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Heterogeneous Catalysis

Cycloisomerization of 2-Alkynylanilines to Indoles Catalyzed by Carbon-Supported Gold Nanoparticles and Subsequent Homocoupling to 3,3′-Biindoles**

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Construction of biologically and pharmaceutically important indole moieties plays a prominent role in classic organic synthesis and modern catalysis. This role is not only due to the significance of the potential applications but also as a standard to calibrate the efficiency of a given method.[1,2]

Despite the fact that the cycloisomerization of 2-alkynylanilines provides one of the most direct and atom-economical manners to assemble indoles,[3,4] there are still no examples of any general protecting-group-free direct catalytic method capable of effecting this transformation heterogeneously.[5] Yet, in homogeneous catalysis this transformation has been successfully performed with gold-based systems.[4a,d,6]

Heterogeneous catalytic non-direct synthesis of indoles had remained unexplored until 2009, when Tokunaga and Haruta reported that indoles could be prepared from 2-alkynylnitrophenyls in moderate to high yields by a reductive cascade process catalyzed by Au/Fe_2O_3 nanoparticles (NPs).[7] However, the reductive nature of those conditions limited the reaction scope and precluded the possibility of further cascade functionalization. Soon after, Somorjai, Toste, and co-workers reported that Pt nanoparticles supported on mesoporous silica are able to efficiently promote the intramolecular heterocyclization of *N*-carbamate protected 2-alkynylanilines to afford the corresponding indole products in excellent yields.[8]

Cationic gold(I) salts have been the more effective catalysts in the homogeneous activation of alkynes for addition of various nucleophiles.[9] We have also recently shown that the cationic nature can be tuned in gold(III) catalyst to achieve a comparable performance.[4f] Furthermore, comprehensive studies by Corma et al.[12] have also demonstrated that cationic gold species could be responsible for alkyne activation rather than reduced metal nanoparticles in analogous heterogeneous transformations,[10,11] such as in the catalytic isomerization of ω-alkynylfurans to phenols, whereby the abundance of Au^{III} has a linear correlation with the catalytic activity of Au/CeO_2 NPs.[12] Analogously, cationic gold NPs have been invoked as the active catalytic species in the cycloisomerization of phenylpropargyl ethers to chromanes or in the oxidative cycloaddition of 1,1,3,3-tetramethyldisiloxane.[13,14] With these considerations in mind, herein we describe an effective general method for the heterogeneous cycloisomerization of 2-alkynylanilines to indoles along with an unprecedented domino cycloisomerization/C–H oxidative homocoupling[15] to furnish pharmaceutically relevant 3,3′-biindolyl products.[16] Novel tetracyclic indoles with a cyclooctatetraene substructure could also be obtained as a result of a cationic AuNP–carbon-support cooperative catalyzed process.

The cycloisomerization of 2-(*p*-tolylethynyl)aniline **1a** to indole **2a** in toluene at 90 °C was selected as a suitable catalytic model system to begin our investigations. Control experiments with catalytic amounts of *p*-toluenesulfonic acid (Table 1, entry 1) resulted in no conversion into indole and confirmed that any catalytic activity could be only ascribed to the corresponding heterogeneous gold catalyst and not to simple acid-assisted events.[17]

We began our screening with widely used gold catalysts immobilized by wet impregnation (WI) over a CeO_2 support. This catalyst afforded moderate yields (51 and 41 %), which depended on catalyst pre-treatment (Table 1, entries 2 and 3). In contrast, gold supported on TiO_2 gave only low yields (13 %) when the impregnation was conducted by deposition–precipitation (entry 4; World Gold Council reference catalyst). Carbon supports were then investigated. Sol immobilization (SI) techniques for pre-forming gold colloids before immobilization onto a carbon support results in some of the most active gold catalysts for a range of oxidation reactions.[18] However, such catalysts showed poor activity for our purpose (11 %, entry 5). Similarly, poor activities were also observed when the preparation method was based on wet impregnation (entry 6). Some improvement in yield (23 %) was achieved by the use of anionic adsorption (AA) method (entry 7).

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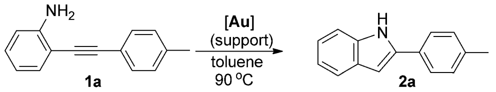
Table 1: Screening of catalysts for cycloisomerization of 2-(*p*-tolylethynyl)aniline (**2a**) to 2-(*p*-tolyl)-1*H*-indole (**2a**).[a]



Entry	1 wt% Au/support	Prep. method	Pre-treatment	Au loading [wt%]	*t* [h]	Yield (NMR) [%][b]
1	*p*-TsOH (0.2 equiv)/–	–	–	–	48	nr
2	/CeO_2[g]	WI[c]	80 °C vac. 4 h	1	48	51
3	/CeO_2	WI	110 °C vac. 17 h	1	48	41
4	/TiO_2	DP[d]	–	1	48	13
5	/carbon G-60	SI[e]	80 °C vac. 4 h	1	48	11
6	/carbon G-60[g]	WI[c]	80 °C vac. 4 h	1	48	11
7	/carbon G-60[g]	AA[f]	80 °C vac. 4 h	1	48	23
8	/carbon G-60	IW[h]	140 °C 18 h	0.5	16	96

[a] **1a** (0.05 mmol), in toluene (0.5 mL, 0.1 M). [b] Filtration through a plug of SiO_2 afforded a clean mixture exclusively consisting of starting material **1a** and indole product **2a**; ratio was determined by relative integration from ^1H NMR spectroscopy. nr = not recorded. [c] Catalyst prepared by the wet impregnation (WI) method and dried under vacuum (vac.) at 80 °C for 4 h. [d] Catalyst obtained from the World Gold Council. [e] Catalyst produced by sol immobilization (SI) followed by reflux and drying under vacuum at 80 °C for 4 h. [f] Catalyst prepared according to an anionic adsorption (AA) procedure and drying under vacuum at 80 °C for 4 h. [g] 2 wt% loading on support. [h] Treated with aqua regia, incipient wetness (IW).

Based on these preliminary results, we envisioned an increase in activity if the preparation method could be optimized in such a way to afford maximum concentration of cationic gold. Hutchings and co-workers have shown that the degree of cationic nature of gold in the carbon supported catalyst that were prepared by incipient wetness methods correlated with excellent performances in the hydrochlorination of acetylene.[11,19,20] We appreciated the analogy with our system and we produced a range of catalysts by incipient wetness (IW) with aqua regia (HNO_3/HCl 1:3) on active carbon following Hutchings' procedure.[20] We were pleased to find that by this strategy, total conversion was attained, and we could even reduce the catalyst loading from 1% to 0.5% and the reaction time from 48 h to 16 h while retaining excellent yields (Table 1, entry 8).

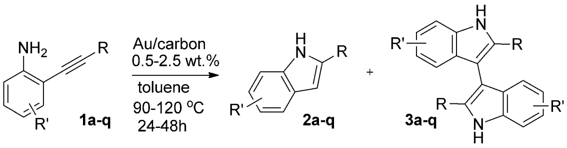
We then studied the effect of varying the substituents on the alkyne moiety and aryl ring over the catalytic activity under several reaction conditions (Conditions A–C, Table 2). For the approximately electroneutral substrates, cycloisomerization took place in high to excellent yields (entries 1, 2, and 9) by using 0.5 wt% catalyst loading at 90 °C in 24 h (conditions A).

As shown in Table 2, the catalytic performance seems to be negatively affected when electron-deficient substrates are employed, requiring higher catalyst loadings and longer reaction times (conditions B) to reach high conversions. For strongly electron-deficient substrates, increased temperatures were also necessary for the reaction to take place (conditions C). Introduction of a chlorine substituent at the aniline 4 or 5 position seems to be beneficial for the catalytic activity (entries 5–8), while replacement of the secondary aryl ring by an aliphatic propyl alkyl group proved detrimental and required harder conditions (entry 3).

In line with the reactivity pattern previously observed, the electron-rich *p*-methoxyphenyl substrate **1c** (entry 14) was converted rather quickly into indole **2c**, but to our surprise some amounts of the homocoupled 3,3′-biindole by-product **3c** were also found in the reaction mixture. Notably, further inspection revealed that a small amount of the homocoupling byproduct could be afforded for electroneutral phenyl alkynylaniline **1c** when higher catalyst loadings and extended reaction times were applied (entry 17). In general, all reactions proceeded cleanly and with excellent yields, except for the *p*-nitrophenyl alkynylaniline **1l**.

We then set to find conditions for quantitative formation of the biindoles **3**. We initially limited the scope to electroneutral and electron-rich alkynylanilines (Table 3). Increase of catalyst loading and

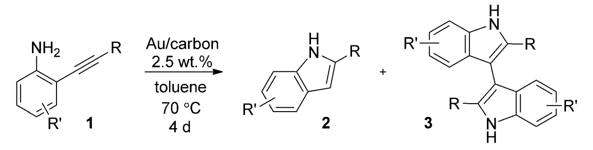
Table 2: Substrate scope for the Au/carbon catalyzed cycloisomerization of 2-alkynylanilines.[a]



Entry	1a–p	R	R′	Cond.[b]	Conv. [%][c]	2:3[c]	Yield of 2 [%][d]
1	**1a**	*p*-MeC_6H_4	H	A	93	100/0	92
2	**1b**	Ph	H	A	89	100/0	87
3	**1d**	*n*-propyl	H	B	91	100/0	87 (91)[e]
4	**1e**	*o*-$NH_2C_6H_4$	H	A	100	100/0	98
5	**1f**	*p*-MeC_6H_4	4-Cl	A	94	100/0	93
6	**1g**	Ph	4-Cl	A	100	100/0	99
7	**1h**	*p*-MeC_6H_4	5-Cl	A	93	100/0	92
8	**1i**	Ph	5-Cl	A	100	100/0	99
9	**1j**	*p*-FC_6H_4	H	A	100	100/0	92
10	**1k**	*p*-$(CH_3CO_2)C_6H_4$	H	B	87	100/0	84
11	**1l**	*p*-$NO_2C_6H_4$	H	B	93	100/0	44
12	**1m**	C_6F_5	H	C	73	100/0	32
13[f]	**1n**	*o*-pyridine	H	C	80	100/0	29
14	**1c**	*p*-$MeOC_6H_4$	H	A	100	88/12	81
15	**1o**	*p*-$MeOC_6H_4$	4-Cl	A	100	100/0	47
16	**1p**	*p*-$MeOC_6H_4$	5-Cl	A	100	75/25	69
17	**1b**	Ph	H	B	100	89/11	86

[a] **1a–q** (0.05–0.5 mmol; see the Supporting Information), toluene (0.1 M), argon. [b] Conditions: A) Au/carbon G-60 (loading, 0.5 wt% on Au), 90 °C, 24 h. B) Au/carbon G-60 (loading, 1.5 wt% on Au), 90 °C, 48 h. C) Au/carbon G-60 (loading, 2.5 wt% on Au), 120 °C, 48 h. [c] Filtration through a plug of SiO_2 afforded the indole product **2a–p** analytically pure with the substrate accounting for the rest of the material, unless otherwise noted. Conversion and ratio of products were determined by ^1H NMR integration of the crude mixture using 1,3,5-trimethoxybenzene (1,3,5-TMB) as internal standard. [d] Yield of isolated indole product **2a–p**. [e] Neat reaction. [f] Reaction concentration: toluene (0.25 M).

Table 3: Substrates and reaction conditions leading to domino cycloisomerization/indole homocoupling on the Au/carbocatalysis.[a]



Entry	Substrate	R	R′	**2**:**3**[b]	Yield of **3** [%][c]
1	**1c**	p-MeOC$_6$H$_4$	H	4/96	74[d]
2	**1o**	p-MeOC$_6$H$_4$	4-Cl	46/54	46
3	**1p**	p-MeOC$_6$H$_4$	5-Cl	0/100	67
4	**1a**	p-MeC$_6$H$_4$	H	29/71	59
5	**1b**	Ph	H	0/100	65
6	**1j**	p-FC$_6$H$_4$	H	31/69	57
7	**1f**	p-MeC$_6$H$_4$	4-Cl	63/37	21
8	**1h**	p-MeC$_6$H$_4$	5-Cl	55/45	35
9	**1d**	n-propyl	H	100/0	0
10	**1e**	o-NH$_2$C$_6$H$_4$	H	100/0	0

[a] **1a–p** (0.25–0.5 mmol; see the Supporting Information), Au/carbon G-60 (loading, 2.5 wt% on Au), 70°C, 96 h, toluene (0.25 M), air unless otherwise stated. [b] Conversion and ratio of products were determined by ^{1}H NMR integration of the crude mixture with 1,3,5-TMB as internal standard. [c] Yield of isolated biindole products **3**. [d] Average of two runs.

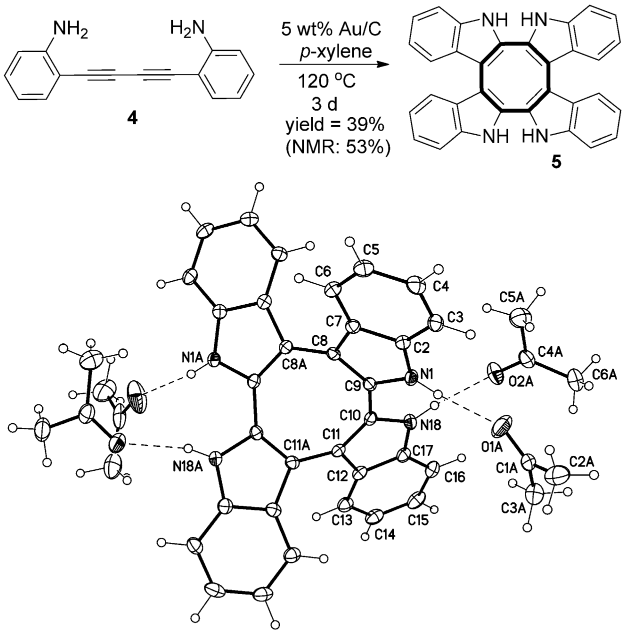


Figure 1. Consecutive cycloisomerisation—homocoupling from bialkynylaniline **4** to tetraindole **5**. Below: X-ray crystal structure of **5** with four co-crystallized acetone molecules (ellipsoids set at 50% probability).[27]

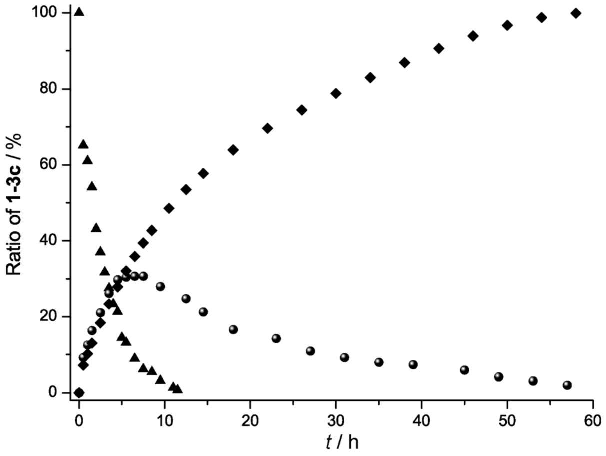
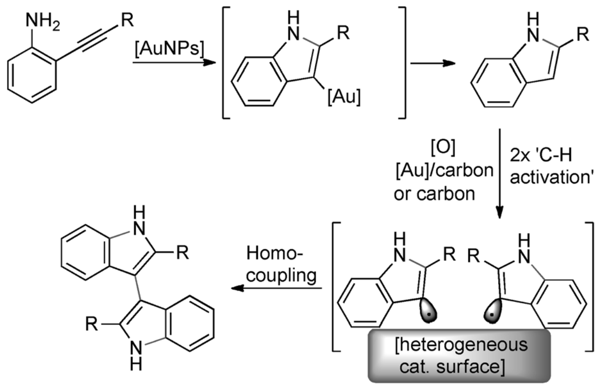


Figure 2. Catalytic formation of indole **2c** (●) and 3,3′-biindole **3c** (◆) of aniline **1c** (▲) in toluene at 70°C as monitored by ^{1}H NMR spectroscopy. The residual toluene peak was used as internal standard.

concentration of starting material, extending reaction time, and using lower temperatures to suppress possible side reactions and improve product stability allowed us to isolate biindole products in fair to good yields (entries 1–5). In few cases the chloride substituent on the aniline ring, particularly when located in position 4, lowered the homocoupling yield (entries 2 and 7). Notably, biindole formation was not detected for n-propyl and o-aniline alkynyl anilines under the studied conditions. To elucidate the competency of the homocoupling reaction we developed reaction conditions for 2,2-biindole **4** double homocoupling to produce 3,3,3′,3′-tetraindole **5** (Figure 1). The unprecedented tetraindole **5** containing the cyclooctatetraene ring was formed by using increased catalyst loading (5 wt%) and higher temperature (120°C) in p-xylene with fair to good yield in 72 h. The product could also be isolated and unambiguously characterized by X-ray diffraction (Figure 1). Recently, 1,8-indole linkages has been utilized in construction of isoelectronic cyclic planar porphyrin-type tetraindole.[21] Instead, the cyclooctatetraene **5** adopts a boat conformation, thus avoiding antiaromatic planar geometry.[22]

To obtain some insights into the mechanism of this novel catalytic system, the progress of the homocoupling reaction was monitored with ^{1}H NMR spectroscopy (Figure 2 and 3). Indole and 3,3′-biindolyl formations are observed clearly from the onset of the reaction (Figure 2), when aniline **1c** was used as starting material under 1 wt% Au/C gold catalysis. It is also clear that, the yield of homocoupling product increases constantly and approaches 100%, whereas the percentage of indole in the reaction media decreases after reaching a maximum concentration of about 30% after about 5 min. We believe that this is a strong indication that after the heterocyclization step, a separate eliminative protodeauration occurs that results in the release of the indole to the reaction media. Subsequently the electron-rich indoles oxidatively react by C–H activation on the gold catalyst, leading to formation of the homocoupling product (Scheme 1).

This is an unprecedented mechanism for this reaction with far-reaching potential applications, that is, C–H activation and C$_{sp^2}$ couplings that urges further investigation. In this view, we monitored the direct homocoupling of indole **2c** to biindole **3c**. The homocoupling results displayed in Figure 3 reveals that the rate of the coupling with 1 wt% Au catalyst is clearly faster in comparison to the cascade reaction from aniline (Figure 2). Surprisingly, the homocoupling reaction



Scheme 1. Proposed mechanism for formation of indoles and homocoupled biindoles.

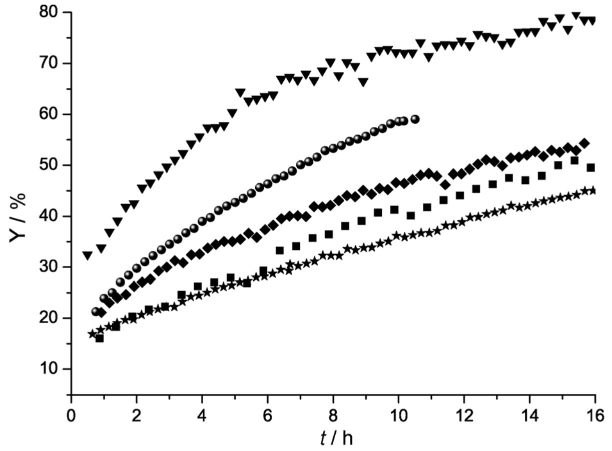


Figure 3. Catalytic formation of 3,3′-biindole **3c** from indole **2c** (as monitored by ^{1}H NMR spectroscopy) in deuterated toluene/MeCN (6:1) at 70°C with 0% (◆,★), 0.1% (■), and 1.0% loadings (▼,●) of Au (wt%) on the carbon support (250 wt%) in an atmosphere of air (●,■,★) and of oxygen (▼,◆). In the case of 1 wt% loadings in air (●), the monitoring was stopped after 10 h. The 1,3,5-trimethoxybenzene peak was used as internal standard.

proceeded decently also when only carbon support treated with aqua regia was used as catalyst. Increasing gold loading on the carbon support or presence of atmospheric oxygen both lead to faster reaction rates. In all cases, the catalysis progressed significantly already before the beginning of the monitoring. As the catalysis proceeded by carbocatalysis on the carbon support alone, and increasingly well as larger amounts of heterogeneous gold were present, the catalysis may be cooperative. The fact that homogeneous gold salts or oxygen atmosphere alone did not notably catalyze the homocoupling also implies that the C–C coupling is a heterogeneous process.

The proposed auto-tandem catalytic mechanism[23] contrasts with that found in previous reports for the AuNP-catalyzed homocoupling formation of 2*H*-chromenes, where a sequential double alkyne activation followed by homocoupling was hypothesized (Scheme 1).[15]

The reusability and leaching of our Au/C (1 wt%) catalyst was studied using the initial model system, 2-alkynylaniline **1a**. After three successive cycles of 16 h, the catalytic performance remained high: 96, 96, and 94%, respectively (Supporting Information). Moreover, when the catalyst was filtered off from the hot mixture after 4 h reaction time with 60% conversion, essentially no further reaction progress was observed in the filtrate heating at 90°C. This is also a further evidence of the heterogeneous nature of the cycloisomerization reaction.

To study the nature of heterogeneous catalysis, we performed some additional tests. The 2-alkynylaniline cycloisomerization to indole was not catalyzed by the plain support treated with aqua regia. Addition of 4-oxo-(2,2,6,6-tetramethylpiperidin-1-yl)-oxy into the reaction mixture inhibited the indole homocoupling, which suggests a radical character for this reaction step. Moreover, addition of 1000 and 2000 ppm of iron on the support upon preparation did have negative influence on the homocoupling catalysis, even though it is known that substoichiometric amounts of homogenous iron can catalyze the oxidative coupling.[15d] Related to this, inductively coupled plasma mass spectrometry (ICP-MS) studies revealed that the carbon support contains only 378 ppm level of Fe and less of other metal impurities (for example Ti = 96, Cr = 16, and Mn = 13 ppm; Supporting Information), which makes trace metal impurity catalysis unlikely. Thus, the homocoupling seems to have a truly carbocatalytic nature. This observation is in line with the recent emergence of oxidative carbocatalysis[24] being also clearly distinct from reported graphite oxide catalyzed Friedel–Crafts addition of unsaturated ketones to indoles.[25] Even though we cannot completely rule out the possibility that the found trace metal impurities could play a role in the reported homocoupling, to the best of our knowledge, this is the first reported carbocatalyzed carbon–carbon homocoupling reaction between aromatic carbons. The involvement of a C_{sp^2}–H activation step suggests that the method has also potential for C–C cross-coupling and C–X heterocoupling reactions.[2d,26]

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[27] CCDC 945482 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.