Structure and Reactivity of a Copper(I)-Fused N-Heterocyclic Carbene Complex: Reactivity toward Styrenic and Strained Alkenes

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Abstract: The synthesis of a fused N-heterocyclic carbene complex is accomplished using a flow-chemistry approach where a fused Nherterocyclic imidazolium chloride is passed through a packed bed of copper(I) oxide. The identity of the resulting complex is confirmed via crystal structure, and the reactivity is examined in the context of alkene hydroboration. We demonstrate that this novel complex can perform the desired reaction whereas the carbene ligand alone cannot.

Key words: boron, copper, flow chemistry, N-heterocyclic carbene complex, catalytic hydroboration, strained alkenes

Copper(I) N-heterocyclic carbene complexes catalyze bis(pinacolato)diboron additions to a wide variety of double bonds including α,β -unsaturated carbonyls, allylic ethers/esters (resulting products shown in Scheme 1), and styrenic substrates.² While iridium,³ rhodium,⁴ and other metal⁵ complexes are known to borylate unfunctionalized double bonds, copper(I) complexes have not been extensively studied.⁶ As part of our ongoing investigation of

NHC–Cu complexes,^{2b,7a–d} we demonstrated that Cu(I)– NHC complexes catalyze the regioselective hydroboration of propargylic ethers using B_2Pin_2 as the boron source.^{2b} These results prompted us to seek copper(I) catalysts that might react with both styrenic and strained double bonds. Herein, we synthesize an imidazo[1,5*a*]pyridine–Cu(I) complex and demonstrate that the complex can catalyze the hydroboration of both norbornene and styrenic substrates while leaving nonstrained double bonds untouched. Control experiments demonstrate clearly that the Cu(I)–NHC complex is required.

N-Heterocyclic carbene–copper complexes can be rapidly synthesized by passing imidazolium chlorides through a packed bed of copper(I) oxide. The method enables gram quantities of complexes to be formed in minutes.⁸ Using this synthetic method, we desired to continue our investigations into reactions that can be catalyzed using nonstandard carbene ligands. Glorius et al. demonstrated that palladium and iridium complexes ligated to imidazo[1,5-a]pyridin-3-ylidene ligands can catalyze Suzuki–Miyaura



Scheme 1 Known reactions catalyzed by NHC-copper chloride complexes

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Scheme 2 Flow synthesis of catalyst 2

cross-couplings of sterically hindered aryl chlorides.⁹ We predicted that copper(I) complexes featuring this ligand might have sufficient reactivity to hydroborate strained and styrenic alkenes. While rhodium and iridium complexes can catalyze both mono- and diborylation of alkenes and simple bases at elevated temperature, such as NaO*t*-Bu, with B₂Pin₂ often lead to diboration of alkenes,¹⁰ very few examples using copper(I) complexes have been reported.⁶

The synthesis of **2** was achieved by passing **1** through a copper(I) oxide column prepared using a mixture of Cu₂O and molecular sieves. The ends of the column were terminated with molecular sieves. A solution of **1** in 80% CH₂Cl₂-toluene was passed through the column while maintaining a temperature of 110 °C. A flow rate of 0.800 mL/min (ca. 2 min residence time) provided complex **2** with 94% yield after concentration (Scheme 2).

A single crystal of **2** was obtained by vapor diffusion of diethyl ether into a solution of **2** in dichloromethane. The colorless cubic-shaped crystals were subjected to X-ray crystallographic analysis. As shown in Figure 1, the asymmetric unit features two molecules of the desired complex. While the bond lengths are consistent with previously observed Cu(I)Cl–NHC complexes,^{7d} the N–C–Cu bond angles are nonsymmetric. The bond angle defined by the N–C–Cu on the side of the mesityl group is larger than the N–C–Cu angle on the side of the heterocycle, demonstrating the openness of the methyl group side. We predict that this open pocket will produce a very active catalyst (Figure 1).



Figure 1 Unit cell of **2e**, showing two crystallographically independent molecules.¹¹ Selected distances [Å] and angles [°]: Cu–Cl 2.0982(6) and 2.1046(6). The mesityl fragment leads to a larger N–C–Cu angle as compared to the N–C–Cu angle on the opposite side of the C–Cu–Cl line (132.9° and 131.6° vs. 123.8° and 124.7°).

As stated in the introduction, NHC–Cu(I)Cl complexes are known to catalyze the addition of B_2Pin_2 to enones, allylic ethers/esters, and alkynes. The next progression in this area is to move towards functionalization of isolated alkenes. The advantage of using copper is that it is much less expensive relative to rhodium and iridium. Thus, optically active complexes can be quickly and cheaply synthesized and assessed for asymmetric induction. To this end, we hypothesized that complex 2 might catalyze the hydroboration of strained alkenes such as norbornene using B_2Pin_2 as a boron source. An additional advantage to this procedure is that B_2Pin_2 is shelf-stable whereas BHbased reagents are more sensitive.

We tested our hypothesis by combining **2** with B_2Pin_2 , NaO*t*-Bu, and methanol. Previous work by Yun and our group have demonstrated that a protic source such as methanol is necessary to provide high-yielding reactions. As shown in Table 1 entries 1 and 2, the reaction produced the desired product in high yield (<30 min).

Table 1 Hydroborylations Experiments



^a Determined by GC analysis using mesitylene as an internal standard at 30 min.

^b Isolated yield after 40 min, see Supporting Information for details.

We then focused our attention on control experiments. Use of catalyst **2**, B_2Pin_2 , with NaOt-Bu, and MeOH in a solution of diethyl ether resulted in 82% yield (Table 1, entry 1). Recently, a number of reactions such as β -borylations have been demonstrated to proceed via carbene-catalyzed pathways that are metal-free.¹² To test whether the observed borylation of norbornene was possible without copper(I), we performed the reaction using the imidazolium chloride (**1**) in the presence of NaOt-Bu – less than 10% conversion was observed (Table 1, entry 5). These data indicate that copper(I) is necessary. We also

examined NaOt-Bu/B₂Pin₂, as previous reports indicated that cyclic alkenes could yield diboration products.¹⁰ However, after 30 minutes at room temperature no evidence of reaction was observed (Table 1, entry 3). We also performed the reaction in the presence of CuCl powder and observed no reaction indicating that the ligand is necessary to produce an active catalyst.

With optimal reaction conditions in hand, we then set out to define the substrate scope of this reaction (Table 2). While we observed mixtures of regioisomers with respect to the strained alkene in unsymmetrical substrates, the reaction functions in the presence of unstrained alkenes (demonstrating excellent chemoselectivity; Table 2, entries 1 and 4), protected alcohols (Table 2, entry 2), and esters (Table 2, entry 5). Styrenics also undergo hydroboration (Table 2, entries 3 and 6). While less strained alkenes, such as cyclohexene, 1-methylcyclopentene, and 1,5-cyclooctadiene, do not react (Table 2, entries 7–9).

Table 2 Hydroboration Scope



^a Isolated yield.

^b Isolated as a 79:21 mixture of regioisomers.

° Isolated as a 69:31 mixture of regioisomers.

^d No reaction was observed even after 24 hours.

The role of methanol was also examined through control and labeling experiments. As shown in Table 1, we ran reactions in the presence and absence of methanol. Uniformly, the presence of methanol provided high-yield outcomes whereas the absence of methanol provides significantly lower yields. When the reaction was run in MeOD, deuterium incorporation was observed in the expected position yielding **6** (Scheme 3 and see Supporting Information). Based on the labeling data and other mechanistic insight provided by the literature, we propose the catalytic cycle provided in Scheme 3.

The catalytic cycle is proposed to begin via CuCl precatalyst exchange with NaOt-Bu or MeOK. The resting state is proposed to be the copper(I) alkoxide. The Cu–Bpin bond is formed via σ -bond metathesis followed by addition of the alkene. The resulting organocuprate intermediate **5** then undergoes methanolysis to produce the desired product and regenerate the catalyst. While the reaction was too fast to determine a kinetic isotope effect, the rate is strongly dependent on MeOH suggesting that the methanolysis step is rate determining.

In conclusion, we present a new Cu(I)–imidazo[1,5-a]pyridin-3-ylidene complex. The crystal structure shows that the Cu–Cl bond is relatively unshielded by the ligand. The complex catalyzes the hydrboration of strained and styrenic alkenes using B₂Pin₂ as the boron source and MeOH as the proton source.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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Scheme 3 Proposed mechanism of hydroboration of norbornene

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