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Article

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Gold(III)-catalyzed decarboxylative C3-benzylation of indole-3-carboxylic acids with benzylic alcohols in water

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KEYWORDS. decarboxylation, gold, water, benzylic alcohol, indole-3-carboxylic acid

Abstract: A strategy for the gold(III)-catalyzed decarboxylative coupling reaction of indole-3-carboxylic acids with benzylic alcohols has been developed. This cascade reaction is devised as a straightforward and efficient synthetic route for 3-benzylindoles in moderate to excellent yields (50-93%). A Hammett study of the protodecarboxylation gives a negative ρ value, suggesting that there is a build-up of positive charge on the indole ring in the transition state. Furthermore, comparison of initial rates in H_2O and in D_2O reveals an observed kinetic solvent isotope effect (KSIE = 2.7). This simple protocol, which affords the desired products with CO_2 and water as the co-products, can be achieved under mild conditions without the need for base or other additives in water.

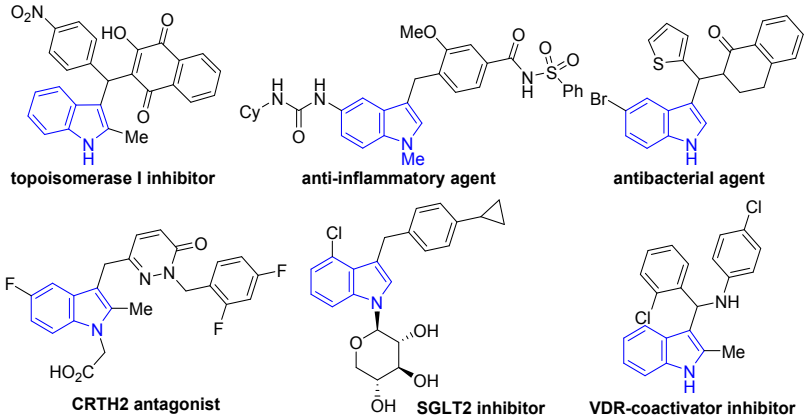
Introduction

Transition metal-catalyzed decarboxylative transformation affords a powerful methodology for C-C bond formation. Carboxylic acids are recognized as atom-economic alternatives to traditional coupling partners in synthetic organic chemistry. In 1930, Shepard *et al*. discovered the copper-promoted decarboxylation reaction.[1] However, this procedure required very high temperatures (260 ^{o}C) and the use of stoichiometric amounts of copper salts. The first report of a catalytic protodecarboxylation of aromatic carboxylic acids was described in 2007 by Gooβen.[2] Subsequently, various transition metals such as Cu,[3]

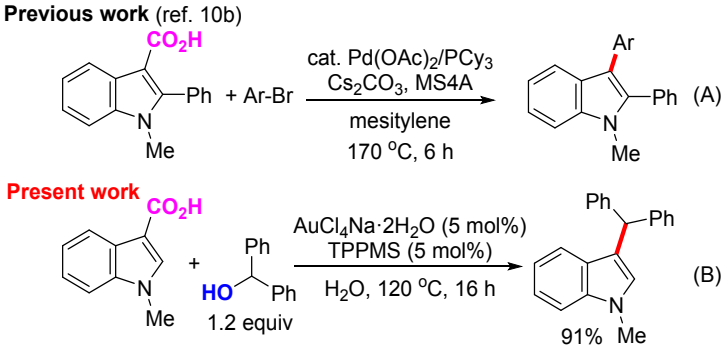
Ag,[4] Pd[5] and Au[6] were successfully utilized for catalytic decarboxylative activation. In 2011, Larrosa *et al.* reported that gold(I)-salts mediated the decarboxylative activation of (hetero)aromatic carboxylic acids at lower temperatures than did copper(I).[6e] In 2013, Nolan *et al.* reported the gold(I) complex, [Au(Ipr)(OH)], promoted the decarboxylation of aromatic carboxylic acids without the use of a silver co-catalyst under mild conditions.[6c]

The indole scaffold is one of the most valuable synthetic targets since it is a common structural motif found in pharmaceuticals and functional materials (Figure 1).[7] Therefore, a dehydrative coupling reaction for the direct introduction of diverse functionalities on indoles is gaining increasing interest.[8] Recently, we developed a green and sustainable strategy for catalytic dehydrative C-C bond formation of indoles with benzylic alcohols.[9] Continuing our studies in the dehydrative coupling strategy, we envisioned its expansion to indole-3-carboxylic acids as a valuable coupling partner with its attractive features of low toxicity, high stability, and easy use.[10,11] Recently, Miura *et al.* reported the Pd-catalyzed decarboxylative C3-arylation of 3-carboxyindoles with aryl bromides (Scheme 1A).[10b] We herein present a strategy for the gold(III)-catalyzed decarboxylative and dehydrative coupling reaction of indole-3-carboxylic acids with benzylic alcohols in water (Scheme 1B). This simple protocol has reduced waste generation, uses safer solvent and reaction conditions, and increases energy efficiency, all of which contribute to the efficiency of a chemical transformation.[11] To the best of our knowledge, this is the first example of using a gold(III) catalyst for the decarboxylative activation of carboxyindoles.

Figure 1. Representative biologically active 3-benzylindoles.



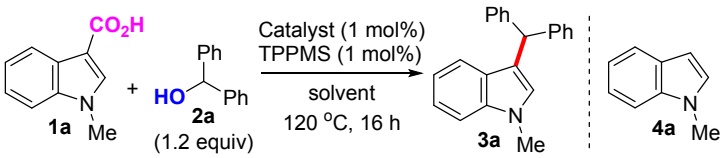
Scheme 1. Decarboxylative coupling reactions.



Results and Discussion

Initially, 1-methylindole-3-carboxylic acid (**1a**) and benzhydrol (**2a**) were chosen as the model compounds to optimize the decarboxylative coupling reaction. The reaction of **1a** with **2a** (1.2 equiv) using $AuCl_4Na·2H_2O$ (1 mol%) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 1 mol%) in water at 120 °C for 16 h gave the corresponding C3-benzylated product **3a** in 61% yield along with protodecarboxylated **4a** in 28% yield (Table 1, entry 1). The yield of **3a** was increased to 91% by use of $AuCl_4Na·2H_2O$ (5 mol%) and TPPMS (5 mol%) (entry 2). In contrast, using only $AuCl_4Na·2H_2O$ resulted in low yield (entry 3). A control experiment using HCl indicated that the Au(III) catalyst was essential in this system (entry 4). With regard to the gold catalysts, $AuCl_4Na·2H_2O$ gave the best result (entry 1 *vs.* entries 5-8). Other transition metals were less effective than $AuCl_4Na·2H_2O$ (entries 9-16). While $Sc(OTf)_3$ generally works as a Lewis acid in water solutions, the desired product **3a** was obtained in only 25% yield (entry 17). Replacing water with organic solvents such as EtOH, DMF and toluene resulted in low yields or no reaction (entries 18-21).

Table 1. Effect of catalysts and solvents[a]



Entry	Catalyst	ligand	Solvents	Yield (%)[b]	
				3a	**4a**
1	$AuCl_4Na·2H_2O$	TPPMS	H_2O	61	28
2[c]	$AuCl_4Na·2H_2O$	TPPMS	H_2O	91	9

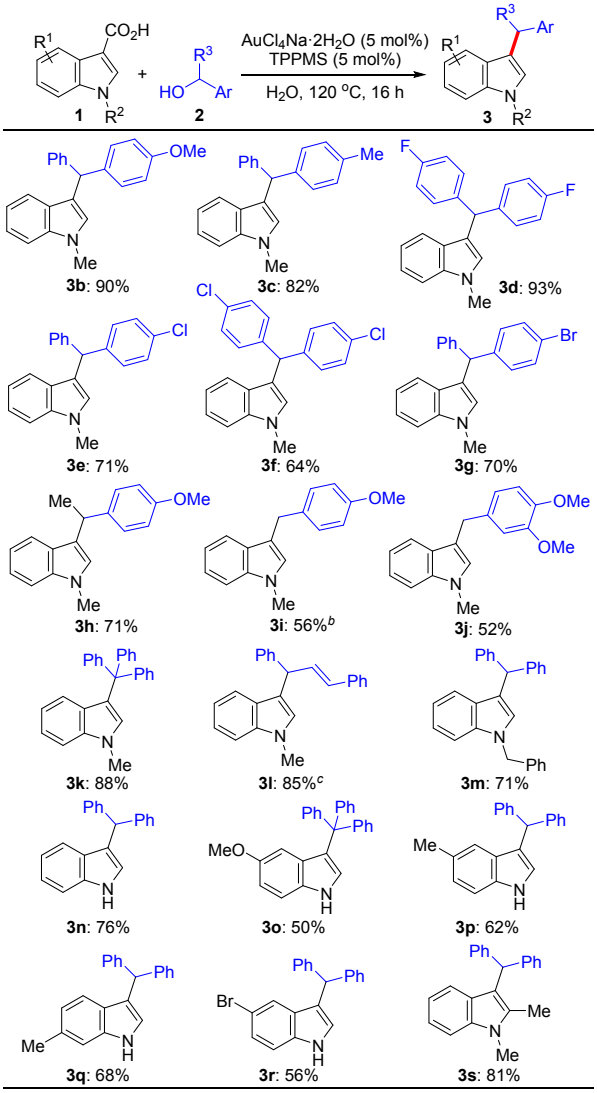
3	$AuCl_4Na·2H_2O$	none	H_2O	18	55
4	HCl	none	H_2O	14	62
5	$HAuCl_4·3H_2O$	TPPMS	H_2O	2	4
6	$AuBr_3$	TPPMS	H_2O	6	9
7	$PicAuCl_2$[d]	TPPMS	H_2O	25	21
8	AuCl	TPPMS	H_2O	17	33
9	$PdCl_2$	TPPMS	H_2O	28	24
10	$CuCl_2$	TPPMS	H_2O	6	58
11	$PtCl_2$	TPPMS	H_2O	25	6
12	$NiCl_2·6H_2O$	TPPMS	H_2O	2	63
13	$FeCl_3·6H_2O$	TPPMS	H_2O	18	40
14	$CoCl_2·6H_2O$	TPPMS	H_2O	3	63
15	$RuCl_3$	TPPMS	H_2O	16	16
16	$IrCl_3·H_2O$	TPPMS	H_2O	24	28
17	$Sc(OTf)_3$	none	H_2O	25	53
18	$AuCl_4Na·2H_2O$	TPPMS	EtOH	16	7
19	$AuCl_4Na·2H_2O$	TPPMS	DMF	0	0
20	$AuCl_4Na·2H_2O$	TPPMS	toluene	9	3
21	$AuCl_4Na·2H_2O$	TPPMS	toluene/H_2O[e]	5	47

[a] Reaction conditions: **1a** (1 mmol), catalyst (1 mol%), TPPMS (1 mol%), **2a** (1.2 equiv), solvent (4 mL), 120 °C, 16 h in a sealed tube under air. [b] The conversion was determined by ^{1}H NMR analysis of the crude product using 4-nitroanisole as an internal standard. [c] $AuCl_4Na·2H_2O$ (5 mol%) and TPPMS (5 mol%) were used. [d] Dichloro(2-pyridinecarboxylato)gold. [e] 1:1.

With the optimized conditions in hand, we examined the substrate scope of the decarboxylative tandem reaction (Scheme 2). First, the scope of alcohols **2** as the coupling partner was examined. Both electron-donating groups (OMe and Me) and electron-withdrawing groups (F and Cl) on the benzene ring of substituted benzhydrols **2** were tolerated well to produce the corresponding C3-benzylated products **3b-g** in moderate to excellent yields (64-93%). The carbon-bromine moiety in **3g** was left intact, which could be employed for further cross-coupling. We explored different benzylic alcohols such as 4-methoxy-α-methylbenzyl alcohol, 4-methoxybenzylalcohol, veratryl Alcohol, trityl alcohol and *trans*-1,3-diphenyl-2-propen-1-ol, which afforded the corresponding products **3h-l** in moderate to excellent yields (52-88%). In contrast, pentafluorobenzhydrol or isopropyl alcohol resulted in no reaction. Since electron-

deficient diarylmethanol or aliphatic alcohol failed to react with **1a**, stability of the diarylcarbocation would be critical to the success of these reactions. Next, the scope of indole-3-carboxylic acids **1** was examined. *N*-Benzylindole-3-carboxylic acid and indole-3-carboxylic acid also led to the desired products **3m-n** in good yields (71-76%). The coupling reactions of indole-3-carboxylic acid with electron-withdrawing (OMe and Me) groups and an electron-withdrawing bromo group on the benzene ring afforded the desired products **3o-r** in moderate to good yields (50-68%). A sterically demanding methyl group at the C2 position was also tolerated in the C3-benzylation (**3s**, 81%). In previous work,[9] we have shown that the reaction of indole 2-carboxylic acids with several benzhydryl alcohols **2** afford the 3-benzylated products with the carboxyl group left intact.

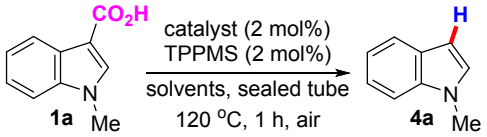
Scheme 2. Scope of carboxylic acids 1 and alcohols 2.[a]



[a] Reaction conditions: **1** (1 mmol), $AuCl_4Na·2H_2O$ (5 mol%), TPPMS (5 mol%), alcohols (**2**, 1.2 equiv), H_2O (4 mL), 120 °C under air in a seald tube. Yield of isolated product. [b] 4-Methoxybenzyl alcohol (1 equiv) was used. [c] $AuCl_4Na·2H_2O$ (2 mol%) was used.

To gain insight into the catalytic decarboxylative activation, several catalysts were investigated (Table 2). As expected, the reaction of **1a** using $AuCl_4Na·2H_2O$ (2 mol%) and TPPMS (2 mol%) in water was extremely rapid at 120 °C, affording the protodecarboxylated product **4a** in 83% yield after only 1 h (entry 1). The use of only $AuCl_4Na·2H_2O$ resulted in decreased yield (entry 2). No reaction occurred without the catalysts or when replacing water with an organic solvent such as DMF (entries 3-4). The use of HCl instead of the Au(III)/TPPMS catalyst also resulted in low yield, since it excluded the Brønsted acid-catalyzed decarboxylative activation pathway (entry 5). The reaction was suppressed by addition of NaOH (1 equiv) (entry 6). The reactions were much slower when using other salts such as Cu(I), Cu(II), Ag(I) Pd(II) and Fe(III) (entries 7-15). These results indicate that the gold(III)/TPPMS catalyst is highly effective as a Lewis acid for the activation of indole-3-carboxylic acid in water.

Table 2. Catalytic decarboxylative activation.[a]

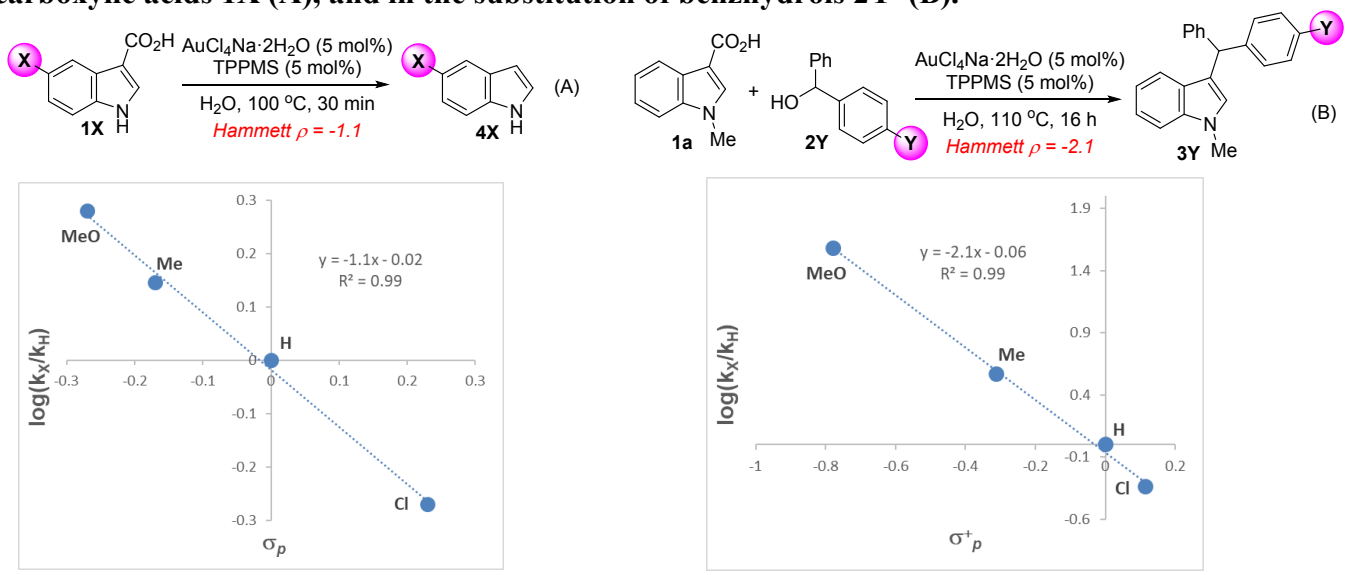


Entr	Catalyst	ligand	Solvent	Yield (%)[b]
1	$AuCl_4Na·2H_2O$	TPPMS	H_2O	83
2	$AuCl_4Na·2H_2O$	none	H_2O	60
3	none	none	H_2O	0
4	$AuCl_4Na·2H_2O$	TPPMS	DMF	0
5	HCl	none	H_2O	18
6[c]	$AuCl_4Na·2H_2O$	TPPMS	H_2O	2
7	Cu_2O	TPPMS	H_2O	25
8	$CuCl_2$	TPPMS	H_2O	15
9	$Cu(OTf)_2$	TPPMS	H_2O	40
10	Ag_2CO_3	TPPMS	H_2O	15
11	AgOAc	TPPMS	H_2O	33
12	Ag_2O	TPPMS	H_2O	36
13	AgOTf	TPPMS	H_2O	37
14	$Pd(OAc)_2$	TPPMS	H_2O	17
15	$FeCl_3·4H_2O$	TPPMS	H_2O	31

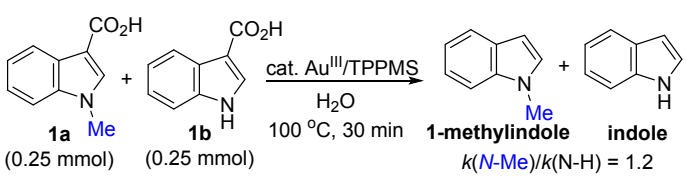
[a] Reaction conditions: **1a** (1 mmol), catalyst (2 mol%), TPPMS (2 mol%), solvent (4 mL), 120 °C, 1 h in a sealed tube under air. [b] NMR yields. [c] NaOH (1 equiv) was added.

To demonstrate the electronic effect of the substituents on the rates of the decarboxylative C3-benzylation, Hammett studies were conducted. First, the relative rates in the protodecarboxylation of various substituted indole-3-carboxylic acids (**1X**) show excellent correlation ($R^2 = 0.99$) between the $\log(k_X/k_H)$ and the σ_p values of the respective substituents, resulting in a negative ρ value (–1.1) (Figure 2A). Furthermore, the C3-benzylation of 1-methylindole-3-carboxylic acid (**1a**) proceeded faster than that of indole-3-carboxylic acid (**1b**) (Scheme 3). These results suggest that there is a build-up of positive charge on the indole ring in the transition state. Next, the relative rates using the *p*-substituted benzhydrols (**2Y**) also showed a negative slope ($\rho = -2.1$, $R^2 = 0.997$) (Figure 2B), indicating a positive charge on the benzylic position in the transition state.

Figure 2. Hammett plot for the rate constants in the protodecarboxylation of substituted indole-3-carboxylic acids 1X (A), and in the substitution of benzhydrols 2Y (B).

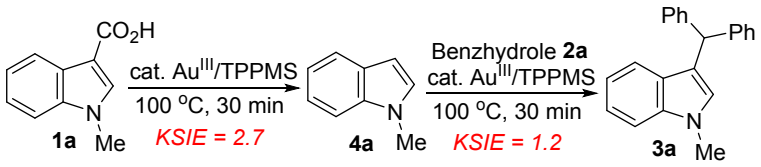


Scheme 3. Competition experiment.



The rates for the decarboxylative activation of **1a** "in H_2O" and "in D_2O" were compared (Scheme 4). The initial rate of the protodecarboxylation was faster "in H_2O" than "in D_2O" with a kinetic solvent isotope effect (KSIE) of 2.7, suggesting that the water molecules stabilized the transition state by hydrogen-bonding interactions that accelerated the decarboxylation rate. Furthermore, a smaller KSIE value of 1.2 was obtained in the dehydrative C-C bond formation step.

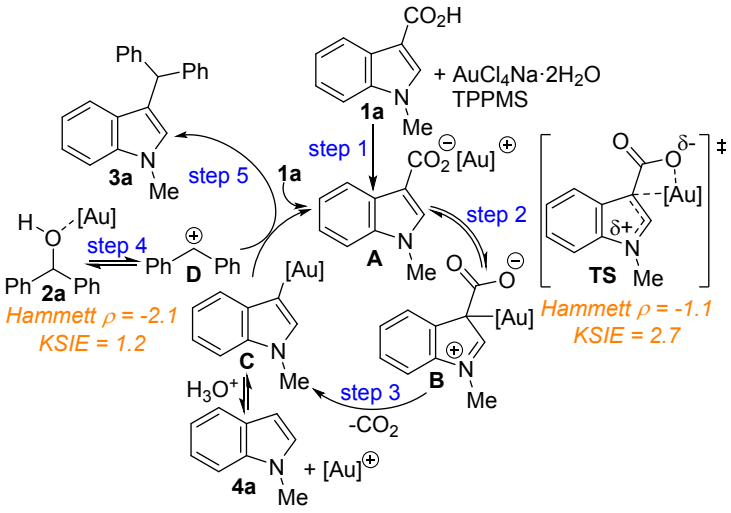
Scheme 4. Deuterium isotope effects.



On the basis of these experimental results and the literature,[6] we propose a catalytic system for the decarboxylative coupling reaction of 1-methylindole-3-carboxylic acid (**1a**) with benzhydrol (**2a**) in water as illustrated in Scheme 5. Initially, $AuCl_4Na{\cdot}2H_2O$ and TPPMS catalysts react with carboxylic acid **1a** to form the gold(III) carboxylate **A** (step 1).[13] Subsequent C3 electrophilic auration of complex **A** proceeds to form zwitter ion **B** *via* a 4-membered transition state **TS** (step 2). This process should be favored by electron-donating groups on **B**, since these will stabilize the positive charge on the indole ring (Hammett $\rho = -1.1$). The intermediate **B** rearomatizes with release of CO_2 to afford the arylgold complex **C**[13] (step 3), which is in equilibrium with 1-methylindole (**4a**). Notably, the use of water as a reaction medium would enhance the decarboxylation (KSIE = 2.7). The sp^3 C-O bond of benzhydrol (**2a**) is activated by the Lewis acidic Au(III) cation species **A** to form the benzylic cation **D** (step 4).[15] The observed negative ρ value of –2.1 is consistent with electrophilic C-O bond cleavage in the transition state which has a build-up of positive charge. Furthermore, the direct substitution of trityl alcohol affords the corresponding desired products **3h** and **3l**, which is in agreement with the reaction proceeding through an S_N1 reaction.

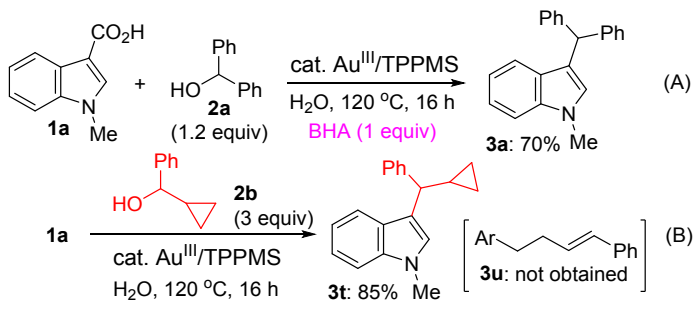
Finally, the C-C bond formation of intermediate **C** (or **4a**) with carbocation **D** leads to the C3-benzylated product **3a** selectively (step 5).

Scheme 5. Proposed mechanism.



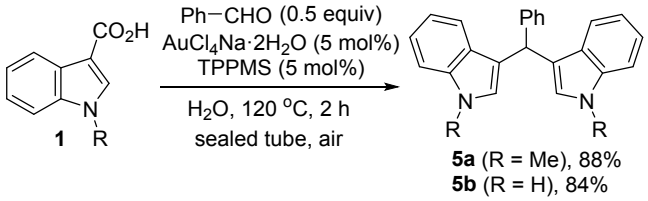
Control experiments were performed to exclude a radical pathway based on a single electron transfer (SET). First, in the presence of a radical scavenger (BHA: 3-*tert*-butyl-4-hydroxyanisole, 1 equiv), desired product **3a** was obtained in 70% NMR yield (Scheme 6A). Next, a radical clock experiment using α-cyclopropylbenzyl alcohol (**2b**) was conducted to observe whether the rapid isomerization of the cyclopropylmethyl radical to the allylmethyl radical occurred (Scheme 6B). As expected, corresponding **3t** was obtained in 85% isolated yield *via* the cyclopropylmethyl cation and not the ring-opened product **3u**.

Scheme 6. Control experiments.



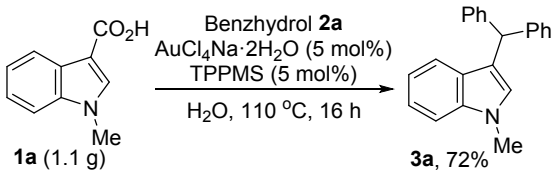
Our catalytic system can be applied to the synthesis of bis(indolyl)methanes **5** (Scheme 7). The gold(III)-catalyzed decarboxylative and dehydrative coupling reaction of indole-3-carboxylic acids **1** with benzaldehyde gave desired **5a-b** in good to excellent yields. After 2 h, the reaction mixture was extracted with AcOEt, then crude products were purified simply by recrystallization from *n*-hexane and AcOEt to give desired products. The developed process avoids the use of column chromatography.

Scheme 7. Synthesis of bis(indolyl)methanes 5.



Finally, to demonstrate the utility of our catalytic system, a gram scale reaction of **1a** (1.05 g, 6 mmol) was carried out (Scheme 8). As expected, the desired **3a** was obtained successfully in 72% isolated yield.

Scheme 8. Scale-up experiment.



Conclusion

In summary, we have demonstrated a gold(III)/TPPMS-catalyzed decarboxylative C-C bond formation of indole-3-carboxylic acids with benzhydryl alcohols in water. This simple protocol provides rapid access to valuable 3-benzylindoles as a common structural motif found in pharmaceuticals in moderate to excellent yields.

Experimental Section

The mass analyzer type is double-focusing magnetic sector mass spectrometer for the HRMS measurements.

General procedure: A mixture of indole-3-carboxylic acids **1** (1 mmol), $AuCl_4Na \cdot 2H_2O$ (20 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) (18 mg, 0.05 mmol) and benzylic alcohols **2** (1.2 mmol) in H_2O (4 mL) was heated at 120 °C for 16 h in a sealed tube under air. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was washed with hexanes, then purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **3**.

3-Benzhydryl-1-methyl-1*H*-indole 3a [1]

Following the scale-up experiment procedure (Scheme 8), **3a** was obtained as a pale yellow solid; mp 142−144 °C; IR (KBr) (cm^{-1}) 3056, 1482; ^1H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H), 5.66 (s, 1H), 6.41 (s, 1H), 6.97 (ddd, *J*=7.8, 6.9, 0.9 Hz, 1H), 7.16-7.31 (m, 13H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 32.8, 49.0, 109.3, 118.4, 119.0, 120.1, 121.8, 126.3, 127.5, 128.4, 128.9, 129.2, 137.6, 144.3; MS(FAB): *m/z* 298 $[M+H]^+$.

3-[(4-Methoxyphenyl)(phenyl)methyl]-1-methyl-1*H*-indole 3b [9]

Following the general procedure, **3b** was obtained as a white solid; 294 mg (90%); mp 98-105 °C; IR (KBr) (cm^{-1}) 3012, 1506; ^1H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.78 (s, 3H), 5.61 (s, 1H), 6.40 (d, *J*=0.8 Hz, 1H), 6.82 (d, *J*=8.8 Hz, 2H), 6.97 (ddd, *J*=8.0, 7.1, 1.0 Hz, 1H), 7.14 (d, *J*=8.4 Hz, 2H), 7.16-7.30 (m, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 32.7, 47.9, 55.2, 109.1, 113.6, 118.6, 118.8, 120.0, 121.6, 126.1, 127.3, 128.2, 128.7, 128.9, 129.9, 136.3, 137.4, 144.5, 157.9; MS(EI): *m/z* 327 (M^+, 100).

1-Methyl-3-[phenyl(*p*-tolyl)methyl]-1*H*-indole 3c [9]

Following the general procedure, **3c** was obtained as a white solid; 202 mg (65%); mp 117-120 °C; IR (KBr) (cm^{-1}) 3024, 2921, 1473; ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.69 (s, 3H), 5.62 (s, 1H), 6.41 (s, 1H), 6.97 (dd, *J*=7.9, 7.1 Hz, 1H), 7.08 (d, *J*=8.4 Hz, 2H), 7.12 (d, *J*=8.1 Hz, 2H), 7.15-7.30 (m,

8H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.1, 32.7, 48.4, 109.1, 118.4, 118.8, 120.0, 121.6, 126.1, 127.4, 128.2, 128.7, 128.8, 128.9, 129.0, 135.6, 137.4, 141.1, 144.3; MS(EI): *m/z* (%) 311 (M^+, 100).

3-[Bis(4-fluorophenyl)methyl]-1-methyl-1*H*-indole 3d [9]

Following the general procedure, **3d** was obtained as a colorless oil; Yield 309 mg (93%); IR (neat) (cm^{-1}) 3054, 1504; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 5.56 (s, 1H), 6.36 (s, 1H), 6.85-7.05 (m, 5H), 7.10-7.23 (m, 6H), 7.28 (d, *J*=8.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 32.8, 47.4, 109.4, 115.3 (d, J_{CF}=22.0 Hz), 118.2, 119.1, 120.0, 122.0, 127.2, 128.8, 130.4 (d, J_{CF}=7.8 Hz), 137.6, 139.8 (d, J_{CF}=2.3 Hz), 161.6 (d, J_{CF}=224.4 Hz); MS(FAB): *m/z* 334 $[M+H]^+$.

3-[(4-Chlorophenyl)(phenyl)methyl]-1-methyl-1*H*-indole 3e [9]

Following the general procedure, **3e** was obtained as a white solid; Yield 236 mg (71%); mp 140-142 °C; IR (KBr) (cm^{-1}) 3052, 1478; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H), 5.70 (s, 1H), 6.71 (s, 1H), 6.90 (t, *J*=7.2 Hz, 1H), 7.11 (d, *J*=7.7 Hz, 1H), 7.10-7.16 (m, 1H), 7.18-7.42 (m, 10H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 32.8, 47.7, 110.3, 117.2, 119.1, 119.7, 121.8, 126.8, 127.2, 128.8, 128.9, 129.1, 130.9, 131.2, 137.6, 143.8, 144.2; MS(FAB): *m/z* 332 $[M+H]^+$, 334 $[M+H+2]^+$.

3-[Bis(4-chlorophenyl)methyl]-1-methyl-1*H*-indole 3f

Following the general procedure, **3f** was obtained as a white solid; Yield 236 mg (64%); mp 137-140 °C; IR (KBr) (cm^{-1}) 3049, 1487; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 5.60 (s, 1H), 6.37 (s, 1H), 6.99 (dd, *J*=7.8, 7.1 Hz, 1H), 7.12-7.31 (m, 12H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 32.8, 47.6, 76.8, 77.1, 77.3, 77.4, 109.4, 117.3, 119.1, 119.7, 122.0, 127.0, 128.5, 128.7, 130.2, 132.2, 137.5, 142.1; MS (EI): *m/z* (%) 365 (M^+, 83), 367 (M^++2, 62), 369 (M^++4, 11), 254 (100); Anal. Calcd for $C_{22}H_{17}Cl_2N$: C, 72.14; H, 4.68; N, 3.82. Found: C, 71.95; H, 4.80; N, 3.76.

3-[(4-Bromophenyl)(phenyl)methyl]-1-methyl-1*H*-indole 3g [9]

Following the general procedure, **3g** was obtained as a white solid. 132 mg (70%) from 198 mg (0.5 mmol) of **3a**; mp 138-140 °C; IR (KBr) (cm^{-1}) 3050, 1613, 1596; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 5.61 (s, 1H), 6.39 (d, *J*=0.9 Hz, 1H), 6.99 (ddd, *J*=7.8, 6.9, 0.9 Hz, 1H), 7.10 (d, *J*=8.2 Hz, 2H), 7.16-7.25 (m, 5H), 7.26-7.31 (m, 3H), 7.39 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.8,

47.8, 110.3, 117.1, 119.1, 119.7, 119.8, 121.9, 126.8, 127.2, 128.9, 129.1, 131.3, 131.7, 137.6, 144.2; MS (FAB): *m/z* 378 $[M+H+2]^+$, 376 $[M+H]^+$.

3-[1-(4-Methoxyphenyl)ethyl]-1-methyl-1*H*-indole 3h [9]

Following the general procedure, **3h** was obtained as a colorless oil. 188 mg (71%); IR (KBr) (cm^{-1}) 2962, 1612, 1512; ^1H NMR (400 MHz, $CDCl_3$): δ 1.89 (d, *J*=7.3 Hz, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 4.54 (q, *J*=7.3 Hz, 1H), 6.99 (s, 1H), 7.02 (d, *J*=8.2 Hz, 2H), 7.21 (t, *J*=7.3 Hz, 1H), 7.35-7.47 (m, 4H), 7.60 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 32.8, 36.3, 55.4, 109.4, 113.9, 118.9, 120.1, 120.6, 121.8, 126.1, 127.5, 128.6, 137.6, 139.4, 158.0; MS (FAB): *m/z* 266 $[M+H]^+$.

3-(4-Methoxybenzyl)-1-methyl-1*H*-indole 3i [9]

Following the general procedure, **3g** was obtained as a colorless oil; Yield 140 mg (56%); IR (neat) (cm^{-1}) 2905, 1471; ^1H NMR (400 MHz, $CHCl_3$): δ 3.72 (s, 3H), 3.78 (s, 3H), 4.04 (s, 2H), 6.73 (s, 1H), 6.82 (d, *J*=8.2 Hz, 2H), 7.06 (dd, *J*=7.8, 6.9 Hz, 1H), 7.20 (d, *J*=8.2 Hz, 2H), 7.21-7.23 (m, 1H), 7.28 (d, *J*=8.2 Hz, 1H), 7.51 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 30.9, 32.7, 55.5, 109.4, 114.0, 115.0, 119.0, 119.5, 121.8, 127.3, 128.1, 129.9, 133.8, 137.5, 158.1; MS(FAB): *m/z* 252 $[M+H]^+$.

3-(3,4-Dimethoxybenzyl)-1-methyl-1*H*-indole 3j [9]

Following the general procedure, **3j** was obtained as a colorless oil. 145 mg (52%); IR (neat) (cm^{-1}) 2935, 1513; ^1H NMR (400 MHz, $CHCl_3$): δ 3.68 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 4.03 (s, 2H), 6.70 (s, 1H), 6.71-6.83 (m, 3H), 7.06 (dd, *J*=7.8, 6.9 Hz, 1H), 7.15-7.30 (m, 2H), 7.52 (dd, *J*=7.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 31.3, 32.7, 56.0, 77.5, 109.3, 111.3, 112.2, 114.7, 118.9, 119.3, 120.7, 121.7, 127.2, 127.9, 134.1, 137.3, 147.3, 149.0; MS (FAB): *m/z* 282 $[M+H]^+$.

1-Methyl-3-trityl-1*H*-indole 3k [16]

Following the general procedure, **3k** was obtained as a white solid; Yield 329 mg (88%); mp 196-198 °C; IR (KBr) (cm^{-1}) 3064, 3027, 1597, 1483; ^1H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 6.64 (d, *J*=8.2 Hz, 1H), 6.78 (ddd, *J*=8.2, 6.9, 0.9 Hz, 1H), 7.12 (d, *J*=7.8, 7.3, 0.9 Hz, 1H), 7.16-7.28 (m, 16H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 32.7, 59.4, 109.0, 118.6, 121.2, 122.9, 125.9, 127.3, 128.2, 130.2, 130.7, 137.7, 146.6; MS(FAB): *m/z* 374 $[M+H]^+$.

(*E*)-3-(1,3-Diphenylallyl)-1-methyl-1*H*-indole 3l [16]

Following the general procedure, **3l** was obtained as a brown oil; Yield 275 mg (85%); IR (neat) (cm^{-1}) 3058, 3025, 1702, 1596; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 5.10 (d, *J*=7.3 Hz, 1H), 6.43 (d, *J*=15.8 Hz, 1H), 6.71 (dd, *J*=15.8, 7.3 Hz, 1H), 6.72 (s, 1H), 7.00 (t, *J*=7.6 Hz, 1H), 7.13-7.38 (m, 12H), 7.41 (d, *J*=8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 32.6, 46.1, 109.2, 117.0, 118.8, 119.9, 121.6, 126.3, 127.1, 127.3, 128.4, 128.4, 130.4, 132.7, 137.4, 137.5, 143.5; MS (FAB): *m/z* 324 $[M+H]^+$.

3-Benzhydryl-1-benzyl-1*H*-indole 3m

Following the general procedure, **3m** was obtained as a pale yellow oil; Yield 221 mg (71 %); IR (neat) (cm^{-1}) 3056, 3026, 1713, 1658; ^1H NMR (400 MHz, $CDCl_3$): δ 5.22 (s, 2H), 5.69 (brs, 1H), 6.54 (d, *J*=0.9 Hz, 1H), 6.96 (ddd, *J*=7.8, 6.9, 0.9 Hz, 1H), 7.04 (d, *J*=6.9 Hz, 2H), 7.11 (dt, *J*=7.3, 1.4 Hz, 1H), 7.17-7.30 (m, 16H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 48.8, 50.0, 109.7, 119.1, 120.1, 121.8, 126.2, 126.4, 128.3, 128.7, 129.0, 137.1, 137.8, 144.0; MS (FAB): *m/z* 373 (M^+); HRMS-FAB: *m/z* (M^+) calcd for $C_{28}H_{23}N$ 373.1830, found 373.1831.

3-Benzhydryl-1*H*-indole 3n [17]

Following the general procedure, **3n** was obtained as a white solid; Yield 215 mg (76%); mp 122-123 °C; IR (KBr) (cm^{-1}) 3384, 3024, 1596, 1494; ^1H NMR (400 MHz, $CDCl_3$): δ 5.67 (s, 1H), 6.57 (d, *J*=1.3 Hz, 1H), 6.98 (t, *J*=7.8 Hz, 1H), 7.13-7.39 (m, 13H), 7.95 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 48.8, 111.0, 119.4, 119.9, 122.1, 124.0, 126.2, 128.3, 129.0, 136.7, 143.9; MS (FAB): *m/z* 284 $[M+H]^+$.

5-Methoxy-3-trityl-1*H*-indole 3o

Following the general procedure, **3o** was obtained as a white solid; Yield 195 mg (50%); mp 269-270 °C; IR (KBr) (cm^{-1}) 3450, 3058, 1623, 1581; ^1H NMR (400 MHz, $CDCl_3$): δ 3.37 (s, 3H), 6.04 (d, *J*=2.3 Hz, 1H), 6.74 (dd, *J*=9.2, 2.8 Hz, 1H), 6.82 (d, *J*=2.8 Hz, 1H), 7.16-7.27 (m, 16H), 7.87 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.5, 59.5, 104.3, 111.6, 112.2, 123.8, 126.1, 126.2, 127.5, 128.4, 130.9, 132.1, 146.5, 155.3; MS(FAB): *m/z* 390 $[M+H]^+$; HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{28}H_{24}NO$ 390.1858, found 390.1857.

3-Benzhydryl-5-methyl-1*H*-indole 3p

Following the general procedure, **3p** was obtained as a white solid; Yield 185 mg (62%); mp 128-129 °C; IR (KBr) (cm^{-1}) 3398, 1491, 1451; ^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 5.64 (s, 1H), 6.52 (d, *J*=1.6 Hz, 1H), 6.99 (dd, *J*=8.2, 1.4 Hz, 1H), 7.03 (s, 1H), 7.17-7.31 (m, 11H), 7.84 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.5, 48.7, 110.7, 119.4, 123.7, 124.2, 126.1, 127.2, 128.2, 128.6, 129.0, 135.0, 144.1; MS(FAB): *m/z* 298 $[M+H]^+$; Anal. Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.80; H, 6.56; N, 4.69.

3-Benzhydryl-6-methyl-1*H*-indole 3q

Following the general procedure, **3q** was obtained as a white solid; Yield 202 mg (68%); mp 134-135 °C; IR (KBr) (cm^{-1}) 3421, 3383, 3024, 1491, 1449; ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 5.64 (s, 1H), 6.48 (dd, *J*=2.3, 0.9 Hz, 1H), 6.81 (dd, *J*=8.2, 0.9 Hz, 1H), 7.09 (d, *J*=7.8 Hz, 1H), 7.14 (s, 1H), 7.16-7.31 (m, 10H), 7.80 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.8, 49.0, 111.1, 119.7, 119.9, 121.3, 123.6, 125.0, 126.3, 128.4, 129.1, 132.0, 137.3, 144.1; MS(FAB): *m/z* 298 $[M+H]^+$; Anal. Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.83; H, 6.53; N, 4.62.

3-Benzhydryl-5-bromo-1*H*-indole 3r [18]

Following the general procedure, **3r** was obtained as a purple amorphous; Yield 203 mg (56%); IR (KBr) (cm^{-1}) 3418, 1493, 1451; ^1H NMR (400 MHz, $CDCl_3$): δ 5.56 (s, 1H), 6.45 (dd, *J*=2.3, 0.9 Hz, 1H), 7.08 (d, *J*=8.7 Hz, 1H), 7.12-7.28 (m, 11H), 7.34 (d, *J*=1.8 Hz, 1H), 7.78 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 48.7, 112.8, 112.9, 120.0, 122.4, 125.2, 125.5, 126.6, 128.6, 128.9, 129.1, 135.4, 143.7; MS (FAB): *m/z* 362 $[M+H]^+$, 364 $[M+H+2]^+$.

3-Benzhydryl-1,2-dimethyl-1*H*-indole 3s

Following the general procedure, **3s** was obtained as a white solid; Yield 252 mg (0.81 mmol); mp 108-109 °C; IR (KBr) (cm^{-1}) 3058, 3022, 1599, 1494; ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.66 (s, 3H), 5.76 (s, 1H), 6.87 (ddd, *J*=7.8, 6.9, 0.9 Hz, 1H), 6.97 (d, *J*=7.8 Hz, 1H), 7.09 (ddd, *J*=8.2, 6.9, 0.9 Hz, 1H), 7.15-7.30 (m, 11H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 10.7, 29.5, 48.0, 108.5, 113.5, 118.7, 119.6, 120.3, 126.0, 127.4, 128.1, 129.1, 133.9, 136.7, 144.1; MS (FAB): *m/z* 312 $[M+H]^+$; Anal. Calcd for $C_{23}H_{21}N$: C, 88.71; H, 6.80; N, 4.50. Found: C, 88.68; H, 6.88; N, 4.44.

3-Benzhydryl-5-bromo-1*H*-indole 3t

Following the general procedure, **3t** was obtained as a pale yellow oil; Yield 222 mg (0.85 mmol); IR (neat) (cm^{-1}) 3056, 3029, 3000, 1724, 1615, 1470; ^1H NMR (400 MHz, $CDCl_3$): δ 0.30-0.40 (m, 2H), 0.53-0.63 (m, 1H), 0.64-0.73 (m, 1H), 1.35-1.45 (m, 1H), 3.47 (d, *J*=9.2 Hz, 1H), 3.77 (s, 3H), 6.93 (ddd, *J*=8.2, 7.6, 0.9 Hz, 1H), 7.05 (s, 1H), 7.12-7.21 (m, 2H), 7.21-7.29 (m, 5H), 7.29-7.35 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 5.18, 6.11, 17.8, 32.9, 48.0, 109.5, 118.9, 119.0, 120.3, 121.8, 126.4, 127.1, 127.9, 128.5, 128.6, 137.7, 145.9; MS (FAB): *m/z* 261 (M^+); HRMS-FAB: *m/z* (M^+) calcd for $C_{19}H_{19}N$ 261.1517, found 261.1517.

Effects of catalysts and solvents (Table 1): A mixture of 1-methylindole-3-carboxylic acid (**1a**) (175 mg, 1 mmol), $AuCl_4Na{\cdot}2H_2O$ (4.0 mg, 0.01 mmol), TPPMS (3.6 mg, 0.01 mmol) and benzhydrol (**2a**) (221 mg, 1.2 mmol) in H_2O (4 mL) was heated at 120 °C for 16 h in a sealed tube under air. After the reaction mixture was cooled, 4-nitroanisole (153 mg, 1 mmol, internal standard) was added to the reaction mixture, which was extracted with $CDCl_3$ (8 mL), then the organic layer was analyzed by ^1H-NMR spectroscopy.

Catalytic decarboxylative activation (Table 2): A mixture of 1-methylindole-3-carboxylic acid (**1a**) (175 mg, 1 mmol), $AuCl_4Na{\cdot}2H_2O$ (8.0 mg, 0.02 mmol), and TPPMS (7.2 mg, 0.02 mmol) in H_2O (4 mL) was heated at 120 °C for 1 h in a sealed tube under air. After the reaction mixture was cooled, 1,3,5-trimethoxybenzene (168.2 mg, 1 mmol, internal standard) was added to the reaction mixture, which was extracted with $CDCl_3$ (8 mL), then the organic layer was analyzed by ^1H-NMR spectroscopy.

Hammett studies (Figure 2A): A mixture of indole-3-carboxylic acids **1X** (0.25 mmol), indole-3-carboxylic acid (**1b**) (40 mg, 0.25 mmol), $AuCl_4Na{\cdot}2H_2O$ (5 mg, 0.0125 mmol), and TPPMS (5 mg, 0.0125 mmol) in H_2O (1 mL) was heated at 100 °C for 30 min in a sealed tube under air. After the reaction mixture was cooled, which was extracted with $CDCl_3$ (8 mL), then the organic layer was analyzed by ^1H-NMR spectroscopy.

Hammett studies (Figure 2B): A mixture of benzhydryl alcohols **2Y** (1 mmol), benzhydrol (**2a**) (184 mg, 1 mmol), 1-methylindole-3-carboxylic acid (**1a**) (175 mg, 1 mmol), $AuCl_4Na·2H_2O$ (8.0 mg, 0.02 mmol), and TPPMS (7.2 mg, 0.02 mmol) in H_2O (4 mL) was heated at 120 °C for 4 h in a sealed tube under air. After the reaction mixture was cooled, which was extracted with $CDCl_3$ (8 mL), then the organic layer was analyzed by ^{1}H-NMR spectroscopy.

Competition experiment (Scheme 3): A mixture of 1-methylindole-3-carboxylic acid (**1a**) (44 mg, 0.25 mmol), indole-3-carboxylic acid (**1b**) (40 mg, 0.25 mmol), $AuCl_4Na·2H_2O$ (5 mg, 0.0125 mmol), and TPPMS (5 mg, 0.0125 mmol) in H_2O (1 mL) was heated at 100 °C for 30 min in a sealed tube under air. After the reaction mixture was cooled, which was extracted with $CDCl_3$ (8 mL), then the organic layer was analyzed by ^{1}H-NMR spectroscopy.

Deuterium isotope effects (Scheme 4): A mixture of 1-methylindole-3-carboxylic acid (**1a**) (88 mg, 0.5 mmol), $AuCl_4Na·2H_2O$ (10 mg, 0.025 mmol), and TPPMS (10 mg, 0.025 mmol) in H_2O (2 mL) was heated at 100 °C for 30 min or 1 h in a sealed tube under air. After the reaction mixture was cooled, 1,3,5-trimethoxybenzene (168.2 mg, 1 mmol, internal standard) was added to the reaction mixture, which was extracted with $CDCl_3$ (8 mL), then the organic layer was analyzed by ^{1}H-NMR spectroscopy.

Control experiments (Scheme 6A): A mixture of 1-methylindole-3-carboxylic acid (**1a**) (88 mg, 0.5 mmol), benzhydrol (**2a**) (110 mg, 0.5 mmol), 4-hydroxy-3-*tert*-butylanisole (BHA) (90 mg, 0.5 mmol), $AuCl_4Na·2H_2O$ (10 mg, 0.025 mmol), and TPPMS (10 mg, 0.025 mmol) in H_2O (2 mL) was heated at 100 °C for 30 min in a sealed tube under air. After the reaction mixture was cooled, 1,3,5-trimethoxybenzene (168.2 mg, 1 mmol, internal standard) was added to the reaction mixture, which was extracted with $CDCl_3$ (8 mL), then the organic layer was analyzed by ^{1}H-NMR spectroscopy.

Control experiments (Scheme 6B): A mixture of 1-methylindole-3-carboxylic acid (**1a**) (175 mg, 1 mmol), α -cyclopropylbenzyl alcohol (248 μL, 3 mmol), $AuCl_4Na·2H_2O$ (20 mg, 0.05 mmol), and TPPMS (20 mg, 0.05 mmol) in H_2O (4 mL) was heated at 120 °C for 16 h in a sealed tube under air. After

cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was washed with hexanes, then purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **3q** (222 mg, 85%).

Synthesis of bis(indolyl)methanes 5 (Scheme 7)

Bis(1-methylindol-3-yl)(phenyl)methane 5a[19]

A mixture of 1-methylindole-3-carboxylic acid (**1a**) (175 mg 1 mmol), $AuCl_4Na{\cdot}2H_2O$ (20 mg, 0.05 mmol), and TPPMS (20 mg, 0.05 mmol) and benzaldehyde (106 mg, 0.5 mmol) in H_2O (4 mL) was heated at 120 °C for 5 h in a sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give desired product **5a** as a pale brown solid. 155 mg (88%) from benzaldehyde (0.5 mmol); mp 199-201 °C; IR (KBr) (cm^{-1}) 3023, 1476; ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 6H), 5.88 (s, 1H), 6.52 (d, *J*=0.9 Hz, 2H), 6.99 (dd, *J*=8.2, 6.9, 0.9 Hz, 2H), 7.16-7.23 (m, 3H), 7.24-7.30 (m, 4H), 7.32-7.40 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 32.8, 40.0, 110.1, 117.8, 118.9, 119.7, 121.6, 126.4, 127.4, 128.4, 128.6, 128.8, 137.5, 145.3; MS (FAB): *m/z* 351 $[M+H]^+$.

Bis(indol-3-yl)(phenyl)methane 5b[19]

Brown solid. 135 mg (84%) from benzaldehyde (0.5 mmol); mp 141-143 °C; IR (KBr) (cm^{-1}) 3395, 1600; ^1H NMR (400 MHz, $CDCl_3$): δ 5.88 (s, 1H), 6.65 (d, *J*=1.4 Hz, 2H), 7.00 (t, *J*=7.3 Hz, 2H), 7.16 (t, *J*=7.3 Hz, 2H), 7.18-7.40 (m, 9H), 7.88 (brs, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 40.0, 112.0, 118.6, 118.7, 119.6, 121.4, 124.1, 126.3, 127.1, 128.5, 128.8, 137.1, 145.5; MS (FAB): *m/z* 323 $[M+H]^+$.

Scale-up experiment (Scheme 8): A mixture of 1-methylindole-3-carboxylic acid (**1a**) (1.05 g, 6.0 mmol), $AuCl_4Na{\cdot}2H_2O$ (119.0 mg, 0.3 mmol), TPPMS (109.3 mg, 0.3 mmol) and benzhydrol (**2a**) (1.33 g, 7.2 mmol) in H_2O (24 mL) was heated at 110 °C for 16 h under air. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over

$MgSO_4$ and concentrated in vacuo. The residue was recrystallized from hexane and AcOEt to give desired product **3a** (1.28 g, 72%) as a pale yellow solid.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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References

(1) Shepard, A. F.; Winslow, N. R.; Johnson, John R. Simple halogen derivatives of furan. *J. Am. Chem. Soc.* **1930**, *52*, 2083-2090.

(2) Gooβen, L. J.; Thiel, W. R.; Rodriguez, N.; Linder, C.; Melzer, B. Copper-Catalyzed Protodecarboxylation of Aromatic Carboxylic Acids. *Adv. Synth. Catal*. **2007**, *349*, 2241-2246.

(3) (a) Moon, P. J.; Fahandej-Sadi, A.; Qian, W.; Lundgren, R. J. Decarboxylative Benzylation of Aryl and Alkenyl Boronic Esters. *Angew. Chem., Int. Ed.* **2018**, *57*, 4612-4616. (b) Shi, X.; Chen, X.; Wang, M.; Zhang, X.; Fan, X. Regioselective Synthesis of Acylated N-Heterocycles via the Cascade Reactions of Saturated Cyclic Amines with 2-Oxo-2-arylacetic Acids. *J. Org. Chem.* **2018**, *83*, 6524-6533. (c) Cadot, S.; Rameau, N.; Mangematin, S.; Pinel, C.; Djakovitch, L. Preparation of Functional Styrenes from Biosourced Carboxylic Acids by Copper Catalyzed Decarboxylation in PEG. *Green Chem.* **2014**, *16*, 3089-3097.

(4) (a) Zeng, X.; Liu, C.; Wang, X.; Zhang, J.; Wang, X.; Hu, Y. Silver-Catalyzed Decarboxylative Acylation of Quinoxalin-2(1H)-ones with α-oxo-carboxylic Acids. *Org. Biomol. Chem.* **2017**, *15*, 8929-8935. (b) Hu, F.; Shao, X.; Zhu, D.; Lu, L.; Shen, Q. Silver-Catalyzed Decarboxylative Trifluoromethylthiolation of Aliphatic Carboxylic Acids in Aqueous Emulsion. *Angew. Chem., Int. Ed.*

2014, *53*, 6105-6109. (c) Grainger, R.; Cornella, J.; Blakemore, D. C.; Larrosa, I.; Campanera, J. M. The *ortho*-Substituent Effect on the Ag-Catalysed Decarboxylation of Benzoic Acids. *Chem. Eur. J.* **2014**, *20*, 16680-16687.

(5) (a) Han, S.; Ren, X.; Wu, Q.; Liang, A.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. Palladium-Catalyzed Decarboxylative Cross-Couplings of 1-Boc-3-iodoazetidine: Regioselective Access to 2-Alkynylazetidines, 3-Alkynylazetidines and 3-Vinylazetidines. *Adv. Synth. Catal.* **2018**, *360*, 2308-2312. (b) Kong, D.; Moon, P. J.; Qian, W.; Lundgren, R. J. Expanding the Limit of Pd-Catalyzed Decarboxylative Benzylations. *Chem. Commun.* **2018**, *54*, 6835−6838. (c) Zheng, C.; Cheng, W.-M.; Li, H.-L.; Na, R.-S.; Shang, R. *Cis*-Selective Decarboxylative Alkenylation of Aliphatic Carboxylic Acids with Vinyl Arenes Enabled by Photoredox/Palladium/Uphill Triple Catalysis. *Org. Lett.* **2018**, *20*, 2559−2563.

(6) (a) Kumar, R.; Krieger, J.-P.; Gomez-Bengoa, E.; Fox, T.; Linden, A.; Nevado, C. The First Gold(III) Formate: Evidence for β-Hydride Elimination. *Angew. Chem., Int. Ed.* **2017**, *56*, 12862-12865. (b) Dupuy, S.; Crawford, L.; Buehl, M.; Nolan, S. P. The Gold(I)-Catalysed Protodecarboxylation Mechanism. *Chem. Eur. J.* **2015**, *21*, 3399-3408. (c) Dupuy, S.; Nolan, S. P. Gold(I)-Catalyzed Protodecarboxylation of (Hetero)Aromatic Carboxylic Acids. *Chem. Eur. J.* **2013**, *19*, 14034-14038. (d) Dupuy, S.; Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J.; Nolan, S. P. Decarboxylation of aromatic carboxylic acids by gold(I)-N-heterocyclic carbene (NHC) complexes. *Chem. Commun.* **2011**, *47*, 5455-5457. (e) Cornella, J.; Rosillo-Lopez, M.; Larrosa, I. A Novel Mode of Reactivity for Gold(I): The Decarboxylative Activation of (Hetero)Aromatic Carboxylic Acids. *Adv. Synth. Catal.* **2011**, *353*, 1359-1366.

(7) (a) Schierle, S.; Flauaus, C.; Heitel, P.; Willems, S.; Schmidt, J.; Kaiser, A.; Weizel, L.; Goebel, T.; Kahnt, A. S.; Geisslinger, G.; Steinhilber, D.; Wurglics, M.; Rovati, G. E.; Schmidtko, A.; Proschak, E.; Merk, D. Boosting Anti-Inflammatory Potency of Zafirlukast by Designed Polypharmacology. *J. Med. Chem*. **2018**, *61*, 5758-5764. (b) Praveen Kumar, V.; Renjitha, J.; Fathimath Salfeena, C. T.; Ashitha, K. T.; Keri, R. S.; Varughese, S.; Balappa Somappa, Sasidhar. Antibacterial and

Antitubercular Evaluation of Dihydronaphthalenone-Indole Hybrid Analogs. *Chem. Biol. Drug Des.* **2017**, *90*, 703-708. (c) Zhang, C.; Qu, Y.; Niu, Bingxuan. Design, Synthesis and Biological Evaluation of Lapachol Derivatives Possessing Indole Scaffolds as Topoisomerase I Inhibitors. *Bioorg. Med. Chem.* **2016**, *24*, 5781-5786. (d) Kaila, N.; Huang, A.; Moretto, A.; Follows, B.; Janz, K.; Lowe, M.; Thomason, J.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. Diazine Indole Acetic Acids as Potent, Selective, and Orally Bioavailable Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 Cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases. *J. Med. Chem.* **2012**, *55*, 5088-5109. (e) Nandhikonda, P.; Lynt, W. Z.; McCallum, M. M.; Ara, T.; Baranowski, A. M.; Yuan, N. Y.; Pearson, D.; Bikle, D. D.; Guy, R. K.; Arnold, L. A. Discovery of the First Irreversible Small Molecule Inhibitors of the Interaction between the Vitamin D Receptor and Coactivators. *J. Med. Chem.* **2012**, *55*, 4640-4651. (f) Yao, C.-H.; Song, J.-S.; Chen, C.-T.; Yeh, T.-K.; Hung, M.-S.; Chang, C.-C.; Liu, Y.-W.; Yuan, M.-C.; Hsieh, C.-J.; Huang, C.-Y.; Wang, M.-H.; Chiu, C.-H.; Hsieh, T.-C.; Wu, S.-H.; Hsiao, W.-C.; Chu, K.-F.; Tsai, C.-H.; Chao, Y.-S.; Lee, J.-C. Discovery of Novel N-β-d-Xylosylindole Derivatives as Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors for the Management of Hyperglycemia in Diabetes. *J. Med. Chem.* **2011**, *54*, 166–178.

(8) (a) Bering, L.; Jeyakumar, K.; Antonchick, A. P. Metal-Free C-O Bond Functionalization: Catalytic Intramolecular and Intermolecular Benzylation of Arenes. *Org. Lett.* **2018**, *20*, 3911−3914. (b) Gregorio, G. D.; Mari, M.; Bartoccini, F.; Piersanti, G. Iron-Catalyzed Direct C3-Benzylation of Indoles with Benzyl Alcohols through Borrowing Hydrogen. *J. Org. Chem.* **2017**, *82*, 8769−8775. (c) Eka, A.; Takigawa, K.; Tanaka, H.; Ito, Y.; Oe, Y.; Ohta, T. Transition-Metal-Catalyzed Regioselective Alkylation of Indoles with Alcohols. *Eur. J. Org. Chem.* **2013**, 6344-6354.

(9) Hikawa, H.; Suzuki, H.; Azumaya, I. Au(III)/TPPMS-Catalyzed Benzylation of Indoles with Benzylic Alcohols in Water. *J. Org. Chem.* **2013**, *78*, 12128-12135.

(10) (a) Vandersteen, A. A.; Mundle, S. O. C.; Kluger, R. Protonated Carbonic Acid and Reactive Intermediates in the Acidic Decarboxylation of Indolecarboxylic Acids. *J. Org. Chem.* **2012**, *77*, 6505-

6509. (b) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. Fluorescent Diarylindoles by Palladium-Catalyzed Direct and Decarboxylative Arylations of Carboxyindoles. *Chem. Eur. J.* **2009**, *15*, 3674-3677. (c) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. Fused Ring Construction around Pyrrole, Indole, and Related Compounds *via* Palladium-Catalyzed Oxidative Coupling with Alkynes. *J. Org. Chem.* **2009**, *74*, 7481-7488.

(11) Preparation of indole-3-carboxylic acids. See: Yoo, W.-J.; Capdevila, M. G.; Du, X.; Kobayashi, S. Base-Mediated Carboxylation of Unprotected Indole Derivatives with Carbon Dioxide. *Org. Lett.* **2012**, *14*, 5326-5329.

(12) (a) Hikawa, H.; Imamura, H.; Kikkawa, S.; Azumaya, I. A Borrowing Hydrogen Methodology: Palladium-Catalyzed Dehydrative *N*-Benzylation of 2-Aminopyridines in Water. *Green Chem.* **2018**, *20*, 3044–3049. (b) Hikawa, H.; Ichinose, R.; Kikkawa, S.; Azumaya, I. A Palladium-Catalyzed Dehydrative *N*-Benzylation/C-H Benzylation Cascade of 2-Morpholinoanilines on Water. *Green Chem.* **2018**, *20*, 1297-1305. (c) Xu, Z.; Yu, X.; Sang, X.; Wang, D. BINAP-Copper Supported By Hydrotalcite s an Efficient Catalyst for the Borrowing Hydrogen Reaction and Dehydrogenation Cyclization under Water or Solvent-Free Conditions. *Green Chem.* **2018**, *20*, 2571-2577. Review see. (d) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. Catalytic Organic Reactions in Water toward Sustainable Society. *Chem. Rev.* **2018**, *118*, 679-746.

(13) (a) Garcia-Moreno, E.; Gascon, S.; Rodriguez-Yoldi, M.; Cerrada, E.; Laguna, M. *S*-Propargylthiopyridine Phosphane Derivatives As Anticancer Agents: Characterization and Antitumor Activity. *Organometallics* **2013**, *32*, 3710-3720. (b) Vergara, E.; Cerrada, E.; Clavel, C.; Casini, A.; Laguna, M. Thiolato Gold(I) Complexes Containing Water-Soluble Phosphane Ligands: A Characterization of their Chemical and Biological Properties. *Dalton Trans.* **2011**, *40*, 10927-10935. (c) Komine, N.; Ichikawa, K.; Mori, A.; Hirano, M.; Komiya, S. Enhanced Reductive Elimination of Dialkylgold(III) Complexes in Water. *Chem. Lett.* **2005**, *34*, 1704-1705.

(14) (a) Biasiolo, L.; Belpassi, L.; Gaggioli, C. A.; Macchioni, A.; Tarantelli, F.; Ciancaleoni, G.; Zuccaccia, D. Cyclization of 2-Alkynyldimethylaniline on Gold(I) Cationic and Neutral Complexes.

Organometallics **2016**, *35*, 595-604. (b) Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. Serendipitous Discovery of the Catalytic Hydroammoniumation and Methylamination of Alkynes. *Angew. Chem. Int. Ed.* **2010**, *49*, 942–945. (c) Hashmi, A. S. K.; Ramamurthi, T. D.; Romingera, F. On the Trapping of Vinylgold Intermediates. *Adv. Synth. Catal.* **2010**, *352*, 971–975.

(15) (a) Morita, N.; Yasuda, A.; Shibata, M.; Ban, S.; Hashimoto, Y.; Okamoto, I.; Tamura, O. Gold(I)/(III)-Catalyzed Synthesis of Cyclic Ethers; Valency-Controlled Cyclization Modes. *Org. Lett.* 2015, *17*, 2668-2671. (b) Das, T.; Debnath, S.; Maiti, R.; Maiti, D. K. Multifold C-C Coupling and Unorthodox Cyclization Catalysis for Selective Synthesis of Indolotriarylmethanes, Indolocarbazoles, and Their Analogues: A Control Experiment Study. *J. Org. Chem.* 2017, *82*, 688-700.

(16) Shirakawa, S.; Kobayashi, S. Surfactant-Type Bronsted Acid Catalyzed Dehydrative Nucleophilic Substitutions of Alcohols in Water. *Org. Lett.* **2007**, *9*, 311-314.

(17) Di Gregorio, G.; Mari, M.; Bartoccini, F.; Piersanti, G. Iron-Catalyzed Direct C3-Benzylation of Indoles with Benzyl Alcohols through Borrowing Hydrogen. *J. Org. Chem.* **2017**, *82*, 8769-8775.

(18) Das, D.; Roy, S. Palladium(II)-Catalyzed Efficient C-3 Functionalization of Indoles with Benzylic and Allylic Alcohols under Co-Catalyst, Acid, Base, Additive and External Ligand-Free Conditions. *Adv. Synth. Catal.* **2013**, *355*, 1308-1314.

(19) Hikawa, H.; Yokoyama, Y. Pd-Catalyzed C-H Activation in Water: Synthesis of Bis(indolyl) methanes from Indoles and Benzyl alcohols. *RSC Adv.* **2013**, *3*, 1061-1064.

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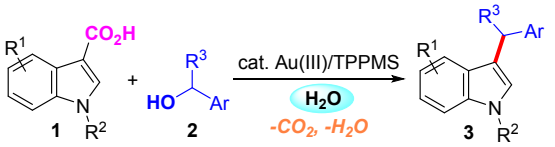

20 examples, 50-93% yield

Decarboxylative and dehydrative coupling reaction in water