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# Gold-Catalyzed Reactions of 2-Alkynyl-phenylamines with α,β-Enones

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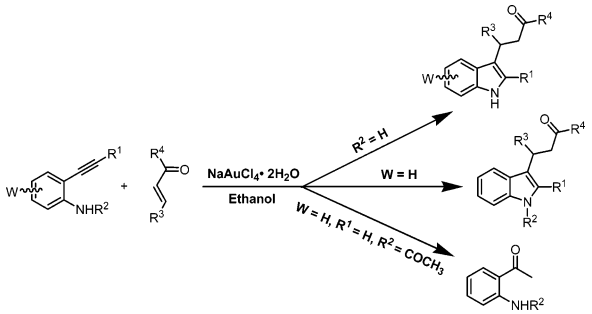


The gold-catalyzed reaction of 2-alkynyl-phenylamines with α,β-enones represents a new general one-pot entry into C-3-alkyl-indoles by sequential reactions. Gold-catalyzed sequential cyclization/alkylation, *N*-alkylation/cyclization, or *N*-alkylation/cyclization/alkylation reactions leading to different indoles can be directed by changing the 2-alkynyl-phenylamine **1**/α,β-enone **3** ratio and the reaction temperature. Unusual gold-catalyzed rearrangement reaction of indoles are observed at 140 °C. New gold-catalyzed formation of propargyl-alkyl ether under mild conditions and the hydration reaction of *N*-acetyl-2-ethynyl-phenylamine are reported.

## Introduction

The synthesis of indoles is currently[1] the object of wide investigation due to their central role as useful building blocks in the synthesis of alkaloids and in the design of therapeutic agents.[2] As the 2-alkynyl-phenylamines derivatives **1** are easily available by established synthetic procedures,[3] the methods for indole syntheses with these compounds as the starting materials are some of the more versatile procedures. Thus far, many reaction conditions have been reported for this purpose. Base-promoted cyclizations of 2-alkynyl-phenylamines **1** or their *N*-protected derivatives have been developed.[4] Electrophilic cyclization of **1** derivatives by $I_2$ or iodinating reagent have been successfully employed in the synthesis of 3-iodoindoles, which in turn have been further functionalized by known palladium methodology.[5] Many transition-metal-assisted protocols have accomplished remarkable improvements in terms of efficiency and functional group compatibility.[6] Applications including both polymer-supported reactions[7] and sequential[8] C-3 functionalization have been established. In this context, 2-substituted-3 alkylindoles have been prepared from *o*-alkynyltrifluroacetanilides either through their domino aminopalladation/reductive elimination reaction[9] or their base-promoted sequential alkylation-cyclization process[10] with alkyl halides. Nevertheless, enhancing the efficiency of the synthesis of the target compounds is still an exciting challenge. The goal of maximizing the efficiency of use of starting materials and of minimizing the creation of waste can be accomplished by increasing the catalog of reactions that are simple additions.[11] Since so few of the existing reactions are additions, synthesis of complex molecules requires the development of new atom-economical methods. Transition metals are a focal point for such invention. Recently, gold derivatives are growing in importance as efficient catalysts of several addition reactions because of their unique properties.[12] Highly effective additions of activated methylene compounds to alkenes[13] by using Au(III) catalysts and to alkynes[14] by means of Au(I) catalysis have been developed. It has been found that $AuCl_3$ can catalyze conjugate addition of electron-rich aromatic rings to methyl vinyl ketone.[15] A highly efficient gold/silver-catalyzed addition of arenes

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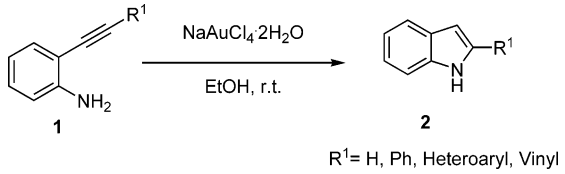
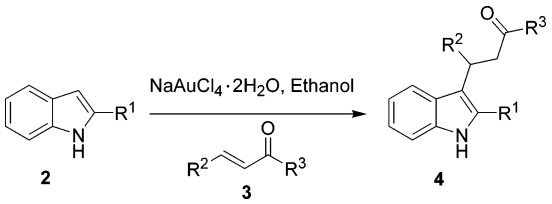
to imines[16] and electron-deficient alkynes[17] has been discovered. Gold-catalyzed addition of heteroatom nucleophiles to alkynes and activated alkenes have been explored.[18] Investigation on synthetic potential of gold-catalyzed reaction of alkynes and/or allenes bearing proximate nucleophiles is currently an attractive research topic.[19]

**SCHEME 1. Gold-Catalyzed Cyclization of 2-Alkynyl-phenylamines**




**SCHEME 2. Gold-Catalyzed Conjugate Addition of Indoles 2 to α,β-Enones**




In this field, we have recently reported the efficient gold-catalyzed cyclization of 2-alkynyl-phenylamines **1** to indoles in ethanol or ethanol/water mixtures at room temperature[20] (Scheme 1).

Moreover, gold salts have been effective catalysts in promoting the conjugate addition reactions of indoles **2** to α,β-enones[21] **3** (Scheme 2).

In this latter case, both the (a) direct auration of indoles **2** at C-3 followed by the addition of indolyl-gold species to α,β-enones and/or (b) gold-catalyzed Friedel−

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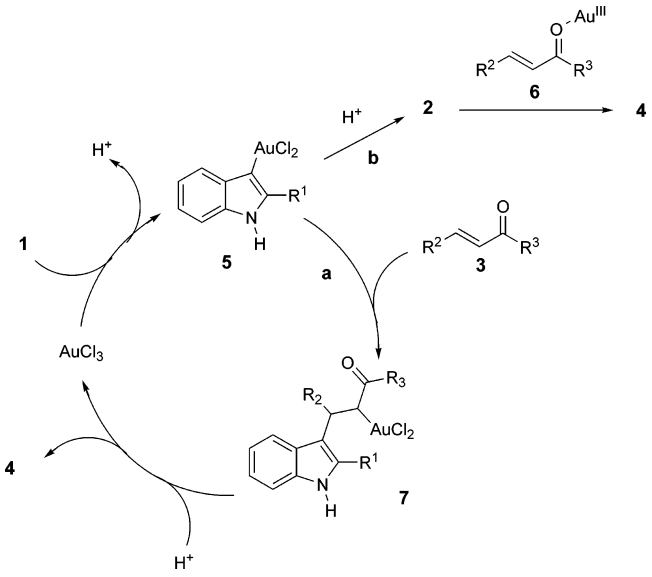
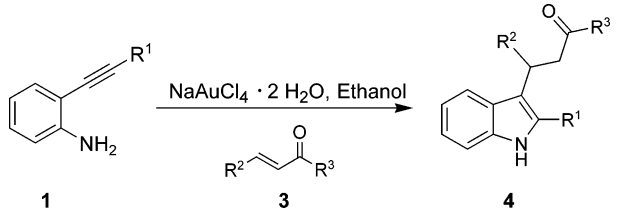
**SCHEME 3. Gold-Catalyzed Conjugate Addition of Indoles 2 to α,β-Enones: Proposed Mechanisms**



**SCHEME 4. Gold-Catalyzed Sequential Cyclization/Conjugate Addition of 2-Alkynyl-phenylamines 1 to α,β-Enones 3**



Crafts-type process can be involved in the reaction pathway (Scheme 3). Aryl/heteroarylgold(III) species are currently reported as the reaction intermediates in the direct C−H functionalization of arenes/heteroarenes.[22]

With the aim to probe the reaction mechanism and to improve the efficiency of the process, we tried to develop the gold-catalyzed sequential cyclization/conjugate addition reaction starting from **1**. Hereafter we show the results of our study.

## Results and Discussion

We are pleased to report that the gold-catalyzed cyclization/conjugate addition-type reaction of 2-alkynyl-phenylamines **1** with α,β-enones **3** can easily occur under very mild reaction conditions, leading to the 3-alkylindoles **4** in moderate to high yields (Scheme 4; Table 1).

Usually, the reaction of **1** with **3** resulted in satisfactory yield at 30 °C. An equimolecular ratio of **1** and **3** were reacted. The reaction proceeds smoothly even with less reactive α,β-enones such as β-disubstituted α,β-enones and cyclic enones. This should suggest the involvement of the formation of Au-complexed enone intermediate **6** because its β-substitution should increase the carbocationic character of the β-carbon. With α,β-unsaturated esters the reaction led only to the isolation of the 2-substituted indole **2** as the reaction product; for example, **1a** reacted with ethyl acrylate to give 2-phenyl-1*H*-indole **2a** in 83% yield.

With regard to **1**, the procedure is compatible with a variety of functional groups. When substitution with electron-withdrawing groups was made in the benzene ring of **1** such as in the case of 2,4-dichloro-6-(3,4-dihydro-naphthalen-1-ylethynyl)-phenylamine **1g** (Table 1, entry 12) and 2,4-dichloro-6-ethynyl-phenylamine **1i** (Table 1, entry 15) the cyclization derivatives 5,7-dichloro-2-(3,4-dihydro-naphthalen-1-yl)-1*H*-indole **2g** and dichloro-1*H*-indole **2i** have been isolated in, respectively, 65% and 24% yield. Increasing the reaction temperature resulted in the formation of the products of sequential cyclization/alkylation reaction in moderate yield (i.e., **4l** was isolated in 28% yield at 45 °C and 45% yield at 80 °C; Table 1, entries 12 and 13). The electronic properties of the aromatic ring have been reported to have an effect on the rate of the Michael reaction of indoles to α,β-enones.[23] The presence of very strong electron-withdrawing groups such as in 1-(2-amino-3-chloro-5-nitro-phenyl)-3-methyl-pent-1-yn-3-ol **1j** could even slow the rate of the annulation process, and the chemoselective formation of the ether 2-chloro-6-(3-ethoxy-3-methyl-pent-1-ynyl)-4-nitro-phenylamine **1k** has been observed (Scheme 5).

Although gold(III) catalysts[24] have been previously reported as efficient catalysts in the synthesis of β-keto enol ethers, to the best of our knowledge this is the first example of gold-catalyzed synthesis of mixed propagyl-ethyl ether.

Usually, the nitrogen of 2-alkynyl-phenylanilins **1** did not require prior protection to avoid their gold-catalyzed competitive aza-Michael[18a,e] reaction with α,β-enones. Nevertheless, the electronic properties of 2-alkynyl-phenylamines **1**, temperature, and **3/1** ratio play a pivotal role on the reaction outcome. Indeed, upon changing the **3/1** ratio from 1 to 2 the gold-catalyzed reaction of **1b** with **3a** in ethanol at 30 °C afforded 4-(2-naphthalen-2-yl-indol-1-yl)-butan-2-one **9a** (30% yield) (Scheme 6).

The formation of **9a** is supposed to be the result of a competitive different sequence involving a gold-catalyzed aza-Michael/cyclization process. Actually, a product deriving from a competitive aza-Michael reaction (4-(2-ethynylphenylamino)butan-2-one **8a**, 33% yield), together with smaller amounts of the aza-Michael/cyclization product **9b** (17% yield) were isolated from the reaction of 2-ethynylaniline **1l**, bearing a terminal triple bond. This latter result indicates that the terminal triple bond is less prone to undergo the cyclization reaction (Scheme 7).[25]

Compound **8a** was an intermediate in the formation of **9b**, as shown by control experiments (Scheme 8).

The better yield of **9b** observed at higher temperature (80% at 60 °C vs 57% at 30 °C) could be explained considering that side polymerization of **8a** can occur when the cyclization is a slow step. Total disappearance of **8a** has been observed in both cases. Moreover, by using a 2-fold excess of **3a** with respect to **1l** and by rising the

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**TABLE 1. Gold-Catalyzed Synthesis of 2,3-Disubstituted Indoles[a] 4 from the Reaction of 2-Alkyny-phenylamines 1 with α,β-Enones 3**

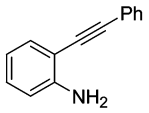
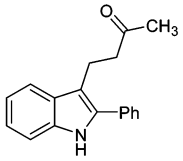
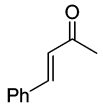
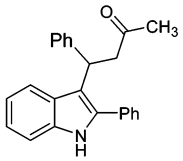
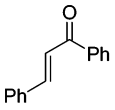
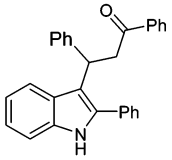
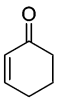
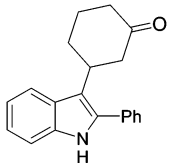
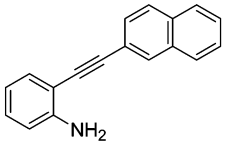
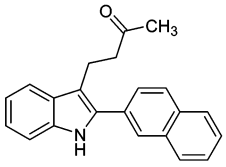
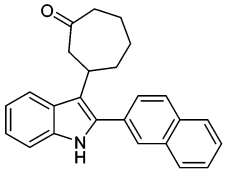
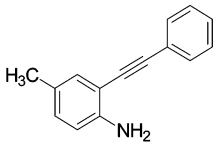
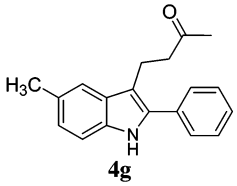
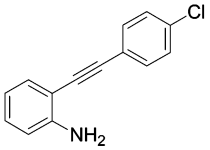
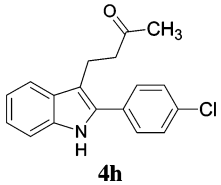
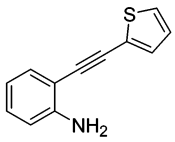
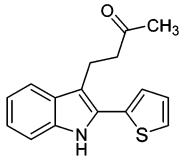
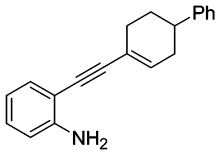
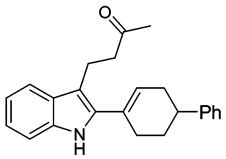
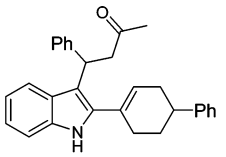
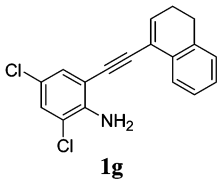
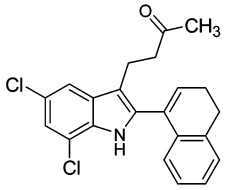
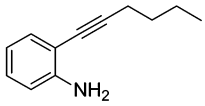
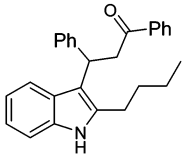
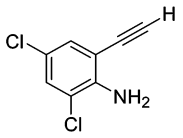
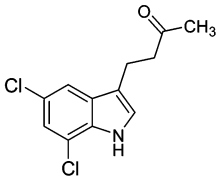
| Entry | Alkyny-phenylamines **1** | α,β-Enones **3** | 2,3-Disubstitutes-indoles **4** | Time/h | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  **1a** |  **3a** |  **4a** | 5 | 74 |
| 2 | **1a** |  **3b** |  **4b** | 2,5 | 88 |
| 3 | **1a** |  **3c** |  **4c** | 9 | 82 |
| 4 | **1a** |  **3d** |  **4d** | 1,5 | 55 |
| 5 |  **1b** | **3a** |  **4e** | 24[c] | 54[d] |
| 6 | **1b** |  **3e** |  **4f** | 6[c] | 68[e] |
| 7 |  **1c** | **3a** |  **4g** | 2,5 | 85 |
| 8 |  **1d** | **3a** |  **4h** | 24 | 86[f] |

**Table 1. (Continued)**

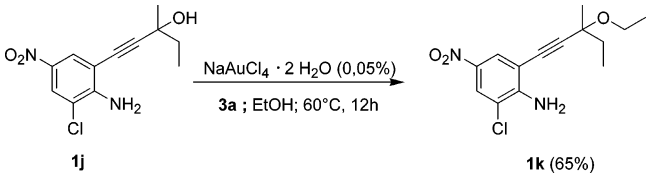
| Entry | Alkyny-phenylamines **1** | α,β-Enones **3** | 2,3-Disubstitutes-indoles **4** | Time/h | Yield (%)[b] |
|---|---|---|---|---|---|
| 9 |  **1e** | **3a** |  **4i** | 1,5 | 88 |
| 10 |  **1f** | **3a** |  **4j** | 23[c] | 95 |
| 11 | **1f** | **3b** |  **4k** | 24[c] | 71 |
| 12 |  **1g** | **3a** |  **4l** | 24[g] | 28[h] |
| 13 | **1g** | **3a** | **4l** | 17[i] | 45[i] |
| 14 |  **1h** | **3c** |  **4m** | 2 | 92 |
| 15 |  **1i** | **3a** |  **4n** | 24 | 51[k] |
| 16 | **1i** | **3a** | **4n** | 15[l] | 57[m] |

[a] Unless otherwise stated, reactions were carried out according to the following procedure: **1/3**/$NaAuCl_4 \cdot 2H_2O$ = 1:1:0.05 in EtOH at 30 °C (0.48−0.95 mmol scale). [b] Yields refer to single runs and are given for isolated products. [c] The reaction was carried out in a mixture ethanol (1 mL)/THF (1 mL) as reaction medium. [d] 2-Naphthalen-2-yl-1*H*-indole **2b** was isolated in 37% yield. [e] 2-Naphthalen-2-yl-1*H*-indole **2b** was isolated in 15% yield. [f] 2-(4-Chloro-phenyl)-1*H*-indole **2d** was isolated in 8% yield. [g] The reaction was carried out at 45 °C. [h] 5,7-Dichloro-2-(3,4-dihydro-naphthalen-1-yl)-1*H*-indole **2g** was isolated in 65% yield. [i] The reaction was carried out at 80 °C. [j] 5,7-Dichloro-2-(3,4-dihydro-naphthalen-1-yl)-1*H*-indole **2g** was isolated in 29% yield. [k] 5,7-Dichloro-1*H*-indole **2i** was isolated in 24% yield. [l] The reaction was carried out at 60 °C. [m] 5,7-Dichloro-1*H*-indole **2i** was isolated in 25% yield.

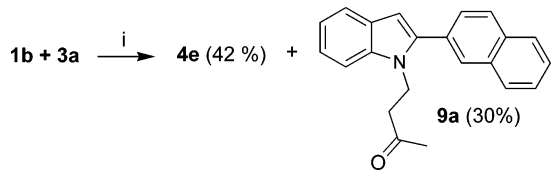
reaction temperature from 30 to 60 °C, product **10a**, deriving from a subsequent Michael addition of **9b** to **3a**, was selectively obtained in 80% yield (Scheme 9).

As expected, both the cyclization reaction and the aza-Michael reaction were completely inhibited when nitrogen nucleophilicity was decreased, as in the case of *N*-(2-acetylphenyl)acetamide **11**, which underwent competitive water addition to the triple bond (Scheme 10). Both Au(III)[18d,j,26] and Au(I)[18f] species have in fact been reported to catalyze the hydration of alkynes.

**SCHEME 5. Gold-Catalyzed Synthesis of 2-Chloro6-(3-ethoxy-3-methyl-pent-1-ynyl)-4-nitro-phenylamine**

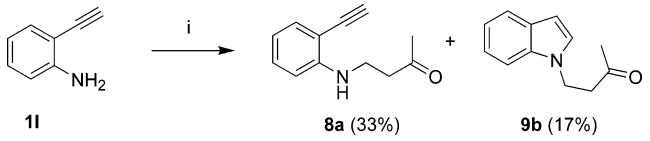



**SCHEME 6. Gold-Catalyzed Sequential Cyclization/Alkylation vs Aza-Michael/Cyclization Process[a]**



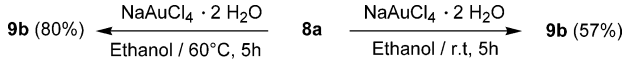

[a] (i) **1b**:**3a**:$NaCuCl_4 \cdot 2H_2O$ = 1:2:0.05; EtOH/THF (1/1); 30 °C, 0.3 h.

**SCHEME 7. Gold-Catalyzed Aza-Michael Alkylation Reaction of 2-Ethynyl-phenylamine 1l[a]**




[a] (i) **1l**:**3a**:$NaAuCl_4 \cdot 2H_2O$ = 1:1:0.05; ethanol/rt, 24 h.

**SCHEME 8. Gold-Catalyzed Cyclization of 4-(2-Ethynyl-phenylamino)-butan-2-one 8a**




The reactivity of *N*-alkylated 2-(phenylethynyl)-phenylamine **8b** was also tested.[27] When 4-(2-phenylethynylphenylamino)butan-2-one **8b** was reacted in EtOH at 140 °C, the formation of C3-alkylated indole **4a** (40% yield) was observed along with the cyclization derivative **9c** and **10b** (Scheme 11).

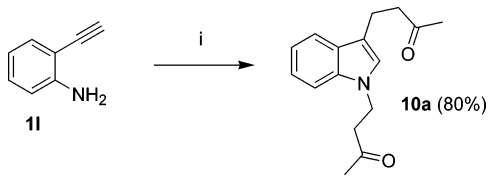
Very likely, **4a** is produced by sequential cyclization/rearrangement reaction. According to this **9c** underwent gold-catalyzed rearrangement to **4a**. The formation, at the same time, of **2a** and **10b** clearly shows that at high temperatures retro aza-Michael/$C_3$-alkylation may occur. Lewis acid catalyzed rearrangements of indoles have been previously described.[28] Furthermore, **8b** can afford the corresponding 1,2,3-trisubstituted indoles **10c** in good yield (Scheme 12).

It worth noting that this new gold-catalyzed sequential reaction can represent a mild and versatile alternative method for the preparation of 1,2,3-trisubstituted indoles, which are targets for antibacterial therapy.[29]

**Reaction Mechanism of the Gold-Catalyzed Sequential Cyclization/Alkylation Reaction of 2-Alkynyl-Phenylamines 1.** As a consequence of the results described above, it appeared that the many "personalities" of gold catalysis could have deserved further investigation to clarify the role of the catalyst in the sequential cyclization/alkylation reaction of **1**. Therefore, we selected reaction **1h** and **3c** as model system to probe the mechanism of gold-catalyzed domino reactions. Our experiments clearly put in evidence that Au(III) show a higher activity compared to that of Pd(II) and Cu(II) catalysts in our sequential process (Scheme 13).

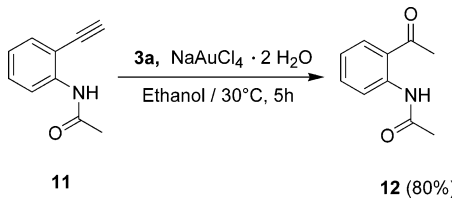
3-Indolyl-gold,[30] 3-indolyl-palladium,[30] and 3-indolyl-copper[6a] species have been previously proposed as intermediates in the cyclization step of **1**. Brønsted acid[31] catalysis in the cyclization step can be ruled out in consequence of the recovering of **1h** and the starting enone **3c** in the presence of *p*-toluenesulfonic acid as the catalyst. Solvolysis products of $AuCl_3$, H [$AuCl_3OCH_2$-$CH_3$] and HCl, should have been serious candidates for active Brønsted acidic catylists[15] under our reaction

**SCHEME 9. Gold-Catalyzed Sequential Aza-Michael/Cyclization/Alkylation Reaction of 2-Ethynyl-phenylamine 1l[a]**

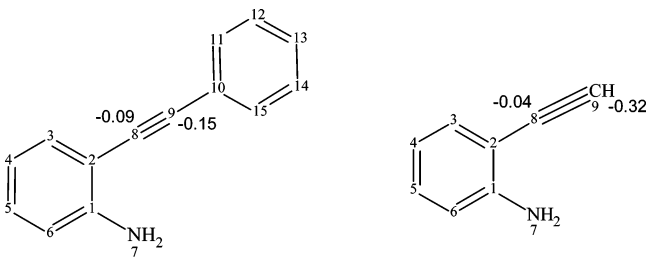



[a] (i) **1l**:**3a**:$NaAuCl_4 \cdot 2H_2O$ = 1:2:0.05; ethanol/60 °C, 24 h.

**SCHEME 10. Gold-Catalyzed Hydration of *N*-(2-Acetyl-phenyl)-acetamide 11**




(25) Electronic effects could account for this. Semiempirical calculations have shown a higher negative charge on the terminal carbon of **1l** than on C-9 of **1a** (the semiempirical calculations provide a charge of −0.09 and −0.15 au for the C-8 and C-9 of **1a,** respectively; the same carbon atom in **1l** shows a charge of −0.04 and −0.32 au, indicating a sharp increase of the negative charge on the acetylenic terminal carbon atom).




**1a** **1l**

(26) (a) Deetlefs, M.; Raubenheimer, H. G.; Esterhuysen, M. W. *Catal. Today* **2002**, *72*, 29. (b) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Tetrahedron Lett.* **2000**, *41*, 9195.

(27) Ross, N. C.; Levine, R. *J. Org. Chem.* **1964**, *29*, 2346.

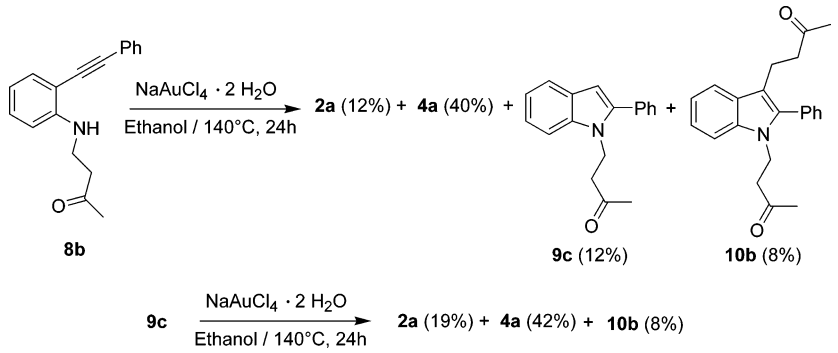
(28) Iqbal, Z.; Jackson, A. H.; Rao, N. K. R. *Tetrahedron Lett.* **1988**, *29*, 2577.

(29) Jennings, L. D.; Foreman, K. W.; Rush, T. S., III; Tsao, D. H. H.; Mosyak, L.; Kincaid, S. L.; Sukhedeo, M. N.; Sutherland, A. G.; Ding, W.; Kenny, C. H.; Sabus, C. L.; Liu, H.; Dushin, E. G.; Moghazeh, S. L.; Labthavikul, P.; Petersen, P. J.; Tuckman, M.; Ruzin, A. V. *Biorg. Med. Chem. Lett.* **2004**, *12*, 5115.

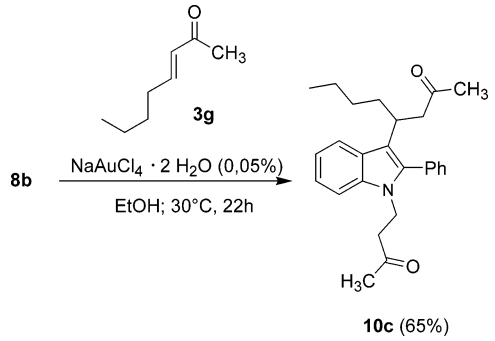
(30) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799.

(31) (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204. Goldfinger, M. B.; Swager, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 7895.

**SCHEME 11. Gold-Catalyzed Sequential Cyclization/Rearrangement of 4-(2-Phenylethynyl-phenylamino)-butan-2-one 8b**




**SCHEME 12. Gold-Catalyzed Sequential Cyclization/Alkylation Reaction of 4-(2-Phenylethynyl-phenylamino)-butan-2-one 8b**




conditions. By contrast, the C-3 alkylation of 2-substituted indole **2h** gave the conjugated addition-type product either under metal salts or Brønsted acidic catalysis. Indeed **2h** afforded the corresponding 3-alkylated indole **4m** in 85% yield under the presence of a catalytic amount of *p*-TsOH (Scheme 14).

Furthermore, the detection by GC−MS of indole derivatives **2** as intermediates during the running of the reaction and its isolation in many cases as byproducts put in evidence that the formation of products **4** is the result of the conjugate-addition-type reaction of **2** with α,β-enones **3**. Then, the catalytic process starts from the coordination of the acetylene moiety of **1** to the transition metal (Scheme 15). The intramolecular nucleophilic attack of the nitrogen to the activated carbon−carbon triple bond leads to the indolyl-metal derivatives **5**. Protonolysis of **5** regenerates the catalyst, which activates the enones **3** to give the electrophile derivative **6**. At last, electrophilic aromatic substitution at the 3-position of the indole **2** provides the 3-alkyl indole derivative **4**.

The results obtained in the Pd-catalyzed sequential reaction of **1h** with **3c** give further support to this proposed mechanism. Indeed, by contrast with the results obtained in the reaction of *N*-protected 2-alkynyl-phenylamines[32] and indoles[33] with alkenes in the presence of palladium(II) catalysts leading to alkenylindoles derivatives **13** (Heck reaction) (Scheme 16), in our conditions the sequential cyclization/alkylation reaction gave hydroalkylation[34] derivative **4m**. Heck products have been observed also in the Pd-catalyzed reaction of 2-methylfuran with olefins bearing electron-withdrawing substituents.[35] Then, the formation of σ-alkyl-palladium **7′** is not involved in the reaction pathway because β-H elimination product **13** has not been observed.

Very likely, an effective catalyst for our sequential cyclization/alkylation reaction should exhibit a dual role catalysis. $MX_n$ should activate the alkyne group toward the intramolecular nucleophilic attack of nitrogen nucleophiles on the carbon−carbon triple bond. $MX_n$ should also catalyze the Friedel−Crafts-type reaction through the formation of a complex with the carbonyl group of α,β-enones **3**. In previous studies the higher efficiency of gold (III) was observed as compared to that of palladium (II)/copper(II) derivatives as dual role catalysts.[36]

## Conclusions

The gold-catalyzed reaction of 2-alkynyl-phenylamines with α,β-enones represents a new general one-pot entry into C-3-alkyl-indoles. Au(III) derivatives show higher activity compared to that of Pd(II) and Cu(II) catalysts. Sequential cyclization/alkylation, *N*-alkylation/cyclization, or *N*-alkylation/cyclization/alkylation reactions leading to different indoles can be directed by changing the 2-alkynyl-phenylamine/α,β-ratio and the reaction temperature. The unusual gold-catalyzed rearrangement reaction of indoles can be observed at 140 C°. The gold-catalyzed formation of propargyl-alkyl ether under mild conditions and hydration reaction of *N*-acetyl-2-ethynylaniline are reported.

## Experimental Section

**General Experimental Procedure for Gold-Catalyzed Sequential Cyclization/Conjugate Addition of 2-Alkynyl-phenylamines 1 to α,β-Enones 3.** To a 1:1 molar ratio solution of 2-alkynyl-phenylamine **1** and α,β-enone **3** in ethanol was added $NaAuCl_4 \cdot 2H_2O$ (5 mol %). The resulting mixture was allowed to react under stirring at 30 °C and the reaction was monitored by TLC or GC−MS. After completion, the solvent was removed by evaporation. To the residue was added

(32) Yasuhara, A.; Kaneto, M.; Sakamoto, T. *Heterocycles* **1998**, *48*, 1793.

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(34) Lu, X.; Lei, A. *Org. Lett.* **2000**, *2*, 2699−2702.

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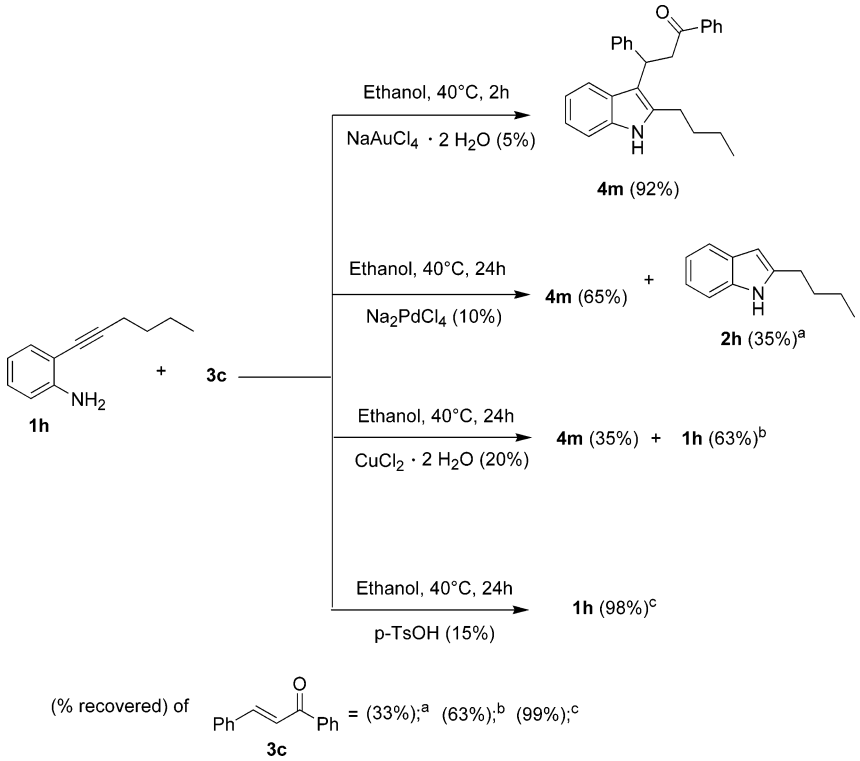
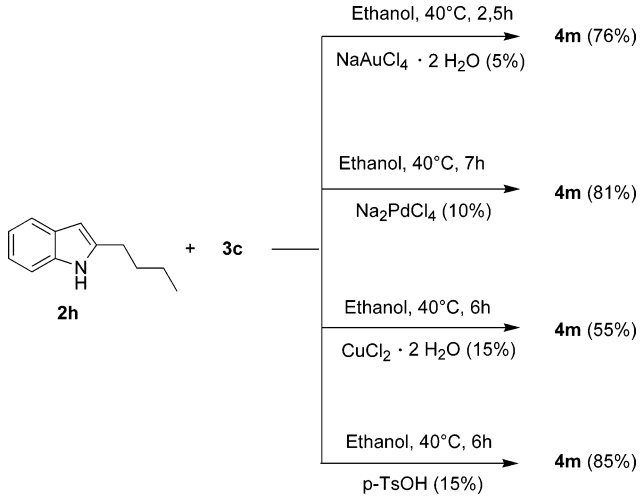
**SCHEME 13. Sequential Cyclization/Alkylation Reaction of 2-Hex-1-ynyl-phenylamine 1h**



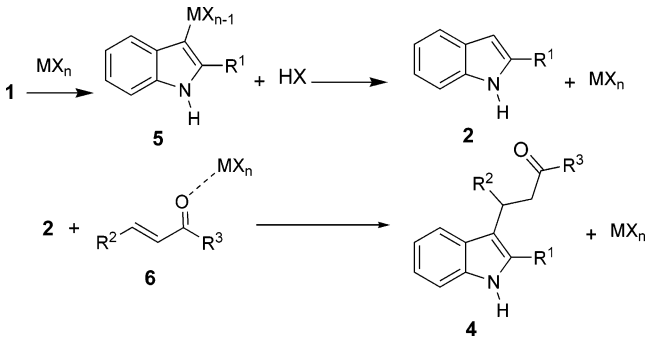

**SCHEME 14. Conjugate Addition Type Reaction of 2-Butyl-1*H*-indole 2h**




acetone (a few mL) to precipitate the catalyst, which was separated by filtration. The filtrate was concentrated and the crude products were purified by chromatography on silica gel (230−400 mesh) eluting with *n*-hexane/ethyl acetate mixtures.

**General Experimental Procedure for Aza-Michael Addition of 2-Alkynyl-phenylamines 1 to α,β-Enones 3.** To a 1:3 molar ratio solution of 2-alkynyl-phenylamine **1** and α,β-enone **3** in acetonitrile was added concentrated (98%) $H_2SO_4$ (10 mol %). The resulting mixture was allotted to react under stirring at room temperature and the reaction was monitored by TLC or GC−MS. After completion, the mixture was diluted with a saturated sodium hydrogencarbonate solution (1 × 50 mL) and extracted with EtOAc. The combined organic layer (150 mL) was washed with brine and dried over anhydrous $Na_2SO_4$. After the removal of the solvent under vacuum, the crude product was purified by chromatography on silica gel (230−400 mesh) eluting with *n*-hexane/ethyl acetate mixtures.

**SCHEME 15. Proposed Mechanism for the $MX_n$-Catalyzed Sequential Cyclization/Alkylation Reaction of 2-Alkynyl-phenylamines 1**

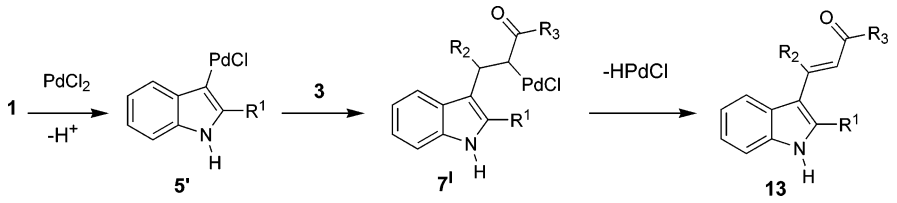



**Gold-Catalyzed Sequential Aza-Michael/Cyclization/Alkylation Reaction.** To a 1:2 molar ratio solution of 2-alkyny-phenylamine **1** and α,β-enone **3** in ethanol was added $NaAuCl_4 \cdot 2H_2O$ (5 mol %). The resulting mixture was allotted to react under stirring at 60 °C and the reaction was monitored by TLC or GC−MS. After completion, the solvent was removed by evaporation. The crude products were purified by chromatography on silica gel (230−400 mesh) eluting with *n*-hexane/ethyl acetate mixtures.

**Procedure for Synthesis of 4-Methyl-2-phenylethynyl-phenylamine 1c.** To a solution of 2-bromo-4-methylaniline (0.60 g, 3.22 mmol) in piperidine (10 mL) was added phenylacetylene (0.49 g, 4.83 mmol), $PdCl_2(PPh_3)_2$ (0.022 g, 0.032 mmol), and CuI (0.003 g, 0.016 mmol). The mixture was stirred at 80 °C for 48 h under $N_2$ and then extracted with 0.1 M HCl (150 mL) and EtOAc (2 × 50 mL). The organic layer was dried ($Na_2SO_4$) and evaporated. Column chromatographic purification on silica gel (230−400 mesh) eluting with *n*-hexane/ethyl acetate 90:10 mixture afforded 4-methyl-2-phenylethynyl-phenylamine **1c** (0.49 g, 74% yield).

**Procedure for Synthesis of 2-(3-Ethoxy-3-methy-pent-1-ynyl)-phenylamine 1k.** To a solution of 2-chloro-6-(3-

**SCHEME 16. Proposed Mechanism for the Palladium-Catalyzed Reaction of 3-Indolyl Palladium with α,β-Enones**




ethoxy-3-methyl-pent-1-ynyl)-4-nitro-phenylamine **1j** (0.10 g, 0.39 mmol) and methyl vinyl ketone **3a** (0.03 g, 0.39 mmol) in ethanol (2 mL) was added $NaAuCl_4 \cdot 2H_2O$ (0.007 g, 0.019 mmol). The resulting mixture was allowed to react under stirring at 60 °C for 12 h. Then, the solvent was removed by evaporation. The residue purified by chromatography on silica gel (230−400 mesh) eluting with *n*-hexane/ethyl acetate 70:30 mixture afforded 2-(3-ethoxy-3-methy-pent-1-ynyl)-phenylamine **1k** (0.086 g, 65% yield).

**Procedure for Synthesis of *N*-(2-Acetyl-phenyl)-acetamide 12.** To a solution of *N*-(2-ethynyl-phenyl)-acetamide **11** (0.10 g, 0.61 mmol) and methyl vinyl ketone **3a** (0.05 g, 0.61 mmol) in ethanol (2 mL) was added $NaAuCl_4 \cdot 2H_2O$ (0.007 g, 0.019 mmol). The resulting mixture was allowed to react under stirring at 30 °C for 24 h. Then, the solvent was removed by evaporation. The residue purified by chromatography on silica gel (230−400 mesh) eluting with *n*-hexane/ethyl acetate 70:30 mixture afforded *N*-(2-acetyl-phenyl)-acetamide **12** (0.080 g, 80% yield).

**Rearrangement of 4-(2-Phenyl-indol-1-yl)-butan-2-one 9c to 4-(2-Phenyl-1*H*-indol-3-yl)-butan-2-one 4a.** To a solution of 4-(2-phenyl-indol-1-yl)-butan-2-one **9c** (0.144 g, 0.55 mmol) in ethanol (2 mL) was added $NaAuCl_4 \cdot 2H_2O$ (0.010 g, 0.027 mmol). The resulting mixture was heated at 140 °C in a steel reactor for 24 h. Then, the solvent was removed by evaporation. The residue purified by chromatography on silica gel (230−400 mesh) eluting with *n*-hexane/ethyl acetate 80:20 mixture afforded 4-(2-phenyl-1*H*-indol-3-yl)-butan-2-one **4a** (0.060 g, 42% yield).

Except for **1c**, all compounds **1** were prepared according to refs 4a and 20. The following products were identified by comparison of their physical and spectral data with those given in the cited references: 2-phenylethynyl-phenylamine[4a] **1a**, 2-(4-chloro-phenylethynyl)-phenylamine[20] **1d**, thiophen-2-yl-ethynyl-phenylamine[4a] **1e**, (4-phenyl-ciclohex-1-enylethynyl)-phenylamine[37] **1f**, 4-dichloro-6-(3,4-dihydro-naphthlen-1-yl-ethynyl)-phenylamine[20] **1g**, 2-hex-1-ynyl-phenylamine[4a] **1h**, 2,4-dichloro-6-ethynyl-phenylamine[20] **1i**, 2-ethynyl-phenylamine[4a] **1m**, 2-phenyl-1*H*-indole[4a] **2a**, 2-(4-chlorophenyl)-1*H*-indole[20] **2d**, 5,7-dichloro-2-(3,4-dihydro-naphthalen-1-yl)-1*H*-indole[20] **2g**, 5,7-dichloro-1*H*-indole[20] **2i**, 2-butyl-1*H*-indole[4a] **2h**, 4-(2-phenyl-1*H*-indol-3-yl)-butan-2-one[21] **4a**, 4-phenyl-4-(2-phenyl-1*H*-indol-3-yl)-butan-2-one[21] **4b**, 3-(2-phenyl-1*H*-indol-3-yl)-cyclohexanone[21] **4d**, 4-(2-thiophen-2-yl-1*H*-indol-3-yl)-ntan-2-one[21] **4i**, 4-[2-(4-phenyl-cyclohex-1-enyl)-1*H*-indol-3-yl]-butan-2-one[21] **4j**, 4-phenyl-4-[2-(4-phenyl-cyclohex-1-enyl)-1*H*-indol-3-yl]-butan-2-one[21] **4k**, 4-(2-butyl-1*H*-indol-3-yl)-4-phenyl-butan-2-one[21] **4m**, 4-(5,7-dichloro-1*H*-indol-3-yl)-butan-2-one[21] **4n**, 4-(1*H*-indol-3-yl)-butan-2-one[23] **4o,** *N*-acetyl-2-ethynylaniline[38] **11**, and *N*-(2-acetyl-phenyl)-acetamide[39] **12**.

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**Supporting Information Available:** Experimental information including characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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