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

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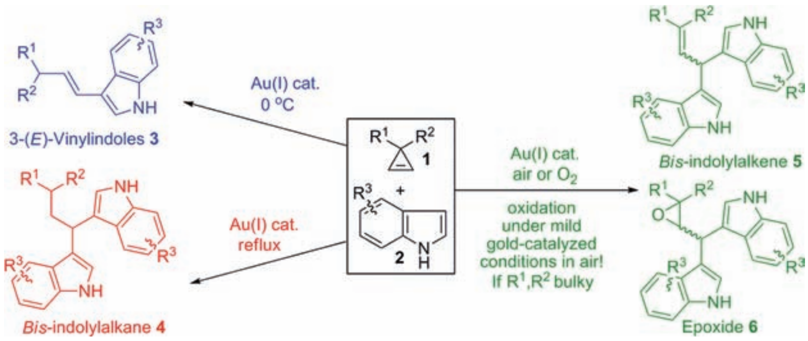
ABSTRACT



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 activity[1] and vinylindoles are valuable synthetic building blocks[2] toward biologically active building blocks such as indole alkaloids,[3] carbazoles,[4] and carbolines.[5] In particular, 3-vinylindoles[6] are useful dienes in [4 + 2] cycloaddtions 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]

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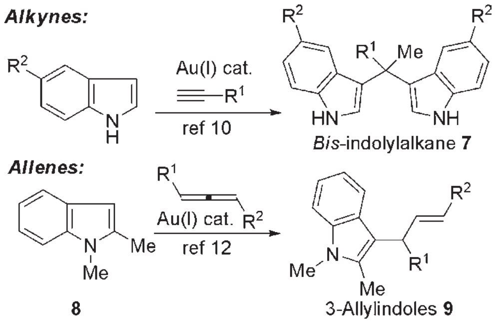
Scheme 1. Gold(I)-Catalyzed Indole Additions to Unactivated Alkynes and Allenes

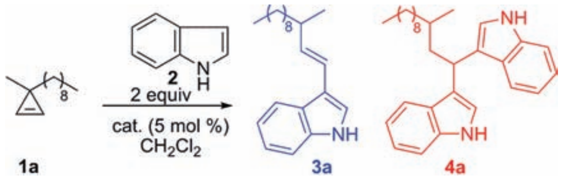


This work: divergent outcomes with ***cyclopropenes:*** producing either 3-vinylindoles **3** or *bis*-indolylalkanes **4**, and in certain cases *bis*-indolylalkenes **5** and epoxide **6**.

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.

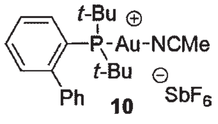
Our investigations commenced with screening conditions using indole and cyclopropene **1a** (entries 1−3, Table 1). Intriguingly, varying levels of **3a** and **4a** were observed, depending on the catalyst and reaction conditions employed. For example, at rt, $\mathrm{PPh_3AuNTf_2}$[16] favored formation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

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



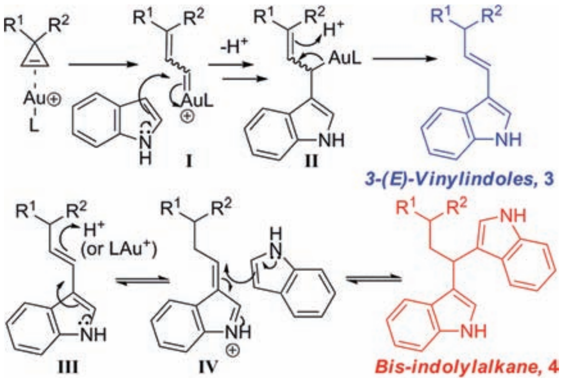
entry	catalyst	temp (°C)	time (h)	**3a:4a**[b]	yield (%)
1	$\mathrm{PPh_3AuNTf}$	rt	3	20:80	53%[c] **4a**
2	**10**	rt	3	88:12	59%[d] **3a**
3[e]	**10**	0	3	80:20	52%[d] **3a**
4	**10**	0	3	>95:5	91%[d] **3a**
5[f]	**10**	reflux	42	1:99>	76%[d] **4a**

[a] See Supporting Information for full optimization studies. [b] Determined by ^{1}H 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.



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



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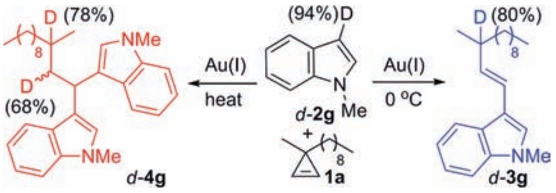
labeling studies using 94% D-labeled *d*-**2g** support our proposed mechanism (Scheme 3).

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.

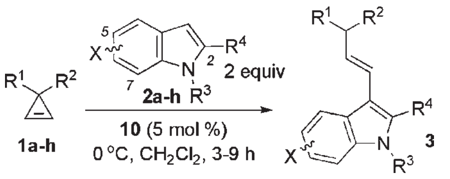
Scheme 3. Deuterium Labelling Studies



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 O_2, air,

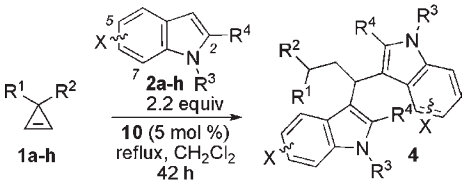
Table 2. Gold(I)-Catalyzed Synthesis of 3-(*E*)-Vinylindoles **3**



entry	R^1	R^2	**1**	indole **2**	yield (%)[a]
1	Me	$(CH_2)_8Me$	**1a**	indole **2a**	91 **3a**
2	Me	$(CH_2)_8Me$	**1a**	5-F-indole **2b**	72 **3b**
3	Me	$(CH_2)_8Me$	**1a**	5-OMe-indole **2c**	65 **3c**
4	Me	$(CH_2)_8Me$	**1a**	5-Cl-indole **2d**	77 **3d**
5	Me	$(CH_2)_8Me$	**1a**	6-Cl-indole **2e**	66 **3e**[c]
6	Me	$(CH_2)_8Me$	**1a**	7-Et-indole **2f**	63 **3f**
7[b]	Me	$(CH_2)_8Me$	**1a**	*N*-Me-indole **2g**	91 **3g**
8	Me	$(CH_2)_8Me$	**1a**	2-Me-indole **2h**	64 **3h**
9[b]	Me	$(CH_2)_2Ph$	**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*-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	$(CH_2)_8Me$	**1a**	indole **2a**	69 **4a**
2	Me	$(CH_2)_8Me$	**1a**	5-F-indole **2b**	67 **4b**
3	Me	$(CH_2)_8Me$	**1a**	5-OMe-indole **2c**	60 **4c**
4	Me	$(CH_2)_8Me$	**1a**	5-Cl-indole **2d**	65 **4d**
5	Me	$(CH_2)_8Me$	**1a**	6-Cl-indole **2e**	48 **4e**
6	Me	$(CH_2)_8Me$	**1a**	7-Et-indole **2f**	51 **4f**
7	Me	$(CH_2)_8Me$	**1a**	*N*-Me-indole **2g**	71 **4g**
8	Me	$(CH_2)_8Me$	**1a**	2-Me-indole **2h**	57 **4h**
9	Me	$(CH_2)_2Ph$	**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*-Pr	**1g**	indole **2a**	29 **4n**
15	Cy	Cy	**1h**	indole **2a**	0 **4o**[d]
16[e]	Bn	*i*-Pr	**1g**	indole **2a**	**5**+**6**

[a] Isolated yields. [b] 5 equiv of indole **2** used. [c] Under N_2. [d] Products: **3o** (11%), **5** (35%), and **6** (13%). [e] Under O_2, rt, 24 h, **5** (35%), **6** (34%).

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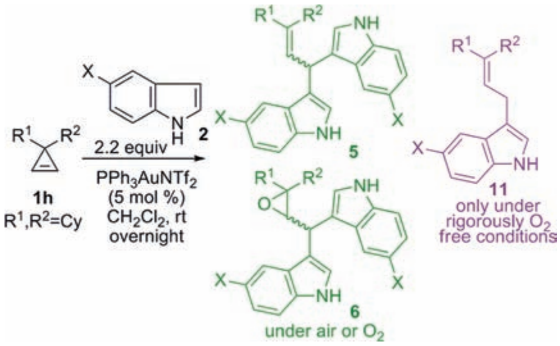
(18) Controls for **1**→**3**: (i) TfOH instead of Au(I) results in no reaction; (ii) addition of DBU to the Au(I)-catalyzed reaction still successfully forms the 3-vinylindole **3**, implying acid catalysis is not involved.

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



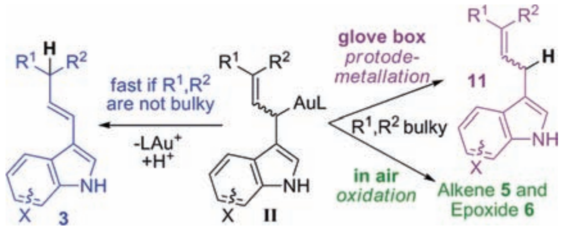
entry^a	atm.	X	yield **5**^{b} (%)	yield **6**^{b} (%)	yield **11**^{c} (%)
1	O_2	OMe	58 (50)^c	28 (27)^c	–
2	air	OMe	49	16	–
3	N_2^{d}	OMe	–	–	44
4	O_2	H	36 (34)^c	44 (28)^c	–
5	O_2	F	35 (34)^c	37 (34)^c	–

^{a} No reaction occurs in the absence of Au(I) catalyst. ^{b} NMR yield by comparison with an internal standard. ^{c} Isolated yield. ^{d} In glovebox.

and N_2 clearly show that O_2/air is required to form **5** and **6** (entries 1–3, Table 4). A rigorously O_2-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 O_2 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).

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/O_2 to yield both **5** and **6**, or protodemetallates to give **11** in the absence of O_2 (Scheme 4). For nonbulky R^1/R^2, facile **II**→**3** outcompetes other potential pathways from **II**. This implies that if an allylgold species[21] 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*-indolyl*alkene* **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.

Acknowledgment. We thank EPSRC (PCY), ScotChem (MSH) and Leverhulme Trust (JJH, F/00 276/O) for funding and EPSRC National Mass Spectrometry Service Centre at Swansea. Johnson Matthey is gratefully acknowledged for a generous loan of gold salts.

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.

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[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.
