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Cu^I click catalysis with cooperative noninnocent pyridylphosphine ligands

Sandra Y. de Boer [a], Yann Gloaguen [a], Martin Lutz [b], Jarl Ivar van der Vlugt [a,*]

[a] *Supramolecular & Homogeneous Catalysis Group, van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands*
[b] *Crystal and Structural Chemistry, Bijvoet Center for Biomolecular Research, Faculty of Science, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands*

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ABSTRACT

We describe the synthesis and characterization of compound **L1H**, 2-di(*tert*-butyl)phosphinomethyl-6-methylpyridine, and the first dimeric Cu^I complex **3** with this novel bidentate NP^{tBu} ligand. We also demonstrate for the first time that this ligand scaffold exhibits noninnocent reactivity through dearomatization behavior, similar to its well-studied tridentate analog **L2H**, 2,6-bis((di-*tert*-butylphosphino)methyl)pyridine PNP^{tBu}. The molecular structure of $[Cu(CCPh)(\mathbf{L2H})]_2$ is reported, which is a rare case of a crystallographically characterized copper-acetylide dimer. We also demonstrate that copper(I) complexes with either ligand **L1H** or **L2H** or their dearomatized counterparts may act as active, cooperative catalysts for the [2+3] polar cycloaddition of azides and acetylenes. These results represent the first indications of selective Cu-based cooperative catalysis, using non-innocent lutidine-based PNP backbone and catalysts **2** and **5** could thus be termed all-inclusive systems for this reaction.

1. Introduction

Nature often employs cooperative substrate activation to enhance selectivity, reactivity or activity, and almost without exception first row transition metals are utilized in metalloenzyme active sites [1]. This activation can be roughly separated into two areas: redox-based reactivity and acid-base related reactivity. Traditionally, the general concept of cooperative interactions has been ignored in synthetic catalyst designs, where ligand and metal have strictly separated roles during the catalytic conversion of substrates, and this is the case for the majority of newly developed systems to facilitate both existing and new catalytic transformations. Only recently, some convincing examples of productive metal–ligand interplay during substrate orientation, activation and/or transformation have been demonstrated. However, there is a striking dichotomy in these literature examples, with first-row transition metals mainly involved in redox-based cooperativity [2], while various expensive second- or third-row transition metals have been involved in other types of substrate activation to an appreciable extent [3]. Hence, the combination of first-row metals and cooperative ligand systems is a relative barren field of research, with potential applications to replace existing processes based on scarce metals with benign, earth-abundant alternatives [4].

Pincer ligands have been around for a few decades now, but research on these well-defined, tridentate scaffolds is still blossoming. The majority of the developed classes of pincer compounds are strictly monoanionic frameworks, predominantly with a deprotonated pivot (heteroatom) donor atom [5–7]. Recently, neutral lutidine-based PNP and PNN pincer scaffolds, which are susceptible to selective deprotonation–rearomatization of the ligand backbone [8], have also been successfully applied in cooperative catalysis [9], mainly with Ru [10] and to a lesser extent with Rh [11] and Ir [12]. Upon dearomatization, the ligand system undergoes a reversible formal charge-switching from neutral to monoanionic. Compared to the varied chemistry detailed for the heavier congeners, strikingly little attention has been paid to the use of first row transition metals with these ligand frameworks to date [13].

Therefore, we started a research program to explore metal–ligand cooperative reactivity with specific focus on first row metals, utilizing *inter alia* cooperative PNP ligands as a reactive scaffold. We have described the stoichiometric reactivity of ligand $\mathbf{PNP^{tBu}}$(**L2H**) with Cu^I, whereby hemilabile coordination of the pyridine-nitrogen donor was observed on going from neutral species **1** to the T-shaped cationic complex **A** (Scheme 1) [14]. Complex **1** selectively reacted with strong bases at the ligand backbone [15], mirroring reactivity described for 2nd and 3rd row metals [10–12] and providing a platform for further investigations with first row metals. Deprotonation of the reactive CH_2-spacer of the **PNP**-backbone resulted in bright orange, neutral T-shaped Cu-complex **2**, featuring ligand scaffold **L2**, which was susceptible to electrophilic addition (C–C bond formation) reactions on the ligand backbone. Reprotonation of **2** with thiophenol and benzyl mercaptan ($pK_a = 15.3$ in DMSO) occurs smoothly and instantaneously at room temperature [16], while boiling this species in ethanol ($pK_a = 29.8$ in DMSO) did not induce any visual change, with the

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* Corresponding author. Tel.: +31 20 5256459; fax: +31 20 5255604.
E-mail address: j.i.vandervlugt@uva.nl (J.I. van der Vlugt).

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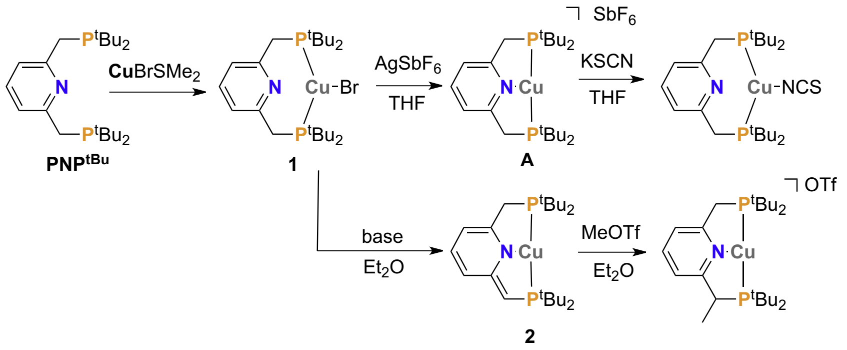


Scheme 1. Synthesis of Cu$^{\text{I}}$ complex **2** featuring a dearomatized PN$^-$P-ligand and the structural resemblance to the cationic derivative **A**.

persistent bright orange color indicative of the intact dearomatized heterocycle.

Alternatively, a 1D coordination polymer based on **L2H** and with the overall formula $[Cu_2Br_2(\mathbf{L2H})]_n$ could be fabricated, which showed identical response to base-mediated deprotonation of the PNP backbone. Subsequent treatment with sufficiently acidic thiols resulted in the formation of unique dinuclear Cu$^{\text{I}}$ complexes featuring bridging thiolate and PNP ligands [16].

Hence, the methodology of dearomatization–reprotonation offers a flexible and versatile route toward Cu$^{\text{I}}$ species bearing functionalities that are otherwise difficult to install. We also reported on the chemistry of ligand **PNP$^{\text{tBu}}$** with nickel [17] and palladium [18], including a direct comparison of dearomatized Pd(alkyl)(**PN$^-$P$^{\text{tBu}}$**) species with their isoelectric PCP analogs in the Suzuki coupling of arylbromides and arylboronic acids.

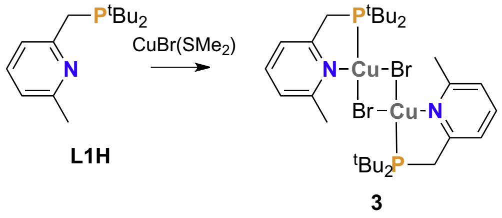
Besides tridentate ligands based on lutidine, also picoline and lutidine-derived NP$^{\text{R}}$-ligands as well as the closely related quinoline analogs have been employed quite extensively in the last decade [19], but the potential noninnocent character of these bidentate analogs of the PNP$^{\text{R}}$ ligand class has been almost completely overlooked to date and practical application of this feature has not been reported so far [20]. Furthermore, very few reports on alkyl-substituted PN ligands have appeared. Given our recent explorations in the first row chemistry of cooperative but very bulky pincer ligands, it was deemed interesting to probe the cooperative reactivity with the sterically more accessible PN ligands while coordinated to Cu$^{\text{I}}$ and thereby expand the toolbox of noninnocent, reactive ligands. We herein describe our initial efforts in this direction with the synthesis and application of Cu-complexes **3** and **4** for the (stoichiometric and catalytic) activation of acetylenes and azides. Furthermore, we have applied complexes **2** and **5**, featuring PNP ligand **L2** and **L2H**, respectively, in the same 'click-reaction'. This is the first example of cooperative copper catalysis with these noninnocent NP and PNP scaffolds.

2. Results and discussion

2.1. Ligand synthesis and Cu$^{\text{I}}$ coordination chemistry

Ligand **L1H** is prepared in a straightforward manner [21] by careful monolithiation of one of the lutidine methyl-groups, followed by phosphorylation using ClP$^{\text{t}}$Bu$_2$ to give a white solid after recrystallization by slow vapor diffusion of hexane into a concentrated dichloromethane solution. The ^{31}P NMR signal appears at δ 35.3 ppm in acetone-d_6. The second, unreacted methyl-group can act both as a spectroscopic handle and as a steric (and electronic) tuning factor upon coordination [22]. By using a lutidine-scaffold instead of picoline, undesirable cyclometallation reactions at the 6-position of the pyridine ring are also efficiently avoided.

Upon combining ligand **L1H** with CuBr(SMe)$_2$ in diethyl ether a light-yellow solid was recovered (Scheme 2) after work-up that showed a broad ^{31}P NMR signal at 26.6 ppm as well as the expected signals in the ^{1}H NMR spectrum for all types of hydrogen atoms present. IR spectroscopy indicated coordination of the pyridine N-atom to the Cu$^{\text{I}}$ center, with two bands at ν 1590 and 1577 cm^{-1}. High resolution FAB-MS showed a peak at m/z 790.0530 for the parent molecule [M+] and a fragmentation pattern indicative of a dimeric structure, which was confirmed by an X-ray crystallographic analysis of single crystals, grown by slow vapor diffusion of pentane into an acetone-d_6 solution. The molecular structure for dimeric complex **3** in the solid state, with bridging bromide ligands, is depicted in Fig. 1.



Scheme 2. Synthesis of complex **3**.

The complex shows overall centrosymmetry and the geometry around the Cu$^{\text{I}}$-center is distorted tetrahedral, with a more acute Br1–Cu1–Br1$^{\text{i}}$ angle of 103.783(9)° and large P–Cu–Br angles of 127.070(16)° and 118.207(16)°. The Cu–N and Cu–P bond distances are within the usual regions [14–16,23].

2.2. Cooperative click reactivity of Cu(PNP) complexes

It was reasoned that compound **2** might be a suitable starting material for the direct preparation of a precatalyst for the [2+3] polar cycloaddition [24] of phenyl acetylene, given that the pK_{a} of this reagent is 28.8 (in DMSO). Reconstitution of the aromatic pyridine heterocycle of the **PN$^-$P$^{\text{tBu}}$** backbone occurred instantaneously upon addition of one equiv phenylacetylene to an orange solution of **2** in diethyl ether, as evidenced by a color change to yellow, and NMR, IR spectroscopic and mass spectrometric analysis of the isolated light-yellow solid confirmed formation of species **5**. Evidently, proton transfer from the acidic phenylacetylene to the dearomatized **L2** backbone, concomitant with formation of the copper–phenylacetylide adduct proceeded smoothly and rapidly at room temperature, which is in contrast with the sluggish formation of a monomeric, two-coordinate Cu$^{\text{I}}$-phenylacetylide complex, reported by Gunnoe [25]. Reaction of the starting (NHC)CuMe-complex with PhCCH, eliminating methane concomitant with formation of the desired copper species, required heating to 60 °C for 22 h to enable complete conversion. This hints towards a different mechanism for both reactions, *i.e.* intermolecular proton-transfer followed by