under solvent-free (neat) conditions at room temperature for 15 min. Then triethylamine (2.25 mmol) was added, and the reaction mixture was stirred under solvent-free (neat) conditions at room temperature for 20 min. Benzaldehyde (**5a**) was obtained in 9 % yield after acid hydrolysis.



Scheme 2. Oxidation of benzylamine to benzaldehyde under neat conditions.

Having optimized the reaction conditions (Table 1, Entry 3), the scope of the reaction was investigated (Scheme 3). In general, all the reactions proceeded without any significant side-



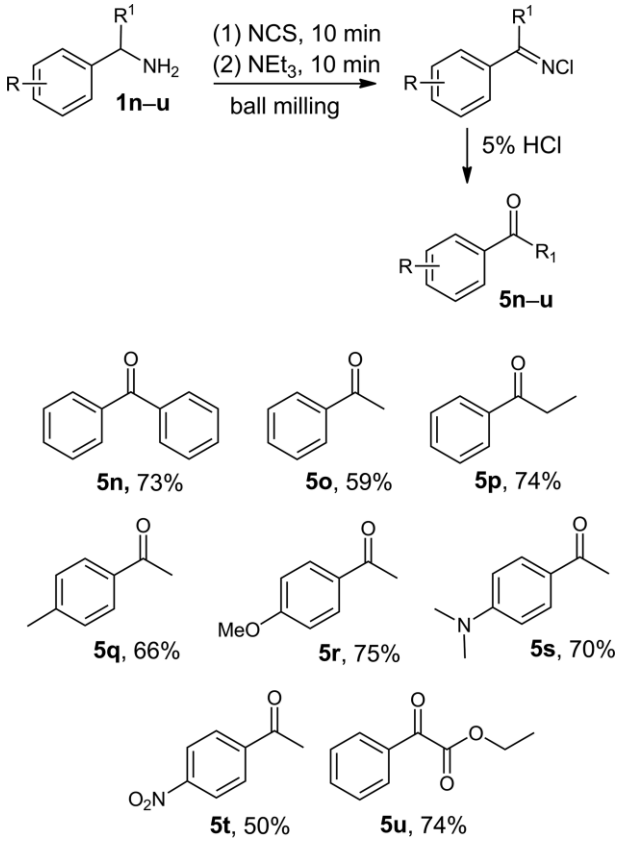
Scheme 3. Oxidation of amines to aldehydes: Scope of the reaction with respect to benzylamines.

products, no overoxidation of the aldehydes to carboxylic acids was observed, and the corresponding carbonyl compounds **5a**–**m** were obtained in satisfactory yields.

The reactions of benzylamines with electron-donating substituents on the aromatic ring (Scheme 3, products **5b**–**5d**, **5j**, and **5k**) gave better results than amines bearing electron-withdrawing substituents (Scheme 3, products **5e**–**5i**). Benzylamines bearing a substituent at the *ortho* position are also suitable substrates for this process (Scheme 3, product **5k**).

The reactions carried out with benzylamines bearing a halide substituent on the aromatic ring (Scheme 3, products **5e**, **5f**, and **5l**) gave the corresponding aldehydes, which could be further transformed by traditional cross-coupling reactions. The oxidation of 1,2,3,4-tetrahydroisoquinoline, a cyclic amine, notably gave selectively only 3,4-dihydroisoquinoline, the corresponding conjugated cyclic imine (Scheme 3, product **5m**). The procedure was applied to aliphatic amines, but at the end of the entire procedure the corresponding *N*,*N*-dichloroamines were recovered and not the corresponding aldehydes.

α-Substituted benzylamines were also successfully transformed into the corresponding ketones by this oxidative procedure. Both symmetrical and unsymmetrical α-substituted benzylamines were easily oxidized to the corresponding ketones (Scheme 4, products **5n**–**5u**). α-Substituted benzylamines bearing both electron-donating and -withdrawing substituents on the aromatic ring worked well in this procedure.



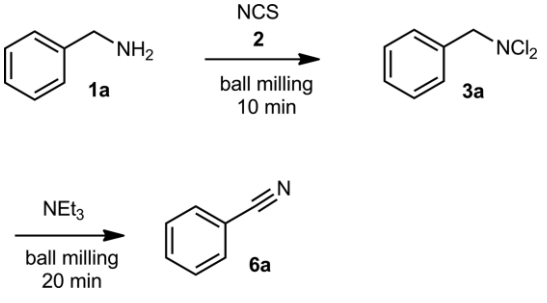
Scheme 4. Oxidation of amines to ketones: Scope of the reaction with respect to α-substituted benzylamines.

Finally, the gram-scale synthesis of product **5a** was performed. Under the optimized conditions, benzylamine (**1a**, 1.0 g, 7.1 mmol) was mixed with *N*-chlorosuccinimide [NCS (**2**), 1.89 g, 14.1 mmol] and then milled in a zirconia jar (50 mL) for 10 min. The corresponding dichloroamine **3a** was quantitatively formed. Then triethylamine (1.48 mL, 10.6 mmol) was added, and the mixture was subjected to mechanical treatment at room temperature for a further 10 min. Upon completion of the ball-milling process and subsequent hydrolysis carried out with 5 % $HCl_{(aq)}$, benzaldehyde (**5a**) was obtained in 83 % yield. The yield and purity were analogous to those of the small-scale reaction, which indicates the flexibility and scalability of the methodology.

Oxidation of Primary Benzylic Amines to Nitriles

After the successful oxidation of primary benzylic amines to aldehydes and ketones, we investigated the possibility of transforming amines into nitriles under ball-milling and solvent-free conditions at room temperature. The same methodology used to oxidize the amines to carbonyl compounds was employed to allow a one-pot oxidation of amines to nitriles but with an increase in the amount of triethylamine and ball-milling time.

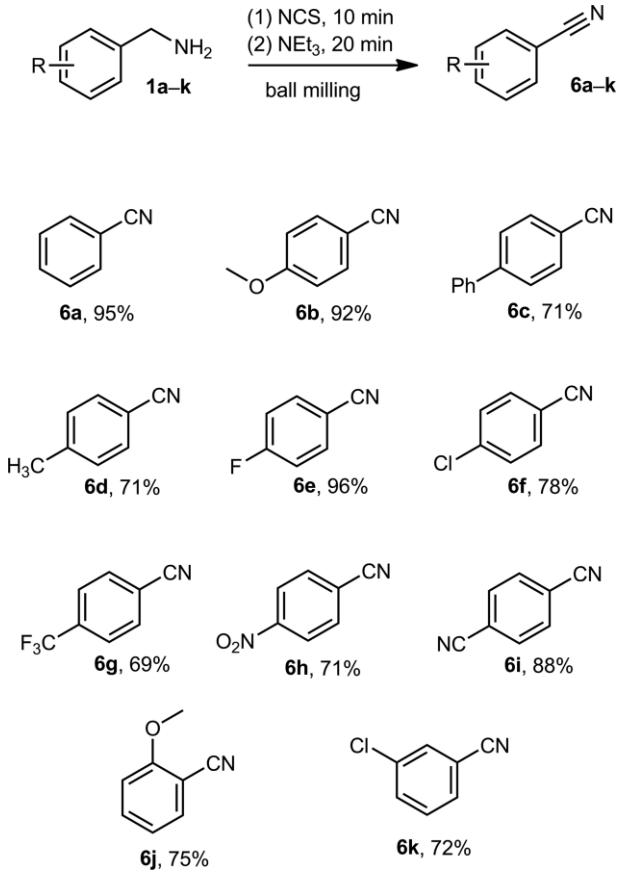
We started our investigation by treating benzylamine (**1a**, 1.5 mmol) with *N*-chlorosuccinimide (**2**, 3 mmol) in a shaker mill consisting of a ZrO_2 milling jar (50 mL) containing two balls (d = 11.2 mm) of the same material at room temperature for 10 min (Scheme 5). The corresponding dichloroamine **3a** was quantitatively formed. Then triethylamine (4.5 mmol) was added, and the mixture was subjected to ball milling at room temperature for 20 min. Upon completion of the ball-milling process, benzonitrile (**6a**) was obtained in 95 % yield (Scheme 5).



Scheme 5. Oxidation of amines to nitriles.

Then the scope of the methodology was tested. Generally, all the reactions proceeded to give the corresponding nitriles **6a**–**k** in satisfactory yields without any significant side-products. The reactions of benzylamines with electron-donating substituents on the aromatic ring (Scheme 6, products **6b**–**6d**) gave yields comparable to those of amines bearing electron-withdrawing substituents (Scheme 6, products **6e**–**6i** and **6k**). Benzylamines with a substituent at the *ortho* position are also suitable substrates for this process (Scheme 6, product **6j**). The reactions carried out with benzylamines bearing a halide substituent on the aromatic ring (Scheme 6, products **6e**, **6f**, and

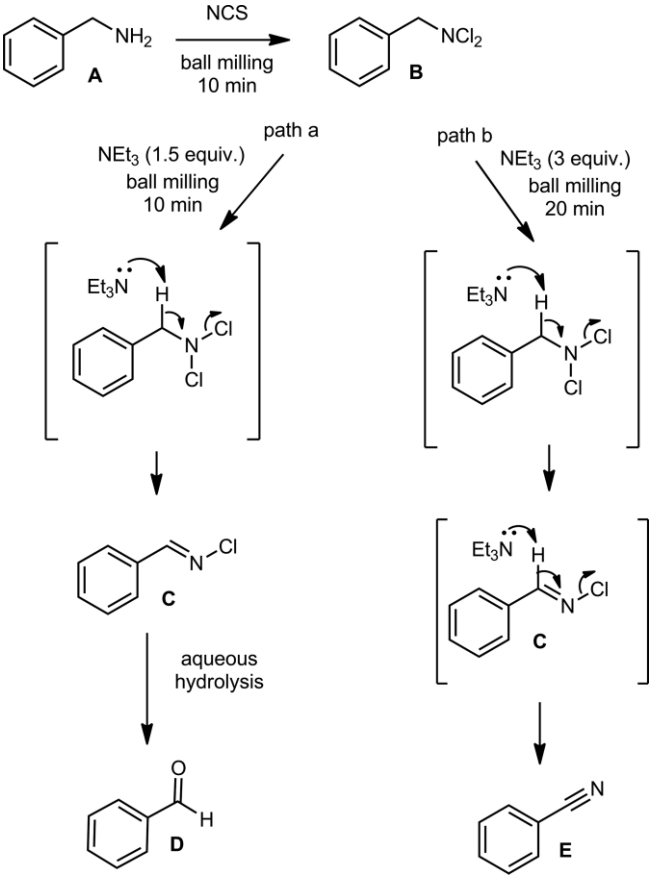
6k) gave the corresponding benzonitriles, which could be further transformed by traditional cross-coupling reactions.



Scheme 6. Oxidation of amines to nitriles: Scope of the reaction with respect to benzylamines.

The gram-scale synthesis of product **6a** was also investigated. Under the optimized conditions for the preparation of nitriles, benzylamine (**1a**, 1.0 g, 7.1 mmol) was mixed with *N*-chlorosuccinimide (**2**, 1.89 g, 14.1 mmol) and then milled in a zirconia jar (50 mL) for 10 min. Then triethylamine (2.95 mL, 21.2 mmol) was added, and the mixture was subjected to mechanical treatment at room temperature for a further 20 min. Upon completion of the ball-milling process benzonitrile (**6a**) was obtained in 94 % yield. Also, the yield and purity were analogous to those of the small-scale reaction.

A plausible reaction mechanism is shown in Scheme 7 in which we propose that benzylamine (**A**) reacted with *N*-chlorosuccinimide (NCS) in the ball-milling process (10 min), probably by a radical pathway, to yield *N*,*N*-dichlorobenzylamine (**B**), which was isolated and characterized. Then **B** reacted with NEt_3 (1.5 equiv.) in the ball-milling process (10 min; Scheme 7, path a)[21] to form *N*-chlorobenzylimine (**C**), which was also isolated and characterized.[22] *N*-Chlorobenzylimine (**C**) was then converted into the corresponding benzaldehyde (**D**) by aqueous hydrolysis. Alternatively, **B** reacted with NEt_3 (3 equiv.) in the ball-milling process (20 min; Scheme 7, path b) to yield benzonitrile (**E**).



Scheme 7. Proposed mechanism for the formation of the carbonyl compounds and nitriles.

Conclusions

We have developed a mild, efficient, and metal-free method for the synthesis of aldehydes, ketones, and nitriles from primary amines under ball-milling conditions, which may constitute a significant addition to the field of mechanochemical synthesis. The method has proved to be compatible with various functional groups and only requires easily accessible starting materials.

Experimental Section

General: All reagents and solvents were used as obtained from commercial sources. All solvents were dried by the usual methods and distilled under argon. Short-column chromatography was generally performed with a column of 4 cm diameter charged with 24 g of silica gel (pore size 60 Å, 32–63 nm particle size), and the reactions were monitored by TLC on Merck Kieselgel 60 F254 plates and visualized by using UV light at 254 nm with $KMnO_4$ and 2,4-DNP staining. An 8000M Mixer/Mill® ball-milling apparatus was used for all reactions with a rotation frequency of 875 rpm. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 or 100 MHz, respectively) using $CDCl_3$ solutions. Chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane standard (TMS: δ = 0.00 ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br., broad. The coupling con-

stants (*J*) are reported in Hertz (Hz). Melting points were determined in open capillary tubes.

General Procedure for the Oxidation of Primary Benzylamines to Carbonyl Compounds: The respective benzylamine **1a**–**1u** (1.5 mmol) and *N*-chlorosuccinimide (**2**, 0.400 g, 3 mmol) were milled in a zirconia vial (50 mL) containing two balls (d = 11.2 mm) of the same material. The reagents were then subjected to ball-milling in a shaker milling device at room temperature for 10 min (the disappearance of benzylamine was monitored by TLC). Then NEt_3 (0.227 g, 2.25 mmol) was added, and the mixture was subjected to ball-milling at room temperature for a further 10 min. Upon completion of the ball-milling process, the jar was opened, and THF (10 mL) was added and the mixture transferred to a round-bottomed flask for the hydrolysis. A 5 % $HCl_{(aq)}$ solution (15 mL) was added and the mixture stirred at room temperature for 2 h and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude products **5a**–**5u** were purified by short-column chromatography (hexane/ethyl acetate).

Compound Characterizations for 5a–5u

Benzaldehyde (5a):[23] Colorless oil; yield: 0.130 g, 82 %. The desired pure product was obtained after short-column chromatography (R_f = 0.314, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.00 (s, 1 H), 7.86 (d, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.1 Hz, 1 H), 7.52 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 136.3, 134.3, 129.6, 128.9 ppm.

4-Methoxybenzaldehyde (5b):[23] Colorless oil; yield: 0.180 g, 88 %. The desired pure product was obtained after short-column chromatography (R_f = 0.344, hexane/ethyl acetate, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (s, 1 H), 7.78 (d, J = 8.5 Hz, 2 H), 6.95 (d, J = 8.6 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.6, 164.4, 131.8, 129.8, 114.1, 55.4 ppm.

1,1′-Biphenyl-4-carbaldehyde (5c):[24] White solid; yield: 0.189 g, 69 % yield; m.p. 56–58 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.4, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 1 H), 7.96 (d, J = 8.1 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.64 (d, J = 7.6 Hz, 2 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.42 (t, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9, 147.2, 139.7, 135.2, 130.2, 129.0, 128.5, 127.7, 127.3 ppm.

4-Methylbenzaldehyde (5d):[25] Colorless oil; yield: 0.122 g, 68 %. The desired pure product was obtained after short-column chromatography (R_f = 0.613, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 7.77 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 7.8 Hz, 2 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.0, 145.5, 134.2, 129.8, 129.7, 21.9 ppm.

4-Fluorobenzaldehyde (5e):[26] Colorless oil; yield: 0.132 g, 71 %. The desired pure product was obtained after short-column chromatography (R_f = 0.59, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1 H), 7.85 (dd, J = 8.6, 5.6 Hz, 2 H), 7.15 (t, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.3, 166.3 (d, J = 255 Hz), 132.8 (d, J = 2.4 Hz), 132.5 (d, J = 9.6 Hz), 116.2 (d, J = 22.2 Hz) ppm.

4-Chlorobenzaldehyde (5f):[27] White solid; yield: 0.116 g, 55 %; m.p. 46–47.5 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.451, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.50 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 140.9, 134.7, 130.8, 129.4 ppm.

4-(Trifluoromethyl)benzaldehyde (5g): Colorless oil; yield: 0.102 g, 39 %. The desired pure product was obtained after short-column chromatography (R_f = 0.433, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.10 (s, 1 H), 8.01 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.0 Hz, 2 H) ppm.[28] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 138.7, 135.6 (q, J = 37.5 Hz), 129.9, 126.1 (q, J = 7.5 Hz), 123.5 (q, J = 270 Hz) ppm.[29]

4-Nitrobenzaldehyde (5h):[25] Yellow solid; yield: 0.093 g, 41 %; m.p. 106–107 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.385, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.16 (s, 1 H), 8.39 (d, J = 8.6 Hz, 2 H), 8.07 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.2, 151.1, 140.0, 130.5, 124.3 ppm.

4-Formylbenzonitrile (5i):[30] White solid; yield: 0.053 g, 27 %; m.p. 102–103 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.333, hexane/ethyl acetate, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 1 H), 7.97 (d, J = 8.1 Hz, 2 H), 7.82 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.6, 138.6, 132.8, 129.7, 117.6, 117.4 ppm.

3,4-Dimethoxybenzaldehyde (5j):[31] White solid; yield: 0.204 g, 82 %; m.p. 42–43 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.379, hexane/ethyl acetate, 3.5:1.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (s, 1 H), 7.45 (dd, J = 8.2, 1.9 Hz, 1 H), 7.40 (d, J = 1.8 Hz, 1 H), 6.97 (d, J = 8.2 Hz, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 154.4, 149.6, 130.1, 126.8, 110.4, 108.9, 56.1, 56.0 ppm.

2-Methoxybenzaldehyde (5k):[27] Yellow oil; yield: 0.126 g, 62 %. The desired pure product was obtained after short-column chromatography (R_f = 0.333, hexane/ethyl acetate, 4.8:0.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.47 (s, 1 H), 7.82 (dd, J = 7.7, 1.8 Hz, 1 H), 7.56–7.52 (m, 1 H), 7.03–6.97 (m, 2 H), 3.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7, 161.8, 135.9, 128.5, 124.8, 120.6, 111.6, 55.6 ppm.

3-Chlorobenzaldehyde (5l):[32] Colorless oil; yield: 0.148 g, 70 %. The desired pure product was obtained after short-column chromatography (R_f = 0.548, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.88 (s, 1 H), 7.75–7.70 (m, 1 H), 7.67 (d, J = 7.7 Hz, 1 H), 7.51–7.46 (m, 1 H), 7.39 (t, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 137.6, 135.1, 134.0, 130.1, 128.8, 127.7 ppm.

3,4-Dihydroisoquinoline (5m):[33] Colorless oil; yield: 0.147 g, 75 %. The desired pure product was obtained after short-column chromatography (R_f = 0.125, hexane/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 7.37 (t, J = 6.8 Hz, 1 H), 7.33–7.27 (m, 2 H), 7.17 (d, J = 7.3 Hz, 1 H), 3.79 (t, J = 7.2 Hz, 2 H), 2.76 (t, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 136.2, 131.0, 128.4, 127.3, 127.2, 127.0, 47.2, 24.9 ppm.

Benzophenone (5n):[34] White solid; yield: 0.199 g, 73 %; m.p. 47–49 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.285, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 7.5 Hz, 4 H), 7.59 (t, J = 7.4 Hz, 2 H), 7.48 (t, J = 7.5 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 137.6, 132.4, 130.0, 128.2 ppm.

Acetophenone (5o):[35] Colorless oil; yield: 0.106 g, 59 %. The desired pure product was obtained after short-column chromatography (R_f = 0.333, hexane/ethyl acetate, 4.7:0.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.3 Hz, 2 H), 7.56–7.50 (m, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 2.57 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9, 137.0, 132.9, 128.4, 128.2, 26.4 ppm.

Propiophenone (5p):[36] Colorless oil; yield: 0.149 g, 74 %. The desired pure product was obtained after short-column chromatography (R_f = 0.354, hexane/ethyl acetate, 4.7:0.3). ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 7.95 (d, J = 7.8 Hz, 2 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 2.98 (q, J = 7.2 Hz, 2 H), 1.21 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 135.9, 131.8, 127.5, 126.9, 30.7, 7.2 ppm.

1-(*p*-Tolyl)ethan-1-one (5q):[37] Colorless oil; yield: 0.133 g, 66 %. The desired pure product was obtained after short-column chromatography (R_f = 0.286, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.1 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 2.59 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 143.8, 134.6, 129.2, 128.4, 26.4, 21.5 ppm.

1-(4-Methoxyphenyl)ethan-1-one (5r):[35] Colorless oil; yield: 0.169 g, 75 %. The desired pure product was obtained after short-column chromatography (R_f = 0.345, hexane/ethyl acetate, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.7 Hz, 2 H), 6.92 (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6, 163.4, 130.5, 130.3, 113.6, 55.4, 26.3 ppm.

1-[4-(Dimethylamino)phenyl]ethan-1-one (5s):[38] White solid: yield: 0.171 g, 70 %; m.p. 103–104 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.345, hexane/ethyl acetate, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.9 Hz, 2 H), 6.65 (d, J = 8.9 Hz, 2 H), 3.05 (s, 6 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 153.3, 130.5, 125.4, 110.6, 40.0, 25.9 ppm.

1-(4-Nitrophenyl)ethan-1-one (5t):[39] White solid; yield: 0.124 g, 50 %; m.p. 76–77 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.7, hexane/ethyl acetate, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.3 Hz, 2 H), 8.11 (d, J = 8.7 Hz, 2 H), 2.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2, 150.4, 141.4, 129.3, 123.8, 27.0 ppm.

Ethyl 2-Oxo-2-phenylacetate (5u):[40] Yellow oil; yield: 0.198 g, 74 %. The desired pure product was obtained after short-column chromatography (R_f = 0.3, hexane/ethyl acetate, 4.2:0.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 7.6 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.50 (t, J = 7.7 Hz, 2 H), 4.45 (q, J = 7.1 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.4, 163.8, 134.8, 132.4, 130.0, 128.8, 62.3, 14.1 ppm.

General Procedure for the Oxidation of Primary Benzylic Amines to Nitriles 6a–6k: The respective benzylamine **1a**–**1k** (1.5 mmol) and *N*-chlorosuccinimide (**2**, 0.400 g, 3 mmol) were milled in a zirconia vial (50 mL) containing two balls (d = 11.2 mm) of the same material. The reagents were then subjected to ball-milling in a shaker milling device at room temperature for 10 min (the disappearance of benzylamine was monitored by TLC). Then NEt_3 (0.455 g, 4.5 mmol) was added, and the mixture was subjected to further milling at room temperature for 20 min. Upon completion of the ball-milling process, the crude product was purified by short-column chromatography (hexane/ethyl acetate) to provide benzonitriles **6a**–**6k**.

Compound Characterizations for 6a–6k

Benzonitrile (6a):[41] Colorless oil; yield: 0.147 g, 95 %. The desired pure product was obtained after short-column chromatography (R_f = 0.314, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.47 (t, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.7, 132.1, 129.1, 118.8, 112.4 ppm.

4-Methoxybenzonitrile (6b):[41] Colorless oil; yield: 0.184 g, 92 %. The desired pure product was obtained after short-column chromatography (R_f = 0.406, hexane/ethyl acetate, 4.3:0.7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 7.2 Hz, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 133.9, 119.2, 114.7, 103.9, 55.5 ppm.

1,1′-Biphenyl-4-carbonitrile (6c):[41] Yellow solid; yield: 0.191 g, 71 %; m.p. 88–89 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.4, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.67 (m, 4 H), 7.59 (d, J = 7.4 Hz, 2 H), 7.51–7.41 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 139.1, 132.5, 129.1, 128.6, 127.7, 127.2, 118.9, 110.8 ppm.

4-Methylbenzonitrile (6d):[42] Colorless oil; yield: 0.124 g, 71 %. The desired pure product was obtained after short-column chromatography (R_f = 0.385, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.0 Hz, 2 H), 7.23 (d, J = 7.5 Hz, 2 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 132.0, 129.8, 119.1, 109.3, 21.8 ppm.

4-Fluorobenzonitrile (6e):[43] Colorless oil; yield: 0.174 g, 96 %. The desired pure product was obtained after short-column chromatography (R_f = 0.59, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, J = 8.7, 5.2 Hz, 2 H), 7.15 (t, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9 (d, J = 254 Hz), 134.5 (d, J = 9 Hz), 117.85, 116.7 (d, J = 13 Hz), 108.42 (d, J = 22 Hz) ppm.

4-Chlorobenzonitrile (6f):[41] White solid; yield: 0.161 g, 78 %; m.p. 91–93 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.344, hexane/ethyl acetate, 4.8:0.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.5 Hz, 2 H), 7.47 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 133.3, 129.7, 117.9, 110.8 ppm.

4-(Trifluoromethyl)benzonitrile (6g):[42] Colorless oil; yield: 0.177 g, 69 %. The desired pure product was obtained after short-column chromatography (R_f = 0.613, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 2 H), 7.76 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.6 (q, J = 33.6 Hz), 132.7, 126.2 (q, J = 3.7 Hz), 123.1 (q, J = 273.5 Hz), 117.4, 116.1 ppm.

4-Nitrobenzonitrile (6h):[44] White solid; yield: 0.157 g, 71 %; m.p. 88–89 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.385, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, J = 8.7 Hz, 2 H), 7.89 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 133.4, 124.3, 118.4, 116.8 ppm.

Terephthalonitrile (6i):[44] White solid; yield: 0.169 g, 88 %; m.p. 222–223 °C. The desired pure product was obtained after short-column chromatography (R_f = 0.333, hexane/ethyl acetate, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.8, 117.0, 116.7 ppm.

2-Methoxybenzonitrile (6j):[42] Colorless oil; yield: 0.150 g, 75 %. The desired pure product was obtained after short-column chromatography (R_f = 0.333, hexane/ethyl acetate, 4.8:0.2) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.46 (m, 2 H), 7.00–6.92 (m, 2 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 134.3, 133.5, 120.6, 116.3, 111.2, 101.4, 55.8 ppm.

3-Chlorobenzonitrile (6k):[43] Colorless oil; yield: 0.148 g, 72 %. The desired pure product was obtained after short-column chromatography (R_f = 0.548, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 1 H), 7.61–7.54 (m, 2 H), 7.43 (t, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3, 133.2, 131.9, 130.5, 130.3, 117.4, 114.0 ppm.

General Procedure for the Synthesis of *N*,*N*-Dichloro-1-phenylmethanamine (3a):[45] Benzylamine (**1a**, 0.212 g, 1.5 mmol) and *N*-chlorosuccinimide (**2**, 0.400 g, 3 mmol) were milled in a zirconia vial

(50 mL) containing two balls (d = 11.2 mm) of the same material. The reagents were then subjected to ball-milling in a shaker milling device at room temperature for 10 min (the disappearance of benzylamine was monitored by TLC). Upon completion of the ball-milling process, the crude product **3a** was purified by short-column chromatography (hexane/ethyl acetate). White solid; yield: 0.174 g, 66 %. The desired pure product was obtained after short-column chromatography (R_f = 0.518, hexane/ethyl acetate, 4.8:0.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 5 H), 4.70 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9, 130.0, 129.2, 128.5, 78.9 ppm.

General Procedure for the Synthesis of (*E*)-*N*-Chloro-1-phenylmethanimine (4a):[46] Benzylamine (**1a**, 0.212 g, 1.5 mmol) and *N*-chlorosuccinimide (**2**, 0.400 g, 3 mmol) were milled in a zirconia vial (50 mL) containing two balls (d = 11.2 mm) of the same material. The reagents were then subjected to ball-milling in a shaker milling device at room temperature for 10 min(the disappearance of benzylamine was monitored by TLC). Then NEt_3 (0.227 g, 2.25 mmol) was added, and the mixture was subjected to milling at room temperature for a further 10 min. Upon completion of the ball-milling process, the crude product was purified by short-column chromatography (hexane/ethyl acetate). White solid; yield: 0.113 g, 54 %. The desired pure product was obtained after short-column chromatography (R_f = 0.392, hexane/ethyl acetate, 4.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 1 H), 7.68 (d, J = 7.5 Hz, 2 H), 7.52–7.42 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 133.2, 132.1, 129.0, 128.0 ppm.

General Procedure for the Synthesis of (*E*)-*N*-Chloro-1-phenylmethanimine (4a) from *N*,*N*-Dichloro-1-phenylmethanamine (3a): *N*,*N*-Dichloro-1-phenylmethanamine (0.264 g, 1.5 mmol) and NEt_3 (0.227 g, 2.25 mmol) were milled in a zirconia vial (50 mL), containing two balls (d = 11.2 mm) of the same material at room temperature for 10 min (the disappearance of *N*,*N*-dichloro-1-phenylmethanamine was monitored by TLC). Upon completion of the ball-milling process, the crude product was purified by short-column chromatography (hexane/ethyl acetate) providing (*E*)-*N*-chloro-1-phenylmethanimine (0.123 g, 59 %).

General Procedure for the Synthesis of Carbonyl Compounds 5 from (*E*)-*N*-Chloro-1-phenylmethanimine (4a): (*E*)-*N*-Chloro-1-phenylmethanimine (**4a**, 0.209 g, 1.5 mmol) was dissolved in THF (10 mL) and the mixture transferred to a round-bottomed flask for the hydrolysis. A 5 % $HCl_{(aq)}$ solution (15 mL) was added to the mixture, which was stirred at room temperature for 2 h and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by short-column chromatography (hexane/ethyl acetate) to provide benzaldehyde **5a** (0.134 g, 84 %).

General Procedure for the Synthesis of Nitriles 6 from *N*,*N*-Dichloro-1-phenylmethanamine (3a): *N*,*N*-Dichloro-1-phenylmethanamine (**3a**, 0.264 g, 1.5 mmol) and NEt_3 (0.455 g, 4.5 mmol) were milled in a zirconia vial (50 mL) containing two balls (d = 11.2 mm) of the same material at room temperature for 20 min (the disappearance of *N*,*N*-dichloro-1-phenylmethanaminewas monitored by TLC). Upon completion of the ball-milling process, the crude product was purified by short-column chromatography (hexane/ethyl acetate) to provide benzonitrile (**6a**, 0.148 g, 96 %).

Acknowledgments

This work was financially supported by the Regione Autonoma della Sardegna within the project "Valorizzazione di biomasse d'interesse regionale attraverso processi chimici a basso impatto ambientale"(CRP 72-Bando "Capitale Umano ad Alta Qualificazione, Annualità 2015_L.R. 7 agosto 2007, no. 7"). S. G. gratefully acknowledges the Sardinia Regional Government for the financial support of her Ph. D. scholarship (P.O.R. Sardegna F.S.E. Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2007–2013-Axis IV Human Resources, Objective l.3, Line of Activity l.3.1).

Keywords: Ball milling · Oxidation · Aldehydes · Ketones · Nitriles · Mechanochemistry

[1] a) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201; b) G. Chu, C. Li, *Org. Biomol. Chem.* **2010**, *8*, 4716–4719; c) P. Galletti, F. Funiciello, R. Soldati, D. Giacomini, *Adv. Synth. Catal.* **2015**, *357*, 1840–1848; d) V. V. Patil, E. M. Gayakwad, G. S. Shankarling, *J. Org. Chem.* **2016**, *81*, 781–786; e) V. V. Patil, G. S. Shankarling, *J. Org. Chem.* **2015**, *80*, 7876–7883; f) X. Wu, C. B. Bheeter, H. Neumann, P. H. Dixneuf, M. Beller, *Chem. Commun.* **2012**, *48*, 12237–12239; g) J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2008**, *47*, 9249–9251; *Angew. Chem.* **2008**, *120*, 9389–9391; h) Y. Wang, H. Kaboyashi, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2012**, *48*, 2642–2644.

[2] a) G. Tojo, M. Fernandez, *Oxidation of Alcohols to Aldehydes and Ketones*, 1st ed., Springer, New York, **2006**.

[3] S. S. Rawalay, H. Shechter, *J. Org. Chem.* **1967**, *32*, 3129–3131.

[4] R. G. R. Bacon, W. J. W. Hanna, *J. Chem. Soc.* **1965**, 4962–4968.

[5] S. Sabhani, M. F. Maleki, *Synlett* **2010**, 383–386.

[6] S. Sobhani, S. Aryanejad, M. F. Maleki, *Helv. Chim. Acta* **2012**, *95*, 613–617.

[7] S. Chandrasekhar, G. P. K. Reddy, C. Nagesh, C. R. Reddy, *Tetrahedron Lett.* **2007**, *48*, 1269–1271.

[8] a) J. Srogl, S. Voltrova, *Org. Lett.* **2009**, *11*, 843–845; b) S.-i. Naya, T. Niwa, R. Negishi, H. Kobayashi, H. Tada, *Angew. Chem. Int. Ed.* **2014**, *53*, 13894–13897; *Angew. Chem.* **2014**, *126*, 14114–14117.

[9] N. Iqbal, E. J. Cho, *Adv. Synth. Catal.* **2015**, *357*, 2187–2192.

[10] R. C. Larock (Ed.), *Comprehensive Organic Transformations*, Wiley-VCH, Weinheim, **1999**, pp. 819–939.

[11] a) For a review of the oxidation of amines, see: D. H. Rosenblatt, E. Burrows in *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives, Supplement F*, vol. 1, part 2 (Ed.: S. Patai), Wiley, Chichester, **1982**, pp. 1085–1149; b) C. R. Noller, *Textbook of Organic Chemistry*, vol. 3, W. B. Saunders Company, Philadelphia, PA, **1966**, p. 229.

[12] a) K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2003**, *42*, 1480–1483; *Angew. Chem.* **2003**, *115*, 1518–1521; b) Y. Zhang, K. Xu, X. Chen, T. Hu, Y. Yu, J. Zhang, J. Huang, *Catal. Commun.* **2010**, *11*, 951–954; c) S. Venkatesan, A. S. Kumar, J.-F. Lee, T.-S. Chan, J.-M. Zen, *Chem. Eur. J.* **2012**, *18*, 6147–6151; d) M. T. Schümperli, C. Hammond, I. Hermans, *ACS Catal.* **2012**, *2*, 1108–1117; e) E. C. Corker, J. Ruiz-Martinez, A. Riisager, R. Fehrmann, *Catal. Sci. Technol.* **2015**, *5*, 5008–5015.

[13] a) J. Kim, S. S. Stahl, *ACS Catal.* **2013**, *3*, 1652–1656; b) D. Damodara, R. Arundhathi, P. R. Likhar, *Adv. Synth. Catal.* **2014**, *356*, 189–198.

[14] a) K. C. Nicolaou, C. J. N. Mathison, *Angew. Chem. Int. Ed.* **2005**, *44*, 5992–5997; *Angew. Chem.* **2005**, *117*, 6146–6151; b) J. Zhang, Z. Wang, Y. Wang, C. Wan, C. Wan, X. Zheng, Z. Wang, *Green Chem.* **2009**, *11*, 1973–1978; c) K. M. Lambert, J. M. Bobbitt, S. A. Eldirany, K. B. Wiberg, W. F. Bailey, *Org. Lett.* **2014**, *16*, 6484–6487; d) K. M. Lambert, J. M. Bobbitt, S. A. Eldirany, L. E. Kissane, R. K. Sheridan, Z. D. Stempel, F. H. Sternberg, W. F. Bailey, *Chem. Eur. J.* **2016**, *22*, 5156–5159.

[15] a) G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668–7700; b) R. S. Varma, *Green Chem.* **2014**, *16*, 2027–2041; c) T. K. Achar, S. Maiti, P. Mal, *RSC Adv.* **2014**, *4*, 12834–12839; I. Dokli, M. Gredicak, *Eur. J. Org. Chem.* **2015**, 2727–2732; d) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413–447; e) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007–4019; f) J.-L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, *3*, 13–19.

[16] R. Mocci, L. De Luca, F. Delogu, A. Porcheddu, *Adv. Synth. Catal.* **2016**, *358*, 3135–3144.

[17] a) M. K. Beyer, H. Clausen-Schaumann, *Chem. Rev.* **2005**, *105*, 2921–2941; b) P. J. Walsh, H. Li, C. A. de Parrodi, *Chem. Rev.* **2007**, *107*, 2503–2545; c) T. K. Achar, P. Mal, *J. Org. Chem.* **2015**, *80*, 666–672; d) L. Li, J.-J. Wang, G.-W. Wang, *J. Org. Chem.* **2016**, *81*, 5433–5439; e) L. Konnert, F. Lamaty, J. Martinez, E. Colacino, *J. Org. Chem.* **2014**, *79*, 4008–4017; f) Z.-J. Jiang, Z.-H. Li, J.-B. Yu, W.-K. Su, *J. Org. Chem.* **2016**, *81*, 10049–10055; g) V. Porte, M. Thioloy, T. Pigoux, T.-X. Metrò, J. Martinez, F. Lamaty, *Eur. J. Org. Chem.* **2016**, 3505–3508; h) T.-X. Métro, J. Bonnamour, T. Reidon, A. Duprez, J. Sarpoulet, J. Martinez, F. Lamaty, *Chem. Eur. J.* **2015**, *21*, 12787–12796; i) A. Beillard, X. Bantreil, T.-X. Mètro, J. Martinez, F. Lamaty, *New J. Chem.* **2017**, *41*, 1057–1063; j) J. G. Hernández, E. Juaristi, *J. Org. Chem.* **2010**, *75*, 7107–7111; k) J. G. Hernández, E. Juaristi, *J. Org. Chem.* **2011**, *76*, 1464–1467; l) J. M. Landeros, E. Juaristi, *Eur. J. Org. Chem.* **2017**, *41*, 687–694.

[18] a) R. Thorwirth, F. Bernhardt, A. Stolle, B. Ondruschka, J. Asghari, *Chem. Eur. J.* **2010**, *16*, 13236–13242; b) I. Huskić, I. Halasz, T. Friščić, H. Vančik, *Green Chem.* **2012**, *14*, 1597–1600; c) G. Cravotto, E. C. Gaudino in *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges* (Eds.: A. Stolle, B. Ranu), RSC Green Chemistry Series, RSC, Cambridge, **2014**, pp. 58–80; d) R. Ghorbani-Vagheri, H. Veisi, *Synthesis* **2009**, *6*, 945–950.

[19] a) L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041–3043; b) L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 1519–1521; c) L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2001**, *66*, 7907–7909; d) M. G. Mura, L. De Luca, M. Taddei, J. M. J. Williams, A. Porcheddu, *Org. Lett.* **2014**, *16*, 2586–2589.

[20] The principal advantages of using NCS include the ease in handling, the mild conditions under which chlorination proceeds, and the simplicity of removal of the innocuous byproduct succinimide.

[21] a) J. M. Antelo, F. Arce, J. Crugeiras, C. Pastoriza, A. Rios, *J. Chem. Res. Synop.* **2001**, 20–21; b) J. M. Antelo, F. Arce, J. Crugeiras, M. Parajò, *J. Phys. Org. Chem.* **1997**, *10*, 631–636; c) S. R. Rajamäki, L. De Luca, F. Capitta, A. Porcheddu, *RSC Adv.* **2016**, *6*, 38553–38557.

[22] *N*,*N*-Dichlorobenzylamine (**B**) and *N*-chlorobenzylimine (**C**) were used in separate reactions as starting materials to prove the pathways leading to compounds **D** and **E**.

[23] A. Wang, H. Jiang, *J. Org. Chem.* **2010**, *75*, 2321–2326.

[24] P. Li, L. Wang, L. Zhang, G.-W. Wang, *Adv. Synth. Catal.* **2012**, *354*, 1307–1318.

[25] W. Han, B. Liu, J. Chen, Q. Zhou, *Synlett* **2017**, *28*, 835–840.

[26] L. Gu, C. Jin, *Chem. Commun.* **2015**, *51*, 6572–6575.

[27] C. M. Nicklaus, P. H. Phua, T. Buntara, S. Noel, H. J. Heeres, J. G. de Vries, *Adv. Synth. Catal.* **2013**, *355*, 2839–2844.

[28] C.-P. Zhang, J. Cai, C.-B. Zhou, X.-P. Wang, X. Zheng, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 9516–9518.

[29] H. Huang, X. Li, C. Yu, Y. Zhang, P. S. Mariano, W. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 1500–1505; *Angew. Chem.* **2017**, *129*, 1522–1527.

[30] E. Barragan, A. Bugarin, *J. Org. Chem.* **2017**, *82*, 1499–1506.

[31] S. H. Christensen, E. P. K. Olsen, J. Rosenbaum, R. Madsen, *Org. Biomol. Chem.* **2015**, *13*, 938–945.

[32] Q. Feng, Q. Song, *J. Org. Chem.* **2014**, *79*, 1867–1871.

[33] D. Leow, *Org. Lett.* **2014**, *16*, 5812–5815.

[34] S. Kamijo, K. Tao, G. Takao, H. Tonoda, T. Murafuji, *Org. Lett.* **2015**, *17*, 3326–3329.

[35] H. Jiang, J. R. Bak, F. J. Lopez-Delgado, K. A. Jorgensen, *Green Chem.* **2013**, *15*, 3355–3359.

[36] M. Iinuma, K. Moriyama, H. Togo, *Eur. J. Org. Chem.* **2014**, 772–780.

[37] B. Skillinghaug, C. Sköld, J. Rydfjord, F. Svensson, M. Behrends, J. Sävmarker, P. J. R. Sjöberg, M. Larhed, *J. Org. Chem.* **2014**, *79*, 12018–12032.

[38] H. Niu, L. Lu, R. Shi, C. W. Chaing, A. Lei, *Chem. Commun.* **2017**, *53*, 1148–1151.

[39] G. Olivo, S. Giosia, A. Barbieri, O. Lanzalunga, S. Di Stefano, *Org. Biomol. Chem.* **2016**, *14*, 10630–10635.

[40] Y. Kumar, Y. Jaiswal, A. Kumar, *J. Org. Chem.* **2016**, *81*, 12247–12257.

[41] B. V. Rokade, S. K. Malekar, K. R. Prabhu, *Chem. Commun.* **2012**, *48*, 5506–5508.

[42] C. Tao, B. Wang, L. Sun, Z. Liu, Y. Zhai, X. Zhang, J. Wang, *Org. Biomol. Chem.* **2017**, *15*, 328–332.

[43] Q. Feng, Q. Song, *Adv. Synth. Catal.* **2014**, *356*, 1697–1702.

[44] Y.-J. Zhuang, J. Liu, Y.-B. Kang, *Tetrahedron Lett.* **2016**, *57*, 5700–5702.

[45] L. Jia, X. Junchao, R. Jiangmeng, Z. Bu-Bing, *Chem. Lett.* **2014**, *43*, 190–192.

[46] R. Kupfer, U. H. Brinker, *J. Org. Chem.* **1996**, *61*, 4185–4186.

Received: May 18, 2017

