

Ag(I) Complexes Bearing *N*-heterocyclic Carbene Catalyzed Formation of Propargylamines by Three-component Coupling Reaction

RAFET KILINCARSLAN*, AHMET KUNDURACIOGLU, NAIM SADIC

Pamukkale University, Department of Chemistry, 20017-Kinikli, Denizli, Turkey

Quaternisation of methylimidazole by bromoalkanes afforded imidazolium salts (1) which were converted to Ag-NHC complexes bearing imidazol-2-ylidenes, [(C_nmim)₂Ag]₂[Ag₂Br₄], 2, using the silver oxide. The catalytic activities of silver-N-heterocyclic carbene (NHC) complexes were investigated in the three-component coupling reaction of aldehyde, alkyne and amine to propargylamines.

Keywords: *N*-heterocyclic carbene, silver, catalytic activity, coupling, propargylamines

N-Heterocyclic carbenes (NHCs) are cyclic constructions which are generally derived from deprotonation of salts of ligands such as imidazoli(ni)um, benzimidazolium, diazepinium, pyrimidium. NHCs are strong σ -donating and weak π -accepting ligands in which a carbene carbon is accompanied by two p-donor nitrogen atoms [1]. Since the first successful synthesis of Ag(I)-NHC complex in 1993, this class of organometallic compounds has been extensively used for transmetallation reactions where the direct synthesis of NHC complexes using other metal ions was either difficult or impossible [2].

NHC-silver complexes have had a significant role in the rapid development of NHC-metal complexes. This valuable use of Ag(I)-NHC complexes was adopted because of their ease of synthesis and stability towards the air and moisture. Furthermore, the transmetallation reactions using Ag(I)-NHC complexes can be carried out under aerobic conditions and even in the presence of moisture. To the date, a number of M-NHC complexes [M = Au(I), Cu(I), Cu(II), Ni(II), Pd(II), Rh(I), Rh(III), Ir(I), Ir(III), Ru(II), Ru(III) and Ru(IV)] have been successfully synthesized using Ag(I)-NHC complexes as ligand (NHC) transfer agents [3-7]. Also, the prominent biological activity of NHC-silver complexes as anticancer and antimicrobial agents has been confirmed [8-10]. However, despite the fact that silver complexes have been extensively used to catalyze the formation of C-C and C-E (E: heteroatom) bonds [11-13], the utility of Ag-NHCs in chemical catalysis remains scarcely explored, and only a few examples were reported. The NHC-silver complexes exhibit good catalytic activities for CO₂ fixation [14], cyanosilylation of imines [15], carbomagnesiation of terminal alkenes [16], diboration of alkenes [17], alkynylation of isatins [18], and ring-opening polymerization of L-lactide [19,20]. This delay may be due to the structural diversity and the lability of the Ag-NHC bond, which could lead to decomposition and also hamper identification of true catalytic species. For example, thermal decomposition of [(emim)₂Ag][AgCl₂] was proposed to give free 1-ethyl-3-methylimidazol-2-ylidene (emim), which catalyzes the ring opening polymerization of L-lactide [21]. It is well-established that in solution the silver NHC complexes, corresponding to [NHC-Ag-X]_n (n = 1-4) formula, are in equilibrium with respect to ionic species [(NHC)₂Ag]⁺[AgX₂]⁻. The steric bulk on the carbene substituents, the nature of halide ion and solvent polarity control the position of equilibrium [22].

In recent years, Ag-NHCs have also been successfully used to catalyze the three-component coupling reaction of aldehyde, alkyne and amine to propargylamines [23-26]. Based on these facts, we wanted to see that a complex capable of providing anionic and cationic species maybe expected to enhance catalytic efficiency for the synthesis of propargylamines in solution used. For this, we decided to ionic Ag-NHCs synthesized by our group, i.e., [(C_nmim)₂Ag]₂[Ag₂Br₄] (C_nmim denotes 1-(C_nH_{2n+1})-3-methylimidazol-2-ylidene; n = 6-12) [14]. As can be seen from figure 1, catalytic efficiencies of this Ag-NHCs report in the three-component coupling reaction of alkyne, aldehyde and amine forming propargylamines.

Experimental part

General considerations

All reactions and manipulations for the preparations of ligands and NHC-silver(I) complexes were carried out under argon in flame-dried glassware using standard Schlenk line techniques. Anhydrous solvents were either distilled from appropriate drying agents or purchased from Merck and degassed prior to use by purging with dry argon and kept over molecular sieves. All other reagents were commercially available and used as received. NMR spectra were recorded at 297 K on a Varian Mercury AS 400 NMR instrument at 400 MHz (¹H), 100.56 MHz (¹³C). Elemental analyses were performed by TUBITAK (Ankara, Turkey) Microlab.

Preparation of ligands

The preparation of imidazolium chlorides (**1a-d**) started from 1-methylimidazole were prepared according the literature [14,30].

Preparation of NHC-Ag(I) catalysts

2 type compounds were prepared according literature [14]. Ag₂O (2.2 mmol) was added to dichloromethane solution of corresponding imidazolium salt (4.0 mmol). The reaction mixture stirred for 12 h at room temperature. After the disappearance of the Ag₂O suspension, the resulting solution was concentrated to 10 mL and added Et₂O. Et₂O phase decanted and dried under vacuum. The white residue recrystallized from CH₂Cl₂/acetonitrile.

[(C₆mim)₂Ag]₂[Ag₂Br₄], **2a**

Yield: 0.88 g (62%); m.p 69-71°C; *Anal.* Calcd. mass fractions of elements, w/%, for C₄₀H₇₂Ag₄Br₄N₈ (M_r = 1416.14) are: C 33.93, H 5.12, N 7.91; found: C 34.04, H

* email : rkilincarslan@pau.edu.tr; Phone: +90 258 2963604

5.23, N 7.87. ¹H NMR (CDCl₃): 6.97 (s, 2H, CH), 4.08 (t, *J*=7.2 Hz, 2H, CH₂), 3.83 (s, 3H, CH₃), 1.80 (t, *J*= 6.0 Hz, 2H, CH₂), 1.31 (s, 6H, CH₂), 0.89 (t, *J*= 8.0 Hz, 3H, CH₃). ¹³C NMR (CDCl₃) δ 181.7, 122.2, 121.1, 52.1, 39.0, 31.6, 26.3, 22.6, 14.1.

[(C₈mim)₂Ag]₂[Ag₂Br₄], **2b**

Yield: 1.15 g (75%); m.p 71-73°C; *Anal.* Calcd. mass fractions of elements, w%, for C₁₆H₈₈Ag₄Br₄N₈ (*M_r* = 1528.36) are: C 37.72, H 5.80, N 7.33; found: C 37.67, H 5.91, N 7.37. ¹H NMR (CDCl₃): δ: 6.97 (s, 2H, CH), 4.08 (t, *J*= 8.0 Hz, 2H, CH₂), 3.84 (s, 3H, CH₃), 1.84 (t, *J*= 8.0 Hz, 2H, CH₂), 1.26-1.31 (m, 12H, CH₂), 0.88 (t, *J*= 8.0 Hz, 3H, CH₃). ¹³C NMR (CDCl₃) δ: 180.9, 122.4, 121.1, 51.9, 38.8, 31.6, 29.0, 26.4, 22.5, 14.0.

[(C₁₀mim)₂Ag]₂[Ag₂Br₄], **2c**

Yield: 1.38 g (84%); m.p 75-77°C; *Anal.* Calcd. mass fractions of elements, w%, for C₃₆H₁₀₄Ag₄Br₄N₈ (*M_r* = 1640.57) are: C 41.00, H 6.39, N 6.83; found: C 41.23, H 6.51, N 6.78. ¹H NMR (CDCl₃): δ: 6.98 (d, *J*= 8 Hz, 2H, CH), 4.02 (t, *J*= 8.0 Hz, 2H, CH₂), 3.78 (s, 3H, CH₃), 1.72 (t, *J*= 8.0 Hz, 2H, CH₂), 1.16 - 1.22 (d, 14H, CH₂), 0.78 (t, *J*= 4.0 Hz, 3H, CH₃). ¹³C NMR (CDCl₃) δ: 181.4, 122.5, 121.3, 52.1, 39.0, 32.0, 31.7, 29.6, 29.4, 29.3, 26.7, 22.8, 14.3.

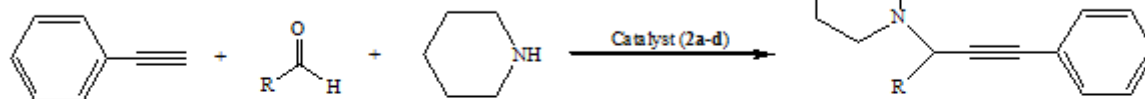
[(C_{*n*}mim)₂Ag]₂[Ag₂Br₄], **2d**

Yield: 1.57 g (90%); m.p 84-86°C; *Anal.* Calcd. mass fractions of elements, w%, for C₃₄H₁₂₀Ag₄Br₄N₈ (*M_r* = 1752.78) are: C 43.86, H 6.90, N 6.39; found: C 44.06, H 6.96, N 6.32. ¹H NMR (CDCl₃): δ: 6.97 (s, 2H, CH), 4.08 (t, *J*= 8.0 Hz, 2H, CH₂), 3.83 (s, 3H, CH₃), 1.80 (t, *J*= 8.0 Hz, 2H, CH₂), 1.31-1.26 (m, 18H, CH₂), 0.88 (t, *J*=8.0 Hz, 3H, CH₃). ¹³C NMR (CDCl₃): δ: 181.6, 122.5, 121.2, 52.2, 39.0, 32.1, 31.7, 30.0, 29.7, 29.5, 29.4, 26.7, 22.8, 14.3.

General procedure for the NHC-Ag(I) catalyzed three-component coupling reaction

In a typical run, a two-necked 25 mL flask fitted with a reflux condenser and septum was charged with phenylacetylene (1.5 mmol), piperidine (1.2 mmol),

Table 1
CATALYTIC EFFECT OF NHC-SILVER(I) CATALYST ON COUPLING REACTION^a



Entry	Catalyst	R	Solvent	Yield (%) ^{b,c}
1	2a	Cy	Dioxane	72
2	2b	Cy	Dioxane	72
3	2c	Cy	Dioxane	74
4	2d	Cy	Dioxane	75
5	2d	Ph	Dioxane	44
6	2d	H	Dioxane	74
7	2d	H	Neat	86

^a Reaction conditions: aldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), NHC-Ag(I) catalyst (3 mol %), dioxane (2.0 ml), argon atmosphere at 80°C for 14h.

^b Yield after purification by silica gel chromatography.

^c Average of two runs.

aldehyde (1.0 mmol) and silver catalyst (3 mol%) in 2 mL of 1,4-dioxane were added. The reaction mixture was stirred at 80°C for given time under an argon atmosphere. After the volatile materials were removed under vacuum, and the products were purified by column chromatography on silica using ethyl acetate/hexane (1/2) as the eluent to give the corresponding propargylic amine [26].

Results and discussions

Synthesis and characterization

The synthesis of a series of NHC-Ag(I) catalysts, **2a-d** is illustrated in figure 1. They were prepared in good yields through a straightforward two-step procedure from commercially available starting materials and reagents similarly to the published procedures [14]. These salts are white, air-stable solids. All isolated NHC-silver(I) complexes are stable to air and moisture and were characterized by using nmr spectroscopy. In the carbon nmr spectra signals observed at around δ: 180 ppm reveal typical coordination of NHCs to Ag [14,27]. These silver complexes (scheme 1) were reported as the first example of the NHC-silver(I) catalyzed cycloaddition of CO₂ to terminal epoxides by our groups and the solid state structure of the C₁₄mim-Ag was identified by X-ray single crystal diffraction method [14].

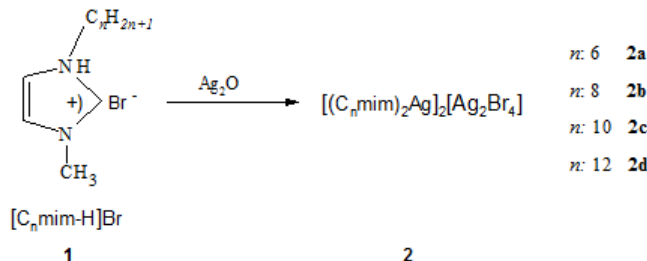


Fig.1. The benzimidazolium salts 1a-d and Ag(I)-NHC complexes 2a-d

Catalytic activity of the NHC-silver(I) complexes

The coupling reaction of alkyne, aldehyde and amine to propargylamines catalyzed by transition metals has attracted considerable attention in recent years, due to the

wide applications of propargylamines as key intermediates in the building of nitrogen-containing biologically active compounds [28]. The first Ag-catalyzed this three-component coupling reaction (A^3 -coupling) developed by Li's group and their silver compounds exhibited highly effective catalytic activity for this three-component coupling reaction [29]. But, only several Ag-NHC systems were performed as catalysts [23-25], and a large part of their were mononuclear Ag-NHC complexes.

Our study showed that all dimeric NHC-silver(I) complexes **2a-d** exhibited effective catalytic activity in the coupling reaction as in table 1. Moderate yields were obtained for coupling reactions. When complex **2d** was used the catalyst, the coupling reaction proceeded slightly faster (entry 4). The propargylamines yield increased as the length of the alkyl chain increased, although substituents did not procedure any further beneficial effect. The three-component coupling reaction was carried out under neat reaction conditions at 80°C and moderate yields of isolated product could be obtained (table 1, entries 1-7). These results show that the use of volatile solvents in the three-component coupling reactions could be avoided which is beneficial to reduce the environmental pollution.

Conclusions

Even though the NHC-Ag(I) complexes, **2a-d** are known in literature by our group, the data obtained from catalytic tests of the three-component coupling reaction of aldehyde, alkyne and amine to propargylamines have been novel obtained by these silver catalysts. Preliminary catalytic study revealed that the complexes exhibit good catalytic activity in three-component coupling reaction. The efficiency slightly depends the length of the alkyl chains on 3N atom. Studies on the structural modification of NHC and the structure-activity relationship of catalysts are ongoing in our laboratory.

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