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Continuous Synthesis and Use of *N*-Heterocyclic Carbene Copper(I) Complexes from Insoluble Cu_2O

Suzanne M. Opalka,[†,‡] Jin Kyoon Park,[†,§] Ashley R. Longstreet,[†] and D. Tyler McQuade*[,†]

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306, United States, Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, United States, and Department of Chemistry and Chemical Institute for Functional Materials, Pusan National University, Busan, 609-735, Korea

mcquade@chem.fsu.edu

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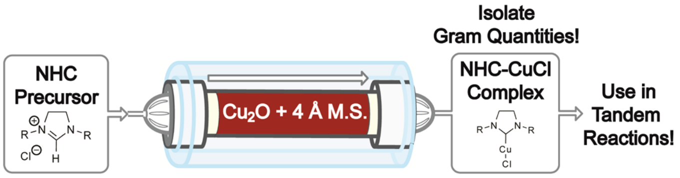
ABSTRACT



It is demonstrated that homogeneous *N*-heterocyclic carbene–copper(I)-chloride complexes can be prepared continuously by flowing NHC precursors through a packed bed of solid Cu_2O suspended in molecular sieves. The method enables the synthesis of a wide range of complexes including those that are challenging to prepare using standard approaches. Our strategy enables both sustained output of complex production for long-term catalytic reactions (greater than 5 h) and for generation of gram quantities for storage (greater than 1 g of complex in ~16 min).

Transition metal complexes are indispensible in the efficient, atom-economical and selective synthesis of molecules.[1] Often these complexes are air and moisture sensitive and require specialized apparatus such as Schlenk-line or gloveboxes to prepare and handle. An alternative approach to preparing sensitive transition metal complexes is continuous synthesis.[2] Continuous transition metal-catalyzed reactions are known and typically rely on supported or homogeneous complexes.[3] Both of these methods work best when the transition metal complex has solution stability in the absence of reagents/starting materials. Recently, we developed a 6-NHC–Cu(I)Cl (**5′**; see Figure 5) complex that exhibits excellent catalytic properties and is a shelf stable solid, but when dissolved in the absence of reagents/starting materials it rapidly decomposes.[4,5] This poor stability hinders the use of this catalyst in flow. In batch, successful use of **5′** requires that we add the complex to the reaction mixture last and as a

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[†] Florida State University
[‡] Cornell University
[§] Pusan National University

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(5) Unless rigorously degassed solvents are used, the catalyst decomposes.

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solid. Despite a few examples,[3e,6] the use of solids in flow is generally avoided, because of pump or reactor clogging. To address this poor solution stability, we speculated that transition metal complexes could be produced using flow chemistry[7] whereby soluble ligands are passed through an insoluble metal source and used immediately in downstream reactions (Figure 1). As we demonstrate herein, this simple idea offers an alternative to glovebox and Schlenk techniques.

Figure 1. Overview for using insoluble metal sources to provide soluble active metal complexes.

To demonstrate this concept, we investigated the synthesis of *N*-heterocyclic carbene (NHC)–copper chloride complexes[8] from insoluble Cu_2O and NHC precursors (Table 1).[9] We speculated that using a packed bed of Cu_2O downstream of the pumps would not only allow for the formation of the desired complex continuously without clogging, but would also increase the rate of complex formation due to increased interaction between solid Cu_2O and solute relative to batch conditions. Herein, we present the use of a packed-bed microreactor to efficiently synthesize known, new, air-sensitive, and chiral NHC–CuCl complexes and illustrate their subsequent use in downstream reactions.

We employed a Vapourtec R series reactor system[10] equipped with a heated tube reactor containing a glass Omnifit column. Optimization reactions were performed using imidazolidinium salt **1a** (Figure 2). We observed high yields of NHC–Cu(I) complexes when an Omnifit column was packed with 1.65 g of a 1:1 mixture of a solid diluent and Cu_2O (< 5 μm particle size). Plugs of pure diluent at each end of the column were necessary to prevent leaching of fine-grained Cu_2O. Diluents such as silica gel, reverse phase silica gel, and molecular sieves all prevented fine Cu_2O from leaching out of the column. Molecular sieves (4 Å), however, were optimal as this material not only filtered fine particles, but also removed water produced during the reaction.[11]

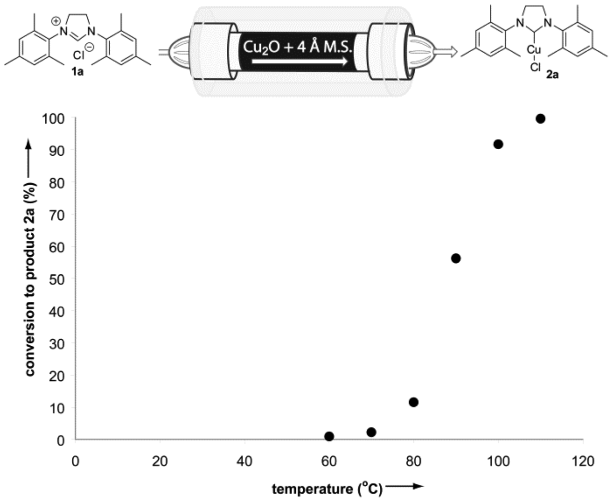

Figure 2. Effect of temperature on reaction conversion with a ~2 min residence time.

We measured the conversion of **1a** to **2a** as a function of column temperature using a 0.800 mL/min flow rate (~2 min residence time; t_R). A steep temperature dependence was observed whereby reaction onset began above 60 °C and showed maximum product formation at 110 °C (Figure 2), resulting in 93% yield of **2a** using a 0.800 mL/min flow rate (Table 1, entry 1).

A 0.800 mL/min flow rate (~2 min t_R) and a 110 °C column temperature were suitable for most substrates. Commonly used imidazolium salts, as well as other more challenging substrates were produced (Table 1). Entries 1 and 2 demonstrate that the flow approach functions well to make known complexes, and entries 3–5 represent new or challenging to produce complexes. For example, **2c** demonstrates that this method can produce complexes that under batch conditions produce a cyclic urea product (Figure 3).[9b] Next, we turned our attention to demonstrating that this method is useful for synthesizing new fused cyclic Cu(I) complexes. For example **2d** (Table 1, entry 4) illustrates that this method can produce other aliphatic flanked carbenes similar to **2c**. Finally, we prepared a mononuclear Cu(I) complex (Table 1, entry 5) to

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demonstrate that multiple copper atoms could be introduced in the same molecule. These examples demonstrate that the flow method enables rapid and easy construction of both known and new compounds.

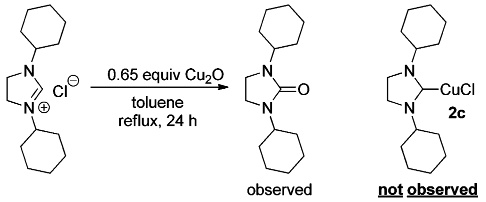


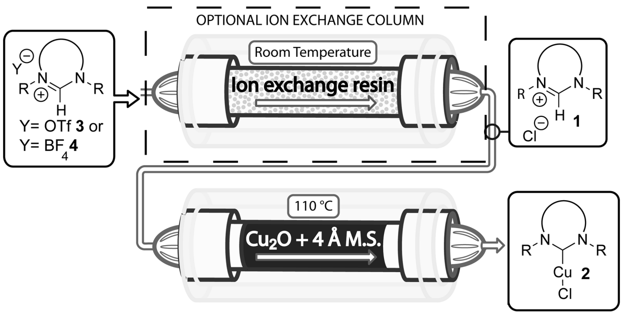
Figure 3. Attempts to produce **2c** failed under batch conditions.[9b]

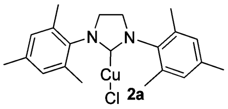
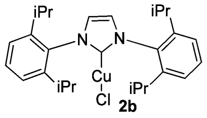
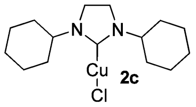
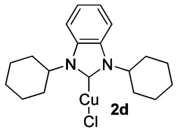
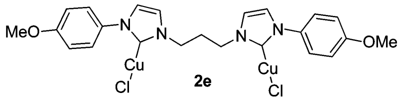
Previous reports show that NHC–Cu(I) complexes formed from Cu_2O require imidazolidinium halide salts, and as expected, we observed no appreciable reaction when the imidazolidinium triflate (**3**) and tetrafluoroborate (**4**) were passed through the Cu_2O packed bed.[9c] This issue represented a significant problem if we wished to use ligand **5** in flow because this material is only isolable as the tetrafluoroborate salt. To overcome this issue, we added an Omnifit column packed with an ion-exchange resin in-line with the Cu_2O packed bed. Passing a solution of **3** or **4** in a 80% CH_2Cl_2/5% MeOH/15% toluene mixture through the columns at a rate of 0.800 mL/min resulted in 95% yield of **2a** (Table 1, entry 1).[12] Thus, with our combined ion exchange and complex generation protocol, other imidazolidinium salts with weakly coordinating anions could be realized using mild Cu_2O conditions.

We then measured the amount of complex **2a** that could be produced before the available Cu_2O reactive sites were depleted. A packed bed containing 825 mg (5.8 mmol) Cu_2O was reacted with an input stream of **1a** (0.2 M). The formation of **2a** was determined by ^{1}H NMR. The sigmoidal shape of the plot shown in Figure 4 suggests that once the accessible/reactive sites of Cu_2O are depleted, the reactivity of the column diminishes rapidly. Regardless, in the 16 min time period where high activity was observed, ~1.0 g (2.5 mmol) of complex **2a** was produced. This result demonstrates that a practical quantity of pure copper complex can be produced very rapidly using this approach.

Producing gram quantities of pure complex is useful, and we use this approach to support our other Cu(I) activities, but the real power of this system is the possibility to produce complexes for extended periods for use as catalysts in downstream processes. We assessed the long-term stability at a catalytically relevant concentration (0.02 M) by passing imidazolidinium salt **1a** through the Cu_2O column. Stable output of complex **2a** was observed for at least 5 h (Figure 4), indicating that a single copper oxide column could be used to run extended catalytic reactions with the goal of producing gram quantities of a downstream reaction. To demonstrate this feature, we generated a catalyst and used the catalyst in a downstream β-borylation of ethyl crotonate. After workup and purification, we produced 11.8 g of the desired borylated product **7a** in only ~40 min (Figure 5A). If the system ran for the full 5 h, then ~90 g of product would have been produced (we stopped the run to reduce the experiment cost).

Table 1. Substrate Scope



entry	product	yield (%)[a]
1[b]		93[e], 95[f]
2[c]		94[e]
3[b]		86[d,e]
4[b]		91[e]
5[c]		93[e]

[a] Isolated yield. [b] Using 80% CH_2Cl_2/20% toluene mixture. [c] Using 5% MeOH/80% CH_2Cl_2/15% toluene. [d] Collected under argon. [e] NHC–Cu(I)-chloride complexes prepared by passing chloride salt **1** through a Cu_2O packed bed without ion exchange column. [f] NHC–Cu(I)-chloride complex prepared using tandem ion exchange/Cu_2O packed bed using OTf or BF_4 salts (same yield). See the Supporting Information for details.

As a final demonstration of how this system enables catalyst synthesis and use, we performed a tandem β-borylation reaction using chiral 6-NHC precursor **5**. Since introduction of **5′** in 2010, we have been interested in using this complex in flow but could not because of the limited solution stability.[4,5] We typically add **5′** as a solid to a borylation, allylation or hydroboration reaction, and the solid dissolves to form the active catalyst. The catalyst decomposes once starting materials are consumed.

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[12] We observed better conversion to product using methanol, indicating it is crucial for full ion exchange at this residence time.

In addition to the solution instability of complex **5′**, the ligand used to prepare **5′** is only stable as the BF_4 salt (**5**).

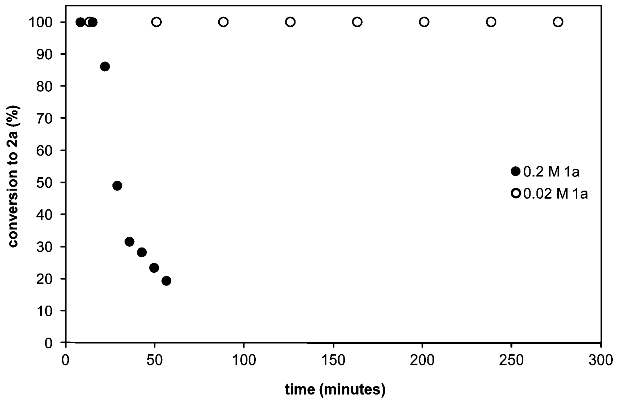

Figure 4. Productivity of an 825 mg column of Cu_2O/4 Å molecular sieve packed bed for the formation of complex **2a**. A 0.02 or 0.2 M solution of imidazolidinium salt **1a** (80% CH_2Cl_2/20% toluene) was passed through a packed bed of Cu_2O/4 Å molecular sieves (1:1 by weight) at 110 °C, entering at the bottom of the column and exiting at the top, with a flow rate of 0.800 mL/min. Fractions were collected, concentrated, and assessed for conversion to product by ^1H NMR.

The tandem ion-exchange/Cu_2O approach (Figure 5) offered an opportunity to generate and use **5′** continuously. A solution of 5 mol % of **5** was pumped at a rate of 1.6 mL/min through an ion-exchange resin (20 °C) followed by a Cu_2O column (110 °C, ~1 min t_R). Subsequent β-borylation in a 0 °C coil provided 93% yield of borylated product **7b** with 85% ee after oxidation (Figure 5B). The induced enantioselectivity indicates that the enantiopure ligand was present.

In conclusion, a simple,[13] rapid method to convert an insoluble inorganic copper source into an NHC–CuCl complex is accomplished by flowing solutions of carbene precursors through a packed bed of Cu_2O. The success of this chemistry relies on the use of a packed bed to facilitate rapid reaction between the insoluble metal source and organic ligand precursor, resulting in a soluble catalytically active complex. The key to using solid Cu_2O in flow is to place the material after the pumps, thereby eliminating the potential of clogging. We also provide an option for synthesizing copper-chloride complexes from other salts by employing an ion-exchange resin. We illustrated the usefulness of this approach by synthesizing gram quantities of a copper complex, running a large scale continuous catalytic reaction, and performing an enantioselective β-borylation reaction. We envision this setup will be useful for rapidly generating and screening NHC–copper catalysts to help accelerate our Cu(I) efforts. We also conjecture that this approach can be used to synthesize other metal catalysts and is a complementary method to glovebox and Schlenk techniques.

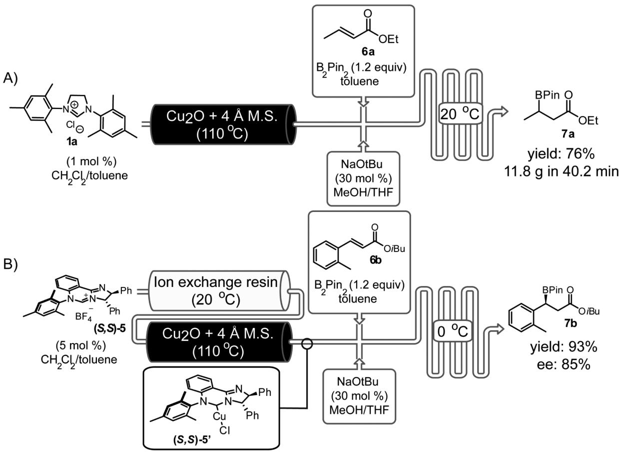

Figure 5. Reactor setups for performing NHC–CuCl catalyzed β-borylation reactions in flow (see the Supporting Information for details). A solution of salt flows through the ion-exchange resin (if needed) followed by Cu_2O/4 Å molecular sieve column. The complex is then precooled in the coil and combined with a precooled solution of B_2Pin_2, unsaturated ester, NaOtBu, and MeOH. The product is collected and purified. (A) Product collected over 40.2 min. (B) Using ion-exchange resin and chiral imidazoquinazolium salt **5**.

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Supporting Information Available. Detailed reactor setup, reaction conditions, characterization data, copies of GC chromatograms and corresponding chiral method as well as ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For an inexpensive flow device, see: Quevedo, E.; Steinbacher, J.; McQuade, D. T. *J. Am. Chem. Soc.* **2005**, *127*, 10498.

The authors declare no competing financial interest.