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An Evaluation of Multiple Catalytic Systems for the Cyanation of 2,3-Dichlorobenzoyl Chloride: Application to the Synthesis of Lamotrigine

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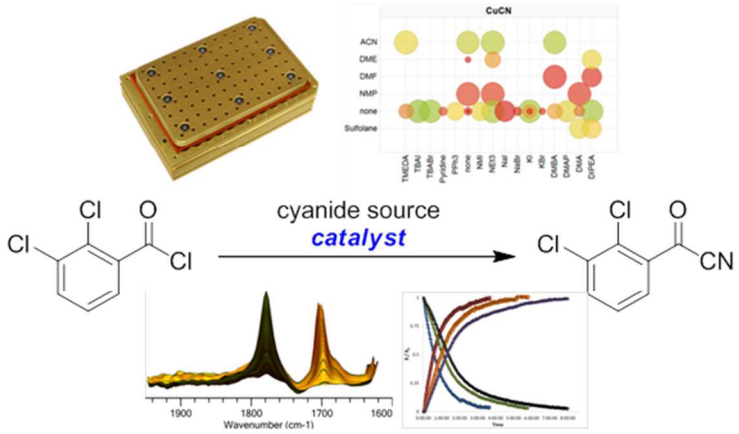


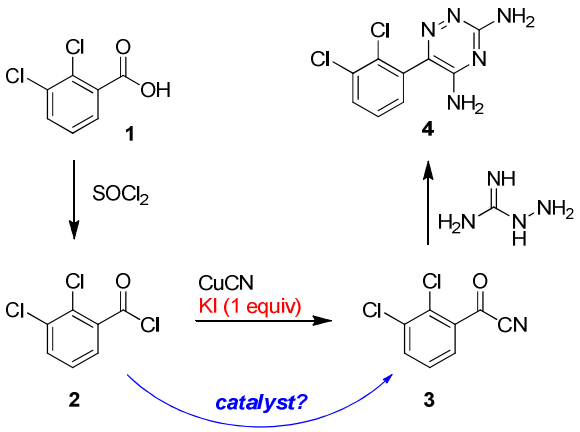
KEYWORDS: acyl cyanide, cyanation, lamotrigine, catalysis, phase-transfer catalysis.

ABSTRACT: 2,3-Dichlorobenzoyl cyanide is a key intermediate in the synthesis of Lamotrigine. An assessment of various catalytic systems for the cyanation of 2,3-dichlorobenzoyl chloride with cyanide salts is described. High-throughput experimentation identified many conditions for effecting the requisite chemistry, including amine bases and phase-transfer catalysts, as well as catalyst-free conditions utilizing acetonitrile as a polar co-solvent. A novel catalyst, $CuBr_2$, was identified by consideration of the possible oxidation of Cu(I) during high throughput screening experimentation. CuCN was found to be the best cyanide source for achieving clean conversion; however, the solubility of CuCN was the major factor limiting reaction rate under many conditions. Improving CuCN solubility by using acetonitrile as solvent enhanced the the reaction rate even in the absence of the catalysts tested but significantly complicated isolation of the product. With no acetonitrile co-solvent, phase-transfer catalysts such as tetrabutylammonium bromide (TBABr) are effective; however, use of TBABr led to inconsistent reaction profiles from run-to-run, due to an unexpected clumping of the CuCN solid. Switching to cetyltrimethylammonium bromide (CTAB) alleviated this clumping behaviour, leading to consistent reactivity. This CTAB-catalyzed process was scaled up, giving 560 kg of 2,3-dichlorobenzoyl cyanide in 77% isolated yield.

Introduction.

Lamotrigine (**4**), first disclosed in the early 1980s by researchers at the Wellcome Foundation,[1] continues to be a front-line anticonvulsant medicine for the treatment of epilepsy, bipolar disorder, and other conditions.[2] In the intervening years, many syntheses of Lamotrigine have been reported, with the vast majority following the general route starting from 2,3-dichlorobenzoic acid (**1**) shown in Scheme 1.[1,3,4] Among these routes, the reported conditions for cyanation of the acid chloride intermediate **2** to give the acyl cyanide **3** are the most varied. Known systems differ in cyanide source, solvent, reaction temperature, and additive / catalyst. Classic methods for the cyanation of acyl chlorides involve high-temperature (>150 °C) treatment with CuCN, often conducted neat.[5] A milder approach for large-scale preparations of Lamotrigine intermediate **3** involves the use of a stoichiometric amount of KI in conjuction with CuCN at lower reaction temperatures.[3a] Because of the simplicity of the organic starting materials, and the high molecular weight of KI, this one additive can constitute an inordinately high proportion of the overall cost of goods. In addition, the correspondingly large mass of iodine-containing waste generated makes the process undesirable from an environmental standpoint. Thus, an inexpensive catalyst capable of achieving comparable or better cyanation activity would greatly improve this process.

Scheme 1. General synthetic sequence for the preparation of Lamotrigine (**4**) from **1**.



A number of potential catalyst systems for the formation of aroyl cyanides have been reported both in the academic and patent literature.[4,6-8] One common approach is the use of phase-transfer catalysts, generally tetraalkylammonium salts such as tetrabutylammonium bromide or iodide.[4a,d,7] Potassium iodide could also potentially be made catalytic, with iodide acting as a nucleophilic catalyst to activate the acid chloride toward cyanation. Finally, combining alternative cyanide sources such as NaCN, $Zn(CN)_2$, or $K_4Fe(CN)_6$ with various catalysts has also been reported previously for cyanation of aroyl chlorides.[3e,4b,8]

Herein we describe our efforts to evaluate multiple catalyst systems for the cyanation of **2** to generate **3**, without increased processing to remove said catalyst, or formation of byproducts. This was achieved by a combined high-throughput screening and reaction profiling approach to ascertain the features and limitations of each system. These experiments led to the discovery of $CuBr_2$ as a previously unreported catalyst for this transformation, as well as identification of cetyltrimethylammonium bromide (CTAB) as a superior phase-transfer catalyst. Informed by small-scale reaction progress experiments, the synthesis of **3** was accomplished using the CTAB system on large scale with a 77% isolated yield.

Results and Discussion.

High throughput screening. In order to rapidly evaluate several sets of reaction conditions for the synthesis of **3**, two high-throughput screens (~0.1 mmol scale) were designed using a qualitative Design of Experiments approach to simultaneously examine three cyanide sources (CuCN, NaCN and $Zn(CN)_2$; data for CuCN and NaCN shown in Figure 1), five co-solvents paired with p-xylene (acetonitrile (ACN), 1,2-dimethoxyethane (DME), *N*,*N*-dimethylformamide (DMF), *N*-methyl-pyrrolidinone (NMP), and sulfolane), and fifteen catalysts. The reactions with NaCN were also run with four different Cu(I) co-catalysts (CuCl, CuBr, CuI, and $Cu[ACN]_4OTf$). To simplify this process, 2,3-dichlorobenzoyl chloride (**2**) was synthesized on a preparative scale[9] and used directly, rather than being generated *in situ* from 2,3-dichlorobenzoic acid (**1**) and thionyl chloride as for the manufacturing process. From these high-throughput experiments, multiple hits were identified (>95% conversion of **2** determined by GC, Figure 1).

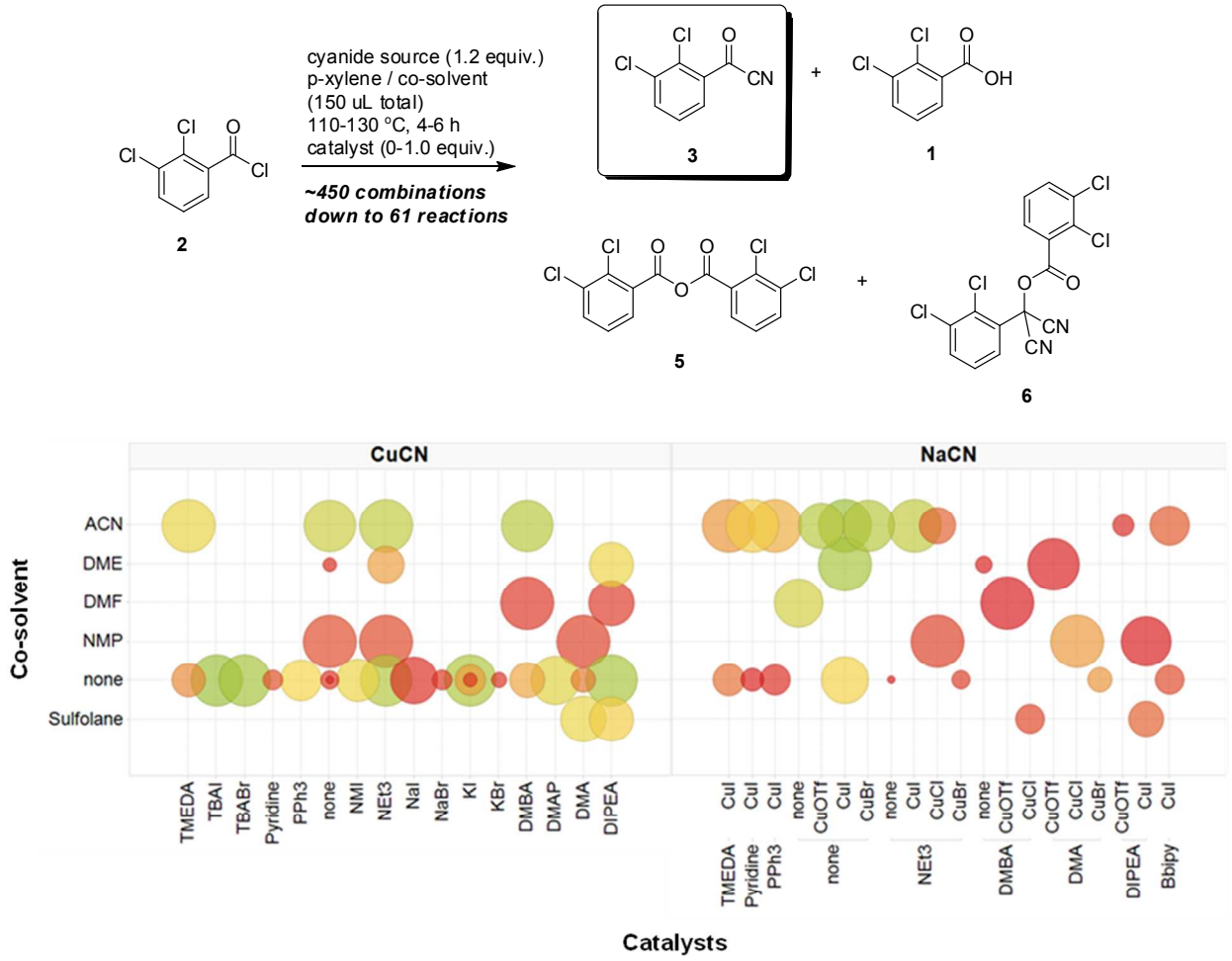


Figure 1. Data visualization of high-throughput experimentation results for reactions with CuCN (left) and NaCN / Cu cat. (right). The y-axis is co-solvent used in conjunction with *p*-xylene, while the x-axis is catalyst (including Cu co-catalyst for NaCN reactions; TMEDA: *N*,*N*,*N*',*N*'-tetramethylethylenediamine; TBAI: tetrabutylammonium iodide; TBABr: tetrabutylammonium bromide; NMI: *N*-methylimidazole; DMBA: *N*,*N*-dimethylbenzylamine; DMAP: 4-dimethylaminopyridine; DMA: *N*,*N*-dimethylaniline; DIPEA: *N*,*N*-diisopropylethylamine; Bbipy: 4,4'-di-*tert*-butylbipyridine). Catalyst charges were typically 10 mol%, with some variability between 5-100 mol%. The size of the points corresponds to % conversion of starting acid chloride 1 (large is high conversion), while the colour of the points represents % product **3** (gradient from red = 0%; to yellow = 50%; to green = 100%). Multiple points under the same set

of conditions represent either repeats, or in the case of KI for cyanation with CuCN and no co-solvent, different equivalents of KI: green point: 1.0 equiv.; yellow point: 0.5 equiv.; red point: 0.1 equiv. Blank areas represent runs not performed. See SI for full numeric table of results, including detailed reagent/catalyst charges for each case.

With *p*-xylene as the solvent and CuCN as the cyanide source, efficient catalysts included the reportedly effective PTCs tetrabutylammonium bromide and iodide (TBABr and TBAI),[4a,d] and aliphatic amines triethylamine and diisopropylethylamine;[4c] notably, these tertiary amines outperformed the common nucleophilic catalyst DMAP. With acetonitrile as a co-solvent (1:1 v/v), no added catalyst was required.[4b] Finally, the combination of NaCN and 10 mol% CuX (X = Cl, Br, I) in 1:1 *p*-xylene/acetonitrile was also effective. Analysis of the crude reaction mixtures by GC revealed the formation of the desired acid cyanide (**3**, 65-75%), and also the carboxylic acid (**1**), anhydride (**5**), and bis(cyanohydrin)-derived ester **6** when using NaCN/CuX.[3e,7] Compounds **1** and **5** were also observed when using stoichiometric KI on high-throughput scale as a positive control, suggesting that adventitious water from atmospheric exposure during reaction set-up is responsible for the hydrolysis side reactivity. Notably, reduction of KI equivalents to 0.5 or 0.1 resulted in only 35% and 7% GC yield respectively. This suggests that iodide is not simply acting as a nucleophilic catalyst in these cases, as the yield is directly proportional to, and never exceeds, the amount of KI added.

Scale up inconsistencies and CuCN solubility. Once several sets of conditions were identified, we prioritized scaling these reactions to ~5 mmol under anhydrous and anaerobic conditions, and developing reaction profiles by using *in situ* ReactIR monitoring of the carbonyl stretches of both **2** (1790 cm^{-1}) and **3** (1700 cm^{-1}). Not only are these two peaks well resolved,

they also have the same absorption coefficient (i.e. **2** and **3** have the same response factor) as confirmed by GC analysis of several timepoints along the profile.[10]

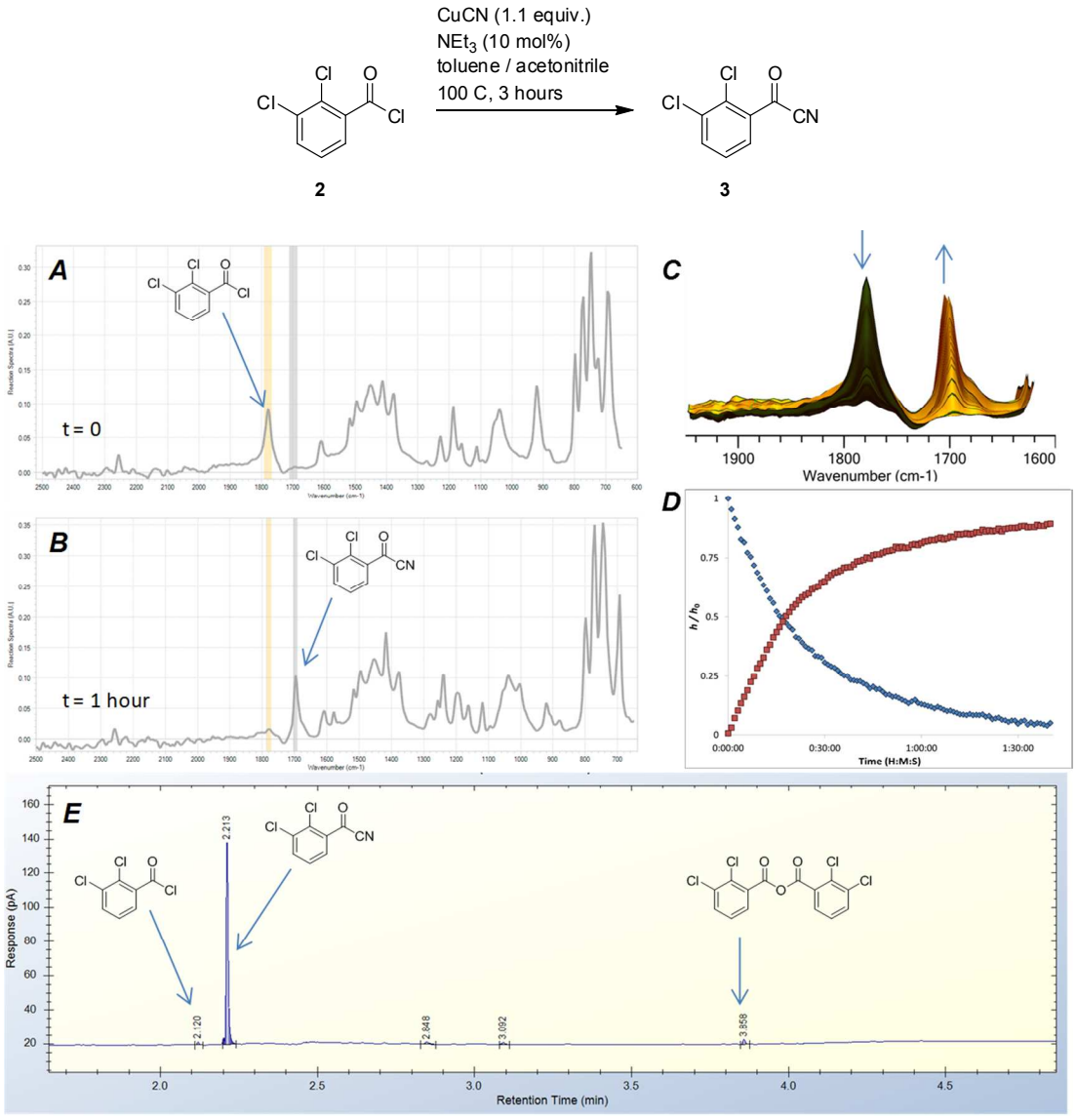


Figure 2. Reaction monitoring data for the cyanation of **1** with CuCN (1.1 equiv.) and NEt_3 (10 mol%) in toluene/acetonitrile (1:1 v/v). ***A***: Solution-phase IR spectrum at reaction start, with C=O stretch for **1** indicated. ***B***: Solution-phase IR spectrum at one hour reaction time, with C=O stretch for **2** indicated. ***C***: Contour-plot of reaction progress as judged by disappearance of C=O stretch at 1790 cm^{-1}, and growth of C=O stretch at 1700 cm^{-1}. ***D***: Reaction profile curve, with

h/h_0 plotted versus time for both **2** (blue) and **3** (red) (h is peak height to single-point baseline, h_0 is initial peak height). *E*: GC trace of reaction mixture after 3 hours (92.4% area for **2**).

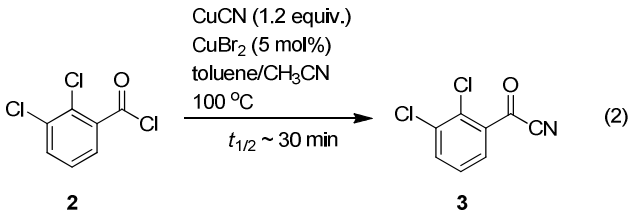
Initially, NEt_3 was investigated as a catalyst using toluene as the reaction solvent. In contrast to screening results, at ~5 mmol scale, no conversion was observed after one hour at 100 °C; over this period, it was evident that the CuCN did not dissolve. Distillation of approximately half of the toluene and addition of an equal volume of acetonitrile initiated the reaction as observed by ReactIR, and complete dissolution of the CuCN was observed after approximately 30 minutes. Since screening had also identified "catalyst-free" conditions with a *p*-xylene-acetonitrile solvent system, the cyanation was repeated on ~5 mmol scale with 1:1 toluene/acetonitrile with no added NEt_3. Again in contrast to the screening results, no conversion was observed after one hour; visually, CuCN had again failed to dissolve. Addition of 10 mol% NEt_3 to this stirring suspension resulted in immediate formation of **3**, and dissolution of CuCN over about 30 minutes. The toluene/acetonitrile/NEt_3 conditions were repeated to generate the reaction data shown in Figure 2; importantly, the degree of hydrolysis to **1** and **5** is greatly diminished under these conditions, as shown in the GC trace (Figure 2, E).

A kinetic analysis[10] of this reaction indicates an overall first-order process, with the rate law shown in equation 1. The apparent zero-order dependence on [CuCN] is almost certainly due to the poor solubility of CuCN in the reaction medium, leading to an effectively constant, low concentration of CuCN until two half-lives have passed (i.e., the reaction is run effectively under *pseudo*-first-order conditions).

$$\text{Rate} = (6.21 \times 10^{-4}\ s^{-1})\ [\mathbf{2}]^1[\text{CuCN}]^0 \qquad (1)$$

(at 100 °C and 10 mol% NEt_3; order in NEt_3 not determined)

The inconsistencies observed between benchtop high-throughput screening experiments and larger-scale anhydrous reactions were disconcerting, as they could indicate the potential for irreproducibility based on unseen reaction variables. One possible reason for this is the presence of water and/or air in the screening reactions; a much larger degree of hydrolysis was certainly observed on small-scale. While trace water would likely be consumed rapidly to generate **1** and/or **5**, adventitious oxygen could effect a small degree of oxidation of Cu(I) to Cu(II) in the CuCN. We hypothesized that a small amount of Cu(II) may be able to catalyze the desired cyanation reaction. Rather than relying on adventitious O_2, $CuBr_2$ was investigated as a possible catalyst to test this hypothesis. At 5 mol% of $CuBr_2$, the conversion of **2** to **3** occurs with a half-life of approximately 30 minutes, which is comparable to rates observed with catalytic NEt_3. While this result supports the hypothesis of a Cu(II)-catalyzed cyanation reaction in the high-throughput experiments, the exact role(s) of Cu(II) in this chemistry is not known, and beyond the scope of the current investigation. Furthermore, we did not identify any clear practical advantage to using $CuBr_2$ *in lieu* of other systems identified in our high-throughput screens.



2 **3** (2)

If CuCN solubility is the key factor in determining a successful reaction, as suggested by the aforementioned kinetic analysis, there should be a pronounced solvent effect on reaction rates; therefore, an evaluation of NEt_3 and $CuBr_2$ as catalysts in acetonitrile as the sole reaction solvent was undertaken, and compared to catalyst-free conditions (Figure 3). With no added catalyst, the cyanation has an initial rate of 1.02×10^{-4} M s^{-1}, whereas use of 5 mol% $CuBr_2$ increases the initial rate by only a factor of 1.3. NEt_3 (10 mol%) effects an increase of 2.4-fold

over the uncatalyzed reaction; however this is in stark contrast to the orders-of-magnitude increase for both of these catalysts observed in the toluene/acetonitrile solvent mixture. These data clearly support the hypothesis that CuCN solubility is the key rate-limiting factor, and also indicate that the catalytic effect of NEt_3 or $CuBr_2$ is negligible when using acetonitrile..

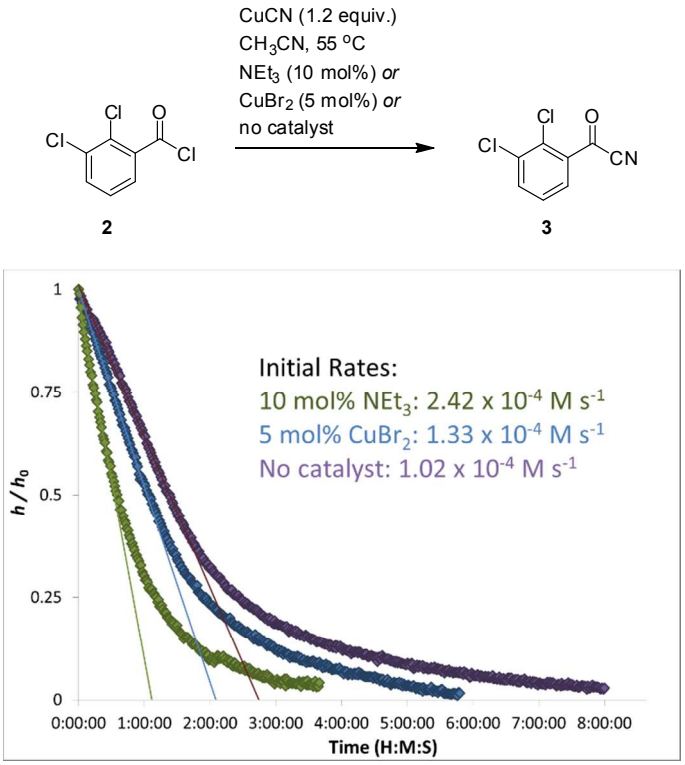


Figure 3. Reaction monitoring data for the cyanation of **2** with CuCN (1.2 equiv.) and NEt_3 (10 mol%, green points), $CuBr_2$ (5 mol%, blue points), or no catalyst (purple points) in acetonitrile at 55 ºC, with initial rates shown. Initial rates were determined by linear regression of the concentration vs. time curve up to 50% conversion.

Phase-Transfer Catalysis. While using either NEt_3 or $CuBr_2$ as a catalyst would be both economical and rapid relative to stoichiometric KI, one clear disadvantage is the need for acetonitrile as a co-solvent. A major issue is that use of this co-solvent would complicate Cu salt removal post-reaction. Under the acetonitrile-only conditions, the reaction mixture is

homogeneous upon complete conversion of **2**, with the Cu(I) salt byproducts clearly in solution. Furthermore, the existing isolation of **3** involves a toluene/petroleum ether crystallization, which would necessitate a complete solvent swap from acetonitrile to toluene, increasing cycle time and adding complexity.

In order to develop the simplest process possible, avoid the aforementioned issues, and enable efficient solvent recycling by using a single reaction solvent, the phase-transfer catalyst TBABr (identified during high-throughput screening) was investigated with toluene as the sole reaction solvent and monitored on ~1 g scale. The cyanation reaction does proceed under these conditions; however, the reaction is slow, the kinetic profile is odd, and reactivity is not consistent from run to run (Figure 4, *top* shows a representative profile). These issues likely arise from mass-transport limitations: in reactions catalyzed by TBABr, the solid CuCN was observed to clump together to form a large mass; this clumping occurs regardless of the order of reagent/solvent addition, and does not appear to be affected by stir rate.

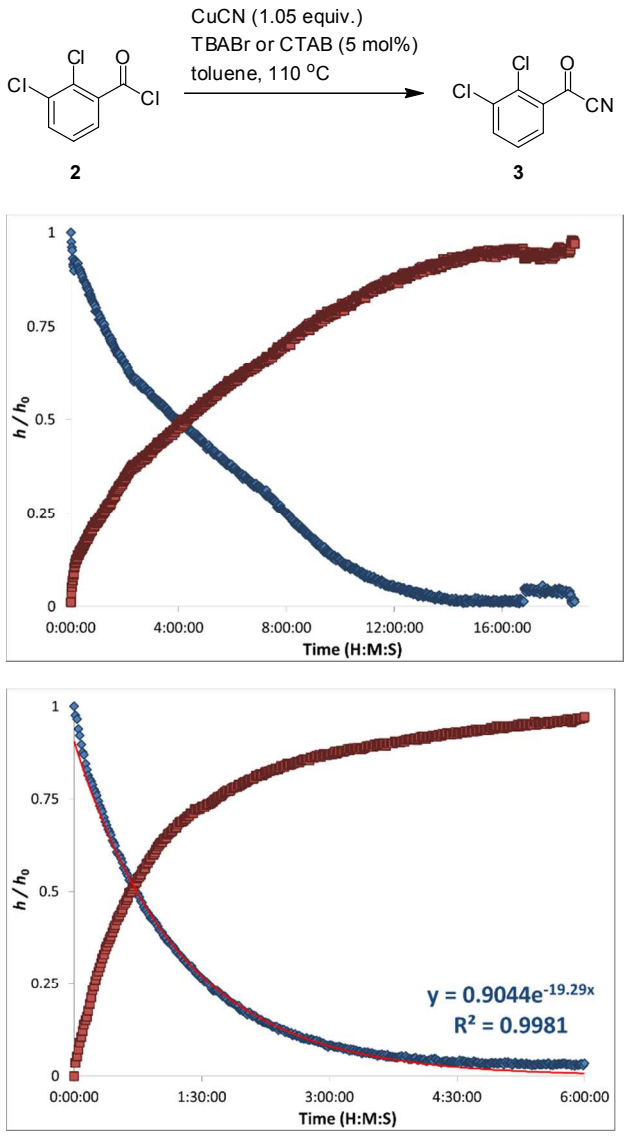
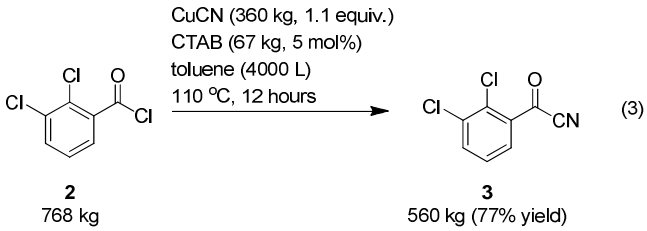


Figure 4. Representative reaction profile curves, for the cyanation of **2** using CuCN (1.05 equiv.) and 5 mol% of either TBABr (*top*, $t_{1/2}$ ~4 hours) or CTAB (*bottom*, $t_{1/2}$ ~40 min, orange line: first-order fit to 95% conversion).

Since CuCN clumping was only observed when using TBABr, and not under any of the previous cyanation conditions, we sought other readily-available phase-transfer catalysts that would not exhibit this behaviour. Due to the observed hydrolytic sensitivity of both acid chloride **2** and desired product **3**, we required use of anhydrous PTCs; unfortunately, many

inexpensive PTCs (such as the Aliquat series) are supplied as aqueous solutions or hydrates, limiting the scope of suitable catalysts. Two inexpensive, (largely) anhydrous, and readily available PTCs were investigated on 1 g scale: benzyltriethylammonium chloride fared poorly (42 hours reaction time with 10 mol% $BnNEt_3Cl$), but cetyltrimethylammonium bromide (CTAB) resulted in rapid, consistent reactivity in toluene (Figure 4, *bottom*). The kinetics of the reaction fit very well to a first-order function up to 95% conversion, with a half-life of approximately 40 minutes at 110 °C. This kinetic behaviour is again consistent with a low, constant concentration of CuCN during the reaction, leading to an apparent zero order in [CuCN], and first order in [**2**]. Due to these favourable kinetics at 5 mol% catalyst, lower or higher CTAB loadings were not explored.

Isolation of **3** generated using CTAB by a simple filtration of the Cu salts and evaporation of the solvent gave a 90% isolated yield of crude product, which was 90% pure based on ^{1}H NMR spectroscopy; the other components were **2** (4%) and **5** (6%). Importantly, the phase-transfer catalyst was not carried through the work-up procedure, which ensures that additional catalyst removal steps are not required. In fact, as a result of the small-scale development work described herein, the preparation of **3** using 5 mol% CTAB was directly scaled to 768 kg input of **2**. For these demonstration runs, the reaction was run at 110 °C for 12 hours to ensure complete conversion. Employing a simple isolation procedure resulted in 77% isolated yield of **3** with 94% purity (eq. 3; average of three runs); the 6% mass balance is comprised of 4% of **1** and 2% of **5**. This material was then successfully used to produce Lamotrigine (**4**).



Conclusions.

As a result of both high-throughput screening and reaction profiling, multiple catalyst systems for the cyanation of 2,3-dichlorobenzoyl chloride (**2**) have been evaluated. While several effective conditions were identified using NaCN, the formation of the homocoupling byproduct **6** (Figure 1) led us to focus on CuCN as the cyanide source. Good to excellent conversion to **3** was effected by the use of simple amines, Cu(II) salts, and phase-transfer catalysts, in addition to "catalyst-free" conditions using acetonitrile as the reaction solvent. In all of these systems, the solubility of CuCN is the crucial factor, and the probable main function of each catalyst or solvent is to influence the rate of CuCN dissolution.

With this in mind, the mechanism of catalysis by NEt_3 and DIPEA is somewhat puzzling. Certainly, one possibility is activation of the acid chloride through formation of a more electrophilic *N*-acylammonium species; however, three pieces of evidence are not fully consistent with this picture. First, DMAP (a generally efficient acylation catalyst) was inferior to NEt_3 and even DIPEA in high-throughput screening; second, *catalytic* KI (another acylation catalyst) gave very poor cyanation in high-throughput screening (<10% yield with 10 mol% KI); and third, NEt_3 increases the cyanation rate only by a factor of 2.4 in acetonitrile (where CuCN solubility is markedly increased) relative to the orders-of-magnitude rate increase in toluene/acetonitrile. Another possibility is that these aliphatic amines act as ligands for Cu, and

assist in breaking up the polymeric chains of solid CuCN. Finally, there is the possibility that a putative *N*-acylammonium species formed by acylation of the amine could also act as a phase-transfer catalyst to bring CuCN into solution. If this is the case, more typical tetraalkylammonium phase-transfer catalysts are evidently superior for this purpose. In any event, it is clear that CTAB is a highly effective PTC, enabling efficient cyanation using CuCN without the need for a polar co-solvent.

Finally, from a mass efficiency and cost standpoint, all of the identified systems are preferrable to the use of stoichiometric KI. While the use of acetonitrile is not desirable due mainly to difficulties in Cu salt removal and solvent swapping and recyclability complications, phase-transfer catalysts are operative in toluene, albeit with markedly different activities. CTAB is a highly effective catalyst for this cyanation, giving a far more reliable reaction profile than TBABr. The estimated reduction in material cost by employing 5 mol% CTAB *in lieu* of stoichiometric KI is ~60% for this stage and ~20% for the entire synthesis, with no increase in cycle time or number of unit operations.

Experimental Section.

Materials. All reagents and solvents were purchased from commercial suppliers and used as received.

NMR Spectroscopy. All NMR spectra were acquired at ambient temperature on a Bruker 400 MHz or 500 MHz spectrometer. Solvents and frequencies for specific data acquisitions are noted for each case.

Gas Chromatography. All GC analyses were conducted using an Agilent 6890 series instrument equipped with a low thermal mass oven unit. The following generic method was used: column: DB-5, length 15 m, diameter 250 μm, film thickness 0.1; inlet: temperature 275 °C, pressure 30 psi, split ratio 100:1; main oven: temperature 275 °C; detector: temperature 320 °C, H_2 flow 40 mL/min, air flow 450 mL/min, make up N_2 flow: 25 mL/min; LTM oven method program: constant pressure mode, initial temperature 50 °C (hold 0.5 min), ramp temperature at 75 °C/min up to 320 °C (hold 2.5 min), ramp temperature at 300 °C/min down to 50 °C. Total run time 7.5 min.

Approximate GC retention times of **1**-**3, 5** using method described above: **1**: 2.40 min; **2**: 2.12 min; **3**: 2.21 min; **5**: 3.85 min.

SAFETY NOTE: Metal cyanide salts, including but not limited to NaCN, CuCN, and $Zn(CN)_2$, are extremely toxic and can liberate hydrogen cyanide (HCN) gas if handled improperly. Great care must be taken when carrying out chemistry using these reagents, particularly on larger scales. All manipulations including weighing materials, charging materials, carrying out reactions, performing workup, isolation, and purification procedures, and quenching of waste, must be performed with sufficient ventilation. In the present case, all chemical waste from cyanide reactions was quenched by disposal into a caustic aqueous solution (pH > 12) before waste disposal.

Synthesis of 2. The preparation of this acid chloride was adapted from a literature procedure.[9] A 100 mL pear-shaped RB-flask containing a stirbar was charged with 25.0 g **1** (131 mmol). The flask was fitted with a water-cooled reflux condenser with a septum on the top joint. Nitrogen was flushed through the system using a needle attached to a rubber hose. The flask was

immersed in a sandbath in a heating mantle, with a probe monitoring the sand temperature. Thionyl chloride (48.9 g, 30.0 mL, 411 mmol, 3.14 equiv.) was added via syringe through the septum at the top of the condenser. The suspension was heated to reflux (sand bath: 80 °C) for 2 hours, during which time the organic solids dissolved in the thionyl chloride. The reaction mixture was then cooled to below the boiling point of thionyl chloride, and the reflux condenser quickly replaced with a hose-adapter connected to a dry ice / isopropanol cold trap preceeding a vacuum pump. The thionyl chloride was distilled off under reduced pressure. Once the volume had reduced by an appropriate amount, anhydrous toluene (10 mL) was added to the residue, and subsequently distilled off under reduced pressure. Once the toluene was removed, the hose adapter was replaced with a short-path distillation apparatus. The desired acid chloride product was isolated by vacuum distillation (sand bath temperature at 150 °C, vacuum at 3-5 mbar), giving a colourless oil that crystallized upon standing at room temperature. Yield: 24.0 g, 88% yield. ^{1}H and ^{13}C NMR spectra are consistent with the reported synthesis.[9] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, J = 7.9 Hz, 1 H); 7.70 (d, J = 7.9 Hz, 1 H); 7.37 (t, J = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.95, 135.69, 135.34, 134.82, 131.35, 130.43, 127.33.

Synthesis of 5 as an impurity marker. This compound was prepared by a modification of a literature procedure.[11] Compound **2** (515.4 mg, 2.461 mmol) was dissolved in dichloromethane (10 mL) in a 20 mL vial. In a separate 20 mL vial, sodium hydroxide (253 mg, 6.33 mmol) was dissolved in water (10 mL). A third 20 mL vial was charged with **1** (1207 mg, 6.32 mmol) and pyridine N-oxide (24.7 mg, 0.260 mmol). The NaOH solution was added via pipette to the **1**/pyridine N-oxide solids, and the suspension stirred at room temperature for 30 min to ensure complete dissolution. Once dissolution of **1** into the aqueous NaOH solution was complete, the DCM solution and the aqueous solution were combined in a 100 mL RB flask

containing a stirbar. The resulting biphasic mixture was stirred at ~1200 rpm at room temperature for one hour. The reaction progress was determined by GC analysis of the DCM layer, indicating complete consumption of **2**, and a new peak at later retention time assigned to **5**. The reaction mixture was diluted with 10 mL DCM, and 10 mL water. The mixture was transferred to a seperatory funnel, and the layers separated. The DCM phase was washed with with 0.02 M NaOH (20 mL), water (2 x 20 mL), and drired over MgSO4. The suspension was filtered, and the organic solvent removed via rotovap to give a white solid (773 mg, 86% crude yield) that was 83% pure by GC analysis. The crude product was recrystallized from refluxing toluene (10 mL) upon cooling to room temperature. The white crystals were collected by suction filtration, and washed with ice-cold toluene (2 x 3 mL) and hexanes (2 x 10 mL) before drying *in vacuo*. Yield: 575 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J*=7.97 Hz, 1 H) 7.74 (dd, *J*=8.07, 1.52 Hz, 1 H) 7.89 (dd, *J*=7.83, 1.57 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.43; 130.31; 132.96; 134.88; 135.39; 159.76. MS (EI): base peak *m/z* = 173/175 [$Cl_2C_6H_3CO^+$], consistent with the literature report.[10]

Synthesis of 3 as a product marker. A 5 mL RB flask containing a stirbar was charged with **2** (200 mg, 0.955 mmol), CuCN (94 mg, 1.055 mmol, 1.1 equiv), and KI (160 mg, 0.964 mmol, 1.01 equiv.). Toluene (0.5 mL) was added. The flask was fitted with a water-cooled reflux condenser equipped with a septum at the top joint. The system was flushed with N_2. The mixture was heated to reflux with using a sandbath/heating mantle. The reaction progress was monitored by periodic aliquots taken via syringe through the reflux condenser and analyzed by GC. After 3 hours at reflux, the mixture was cooled to room temperature. The suspension was filtered via suction filtration through a small plug of Celite to remove inorganic salts. The solvent from the filtrate was removed *in vacuo* to give the crude product (160 mg, 84% yield).

^{1}H and ^{13}C NMR spectroscopy and GC analysis reveal the presence of 8 mol% of **5**. Further purification of this material was not carried out. ^{1}H NMR ($CDCl_3$, 500 MHz): **3** (rel. integ.: 1.0): δ 8.08 (dd, *J* = 7.78, 1.07 Hz, 1 H); 7.84 (dd, *J*=7.93, 1.22 Hz, 1 H); 7.49 (t, *J*=8.09 Hz, 1 H); **5** (rel. integ.: 0.20): δ 7.88 (dd, *J*=7.93, 1.22 Hz, 1 H); 7.72 (dd, *J*=7.93, 1.22 Hz, 1 H); 7.36 (t, *J*=7.93 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz) **3**: δ 112.83; 127.92; 132.69; 132.71; 133.59; 136.48; 137.00; 165.15; **5**: 127.49; 130.32; 132.91; 134.90; 135.36; 159.70. GC analysis (peak area%): **3**: 92.5%; **5**: 7.5%.

Procedure for high-throughput screening experiments. Small-scale HTS reactions were carried out with 20 mg (0.1 mmol) of **2**, with 0.15 mL solvent ([**2**] = 0.64 M). Solid reagents were dosed using a FlexiWeigh (Mettler Toledo) instrument into a 48-well array of 1.5 mL crimp-cap HPLC vials containing micro stirbars. (NOTE: After dispensing metal cyanides, all potentially contaminated surfaces were thoroughly cleaned with bleach.) All liquid reagents and solvents were dispensed via micropipette to the appropriate vials according to the experimental design. Once all materials were charged, each vial was sealed with an aluminum crimp-cap containing a PTFE/silicone/PTFE septum. The septa were pierced with a wide-bore needle to allow gas ingress/egress. The vials (arrayed in a metal plate) were heated to the desired reaction temperature under 5 barg nitrogen inside a Cat96 pressure reactor (HEL). At the end of the reaction time, the reactor was cooled to room temperature and vented to atmosphere. The plate was removed, and the caps removed. Each vial was diluted with 1 mL dichloromethane. The plate was placed on a stirplate to ensure complete dissolution of any organic products. The resulting suspensions were centrifuged prior to analysis by GC.

Procedure for reaction profiling experiments of the cyanation of 2. An oven-dried, nitrogen-flushed 50 mL, 3-necked RB flask containing a stirbar was charged with **2** (1.00 g, 4.78

mmol) and anhydrous reaction solvent(s) (4-8 mL). The flask was fitted with a water-cooled reflux condenser, a ReactIR probe, and a septum. The reaction mixture was brought to the desired temperature using a sandbath/heating mantle. Once reaction temperature had stabilized, the reflux condenser was quickly removed and CuCN (1.05-1.2 equiv) was carefully added as a solid with vigorous stirring. For reactions with a solid catalyst ($CuBr_2$, PTCs), the catalyst was co-mixed with the CuCN. For reactions with a liquid catalyst (NEt_3), the catalyst was added via syringe through the septum. The reaction progress was monitored by IR spectra acquired every minute, and conversion determined by the relative heights of the carbonyl peaks for **2** (1790 cm^{-1}) and **3** (1700 cm^{-1}).

Procedure for large-scale preparation of 3. A glass-lined reactor was charged with a toluene solution of **2** (768 kg, 3667 mol, dissolved in 1 vol toluene), CuCN (360 kg, 4019 mol), and CTAB (67 kg, 184 mol) at room temperature. The reaction mixture was heated to 110 °C with stirring for 12 hours. The reactor was then cooled to room temperature. Toluene (2100 L) was charged, and the suspension filtered to remove the Cu salt byproducts and unreacted CuCN. These waste salts were washed with an additional portion of toluene (1400 L). Toluene was distilled from the combined organic solution under vacuum. Petroleum ether (1800 L) was added to the crude product, and the suspension was stirred for 12 hours at 15-20 °C. The product was collected by filtration to yield 560 kg of **3** (77% yield, 94% assay by HPLC, balance is 2,3-dichlorobenzoic acid **1** and corresponding anhydride **5**, average of three runs).

ASSOCIATED CONTENT

The following files are available free of charge via the Internet at http://pubs.acs.org.

Full table of HTS experimental data, kinetic plots, and representative characterization data (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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