Efficient Gold(I) Acyclic Diaminocarbenes for the Synthesis of Propargylamines and Indolizines

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S *Supporting Information*

ABSTRACT: Mononuclear gold(I) acyclic diaminocarbenes (ADCs) were prepared by the reaction of 1,2-cyclohexanediamine with the corresponding isocyanide complexes [AuCl(CNR)] (R = Cy, ^tBu). The three-component coupling of aldehydes, amines, and alkynes was investigated by using these gold(I) ADC complexes. The new gold(I) metal complexes are highly efficient catalysts for the synthesis of propargylamines and indolizines in the absence of solvent and in mild conditions. This method affords the corresponding final products with excellent yields in short reaction times. Additionally, chiral gold(I) complexes with ADCs have been prepared and tried in the enantioselective synthesis of propargylamines.

INTRODUCTION

The chemistry of gold has attracted the interest of many research groups because of the properties presented by its complexes covering different areas of investigation, such as in medicine as anticancer agents,[1−10] in materials chemistry for their optical properties,[11−13] or in catalysis because gold is able to promote several organic transformations.[14−23]

In this field, *N*-heterocyclic carbenes (NHCs)[24,25] are a kind of privileged scaffolds efficiently employed as ligands in gold compounds with applications in catalysis,[26,27] medicine,[28,29] and optical materials.[30] However, some of these NHCs still present some drawbacks. Nowadays, acyclic diaminocarbenes (ADCs) have become a promising alternative to NHCs for transition-metal-catalyzed organic transformations.[31] ADCs are free of some disadvantages that are present in the NHCs, such as the difficulty in their preparation when NHCs are unsymmetrically substituted or chiral, or when NHCs are used as ligands with steric hindrance. Remarkably, among them, gold(I) ADC complexes have received less attention in comparison with their cyclic analogues. Therefore, the search for new interesting examples is still an open challenging area of research.[32,33]

Multicomponent (MC) processes are of great interest because of their atom efficiency, affording structural diversity and complexity in a single reaction step. Their development has attracted the attention and efforts of many research groups over the years for obtaining numerous compound libraries with combinatorial chemistry. Moreover, MC reactions (MCRs) have played an important role in the progress for drug discovery.[34,35] Among these processes, the formation of propargylamines via a three-component coupling procedure, commonly called A³-coupling reaction, is an interesting approach center of continuous investigations.[36−40] Propargylamines are versatile building blocks for the synthesis of nitrogen-containing molecules. The structural core of the resulting amine derivatives is present in many natural products and drug candidates (Figure 1).[41−45] Some examples such as pargyline,[46] rasagyline,[47] and selegiline[48] have found applications in the treatment of neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases.[49,50]

Therefore, the development of a new synthetic procedure to obtain propargylamines is a very attractive aim because they are useful intermediates. Interestingly, the use of gold-based catalysts in these A³-coupling procedures has been shortly explored.[51−61]

The synthesis of indolizines in a tandem reaction involving an MC approach is also an interesting active goal.[62,63] Indolizines, one of the most important *N*-fused heterocyclic skeletons, are found in a variety of biological active compounds (Figure 1). Indolizines display a broad spectrum of potential pharmacological activities and are used in a variety of applications for drug discovery.[64]

Gold-based catalysts have been scarcely used for the preparation of indolizines.[65−70] It is worth mentioning that
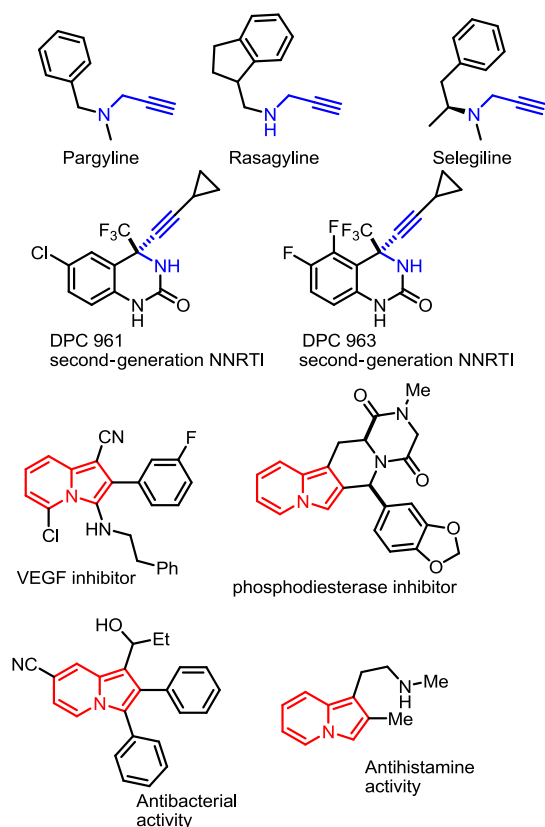
Figure 1. Biologically active propargylamines and indolizines. NNRTI: non-nucleoside reverse transcriptase inhibitor; VEGT: vascular endothelial growth factor.

only one example where the authors carry out a tandem multicomponent strategy has been described.[67] Because of the scarce background found in the literature for this process using gold catalysts along with the interesting biological properties exhibited by indolizines, the search for novel efficient and eco-friendly protocols using benign catalysts still remains a challenging task.

With all these ideas in mind, we planned the preparation of new and challenging gold(I) ADC complexes. Moreover, the resulting carbenes could be promising catalysts in different organic processes. Here, we report on the synthesis of such ADC gold derivatives and the study of their applications in the synthesis of propargylamines and indolizines through MCRs.

■ RESULTS AND DISCUSSION

The common synthesis of metal acyclic carbenes is based on the nucleophilic attack of an amine over a metal isocyanide complex. This procedure does not proceed easily for all the amines, and in some cases with aryl or less activated amines, the reaction does not work.[71] (±)-1,2-Cyclohexanediamine (2a), as a racemic mixture of *trans* isomers, has been employed by the first time for the preparation of gold ADCs 3a and 3b using isocyanides 1a and 1b following the reaction depicted in Scheme 1.

Acyclic carbenes 3a and 3b were easily prepared via the reaction of the isocyanide chloride gold(I) compound and the racemic mixture of 1,2-cyclohexanediamine (2a) at room temperature, giving rise to very good yields in both cases. It is remarkable that the mononuclear complexes are also obtained even in the case where a 2:1 molar ratio is used. Probably, the

Scheme 1. Synthesis of ADC Gold Carbene Complexes
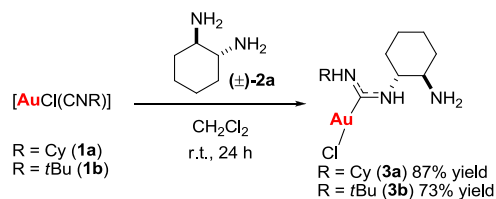
high insolubility of compounds 3a and 3b in dichloromethane is a driving force to solely produce the mononuclear species. Complexes 3a and 3b are sparingly soluble in common organic solvents. The ^{1}H NMR spectrum of complex 3b carried out in methanol-d_4 shows the expected resonances for the cyclohexyl skeleton, with two multiplets for the −CH− protons, four multiplets for the −CH$_2$− protons, and a singlet for the *tert*-butyl protons. The amine protons are not observed as they interchange with the deuterium of the solvent. In the ^{13}C-attached proton test (APT) NMR spectrum, all the signals can be easily assigned (Figure S4) and corroborate the inequivalence of all the carbons in the cyclohexyl moiety, thus indicating that only one gold center has formed the ADC unit. The resonance due to the carbene carbon atom appears at 192.0 ppm.

In contrast, in complex 3a because of the higher steric hindrance of the substituents and also because the carbene C−N bond shows a considerable multiple character in this type of complexes, an important restriction to rotation is produced, giving rise to stereoisomers or rotamers (see Figure 2).
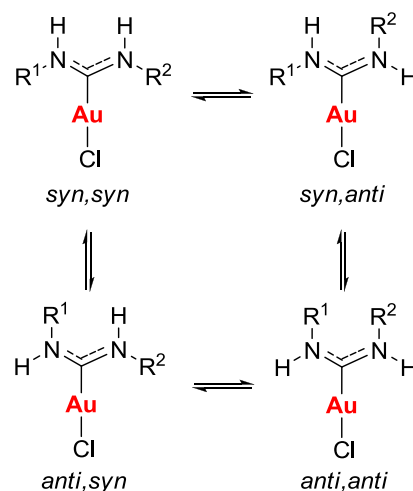

Figure 2. Different structural conformations for ADCs.

For this reason, complex 3a shows a very complicated ^{1}H NMR spectrum, and the resonances of the −CH$_2$− protons at the cyclohexyl ring appear as multiplets. It is possible to observe the resonances of the cyclohexyl −CH− protons in the less congested area in three different rotamers, with two of them in higher proportion. In the ^{13}C-APT NMR spectrum, two resonances with different intensities are observed for the carbene carbon atoms, which are probably due to the two major rotamers. The matrix-assisted laser desorption ionization mass spectra show the cationic peak arising at the loss of the chlorine ligand for complex 3a at m/z = 420.1759 [M − Cl]$^+$ and both the molecular peak [M + H]$^+$ at m/z = 430.1327 and the cationic [M − Cl]$^+$ at m/z = 394.1524 for complex 3b.

Additionally, the analytical data for these complexes also agree with the proposed formulation. In the infrared (IR) spectra, the most significant absorptions are the ν(Au−Cl), which appears at around 320 cm^{-1}, and the ν(N−H) in the range 2600−3000 cm^{-1}.

With both gold complexes in hand and in the context of our research program focused on the development of new catalytic processes, we first centered our attention in the preparation of propargylamines 7 via the A^3-coupling reaction following an easy and straightforward procedure. To test the efficiency of our precatalytic structures 3a,b, the viability of the reaction model illustrated in Table 1 was initially explored.

Table 1. Screening of the A^3-Coupling Reaction^a
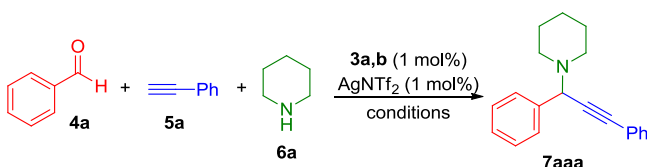
entry	cat.	solvent	t (h)	T (°C)	conv. (%)^b
1	3a−AgNTf$_2$	MeOH-d_4	5	60	85
2	3a−AgNTf$_2$	CD$_3$CN	5	60	46
3	3a−AgNTf$_2$	CD$_3$CN	5	70	85
4	3a−AgNTf$_2$	toluene-d_8	5	60	56
5	3a−AgNTf$_2$	toluene-d_8	5	70	70
6	3a−AgNTf$_2$		5	60	>99
7	3a^c		5	60	n.r.
8	AgNTf$_2$		5	60	20
9	3b−AgNTf$_2$		5	60	90

^{a}Reaction conditions: benzaldehyde 4a (0.25 mmol), piperidine 6a (0.275 mmol), phenylacetylene 5a (0.3 mmol), 3a,b (0.0025 mmol), AgNTf$_2$ (0.0025 mmol), and solvent 0.7 mL. ^{b}The conversions of the reactions are given by ^{1}H NMR using mesitylene as the internal standard. ^{c}Without addition of AgNTf$_2$.

In the first screening of solvent at 60 °C, encouraging results were found with MeOH-d_4 for 1 mol % of the catalyst (Table 1, entry 1) after short reactions times (5 h). In contrast, with CD$_3$CN and toluene-d_8, better conversions were only achieved when the temperature of the reaction was increased until 70 °C for the same reaction time (entries 3 and 5). Interestingly, a complete conversion was observed when the reaction was performed in the absence of solvent at 60 °C after 5 h of the reaction (entry 6). It is worth noting that the gold *precatalyst* 3a does not promote the reaction in the absence of the Ag species (entry 7). The same is observed when the reaction was performed only with the cocatalyst AgNTf$_2$ (entry 8). A good result was obtained using catalyst 3b (entry 9), although a slight lower conversion was observed in comparison with catalyst 3a. With the best reaction conditions found, different aldehydes 4a−c, acetylenes 5a,b, and amines 6a−f were explored to extend the scope of the reaction. The results are shown in Table 2.

Very good results were obtained for the complete scope of the reaction using different cyclic secondary amines such as piperidine (6a), morpholine (6b), or pyrrolidines (6c and 6e) and even noncyclic secondary amines such as Et$_2$NH (6d) and Bu$_2$NH (6f). Good results were also achieved for the use of different aldehydes (4a−c) and acetylenes (5a and 5b). For aldehydes 4b,c, which are solids, the addition of a small amount of 100 μL CH$_3$CN was needed prior to the reaction.

Otherwise, the crude mixture becomes very dense, and the stirring is really difficult. It is remarkable that our work is one of the scarce examples in which a gold catalyst is used to promote this process, in addition of using very low catalyst loading (1 mol %) and short reaction times (5 h). Our reaction represents an improvement in the synthesis of propargylamines in comparison with other reported examples where several metal complexes or metal salts such as Ag(I),[72] Cu(I),[73] Zn(II),[74,75] or Ir(II)[76] have been employed, among others, because in our case lower catalyst loading, shorter reaction times, and lower temperature were able to promote the process. Moreover, this is one of the scarce examples where Au(I) has been used against the examples reported with Au(III) and even in the absence of solvent and without inert atmosphere. Additionally, in many cases, the authors only used their catalysts to obtain propargylamines. In contrast and encouraged by these results, following this simple and effective method, our next step was to apply this catalytic system in the synthesis of indolizines 8 (Table 3).

Under the same optimized reaction conditions, the corresponding 1-aminoindolizine products 8 were obtained with very good yields in short reaction times. The generality of the protocol was evaluated by the synthesis of differently substituted 1-aminoindolizines 8. Thus, the reaction between pyridine-2-carboxaldehyde (4d) and 2-quinolinecarboxalde-hyde (4e) with various secondary amines and terminal alkynes 5a,b affords the desired product in all cases using 1 mol % of catalysts 3a. Interestingly, less studied alkynes 5c and 5d also provided the corresponding final products with moderate yields, although the starting material remained unreacted. Maybe longer reaction times would afford better yields. When the process was performed with aldehyde 4d, the reactions worked with cyclic secondary amines 6a−c and even noncyclic secondary amines 6d,f, more scarcely employed until now in this process. Interestingly, 2-quinolinecarboxaldehyde (4e) was also efficiently employed in the reaction with piperidine 6a and different noncyclic secondary amines 6d,f,g, giving rise to the corresponding aminoindolizine products 8 with very good results. On the other hand, when aldehyde 4e was used, the final products were obtained with yield values that were a bit lower compared with those achieved with 4d. In order to check the effectiveness of catalyst 3b, we tested some model reactions, and in all of them, very good results were obtained (Table 3).

The formation of the propargylamines 7 and the corresponding indolizines 8 can be explained by a plausible mechanism depicted in Scheme 2 and based on the chemistry of gold[14−23] (routes a and b). In both cases, the aldehyde initially reacts with the secondary amine to generate the iminium ion A. Because the bases present in the reaction are not able to deprotonate the terminal alkyne by themselves, the formation of an intermediate π-metal−alkyne complex is envisioned, involving a C−H activation of the alkyne by the gold catalyst. Complex B should make the alkyne proton more acidic for further abstraction. The in situ generated metal acetylide C reacts with the iminium ion A, giving rise to the formation of the propargylamines 7, releasing the gold catalyst for the subsequent catalytic cycle (Scheme 2, route a). Otherwise, if we have a pyridine aldehyde derivative (Scheme 2, route b) once the corresponding propargylamine D is generated, it undergoes a cyclization (5 endo-dig) affording intermediate E. In this step, a plausible activation of the alkyne by the metal to allow the cyclization is assumed. A subsequent

Table 2. Catalytic Synthesis of Propargylamines 7 via the Three-Component Addition Reaction
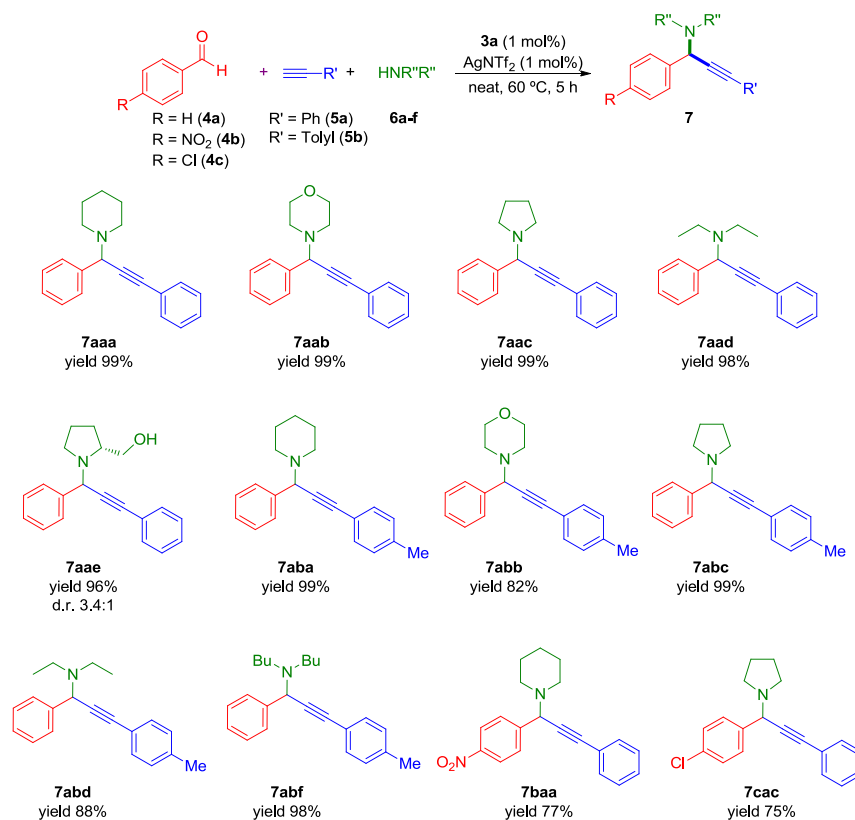
isomerization of **E** and final protodeauration of **F** would release the gold catalyst to start with the catalytic cycle.

At this stage, we planned to synthesize chiral-related catalysts following the same synthetic procedure (Scheme 3). For such a purpose, chiral amines **2b** and **2c** were selected. Chiral symmetric carbene **3c** and nonsymmetric carbene **3d** were easily prepared via the reaction of isocyanide **1a** and the chiral amines **2b** and **2c**, affording the chiral ADCs in very good yields.

Surprisingly, the chiral complex **3c**, which is analogous to the racemic mixture **3a**, was obtained as the dinuclear species. As this compound has a greater solubility in dichloromethane, it does not precipitate from the reaction media, and then the reaction proceeds to the complete nucleophilic attack of both amine units. To shed more light on this matter, we have measured the optical rotation of compound **3a** in methanol, which interestingly has a slightly different value from zero ($[\alpha]_D^{20}$ −1.12), whereas the optical rotation of complex **3c** is $[\alpha]_D^{20}$ −26.07. Therefore, we propose that there was a slight enrichment in one of the enantiomers (1S,2S) because of the high insolubility of this mononuclear species compared to that of the dinuclear **3c**, which is the 1R,2R enantiomer.

The analytical data and the mass spectrum corroborate the proposed formulation. Complex **3c** shows NMR spectra with a different integral ratio for the cyclohexyl protons, similar to that of the racemic mixture **3a**, with the presence of rotamers. In this case, three resonances for the carbene carbon atom are clearly observed at 190.9, 185.9, and 185.8 ppm, indicating the presence of three different rotamers. For complex **3d**, three rotamers are also clearly observed in the ^{1}H NMR spectrum for the resonances of the tolyl group. The ν(Au−Cl) and ν(N−H) absorptions are also observed in the IR spectra of

these compounds. The analytical data for both complexes agree with the proposed formulation.

Interestingly, with these two chiral structures, we have demonstrated the possibility to easily obtain chiral or unsymmetrically substituted ADCs, also using substituents with steric properties, which is still a challenging task in the preparation of NHCs. Furthermore, we set out on the exploration of the reactivity of these promising structures to generate propargylamines **7aaa** and **7aab**. Although at this point only <10% of enantiomeric excess has been reached in a model reaction between benzaldehyde **4a**, phenylacetylene **5a**, and morpholine **6b**, more efforts are necessary to improve these values and they are currently ongoing in our lab.

■ CONCLUSIONS

In summary, new gold(I) ADCs have been synthesized following a straightforward protocol. This synthetic method of the ADC metal complexes offers a great versatility for the synthesis of gold(I) species with different scaffolds, including chiral derivatives. These precatalysts have resulted to be efficient for the preparation of propargylamines and indolizines. These interesting scaffolds have been achieved following an easy and green protocol by a three-component coupling of carboxaldehydes, secondary amines and terminal alkynes. The potential of our procedure is reflected by the substrate scope, the operational simplicity, short reaction times, and good to excellent isolated yields. We believe that these MCRs demonstrate the strong capacity of our complex to act as an efficient catalyst. In addition, the reactions were performed under solvent-free conditions, an important feature from a sustainable point of view, without inert atmosphere and in the presence of light, in contrast to previous reported

Table 3. Scope for the Gold(I)-Catalyzed Multicomponent Synthesis of Aminoindolizines 8
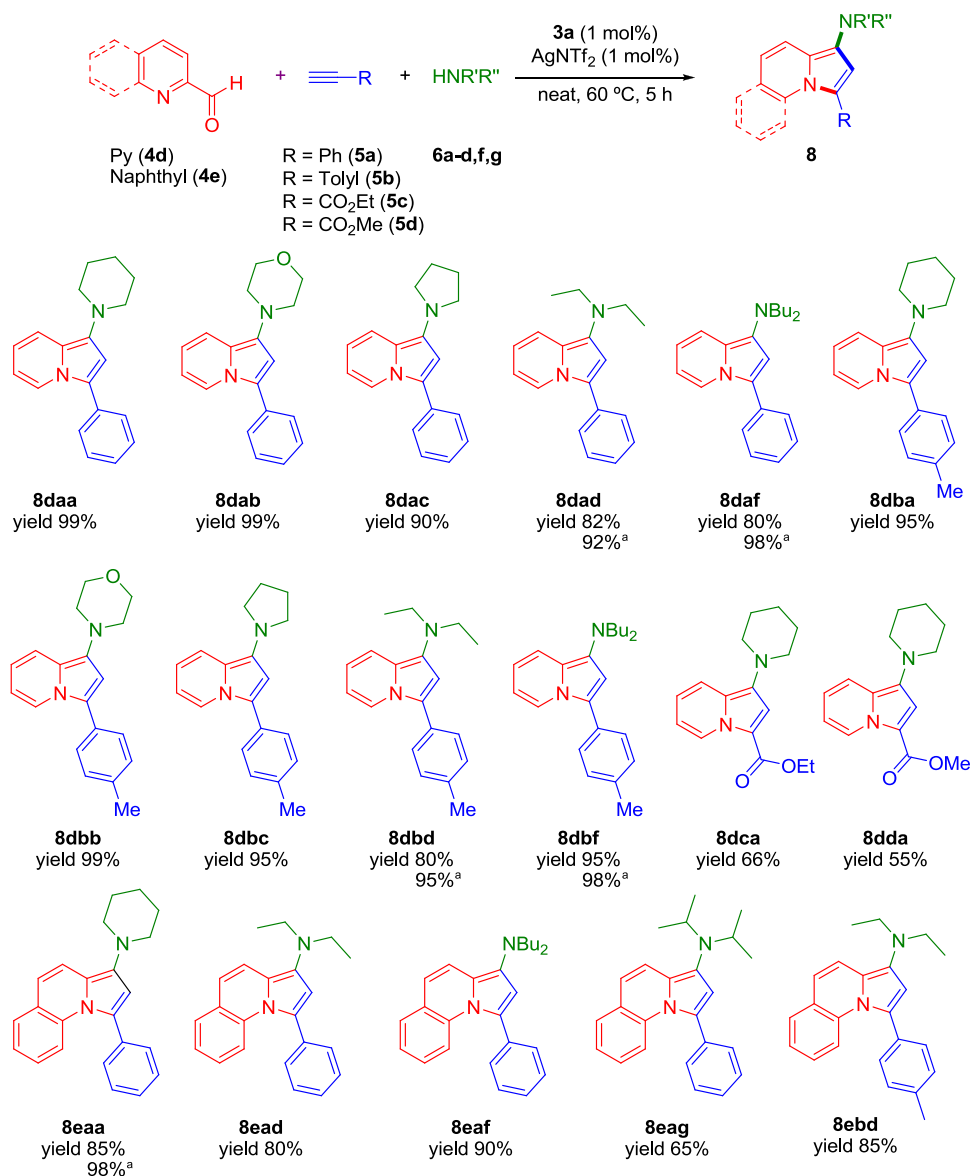
*Results obtained with catalyst **3b**.

examples. The chiral version of these catalysts has also been synthesized, and the asymmetric catalysis in the reaction of propargylamines has been tried. The results were not good probably because the chiral center is far from the catalytic site of the complex. We cannot discard that the free single bond rotations in the chiral catalysts, leading to multiple transition states, would also be responsible for the low ee. Further studies to improve the design of the catalysts are ongoing in our laboratory.

■ EXPERIMENTAL DETAILS

Instrumentation. Purification of reaction products was carried out by column chromatography using silica gel (0.063–0.200 mm). Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. ^{1}H and ^{13}C-$\{^{1}$H$\}$-APT NMR spectra were recorded at room temperature on a Bruker AVANCE 400 spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) or on a Bruker AVANCE II 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz), with chemical shifts (ppm)

reported relative to the solvent peaks of the deuterated solvent. $CDCl_3$, CD_2Cl_2, CD_3COCD_3, and CD_3OD were used as the deuterated solvents. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.28 ppm), CH_2Cl_2 (5.32 ppm), CH_3COCH_3 (2.05 ppm), and CH_3OH (3.31) for ^{1}H NMR and to the central line of $CDCl_3$ (77 ppm), CD_2Cl_2 (54 ppm), CD_3COCD_3 (29.84 ppm), and CD_3OD (49.0 ppm) for ^{13}C-APT-NMR. Mass spectra were recorded on Bruker ESQUIRE 3000 PLUS, with the electrospray ionization technique. The attenuated total reflection (ATR)–Fourier transform infrared (FTIR) spectra of solid samples were recorded on a PerkinElmer FTIR spectrometer equipped with a universal ATR sampling accessory.

Starting Materials. All reactions were performed under air atmosphere and solvents were used as received without further purification or drying. The starting materials [AuCl(CNR)] were prepared according to published procedures.[77−79] Starting materials, yields, and spectroscopic data for compounds **7abf**, **8dad**, **8dbf**, **8ead**, **8eag**, and **8ebd** are described

Scheme 2. Plausible Mechanistic Reaction
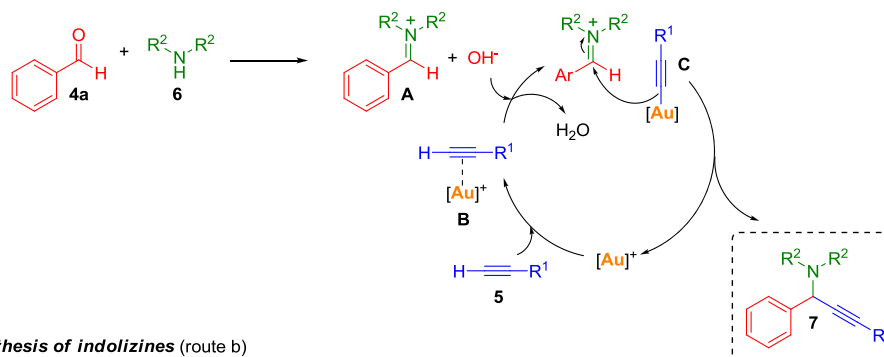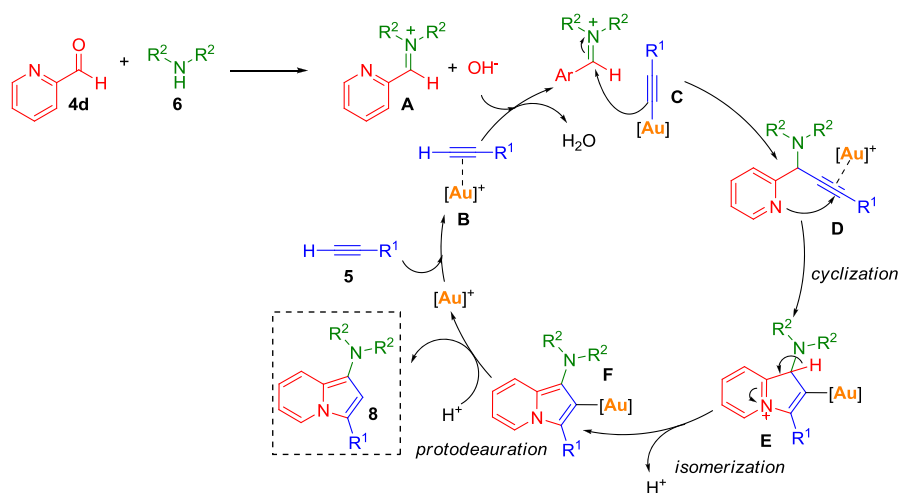
Scheme 3. Synthesis of Chiral Gold ADCs
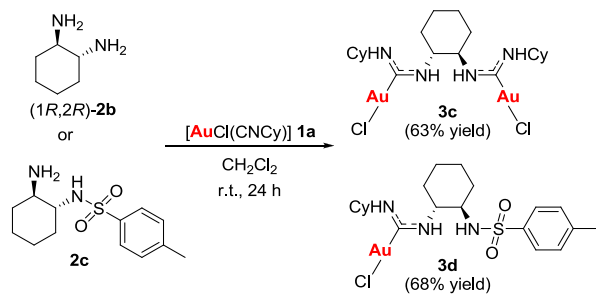
in the Supporting Information. ^{1}H and ^{13}C NMR spectra for compounds **7aaa**,[80] **7aab**,[81] **7aac**,[81] **7aad**,[81] **7aba**,[82] **7abb**,[83] **7abc**,[84] **7abd**,[85] **7baa**,[86] **7cac**,[87] **8daa**,[67] **8dab**,[67] **8dac**,[67] **8daf**,[88] **8dba**,[88] **8dbb**,[89] **8eaa**,[67] and **8eaf**[90] are consistent with the values previously reported in the literature.

General Procedure for the Synthesis of Complexes 3a−d. A mixture of [AuCl(CNR)] R = Cy (0.0683 g, 0.2 mmol), R = ^{t}Bu (0.0613 g, 0.2 mmol) and 1,2-cyclohexanediamine (as a racemic mixture of *trans* isomers, **2a**) (0.0228 g, 0.2 mmol) or (1*R*,2*R*)-1,2-cyclohexanediamine (**2b**) (0.0114 g, 0.1 mmol) or (1*R*,2*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine (**2c**) (0.0537 g, 0.2 mmol) in dichloromethane (20 mL) was stirred at room temperature for 24 h (**3a,b,d**) or 4 days (**3c**). Complexes **3a** and **3b** precipitated as white solids and were filtered off. For compounds **3c** and **3d**, the volume was reduced to 5 mL, and addition of *n*-hexane afforded the complexes as white solids.

General Procedure for the Au-Catalyzed Three-Component Synthesis of Propargylamines 7. To a mixture of gold complex **3a** (2 mg, 0.0025 mmol) and AgNTf$_2$ (0.97 mg, 0.0025 mmol), aldehyde **4a−c** (0.25 mmol), amine **6a−f** (0.275 mmol), and acetylene **5a,b** (0.30 mmol) were added under solvent-free conditions. The resulting reaction mixture was stirred at 60 °C for 5 h and monitored by thin-layer chromatography. After this reaction time, products **7** were isolated by flash chromatography (SiO$_2$, using Hex/Et$_2$O 95:5). The yields are reported in Table 2.

General Procedure for the Au-Catalyzed Three-Component Synthesis of Indolizines 8. To a mixture of gold complex **3a** (3.99 mg, 0.005 mmol) and AgNTf$_2$ (1.94 mg, 0.005 mmol), aldehyde **4d,e** (0.50 mmol), amine **6a−d, f, g** (0.55 mmol), and acetylene **5a,b** (0.60 mmol) were added under solvent-free conditions. The resulting reaction mixture was stirred at 60 °C for 5 h and monitored by thin-layer chromatography. After the reaction time, products **8** were isolated by flash chromatography (SiO$_2$, using Hex/Et$_2$O 95:5). The yields are reported in Table 3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01352.

Characterization of all new compounds and ^{1}H and ^{13}C-APT NMR spectra (PDF)

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Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

■ REFERENCES

(1) Tiekink, E. R. T. Gold Compounds in Medicine: Potential Anti-Tumour Agents. *Gold Bull.* **2003**, *36*, 117−124.

(2) Maia, P. I. d. S.; Deflon, V. M.; Abram, U. Gold(III) complexes in medicinal chemistry. *Future Med. Chem.* **2014**, *6*, 1515−1536.

(3) Berners-Price, S. J.; Filipovska, A. Gold compounds as therapeutic agents for human diseases. *Metallomics* **2011**, *3*, 863−873.

(4) Ott, I. On the medicinal chemistry of gold complexes as anticancer drugs. *Coord. Chem. Rev.* **2009**, *253*, 1670−1681.

(5) Bertrand, B.; Casini, A. A golden future in medicinal inorganic chemistry: the promise of anticancer gold organometallic compounds. *Dalton Trans.* **2014**, *43*, 4209−4219.

(6) Zou, T.; Lum, C. T.; Lok, C.-N.; Zhang, J.-J.; Che, C.-M. Chemical biology of anticancer gold(III) and gold(I) complexes. *Chem. Soc. Rev.* **2015**, *44*, 8786−8801.

(7) Yeo, C.; Ooi, K.; Tiekink, E. Gold-Based Medicine: A Paradigm Shift in Anti-Cancer Therapy? *Molecules* **2018**, *23*, 1410.

(8) Visbal, R.; Fernández-Moreira, V.; Marzo, I.; Laguna, A.; Gimeno, M. C. Cytotoxicity and biodistribution studies of luminescent Au(I) and Ag(I) N-heterocyclic carbenes. Searching for new biological targets. *Dalton Trans.* **2016**, *45*, 15026−15033.

(9) Gutiérrez, A.; Gracia-Fleta, L.; Marzo, I.; Cativiela, C.; Laguna, A.; Gimeno, M. C. Gold(I) thiolates containing amino acid moieties. Cytotoxicity and structure-activity relationship studies. *Dalton Trans.* **2014**, *43*, 17054−17066.

(10) Goitia, H.; Nieto, Y.; Villacampa, M. D.; Kasper, C.; Laguna, A.; Gimeno, M. C. Antitumoral Gold and Silver Complexes with Ferrocenyl-Amide Phosphines. *Organometallics* **2013**, *32*, 6069−6078.

(11) Crespo, O.; Gimeno, M. C.; Laguna, A.; Larraz, C.; Villacampa, M. D. Highly Luminescent Gold(I)-Silver(I) and Gold(I)-Copper(I) Chalcogenide Clusters. *Chem.—Eur. J.* **2007**, *13*, 235−246.

(12) Czerwieniec, R.; Hofbeck, T.; Crespo, O.; Laguna, A.; Gimeno, M. C.; Yersin, H. The Lowest Excited State of Brightly Emitting Gold(I) Triphosphine Complexes. *Inorg. Chem.* **2010**, *49*, 3764−3767.

(13) Crespo, O.; Gimeno, M. C.; Jones, P. G.; Laguna, A.; López-de-Luzuriaga, J. M.; Monge, M.; Pérez, J. L.; Ramón, M. A. Luminescent nido-Carborane−Diphosphine Anions [(PR₂)₂C₂B₉H₁₀]⁻ (R = Ph,ⁱPr). Modification of Their Luminescence Properties upon Formation of Three-Coordinate Gold(I) Complexes. *Inorg. Chem.* **2003**, *42*, 2061−2068.

(14) Hashmi, A. S. K.; Hutchings, G. J. Gold Catalysis. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936.

(15) Hashmi, A. S. K. Gold-Catalyzed Organic Reactions. *Chem. Rev.* **2007**, *107*, 3180−3211.

(16) Fürstner, A.; Davies, P. W. Catalytic Carbophilic Activation: Catalysis by Platinum and Gold π Acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449.

(17) Li, Z.; Brouwer, C.; He, C. Gold-Catalyzed Organic Transformations. *Chem. Rev.* **2008**, *108*, 3239−3265.

(18) Arcadi, A. Alternative Synthetic Methods through New Developments in Catalysis by Gold. *Chem. Rev.* **2008**, *108*, 3266−3325.

(19) Jiménez-Nuñez, E.; Echavarren, A. M. Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective. *Chem. Rev.* **2008**, *108*, 3326−3350.

(20) Gorin, D. J.; Sherry, B. D.; Toste, F. D. Ligand Effects in Homogeneous Au Catalysis. *Chem. Rev.* **2008**, *108*, 3351−3378.

(21) Garayalde, D.; Nevado, C. Synthetic applications of gold-catalyzed ring expansions. *Beilstein J. Org. Chem.* **2011**, *7*, 767−780.

(22) Rudolph, M.; Hashmi, A. S. K. Gold catalysis in total synthesis—an update. *Chem. Soc. Rev.* **2012**, *41*, 2448−2462.

(23) Sengupta, S.; Shi, X. Recent Advances in Asymmetric Gold Catalysis. *ChemCatChem* **2010**, *2*, 609−619.

(24) Lin, I. J. B.; Vasam, C. S. Review of gold(I) N-heterocyclic carbenes. *Can. J. Chem.* **2005**, *83*, 812−825.

(25) Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. Beyond Conventional N-Heterocyclic Carbenes: Abnormal, Remote, and Other Classes of NHC Ligands with Reduced Heteroatom Stabilization. *Chem. Rev.* **2009**, *109*, 3445−3478.

(26) Díez-González, S.; Marion, N.; Nolan, S. P. N-Heterocyclic Carbenes in Late Transition Metal Catalysis. *Chem. Rev.* **2009**, *109*, 3612−3676.

(27) Nolan, S. P. The Development and Catalytic Uses of N-Heterocyclic Carbene Gold Complexes. *Acc. Chem. Res.* **2011**, *44*, 91−100.

(28) Oehninger, L.; Rubbiani, R.; Ott, I. N-Heterocyclic carbene metal complexes in medicinal chemistry. *Dalton Trans.* **2013**, *42*, 3269−3284.

(29) Liu, W.; Gust, R. Metal N-heterocyclic carbene complexes as potential antitumor metallodrugs. *Chem. Soc. Rev.* **2013**, *42*, 755−773.

(30) Visbal, R.; Gimeno, M. C. N-heterocyclic carbene metal complexes: photoluminescence and applications. *Chem. Soc. Rev.* **2014**, *43*, 3551−3574.

(31) Boyarskiy, V. P.; Luzyanin, K. V.; Kukushkin, V. Y. Acyclic diaminocarbenes (ADCs) as a promising alternative to N-heterocyclic carbenes (NHCs) in transition metal catalyzed organic transformations. *Coord. Chem. Rev.* **2012**, *256*, 2029−2056.

(32) Slaughter, L. M. Acyclic Aminocarbenes in Catalysis. *ACS Catal.* **2012**, *2*, 1802−1816.

(33) Barbazanges, M.; Fensterbank, L. Chiral Acyclic Diaminocarbene Complexes: a New Opportunity for Gold Asymmetric Catalysis. *ChemCatChem* **2012**, *4*, 1065−1066.

(34) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.

(35) *Multicomponent Reactions: Concepts and Applications for Design and Synthesis*; Herrera, R. P., Marqués-López, E., Eds.; John Wiley & Sons: Hoboken, New Jersey, 2015.

(36) Wei, C.; Li, Z.; Li, C.-J. The Development of A³-Coupling (Aldehyde-Alkyne-Amine) and AA³-Coupling (Asymmetric Aldehyde-Alkyne-Amine). *Synlett* **2004**, 1472−1483.

(37) Yoo, W.-Y.; Zhao, L.; Li, C.-J. The A³-Coupling (Aldehyde−Alkyne−Amine) Reaction: A Versatile Method for the Preparation of Propargylamines. *Aldrichimica Acta* **2011**, *44*, 43−51.

(38) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. A walk around the A³-coupling. *Chem. Soc. Rev.* **2012**, *41*, 3790−3807.

(39) Abbiati, G.; Rossi, E. Silver and gold-catalyzed multicomponent reactions. *Beilstein J. Org. Chem.* **2014**, *10*, 481−513.

(40) Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. Synthesis and Reactivity of Propargylamines in Organic Chemistry. *Chem. Rev.* **2017**, *117*, 14091−14200.

(41) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. Lithium Alkoxides of Cinchona Alkaloids as Chiral Controllers for Enantioselective Acetylide Addition to Cyclic *N*-Acyl Ketimines. *J. Org. Chem.* **1995**, *60*, 1590−1594.

(42) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. An Efficient Chiral Moderator Prepared from Inexpensive (+)-3-Carene: Synthesis of the HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor DPC 963. *Org. Lett.* **2000**, *2*, 3119−3121.

(43) Jiang, B.; Xu, M. Highly Enantioselective Construction of Fused Pyrrolidine Systems That Contain a Quaternary Stereocenter: Concise Formal Synthesis of (+)-Conessine. *Angew. Chem., Int. Ed.* **2004**, *43*, 2543−2546.

(44) Gommermann, N.; Knochel, P. Practical highly enantioselective synthesis of terminal propargylamines. An expeditious synthesis of (S)-(+)-coniine. *Chem. Commun.* **2004**, 2324−2325.

(45) Xu, Q.; Rozners, E. Asymmetric Synthesis of *trans*-3,4-Dialkyl-*γ*-butyrolactones via an Acyl-Claisen and Iodolactonization Route. *Org. Lett.* **2005**, *7*, 2821−2824.

(46) Langston, J.; Irwin, I.; Langston, E.; Forno, L. Pargyline prevents MPTP-induced parkinsonism in primates. *Science* **1984**, *225*, 1480−1482.

(47) Chen, J. J.; Swope, D. M. Clinical Pharmacology of Rasagiline: A Novel, Second-Generation Propargylamine for the Treatment of Parkinson Disease. *J. Clin. Pharmacol.* **2005**, *45*, 878−894.

(48) Birks, J.; Flicker, L. Selegiline for Alzheimer's disease. *Cochrane Database of Systematic Reviews*; John Wiley & Sons, Ltd: Chichester, U.K., 2003; Vol. *1*.

(49) Baranyi, M.; Porceddu, P. F.; Gölöncsér, F.; Kulcsár, S.; Otrokocsi, L.; Kittel, A.; Pinna, A.; Frau, L.; Huleatt, P. B.; Khoo, M.-L.; Chai, C. L. L.; Dunkel, P.; Mátyus, P.; Morelli, M.; Sperlágh, B. Novel (Hetero)arylalkenyl propargylamine compounds are protective in toxin-induced models of Parkinson's disease. *Mol. Neurodegener.* **2016**, *11*, 6.

(50) Bolea, I.; Gella, A.; Unzeta, M. Propargylamine-derived multitarget-directed ligands: fighting Alzheimer's disease with mono-amine oxidase inhibitors. *J. Neural Transm.* **2013**, *120*, 893−902.

(51) Wei, C.; Li, C.-J. A Highly Efficient Three-Component Coupling of Aldehyde, Alkyne, and Amines via C−H Activation Catalyzed by Gold in Water. *J. Am. Chem. Soc.* **2003**, *125*, 9584−9585.

(52) Kantam, M. L.; Prakash, B. V.; Reddy, C. R.; Sreedhar, B. Layered Double Hydroxide-Supported Gold Catalyst for Three-Component Aldehyde-Amine-Alkyne Coupling. *Synlett* **2005**, 2329−2332.

(53) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. Gold(III) Salen Complex-Catalyzed Synthesis of Propargylamines via a Three-Component Coupling Reaction. *Org. Lett.* **2006**, *8*, 1529−1532.

(54) Kidwai, M.; Bansal, V.; Kumar, A.; Mozumdar, S. The first Au-nanoparticles catalyzed green synthesis of propargylamines via a three-component coupling reaction of aldehyde, alkyne and amine. *Green Chem.* **2007**, *9*, 742−745.

(55) Lo, V. K.-Y.; Kung, K. K.-Y.; Wong, M.-K.; Che, C.-M. Gold(III) (C^N) complex-catalyzed synthesis of propargylamines via a three-component coupling reaction of aldehydes, amines and alkynes. *J. Organomet. Chem.* **2009**, *694*, 583−591.

(56) Elie, B. T.; Levine, C.; Ubarretxena-Belandia, I.; Varela-Ramírez, A.; Aguilera, R. J.; Ovalle, R.; Contel, M. Water-Soluble (Phosphane)gold(I) Complexes - Applications as Recyclable Catalysts in a Three-Component Coupling Reaction and as Antimicrobial and Anticancer Agents. *Eur. J. Inorg. Chem.* **2009**, 3421−3430.

(57) Lili, L.; Xin, Z.; Jinsen, G.; Chunming, X. Engineering metal-organic frameworks immobilize gold catalysts for highly efficient one-pot synthesis of propargylamines. *Green Chem.* **2012**, *14*, 1710−1720.

(58) Kung, K. K.-Y.; Lo, V. K.-Y.; Ko, H.-M.; Li, G.-L.; Chan, P.-Y.; Leung, K.-C.; Zhou, Z.; Wang, M.-Z.; Che, C.-M.; Wong, M.-K.

Cyclometallated Gold(III) Complexes as Effective Catalysts for Synthesis of Propargylic Amines, Chiral Allenes and Isoxazoles. *Adv. Synth. Catal.* **2013**, *355*, 2055−2070.

(59) Montanel-Pérez, S.; Herrera, R. P.; Laguna, A.; Villacampa, M. D.; Gimeno, M. C. The fluxional amine gold(III) complex as an excellent catalyst and precursor of biologically active acyclic carbenes. *Dalton Trans.* **2015**, *44*, 9052−9062.

(60) von Wachenfeldt, H.; Polukeev, A. V.; Loganathan, N.; Paulsen, F.; Röse, P.; Garreau, M.; Wendt, O. F.; Strand, D. Cyclometallated gold(III) aryl-pyridine complexes as efficient catalysts for three-component synthesis of substituted oxazoles. *Dalton Trans.* **2015**, *44*, 5347−5353.

(61) Zhang, X.; Corma, A. Supported Gold(III) Catalysts for Highly Efficient Three-Component Coupling Reactions. *Angew. Chem., Int. Ed.* **2008**, *47*, 4358−4361.

(62) Liu, Y. Recent advances on diversity oriented heterocycle synthesis via multicomponent tandem reactions based on A^3 coupling. *ARKIVOC* **2014**, No. i, 1−20.

(63) Sadowski, B.; Klajn, J.; Gryko, D. T. Recent advances in the synthesis of indolizines and their *π*-expanded analogues. *Org. Biomol. Chem.* **2016**, *14*, 7804−7828.

(64) Singh, G. S.; Mmatli, E. E. Recent progress in synthesis and bioactivity studies of indolizines. *Eur. J. Med. Chem.* **2011**, *46*, 5237−5257.

(65) Seregin, I. V.; Gevorgyan, V. Gold-Catalyzed 1,2-Migration of Silicon, Tin, and Germanium en Route to C-2 Substituted Fused Pyrrole-Containing Heterocycles. *J. Am. Chem. Soc.* **2006**, *128*, 12050−12051.

(66) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. Mechanistically Diverse Copper-, Silver-, and Gold-Catalyzed Acyloxy and Phosphatyloxy Migrations: Efficient Synthesis of Heterocycles via Cascade Migration/Cycloisomerization Approach. *J. Am. Chem. Soc.* **2007**, *129*, 9868−9878.

(67) Yan, B.; Liu, Y. Gold-Catalyzed Multicomponent Synthesis of Aminoindolizines from Aldehydes, Amines, and Alkynes under Solvent-Free Conditions or in Water. *Org. Lett.* **2007**, *9*, 4323−4326.

(68) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. Multi-substituted *N*-fused heterocycles via transition metal-catalyzed cycloisomerization protocols. *Tetrahedron* **2008**, *64*, 6876−6883.

(69) Liu, R.-R.; Ye, S.-C.; Lu, C.-J.; Xiang, B.; Gao, J.; Jia, Y.-X. Au-catalyzed ring-opening reactions of 2-(1-alkynyl-cyclopropyl)pyridines with nucleophiles. *Org. Biomol. Chem.* **2015**, *13*, 4855−4858.

(70) Li, X.; Xie, X.; Liu, Y. Gold(I)-Catalyzed Cascade Hydro-arylation/Cycloaromatization to Indolizines via Pyridine Ring Construction. *J. Org. Chem.* **2016**, *81*, 3688−3699.

(71) Crespo, O.; Gimeno, M. C.; Laguna, A.; Montanel-Pérez, S.; Villacampa, M. D. Facile Synthesis of Gold(III) Aryl-Carbene Metallacycles. *Organometallics* **2012**, *31*, 5520−5526.

(72) Li, Y.; Chen, X.; Song, Y.; Fang, L.; Zou, G. Well-defined *N*-heterocyclic carbene silver halides of 1-cyclohexyl-3-arylmethylimida-zolylidenes: synthesis, structure and catalysis in A^3-reaction of aldehydes, amines and alkynes. *Dalton Trans.* **2011**, *40*, 2046−2052.

(73) Choi, J.; Lim, J.; Irudayanathan, F. M.; Kim, H.-S.; Park, J.; Yu, S. B.; Jang, Y.; Raja, G. C. E.; Nam, K. C.; Kim, J.; Lee, S. Copper-Catalyzed Double Decarboxylative Coupling Reactions of Alkynyl Carboxylic Acid and Glyoxylic Acid: Synthesis of Propargyl Amines and Imidazopyridines. *Asian J. Org. Chem.* **2016**, *5*, 770−777.

(74) Mishra, S.; Bagdi, A. K.; Ghosh, M.; Sinha, S.; Hajra, A. Zinc iodide: a mild and efficient catalyst for one-pot synthesis of aminoindolizines via sequential A^3 coupling/cycloisomerization. *RSC Adv.* **2014**, *4*, 6672−6676.

(75) Obst, M.; Srivastava, A.; Baskaran, S.; König, B. Preparation of Propargyl Amines in a ZnCl$_2$−Dimethylurea Deep-Eutectic Solvent. *Synlett* **2018**, *29*, 185−188.

(76) Sakaguchi, S.; Mizuta, T.; Furuwan, M.; Kubo, T.; Ishii, Y. Iridium-catalyzed coupling of simple primary or secondary amines, aldehydes and trimethylsilylacetylene: preparation of propargylic amines. *Chem. Commun.* **2004**, 1638−1639.

(77) White-Morris, R. L.; Olmstead, M. M.; Balch, A. L.; Elbjeirami, O.; Omary, M. A. Orange Luminescence and Structural Properties of Three Isostructural Halocyclohexylisonitrilegold(I) Complexes. *Inorg. Chem.* **2003**, *42*, 6741−6748.

(78) McCleverty, J. A.; da Mota, M. M. M. Isocyanide and carbene complexes of gold(I). The stepwise formation of formamidines. *J. Chem. Soc., Dalton Trans.* **1973**, 2571−2574.

(79) Hashmi, A. S. K.; Yu, Y.; Rominger, F. Efficient One-Pot Synthesis of Unsymmetrical Gold(I) *N*-Heterocyclic Carbene Complexes and Their Use as Catalysts. *Organometallics* **2012**, *31*, 895−904.

(80) Leadbeater, N. E.; Torenius, H. M.; Tye, H. Microwave-assisted Mannich-type three-component reactions. *Mol. Diversity* **2003**, *7*, 135−144.

(81) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. Microwave-Promoted Three-Component Coupling of Aldehyde, Alkyne, and Amine via C−H Activation Catalyzed by Copper in Water. *Org. Lett.* **2004**, *6*, 1001−1003.

(82) Mitamura, T.; Ogawa, A. Copper(0)-Induced Deselenative Insertion of *N,N*-Disubstituted Selenoamides into Acetylenic C−H Bond Leading to Propargylamines. *Org. Lett.* **2009**, *11*, 2045−2048.

(83) Sun, R.; Liu, J.; Yang, S.; Chen, M.; Sun, N.; Chen, H.; Xie, X.; You, X.; Li, S.; Liu, Y. Cp$_2$TiCl$_2$-catalyzed *cis*-hydroalumination of propargylic amines with Red-Al: stereoselective synthesis of Z-configured allylic amines. *Chem. Commun.* **2015**, *51*, 6426−6429.

(84) Buckley, B. R.; Khan, A. N.; Heaney, H. Mannich Reactions of Alkynes: Mechanistic Insights and the Role of Sub-Stoichiometric Amounts of Alkynylcopper(I) Compounds in the Catalytic Cycle. *Chem.—Eur. J.* **2012**, *18*, 3855−3858.

(85) Lin, Z.; Yu, D.; Zhang, Y. Propargylic amines constructed via copper-catalyzed three-component coupling of terminal alkynes, benzal halides and amines. *Tetrahedron Lett.* **2011**, *52*, 4967−4970.

(86) Layek, K.; Chakravarti, R.; Kantam, M. L.; Maheswaran, H.; Vinu, A. Nanocrystalline magnesium oxide stabilized gold nanoparticles: an advanced nanotechnology based recyclable heterogeneous catalyst platform for the one-pot synthesis of propargylamines. *Green Chem.* **2011**, *13*, 2878−2887.

(87) Zhao, Y.; Zhou, X.; Okamura, T.-A.; Chen, M.; Lu, Y.; Sun, W.-Y.; Yu, J.-Q. Silver supramolecule catalyzed multicomponent reactions under mild conditions. *Dalton Trans.* **2012**, *41*, 5889−5896.

(88) Albaladejo, M. J.; Alonso, F.; Yus, M. Synthesis of Indolizines and Heterocyclic Chalcones Catalyzed by Supported Copper Nanoparticles. *Chem.—Eur. J.* **2013**, *19*, 5242−5245.

(89) Mishra, S.; Bagdi, A. K.; Ghosh, M.; Sinha, S.; Hajra, A. Zinc iodide: a mild and efficient catalyst for one-pot synthesis of aminoindolizines via sequential A^3 coupling/cycloisomerization. *RSC Adv.* **2014**, *4*, 6672−6676.

(90) Albaladejo, M. J.; Alonso, F.; González-Soria, M. J. Synthetic and Mechanistic Studies on the Solvent-Dependent Copper-Catalyzed Formation of Indolizines and Chalcones. *ACS Catal.* **2015**, *5*, 3446−3456.