ORGANOMETALLICS
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Cyanation of Aryl Chlorides Using a Microwave-Assisted, Copper-Catalyzed Concurrent Tandem Catalysis Methodology

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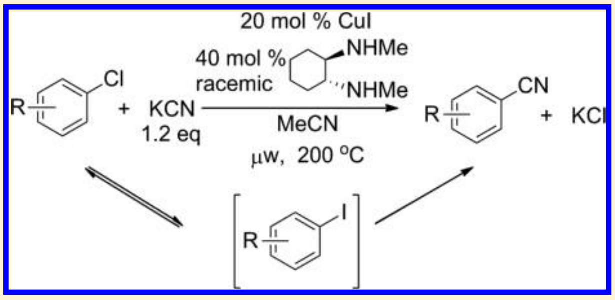
Supporting Information

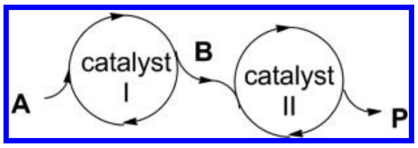
ABSTRACT: A microwave-assisted, copper-catalyzed concurrent tandem catalytic (CTC) methodology has been developed for the cyanation of aryl chlorides, where the aryl chloride is first converted to an aryl iodide via halogen exchange and the aryl iodide is subsequently transformed to the aryl nitrile. A variety of aryl chlorides were converted to aryl nitriles in 44−97% yield using 20 mol % of CuI, 40 mol % of *N*,*N*′-cyclohexane-1,2-diamine, and 1.2 equiv of KCN in acetonitrile at 200 °C after 1−2 h. The same copper/ligand system served as a multifunctional catalyst for both steps of the concurrent catalytic process. Unlike our previously reported CTC hydrodehalogenation of aryl chlorides, CTC cyanation was catalytic in iodide. Kinetic simulations of the proposed CTC mechanism were consistent with experimental results and stipulate the relative reaction rates of the two catalytic cycles necessary to achieve reasonable yields of product.



INTRODUCTION

As described by Baker and Bazan,[1] concurrent tandem catalysis (CTC) is defined as a transformation in which two or more catalytic cycles operate in a cooperative manner in a single reactor (Scheme 1).

Scheme 1. A Concurrent Tandem Catalytic (CTC) Cycle[a]



[a] Adapted from ref 1.

One advantage of CTC over one-pot, sequential tandem catalytic processes is that “efficient catalysts may allow the coupling of equilibrium-limited reactions with subsequent exothermic ones.”[1] Recently we developed such a microwave-assisted CTC methodology in which aryl chlorides or aryl bromides, in equilibrium with aryl iodides, were converted to arenes through a hydrodehalogenation reaction mediated by the same metal−ligand system that performed the halogen exchange (Scheme 2).[2] This methodology allowed the exploitation of the greater reactivity of C−I bonds over C−Cl and C−Br bonds[3] despite the presence of an equilibrium-limited first step in the case of aryl chloride to aryl iodide halogen exchange.[4,5] In our reported CTC hydrodehalogenation, the aryl chloride-aryl iodide halogen exchange equilibrium was shifted to the right by the consumption of the aryl iodide produced in the first catalytic reaction.

Having established the feasibility of a CTC cycle involving halogen exchange followed by hydrodehalogenation, we now demonstrate our ability to generalize this methodology by varying the second catalytic step. We chose one of the synthetically powerful carbon−carbon bond-forming reactions involving an aryl halide substrate, specifically the cyanation of aryl chlorides to produce aryl nitriles. Aryl nitriles have important applications as natural products, pharmaceuticals, agrochemicals, and dyes.[6] Additionally, they function as synthetic intermediates for a multitude of other functional groups. Palladium-catalyzed cyanations of aryl chlorides are known,[7−13] but there are relatively fewer examples of copper-catalyzed reactions. Previous reports of copper-catalyzed cyanation of aryl halides focused on aryl iodide and bromide substrates[4,14] or included only highly activated aryl chloride substrates.[15−18] Buchwald has reported a domino (CTC) halogen exchange−cyanation method for the copper-catalyzed cyanation of aryl bromides in the presence of 10 mol % of CuI, 20 mol % of KI, 1 equiv of *trans*-*N*,*N*′-dimethylethylenediamine, and 1.2 equiv of NaCN in toluene at 110−130 °C for 24 h.[5] The reaction tolerated a variety of functional groups and heteroatoms and produced good to excellent yields of the corresponding aryl nitriles after 24 h with conventional heating methods. However, no mention of the use of aryl chloride substrates was made. Given Buchwald’s work and our previous success with CTC hydrodehalogenation, we were subsequently able to develop a microwave-assisted, copper-catalyzed CTC cyanation of aryl chlorides.

RESULTS AND DISCUSSION

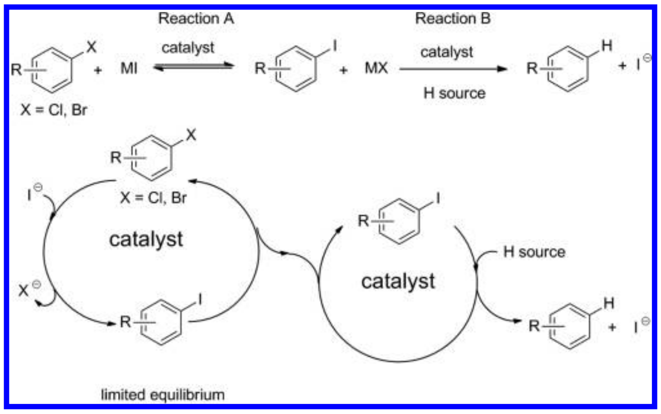
Reaction conditions were screened to optimize the microwave-assisted CTC cyanation method using 4-chlorotoluene as the substrate. The initial conditions examined were predicated upon both Buchwald’s reported conditions for CTC cyanation

Received: May 14, 2013

of aryl bromides[5] (vide supra) and our experience with CTC hydrodehalogenation of aryl chlorides and aryl bromides,[2] where a multifunctional copper/diamine species was the catalyst for both cycles. The highest conversion of aryl chloride (86%) and highest yield of 4-toluinitrile (78%) were obtained using 20 mol % of CuI, 40 mol % of *N*,*N'*-cyclohexane-1,2-diamine (ligand **1**), and 1.2 equiv of KCN in acetonitrile at 200 °C after heating for 1 h (Table 1, entry 1). The same reaction conducted at 150 °C (entry 2), the temperature at which aryl bromides could be converted to aryl nitriles after 1 h under microwave heating using ligand **2**, yielded only 10% of the desired product. Performing the reaction with heating to 200 °C in a high-temperature fluid bath instead of the microwave reactor resulted in only a trace of product being formed (entry 3). Attempting the reaction with ligand **2** at 200 °C produced only 6% product (entry 4). Decreasing catalyst/ligand loading by half (entry 5) led to only a slightly lower yield of product, but given the high temperatures required for CTC cyanation of aryl chlorides and concerns over catalyst stability, 20 mol % of copper iodide and 40 mol % of ligand **1** was deemed optimal. Lower conversions and yields were obtained when the cyanide source was NaCN (entry 6) or $K_3Fe(CN)_6$[19] (entry 7). Similar to Buchwald's CTC cyanation of aryl bromides, CTC cyanation of aryl chlorides occurred in the presence of only a catalytic amount of iodide (0.2 equiv present from 20 mol % of CuI); addition of NaI to increase the total amount of iodide to 2 equiv led to a decrease in yield of 4-toluinitrile (entry 8) due to the incomplete conversion of aryl iodide and the formation of toluene via hydrodehalogenation.

The optimized reaction conditions for CTC cyanation were applied to a variety of aryl chlorides (Table 2). For most substrates, yields of aryl nitriles ranged between 44 and 97%. The reaction is sensitive to steric crowding, as in the case of 2-chlorotoluene (entry 2, trace amount of product formed), but 1-chloronaphthalene was converted to the corresponding product in 44% yield. Fortunately, unlike CTC hydrodehalogenation, the presence of heteroatoms was well-tolerated by the cyanation reaction. Cyanation occurred in the presence of functional groups such as an alcohol (entry 4), a ketone (entry 5), an ether (entry 6), and both nitrogen- and sulfur-containing heterocycles (entries 7 and 8). By maintaining a catalyst loading of 20 mol % per C−Cl bond, 1,4-dichlorobenzene was converted to 1,4-dicyanobenzene in 27% yield (entry 9). A complex reaction mixture was observed in this reaction, which included products

Scheme 2. CTC Methodology for the Hydrodehalogenation of Aryl Chlorides and Aryl Bromides



Scheme 3. CTC Methodology for the Cyanation of Aryl Chlorides

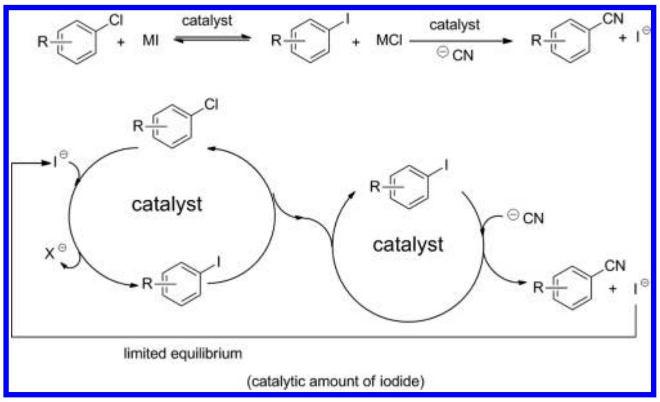
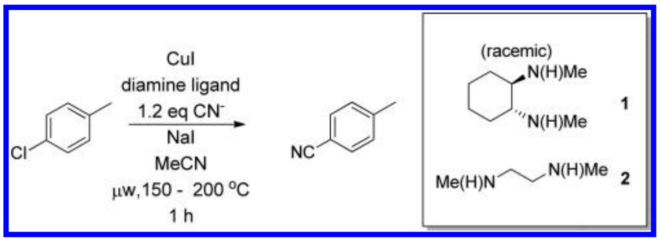


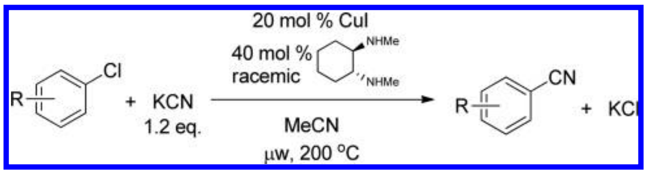
Table 1. Screening Conditions for Cyanation of 4-Chlorotoluene

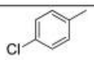
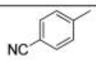
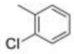
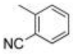
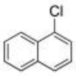
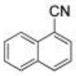
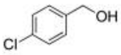
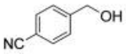
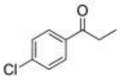
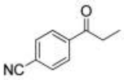
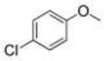
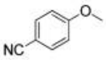
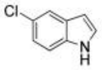
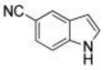
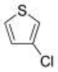
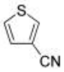
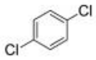
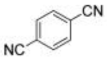


entry	amt of CuI (mol %)	ligand	amt of ligand (mol %)	CN^- source	amt of NaI (equiv)	*T* (°C)	conversn of ArCl[a] (%)	yield of ArCN[b] (%)
1	20	**1**	40	KCN	0	200	86	78
2	20	**1**	40	KCN	0	150	11	10
3	20	**1**	40	KCN	0	200[c]	1	trace
4	20	**2**	40	KCN	0	200	9	6
5	10	**1**	20	KCN	0	200	76	72
6	20	**1**	40	NaCN	0	200	67	66
7	20	**1**	40	$K_3Fe(CN)_6$	0	200	53	53
8	20	**1**	40	KCN	2	200	77	29
9	20	**1**	40	none	0	200	26	0
10	20[d]	**1**	40	NaCN[e]	0	200	21	2

[a]Determined by GC. [b]GC yield versus standard (*n*-decane). [c]Conducted using thermal heating (oil bath) instead of microwave heating. [d]CuCN instead of CuI. [e]Conducted with NaCN because the reaction with KCN could not reach the desired reaction temperature.

Table 2. Microwave-Assisted Copper-Catalyzed Cyanation of Aryl Chlorides To Form Aryl Nitriles via Concurrent Tandem Catalysis



Entry	ArCl	ArCN	time (hr)	Yield, %[a]
1			2	74
2			2	trace
3			1	44
4			1	81
5			1	97
6			1	62
7			1	88[b]
8			1	79[c]
9			1	26[d]

[a]Isolated yields (average of two runs). [b]≥90% purity as determined by ^{1}H NMR spectroscopy and GCMS; the impurity is due to the presence of a small amount of dimerization of the indole. [c]GC yield due to volatility of the product. [d]Reaction performed with 40 mol % CuI, 40 mol % ligand, and 4 equiv of KCN.

derived from various combinations of cyanation and hydrodehalogenation reactions.

Evidence that the cyanation reaction was taking place via the proposed CTC cycle shown in Scheme 3 came from experiments similar to those conducted for CTC hydrodehalogenation. First, the cyanide source was confirmed to be KCN (versus the acetonitrile solvent[20,21]) by conducting the cyanation of 4-chlorotoluene in the absence of the cyanide salt (Table 1, entry 9), which resulted in no formation of 4-toluinitrile. In order to establish that aryl iodide was an important intermediate to the transformation, the cyanation of 4-chlorotoluene was performed in the complete absence of iodide by replacing CuI with CuCN (Table 1, entry 10). The result was only a 2% yield of 4-toluinitrile and 17% consumption of 4-chlorotoluene, indicating that the direct cyanation of the aryl chloride was approximately 30 times slower than the corresponding reaction in the presence of 20 mol % of iodide (Table 1, entry 6).

In the case of CTC hydrodehalogenation, the observation of up to 40 mol % of aryl iodide being formed and then consumed during the course of the reaction of 4-chlorotoluene to produce toluene was consistent with the proposed CTC mechanism (Figure 1a). When this study was repeated for CTC cyanation using 4-chloropropiophenone as the substrate, 4-iodopropiophenone was not detected by GC-MS at any point in the reaction (Figure 1b). However, the observation of an aryl iodide intermediate for a given CTC reaction should be dependent upon the relative rates of the two catalytic cycles (Scheme 3). If cyanation of aryl iodide were fast relative to the halogen exchange step to convert aryl chloride to aryl iodide, any aryl iodide formed would be quickly converted to aryl nitrile and would not form in detectable quantities in the experimental data shown in Figure 1.

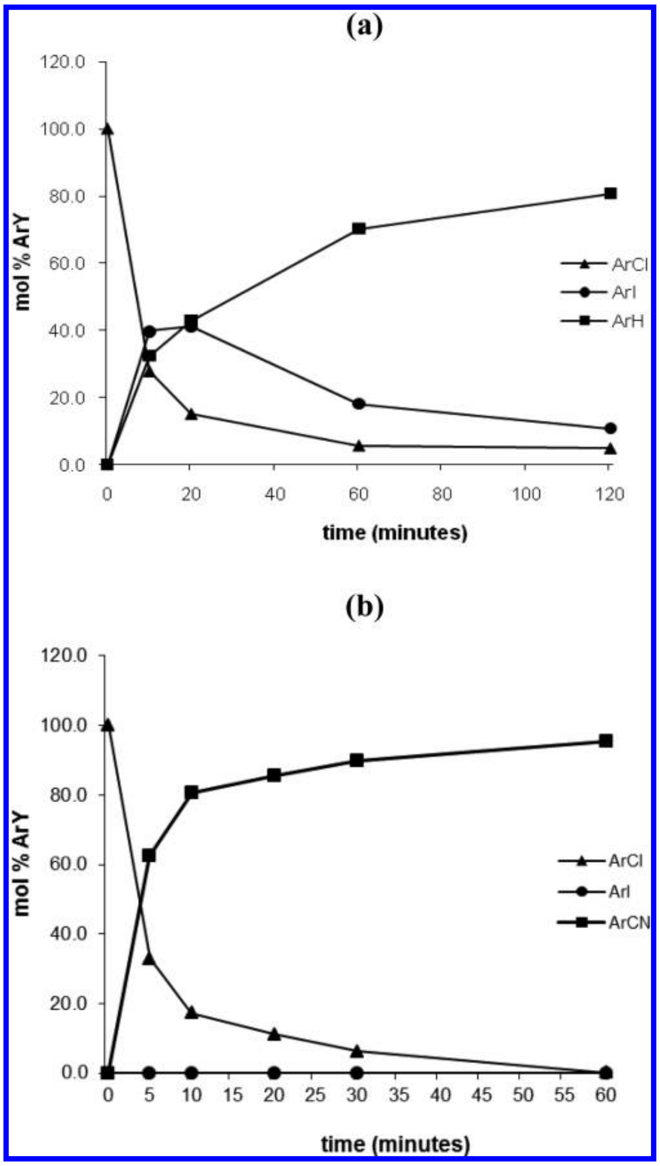


Figure 1. (a) Copper-catalyzed hydrodehalogenation of 4-chlorotoluene, performed using 20 mol % of CuI, 1.5 equiv of ligand **1**, 2 equiv of NaI, and acetonitrile as solvent at 200 °C using microwave radiation. (b) Copper-catalyzed cyanation of 4-chloropropiophenone, performed using 20 mol % of CuI, 40 mol % of ligand **1**, 1.2 equiv of KCN, and acetonitrile as solvent at 200 °C using microwave radiation.

Kinetic modeling of the CTC cycle outlined in Scheme 3 confirms this hypothesis. The simplified reaction shown in eq 1

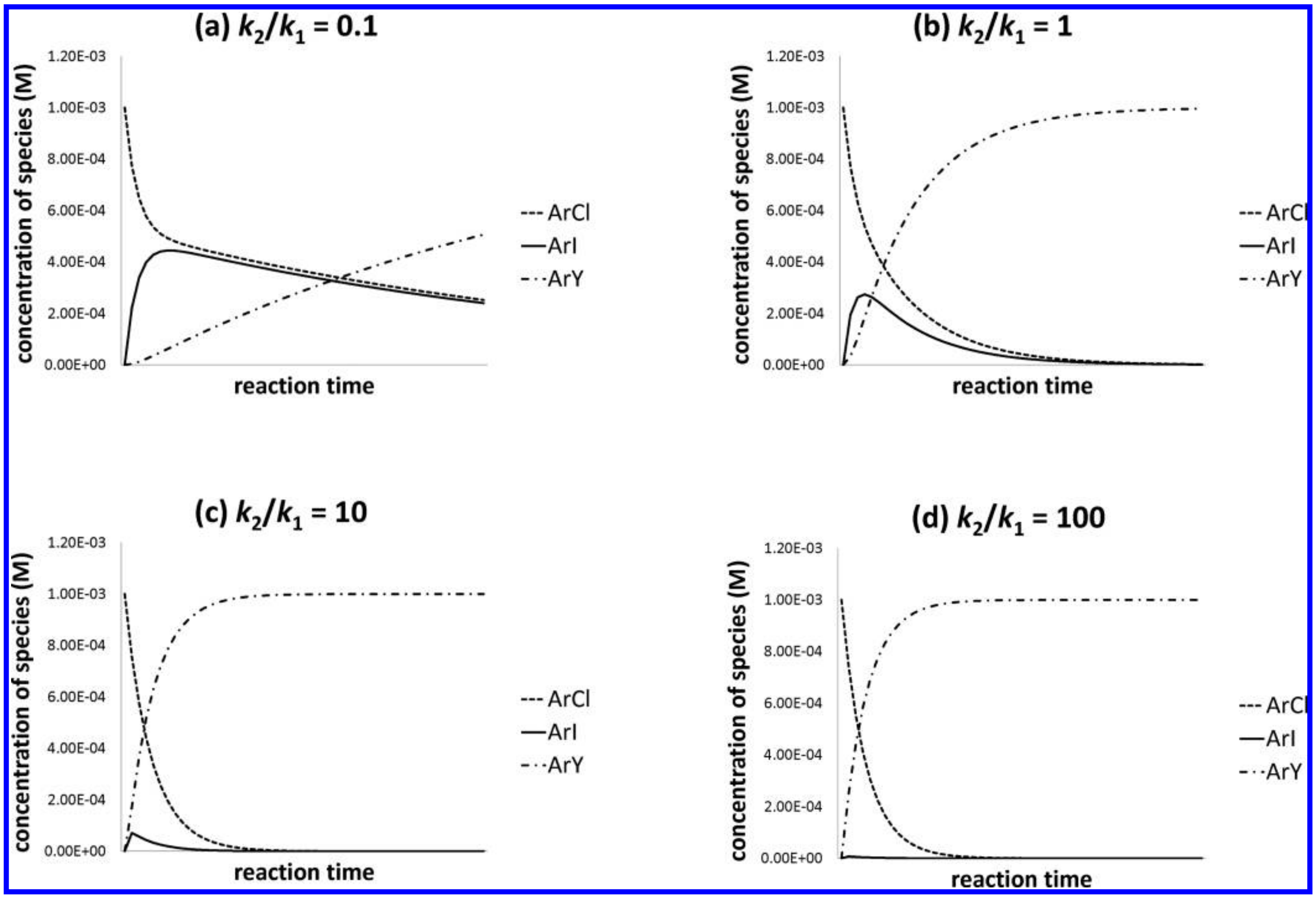


Figure 2. Kinetic simulations of the consumption of ArCl and ArI and the production of ArI and ArY as a function of reaction time according to the proposed mechanism in eq 1 and Scheme 3 (Y = CN), where the rate of formation of ArY from ArI (k_2) is (a) 10 times slower, (b) as fast, (c) 10 times faster, and (d) 100 times faster than the rate of formation of ArI from ArCl (k_1).

was modeled in GEPASI,[22] where k_1, k_{-1}, and k_2 are pseudo rate constants for the reactions in the two catalytic cycles: Y = H, CN in the case of hydrodehalogenation and cyanation, respectively.

$$\mathrm{ArCl} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ArI} \xrightarrow{k_2} \mathrm{ArY} \tag{1}$$

The initial conditions of the simulation were set where [ArCl] = 1.0 mM and [ArI] = [ArY] = 0 mM. All rate laws involving ArCl and ArI were assumed to be first order in substrate. From our previous study on halogen exchange between aryl chlorides and aryl iodides under our CTC conditions,[2] we observed K_{eq} (or k_1/k_{-1}) ≈ 1 for 4-iodotoluene/4-chlorotoluene and K_{eq} (or k_1/k_{-1}) ≈ 0.37 for 4-iodopropiophenone/propiophenone in acetonitrile at 200 °C in the presence of 2 equiv of NaI. In order to observe the effect of changing rate constant k_2 relative to k_1, the values of k_1 and k_{-1} were held constant at 1.0 M/s while k_2 was varied from 0.1 to 100 in logarithmic steps. The results of the simulation are shown in Figure 2. For all cases, as k_2 increases relative to k_1, the amount of ArI present at any given time in the reaction decreases. In Figure 2a−c, it is apparent that when the magnitude of k_2 is less than, similar to, or 1 order of magnitude greater than k_1, one can expect to observe ArI as an intermediate in the catalytic reaction. Figure 2b, where $k_2/k_1 = 1$, resembles the data in Figure 1a, the CTC hydrodehalogenation reaction. However, as the magnitude of k_2 increases and becomes 100 times larger than k_1 (Figure 2d), the concentration of ArI remains low during the course of the reaction and becomes unobservable. This prediction is consistent with the absence of ArI in the plot of species concentration versus time for CTC cyanation (Figure 1b) and indicates that the rate of cyanation of aryl iodide is at least 100 times faster than halogen exchange to form aryl iodide from aryl chloride.

The ability to simulate the kinetics of a CTC reaction also gave us the opportunity to explore the potential limitations of using an irreversible second catalytic step to drive the first catalytic step that is equilibrium-limited where the equilibrium favors ArCl. In principle, a CTC reaction with a very small K_{eq} value would be still be capable of generating 100% yield of product at very long reaction times, with the second catalytic step pushing the equilibrium of the first step toward formation of ArI. However, in practice, catalyst lifetime and substrate and product stability are real-world constraints. We have observed experimentally a wide variety of product yields ranging from trace amounts to 97% after reaction times of 1−2 h at 200 °C under conditions of CTC hydrodehalogenation and CTC cyanation. The kinetic simulation program was used to determine how much final product ArY can be generated at practical reaction times for different magnitude of rate constants k_1, k_{-1}, and k_2.

As before, the initial conditions of the simulation were [ArCl] = 1.0 mM and [ArI] = [ArY] = 0 mM and rate laws involving ArCl and ArI were assumed to be first order in substrate. The equilibrium constant of the first step, K_{eq}, was varied in two different ways, either by changing k_1 while holding k_{-1} constant or by varying k_{-1} while holding k_1 constant. First, we conducted

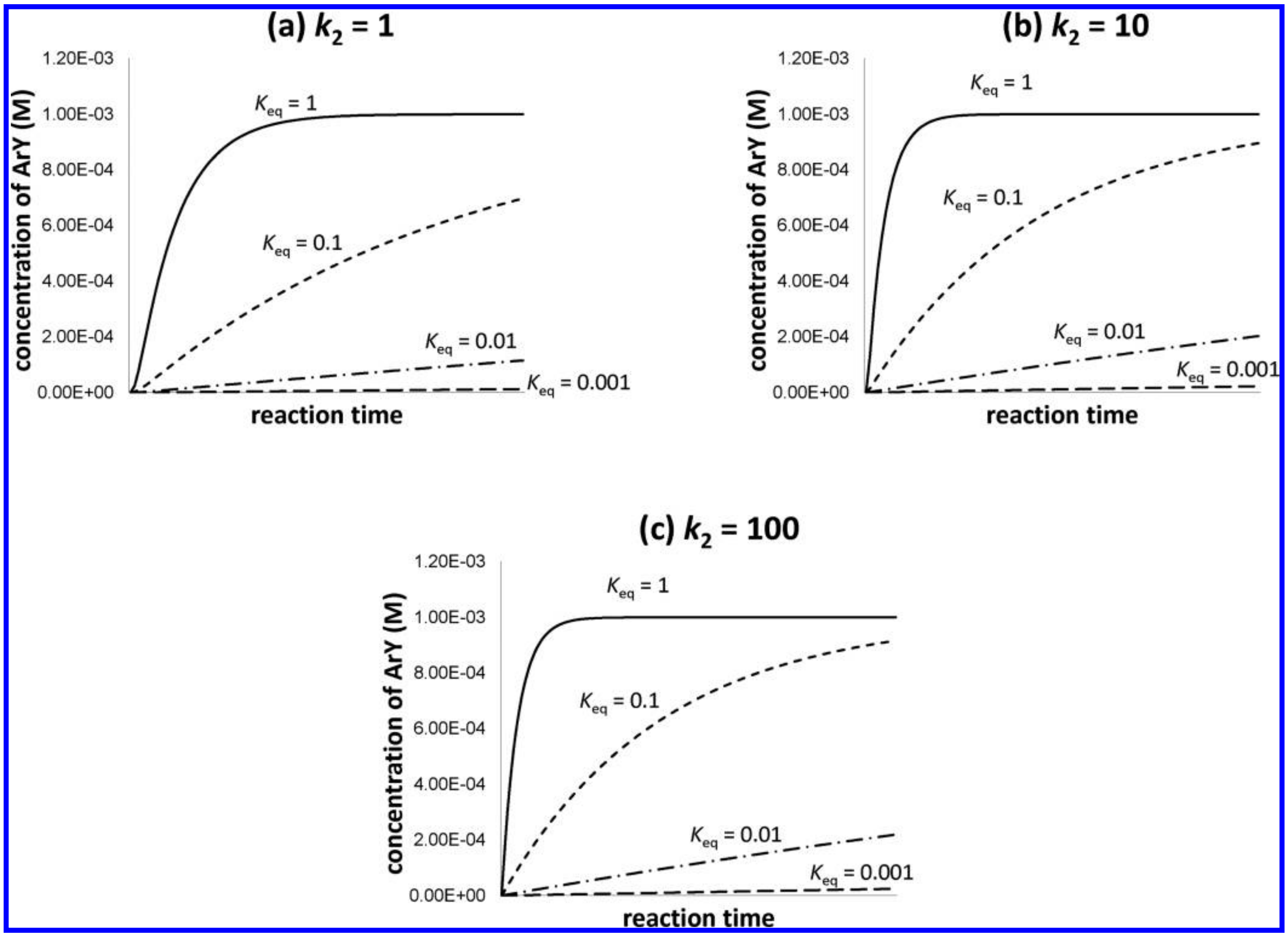


Figure 3. Kinetic simulations of the production of ArY according to the proposed mechanism in eq 1 and Scheme 3 (Y = CN), where the rate constant for formation of ArY from ArI (k_2) is (a) 1, (b) 10, and (c) 1000 times faster than the rate of formation of ArI from ArCl (k_1).

the simulation by holding k_{-1} constant at 1.0 M/s while varying k_1 from 10^{-3} to 1.0 M/s in logarithmic steps at different values of k_2 ranging from 1.0 to 100 M/s in logarithmic steps. The evolution of product ArY as a function of time is shown for $k_2 = 1$ (Figure 3a), $k_2 = 10$ (Figure 3b), and $k_2 = 100$ (Figure 3c). When $k_1 = k_2 = 1.0$ M/s (Figure 3a), the effect of decreasing K_{eq} by each order of magnitude is to take the reaction from being capable of reaching 100% yield in a reasonable reaction time to less than 80% yield in the same amount of time. As expected, the rates of formation for ArY in Figure 3b,c are identical, since formation of ArI from ArCl is the rate-determining step in the CTC reaction when $k_2 \geq k_1$ and the magnitude of k_2 has no influence on the rate of formation of ArY. When k_2 is 1 or 2 orders of magnitude larger than k_1, useful amounts of product (>80%) can still be achieved at reasonably short reaction times only if $K_{eq} \geq 0.1$.

An interesting situation arises when the rate constant k_2 was changed relative to K_{eq} by holding k_1 constant at 1.0 M/s at values of k_2 ranging from 1 to 100 M/s while k_{-1} was varied from 1 to 1000 M/s in logarithmic steps, effectively varying K_{eq} from 1 to 10^{-3}. The results of the simulations are shown in Figure 4.

Figure 4 demonstrates that in order for useful amounts of ArY (>80% yield to be worth isolating from a mixture) to be generated, the ratio k_2/K_{eq} must be no smaller than 0.1. That is, a successful CTC methodology with a small K_{eq} value governing the first catalytic cycle due to a large k_{-1} value must have a sufficiently fast rate for the second catalytic cycle to compensate if useful amounts of ArY are to be generated from ArCl. These simulations indicate that, during future screenings for other CTC methodologies involving halogen exchange, an effective strategy to achieve good yields of the final products is to choose the most active catalysts and coupling partners for the conversion of aryl iodide in the second catalytic cycle. This insight suggests that employing two different catalysts, one for halide exchange and the other specifically optimized to conduct the second reaction involving aryl iodide, may be advantageous over using a single, multifunctional catalyst. We hope to find such an approach particularly helpful for devising CTC processes starting with aryl chlorides that take place at lower temperatures.

In conclusion, we have described here a microwave-assisted CTC methodology for the cyanation of aryl chlorides where the first step of the tandem catalytic cycle is halogen exchange to form aryl iodides. Yields of up to 97% aryl nitrile were obtained. Kinetic simulations assisted in our understanding of the mechanism of CTC cyanation and define some key parameters in designing a successful CTC methodology. In the future, we look forward to expanding the repertoire of CTC reactions starting with aryl chlorides and bromides to include C−N and C−O bond formation as well as further examples of carbon−carbon coupling reactions. We also hope to perform mechanistic studies on CTC hydrodehalogenation and CTC cyanation in order to further expand the scope and utility of these methodologies.

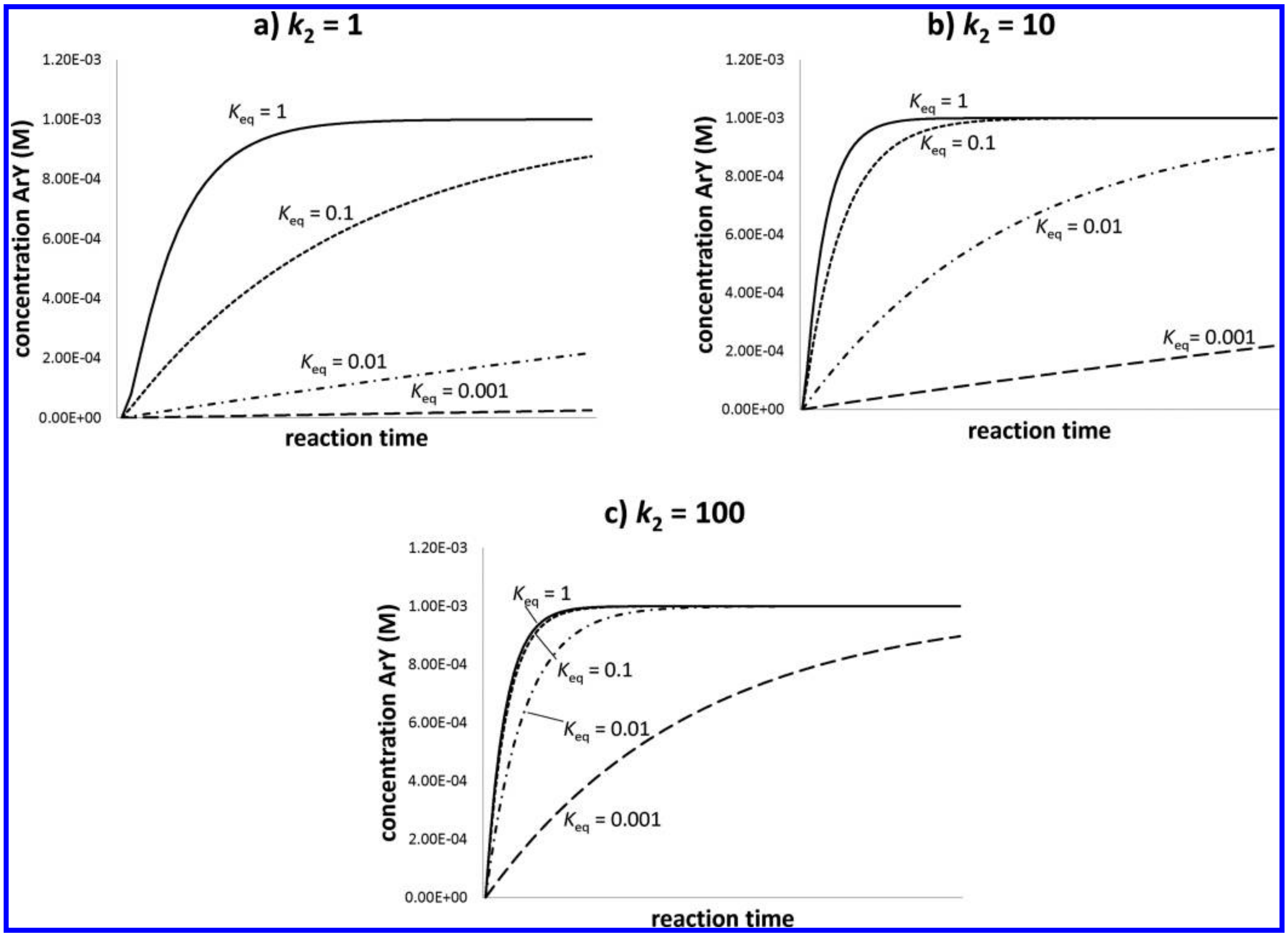


Figure 4. Kinetic simulations of the production of ArY according to the proposed mechanism in eq 1 and Scheme 3 (Y = CN), where the rate constant for formation of ArCl from Ar I (k_{-1}) is 1−1000 times faster than the rate of formation of ArY from ArI (k_2) for (a) $k_2 = 1$, (b) $k_2 = 10$, and (c) $k_2 = 100$.

■ EXPERIMENTAL SECTION

General Considerations. All manipulations were carried out using standard nitrogen drybox techniques. Anhydrous acetonitrile and copper(I) iodide were purchased from Acros and used as received. *trans-N*,*N*′-Dimethylcyclohexane-1,2-diamine was purchased from Aldrich and used as received. Microwave reactions were performed in a CEM Discover microwave reactor. GC/MS analysis was performed on a Shimadzu GCMS-QP5050A instrument with a Restek Rxi-5 ms capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness, 5% diphenyl/95% dimethylpolysiloxane). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX-400 spectrometer and were referenced to residual protio solvent peaks. Melting points were measured on an Electrothermal Mel-temp melting point device.

General Procedure for the Copper-Catalyzed Conversion of Aryl Chlorides into Aryl Nitriles. In a nitrogen-filled glovebox, CuI (38 mg, 0.20 mmol, 20 mol %), KCN (78 mg, 1.2 mmol), and an aryl chloride (1.0 mmol) were weighed into an oven-dried microwave tube containing a small stir bar. Acetonitrile (0.5 mL) was added by syringe and then *trans-N*,*N*′-dimethylcyclohexane-1,2-diamine (63.8 μL, 0.40 mmol, 40 mol %) was added by positive displacement pipet, the sample was stirred, and a septum-lined cap was added. The initial reaction mixture appeared as a clear or pale yellow liquid over a white solid. After the tube was removed from the box, the reaction was performed in a CEM Discover microwave reactor for 60−120 min at 200 °C and 250 W (with power adjustments to maintain temperature), with a 2 min ramp time. After it was cooled, the reaction mixture contained a dark brown liquid over a solid (the color was difficult to determine due to the dark color of the liquid). The product mixture was quenched with 4 mL of a 30% aqueous ammonia solution, and the product was extracted with 4 × 10 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate, and the solvent was evaporated under vacuum. The resulting brown oil was purified by column chromatography on silica.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving characterization data for all isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.K.K. and M.M.C. gratefully acknowledge the Office of Naval Research for partial support of this work on funding document NN00014110WX30241. S.L. and A.H.R.M. thank the Naval Academy Research Council and the Office of Naval Research for partial support of this work on funding document N0001409WR40059. We thank Prof. Lyle Isaacs at the University of Maryland College Park for assistance with GEPASI.

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