DOI: 10.1002/adsc.201700126
Advanced Synthesis & Catalysis

Gold(I)-catalyzed synthesis of dihydrodibenzoquinolizinium salts

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Received: February 2, 2017; Revised: April 19, 2017; Published online: ■■ ▮▮, 0000

Dedicated to Professor Dirk Tourwé on the occasion of his 70th birthday.

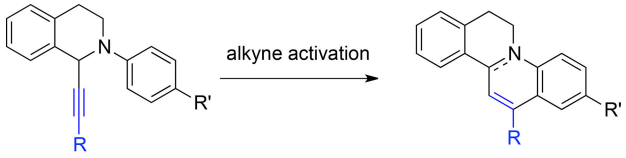
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201700126

Abstract: A gold-catalyzed cyclization of 1-alkynyl-2-aryl tetrahydroisoquinolines is described for the synthesis of novel dihydrodibenzoquinolizinium salts. The reaction mechanism is likely to involve a 6-*endo*-*dig* cyclization and subsequent oxidation by air to give a relatively stable arylgold intermediate. This gold species undergoes protodeauration under acidic conditions to afford the title compounds. An NMR study was performed to gain further evidence and insight on the presence of the arylgold intermediate and the reaction mechanism.

Keywords: Cyclization; Gold; Homogeneous catalysis; Nitrogen heterocycles; Oxidation

Introduction

Homogeneous gold catalysis has proven to be an increasingly valuable addition to the organic chemist's toolbox.[1] In particular, the activation of triple bonds towards a nucleophilic attack has opened synthetic pathways to a large number of biologically active motifs.[2] A number of the pioneering reactions in this field started from α-heteroatom substituted alkynes.[3] The recent surge in "cross-dehydrogenative coupling" (CDC) reactions will undoubtedly boost this research further as it offers facile entries to these particular starting materials.[4] For example, substituted *N*-phenyl propargylamines are readily available via this methodology and can be transferred chemoselectively to quinolines[5] and indoles[6] via a 6-*endo*-*dig* or 5-*exo*-*dig* cyclization respectively. To our knowledge, related 1-alkynyl-2-aryl tetrahydroisoquinolines **1** have never been employed as starting materials in a cyclization strategy (Scheme 1). Due to our group's ongoing interest in employing gold-catalyzed reactions towards relevant polyheterocycles,[7] we envisaged these 1-alkynyl-2-aryl tetrahydroisoquinolines **1** as promising starting materials for the synthesis of tetrahydrodibenzoquinolizines or their oxidized analogues.



1 2

Scheme 1. Proposed cyclization of **1** to polycyles **2**.

Results and Discussion

The aforementioned starting materials **1** were synthesized from commercially available substrates in a simple two-step process. A Cu(I)-catalyzed cross-coupling of tetrahydroisoquinoline (THIQ) with an aryliodide afforded *N*-arylated THIQs.[8] A subsequent cross dehydrogenative coupling with a terminal alkyne, afforded the desired substrates **1**.[9]

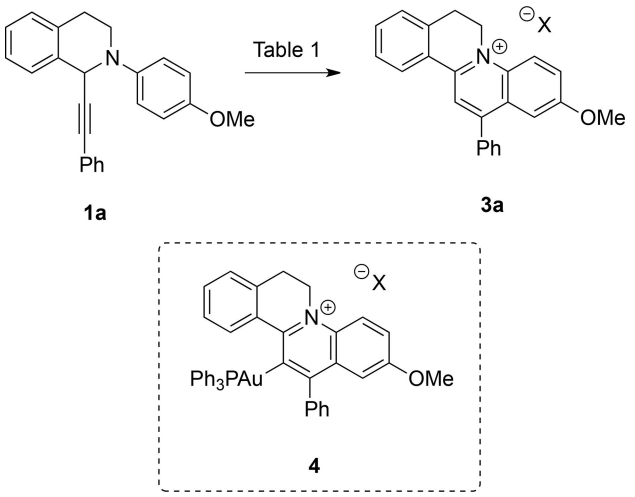
One of the available substrates **1a** was chosen as a model substrate and subjected to various catalytic systems, as summarized in Table 1

Initial attempts (entries 1–4) provided a proof-of-concept as a transformation of **1a** towards **3a** was observed, although in relatively low conversions. When $AuPPh_3$ type catalysts were evaluated, the formation of an intermediate arylgold species **4** was detected in the reaction mixture pointing to a slow protodeauration as a final step towards **3a**. This unexpected compound **4** could be isolated in trace amounts *via* preparative HPLC and was analyzed by LC-MS and NMR. In subsequent attempts, a number of variables were tested to get an insight in the

Table 1. Evaluation of catalytical systems for conversion of **1a** to **3a**.

Entry	Conditions	Conversion (%)
1	$AuPPh_3Cl/AgOTf$	<20
2	$AuPPh_3Cl/AgNTf_2$	24
3	$Au(pic)Cl_2$	32
4	$AuCl_3$	<20
5	$AuPPh_3Cl/AgNTf_2$, Ar atm.	Trace
6	$AuPPh_3Cl/AgNTf_2$, O_2 atm.	Trace
7	$AuPPh_3Cl/AgNTf_2$, 1eq DDQ, Ar atm.	Complex mixture
8	$AuPPh_3Cl/AgNTf_2$, 1eq TFA	75
9	$AuPPh_3Cl/AgNTf_2$, 2eq TFA	52
10	$AgNTf_2$, 1eq TFA	22
11	1eq TFA	0
12	1eq. MsOH	0
13	Excess MsOH	0
14	$AuPPh_3Cl/AgNTf_2$, 1eq MsOH	85
15	**$AuPPh_3Cl/AgNTf_2$, 1.1eq MsOH**	**94**
16	$AuPPh_3Cl/AgNTf_2$, 1.5eq MsOH	82
17	$Au(pic)Cl_2$, 1eq MsOH	45
18	$AuPPh_3Cl/AgNTf_2$, H_2O	63

[a] Test reactions were typically performed on a 75 µmol scale in CH_2Cl_2 at room temperature for 16 h under air atmosphere, using 10 mol% of (co–)catalyst.
[b] Conversion as observed via HPLC analysis.



Scheme 2. Evaluation of catalytic systems.

reaction mechanism and optimize conversion. The obtained **3a** can be related to annulated quaternary quinolinium compounds (e.g. berberine), which represent an important class of natural products with a wide array of bioactivities.[10] To our surprise, there are only a few reports available towards these polyheterocycles **3**.[11]

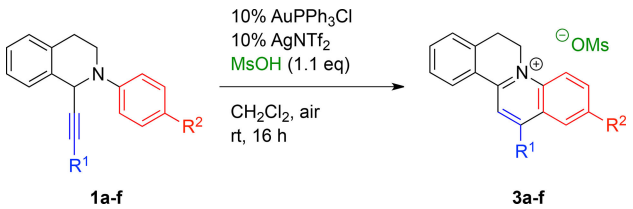
Performing the reaction under inert atmosphere (entry 5) resulted in a lack of conversion towards **3a**, suggesting the need for either oxygen or moisture present in air. An oxygen atmosphere or the addition of external oxidants was also found to be unsuitable to drive the conversion to completion (entry 6–7; both under dry conditions). This further strengthened our hypothesis that protodeauration of **4** to **3a** was the bottleneck in this reaction.

Addition of an equivalent of trifluoroacetic acid (entry 8) to the reaction mixture facilitated the protodeauration step,[12] significantly boosting the observed conversion to 75%. Further increasing the amount of acid gave an adverse effect on the conversion (entry 9). Control experiments using only $AgNTf_2$ and/or TFA resulted in low or no conversion (entries 10–11), proving the necessity for the gold catalyst to enable a clean conversion at room temperature.

In an attempt to increase conversions further, TFA was substituted by the stronger methanesulfonic acid. Further optimization of the amount of equivalents of MsOH used (entry 15) resulted in excellent conversions towards **3a**. Comparing entries 2 and 15, the addition of MsOH proved to be essential for increasing conversion. Remarkably, this increase was not observed when a gold (III) catalytical system was used, as shown in entries 3 and 17. Taking into account that MsOH is a much stronger acid than TFA, two additional control experiments (entries 12–13) were performed but no conversion towards **3a** was detected.

Considering that water as a proton source was sufficient to get low conversion, it was also tested if a biphasic approach (i.e. a large excess of water) could also afford the desired polycyclic **3a**. While conversions were lower as compared to the addition of acids, we observed that **3a** showed good solubility in aqueous media. This observation was used to facilitate workup: after quenching the slight excess MsOH with a solid-supported base, **3a** was extracted into the aqueous phase. Removal of water via evaporation or freeze-drying afforded the desired **3a** deemed pure via HPLC/NMR, effectively removing the need for tedious chromatographic purification.

Subsequently, a number of 1-alkynyl-2-aryl tetrahydroisoquinolines **1** were subjected to the optimized reaction conditions to investigate the scope of the reaction (Scheme 3, Table 2). Structures similar to the one used for catalyst screening (**3a–c**, Table 2) were



Scheme 3. Scope evaluation using optimized conditions.

isolated in decent yields. An ester and alkyl group were also tolerated (Entries **3d–e**), where it is noteworthy that the electron withdrawing ester moiety did not shift the reactivity towards attack at the β-carbon. Removal of the electron donating group at the *N*-aryl group (R^2) still resulted in the formation of **3f** although a lower conversion and isolated yield was observed.

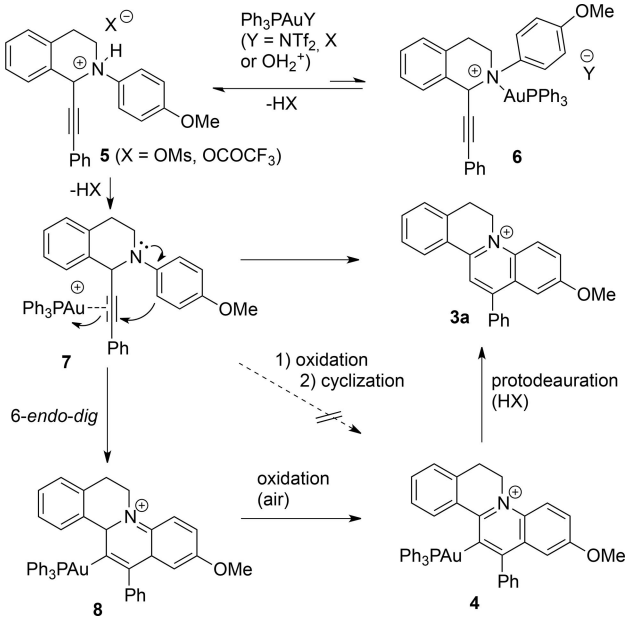
Table 2. Evaluation of scope towards **3**.

Product	R^1	R^2	Isolated yield (%)
3a	Ph	OMe	55
3b	4-MePh	OMe	43
3c	3-FPh	OMe	55
3d	COOEt	OMe	46
3e	Butyl	OMe	73
3f	Ph	H	35

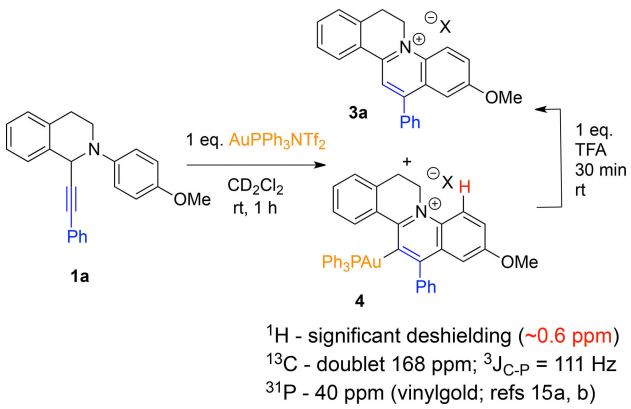
A plausible mechanism for the gold-catalyzed cyclization is shown in Scheme 4. Activation of the triple bond in **5** by the cationic gold catalyst, via the free base **1a** present in the mixture through acid-base equilibrium could facilitate a nucleophilic attack by the aromatic system, resulting in a 6-*endo-dig* cyclization. The presence of acid also helps in preventing deactivation of the catalyst by formation of complexes such as **6**. Considering the observation of arylgold species **4** in several reaction mixtures, a swift oxidation of the proposed intermediate **8** to **4** gives rise to aromatic stabilization.[13] A reverse order of events where oxidation occurs first, followed by cyclization (e.g. by electrocyclization) is not probable given the negative results obtained by performing the reaction under oxygen atmosphere and the fact that no arylgold species **4** would be obtained in this case. Also a [3,3]-sigmatropic rearrangement as reported by Blechert for *N*-arylpropargylamines is unlikely because the reaction proceeds at room temperature and a strained cyclic allene would be formed as intermediate.[14] The formation of vinyl- and arylgold species as catalytic resting states has been described and can give rise to isolable monoaurated, diaurated or Au/Ag-dimetallated species.[13,15] In our case no dimetalated compounds were observed via MS or ^{31}P NMR analysis of the reaction mixture in CD_2Cl_2. This corroborates with the findings of Gagné and Hammond that monometallated species are generally observed with electron deficient aryl or vinyl species.

The arylgold species **4** is then protodeaurated under acidic conditions to afford the desired end product **3a**. This proposed mechanism is consistent with the observed necessities for air and acid to be present in the reaction.

An NMR study was performed in an attempt to gain further evidence for the proposed mechanism. An equimolar amount of a preformed and filtered gold catalyst in CD_2Cl_2 was added to a solution of **1a** in CD_2Cl_2 and stirred at room temperature. The reaction was followed via ^{1}H, ^{13}C and ^{31}P NMR on regular intervals. After one hour, near full consumption (>95%) of **1a** was observed. The reaction mixture appeared to consist of **4** and **3a** in a 1:2.5 ratio. Several NMR spectra were indeed in agreement with the proposed arylgold intermediate **4**: significant deshielding of nearby aromatic protons, a doublet in ^{13}C NMR with a $^3J_{C\text{-}P}$ coupling constant similar to that of other C–Au-P systems and a singlet at 40 ppm in ^{31}P NMR (Figure 1, Scheme 5).[15a,b] The significant



Scheme 4. Proposed mechanism for gold-catalyzed cyclization of **1a** to **3a**.



Scheme 5. NMR study to validate the formation of arylgold species **4**.

amount of protodeauration already observed here could be explained by the formation of $HNTf_2$ in situ.

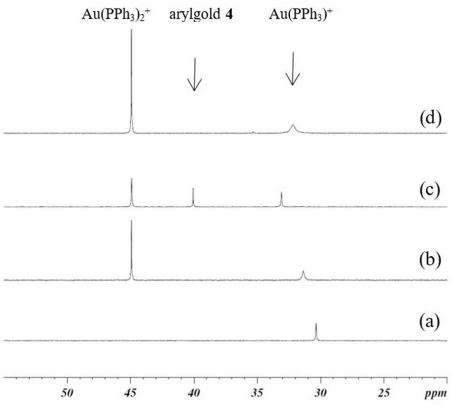


Figure 1. ^{31}P NMR spectra in CD_2Cl_2 for (a) $Ph_3PAuNTf_2$, (b) PPh_3AuNTf_2 after several days in CD_2Cl_2, (c) Reaction of **1a**, and 1 eq. PPh_3AuNTf_2 after 1 h, (d) Reaction of **1a**, and 1 eq. PPh_3AuNTf_2 after 1 h, followed by quenching with TFA.

The reaction mixture was subsequently quenched via addition of 1 equivalent of TFA. Full protodeauration of **4** to **3a** occurred in ~30 min. As can be seen from Figure 1c and 1d, significant catalyst decomposition is observed during the reaction shown by the presence of a signal at 45 ppm in ^{31}P NMR, which is most probably a $Au(PPh_3)_2^+$ species.[16] This hypothesis was strengthened further by acquisition of a direct ESI-MS spectrum from the NMR sample, which cleanly showed an m/z of 338 (**3a**) and 721 ($Au(PPh_3)_2^+$). This is in correspondence with the known decomposition of PPh_3AuOTf where it has been shown that the presence of π-substrates and water significantly accelerates decomposition to amongst others $Au(PPh_3)_2^+$ species.[16]

When a similar reaction was performed under basic conditions (1 equiv. of NEt_3), the protodeauration step slowed down significantly, and the gold intermediate **4** could be isolated via chromatography from the reaction mixture.[17]

In an attempt to detect intermediate vinyl gold species **8**, a reaction in an NMR-tube under Ar atmosphere was performed in the presence of Et_3N (1 equiv.) to prevent protodeauration. After reaction for 4 h, the mixture contained next to starting material and the arylgold **4** also an unidentifiable reaction intermediate (ratio 1:2:1, resp.). The latter disappeared after prolonged standing of the sample resulting in only **4** and **3a** (leaving a gold mirror on the NMR tube after 2 days). Due to the complexity of the obtained NMR spectrum and lability of this intermediate, the intermediacy of vinylgold species **8** could not be proven.

In the optimized reaction conditions, MsOH and most probably also traces of water are present from the very start of the reaction. Therefore, the NTf_2 counterion of the used catalysts is likely to be interchanged with present coordinating groups. It is known that PPh_3AuNTf_2 reacts with water to give less reactive PPh_3AuOH which can further lead to dimeric hydroxonium or trimeric $(Ph_3PAu)_3O^+$ species with a characteristic peak at 23.9 ppm in ^{31}P NMR.[18] In our case, we did not observe such species because of the presence of the Bronsted acid which is known to reactivate formed PPh_3AuOH.[19] As such the addition of MsOH to the mixture could perform a triple role in this reaction: reactivation of the catalyst, enhancing the protodeauration rate and neutralizing the basic tetrahydroisoquinoline nitrogen which has been linked to deactivation of the gold catalyst in related systems.[20]

Conclusion

In conclusion, a gold-catalyzed cyclization of 1-alkynyl-2-aryl tetrahydroisoquinolines towards novel dihydrodibenzoquinolizinium salts was developed. These compounds could be isolated from the reaction mixture via a simple extraction protocol, avoiding the need for chromatographic purification. The reaction mechanism is likely to involve a 6-*endo-dig* cyclization and subsequent oxidation by air to a relatively stable arylgold intermediate that undergoes protodeauration. The presence of this arylgold intermediate could be demonstrated via MS and NMR.

Experimental Section

The gold-catalyzed cyclization of **1a** to **3a** is given as a representative example.

$(Ph_3P)AuCl$ (14.6 mg, 0.029 mmol) and $AgNTf_2$ (11.4 mg, 0.029 mmol) were dissolved in dichloromethane (2.9 mL) and allowed to stir at room temperature for 15 minutes, resulting in the precipitation of AgCl. To this suspension was added **1a** (100.0 mg, 0.29 mmol). After an additional 5 minutes of stirring, methanesulfonic acid (21 µL, 0.32 mmol) was added and the resulting reaction mixture was allowed to stir overnight. The acidic excess was quenched *via* addition of a solid supported base (ISOLUTE Si-trisamine, loading 1.18 mmol/g; 127 mg, 0.15 mmol) and this mixture was filtered through a small cotton plug. The organic phase was then extracted with distilled water (5×3 mL). The combined water phases were freeze-dried to afford **3a** as an orange solid in 55% yield (64.0 mg, 0.15 mmol). **IR** (neat) 1615, 1596, 1560, 1383, 1277, 1238, 1221, 1209, 1039, 1020, 821, 784, 755 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.23 (d, J=9.9 Hz, 1H), 8.09 (s, 1H), 8.02–7.94 (m, 2H), 7.68–7.59 (m, 5H), 7.56–7.48 (m, 2H), 7.36 (d, J=2.9 Hz, 1H), 5.51 (t, =6.9 Hz, 2H), 3.88 (s, 3H), 3.60 (t, 6.8 Hz, 2H), 2.80 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.2, 156.5, 148.3, 137.0, 135.8, 135.5, 134.5, 130.9, 129.6, 129.3, 129.0, 128.8, 127.9, 127.2, 122.9, 119.9,

107.6, 56.3, 49.1, 39.7, 27.0. **HRMS** M^+ calculated 338.1539 found 338.1539.

Acknowledgements

The authors acknowledge the Vrije Universiteit Brussel (*starting grant for GV and AAP-PhD Fellowship for NM*) *and the Research Fund-Flanders* (*FWO-KN249*) *for financial support.*

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Adv. Synth. Catal. **2017**, *359*, 1–6

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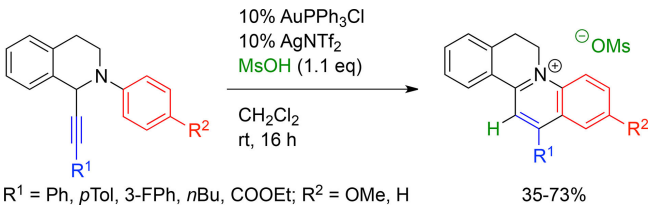

R^1 = Ph, *p*Tol, 3-FPh, *n*Bu, COOEt; R^2 = OMe, H

35-73%