Heterocycles

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Umpolung Reactivity of Indole through Gold Catalysis**

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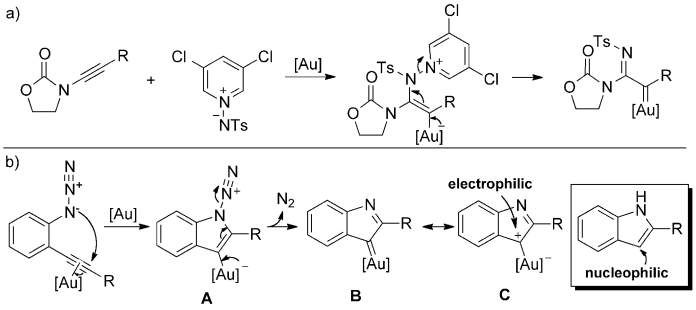
The 3-position of indole is highly electron rich and typically functions as the primary nucleophilic site that reacts with a large array of electrophiles, thereby leading to various functionalized indoles.[1] The reversal of this prime reactivity, that is, making the 3-position of indole electrophilic, would be of significant synthetic utility and provide a complementary strategy to access derivatives[2] otherwise difficult to prepare conventionally. This umpolung[3] reactivity of indole has, however, only been realized in a limited number of cases.[4]

For the past few years we have engaged in extensive studies of gold-catalyzed intra-[5] and intermolecular[6] alkyne oxidations using oxygen-delivering oxidants,[7] wherein reactive α-oxo gold carbene intermediates are presumably generated[8] and responsible for the diverse reaction outcomes. Lately we extended this strategy to the use of nitrene precursors as oxidants, thus providing access to reactive α-imino gold carbenes (Scheme 1 a);[9] however, the chemistry has so far been limited to ynamides,[10] which are activated alkynes. In our effort to expand the scope of this type of gold-catalyzed nitrene transfer,[11] we decided to use an azido group as a nitrene precursor, a choice that was inspired by previous studies of gold-[12] and platinum-catalyzed[13] pyrrole synthesis. We reasoned that closely and rigidly positioned C≡C bonds in *ortho*-azidoarylalkynes might facilitate an intramolecular nitrene transfer from the azido group. Importantly, the thus-formed gold carbene **B** would serve as an electrophilic indole equivalent, as depicted in its resonance form **C**, thereby realizing umpolung reactivity of the 3-position of indole (Scheme 1 b).[14]



Scheme 1. Gold-catalyzed nitrene transfer: realizing umpolung reactivity at the 3-position of indole. Ts = 4-toluenesulfonyl.

We started by using *ortho*-azidophenylalkyne (**1a**) as the substrate and anisole as the nucleophile, and the initial reaction was run in toluene using $Ph_3PAuNTf_2$[15] as the catalyst. To our delight, the desired indole regioisomers **2a** and **2a′** were indeed formed (Table 1, entry 1), thus confirming that the azido group could function as a nitrene precursor and a gold carbene of type **B** might be indeed formed. Moreover, this proposed reactive intermediate seemingly reacted mainly via its cationic resonance form **C**[16] as no Büchner reaction,[17] that is, the formation of cycloheptatriene products that is characteristic of carbene chemistry, occurred. The regioselectivity on the anisole ring is consistent with an electrophilic aromatic substitution mechanism. To our surprise, the majority of the gold intermediate **B**/**C** reacted with the solvent toluene, thereby yielding a mixture of regioisomers (*p*-**3**/*o*-**3**/*m*-**3** = 41:11:8 %). Although the concentration of toluene is approximately 190 times that of anisole, anisole is much more nucleophilic than toluene.[18] These results indicate that the intermediate **C** is strongly electrophilic and hence less selective. This conclusion is consistent with the ratio of *p*-**3** versus *m*-**3** (ca. 5), which is lower than that in the case of nitration (>10),[19] thus suggesting that **C** might be even more electrophilic than NO_2^+. Since products of type **2a**, **2a′**, and **3** are also good nucleophiles, we anticipated that it is essential to use excess intended nucleophiles to minimize their competing reactions with highly electrophilic **C**.

Other solvents were screened to minimize solvent participation (Table 1, entries 2–4). Whereas benzene also interfered the desired reaction (entry 2), neither 1,2-DCE (entry 3) nor chlorobenzene (entry 4) did; a better reaction yield was realized in 1,2-DCE. Examination of different gold catalysts (entries 5–10) at a beneficial higher reaction temperature (comparing entries 3 and 5) revealed that $IPrAuNTf_2$ (entry 6) gave the best yield and bulky *t*BuXPhosAuNTf$_2$ gave the best *para*/*ortho* ratio (entry 8). We also ran the reaction using anisole as the solvent at a higher concentration (0.2 M). Somewhat to our surprise, the reaction was dramatically faster and finished after 5 minutes at 80 °C; moreover, the yield was excellent. Perhaps even more surprising is that the *para*/*ortho* ratio decreased as the reaction temperature was lowered (compare entries 11–13). This may suggest the involvement of another reaction mechanism. As shown in Scheme 2, at a higher temperature (e.g., 80 °C) the formation of **B**/**C** should be facilitated, but at a lower temperature (e.g., −20 °C) its precursor, that is, **A**, may persist and play an increasing role in the reaction by reacting with nucleophiles

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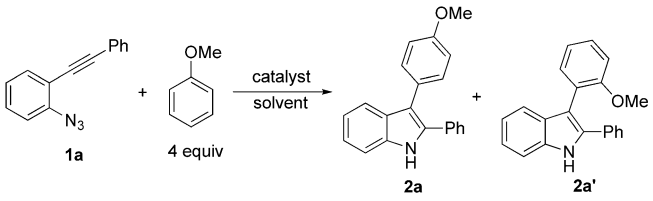
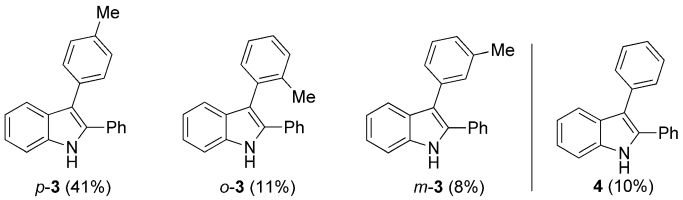
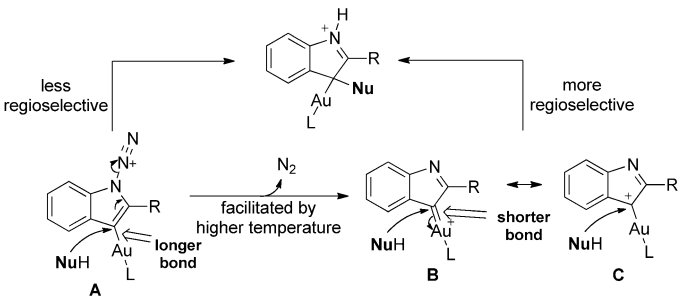
Table 1: Initial discovery and reaction conditions optimization.[a]



Entry	Catalyst	Solvent	T [°C]	t	Yield [%][b]	**2a**/**2a′**
1	$Ph_3PAuNTf_2$	toluene	60	11 h	20[c]	2.4
2	$Ph_3PAuNTf_2$	benzene	60	11 h	40[d]	2.4
3	$Ph_3PAuNTf_2$	1,2-DCE	60	11 h	52	1.9
4	$Ph_3PAuNTf_2$	PhCl	60	11 h	44	2.1
5	$Ph_3PAuNTf_2$	1,2-DCE	80	11 h	60	1.9
6	$IPrAuNTf_2$	1,2-DCE	80	11 h	81	4.3
7	Cy-JohnPhos-$AuNTf_2$	1,2-DCE	80	11 h	60	2.7
8	*t*BuXPhosAuNTf_2	1,2-DCE	80	11 h	66	8.6
9	$(ArO)_3PAuNTf_2$[e]	1,2-DCE	80	11 h	73	2.0
10	$AuCl_3$	1,2-DCE	80	11 h	<20	–
11	*t*BuXPhosAuNTf_2	anisole (0.2 M)	80	5 min	>95[f]	6.5
12	*t*BuXPhosAuNTf_2	anisole (0.2 M)	40	1.5 h	>95	5.2
13	*t*BuXPhosAuNTf_2	anisole (0.2 M)	−20	12 h	>95	3.9

[a] [**1**] = 0.05 M. [b] Estimated by ^{1}H NMR spectroscopy using diethyl phthalate as the internal reference. [c] The regioisomers **3** (see below) were formed from reaction with the solvent, toluene. [d] 2,3-Diphenylindole (**4**; see below) was formed in 10% yield. [e] Ar = 2,4-di-*tert*-butylphenyl. [f] Yield of isolated product: 89%. 1,2-DCE = 1,2-dichloroethane.



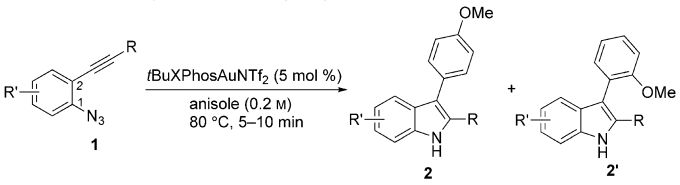


Scheme 2. Rationale for the inverse relationship between regioselectivities and reaction temperatures.

through an S_N2' process. Since the Au–C bond length in **B**/**C** should be shorter than the Au–C bond in **A**, one might expect that the more the reaction goes through **B**/**C** the more regioselective it is and the bulky ligand (i.e., *t*BuXPhos) can be more sterically imposing.[20]

The scope of the *o*-azidoarylalkynes was subsequently examined by first varying the alkyne substituent. By using

Table 2: The scope of *o*-azidoarylalkyne substrates.[a]



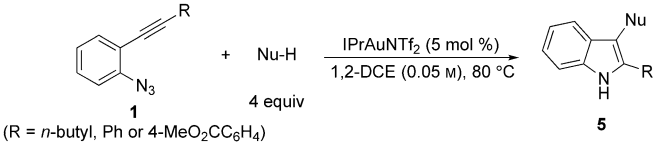
Entry	**1** (R)	R′	**2**	**2**/**2′**	Yield [%][b]
1	**1b** (*n*-butyl)	H	**2b**	7:1	74
2	**1c** ($PhCH_2CH_2$)	H	**2c**	5:1	83
3	**1d** ($BnOCH_2$)	H	**2d**	5:1	51[c]
4	**1e** (cyclopropyl)	H	**2e**	8:1	76
5	**1f** (cyclopentyl)	H	**2f**	15:1	75
6	**1g** (cyclohexyl)	H	**2g**	16:1	82
7	**1h** (*tert*-butyl)	H	**2h**	25:1	75
8	**1i** (H)	H	**2i**	3:1	91
9	**1j** (p-$MeOC_6H_4$)	H	**2j**	7:1	76
10	**1k** (p-$MeO_2CC_6H_4$)	H	**2k**	7:1	95
11	**1l** (*n*-butyl)	4,6-Me_2	**2l**	8:1	82
12[d]	**1m** (*n*-butyl)	3,5-Cl_2	**2m**	7:1	78

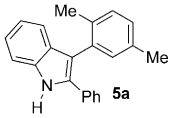
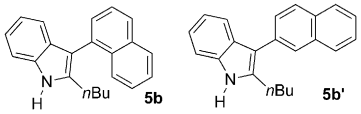
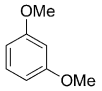
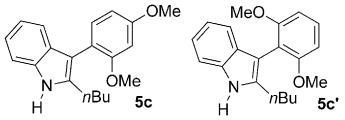
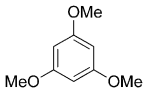
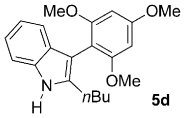
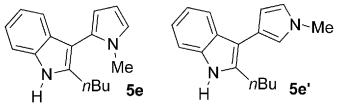
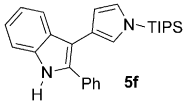
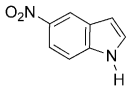
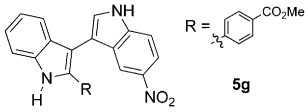
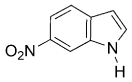
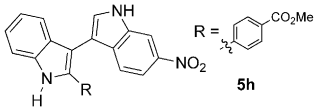
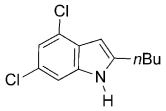
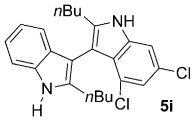
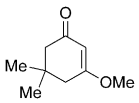
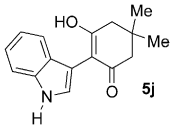
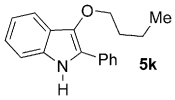
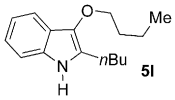
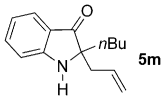
[a] Reaction was run in a vial. [b] Combined yield of **2** and **2′** upon isolation. [c] About 4% of **7** [see Eq. (2)] was formed. [d] Reaction time: 1 h.

anisole as the solvent, primary alkyl groups such as *n*-butyl (Table 2, entry 1) and phenethyl (entry 2) reacted smoothly. A lower yield was obtained with **1d** containing a benzyl ether (entry 3), and cyclic secondary alkyl groups (entries 4–6) as well as a *tert*-butyl group (entry 7) all led to good yields. Interestingly, substrate **1i** having a terminal alkyne also worked (entry 8), and aryl groups with either a *p*-MeO (entry 10) or a *p*-methoxycarbonyl group (entry 11) were readily tolerated and the corresponding indoles were isolated in good to excellent yields. In all the cases, the regioselectivities correlated well with the bulk of the substitutent, and the best **2**/**2′** ratio was realized with the *tert*-butyl alkyne **1h** (entry 7). In addition, substrates with substituted benzene rings reacted with good efficiencies, thus affording highly substituted indole products (entries 11 and 12).

The applicability of this chemistry to other nucleophiles was then probed by using the reaction conditions from entry 6 in Table 1, and the successful examples are shown in Table 3. As expected, *p*-xylene, when used as the solvent, served as a suitable nucleophile for this chemistry (entry 1). In the case of naphthalene, the α position is preferred because of its stronger nucleophilicity (entry 2). More-activated benzene rings (entries 3 and 4) gave good yields of the desired products, and a good selectivity (10:1) was observed with 1,3-dimethoxybenzene, thus reflecting the more congested nature of the 2-position. In the case of *N*-methylpyrrole, apparently the electronic and the steric factors were working against each other, therefore no regioselectivity was observed (entry 5); however, the overall efficiency was excellent. Increasing the steric hindrance at the pyrrole 2-position by installing a TIPS group on the ring nitrogen atom indeed made the reaction proceed selectively at the 3-position (entry 6). When *N*-benzylindole was used as

Table 3: The scope of different nucleophiles.[a]

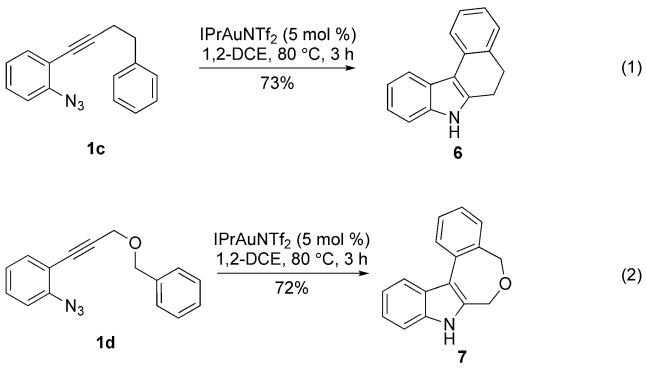


Entry	NuH	*t* [h]	**5**	**5/5′**[b]	Yield [%][c]
1	*p*-xylene[d]	5	 **5a**	–	70
2		3	 **5b** **5b'**	6:1	78
3		3	 **5c** **5c'**	10:1	84
4		3	 **5d**	–	84
5		8	 **5e** **5e'**	1:1	91
6[e]		12	 **5f**	–	69[f]
7		3	 **5g**	–	83
8		3	 **5h**	–	81
9		3	 **5i**	–	64
10		1	 **5j**	–	49
11	*n*BuOH	15	 **5k**	–	66
12	*n*BuOH	12	 **5l**	–	62
13	allyl alcohol	10	 **5m**	–	65

[a] [**1**] = 0.1 M. [b] Regioisomers not separated. Ratio determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] Used as solvent. [e] 10 mol% of IPrAuNTf$_2$ used. [f] The regioselectivity is >9:1, and the yield reported is that of the major isomer. Bn = benzyl; TIPS = triisopropylsilyl.

the nucleophile, to our surprise, at least three inseparable regioisomers were formed, suggesting that its benzene ring participated in this reaction as the nucleophilic site. To our delight, with the strongly electron-withdrawing nitro group on the indole benzene ring, the substitution selectively occurred on the 3-position, thus affording nonsymmetrical 3,3′-bis(indole)s with good yields (entries 7 and 8). The use of the more polar azidoalkyne substrate **1k** facilitated purification of the products. With the indole 2-position substituted and its benzene ring again deactivated, the electrophilic substitution proceeded as expected at the 3-position to yield the bis(indole) **5i**. Notably, the 3,3-bis(indole) structure has been found in natural products[21] and compounds of medical interest,[22] and their syntheses often require multiple steps.[23] Dimedone methyl ether could react as a nucleophile as well, albeit accompanied by in situ hydrolysis and in a relatively low reaction yield (entry 10). In addition to carbon nucleophiles, alcohols could react with intermediates of type **C** (entries 11 and 12). The moderate yields were to some extent due to the susceptibility of the products towards aerobic oxidation. Interestingly, with allyl alcohol as the nucleophile, the product underwent a one-pot Claisen rearrangement, thus yielding the indol-3-one **5m** in a serviceable yield (entry 13). Notably, no desired product was observed when using *N*-methyltosylamide as the nucleophile.

This umpolung reactivity of indole was briefly tested in intramolecular scenarios. With the azidoalkyne **1c**, in the absence of an external nucleophile such as anisole (e.g., in Table 2, entry 2), the tethered benzene ring reacted as the nucleophile, efficiently trapping the electrophilic indole 3-position, and thereby forming the tetracyclic product **6** in a good yield [Eq. (1)]. To our surprise even a seven-membered ring **7** could be readily formed through this intramolecular trapping [Eq. (2)]; moreover, this



reaction appeared to be rather facile as the tetracyclic product **7** was formed in approximately 4% yield even when the anisole was used as the solvent (Table 2, entry 3), again implicating the high electrophilicity of the intermediate **B**/**C**.

In summary, we have developed a new approach to achieving umpolung reactivity of indole at the 3-position through gold catalysis. By using an *ortho*-azido group to deliver a nitrene intramolecularly, an arylalkyne can be converted into a gold carbene intermediate containing the indole skeleton that is highly electrophilic at the 3-position. The reaction of this electrophilic indole intermediate with various nucleophiles provides a novel and expedient synthesis of a range of functional indoles.

Experimental Section

General procedure for the gold-catalyzed formation of indole **5**: *o*-Azidoarylalkyne **1** (0.30 mmol) and $IPrAuNTf_2$ (12.9 mg, 0.015 mmol) were added to a solution of a nucleophile (1.2 mmol) in 1,2-DCE (3 mL) at room temperature. The reaction mixture was heated at 80°C, and the progress of the reaction was monitored by TLC. The reaction typically took 3 h. Upon completion, the mixture was concentrated and the residue was purified by silica gel flash chromatography (eluent: hexanes/ethyl acetate) to afford the desired products.

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Keywords: catalysis · gold · indole · nitrenes · umpolung

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