

Divergent Outcomes of Gold(I)-Catalyzed Indole Additions to 3,3-Disubstituted Cyclopropenes

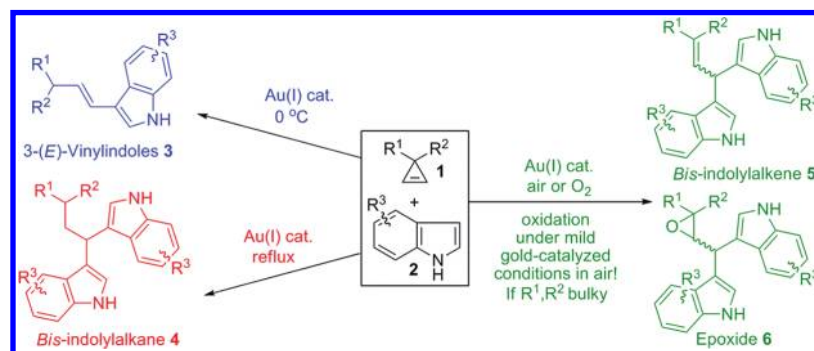
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ABSTRACT



Depending on the conditions employed, gold(I)-catalyzed addition of indoles to 3,3-disubstituted cyclopropenes can be controlled to yield either 3-(*E*)-vinylindoles (**3**) or bis-indolylalkanes (**4**). If the cyclopropene substituents are sterically bulky, unprecedented gold-catalyzed oxidation under air occurs to yield bis-indolylalkene (**5**) and epoxide (**6**) at room temperature.

The indole skeleton is a key structural unit in many natural products and pharmaceutical compounds. For example, bis-indolylalkanes have been shown to exhibit potent antitumor activity¹ and vinylindoles are valuable synthetic building blocks² toward biologically active building blocks such as indole alkaloids,³ carbazoles,⁴ and carbolines.⁵ In particular, 3-vinylindoles⁶ are useful dienes in [4 + 2] cycloadditions toward polycyclic heterocycles.⁷

In the field of gold(I) catalysis,⁸ indole derivatives have been explored as intermolecular nucleophiles for additions to unactivated alkynes and allenes.⁹ In the case of unactivated alkynes, indole reacts twice to yield the corresponding bis-indolylalkanes **7** (Scheme 1).¹⁰ Gold(I)-catalyzed addition of indole derivatives to allenes appears to be a bit more difficult:¹¹ allenes were only reported to react with more nucleophilic indoles (e.g., *N*-alkylated **8**) to form 3-allylindoles **9**.¹²

(1) For the latest review on bis-indolylalkanes, see: Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250 and references cited therein.

(2) For a review, see: Pindur, U. *Heterocycles* **1988**, *27*, 1253.

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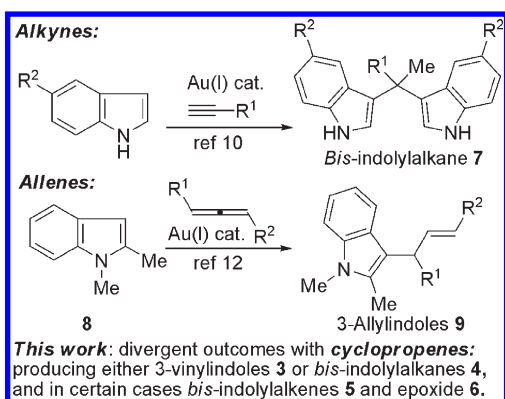
(6) For selected recent examples, see: (a) Low, K. H.; Magomedov, N. A. *Org. Lett.* **2005**, *7*, 2003. (b) Fridkin, G.; Boutard, N.; Lubell, W. D. *J. Org. Chem.* **2009**, *74*, 5603. (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (d) Reddy, M. V. R.; Billa, V. K.; Pallela, V. R.; Mallireddigari, M. R.; Boominathan, R.; Gabriel, J. L.; Reddy, E. P. *Bioorg. Med. Chem.* **2008**, *16*, 3907.

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Scheme 1. Gold(I)-Catalyzed Indole Additions to Unactivated Alkynes and Allenes

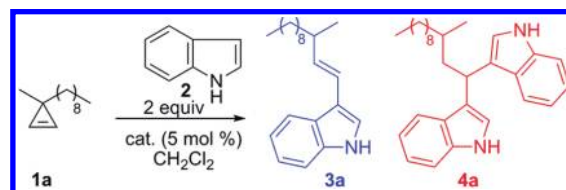


One of the research efforts within our group is to explore the diverse chemistry of gold-catalyzed reactions with cyclopropenes.^{13–15} In this communication, we present a gold(I)-catalyzed *controlled* approach toward either 3-(*E*)-vinylindoles **3** or *bis*-indolylalkane **4** from indole additions to 3,3-disubstituted cyclopropenes **1**. Furthermore, we disclose a highly unusual outcome when both substituents R^1, R^2 on **1** are bulky (e.g., Cy): in this case, oxidation products *bis*-indolylalkene **5** and epoxide **6** are observed with only air as the oxidant.

Our investigations commenced with screening conditions using indole and cyclopropene **1a** (entries 1–3, Table 1). Intriguingly, varying levels of **3a** and **4a** were observed, depending on the catalyst and reaction conditions employed. For example, at rt, PPh_3AuNTf_2 ¹⁶ favored formation of **4a** whereas catalyst **10**¹⁷ favors **3a**.

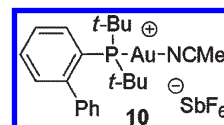
The proposed mechanism for the formation of **3** and **4** is shown in Scheme 2. Gold(I) catalyzes the ring opening of

Table 1. Initial Studies: Gold(I)-Catalyzed Intermolecular Reaction between Cyclopropene **1a** and Indole **9**^a



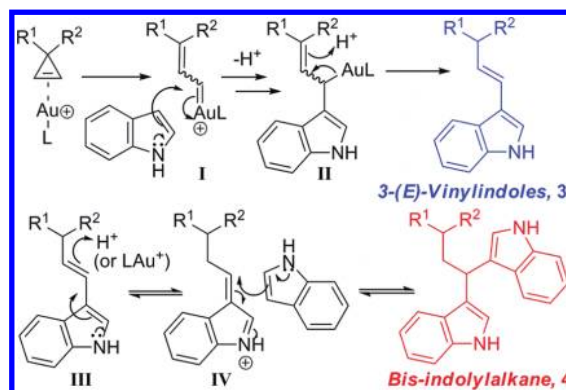
entry	catalyst	temp (°C)	time (h)	3a: 4a ^b	yield (%)
1	PPh_3AuNTf	rt	3	20:80	53% ^c 4a
2	10	rt	3	88:12	59% ^d 3a
3 ^e	10	0	3	80:20	52% ^d 3a
4	10	0	3	>95:5	91% ^d 3a
5 ^f	10	reflux	42	1:99>	76% ^d 4a

^a See Supporting Information for full optimization studies. ^b Determined by ¹H NMR analysis of the crude mixture. ^c Isolated yield. ^d NMR yield by comparison with an internal standard. ^e 1 equiv of indole **2** employed. ^f 2.2 equiv of indole **2** employed.



cyclopropene to form a carbene/cationic intermediate **I**,^{13a,15f,15g} which is trapped by indole to give intermediate **II**. **II** then deaurates/protonates to yield vinylindole **3**. Under optimized conditions, vinylindole **3** can be further activated by Au(I) or H^+ (**III**) to allow the attack of a second equivalent of indole with intermediate **IV** to produce *bis*-indolylalkane **4**.¹⁸ To ascertain if **3**→**4** is Au(I) or H^+ catalyzed,^{6b} isolated **3h** was resubjected to 2-methylindole and catalyst **10** in the presence and absence of 2,6-di-*tert*-butylpyridine (to quench any H^+ that might be present). *Bis*-indolylalkane **4h** is only successfully produced in the absence of 2,6-di-*tert*-butylpyridine, implying that **3**→**4** is either H^+ catalyzed or assisted. Deuterium

Scheme 2. Proposed Mechanism for the Gold(I)-Catalyzed Indole Additions to Cyclopropenes



(10) (a) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (b) Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *J. Organomet. Chem.* **2009**, *694*, 546. With propargyl carboxylates, indoles trap the rearranged gold(I)-carbene intermediates to form vinylindoles: (c) Amijs, C. H. M.; López-Carrillo, V.; Echavarren, A. M. *Org. Lett.* **2007**, *9*, 4021. For intramolecular, see: (d) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.

(11) Tarselli, M. A.; Liu, A.; Gagne, M. R. *Tetrahedron* **2009**, *65*, 1785.

(12) (a) Toups, K. L.; Liu, G. T.; Widenhoefer, R. A. *J. Organomet. Chem.* **2009**, *694*, 571. For enantioselective version: (b) Wang, M.-Z.; Zhou, C.-Y.; Guo, Z.; Wong, L.-M.; Wong, M.-K.; Che, C.-M. *Chem.—Asian. J.* **2011**, *6*, 812. For additions to allenamides: (c) Kimber, M. C. *Org. Lett.* **2010**, *12*, 1128.

(13) (a) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2008**, 6405. (b) Hadfield, M. S.; Lee, A.-L. *Org. Lett.* **2010**, *12*, 484. (c) Hadfield, M. S.; Bauer, J. T.; Glen, P. E.; Lee, A.-L. *Org. Biomol. Chem.* **2010**, *8*, 4090. (d) Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2011**, 47, 1333.

(14) Recent reviews on cyclopropene chemistry: (a) Zhu, Z.-B.; Wei, Y.; Shi, M. *Chem. Soc. Rev.* **2011**, *40*, 5534. (b) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117.

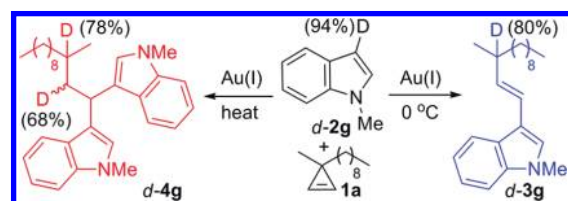
(15) For other gold(I)-catalyzed reactions with cyclopropenes, see: (a) Zhu, Z.-B.; Shi, M. *Chem.—Eur. J.* **2008**, *14*, 10219. (b) Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956. (c) Li, C.; Zeng, Y.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 6413. (d) Miede, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 4144. (e) Seraya, E.; Slack, E.; Ariafard, A.; Yates, B. F.; Hyland, C. J. T. *Org. Lett.* **2010**, *12*, 4768. (f) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510. (g) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., III; Toste, F. D. *Nature Chem.* **2009**, *1*, 482. Review: (h) Miede, F.; Meyer, C.; Cossy, J. *Beilstein J. Org. Chem.* **2011**, *7*, 717.

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labeling studies using 94% D-labeled *d*-**2g** support our proposed mechanism (Scheme 3).

Since our proposed mechanism can account for the formation of **4** from **3** (Scheme 2), we argued that the reaction conditions could in principle be controlled to be trapped at the vinylindole **3** stage, or forced to completion to produce the *bis*-indolylalkanes **4**. To this end, the conditions were successfully optimized to selectively produce either **3a** or **4a** (entries 4–5, Table 1; for full optimization studies, see Supporting Information (SI)). Pleasingly, the vinylindole **3a** could be produced in a high 91% yield.¹⁹ It is interesting to note that 2 equiv of indole **2** produce optimal yields of vinylindole **3a** (*cf.* entry 3) and it is the extended time and temperature that drive the reaction fully toward **4a**. With the two optimized conditions in hand, we set about exploring the scope and generality of the reaction.

Scheme 3. Deuterium Labelling Studies



A series of different indoles and substrates were successfully employed to form vinylindoles **3a–n** (Table 2, entries 1–14). Both electron-donating and -withdrawing substituents are viable nucleophiles (entries 2–6) as are N-Me and 2-substituted indoles (entries 7 and 8). The substituents on the cyclopropene can also be varied to afford vinylindoles **3i–n** in good yields (entries 9–14). Even an aryl substituted cyclopropene, which can undergo intramolecular rearrangement,^{13a,15a,15b} reacts smoothly to produce **3k** (entry 11). Vinylindole **3** is still formed in good yields if one of the substituents **R**² is bulky (entries 12–13), but if both **R**¹ and **R**² become progressively bulkier (entries 14–15), the yield of **3** drops (*vide infra*).

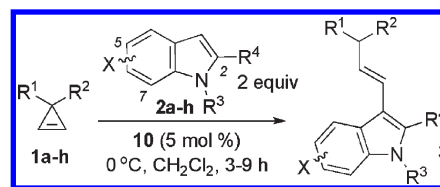
Switching the conditions to a higher temperature and longer time allows for the formation of a series of the corresponding *bis*-indolylalkanes **4a–4n** (Table 3). However, no **4o** is observed with bulky (**R**¹, **R**² = Cy) substituents (entry 15). Instead, oxidation products **5** and **6** are surprisingly observed. Since gold(I) is usually reported to be stable to oxidation by air at RT,⁸ formation of oxidation products **5** and **6** under mild RT conditions is highly unusual.²⁰ Control reactions carried out under O₂, air,

(17) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146.

(18) Controls for **1**→**3**: (i) TfOH instead of Au(I) results in no reaction; (ii) addition of DBU to the Au(I)-catalyzed reaction still successfully forms the 3-vinylindole **3**, implying acid catalysis is not involved.

(19) NMR yields as *alkyl* substituted 3-vinylindoles are known to have limited stability and will decompose readily upon standing and/or isolation: see ref 6a. For further details, see Supporting Information.

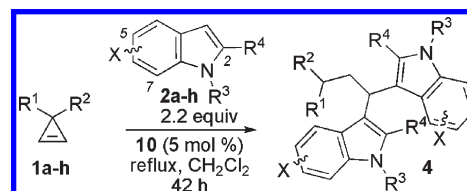
Table 2. Gold(I)-Catalyzed Synthesis of 3-(*E*)-Vinylindoles **3**



entry	R ¹	R ²	1	indole 2	yield (%) ^a
1	Me	(CH ₂) ₈ Me	1a	indole 2a	91 3a
2	Me	(CH ₂) ₈ Me	1a	5-F-indole 2b	72 3b
3	Me	(CH ₂) ₈ Me	1a	5-OMe-indole 2c	65 3c
4	Me	(CH ₂) ₈ Me	1a	5-Cl-indole 2d	77 3d
5	Me	(CH ₂) ₈ Me	1a	6-Cl-indole 2e	66 3e ^c
6	Me	(CH ₂) ₈ Me	1a	7-Et-indole 2f	63 3f
7 ^b	Me	(CH ₂) ₈ Me	1a	<i>N</i> -Me-indole 2g	91 3g
8	Me	(CH ₂) ₈ Me	1a	2-Me-indole 2h	64 3h
9 ^b	Me	(CH ₂) ₂ Ph	1b	indole 2a	81 3i
10 ^b	Me	Bn	1c	indole 2a	73 3j
11 ^d	Me	Ph	1d	indole 2a	83 3k
12	Me	Cy	1e	indole 2a	70 3l ^e
13	Me	Ad	1f	indole 2a	81 3m ^e
14 ^d	Bn	<i>i</i> -Pr	1g	indole 2a	28 3n ^f
15	Cy	Cy	1h	indole 2a	7 3o ^g

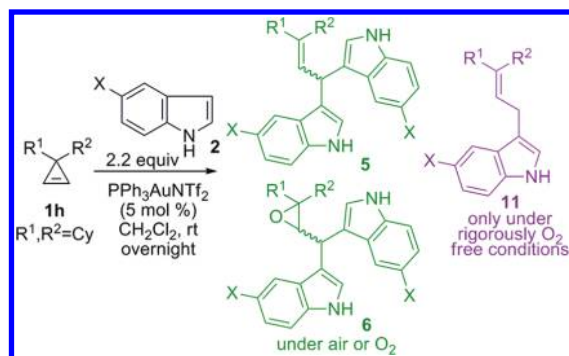
^a NMR yield with an internal standard. ¹⁹ All reactions carried out in air unless otherwise stated. ^b 1–1.05 equiv of indole **2** used. ^c Reaction time 16.5 h. ^d 5 equiv of indole **2** used. ^e Trace side products: **5/6**. ^f Other products **5** (15%) and **6** (28%). ^g Other products **5** (18%) and **6** (10%).

Table 3. Gold(I)-Catalyzed Synthesis of *Bis*-indolylalkanes **4**



entry	R ¹	R ²	1	indole 2	yield (%) ^a
1	Me	(CH ₂) ₈ Me	1a	indole 2a	69 4a
2	Me	(CH ₂) ₈ Me	1a	5-F-indole 2b	67 4b
3	Me	(CH ₂) ₈ Me	1a	5-OMe-indole 2c	60 4c
4	Me	(CH ₂) ₈ Me	1a	5-Cl-indole 2d	65 4d
5	Me	(CH ₂) ₈ Me	1a	6-Cl-indole 2e	48 4e
6	Me	(CH ₂) ₈ Me	1a	7-Et-indole 2f	51 4f
7	Me	(CH ₂) ₈ Me	1a	<i>N</i> -Me-indole 2g	71 4g
8	Me	(CH ₂) ₈ Me	1a	2-Me-indole 2h	57 4h
9	Me	(CH ₂) ₂ Ph	1b	indole 2a	69 4i
10	Me	Bn	1c	indole 2a	61 4j
11 ^b	Me	Ph	1d	indole 2a	62 4k
12	Me	Cy	1e	indole 2a	56 4l
13	Me	Ad	1f	indole 2a	79 4m
14 ^c	Bn	<i>i</i> -Pr	1g	indole 2a	29 4n
15	Cy	Cy	1h	indole 2a	0 4o ^d
16 ^e	Bn	<i>i</i> -Pr	1g	indole 2a	5+ 6

^a Isolated yields. ^b 5 equiv of indole **2** used. ^c Under N₂. ^d Products: **3o** (11%), **5** (35%), and **6** (13%). ^e Under O₂, rt, 24 h, **5** (35%), **6** (34%).

Table 4. Gold(I)-Catalyzed Reactions with **1h**

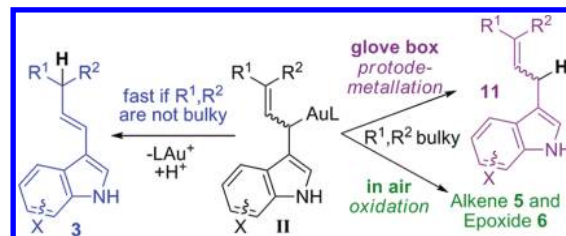
entry ^a	atm.	X	yield 5 ^b (%)	yield 6 ^b (%)	yield 11 ^c (%)
1	O ₂	OMe	58 (50) ^c	28 (27) ^c	—
2	air	OMe	49	16	—
3	N ₂ ^d	OMe	—	—	44
4	O ₂	H	36 (34) ^c	44 (28) ^c	—
5	O ₂	F	35 (34) ^c	37 (34) ^c	—

^aNo reaction occurs in the absence of Au(I) catalyst. ^bNMR yield by comparison with an internal standard. ^cIsolated yield. ^dIn glovebox.

and N₂ clearly show that O₂/air is required to form **5** and **6** (entries 1–3, Table 4). A rigorously O₂-free reaction produces neither **5** nor **6**, yielding instead the allylindole **11** (presumably from direct protodemetalation of **II**) as the major product (entry 3, Table 4). Resubjection of isolated **5**, **6**, **11**, or **3o** to the reaction conditions under O₂ provides only recovered substrates, indicating that **6** is not formed from **5** and *vice versa*, and neither are formed from **11** or **3**. It is also worth noting that **5** and **6** are never observed with nonbulky substituents (**1a–1d**), but begin to be observed as trace side products when only one substituent is bulky (**1e–1f**, see SI), and switch to become the major products when both substituents are bulky (**1h**). The outcome for **1g** is in between the two extremes and can be altered depending on the reaction conditions (entry 14 vs 16, Table 3).

(20) Review of oxidation by gold: (a) Pina, C. D.; Falletta, E.; Prati, L.; Rossi, M. *Chem. Soc. Rev.* **2008**, *37*, 2077. Oxidations utilizing homogeneous Au(I) catalysts with only air/O₂ as the oxidant are rare and occur at > rt: (b) Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 18004. (c) Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc.* **2006**, *128*, 11332. (d) Lu, B.-L.; Shi, M. *Chem.—Eur. J.* **2011**, *17*, 9070.

With these observations in hand, we propose that bulky substituents render intermediate **II** more stable and less prone to facile **II**→**3** conversion, and it is the allylgold intermediate **II** which is oxidized under air/O₂ to yield both **5** and **6**, or protodemetalates to give **11** in the absence of O₂ (Scheme 4). For nonbulky R¹/R², facile **II**→**3** outcompetes other potential pathways from **II**. This implies that if an allylgold species²¹ such as **II** can be designed to be more stable, it could open the door to unprecedented mild gold oxidation pathways under air.

Scheme 4. Proposed Different Outcomes from Intermediate **II**

In conclusion, the gold(I)-catalyzed reaction of various indoles to 3,3-disubstituted cyclopropenes can be *controlled* to provide either 3-(*E*)-vinylindoles **3** or *bis*-indolylalkanes **4**. As the substituents on cyclopropene become progressively bulkier, oxidation products *bis*-indolylalkene **5** and epoxide **6** are surprisingly formed. Further work to elucidate the mechanism of this oxidation reaction is underway and will be reported in due course.

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Supporting Information Available. Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(21) For evolution of allyl-Au(I) intermediates by protonolysis, see: Porcel, S.; López-Carrillo, V.; García-Yebra, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1883.

The authors declare no competing financial interest.