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[Cu(NHC)(OR)] (R = C(CF₃)₃) complexes for N–H and S–H bond activation and as pre-catalysts in the Chan–Evans–Lam reaction†

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The synthesis, isolation, and full characterization of a series of NHC–copper perfluoro–alkoxide complexes are reported. Their exceptional stability resides with the steric hindrance of the non-fluoro-*tert*-butyl alkoxide moiety, which exhibits a strong electron withdrawing effect. These new Cu(I) complexes are synthons that can permit the activation of acidic N–H and S–H bonds. The well-defined [Cu(IPr)(OC(CF₃)₃)] was investigated as a pre-catalyst in the Chan–Evans–Lam reaction.

Nonafluoro-*tert*-butyl alcohol (NFTBA) is a polar, strong H-bond donating solvent, and is the least explored member among the family of fluorinated alcohols that include 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). Its less frequent use can be reasoned from its higher cost and its rather unique physical/chemical properties: NFTBA has a $pK_a = 5.4$ in water and its boiling point is 45 °C.¹ These properties make it behave almost as a volatile carboxylic acid. It was recently used as a solvent for catalytic selective oxidation,^{2,3} as an additive for organocatalyzed reactions⁴ and it has been adopted as a valuable building block for ¹⁹F magnetic resonance imaging.⁵ It has been scarcely used as a reagent; one notable example is its role in C–O coupling reactions.⁶ It has been adopted as a ligand for metal centres such as aluminium,^{7,8} molybdenum and tungsten,⁹ palladium¹⁰ and copper,^{11,12} and some 21 metals from the Periodic Table (see ESI† for full references) for both complexes and salts, although the design of those NFTBA containing compounds has never incorporated other important and widely used families of ligands such as NHCs. NHCs have proven to be a particularly important ligand family, able to stabilize and protect metals prone to oxidation.¹³ Copper is one of the most

earth abundant metals, but it also undergoes facile oxidation and thus, this reaction route accounts for several examples where, due to reactions with oxygen, decomposition of its complexes is observed.

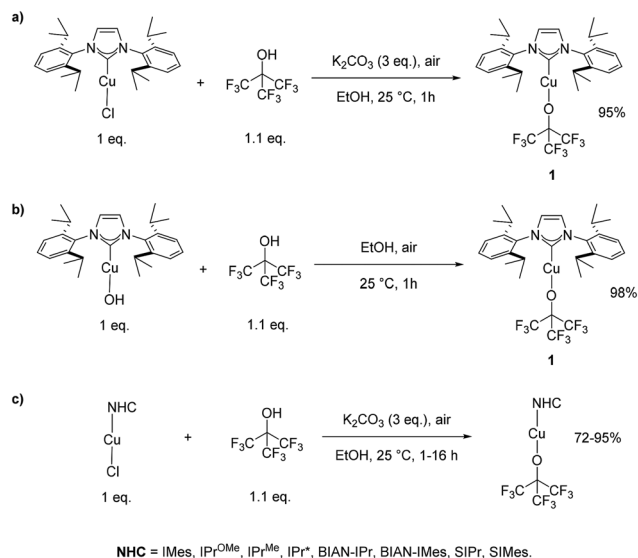
The combination of NHC-type ligands with Cu–alkoxide species has proven to lead to significant advances in copper-mediated catalysis.^{14–18} The alkoxide moiety has been shown to be a useful fragment in conferring to the NHC–Cu complex the required stability to act as a synthon, allowing easy access to a plethora of other useful copper(I) complexes. One of the key representative compounds in this regards is [Cu(IPr)(O^{*t*}Bu)] (IPr = [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene]), which can act as an excellent pre-catalyst in many catalytic transformations.^{19–24} Another important copper synthon is the remarkably stable copper(I) hydroxide complex [Cu(IPr)(OH)] which is capable of activating numerous X–H bonds, including all hybridizations of C–H (*i.e.*, sp, sp², sp³), N–H, P–H, O–H, S–H bonds.²⁵ Despite numerous advantages, such as their excellent reactivity, these Cu–OR (where R is not H) complexes have some limitations. Firstly, their synthesis requires the use of a strong base and usually anaerobic conditions. Secondly, the handling of copper-alkoxide complexes generally necessitates anaerobic conditions and anhydrous solvents, as these are sensitive to both air and moisture. A notable exception is [Cu(IPr)(OH)], which displays remarkable stability.²⁵

As a key complex, the very sensitive [Cu(IPr)(O^{*t*}Bu)] is a salient example. We thus reasoned that we could use the nonafluoro-*tert*-butoxide group's unique properties to generate more stable copper complexes and that this would enable a comparison with the stability and chemistry displayed by the recently reported [Cu(IPr)(O(C(H)(CF₃)₂))].²⁶

The synthesis of the first NHC–copper–NFTBA complex was achieved by reacting [Cu(IPr)Cl] with 1.1 eq. of NFTBA in EtOH in the presence of 3 eq. of K₂CO₃ and conducting the reaction in air at 25 °C for 1 hour. The desired copper-alkoxide complex [Cu(IPr)(OC(CF₃)₃)] (**1**) was obtained in excellent yield using this simple procedure (Scheme 1a).

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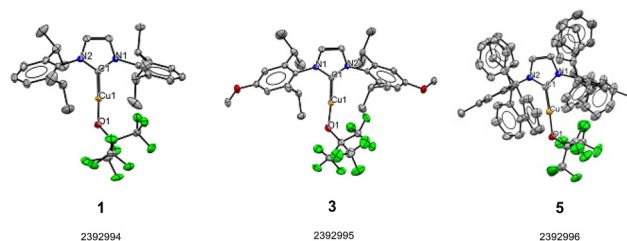
Scheme 1 Syntheses of $[\text{Cu}(\text{IPr})(\text{OC}(\text{CF}_3)_3)]$ (**1**) using (a) $[\text{Cu}(\text{IPr})(\text{Cl})]$, (b) $[\text{Cu}(\text{IPr})(\text{OH})]$, (c) general synthesis of $[\text{Cu}(\text{IPr})(\text{OC}(\text{CF}_3)_3)]$.

Complex **1** was also obtained in a slightly higher yield of 98%, using the $[\text{Cu}(\text{IPr})(\text{OH})]$ complex as the copper source on a larger scale (500 mg of starting material instead of 100 mg, Scheme 1b). Once a simple protocol was established, we explored its compatibility and reactivity to support other Cu-NHC relatives (Scheme 1c). Nine NHC-Cu(I)-NFTBA complexes have been successfully synthesized in good to excellent yields using this simple protocol (Scheme 2).

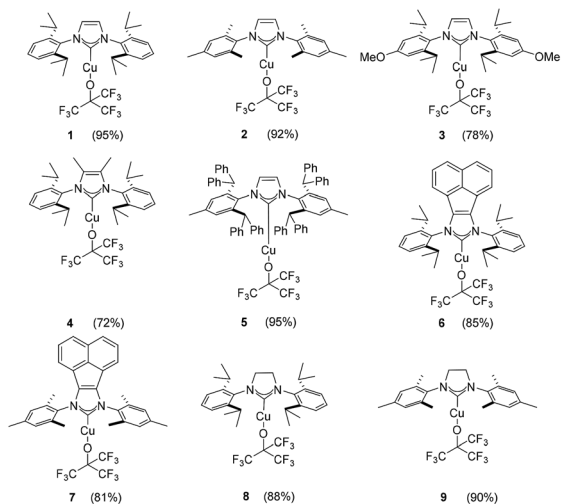
Notably, lower yields were obtained in cases where the most electron donating NHCs (compounds **3** and **4**) were used. In addition, the reactions with $[\text{Cu}(\text{BIAN-IPr})(\text{Cl})]$ and $[\text{Cu}(\text{BIAN-IMes})(\text{Cl})]$ required longer reaction time to reach completion, with respect to other (smaller) substrates, delivering products **6** and **7**, respectively. We suspect the strong electron-

withdrawing property of the fluoroalkyl groups creates a stable Cu-O bond in **1**. Interestingly, the Cu-O bond length in $[\text{Cu}(\text{IPr})(\text{O}^t\text{Bu})]$ is slightly shorter (1.8104(13) Å) than the one measured for $[\text{Cu}(\text{IPr})(\text{OC}(\text{CF}_3)_3)]$ (**1**) (1.8403(18) Å) (see Scheme 3).²⁷ Next, to highlight the versatility of $[\text{Cu}(\text{IPr})(\text{OC}(\text{CF}_3)_3)]$ (**1**) as a synthon, its reactivity towards H-X activation was examined (Scheme 4).

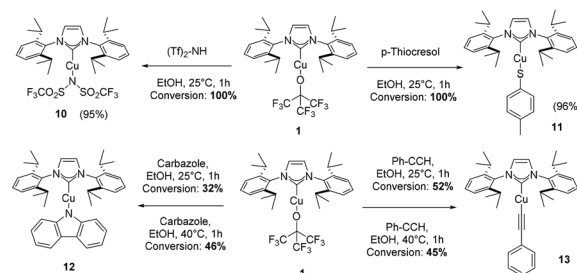
We initially tested the displacement/removal of the NFTBA moiety from **1** by simple protonolysis/ligand exchange with 1 equivalent of a protic ligand. As shown in Scheme 4, four ligands were able to displace the alkoxy fragment, leading to the formation of complexes **10–13**. Gratifyingly, full conversion was achieved for the isolation of **10** and **11**, due to high nucleophilicity of *p*-thiocresol and trifluoromethanesulfonimide. Unfortunately, the substitution with carbazole in EtOH at room temperature afforded only 32% conversion to **12**, which was increased to 46% by heating the reaction mixture to 40 °C. The substitution of phenylacetylene also led to a 52% conversion, which decreased to 45% at 40 °C, probably due to the intrinsic instability of **13** in solution at more elevated temperatures than 25 °C. The lower reactivity of **1** highlights its increased stability given by steric hindrance of three CF_3 groups and the overall stronger electronegativity effect which pulls electron density away from the oxygen atom. Synthon **1** was unreactive with pyrazole, 1,2,4-triazole, 1,2,4,5-tetrafluorobenzene, nitromethane, phenylboronic acid and phenylboronic acid pinacol ester under the same conditions presented for $[\text{Cu}(\text{IPr})(\text{HFIP})]$ (see ESI†).²⁶ Similarly to the work of Dhiman, the reactivity of **1** as a nucleophile was investigated by carrying out stoichiometric reactions with hetero-aryl chlor-



Scheme 3 XRD molecular structures of compounds **1**, **3** and **5**. Thermal displacement ellipsoids shown at the 50% probability level. H-atoms are omitted for clarity. CCDC 2392994–2392996 contain the supplementary crystallographic data for this paper.†

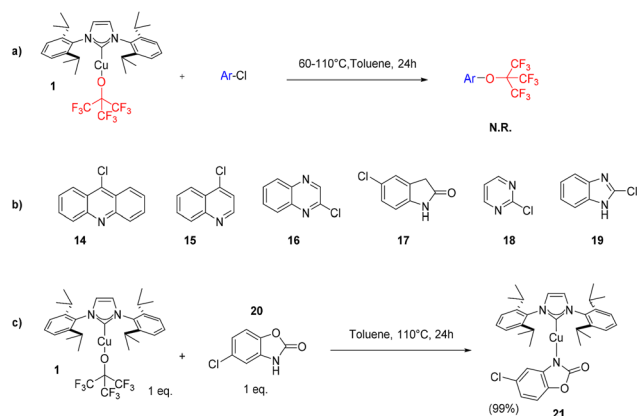


Scheme 2 Overview of the synthesized $[\text{Cu}(\text{NHC})(\text{OC}(\text{CF}_3)_3)]$ complexes.



Scheme 4 Reactions making use of the $[\text{Cu}(\text{IPr})(\text{OC}(\text{CF}_3)_3)]$ (**1**) synthon.





Scheme 5 (a) Unsuccessful nucleophilic substitution using [Cu(IPr)(OC(CF₃)₃)] (**1**), (b) series of unreactive aryl chlorides for the reaction shown above, (c) successful reaction using the [Cu(IPr)(OC(CF₃)₃)] (**1**) synthon.

ides, to form aryl fluoroalkoxides by nucleophilic substitution *via* heating the reaction of **1** with hetero-aryls **14–19** at 60 and 110 °C, in toluene (Scheme 5a).²⁸ In the reaction between **1** and **19**, decomposition of the former was observed, whereas for the reactions with reactants **14–18**, **1** remained unreactive and intact. Employing chlorzoxazone (**20**) as reagent led to 99% yield of **21** (Scheme 5c). This affords the first cyclic carbamate copper complex in the literature. The single-crystal XRD structure of **21** is provided in the ESI (CCDC 2392997†). Finally, we investigated the catalytic activity of **1** and other NHC–Cu–NFTBA complexes. Our first attempt was to replace the air- and moisture-sensitive [Cu(IPr)(O^tBu)] as a pre-catalyst with our thermally, air- and moisture-stable [Cu(IPr)(OC(CF₃)₃)] (**1**). [Cu(IPr)(O^tBu)] has been widely used as a precursor to copper hydride species formed with the aid of silanes such as (EtO)₃SiH or PMHS, as H sources. The copper hydride species is the main catalyst for a wide array of many catalytic reactions such as reduction of α,β-unsaturated carbonyl compounds,²⁹ the hydrogenation of alkenes and alkynes,³⁰ and the hydrosilylation of hindered and functionalized ketones.³¹ The copper hydride species are quite unstable, hence their highly reactive nature towards several substrate classes.²⁷ Thus, we explored reactions of [Cu(IPr)(OC(CF₃)₃)] (**1**) with (EtO)₃SiH or PMHS (Table 1). **1** was found completely unreactive under these conditions, showcasing its outstanding stability (see ESI† for reaction conditions). We next explored the possible catalytic activity of the new complexes in the Chan–Evans–Lam (CEL) reaction, employing **1** as pre-catalyst. There are many examples of copper species involved in CEL systems, mostly employing Cu(II) complexes, with very few examples of NHC-containing complexes.³² In most recent examples, the catalyst loading required for CEL coupling is between 5 and 10 mol%,³³ (with only two exceptions in literature presenting 0.1–1 mol% catalyst loading^{34,35}) so we began an exploration of this catalytic transformation using 5 mol% as catalyst loading involving phenylboronic acid and imidazole as the limiting reagent (Table 1). The initial comparison of entries 1 and 4

Table 1 Optimization for the Chan–Evans–Lam reaction of imidazole with phenylboronic acid^a

Entry	Mol% (cat.)	Solvent (mL)	T (°C)	Time (h)	Base	Yield ^b (%)
1	5	MeOH (3)	60	20	Na ₂ CO ₃	58 ^c
2	5	MeOH (3)	60	5	Na ₂ CO ₃	57 ^c
3	5 ^e	MeOH (3)	60	5	Na ₂ CO ₃	52 ^c
4	5	MeOH (3)	60	20	Na ₂ CO ₃	68
5	5	MeOH (1)	60	20	Na ₂ CO ₃	78 ^c
6	5	MeOH (1)	60	20	Na ₂ CO ₃	94 (92) ^d
7	5	MeOH (1)	60	10	Na ₂ CO ₃	85
8	0	MeOH (1)	60	20	Na ₂ CO ₃	0
9	5	EtOH (1)	60	20	Na ₂ CO ₃	82
10	5	IPrOH (1)	60	20	Na ₂ CO ₃	80
11	5	Acetone (1)	60	20	Na ₂ CO ₃	0
12	5	MeOH (1)	60	20	K ₂ CO ₃	90
13	5	MeOH (1)	60	20	K ₃ PO ₄	89
14	5	MeOH (1)	60	20	No base	0
15	5	MeOH (1)	RT	20	Na ₂ CO ₃	28
16	5 ^e	MeOH (1)	RT	20	Na ₂ CO ₃	22
17	5	MeOH (1)	40	20	Na ₂ CO ₃	83
18	5	MeOH (1)	50	20	Na ₂ CO ₃	88
19	5	MeOH (1)	60	5	Na ₂ CO ₃	77
20	2.5	MeOH (1)	60	20	Na ₂ CO ₃	90
21	2.5 ^e	MeOH (1)	60	20	Na ₂ CO ₃	82
22	2.5 ^e	MeOH (1)	60	7	Na ₂ CO ₃	79
23	5 ^f	MeOH (1)	60	20	Na ₂ CO ₃	94
24	5 ^f	MeOH (1)	60	5	Na ₂ CO ₃	88
25	5 ^f	MeOH (1)	60	7	Na ₂ CO ₃	93
26	2.5 ^f	MeOH (1)	60	7	Na ₂ CO ₃	90
27	2.5 ^{e,f}	MeOH (1)	60	7	Na ₂ CO ₃	85

^a Reaction conditions: **27** (0.50 mmol, 2 eq.), **28** (0.25 mmol, 1 eq.), Na₂CO₃ (0.50 mmol, 2 eq.), Cat. (5 mol%), MeOH (1.0 mL), 60 °C, 20 h, under air with an air-filled balloon above the vial. ^b NMR yield were calculated with 3-methoxy-benzene as internal standard. Average of two runs. ^c Reaction carried in closed vial without the air-filled balloon. ^d Isolated yield. ^e [Cu(IPr)Cl] used as catalyst. ^f Oxygen-filled balloon above the vial.

with 5 and 6 shows that a smaller amount of solvent increases the yields, and by comparing entries 1 and 5 with 4 and 6 it is found that a higher level of oxygen is a detrimental factor for maximum efficiency. After screening several solvents (Table 1, entries 6, 9, 10 and 11), methanol was found to be the best, affording 94% of the desired product. The use of base is essential for the reaction to proceed (Table 1, entry 14), with Na₂CO₃ affording the highest yield of **24** (Table 1, entries 6, 12 and 13). Lowering the catalyst loading to 2.5 mol% resulted in negligible change in the isolated yield (Table 1, entries 20 and 26).

Lastly, the amount of oxygen was increased in the reactor by affixing a balloon of pure oxygen gas to the vial. This increased oxygen concentration did not lead to higher conversion to product, but the reaction kinetics are greatly accelerated. Indeed, by comparing entries 6 and 25, the reaction time can be decreased to 7 hours leading to an excellent yield. We next examined the activity of [Cu(IPr)(Cl)] for the sake of com-

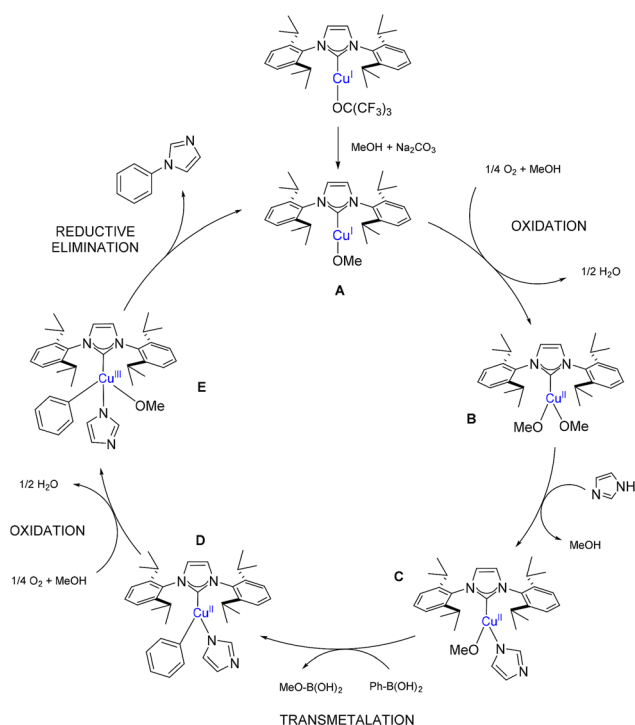


parison. Under these conditions, the activity of $[\text{Cu}(\text{IPr})(\text{Cl})]$ does not significantly differ from that displayed by **1**.

A proposed mechanism for CEL coupling using **1** as pre-catalyst is shown in Scheme 6 and is supported by previous mechanistic studies carried out under similar reaction conditions.^{36,37} $[\text{Cu}(\text{IPr})(\text{OMe})]$ (**A**) is believed to be the active catalytic species which undergoes aerobic oxidation forming a $\text{Cu}(\text{II})$ species (**B**). The two methoxide ligands on **B** are displaced with the nucleophilic amine by ligand exchange and with the phenylboronic acid *via* transmetalation, forming **D**. The final $\text{Cu}(\text{III})$ species (**E**) is formed by a second aerobic oxidation that subsequently undergoes reductive elimination, yielding the coupling product and the starting catalytic species **A**.

The active species in the CEL reactions remains a matter of debate, however, the present study encourages us to explore the CEL reaction in more detail with very simple catalyst. Such studies are presently ongoing in our laboratories.

In summary, we have developed a simple and efficient protocol to isolate air-stable NHC-containing copper perfluorinated alkoxide compounds. We have shown that complex **1** exhibits chemical versatility as an air-stable synthon in reactions involving N–H and S–H bond activations. Additionally, we have shown that **1** is an effective pre-catalyst for an early example of the Chan–Evans–Lam coupling reaction. Further studies involving this and related congeners in stoichiometric and catalytic reactions are ongoing in our laboratories.



Scheme 6 Proposed mechanism for the Chan–Evans–Lam reaction using $[\text{Cu}(\text{IPr})(\text{OC}(\text{CF}_3)_3)]$ (**1**) as pre-catalyst.

Data availability

All data included and leading to conclusions presented in this manuscript are included in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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