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Mechanochemically Activated Oxidative Coupling of Indoles with Acrylates through C−H Activation: Synthesis of 3-Vinylindoles and β,β-Diindolyl Propionates and Study of the Mechanism

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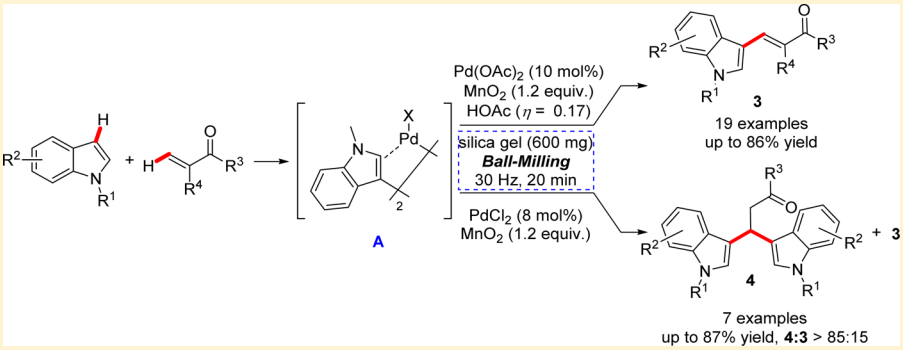
Supporting Information



ABSTRACT: Construction of 3-vinylindoles (**3**) and β,β-diindolyl propionates (**4**) through solvent-free C−H functionalization has been explored under high-speed ball-milling conditions. The reaction selectivity is influenced by the catalyst dramatically: $Pd(OAc)_2$ provides **3** in moderate to good yields, whereas PdX_2 (X = Cl, I) affords **4** as the major products. The reaction mechanism has been further studied by using electrospray ionization mass spectrometry, implicating the dimeric palladium complex **A** as the key intermediate in an explanation of the selectivity.

INTRODUCTION

Mechanochemically promoted organic reactions have aroused considerable attention due to their emergent advantages of high reaction rate, new reactivity, excellent stoichiometry control, and reactant solubility ignorance.[1] Among these excellent results, series of valuable transition-metal-catalyzed cross-coupling reactions have been reported with the aid of this unusual method,[2] providing comparable results within much shorter reaction times. Very recently, after the discovery of C−H palladation under high-speed ball-milling (HSBM) conditions,[3] pioneer works of inert C−H functionalization were achieved by Bolm et al.,[4] which showed the potential application of mechanochemistry for developing highly efficient solvent-free C−H functionalization reactions.

Among the prevalent indole scaffolds in nature, 3-vinylindoles have attracted continuous interest from the industrial and academic communities because of their biological and pharmaceutical properties,[5] and the structure can be easily accessed through direct alkenylation.[6] As part of our continuous pursuit of greener synthesis under solvent-free HSBM conditions,[7] the direct alkenylation of indoles and acrylates was undertaken to further improve its greenness. The reaction proceeded well with $Pd(OAc)_2$, affording 3-vinylindoles (**3**) smoothly as expected. However, during the optimization, unexpected β,β-diindolyl propionates (**4**) were separated as the main products using $PdCl_2$ or PdI_2 as catalyst. According to a literature survey, several cases of metal-catalyzed β,β-diindolyl propionate synthesis were reported (Scheme 1),[8] and most of the cases underwent a nucleophilic addition pathway to introduce the second indolyl motif. Herein, we report a selective synthesis of 3-vinylindoles and β,β-diindolyl propionates through C−H activation under HSBM conditions (Scheme 1). The reaction mechanism was primarily disclosed on the basis of electrospray ionization mass spectrometry (ESI-MS) to shed some light on the cause of selectivity.

RESULTS AND DISCUSSION

At the beginning, a reaction mixture of *N*-methylindole (**1a**) and ethyl acrylate (**2a**) was treated with $Pd(OAc)_2$ (10 mol %) and $Cu(OAc)_2·H_2O$ (2.0 equiv), affording the 3-alkenylated product **3aa** with 39% yield (Table 1, entry 1). Then,

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Scheme 1. Synthesis of *β,β*-Diindolyl Propionates

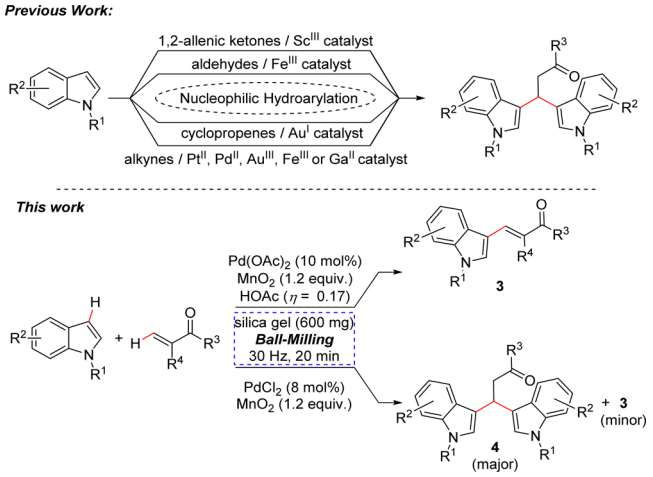
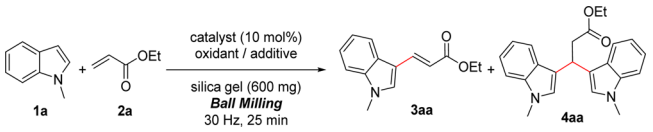


Table 1. Optimization Studies of the Reaction Conditions[a]



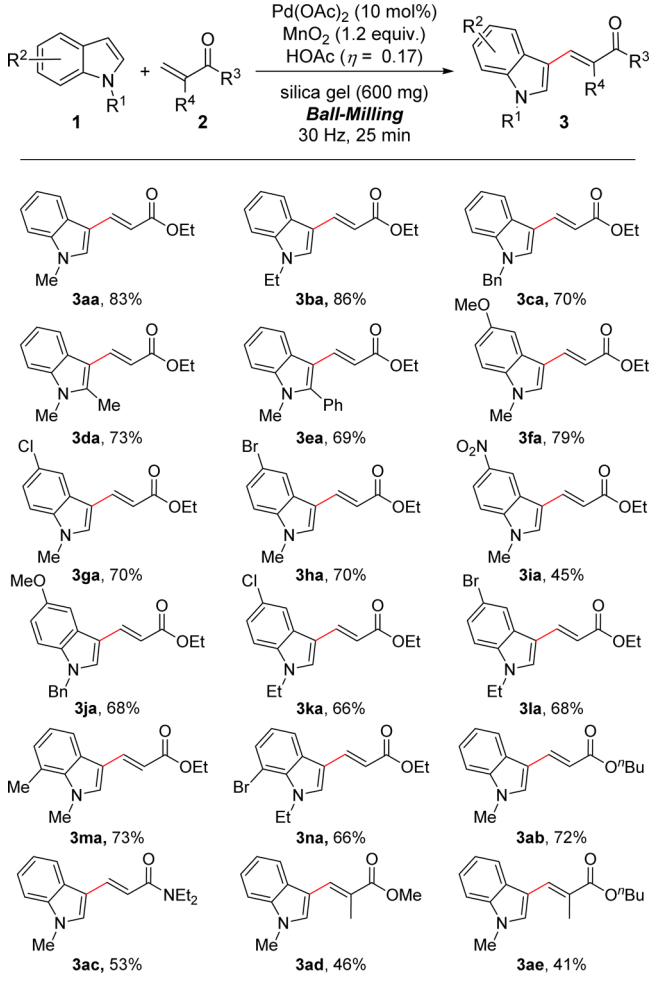
				yield (%)[c]	
entry	catalyst	oxidant (amt (equiv))	additive (η)[b]	3aa	4aa
1	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$ (2.0)		39	
2	$Pd(OAc)_2$	AgOAc (2.0)		45	
3	$Pd(OAc)_2$	CuO (2.0)		50	
4	$Pd(OAc)_2$	MnO_2 (2.0)		61	
5	$Pd(OAc)_2$	air (1 atm)[d]		18	
7	$Pd(OAc)_2$	MnO_2 (1.2)		62	
8	$Pd(OAc)_2$	MnO_2 (0.8)		48	
9	$Pd(OAc)_2$	MnO_2 (1.2)	HOAc (0.17)	83	
10	$Pd(OAc)_2$	MnO_2 (1.2)	TFA (0.17)	39	
11	$Pd(OAc)_2$	MnO_2 (1.2)	H_2O (0.17)	45	
12	$Pd(OAc)_2$	MnO_2 (1.2)	DMSO (0.17)	72	
13	$Pd(TFA)_2$	MnO_2 (1.2)		31	
14	$Pd(TFA)_2$	MnO_2 (1.2)	HOAc (0.16)	75	
15	$PdCl_2$	MnO_2 (1.2)	HOAc (0.17)	15	68
16	$PdCl_2$	MnO_2 (1.2)		11	78
17	PdI_2	MnO_2 (1.2)	HOAc (0.17)	20	65
18	PdI_2	MnO_2 (1.2)		12	75
19	$PdCl_2$[e,f]	MnO_2 (1.2)		9	78
20	$PdCl_2$[g]	MnO_2 (1.2)		9	57

[a]Reaction conditions unless specified otherwise: **1a** (1 mmol), **2a** (1 mmol), catalyst (0.1 equiv), oxidant, additive, and silica gel (600 mg) were placed in a stainless-steel vessel with two stainless-steel balls (ø = 1.2 cm). Ball milling conditions: 25 min at 30 Hz. [b]$\eta = V$(liquid; mL)/m(sample; mg). [c]Yield based on **1a**. [d]No air exchange was performed during the milling process. [e]$PdCl_2$ (8 mol %). [f]The selectivity was influenced by the ratio of **1a** and **2a**: 13:87 (**3aa**:**4aa**) for 2:1 (**1a**:**2a**), 12:88 for 2:1.5, 11:89 for 2:1.7, and 10:90 for 1:1. [g]$PdCl_2$ (5 mol %).

optimization studies for this model reaction were performed, and selected results are summarized in Table 1. First, several oxidants were tested, and the yields were elevated to 61% by using MnO_2 (Table 1, entries 1−5). Further screening showed that the reaction still worked well when the amount of MnO_2 was reduced to 1.2 equiv (Table 1, entries 7 and 8). With the inspiration of the liquid-assisted grinding (LAG) effect of additives on mechanochemical reactions,[1d,9] several commonly used solvents and additives were tested, and acetic acid was proved to be the optimum species, giving the highest yield of 83% (Table 1, entries 9−12). A low yield was obtained when triflate anion was used (Table 1, entry 10). Subsequent results with $Pd(TFA)_2$ (Table 1, entries 13 and 14) indicate that the anion may have a strong influence on the outcome. Thus, the two catalysts $PdCl_2$ and PdI_2 were further tested. Unexpectedly, the *β,β*-diindolyl propionate **4aa** was separated as the major product from the reaction mixture (Table 1, entries 15 and 17). To our delight, higher selectivity could be obtained by removing acetic acid in these cases (Table 1, entries 16 and 18). Further decreasing the amount of $PdCl_2$ to 8 mol % afforded **4aa** without erosion in yield (Table 1, entries 19 and 20). Comprehensive optimizations of the mechanochemical process for the synthesis of 3-vinylindole (conditions A) and *β,β*-diindolyl propionate (conditions B) were performed, including grinding frequency, time, and grinding auxiliary (Tables S1−S4 in the Supporting Information).

With the optimal conditions in hand, the scope of direct alkenylation (conditions A) was investigated first (Table 2). A range of indoles **1a−n** was reacted with ethyl acrylate (**2a**), affording the desired 3-vinylindoles in moderate to good yield

Table 2. Scope of 3-Vinylindoles[a,b]



[a]Reaction conditions A: **1** (1.0 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), MnO_2 (1.2 equiv), HOAc (η = 0.17), and silica gel (600 mg) were placed in a stainless-steel vessel with two stainless-steel balls (ø = 1.2 cm). Ball milling conditions: 25 min at 30 Hz. [b]Yield based on **1**.

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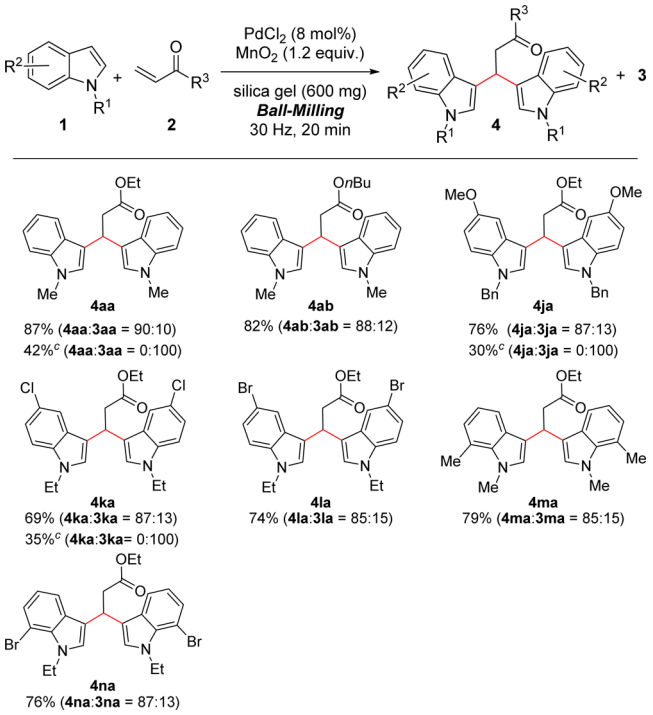
Table 3. Scope of *β,β*-Diindolyl Propionates[a,b]



[a]Reaction conditions B: **1** (1.0 mmol), **2** (1.0 mmol), $PdCl_2$ (8 mol %), MnO_2 (1.2 equiv), and silica gel (600 mg) were placed in a stainless-steel vessel with two stainless-steel balls (ø = 1.2 cm). Ball milling conditions: 20 min at 30 Hz. [b]Total yield based on **1**. [c]Yields of comparative experiments: **1** (1.0 mmol), **2** (1.0 mmol), $PdCl_2$ (10 mol %), MnO_2 (1.2 equiv), and DMF (10 mL) at 100 °C overnight.

(**3aa**−**na**). The best result was obtained by using *N*-ethylindole (**3ba**); changing the protecting group to benzyl led to a moderate yield of 70% (**3ca**). Other substitutions on indoles were well tolerated to provide products **3** smoothly, among which the 5-nitro-substituted substrate **3i** was proved to be less reactive than others. Acrylate derivatives **2b**−**e** were also tested with **1a**. Low yields were obtained using methacrylates **2d**,**e**, which may be due to the steric hindrance.[10]

Afterward, indoles were treated with acrylic esters under conditions B (Table 3). *N*-Methylindoles **1a** reacted smoothly with **2a**,**b** to afford *β,β*-diindolyl propionates **4aa**,**ab** along with the corresponding 3-vinylindoles in total yields of 87% and 82% (**4aa**:**3aa** = 90:10, **4ab**:**3ab** = 88:12), respectively. Indoles bearing either electron-donating or electron-withdrawing groups on the aryl ring also reacted well with **2a**, giving the desired **4ja**−**4na** as the main products with moderate to good yields and selectivity. For comparison, reactions involving **1a**,**j**,**k** were conducted in DMF, where only 3-vinylindoles were detected without any trace of *β,β*-diindolyl propionates, indicating that this HSBM-promoted reaction may follow a mechanism different from that of solvent-based reactions.

Further disclosure of the reaction mechanism was performed on the basis of previous works.[9,11] ESI-MS, a powerful tool for mechanistic studies,[12] was chosen here to capture the intermediates that were generated during the reaction. First, two mixtures of $PdCl_2$ and **1a** treated by 30 s of grinding (HSBM sample, Figure 1a) and 30 min of reflux in DMF (DMF sample, Figure 1b) were analyzed quickly by ESI(+)-MS,[13] where special attention was paid to the range between *m*/*z* 200 and 700. Differences arose at *m*/*z* 542.2 and 273.2. The former cluster assigned as $[Pd_2(\mathbf{1a}\text{-H})_2(Cl)_2 + H]^+$ appeared exclusively in the HSBM sample, whereas the cluster at *m*/*z* 273.2 assigned as $[Pd(\mathbf{1a}\text{-H})(Cl) + H]^+$ was found in the DMF sample. The signal at *m*/*z* 261.9 was thought to be the homocoupling product (**5a**) of indoles and was further confirmed by HPLC (Figure S4 in the Supporting Information). Inspired by the solvent-labile intermediate captured by Friščić et al.,[11b] we hypothesized that the $Pd_2(\mathbf{1a}\text{-H})_2(Cl)_2$ may also be a solvent-sensitive species, which was supported by attenuation of the corresponding signals during the analysis

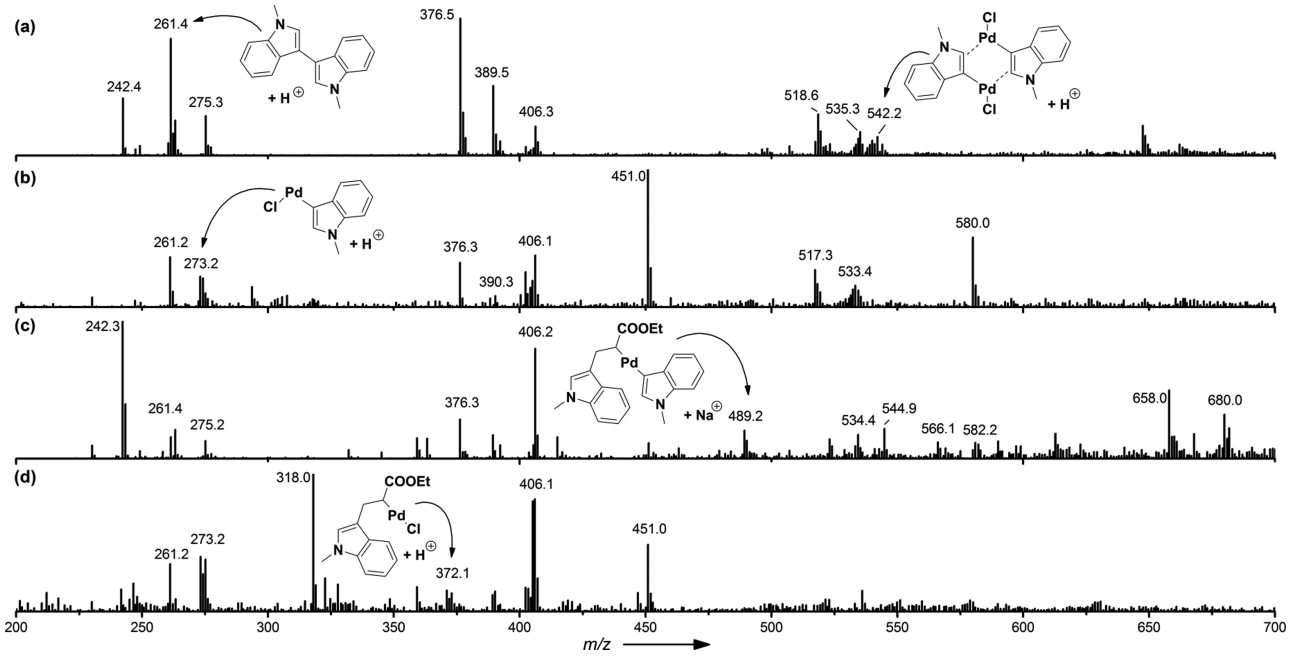


Figure 1. ESI-MS spectra of $PdCl_2$-catalyzed reactions: (a) $PdCl_2$ with **1a** with 30 Hz grinding for 30 s; (b) $PdCl_2$ with **1a** in DMF refluxed for 30 min; (c) $PdCl_2$ with **1a** and **2a** with 30 Hz grinding for 30 s; (d) $PdCl_2$ with **1a** and **2a** in DMF refluxed for 30 min.

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(Figure S2 in the Supporting Information). Continuously, two other samples of $PdCl_2$, **1a**, and **2a** under different conditions were compared, and the intermediates after insertion were found in both spectra (Figure 1c,d). However, in the HSBM sample, the intermediate $[Pd(\mathbf{3a} + H)(\mathbf{1a}\text{-}H) + Na]^+$ at m/z 489.1 with an indolyl ligand was apt to give the β,β-diindolyl propionate product after several additional steps.

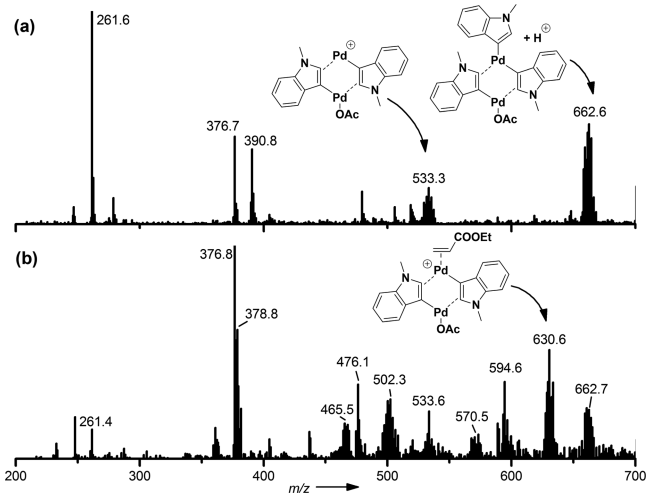
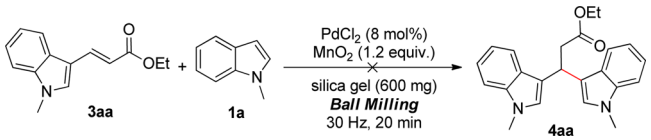


Figure 2. ESI-MS spectra of $Pd(OAc)_2$-catalyzed HSBM reactions (conditions A): (a) $Pd(OAc)_2$ with **1a** with 30 Hz grinding for 30 s; (b) $Pd(OAc)_2$ with **1a** and **2a** with 30 Hz grinding for 30 s.

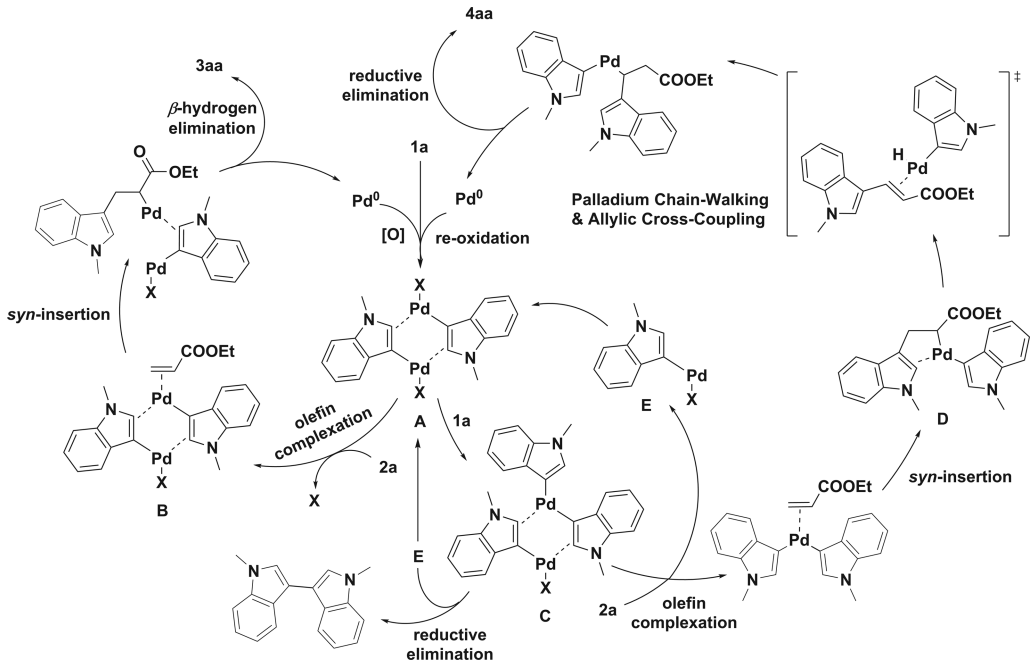
Subsequently, the reaction performed under conditions A was further scrutinized to illustrate the selectivity. A dimeric complex was found at m/z 533.3 that was similar to $[Pd_2(\mathbf{1a}\text{-}H)_2OAc]^+$, showing that both conditions started with the same intermediate (Figure 2a). When **2a** was added, a cluster at m/z 630.6 was detected and assigned as $[Pd_2(\mathbf{1a} - H)_2(\mathbf{2a})OAc]^+$ (Figure 2b). A similar homocoupling product appeared again and was thought to be the reductive elimination product from $[Pd_2(\mathbf{1a} - H)_3OAc]^+$ (m/z 662.6). Additionally, samples without LAG were examined carefully, implicating the reaction to undergo a similar pathway (Figure S3 in the Supporting Information).

On the basis of previous studies[6b] and our results, a plausible mechanism for the selective synthesis of 3-vinylindoles and β,β-diindolyl propionates was proposed (Scheme 2). The reactions started with palladation at the C-3 position, followed by intermolecular coordination to give the dimeric palladium complex **A**. Then, this key intermediate entered two catalytic cycles with the rate control of olefin complexation and second palladation.[14] With acetate anion (conditions A), the intermediate **A**-OAc underwent a fast olefin complexation, followed by classical steps as in the Heck reaction mechanism.[14] A small amount of **5** was separated, indicating that the second palladation of indole also occurred under conditions A. In contrast, with chloride or iodide anion (conditions B), the solvent-labile intermediate **A**-Cl (or **A**-I) was much more stable with ball milling but with a slower rate of the olefin complexation; thus, another palladation occurred to give complex **C**. After olefin complexation and the following syn insertion, intermediate **D** was formed, which was hypothesized to undergo a palladium chain-walking/allylic cross-coupling pathway[15] and the possibility of catalytic hydroarylation was ruled out by a failed control experiment between **1a** and **3aa** under conditions B (Scheme 3).

Scheme 3. Control Experiment for the Formation of 4aa



Scheme 2. Proposed Mechanism of HSBM-Promoted Selective Synthesis of 3-Vinylindoles and β,β-Diindolyl Propionate



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CONCLUSION

In summary, we have described a facile protocol for the selective synthesis of 3-vinylindoles and β,β-diindolyl propionates under solvent-free HSBM conditions. With the assistance of ESI-MS, a plausible mechanism was proposed, in which the selectivity was controlled by the olefin complexation rate of the dimeric palladium intermediate **A** with different anion. In addition, a solvent-labile dimeric palladium intermediate may also account for the different outcomes between HSBM and DMF, which shed light on new reactivity involving a solvent-labile intermediate under mechanochemical conditions.

EXPERIMENTAL SECTION

General Information. All the reagents were used as received, unless otherwise indicated. TLC analysis was performed using precoated glass plates. All of the the HSBM reactions were conducted in a Mixer Miller with 50 mL stainless-steel grinding vessels and two stainless-steel balls (ø = 1.2 cm). Melting points (mp) were obtained on a digital melting point apparatus and are uncorrected. NMR spectra were recorded with a 400 MHz spectrometer for ^{1}H and 100 MHz for ^{13}C, and TMS was used as an internal standard. Mass spectra were recorded with a HRMS-ESI-Q-TOF and a low-resolution MS instrument using an ESI ion source.

Typical Procedure for Synthesis of (*E*)-Ethyl 3-(1-Methyl-1*H*-indol-3-yl)acrylate (3aa).[6e] A mixture of the substrate *N*-methylindole (1.0 mmol, 131 mg, 1.0 equiv), ethyl acrylate (1.0 mmol, 100 mg, 1.0 equiv), MnO_2 (1.2 mmol, 104 mg, 1.2 equiv), $Pd(OAc)_2$ (0.1 mmol, 22.5 mg, 0.1 equiv), HOAc (60 μL), and silica gel (0.6 g) was placed in a screw-capped stainless-steel vessel, along with two stainless-steel balls (12 mm). Then, the vessel was placed in the mixer mill, and the contents were milled at 30 Hz for 25 min. At the end of the experiment, all of the reaction mixture was scratched off from the vessel and dissolved in ethyl acetate followed by washing with brine, and the organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (eluents: petroleum ether/ethyl acetate 10/1) to give the desired product **3aa** as white crystals (190.0 mg, 83% yield): mp 94−95 °C (lit. mp 96−97 °C);[6e] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.79 [m, 2H, including 7.81 (d, *J* = 16.0 Hz, 1H)], 7.27−7.25 (m, 1H), 7.25−7.20 (m, 1H), 7.19−7.16 (m, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 4.20 (q, *J* = 7.12 Hz, 2H), 3.74 (s, 3H), 1.29 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.6, 137.5, 132.7, 125.5, 122.5, 120.8, 120.2, 112.2, 111.7, 109.6, 60.08, 33.39, 14.90; MS (ESI) 230.4 ([M + H]$^+$).

(E)-Ethyl 3-(1-ethyl-1H-indol-3-yl)acrylate (**3ba**): white crystals (209.0 mg, 86% yield); mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.85 [m, 2H, including 7.88 (d, *J* = 16.0 Hz, 1H)], 7.41−7.20 (m, 4H), 6.39 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.12 Hz, 2H), 4.18 (q, *J* = 7.28 Hz, 2H), 1.50 (t, *J* = 7.28 Hz, 3H), 1.35 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.1, 137.9, 137.0, 131.2, 126.1, 122.7, 121.1, 120.6, 112.4, 112.1, 109.9, 60.0, 41.4, 15.4, 14.6; HRMS (ESI) $C_{15}H_{17}NO_2$ ([M + H]$^+$) calcd 244.1332, found 244.1332.

(E)-Ethyl 3-(1-benzyl-1H-indol-3-yl)acrylate (**3ca**):[16] light yellow oil (213.8 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.91 (m, 1H), 7.88 (d, *J* = 16.0 Hz, 1H), 7.39 (s, 1H), 7.34−7.27 (m, 4H), 7.27−7.22 (m, 3H, including $CDCl_3$), 7.15−7.10 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 5.31 (s, 2H), 4.26 (q, *J* = 7.12 Hz, 2H), 1.35 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.9, 137.6, 137.5, 136.0, 132.1, 128.8 (2C), 127.9, 126.8 (2C), 126.2, 122.9, 121.3, 120.5, 113.1, 112.6, 110.3, 60.0, 50.4, 14.6; MS (ESI) 306.1 ([M + H]$^+$).

(E)-Ethyl 3-(1,2-dimethyl-1H-indol-3-yl)acrylate (**3da**): pink crystals (177.6 mg, 73% yield); mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 16.0 Hz, 1H), 7.89−7.85 (m, 1H), 7.30−7.17 (m, 3H), 6.40 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.12 Hz, 2H), 3.67 (s, 3H), 2.52 (s, 3H), 1.35 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.4, 141.5, 137.4, 137.2, 125.3, 121.8, 121.0, 120.0, 111.0, 109.1, 108.6, 59.8, 29.7, 14.5, 10.6; HRMS (ESI) $C_{15}H_{17}NNaO_2$ ([M + Na]$^+$) calcd 266.1151, found 226.1142.

(E)-Ethyl 3-(1-methyl-2-phenyl-1H-indol-3-yl)acrylate (**3ea**): white crystals (210.5 mg, 69% yield); mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 16.0 Hz, 1H), 7.55−7.44 (m, 3H), 7.41−7.21 (m, 5H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.19 (q, *J* = 7.12 Hz, 2H), 3.62 (s, 3H), 1.29 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.2, 138.6, 137.8, 130.8 (2C), 130.0, 129.1, 128.5 (2C), 125.5, 122.9, 121.6, 120.6, 112.9, 110.4, 109.9, 59.9, 31.2, 14.6; HRMS (ESI) $C_{20}H_{19}NNaO_2$ ([M + Na]$^+$) calcd 328.1308, found 328.1317.

(E)-Ethyl 3-(5-methoxy-1-methyl-1H-indol-3-yl)acrylate (**3fa**): white crystals (204.6 mg, 79% yield); mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 16.0 Hz, 1H), 7.30−7.28 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 4.26 (q, *J* = 7.12 Hz, 2H), 3.90 (s, 3H), 3.77 (s, 3H), 1.35(t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.1, 155.2, 137.9, 133.1, 133.0, 126.4, 112.7, 111.6, 111.4, 110.6, 102.4, 60.0, 56.0, 33.4, 14.6; HRMS (ESI) $C_{15}H_{17}NNaO_3$ ([M + Na]$^+$): calcd 282.1101, found 282.1092.

(E)-Ethyl 3-(5-chloro-1-methyl-1H-indol-3-yl)acrylate (**3ga**):[17] white crystals (184.1 mg, 70% yield); mp 114−116 °C (lit. mp 112−113 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.32 (s, 1H), 7.26−7.21 (m, 2H), 6.33 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.12 Hz, 2H), 3.79 (s, 3H), 1.35 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.7, 137.0, 136.1, 133.7, 126.9, 126.6, 122.9, 119.8, 112.8, 111.3, 110.8, 60.1, 33.3, 14.5. MS (ESI) 264.5 ([M + H]$^+$).

(E)-Ethyl 3-(5-bromo-1-methyl-1H-indol-3-yl)acrylate (**3ha**):[18] light yellow crystals (215.2 mg, 70% yield); mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−8.00 (m, 1H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.37 (dd, *J* = 8.8 Hz, 2.0 Hz 1H), 7.31 (s, 1H), 7.19 (m, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.12 Hz, 2H), 3.79 (s, 3H), 1.37 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.3, 136.7, 136.1, 133.3, 127.0, 125.3, 122.7, 114.4, 112.8, 111.2, 111.1, 60.3, 33.6, 14.9. MS (ESI) 308.9 ([M + H]$^+$).

(E)-Ethyl 3-(1-methyl-5-nitro-1H-indol-3-yl)acrylate (**3ia**): yellow crystals (123.3 mg, 45% yield); mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.0 Hz, 1H), 8.21−8.16 (m,1H), 7.83 (d, *J* = 16.0 Hz, 1H), 7.47 (s, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.12 Hz, 2H), 3.88 (s, 3H), 1.37 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 142.1, 140.1, 135.4, 134.5, 124.9, 118.1, 117.0, 114.9, 113.9, 109.7, 60.5, 34.0, 14.9; HRMS (ESI) $C_{14}H_{14}N_2NaO_4$ ([M + Na]$^+$) calcd 297.0846, found 297.0859.

(E)-Ethyl 3-(1-benzyl-5-methoxy-1H-indol-3-yl)acrylate (**3ja**): white crystals (227.8 mg, 68% yield); mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.0 Hz, 1H), 7.35 (s, 1H), 7.33−7.25 (m, 4H), 7.19−7.07 (m, 3H), 6.89−6.83 (m, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.26 (s, 2H), 4.25 (q, *J* = 7.12 Hz, 2H), 3.88 (s, 3H), 1.34 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.6, 154.9, 137.5, 135.7, 132.2, 132.0, 128.5 (2C), 127.6, 126.5 (2C), 112.7, 112.0, 111.9, 111.0, 102.5, 102.4, 60.1, 56.1, 50.8, 14.9. HRMS (ESI) $C_{21}H_{21}NNaO_3$ ([M + Na]$^+$) calcd 358.1414, found 358.1409.

(E)-Ethyl 3-(5-chloro-1-ethyl-1H-indol-3-yl)acrylate (**3ka**): white crystals (183.1 mg, 66% yield); mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.6 Hz, 1H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.39 (s, 1H), 7.29−7.19 (m, 3H, including $CDCl_3$), 6.33 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.12 Hz, 2H), 4.15 (q, *J* = 7.28 Hz, 2H), 1.49 (t, *J* = 7.28 Hz, 3H), 1.35 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 136.9, 135.0, 131.8, 131.7, 126.7, 122.7, 119.9, 112.7, 111.5, 110.7, 60.3, 41.8, 15.6, 14.9; HRMS (ESI) $C_{15}H_{17}ClNO_2$ ([M + H]$^+$) calcd 278.0942, found 278.0933.

(E)-Ethyl 3-(5-bromo-1-ethyl-1H-indol-3-yl)acrylate (**3la**): yellow oil (218.9 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.6 Hz, 1H), 7.82 (d, *J* = 16.0 Hz, 1H), 7.42−7.32 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.28 Hz, 2H), 4.16 (q, *J* = 7.12 Hz, 2H), 1.50 (t, *J* = 7.28 Hz, 3H), 1.37 (t, *J* = 7.12 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.1, 136.5, 135.0, 131.3, 127.0, 125.0, 122.6, 114.0, 112.5, 111.1, 110.8, 60.0, 41.5, 15.3, 14.6; HRMS (ESI) $C_{15}H_{16}BrNaNO_2$ ([M + Na]$^+$) calcd 344.0257, found 344.0232.

(E)-Ethyl 3-(1,7-dimethyl-1H-indol-3-yl)acrylate (**3ma**): light yellow crystal (177.0 mg, 73% yield); mp 106−108 °C; ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 7.84 (d, J = 16.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.21 (s, 1H), 7.08 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 4.0 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 4.25 (q, J = 7.12 Hz, 2H), 4.04 (s, 3H), 2.75 (s, 3H), 1.34 (t, J = 7.12 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 137.6, 134.2, 127.2, 125.5, 121.8, 121.3, 118.4, 112.4, 111.6, 60.0, 37.4, 19.8, 14.6; HRMS (ESI) $C_{15}H_{17}NNaO_2$ ($[M + Na]^+$) calcd 266.1151, found 266.1151.

*(E)-Ethyl 3-(7-bromo-1-ethyl-1H-indol-3-yl)acrylate (**3na**):* white crystals (212.5 mg, 66% yield); mp 115−116 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87−7.79 [m, 2H, including 7.83 (d, J = 16.0 Hz, 1H)], 7.44−7.40 (m, 1H), 7.37 (s, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 4.60 (q, J = 7.16 Hz, 2H), 4.25 (q, J = 7.12 Hz, 2H), 1.49 (t, J = 7.16 Hz, 3H), 1.34 (t, J = 7.12 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.7, 136.6, 133.3, 129.6, 128.1, 122.0, 119.5, 113.6, 112.0, 104.1, 60.1, 43.9, 17.7, 14.6; HRMS (ESI) $C_{15}H_{17}BrNO_2$ ($[M + H]^+$) calcd 322.0437, found 322.0422.

*(E)-Butyl 3-(1-methyl-1H-indol-3-yl)acrylate (**3ab**):*[6c] yellow oil (185.0 mg, 72% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.83 [m, 2H, including 7.86 (d, J = 16.0 Hz, 1H)], 7.35−7.21 (m, 4H), 6.39 (d, J = 16.0 Hz, 1H), 4.20 (t, J = 6.6 Hz, 2H), 3.81 (s, 3H), 1.74−1.65 (m, 2H), 1.52−1.40 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2, 137.9, 137.7, 132.8, 122.8, 121.1, 120.5, 112.7, 112.1, 109.8, 64.0, 33.2, 31.1, 19.4, 13.9; MS (ESI) 258.6 ($[M + H]^+$).

*(E)-N,N-Diethyl-3-(1-methyl-1H-indol-3-yl)acrylamide (**3ac**):*[19] yellow oil (135.7 mg, 53% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 16.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.36−7.20 (m, 5H, including $CDCl_3$), 6.81 (d, J = 16.0 Hz, 1H), 3.80 (s, 1H), 3.58−3.45 (m, 4H), 1.31−1.22 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 137.9, 135.6, 132.2, 126.0, 120.7, 120.2, 118.9, 112.4, 109.8, 60.4, 58.4, 33.1, 18.5, 14.3; MS (ESI) 257.1 ($[M + H]^+$).

*(E)-Methyl 2-methyl-3-(1-methyl-1H-indol-3-yl)acrylate (**3ad**):* yellow oil (105.3 mg, 46% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.39−7.27 (m, 3H), 7.26−7.17 (m, 2H, including $CDCl_3$), 3.85 (s, 3H), 3.82 (s, 3H), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 136.4, 130.0, 128.3, 122.7, 121.8, 120.4, 118.9, 111.8, 109.4, 51.9, 33.4, 15.3; HRMS (ESI) $C_{14}H_{15}NNaO_2$ ($[M + Na]^+$) calcd 252.0995, found 252.0993.

*(E)-Butyl 2-methyl-3-(1-methyl-1H-indol-3-yl)acrylate (**3ae**):* yellow oil (111.1 mg, 41% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.38−7.27 (m, 3H), 7.25−7.18 (m, 2H, including $CDCl_3$), 4.22 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 2.18 (s, 3H), 1.79−1.66 (m, 2H), 1.53−1.42 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.4, 136.0, 129.7, 129.4, 128.0, 122.4, 121.9, 120.1, 118.7, 111.7, 109.2, 64.6, 33.6, 31.3, 19.8, 15.6, 14.3; HRMS (ESI) $C_{17}H_{22}NO_2$ ($[M + H]^+$) calcd 272.1645, found 272.1635.

Typical Procedure for Synthesis of Ethyl 3,3-Bis(1-methyl-1*H*-indol-3-yl)propionate (4aa).[8e] A mixture of the substrate *N*-methylindole (1.0 mmol, 131.2 mg, 1.0 equiv), ethyl acrylate (1.0 mmol, 100.1 mg, 1.0 equiv), MnO_2 (1.2 mmol, 104.3 mg, 1.2 equiv), $PdCl_2$ (0.08 mmol, 14.2 mg, 0.08 equiv), and silica gel (0.6 g) were placed in a screw-capped stainless-steel vessel, along with two stainless-steel balls (12 mm). Then, the vessel was placed in the mixer mill, and the contents were milled. At the end of the experiment, all of the reaction mixture was scratched off from the vessel and dissolved in ethyl acetate followed by washing with brine, and the organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (eluents: petroleum ether/ethyl acetate 18/1) to give the desired product **4aa** as white crystals (149.0 mg, 78% yield): mp 109−111 °C (lit. mp 113−115 °C);[8e] ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.23 (m, 2H), 7.19−7.15 (m, 2H), 7.04−7.00 (m, 2H), 6.85 (s, 1H), 5.09 (t, J = 7.6 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.70 (s, 6H), 3.15 (d, J = 7.6 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.2, 137.1 (2C), 126.9 (2C), 126.2 (2C), 121.3 (2C), 119.5 (2C), 118.5 (2C), 117.3 (2C), 109.0 (2C), 60.2, 41.6, 0.32.7, 30.8 (2C), 14.2; MS (ESI) 383.8 ($[M + H]^+$).

*Butyl 3,3-bis(1-methyl-1H-indol-3-yl)propionate (**4ab**):* white crystals (139.4 mg, 72% yield); mp 93−95 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.55 (m, 2H), 7.26−7.13 (m, 4H), 7.05−7.00 (m, 2H), 6.8 (s, 2H), 5.08 (t, J = 7.72 Hz, 1H), 3.95 (t, J = 6.6 Hz, 2H), 3.66 (s, 6H), 3.15 (d, J = 7.72 Hz, 2H), 1.47−1.38 (m, 2H), 1.21−1.11 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.6, 137.1 (2C), 127.0 (2C), 126.3 (2C), 121.3 (2C), 119.5 (2C), 118.5 (2C), 117.3 (2C), 109.0 (2C), 64.1, 41.7, 32.7, 30.9 (2C), 30.7, 19.1, 13.7; HRMS (ESI) $C_{25}H_{28}N_2NaO_2$ ($[M + Na]^+$) calcd 411.2043, found 411.2056.

*Ethyl 3,3-bis(1-benzyl-5-methoxy-1H-indol-3-yl)propionate (**4ja**):* white crystals (204.2 mg, 66% yield); mp 104−106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.20 (m, 6H), 7.07 (d, J = 8.8 Hz, 2H), 7.04−6.98 (m, 6H), 6.97 (s, 2H), 6.75 (dd, J = 8.8 Hz, 2.4 Hz, 2H), 5.21 (s, 4H), 5.01 (t, J = 7.6 Hz, 1H), 4.00 (q, J = 7.12 Hz, 2H), 3.70 (s, 6H), 3.16 (d, J = 7.6 Hz, 2H), 1.07 (t, J = 7.12 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.2, 153.5 (2C), 137.7 (2C), 132.2 (2C), 128.5 (4C), 127.3 (2C), 126.4 (2C), 126.3 (4C), 117.2 (2C), 111.7 (2C), 110.3 (2C), 101.9 (2C), 60.3, 55.9 (2C), 50.2 (2C), 41.1, 31.1, 14.2; HRMS (ESI) $C_{37}H_{36}N_2NaO_4$ ($[M + Na]^+$) calcd 595.2567, found 595.2577.

*Ethyl 3,3-bis(5-chloro-1-ethyl-1H-indol-3-yl)propionate (**4ka**):* white crystals (136.6 mg, 60% yield); mp 126−128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 2.0 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.11−7.05 (m, 2H), 6.95 (s, 2H), 4.94 (t, J = 7.6 Hz, 1H), 4.11−3.98 (m, 6H), 3.10 (d, J = 7.6 Hz, 2H), 1.39 (t, J = 7.2 Hz, 6H), 1.11 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.9, 134.6 (2C), 127.9 (2C), 125.8 (2C), 124.3 (2C), 121.6 (2C), 118.9 (2C), 116.5 (2C), 110.2 (2C), 60.4, 41.3, 41.1 (2C), 30.9, 15.6 (2C), 14.2; HRMS (ESI) $C_{25}H_{26}Cl_2N_2NaO_2$ ($[M + Na]^+$) calcd 479.1264, found 479.1240.

*Ethyl 3,3-bis(5-bromo-1-ethyl-1H-indol-3-yl)propionate (**4la**):* white crystals (192.1 mg, 63% yield); mp 89−91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 2.0 Hz, 2H), 7.25−7.21 (m, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.93 (s, 2H), 4.94 (t, J = 7.6 Hz, 1H), 4.17−3.94 (m, 6H), 3.10 (d, J = 7.6 Hz, 2H), 1.39 (t, J = 7.2 Hz, 6H), 1.12 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.9, 134.9 (2C), 128.6 (2C), 125.7 (2C), 124.1 (2C), 122.0 (2C), 116.4 (2C), 112.0 (2C), 110.7 (2C), 60.4, 41.3, 41.1 (2C), 30.8, 15.6 (2C), 14.2. HRMS (ESI) $C_{25}H_{26}Br_2N_2NaO_2$ ($[M + Na]^+$) calcd 567.0253, found 567.0252.

*Ethyl 3,3-bis(1,7-dimethyl-1H-indol-3-yl)propionate (**4ma**):* white crystals (130.3 mg, 67% yield); mp 126−127 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H), 6.92−6.81 (m, 4H), 6.70 (s, 2H), 5.00 (t, J = 7.72 Hz, 1H), 4.02 (q, J = 7.12 Hz, 2H), 3.94 (s, 6H), 3.08 (d, J = 7.72 Hz, 2H), 2.72 (s, 6H), 1.12 (t, J = 7.12 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.3, 135.8 (2C), 128.0 (2C), 124.0 (2C), 121.0 (2C), 118.8 (2C), 117.6 (2C), 116.9 (2C), 60.3, 41.5, 36.7 (2C), 30.4, 19.9 (2C), 14.3; HRMS (ESI) $C_{25}H_{28}N_2NaO_2$ ($[M + Na]^+$) calcd 411.2043, found 411.2050.

*Ethyl 3,3-bis(7-bromo-1-ethyl-1H-indol-3-yl)propionate (**4na**):* white crystals (179.3 mg, 66% yield); mp 89−91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.6 Hz, 1.2 Hz, 2H), 7.30 (dd, J = 7.6 Hz, 1.2 Hz, 2H), 6.87−6.80 (m, 4H), 5.00 (t, J = 7.6 Hz, 1H), 4.61−4.38 (m, 4H), 4.03 (q, J = 7.2 Hz, 2H), 3.09 (d, J = 7.6 Hz, 2H), 1.39 (t, J = 7.2 Hz, 6H), 1.12 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.9, 132.6 (2C), 130.4 (2C), 127.9 (2C), 126.7 (2C), 119.8 (2C), 118.7 (2C), 117.2 (2C), 103.5 (2C), 60.4, 43.1 (2C), 41.2, 30.5, 17.8 (2C), 14.3; HRMS (ESI) $C_{25}H_{26}Br_2N_2NaO_2$ ($[M + Na]^+$) calcd 567.0253, found 567.0277.

General Procedure for ESI(+)-MS Experiments for Reactions under HSBM Conditions. In a 50 mL screw-capped stainless-steel vessel were placed the reactants, forming a dark brown mixture after 30 s of grinding at 30 Hz. The sample was diluted with 2 mL of HPLC-grade methanol and filtered by an organic ultrafilter membrane (0.45 μm). The diluted solution was subjected to ESI-MS analysis. The injection speed of the diluted reaction solution was set at 5 μL/min.

General Procedure for ESI(+)-MS Experiments for Reactions in Solution. In a 20 mL reaction tube were placed the reactant (0.5 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), and solvent (2 mL), and the mixture was heated to 80 °C for 0.5 h. Then the mixture was diluted with 2 mL of HPLC-grade methanol and filtered by an organic

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ultrafilter membrane. The diluted solution was subjected to ESI-MS analysis. The injection speed of the diluted reaction solution was set at 5 μL/min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01138.

Detailed optimization of mechanochemistry parameters, calculation of *E* factors, spectra for ESI(+)-MS studies, HPLC chromatograms for **5a**, and ^{1}H and ^{13}C NMR spectra for **3** and **4** (PDF)

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Notes

The authors declare no competing financial interest.

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