

C–H activation of indoles for the sustainable synthesis of pharmaceuticals

ERASMUS DISSERTATION

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1 Introduction

In the last decade, new methods have been pursued for the synthesis of organic molecules. Reactions that can directly activate C–H bonds are promising to avoid long synthetic pathways with multiple wasteful reaction steps.^{1,2} Due to their importance in bio-active molecules such as pharmaceuticals, this work focuses on the coupling of indoles *via* C–H activation. This is a one-step approach with the simple, unfunctionalized indole as cheap reactant. In contrast, traditional methods such as the Suzuki coupling produce stoichiometric waste and require expensive pre-activated reagents.

The Pd-catalyzed C–H/C–H coupling of *N*-protected indoles is previously reported with Cu(II) and Ag(I) salts as the terminal oxidant.^{3,4} While this new method could decrease the number of steps, the reduced Cu(0) and Ag(0) is generated as stoichiometric metal waste. As a consequence, the reaction remains unsatisfactory for industrial applications from both an environmental and economic perspective.

This research focuses on the use of oxygen as a green alternative for the oxidation of the Pd-catalyst, which generates H₂O as an environmentally harmless side-product. The use of Pd-metal in the reaction is reduced from 5 at 1 mol%, which also renders the reaction more cost-efficient. The concentration of carboxylic acid ligand was crucial for the increase in activity. Furthermore, the influence of the electrophilicity of the Pd-catalyst on the reaction is investigated. A large effect on the regioselectivity of the reaction was found, which is very important in drug synthesis to minimize side-product formation. Alternatively, the reaction was shown to proceed with the unprotected indole as well, but with a lower catalytic activity.

2 Materials and methods

2.1 Materials

All chemicals were used as received from commercial suppliers: 1-methylindole, 1-acetylindole, indole, palladium(II)acetate (Acros Organics, 99.9%), palladium(II)benzoate (Strem Chemicals, 99%), palladium(II)pivalate (Strem Chemicals, 99%), DMSO, butyl acetate, propylene carbonate, acetone, mesitylene, ethyl acetate, acetonitrile, decane (Carl Roth, 99%), acetic acid glacial (Acros Organics, 99.7%), benzoic acid (Acros Organics, 99%), pivalic acid, 2-methylbenzoic acid, 3-methylbenzoic acid, 4-methylbenzoic acid, 2-hydroxybenzoic acid, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, 2-methoxybenzoic acid, 3-methoxybenzoic acid, 4-methoxybenzoic acid, 2-fluorobenzoic acid, 3-fluorobenzoic acid, 4-fluorobenzoic acid, 2-trifluoromethyl benzoic acid, 3-trifluoromethylbenzoic acid, 4-trifluoromethylbenzoic acid, 2-nitrobenzoic acid, 3-nitrobenzoic acid, 4-nitrobenzoic acid.

2.2 Experimental method

The reaction mixture is formed in a glass liner with 0.15 mmol of heteroaromatic reagent, 0.0015 mmol of Pd(OAc)₂, 0.10 mmol of decane as internal standard, a variable percentage of ligand and a solvent, in a total volume of 1 mL. The glass liner is loaded in a stainless steel autoclave equipped with a manometer. The air is flushed and pressurized with oxygen at 16 bar (in general). The reactor is heated at a certain temperature and with magnetic stirring at 500 rpm. After a general reaction time of 3 hours, the reactors are cooled down, the pressure is released and the glass liner is retrieved for sample preparation. A homogeneous sample is obtained with a syringe, which is consequently filtered using a disposable syringe filter (CHROMAFIL polytetrafluoroethylene, pore size 20 μm). In case non-volatile carboxylic acids are used (e.g. benzoic acid derivatives), N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) is added and sampling is performed after 30 minutes. The reaction products are analyzed *via* GC-FID for quantification and GC-MS for identification.

2.3 Analysis and characterization

2.3.1 Gas Chromatography - Flame Ionization Detector

The instrument is used for quantitative analyzing was a Shimadzu 2010 Gas Chromatograph and is equipped with an AOC-20c autosampler, Aoc-20i autoinjector and a CP-Sil 8 column. Flame Ionization Detector is based in the combustion of the different organic molecules that leave the column in the time, according to its boiling point and interaction with stationary phase.

2.3.2 Gas Chromatography – Mass Spectrometry Detector

For product identification, mass spectra were obtained *via* GC-MS (Agilent 6890 equipped with HP-5MS column and a 5973 MSD mass spectrometer with electron impact ionization). The molecules were identified according to its mass/charge ratio.

2.3.3 Data analysis

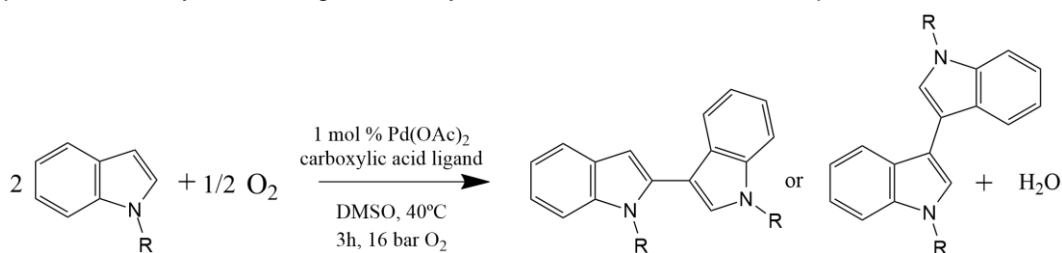
The area peaks allow for the calculation of the yield (%), conversion (%) and regioselectivity as main parameters for the evaluation of catalyst performance. With a calibration curve, the relative sensitivity of the products for the FID detector was determined in combination with decane as the internal standard.

3 Results and discussion

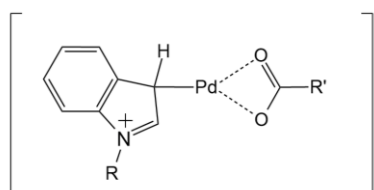
In this research, the palladium-catalyzed C–H/C–H coupling of indoles was investigated. Various general reaction conditions were tested, such as the acetic acid (AcOH) concentration, different solvents, H₂O and oxygen pressure. A large effect of AcOH on the catalyst performance was observed. Consequently, other carboxylic acid ligands were screened, such as pivalic acid and benzoic acid derivatives. To further optimize the reaction, the effect of electron-donating and -withdrawing substituents on the benzoic acid ligands was assessed. Finally, two other indole reactants (1-acetylindole and indole) were tested to expand the substrate scope of the reaction.

Under the general reaction conditions, palladium(II)acetate (Pd(OAc)₂) was used as the catalyst precursor in combination with an excess of carboxylic acid ligand (Scheme 1). The reaction was performed in dimethyl-sulfoxide (DMSO) at 40° C for 3 hours, and an excess of oxygen pressure (16 bar) was used.

With 1-methylindole as reactant, the 1,1'-dimethyl-2,3'-bisindole and 1,1'-dimethyl-3,3'-bisindole products were observed. It should be noted that 1,1'-dimethyl-2,2'-bisindole was not observed by GC analysis. The preferential formation of products coupled at the C3 position is explained by an electrophilic substitution, due to the stabilization of the positively charged intermediate on the nitrogen atom (Scheme 2). In this work, the regioselectivity of the reaction is defined as the ratio between 1,1'-dimethyl-2,3'-bisindole and 1,1'-dimethyl-3,3'-bisindole, in which the first regioisomer was observed as the majority product. Interestingly, in the two C–H activation steps of the reaction, the palladium catalyst has a high tendency to attack both the C2 and C3 position.



Scheme 1. Dimerization reaction activated by Pd(OAc)₂ with general conditions.



Scheme 2. Resonant form with largest contribution of the reaction of aromatic electrophilic substitution in the C3 atom.

3.1 General reaction conditions

First, the influence of AcOH concentration on the reaction was tested (Figure 1). In the absence of additional AcOH, only low yield of the 1,1'-dimethyl-2,3'-bisindole product was obtained. A clear optimum is observed for 75 mol% AcOH with a maximum yield of 46% and a regioselectivity of 11:1. However, a higher concentration of AcOH slows down the reaction rate. The large impact of the AcOH on the activity of the palladium-catalyst is explained by its role as a ligand. The acetate ligand might be directly involved in the C–H activation step, resulting in an overall increase in reaction rate. Alternatively, too high concentrations might saturate the catalyst and hinder its coordination to the indole reactant.

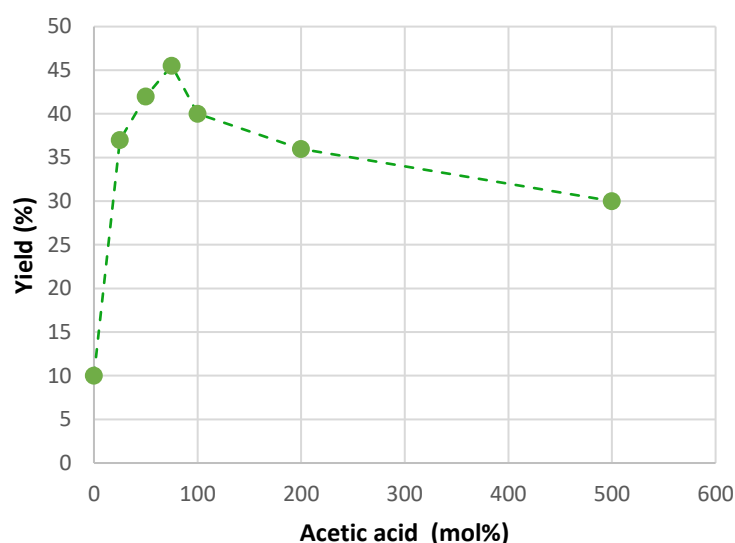


Figure 1. Influence of acetic acid concentration on the yield of 1,1'-dimethyl-2,3'-bisindole. Reaction conditions: Pd(OAc)₂ (1 mol%), AcOH (0-500 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 3 h.

Several solvents were tested as alternatives to DMSO: butyl acetate, propylene carbonate, acetone, mesitylene, ethylacetate and acetonitrile. In each case, less than 5% yield of the 1,1'-dimethyl-2,3'-bisindole product was observed. It was concluded that none of these solvents are comparable to DMSO in terms of reaction performance. This indicates that the coordination of DMSO to the catalyst is beneficial for the reaction. Furthermore, the influence of small quantities of H₂O on the reaction rate was investigated (Figure 2). Upon the addition of 50 to 100 mol% of H₂O, a decrease of up to one third of the original yield was observed. This shows that the coordination of H₂O also has a negative effect on the activity of the catalyst.

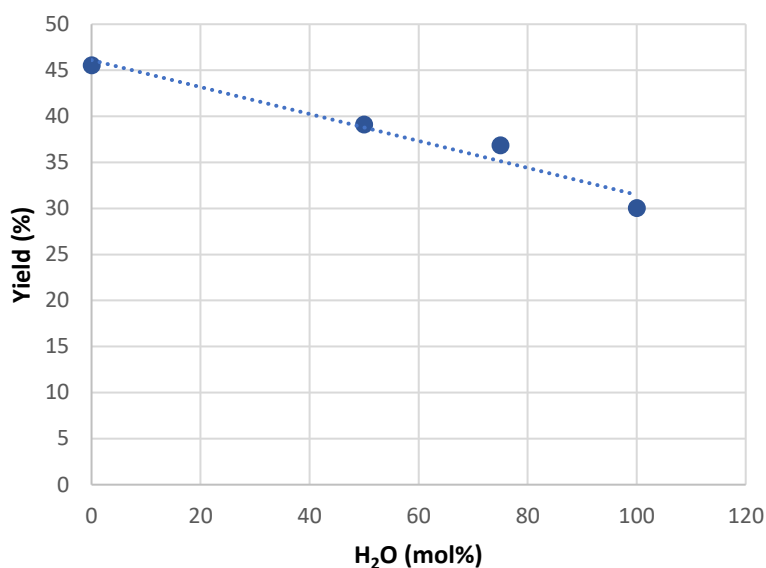


Figure 2. Influence of H₂O on the yield of 1,1'-dimethyl-2,3'-bisindole. Reaction conditions: Pd(OAc)₂ (1 mol%), AcOH (75 mol%), H₂O (50-100 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 3 h.

To investigate the kinetics of the reaction, a time profile was prepared (Figure 3). For the short reaction times from 30 min to 3 h, it shows a linear behaviour of 1,1'-dimethyl-2,3'-bisindole product formation. Initially, a high turnover frequency of the catalyst is observed. However, for longer reaction times a decrease in reaction rate is observed. After 22h, the reaction shows almost complete conversion and reaches a maximum of 88% yield. There are two effects that can explain the decrease in reaction rate. First, the reaction produces H₂O as a by-product. It was previously shown that H₂O has a negative influence on the reaction rate. Secondly, the reaction kinetics is expected to be dependent on the 1-methylindole concentration (at least first order or higher). The conversion of the 1-methylindole reactant results in a lower concentration during the course of the reaction, which slows down the overall rate.

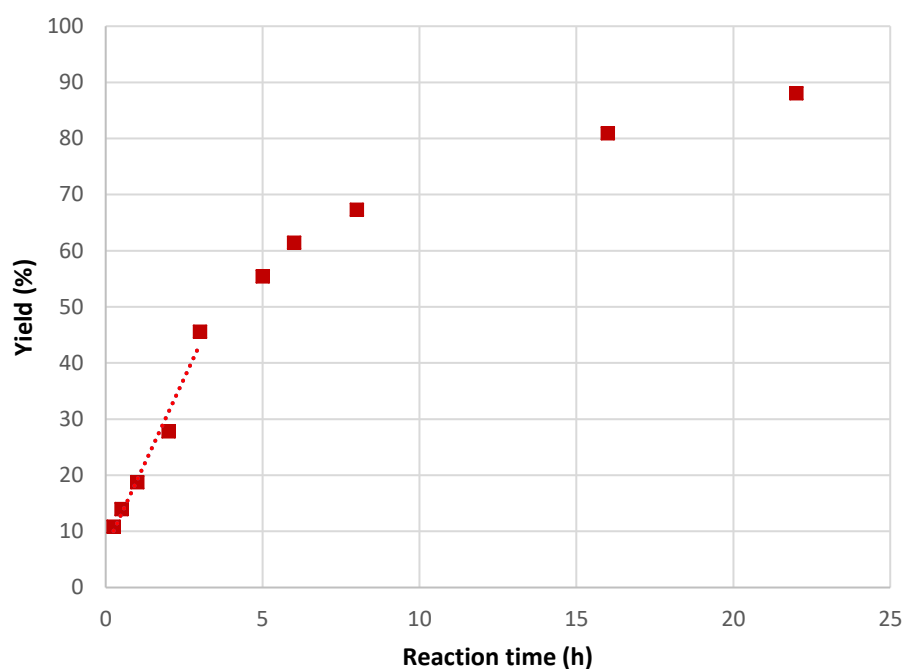


Figure 3. Time profile of the yield of 1,1'-dimethyl-2,3'-bisindole. Reaction conditions: Pd(OAc)₂ (1 mol%), AcOH (75 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 0.5-22 h.

Furthermore, the oxygen pressure was also decreased from 16 to 8 bar to evaluate its effect on the reaction rate (Figure 4). Only a small decrease from 46% to 41% yield was observed. This shows that high oxygen pressures (>8 bar) are not strictly necessary for the reaction, and that the reoxidation of Pd⁰ is not rate-limiting for the overall reaction rate. Nevertheless, a high pressure of 16 bar of O₂ was maintained in the following experiments, to exclude the influence of the reoxidation step on the reaction rate.

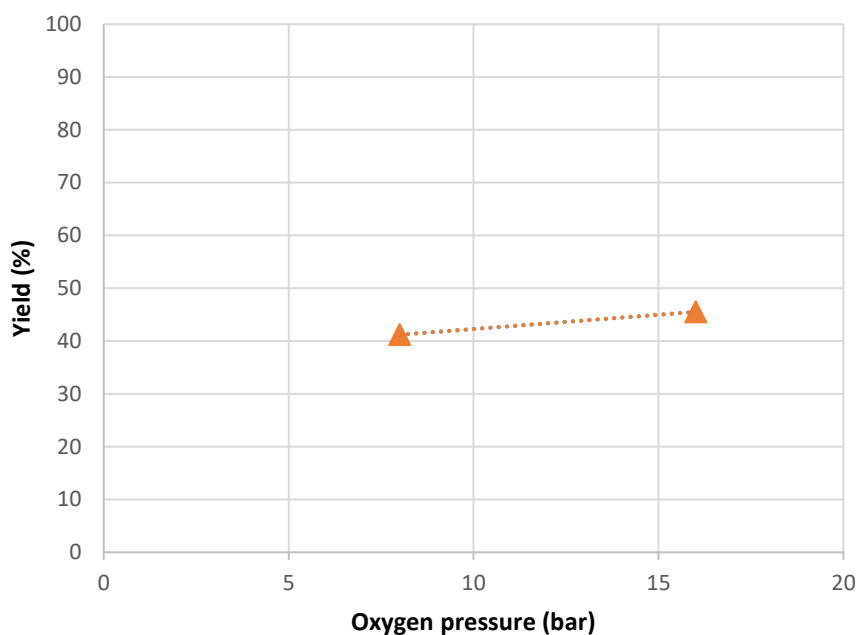


Figure 4. Effect of oxygen pressure on the yield of 1,1'-dimethyl-2,3'-bisindole. Reaction conditions: Pd(OAc)₂ (1 mol%), AcOH (75 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 8 or 16 bar O₂, 40° C, 3 h.

3.2 Screening of carboxylate ligands

In view of the interesting results obtained with acetic acid as ligand, other carboxylic acids, such as benzoic acid (BZA) and pivalic acid (PivOH), were used. The influence of its concentration on the reaction was tested (Figure 5). The shape of the curve of the BZA influence is similar to the AcOH concentration. A clear optimum is also observed for a concentration of 75 mol%, with a maximum yield of 42% 1,1'-dimethyl-2,3'-bisindole. This is slightly lower than the optimal yield for AcOH as a ligand. The regioselectivity also equals to 11:1. A decreased yield is also observed for the lower and higher concentrations of BZA. Again, this demonstrates the participation of BZA as a ligand in the catalytic cycle, most likely in the C–H activation step. Furthermore, concentrations higher than 75% might also saturate the catalyst. For PivOH as a ligand, a lower maximum yield of 30% was obtained with a regioselectivity of 8:1.

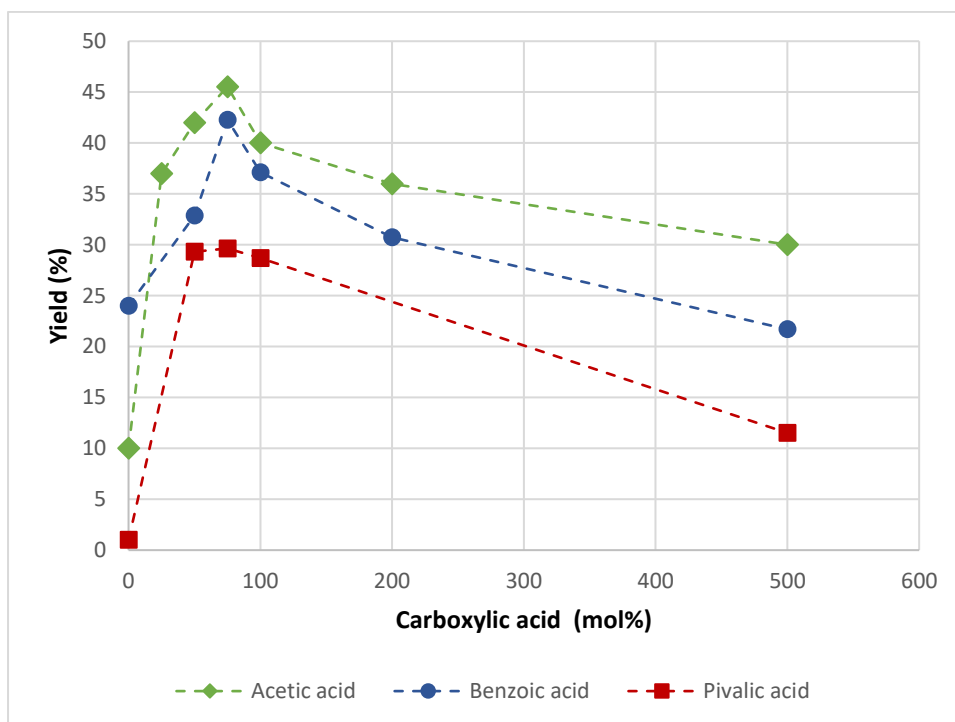


Figure 5. Influence of carboxylic acid concentration (acetic acid, benzoic acid and pivalic acid) on the yield of 1,1'-dimethyl-2,3'-bisindole. Reaction conditions: Pd(OAc)₂, Pd(benzoate)₂ or Pd(OPiv)₂ (1 mol%) without additional carboxylic acid ligand (0 mol%) or Pd(OAc)₂ (1 mol%) with AcOH, BZA or PivOH (50-500 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 3 h.

In both cases, the catalyst precursor Pd(OAc)₂ was also replaced by palladium(II)benzoate and palladium(II)pivalate with an additional 100 mol% of the respective ligand. The yields and regioselectivities with each catalyst precursor were compared for each ligand (Table 1). For the BZA those were almost the same, confirming the fast exchange of acetate for benzoate on the Pd-complexes due to the excess of the ligand and higher acidity of benzoic acid. However, for the PivOH those were very different. It was observed that Pd(OPiv)₂ is poorly soluble, which can explain these results.

	Yield (%)	
	Catalyst precursor: Pd(OAc) ₂	Catalyst precursor: Pd(BZA) ₂ or Pd(OPiv) ₂
+ 100 mol% BZA	37	39
+ 100 mol% PivOH	29	2

Table 1. Comparison of yields (%) of 1,1'-dimethyl-2,3'-bisindole for different catalyst precursor of Palladium. Reaction conditions: catalyst precursor (1 mol%), ligand (100 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 3 h.

Because the BZA ligand showed promising results, all regioisomers (*ortho*-, *meta*- and *para*-substituted) of trifluoromethyl benzoic acid, nitrobenzoic acid, fluorobenzoic acid, hydroxybenzoic acid, methoxybenzoic acid and methylbenzoic acid were tested (Table 2).

Ligand (75%)	Yield (%)	Regioselectivity*
<i>o</i>-trifluoromethylbenzoic acid	9.7	5
<i>m</i>-trifluoromethylbenzoic acid	19.8	22
<i>p</i>-trifluoromethylbenzoic acid	13.0	3
<i>o</i>-nitrobenzoic acid	5.0	1
<i>m</i>-nitrobenzoic acid	20.4	4
<i>p</i>-nitrobenzoic acid	11.3	3
<i>o</i>-fluorobenzoic acid	27.9	7
<i>m</i>-fluorobenzoic acid	30.0	10
<i>p</i>-fluorobenzoic acid	12.9	8
<i>o</i>-hydroxybenzoic acid	11.3	1
<i>m</i>-hydroxybenzoic acid	11.5	13
<i>p</i>-hydroxybenzoic acid	28.3	14
<i>o</i>-methoxybenzoic acid	27.7	26
<i>m</i>-methoxybenzoic acid	6.1	10
<i>p</i>-methoxybenzoic acid	38.7	14
<i>o</i>-methylbenzoic acid	28.0	10
<i>m</i>-methylbenzoic acid	31.0	14
<i>p</i>-methylbenzoic acid	37.8	13

Table 2. Influence of benzoic acid derivatives on the yield and regioselectivity of 1,1'-dimethyl-2,3'-bisindole. Reaction conditions: Pd(OAc)₂ (1 mol%), ligand (75 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 3 h. *Regioselectivity expressed as the ratio between 1,1'-dimethyl-2,3'-bisindole and 1,1'-dimethyl-3,3'-bisindole.

Neither of these ligands reached higher yields than BZA or AcOH. However, a strong influence on the regioselectivity is observed, which becomes clear from the *p*-isomers (Table 3). The selectivity for the 1,1'-dimethyl-2,3'-bisindole over the 1,1'-dimethyl-3,3'-bisindole is higher for the *p*-hydroxy-, *p*-methoxy- and *p*-methylbenzoic acid ligands. As indicated by their pK_a, these compounds are less acidic due to their electron-donating substituents. These give up electronic density to the ring, which makes the O–H bond stronger. Consequently, the palladium compounds formed with these ligands are less electrophilic, which does not promote the aromatic electrophilic substitution in the C3 of the 1-methylindole. Therefore a higher regioselectivity for the 1,1'-dimethyl-2,3'-bisindole over the 1,1'-dimethyl-3,3'-bisindole is found than for the BZA ligand. Moreover, the second product is formed to a larger extent with *p*-fluorobenzoic acid,

p-trifluoromethylbenzoic acid and *p*-nitrobenzoic acid. These electron-withdrawing substituents make the palladium compound more electrophilic, which assists the C3 substitution and results in a decrease in regioselectivity.

The *p*-methoxybenzoic acid and *p*-methylbenzoic acid emerged as promising ligands. Although the yields are slightly lower than BZA and AcOH, these ligands give better regioselectivity (14:1 and 13:1). Although the reaction rates are lower, it is expected that these ligands could result in a higher yield at full conversion, since a lower amount of side-products are formed.

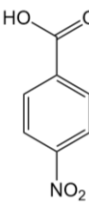
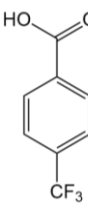
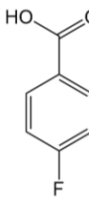
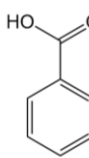
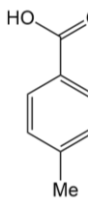
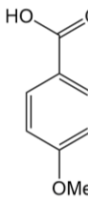
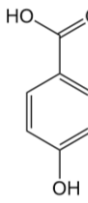
							
pK_a	3.4	3.7	4.1	4.2	4.4	4.5	4.6
Regioselectivity*	3	4	8	11	13	14	14
Yield (%)	11.3	13.0	12.9	42.3	37.8	38.7	28.3

Table 3. Influence of *p*-substituted BZA derivatives on the regioselectivity and yield of 1,1'-dimethyl-2,3'-bisindole. Reaction conditions: Pd(OAc)₂ (1 mol%), ligand (75 mol%), 1-methylindole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 3 h. *Regioselectivity expressed as between as 1,1'-dimethyl-2,3'-bisindole and 1,1'-dimethyl-3,3'-bisindole.

3.3 Expanding the substrate scope

To expand the substrate scope of the reaction, the reactant was changed to 1-acetylindole and indole. The methyl substituent was exchanged for the acetyl group, which is a protecting group that is more commonly used in organic synthesis, because the acetyl group is easily deprotected in H₂O under strong acidic conditions. In addition, the reaction was also tested in the absence of protecting group, which allows shorter reaction sequences without protection and deprotection steps.

The 1-acetylintole was tested with the general reaction conditions, both in the absence of ligand and in the presence of 75 mol% AcOH, BZA and PivOH. No coupling products were detected in the product mixture, even for reaction temperatures above 100° C. Moreover, degradation of the 1-acetylintole reactant was observed at a temperature higher than 100°C. Therefore, it was concluded that the stability of 1-acetylintole does not allow temperatures over 100°C in harsh aerobic conditions (16 bar O₂). Interestingly, reactions with indole resulted in coupling products, although in smaller yields than for 1-methylindole as the reactant. While the products were confirmed *via* GC-MS, the analysis has not been conclusive in identifying the exact regioisomer. Furthermore, it should be noted that the reported yields for the bisindole compound are still estimated yields, using the same calibration curve as the 1,1'-dimethyl-2,3'-bisindole. The three standard carboxylic acids (AcOH, BZA, PivOH) were also tested for this reaction (Figure 6). The BZA ligand was slightly better, with a maximum estimated yield of 7.5%. Furthermore, the results show that the presence of additional ligands is necessary for the reaction to proceed.

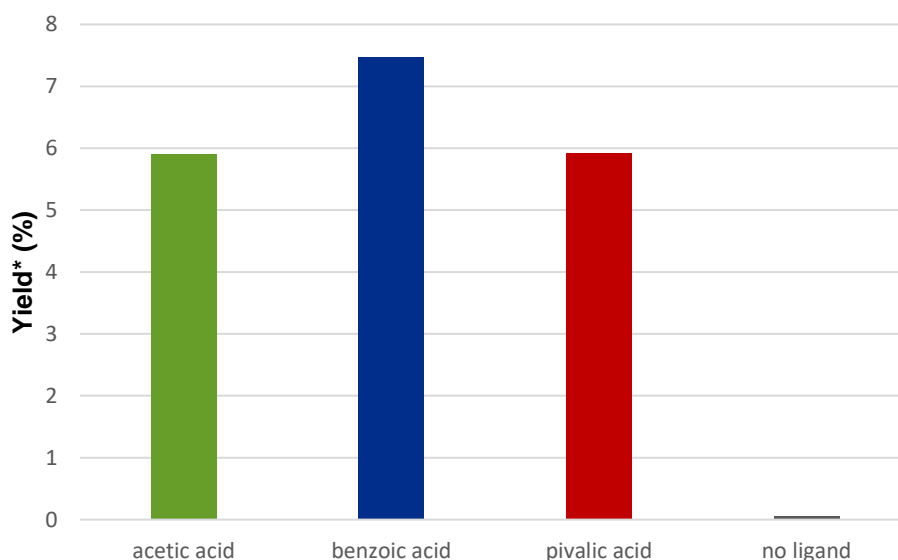


Figure 6. Influence of ligands in the indole coupling reaction. Reaction conditions: Pd(OAc)₂ (1 mol%), AcOH/BZA/PivOH/none (75 mol%), indole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40° C, 3 h. * Yield estimated with response factor of 1,1'-dimethyl-2,3'-bisindole.

To further optimize the yield, higher temperatures were tested (Figure 7) using BZA as ligand. A clear optimal temperature was found at 60°C, with an estimated yield of 11%. For higher temperatures, a strong decrease in the reaction rate was noticed, presumably to (aerobic) degradation of the indole reactant. Finally, the BZA ligand was also exchanged for other BZA derivatives (Table 4): *p*-trifluoromethyl benzoic acid, *p*-nitrobenzoic acid, *p*-fluorobenzoic acid, *p*-hydroxybenzoic acid, *p*-methoxybenzoic acid and *p*-methylbenzoic

acid. Only a slight decrease in reaction yield was found for the ligands bearing electron-donating groups (*p*-methylbenzoic acid, *p*-methoxybenzoic acid and *p*-hydroxybenzoic acid). However, a larger decrease in reaction rate was found for the ligands with electron-withdrawing substituents (*p*-trifluoromethylbenzoic acid, *p*-nitrobenzoic acid and *p*-fluorobenzoic acid).

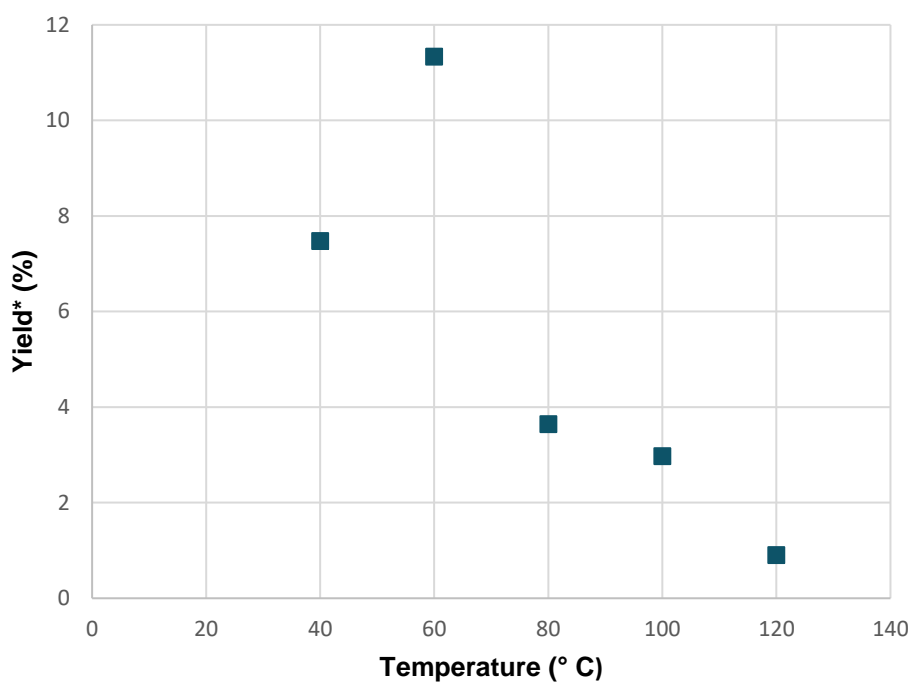


Figure 7. Influence of temperature in the indole coupling reaction. Reaction conditions: Pd(OAc)₂ (1 mol%), BZA (75 mol%), indole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 40-120° C, 3 h. * Yield estimated with response factor of 1,1'-dimethyl-2,3'-bisindole.

Ligand (75 mol%)	Yield* (%)
<i>p</i> -methylbenzoic acid	10.9
<i>p</i> -methoxybenzoic acid	9.6
<i>p</i> -hydroxybenzoic acid	9.0
<i>p</i> -nitrobenzoic acid	5.2
<i>p</i> -fluorobenzoic acid	2.0
<i>p</i> -trifluoromethylbenzoic acid	7.1
benzoic acid	11.0

Table 4. Influence of benzoic acid derivatives in the indole coupling reaction. Reaction conditions: Pd(OAc)₂ (1 mol%), ligand (75 mol%), indole (0.15 mmol), DMSO (1 mL), 16 bar O₂, 60° C, 3 h. * Yield estimated with response factor of 1,1'-dimethyl-2,3'-bisindole.

When comparing the reaction rates with the different indole derivatives, it becomes clear that the reactivity corresponds well with their electron density (Table 5). This indicates that the C–H activation occurs *via* an electrophilic substitution. In the first case, the methyl-group is an electron-donating substituent, and therefore increases the electronic density of the heteroaromatic ring. This stabilizes the positively charged intermediate, which explains why 1-methylindole obtains the best yields under mild reaction conditions. On the other hand, a lower yield of the indole without substituent was obtained, for a slightly higher temperature. Finally, the 1-acetylindole has an electron-withdrawing substituent, which results in the destabilization of the positively charged intermediate. This explains why the reaction was not successful, even at higher temperatures.

	Reaction rate* (mmol/h)	Temperature (°C)
	0.0115	40
	0.00275	60
	0	< 100

Table 5. Comparison of the best results for each indole reagent. Reaction conditions: Pd(OAc)₂ (1 mol%), AcOH and BZA (75 mol%), indole compound (0.15 mmol), DMSO (1 mL), 16 bar O₂, 3 h. * Reaction rate calculated with estimated yield (response factor of 1,1'-dimethyl-2,3'-bisindole).

4 Conclusion

In this work, the Pd-catalyzed C–H/C–H coupling of indoles was demonstrated with oxygen as the oxidant, resulting in a sustainable reaction with H₂O as the only stoichiometric by-product. The asymmetric 1,1'-methyl-2,3'-bisindole coupling product was obtained in 88% yield at a low temperature of 40°C. The catalytic activity was increased, allowing a decrease in Pd-loading from 5 to 1 mol% compared to the state-of-the-art. Furthermore, it was shown that the regioselectivity of the reaction can be influenced by changing the electronic properties of the carboxylate ligand. A decrease in reactivity was observed for indole substrates with lower electron density (indole and 1-acetylindole), which indicates that the reaction occurs *via* an electrophilic attack of the Pd-catalyst.

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