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

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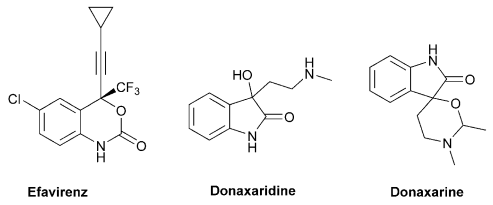
N-Heterocyclic carbene (NHC) silver(I) complexes were employed efficiently in the alkynylation of ketones. These cationic complexes were highly active and efficient under mild conditions and in air without the need for an additive. The mechanism of this transformation was investigated. Experiments suggest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

Introduction

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



Efavirenz Donaxaridine Donaxarine

Figure 1. Examples of natural product and pharmaceutical reagents.

Propargylic alcohols are principally synthesised by 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 the 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.[8–12] In 2007, Shibasaki and co-workers reported a methodology using a copper salt with Xantphos or phenanthroline as the ligand (10 mol%) in the presence of potassium *tert*-butoxide, which allowed the direct alkynylation of trifluoromethyl ketones in toluene at 100 °C (or THF at 60 °C) for 12–24 h.[9] In parallel, Deng and Li described an aqueous process that showcased silver(I)/phosphine as an efficient system for such a transformation. However, long reactions times (1–2 days) were required, and the reaction had to be conducted under an inert atmosphere.[10]

During the last decade, metal-N-heterocyclic carbene (NHC) systems have become catalysts of choice that present outstanding reactivity and stability.[13] Recently, Li and co-workers 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 di-*iso*-propylethylamine (DIPEA, 10 mol%).[11] McQuade and co-workers demonstrated [Cu(Cl)(IPr)] (IPr = *N*,*N*′-bis[2,6-(di-*iso*-propyl)phenyl]imidazol-2-ylidene) and sodium *tert*-butoxide as a catalytically active system for the alkynylation of trifluoromethyl ketones.[12] However, as a result of 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] Although 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] Therefore, we 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 the solvent in air and without the need for any additive.

Results and Discussion

N-Benzylisatin and phenylacetylene were selected as benchmark substrates for the optimisation of the reaction conditions. [Cu(IPr)(ICy)]BF_4 (**1**; ICy = *N*,*N*′-dicyclohexylimidazol-2-ylidene) and [Cu(IPr)(I*t*Bu)]BF_4 (**2**; I*t*Bu = *N*,*N*′-di-*tert*-butylimidazol-2-yli-

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dene) were chosen as they are efficient catalysts for the [3+2] cycloaddition and permit the direct C–H activation of alkynes without additives.[14] The silver analogues [Ag(IPr)(ICy)]BF_4 (**3**) and [Ag(IPr)(I*t*Bu)]BF_4 (**4**) were also evaluated (Figure 2).

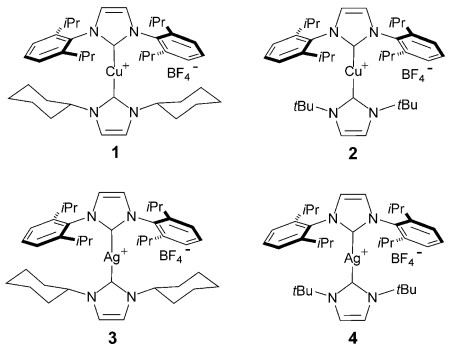
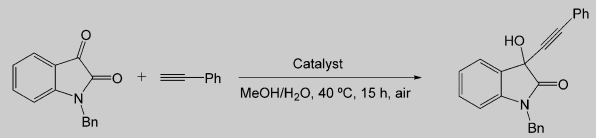


Figure 2. Bis-NHC copper(I) and silver(I) complexes used in this study.

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

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



5a 6a 7aa

Entry	Complex	Catalyst [mol%]	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 ^1H NMR spectroscopy based on *N*-benzylisatin, minimum average of four reactions. [c] RT. [d] 60 °C.

Solvent optimisation was performed (see the Supporting Information), which led us to a mixture of MeOH and H_2O in a 1:1 ratio as the optimal reaction medium. Under such conditions, complex **3** provides superior catalytic activity than its I*t*Bu analogue **4** (Table 1, entries 10 and 11). A further decrease of the catalyst loading to 0.5 mol% leads to a good conversion if the reaction mixture is heated to 60 °C (Table 1, entry 17).

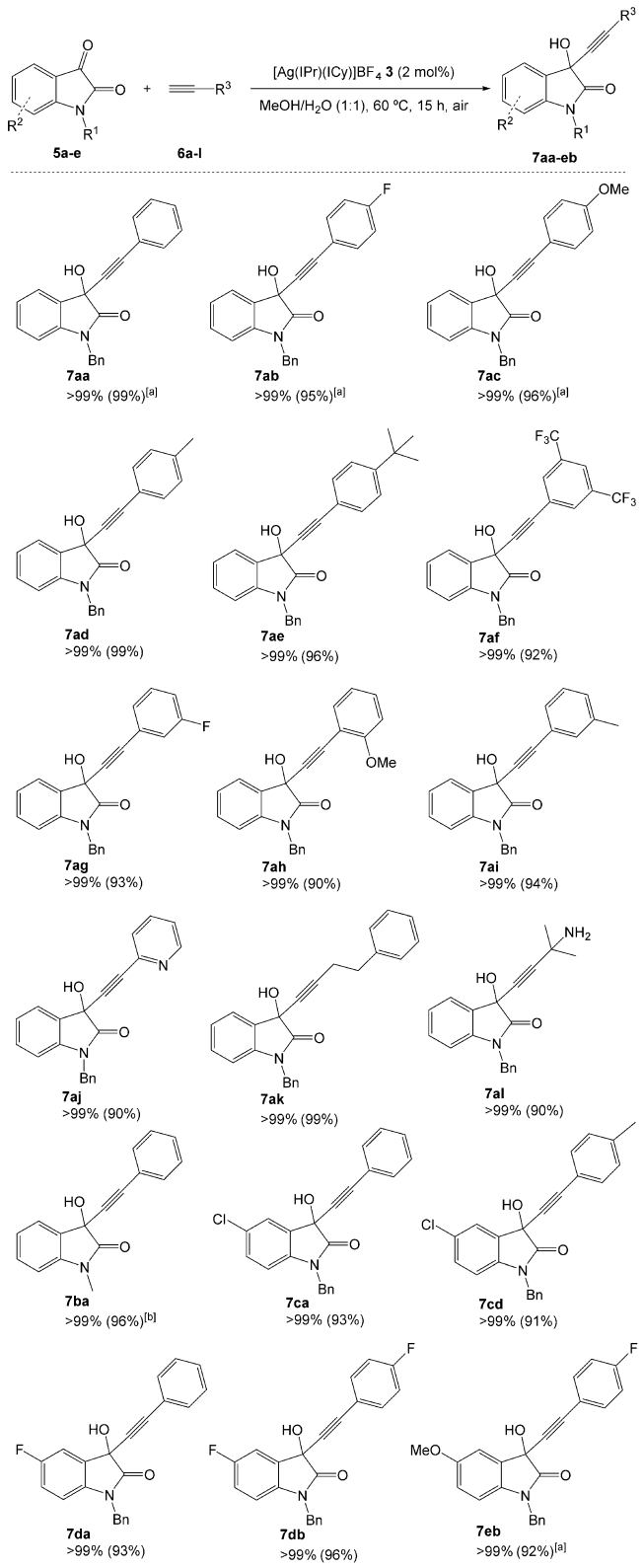
The scope of the reaction was examined (Scheme 1). *N*-Benzylisatin was converted successfully in a series of propargylic alcohols using aryl- and alkyl-substituted alkynes. In all cases, quantitative conversion is observed with isolated yields that ranged from 90 to 99%, which demonstrates the selectivity of the process. Phenyl acetylene derivatives substituted with a range of functional groups (F, OMe, Me, *t*Bu, CF_3) are converted efficiently (**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 performed 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 the 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.

Next, we turned our attention to the acyclic trifluoromethyl ketone trifluoroacetophenone. In this case, the reaction is catalysed efficiently using only 1 mol% of **3** in water and 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 that bear electron-withdrawing and -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**), which extends the scope to alkyl-substituted alkynes.

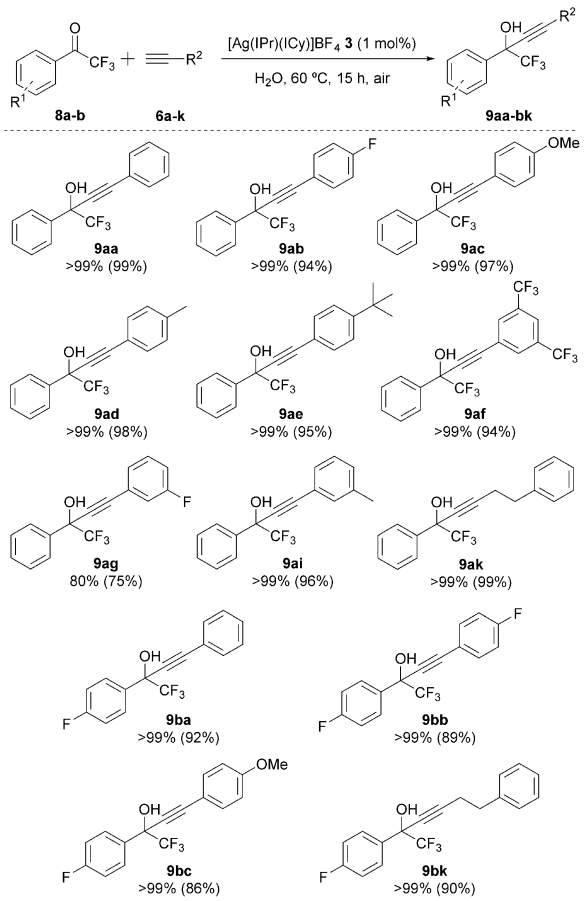
Mechanistic studies

To obtain information on the nature of the organometallic intermediates involved in these reactions, **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, and the Supporting Information). The intermediate acetylide **A** can itself catalyse the reaction (Scheme 4). The species **A** was reacted with *N*-benzylisatin, which interestingly leads to the formation of an unstable new species, presumably intermediate **C** (Scheme 5).

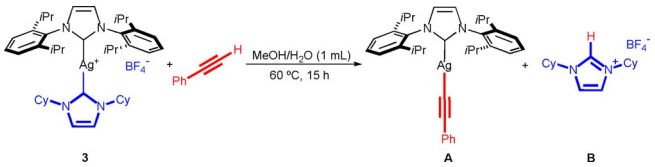
Based on these observations, a catalytic cycle is proposed (Scheme 5) in which the bis-NHC Ag pre-catalyst leads to the acetylide derivative **A** that can then react with the ketone to form an alkoxide intermediate. The latter can be protonated by the imidazolium salt **B** released during the first step, which liberates the product and regenerates the catalyst. An alterna-



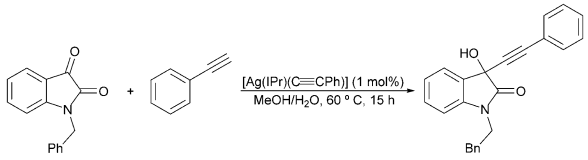
Scheme 1. Alkynylation of isatin derivatives. Reaction conditions: Isatin (0.25 mmol), alkyne (0.375 mmol), **3** (2 mol%), methanol/water (1:1, 1 mL), 60 °C, 15 h. Conversion determined by ^{1}H NMR based on the isatin derivative, average of two reactions. Isolated yield is shown in parentheses. [a]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



Scheme 2. Scope of trifluoromethyl ketones. 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 is shown in parentheses.

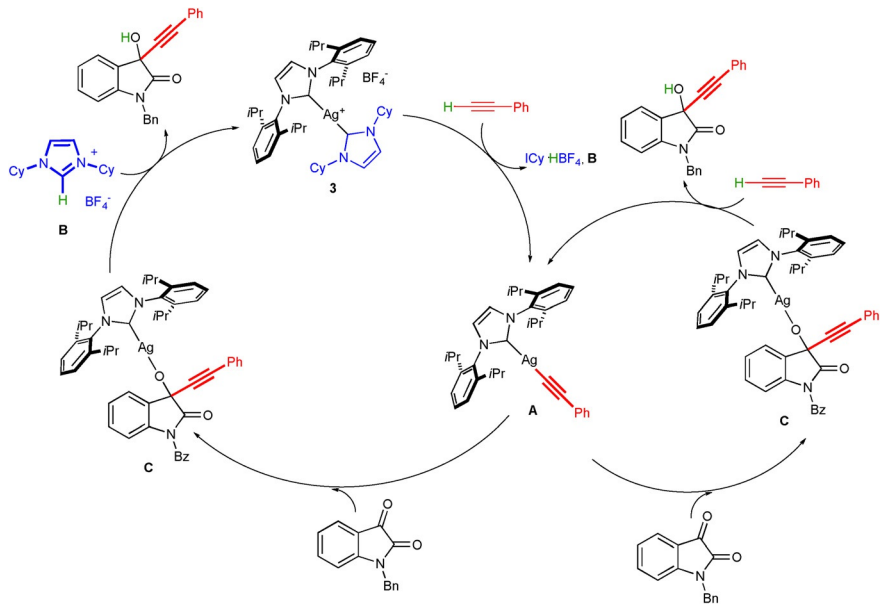


Scheme 3. Stoichiometric reaction between **3** and phenylacetylene.



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

tive catalytic cycle might also be operative in which the proton that leads 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-N-heterocyclic carbene (NHC) silver complexes were shown to promote the alkynylation of ketones efficiently. The NHC silver(I) complexes were 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 under mild conditions with 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 h. The reaction mixture was allowed to cool to RT. The aqueous layer was extracted with ethyl acetate (2× 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 recrystallisation or flash chromatography (SiO_2).

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Keywords: alkynes · carbene ligands · copper · ketones · silver

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