Gold(I)-catalysed arylation of 1,6-enynes: different site reactivity of cyclopropyl gold carbenes†

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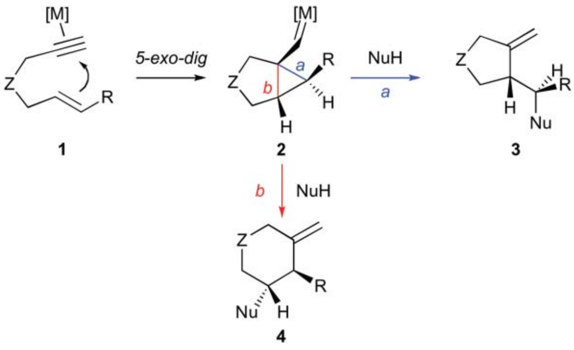
Gold(I)-catalysed addition of electron-rich arenes and heteroarenes to 1,6-enynes gives two different types of products by reaction of the intermediate cyclopropyl gold carbenes at the cyclopropane or at the carbene.

Work on metal-catalysed reactions of 1,6-enynes[1–3] carried out with Pt(II),[4–6] Pd(II),[7] and Au(I)[8,9] catalysts has identified two general manifolds upon monocoordination of the metal fragment to the alkyne: a 5-*exo-dig* process *via anti*-cyclopropyl metal carbenes **2** (Scheme 1),[8] along with the relatively less common 6-*endo-dig* cyclisation.[8,10] Attack of a nucleophile NuH (water or an alcohol) to intermediate **2** leads to five- or six-membered ring compounds **3** and **4**, respectively. In the absence of nucleophiles, the intermediate **2** can undergo single- or double-cleavage rearrangement reactions leading to 1,3-dienes.[9d]

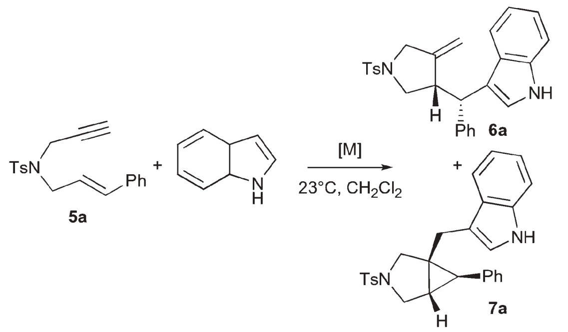
Until now, additions to 1,6-enynes *via* intermediates **2** have been restricted to water or alcohols as nucleophiles.[3–8,9a,b,e] Herein we report the gold(I)-catalysed addition of electron-rich arenes and heteroarenes to 1,6-enynes that reveal that intermediates **2** are bifunctional electrophiles, being able to react at the cyclopropane or at the carbene.[11]

As an extension of our work on the intra- and intermolecular reaction of indoles with alkynes catalysed by gold,[12,13] we decided to explore the corresponding reaction of indoles and electron-rich arenes with 1,6-enynes by using cationic gold complexes as catalysts. Reaction between enyne **5a** and indole afforded a 4 : 1 mixture of adducts **6a** and **7a** with cationic catalyst **8**[9c,14] (Table 1, entry 1). A more selective transformation was found with a catalyst formed *in situ* from complex **9**[15] and AgSbF$_6$, which lead to **6a** and **7a** in a 10 : 1 ratio (Table 1, entry 2). Neutral complex **9**, AuCl and AuCl$_3$ were not effective as catalysts (Table 1, entries 3–5). A result similar to that obtained with cationic complex **8** was achieved with a catalyst formed from complex **10** and AgSbF$_6$,[9c,16] although the reaction was slower (Table 1, entry 6). No reaction was observed with 5 mol% AgSbF$_6$ (Table 1, entry 7).



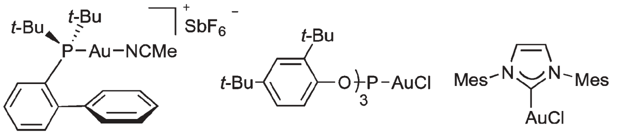
Scheme 1

Table 1 Metal-catalysed reaction of enyne **5a** with indole



Entry	[M]	*t*/h	Products (ratio)	Yield (%)
1	**8**	1	**6a** + **7a** (4 : 1)	74
2	**9**/AgSbF$_6$	1	**6a** + **7a** (10 : 1)	68
3	**9**	60	—	—
4	AuCl	192	—	—
5	AuCl$_3$	192	—	—
6	**10**/AgSbF$_6$	19	**6a** + **7a** (0.8 : 1)	72
7	AgSbF$_6$	60	—	—

[a] Reactions carried out with 5 mol% [M] in CH$_2$Cl$_2$ at room temperature.



8 **9** **10**

In general, best results were obtained with just 1.1 equiv of the arene or indole and by using the catalyst formed *in situ* from complex **9** and AgSbF$_6$ (Table 2). Thus, enyne **5a** reacted with indole-5-carbonitrile, 1,3,5-trimethoxybenzene and benzodioxole to give **6b–d** (entries 1–3). Reaction of **5a** with 2,6-di-*tert*-butylphenol gave the expected product of *para* arylation **6e** (entry 4). As the skeletal rearrangement of enynes **5b,c** bearing a trisubstituted double bond is a fast process even at low temperatures,[9d] reactions with indole and 5-methoxyindole with

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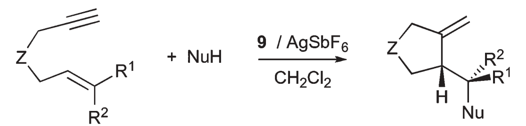
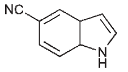
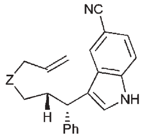
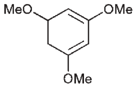
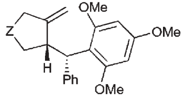
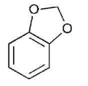
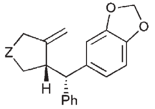
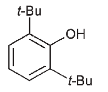
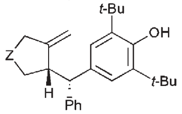
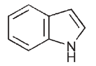
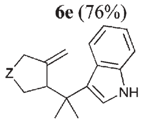
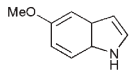
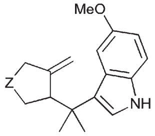
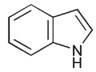
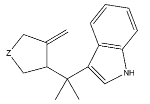
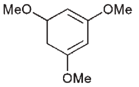
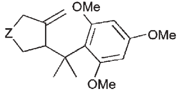
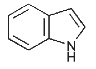
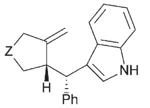
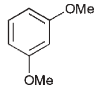
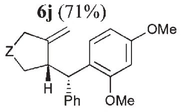
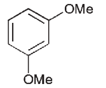
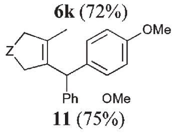
† Electronic supplementary information (ESI) available: Experimental procedures and analytical and spectroscopic data for new compounds. See DOI: 10.1039/b615335f

Table 2 Gold(I)-catalysed reaction of enynes



5a: Z = NTs, R^1 = Ph, R^2 = H
5b: Z = $C(CO_2Me)_2$, R^1 = R^2 = Me
5c: Z = $C(SO_2Ph)_2$, R^1 = R^2 = Me
5d: Z = $C(CO_2Me)_2$, R^1 = Ph, R^2 = H

Entry	Enyne	NuH	T/°C, t/h	Product (yield, %)
1	**5a**		23, 48	 **6b** (49%)
2	**5a**		23, 2	 **6c** (66%)
3	**5a**		−40, 4	 **6d**(74%)
4	**5a**		−40, 4	 **6e** (76%)
5	**5b**		−50, 5	 **6f** (78%)
6	**5b**		−50, 5	 **6g** (63%)
7	**5c**		−50, 1	 **6h** (78%)
8	**5c**		−50, 1	 **6i** (60%)
9	**5d**		23, 1	 **6j** (71%)
10	**5d**		−40, 3	 **6k** (72%)
11	**5d**		23, 2	 **11** (75%)

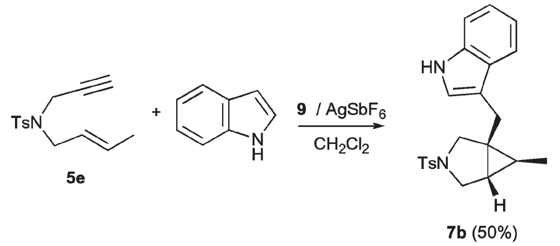
[a] Reactions carried out with catalyst **9** (5 mol%), $AgSbF_6$ (5 mol%) in CH_2Cl_2.

catalyst **9**/$AgSbF_6$ had to be performed at −50 °C to give adducts **6f–h** in 63–78% yields (Table 2, entries 5–7). Enyne **5c** also reacted with 1,3,5-trimethoxybenzene at −50 °C to afford **6i** in 60% yield (Table 2, entry 8). Reaction of enyne **5d** with indole and 1,3-dimethoxybenzene provided **6j** and **6k**, respectively (Table 2, entries 9 and 10). In the later case, the reaction had to be performed at −40 °C to avoid the isomerisation of the exocyclic double bond that leads to **11** when the reaction was carried out at room temperature (entry 11).

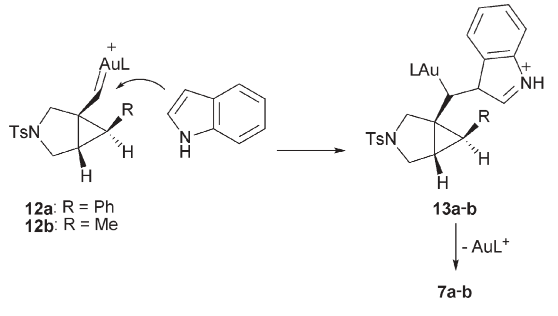
Single stereoisomers were obtained in the case of **6a–e** and **6j,k** and their configurations were assigned on the basis of previous work on the hydroxy- and alkoxy-cyclization reactions.[4–8] Although products of type **3** were obtained as the major or exclusive products in the reactions of enynes **5a–d** using complex **9** and $AgSbF_6$, enyne **5e** reacted with indole to give cyclopropane **7b** as the major product (Scheme 2) . A slower transformation was observed with $[AuCl(PPh_3)]/AgSbF_6$. It is interesting that in these reactions of 1,6-enynes we never observed products of direct attack of the nucleophilic arene or heteroarene to the alkyne.[12,13,17–20]

Formation of products **6a–k** and **11** can be rationalised as shown in Scheme 1 as a result of the attack of the electron-rich arene or indole to intermediate **2** (M = AuL^+). Mechanistically, this reaction is related to the intramolecular [4 + 2] cycloaddition of arylalkynes to alkenes catalyzed by cationic Au(I) complexes.[9c] On the other hand, cyclopropyl derivatives **7a,b** presumably arise by reaction of intermediates **12a,b** with indole to form intermediates **13a,b**, which evolve by rearomatisation and protodemetalation to form **7a,b** (Scheme 3). Intra- and intermolecular trapping of carbenes of type **2** (M = AuL^+)[9f,15] and other gold carbenes[21] with olefins has been shown to afford cyclopropanes. However, products of C–H functionalisation of aromatic compounds have also been found in reactions of certain gold carbenes.[21]

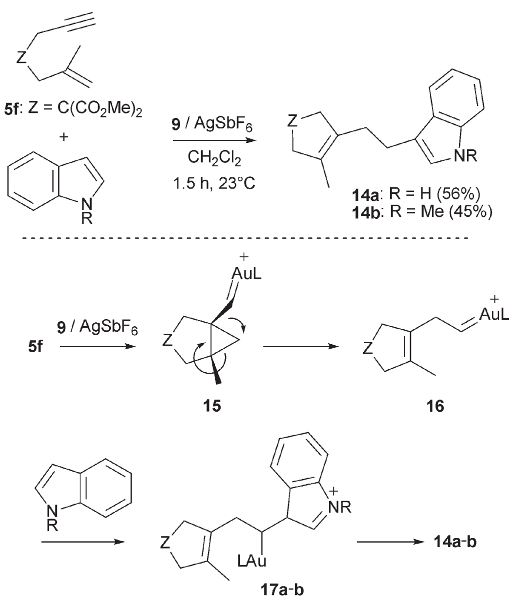
Remarkably, reaction of enyne **6** with indole and *N*-methylindole affords adducts **14a,b** (Scheme 4). These results



Scheme 2



Scheme 3



Scheme 4

indicate that under these conditions, the initially formed cyclopropyl gold carbene **15** undergoes a diatropic shift (double cleavage rearrangement) to form a second carbene **16**[9c,15] which reacts with the indoles to form intermediates **17a,b** and then **14a,b** by a process similar to that shown before in the transformation of **12a,b** into **7a,b**. Gold(I) carbene **16** is probably more electrophilic than **15**, being non-conjugated with the cyclopropane and less sterically hindered. Although a mechanism *via* cyclopropanation of the indoles is also conceivable,[22] *N*-methoxycarbonylindole, which affords stable cyclopropanes with metal carbenes,[23] does not react with **5f** under these conditions.

In summary, we have found that cyclopropyl gold–carbene intermediates formed from 1,6-enynes act as bifunctional electrophiles, reacting at the cyclopropane or at the carbene with electron-rich arenes and heteroarenes. The reactions of electrophilic gold carbenes with indoles are significant and point to new applications of gold(I)-catalysed reactions of alkynes in organic synthesis.

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