# Selective 2,3’-Homodimerization of Indoles Using Mechanochemistry: A Convenient Synthesis 2,3’-Biindoles.

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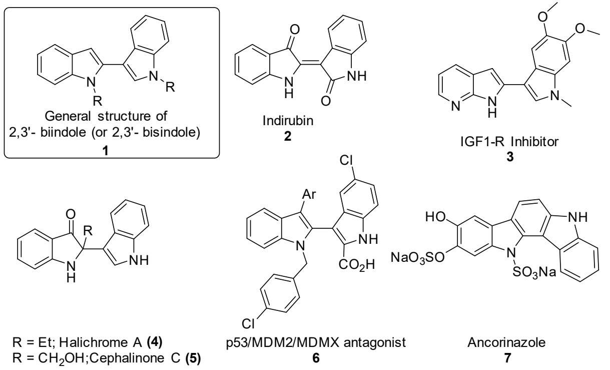
**Abstract:** 2,3-biindole (or 2,3-bisindole) is an important structural feature found in many biologically active synthetic and natural products. Though many excellent methods have been reported to achieve selective 2,3’ homodimerization of indole to produce 2,3-biindole compounds, most of them need strong co-oxidants and other additives to enable the reactions. In recent times, mechanochemistry is picking up as a promising sustainable environmentally-benign tool in modern organic chemistry. Because, mechanochemistry not only presents a fair deal to avoid the use of environmentally hazardous, unsafe, expensive large quantities of solvents (waste reduction), it is also found to accelerate reactions and even enable new chemical transformations. We herein report such greener, atom-economical, solvent-free and oxidant-free Pd-catalyzed 2,3’ homodimerization of two indolyl groups to furnish 2,3-biindole compounds in an environment-friendly fashion using Liquid Assisted Grinding (LAG) mechanochemical process.

## Introduction

Development of the sustainable chemical processes by discovering environmentally benign synthetic methodologies is the most important challenge to current researchers.[1] As highlighted by Anastas et al., some of the important aspects of “twelve principles of green chemistry” include waste prevention, atom economy, less hazardous synthesis, use of benign solvents and reagents, energy efficiency, etc.,.[1] Indeed, mechanochemistry fulfils majority of these green chemistry principles. Therefore, mechanochemistry[2-3] has been gaining tremendous attention of the modern organic chemists as a promising viable environmentally-friendly tool to develop sustainable organic chemical processes. Because, first of all, mechanochemistry uses green & cheaper mechanical force to accelerate or/and enable chemical transformations. Secondly, it not only allows us to avoid the use of environmentally hazardous and unsafe large quantities of solvents (major industrial waste) and other expensive additives, but it also adds several other benefits such faster reaction times, less energy usage, efficiency etc., thus fulfilling major principles of green chemistry principle[2-3] Biindole (or bisindole) is an important sub-class of Indole compounds that appears in several natural products and possess diverse biological properties.[4-7] Particularly, biindole moiety formed by direct 2,3′-linkage between two indole monomeric units, which are known as 2,3′-biindoles (or 2,3′-bisindoles), deserve a special place in the list of indole-containing heterocycles due to their historical importance and also due to their many biological activities (Figure 1).[5-7] For example, Indirubin (**2**) is an active ingredient in Chinese medicine used for various treatments like anti-cancer chronic myelocytic leukemia.[5] Other 2,3′-biindole-containing natural products, such as ancorinazole (**7**), Halichrome-A (**4**), and Cephalinone-C (**5**), are found to exhibit important biological properties.[6] Also, certain synthetic 2,3′-biindoles showed biological properties such as inhibition of protein–protein interaction of p53 and MDM2/X (**6**) (a promising non genotoxic anticancer target) and Insulin-like growth factor IGF1-R (**3**)(anticancer target).[7]

**Figure 1.** Representative examples of biologically active 2,3-biindole.



Due to such interesting properties and uses, a great amount of research has been done to develop various methods to construct selectively 2,3′-diindole moiety. It is important to note that the feasibility to extend the regular biaryl synthesis’ methods (like Suzuki, Ullman or Stille) to biindole synthesis is very low which is attributed to known poor stability nature of indoles halides, triflates, boronic acids, and corresponding metal species of the indole structure.[8] Alternatively, diindole scaffold is constructed via multi-step protocols involving constructions of indole rings from highly functionalized starting materials.[9] Therefore, direct C-C bond coupling of indole selectively to obtain 2,3′-biindole scaffold attracts a special attention. Accordingly, significant efforts have been made to achieve selective 2,3′-C-C bond formation between two indolyl groups to furnish 2,3′-biindole compounds. [10-12] They include i) homocoupling (homodimerization) of indoles by acid-catalysed dimerization accompanied by dehydrogenation,[10] ii) oxidative homodimerization of two indoles to obtain 2,3'-biindoles (such as NBS, $I_2$, $Na_2S_2O_4$, TEMPO etc., as strong oxidants),[11] and iii) metal(Pd, Cu, Co, Rh etc.,)-catalyzed homodierization in presence oxidants/additives {such as $Cu(OAc)_2$, $AgNO_3$, mCPBA, $K_4[Fe(CN)_6]$, AgOAc, AcOH etc}.[12] Though all of them present nice alternative methods to achieve selective homodimerization of two indolyl groups to furnish 2,3′-biindole compounds, they employ strong oxidants, additives or acids in large excess to enable the reactions (Scheme 1). Therefore, in continuation of efforts to adapt newer sustainable technologies,[13] we herein report a greener, atom-economical, solvent-free, oxidant-free, faster Pd-catalyzed 2,3'-homodimerization of two indolyl groups to furnish 2,3′-biindole compounds in an environment-friendly fashion using mechanochemistry (Scheme **1c**).

**Scheme 1.** Pd-catalyzed 2,3'-dimerization of indoles to obtain 2,3-biindole.

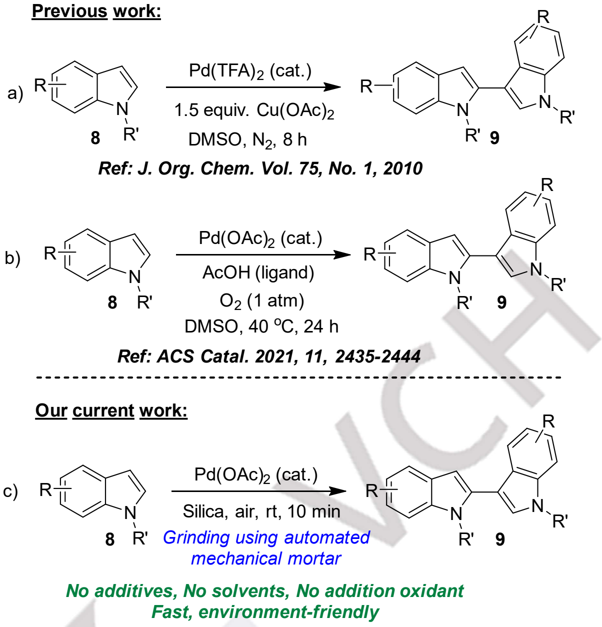
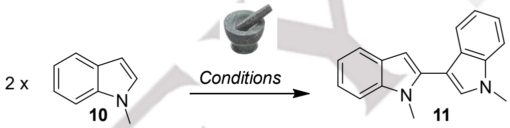


**Table-1:** Selected optimization reactions.[a,b]



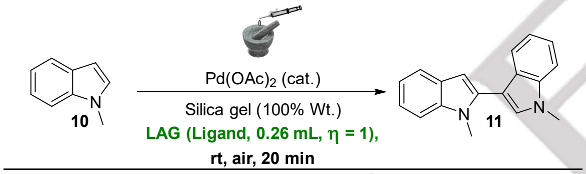
| Entry | Catalyst | Additive (Wt.%) | Grinding Time (Min.) | Conversion[a,b,c] (%) |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (5 mol%) | Silica gel (100%)/ $MnO_2$ (1.2 eq.) | 10 | 4 |
| 2 | $Pd(OAc)_2$ (5 mol%) | $MnO_2$ (1.2 eq.) | 10 | trace |
| 3 | $Pd(OAc)_2$ (5 mol%) | Silica gel (100%) | 10 | 6 |
| 4 | $Pd(OAc)_2$ (5 mol%) | -- | 10 | trace |
| 5 | $Pd(PPh_3)_4$ (5 mol%) | Silica gel (100%) | 10 | no reaction |
| 6 | $PdCl_2(PPh_3)_2$ (5 mol%) | Silica gel (100%) | 10 | no reaction |
| 7 | $PdCl_2$ (5 mol%) | Silica gel (100%) | 10 | no reaction |
| 8 | $Pd(TFA)_2$ (5 mol%) | Silica gel (100%) | 10 | no reaction |
| 9 | $Pd(OAc)_2$ (10 mol%) | Silica gel (100%) | 20 | 12 |
| 10 | $Pd(OAc)_2$ (10 mol%) | Neutral alumina (100%) | 20 | 8 |
| 11 | $Pd(OAc)_2$ (10 mol%) | Basic alumina (100%) | 20 | 5 |
| 12 | $Pd(OAc)_2$ (10 mol %) | celite (100) | 20 | 8 |
| 13 | $Cu(OAc)_2$ (10 mol %) | Silica gel (100%) | 20 | no reaction |
| 14 | $Cu(OTf)_2$ (10 mol %) | Silica gel (100%) | 20 | no reaction |
| 15 | $Pd(OAc)_2$ (20 mol%) | Silica gel (100%) | 20 | 18 |
| 16 | $Pd(OAc)_2$ (20 mol%) | Silica gel (200%) | 20 | 15 |
| 17 | $Pd(OAc)_2$ (20 mol%) | Silica gel (100%) | 20 (under $N_2$ atmosphere)[c] | trace |

a: Product formation was estimated by $^1H$ NMR analysis of crude reaction mixture by integrating relative ratios of **11** vs **10.**
b: Unreacted starting material (**10**) was intact and no other byproducts formed.
c: All other reactions were carried under air atmosphere except entry 17.

## Results and Discussion:

First, to evaluate our idea to enable the homodimerization of indole under mechanochemistry conditions, we subjected the N-Methyl indole (**10**) to various conditions under mechanochemical grinding. When we treated mixture of N-Methyl indole (**10**) and ($MnO_2$) absorbed on silica gel to mechanochemical grinding in the presence of $Pd(OAc)_2$ (cat.), we were pleased to see the selective 2,3'-dimerization though the conversion was very low (~4%) while most the unreacted starting material remained intact (entry 1). Then we studied other conditions. We observed even lower conversion (traces) when the mixture of N-Methyl indole (**10**) and ($MnO_2$) was subjected to Pd-catalyzed mechanochemical grinding (without silica gel) (entry 2). But, when the mixture of N-Methyl indole (**10**) and silica gel (without oxidant) was subjected to Pd-catalyzed mechanochemical grinding, formation selective 2,3'-dimerization product was observed with slightly improved conversion (~6%) (entry 3). Encouraged by these results, we examined various other conditions with different catalysts, loadings and solid support materials. Best result with 18% conversion was obtained when the mixture of N-Methyl indole (**10**), silica gel (100% wt%) was subjected to Pd-catalyzed mechanochemical grinding using 20 mol% $Pd(OAc)_2$ for 20 mins (entry 15).

**Table-2:** Liquid Assisted Grinding (LAG): screening of various liquid assistors (ligands).[a,b,c]

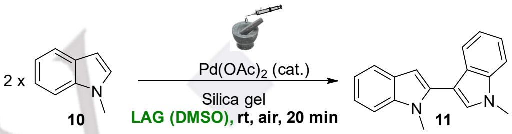


| Entry | Catalyst | Ligand (Liquid assistor) | Conversion[a,b,c] (%) |
|---|---|---|---|
| 1 | 10 mol % $Pd(OAc)_2$ | DMF | 24 |
| **2** | **10 mol % $Pd(OAc)_2$** | **DMSO** | **40** |
| 3 | 10 mol % $Pd(OAc)_2$ | DMC | 16 |
| 4 | 10 mol % $Pd(OAc)_2$ | Xylene | 25 |
| 5 | 10 mol % $Pd(OAc)_2$ | Anisole | 23 |
| 6 | 10 mol % $Pd(OAc)_2$ | *n*-BuOH | 35 |
| 7 | 10 mol % $Pd(OAc)_2$ | 2-MeTHF | 34 |
| 8 | 10 mol % $Pd(OAc)_2$ | 1-Heptanol | 28 |
| 9 | 10 mol % $Pd(OAc)_2$ | Glyceroll | 23 |
| 10 | 10 mol % $Pd(OAc)_2$ | AcOH | 15 |
| **11** | **20 mol % $Pd(OAc)_2$** | **DMSO** | **58** |

a: All the reactions were performed on 262 mg (2.0 mmol) scale of starting material. Accordinly eta (η) value was fixed at '1' by using 0.26 mL of DMSO.
b: Product formation was estimated by $^1H$ NMR analysis of crude reaction mixture by integrating relative ratios of **11** vs **10**).
c: Unreacted starting material (**10**) was intact and no other byproducts formed.

Then, with the aim to further improve conversions in this interesting Pd-catalyzed mechanochemical grinding for selective 2,3'-dimerization of N-Methyl indole (**10**), we turned our attention to a new optimization strategy recently being followed in mechanochemistry, known as the 'Liquid Assisted Grinding (LAG)[14] (Table 2). It is important to mention here that the Liquid-assisted grinding (LAG)[14] is the new advancement in mechanochemistry technology where the addition of a very minor amount of liquid (as liquid assistor or ligand) is used to accelerate or enable a mechanochemical solid-state reaction.[15] To validate the liquid-assisted grinding effect, we subjected the mixture of N-Methyl indole (**10**), 20 mol% $Pd(OAc)_2$ and silica gel (100% wt%) to open-air mechanochemical grinding in presence 0.26 mL [η (eta)= 1] of DMF as the liquids assistors for 20 mins and (entry 1) and found that conversion reasonably improved to 24% (entry 1, Table 2). Then, we screened different liquid assistors (LAG) keeping the *eta* value at constant (η = 1). We were delighted to observe that all the liquid assistors had a positive impact on the conversions. The best result with the significant improvement in the conversion (up to 40%, entry 2) was observed when 0.26 mL [η (eta)= 1] of DMSO was used as the liquid assistor. Conversion further improved to 58% when the same LAG was carried out using DMSO [η (eta)= 1] with 20 mol% $Pd(OAc)_2$ (entry 11, Table 2)

**Table-3:** Liquid Assisted Grinding (LAG): screening of various eta (η) value of DMSO (the best liquid assistor)[a,b,c]

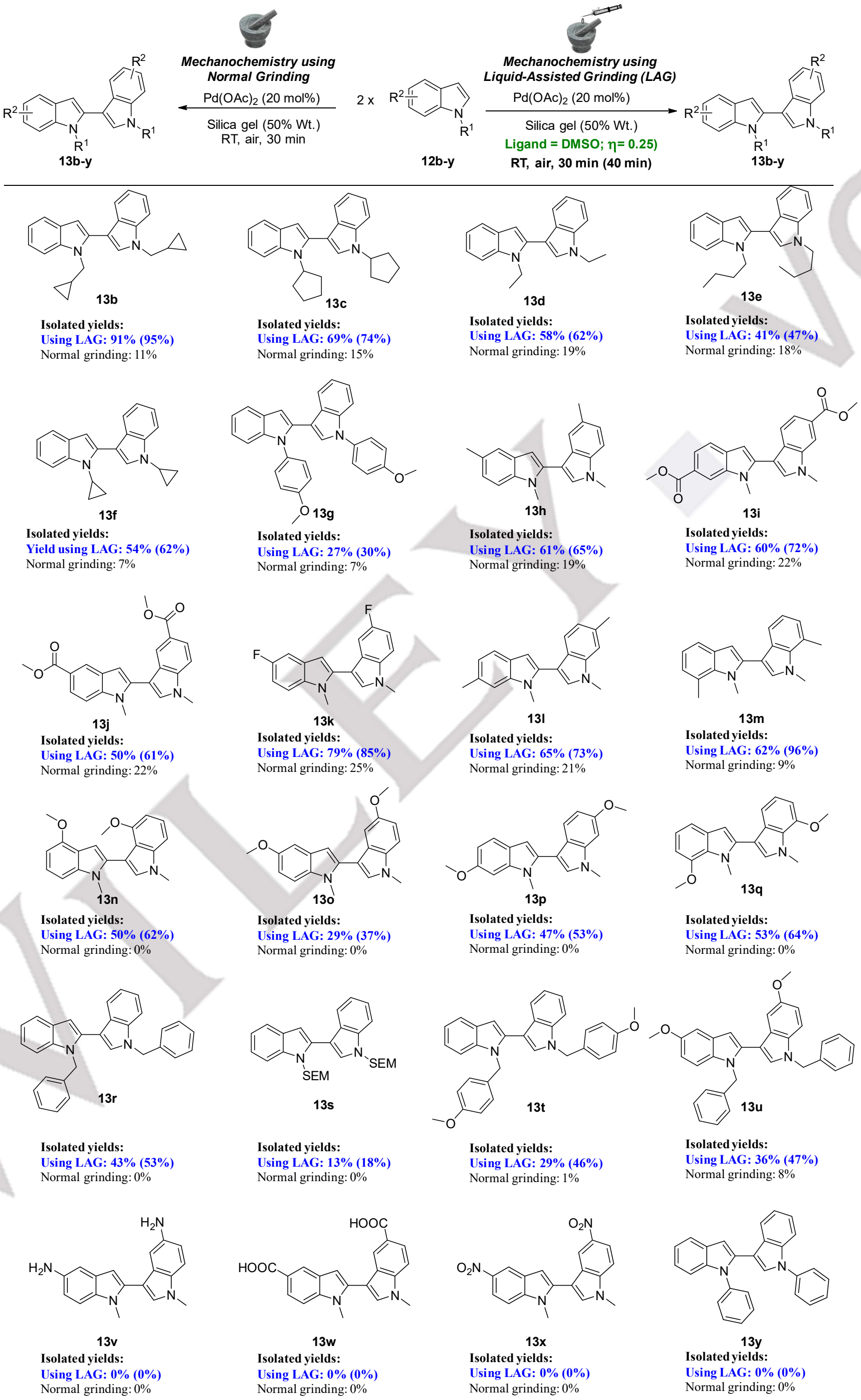


| Entry | Pd(OAc)2 (mol%) | Silica gel (Wt. %) | η (mL) | Conversion[a,b,c] (%) |
|---|---|---|---|---|
| 1 | 10 | 100 | 0 (0) | 12 |
| 2 | 10 | 100 | 1 (0.26) | 40 |
| 3 | 10 | 100 | 2 (0.52) | 24 |
| 4 | 10 | 100 | 0.5 (0.13) | 22 |
| 6 | 10 | 100 | 0.1 (0.026) | 18 |
| 7 | 10 | 0 | 1 (0.26) | 21 |
| 8 | 10 | 200 | 1(0.26) | 22 |
| 9 | 20 | 100 | 0 (0) | 18 |
| 10 | 20 | 100 | 1(0.26) | 58 |
| 11 | 20 | 100 | 0.5 (0.13) | 48 |
| 12 | 20 | 100 | 1.5 (0.39) | 39 |
| 13 | 20 | 100 | 2 (052) | 35 |
| 14 | 20 | 50 | 1 (0.26) | 45 |
| 15 | 20 | 50 | 0.75 (0.19) | 44 |
| 16 | 20 | 50 | 0.5 (0.13) | 67 |
| **17** | **20** | **50** | **0.25 (0.065)** | **71** |
| 18 | 20 | 50 | 0.1 (0.026) | 64 |
| 19 | 20 | 75 | 0.75 (0.19) | 42 |
| 20 | 20 | 75 | 0.25 (0.065) | 41 |
| **21** | **20** | **50** | **0.25 (0.065)** | **84** (t = 30 mins)[c] |
| **22** | **20** | **50** | **0.25 (0.065)** | **95** (t = 40 mins)[c] |
| 23 | 15 | 50 | 0.25 (0.065) | 50 |
| **24** | **25** | **50** | **0.25 (0.065)** | **73** |
| 25 | 5 | 50 | 0.25 (0.065) | 14 |
| 26 | 10 | 50 | 0.25 (0.065) | 22 |

a: All the reactions were performed on 262 mg (2.0 mmol) scale of starting material.
b: Product formation was estimated by $^1H$ NMR analysis of crude reaction mixture by integrating relative ratios of **11** vs **10**.
c: All reactions were carried out for 20 mins except entries 21 and 22

Intrigued by the power of liquid assistance in mechanochemistry, we have further taken up the study to evaluate impact of *eta* (η) value on conversions. As DMSO was found to be the best liquid assistor in this Pd-catalyzed LAG (liquid assisted Grinding), we subjected the mixture of N-Methyl indole (**10**) and silica gel (100% wt/wt) to Pd-catalyzed LAG using DMSO as the liquids assistor at various *eta* (η) value, catalyst loading and also silica gel loading (Table 3). We were pleased to see the significant improvement in the conversion at lower *eta* (η) value. The best result of 71% conversion was observed when Pd-catalyzed LAG was carried out on the mixture of N-Methyl indole (**10**) and

**Table-4:** Substrate scope of the methodology.



**13b**
Isolated yields:
Using LAG: 91% (95%)
Normal grinding: 11%

**13c**
Isolated yields:
Using LAG: 69% (74%)
Normal grinding: 15%

**13d**
Isolated yields:
Using LAG: 58% (62%)
Normal grinding: 19%

**13e**
Isolated yields:
Using LAG: 41% (47%)
Normal grinding: 18%

**13f**
Isolated yields:
Yield using LAG: 54% (62%)
Normal grinding: 7%

**13g**
Isolated yields:
Using LAG: 27% (30%)
Normal grinding: 7%

**13h**
Isolated yields:
Using LAG: 61% (65%)
Normal grinding: 19%

**13i**
Isolated yields:
Using LAG: 60% (72%)
Normal grinding: 22%

**13j**
Isolated yields:
Using LAG: 50% (61%)
Normal grinding: 22%

**13k**
Isolated yields:
Using LAG: 79% (85%)
Normal grinding: 25%

**13l**
Isolated yields:
Using LAG: 65% (73%)
Normal grinding: 21%

**13m**
Isolated yields:
Using LAG: 62% (96%)
Normal grinding: 9%

**13n**
Isolated yields:
Using LAG: 50% (62%)
Normal grinding: 0%

**13o**
Isolated yields:
Using LAG: 29% (37%)
Normal grinding: 0%

**13p**
Isolated yields:
Using LAG: 47% (53%)
Normal grinding: 0%

**13q**
Isolated yields:
Using LAG: 53% (64%)
Normal grinding: 0%

**13r**
Isolated yields:
Using LAG: 43% (53%)
Normal grinding: 0%

**13s**
Isolated yields:
Using LAG: 13% (18%)
Normal grinding: 0%

**13t**
Isolated yields:
Using LAG: 29% (46%)
Normal grinding: 1%

**13u**
Isolated yields:
Using LAG: 36% (47%)
Normal grinding: 8%

**13v**
Isolated yields:
Using LAG: 0% (0%)
Normal grinding: 0%

**13w**
Isolated yields:
Using LAG: 0% (0%)
Normal grinding: 0%

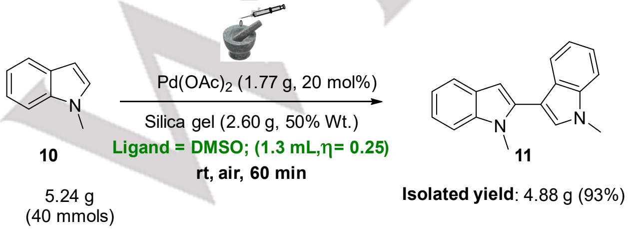
**13x**
Isolated yields:
Using LAG: 0% (0%)
Normal grinding: 0%

**13y**
Isolated yields:
Using LAG: 0% (0%)
Normal grinding: 0%

silica gel (50% wt%) with 0.065 mL [η = 0.25] DMSO (entry 17, Table 3). It is worthwhile to mention that *eta* (η) value was found to be dependent on silica gel loading. For example, when silica gel loading was taken at 100% wt/wt [w.r.t N-Methyl indole (**10**)], the best *eta* (η) value was found to 1.0 with 58% conversion (entry 10, Table 3). But, when silica gel loading was taken at 50% wt/wt [w.r.t N-Methyl indole (**10**)], the best *eta* (η) value was found to 0.25 with 71% conversion (entry 17, Table 3). When catalyst loading was further increased to 25 mol%, conversion was slightly improved to 73% (entry 24, Table 3). However, excellent conversions of 84% and 95% were obtained when the mixture of N-Methyl indole (**10**), 20 mol% Pd(OAc)$_2$, and silica gel (50% wt%) with 0.065 mL [η = 0.25] DMSO was subjected Liquid assisted Grinding for an extended time of 30 mins and 40 mins respectively (entries 21 & 22, Table 3).

Encouraged by these results and to prove the generality of our Pd-catalyzed LAG (liquid assisted Grinding) for the selective 2,3'-dimerization of N-Methyl indole (**10**) to provide 2,3'-bisindoles, we subjected various other indole derivatives (**12b-y**) to the standard Pd-catalyzed LAG conditions and summarized all the results in Table 4. For comparison, we have also subjected same set of the example to normal mechanochemical grinding (i.e., without using any liquid assistor) and summarized the results in the same table (Table 4). in the case of N-Alkyl indoles (**12b-f**), corresponding 2,3'-biindoles (**13b-f**) were isolated in moderate to excellent yields (45-91% with 30 mins grinding time and 62-95% with 40 mins grinding time). In the case of N-aryl (**13g**), reaction was found to be a bit slow with relatively lower isolated yield. We have also studied tolerance of substituents on phenyl ring of the indole group. As can be seen from the table-4, various groups of different nature (EWG, EDG, halogen, & methyl group) were well tolerated providing corresponding 2,3'-biindoles (**13h-q**) in good yields under the optimized Pd-catalyzed LAG conditions via the selective 2,3'-dimerization. We have studied some N-protecting groups (Bn, PMB, SEM) in this Pd-catalyzed LAG (liquid assisted Grinding) for selective 2,3'-dimerization of *N*-protected indoles and found that they were also well tolerated and provided corresponding *N*-protected 2.3'-biindoles (**13r-u**) in moderate yields. It is worth mentioning here that all the examples when subjected to normal Pd-catalyzed mechanochemical grinding, using optimized best condition, corresponding 2.3'-biindoles (**13b-y**) were isolated in very poor yields (0-25%). In many cases, there was no conversion at all under normal Pd-catalyzed mechanochemical grinding (**13n-s,** and **13v-y**).

**Scheme 2.** Scalability scope study



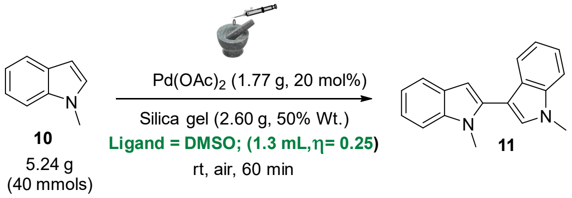
| Entry | Time (mins) | Conversion (%)$^{a,b}$ |
|---|---|---|
| 1 | 20 | 68% |
| 2 | 30 | 80% |
| 3 | 40 | 88% |
| 4 | 50 | 93% |
| 5 | 60 | 97% |

a: Product formation was estimated by $^1$H NMR analysis of crude reaction mixture by integrating relative ratios of **11** vs **10**.
b: Unreacted starting material (**10**) was intact and no other byproducts formed.

To understand the scalability of this environment-friendly Pd-catalyzed LAG (liquid Assisted Grinding) for selective 2,3'-homodimerization of indoles, we have subjected 5.24 g of N-Methyl indole (**10**) to the optimized Pd-catalyzed LAG and monitored conversions at various intervals (Scheme 2). We were pleased to find that the reaction went smoothly even on a large scale with complete conversion (97% conversion) at 60 mins. Column chromatography after 60 mins provided the pure 2,3'-biindoles in 93% (4.88 g) isolated yield (Scheme 2).

Next, we conducted a study on the recyclability of silica gel as well as Pd-catalyst (Scheme 3). Accordingly, a mixture of 5.24 g of N-Methyl indole (**10**), 2.62 g of silica gel and 1.77 g of Pd(OAc)$_2$ was subjected to the optimized liquid-assisted grinding for 60 mins (i.e., until the reaction reached complete conversion). We then washed the reaction mass thoroughly using 20% EtOAc in hexanes to extract all the product (monitored by TLC). While the filtrate yielded the desired product in 96% yield, the mass of solid residue recovered after filtration was quantitative.[16] Subsequently, we subjected another lot of N-Methyl indole (**10**) to the standard Pd-catalyzed LAG condition using the recovered black solid residue as-is [i.e., without adding additional silica gel or Pd(OAc)$_2$] (cycle-2). We repeated the same procedure for another run (cycle-3) and summarized all the results in Scheme 3. As shown in the Scheme 3, there was a gradual depletion in conversion which is presumably due to the formation of inactive Pd-black.[16,17]

**Scheme 3.** Study on the recyclability of silica gel as well as Pd-catalyst.

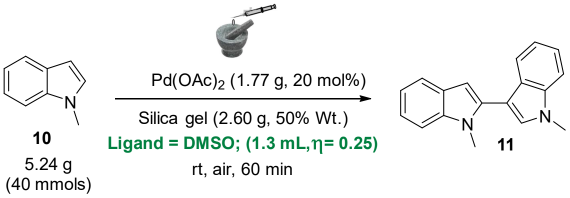


| Entry | Cycle$^a$ | Conversion (%)$^{b,c}$ |
|---|---|---|
| 1 | 1 | 96% |
| 2 | 2 | 39% |
| 3 | 3 | 10% |

a: After the first experiment (cycle 1), solid residue recovered after filtration was used in next consecutives cycles 2&3 without adding additional Silical gel and Pd(OAc)$_2$.
b: Product formation was estimated by $^1$H NMR analysis of crude reaction mixture by integrating relative ratios of **11** vs **10**.
c: Unreacted starting material (**10**) was intact and no other byproducts formed.

Subsequently, we investigated the recyclability of silica gel to primarily demonstrate the reduction of solid waste in the form of silica gel (Scheme 4). To this end, we subjected N-Methyl indole (10) to standard Pd-catalyzed LAG conditions. After cycle 1, the recovered solid residue was reused as-is in the next cycle using 20 mol% Pd(OAc)$_2$ (without adding additional silica gel). We were pleased to observe that the desired product formed in excellent yield. Encouraged by this, we repeated the recycling experiments for an additional four consecutive cycles (Scheme 4). We were delighted to find that there was no significant loss of conversion, even after 5 cycles. These successful recyclability experiments clearly demonstrate that silica gel can be recycled, further reducing solid waste (in the form of silica gel), making the process more environmentally friendly.

**Scheme 4.** Study on the recyclability of silica gel.



| Entry | Cycle[a] | Conversion (%)[b,c] |
|---|---|---|
| 1 | 1 | 96% |
| 2 | 2 | 93% |
| 3 | 3 | 92% |
| 4 | 4 | 91% |
| 5 | 5 | 91% |

a: After the first experiment (cycle 1), solid residue recovered after filtration was used in next consecutive cycles 2-5 without adding additional Silical gel.

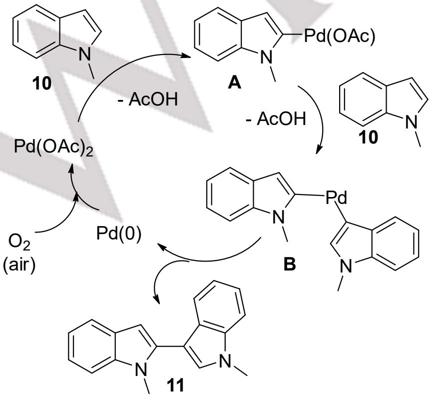
b: Product formation was estimated by $^1$H NMR analysis of crude reaction mixture by integrating relative ratios of **11** vs **10**.

c: Unreacted starting material (**10**) was intact and no other byproducts formed.

## Mechanism:

Based on our results and other known literature reports,[12a, 18-20] we propose that under our silica gel conditions, palladation first preferentially occurs at 2-position of the indole ring forming an intermediate **A**[21] (Scheme 5). Then, it reacts with another indole moiety in electrophilic addition manner forming 2.3'-diindolyl palladium species **B** as the second intermediate. Subsequently, **B** undergoes reductive elimination resulting in the formation of 2.3'-biindole derivative in a selective manner under environment-friendly Liquid Assisted Mechanochemistry conditions using $O_2$ from air (Scheme 5).

**Scheme 5.** Proposed Plausible Mechanism



## Conclusion:

In conclusion, we developed an atom-economical, solvent-free and oxidant-free mechanochemical Pd-catalyzed 2,3'-homodimerization of indoles furnishing 2,3′-biindole moiety in an environment-friendly fashion. During this study, we looked into various ways to improve yields in mechanochemical process, accordingly screened several conditions and finally developed an excellent example of Liquid Assisted Grinding (LAG) mechanochemical process to achieve complete conversion (~97%) in Pd-catalyzed 2,3'-homo dimerization of indoles. 2,3'-biindole (or 2,3'-bisindole) is an important structural feature found in many biologically active synthetic and natural products. And, most of known literature methods found to use strong co-oxidants and other additives for selective homo dimerization to produce 2,3'-biindole. But, our procedure demonstrates several advantages satisfying many of the 'sustainable green chemical processes principles" (such as, atom economical process - no by-products formation; avoidance chemical wastage - no solvent usage & recycling of Silica gel, no by-products; avoidance of hazardous reagents – no need of strong oxidants; less energy usage - fast reaction; usage of environmentally benign & cheaper materials – use of Silica gel, etc.,). We proposed a plausible mechanism via a 2.3'-diindolyl palladium species which undergoes reductive elimination resulting in the formation of 2.3'-biindole. We further demonstrated the scalability of the reaction by performing reaction on 5.24 g (40 mmols) scale producing 2,3'-biindole in 93% isolated yield. We strongly believe that this protocol will serve as a greener & sustainable chemical process of choice for future large-scale synthesis of useful 2,3'-biindoles.

## Experimental Section:

**1. Synthesis of N, N-dimethyl-2,3-biindole 11 (5.24 g scale)**[22]

In an oven-dried mortar, 1-alkyl-1H-indole (5.24 g, 40 mmol, 1.0 equiv.), Pd(OAc)2 (1.79 g, 8 mmol, 20 mol%), Silica gel (2.62 g, 50% wt. to Indole derivative) and DMSO (1.31 mL, η = 0.25) were taken and gently ground by pestle (using electric Agate Mortar Pestle). After 60 mins, additional silica gel was added to the resultant black reaction mixture (to make a free-flowing powder) and purified by column chromatography (0-40% EtOAc/Hexane) to afford the title compound (**11**) as white solid (5.08 g, 97% yield). MP: 85-90 ºC. 1H NMR (400 MHz, DMSO-d6): δ7.70 (dd, J = 8.0, 0.8 Hz, 1H), 7.64 (dd, J = 7.6, 0.8 Hz, 1H), 7.37 (t, J = 8.4 Hz, 2H), 7.32-7.28 (m, 1H), 7.24 – 7.15 (m, 4H), 6.612 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H). 13C{1H} NMR (100 MHz, DMSO-d6): δ 137.9, 136.9, 135.1, 128.4, 128.4, 127.7, 122.3, 121.0, 120.3, 120.2, 120.0, 119.5, 109.5, 109.4, 107.3, 101.3, 33.0, 31.0. MS (MM) m/z 261.1 [M+H] +. HRMS (ESI/Q-TOF) m/z: [M+H] + Calcd. for C18H17N2 261.1391; Found 261.1430.

**2. Procedure with recycled Silica gel and Pd(OAc)$_2$:**

In an oven-dried mortar, 1-alkyl-1H-indole (5.24 g, 40 mmol, 1.0 equiv.), Pd(OAc)$_2$ (1.79 g, 8 mmol, 20 mol%), Silica gel (2.62 g, 50% wt. to Indole derivative) and DMSO (1.31 mL, η = 0.25) were taken and gently ground by pestle (using electric Agate Mortar

Pestle). After 60 mins, the resultant black reaction mixture was washed thoroughly by filtration using 20% EtOAc in hexanes to extract the product (monitored by TLC). Filtrate provided the desired product in 96% yield (>95% purity) (Cycle 1). Collected solid residue was reused as-is in the next LAG on another lot of N-Methyl indole (**10**) without adding additional silica gel or Pd(OAc)2) (cycle-2). After 60 mins, $^1$H NMR analysis of the crude product extracted from the resultant black reaction mixture indicated 39% product while the unreacted starting material was intact. The same process was repeated for three consecutive cycles and recorded conversion each time using $^1$H NMR analysis of crude product extracted from the resultant black reaction mixture following a standard procedure.

**3. Procedure with recycled Silica gel:**

In an oven-dried mortar, 1-alkyl-1H-indole (5.24 g, 40 mmol, 1.0 equiv.), $Pd(OAc)_2$ (1.79 g, 8 mmol, 20 mol%), Silica gel (2.62 g, 50% wt. to Indole derivative) and DMSO (1.31 mL, $\eta$ = 0.25) were taken and gently ground by pestle (using electric Agate Mortar Pestle). After 60 mins, the resultant black reaction mixture was washed thoroughly by filtration using 20% EtOAc in hexanes to extract the product (monitored by TLC). Filtrate provided the desired product in 98% conversion ($^1$H NMR analysis of crude product extracted from resultant black reaction mixture following a standard procedure) (Cycle 1). Then, the collected solid residue was reused as-is in the next LAG on another lot of N-Methyl indole (10) and 20 mol% $Pd(OAc)_2$ (i.e., without adding additional silica gel) (cycle-2). The same process was repeated for five consecutive cycles, and the conversions were recorded each time using $^1$H NMR analysis of crude product extracted from the resultant black reaction mixture following a standard procedure.

## Supporting Information:

The authors have cited additional references within the Supporting Information.[22]

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## Conflict of Interests:

The authors declare no conflict of interest.

## Data Availability Statement:

The data that support the findings of this study are available in the supplementary material of this article

**Keywords:** Mechanochemistry. Liquid Assisted Grinding. 2,3'-Biindole (or 2,3'-Bisindole). Homodimerization. Solvent-free Pd-catalysis

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15. It is important to note that though mechanochemistry has been known to researchers since centuries, but it remained largely dormant or less explored until recently. Apart from lack of better equipment, this slow growth of mechanochemistry in the past can be attributed to the lack of understanding about the optimization techniques, i.e., how to optimize reactions to improve yields and selectivity by varying different reaction parameters. One such new parameter is the Liquid-assisted grinding (LAG)[13]. Liquid-assisted grinding (LAG) mechanochemistry is the new advancement of mechanochemistry technology where the addition of a very small amount of liquid is used to accelerate or enable a mechanochemical solid-state reaction.14-15 To validate the liquid-assisted grinding effect.
16. The recovered solid residue, which is a mixture of silica gel and Pd(OAc)$_2$, appeared black, presumably due to the formation of Pd-black. This is a known persistent problem in Pd(OAc)$_2$-catalyzed reactions, where Pd aggregates to form stable Pd-black, leading to a considerable loss of catalytic activity[21].
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19. Deprez et.al.,[20a] explained in their work that when a more electron-deficient Pd(II) catalyst (i.e., Pd(OAc)2) is used, palladation on indole ring would favour the formation 2-indole Pd(II) complex under acid conditions. This was further ascertained by Shi and co-workers[20b]. We believe that in our case where silica gel was used as solid binding for grinding created required acidic conditions and thus favouring first palladation at 2-position of the indole ring[21].
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21. It is worth mentioning here that Zunjun et.,[12a] suggested formation similar intermediate **A** in their work, but in a different path. They proposed that the palladation might first occur at C3-position of indoles which subsequently migrates to the 2-position to intermediate.
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## Entry for the Table of Contents

2,3-biindole (or 2,3-bisindole) is an important structural feature found in many biologically active synthetic and natural products. We herein report a greener, atom-economical, solvent-free, and oxidant-free Pd-catalyzed 2,3'homodimerization of two indolyl groups to furnish 2,3-biindole compounds in an environment-friendly fashion using Liquid Assisted Grinding (LAG) mechanochemical process.