# Silver(I) versus Gold(I) Catalysis in Benzannulation Reaction: A Versatile Access to Acridines

Thomas Godet, Philippe Belmont*

Laboratoire de Synthèse et Méthodologie Organiques, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), Université Lyon 1, CNRS, UMR 5246, Bâtiment CPE, 43 boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France
Fax +33(4)72432963; E-mail: philippe.belmont@univ-lyon1.fr

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**Abstract:** A silver/gold-catalysed benzannulation reaction is described. In the presence of catalytic amounts of gold and/or silver salts, the reaction of silyl enol ethers onto alkynes occurs under mild conditions to produce the corresponding polycyclic aromatic systems (acridine, quinoline or naphthalene cores) in good to high yields. Among the catalysts investigated, AgOTf has been chosen as a general catalyst for this reaction which likely proceeds through silver(I) activation of the alkynyl moiety leading to a subsequent cycloisomerisation reaction.

**Key words:** silver, gold, benzannulation, acridine, quinoline

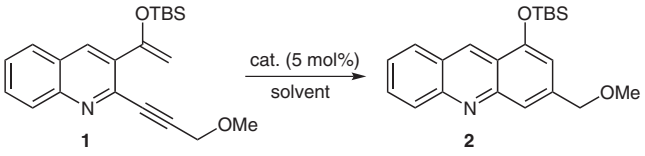
Polycyclic aromatic systems (PAS) made of fused aromatic rings such as naphthalene, anthracene, acridine and quinoline are of particular interest due to their physical and biological properties.[1–8]

Physical properties are typically illustrated among others[1] by superconductivity[2] and fluorescence.[3] PAS have a broad range of biological applications from dyes (ethidium bromide)[4] to therapeutics as anticancer agents (acridine derivatives,[5] carbazoles[6]), antibiotics (tetracycline or quinolone derivatives)[7] or antimalarial agents (quinoline or acridine derivatives).[8]

Benzannulation has gained considerable interest since a single step is required to create an aromatic moiety. Benzannulation reactions[9] are carried out through Brønsted acid[10] or Lewis acid[11] catalysis, under anionic[12] or radical conditions,[13] with vinyl ketenes,[14] transition metals catalysis (Rh,[15,16] Ru,[15–17] Pt,[15] Pd,[15,18] Au,[15,19] Co,[20] In,[21] Ga,[22] Cu,[23] Ni,[16] Ag[24]), thermal conditions,[25] under pyrrolysis[26] or using stoichiometric metallic systems (Ag,[15] Cr,[27] W,[28] Te,[29] Yb,[30] Ni[31]). Among transition metals, gold is highly valuable and efficient due to the wide range of reaction outcomes.[32] We thus first turned our attention to gold-catalysed benzannulation reactions in order to access acridine derivatives under smooth conditions.

Previous work from our group[33] reported the synthesis of acridines in moderate yields via a rhodium(I)-catalysed benzannulation reaction, inspired by an earlier report from Dankwardt.[15] Best results were obtained in refluxing toluene but the introduction of up to 10 mol% of catalyst under inert atmosphere was mandatory in most cases and poor to fair yields ranging from 40% to 70% were obtained. These first results led us to envision new catalytic systems.

**Table 1** Transition-Metal-Catalysed Benzannulation Reaction[a]




1 2

| Entry | Catalyst | Solvent | Temp (°C) | Conversion (%)[c] |
|---|---|---|---|---|
| 1 | $[Rh(CO)_2Cl]_2$[b] | Toluene | reflux | 56 |
| 2 | $AuCl_3$ | $CH_2Cl_2$ | r.t. | 0[d] |
| 3 | $AuCl_3$ | $C_2H_4Cl_2$ | 50 | 12[d] |
| 4 | $AuCl(PPh_3)$ | $C_2H_4Cl_2$ | reflux | 0[d] |
| 5 | $AuCl(PPh_3)$–$AgSbF_6$ | $C_2H_4Cl_2$ | 50 | >95[e] |
| 6 | $AgSbF_6$ | $C_2H_4Cl_2$ | 50 | >95[e] |
| 7 | TFA[f] | $C_2H_4Cl_2$ | 50 | <5[d] |

[a] Concentration of the reaction mixture was 0.01 M.
[b] The amount of the catalyst used was 10 mol%.
[c] Conversion was determined by $^1H$ NMR.
[d] Overnight reaction.
[e] Reaction time: 1 h.
[f] TFA: trifluoroacetic acid.

We chose quinoline derivative **1** as a model substrate. Exposure to a catalytic amount (5%) of $[Rh(CO)_2Cl]_2$ promoted its conversion to **2** in a 56% yield (Table 1, entry 1). Thereafter, we first turned our attention to gold species such as $AuCl_3$ and $AuCl(PPh_3)$.[34] At room temperature (Table 1 entry 2), gold(III) salt did not give the desired product, whereas at 50 °C (Table 1, entry 3), a poor but, nonetheless, encouraging conversion rate of 12% was obtained. With gold(I), no better results were achieved since no benzannulation took place either at room temperature or in refluxing 1,2-dichloroethane (Table 1, entry 4). We then turned our attention to activated gold(I) complexes.[35] With $AuSbF_6(PPh_3)$ [formed in situ from $AuCl(PPh_3)$ and $AgSbF_6$ in equimolar quantities], we obtained the desired polycyclic system, as a single product and in high conver-

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**Table 2** Screening of Silver Species[a]

| Catalyst[b] | Time (h) | Conversion (%)[c] | $pK_A$ |
|---|---|---|---|
| $AgSbF_6$ | 1 | >95 | <0 |
| $AgPF_6$ | 1 | >95 | <0 |
| AgOTf | 0.5 | >95 | <0 |
| $AgNO_3$ | 1.5 | >95 | <0 |
| $AgCO_2CF_3$ | 0.5 | >95 | <0 |
| $Ag_2SO_4$ | overnight | NA | 2 |
| AgF | overnight | NA | 3.2 |
| AgOAc | overnight | NA | 4.8 |
| $Ag_2CO_3$ | overnight | NA | 10.3 |
| $Ag_2O$ | overnight | NA | 15.7 |

[a] Reaction conditions: catalyst (5 mol%), $C_2H_4Cl_2$, 50 °C.
[b] OTf: trifluoromethanesulfonate. OAc: acetate.
[c] Determined by $^1H$ NMR. NA: Not Applicable.

sion rate (>95%, Table 1, entry 5). Interestingly, control experiments with only the silver species led to the same results within one hour (Table 1, entry 6). Finally, the addition of 5 mol% of TFA led to traces of the acridine product, ruling out the possibility of a Brönsted acid catalysed reaction (Table 1, entry 7).

Few investigations concerning the catalytic applications of silver have been reported in the literature.[36,37] We thus became interested in the behaviour of silver species and screened different silver-based catalysts on the same model reaction (Table 2).

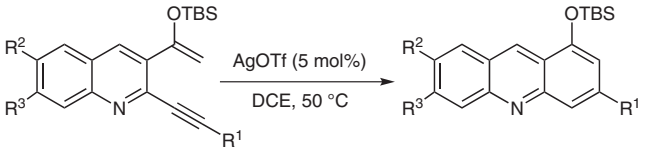
As we previously reported,[38] we found a good correlation between the reactivity of silver species and the $pK_A$ of their counteranion since only the silver salts having counteranions with $pK_A$ values below zero were efficient catalysts (Table 2). These silver salts are known for forming π-complexes with alkynes, thus acting as transition metal catalysts, and they gave here a quantitative conversion of quinoline **1** to acridine **2**.

Other silver species such as $Ag_2CO_3$ and $Ag_2O$ are mainly characterised through their oxidising properties of oxygenated functions.[39] They act as Lewis acids, interacting with oxygen atoms. Such activation does not allow the cycloisomerisation to occur since the alkynyl group activation seems mandatory.

Having established a standard reaction protocol, we examined the current benzannulation reaction with various combinations of alkynyl substituents and aromatic cycles (with or without nitrogen). The results are shown in Table 3 and Table 4.

Good results are obtained with alkyl (Table 3, entries 1, 4, 6–8 and 10), silyl (Table 3, entry 5) and aryl substituents (Table 3, entries 2, 9 and 11). It is noteworthy that sensitive protecting groups such as acetal remained untouched under these conditions (Table 3, entry 7). Sterically hindered substituents did not disfavour the course of the reaction (Table 3, entries 4 and 5). Remarkably, a ferrocenyl

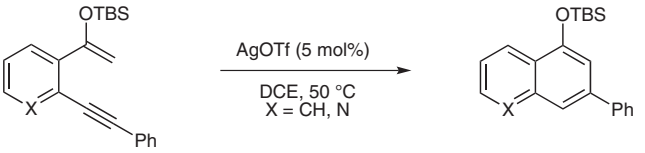
**Table 3** Silver-Catalysed Synthesis of Substituted Acridines

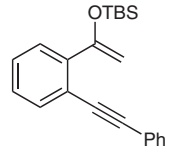
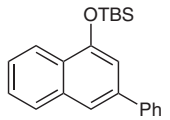
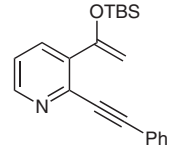
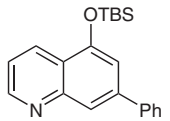



| Entry | $R^1$ | $R^2$, $R^3$ | Yield (%) |
|---|---|---|---|
| 1 | $CH_2OMe$ | H, H | quant |
| 2 | Ph | H, H | quant |
| 3 | Fc[a] | H, H | 47[b] |
| 4 | *t*-Bu | H, H | 95 |
| 5 | TMS | H, H | 92 |
| 6 | cyclopropyl | H, H | 98 |
| 7 | $CH_2OTHP$ | H, H | 89 |
| 8 | $CH_2N(Me)Bn$ | H, H | 97 |
| 9 | 4-py | H, H | quant |
| 10 | Bu | OMe, H | 95 |
| 11 | 2-$MeO_2CC_6H_4$ | OMe, H | 92 |

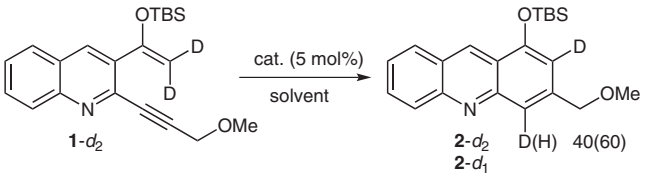
[a] Fc: ferrocenyl.
[b] The yield was 72% based on the recovered starting material.

**Table 4** Application to Related Polycyclic Systems

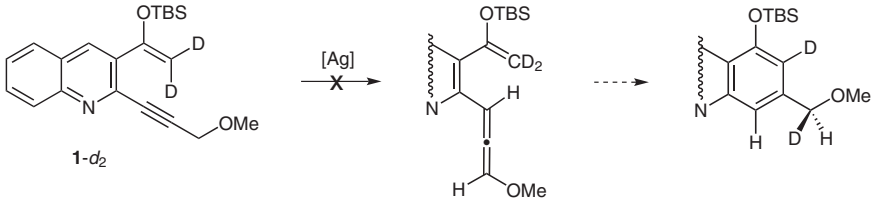



| Entry | Starting material | Product | Conversion (%) |
|---|---|---|---|
| 1 |  |  | >95 |
| 2 |  |  | >95 |






**Scheme 1** Isotopic labelling experiment




**Scheme 2** Hypothetical formation of an allenyl intermediate

moiety led to the expected product but in a moderate yield (47%), along with the unreacted starting material (entry 3). Such a result might be explained through a stable complexation of silver to the iron atom of the ferrocenyl moiety[40] and not through a reduction of silver(I).[41]

Moreover, we found that the benzannulation reaction proceeded nicely to form naphthalene (Table 4, entry 1) and quinoline rings (Table 4, entry 2) with high conversion, attesting that neither the aromatic nitrogen nor the extra benzene ring interfere in the reaction.

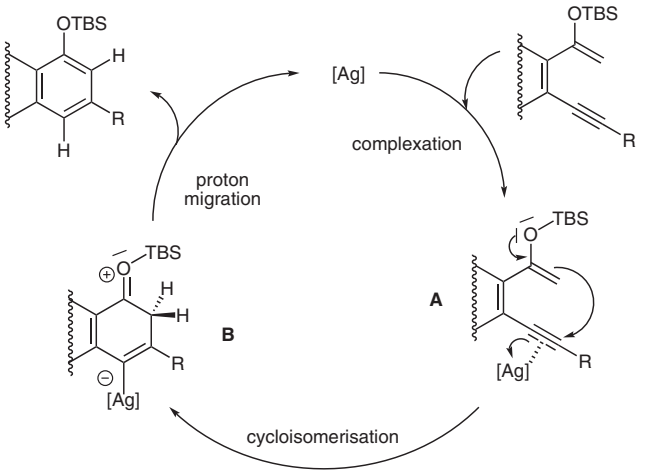
In order to get insights into the reaction mechanism, we performed the reaction using a $D_2$ labelled silyl enol ether (**1**-$d_2$, Scheme 1). Performing this reaction in $C_2H_4Cl_2$ led to the formation of a mixture of deuterated and nondeuterated products in a ratio of 40:60, probing the feasibility of an intra-molecular deuterium 1,3-migration.

Moreover, as shown in Scheme 2, the absence of any deuterium insertion in the $CH_2$ group α to the alkynyl moiety apparently rules out the possibility of an allenyl intermediate.

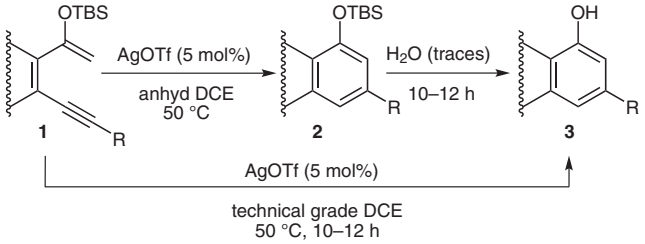
These results led us to envision the following reaction mechanism (Scheme 3). First, we propose that the reaction begins upon complexation of the alkynyl moiety by silver(I) species to give the silver-alkynyl complex **A** (Scheme 3), which is supported by our previous work related to the carbophilic properties of these silver species.[38] A 6-*endo-dig* cycloisomerisation would then occur, from the electron-rich alkene towards the electron-deficient complexed alkyne, thanks to the electronic assistance of the silyl enol ether, leading to the zwitterionic intermediate **B** (Scheme 3). A proton migration driven by the aromatisation of the newly generated ring system would then lead to the desired product and to the regeneration of the silver catalyst.

Interestingly, the use of anhydrous 1,2-dichloroethane led to the exclusive formation of the TBS-protected alcohol acridine (**2**, Scheme 4) within 30 minutes, whereas the addition of traces of water (or the use of technical grade 1,2-dichloroethane) enabled the complete deprotection of the alcohol group (**3**, Scheme 4) in an overnight reaction.[42]

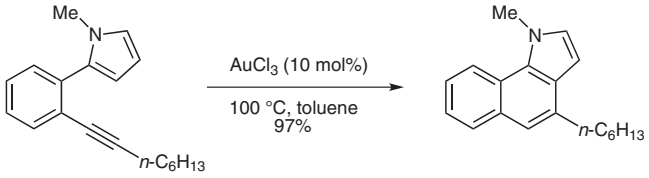
In conclusion, we have demonstrated that silver salts can promote catalytically benzannulation reactions.[43] The reaction proceeds under smooth conditions and the choice of the counteranion is crucial to obtain good to excellent yield of highly substituted acridine, quinoline, or naphthalene nuclei.




**Scheme 3** Proposed mechanism




**Scheme 4** Silver-catalysed deprotection of a silyl alcohol protected group (R = $CH_2OMe$)




**Scheme 5** Dankwardt´s work; see refs. 15 and 34

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(43) **Typical Procedure**: To a flask charged with silyl enol ether quinoline (0.1 mmol)[44] dissolved in anhyd 1,2-dichloroethane (10 mL), was added silver catalyst (5 mol%). The reaction mixture was stirred at 50 °C until the reaction was judged complete by TLC analysis (0.5–2 h). The crude mixture was dissolved in $CH_2Cl_2$ and washed with a sat. aq solution of $NaHCO_3$ (3 ×). The organic phase was dried over $Na_2SO_4$, filtered and the solvents were removed in vacuo. If needed, the residue was loaded on a silica gel column and elution with the appropriate mixture of cyclohexane and EtOAc yielded the pure cyclised products.
Selected spectroscopic data for entry 8, Table 3: isolated as a yellow oil (97%). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.04 (s, 1 H), 8.20 (app d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 8.02 (app d, $^3J_{H,H}$ = 8.3 Hz, 1 H), 7.77 (s, 1 H), 7.77 (ddd, $^3J_{H,H}$ = 8.7, 6.7 Hz, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.51 (ddd, $^3J_{H,H}$ = 8.0, 6.6 Hz, $^4J_{H,H}$ = 0.8 Hz, 1 H), 7.43–7.45 (m, 2 H), 7.34 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H), 7.26 (m, 1 H), 7.03 (d, $^4J_{H,H}$ = 1.0 Hz, 1 H), 3.69 (s, 2 H), 3.63 (s, 2 H), 2.26 (s, 3 H), 1.15 (s, 9 H), 0.37 (s, 6 H). $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 151.6, 150.2, 149.2, 143.2, 139.6, 131.8, 130.5, 129.2, 128.9, 128.9, 128.4, 127.1, 126.0, 125.3, 122.3, 121.3, 111.7, 62.2, 62.2, 42.6, 26.1, 18.7, –4.1. MS (ESI+): *m/z* (%) = 443 (100) $[M + H]^+$. HRMS (CI): *m/z* calcd for $C_{28}H_{35}N_2OSi^+$: 443.2519; found: 443.2522.

(44) Silyl enol ether quinolines (Table 3) were prepared following a published procedure. Please see ref. 33.