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Structure Ligation Relationship of Amino Acids for the Selective Indole C-H Arylation Reaction: L-Aspartic acid as Sustainable Alternative of Phosphines Ligands

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Abstract: The **S**tructure **L**igation **R**elationship (SLR) of free amino acids (AAs) under Pd-catalysis were examined for the chemo- and regio-selective indole C–H arylation reactions. While the majority of AAs were minor or ineffective, the L-aspartic acid (L-Asp) stands out promising to deliver high-value C3–arylated indoles with excellent chemo- (C vs N) and regioselectivity (C3 vs C2) with high functional group tolerance. Thus, the protocol offers a cost-effective and sustainable alternative of phosphine-based ligands for the indole C3-H arylation reactions. Preliminary mechanistic investigations suggested the simultaneous involvement of $-NH_2$, $\alpha-CO_2H$, and $\beta-CO_2H$ functionalities of L-Asp and found critical for its ligation efficiency. The developed catalytic system was compatible with the tandem decarboxylation/arylation procedure for the chemoselective synthesis of 3-aryl indoles.

Keywords: Amino Acids; Structure ligation relationship; Indole C-H arylation; Palladium; Phosphine free

It has been known that amino acid (AA) coordination around a Pd affects its reactivity and selectivity in the elementary reactions and thereof resulting Pd-complexes are capable of interacting with, cleaving, and mediating the functionalization of C–H bonds differently.[1] Thus, the development of AA as a ligand, particularly mono-N-protected amino acid (MPAA), to promote and control C-H functionalization reactions is now a forefront exercise.[2] Despite this notable progress, the utilization of free-AA as a ligand for the direct and selective C–H arylation reactions are still in infancy.[3]

Indoles constitute an important building block of pharmaceuticals (including natural products), agrochemicals, and functional materials.[4] Consequently, the synthetic design and development of new reactions for its functionalizations is an essential concern.[5] In this context, direct arylation of

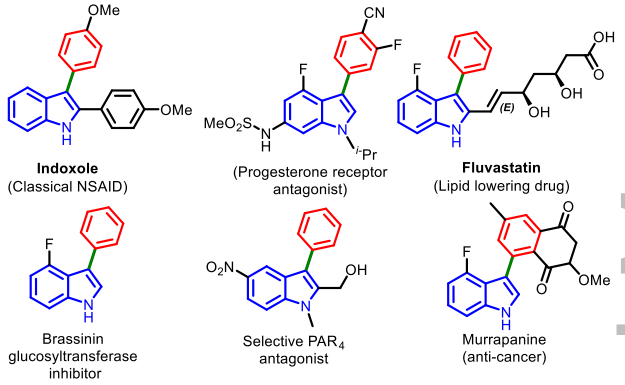

Figure 1. Representative examples of bioactive C-aryl indoles

indole is a valuable strategy for the synthesis of high-value C3-arylated indoles. Such manipulations are typically achieved under transition-metal, particularly palladium catalysis[6] (Scheme 1). However, these reactions offer competing reaction pathways resulting in multiple products, thus possess a significant challenge. Transition-metal-free protocols[7] were attempted; however, the need for highly reactive arylating agents such as hypervalent iodine reagents and diazonium salts, poor yields in case of C2-substituted indoles, and low regioselectivity due to benzyne-like intermediates limit their synthetic utility and applications. In a recent study, Chloé Thieuleux and Jérôme Canivet highlighted the use of sterically hindered, non-nucleophilic lithium bis(trimethylsilyl)amide (LiHMDS) as a base and directing group in controlling the C3-selectivity during the direct arylation of indole under Pd-catalysis.[8] Although it offers exceptional selectivity, the use of highly toxic and inflammable LiHMDS,

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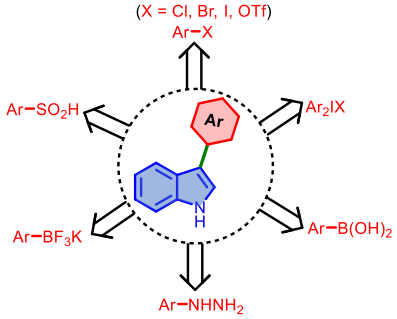
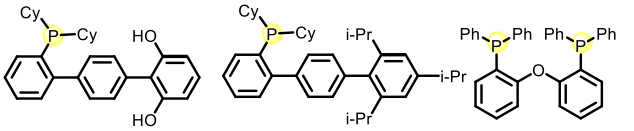
the requirement of globe box, and inconsistent yields are the major drawbacks.

Reported synthetic strategies for the indole C3-H arylation



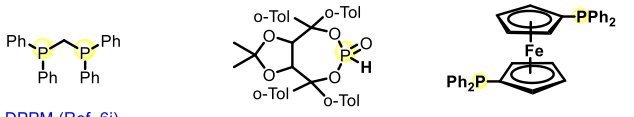
Reported phosphine ligands for the synthesis of 3-aryl indoles



Cy-DTHP (Ref. 6a)
Limitations
Multistep synthesis of ligand
3 molar equiv of base
Use of additive (HBF_4)
Poor yield in 2-Me-indole
Phosphine toxicity

XPhos (Ref. 6b)
Limitations
High cost of ligand
($ 645, 25 g)
Specialized substrates
Phosphine toxicity

DPEPhos (Ref. 6e)
Limitations
High cost
($ 136, 25 g)
High temp (140 °C)
Additional oxidant
Poor substrate scope
Phosphine toxicity

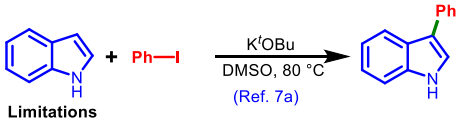


DPPM (Ref. 6i)
Limitations
High cost ($ 172, 25 g)
Poor selectivity
Poor functional grp. tolerance
Relatively high temperature
Phosphine toxicity

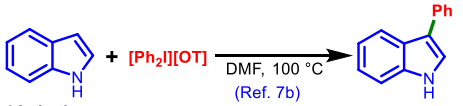
HASPO (Ref. 6j)
Limitations
Multistep synthesis of ligand
Moderate yields
Poor functional grp. tolerance
Phosphine toxicity

DPPF (Ref. 6x)
Limitations
High cost of ligand
($ 408, 25 g)
Poor selectivity
Phosphine toxicity

Reported metal-free indole C3-H arylation protocol

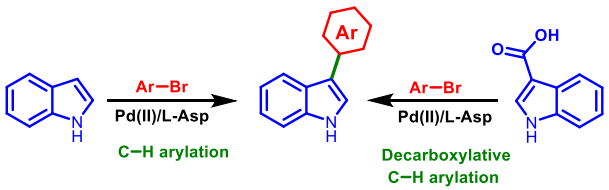


Limitations
Requirement of glove box; Degassing of solvent via freeze-pump-thaw; Relatively poor selectivity (C vs N), Relatively poor yields and fuctional group tolerance



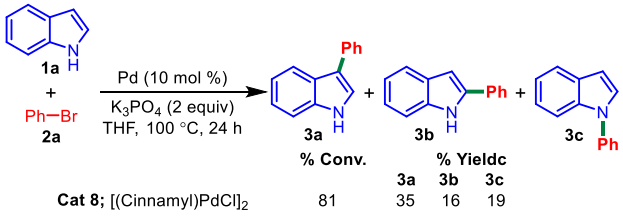
Limitations
Prepartion of arylating reagents; Requirement of glove box; Additional purification and drying of solvent; Relatively poor selectivity (C vs N), Relatively poor yields and fuctional group tolerance

Present work: L-Asp as potential alternative of phosphines



- **Use of L-Aspartic acid as ligand ($ 145 for 500 g)**
- No requirement of glove box
- No additional purification/drying of solvent
- Excellent selectivity (C3 vs C2; C vs N)
- Excellent functional group (-F, -Cl, $-CF_3$, $-NO_2$, -Me, -OMe, $-OCH_2O-$, Bn, $-CH_2Br$) tolerance
- Superior yields

Scheme 1. Reported indole C^3–H-arylation protocol, employed various phosphine ligands, and the present work



	% Conv.	% Yieldc		
		3a	3b	3c
Cat 8; [(Cinnamyl)PdCl]$_2$	81	35	16	19

Tested Pd Sources

Cat 1; $Pd(PPh_3)_4$, **Cat 2;** $Pd(dba)_2$, **Cat 3;** $PdCl_2$, **Cat 4;** $Pd(OAc)_2$, **Cat 5;** $Pd(TFA)_2$, **Cat 6;** $Pd(PPh_3)_2Cl_2$, **Cat 7;** [PdCl(allyl)]$_2$, **Cat 8;** [(cinnamyl)PdCl]$_2$

$Pd(dba)_2$, Bis(dibenzylideneacetone)palladium(0); $Pd(TFA)_2$, Palladium(II) trifluoroacetate; [(cinnamyl)PdCl]$_2$, Palladium(1-phenylallyl)chloride dimer

NOTE: For dimeric Pd-complexes (**Cat 7** and **Cat 8**), 10 mol% Pd corresponds to 5 mol% of Pd-complex (catalyst)

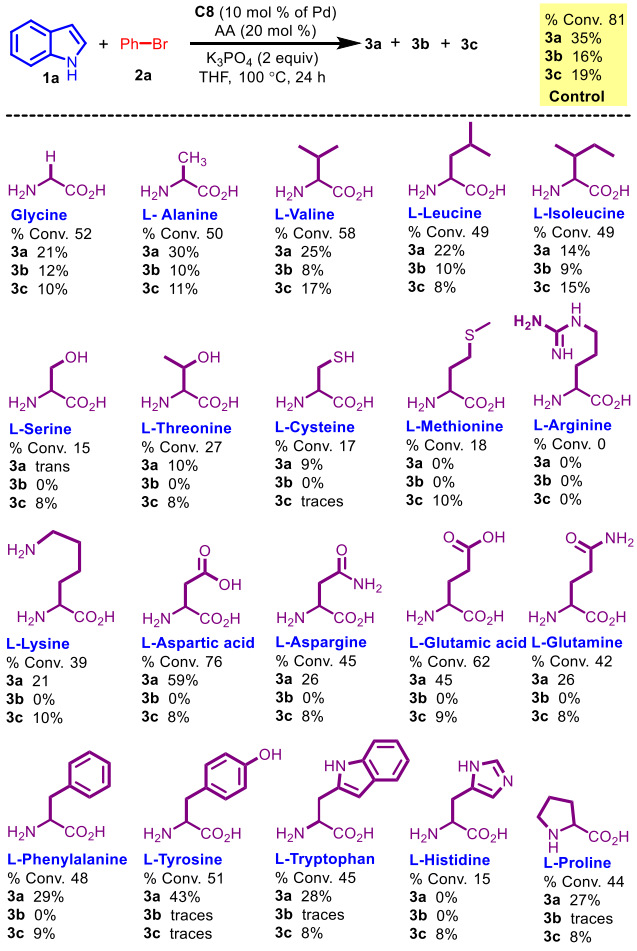
Scheme 2. Optimal Pd-source for the direct C-H arylation of (NH)-indoles

Great advancement has been achieved in this area employing ligands to tune the reactivity and selectivity, however, the use of phosphines remains the major limitations (Scheme 1). In this context, the introduction of sustainability is an ongoing demand and invites worldwide scientific quest to uncover and develop a sustainable alternative of phosphines for indole C-H arylation reactions.[9] In this context, the present work describes the general **S**tructure **L**igation **R**elationship (**SLR**) of free AAs for the chemo- and regio-selective indole C–H arylation reaction under Pd-catalysis and reported L-aspartic acid (L-Asp) as a sustainable alternative of phosphines for the indole C3-H arylation with excellent chemo- and regiocontrol and wide range of functional groups tolerance.

The study began with evaluating different Pd-salts (complexes) to discover the most active Pd-source for the arylation of indole in the absence of additional ligand. Treatment of (NH)-indole **1a** with bromobenzene **2a** in THF under the basic condition in presence of different Pd-catalysts resulted in the identification of [(cinnamyl)PdCl]$_2$ (**Cat 8**) as the most active catalyst with the formation of **3a** (35%), **3b** (16%), and **3c** (19%) (Scheme 2 and ESI). The relative catalytic efficiency of different active Pd-catalysts was [(cinnamyl)PdCl]$_2$ > $Pd(OAc)_2$ > $PdCl_2$ > $Pd(TFA)_2$ ≈ [PdCl(allyl)]$_2$. No products (**3a**/**3b**/**3c**) formation was observed in the case of $Pd(PPh_3)_4$, $Pd(dba)_2$, and $Pd(PPh_3)_2Cl_2$ (**1a** was found intact) (Scheme 2 and ESI).

With the identified optimal Pd-source, the ligation efficiency of naturally occurring free AAs for the C–H arylation of indoles were examined next. The model reactions involving **1a** and **2a** in the presence of **Cat 8** were performed but with AA present (Scheme 3). While the complete shutdown of the reaction was observed in case of L-Arg, in most cases, AAs (L-Gly, L-Ala, L-Val, L-Leu, L-Iso, L- Ser, L-

Thr, L-Cys, L-Met, L-Lys, L-Gln, L-Asn, L-His, L-Phe, L-Tyr, L-Trp, L-Pro) inhibit the reactions to a variable degree with an improvement in the selectivity compared to control (AA free condition using **C8** as Pd-precursor). Out of promising AAs (L-Glu and L-Asp), the L-Asp



1a (0.2 mmol) was treated with **2a** (0.3 mmol, 1.5 equiv) in presence of Pd-catalyst **C8** (10 mol %) and different AA (20 mol %) in THF at 100 °C for 24 h. %Conversion based on ^{1}H NMR. %Yield represent isolated and purified yield.

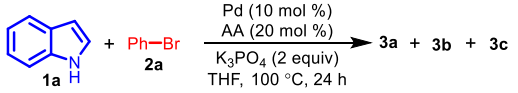
Scheme 3. Evaluation of Free AAs as the ligand for the selective C–H arylation of indoles under Pd-catalysis.

stands out best resulting in 76% conversion with a 59% isolated yield of **3a**. No C2-arylation (**3b**) was observed, however, traces of *N*- arylation (**3c**) were formed (Scheme 3). To be noted, in some cases, degradation of starting **1a** (oxidation to indoline-2,3-dione) was observed (^{1}H NMR).

This unprecedented but highly selective reaction in presence of L-Asp excited us to investigate and explore their ligation property further. First, we validated this observation with other active Pd-precursors (of Scheme 2) such as $PdCl_2$ and $Pd(OAc)_2$ with most effective AA (L-Asp), moderately active AA (L-Ala), poorly active AA ligand (L-Met), and non-active AA (L–Arg) ligands. A similar trend was observed, suggesting the free AAs, in general, inhibit the catalytic activity of Pd (to a variable degree) during the reaction of **1a** with **2a**, the L-Asp being the optimal resulting the superior yield and selectivity (Table 1). Further studies revealed a 1:1 relative ratio of Pd(II) and L-Asp is optimal.

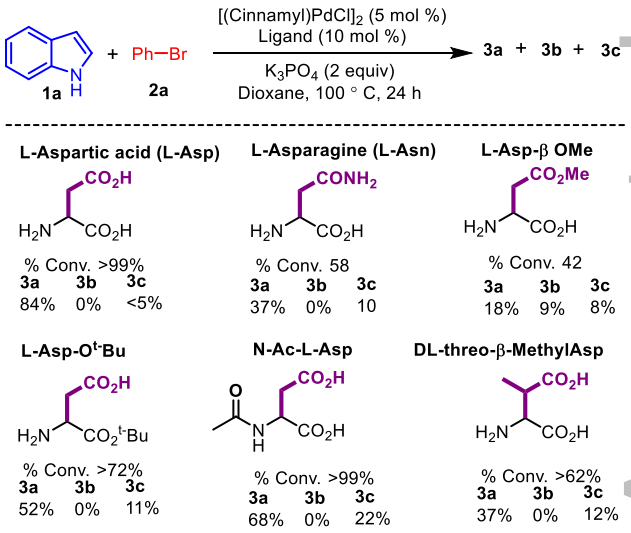
The effect of solvents, bases, and other reaction parameters to offer optimized reaction conditions with improved yields was explored (see ESI). It was delighted to note the use of 1,4-dioxane and K_3PO_4 in

Table 1. Validation of AA-ligated catalytic palladium inhibition empowering selectivity control.[a]



Entry	Pd-cat.	AA	% conv.[b]	%yield[c] 3a	3b	3c
1	**Cat 3**	L-Asp	42	25	0	9
2		L-Ala	31	18	0	traces
3		L-Met	0[d]	n/a	n/a	n/a
4		L-Arg	traces[d]	n/a	n/a	n/a
5	**Cat 4**	L-Asp	28	16	0	0
6		L-Ala	0[d]	n/a	n/a	n/a
7		L-Met	0[d]	n/a	n/a	n/a
8		L-Arg	0[d]	n/a	n/a	n/a

[a]**1a** (0.1 mmol) was treated with **2a** (0.15 mmol, 1.5 equiv) in presence of selected Pd-catalyst (10 mol %) and AA (10 mol %) in THF (1 mL) at 100 °C for 24 h. [b]Based on ^{1}H NMR. [c]Isolated yield. [d]**1a** was found intact.



Scheme 4. Preliminary mechanistic investigations

presence of 5 mol% of $[(cinnamyl)PdCl]_2$ and 10 mol% L-Asp improved the yield up to 84% (**3a**) with exceptional regio- (C3 vs C2) & chemoselectivity (C vs N). Catalytic tests with lower amounts of Pd were examined carefully. A 51% yield of **3a** was obtained with 2.5 mol% $[(cinnamyl)PdCl]_2$ and further lowering the Pd level reduced the **3a** yields

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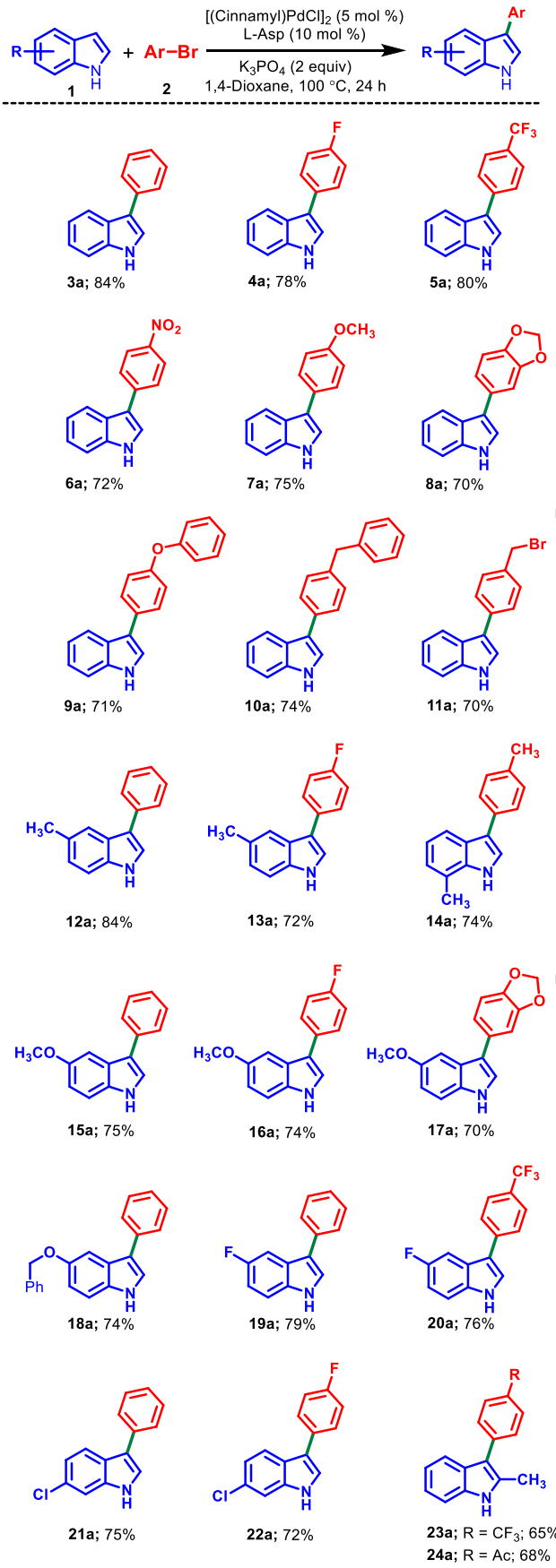
drastically. A similar yield and selectivity were obtained using isomeric D-Asp indicating the chirality of AAs was insignificant in this regard.

Predicting the valid mechanism to explain the selectivity control of L-Asp ligated Pd(II)-catalyzed indole C3–H arylation is under progress. At this stage, we don't have clear explanations for the selectivity attributed to L-Asp, however, based on limited

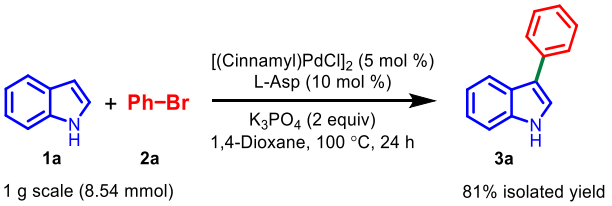


Scheme 5: C3-arylation of various indoles (**1**) with aryl bromides (**2**) under optimized conditions unless otherwise noted. The indicated yields represent the isolated and purified yield.

preliminary studies, the following description can be made. The selectivity control attributed to L-Asp (and L-Glu) could be the outcome of the stabilization of desirable cationic palldo-indole resulting in C3-aryl indoles via combined electrostatic interaction and hydrogen bonding between cationic Pd-complex and L-Asp.[6p, 10] Further, L-Asp ligated Pd(II)-complexes offer a distorted parallelogram geometry resulting in steric influence towards C3–H arylation reactions,[11] although they are less common than electronic control. To gain a better understanding of the role of α/β–carboxyl and amino functionality of L-Asp, the structural analogs of L-Asp but lacking free β–CO_2H acids such as L-Asn and L-Asp-β-OMe, lacking free α–CO_2H (3-amino-4-tert-butoxy-4-oxobutanoic acid), and lacking free –NH_2 (N-Ac-L-Asp) were investigated for the model reaction involving **1a** and **2a** under optimized conditions. An inferior yield (**3a**) and selectivity were obtained suggesting the essentially (simultaneous involvement) of the α–NH_2 and α- & β–CO_2H functionalities of L-Asp for their optimal ligation efficiency (Scheme 4). We further examine the effect of β-substitution on the L-Asp ligation efficiency using DL-threo-β-methylaspartic acid; an inferior result obtained suggesting the possible interference of β-methyl to the ligation efficiency of L-Asp.

Towards the end, we took this opportunity to develop a generalized sustainable protocol for the C3–arylation of indoles using L-Asp as a ligand to generate the diverse range of high-value C3–aryl indoles. As summarized in Scheme 5, reactions work well with variable electronically substituted indoles and bromobenzenes to deliver the desired C3–aryl indoles with good to excellent yields and superior chemo- (C vs N) and regioselectivity (C3 vs C2). Practically no C2-arylated products were obtained, however, in a few cases, *N*-arylated products were noticed.

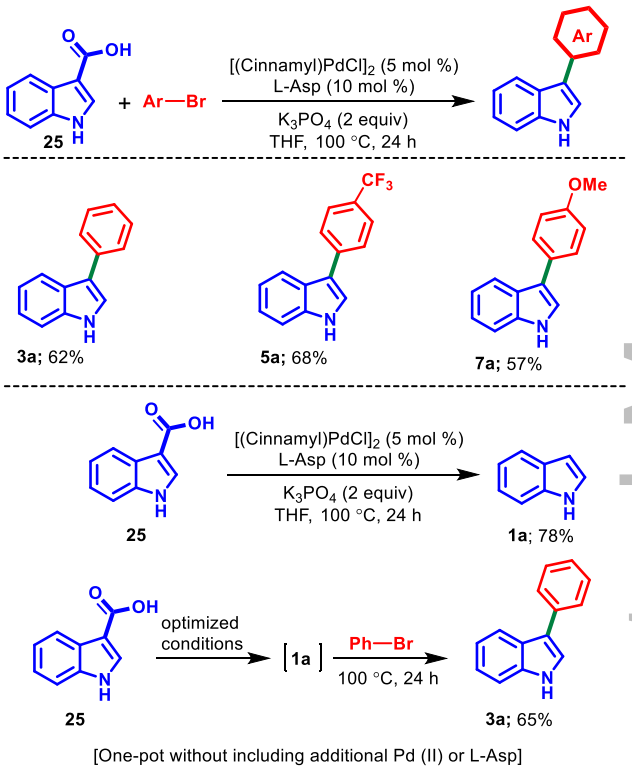
Various functional groups tolerated well including but not limited to halogens (–F, –Cl), –CF_3, –Me, –OMe, –OBn, –C(O)Me, –$O(CH_2)O$-, -OPh, -CH_2Br. The use of 2-methyl indole (**23a**, **24a**) as a reacting partner afforded good yields and strong chemoselectivity (C *vs* N). Important to mention, in the case of 4-bromobenzyl bromide, the exclusive formation of 3-(4-(bromomethyl)phenyl)-1*H*-indole (**11a**) was observed suggesting the preferential participation of aromatic C–Br over aliphatic (benzylic) C–Br bond. To be noted, the reactions proceed essentially with (NH)-indoles as no C-H arylation products were observed during the reaction of (N-Me)-indole and (N-Bn)-indole with **2a**. Further, only traces of **3a** was obtained during the reaction of **1a** with chlorobenzene.



Scheme 6. Demonstration of gram-scale reaction

To demonstrate the scalability and utility of the protocol, the reaction was also performed on a gram scale (8.54 mmol). Treatment of **1a** (1 g, 8.54 mmol) with **2a** under optimized condition resulted in the formation of **3a** in 81% yield (Scheme 6).

We further demonstrated a cascade decarboxylative indole C3–H arylation under Pd/L-Asp catalysis. Treatment of indole-3-carboxylic acid **25** with aryl bromides under adapted optimized conditions (use of THF instead of 1,4-dioxane) resulted in 3-arylated indoles in synthetically good yields with excellent selectivity. The mechanistic study suggested the cascade process involving the decarboxylation of indole-3-carboxylic acid **25** to indole **1a** followed by Pd-catalyzed C–H arylation. (Scheme 7).



Scheme 7. Tandem decarboxylation/arylation procedure for the chemoselective synthesis of 3-aryl indole

Experimental Section

Representative procedure for C3-arylation of indole: To dried tube equipped with a stir bar, $[(cinnamyl)PdCl]_2$ (5.2 mg, 0.01 mmol, 5 mol%), L-aspartic acid (2.7 mg, 0.02 mmol, 10 mol%), indole **1a** (23.4 mg, 0.2 mmol), bromobenzene **2a** (31.1μL, 47.1 mg, 0.3 mmol, 1.5 equiv), K_3PO_4 (84.9 mg, 0.4 mmol, 1.5 equiv), and 1,4–Dioxane (1 mL) were added and the resultant reaction mixture was stirred at 100 °C for 24 h. The cooled (room temp.) reaction mixture was subject to aq. workup and extracted with EtOAc. The collected organic layers were dried over

anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and pass through the column (eluent: Hexane/EtOAc) to get analytically pure product **3a,** white solid (32.4 mg, 84%); mp: 84–85 °C; **^{1}H NMR** (500 MHz $CDCl_3$): δ 8.15 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 8.0, 1.5 Hz,2H), 7.44 (t, J = 7.7 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.19 (td, J = 7.4, 6.9, 1.1 Hz, 1H); **^{13}C NMR** (125 MHz $CDCl_3$): δ 136.7, 135.6, 128.8, 127.5, 126.0, 125.8, 122.5, 121.8, 120.4, 119.9, 118.4, 111.4;**HRMS** (ESI-TOF) *m/z*: $[M + H]^+$Calcd for $C_{14}H_{11}N$ 194.0964, Found 194.0961.

Representative tandem decarboxylation/C3-arylation of indole: To dried tube equipped with a stir bar, $[(cinnamyl)PdCl]_2$ (5.2 mg, 0.01 mmol, 5 mol%), L-Aspartic acid (2.7 mg, 0.02 mmol, 10 mol%), 1*H*-indole-3-carboxylic acid **25** (32.2 mg, 0.2 mmol), bromobenzene **2a** (31.1 µL, 47.1 mg, 0.3 mmol, 1.5 equiv), K_3PO_4 (84.9 mg, 0.4 mmol, 2 equiv), and THF (1 mL) were added and the resultant reaction mixture was stirred at 100 °C for 24 h. The cooled (room temp.) reaction mixture was subject to aq. workup and extracted with EtOAc. The collected organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and pass through the column (eluent: Hexane/EtOAc) to get analytically pure product **3a** (23.9 mg, 62%).

Acknowledgments

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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