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Decarboxylative Addition of Propiolic Acids with Indoles to Synthesize Bis(indolyl)methane Derivatives with a Pd(II)/LA Catalyst

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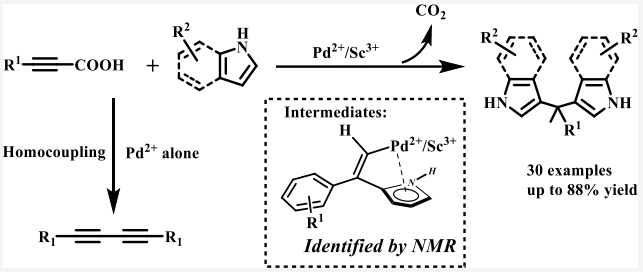
ABSTRACT: Exploring new protocols for efficient organic synthesis is crucial for pharmaceutical developments. The present work introduces a Pd(II)/LA-catalyzed (LA: Lewis acid) decarboxylative addition reaction for the synthesis of bis(indolyl)-methane derivatives. The presence of Lewis acid such as $Sc(OTf)_3$ triggered Pd(II)-catalyzed decarboxylative addition of propiolic acids with indoles to offer the bis(indolyl)methane derivatives in moderate to good yields, whereas neither Pd(II) nor Lewis acid alone was active for this synthesis. The catalytic efficiency of $Pd(OAc)_2$ was highly dependent on the Lewis acidity of the added Lewis acid, that is, a stronger Lewis acid provided a higher yield of the bis(indolyl)methane derivatives. Meanwhile, this Pd(II)/LA-catalyzed decarboxylative addition reaction showed good tolerance toward versatile electron-rich or -deficient substituents on the indole skeleton and on the benzyl ring of propiolic acids. The studies on the in situ ^{1}H NMR kinetics of this Pd(II)/Sc(III) catalysis disclosed the formation of a transient vinyl-Pd(II)/Sc(III) intermediate generated by the pyrrole addition to the alkynyl-Pd(II)/Sc(III) species after decarboxylation, which was scarcely observed before.



1. INTRODUCTION

Exploring new methodology for efficient organic synthesis is among the most attractive topics in chemical science because of its fantasy in creating new compounds for pharmaceutical and material applications with it reducing the pollution in synthesis. In recent years, cooperatively bimetallic catalysis has received increasing attention in organic synthesis, and Wacker-type oxidation with inspired Pd(II)/Cu(II) catalysis possibly represents one of the most attractive bimetallic oxidation methods in organic synthesis, in which Cu(II) is generally believed to serve as the oxidant to regenerate the active Pd(II) species from the reduced Pd(0) in the catalytic cycle.[1−3] During the mechanistic studies of redox enzymes with inorganic models, we observed that increasing the positive net charge of an active metal ion through protonation can significantly accelerate its electron transfer rate, which inspired us to explore Lewis acid-promoted catalytic oxidations with redox catalysts (Brönsted acid vs Lewis acid).[4,5] Following up this concept, we unexpectedly found that adding certain non-redox metal ions such as Sc^{3+} can significantly accelerate Pd(II)-catalyzed aerobic olefin oxidation to ketone, even much more efficiently than the corresponding Pd(II)/Cu(II) catalysis, and the promotional effect was obviously dependent on the Lewis acidity of the added non-redox metal ions as Lewis acid.[6] This phenomenon has disclosed that in addition to its redox properties, the Lewis acid properties of the Cu^{2+} cation may have also played significant roles in Pd(II)/Cu(II)-catalyzed organic syntheses in certain cases, which inspired us to explore Lewis acid-promoted Pd(II) catalysis in organic synthesis, defined as Pd(II)/LA catalysis. Up to now, this strategy has been successful in olefin oxidation, olefin isomerization, alkyne oxidation, oxidative dehydrogenation, benzene hydroxylation, nitrile hydration, and oxidative olefination/annulation of benzamides,[6,7] and it has also been expanded to Ni(II)/LA-catalyzed oxidative S−P bond formation.[8]

The present work introduces the application of this Pd(II)/LA catalysis in decarboxylative addition of propiolic acids to indoles and pyrroles for the syntheses of bis(indolyl)methane and bis(pyrrolyl)methane derivatives, in which bis(indolyl)-methane derivatives have been disclosed to have promising antibacterial and antifungal activities.[9] In the literature, a list of methodologies was explored to synthesize bis(hetero)methane derivatives;[10] among them, bis(indolyl)methane derivatives were mainly synthesized through (1) arylation of aryl ketones followed by addition of indoles (Scheme 1a),[11] (2) reductive alkylation of indoles with aryl ketones and aldehydes (Scheme 1b),[12] (3) alkyne addition with indoles (Scheme 1c),[13] (4) Friedel−Crafts alkylation of trifluoromethylated 3-indolylmethanols with 2-substituted indoles (Scheme 1d),[14] (5)

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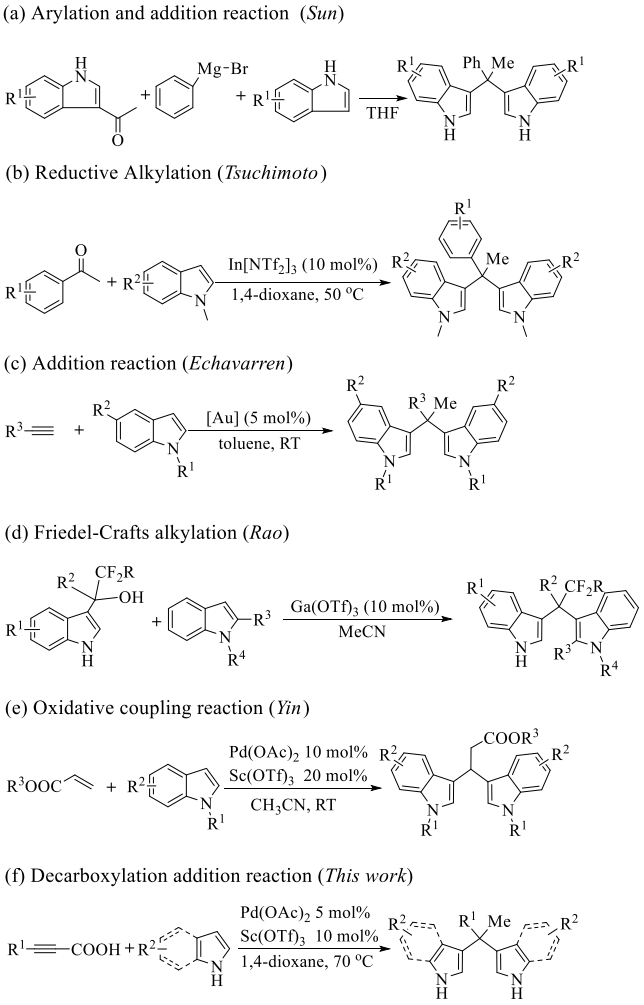
Scheme 1. Synthesis of Bis(indolyl)methanes



oxidative coupling of olefin with indoles (Scheme 1e),[15] and so forth. While all of these methodologies demonstrated their specific merits in bis(indolyl)methane derivative syntheses, for example, a Lewis acid-catalyzed reaction such as $GaCl_3$- and $In(OTf)_3$-catalyzed addition of indoles to alkynes represents a simple protocol for their syntheses,[13c] they also face different challenges such as starting material limits, the structural limits of the final bis(indolyl)methane product, and so forth. Decarboxylative coupling is a new protocol for C−C bond formation in addition to well-known protocols through C−H and C−X bond activation.[16] Herein, we report a Pd(II)/LA-catalyzed decarboxylative addition of propiolic acids with indoles and pyrroles to synthesize bis(indolyl)methane and bis(pyrrolyl)methane derivatives, respectively (Scheme 1f), which complements our previous oxidative coupling protocol suitable for electron-deficient olefins.[15a] Interestingly, the decarboxylation coupling and the next indole/pyrrole addition reaction in this work dominantly happened on the olefinic carbon proximal to the aromatic ring, in which a vinyl-Pd(II)/Sc(III) complex, generated by pyrrole addition to the alkynyl-Pd(II)/Sc(III) species after decarboxylation, was observed as an intermediate through ^{1}H NMR kinetic studies.

2. RESULTS AND DISCUSSION

In the initial tests, the condition optimizations were carried out with phenylpropiolic acid (**1a**) and indole (**2a**) as the model substrates. As shown in Table 1, the expected decarboxylative addition reaction did not happen using 5 mol % $Pd(OAc)_2$ alone as the catalyst in 1,4-dioxane at 70 °C (Table 1, entry 1); only the homocoupling product of phenylacetylene was obtained after Pd(II)-catalyzed decarboxylation of phenylpropiolic acid as that in the literature.[17] Next, different Lewis acids were tested as the additives to the $Pd(OAc)_2$ catalyst (Table 1, entries 2−11). Although adding 10 mol % NaOTf to $Pd(OAc)_2$ did not provide bis(indolyl)methane as the product, it was obtained when bivalent metal ions were added as the Lewis acid (Table 1, entries 2−6). For example, adding $Zn(OTf)_2$ to $Pd(OAc)_2$ provided 28% yield of **3aa** with only 4% yield of α-addition product **4aa**; using $Cu(OTf)_2$ as the source of Lewis acid also provided 26% yield of **3aa** with the yield of **4aa** increasing up to 16%. Remarkably, the trivalent metal ions such as Bi^{3+}, Al^{3+}, Yb^{3+}, Y^{3+}, and Sc^{3+} exhibited a much better promotional effect than bivalent metal ions for **3aa** synthesis, while the yield of **4aa** did not increase too much (Table 1, entries 7−11), and adding $Sc(OTf)_3$ afforded **3aa** in the highest yield than other trivalent metal ions, giving 80% yield of **3aa** with only 8% of **4aa** (Table 1, entry 11). Clearly, the promotional effects were positively correlated with the acidity of the added Lewis acids, whereas using Lewis acid alone was ineffective for this reaction, and the substrate **1a** could not be decarboxylated with Lewis acid alone (Table 1, entry 16). In addition, this Pd(II)/LA catalysis demonstrated higher activity in **3aa** synthesis in ether-type solvents such as 1,4-dioxane and ethylene glycol diethyl ether than that in other solvents such as DMSO, MeCN, and HOAc (Table 1, entries 11−15). Notably, combining Lewis acids with $Pd(OAc)_2$ to generate a Pd(II)/LA catalyst led to no homocoupling product formation from propionic acid, and no palladium black was observed after the reaction, whereas both the homocoupling product and palladium black were clearly observed with $Pd(OAc)_2$ alone as the catalyst, indicating that in situ generation of a Pd(II)/LA catalyst led to a distinct reactivity different from that when using $Pd(OAc)_2$ alone.

The ratio of **1a** and **2a** substrates and the reaction temperature were further optimized using Pd(II)/Sc(III) as the catalyst, and it was found that the ratio of 1/5 between **1a** and **2a** provided the best results at the reaction temperature of 70 °C in 1,4-dioxane solvent (Table S1, entries 1−5). Based on these conditions, the influence of the Pd(II)/Sc(III) ratio on the catalytic efficiency of the model reaction was next investigated (Table S2). As shown, in the absence of $Sc(OTf)_3$, using $Pd(OAc)_2$ alone as a catalyst, only the homocoupling product of phenylacetylene was obtained (Table S2, entry 1). Adding $Sc(OTf)_3$ significantly improved the catalytic efficiency for the decarboxylative addition reaction. Even in the case of adding 0.5 mol % $Sc(OTf)_3$ to 5 mol % $Pd(OAc)_2$, it also provided 7% yield of **3aa** (Table S2, entry 2). When adding 5 mol % $Sc(OTf)_3$ to 5 mol % $Pd(OAc)_2$, it gave 63% yield of **3aa** with trace **4aa** formation (Table S2, entry 5), and using 10 mol % $Sc(OTf)_3$ and 5 mol % $Pd(OAc)_2$ provided **3aa** in 80% yield with 8% yield of **4aa** formation (Table S2, entry 6); further increasing the $Sc(OTf)_3$ loading did not provide any more improvement on catalytic efficiency.

In order to reveal the role of $Sc(OTf)_3$ in catalysis, a series of control experiments was carried out next under the optimal conditions (Table 2). As shown, in the absence of $Sc(OTf)_3$, using $Pd(OAc)_2$ alone as a catalyst, no **3aa** or **4aa** was detected (Table 2, entry 1). The product **3aa** was generated only when $Pd(OAc)_2$ and Lewis acid such as $Sc(OTf)_3$ were employed

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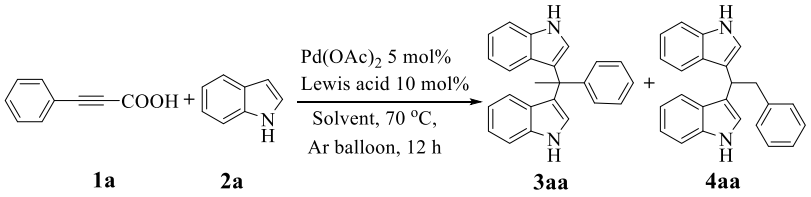
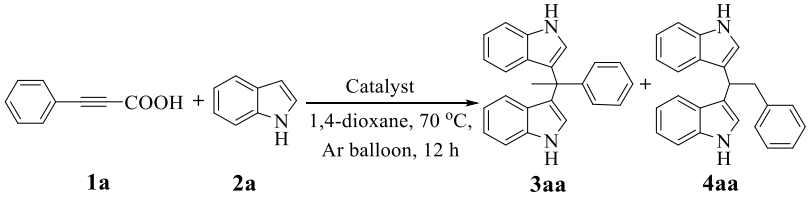
Table 1. Optimization of the Reaction Conditions for the Model Reaction[a]



entry	catalyst	additives	solvent	yield (%)[b] 3aa	4aa
1	$Pd(OAc)_2$		1,4-dioxane	nd	nd
2	$Pd(OAc)_2$	NaOTf	1,4-dioxane	nd	nd
3	$Pd(OAc)_2$	$Ba(OTf)_2$	1,4-dioxane	3	nd
4	$Pd(OAc)_2$	$Mg(OTf)_2$	1,4-dioxane	6	nd
5	$Pd(OAc)_2$	$Zn(OTf)_2$	1,4-dioxane	28	4
6	$Pd(OAc)_2$	$Cu(OTf)_2$	1,4-dioxane	26	16
7	$Pd(OAc)_2$	$Bi(OTf)_3$	1,4-dioxane	38	15
8	$Pd(OAc)_2$	$Al(OTf)_3$	1,4-dioxane	45	13
9	$Pd(OAc)_2$	$Yb(OTf)_3$	1,4-dioxane	59	trace
10	$Pd(OAc)_2$	$Y(OTf)_3$	1,4-dioxane	61	trace
11	$Pd(OAc)_2$	$Sc(OTf)_3$	1,4-dioxane	80	8
12	$Pd(OAc)_2$	$Sc(OTf)_3$	MeCN	19	13
13	$Pd(OAc)_2$	$Sc(OTf)_3$	ethylene glycol diethyl ether	70	8
14	$Pd(OAc)_2$	$Sc(OTf)_3$	DMSO	nd	nd
15	$Pd(OAc)_2$	$Sc(OTf)_3$	HOAc	trace	trace
16		$Sc(OTf)_3$	1,4-dioxane	nd	nd

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), solvent (1.0 mL), $Pd(OAc)_2$ (5 mol %), Lewis acid (10 mol %), Ar balloon, 70 °C, and 12 h. [b]Isolated yield.

Table 2. Control Experiments for the Model Reaction[a]



entry	catalyst	yield (%)[b] 3aa	4aa
1	$Pd(OAc)_2$	nd	nd
2	$Pd(OAc)_2$ + $Sc(OTf)_3$	80	8
3	$Pd(OAc)_2$ + HOTf (30 mol %)	30	20
4	$Pd(OAc)_2$ + NaOTf (30 mol %)	trace	trace
5	$Pd(OTf)_2$	trace	trace
6	$Pd(OAc)_2$ + $Zn(OTf)_2$	28	4
7	$Pd(OAc)_2$ + $Zn(BF_4)_2$	34	5

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), 1,4-dioxane (1.0 mL), $Pd(OAc)_2$ (5 mol %), Lewis acid (10 mol %), Ar balloon, 70 °C, and 12 h. [b]Isolated yield.

together as a catalyst (Table 2, entry 2), which clearly supported that adding Lewis acid triggered the catalytic activity of $Pd(OAc)_2$ for the decarboxylative addition reaction. The role of the anion in this reaction was also addressed by adding HOTf or NaOTf instead of the salts of bivalent or trivalent metal ions. When 30% mol HOTf was added instead of Lewis acid, the desired product **3aa** was formed in only 30% yield; however, the α-addition byproduct **4aa** was also formed in 20% yield (Table 2, entry 3). Plausibly, the substrate **1a** was unstable under acidic conditions;[18] after its decarboxylation, both the α-addition and β-addition reaction could proceed feasibly, leading to the low selectivity to **3aa**. Adding Sc^{3+} possibly enhanced the electrophilic properties of the Pd^{2+} cation (vide infra); thus, the Markovnikov adduct product **3aa** dominated with trace **4aa** formation.[19] To address whether the OTf^- anion of $Sc(OTf)_3$ played the key role instead of the Sc^{3+} cation through the ligand exchange between $Pd(OAc)_2$ and $Sc(OTf)_3$, 30% mol NaOTf was tested as the additives; however, only trace **3aa** was detected as the product (Table 2, entry 4). In addition, using $Pd(OTf)_2$ as a catalyst also provided only trace **3aa** formation (Table 2, entry 5). When 5% mol $Zn(BF_4)_2$ was added instead of $Zn(OTf)_2$, the product **3aa** was formed in 34% yield, even higher than 28% yield of **3aa** with $Zn(OTf)_2$ as additives (Table 2, entries 6 and 7).

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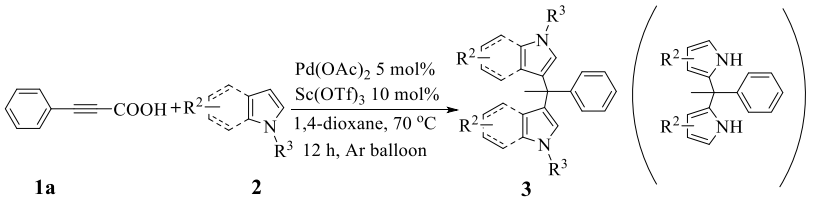
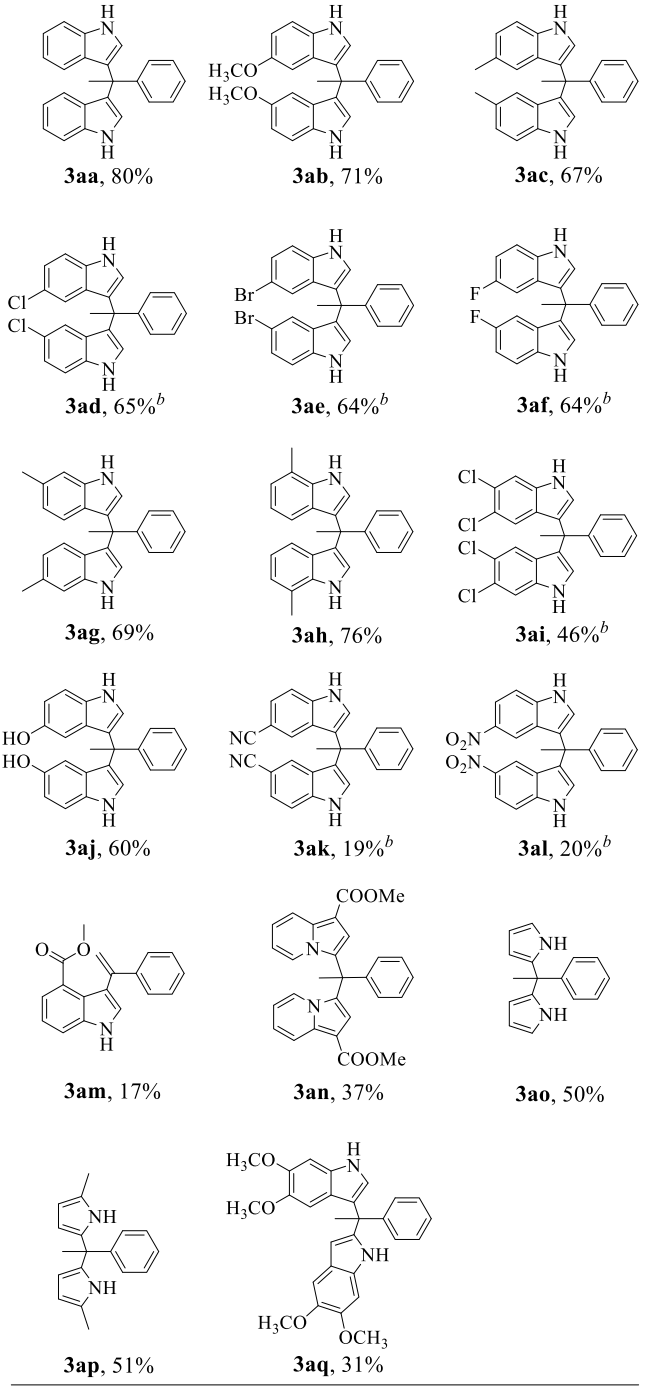
Scheme 2. Substrate Scope of Reactions Using Indole[a]





[a]Reaction conditions: **1a** (0.2 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), $Sc(OTf)_3$ (10 mol %), 1,4-dioxane (1 mL), Ar balloon, 70 °C, and 12 h. [b]24 h.

Clearly, these results supported that it was the Lewis acid cation, rather than its counteranion, OTf^-, that improved the catalytic efficiency of $Pd(OAc)_2$ in this decarboxylation addition reaction, and the promotional effect was positively

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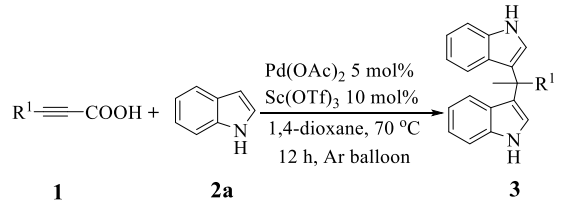
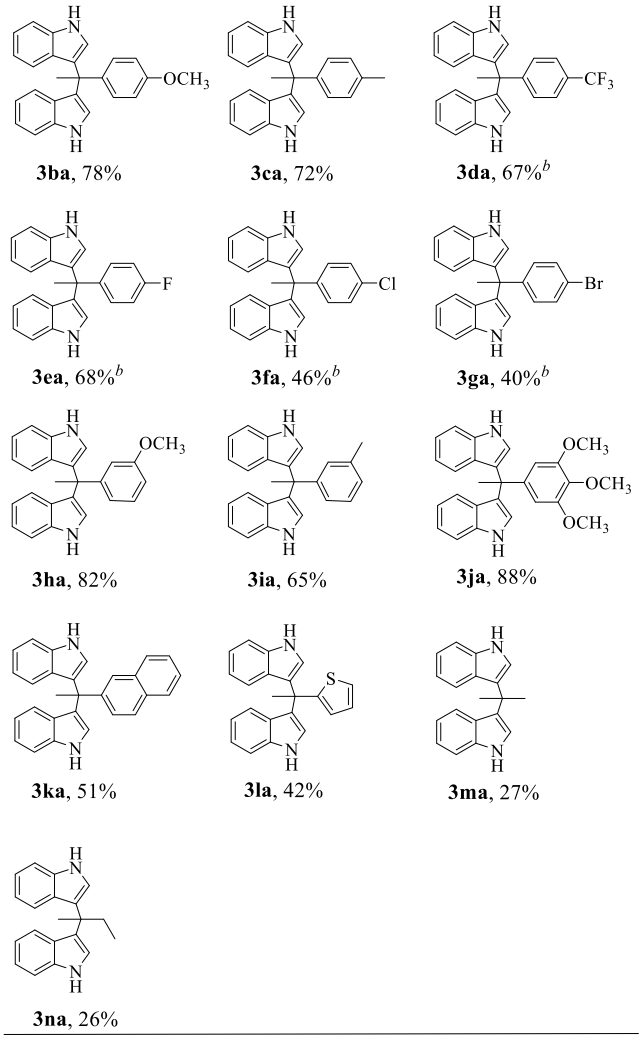
correlated with the acidity of the added Lewis acids, as disclosed in Table 1.

To evaluate the substrate scope of this reaction with a $Pd(OAc)_2/Sc(OTf)_3$ catalyst, a variety of indoles were first investigated as the substrate in reaction with phenylpropiolic acid **1a**. As summarized in Scheme 2, the reaction proceeded smoothly to provide bis(indolyl)methanes as the product. The indole bearing a methyl or methoxy group at the C5 position reacted smoothly with **1a**, giving 71 and 67% yields, respectively (**3ab** and **3ac**), and it bearing an electron-withdrawing group at the C5 position also gave similar yields (**3ad** and **3af**). The C6- and C7-substituted indole derivatives were also tolerated with this reaction, giving 67 and 76% yields, respectively (**3ag** and **3ah**). Unfortunately, when the C2-substituted indoles such as 2-phenylindole and 2-methylindole were employed as the substrate, no bis(indolyl)methane was observed, possibly due to the influence of steric hindrance. Indole having multiple electron-withdrawing groups on the phenyl ring gave a moderate yield (46%, **3ai**). Other functional group-substituted indoles such as 5-hydroxyindole, 5-cyanoindole, and 5-nitroindole reacting with **1a** gave 60, 19, and 20% yields, respectively (**3aj**−**3al**). Interestingly, methyl indole-4-carboxylate **2m** as the substrate gave 17% yield of **3am**, which is a decarboxylative addition product without further addition of the second **2m** substrate, possibly due to the steric hindrance; remarkably, the formation of this product provided a valuable mechanistic clue for this Pd(II)/LA catalysis. In addition, using dimethyl indolizine-1,2-dicarboxylate instead of indole as the substrate provided 37% yield of bis(indolizinyl)-methane (**3an**). Since **3an** is not very stable, the real yield of **3an** may be higher than 37% in the present study. Pyrrole and 2-methyl-1*H*-pyrrole also reacted with **1a** smoothly, giving 50 and 51% yields of bis(pyrrolyl)methanes (**3ao** and **3ap**), respectively. Notably, 5,6-dimethoxyindole **2q** as the substrate gave 31% yield of **3aq**, which is a new decarboxylative addition product that was never reported before. Unlike other substrates, here, the addition reaction occurred at the C2 and C3 positions of the two **2q** molecules. In addition, N-protected indole **2** such as 1-methylindole was also tested as the substrate, and it showed good reactivity; however, the expected product was not stable enough to achieve the NMR analysis.

Next, the scope of phenylpropiolic acid derivatives was investigated, which is summarized in Scheme 3. The electronic nature of the phenylpropiolic acid derivatives significantly affected the yield of bis(indolyl)methane. As shown, phenylpropiolic acids with an electron-donating functional group on the phenyl ring (**3ba** and **3ca**) provided higher yield than those having an electron-withdrawing group (**3da**−**3ga**). Aryl propiolic acids with a methoxy and methyl group at the meta position afforded bis(indolyl)methanes **3ha** and **3ia** in 82 and 65% yields, respectively. Phenylpropiolic acid with multiple electron-donating groups on the phenyl ring gave **3ja** in 88% yield, and naphthyl propiolic acid as the substrate also gave **3ka** in 51% yield. In addition, 2-thiophenyl propiolic acid as the substrate gave **3la** in 42% yield, and the alkyl-substituted alkynoic acids also gave **3ma** and **3na** in 27 and 26% yields, respectively. In the literature, Statti even disclosed the good anti-cancer activity of **3ja**, in which **3ja** was synthesized through condensation of 3,4,5-trimethoxyacetophenone with indole in the presence of HCl (26% yield) or $(COOH)_2{\cdot}2H_2O$/CTAB (62% yield, CTAB: *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide).[20] Most recently, Szpilman

Scheme 3. Scope of Reactions Using Phenylpropiolic Acid[a]





[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), $Sc(OTf)_3$ (10 mol %), 1,4-dioxane (1 mL), Ar balloon, 70 °C, and 12 h. [b]24 h.

reported an $InCl_3$-catalyzed vinyl azide reaction with indole to provide **3ja** in 88% yield, where the treatment of vinyl azide must be done with proper safety precautions.[21] Apparently, the method disclosed in the present study is more attractive than that in previous studies for **3ja** synthesis. Accordingly, the synthesis of **3ja** was carried out next in the gram scale, which provided 86% yield of **3ja** (1.1 g, 86%, Scheme 4), almost identical to that in Scheme 3, indicating that this new methodology is potentially applicable in the large-scale synthesis of **3ja**.

In order to investigate the active catalyst in this Pd(II)/LA-catalyzed decarboxylative addition reaction, the UV−vis spectra of the Pd(II)/Sc(III) catalyst were investigated,

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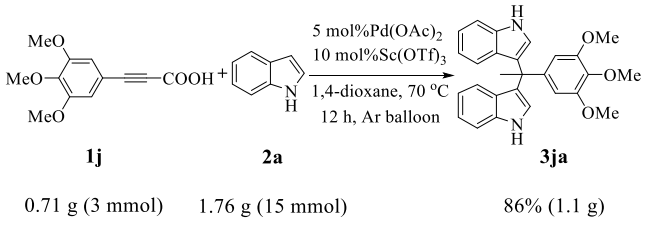
Scheme 4. Gram-Scale Synthesis of Bis(indolyl)methane 3ja



1j **2a** **3ja**

0.71 g (3 mmol) 1.76 g (15 mmol) 86% (1.1 g)

which are displayed in Figure 1. As shown, $Pd(OAc)_2$ demonstrated an absorbance band around 400 nm due to the ligand-to-metal charge transfer from the acetate ligand to the Pd^{2+} cation. Adding $Sc(OTf)_3$ to $Pd(OAc)_2$ led to the generation of a new absorbance band with a maximum near 321 nm, and with increasing the concentration of the Pd(II)/LA catalyst, the new absorbance band increased proportionately as well (Figure S2), thus indicating the formation of a new Pd(II) species. The migration of chemical shifts caused by adding $Sc(OTf)_3$ was also observed in ^1H NMR spectra (Figure 2). As shown in Figure 2b, $Pd(OAc)_2$ alone in DMSO-d_6 reveals a chemical shift of 1.78 ppm, corresponding to the methyl group of acetate in the $Pd_3(OAc)_6$ trimer in which all of the acetates serve as bridges like those in the literature.[22] Adding $Sc(OTf)_3$ to $Pd(OAc)_2$ downshifted the methyl group of acetate from 1.78 to 1.91 ppm (Figure 2a vs 2b), and a similar methyl peak of the acetate at δ_H = 1.91 ppm was also observed in Pd(II)/Sc(III)-catalyzed decarboxylative addition reaction in its ^1H NMR kinetic studies (vide infra, Figures 3c–e and S3). Accordingly, a similar hetero-bimetallic Pd(II)/Sc(III) species having two acetate bridges can be assigned to this new Pd(II) species and that in our previous studies,[7] and the downshift of the methyl group was caused by the more positively charged Sc^{3+} cation in the hetero-bimetallic Pd(II)/Sc(III) species than the +2 charged Pd^{2+} cation in the $Pd_3(OAc)_6$ trimer.

To obtain the mechanistic clues for this Pd/LA-catalyzed decarboxylative addition reaction, a series of control experiments was carried out, as shown in Scheme 5. In the literature, Lewis acid-catalyzed indole addition of phenylacetylene to give bis(indolyl)methane products was even reported;[13c] accordingly, one may suspect that a pathway of Pd(II)-catalyzed decarboxylation of phenylpropiolic acid to phenylacetylene followed by Lewis acid-catalyzed indole addition may be present here. To address this issue, the control experiments using phenylacetylene instead of phenylpropiolic acid as the substrate were carried out under the standard conditions, and the results are summarized in Table S3. As shown, when phenylacetylene was employed as the substrate, only 15% yield of the product **3aa** was observed with the Pd(II)/Sc(III) catalyst (Scheme 5, eq 1, also Table S3, entry 1), which is much lower than that using phenylpropiolic acid as the substrate (80% yield, Table 1, entry 11), and 31% of phenylacetylene still remained after the reaction in GC analysis (Figure S1). In the case of using $Sc(OTf)_3$ alone as a catalyst, it provided **3aa** in only 17% yield (Table S3, entry 2), also much lower than that using phenylpropiolic acid as the substrate (80% yield, Table 1, entry 11). Clearly, if Pd(II)-catalyzed decarboxylation followed by Lewis acid-catalyzed indole addition happened in this Pd/LA-catalyzed decarboxylative addition reaction, its efficiency should be much lower than that observed in Table 1. Also, if phenylacetylene was the intermediate for the product **3aa** formation in this reaction, using phenylacetylene as the reactant should provide a much higher yield than 15% of **3aa**, and it should be completely converted, not as 31% of phenylacetylene still remained after the reaction. Additionally, in the ^1H NMR kinetic monitoring of Pd(II)/Sc(III)-catalyzed decarboxylative addition of phenylpropiolic acid with pyrrole, no signals of phenylacetylene were observed to indicate it as the intermediate for this reaction (Figures S4, S9–S11). Taken together, the pathway of Pd(II)-catalyzed decarboxylation of phenylpropiolic acid to phenyl-

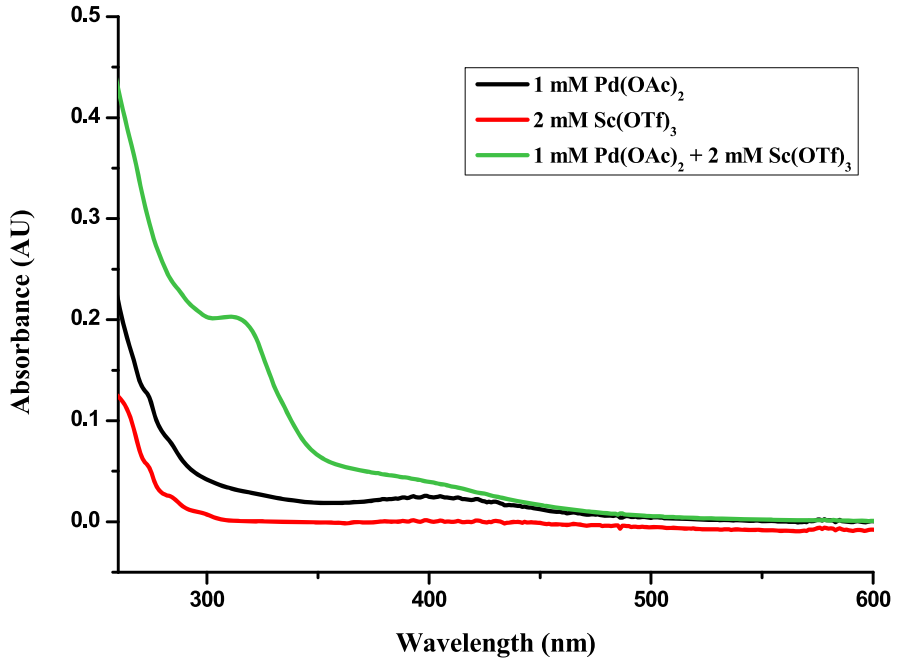


Figure 1. UV–vis spectra of $Pd(OAc)_2$ and $Sc(OTf)_3$ in 1,4-dioxane.

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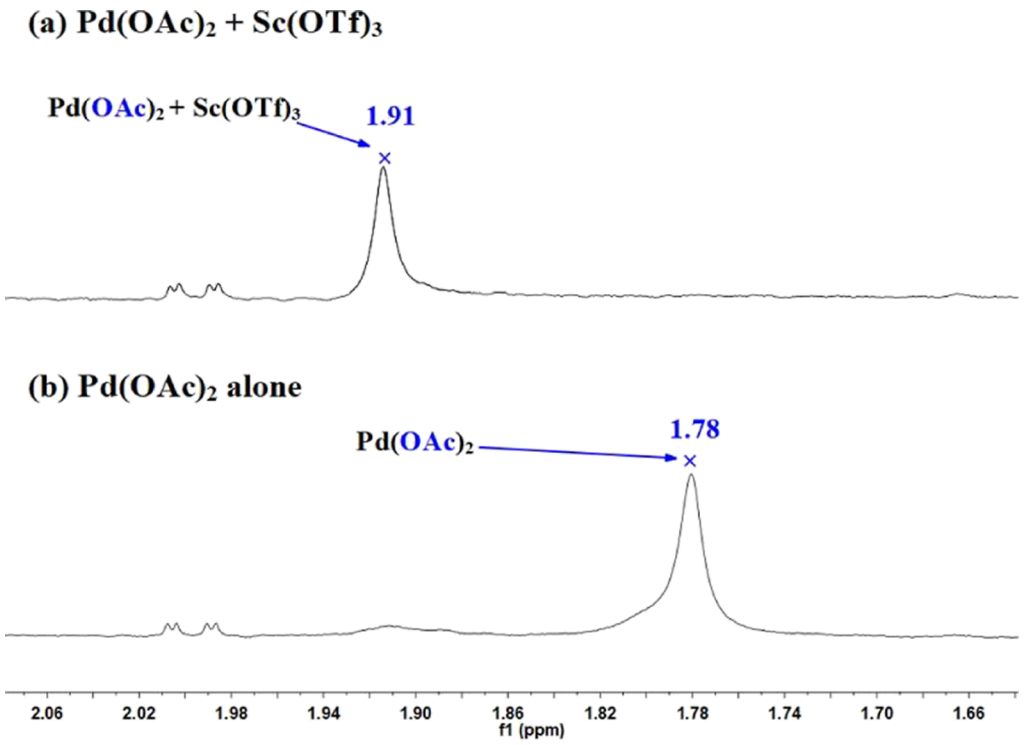

Figure 2. ^{1}H NMR spectra of $Pd(OAc)_2$ and $Sc(OTf)_3$ in DMSO-d_6 containing 1,4-dioxane (v/v, 0.4/0.2 mL).

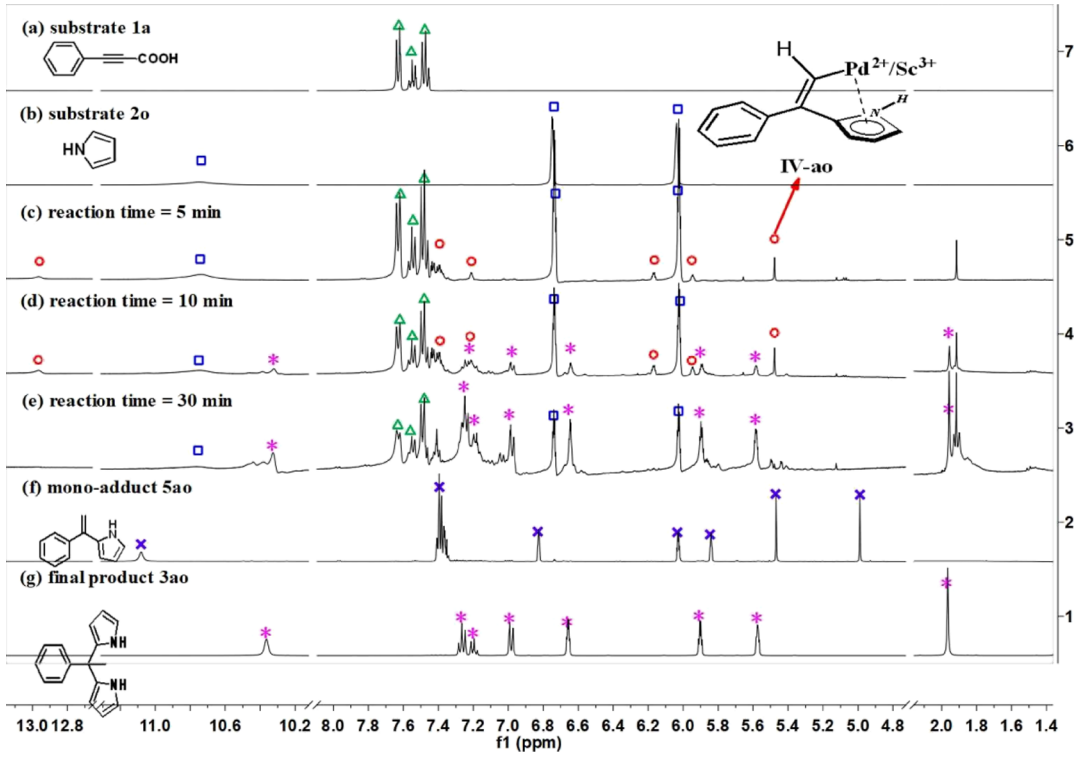

Figure 3. Selected ^{1}H NMR spectra of the decarboxylative addition of phenylpropionic acid (**1a**) to pyrrole (**2o**) in DMSO-d_6 containing 1,4-dioxane (v/v, 0.4/0.2 mL) at room temperature.

acetylene followed by Lewis acid-catalyzed indole addition could be clearly excluded here.

Next, when using equal equivalence of indole and 2-methyl-1*H*-pyrrole to react with phenylpropiolic acid, the product **3aa** and **5aap** were generated in 7 and 9% yields, respectively, and no product **3ap** was observed (Scheme 5, eq 2). As both observed products contained an indolyl unit and a benzyl unit, 3-(1-phenylvinyl)-1*H*-indole **5aa** was possibly the intermediate in this reaction, which was also evidenced by the formation of **3am** as the product in the abovementioned substrate scope section (vide supra, Scheme 2). Accordingly, **5aa** was synthesized according to the literature[11] and employed as the

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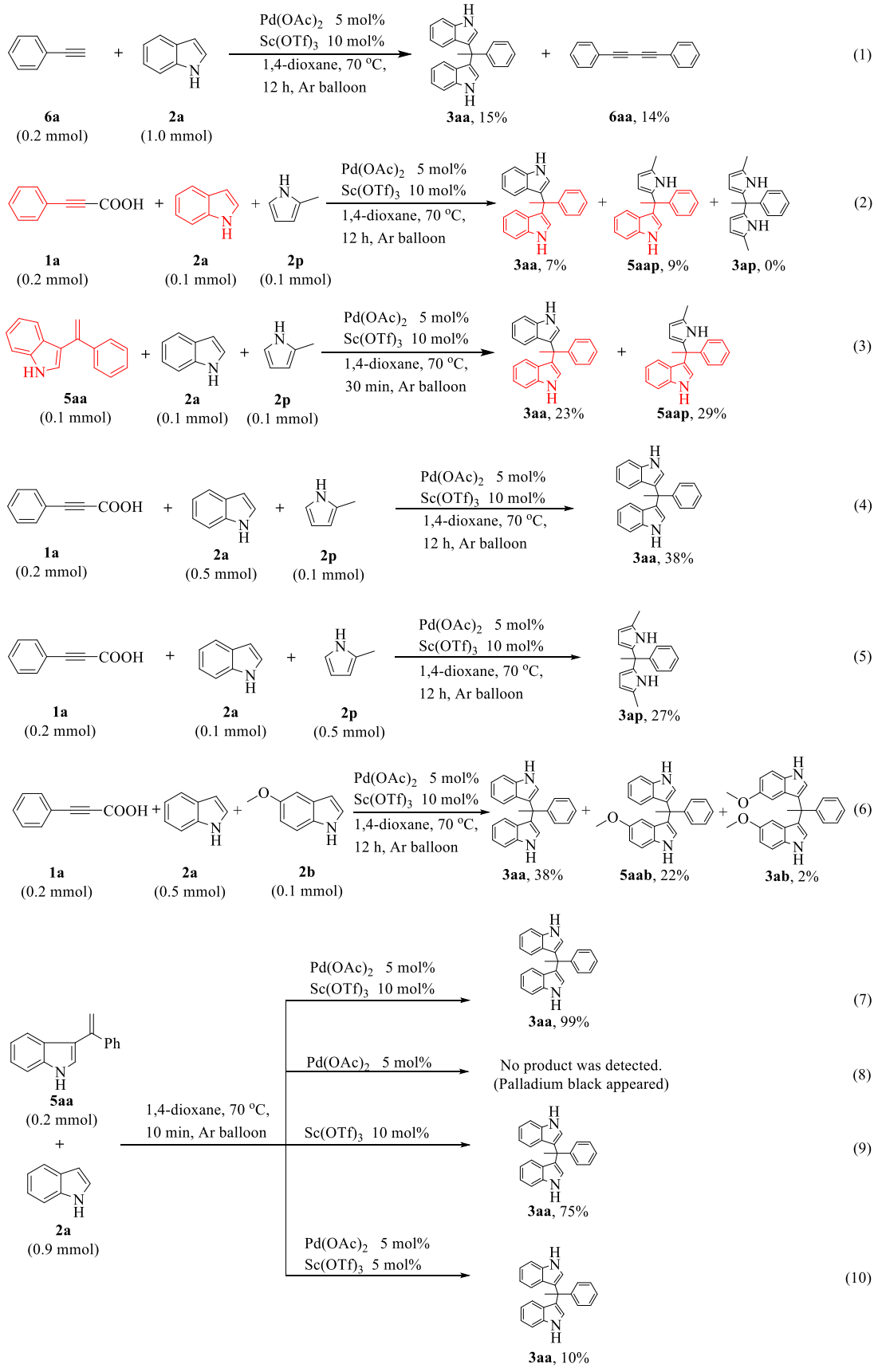
Scheme 5. Experiments for Mechanistic Studies



substrate to react with both indole and 2-methyl-1*H*-pyrrole, which gave the product **3aa** and **5aap** in 23 and 29% yields, respectively, thus suggesting that **5aa** was involved as the intermediate in this decarboxylative addition reaction (Scheme

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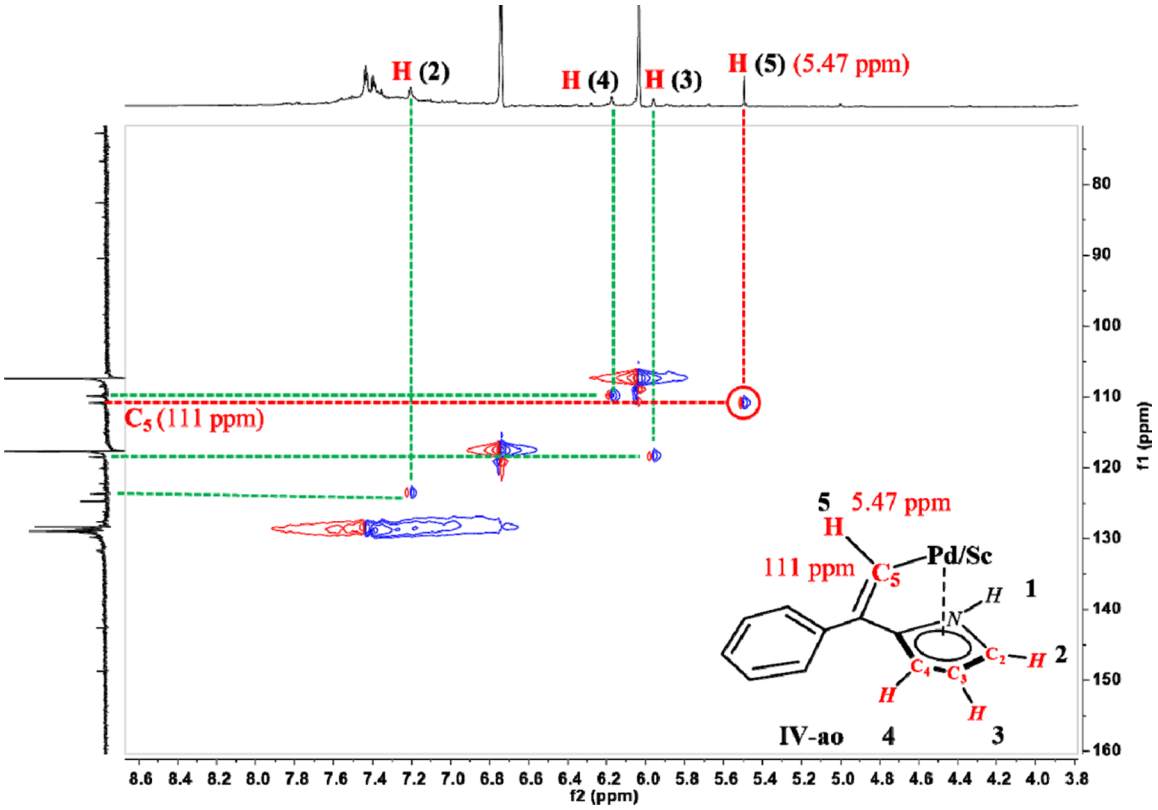

Figure 4. ^{1}H-^{13}C HSQC spectrum of the decarboxylative addition of phenylpropiolic acid (**1a**) with pyrrole (**2o**).

5, eq 3). Notably, if indole or 2-methyl-1*H*-pyrrole was in much excess than the other, the major product was bis(indolyl)methane **3aa** or bis(pyrrolyl)methane **3ap**, respectively (Scheme 5, eqs 4 and 5). When using one equivalent of indole **2b** with indole **2a** in excess as the substrate mixture to react with phenylpropiolic acid, the product **3aa** and **3ab** were generated in 38 and 2% yields, respectively, and remarkably, 22% yield of bis(indolyl)methane product **5aab** bearing two different indole rings was generated as a mixed bis(indolyl)-methane product (Scheme 5, eq 6). Using **5aa** as the substrate to react with indole in the presence of the Pd(II)/Sc(III) catalyst for 10 min provided bis(indolyl)methane product **3aa** in 99% yield (Scheme 5, eq 7), while the product **3aa** was also obtained in 75% yield when employing Sc(III) alone as a catalyst (Scheme 5, eq 9). However, no product **3aa** was observed when using Pd(II) alone as a catalyst under the identical conditions, but a lot of palladium black was observed after the reaction (Scheme 5, eq 8); in contrast, no palladium black was observed when using Pd(II)/Sc(III) as a catalyst for this control experiment (Scheme 5, eq 7). Surprisingly, when adding 5 mol % $Sc(OTf)_3$ to 5 mol % $Pd(OAc)_2$ as the catalyst, only 10% yield of **3aa** was obtained (Scheme 5, eq 10). In the complimentary tests, the product **3aa** could also be obtained in 27% yield after reaction for 12 h when using $Zn(OTf)_2$ alone as a catalyst (Table S4); apparently, the second step is a Lewis acid-catalyzed addition reaction.

Significantly, 1:1 ratio of Pd(II)/Sc(III) was almost inactive for this second-step reaction, which is an addition reaction, whereas 1:2 ratio of the Pd(II)/Sc(III) or Sc(III) alone was highly active for this addition reaction (Scheme 5, eqs 7 and 10). These results indicated that the presence of the Pd(II) unit in the hetero-bimetallic Pd(II)/Sc(III) species has weakened the Lewis acidity of the Sc^{3+} cation, thus making its catalysis much less efficient than Sc^{3+} alone, which is a Lewis acid-catalyzed addition reaction (Scheme 5, eqs 9 vs 10). An identical information was also confirmed by comparing the catalytic efficiencies between Pd(II)/Zn(II) and Zn(II) as a catalyst, in which $Zn(OTf)_2$ alone as a catalyst offered 27% of **3aa** from **5aa** and **2a** in 12 h, whereas 1:1 ratio of the Pd(II)/Zn(II) was inactive (Table S4). Taken together, these data supported that the formation of the heterometallic Pd(II)/LA species significantly weakened the Lewis acidity of the LA in the cluster; on the other hand, it should have simultaneously strengthened the electrophilic properties of the Pd(II) unit in this Pd(II)/LA species, making it more active in Pd(II)-catalyzed syntheses, as demonstrated in this decarboxylative addition reaction and that in previous studies.[7]

In order to detect the potential intermediate in situ generated in this decarboxylative addition reaction, ^{1}H NMR kinetic studies of the Pd(II)/Sc(III)-catalyzed decarboxylative addition reaction between phenylpropiolic acid (**1a**) and pyrrole (**2o**) were performed, as shown in Figure 3. The selection of **2o** rather than indole in this study was based on the purpose of simplifying the ^{1}H NMR spectrum in kinetic studies. The ^{1}H NMR spectra of **1a** and **2o** in pure DMSO-d_6 are displayed in Figure 3a,b. After reaction for 5 min under the standard conditions, the reaction mixtures of **1a** and **2o** were taken out for the ^{1}H NMR examination in DMSO-d_6 immediately (Figure 3c), and it was found that large amounts of **1a** and **2o** still remained with a set of new peaks observed (marked in a red circle in Figure 3). After 10 min, these new peaks grew up quickly, and the peaks of the product **3ao** were also observed as compared with its authentic sample (Figure 3d vs 3g). After 30 min, the set of these new peaks disappeared with the peaks of the product **3ao** growing up (Figure 3e). Clearly, this set of new peaks in the ^{1}H NMR spectrum

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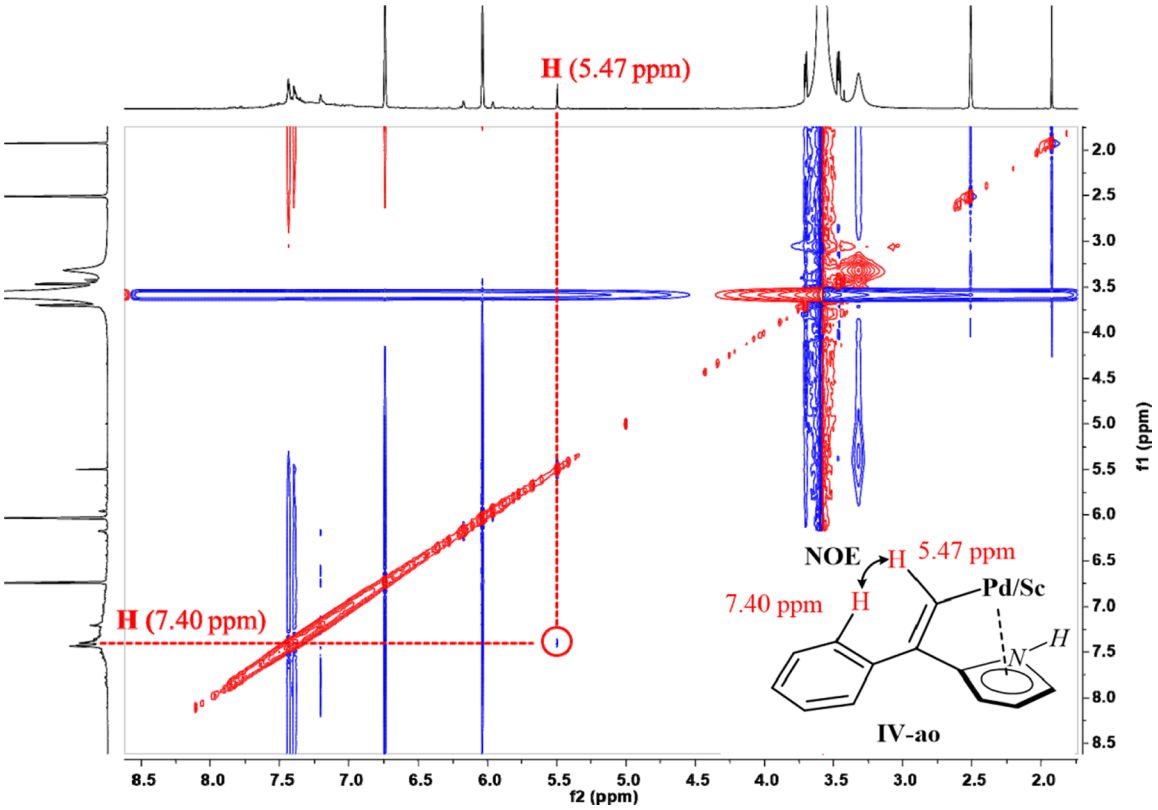

Figure 5. ^{1}H-^{1}H NOESY spectrum of the decarboxylative addition of phenylpropiolic acid (**1a**) with pyrrole (**2o**).

indicated the occurrence of a transient intermediate in the reaction, which can be transformed to the final product **3ao** with the reaction proceeding.

In Figure 3c, the ^{1}H NMR spectrum of these new peaks shows ABC system peaks with equal intensity in the aromatic region (δ_H = 5.94, 6.17, and 7.20 ppm, Figure 3c). After comparing with the pyrrolyl protons in 2-(1-phenylvinyl)-1*H*-pyrrole (**5ao**) which was independently synthesized according to the literature as the authentic sample (Figure 3f),[23] these new ABC system peaks can be assigned to the pyrrolyl protons of the transient intermediate (Figures 3c,f and S5). According to the ^{1}H NMR assignments of the pyrrolyl unit in **5ao**,[23] here, the peak at δ_H = 7.20 ppm can be assigned to the proton at the 2 position of the pyrrolyl ring in the transient intermediate, while the peaks at δ_H = 6.17 and 5.94 ppm can be assigned to the protons at the 4 and 3 positions, respectively (see also Figure S5a′,b′ for clear details); the multiple signals of the new transient intermediate in the aromatic region (δ_H around 7.40 ppm) can be assigned to its corresponding aromatic protons. As only one singlet peak (no doublet peak) was observed in the region of the olefinic proton (δ_H = 5.47 ppm), it could be concluded that the transient intermediate was not **5ao**. Compared with the authentic ^{1}H NMR graph of the authentic **5ao** sample, the pyrrolyl protons of the transient intermediate showed a great downshift (see Figure S5 for clear details), especially for the N−H (downshifted from 11.08 to 12.96 ppm) and the pyrrolyl proton adjacent to the N−H group (downshifted from 6.82 to 7.20 ppm). It is worth mentioning that in the ^{1}H NMR spectrum of the reaction mixtures, the methyl group of acetate from the Pd(II)/Sc(III) catalyst retained the identical chemical shift as that in the ^{1}H NMR studies of the catalyst (Figures 2 vs 3), indicating that during the reaction, the catalyst retained its hetero-bimetallic Pd(II)/Sc(III) structure. According to these clues and those from control experiments, this transient intermediate can be assigned as a vinyl-Pd(II)/Sc(III) intermediate **IV-ao**, as shown in Figure 3.

To confirm the vinyl-Pd(II)/Sc(III) structure, the ^{1}H-^{13}C HSQC experiment was conducted for the mixtures of **1a** and **2o** after reaction for 5 min under the standard conditions. As shown in Figure 4, the ^{1}H-^{13}C HSQC spectrum disclosed that the carbon linked to the singlet proton at δ_H = 5.47 ppm of the intermediate **IV-ao** is in sp^2 hybridization having the chemical shift around 111 ppm, thus confirming that the intermediate **IV-ao** is a vinyl-Pd(II) complex. Furthermore, the ^{1}H-^{1}H NOESY spectrum disclosed that this singlet proton at δ_H = 5.47 ppm is correlated with the corresponding aryl proton at δ_H = 7.4 ppm of the same intermediate **IV-ao** (Figure 5), thus confirming that this proton is cis to the aromatic ring, that is, Pd(II) and the pyrrolyl ring are cis about the C=C bond. The sharp downshift of the N−H proton from 11.08 to 12.96 ppm in **IV-ao** can be attributed to the unsymmetrical η5-coordination of the Pd^{2+} cation on the pyrrolyl ring, a cation−π coordination mode in which the N lone pair of pyrrolyl contributes a lot in the η^5-coordination; such a cation−π coordination mode similarly causes the downshift of the neighboring proton of the pyrrolyl nitrogen atom from 6.82 to 7.20 ppm. Because of the unsymmetrical η^5-coordination of the Pd^{2+} cation on the pyrrolyl ring, the coplanar geometry of benzyl, alkenyl, and pyrrolyl groups was broken in this vinyl-Pd(II)/Sc(III) intermediate, thus breaking the conjugated π bond system, which exists in **5ao**.

Notably, one of two alkenyl protons in **5ao** also appears at the nearly identical chemical shift of the alkenyl proton in **IV-ao** (5.468 vs 5.472 ppm, see Figure S5 for clear details). Generally, one may expect that the chemical shift of the

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neighboring proton of the vinyl-Pd(II)/Sc(III) intermediate should upshift when compared with that in **5ao**. This phenomenon can be rationalized as that while the shielding effect of the Pd(II) causes the alkenyl proton to upshift, the breaking of the conjugated π bond system in **IV-ao** may have caused the contrast deshielding effect. Two distinct effects compensated together, resulting in the chemical shift of the alkenyl proton in **IV-ao** almost unchanged (5.468 vs 5.472 ppm), while others including pyrrolyl and benzyl protons still downshifted, as displayed in Figure S5. A similar vinyl-Pd(II)/Sc(III) intermediate was also observed in the ^{1}H NMR kinetics when using 3-(4-chlorophenyl)propiolic acid as the substrate (Figure S6). To the best of our knowledge, except in Pd(II)-catalyzed C−X (X = Cl, Br, and I) activation of halogenated alkene, the vinyl-Pd(II) intermediate was scarcely identified in Pd(II)-catalyzed C−H activation of alkene until now, although it may occur as an intermediate in many alkene functionalization reactions.[24]

The ^{1}H NMR kinetic studies of the Pd(II)/Sc(III)-catalyzed decarboxylative addition reaction between phenylpropiolic acid (**1a**) and indole (**2a**) were also carried out, as shown in Figure S7. However, no clean intermediate such as **IV-ao** could be assigned except that two small new peaks in the olefinic region (δ_H = 5.51 and 5.32 ppm, Figure S7) were observed. After comparing with the alkenyl protons of 3-(1-phenylvinyl)-1*H*-indole (**5aa**) which was independently synthesized according to the literature as the authentic sample (Figure S7g),[11] the two protons at the chemical shift of 5.51 and 5.32 ppm can be assigned to the intermediate **5aa**, and **5aa** reacts feasibly with the second indole to give the final bis(indolyl)methane product, as shown in Figure 3. In the case of using indole-4-carboxylate **2m** as the substrate, the mono-adduct product **3am** was obtained as the final product due to the steric hindrance, as demonstrated above (Scheme 2).

Interestingly, the vinyl-Pd(II)/Sc(III) intermediate was not observed in decarboxylative addition of propionic acids with indole, which can be rationalized by that its addition reaction occurs at the 3 position of indole (unlike at the 2 position of pyrrole), making it impossible to form an intermediate such as **IV-ao** due to the steric hindrance. Without the stabilization of unsymmetrical η5-coordination of the Pd^{2+} cation on the pyrrolyl ring, after its formation, it could be immediately transformed to the mono-adduct product such as **5aa**, which was traced by the occurrence of its olefinic protons, as shown in Figure S7, and next, Lewis acid-catalyzed addition of the second indole to the mono-adduct product happened feasibly to give the final bis(indolyl)methane product. On the other hand, in the case of pyrrole as the substrate, because of the stabilization of the unsymmetrical η5-coordination of the Pd(II)/Sc(III) intermediate on the pyrrolyl ring, it can be identified as the intermediate in the reaction mixtures by ^{1}H NMR studies, and next, Lewis acid-catalyzed direct addition of pyrrole to this intermediate led to the formation of the final bis(pyrrolyl)methane product. The absence of the mono-adduct product such as **5ao** was supported by the failure of tracing its olefinic protons in the ^{1}H NMR kinetic studies, as shown in Figure 3.

In the ^{1}H NMR kinetics of the semi-reaction, after adding the Pd(II)/Sc(III) catalyst to the solution of **1a** in deuterated 1,4-dioxane at 70 °C, the signals of phenylpropionic acid **1a** disappeared gradually in its ^{1}H NMR spectrum (Figure S8), indicating that the decarboxylative reaction happened. However, because of the absence of the other substrate, that is, indole, the resulting ^{1}H NMR spectra became complicated with the disappearance of **1a**, indicating the instability of the resulting decarboxylating intermediate. On the other side, the signals of indole remained clear after adding the Pd(II)/Sc(III) catalyst to its deuterated 1,4-dioxane solution, indicating that the Pd(II)/Sc(III) catalyst did not react directly with indole under current reaction conditions. Taken together, these clues indicated that this Pd(II)/Sc(III)-catalyzed decarboxylative addition of propiolic acids with indoles started from decarboxylation of propiolic acid rather than activation of the C−H bond in indole.

Because a pathway of Pd(II)-catalyzed decarboxylation of phenylpropiolic acid to phenylacetylene followed by Lewis acid-catalyzed indole addition has been excluded in the present studies (vide supra), a phenylethynyl-Pd(II)/Sc(III) intermediate may be generated after Pd(II)/Sc(III)-catalyzed phenylpropiolic acid decarboxylation, and a following pyrrole addition to this intermediate leads to the observed intermediate **IV-ao** formation in Figure 3. However, such a phenylethynyl-Pd(II)/Sc(III) intermediate was not observed in ^{1}H NMR kinetic studies, plausible due to its instability. In order to address whether the addition of the weakly nucleophilic indole to the phenylethynyl-Pd(II)/Sc(III) species can happen or not, a series of controlled experiments to investigate the nucleophilic addition reactivity of the plausible phenylethynyl-Pd(II)/Sc(III) were carried out, as shown in Table S5.

First, the stable phenylethynyl-Cu(I) reagent **7a** was synthesized according to the literature.[25] Then, a series of controlled experiments were designed to check its reactivity with indole in the absence/presence of $Pd(OAc)_2$ and/or $Sc(OTf)_3$. As shown in Table S5, (1)when using **7a** as the substrate to react directly with indole in HOAc, no product was detected (Table S5, entry 1), indicating that nucleophilic addition of indole to the phenylethynyl-Cu(I) moiety is not accessible; (2) adding $Pd(OAc)_2$ as the catalyst to this reaction provided 5% yield of **6aa** as a homocoupling product with bulky palladium black formation (Table S5, entry 2), which may proceed through transmetallation of the phenylethynyl-Cu(I) with Pd(II) to generate the phenylethynyl-Pd(II) intermediate, followed by the homocoupling reaction to give **6aa** as the product; however, no indole addition product **3aa** was observed, indicating that the nucleophilic addition of indole to a nucleophilic phenylethynyl-Pd(II) moiety is not accessible; (3) In the absence of indole, reaction of phenylethynyl-Cu(I) with $Pd(OAc)_2$ also provided only 7% yield of **6aa** as the homocoupling product (Table S5, entry 4); (4) using $Sc(OTf)_3$ alone as the catalyst provided 8% yield of **3aa** as the indole addition product, which may be explained as a Lewis acid-catalyzed indole addition reaction under the reaction conditions (Table S5, entry 3); and (5) Remarkably, using $Pd(OAc)_2/Sc(OTf)_3$ as the catalyst provided 36% yield of **3aa** with 8% yield of **6aa** product (Table S5, entry 5), in which the yield of the indole addition product **3aa** was much higher than that when using $Sc(OTf)_3$ alone as the catalyst, which cannot be explained as a Sc^{3+}-catalyzed indole addition. Accordingly, this higher yield of **3aa** can be rationalized by the indole addition to the C≡C triple bond of the phenylethynyl-Pd(II)/Sc(III) intermediate, generated by transmetallation of phenylethynyl-Cu(I) to the Pd(II)/Sc(III) species, which is more electron-deficient than that in the phenylethynyl-Pd(II) intermediate, thus making indole addition become accessible, even though indole is a weakly nucleophilic reagent.

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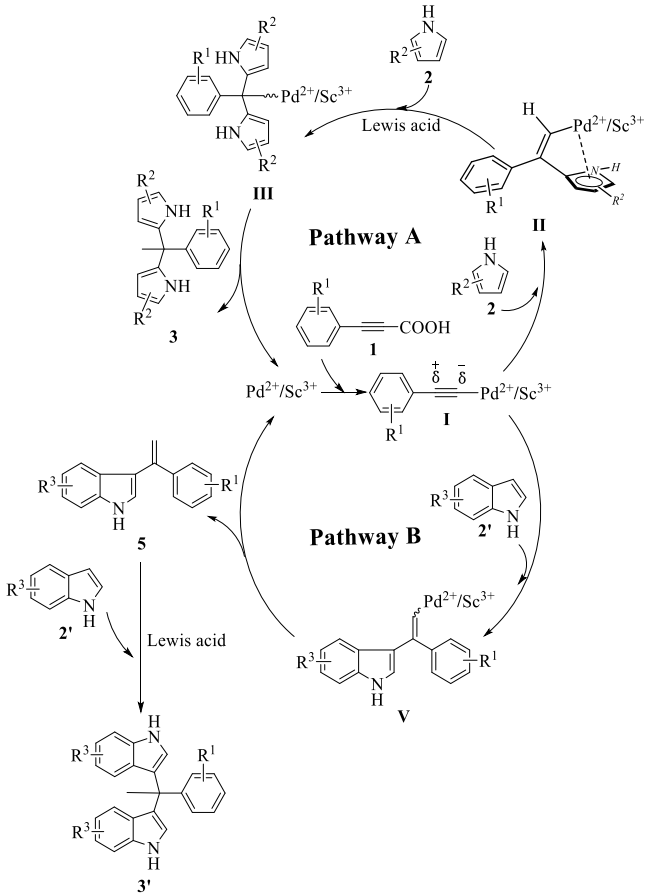
Due to the instability of the phenylethynyl-Pd(II)/Sc(III) intermediate, it was also not observed in the abovementioned phenylethynyl-Cu(I) reaction with Pd(II) or Pd(II)/Sc(III) in the presence/absence of indole; however, from the clues of the homocoupling product formation in the presence of Pd-$(OAc)_2$, it can be reasonably suspected that it can occur through transmetallation reaction between phenylethynyl-Cu(I) and Pd(II) or Pd(II)/Sc(III). Remarkably, nucleophilic addition of indole to a nucleophilic phenylethynyl-Pd(II) intermediate is not accessible, whereas it is accessible for the phenylethynyl-Pd(II)/Sc(III) intermediate to generate the **3aa** product, as disclosed (Table S5, entries 2 vs 5). Similarly, in our decarboxylative addition reaction, using $Pd(OAc)_2$ alone as the catalyst only provided the homocoupling product without indole addition product formation, but the homocoupling product was observed (Table 1, entry 1); however, the presence of $Sc(OTf)_3$ makes indole addition become accessible, leading to 80% yield of **3aa** with 8% yield of **4aa** formation (Table 1, entry 11), indicating that the C≡C triple bond of the phenylethynyl-Pd(II)/Sc(III) intermediate is more electron-deficient than that of the phenylethynyl-Pd(II), thus making indole addition become accessible in our studies, even though indole is a weakly nucleophilic reagent.

Accordingly, a simplified mechanism of Pd(II)/Sc(III)-catalyzed decarboxylative addition of propiolic acids with indole or pyrrole reaction is proposed in Scheme 6. First, a hetero-bimetallic Pd(II)/Sc(III) species was in situ generated as the key active species for the decarboxylative addition reaction. The catalysis was triggered through decarboxylation of propiolic acid by the Pd(II)/Sc(III) species to generate the phenylethynyl-Pd(II)/Sc(III) intermediate **I**. The presence of the Sc^{3+} cation makes the Pd^{2+} cation more electron-deficient, and the carbon of the α-position in the intermediate **I** is partially, positively charged, which makes its C≡C triple bond electrophilic addition with substrate **2** or **2″** become accessible and give the intermediate **II** and **V**. For the pyrrole derivatives **2**, the addition reaction occurs at the 2 position of the pyrrolyl ring (Scheme 6, pathway A), which makes the unsymmetrical η5-coordination of the Pd(II)/Sc(III) intermediate to the pyrrolyl ring, a cation−π coordination mode in which the N lone pair of pyrrole contributes a lot in the η5-coordination, become possible, giving a relatively stable vinyl-Pd(II)/Sc(III) intermediate **II**, which was successfully identified in ^{1}H NMR kinetic studies. Here, releasing the Pd(II)/Sc(III) species from the intermediate **II** is not favorable, as no olefinic protons of the mono-adduct such as **5ao** are traced in Figure 3. Thus, the intermediate **II** directly reacts with another substrate **2** via Lewis acid-catalyzed addition to provide the intermediate **III**. Then, releasing the Pd(II)/Sc(III) species from the intermediate **III** gives the bis(pyrrolyl)methane **3** as the final product to achieve the catalytic cycle. Unlike the pathway A, for the indole addition, the reaction preferably occurs at the 3 position of indole derivatives **2″** to give the intermediate **V** (Scheme 6, pathway B). Releasing the Pd(II)/Sc(III) species from the intermediate **V** generates the mono-adduct product **5**, which was traced by the occurrence of its olefinic protons in ^{1}H NMR kinetic studies (Figure S7). Next, **5** reacts feasibly with another substrate **2″** via Lewis acid-catalyzed addition to provide the bis(indolyl)methane as the final product **3″** to achieve the catalytic cycle.

Scheme 6. Proposed Mechanism for the Pd(II)/Sc(III)-Catalyzed Decarboxylative Addition Reaction



3. CONCLUSIONS

In summary, a new protocol was explored for the synthesis of bis(indolyl)methane and bis(pyrrolyl)methane derivatives through decarboxylative addition reaction of propiolic acids and indoles/pyrroles with a Pd(II)/LA catalyst. It was found that adding Lewis acid such as $Sc(OTf)_3$ to the $Pd(OAc)_2$ catalyst triggered this catalysis, providing the desired products in moderate to good yields, whereas neither Pd(II) nor Sc(III) alone was active for this synthesis. The promotional effect was highly dependent on the Lewis acidity of the added Lewis acid, that is, a stronger Lewis acid provided a higher yield. Through the UV−vis and ^{1}H NMR characterizations, a hetero-bimetallic Pd(II)/Sc(III) species having two acetate bridges was proposed as the active species for this catalysis as that in previous studies, and a vinyl-Pd(II)/Sc(III) intermediate was identified in ^{1}H NMR kinetic studies of Pd(II)/Sc(III)-catalyzed decarboxylative addition of pyrrole to phenylpropionic acid, which was scarcely identified in Pd(II)-catalyzed alkene functionalization reaction except in Pd(II)-catalyzed C−X (X = Cl, Br, and I) activation of halogenated alkene. In addition, the present work also further convinced that the presence of Lewis acid can modulate the reactivity and improve the catalytic efficiency of a redox metal ion such as Pd(II), thus providing a new strategy for the catalyst design of these transition metal ion-mediated organic syntheses.

4. EXPERIMENTAL SECTION

4.1. Materials and Analytical Methods. All reagents were purchased from commercial suppliers and used without further purification. The propiolic acids **2b−2m** and intermediate **5aa** were

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synthesized following the literature with modifications.[11,26] UV−vis spectra were collected on an Agilent Technologies Cary-8454 UV−vis spectrometer. The reactions were monitored by TLC with Haiyang GF-254 silica gel plates (Qingdao Haiyang Chemical Industry Co. Ltd, Qingdao, China) using UV light and bromocresol green as visualizing agents as needed. Flash column chromatography was performed using a 200−300-mesh silica gel at increased pressure. ^{1}H NMR spectra and ^{13}C NMR spectra were, respectively, recorded on Brüker AV-400 spectrometers and Brüker AV-600 spectrometers. Chemical shifts (δ) were expressed in ppm with TMS as the internal standard, and coupling constants (J) were reported in Hz. High-resolution mass spectra were obtained on a mass spectrometer using APCI FT-ICR mass spectrometry. Melting points were collected on an INESA automatic melting point tester (WRS-1C).

4.2. General Procedure for the Synthesis of 3. In a typical procedure, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $Sc(OTf)_3$ (9.9 mg, 0.02 mmol) were dissolved in 1,4-dioxane (1 mL) in a glass tube. Then, propiolic acids **1** (0.2 mmol) and indole derivatives **2** (1.0 mmol) were added in the glass tube connected with an Ar balloon. The reaction mixtures were heated in an oil bath with stirring at 70 °C for 12 h. After the reaction, the solvent was removed under reduced pressure. The raw product was purified by column chromatography on a silica gel (petroleum ether/EtOAc: 1/1−20/1) to give the desired product **3**.

4.3. General Procedure for the Controlled Experiments with Phenylacetylene as the Substrate. In a typical procedure, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $Sc(OTf)_3$ (9.9 mg, 0.02 mmol) were dissolved in 1,4-dioxane (1 mL) in a glass tube. Then, phenylacetylene **6a** (20.4 mg, 0.2 mmol) and indole **2a** (117.1 mg, 1.0 mmol) were added in the glass tube connected with an Ar balloon. The reaction mixtures were heated in an oil bath with stirring at 70 °C for 12 h. After the reaction, the solvent was removed under reduced pressure. The raw product was purified by column chromatography on a silica gel (petroleum ether/EtOAc: 1/1−100/1) to give the desired product **3aa** and **6aa**.

4.4. General Procedure for the Controlled Experiments with Phenylethynyl-Cu(I) Reagent as the Substrate. In a typical procedure, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $Sc(OTf)_3$ (9.9 mg, 0.02 mmol) were dissolved in 1,4-dioxane (1 mL) in a glass tube. Then phenylethynyl-Cu(I) **7a** (32.9 mg, 0.2 mmol) and indole **2a** (117.1 mg, 1.0 mmol) were added in the glass tube connected with an Ar balloon. The reaction mixtures were heated in an oil bath with stirring at 70 °C for 12 h. After the reaction, the solvent was removed under reduced pressure. The raw product was purified by column chromatography on a silica gel (petroleum ether/EtOAc: 1/1−100/1) to give the desired product **3aa** and **6aa**.

4.5. General Procedure for the Synthesis of 3-(1-Phenylvinyl)-1*H*-indole (5aa). According to the literature,[11] under N_2, 1-(1*H*-indol-3-yl)ethan-1-one (5 mmol, 0.8 g) was added in dry THF (20 mL) at 0 °C; then, ArMgBr (12.5 mmol, 1.0 M solution in THF) was added dropwisely. The reaction mixtures were warmed to 50 °C and stirred at the same temperature for 12 h. Then, the reaction mixtures were cooled to 0 °C, and a saturated aqueous NH_4Cl solution (20 mL) was added dropwisely. After the organic layer was separated, the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residues were dissolved in CH_2Cl_2 (25 mL), to which was added anhydrous $MgSO_4$ (2.5 g) followed by a silica gel (200−300 mesh particle size, 2.5 g). The mixtures were then stirred at room temperature for 5 h, then filtered, and washed with Et_2O. The filtrate was concentrated, and the resulting residues were purified by silica gel chromatography to afford the desired **5aa** as a white solid alkene product **5aa** (910 mg, 83% yield).

4.6. General Procedure for the Synthesis of 2-(1-Phenylvinyl)-1*H*-pyrrole (5ao). According to the literature,[23] a NMR tube was charged with 21.5 μL (196 μmol; 1 equiv) of phenylacetylene and 0.56 mL of acetonitrile. Then, 67.9 μL (979 μmol; 5 equiv) of pyrrole and 3.4 mg (4 μmol; 0.02 equiv) of $IPrAuNTf_2$ were next added in the NMR tube. The reaction was terminated after reaction 5 h, and the solvent was removed under reduced pressure. After purification by column chromatography (SiO_2, PE/EA = 40:1), it afforded **5ao** (21.9 mg, 66% yield) as a yellowish oil.

*4.6.1. 3,3′-(1-Phenylethane-1,1-diyl)bis(1H-indole) (**3aa**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(1*H*-indole) (**3aa**) (53.8 mg, 0.16 mmol, 80% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 2H), 7.34 (d, J = 7.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.23−7.14 (m, 5H), 7.08 (t, J = 7.5 Hz, 2H), 6.89 (t, J = 7.5 Hz, 2H), 6.42 (d, J = 1.7 Hz, 2H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.1, 137.1, 128.2, 127.9, 126.5, 125.9, 124.7, 123.5, 122.2, 121.6, 119.0, 111.3, 43.8, 28.9; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{20}N_2$, 335.1554; found, 335.1550.

*4.6.2. 3,3′-(1-Phenylethane-1,1-diyl)bis(5-methoxy-1H-indole) (**3ab**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5-methoxy-1*H*-indole (**2b**) (147 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(5-methoxy-1*H*-indole) (**3ab**) (53.8 mg, 0.142 mmol, 71% yield); yellowish solid (petroleum ether/ethyl acetate = 4/1); melting point: 259−261 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (d, J = 1.9 Hz, 2H), 7.33 (d, J = 7.3 Hz, 2H), 7.24 (d, J = 8.8 Hz, 4H), 7.17 (d, J = 7.2 Hz, 1H), 6.77 (d, J = 2.5 Hz, 2H), 6.65 (dd, J = 8.8, 2.4 Hz, 2H), 6.43 (d, J = 2.3 Hz, 2H), 3.45 (s, 6H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 152.6, 148.6, 132.7, 128.3, 128.0, 126.9, 126.0, 124.6, 122.8, 112.4, 110.5, 103.8, 55.5, 43.5, 29.5; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{26}H_{24}N_2O_2$, 395.1765; found, 395.1761.

*4.6.3. 3,3′-(1-Phenylethane-1,1-diyl)bis(5-methyl-1H-indole) (**3ac**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5-methyl-1*H*-indole (**2c**) (131.2 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(5-methyl-1*H*-indole) (**3ac**) (48.8 mg, 0.134 mmol, 67% yield); yellowish solid (petroleum ether/ethyl acetate = 4/1); melting point: 218−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 2H), 7.37 (d, J = 7.2 Hz, 2H), 7.21 (dd, J = 14.3, 7.8 Hz, 5H), 7.12 (s, 2H), 6.95 (d, J = 8.1 Hz, 2H), 6.47 (d, J = 1.8 Hz, 2H), 2.34 (s, 3H), 2.29 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 148.9, 136.0, 128.2, 128.0, 126.7, 126.5, 126.0, 124.1, 122.9, 122.6, 121.2, 111.8, 43.7, 29.4, 21.9; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{26}H_{24}N_2$, 363.1867; found, 363.1856.

*4.6.4. 3,3′-(1-Phenylethane-1,1-diyl)bis(5-chloro-1H-indole) (**3ad**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5-chloro-1*H*-indole (**2d**) (151.6 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(5-chloro-1*H*-indole) (**3ad**) (52.7 mg, 0.13 mmol, 65% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.11 (dd, J = 23.4, 10.5 Hz, 7H), 6.96 (d, J = 8.6 Hz, 2H), 6.48 (d, J = 1.8 Hz, 2H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 148.0, 136.0, 128.3, 128.0, 127.5, 126.4, 125.7, 123.1, 122.7, 121.1, 120.2, 113.7, 43.4, 29.7; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{18}Cl_2N_2$, 403.0774; found, 403.0773.

*4.6.5. 3,3′-(1-Phenylethane-1,1-diyl)bis(5-bromo-1H-indole) (**3ae**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5-bromo-1*H*-indole (**2e**) (196 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(5-bromo-1*H*-indole) (**3ae**) (63.3 mg, 0.128 mmol, 64% yield); yellowish solid (petroleum ether/ethyl acetate = 10/1); melting point: 251−253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.11 (s, 2H), 7.36 (d, J = 9.1 Hz, 2H), 7.28 (d, J = 4.2 Hz, 4H), 7.21 (dd, J = 8.4, 4.1 Hz, 1H), 7.14−7.09 (m, 4H), 6.86 (d, J = 2.4 Hz, 2H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 148.0, 136.2, 128.3, 128.2, 128.00, 126.4, 125.5, 123.6, 123.2, 122.6, 114.2, 111.2, 43.4, 29.7; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{18}Br_2N_2$, 490.9764; found, 490.9754.

*4.6.6. 3,3′-(1-Phenylethane-1,1-diyl)bis(5-fluoro-1H-indole) (**3af**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5-fluoro-1*H*-indole (**2f**) (135.1 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(5-fluoro-1*H*-indole) (**3af**) (47.7 mg, 0.128 mmol, 64% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 2H), 7.34 (d, J = 7.3 Hz, 2H), 7.27−7.16 (m, 5H), 6.86 (dd, J

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= 16.2, 9.3 Hz, 4H), 6.67 (s, 2H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 157.4 (d, J_{C-F} = 4.7 Hz), 148.1, 134.1, 128.1 (d, J_{C-F} = 18.5 Hz), 126.6 (d, J_{C-F} = 9.8 Hz), 126.3, 125.9, 123.1 (d, J_{C-F} = 4.7 Hz), 113.0 (d, J_{C-F} = 9.9 Hz), 109.2 (d, J_{C-F} = 26.3 Hz), 105.7, 105.5, 43.3, 29.5; ^{19}F NMR (376 MHz, DMSO-d_6): δ −125.3 (td, J = 9.8, 4.5 Hz); HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{18}F_2N_2$, 371.1365; found, 371.1357.

*4.6.7. 3,3′-(1-Phenylethane-1,1-diyl)bis(6-methyl-1H-indole) (**3ag**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 6-methyl-1*H*-indole (**2g**) (131.2 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(6-methyl-1*H*-indole) (**3ag**) (50.3 mg, 0.138 mmol, 69% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 221−223 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 2H), 7.28 (d, J = 7.7 Hz, 2H), 7.15−7.06 (m, 5H), 6.97 (s, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.36 (d, J = 1.8 Hz, 2H), 2.32 (s, 6H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 148.9, 137.9, 130.1, 128.0, 127.7, 125.7, 124.5, 123.3, 122.9, 121.1, 120.0, 111.5, 43.5, 29.1, 21.1; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{26}H_{24}N_2$, 363.1867; found, 363.1857.

*4.6.8. 3,3′-(1-Phenylethane-1,1-diyl)bis(7-methyl-1H-indole) (**3ah**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 7-methyl-1*H*-indole (**2h**) (131.2 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(7-methyl-1*H*-indole) (**3ah**) (55.4 mg, 0.152 mmol, 76% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 224−226 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 2H), 7.25 (d, J = 6.8 Hz, 2H), 7.12−7.05 (m, 5H), 6.84 (d, J = 6.9 Hz, 2H), 6.77 (t, J = 7.5 Hz, 2H), 6.24 (d, J = 2.0 Hz, 2H), 2.29 (s, 6H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 148.8, 136.9, 128.1, 127.8, 126.2, 125.8, 123.8, 123.5, 121.4, 121.0, 119.2, 118.5, 43.6, 29.2, 16.9; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{26}H_{24}N_2$, 363.1867; found, 363.1859.

*4.6.9. 3,3′-(1-Phenylethane-1,1-diyl)bis(5,6-dichloro-1H-indole) (**3ai**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5,6-dichloro-1*H*-indole (**2i**) (186 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(5,6-dichloro-1*H*-indole) (**3ai**) (43.6 mg, 0.092 mmol, 46% yield); yellowish solid (petroleum ether/ethyl acetate = 4/1); melting point: 185−187 °C; ^1H NMR (600 MHz, DMSO-d_6): δ 11.20 (s, 2H), 7.62 (s, 2H), 7.30−7.20 (m, 5H), 7.05 (s, 2H), 6.95 (d, J = 2.4 Hz, 2H), 2.19 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 147.6, 136.4, 135.9, 128.4, 126.8, 126.3, 125.2, 122.6, 121.7, 121.0, 119.9, 113.7, 43.2, 29.7; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{16}Cl_4N_2$, 470.9995, found, 470.9987.

*4.6.10. 3,3′-(1-Phenylethane-1,1-diyl)bis(1H-indol-5-ol) (**3aj**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 1*H*-indol-5-ol (**2j**) (133.2 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(1*H*-indol-5-ol) (**3aj**) (44.2 mg, 0.12 mmol, 60% yield); yellowish solid (petroleum ether/ethyl acetate = 3/1); melting point: 191−193 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (d, J = 2.2 Hz, 2H), 8.42 (s, 2H), 7.34−7.30 (m, 2H), 7.25 (t, J = 7.6 Hz, 2H), 7.19−7.15 (m, 2H), 7.13 (s, 1H), 6.59 (d, J = 2.5 Hz, 2H), 6.54 (d, J = 2.3 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.49 (d, J = 2.2 Hz, 2H), 2.17 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 149.9, 132.1, 128.2, 128.0, 127.2, 124.4, 122.3, 112.2, 111.3, 105.8, 43.5, 28.9; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{20}N_2O_2$, 367.1452; found, 367.1455.

*4.6.11. 3,3′-(1-Phenylethane-1,1-diyl)bis(1H-indole-5-carbonitrile) (**3ak**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 1*H*-indole-5-carbonitrile (**2k**) (142.2 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(1*H*-indole-5-carbonitrile) (**3ak**) (14.7 mg, 0.038 mmol, 19% yield); yellowish solid (petroleum ether/ethyl acetate = 2/1); melting point: 261−263 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 2H), 7.76 (s, 1H), 7.54 (s, 1H), 7.41 (d, J = 4.1 Hz, 2H), 7.36 (t, J = 7.7 Hz, 3H), 7.30 (d, J = 2.4 Hz, 3H), 7.18 (s, 1H), 6.87 (d, J = 1.8 Hz, 2H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 147.7, 139.3, 128.5, 128.0, 126.7, 126.6, 126.3, 126.1, 123.9, 123.8, 121.2, 113.6, 100.7, 43.4, 29.9; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{26}H_{18}N_4$, 385.1459; found, 385.1448.

*4.6.12. 3,3′-(1-Phenylethane-1,1-diyl)bis(5-nitro-1H-indole) (**3al**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5-nitro-1*H*-indole (**2l**) (162.1 mg, 1.0 mmol) afforded 3,3′-(1-phenylethane-1,1-diyl)bis(5-nitro-1*H*-indole) (**3al**) (17.1 mg, 0.04 mmol, 20% yield); yellowish solid (petroleum ether/ethyl acetate = 2/1); melting point: 199−201 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 11.73 (d, J = 1.6 Hz, 2H), 7.93 (d, J = 2.3 Hz, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.89 (d, J = 2.2 Hz, 2H), 7.57 (s, 1H), 7.55 (s, 1H), 7.32 (d, J = 4.2 Hz, 4H), 7.26 (dd, J = 8.3, 4.1 Hz, 1H), 7.18 (d, J = 2.4 Hz, 2H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 147.4, 140.8, 140.3, 128.6, 127.9, 126.8, 125.6, 125.3, 117.8, 116.8, 112.8, 43.5, 30.3; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{18}N_4O_4$, 425.1255; found, 425.1245.

*4.6.13. Methyl 3-(1-Phenylvinyl)-1H-indole-4-carboxylate (**3am**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and methyl 1*H*-indole-4-carboxylate (**2m**) (175.2 mg, 1.0 mmol) afforded methyl 3-(1-phenylvinyl)-1*H*-indole-4-carboxylate (**3am**) (9.4 mg, 0.034 mmol, 17% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 222−224 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.58 (dd, J = 8.1, 0.9 Hz, 1H), 7.51 (dd, J = 7.4, 0.9 Hz, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.37−7.33 (m, 2H), 7.25 (dd, J = 8.8, 6.9 Hz, 4H), 5.69 (d, J = 1.5 Hz, 1H), 5.38 (d, J = 1.5 Hz, 1H), 3.42 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 168.4, 144.2, 141.0, 137.9, 128.6, 128.4, 127.7, 126.6, 124.7, 123.2, 121.6, 120.9, 116.7, 116.2, 111.7, 51.3; HRMS (APCI) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}NO_2$, 278.1176; found, 278.1177.

*4.6.14. Dimethyl 3,3′-(1-Phenylethane-1,1-diyl)bis(indolizine-1-carboxylate) (**3an**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and methyl indolizine-1-carboxylate (**2n**) (175.2 mg, 1.0 mmol) afforded dimethyl 3,3′-(1-phenylethane-1,1-diyl)bis(indolizine-1-carboxylate) (**3an**) (33.5 mg, 0.074 mmol, 37% yield); yellowish solid (petroleum ether/ethyl acetate = 10/1); melting point: 297−299 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, J = 7.9 Hz, 2H), 7.64 (s, 2H), 7.37 (d, J = 6.3 Hz, 3H), 7.12 (s, 4H), 6.84 (s, 2H), 6.66 (d, J = 5.4 Hz, 2H), 3.76 (d, J = 4.4 Hz, 6H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 164.5, 142.5, 136.9, 129.3, 128.3, 128.0, 125.8, 123.2, 119.5, 116.6, 113.2, 102.4, 51.2, 45.3, 25.4; HRMS (APCI) m/z: $[M + H]^+$ calcd for $C_{28}H_{24}N_2O_4$, 453.1809; found, 453.1802.

*4.6.15. 2,2′-(1-Phenylethane-1,1-diyl)bis(1H-pyrrole) (**3ao**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 1*H*-pyrrole (**2o**) (67.1 mg, 1.0 mmol) afforded 2,2′-(1-phenylethane-1,1-diyl)bis(1*H*-pyrrole) (**3ao**) (23.6 mg, 0.1 mmol, 50% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 221−223 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 2H), 7.28 (s, 1H), 7.24 (d, J = 7.0 Hz, 2H), 7.15−7.10 (m, 2H), 6.68 (d, J = 1.4 Hz, 2H), 6.18 (dd, J = 5.8, 2.8 Hz, 2H), 5.98 (d, J = 3.3 Hz, 2H), 2.04 (d, J = 15.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 149.3, 138.0, 128.1, 127.6, 126.3, 117.6, 106.7, 106.4, 44.7, 28.5; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{16}H_{16}N_2$, 235.1241; found, 235.1241.

*4.6.16. 5,5′-(1-Phenylethane-1,1-diyl)bis(2-methyl-1H-pyrrole) (**3ap**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 2-methyl-1*H*-pyrrole (**2p**) (81.1 mg, 1.0 mmol) afforded 5,5′-(1-phenylethane-1,1-diyl)bis(2-methyl-1*H*-pyrrole) (**3ap**) (27 mg, 0.102 mmol, 51% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 161−162 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 2H), 7.28 (s, 1H), 7.23 (d, J = 6.9 Hz, 2H), 7.17−7.13 (m, 2H), 5.85−5.74 (m, 4H), 2.20 (s, 6H), 1.99 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 149.7, 136.6, 128.0, 127.6, 126.7, 126.2, 106.2, 104.5, 44.6, 28.5, 13.4; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{18}H_{20}N_2$, 263.1554; found, 263.1554.

*4.6.17. 3-(1-(5,6-Dimethoxy-1H-indol-2-yl)-1-phenylethyl)-5,6-dimethoxy-1H-indole (**3aq**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol) and 5,6-dimethoxy-1*H*-indole (**2q**) (177.1 mg, 1.0 mmol) afforded 3-(1-(5,6-dimethoxy-1*H*-indol-2-yl)-1-phenylethyl)-5,6-dimethoxy-1*H*-indole (**3aq**) (28.3 mg, 0.062 mmol, 31% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 385−387 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 10.43 (s, 1H), 7.31−7.17 (m, 5H), 6.94 (s, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 6.71 (d, J = 2.3 Hz, 1H), 6.17 (s, 1H), 5.78 (d, J = 1.7 Hz, 1H), 3.72 (d, J = 4.3 Hz, 6H), 3.69 (s, 3H), 3.28 (s, 3H), 2.15 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 148.3, 146.5, 146.2,

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145.1, 144.6, 143.9, 131.8, 131.2, 128.1, 128.0, 126.3, 122.4, 122.1, 120.6, 119.4, 103.9, 103.2, 100.2, 95.7, 95.6, 56.7, 56.2, 56.1, 56.1, 44.5, 28.9; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{28}H_{28}N_2O_4$, 455.1976; found, 455.1971.

*4.6.18. 3,3′-(1-(4-Methoxyphenyl)ethane-1,1-diyl)bis(1H-indole) (**3ba**).* 3-(4-Methoxyphenyl)propiolic acid (**1b**) (35.2 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(4-methoxyphenyl)ethane-1,1-diyl)bis(1*H*-indole) (**3ba**) (52.5 mg, 0.156 mmol, 78% yield); yellowish solid (petroleum ether/ethyl acetate = 4/1); melting point: 225−227 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 2H), 7.30 (d, J = 7.8 Hz, 3H), 7.24 (s, 2H), 7.09 (t, J = 7.2 Hz, 3H), 6.91 (t, J = 7.3 Hz, 2H), 6.72 (d, J = 8.3 Hz, 2H), 6.49 (s, 2H), 3.71 (s, 3H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 157.5, 141.1, 137.5, 129.0, 126.5, 123.7, 123.5, 121.4, 120.7, 118.0, 112.9, 111.6, 56.7, 42.8, 29.0; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{25}H_{22}N_2O$, 365.1659; found, 365.1647.

*4.6.19. 3,3′-(1-(p-Tolyl)ethane-1,1-diyl)bis(1H-indole) (**3ca**).* 3-(*p*-Tolyl)propiolic acid (**1c**) (32 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(*p*-tolyl)ethane-1,1-diyl)bis-(1*H*-indole) (**3ca**) (50.5 mg, 0.144 mmol, 72% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 2H), 7.30 (d, J = 7.7 Hz, 2H), 7.24 (d, J = 7.6 Hz, 4H), 7.10 (t, J = 7.2 Hz, 2H), 7.01 (d, J = 7.3 Hz, 2H), 6.91 (d, J = 7.0 Hz, 2H), 6.48 (s, 2H), 2.36−2.16 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 145.6, 137.5, 134.7, 128.2, 127.9, 126.5, 123.5, 121.4, 120.7, 118.0, 111.6, 43.1, 29.0, 18.2; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{25}H_{22}N_2$, 349.1710; found, 349.1710.

*4.6.20. 3,3′-(1-(4-(Trifluoromethyl)phenyl)ethane-1,1-diyl)bis-(1H-indole) (**3da**).* 3-(4-(Trifluoromethyl)-phenyl)propiolic acid (**1d**) (42.8 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(4-(trifluoromethyl)phenyl)ethane-1,1-diyl)-bis(1*H*-indole) (**3da**) (54.2 mg, 0.134 mmol, 67% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 2H), 7.46 (q, J = 8.6 Hz, 4H), 7.27 (dd, J = 12.2, 8.2 Hz, 4H), 7.13 (t, J = 7.5 Hz, 2H), 6.93 (t, J = 7.5 Hz, 2H), 6.54 (d, J = 1.5 Hz, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 153.4, 137.5, 128.8, 126.2, 124.6, 123.8, 122.4, 121.1, 120.9, 118.4, 111.9, 43.8, 29.0; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{25}H_{19}F_3N_2$, 403.1428; found, 403.1417.

*4.6.21. 3,3′-(1-(4-Fluorophenyl)ethane-1,1-diyl)bis(1H-indole) (**3ea**).* 3-(4-Fluorophenyl)propiolic acid (**1e**) (32.8 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(4-fluorophenyl)ethane-1,1-diyl)bis(1*H*-indole) (**3ea**) (48.2 mg, 0.136 mmol, 68% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 122−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 2H), 7.33−7.23 (m, 6H), 7.11 (t, J = 7.5 Hz, 2H), 6.89 (dt, J = 17.1, 8.0 Hz, 4H), 6.49 (d, J = 1.4 Hz, 2H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.4 (d, J_{C-F} = 252.5 Hz), 159.9, 143.8 (d, J_{C-F} = 3.0 Hz), 137.2, 129.7 (d, J_{C-F} = 7.7 Hz), 126.3, 124.5, 123.4, 122.0, 121.7, 119.1, 114.5 (d, J_{C-F} = 21.2 Hz), 111.3, 43.4, 29.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.9 (td, J = 8.9, 4.5 Hz); HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{19}FN_2$, 353.1460; found, 353.1450.

*4.6.22. 3,3′-(1-(4-Chlorophenyl)ethane-1,1-diyl)bis(1H-indole) (**3fa**).* 3-(4-Chlorophenyl)propiolic acid (**1f**) (36.1 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(4-chlorophenyl)ethane-1,1-diyl)bis(1*H*-indole) (**3fa**) (32.5 mg, 0.092 mmol, 46% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 2H), 7.28 (d, J = 7.2 Hz, 6H), 7.18−7.10 (m, 4H), 6.93 (t, J = 7.5 Hz, 2H), 6.52 (d, J = 1.6 Hz, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.7, 137.1, 131.6, 129.6, 127.9, 126.3, 124.2, 123.4, 122.0, 121.7, 119.1, 111.3, 43.5, 28.8; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{19}ClN_2$, 369.1164; found, 369.1154.

*4.6.23. 3,3′-(1-(4-Bromophenyl)ethane-1,1-diyl)bis(1H-indole) (**3ga**).* 3-(4-Bromophenyl)propiolic acid (**1g**) (45 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(4-bromophenyl)ethane-1,1-diyl)bis(1*H*-indole) (**3ga**) (33.2 mg, 0.08 mmol, 40% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 2H), 7.37−7.28 (m, 6H), 7.23 (d, J = 2.6 Hz, 2H), 7.13 (t, J = 7.4 Hz, 2H), 6.94 (t, J = 7.5 Hz, 2H), 6.58 (d, J = 1.8 Hz, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 147.2, 137.1, 130.9, 130.0, 126.2, 124.1, 123.4, 121.9, 121.7, 119.8, 119.1, 111.3, 43.5, 28.7; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{24}H_{19}BrN_2$, 413.0659; found, 413.0654.

*4.6.24. 3,3′-(1-(3-Methoxyphenyl)ethane-1,1-diyl)bis(1H-indole) (**3ha**).* 3-(3-Methoxyphenyl)propiolic acid (**1h**) (35.2 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(3-methoxyphenyl)ethane-1,1-diyl)bis(1*H*-indole) (**3ha**) (60 mg, 0.164 mmol, 82% yield); yellowish solid (petroleum ether/ethyl acetate = 4/1); melting point: 211−213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 7.10 (dd, J = 16.9, 8.5 Hz, 3H), 6.91 (dd, J = 17.4, 10.3 Hz, 4H), 6.71 (d, J = 8.4 Hz, 1H), 6.42 (s, 2H), 3.63 (s, 3H), 2.25 (d, J = 28.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 157.4, 140.9, 137.5, 129.1, 126.5, 123.7, 123.6, 121.5, 120.9, 118.3, 113.3, 112.0, 55.3, 42.9, 29.7; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{25}H_{22}N_2O$, 365.1659; found, 365.1651.

*4.6.25. 3,3′-(1-(m-Tolyl)ethane-1,1-diyl)bis(1H-indole) (**3ia**).* 3-(*m*-Tolyl)propiolic acid (**1i**) (32 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(*m*-tolyl)ethane-1,1-diyl)bis-(1*H*-indole) (**3ia**) (45.6 mg, 0.13 mmol, 65% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.26−7.19 (m, 3H), 7.11 (dd, J = 14.5, 7.2 Hz, 4H), 6.98 (d, J = 7.1 Hz, 1H), 6.90 (t, J = 7.5 Hz, 2H), 6.47 (d, J = 1.7 Hz, 2H), 2.31 (s, 3H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 148.0, 137.2, 137.1, 128.7, 127.7, 126.6, 126.5, 124.8, 123.5, 122.2, 121.5, 118.9, 111.2, 43.7, 28.8, 21.8; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{25}H_{22}N_2$, 349.1710; found, 349.1701.

*4.6.26. 3,3′-(1-(3,4,5-Trimethoxyphenyl)ethane-1,1-diyl)bis(1H-indole) (**3ja**).* 3-(3,4,5-Trimethoxyphenyl)propiolic acid (**1j**) (47.2 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(3,4,5-trimethoxyphenyl)ethane-1,1-diyl)bis(1*H*-indole) (**3ja**) (75.0 mg, 0.176 mmol, 88% yield); yellowish solid (petroleum ether/ethyl acetate = 4/1); melting point: 386−388 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.6 Hz, 2H), 6.79−6.74 (m, 4H), 6.63 (s, 2H), 3.63 (s, 3H), 3.50 (s, 6H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 152.3, 144.5, 137.4, 136.3, 126.5, 123.8, 123.2, 121.5, 120.9, 118.3, 112.0, 106.5, 60.5, 56.2, 43.8, 29.7; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{27}H_{26}N_2O_3$, 425.1871; found, 425.1867.

*4.6.27. 3,3′-(1-(Naphthalen-2-yl)ethane-1,1-diyl)bis(1H-indole) (**3ka**).* 3-(Naphthalen-2-yl)propiolic acid (**1k**) (39.2 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(naphthalen-2-yl)ethane-1,1-diyl)bis(1*H*-indole) (**3ka**) (39.4 mg, 0102 mmol, 51% yield); yellow solid (petroleum ether/ethyl acetate = 7/1); melting point: 266−268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (d, J = 1.7 Hz, 2H), 7.83 (dd, J = 7.9, 5.7 Hz, 2H), 7.77−7.68 (m, 2H), 7.49 (dd, J = 8.7, 1.8 Hz, 1H), 7.46−7.39 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.00 (dd, J = 11.2, 3.9 Hz, 2H), 6.78−6.71 (m, 4H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.4, 137.5, 133.2, 131.9, 128.4, 127.7, 127.6, 127.3, 126.5, 126.2, 125.9, 125.6, 124.0, 123.1, 121.4, 121.0, 118.5, 112.1, 43.8, 29.4; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{28}H_{22}N_2$, 385.1710; found, 385.1709.

*4.6.28. 3,3′-(1-(Thiophen-2-yl)ethane-1,1-diyl)bis(1H-indole) (**3la**).* 3-(Thiophen-2-yl)propiolic acid (**1l**) (30.4 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(1-(thiophen-2-yl)ethane-1,1-diyl)bis(1*H*-indole) (**3la**) (28 mg, 0.082 mmol, 42% yield); yellowish solid (petroleum ether/ethyl acetate = 5/1); melting point: 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.11 (t, J = 7.3 Hz, 3H), 6.93 (t, J = 7.5 Hz, 2H), 6.86 (s, 2H), 6.63 (d, J = 1.8 Hz, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 154.6, 137.1, 126.2, 126.1, 125.0, 124.6, 123.6, 123.1, 121.9, 121.6,

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119.1, 111.3, 41.9, 30.3; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{22}H_{18}N_2S$, 341.1118; found, 341.1116.

*4.6.29. 3,3′-(Propane-2,2-diyl)bis(1H-indole) (**3ma**).* But-2-ynoic acid (**1m**) (16.8 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(propane-2,2-diyl)bis(1*H*-indole) (**3ma**) (14.8 mg, 0.054 mmol, 27% yield); yellowish solid (petroleum ether/ethyl acetate = 6/1); melting point: 165−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.07 (t, J = 7.4 Hz, 4H), 6.88 (t, J = 7.5 Hz, 2H), 1.92 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 137.5, 126.5, 124.2, 121.2, 120.7, 120.7, 118.0, 111.8, 34.6, 30.5; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{19}H_{18}N_2$, 273.1397; found, 273.1400.

*4.6.30. 3,3′-(Butane-2,2-diyl)bis(1H-indole) (**3na**).* Pent-2-ynoic acid (**1n**) (19.6 mg, 0.2 mmol) and 1*H*-indole (**2a**) (117.2 mg, 1.0 mmol) afforded 3,3′-(butane-2,2-diyl)bis(1*H*-indole) (**3na**) (15 mg, 0.052 mmol, 26% yield); yellowish solid (petroleum ether/ethyl acetate = 6/1); melting point: 179−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.98 (t, J = 5.9 Hz, 4H), 6.76 (t, J = 7.5 Hz, 2H), 2.33 (q, J = 7.3 Hz, 2H), 1.73 (s, 3H), 0.68 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 137.5, 126.5, 123.0, 122.0, 120.7, 120.6, 117.9, 111.7, 38.2, 32.6, 26.6, 9.3; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{20}H_{20}N_2$, 287.1554; found, 287.1556.

*4.6.31. 3-(1-(5-Methyl-1H-pyrrol-2-yl)-1-phenylethyl)-1H-indole (**5aap**).* 3-(1-Phenylvinyl)-1*H*-indole (**5aa**) (21.9 mg, 0.1 mmol), 1*H*-indole (**2a**) (11.7 mg, 0.1 mmol), and 2-methyl-1*H*-pyrrole (**2o**) (8.1 mg, 0.1 mmol) afforded 3-(1-(5-methyl-1*H*-pyrrol-2-yl)-1-phenylethyl)-1*H*-indole (**5aap**) (8.7 mg, 0.029 mmol, 29% yield); yellowish solid (petroleum ether/ethyl acetate = 6/1); melting point: 171−173 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (s, 1H), 10.11 (s, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.26−7.15 (m, 5H), 6.98 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.74 (dd, J = 10.0, 4.8 Hz, 2H), 5.53 (s, 1H), 5.32 (s, 1H), 2.13 (s, 3H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 149.0, 137.4, 137.3, 128.0, 127.9, 126.5, 126.5, 126.1, 123.7, 123.6, 121.3, 120.9, 118.4, 111.9, 106.3, 104.6, 43.9, 28.9, 13.4; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{21}H_{20}N_2$, 299.1554; found, 299.1546.

*4.6.32. 2-(1-Phenylvinyl)-1H-pyrrole (**5ao**).* Yellowish oil (petroleum ether/ethyl acetate = 40/1, 21.9 mg, 66% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H), 7.42−7.35 (m, 5H), 6.83 (d, J = 1.5 Hz, 1H), 6.05−5.97 (m, 1H), 5.84 (t, J = 3.5 Hz, 1H), 5.47 (s, 1H), 4.99 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 141.6, 141.3, 131.6, 128.6, 128.5, 128.2, 120.1, 109.7, 108.7, 108.6.

*4.6.33. 3,3′-(2-Phenylethane-1,1-diyl)bis(1H-indole) (**4aa**).*[19] It is a known byproduct in **3** synthesis, as shown in Section 4.2 (**4aa**, 5.38 mg, 0.016 mmol, 8% yield): yellowish oil (petroleum ether/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.12 (t, J = 7.5 Hz, 2H), 6.96 (q, J = 6.6 Hz, 7H), 6.64−6.50 (m, 2H), 4.84 (t, J = 7.2 Hz, 1H), 3.40 (d, J = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.8, 136.6, 130.4, 127.0, 126.1, 122.0, 119.7, 119.6, 119.2, 118.8, 115.8, 111.2, 37.2, 34.5.

*4.6.34. 3-(1-Phenylvinyl)-1H-indole (**5aa**).* Yellowish oil (petroleum ether/ethyl acetate = 5/1, 910 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 63.7 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 3.8 Hz, 2H), 7.37−7.27 (m, 4H), 7.20 (t, J = 7.5 Hz, 1H), 7.08 (dd, J = 12.9, 4.8 Hz, 2H), 5.58 (s, 1H), 5.42 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.3, 142.5, 136.6, 128.2, 127.7, 126.3, 124.4, 122.3, 120.8, 120.1, 118.1, 112.2, 111.3.

*4.6.35. 1,4-Diphenylbuta-1,3-diyne (**6aa**).*[17] It is a byproduct in **3aa** synthesis, as shown in Section 4.3 (**6aa**, 5.7 mg, 0.016 mmol, 14% yield): White solid (petroleum ether/ethyl acetate = 1/0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59−7.53 (m, 4H), 7.43−7.34 (m, 6H).

*4.6.36. 3-(1-(1H-Indol-3-yl)-1-phenylethyl)-5-methoxy-1H-indole (**5aab**).* 3-Phenylpropiolic acid (**1a**) (29.2 mg, 0.2 mmol), 1*H*-indole (**2a**) (58.5 mg, 0.5 mmol), and 5-methoxy-1*H*-indole (**2b**) (14.7 mg, 0.1 mmol) afforded 3-(1-(1*H*-indol-3-yl)-1-phenylethyl)-5-methoxy-1*H*-indole (**5aab**) (16.1 mg, 0.044 mmol, 22% yield); Back oil (petroleum ether/ethyl acetate = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.78−7.73 (m, 1H), 7.49−7.41 (m, 2H), 7.40−7.34 (m, 2H), 7.32−7.27 (m, 2H), 7.26−7.21 (m, 2H), 7.21−7.15 (m, 1H), 7.02−6.95 (m, 1H), 6.84 (dd, J = 8.8, 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.66 (d, J = 2.6 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 3.64 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.2, 147.9, 137.1, 132.3, 128.1, 127.8, 126.9, 126.5, 125.8, 124.6, 124.4, 124.0, 123.5, 122.1, 121.5, 118.9, 111.7, 111.5, 111.2, 104.2, 55.8, 43.7, 28.7; HRMS (APCI) m/z: $[M - H]^-$ calcd for $C_{25}H_{22}N_2O$, 365.1659; found, 365.1653.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00762.

General methods, optimizations of reaction conditions, and ^{1}H NMR, ^{13}C NMR, and HRMS spectra (PDF)

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Notes

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■ REFERENCES

(1) (a) He, R.; Huo, X.; Zhao, L.; Wang, F.; Jiang, L.; Liao, J.; Zhang, W. Stereodivergent Pd/Cu Catalysis for the Dynamic Kinetic Asymmetric Transformation of Racemic Unsymmetrical 1,3-Disubstituted Allyl Acetates. *J. Am. Chem. Soc.* **2020**, *142*, 8097−8103. (b) Wu, Y.; Huo, X.; Zhang, W. Synergistic Pd/Cu Catalysis in Organic Synthesis. *Chem.—Eur. J.* **2020**, *26*, 4895−4916. (c) Wan, X.; Sun, M.; Wang, J.-Y.; Yu, L.; Wu, Q.; Zhang, Y.-C.; Shi, F. Regio- and Enantioselective Ring-opening Reaction of Vinylcyclopropanes with Indoles under Cooperative Catalysis. *Org. Chem. Front.* **2021**, *8*, 212−223.

(2) Michel, B. W.; Steffens, L. D.; Sigma, M. S. *The Wacker Oxidation*; Organic Reactions, Inc. Published, 2014; Vol. *84*.

(3) Clement, W. H.; Selwitz, C. M. Improved Procedures for Converting Higher α-Olefins to Methyl Ketones with Palladium Chloride. *J. Org. Chem.* **1964**, *29*, 241−243.

(4) (a) Chen, Z.; Yang, L.; Choe, C.; Lv, Z.; Yin, G. Non-redox Metal Ion Promoted Oxygen Transfer by a Non-heme Manganese Catalyst. *Chem. Commun.* **2015**, *51*, 1874−1877.

(5) (a) Zhang, J.; Yang, H.; Sun, T.; Chen, Z.; Yin, G. Nonredox Metal-Ions-Enhanced Dioxygen Activation by Oxidovanadium(IV) Complexes toward Hydrogen Atom Abstraction. *Inorg. Chem.* **2017**, *56*, 834−844.

(6) Qin, S.; Dong, L.; Chen, Z.; Zhang, S.; Yin, G. Non-redox Metal Ions can Promote Wacker-type Oxidations Even Better Than Copper(II): a New Opportunity in Catalyst Design. *Dalton Trans.* **2015**, *44*, 17508−17515.

(7) (a) Senan, A. M.; Qin, S.; Zhang, S.; Lou, C.; Chen, Z.; Liao, R.-Z.; Yin, G. Nonredox Metal-Ion-Accelerated Olefin Isomerization by Palladium(II) Catalysts: Density Functional Theory (DFT) Calculations Supporting the Experimental Data. *ACS Catal.* **2016**, *6*, 4144−4148. (b) Xue, J.-W.; Zeng, M.; Hou, X.; Chen, Z.; Yin, G. Catalytic Oxidation of Alkynes into 1,2-Diketone Derivatives by Using a Pd^{II}/Lewis-Acid Catalyst. *Asian J. Org. Chem.* **2018**, *7*, 212−219. (c) Lou, C.; Qin, S.; Zhang, S.; Lv, Z.; Senan, A. M.; Chen, Z.; Yin, G. Non-redox Metal Ions Promoted Oxidative Dehydrogenation of Saturated C-C Bond by Simple $Pd(OAc)_2$ Catalyst. *Catal. Commun.* **2017**, *90*, 5−9. (d) Guo, H.; Chen, Z.; Mei, F.; Zhu, D.; Xiong, H.; Yin, G. Redox Inactive Metal Ion Promoted C-H Activation of Benzene to Phenol with Pd^{II}(bpym): Demonstrating New Strategies in Catalyst Designs. *Chem.—Asian J.* **2013**, *8*, 888−891. (e) Zhang, S.; Xu, H.; Lou, C.; Senan, A. M.; Chen, Z.; Yin, G. Efficient Bimetallic Catalysis of Nitrile Hydration to Amides with a Simple $Pd(OAc)_2$/Lewis Acid Catalyst at Ambient Temperature. *Eur. J. Org. Chem.* **2017**, *2017*, 1870−1875. (f) Xue, J.-W.; Zeng, M.; Jiang, H.; Li, K.; Chen, Z.; Yin, G. Palladium(II)/Lewis Acid-Catalyzed Oxidative Olefination/Annulation of N-Methoxybenzamides: Identifying the Active Intermediates through NMR Characterizations. *J. Org. Chem.* **2020**, *85*, 8760−8772.

(8) Xue, J.-W.; Zeng, M.; Zhang, S.; Chen, Z.; Yin, G. Lewis Acid Promoted Aerobic Oxidative Coupling of Thiols with Phosphonates by Simple Nickel(II) Catalyst: Substrate Scope and Mechanistic Studies. *J. Org. Chem.* **2019**, *84*, 4179−4190.

(9) (a) Rahimi, M.; Huang, K.-L.; Tang, C. K. ′-Diindolylmethane (DIM) Inhibits the Growth and Invasion of Drug-resistant Human Cancer Cells Expressing EGFR Mutants. *Cancer Lett.* **2010**, *295*, 59−68. (b) Hsu, E. L.; Chen, N.; Westbrook, A.; Wang, F.; Zhang, R.; Taylor, R. T.; Hankinson, O. ′-Diindolylmethane for Breast and Ovarian Cancers. *Cancer Lett.* **2008**, *265*, 113−123.

(10) (a) Mao, Y.; Lu, Y.; Li, T.; Wu, Q.; Tan, W.; Shi, F. Brønsted Acid-Catalyzed Substitution Reactions of 2-Indolylmethanols with Tryptophols: Chemoselective Synthesis of 2,2′-Bisindolylmethanes. *Chin. J. Org. Chem.* **2020**, *40*, 3895−3907. (b) Zhou, J.; Li, T. Z.; Sun, Y. W.; Du, B. X.; Tan, W.; Shi, F. Chiral Brønsted Acid-Catalyzed Asymmetric 1,4-Addition of Benzofuran-Derived Azadienes with 3-Substituted indoles. *ChemCatChem* **2020**, *12*, 4862−4870. (c) Wang, J.-R.; Jiang, X.-L.; Hang, Q.-Q.; Zhang, S.; Mei, G.-J.; Shi, F. Catalytic Asymmetric Conjugate Addition of Indoles to para-Quinone Methide. *J. Org. Chem.* **2019**, *84*, 7829−7839. (d) Wang, H.-Q.; Xu, M.-M.; Wan, Y.; Mao, Y.-J.; Mei, G.-J.; Shi, F. Application of 7-Indolylmethanols in Catalytic Asymmetric Arylations with Tryptamines: Enantioselective Synthesis of 7-indolylmethanes. *Adv. Synth. Catal.* **2018**, *360*, 1850−1860. (e) He, Y.-Y.; Sun, X.-X.; Li, G.-H.; Mei, G.-J.; Shi, F. Substrate-Controlled Regioselective Arylations of 2-Indolylmethanols with Indoles: Synthesis of Bis(indolyl)methane and 3,3′-Bisindole Derivatives. *J. Org. Chem.* **2017**, *82*, 2462−2471. (f) Sun, X.-X.; Du, B.-X.; Zhang, H.-H.; Ji, L.; Shi, F. ′Catalytic Asymmetric Arylation of 3-Indolylmethanols: Enantioselective Synthesis of 3,3′-Bis(indolyl)oxindoles with High Atom Economy. *ChemCatChem* **2015**, *7*, 1211−1221. (g) Zhou, L.-J.; Zhang, Y.-C.; Zhao, J.-J.; Shi, F.; Tu, S.-J. Organocatalytic Arylation of 3-Indolylmethanols via Chemo- and Regiospecific C6-Functionalization of Indoles. *J. Org. Chem.* **2014**, *79*, 10390−10398.

(11) Wang, Z.; Ai, F.; Wang, Z.; Zhao, W.; Zhu, G.; Lin, Z.; Sun, J. Organocatalytic Asymmetric Synthesis of 1,1-Diarylethanes by Transfer Hydrogenation. *J. Am. Chem. Soc.* **2015**, *137*, 383−389.

(12) (a) Nomiyama, S.; Hondo, T.; Tsuchimoto, T. Easy Access to a Library of Alkylindoles: Reductive Alkylation of Indoles with Carbonyl Compounds and Hydrosilanes under Indium Catalysis. *Adv. Synth. Catal.* **2016**, *358*, 1136−1149. (b) Palmieri, A.; Petrini, M. Recent Advances in the Synthesis of Unsymmetrical Bisindolylmethane Derivatives. *Synthesis* **2018**, *51*, 829−841.

(13) (a) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. Intra- and Intermolecular Reactions of Indoles with Alkynes Catalyzed by Gold. *Chem.—Eur. J.* **2007**, *13*, 1358−1373. (b) McLean, E. B.; Cutolo, F. M.; Cassidy, O. J.; Burns, D. J.; Lee, A.-L. Selectivity Control in Gold-Catalyzed Hydroarylation of Alkynes with Indoles: Application to Unsymmetrical Bis(indolyl)methanes. *Org. Lett.* **2020**, *22*, 6977−6981. (c) Yadav, J. S.; Reddy, B. V. S.; Padmavani, B.; Gupta, M. K. Gallium(III) Halide-Catalyzed Coupling of Indoles with Phenylacetylene: Synthesis of Bis(indolyl)phenylethanes. *Tetrahedron Lett.* **2004**, *45*, 7577−7579.

(14) Ling, Y.; An, D.; Zhou, Y.; Rao, W. $Ga(OTf)_3$-Catalyzed Temperature-Controlled Regioselective Friedel-Crafts Alkylation of Trifluoromethylated 3-Indolylmethanols with 2-Substituted Indoles: Divergent Synthesis of Trifluoromethylated Unsymmetrical 3,3′-and 3,6′-Bis(indolyl)methanes. *Org. Lett.* **2019**, *21*, 3396−3401.

(15) (a) Zhang, S.; Chen, Z.; Qin, S.; Lou, C.; Senan, A. M.; Liao, R.-Z.; Yin, G. Non-redox Metal Ion Promoted Oxidative Coupling of Indoles with Olefins by the Palladium(II) Acetate Catalyst through Dioxygen Activation: Experimental Results with DFT Calculations. *Org. Biomol. Chem.* **2016**, *14*, 4146−4157. (b) Zhang, Y.; Zhang, S.-X.; Fu, L.-N.; Guo, Q.-X. Highly Efficient Atom-Economic Synthesis

of Chiral Bis(indolyl)methanes Bearing Quaternary Stereogenic Carbon Centers. *ChemCatChem* **2017**, *9*, 3107−3110.
(16) (a) Wei, Y.; Hu, P.; Zhang, M.; Su, W. Metal-Catalyzed Decarboxylative C-H Functionalization. *Chem. Rev.* **2017**, *117*, 8864−8907. (b) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions. *Chem. Rev.* **2011**, *111*, 1846−1913. (c) Park, K.; Lee, S. Transition Metal-catalyzed Decarboxylative Coupling Reactions of Alkynyl Carboxylic Acids. *RSC Adv.* **2013**, *3*, 14165−14182. (d) Waetzig, S. R.; Tunge, J. A. Palladium-Catalyzed Decarboxylative sp^3-sp^3 Coupling of Nitrobenzene Acetic Esters. *J. Am. Chem. Soc.* **2007**, *129*, 14860−14861. (e) Drapeau, M. P.; Bahri, J.; Lichte, D.; Gooßen, L. J. Decarboxylative ipso Amination of Activated Benzoic Acids. *Angew. Chem., Int. Ed.* **2019**, *58*, 892−896. (f) Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. One-Pot Synthesis of Diarylalkynes Using Palladium-Catalyzed Sonogashira Reaction and Decarboxylative Coupling of sp Carbon and sp^2 Carbon. *Org. Lett.* **2008**, *10*, 945−948. (g) Yu, S.; Cho, E.; Kim, J.; Lee, S. Palladium-Catalyzed Decarboxylative Coupling of Alkynyl Carboxylic Acids and Alkenyl Tosylates for the Synthesis of Enynones. *J. Org. Chem.* **2017**, *82*, 11150−11156. (h) Han, S.; Kim, H.-S.; Zhang, M.; Xia, Y.; Lee, S. Ni/Cu-Catalyzed Decarboxylative Addition of Alkynoic Acids to Terminal Alkynes for the Synthesis of gem-1,3-Enynes. *Org. Lett.* **2019**, *21*, 5426−5431.
(17) Park, J.; Park, E.; Kim, A.; Park, S.-A.; Lee, Y.; Chi, K.-W.; Jung, Y. H.; Kim, I. S. Pd-Catalyzed Decarboxylative Coupling of Propiolic Acids: One-Pot Synthesis of 1,4-Disubstituted 1,3-Diynes via Sonogashira Homocoupling Sequence. *J. Org. Chem.* **2011**, *76*, 2214−2219.
(18) Ling, F.; Xiao, L.; Fang, L.; Feng, C.; Xie, Z.; Lv, Y.; Zhong, W. $B(C_6F_5)_3$-Catalyzed Markovnikov Addition of Indoles to Aryl Alkynes: an Approach toward Bis(indolyl)alkanes. *Org. Biomol. Chem.* **2018**, *16*, 9274−9278.
(19) Xia, D.; Wang, Y.; Du, Z.; Zheng, Q.-Y.; Wang, C. Rhenium-Catalyzed Regiodivergent Addition of Indoles to Terminal Alkynes. *Org. Lett.* **2012**, *14*, 588−591.
(20) Marrelli, M.; Cachet, X.; Conforti, F.; Sirianni, R.; Chimento, A.; Pezzi, V.; Michel, S.; Statti, G. A.; Menichini, F. Synthesis of a New Bis(indolyl)methane That Inhibits Growth and Induces Apoptosis in Human Pprostate Cancer Cells. *Nat. Prod. Res.* **2013**, *27*, 2039−2045.
(21) More, A. A.; Szpilman, A. M. Indium(III) Catalyzed Reactions of Vinyl Azides and Indoles. *Org. Lett.* **2020**, *22*, 3759−3764.
(22) (a) Nosova, V. M.; Ustynyuk, Y. A.; Bruk, L. G.; Temkin, O. N.; Kisin, A. V.; Storozhenko, P. A. Structure of Complexes Formed by Dissolution of Palladium Diacetate in Methanol and Chloroform. In Situ NMR Study. *Inorg. Chem.* **2011**, *50*, 9300−9310. (b) Bakhmutov, V. I.; Berry, J. F.; Cotton, F. A.; Ibragimov, S.; Murillo, C. A. Non-trivial Behavior of Palladium(II) Acetate. *Dalton Trans.* **2005**, 1989−1992.
(23) Schießl, J.; Rudolph, M.; Hashmi, A. S. K. The Gold-Catalyzed Hydroarylation of Alkynes with ElectronRich Heteroarenes − A Kinetic Investigation and New Synthetic Possibilities. *Adv. Synth. Catal.* **2017**, *359*, 639−653.
(24) (a) Jiang, T.; Zhang, H.; Ding, Y.; Zou, S.; Chang, R.; Huang, H. Transition-Metal-Catalyzed Reactions Involving Reductive Elimination between Dative Ligands and Covalent Ligands. *Chem. Soc. Rev.* **2020**, *49*, 1487−1516. (b) Kotov, V.; Scarborough, C. C.; Stahl, S. S. Palladium-Catalyzed Aerobic Oxidative Amination of Alkenes: Development of Intra- and Intermolecular Aza-Wacker Reactions. *Inorg. Chem.* **2007**, *46*, 1910−1923.
(25) Mo, X.; Chen, B.; Zhang, G. Copper-Catalyzed Enantioselective Sonogashira Type Coupling of Alkynes with a-Bromoamides. *Angew. Chem., Int. Ed.* **2020**, *59*, 13998−14002.
(26) Ponpandian, T.; Muthusubramanian, S. Copper Catalysed Domino Decarboxylative Cross Coupling-cyclisation Reactions: Synthesis of 2-Arylindoles. *Tetrahedron Lett.* **2012**, *53*, 4248−4252.

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