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Ancillary ligand-free copper catalysed hydrohydrazination of terminal alkynes with NH_2NH_2†

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An efficient and selective Cu-catalysed hydrohydrazination of terminal alkynes with parent hydrazine is reported. The methodology tolerates a broad range of functional groups, allows for the synthesis of symmetrical and unsymmetrical azines, and can be extended to hydrazine derivatives and amines.

Driven by environmental and industrial concerns, the development of sustainable methodologies providing clean and selective synthetic transformations has risen over the years to become a major societal challenge.[1] In this context, the development of atom-efficient routes to carbon–nitrogen containing products using readily accessible bulk materials such as parent hydrazine is of special interest. However, NH_2NH_2 is a strong reducing agent, which can induce the formation of inactive metal(0),[2] or lead to the formation of inert Werner complexes.[3] Consequently, very few examples of catalytic reactions involving this reagent have been reported. Lundgren and Stradiotto,[4] and Buchwald *et al.*[5] have demonstrated that Pd- and Cu-catalysed cross-coupling of hydrazine with aryl chlorides and tosylates was possible providing the use of an electron rich bulky P-ligand. We[6] and others[7] have also shown that the hydrohydrazination of unactivated alkynes and allenes is efficiently promoted by cationic (L)Au(I) complexes (L: CAAC,[8] *Pyr*NHC,[9] MIC,[10] BAC,[11] saNHC[12]) (Fig. 1).

Based on the positive results observed with gold catalysts,[13] we questioned if copper complexes could also promote the hydrohydrazination of alkynes. It is interesting to note that so far, even for the hydroamination reaction, there are only a few reports dealing with the Cu-catalysed intermolecular version,[14] although there are examples of intramolecular reactions.[15]

Optimization of the reaction was performed using a stoichiometric mixture of parent hydrazine and phenylacetylene, as a model substrate, at 100 °C for 12 h with 5 mol% of copper complex (Table 1). In the presence of 5 mol% $KB(C_6F_5)_4$ (KBArF), both (IPr)CuCl[16] and (CAAC)CuCl[17] showed moderate activity (entries 1 and 2), while the bulkier (IPr*)CuCl[18] afforded complete conversion,

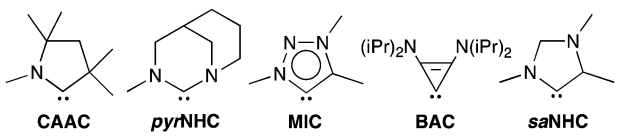
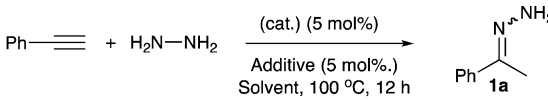
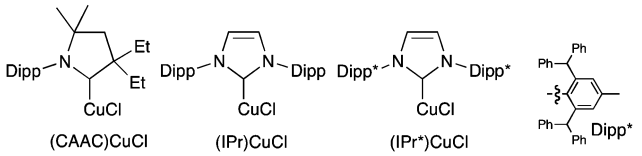


Fig. 1 Carbene ligands previously used in gold-catalysed hydrohydrazination.

Table 1 Optimization of the reaction conditions



Entry	Catalyst	Additive	Solvent	**1a**[a] (%)
1	(IPr)CuCl	KBArF	Benzene	66
2	(CAAC)CuCl	KBArF	Benzene	64
3	(IPr*)CuCl	KBArF	Benzene	83[b]
4	(CAAC)CuOTf	—	Benzene	22
5	—	KBArF	Benzene	0
6	CuCl	—	Benzene	0
7	(IPr*)CuCl	—	Benzene	0
8	CuCl	KBArF	Benzene	99
9	$CuCl_2$	KBArF	Benzene	86
10	CuCl	KBArF	THF	0
11	CuCl	KBArF	$CHCl_3$	0
12	CuCl	KBArF	Toluene	99
13	CuCl	$KBPh_4$	Benzene	<1
14	CuCl	$KSbF_6$	Benzene	<1
15	CuCl	AgOTf	Benzene	<1
16	CuCl	HBArF	Benzene	0
17	—	HBArF	Benzene	0
18	CuCl	KBArF/Hg(0)	Benzene	99



[a] Determined by ^1H NMR spectroscopy using hexamethylbenzene as internal standard. [b] Isolated.

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allowing the isolation of **1a** in 83% yield (entry 3). (CAAC)CuOTf[17] showed minimal activity likely due to the coordinating nature of the OTf counter-anion (entry 4). At this stage, control experiments were performed to confirm these initial observations. To our surprise, while no reaction was observed using either KBarF, (IPr*)CuCl or CuCl alone (entries 5–7), quantitative formation of hydrazine **1a** occurred in the presence of a stoichiometric mixture of CuCl/KBArF (5 mol%) (entry 8). Replacing CuCl by $CuCl_2$ also led to full conversion albeit in lower yield (86% – entry 9). Noteworthy, the reaction appears to be limited to non-polar solvents such as benzene or toluene (entries 10–12). Potassium or silver salts with weakly coordinating anions are broadly used for the *in situ* preparation of cationic metal species. However, as previously observed by Hashmi *et al.* with the (saNHC)AuCl system,[7] replacing KBArF by $KBPh_4$, $KSbF_6$, or AgOTf, inhibits the reaction (entries 13–15). Since Bergman *et al.*[19] have shown that the hydroamination of alkenes with anilines could be promoted by $H(Et_2O)_{2.5}B(C_6F_5)_4$, we tested the hydrohydrazination in the presence of 5 mol% of HBArF, but no conversion occurred (entries 16 and 17). Finally, a mercury test was performed to evaluate alternative heterogeneous catalytic pathways involving the formation of colloidal copper nanoparticles (entry 18). Under these conditions, catalysis still proceeded which is consistent with a homogeneous catalytic system.

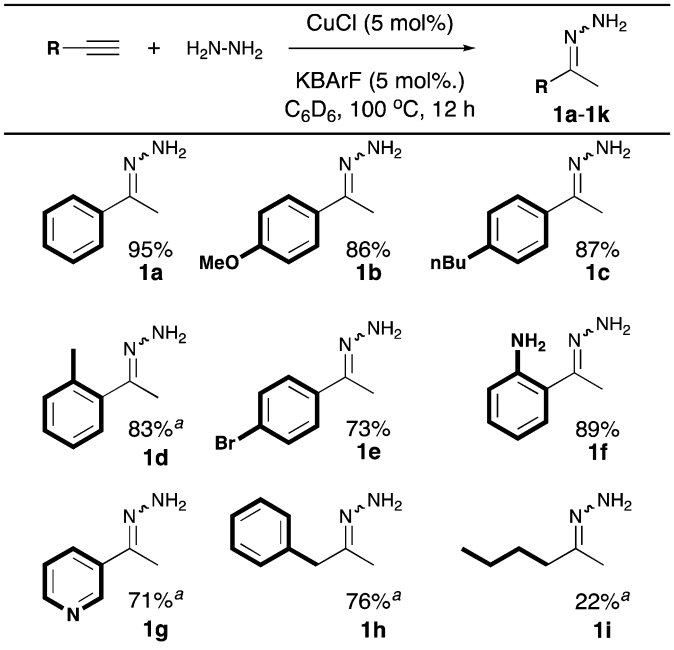
We then evaluated the scope of the reaction using CuCl (5 mol%), KBArF (5 mol%), and benzene as solvent. Under these conditions, a broad range of terminal aryl alkynes was reacted with parent hydrazine to yield the hydrazones **1a–1i** in good to excellent yields (Table 2). The reaction also appears to work with benzyl alkyne but is slower with alkyl substituted alkynes as observed with 1-hexyne, since compound **1i** was obtained in only 22% yield after 16 h. However, this protocol is quite straightforward as demonstrated by a gram-scale synthesis using phenylacetylene and parent hydrazine. Under the optimized conditions, 1.17 g (89% yield) of hydrazone **1a** was obtained.

To demonstrate the broad scope of this ancillary ligand-free copper catalysed process, phenyl acetylene was reacted with 1,1-dimethylhydrazine and phenylhydrazine, as well as with primary amines such as *n*-propylamine and aniline, and the corresponding products were obtained in greater than 78% yield (Table 3).

During our study we observed the formation of trace amounts of azines **2**. These products, which result from a bis-hydrohydrazination reaction, are formed whenever parent hydrazine was used sub-stoichiometrically. Azines have been used as synthetic intermediates,[20] and recently received much attention due to their interesting physical[21] and biological properties.[22] Under the standard conditions, using half equivalent of parent hydrazine we were able to obtain the corresponding azines **2a–2d** in good to excellent yields (Table 4). Furthermore, by sequential addition of two different alkynes, we were able to cleanly prepare unsymmetrical azines **2e–2f** (Table 5).

In summary, we have reported the first examples of copper-catalysed hydrohydrazination of terminal alkynes with NH_2NH_2.

Table 2 Scope of the hydrohydrazination of terminal alkynes with NH_2NH_2



[a] 16 h reaction time.

Table 3 Hydrohydrazination and hydroamination of phenyl acetylene

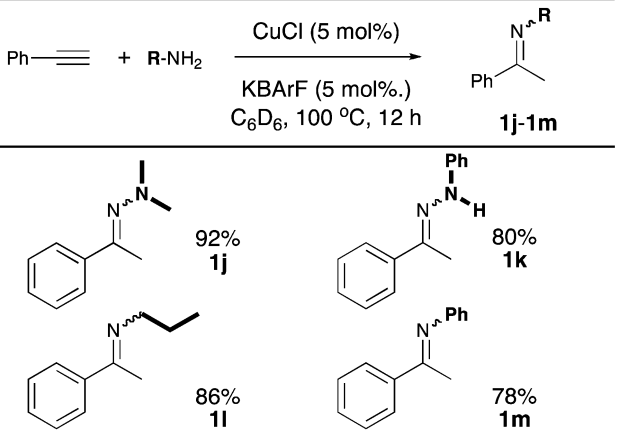


Table 4 Bis(hydrohydrazination) of terminal alkynes

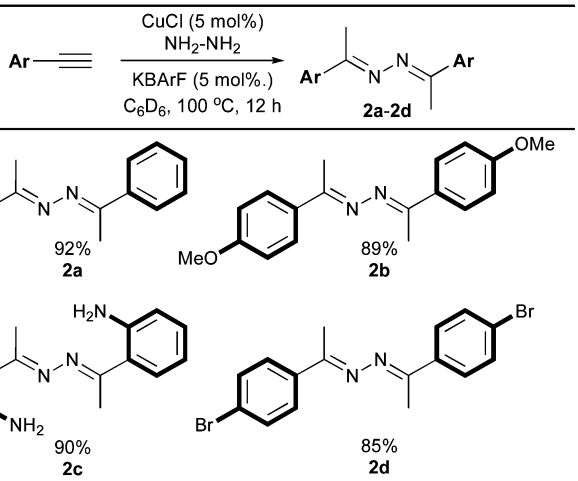
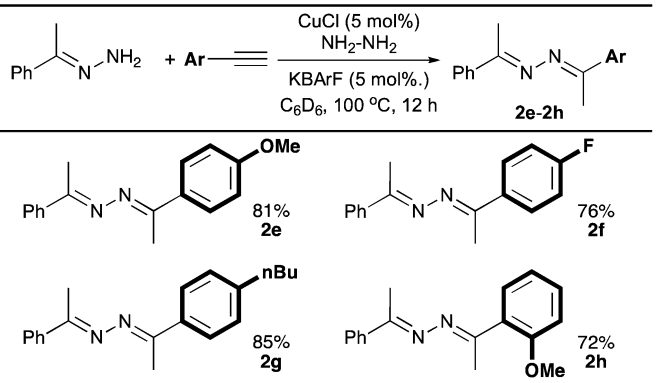


Table 5 Stepwise synthesis of unsymmetrical azines



The methodology tolerates a broad range of functional groups, allows for the synthesis of symmetrical and unsymmetrical azines, and can be extended to hydrazine derivatives and amines. In contrast to other metal catalysed reactions allowing the functionalization of parent hydrazine,[4–7] the process reported here is ancillary ligand-free and therefore economically viable.

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