Gold Catalysis

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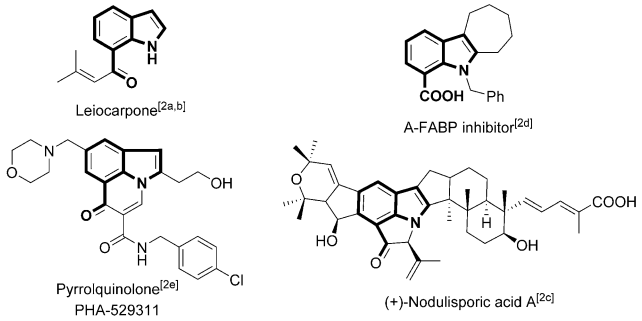
# Gold-Catalyzed C–H Annulation of Anthranils with Alkynes: A Facile, Flexible, and Atom-Economical Synthesis of Unprotected 7-Acylindoles

*Hongming Jin, Long Huang, Jin Xie, Matthias Rudolph, Frank Rominger, and A. Stephen K. Hashmi**

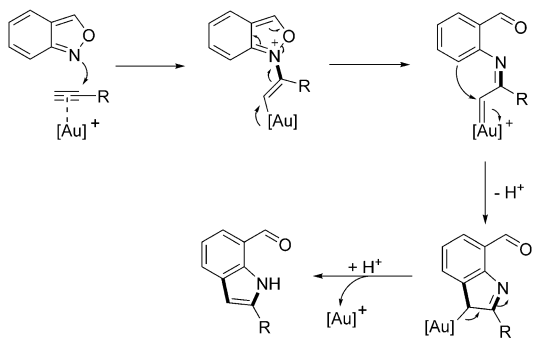
***Abstract:*** *The gold-catalyzed C–H annulation of anthranil derivatives with alkynes offers a facile, flexible, and atom-economical one-step route to unprotected 7-acylindoles. An intermediate α-imino gold carbene, generated by an intermolecular reaction, promotes ortho-aryl C–H functionalization to afford the target products. The transformation proceeds with a broad range of substrates under mild conditions. Moreover, the obtained functionalized indole products represent a versatile platform for the construction of diverse indolyl frameworks.*

Indoles have attracted immense attention owing to their ubiquitous presence in natural products, materials, and pharmaceuticals.[1] Among indoles, 7-acylindoles serve not only as a class of bioactive molecules (Scheme 1) but also as key building blocks with orthogonal chemical reactivity.[2] However, traditional methodologies[3] such as the Fischer, Larock, or Bartoli syntheses usually show low functional-group tolerance, and difficulties in installing aldehydes and ketones make it a challenge to construct 7-acylindoles. Hence, the development of a general synthetic strategy for the efficient construction of a diversified scaffold of 7-acylindole would be highly desirable.




***Scheme 1.*** Selected bioactive compounds based on 7-acylindoles.

In recent years, transition-metal-catalyzed synthesis of functionalized indoles has experienced significant development.[1f,4] Gold catalysis[5,6,7e] in particular has had a strong impact on this field of synthetic chemistry. For instance, gold-catalyzed intramolecular annulation[5] of 2-alkynyl arylazides has opened up an efficient access to indolyl[6b,d] and pseudoindoxyl[6a,c] skeletons, based on α-imino gold carbenes as key electrophilic intermediates. However, access to α-imino gold carbenes through intramolecular nitrene transfer can limit the generality and flexibility of the obtained products. Regarding this drawback, an intermolecular approach for the generation of a gold nitrene en route to functionalized heterocyclic compounds would represent an attractive strategy. In line with this principle, Davies et al. and Ye et al. were able to accomplish gold-catalyzed intermolecular cycloaddition for the preparation of polysubstituted oxazoles[7a,b] and pyrroles.[7c] Very recently, the gold-catalyzed intermolecular transformation of benzyl azides with ynamides was also reported by Ye's group.[7d] However, the α-imino gold carbenes that are produced through the intermolecular approach have so far been limited to polarized alkynes. Inspired by these reports and in continuation of our work on indole chemistry,[8] we envisioned that a gold-catalyzed intermolecular transformation of anthranil with alkynes could produce α-imino gold carbene intermediates. Based on the high electrophilicity of the α-imino gold carbenoid, an intramolecular *ortho*-aryl C–H insertion could then afford the desired 7-formyl indoles (Scheme 2). Herein, we report our results on the unprecedented gold-catalyzed C–H annulation




***Scheme 2.*** Planned gold-catalyzed annulation of anthranils with alkynes.

[*] H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger, A. S. K. Hashmi
Institut für Organische Chemie, Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail: hashmi@hashmi.de
A. S. K. Hashmi
Chemistry Department, Faculty of Science
King Abdulaziz University
Jeddah 21589, Saudi Arabia

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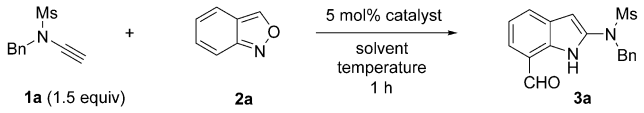
***Table 1:*** Optimization of the Reaction Conditions.[a]




**1a** (1.5 equiv) **2a** **3a**

| Entry | Catalyst | Solvent | *T* [°C] | Yield [%][b] |
|---|---|---|---|---|
| 1 | none | $ClCH_2CH_2Cl$ | RT | n.d. |
| 2 | $Ph_3PAuCl/AgNTf_2$ | $ClCH_2CH_2Cl$ | 0 | 36 |
| 3 | JohnPhosAuCl/$AgNTf_2$ | $ClCH_2CH_2Cl$ | 0 | 49 |
| 4 | $^t$BuXPhosAuCl/$AgNTf_2$ | $ClCH_2CH_2Cl$ | 0 | 33 |
| 5 | $(ArO)_3PAuCl$[c]/$AgNTf_2$ | $ClCH_2CH_2Cl$ | 0 | 64 |
| 6 | $AuBr_3$ | $ClCH_2CH_2Cl$ | 0 | 35 |
| 7 | IPrAuCl/$AgNTf_2$ | $ClCH_2CH_2Cl$ | 0 | 73 |
| 8 | IPrAuCl/$AgNTf_2$ | $ClCH_2CH_2Cl$ | −20 | 84 |
| 9 | IPrAuCl/$AgSbF_6$ | $ClCH_2CH_2Cl$ | −20 | 74 |
| 10 | IPrAuCl/$AgBF_4$ | $ClCH_2CH_2Cl$ | −20 | 58 |
| 11 | IPrAuCl/AgOTf | $ClCH_2CH_2Cl$ | −20 | 32 |
| **12** | **IPrAuCl/$AgNTf_2$** | **$PhCF_3$** | **−20** | **90 (85)**[d] |
| 13 | IPrAuCl/$AgNTf_2$ | PhMe | −20 | 81 |
| 14 | IPrAuCl/$AgNTf_2$ | PhCl | −20 | 71 |
| 15 | IPrAuCl/$AgNTf_2$ | $CH_2Cl_2$ | −20 | 72 |
| 16 | IPrAuCl/$AgNTf_2$ | $CH_3CN$ | −20 | 22 |
| 17 | IPrAuCl/$AgNTf_2$ | THF | −20 | 46 |
| 18 | IPrAuCl/$AgNTf_2$ | $Et_2O$ | −20 | 30 |

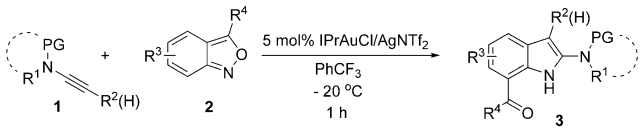
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol); a solution of **1a** (1 mL) was added over 3 mins to a solution of **2a** (1 mL) and the catalyst at the given temperature, with a reaction time of 1 h. [b] Measured by $^1$H NMR with 4-(dimethylamino)benzaldehyde as the internal standard. n.d. = not detected. [c] Ar = 2,4-di-*tert*-butylphenyl. [d] Yield of isolated product.

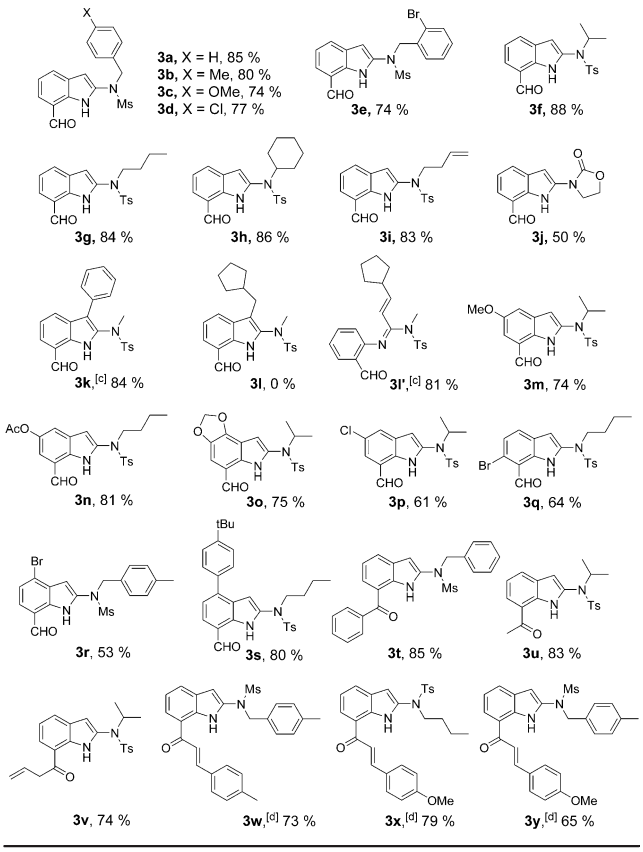
of anthranils with alkynes under mild reaction conditions. Notably, the reaction also proceeds smoothly with ynamides, non-polarized alkynes, and non-terminal alkynes. The process enables the facile, flexible, and atom-economical synthesis of 7-acylindolyl frameworks.

Initially, we performed a screening of the reaction conditions with ynamide **1a**, since such substrates usually possess high reactivity in gold-catalyzed reactions as a result of their electronic properties[7a–d,9] (Table 1). Treatment of ynamide **1a** and anthranil **2a** with $Ph_3PAuCl/AgNTf_2$ at 0 °C afforded the expected product **3a** in 36 % yield (entry 2). The control experiment without catalyst showed no reaction even at room temperature (entry 1). Among the screened gold catalysts, the catalyst with an NHC ligand (entry 7) showed higher activity than those with phosphane and phosphite ligands (entries 3–5). $AuBr_3$ was also less efficient (entry 6). The yield increased to 84 % upon decreasing the reaction temperature to −20 °C (entry 8). Further improvement was achieved by screening different silver salts (entries 9 and 10) and solvents (entries 11–18). Finally, up to 90 % yield of **3a** was gained by employing 5 mol % IPrAuCl/$AgNTf_2$ as the catalyst in $PhCF_3$ at −20 °C (entry 12).

Under the optimized conditions, the scope of the reaction was explored (Table 2). Ynamides reacted with excellent to moderate yields (**3a**–**3j**). A broad set of substituents at the ynamide nitrogen atom turned out to be compatible. 7-Formyl indole **3e**, which was prepared from *N*-(2-bromophenyl) ynamide in good yield, is a potential precursor for the synthesis of 1,2-fused indoles according to a method from

***Table 2:*** Scope of the synthesis of anthranils with ynamides.[a,b]




[a] Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol); a solution of **1** (1 mL) was added over 3 min to a solution of **2** (1 mL) and 5 mol % IPrAuCl/$AgNTf_2$ at −20 °C, and then the mixture was stirred for 1 h. [b] Yield of isolated product. [c] Reaction temperature: 65 °C; 4 Å MS. [d] A mixture of $ClCH_2CH_2Cl$ (0.5 mL) and $PhCF_3$ (1.5 mL) as solvent.

Perumal's group.[4g] Among the tested protecting groups on the ynamides, besides tosyl and mesyl, the oxazolidinone-derived ynamide also underwent annulation to afford the product **3j** in moderate yield. Non-terminal ynamides were also investigated. While the targeted product **3k** was prepared from phenyl-substituted ynamide in good yield, the alkyl-substituted ynamide afforded the unsaturated product **3l′** rather than **3l**. Various substituted anthranils were applied for the synthesis of diversified 7-acylindoles (**3m**–**3y**). Owing to the mild reaction conditions, a large array of functional groups, including chloride (**3p**), bromide (**3q**, **3r**), acetal (**3o**), ester (**3n**), alkene (**3v**), and α,β-unsaturaed ketone (**3w**–**3y**) substituents were all tolerated, which enormously enhances the range of obtained substrates. The reaction of anthranils with electron-donating groups usually proceeded with higher yields, which suggests an electrophilic aromatic substitution mechanism. For a structural confirmation of the 7-acylindolyl framework, a single-crystal X-ray structure analysis[10] of **3q** was conducted (Figure 1).

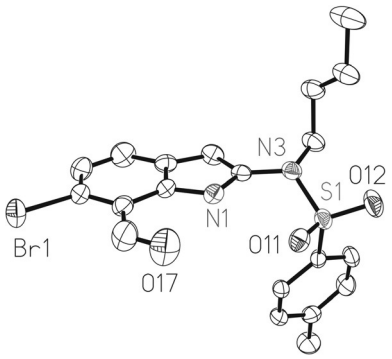
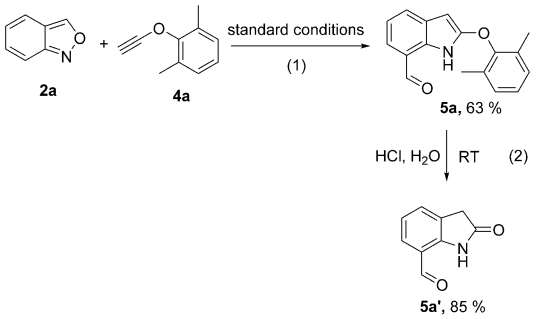



***Figure 1.*** Solid-state molecular structure of **3q**.



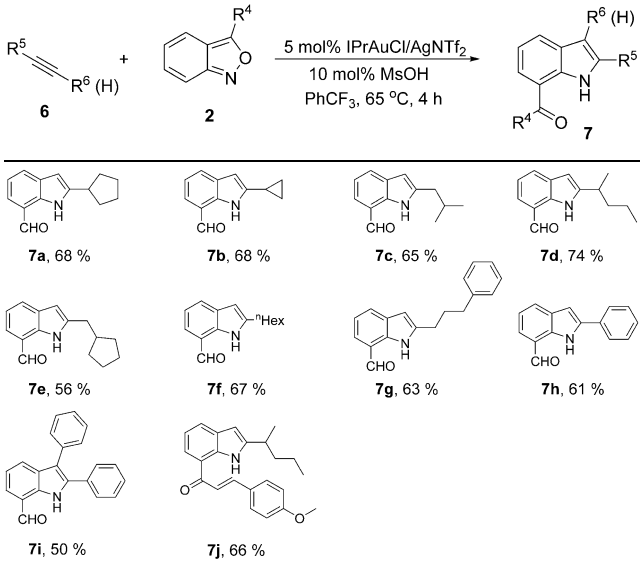

***Scheme 3.*** The reaction of anthranil with aryl alkynyl ether.

The transformation was not limited to ynamides. Treatment of anthranil with aryl alkynyl ether **4a** under the standard reaction condition furnished the 2-oxo product **5a** in 63% yield (Scheme 3, Step 1). 7-Formyl oxindole **5a′**, a promising novel antioxidant,[11] was easily synthesized through hydrolysis of **5a** under acid condition (Scheme 3, Step 2).

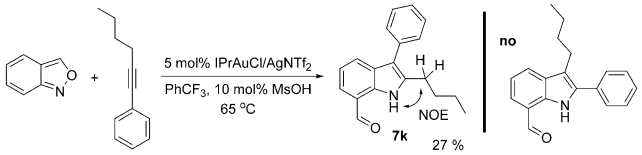
To extend the substrate scope further, non-polarized alkynes were used too. However, owing to their decreased reactivity, the reaction did not work under the standard conditions. But by raising the temperature and extending the reaction time, the yield of the expected product could be gradually increased.[12] A more efficient conversion rate of anthranil was enabled by the addition of 10 mol% MsOH (which might facilitate the deauration process) and by using an excess of alkyne (MsOH alone is not catalytically active). Following this procedure afforded the products in moderate yields. Under the adjusted conditions, both alkyl and aryl alkynes were suitable for the construction of C2-functionalyzed and C2,C3-diarylated products (Table 3, **7a**–**7i**). The 7-substituted indole **7j**, which is a key precursor for synthesizing pyrrolquinolone derivatives,[13] could conveniently be prepared despite the conjugated double bond.

Finally, we used an unsymmetrically alkyl/aryl-substituted alkyne. In this case, a low yield of 2-alkyl-3-aryl indol **7k** was obtained (assigned by NOE) and no other indole isomer was formed (Scheme 4). The low yield might result from a competing hyride-shift pathway if the carbenoid is formed next to the alkyl tether (similar to the formation of **3l′**).

***Table 3:*** Scope with respect to the alkynes.[a,b]

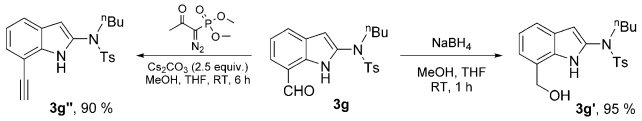



[a] Reaction conditions: **6** (0.8 mmol) and **2** (0.2 mmol) were heated for 4 h at 65 °C in 2 mL $PhCF_3$. [b] Yield of isolated product.




***Scheme 4.*** Conversion of an unsymmetrical alkyne.

Owing to the presence of both electrophilic and nucleophilic sites, 7-formyl indoles have been utilized as flexible scaffolds for the syntheses of 1,7-fused indoles, most of which exhibit significant biological activity.[13,14] While numerous studies have focused on the reactions of indoles with electrophiles, we focused our attention on nucleophilic transformations of 7-acyl indoles. For instance, reduction of **3g** afforded the 7-alkylated product **3g′**, and the unprotected 7-alkynyl indole **3g″** could be obtained easily in excellent yield through Seyferth–Gilbert homologation (Scheme 5).




***Scheme 5.*** Application to the preparation of diverse 7-substituted indoles.

In summary, a novel, short, and atom-economical synthesis of 7-acyl indoles through gold-catalyzed C–H annulation of anthranils with alkynes was developed. The substrate scope is remarkably broad and the benign reaction conditions tolerate a diverse set of functional groups, which further strengthens the synthetic impact of this method. The obtained

indoles are highly interesting building blocks, for example, for the synthesis of 7-substiuted indolyl and fused indolyl frameworks. Based on the availability of the starting materials and the enormous gain in molecular complexity, we believe that this method will serve as powerful tool for organic synthesis.

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**Keywords:** alkynes · C—H functionalization · gold carbenoids · gold catalysis · indoles

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