$AuCl_3$-Catalyzed Tandem Reaction of *N*-(*o*-Alkynylphenyl)imines: A Modular Entry to Polycyclic Frameworks Containing an Indole Unit

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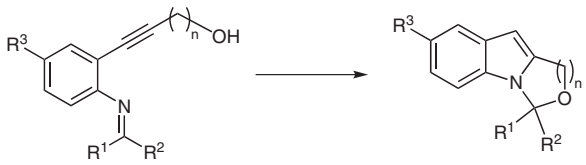
Abstract: A highly efficient tandem cyclization reaction of *N*-(*o*-alkynylphenyl)imines leading to ring-fused indoles was developed by using gold(III) as a catalyst under extremely mild reaction conditions.

Key words: cyclization, gold, indoles, *N*-(*o*-alkynylphenyl)imines

Indoles are important chemicals that exhibit a wide range of biological activities. They are found as key structural elements in many naturally occurring compounds.[1] As a consequence, much attention has been paid to the synthesis of indole derivatives. In addition to classical methods (e.g., the Fischer synthesis,[2] the Reissert synthesis,[3] the Madelung synthesis[4]), numerous transition-metal-catalyzed heteroannulation reactions have been developed with remarkable improvements in terms of efficiency and wide scope of application.[5] A particularly attractive methodology is based on transition-metal-catalyzed cyclization of *o*-alkynylaniline derivatives.[6] Hiroya developed an efficient Cu(II)-catalyzed indoles formation by cyclization of 2-ethynyl aniline derivatives.[7] Yamamoto and coworkers reported that tandem cyclization of 2-alkynylaniline proceeded successfully to give the nucleophile incorporated indoles in the presence of certain nucleophiles, such as allyl carbonate and alcohol.[8] Nevertheless, the development of synthetic routes that allow the facile assembly of indole derivatives under mild conditions still remains an important objective.

Previous investigations have shown that Au(III) salts and Au(I) complexes display considerable catalytic activity under moderate conditions.[9] The activation of alkynes or allenes with carbophilic, Lewis acidic gold salts is the most widespread application of homogeneous gold catalysis, and it is also utilized for the construction of carbocyclic or heterocyclic compounds.[10] Recently, the design of gold-catalyzed tandem nucleophilic additions that preserve atom economy in a one-pot reaction has attracted attention because of the application to efficient construction of molecular structures.[11] As a continuation of our interest in the design and discovery of new reactions for the synthesis of heterocycles,[12] we envisioned that *N*-(*o*-alkynylphenyl)imines **1** might cyclize via the formation of an iminium ion, which is trapped by a tethered nucleophile to afford ring-fused indoles in a novel tandem reaction process (Scheme 1). Herein, we present a convenient and efficient method for the synthesis of ring-fused indoles starting from compounds of type **1** catalyzed by gold(III) under mild conditions.



Scheme 1

We initially examined the reaction of 3-[2-(diphenyl-methyleneamino)phenyl]prop-2-yn-1-ol (**1a**) using different metal catalysts in CH_2Cl_2 at room temperature (Table 1). To our delight, the ring-fused indole **2a** was formed in all cases as the only major product. Lewis acids such as $Cu(OTf)_2$, AgO_2CCF_3, $Hg(O_2CCF_3)_2$, and $AgBF_4$ were active, but only modest yields were obtained after long reaction time. In contrast, employment of $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Cu(OAc)_2$, and CuI catalysts under these conditions resulted in low yields, and the reactions were generally much more sluggish. Significantly, we found that $AuCl_3$ was a particularly efficient catalyst for this reaction. With only 3 mol% of this catalyst, the ring-fused indole formation was complete after less than 30 minutes at room temperature to afford **2a** in 90% yield (Table 1, entry 4). It was found that decreasing the catalyst load to 1 mol% of $AuCl_3$ had virtually no effect on the reaction course, producing **2a** in 84% yield (Table 1, entry 5), though the reaction was slower. The molecular structure of **2a** was confirmed by single-crystal X-ray diffraction analysis (Figure 1).[13]

Next we investigated the annulation reaction of various *N*-(*o*-propynolphenyl)imines **1**. The results summarized in Table 2 proved that this sequential reaction indeed provided a straightforward entry to a variety of fused tricyclic compounds with an indole unit in good to high yields. The substituent on the aromatic ring of R^1 and R^2 did not affect the efficiency of the reaction. For imines **1** having an electron-withdrawing or an electron-donating group on the benzene ring, these reactions proceeded smoothly to give the corresponding cyclization products. Employing *N*-(*o*-propynolphenyl)phenylimine as a substrate, the annula-

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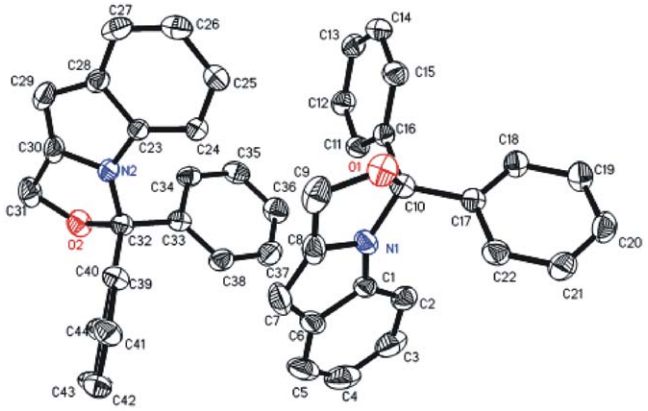
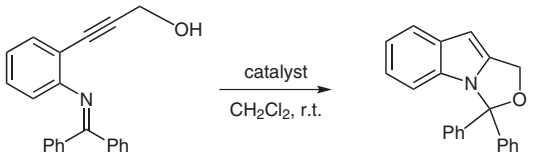


Figure 1

Table 1 Effect of Catalyst on the Reaction of **1a** To Give **2a**[a]



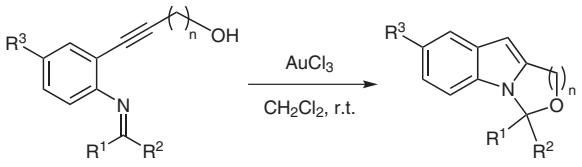
Entry	Catalyst	Amount (mol%)	Time (h)	Yields (%)[b]
1	–	–	24	0
2	$Cu(OTf)_2$	3	3	76
3	AgO_2CCF_3	3	3	81
4	$AuCl_3$	3	0.5	90
5	$AuCl_3$	1	2	84
6	$Pd(OAc)_2$	5	24	45 (43)[c]
7	$PdCl_2(PPh_3)_2$	5	24	48 (38)[c]
8	$Hg(O_2CCF_3)_2$	10	10	57
9	$AgBF_4$	3	3	82
10	CuI	10	24	37 (50)[c]
11	$Cu(OAc)_2$	10	24	21 (71)[c]

[a] All of the reactions were carried out on a 0.5 mmol scale.
[b] Isolated yields.
[c] Starting material was recovered in parentheses.

tion failed, and a complex mixture of unidentified products was obtained under the reaction conditions (Table 2, entry 4). This transformation can be successfully extended to a variety of *N*-(*o*-hydroxyalkynylphenyl)imines **1** leading to the generation of the corresponding ring-fused indoles in 58–93% yield (Table 2, entries 11–26).[14] Their structures were assigned on the basis of ^{1}H NMR, ^{13}C NMR, IR spectra, and MS data.

On the basis of the above observations, a plausible mechanisms is proposed for this novel Au(III)-catalyzed transformation (Scheme 2). A cationic Au(III) species first coordinates to the triple bond to generate an intermediate

Table 2 Gold(III)-Catalyzed Tandem Cyclization of **1**[a]

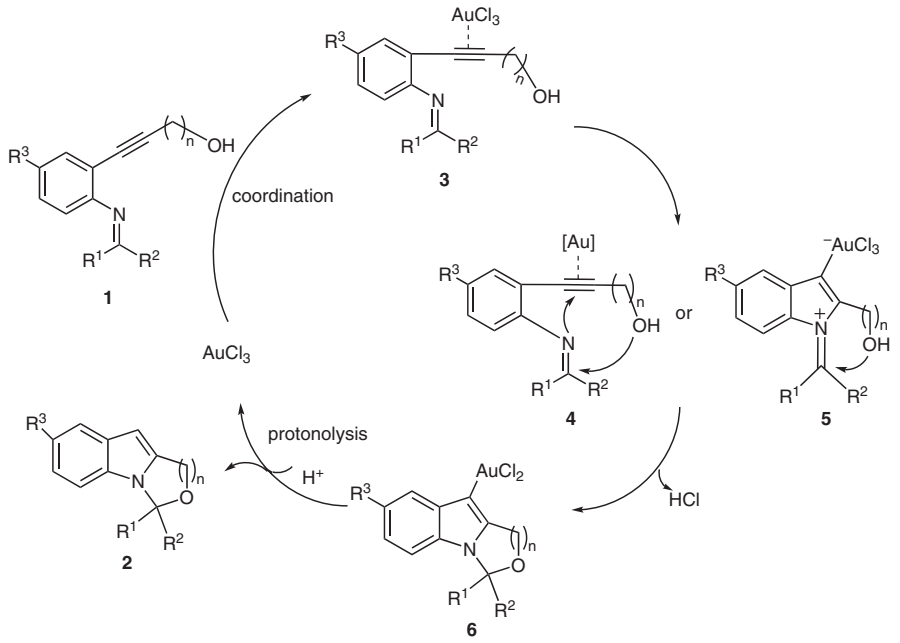


1 **2**

Entry	R^1	R^2	R^3	n	Yields (%)[b]
1	Ph	Ph	H	1	**2a**, 90
2	4-FC_6H_4	4-FC_6H_4	H	1	**2b**, 88
3	Ph	4-ClC_6H_4	H	1	**2c**, 91
4	Ph	H	H	1	complex[c]
5	Ph	3-$MeOC_6H_4$	H	1	**2d**, 79
6	Ph	4-$MeOC_6H_4$	H	1	**2e**, 83
7	Ph	Ph	Me	1	**2f**, 94
8	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	1	**2g**, 80
9	Ph	4-ClC_6H_4	Me	1	**2h**, 89
10	4-FC_6H_4	4-FC_6H_4	Me	1	**2i**, 90
11	Ph	Ph	H	2	**2j**, 92
12	4-FC_6H_4	4-FC_6H_4	H	2	**2k**, 89
13	Ph	4-ClC_6H_4	H	2	**2l**, 87
14	Ph	3-$MeOC_6H_4$	H	2	**2m**, 84
15	Ph	H	H	2	**2n**, 58
16	Ph	Ph	Me	2	**2o**, 93
17	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	2	**2p**, 78
18	Ph	4-ClC_6H_4	Me	2	**2q**, 91
19	4-FC_6H_4	4-FC_6H_4	Me	2	**2r**, 90
20	Ph	Ph	H	3	**2s**, 88
21	4-FC_6H_4	4-FC_6H_4	H	3	**2t**, 92
22	Ph	4-ClC_6H_4	H	3	**2u**, 87
23	Ph	Ph	Me	3	**2v**, 90
24	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	3	**2w**, 91
25	Ph	4-ClC_6H_4	Me	3	**2x**, 88
26	4-FC_6H_4	4-FC_6H_4	Me	3	**2y**, 89

[a] Unless noted, all of the reaction was carried out using **1** (0.5 mmol) and $AuCl_3$ (3 mol%) at r.t. for 30 min.
[b] Isolated yields.
[c] Decomposition of starting material was observed.

3, which enhances the electrophilicity of the alkyne. The subsequent domino nucleophilic attack/*anti-endo-dig* cyclization affords organogold intermediate **6**. Protonolysis of the resulting organogold intermediate **6** gives product **2**



Scheme 2

and regenerates the gold catalyst. Alternatively, the reaction may involve the intermediate iminium ion **5**,[15] which is formed by the intramolecular addition of the nitrogen atom of the imine to the gold-coordinated alkynes. The iminium ion **5** undergoes the subsequent reaction with a tethered nucleophile followed by protonation to regenerate the Au(III) catalyst and afford the final product **2**.

In conclusion, we have developed a gold-catalyzed domino reaction of *N*-(*o*-alkynylphenyl)imines that provides an efficient route to ring-fused indoles under mild conditions. The substrates can be readily prepared from the corresponding *o*-iodoanilines, ketones, and alkynes. Further studies to elucidate the precise mechanism of this reaction and to extend the scope of synthetic utility are in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) For reviews on indole chemistry, see: (a) Sundberg, R. L. *Indoles*; Academic Press: London, **1996**. (b) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*; Pergamon Press: Oxford, **2000**, Chap. 4. (c) Joule, J. A. In *Science of Synthesis (Houben-Weyl: Methods of Molecular Transformations)*, Vol. 10; Thomas, E. J., Ed.; Thieme: Stuttgart, **2000**. (d) For other references, see: Li, J. J.; Gribble, G. W. *In Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, **2000**, Chap. 3. (e) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (f) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, **1996**.

(2) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**. (b) Shriner, R. L.; Ashley, W. C.; Welch, E. *Org. Synth., Coll. Vol. III*; Wiley: New York, **1955**, 725–727; and references therein. (c) Rogers, C. U.; Corson, B. B. *Org. Synth., Coll. Vol. IV*; Wiley: New York, **1963**, 884.

(3) Noland, W. E.; Baude, F. J. *Org. Synth. Collect. Vol. V*; Wiley: New York, **1973**, 567.

(4) Tyson, F. T. *Org. Synth. Collect. Vol. III*; Wiley: New York, **1955**, 479.

(5) For review on the palladium-catalyzed indole synthesis, see: (a) For selected examples, see: Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Pal, M.; Subramanian, V.; Batchu, V. R.; Dager, I. *Synlett* **2004**, 1965. (c) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017. (d) Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693. (e) Yu, M. S.; Leon, L. L.; McGuire, M. A.; Botha, G. *Tetrahedron Lett.* **1998**, *39*, 9347. (f) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2501. (g) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (h) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412. (i) Yamazaki, K.; Kondo, Y. *Chem. Commun.* **2002**, 210.

(6) For transition-metal-catalyzed cyclizations in indole synthesis, see the following: Cu(I): (a) Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem.* **1996**, *61*, 5804. (b) Cu(II): Nishikawa, T.; Ishikawa, M.; Isobe, M. *Synlett* **1999**, 123. (c) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841. (d) Hg(stoichiometric): Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277. (e) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218.

(7) (a) Hiroya, K.; Itoh, S.; Ozawa, M. *J. Org. Chem.* **2004**, *69*, 1126. (b) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277.

(8) (a) Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11940. (b) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662. (c) Kamijo, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 3230. (d) Kamijo, S.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 4764.

(9) For reviews on gold-catalyzed reactions, see: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (c) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (e) Gorin, D. J.; Toste, F. D. *Nature (London)* **2007**, *446*, 395. (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (g) Marion, N.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2750. (h) Hashmi, A. S. K. *Nature (London)* **2007**, *449*, 292. (i) Dyker, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4237. (j) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (k) Brown, R. C. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 850. (l) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2005**, *44*, 6990. (m) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 200. (n) Li, Z. J.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (o) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, *(v)*, 6.

(10) (a) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (b) Barluenga, J.; Dieguez, A.; Fernandez, A.; Rodriguez, F.; Fananas, F. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2091. (c) Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727. (d) Hashmi, A. S. K.; Salathe, R.; Frey, W. *Synlett* **2007**, 1763. (e) Dube, P.; Toste, D. F. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (f) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620. (g) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485. (h) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (i) Brouwer, C.; Rahaman, R.; He, C. *Synlett* **2007**, 1785. (j) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473. (k) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081. (l) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (m) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. (n) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; *Angew. Chem.* **2000**, *112*, 2382.

(11) (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (b) Leseurre, L.; Toullec, P. Y.; Genet, J. P.; Michelet, V. *Org. Lett.* **2007**, *9*, 4049. (c) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1141. (d) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070. (e) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (f) Zhang, J.; Schmalz, H. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 6704. (g) Lin, C. C.; Teng, T. M.; Odedra, A.; Liu, R. S. *J. Am. Chem. Soc.* **2007**, *129*, 3798. (h) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489.

(12) (a) Fu, W. J.; Huang, X.; Li, Y. *Synlett* **2007**, 321. (b) Huang, X.; Fu, W. J. *Tetrahedron Lett.* **2008**, *49*, 2359. (c) Fu, W. J.; Huang, X. *Tetrahedron Lett.* **2008**, *49*, 562.

(13) The crystal data of **2a** has been deposited in CCDC with number 710261. X-ray data for compound **2a**: $C_{44}H_{34}N_2O_2$; *Mw* = 622.73; triclinic; space group: P-1; lattice parameters: *a* = 10.5127 (12) Å, *b* = 11.3097 (13) Å, *c* = 14.1538 (16) Å, α = 85.2950 (10)°, β = 81.3660 (10)°, γ = 78.5540 (10)°, *V* = 1628.3 (3) Å^3; D_{calc} = 1.270 g/cm^3; *F*000 = 656; residuals: R; *Rw*: 0.0578, 0.1065.

(14) **General Procedure**
To a solution of *N*-(*o*-alkynylphenyl) imines **1** (0.5 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of $AuCl_3$ (3 mol%) in MeCN (0.05 M). The mixture was stirred for 30 min at r.t. After evaporation of the solvent, the residue was purified by column chromatography on SiO_2 (PE–EtOAc, 25:1) to afford **2**.

(15) (a) Kamijo, S.; Sasaki, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 35. (b) Halim, R.; Scammells, P. J.; Flynn, B. L. *Org. Lett.* **2008**, *10*, 1967.