Continuous Synthesis and Use of N-Heterocyclic Carbene Copper(I) Complexes from Insoluble Cu$_2$O

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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$_2$O 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 indispensable in the efficient, atom-economical and selective synthesis of molecules. 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. Continuous transition metal-catalyzed reactions are known and typically rely on supported or homogeneous complexes. Both of these methods work best when the transition metal complex has solution stability in the absence of reagents/startling 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/startling materials it rapidly decomposes. 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

solid. Despite a few examples, 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 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.

We employed a Vapourtec R series reactor system 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 Cu2O (< 5 μm particle size). Plugs of pure diluent at each end of the column were necessary to prevent leaching of fine-grained Cu2O. Diluents such as silica gel, reverse phase silica gel, and molecular sieves all prevented fine Cu2O 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

To demonstrate this concept, we investigated the synthesis of N-heterocyclic carbene (NHC)–copper chloride complexes from insoluble Cu2O and NHC precursors (Table 1).⁹ We speculated that using a packed bed of Cu2O 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 Cu2O 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 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; tR). 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 tR) 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). 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 carbene species 2e. Finally, we prepared a mononuclear Cu(I) complex (Table 1, entry 5) to

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

Figure 2. Effect of temperature on reaction conversion with a ~2 min residence time.
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 Cu2O require imidazolidinium halide salts, and as expected, we observed no appreciable reaction when the imidazolidinium triflate (3) and tetrafluoroborate (4) were passed through the Cu2O 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 inline with the Cu2O packed bed. Passing a solution of 3 or 4 in a 80% CH2Cl2/5% 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 Cu2O conditions.

We then measured the amount of complex 2a that could be produced before the available Cu2O reactive sites were depleted. A packed bed containing 825 mg (5.8 mmol) Cu2O was reacted with an input stream of 1a (0.2 M). The formation of 2a was determined by 1H NMR. The sigmoidal shape of the plot shown in Figure 4 suggests that once the accessible/reactive sites of Cu2O 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 Cu2O 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).

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.

Table 1. Substrate Scope

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<thead>
<tr>
<th>entry</th>
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<th>yield (%)</th>
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<td>1b</td>
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<tr>
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<td>3b</td>
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<tr>
<td>4b</td>
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<td>91'</td>
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<tr>
<td>5c</td>
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* Isolated yield. † Using 80% CH2Cl2/20% toluene mixture. ‡ Using 5% MeOH/80% CH2Cl2/15% toluene. § Collected under argon.

NHC–Cu(I)-chloride complexes prepared by passing chloride salt 1 through a Cu2O packed bed without ion exchange column. NHC–Cu(I)-chloride complex prepared using tandem ion exchange/Cu2O packed bed using OTf or BF4 salts (same yield). See the Supporting Information for details.

(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 ($5$).

The tandem ion-exchange/Cu$_2$O 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 (20/80 C) followed by a Cu$_2$O column (110 °C, ~1 min $t_R$). Subsequent $\beta$-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, 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$_2$O. 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$_2$O 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 $\beta$-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.

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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 $^1$H and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.