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Generation of gold carbenes in water: efficient intermolecular trapping of the α-oxo gold carbenoids by indoles and anilines†

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The efficient intermolecular reaction of gold carbene intermediates, generated *via* gold-catalyzed alkyne oxidation, with indoles and anilines has been realized in aqueous media. Importantly, it was revealed for the first time that water could dramatically suppress the undesired over-oxidation, providing a general and practical solution to the problem of over-oxidation in gold-catalyzed intermolecular alkyne oxidation with external nucleophiles. This strategy was successfully applied to the formal synthesis of the Pfizer's chiral endothelin antagonist UK-350,926.

Introduction

The generation of α-oxo gold carbenes *via* gold-catalyzed intermolecular alkyne oxidation represents a significant advance in gold catalysis,[1] and various efficient synthetic methods have been developed based on this approach by Zhang,[2] Liu,[3] and others.[4,5] Despite these significant achievements, intermolecular alkyne oxidation with external nucleophiles remains a particularly challenging task. There are two major reasons for this: (1) most external nucleophiles can also attack alkynes directly, catalyzed by gold species; and (2) this type of α-oxo gold carbene is highly reactive and often suffers the competing over-oxidation of the carbene center by the oxidant[5,3g], in addition to many other side reactions. To date, successful intermolecular examples of this reaction have been quite scarce,[4a] except for some reactions which have to rely on P,N- or P,S-bidentate ligands and the slow addition of oxidants *via* a syringe pump,[2b,c] or the use of the external nucleophiles as the reaction solvent to minimize the second oxidation.[2f]

Recently, the use of an environmentally friendly reaction medium, particularly water, has attracted much attention.[6] Although many types of transition metal-catalyzed reactions, including olefin metathesis, Mizoroki–Heck reaction, Suzuki reaction, and Sonogashira reaction in water have been achieved, the investigation of gold-catalyzed reactions conducted in aqueous media is still limited[7] and generally focused on reactions catalyzed by water-soluble gold complexes.[8] Competitive hydration of the substrates is probably the major reason for this paucity when gold-catalyzed transformations of alkynes are performed in water.[9] Herein we present the first example of the generation of gold carbenes through intermolecular alkyne oxidation in aqueous media, and efficient intermolecular trapping of the α-oxo gold carbenes by indoles and anilines. Importantly, it was revealed for the first time that water could dramatically suppress the undesired over-oxidation of gold carbene, making this approach a viable synthetic methodology, which is complementary to the traditional generation of metal carbenoids in organic solvents from diazo compounds. The synthetic utility is also demonstrated by the formal synthesis of the Pfizer's chiral endothelin antagonist UK-350,926.

Results and discussion

During the last decade, a lot of attention has been paid to the development of transition-metal (M = Rh, Ru, Cu, Pd, Fe, In) catalyzed C–H functionalization of indoles by carbenoids derived from diazo compounds, allowing efficient access to indole derivatives.[10,11] However, the use of hazardous, not easily accessible and potentially explosive α-diazo ketone precursors has severely limited its further synthetic applications and the molecular flexibility. Moreover, it remains challenging to control the regioselectivity and chemoselectivity of the C–H insertion reaction, N–H insertion reaction and the cyclopropanation reaction. Therefore, the development of an alternative approach is still highly desirable. We envisioned that using the above-mentioned oxidative approach, α-oxo gold carbenoids of type **I** would be readily accessed by using ynamide **2**, instead of the corresponding hazardous and potentially explosive α-diazoamide, and its subsequent C–H functionalization of indole **1** would deliver **3** in a non-diazo approach (Scheme 1).

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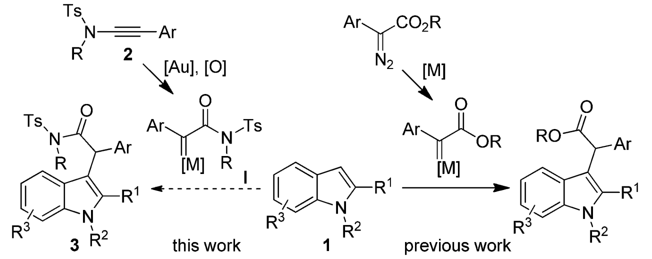
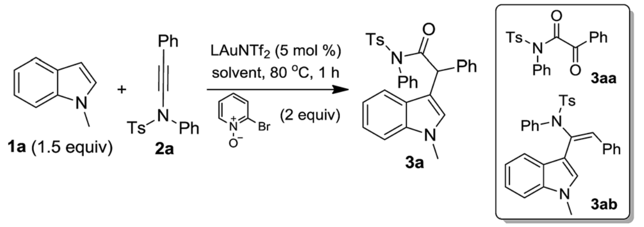


Scheme 1 Initial design.

At the outset, we used *N*-methylindole **1a** and ynamide substrate **2a** as the reacting partners, and 2-bromopyridine *N*-oxide as the oxidant (see ESI† for the screening of different oxidants and solvents), and some of the results are listed in Table 1. Initially, diketone compound **3aa** was detected as a major product with various typical gold catalysts with a range of electronic and steric characteristics (Table 1, entries 1–8). To suppress the over-oxidation of ynamide into the diketone, we then performed the reaction by slow addition of the oxidant into the reaction mixture using a syringe pump, which was utilized in previous intermolecular trapping of α-oxo gold carbenes.[2b,c] However, in this case, only enamide **3ab** was produced through a gold-catalyzed direct addition of indole **1a** to alkyne **2a** (Table 1, entries 9–10).[12] To our delight, it was found that the reaction yields could be substantially improved when the reaction was run in 10 : 1 DCE–H_2O mixed solvent (Table 1, entries 11–13). Further studies revealed that increasing the ratio of H_2O–DCE offered a further improvement (Table 1, entries 14–19) and excellent yield could be achieved using 10 : 1 H_2O–DCE as the solvent (Table 1, entries 17–19). Strikingly, the reaction could proceed equally well even in neat H_2O when 5 mol% $IPrAuNTf_2$ was employed as the catalyst, and the desired indole derivative **3a** could be furnished in 88% yield (Table 1, entry 21). Notably, without a gold catalyst, the reaction failed to give even a trace of **3a**, and $PtCl_2$ and $AgNTf_2$ were not effective in promoting this reaction (8 and 25%, respectively).

Table 1 Optimization of reaction conditions[a]

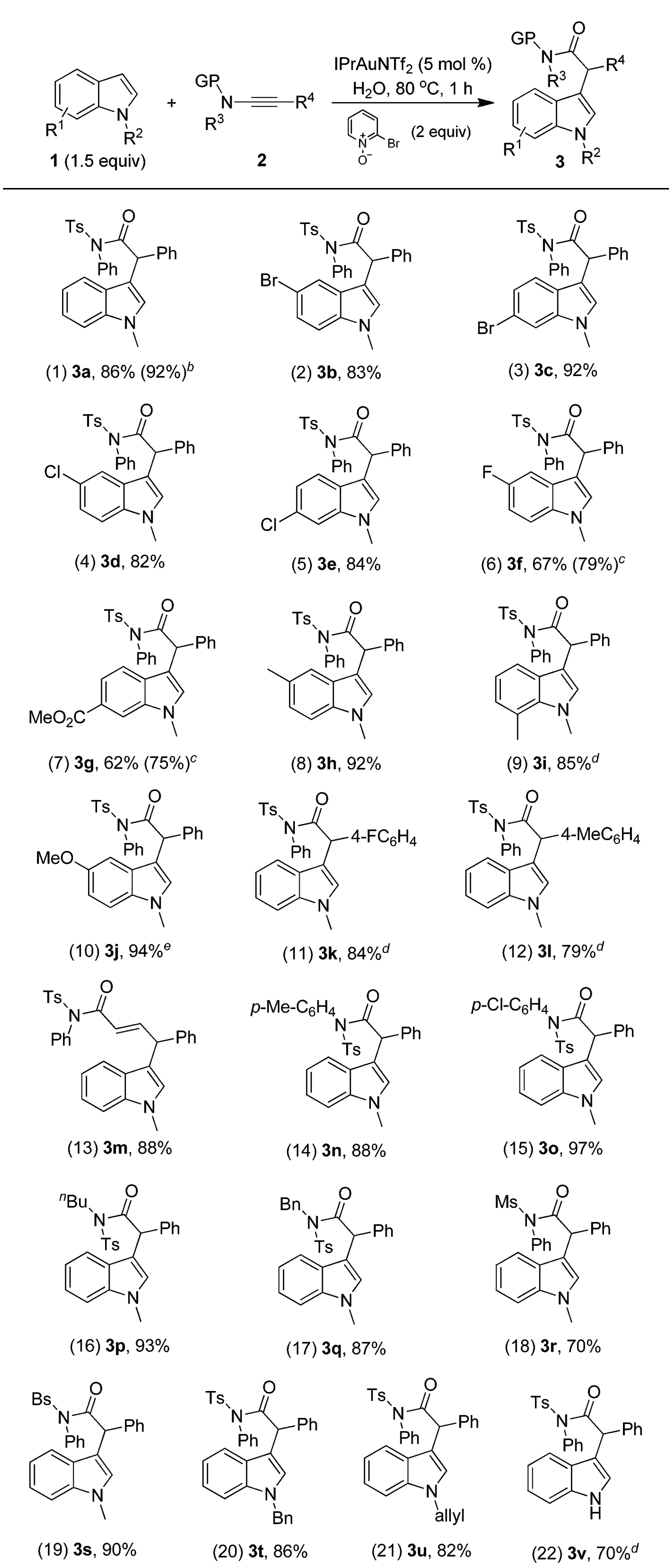


Entry	Gold catalyst	Solvent	Yield[b] (%) 3a	3aa	3ab
1	$Ph_3PAuNTf_2$	DCE	25	65	2
2	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	DCE	9	68	3
3	Cy-JohnPhosAuNTf$_2$	DCE	15	76	2
4	XPhosAuNTf$_2$	DCE	17	40	4
5	BrettPhosAuNTf$_2$	DCE	19	29	7
6	IMesAuNTf$_2$	DCE	24	36	<2
7	IPrAuNTf$_2$	DCE	26	35	<2
8	$Et_3PAuNTf_2$	DCE	44	55	<2
9[c]	$Et_3PAuNTf_2$	DCE	<2	<2	90
10[d]	$Et_3PAuNTf_2$	DCE	<2	<2	85
11	$Ph_3PAuNTf_2$	DCE–H_2O = 10 : 1	40	55	<2
12	IPrAuNTf$_2$	DCE–H_2O = 10 : 1	36	45	<2
13	$Et_3PAuNTf_2$	DCE–H_2O = 10 : 1	52	47	<2
14	$Ph_3PAuNTf_2$	DCE–H_2O = 1 : 1	60	35	<2
15	IPrAuNTf$_2$	DCE–H_2O = 1 : 1	43	48	<2
16	$Et_3PAuNTf_2$	DCE–H_2O = 1 : 1	70	28	<2
17	$Ph_3PAuNTf_2$	DCE–H_2O = 1 : 10	85	<2	5
18	IPrAuNTf$_2$	DCE–H_2O = 1 : 10	87	<2	<2
19	$Et_3PAuNTf_2$	DCE–H_2O = 1 : 10	86	4	<2
20	$Ph_3PAuNTf_2$	H_2O	41	<2	46
21	IPrAuNTf$_2$	H_2O	88	<2	<2
22	$Et_3PAuNTf_2$	H_2O	56	<2	12

[a] Reaction run in vials with DCE and/or deionized water; [**2a**] = 0.1 M. [b] Measured by ^1H NMR using diethyl phthalate as the internal standard. [c] The oxidant was introduced into the reaction mixture over a 1 h period using a syringe pump. [d] The mixture of oxidant and **1a** were introduced into the reaction mixture over a 1 h period using a syringe pump.

With the optimized reaction conditions in hand, the scope of the transformation was explored with a range of indoles and ynamides. As shown in Table 2, the reaction proceeded smoothly with various substrates, and the yields ranged from 70% to 97%. Importantly, only C3-alkylated products were formed in all cases. We first examined various substituted indoles with ynamide substrate **2a** and were pleased to find that the reaction provided the desired indole derivatives **3a**–**3j** in good to excellent yields (Table 2, entries 1–10). In the case of the indoles bearing strongly electron-withdrawing groups, improved yields could be obtained by using a slight excess of ynamide **2a** (Table 2, entries 6–7). Then, various ynamides **2** were investigated and the reaction also proceeded well, affording the corresponding products **3k**–**3s** in good to excellent yields (Table 2, entries 11–19). In case of 3-en-1-ynamide **2d**, the reaction gave α, β-unsaturated imide **3m** as a single isomer in 88% yield (Table 2, entry 13). Notably, when R^3 is an alkyl group, the desired **3p** and **3q** were formed in 93% and 87% yield, respectively, and no carbene insertion into a CH bond was observed (Table 2, entries 16–17). In addition, ynamides containing a Ms or a Bs group also worked well to give the desired **3r** and **3s** in 70% and 90% yields, respectively (Table 2, entries 18–19). Other *N*-substituted indoles were also suitable substrates for this reaction to furnish the corresponding functionalized indoles **3t**–**3u** in good yields (Table 2, entries 20–21). Even for unprotected indole substrate, this reaction still led to a respectable 70% yield and no *N*-alkylated product was formed (Table 2, entry 22).[11m,n] It should be mentioned that in some cases, slightly improved yields could be achieved by using 1.05 equiv. of indole in order to prohibit the background enamide formation (Table 2, entry 9, entries 11–12 and entry 22). To further test the practicality of the current catalytic system, the reaction was carried out in a gram scale in the presence of 2.5 mol% gold catalyst and the desired product **3a** was afforded in 92% yield, highlighting the synthetic utility of this chemistry (Table 2, entry 1). Finally, X-ray diffraction studies of product **3b** further confirmed our structural assignments.[13]

Table 2 Reaction scope with different indoles **1** and ynamides **2**[a]



(1) **3a**, 86% (92%)[b]

(2) **3b**, 83%

(3) **3c**, 92%

(4) **3d**, 82%

(5) **3e**, 84%

(6) **3f**, 67% (79%)[c]

(7) **3g**, 62% (75%)[c]

(8) **3h**, 92%

(9) **3i**, 85%[d]

(10) **3j**, 94%[e]

(11) **3k**, 84%[d]

(12) **3l**, 79%[d]

(13) **3m**, 88%

(14) **3n**, 88%

(15) **3o**, 97%

(16) **3p**, 93%

(17) **3q**, 87%

(18) **3r**, 70%

(19) **3s**, 90%

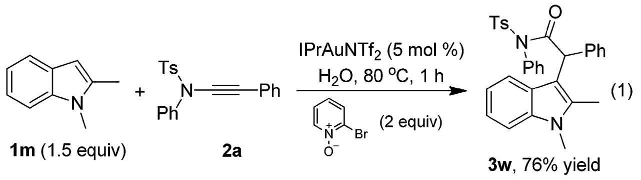
(20) **3t**, 86%

(21) **3u**, 82%

(22) **3v**, 70%[d]

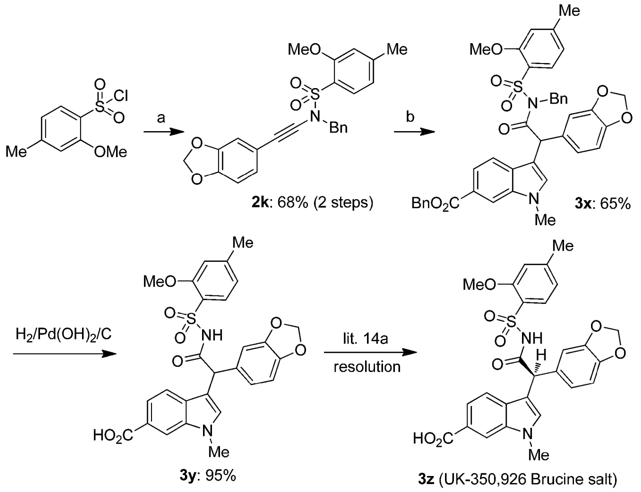
[a] Reactions run in vials; [**2**] = 0.1 M; isolated yields are reported. [b] 5.0 mmol scale, 2.5 mol% gold catalyst was used, 4 h. [c] Indole **1** (1.0 equiv.), ynamide **2a** (1.5 equiv., added in two portions), 2 h. [d] 1.05 equiv. of indole **1** was used [e] Using H_2O–DCE = 10 : 1 as the solvent.

This chemistry can also be extended to 2-substituted indole substrate **1m** under the optimized reaction conditions, leading to the formation of the desired product **3w** in 76% yield, as shown in eqn (1).

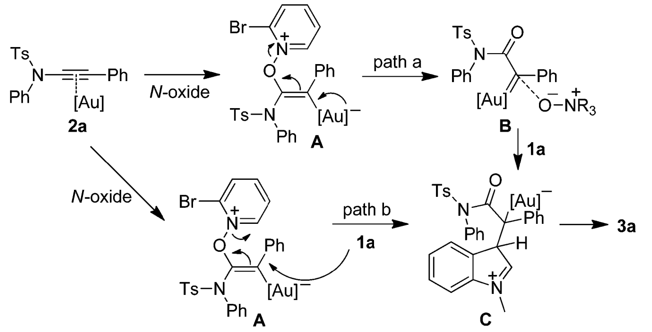


The significance of this chemistry is additionally demonstrated by its application to the formal synthesis of Pfizer's chiral endothelin antagonist UK-350,926 (**3z**),[14] as depicted in Scheme 2. Ynamide substrate **2k** was prepared from 2-methoxy-4-methylbenzenesulfonyl chloride[14e] in a two-step process involving a copper-catalyzed amidation of an alkynyl bromide compound. Then, the reaction of the ynamide **2k**, indole **1n**, and oxidant in the presence of 5 mol% $IPrAuNTf_2$ in water at 80 °C for 4 h gave the compound **3x** in 65% yield. Indole **3x** was subjected to hydrogenation to afford **3y**, which was then transformed to **3z** in one step using a dynamic resolution process.[14a] This total synthesis of racemic UK-350,926 constitutes a short, four-step sequence from the above sulfonyl chloride in a 42% overall yield.

Two plausible mechanisms to rationalize the formation of indole **3a** are proposed (Scheme 3). Path a is generally believed for the gold-catalyzed oxidative processes involving the α-oxo gold carbene intermediate **B**, which could be further trapped by indole **1a** to deliver the final product **3a**. Another pathway, path b, may involve the generation of intermediate **C** by a direct intermolecular S_N2' reaction. The intermediate **C** then undergoes protodeauration to furnish product **3a** along with the regeneration of the gold catalyst.

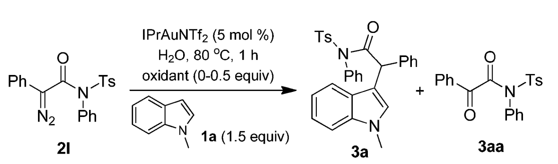


Scheme 2 Formal synthesis of Pfizer's chiral endothelin antagonist UK-350,926. Reagents and conditions: (a) $BnNH_2$ (1.1 equiv.), Et_3N, rt, 4 h; 5-(bromoethynyl)benzo[*d*][1,3]dioxole (1.0 equiv.), $CuSO_4\cdot5H_2O$ (0.1 equiv.), 1,10-phenanthroline (0.2 equiv.), K_2CO_3 (3.0 equiv.), toluene, 80 °C, 10 h; (b) $IPrAuNTf_2$ (5 mol%), benzyl 1-methyl-1*H*-indole-6-carboxylate **1n** (1.0 equiv.), **2k** (1.5 equiv.), 2-bromopyridine *N*-oxide (2.0 equiv.), H_2O, 80 °C, 4 h.



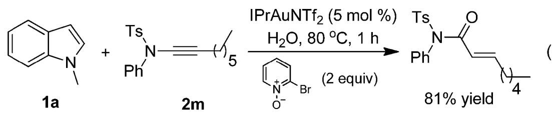
Scheme 3 Possible reaction mechanisms.

To probe the feasibility of the two reaction paths (a and b), we first prepared the diazo compound **2l**. As shown in eqn (2), it was found that the reaction of **2l** with indole **1a** indeed produced the desired **3a** in 48% yield. In particular, 62% yield could be achieved in the presence of 0.5 equiv. of oxidant, which was supposed to facilitate the generation of gold carbene **B** through a stabilization effect, as previously reported by Liu.[3b] Moreover, a similar water effect was observed, as in its absence the reaction efficiency decreased dramatically and the ketoimide **3aa** was formed in a much increased yield. In addition, the reaction of **1a** with **2m** only resulted in the formation of the α, β-unsaturated imide product (eqn (3)).[4i] These results suggest that the reaction presumably goes through the path a and the α-oxo gold carbene intermediate **B** is most likely generated. Notably, the reaction pathway involving the trapping of α-oxo gold carbenes by water, followed by nucleophilic attack by the indole is much less probable because the reaction of α-hydroxyimide **3aa′** with **1a** failed to produce **3a** and also no **3aa′** formation was observed in the reaction system (eqn (4)). More importantly, the inactivity of insertion to the O–H bond of water guaranteed further transformations of the derived gold carbene in aqueous solution.[15] In addition, we also prepared **3aa** and subjected it to the optimal reaction conditions, and no **3a** was obtained, which rules out diketone **3aa** as an intermediate on the way to product **3a** (eqn (4)).

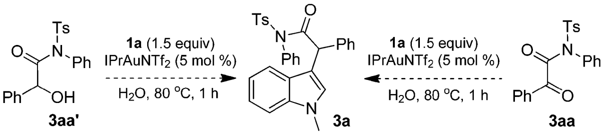


(2)

no 2-bromopyridine *N*-oxide: **3a**, 48%; no **3aa**
0.5 equiv of 2-bromopyridine *N*-oxide: **3a**, 62%; **3aa**, <5%
0.5 equiv of 2-bromopyridine *N*-oxide (in DCE): **3a**, 24%; **3aa**, 18%

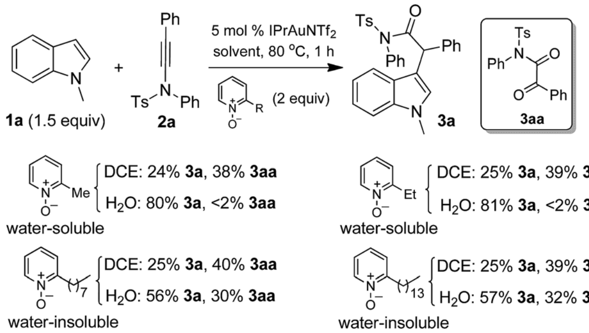


(3)



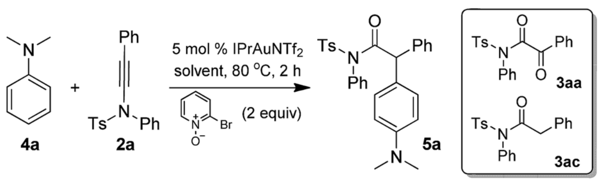
(4)

While the role of H_2O in this reaction remains to be clearly established, we suspected that the water-soluble organic oxide (2-bromopyridine *N*-oxide) in this system exists mainly in the aqueous phase, whereas the catalyst and internal alkynes and indole nucleophiles form insoluble organic mesophases, in which the reactions take place. As a result, this mesophase system maintains the proper concentration of the external oxidants thus avoiding the double oxidation of the alkynes and favoring the nucleophilic addition of indole to gold carbenes, which is equivalent in nature to the reaction conditions using the slow addition of an oxidant.[16] Indeed, it was found that when the reaction was run in water by using water-insoluble *N*-oxides (even at 80 °C), significant formation of diketone **3aa** was observed (eqn (5)). In addition, kinetic experiments showed that the reaction proceeded much slower in water than in DCE (5 min *vs.* 1 h, see ESI† for the detailed kinetic study of the reaction), further supporting the above speculation that the concentration of the water-soluble *N*-oxides in the reaction phase was kept at a low level.



(5)

We next considered the possibility of extending the reaction to other electron-rich aromatics. To our delight, the reaction of the ynamide **2a** with *N*,*N*-dimethyl aniline **4a** in the presence of 5 mol% $IPrAuNTf_2$ and 2 equiv. of 2-bromopyridine *N*-oxide could proceed smoothly in water, delivering the desired **5a** in 78% yield (as determined by NMR), as depicted in eqn (6). In contrast, when the reaction was carried out in DCE, **5a** was obtained only in 10% yield and a significant formation of diketone **3aa** could be observed, thus demonstrating again that the role of water here serves to dramatically promote this oxidative gold catalysis. The use of 3 equiv. of **4a** minimized the formation of hydration byproduct **3ac**,[18,5a] leading to a further improved yield.



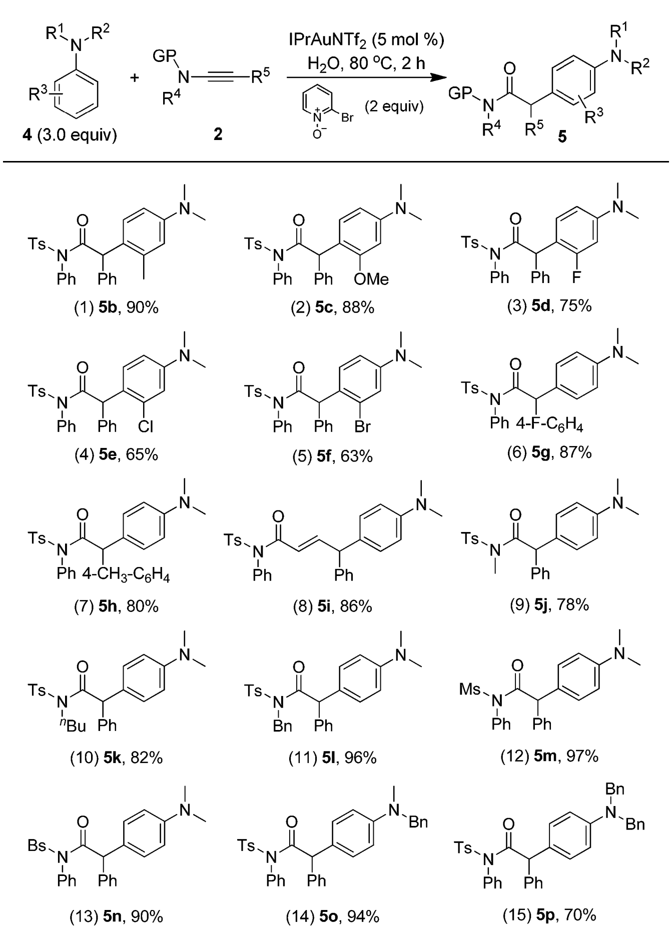
(6)

Conditions	Yield[a] 5a	3aa	3ac
DCE, **4a** (2 equiv)	10%	37%	<2%
H_2O, **4a** (2 equiv)	78%	<1%	12%
H_2O, **4a** (3 equiv)	90%[b]	<1%	<5%

[a] Measured by ^1H NMR using diethyl phthalate as the internal standard.
[b] Yield of isolated **5a** was 89%.

There are several well-documented examples of intramolecular trapping of α-oxo gold carbenoids by aromatic substitution reaction,[2d,5b,17] however, to our best knowledge, examples of the intermolecular version have not been reported. We then examined the scope of this intermolecular aromatic substitution of *N*,*N*-disubstituted anilines **4** with α-oxo gold carbenoids generated *via* oxidation of ynamides **2**. As summarized in Table 3, all of the reactions took place smoothly and afforded the corresponding product **5** in largely good to excellent yields. In entries 1–5, this reaction works satisfactorily with various types of *N*,*N*-dimethyl aniline derivatives **4b–4f**; their electrophilic aromatic substitution products **5b–5f** were obtained in 63–90% yields. The reactions were also extensible to different ynamides **2**, which delivered the desired **5g–5l** in 78–96% yields (Table 3, entries 6–11). Notably, the reaction with 3-en-1-ynamide **2d** afforded α, β-unsaturated imide **5i** as a single isomer in 86% yield (Table 3, entry 8 *vs.* Table 2, entry 13). Entries 12 and 13 show our reactions with Ms and Bs protected ynamides **2i–2j**, resulting in excellent yields of the desired products **5m–5n** (97% and 90% isolated yields). This reaction also worked well for other types of *N*,*N*-disubstituted anilines **4g–4h**, giving the desired products **5o–5p** in 94% and 70% yields, respectively (Table 3, entries 14–15). The molecular structure of **5f** was confirmed by X-ray diffraction.[13]

Table 3 Reaction scope with different tertiary anilines **4** and ynamides **2**[a]



(1) **5b**, 90% (2) **5c**, 88% (3) **5d**, 75%

(4) **5e**, 65% (5) **5f**, 63% (6) **5g**, 87%

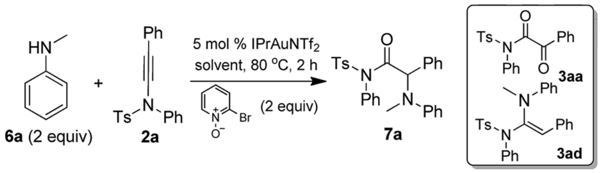
(7) **5h**, 80% (8) **5i**, 86% (9) **5j**, 78%

(10) **5k**, 82% (11) **5l**, 96% (12) **5m**, 97%

(13) **5n**, 90% (14) **5o**, 94% (15) **5p**, 70%

[a] Reactions run in vials; [2] = 0.1 M; isolated yields are reported.

Interestingly, when we tested the above oxidative gold catalysis on the secondary aniline **6a**, no aromatic substitution product was observed. Instead, the intermolecular N–H insertion product **7a** was isolated, albeit in low yield. As shown in eqn (7), water indeed significantly inhibited the formation of diketone byproduct **3aa**, however, the formation of background enamide **3ad** became dominant, which could be rationalized by a gold-catalyzed direct addition of *N*-methylaniline **6a** to ynamide **2a**. Gratifyingly, the yield could be substantially improved by simply tuning of the ratio of H_2O–DCE.



(7)

Conditions	Yield[a] 7a	3aa	3ad
DCE	75%	18%	<1%
H_2O	30%	<1%	48%
DCE/H_2O = 1/1	83%[b]	<1%	<2%

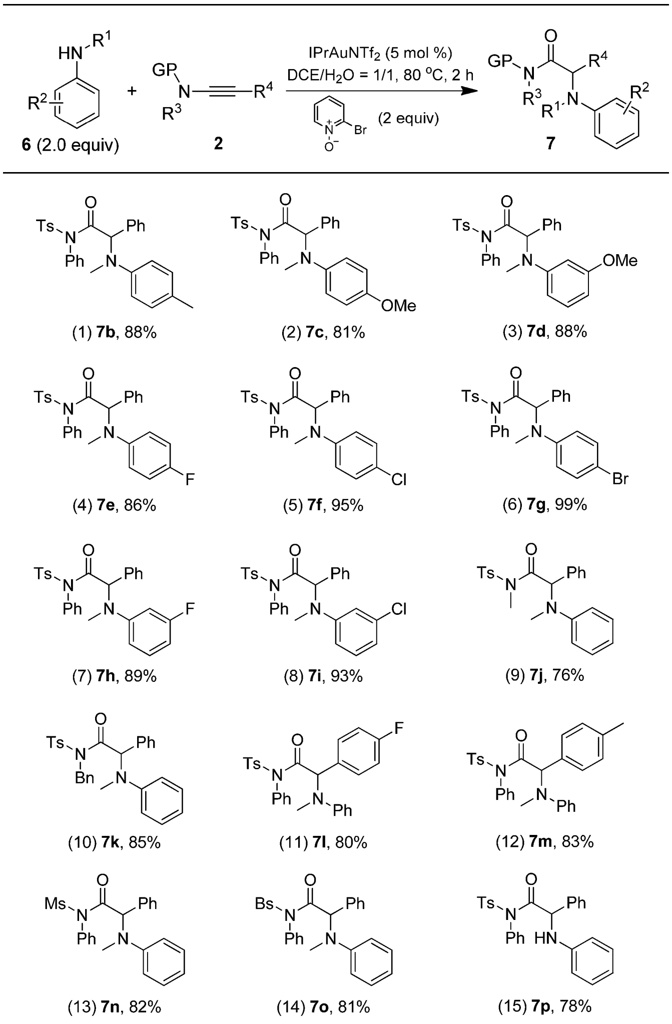
[a] Measured by ^1H NMR using diethyl phthalate as the internal standard.
[b] Yield of isolated **7a** was 81%.

Although intramolecular trapping of this type of gold carbenes *via* facile O–H[2i,j] and N–H[19,2g] insertions has been well established, no success has been achieved with the intermolecular version to date.[3g] With the optimized reaction conditions in hand, the reaction scope was then studied. As depicted in Table 4, a broad variety of α-amino amides **7** could be readily obtained under the above optimized conditions. The reaction of ynamide **2a** with various *N*-methyl anilines **6b–6i** was first examined. The yields for both electron-deficient and electron-rich aniline substrates varied from good to excellent (Table 4, entries 1–8). Different ynamides **2** turned out to be suitable starting materials as well, leading to the corresponding α-amino amides **7** in good yields (Table 4, entries 9–14). In addition to secondary anilines, primary aniline **6j** also proved to be a viable substrate affording **7p** in 78% yield (Table 4, entry 15). Importantly, only intermolecular N–H insertions into the α-oxo gold carbenoids occurred in all cases, and essentially no competing aromatic substitution reaction was observed, thereby providing environmental and non-diazo advantages over previously reported protocols.[20]

Conclusions

In summary, the challenging intermolecular trapping of α-oxo gold carbenes by external nucleophiles such as indoles and anilines has been achieved. Different from the well known Cu, Rh, and Ru carbenoids, which were formed from the metal-catalyzed decomposition of diazo compounds and normally in organic solvents, this carbenoid species is generated through gold-catalyzed intermolecular alkyne oxidation and its relevant

Table 4 Reaction scope with different secondary or primary anilines **6** and ynamides **2**[a]



(1) **7b**, 88%
(2) **7c**, 81%
(3) **7d**, 88%
(4) **7e**, 86%
(5) **7f**, 95%
(6) **7g**, 99%
(7) **7h**, 89%
(8) **7i**, 93%
(9) **7j**, 76%
(10) **7k**, 85%
(11) **7l**, 80%
(12) **7m**, 83%
(13) **7n**, 82%
(14) **7o**, 81%
(15) **7p**, 78%

[a] Reactions run in vials; $[\mathbf{2}] = 0.1$ M; isolated yields are reported.

reactions can be performed in aqueous media, thus making this non-diazo protocol very practical and environmentally friendly. Significantly, it was revealed that water could dramatically inhibit the formation of diketone byproducts, which might serve as a general solution to the over-oxidation in oxidative gold catalysis. This new method enables a succinct and practical formal synthesis of the Pfizer's chiral endothelin antagonist UK-350,926. Studies to elucidate the detailed mechanism and further application of this water-assisted protocol for the oxidative gold catalysis will be pursued further in our laboratory.

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