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Reusable and highly active supported copper(i)–NHC catalysts for Click chemistry

Immobilised [Cu(NHC)] catalysts are reported for the Click preparation of 1,2,3-triazoles; these are highly active, easy to prepare and to recycle.
Reusable and highly active supported copper(i)–NHC catalysts for Click chemistry†


Immobilised [Cu(NHC)] catalysts are reported for the preparation of 1,2,3-triazoles. In addition to showing outstanding catalytic activity, the catalyst systems are easy to prepare and can be recycled many times.

The copper-mediated cycloaddition reaction of azides and alkynes is a recent example of how metal catalysis can have an impact on a wide range of scientific disciplines. It has been thrust into the spotlight by its use as a proof of concept for the Click philosophy postulated by Sharpless. The reported applications for this cycloaddition reaction are numerous and diverse, but the development of true Click transformations still relies on the significant efforts being devoted to improve the understanding of the mechanism(s) involved, as well as on the development of ligand-modified systems. Among the families of ligands reported for this reaction, N-heterocyclic carbenes (NHCs) are prominent as they produce highly robust catalysts capable of conferring outstanding catalytic activity on the copper centre, often at extremely low catalytic loadings.

The immobilisation of metals on nanoparticles allows the properties and flexibility of a metal–ligand unit to be harnessed while exploiting the advantages of attachment to a surface. An enhanced Click catalyst for the cycloaddition of azides and alkynes could thus be achieved by a system that combines the exceptional activity of copper–NHC systems with the easy separation and recyclability of a heterogeneous catalyst. In this quest, it was decided to use [Cu(IAd)] [IAd = 1,3-di(adamantyl)imidazol-2-ylidene] as the starting point due to its superior reactivity when compared to other neutral [Cu(NHC)] complexes. Thus, it was anticipated that an analogue of the IAd ligand could be immobilised on silica through a hydroxyl substituent on the NHC backbone. Precedents in the literature for such architectures (sometimes referred to as switchable carbenes) include copper(i) complexes. More importantly, the modification of the ligand backbone minimises the changes around the metal centre, as significantly diminished catalytic activities are often reported for catalysts attached to surfaces via the substituent on the N atoms of the NHC ligand.

Following the reported synthetic route for the preparation of 4-hydroxyimidazol-2-ium salts bearing aromatic groups on the nitrogen atoms, the known adamantylformamidine 1 was prepared. However, under acylation conditions decomposed to give 2 as the sole isolated product (Scheme 1). This reactivity might be attributed to the fragility of allyl formamidines when compared to their aryl analogues. Thus, construction of the ligand was commenced instead from the backbone. The preparation of the ligand [IAd]HBF₄ 5 HBF₄ was then accomplished in three simple steps from adamantyl amine, starting with its acylation by chloroacetyl chloride, followed by amine alkylation (Scheme 1). Subsequent cyclisation with triethyl orthoformate led to the isolation of 5-HBF₄. Gratifyingly, it was found that all these reactions could be run in air with no need for purification on silica gel.

It is important to note that, for known 4-hydroxyimidazolium ligands (and their 4-amino analogues), the enol tautomer is so favourable that no 4-oxo-1,3-diarylimidazolium derivatives are observed. In contrast, the 1H NMR spectrum of 5-HBF₄ showed two singlets at 6.16 and 4.10 ppm, attributed to the enol and keto tautomers, respectively. The integration of these signals indicated a 1:1 equilibrium between both forms of [IAd]HBF₄.

Scheme 1 Synthesis of [IAd]HBF₄ 5 HBF₄.
The new azolium salt was then immobilised on three different carrier materials, namely silica flakes, silica nanoparticles and magnetite/silica nanoparticles. This was achieved by reaction of these supports with 5-HBF$_4$ in hot DMF in the presence of molecular sieves. The anchored ligands were then treated with CuI under otherwise identical conditions to those reported for the preparation of [CuI(Ad)] to give the corresponding supported [CuI(5)] complexes (Scheme 2).

Transmission Electron Microscopy (TEM) revealed that the silica nanoparticles, SiNP[CuI(5)], possessed an average diameter of 150.4 (±3.3) nm, while those with a magnetite core Fe$_3$O$_4$Si[CuI(5)], were 47.7 (±3.8) nm in size. All three functionalised silica materials showed the presence of copper, as determined by Energy Dispersive X-Ray Spectroscopy (EDS). Infrared spectroscopy provided limited information due to the small proportion of surface units compared to the bulk material of the nanoparticles. Initially, mass balance calculations were used to determine the loading of copper surface units on the nanoparticles but this was replaced by Inductively Coupled Plasma (ICP) analysis to provide the mmolCu per mg loading for the materials.

With the supported copper complexes in hand, the influence of the support on the catalytic activity was examined, along with the recycling efficiency of each system. Hence, the three prepared catalysts were applied to the model reaction of benzyl azide 6a and phenylacetylene on water at room temperature (Scheme 3). In the first cycle, all catalysts led to the quantitative formation of triazole 7a after overnight reactions with only 1 mol% [Cu]. After dissolving the formed triazoles in ETOAc, the reaction mixtures were centrifuged, and the catalysts were collected by filtration or using a magnet, washed, dried under vacuum and reused in a new cycle. The catalyst supported on silica flakes lost its catalytic activity by the fifth cycle, whereas the copper-functionalised silica nanoparticles led to diminished conversions after only 3 cycles (53% conversion, respectively). However, the copper complex supported on water at room temperature (Scheme 3). In the first cycle, all catalysts led to the quantitative formation of triazole 7a after overnight reactions with only 1 mol% [Cu]. After dissolving the formed triazoles in ETOAc, the reaction mixtures were centrifuged, and the catalysts were collected by filtration or using a magnet, washed, dried under vacuum and reused in a new cycle. The catalyst supported on silica flakes lost its catalytic activity by the fifth cycle, whereas the copper-functionalised silica nanoparticles led to diminished conversions after only 3 cycles (53% conversion, respectively). However, the copper complex supported on silica flakes, Fe$_3$O$_4$/Si[CuI(5)], showed extremely low copper contamination (around 3% of the original metal loading). TEM and EDS analysis of the used Cu–silica–magnetite catalyst demonstrated no discernible change of structure and showed no evidence of formation of copper nanoparticles.

In conclusion, a supported copper(I) catalyst has been developed that combines high recyclability with the remarkable activity of [Cu(NHC)] systems in the cycloaddition reaction of azides and alkynes. Importantly, in terms of its wider utility, the new system does not require a lengthy or complicated synthetic sequence for its preparation. The activity of the supported catalyst is comparable to its homogeneous analogue while permitting the reuse of the catalyst up to ten times after simple decantation in the presence of a hand-held magnet.
Imperial College and EPSRC are gratefully acknowledged for financial support of this work.

Notes and references


