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Sequential alkylation/gold-catalyzed annulation reactions of anilines with propargylic bromide derivatives

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ABSTRACT

Preliminary results of sequential alkylation/gold-catalyzed annulation reactions of anilines with propargylic bromide derivatives to provide quinoline scaffolds are described. The efficiency of $NaAuCl_4{\cdot}2H_2O$ in the sequential procedure was investigated and compared with different transition metal salts and Au(I) complexes. Selectivity of the reaction of aniline derivatives with propargylic bromides has also been investigated.

Heterocyclic compounds, particularly some fused heterocycles, play great relevance in pharmaceutical and agrochemical fields.[1] Although a variety of synthetic methods for the synthesis of these important frameworks have been developed, most of them involve their preparation through a stepwise process. In recent years, one-pot synthetic sequences have been recognized as more sustainable approaches to target molecules by minimizing the number of steps and the amount of time, labor, and waste.

Gold catalysis represents an important and powerful tool for the promotion of one-pot synthesis of fused heterocycles from readily available starting materials.[2]

The cyclization of substituted propargylic aryl ethers[3] or propagylic anilines[4] by electrophiles to 3,4-disubstituted 2*H*-benzopyrans or substituted quinolines has been examined. The cyclization of aryl-substituted alkynes via intramolecular hydroarylation has proven to be an efficient method for the construction of carbocycles[5] and heterocycles.[6] In particular, azaanthraquinone assembly from *N*-propargylamino quinone via a Au(I)-catalyzed[7] or iodine- induced 6-*endo-dig* electrophilic cyclization[8] has been investigated. A number of important heterocyclic motifs including 2*H*-chromenes, coumarins, benzofurans, and dihydroquinolines were formed expeditiously from readily accessible starting materials through protocols involving Au(I)-catalyzed intramolecular hydroarylation (IMHA) of terminal alkynes.[9] The access to differently site-iodinated relevant heterocyclic frames was achieved by judicious ligand tuning in gold(I)-catalyzed IMHA of simple tethered iodoalkynyl and arene partners.[10] An efficient synthesis of *exo*-methylene tetrahydroquinolines and dihydroquinolines was developed from readily accessible *N*-aminophenyl propargyl malonates.[11] The hydroarylation process, which could be performed with a low loading of $[XPhosAu(NCMe)]SbF_6$ in nitromethane at 100 °C (1 mol %), proved to be rapid and general allowing the presence of a plethora of functional groups on the aromatic ring. Furthermore, the dihydroquinolines were shown to easily rearrange to functionalized indoles under photochemical conditions. Analogously the formation of 4-*exo*-methylene-1,2-dihydrocinnolines by $[XPhosAu(NCMe)]SbF_6$ was allowed by IMHA of *N*-propargyl-*N*′-arylhydrazinecarboxylic acid methyl ester.[12]

Interestingly, iron complex $Fe(OTf)_3$ has been, also, proven to be an effective catalyst for IMHA of aryl-substituted alkynes to form 1,2-dihydroquinolines and phenanthrenes in good to high yields.[13] Moreover, 3*H*-pyrano[3,2-*f*]quinoline-3-one, 4-methyl-4,7-phenanthrolin-3(4*H*)-one, and 1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives have been synthesized by hitherto unreported silver-catalyzed 6-*endo-dig* mode of cycloisomerization from various N-propargylated heterocyclic compounds.[14]

The preparation of the N-propargylated intermediates usually involves the *N*-alkylation reaction of aniline derivatives with propargyl bromides.

Interestingly, the Rh(I)-catalyzed amino-Claisen rearrangement of *N*-propargylanilines led to the formation of indole derivatives which have been also obtained through a one-pot procedure by

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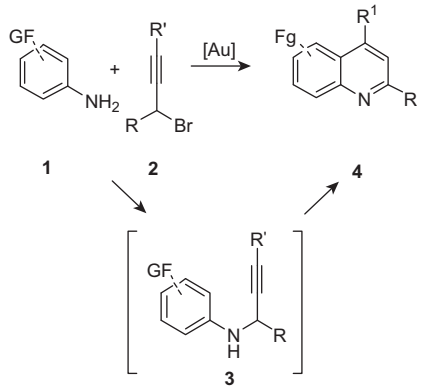
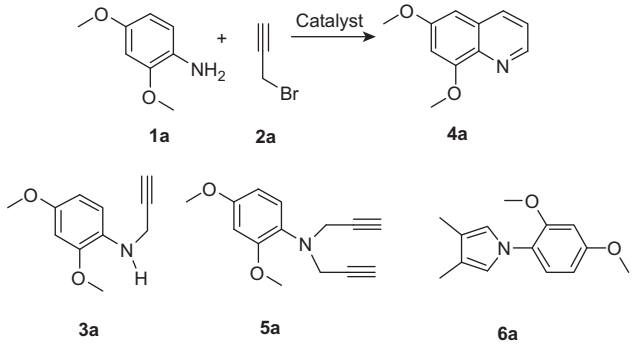
the rhodium-catalyzed reaction of *N*-alkylaniline with propargyl bromide in the presence of K_2CO_3 in hexafluoroisopropyl alcohol.[15] By contrast, the one-pot synthesis of quinolines which should occur via the divergent 6-*endo* annulation pathway has not been yet reported.



Scheme 1. Sequential synthesis of quinolines.



Scheme 2. Transition-metal catalyzed reaction of **1a** with **2a**.

Herein, we report our preliminary results of sequential alkylation/gold-catalyzed annulation reactions of anilines **1** with propargylic bromide derivatives **2** directed toward the synthesis of quinoline scaffolds **4** (Scheme 1).

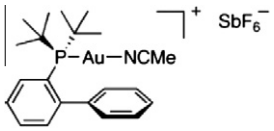
We selected the reaction of 2,4-dimethoxyaniline **1a** with propargyl bromide **2a** under the presence of a gold catalyst for initial studies (Scheme 2).

Some of our results of the screening of the reaction conditions are summarized in Table 1. The recent discovery of the high efficiency of the stable and commercially available Au(I) complex **A** in the IMHA of alkynes[9] prompted us to investigate its effectiveness in our sequential process. The reaction of an excess of **1a** with propargyl bromide **2a** (**1a**:**2a**:**A** = 3:1:7%) in toluene at 100 °C (Table 1, entry 1) gave after 24 h the corresponding quinoline derivative **4a**, but only in 28% yield (the N-alkylated derivative intermediate 2,4-dimethoxy-*N*-(propen-2-yn-1-yl)-aniline **3a** was isolated in 48% yield). The formation of **4a** can be considered to occur via the gold-catalyzed annulation/aromatization reaction of **3a** generated in situ from the alkylation reaction of **1a** with **2a**.

When ethanol was employed as the solvent, the yield of **4a** increased to 48% (Table 1, entry 2), but the formation of pyrrole **6a** was observed as a side-product of the reaction. Very likely, the in situ generated nitrogen-tethered 1,6-diynes **5a** underwent under the reaction conditions a gold(I)-catalyzed cycloisomerization to provide pyrrole **6a**.[16]

While the catalyst was switched to $NaAuCl_4{\cdot}2H_2O$, different reaction conditions were screened. In toluene as solvent at 100 °C only the formation of the N-alkylation and the N,N-dialkylated derivatives was observed (Table 1, entry 3). Again ethanol resulted in a better solvent for the sequential process. It should be mentioned that an equal ratio of **1a** and **2a** failed to give satisfactory results, but, by adding an organic or inorganic base to a 1:1 or 1:1.5 mixture of **1a** and **2a**, respectively, the subsequent treatment with $NaAuCl_4{\cdot}2H_2O$ significantly improved the yield of **4a** (Table 1, entries 4 and 5). Under these latter conditions the N,N-dialkynyl derivatives **5a** (Table 1, entry 4) and pyrrole **6a** (Table 1, entry 5) were isolated as by-products. Quinoline **4a** was isolated in 64% yield as the only reaction product when the reaction of an excess of **1a** with **2a** was carried out in ethanol at 70 °C for 24 h in the presence of $NaAuCl_4{\cdot}2H_2O$ as the catalyst (7 mol %) (Table 1, entry

Table 1
Different conditions screened[a]

Entry	Catalyst (mol %)	**3a** Yield (%)	**4a** Yield (%)	**5a** Yield (%)	**6a** Yield (%)
1[b]		48	28	—	—
2[c]	**A** (7%)	—	48		13
3[b]	$NaAuCl_4{\cdot}2H_2O$ (7%)	74	—	10	—
4[d]	$NaAuCl_4{\cdot}2H_2O$ (5%)	—	58	12	—
5[e]	$NaAuCl_4{\cdot}2H_2O$ (7%)	—	38	—	8
6[c]	$NaAuCl_4{\cdot}2H_2O$ (7%)	—	64	—	—
7[c]	AgOTf (7%)	68	10	—	—
8[c]	$FeCl_3{\cdot}6H_2O$ (7%)	46	7	18	
9[c]	CuBr (7%)	—	38	—	—
10[c]	CuCl (7%)	—	41	—	—
11[c]	$Cu(NO_3)_2{\cdot}6H_2O$ (7%)	—	41	—	—
12[c]	$CuSO_4{\cdot}5H_2O$ (7%)	—	28	—	—
13[c]	$Cu(OTf)_2$ (7%)	—	41	—	—
14[c]	$Cu(OAc)_2$ (7%)	18	24	—	—
15[c]	$CuCl_2{\cdot}5H_2O$ (7%)	22	24		

[a] Yields refer to single non optimized runs, and are given for pure isolated products.
[b] Reaction was carried in toluene at 100 °C for 24 h by using the following molar ratios: [**1a**]:[**2a**] = 3:1.
[c] Reaction was carried in ethanol at 70 °C for 24 h by using the following molar ratios: [**1a**]:[**2a**] = 3:1.
[d] Reaction was carried in ethanol at 70 °C for 24 h by using the following conditions: [**1a**]:[**2a**]:[DBU] = 1:1:1.
[e] Reaction was carried in ethanol at 70 °C for 24 h by using the following conditions: [**1a**]:[**2a**]:[K_2CO_3] = 1:1.5:1.5.

Table 2
Different conditions screened for the *N*-alkylation reaction of the aniline **1a** with propargyl bromide **2a** **1a** + **2a** $\xrightarrow[\text{Solvent, Base}]{\text{Temperature (°C) Time (h)}}$ **3a** + **5a**

Entry	Molar Ratio[**1a**]:[**2a**]:base	Base	Solvent	Temperature (°C)/time (h)	**3a**[a] (yield %)	**5a**[a] (yield %)
1	[3.0]:[1.0]:[—]	—	Toluene	80/2.0	73	10
2	[1.0]:[1.0]:[1.0]	DBU	Ethanol	70/6.5	57	12
3	[2.3]:[1.0]:[1.0]	DBU	Ethanol	70/6.5	66	10
4	[1.0]:[1.0]:[2.0]	K_2CO_3	Ethanol	70/4.0	70	—
5	[1.0]:[1.5]:[1.5]	K_2CO_3	Ethanol	70/4.0	90	—

[a] Yields refer to single non optimized runs, and are given for pure isolated products.

Table 3
Different conditions screened for the gold-catalyzed IMHA reaction of the 2,4-dimethoxy-*N*-(propen-2-yn-1-yl)-aniline **3a** **3a** $\xrightarrow[\text{Solvent, Catalyst}]{\text{Temperature(°C)Time(h)}}$ **4a**

Entry	Catalyst	Solvent	Temperature (°C)/Time (h)	**4a**[a] (yield %)
1	**A** (5%)	Ethanol	70/6.0	76
2	**A** (5%)	DCE	70/6.0	74
3	$NaAuCl_4{\cdot}2H_2O$ (5%)	Ethanol	70/23	65
4	Ph_3PAuCl (10%)/AgOTf (10%)	HOAc	100/1.0	Quantitative

[a] Yields refer to single non optimized runs, and are given for pure isolated products.

6). For a further optimization of the reaction conditions we have, also, used various metal catalysts. Among the catalysts used, AgOTf[14] and $FeCl_3{\cdot}6H_2O$[17] gave very poor yield of quinoline **3a** (Table 1, entries 7 and 8). Better results salts were observed with copper salts[18] (Table 1, entries 9–15), but gold catalysts[19] proved to be the most effective in promoting the sequential process to quinoline **4a**.

Control experiments indicated the influence of the reaction conditions in the N-alkylation step (Table 2) as well as in the IMHA step (Table 3). We failed to avoid the N,N-dialkylative process by using DBU[20] as the base in ethanol (Table 2, entries 2 and 3). In the absence of the gold catalyst, the formation of the side-product **5a** can be suppressed by the use of K_2CO_3 even in the presence of an excess of propargyl bromide **2a** which leads to a better yield of intermediate **3a** (Table 2, entries 2 and 3).

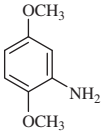
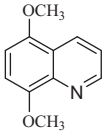
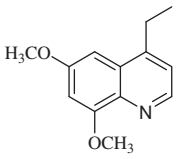
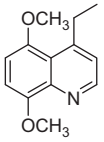
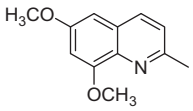
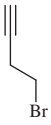
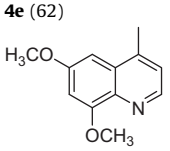
The gold-catalyzed IMHA step deserves further comment. Au(I)-catalyzed IMHA reactions of terminal alkynes have been previously investigated.[7,9,12] In toluene as the solvent the gold(I)-catalyzed IMHA allowed to isolate quinoline **4a** in 28% yield (Table 1, entry 1). According to the literature[21] Au(III) is not effective in promoting the IMHA in toluene (Table 1, entry 3). Remarkably, in ethanol as the solvent, both the Au(I) catalyst **A** and $NaAuCl_4{\cdot}2H_2O$ accomplished the formation of **4a** in comparable yield (Table 3, entry 1 vs 3). Interestingly catalyst A was as effective in the more eco-friendly ethanol as in the halogenated 1,2-dichlorethane (DCE) (Table 2, entry 3). Beneficial effect of the ethanol as the reaction medium for gold-catalyzed annulation reactions has been highlighted.[22] According to previous results[7] the IMHA reaction of **3a** in HOAc as the solvent completed in just 1 h, but the use of this latter solvent is incompatible with the sequential N-alkylation/IMHA process. Furthermore, the gold catalysis seems to play a relevant role for the transformation of the in situ generated 2,4-dimethoxy-N,N-bis(propen-2-yn-1-yl)aniline **5a** into the corresponding pyrrole derivative **6a**.

In order to explore the scope of the sequential gold-catalyzed approach to quinolines **3**, anilines **1a**–**b** were reacted with the alkynyl bromides **2a**–**d** (Table 4).[23]

The use of terminal alkyne **2a**, of the internal alkyne 1-bromopent-2-yne **2b** and the branched derivative 3-bromobut-1-yne **2c** is compatible with this protocol. The 4-bromobut-1-yne derivative **2d** should lead to the corresponding *N*-butynyl aniline derivative intermediates which via, in this case, a 6-*exo*-cyclization to *exo*-methylenetetrahydroquinoline derivatives might undergo isomerization to the corresponding 4-methylquinolines.

The cyclization of *N*-butynyl tosylaniline has not been previously observed to occur under gold catalysis, while the *N*-(but-3-yn-1-yl) *N*-methylaniline gave the 1-methyl-4-methylidene-1,2,3,4-terahydroquinoline in 11% yield when the IMHA reaction was conducted in nitromethane at 100 °C with [XPhosAu(NCMe)]SbF_6 as catalyst.[11] An encouraging 20% yield of **4f** was observed under our sequential conditions.

Table 4
Scope of the sequential process

Entry	**1**	**2**	Catalyst (mol %)	**4**[a,b] (yield %)
1	**1a**	**2a**	$NaAuCl_4{\cdot}2H_2O$ (7%)	**4a** (64)
2	**1a**	**2a**	**A** (7%)	**4a** (48)
3	 **1b**	**2a**	$NaAuCl_4{\cdot}2H_2O$ (7%)	 **4b** (60)
4	**1b**	**2a**	**A** (7%)	**4b** (43)[c]
5	**1a**	 **2b**	$NaAuCl_4{\cdot}2H_2O$ (7%)	 **4c** (67)
6	**1b**	**2b**	$NaAuCl_4{\cdot}2H_2O$ (7%)	 **4d** (60)
7	**1a**	 **2c**	$NaAuCl_4{\cdot}2H_2O$ (7%)	 **4e** (62)
8	**1a**	 **2d**	$NaAuCl_4{\cdot}2H_2O$ (7%)	 **4f** (20)

[a] Yields refer to single non optimized runs, and are given for pure isolated products.
[b] The reactions were carried out at 70 °C in ethanol using the following molar ratios: [**1**]:[**2**] = 3:1.
[c] Compound **6b** was isolated in 12% yield.

In summary, our preliminary results show the feasibility of the one-pot/one-flask synthesis of functionalized quinolines from commercial available anilines and propargylic bromide derivatives. The formation of the quinolines proceeds through the sequential N-propargylation of aniline derivative followed by regioselective 6-*endo*-*dig* transition metal-catalyzed intramolecular hydroarylation of the *N*-propargylamine intermediate and aromatization reaction. $NaAuCl_4{\cdot}2H_2O$ represents a suitable catalyst for the sequential procedure which occurs under mild reaction conditions in the eco-friendly ethanol as the reaction medium. The catalytic efficiency of both Au(III) and Au(I) catalysts in the sequential process has been investigated and compared with different transition metal salts.

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23. *General procedure for the alkylation/gold-catalyzed annulation reactions of anilines with propargylic bromide derivatives*: to a solution of aniline **1** (2.0 mmol) in absolute ethanol (2 mL) were added propargylic bromide **2** (0.66 mmol) and $NaAuCl_4{\cdot}2H_2O$ (0.05 mmol). The resulting mixture was heated at 70 °C for 24 h. The reaction was monitored by TLC. After cooling, the solvent was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and extracted three times with a saturated solution of $NaHCO_3$. The combined aqueous extracts were extracted three times with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, *n*-hexanes–ethyl acetate mixtures) to give quinoline **4**. ^{1}H NMR and ^{13}C NMR of compounds **4**. Compound **4a**: ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 3H), 3.99 (s, 3H), 6.57 (d, J = 2.5 Hz, 1H), 6.65 (d, J = 2.5 Hz, 1H), 7.30 (dd, J = 8.4 Hz, J = 4.2 Hz, 1H), 7.93 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 8.70 (ddd, J = 4.2 Hz, J = 1.6 Hz, J = 0.55 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 55.3, 55.8, 96.6, 101.0, 121.9, 129.8, 134.5, 136.7, 146.5, 156.1, 158.1. Compound **4b**: ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3H), 4.03 (s, 3H), 6.75 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 7.43 (dd, J = 8.5 Hz, J = 4.3 Hz, 1H), 8.55 (dd, J = 8.5 Hz, J = 1.7 Hz, 1H), 8.95 (dd, J = 4.3 Hz, J = 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 55.7, 55.9, 103.6, 106.8, 120.8, 121.6, 130.9, 140.2, 148.5, 149.2, 149.4. Compound **4c**: ^{1}H NMR ($CDCl_3$): δ = 1.37 (t, J = 7.42 Hz, 3H), 3.00 (q, J = 7.42 Hz, 2H), 3.92 (s, 3H), 4.04 (s, 3H), 6.70 (d, J = 2.47 Hz, 1H), 6.78 (d, J = 2.20 Hz, 1H), 7.22 (d, J = 4.12 Hz, 1H), 8.67 (d, J = 4.40 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 13.2, 25.2, 55.2, 55.9, 92.8, 100.3, 120.4, 128.8, 136.5, 146.4, 147.8, 156.7, 157.8. Compound **4d**: ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, J = 7.3 Hz, 3H), 3.27 (q, J = 7.4 Hz, 2H), 3.88 (s, 3H), 4.02 (s, 3H), 6.74 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 4.4 Hz, 1H), 8.77 (d, J = 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 15.5, 29.8, 55.3, 55.8, 104.3, 106.2, 120.7, 122.1, 141.3, 148.9, 149.5, 150.4, 151.4. Compound **4e**: ^{1}H NMR ($CDCl_3$): δ = 2.74 (s, 3H), 3.88 (s, 3H), 4.03 (s, 3H), 6.61 (d, J = 2.5 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 25.2, 55.3, 55.9, 96.7, 100.9, 122.8, 127.9, 135.0, 136.1, 155.3, 155.5, 157.3. Compound **4f**: ^{1}H NMR ($CDCl_3$): δ = 2.63 (s, 3H), 3.94 (s, 3H), 4.05 (s, 3H), 6.72 (d, J = 2.5 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H), 7.23 (d, J = 4.4 Hz, 1H), 8.63 (d, J = 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 19.3, 55.4, 56.0, 93.2, 100.6, 122.9, 129.7, 130.9, 142.5, 146.3, 156.7, 158.0.