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Combining Zn ion catalysis with homogeneous gold catalysis: an efficient annulation approach to *N*-protected indoles†

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The Fischer indole synthesis is perhaps the most powerful method for indole preparation, but it often suffers from low regioselectivities with unsymmetrical aliphatic ketone substrates and strongly acidic conditions and is not suitable for α,β-unsaturated ketones. In this edge article, we disclose an efficient synthesis of *N*-protected indoles from *N*-arylhydroxamic acids/*N*-aryl-*N*-hydroxycarbamates and a variety of alkynes *via* cooperative gold and zinc catalysis. The zinc catalysis is similar to the related zinc ion catalysis in metalloenzymes such as human carbonic anhydrase II and substantially enhances the *O*-nucleophilicity of *N*-acylated hydroxylamine by forming the corresponding Zn chelates. The Zn chelates can attack gold-activated alkynes to form *O*-alkenyl-*N*-arylhydroxamates, which can undergo facile 3,3-sigmatropic rearrangements and subsequent cyclodehydrations to yield *N*-protected indole products. This new chemistry offers several important improvements over the Fischer indole synthesis: (a) the reaction conditions are mildly acidic and can tolerate sensitive groups such as Boc; (b) broader substrate scopes including substrates with pendant carbonyl groups (reactive in the Fischer chemistry) and alkyl chlorides; (c) better regioselectivities for the formation of 2-substituted indoles under much milder conditions; (d) 2-alkenylindoles can be prepared readily in good to excellent yields, for which Fischer chemistry could not be used; (e) with internal alkynes both steric and electronic controls are available for achieving good regioselectivities, while Fischer chemistry is in general problematic.

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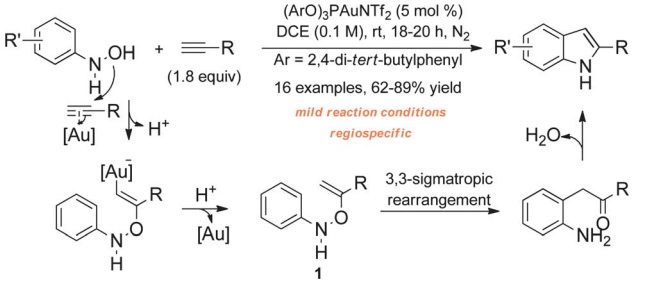
Introduction

The Fischer indole synthesis[1] is arguably the most versatile method for indole synthesis and has been subjected to extensive modifications/improvements[2] since the original report by Fischer's group[3] more than one hundred years ago. This one-step annulation between an arylhydrazine and a ketone under strongly acidic conditions relies on a key 3,3-sigmatropic rearrangement of the *N*-alkenyl-*N*′-arylhydrazine intermediate, and many syntheses of indole alkaloids have used it as the key transformation.[4] Notwithstanding, its synthetic potential is limited by several drawbacks associated with the formation of *N*-alkenylhydrazine precursors *via* hydrazone tautomerization; the most notable is the often poor regioselectivities with unsymmetrical aliphatic ketones. In addition, 2-alkenylindoles cannot be prepared *via* this method except for a few special cases.[5] While catalytic hydroamination of alkynes has been developed as an alternative approach to accessing *N*-arylhydrazones, the same drawbacks remain, and the reported reaction scopes are mostly limited to arylalkynes.[6]

On the other hand, analogous indole syntheses based on 3,3-rearrangements of *O*-alkenyl-*N*-arylhydroxylamines or its derivatives[7] such as the Bartoli indole synthesis[8] have been developed; while these rearrangements involving fragmentations of weaker N–O bonds typically proceed at much lower temperatures than in the Fischer indole synthesis, there is a lack of a general and straightforward method for the generation of *O*-alkenylhydroxyamine intermediates.[7] For the Bartoli reaction, it is severely limited by the requirement of an *ortho* substituent in the nitroarene substrate, and its functional group tolerance is rather poor due to the use of excess Grignard reagents (at least 3 equivalents).



Scheme 1 Regiospecific formation of 2-alkylindoles from aliphatic terminal alkynes *via* gold-catalyzed O-additions of hydroxylamines to C–C triple bonds.

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We[9] reported previously that this type of intermediate (*i.e.*, **1**, Scheme 1) could be formed *via* the addition of the HO group of an *N*-arylhydroxylamine onto a terminal aliphatic alkyne in the presence of a gold catalyst.[10,11] Followed by one-pot sequential 3,3-rearrangement and dehydrative cyclization, this gold catalysis affords 2-alkylindole products at ambient temperature. Two notable features of this method are the exceedingly mild reaction conditions (tolerance of a THP ether) and the excellent regioselectivities. In comparison, the Fischer synthesis requires heating and harsh acidic conditions (*e.g.*, 5% P_2O_5 per neat MsOH[12] or neat PPA[13]) to convert methyl ketones into 2-alkylindoles, albeit only with low to moderate regioselectivities.

Although this chemistry represents a significant improvement in the synthesis of 2-alkylindoles over the Fischer indole synthesis, our attempts to extend it to the synthesis of other types of indoles were thwarted by inherent slow reactions and limited thermostabilities of *N*-arylhydroxylamines.[9] The aliphatic terminal alkynes used in our previous studies appear to be the best substrates for the chemistry, but the reactions still required 18 h or more to reach completion at room temperature. Increasing reaction temperature was detrimental as *N*-arylhydroxylamines easily underwent disproportionation and/or decomposition. When less reactive internal alkynes, arylalkynes and enynes were employed, the reaction yields were <15%. As a result, the strategy outlined in Scheme 1 is very limited and could only be applied to aliphatic terminal alkynes. A new synthetic approach to *O*-alkenyl-*N*-arylhydroxylamines or their derivatives is imperative in order to establish a broadly applicable and improved/complementary alternative to the Fischer indole synthesis. Additional drawbacks with the published work are the need to use excess alkynes (typically 1.8 equiv.) in order to compensate the competing C≡C triple bond hydration and often difficulties in separating the formed methyl ketones.

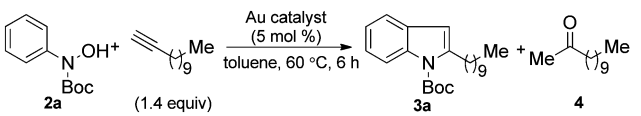
We reasoned that the thermostability of *N*-arylhydroxylamines can be much improved by converting them into hydroxamic acids or *N*-hydroxycarbamates; however, this modification is at the expense of the nucleophilicity of the HO group and hence the reaction rates. Although increasing the reaction temperature might compensate the rate loss, little improvement over the already long reaction duration could be expected unless a new design can be introduced. Herein, we disclose a solution by employing a rare cooperative gold and zinc catalysis,[14] which enables an efficient synthesis of *N*-protected indoles by using hydroxamic acids or *N*-hydroxycarbamates as substrates; notably, the Zn catalysis is similar to metal ion catalysis in metalloenzymes.

Results and discussion

We began the reaction condition studies by using *tert*-butyl *N*-hydroxy-*N*-phenylcarbamate **2a** as the substrate. While **2a** and its congeners in this work were prepared *via* sequential nitroarene reduction and protection,[15] they could also be prepared *via* Cu-[16] or Pd-catalyzed[17] cross coupling reactions. In the presence of a slight excess of 1-dodecyne and catalytic $Ph_3PAuNTf_2$, little indole **3a** was formed in toluene at 60 °C after 6 h. Instead, the hydration product, methyl ketone **4**, became significant over time (Table 1, entry 1). This result confirmed our initial fear that heating the reaction could not compensate the diminished nucleophilicity of **2a**. Further increasing the reaction temperature led to gold decomposition, and variation of other reaction conditions did not offer much improvement. We concluded that a new strategy had to be developed to dramatically improve this chemistry.

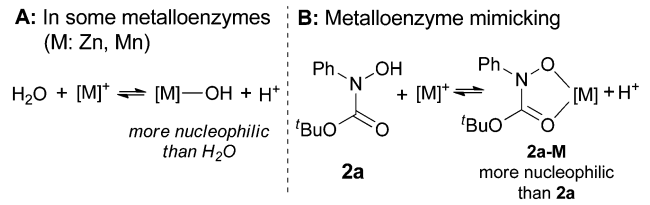
Inspired by the role of metal ions in enhancing the nucleophilicity of H_2O by forming metal hydroxides in metalloenzyme catalysis (Scheme 2A),[18] we wondered whether the nucleophilicity of **2a** would be enhanced in a similar manner. As shown in Scheme 2B, **2a** could react with a metal ion to form metal chelate **2a-M** and a proton reversibly. Due to the bidentate nature of the deprotonated **2a**, **2a-M** should be formed in a significant amount.[19] As in metalloenzyme catalysis, **2a-M** should be more nucleophilic than **2a** due to the increased negative charge on the deprotonated oxygen. The most common metal employed in hydrolytic or hydration metalloenzymes (*e.g.*, human carbonic anhydrase II) is Zn^{2+}. To our delight, when $Zn(OTf)_2$ (5 mol%) was added, the reaction was drastically accelerated, and **3a** was formed in 62% yield in 6 h (Table 1, entry 2). Other metal salts (Table 1, entries 3–5), however, did not work nearly as well. Subsequent variation of the gold

Table 1 Screening gold catalysts and reaction conditions[a]



Entry	Catalyst	Additive (5 mol%)	Yield[b] 3a	4
1	$Ph_3PAuNTf_2$	—	2%[c]	26%
2	$Ph_3PAuNTf_2$	$Zn(OTf)_2$	62%	45%
3	$Ph_3PAuNTf_2$	$Sc(OTf)_3$	20%	60%
4	$Ph_3PAuNTf_2$	$Cu(OTf)_2$	4%	54%
5	$Ph_3PAuNTf_2$	$Dy(OTf)_3$	23%	62%
6	$(4\text{-}CF_3Ph)_3PAuNTf_2$	$Zn(OTf)_2$	77%	37%
7	$IPrAuNTf_2$	$Zn(OTf)_2$	40%[c]	60%
8	$(\mathbf{ArO})_3PAuNTf_2$[d]	$Zn(OTf)_2$[e]	91%[f]	36%
9	$(\mathbf{ArO})_3PAuOTf$[d]	$Zn(OTf)_2$[e]	90%	38%
10	$Et_3PAuNTf_2$	$Zn(OTf)_2$	41%[c]	11%
11	$BrettphosAuNTf_2$	$Zn(OTf)_2$	83%	39%
12	Dichloro(2-picolinato)gold(III)	$Zn(OTf)_2$	0%[c]	1%
13	$Ph_3PAuCl/AgClO_4$	$Zn(OTf)_2$	20%[c]	21%
14	$PtCl_2$	$Zn(OTf)_2$	5%[c]	24%
15	—	$Zn(OTf)_2$	—	—
16	$(\mathbf{ArO})_3PAuNTf_2$[d]	—[g]	4%[c]	76%
17	$(\mathbf{ArO})_3PAuNTf_2$[d]	HOTf (10%)[h]	6%[c]	64%
18	$(\mathbf{ArO})_3PAuNTf_2$[d]	$Zn(OTf)_2$[e,i]	48%[c]	27%

[a] Reaction run in oven-dried vials with anhydrous toluene; [**2a**] = 0.1 M. [b] Estimated by ^1H NMR using diethyl phthalate as the internal reference; to be consistent, the yield of **4** is also based on **2a**. [c] **2a** left. [d] **Ar** = 2,4-di-*tert*-butylphenyl. [e] Reaction time: 2 h. [f] 90% isolated yield. [g] Reaction time: 12 h. [h] Reaction time: 3 h. [i] $NaHCO_3$ (1 equiv.) added; reaction time: 12 h; 51% of the alkyne remained.



Scheme 2 Enhancing the nucleophilicity of **2a** by a metal ion.

catalyst (entries 6–13) showed that $(\mathbf{Ar}O)_3PAuNTf_2$ (**Ar** = 2,4-di-*tert*-butylphenyl)[20] gave the best yield of the desired product (Table 1, entry 8). While the related gold triflate was nearly as effective (entry 9), $PtCl_2$ was ineffective (Table 1, entry 14), and no reaction was detected without gold (entry 15). The importance of $Zn(OTf)_2$ was again confirmed as only a little product was formed in its absence (Table 1, entry 16) or by replacing it with HOTf (10 mol%) (Table 1, entry 17). The latter result indicates that the Brønsted acid generated in Scheme 2B is not responsible for the dramatic rate acceleration, but it is crucial for catalyst turnover as the reaction was substantially slowed in the presence of $NaHCO_3$ (1 equiv., entry 18).

It is noteworthy that only 5 mol% of $Zn(OTf)_2$ was needed, therefore making this reaction an interesting cooperation between a gold catalysis and a Zn catalysis. Notably, this type of cooperative dual metal catalysis involving gold is rare.[21]

The scope of the reaction was then studied. As shown in Table 2, various functionalized aliphatic terminal alkynes were readily allowed, and the desired 2-substituted indoles **3** were formed regiospecifically in mostly good to excellent yield (entries 1–10). Comparing to our previous chemistry based on *N*-arylhydroxylamines, this method requires shorter reaction time (2–8 h *vs.* ~20 h) and less alkyne (1.4 equiv. *vs.* 1.8 equiv.), generally results in higher yields and allows much easier product purification. Albeit the raised reaction temperature (60 °C) and the use of Lewis acid $Zn(OTf)_2$, the reaction conditions were still very mild as the Boc group was not touched. In comparison, the Fischer method, in addition to the aforementioned issues (*i.e.*, harsh acidic conditions and moderate regioselectivities), could not afford the *N*-unprotected forms of chloroindole **3f** (entry 5), due to the interference of the chloro group,[22] and may not be applicable to the synthesis of indole **3h** (entry 7), due to likely elimination of benzyl alcohol from the corresponding methyl ketone substrate under strongly acidic conditions.

To our delight, substituents on the benzene ring *para* to the hydroxylamine moiety can vary from electron-withdrawing ones (entries 11 and 12) to electron-donating ones (entries 13–15) with good to excellent reaction efficiencies. With an electron-donating *p*-MeO group, the *N*-Boc hydroxylamine was labile at the reaction temperature, and the yield was only 40%; however, swapping the Boc group with an acetyl provided sufficient substrate stability, and the yield was improved to 80% in the presence of 10% $Zn(OTf)_2$ (entry 15). Notably, the corresponding free hydroxylamine, *N*-(4-methoxyphenyl)hydroxylamine, is labile even at ambient temperature and, therefore, could not be employed in our previous indole chemistry.[9] An *ortho*-Me group led to 25% yield of the desired product, which is attributed to sterics but can be complemented by the Bartoli reaction. A *meta*-Me group led to a good combined yield, albeit with a low regioselectivity (entry 14). While this chemistry provides indoles with the nitrogen protected by readily removable Boc groups, other groups such as methoxycarbonyl (entries 12, 14 and 16) and acetyl (entries 15 and 17) can also be incorporated. Since protection of the indole NH group is often required in multi-step synthesis and acyl or alkoxycarbonyl groups are frequently used for this purpose, this chemistry, directly offering such *N*-protected indoles, could prove to be advantageous in the total synthesis of indole alkaloids.

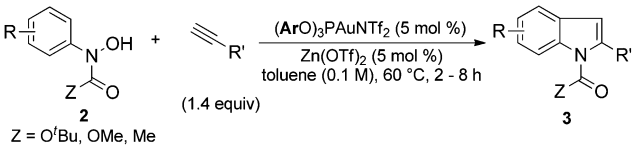
Although the above studies have firmly established that this novel dual Zn/Au catalysis is better than our previous study in the synthesis of 2-alkylindoles in terms of reaction scope, synthetic efficiency, reaction time and ease of purification, a categorical superiority by the new approach would be ascertained by expanding the reaction scope beyond what the previous method would achieve. With this in mind, we examined terminal enynes and internal alkynes, both of which were not suitable substrates in our previous work.

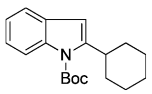
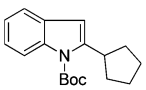
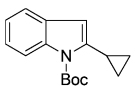
In the case of terminal enyne substrates, 2-alkenylindoles were the expected products. Notably, they could not be prepared *via* the Fischer indole synthesis,[5] either, as the ketone substrates, α,β-unsaturated ketones, typically react with arylhydrazines to form pyrazolines.[23]

To our delight, with this cooperative Au/Zn catalysis, these synthetically useful diene-type indoles[24] were readily prepared by using terminal enynes as substrates. As shown in Table 3, different alkenyl groups (entries 1–5) including sterically demanding cyclohexenyl (entry 1) and conjugated β-styryl (entry 3) were smoothly installed at the indole 2-position. Similar to aliphatic terminal alkynes, the reaction was regiospecific, and no 3-alkenylindole was observed. In entry 5, the increased product *E*/*Z* ratio might be due to acid-promoted isomerization. Both electron-withdrawing and electron-donating substituents on the benzene ring were readily allowed (entries 6–11), and other nitrogen protecting groups such as methoxycarbonyl (entries 8, 10 and 12) and acetyl (entries 2, 11 and 13) could easily replace the Boc group. In the cases of *N*-methoxycarbonyl groups, 1,2-dichloroethane was a better solvent. Of note, for all the cases involving more sterically demanding cyclohexenyl groups, the cyclodehydrative indole formation did not complete until further heating at 80 °C for 4–8 h.

An inherent issue with the Fischer indole synthesis is the low regioselectivity[25] with unsymmetric ketones with the following generic formulae, $R^1CH_2C(O)CH_2R^2$ (R^1, $R^2 \neq$ H, Ar). To probe whether our chemistry offers a solution to this long standing problem, we examined various internal alkynes by using *N*-hydroxy-*N*-phenylacetamide (**2b**) as the substrate. The results are shown in Table 4. First of all, internal alkynes with moderate steric demand were allowed, but due to their decreased reactivities compared to the terminal ones, the reactions were slower (18–30 h) even with increased amounts of $Zn(OTf)_2$ (20 mol%); moreover, much more thermostable IPrAuOTf, though less reactive, was a better catalyst than $(\mathbf{Ar}O)_3PAuNTf_2$ as the reaction could not proceed to completion with the latter as

Table 2 Formation of *N*-protected 2-alkylindoles[a]



1		2		3	
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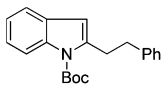
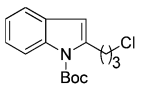
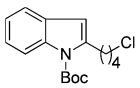
4		5		6	
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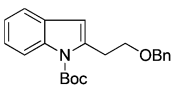
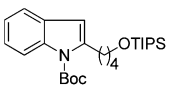
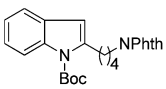
7		8		9	
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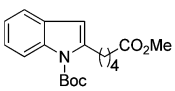
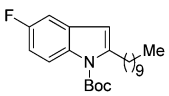
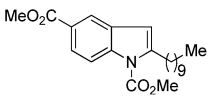
10		11		12	
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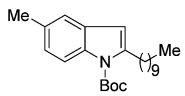
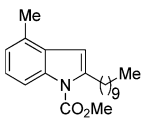
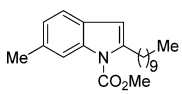
13		14[b]	 		
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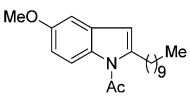
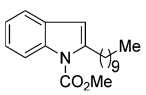
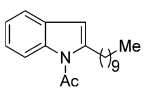
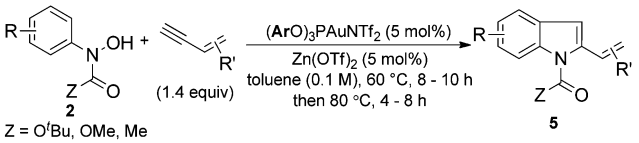
15[b,c]		16[b,d]		17	
	3p, 80%		**3q**, 81%[c]		**3r**, 90%

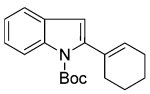
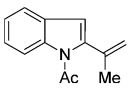
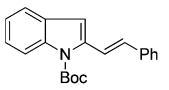
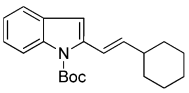
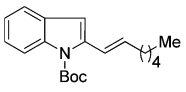
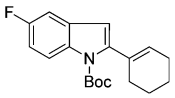
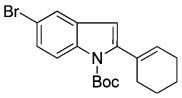
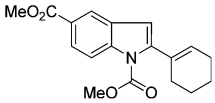
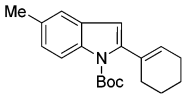
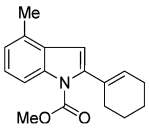
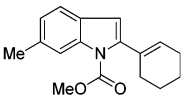
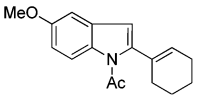
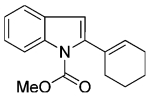
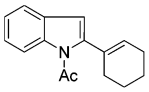
[a] Reactions run in oven-dried vials; isolated yields are reported; **Ar** = 2,4-di-*tert*-butylphenyl. [b] 2 equivalents of dodecyne. [c] 10% Zn(OTf)$_2$. [d] DCE as solvent.

the catalyst. With the symmetric 6-dodecyne, the indole product **6a** was isolated in 74% yield (entry 1). With methylalkynes (entries 2–7), the regioisomers with the methyl group at the 2 position were always favored, apparently due to its smaller size. With primary groups at the other end, the selectivities were around 6–8 : 1 (entries 2, 4, and 5). Interestingly, a similar selectivity was observed with a Ph group (entry 7), suggesting that steric control is dominating over electronics. By increasing the steric size of the group (*i.e.*, a cyclohexyl group, entry 3), the selectivity was enhanced to >19 : 1. There is a notable electronic effect when a strongly inductive PhthN group is present (entry 6, *vide infra*), and the selectivity and the yield were synthetically desirable. While the above products could be obtained selectively by the Fischer indole synthesis using the corresponding methyl ketones in most cases, the successful formation of the ketone product **6d** shows another example of functional group tolerance offered by this chemistry but unattainable by the Fischer approach.

For internal alkynes with one end substituted by a primary alkyl group, the one with a cyclohexyl group on the other end of the alkyne (*i.e.*, but-1-ynylcyclohexane) was apparently sterically too demanding, and the reaction was very sluggish (21% yield). With a smaller isobutyl group, the reaction proceeded well (entry 8), and the small steric difference between the two alkyne ends was reflected by a 2.5/1 regioselectivity, favoring the one with ethyl at the indole 2 position. With differently protected hydroxyethyl groups (entries 9–11), the trend of regioselectivities clearly correlated with the inductive effect of the protecting groups. Hence, a synthetically useful selectivity (10.3 : 1, entry 9) was achieved by using a trifluoroacetate substrate. A somewhat synergy between sterics and induction resulted in an even better regioselectivity for the indole product **6l** (entry 12). It is important to note that the trifluoroacetyl group can be easily removed, therefore making this chemistry a convenient and regioselective approach to various 2-substituted indole-3-ethanols. In comparison, a recent gold catalysis using phenylhydrazine and hex-3-yn-1-ol under strong conditions (TsOH, toluene, 100 °C) led to the fully deprotected **6i** as a minor isomer,[26] and the Fischer method would most likely offer a similar result. These results demonstrated that unattainable

Table 3 Formation of *N*-protected 2-alkenylindoles[a]



1		2[b,c]		3[c]	
	5a, 83%		**5b**, 68%		**5c**, 74%
4[c]		5[c,d]		6	
	5d, 90%		**5e**, 86%		**5f**, 75%
7		8[e]		9	
	5g, 65%		**5h**, 77%		**5i**, 80%
10[e]				11[b,f]	
	5j, 71% (1.5 : 1)				**5k**, 75%
12[e]		13			
	5l, 86%		**5m**, 92%		

[a] Reactions run in oven-dried vials; isolated yields are reported; **Ar** = 2,4-di-*tert*-butylphenyl. [b] 2 equiv. of the enyne. [c] The reaction was run at 60 °C for 12 h. [d] The enyne *E*/*Z* = 9 : 1, and the product *E*/*Z* > 19 : 1. [e] Solvent: DCE. [f] 10 mol% of $Zn(OTf)_2$.

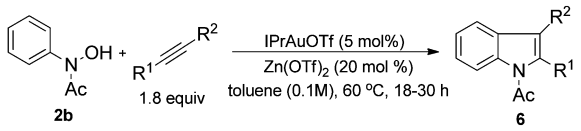
regioselectivities in the Fischer chemistry could be realized by judicial choices of protecting groups in this dual metal catalysis.

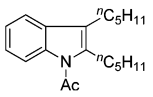
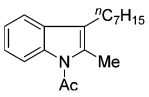
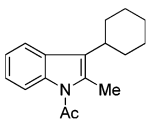
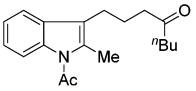
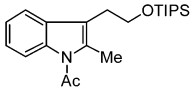
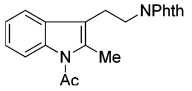
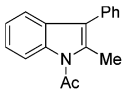
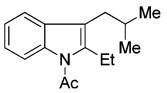
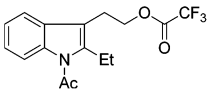
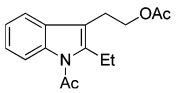
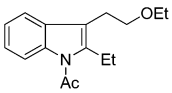
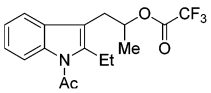
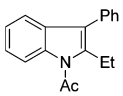
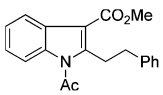
Compared to the methyl group in entry 7, the use of an Et group in entry 13 expectedly led to a decreased regioselectivity, although the Ph group at the 3 position was still favored. A more electronically biased triple bond in entry 14 led selectively to the regioisomer following an initial Michael-type addition.[27]

A reaction mechanism is proposed in Scheme 3. First, the hydroxamic acid or related acylated substrate **2** is activated *via* the formation of the zinc chelate **2-Zn**. This more *O*-nucleophilic intermediate can then attack the gold-activated alkyne effectively, forming the precursor (*i.e.*, **7**) for the 3,3-sigmatropic rearrangement upon subsequent protodeauration. After the rearrangement, a subsequent cyclodehydration, most likely facilitated by the Lewis acidic $Zn(OTf)_2$, leads to the desired indole product.

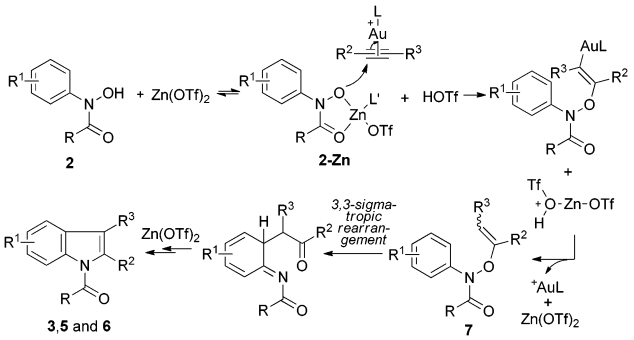
The observed regioselectivities are rationalized in Fig. 1: first of all, the zinc hydroxamate **2-Zn** is sterically bulky, likely due to additional ligands on the metal, and preferably attacks the less hindered end of internal alkynes (Fig. 1A). With terminal alkynes including enynes, the internal end of the C≡C triple bond is much less negatively charged than the terminus [*e.g.*, the difference of the natural charges (NC) of the alkyne ends computed by using DFT calculations (B3LYP/6-31G*) is 0.22 with R = Et, Fig. 1B], which is also reflected by the ^{13}C chemical shifts.[28] The electronic difference totally overrides the steric disparity, resulting in an exclusive nucleophilic attack at the more electrophilic internal end. For alkynes with conjugated electron-withdrawing groups, the polarization of the triple bond is again significant; for example, in Fig. 1C, ΔNC and $\Delta\delta(^{13}C)$ between the two sp-hybridized carbons are 0.249 and 15.33 ppm, respectively; the electronic difference, quantitatively similar to that in the terminal alkyne 1-butyne (Fig. 1B), is consistent with the observed excellent selectivity. For those with non-conjugated electron-withdrawing groups, the often overlooked inductive effects[29] can be significant. Such an induction results in less electron density at the distal end of the C≡C triple bond than at the proximal end, which is confirmed by the calculated NCs and the observed ^{13}C chemical shifts of the alkyne substrates for entries 6 and 9–11 in Table 4 (Fig. 1D). This electronic bias predicts correctly the selective attack by the nucleophilic hydroxamate at the distal end in the absence of significant steric disparity and, moreover, correlates in a roughly quantitative manner with the regioselectivity observed in entries 9–11,Table 4.

Table 4 Regioselective formation of *N*-acetyl-2,3-disubstituted indoles[a]



1		2		3	
	6a, 74%		**6b**, 61% (7.4 : 1)[b]		**6c**, 67% (>19 : 1)[b]
4		5		6	
	6d, 68% (6.8 : 1)[b]		**6e**, 52% (6 : 1)[b]		**6f**, 80% (16.6 : 1)[b]
7		8		9	
	6g, 61% (8 : 1)[b]		**6h**, 75% (2.5 : 1)[c,d]		**6i**, 65% (10.3 : 1)[c]
10		11		12	
	6j, 77% (5.6 : 1)[c]		**6k**, 86% (2 : 1)[c]		**6l**, 69% (12 : 1)[c]
13		14		15	
	6m, 70% (2.9 : 1)[c]		**6n**, 66% (>20 : 1)		

[a] Reactions run in oven-dried vials; isolated yields of the major isomers are reported if not specified. [b] Regioselectivity; the major isomer is shown. [c] Overall yields of both isomers are reported. [d] 2 equiv. of 6-methylhept-3-yne was used.



Scheme 3 Proposed reaction mechanism.

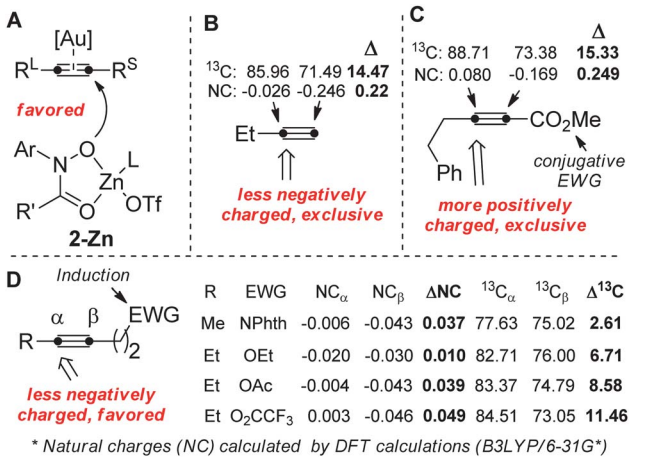
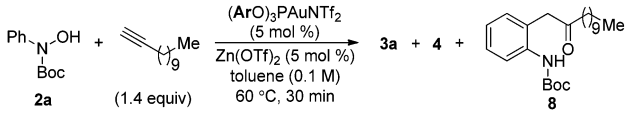


Fig. 1 Rationales for the reaction regioselectivity on alkynes.

To substantiate the notion that catalytic $Zn(OTf)_2$ enhances the nucleophilicity of *N*-arylhydroxamic acids/*N*-aryl-*N*-hydroxycarbamates, we probed the competition between the addition of **2a** to 1-dodecyne and its hydration by varying the amount of the metal salt. As shown in Table 5, the reactions were stopped after 30 min in order to glean early stage rate differences. When toluene saturated with H_2O was used as the solvent, there was a clear correlation between the amount of $Zn(OTf)_2$ and the ratio of products due to **2a** addition (*i.e.*, **3a** and **8**) and hydration (*i.e.*, **4**), suggesting that $Zn(OTf)_2$ increases the rate of **2a** addition (entries 1–5). Notably, the amount of the hydration product, methyl ketone **4**, did not change much as the amount of the zinc salt increased, indicating that hydration was not much affected by the salt. Under anhydrous conditions, water was generated upon the cyclodehydration of **8**. Again, a positive correlation was observed when the amount of $Zn(OTf)_2$ was varied from 0%

Table 5 Examination of the role of $Zn(OTf)_2$[a]



			Yield[b]			
Entry	Toluene	$Zn(OTf)_2$	**3a**	**4**	**8**	(**3a** + **8**)/**4**
1	Wet[c]	0	<1	18%	<1	—
2	Wet[c]	1 mol%	9%	19%	16%	1.3
3	Wet[c]	5 mol%	29%	21%	27%	2.7
4	Wet[c]	10 mol%	50%	21%	25%	3.6
5	Wet[c]	20 mol%	67%	21%	19%	4.1
6	Anhydrous[d]	0	0	1.4%	0	0
7	Anhydrous[d]	1 mol%	13%	7%	16%	4.1
8	Anhydrous[d]	5 mol%	41%	9%	25%	7.3
9	Anhydrous[d]	10 mol%	57%	11%	20%	7.0
10	Anhydrous[d]	20 mol%	78%	17%	13%	5.4

[a] [**2a**] = 0.1 M; **Ar** = 2,4-di-*tert*-butylphenyl. [b] NMR yield estimated by using diethyl phthalate as the internal reference. [c] Saturated with deionized water, and reactions run in vials. [d] Reaction run in Schlenk tubes.

(entry 6) to 5 mol% (entry 8); moreover, the preference toward **2a** addition was expectedly better than in wet toluene. The decreased preferences in entries 9 and 10 reflect the significant increase of the amount of by-product H_2O, which leads to increasing hydration. These results are consistent with the proposed role of $Zn(OTf)_2$. Expectedly, it, being Lewis acidic, also facilitated the cyclodehydration (comparing the ratios of **8**/**3a**); notably, the gold catalyst can also promote the process, albeit much slower (93% **8** converted into **3a** in the presence of 5 mol% $(\mathbf{Ar}O)_3PAuNTf_2$ in toluene at 60 °C for 6 h).

Conclusions

We have developed an efficient and general synthesis of *N*-protected indoles *via* the annulation of *N*-arylhydroxamic acids/*N*-aryl-*N*-hydroxycarbamates and alkynes. It is synthetically superior to our previous chemistry based on *N*-hydroxylamines. The reaction scope is broad, and the reaction conditions are mild. The indole nitrogens are substituted with acyl or alkoxycarbonyl groups, which could be advantageous as these groups often offer desirable *N*-protection in complex molecule synthesis. With terminal alkynes, this reaction is regiospecific and offers 2-substituted indoles and tolerates a range of functional groups. Notably, various 2-alkenylindoles, useful substrates for the Diels–Alder reaction as dienes but not accessible *via* the Fischer indole synthesis, can be readily prepared from 3-en-1-ynes. This chemistry also works with internal alkynes of moderate steric demand, and the regioselectivity can be controlled both by sterics and/or by electronics: the small substituent on the C≡C triple bond ends up selectively at the indole 2-position, and the electron-withdrawing groups direct the substituents to the indole 3 positions *via* either induction or conjugation. With judicial choices of protecting groups, good to excellent regioselectivities with internal alkynes can be achieved. Importantly, this chemistry is a rare example of cooperative dual catalysis involving gold and the first example of gold-catalyzed intermolecular addition of hydroxamic acids/*N*-aryl-*N*-hydroxycarbamates to alkynes. Catalytic $Zn(OTf)_2$ enhances the nucleophilicity of these hydroxylamine derivatives *via* the formation of deprotonated chelates, which is similar to the metal ion catalysis in metalloenzymes.

Acknowledgements

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Notes and references

1 (*a*) B. Robinson, *The Fischer Indole Synthesis*, Wiley, Chichester, New York, 1982; (*b*) R. S. Downing and P. J. Kunkeler, in *Fine Chemicals Through Heterogenous Catalysis*, ed. R. A. Sheldon and H. Bekkum, Wiley-VCH, Weinheim; New York, 2001, pp. 178–183; (*c*) D. L. Hughes, *Org. Prep. Proced. Int.*, 1993, **25**, 607–632.

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