Light-Stable Silver *N*-Heterocyclic Carbene Catalysts for the Alkynylation of Ketones in Air

Faïma Lazreg, Mathieu Lesieur, Andrew J. Samson and Catherine S. J. Cazin *[a]

Dedication ((optional))

Abstract: *N*-Heterocyclic carbene (NHC) silver(I) complexes were efficiently employed in the alkynylation of ketones. These cationic complexes were found highly active and efficient under mild conditions without the need of additive, and in air. The mechanism of this transformation was investigated. Experiments suggest the formation of a silver-acetylide key intermediate and the release of one ligand from the silver centre enabling the transformation.

Introduction

Propargylic alcohols are well-known building blocks in organic chemistry.[1] Easily functionalized, these precursors lead to a variety of molecules such as allenes, alkenes, vinylsilanes,[1] and find useful applications in the synthesis of natural products or pharmaceutical agents such as Efavirenz[2] or Donaxarine[3] (Figure 1).

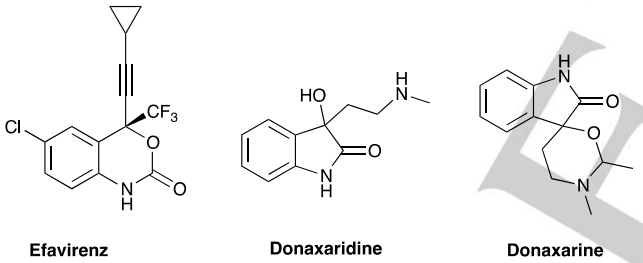

Figure 1. Examples of natural product and pharmaceutical reagents.

Propargylic alcohols are principally synthesized *via* the alkynylation of aldehydes or ketones, but their assembly usually requires the presence of a zinc, lithium or Grignard reagent to activate the alkyne.[4,5] Interestingly, numerous advances have been reported in the area of C-H activation of alkynes.[6] Despite the recent work reported on direct alkynylation of aldehydes, ketones have remained a more challenging functionality to activate.[4,5,7] Amongst ketones, much less attention has focused on trifluoromethyl-ketone and isatin (1*H*-indole-2,3-dione) derivatives.[8-10,12,13] In 2007, Shibasaki reported a methodology using a copper salt with Xantphos or phenanthroline as ligand (10 mol%) in the presence of potassium *tert*-butoxide, allowing the direct alkynylation of trifluoromethyl-ketones in toluene at 100°C (or THF at 60°C) for 12 to 24 h.[9] In parallel, Li described an aqueous process showcasing silver(I)/phosphine as an efficient system for such a transformation. In the latter case, long reactions times (1 to 2 days) were required and the reaction had to be conducted under an inert atmosphere.[10] During the last decade, metal-NHC (NHC = *N*-heterocyclic carbene) systems have become catalysts of choice, presenting outstanding reactivity and stability.[11] Recently, Li reported an "on water" alkynylation of isatin using 5 mol% of [Ag(Cl)(IMes)] (IMes = *N*,*N*'-bis{2,4,6-(trimethyl)phenyl} imidazol-2-ylidene) in the presence of DIPEA (di-*iso*-propylethylamine, 10 mol%).[12] McQuade and co-workers showed [Cu(Cl)(IPr)] (IPr = *N*,*N*'-bis{2,6-(di-*iso*-propyl) phenyl}imidazol-2-ylidene) and sodium *tert*-butoxide as catalytically active system for the alkynylation of trifluoromethyl-ketones.[13] However, due to the formation of a *tert*-butoxide species, an inert atmosphere was required. Recently, our group reported the synthesis of heteroleptic bis-NHC copper(I) and silver (I) complexes.[14,15] While the latter have not yet been tested in catalysis, the former have shown excellent activity in the [3+2] cycloaddition of alkynes and azides.[14] Mechanistic studies have shown that the reaction likely proceeds through an acetylide complex, which could also be a key intermediate in the alkynylation of ketones.[9] We therefore reasoned that heteroleptic bis-NHC Cu and Ag complexes could be efficient catalysts in such a transformation.

Herein, we report the high efficiency of such complexes for the alkynylation of trifluoromethyl ketones and isatin derivatives using water or methanol/water mixtures as solvent, in air, and without the need for any additive.

Results and Discussion

N-benzylisatin and phenylacetylene were selected as benchmark substrates for the reaction conditions optimization. [Cu(IPr)(ICy)]BF_4 **1** (ICy = *N*,*N*'-dicyclohexyl imidazol-2-ylidene) and [Cu(IPr)(ItBu)]BF_4 **2** (ItBu = *N*,*N*'-di-*tert*-butyl imidazol-2-ylidene) were chosen as they are efficient catalysts for the [3+2] cycloaddition and permit the direct C-H activation of alkynes without additives.[14] Their silver analogues **3** and **4** were also evaluated (Figure 2).

[a] F. Lazreg, M. Lesieur, A. J. Samson Dr, C.S.J., Cazin
EaStCHEM School of Chemistry
University of St Andrews
KY16 9ST, St Andrews, U.K.
E-mail: cc111@st-andrews.ac.uk

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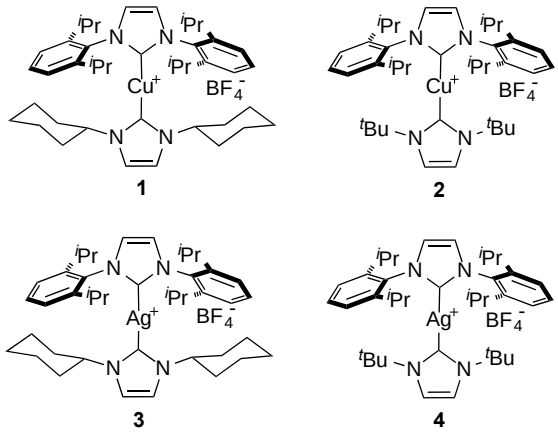


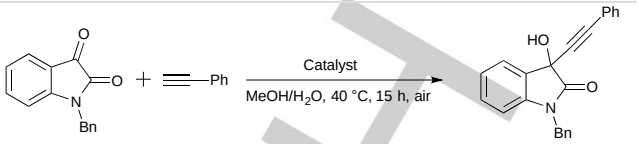
Figure 2. Bis-NHC copper(I) and silver(I) complexes used in this study.

Comparison of the four complexes, in water, using 2.5 mol% loading, shows that, whilst the Cu catalysts are moderately active, the Ag analogues lead in quantitative manner to the propargylic alcohol (Table 1, entries 1-4). No particular precaution was taken to avoid the presence of light when using silver(I) complexes (**3** and **4**). Decreasing the catalyst loading to 2 mol% showed no loss in catalytic activity. A further decrease to 1 mol% Ag leads to poor conversion (Table 1, entries 7-9).

Solvent optimisation was performed (see ESI), which led us to a mixture of MeOH and H_2O in a 1:1 ratio as the optimal reaction medium. Under such conditions, $[Ag(IPr)(ICy)]BF_4$ **3** provides superior catalytic activity than its ItBu analogue complex **4** (Table 1, entries 10 and 11). Further decrease of the catalyst loading to 0.5 mol% leads to good conversion providing that the reaction mixture is heated to 60ºC (Table 1, entry 17).

The scope of the reaction was examined (Scheme 1). *N*-benzylisatin was successfully converted in a series of propargylic alcohols using aryl and alkyl-substituted alkynes. In all cases, quantitative conversion is observed, with isolated yields ranging from 90% to 99%, demonstrating the selectivity of the process. Phenyl acetylene derivatives substituted with a range of functional groups (F, OMe, Me, ^{t}Bu, CF_3) are efficiently converted (**7aa-i**). This is also the case with alkynes substituted with a heterocycle (**7aj**), alkyl and amino groups (**7ak-l**). *N*-Methylated isatin can also be converted, however, in this case, no methanol was used, and the reaction was carried out in water (**7ba**). The versatility of the methodology is further showcased by the reactivity of isatins substituted by electron-donating and withdrawing groups (**7ca**, **7cd**, **7da**, **7db**, **7eb**). All these reactions lead to complete conversion to the alkynylation product in air, in the presence of light, using 2 mol% of catalyst (for **7aa-c** and **7eb**, only 1 mol% was used). Notably, ethyltrimethylsilane as well as prop-2-yn-1-ol were tested, however no conversion towards the desired products was observed.

Table 1. Optimisation of bis-NHC silver(I) and copper(I) complexes.[a]

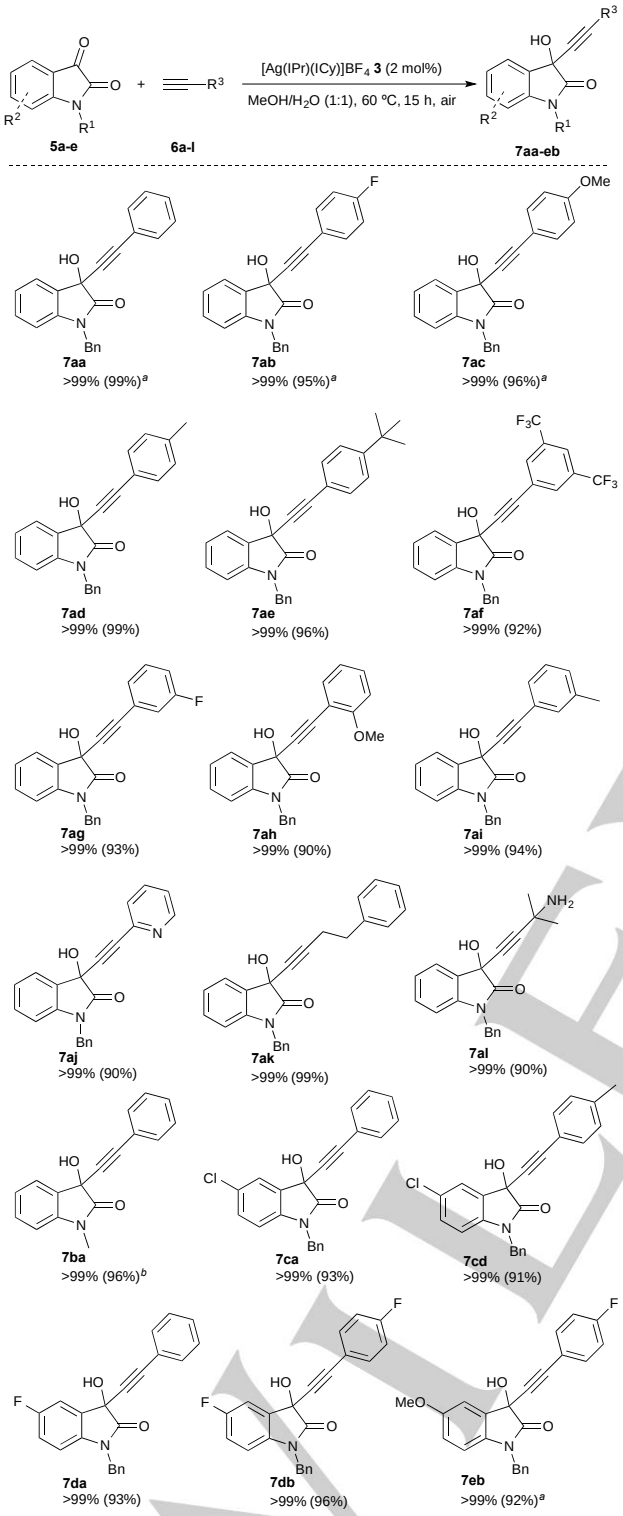


5a **6a** **7aa**

Entry	Complex	Catalyst (mol%)	Ratio MeOH/H_2O	Conversion (%)[b]
1	**1**	2.5	0:1	15
2	**2**	2.5	0:1	15
3	**3**	2.5	0:1	>99
4	**4**	2.5	0:1	>99
5	**3**	2	0:1	>99
6	**4**	2	0:1	98
7	**3**	1	0:1	30
8	**4**	1	0:1	26
9	**4**	1	1:0	30
10	**3**	0.5	1:1	40
11	**4**	0.5	1:1	10
12	**3**	0.5	8:2	8
13	**4**	0.5	8:2	4
14	**3**	0.5	2:8	20
15	**4**	0.5	2:8	20
16	**3**	0.5	1:1	10[c]
17	**3**	0.5	1:1	73[d]

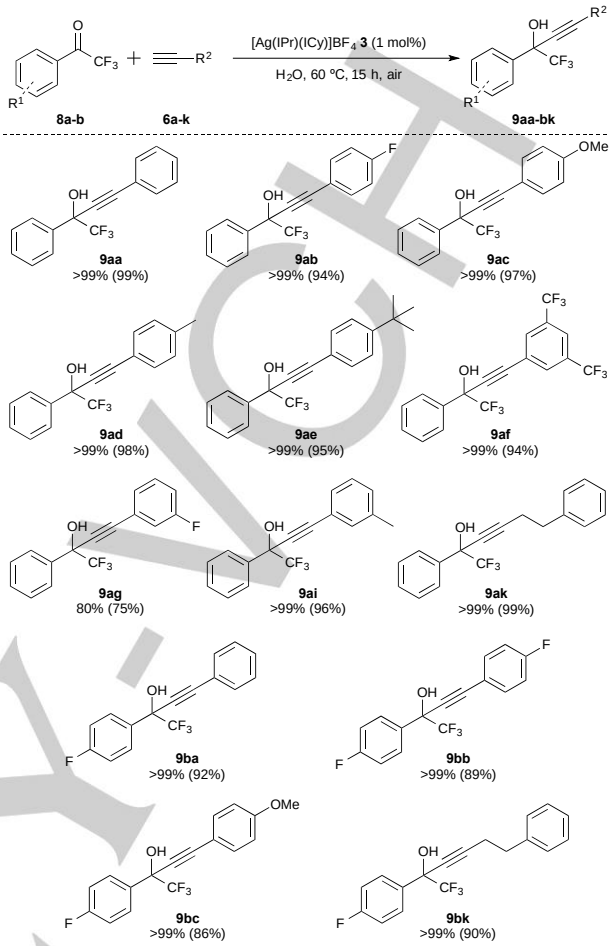
[a] Reaction conditions: *N*-benzylisatin (0.25 mmol, 59.3 mg), phenylacetylene (0.37 mmol, 41.2 µL), solvent (1 mL), 40 °C, 15 h, in air. [b] Conversion determined by ^{1}H-NMR, based on *N*-benzylisatin, minimum average of 4 reactions. [c] RT. [d] 60 °C.

Next, we turned our attention to the acyclic trifluoro-methyl ketone trifluoroacetophenone. In this case, the reaction is efficiently catalysed using only 1 mol% of $[Ag(IPr)(ICy)]BF_4$ **3**, in water, in air and in the presence of light (Scheme 2). The scope of the reaction was investigated, and a series of propargylic alcohols was synthesised in good to excellent isolated yields (75-99%). Phenyl acetylene derivatives bearing electron withdrawing and electron donating groups (F, CF_3, Me, ^{t}Bu, OMe) are well tolerated. Alkynes other than phenyl acetylene derivatives can be used, as shown with 4-phenyl-1-butyne (**9ak**, **9bk**), hence extending the scope to alkyl-substituted alkynes.



Reaction conditions: isatin (0.25 mmol), alkyne (0.375 mmol), **3** (2 mol%), methanol/water (1:1, 1 mL), 60ºC, 15 h. Conversion determined by ^{1}H-NMR, based on the isatin derivative, average of 2 reactions. Isolated yield in parentheses.
[a] 1 mol% of catalyst **3**.
[b] Only in water.

Scheme 1. Alkynylation of isatin derivatives.

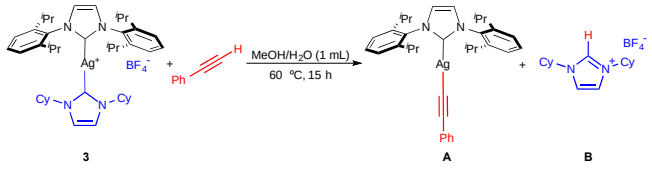


Reaction conditions: trifluoromethyl ketone (0.25 mmol), alkyne (0.375 mmol), **3** (1 mol%), water (1 mL), 60 °C, 15 h. Conversion determined by ^{1}H-NMR, based on the isatin derivative, average of two reactions. Isolated yield in parentheses.

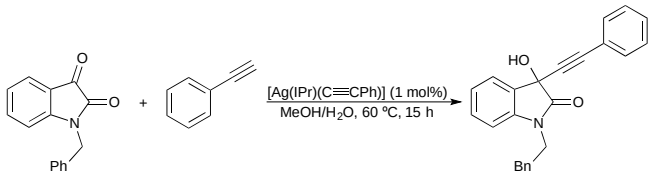
Scheme 2. Scope of trifluoromethyl ketones.

Mechanistic Studies.

In order to obtain information on the nature of organometallic intermediates involved in these reactions, [Ag(IPr)(ICy)]BF_4 **3** was reacted with an excess of phenylacetylene at 60 °C in methanol/water for 15 h (Scheme 3). This led to the formation of the silver acetylide complex **A** with the concomitant loss of the imidazolium salt ICy·HBF_4 **B** (Scheme 3).[16] It was also shown that the intermediate acetylide **A** can itself catalyse the reaction (Scheme 4). The species **A** was reacted with benzylisatin. Interestingly, the reaction leads to the formation of an unstable new species, presumably intermediate **C** (Scheme 5).

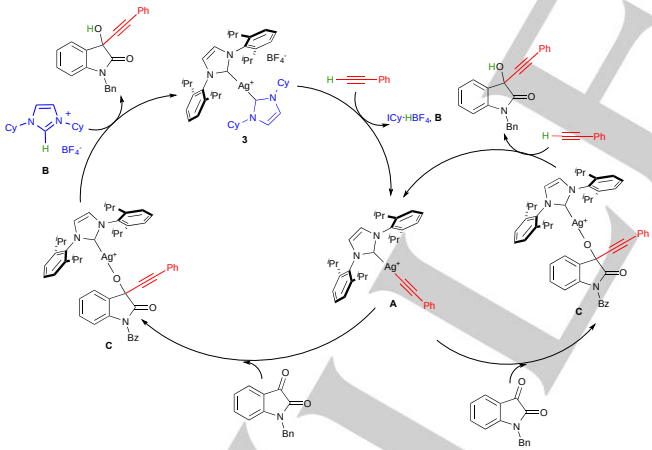


Scheme 3. Stoichiometric reaction between complex **3** and phenylacetylene.



Scheme 4. Catalytic reaction involving the acetylide silver(I) complex **A.**

Based on these observations, a catalytic cycle is proposed (Scheme 5), where the bis-NHC Ag pre-catalyst leads to the acetylide derivative **A** which can then react with the ketone to form an alkoxide intermediate. The latter can be protonated by the imidazolium salt **B** released during the first step, hence liberating the product and regenerating the catalyst. An alternative catalytic cycle might also be operative, in which the proton leading to the liberation of the alcohol product comes from the alkyne itself (Scheme 5, right-hand side). On-going computational studies are directed to answer these questions about the preferred reaction pathway.



Scheme 5. Proposed mechanism for the alkynylation of isatin.

Conclusions

Cationic heteroleptic bis-NHC silver complexes were shown to efficiently promote the alkynylation of ketones. The NHC-silver(I) complexes were shown to be more efficient in aqueous media than their copper(I) analogues. An excellent catalytic activity was observed with only 1 mol% of catalyst, without the need of additives, in the presence of air and light, using mild conditions and water as the solvent. Stoichiometric experiments support the release of one NHC and the formation of a silver(I) acetylide species as key elements of the catalytic cycle. On-going studies are directed to further extend the scope of this transformation towards unactivated and other ketone substrates.

Experimental Section

General procedure for catalysis: A vial was charged with [Ag(IPr)(ICy)]BF_4 (1.0 mol%), the ketone (0.25 mmol), the alkyne (0.375 mmol), and the solvent (1 mL). The reaction mixture was stirred at 60°C for 15 hours. The reaction mixture was allowed to cool to room temperature. The aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (20 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by recrystallization or by flash chromatography (SiO_2).

Acknowledgements

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Keywords: Alkynylation •Silver •Copper • Carbene • Air

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[16] See Supporting Information.

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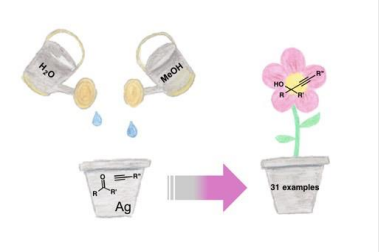
FULL PAPER

An efficient methodology for the alkynylation of ketones was developped based on NHC-silver(I) complexes, in air.



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