



HAL
open science

Regiospecificity in Ligand-Free Pd-Catalyzed C–H Arylation of Indoles: LiHMDS as Base and Transient Directing Group

Yorck Mohr, Marc Renom-Carrasco, Clément Demarcy, Elsje Alessandra Quadrelli, Clément Camp, Florian Wisser, Eric Clot, Chloé Thieuleux, Jérôme Canivet

► **To cite this version:**

Yorck Mohr, Marc Renom-Carrasco, Clément Demarcy, Elsje Alessandra Quadrelli, Clément Camp, et al.. Regiospecificity in Ligand-Free Pd-Catalyzed C–H Arylation of Indoles: LiHMDS as Base and Transient Directing Group. *ACS Catalysis*, 2020, 10 (4), pp.2713-2719. 10.1021/acscatal.9b04864 . hal-02493979

HAL Id: hal-02493979

<https://hal.umontpellier.fr/hal-02493979v1>

Submitted on 18 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Regiospecificity in Ligand-Free Pd-Catalyzed C-H Arylation of Indoles: LiHMDS as Base and Transient Directing Group

Yorck Mohr,^[a] Marc Renom-Carrasco,^[b] Clément Demarcy,^[b] Elsje Alessandra Quadrelli,^[b] Clément Camp,^[b] Florian M. Wissler,^[a] Eric Clot,^[c] Chloé Thieuleux*^[b] and Jérôme Canivet*^[a]

^[a]Univ. Lyon, Université Claude Bernard Lyon 1, CNRS, IRCELYON - UMR 5256, 2 Av. Albert Einstein, 69626 Villeurbanne, France

^[b]Univ. Lyon, Université Claude Bernard Lyon 1, CPE Lyon, CNRS, C2P2 - UMR 5265, 43 Bvd. du 11 Novembre 1918, 69616 Villeurbanne, France

^[c]Institut Charles Gerhardt Montpellier, Université de Montpellier, UMR 5253 CNRS, ENSCM, 8 rue de l'Ecole Normale, Montpellier 34296, France

ABSTRACT: A highly efficient catalyst-base pair for the C-H arylation of free (NH)-indoles in the C-3 position is reported. Ligand-free palladium acetate coupled with lithium hexamethyldisilazide (LiHMDS) catalyzed the regiospecific, *i.e.* 100% regioselective, C-3 arylation of indoles with high turnover numbers. This catalytic system has been successfully applied to a wide range of substrates including various functional aryl halides and indolic cores. The unique role of LiHMDS as both a base and unexpected transient directing group has been revealed experimentally and elucidated computationally, in line with a Heck-type insertion-elimination mechanism.

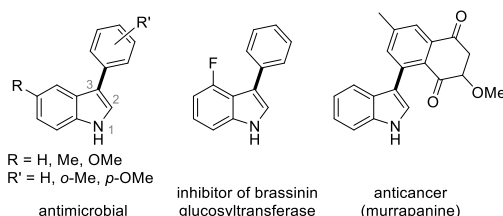
KEYWORDS: cross-coupling, indole, C-H arylation, palladium, LiHMDS.

Heterobiaryls and in particular those containing indolic cores are ubiquitous motifs in active pharmaceutical ingredients (API) of marketed drugs.¹⁻³ Their synthesis often involves at least one catalytic step based on carbon-carbon coupling reactions such as the Pd-catalyzed aryl boronate/aryl halide Suzuki-Miyaura cross-coupling reaction.⁴ Only in the last decade, the formidable challenge of activating aromatic C-H bonds has led to reduced synthetic steps and improved atom economy.⁵⁻¹⁰

Heteroarene C-H arylation is reported to proceed following three main pathways, often supported by DFT calculations: electrophilic aromatic substitution,¹¹ concerted metalation-deprotonation¹²⁻¹⁶ or Heck-type carbo-metalation.^{17,18} The reaction's regioselectivity is often a key to discriminate mechanisms for a given catalytic system and is mostly explained on the basis of the substrate's electronic or steric properties, the directing effect of a ligand on the catalyst or the presence of permanent or transient directing groups.¹⁸⁻²⁴

Regarding free (NH)-indoles, their C-H arylation at the C-3 position combined with regioselectivity and high activity has never been accomplished so far. The few reported systems which show high selectivities for the C-3 arylated products display only moderate TON values up to 81 (the catalysts in these cases are mostly Pd- or Ir-based systems).²⁵⁻³² Yields of up to 76% for the C-3 arylated product (after 35 hours) were obtained *via* a transition metal-free system developed by Chen and Wu using four equivalents of potassium *tert*-butoxide and an excess of indole.³³ However, this system led to mixtures of regioisomers. Another metal-free system for the arylation of indoles was described by Ackermann *et al.* using substituted diaryliodonium salts as reagents without any catalyst.³⁴ This procedure gave rise to almost exclusively C-3 arylation albeit in moderate

yields. Despite these synthetic limitations, C-3 arylated indoles are considered to be promising API, for instance, as antimicrobial agents, enzyme inhibitors and anticancer drugs (Scheme 1).³⁵⁻⁴¹

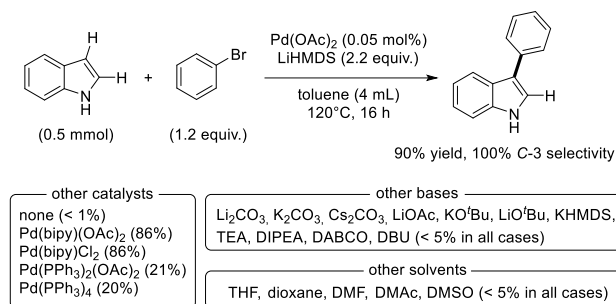


Scheme 1. API based on C-3 arylated free (NH)-indoles and their biological activity.³⁵⁻³⁸

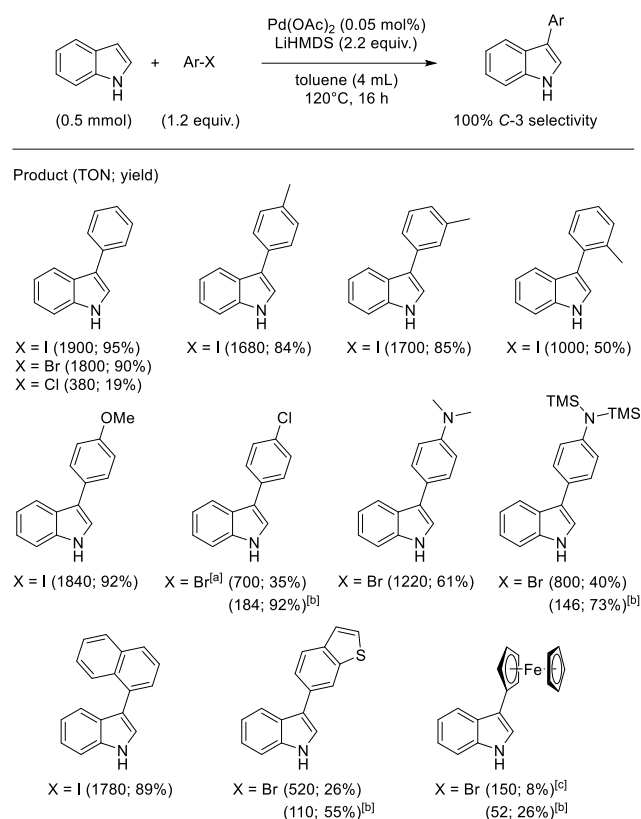
In this context, we report here the ligand-free palladium-catalyzed regiospecific, *i.e.* 100% regioselective, C-3 arylation of free (NH)-indole derivatives. Catalyzed by a standard palladium salt, the reaction mechanism is driven by a specific lithiated base whose dual role is crucial as demonstrated experimentally and elucidated by DFT calculations.

After extensively screening reaction parameters (Scheme 2 and SI), we determined that palladium acetate, with a loading as low as 0.05 mol%, efficiently catalyzed the phenylation of 1*H*-indole with 100% selectivity for the C-3 position using lithium hexamethyldisilazide (LiHMDS) as base and bromobenzene as the arylating agent, in toluene at 120°C. After 16 hours, the product was isolated with a yield of 90%, corresponding to a TON of 1800 moles of isolated 3-phenyl-1*H*-indole *per* mole of palladium. In toluene, classical inorganic bases such as carbonates or acetates with lithium, potassium and caesium as counter-cations, gave very poor yields. Organic bases such as

triethylamine (TEA), diisopropylethylamine (DIPEA), 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were found to be inefficient. Lithium and potassium *tert*-butoxide did not allow the arylation to proceed in toluene, in contrast to the activity reported by Chen and Wu in dimethylsulfoxide (DMSO).³³



Scheme 2. The Pd(OAc)₂/LiHMDS catalytic system for efficient C-3 arylation of 1H-indole and overview of screened parameters.

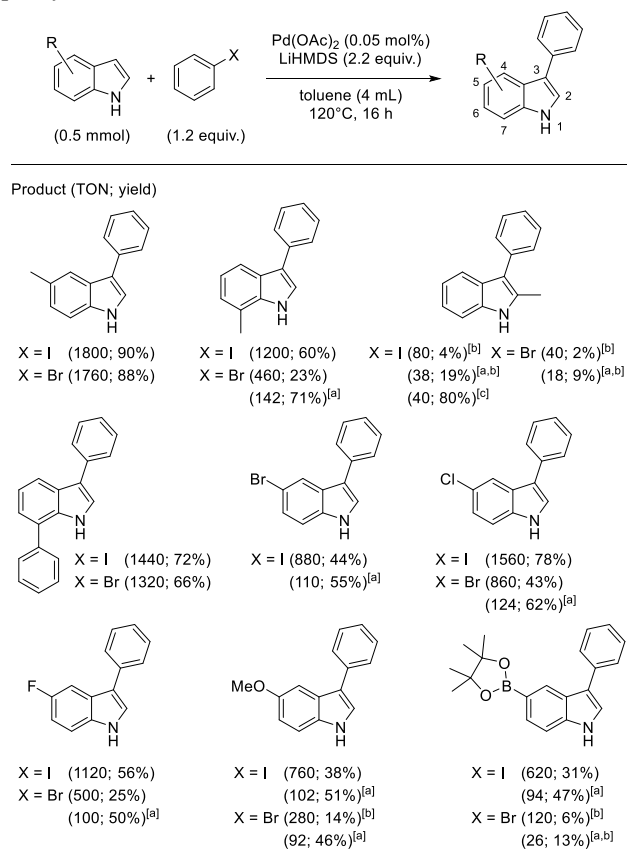


Scheme 3. Scope of aryl halides. TON are calculated from isolated yields if not otherwise stated. ^[a] 3 equivalents of 1-bromo-4-chlorobenzene were used. ^[b] 0.5 mol% of Pd(OAc)₂ used. ^[c] TON calculated from GC-FID yield.

Using LiHMDS, solvents other than toluene and mesitylene, such as tetrahydrofuran (THF), dioxane, dimethylformamide (DMF), dimethylacetamide (DMAc) and DMSO, gave essentially *N*-arylation or no reaction at all (see SI, Table S7). In contrast to the work of Chen and Wu who noticed a change in selectivity towards *N*-arylation in the presence of oxygen,³³ here the standard reaction with bromobenzene and a metal loading as low as 0.05 mol% did not require an anhydrous or deoxygenated solvent but could be performed in technical grade toluene without affecting neither yield nor regioselectivity (Table S7).

To demonstrate the versatility of the present catalytic system, different aryl electrophiles were evaluated (Scheme 3). The C-3 indole arylation was found to proceed efficiently using either iodo- (TON = 1900), bromo- (TON = 1800) or chlorobenzene (TON = 380) with the Pd(OAc)₂/LiHMDS catalytic system. High activity was also achieved using *p*-iodoanisole (TON = 1840) and *p*-bromodimethylaniline (TON = 1220). When *N,N*-bis(trimethylsilyl)-protected 4-bromo-aniline was used as substrate, the coupling at the C-3 position also proceeded efficiently (TON = 800). Using three equivalents of 1-bromo-4-chlorobenzene as arylating agent gave rise to 3-(4-chlorophenyl)-1H-indole with a TON of 700. Here the superior reactivity of the bromide compared to the chloride moiety allowed reaching 100% chemoselectivity. Further aromatic systems, like naphthalene, benzothiophene and ferrocene could be used efficiently as electrophiles with average to high activity and full regioselectivity. Noteworthy, the Pd(OAc)₂/LiHMDS system allowed preparing 3-(*o*-tolyl)indole, which cannot be obtained using the previously reported transition metal-free system, since the latter operates *via* a benzyne intermediate.³³

The scope of applicable functionalized indoles is presented in Scheme 4. The C-3 arylation efficiently proceeded with both phenyl iodide and bromide in most cases.



Scheme 4. Scope of functionalized indoles. TON are calculated from isolated yields if not otherwise stated. ^[a] 0.5 mol% of Pd(OAc)₂ used. ^[b] TON calculated from GC-FID yield. ^[c] 2.0 mol% of Pd(OAc)₂ used.

Indoles functionalized either at the C-5 or C-7 positions can be efficiently arylated leading to a 100% regioselectivity in all but one case. Only for 5-methyl-1H-indole, traces of a presumably *N*- or C-2 arylated product were detected with, nonetheless, a selectivity of 99% for the C-3 arylated product (Figure S3). 2-

Methyl-1*H*-indole can also be C-3 arylated with, however, a TON one order of magnitude lower than other functionalized indoles. This lower activity is probably due to steric hindrance resulting from the presence of the methyl group. Similarly, the use of 2-phenylindole as substrate leads to no reaction.

Overall, the Pd(OAc)₂/LiHMDS catalytic system is tolerant to various halide, methoxy, substituted amino, and boronate substituents (Scheme 3 & 4), offering the possibility for further functionalization of the 3-phenyl-1*H*-indole moiety. Unfortunately, compounds bearing nitro or trifluoromethyl groups, either at the electrophile or the indolic core, decompose under the reaction conditions. Aryl halides based on pyridine or with protic functional groups (-OH, -NH₂) did not react with 1*H*-indole (see SI, Scheme S1).

Following the concept of “homeopathic” catalysis introduced by Beletskaya and Cheprakov⁴² and demonstrated by de Vries and co-workers for ligand-free Pd-catalyzed C-C coupling reactions,^{43,44} we tested the Pd(OAc)₂/LiHMDS catalytic system at Pd loadings as low as 5 ppm with respect to the quantity of indole (i.e. 0.0005 mol%) and a TON of *ca.* 16000 was reached without affecting the selectivity for the C-3 arylated product (Table 1, entry 8). However, the yield decreased significantly at such a low palladium loading.

Table 1. Effect of lowering the palladium loading down to the ppm level.^[a]

Entry	Pd loading (mol%)	Time (h)	Temperature (°C)	C-3 yield (%) ^[b]	TON ^[c]
1	0.05	16	120	90	1800
2 ^[d]	0.05	1	120	29	570
3 ^[d]	0.05	2	120	58	1200
4 ^[d]	0.05	1	150	81	1600
5	0.01	16	120	46	4600
6	0.002	16	120	13	6300
7 ^[d]	0.002	16	150	23	11400
8	0.0005	112	120	8	15700
9	0	112	120	0	n.d.
10 ^[d]	0	16	150	0	n.d.

^[a] Reaction conditions: 1*H*-indole (0.5 mmol), bromobenzene (0.6 mmol), palladium acetate and LiHMDS (1.1 mmol) in toluene (4 mL) at 120°C. ^[b] GC-FID yields with dodecane as internal standard. ^[c] Turnover number defined as (moles of 3-phenylindole)/(moles of palladium) (n.d.: not determined). ^[d] Reaction performed under microwave irradiation (300 W).

We also investigated the use of microwave irradiation as heating protocol.⁴⁵⁻⁴⁷ In the presence of 0.05 mol% of palladium and under microwave irradiation, a TON of 1200 was reached at 120°C after two hours and a TON of 1600 was obtained at 150°C after only one hour of reaction (Table 1, entries 3 and 4, respectively). In the latter case, the turnover frequency (TOF), defined as moles of 3-phenyl-1*H*-indole *per* mole of palladium *per* hour, reaches a value of 1600 h⁻¹, which represents one of the highest TOF for metal-catalyzed C-H arylation reactions reported so far.^{48,49} Furthermore, using only 20 ppm of palladium acetate, the 3-phenyl-1*H*-indole was obtained with full regioselectivity and a TON of 11400 (Table 1, entry 7). In the absence of palladium, under microwave heating, only the formation of traces of *N*-arylated indole were observed after 16 hours (Table 1, entry 10 and SI).

From a mechanistic point of view, since the use of LiHMDS was key for both activity and selectivity, a series of experiments was carried out to gain more insight into the role of the lithiated base (Table 2). Under optimized conditions, we found that reducing the amount of LiHMDS from 2.2 equiv. to 1.5 or 1.0 equiv. drastically lowered the yield of the reaction from 90% to 38% and 0.6%, respectively (Table 2, entries 1-3), thus suggesting that two equivalents of LiHMDS are mandatory. When using NaHMDS, KHMDS or Mg(HMDS)₂ instead of LiHMDS, very low arylation yields were observed (0.05 mol% Pd, Table 2, entries 4-6). When 5 mol% Pd were used, Mg(HMDS)₂ was found to be capable to drive the reaction with however a lower regioselectivity (33% yield, 96% selectivity, Table S1 and S2), whereas KHMDS was not. It is noteworthy that Sames and coworkers also reported in 2005 the use of Mg(HMDS)₂ as base for this reaction, among a series of Mg salts, albeit with the formation of both C-2 and C-3 arylated products and the nature of the magnesium salt of indole as well as its role in the reaction mechanism not being elucidated.²⁵

The use of alternative lithiated bases such as lithium diisopropylamide (LDA, pKa ~ 36), which is a stronger lithiated base than LiHMDS (pKa ~ 26), or *n*-butyl lithium (BuLi, pKa ~ 50) gave rise to only 0.3% yield (Table 2, entry 7) or no arylated product (Table 2, entry 8), respectively.

Table 2. Evaluation of the effect of different lithiated and different silazide bases on the catalytic performance.^[a]

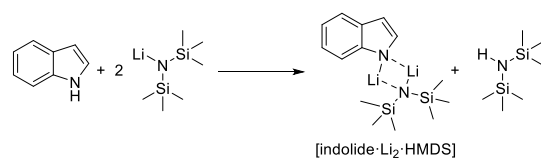
Entry	Base (equiv.)	C-3 yield (%) ^[b]	TON ^[c]
1	LiHMDS (2.2)	90	1800
2	LiHMDS (1.5)	38	750
3	LiHMDS (1)	0.6	11
4	NaHMDS (2.2)	0.4	8
5	KHMDS (2.2)	0.2	4
6	Mg(HMDS) ₂ (2.2)	1.5	30
7	LDA (2.2)	0.3	6
8	BuLi (2.2)	0	n.d.
9	BuLi (0.9) + LiHMDS (1.3) ^[d]	84	1680
10	BuLi (0.9) + NaHMDS (1.3) ^[d]	0.3	6
11	LiHMDS (1.1) + NaHMDS (1.1) ^[d]	1.3	26

^[a] Reaction conditions: 1*H*-indole (0.5 mmol), bromobenzene (0.6 mmol), palladium acetate (0.25 μmol) and base in toluene (4 mL) at 120°C for 16 h. ^[b] GC-FID yields with dodecane as internal standard. ^[c] Turnover number defined as (moles of 3-phenylindole)/(moles of palladium) (n.d.: not determined). ^[d] Indole and the two bases were stirred in toluene for 15 min prior to the addition of bromobenzene and Pd(OAc)₂.

To further elucidate the role of both the lithium cation and the hexamethyldisilazide anion (HMDS⁻) in the reaction, different base combinations were evaluated. A mixture of BuLi and LiHMDS gave comparable results to those found under standard conditions (Table 2, entry 9). In contrast, when one equivalent of Li was removed from the reaction mixture by using either BuLi/NaHMDS or LiHMDS/NaHMDS, almost all the activity was suppressed (Table 2, entries 10 and 11) similar to when one equivalent of LiHMDS was employed (Table 2 entry 3). Thus, the palladium-based catalytic system requires two equivalents of base, at least one being HMDS⁻, and two equivalents of Li⁺ with respect to the substrate.

Further, the product of mixing 1*H*-indole with two equivalents of LiHMDS was isolated as a white powder and characterized by liquid and solid-state NMR spectroscopy as well as ICP-OES and elemental analysis (see SI). ¹H and ¹³C liquid state NMR spectra of the isolated precipitate recorded at 105°C in toluene-*d*8 show the presence of indolide and HMDS⁻ in a 1:1 ratio (Figure S55 and S56). In addition, well-resolved ¹³C Cross-Polarization (CP) Magic Angle Spinning (MAS) solid-state NMR spectra were obtained with chemical shifts in good agreement to those obtained from liquid state ¹³C NMR (Figure S56 and S59) spectroscopy. ICP-OES and elemental analysis evidence the presence of two Li cations, which appear as a single signal in both the liquid-state and the MAS solid-state ⁷Li NMR spectra at -1.5 ppm and -2.5 ppm, respectively (Figure S57 and S60). In contrast, the ⁷Li NMR signal of LiHMDS in toluene-*d*8 at 105°C is found at +1.4 ppm (Figure S63), confirming a different chemical environment of Li in the two compounds. Furthermore, ¹H-¹H NOESY experiments display a correlation between the methyl groups of the HMDS⁻ moiety and several indole protons at 105°C in toluene-*d*8 (Figure S58).

These data strongly suggest that, as it is known for lithium bis(silyl)amides,^{50–53} the lithiated compound is present predominantly as a bis-lithium indolide hexamethyldisilazide species with the general formula [indolide·Li₂·HMDS] (Scheme 5), the presence of larger aggregates being however not excluded.⁵⁴



Scheme 5. Postulated reactivity of 1*H*-indole with two equivalents of LiHMDS leading to [indolide·Li₂·HMDS] as a key intermediate.

When the deprotonation of indole is carried out in the presence of two equivalents of Li⁺ and one equivalent of HMDS⁻ at room temperature, [indolide·Li₂·HMDS] precipitates in toluene but then dissolves back upon heating above 100°C. In contrast, the use of other lithiated bases gave precipitates that were not soluble even at 120°C in toluene (Figure S52). This unique solubility of [indolide·Li₂·HMDS] was confirmed by *in-situ* liquid state NMR spectroscopy. Hexamethyldisilazane was the sole product observed in the ¹H spectrum of a 1:2 mixture of 1*H*-indole and LiHMDS in toluene-*d*8 at room temperature. Furthermore, no soluble Li species were detected, *i.e.* no signal in the ⁷Li NMR spectrum. This evidences that at room temperature all indole and Li species are insoluble. Upon heating to 105°C the signals belonging to the [indolide·Li₂·HMDS] species become visible in both ¹H and ⁷Li NMR spectra (Figure S53 and S54).

A catalytic test was carried out with the isolated precipitate [indolide·Li₂·HMDS] without adding any additional base under standard conditions (see SI), giving 3-phenyl-1*H*-indole in 85% yield. In light of these observations, only the combination of indole with two equivalents of Li⁺ and one equivalent of HMDS⁻ gives rise to a soluble reaction intermediate [indolide·Li₂·HMDS] which can be readily arylated by the palladium catalyst.

To get deeper insight into the possible reaction mechanism, deuterium-labelling experiments were performed. When (2-²H)-1*H*-indole was used as a substrate, the final product was

obtained with complete deuterium retention leading to 3-phenyl-(2-²H)-1*H*-indole, which excludes any C-H activation at the C-2 position. This is further supported by the fact that 2-methyl-1*H*-indole could be C-3 arylated (Scheme 4 and section 4 of SI). As a blank experiment, we performed the reaction using 3-methyl-1*H*-indole as substrate and the starting reagents were quantitatively recovered showing that neither C-2 nor *N*-arylation occurred as side reactions (Scheme S1). Using 1-methyl-1*H*-indole, also no reaction was observed, highlighting the importance of this position in the reaction mechanism (Scheme S1).

When the reaction was carried out using (3-²H)-1*H*-indole and 1*H*-indole as substrates in parallel reactions or in a 1:1 mixture for an intermolecular competition experiment, no kinetic isotopic effect (KIE) was observed, $k_H/k_D = 1$ (Figure S64–S66). Thus, the C-H cleavage at the C-3 position is not the rate-determining step.⁵⁵ The absence of any KIE makes a CMD mechanism very unlikely, and thus is not considered any further.^{18,56}

Calculations performed at the DFT level allow to draw the energy profile of the reaction between phenyl bromide and indole catalyzed by Pd(II) in the presence of two equivalents of LiHMDS (Figure 1). The calculations clearly show that a mechanism based on the insertion of a Pd-aryl into the indole C-2=C-3 bond (carbo-palladation) followed by a base-assisted elimination in a Heck-type mechanism is much more favored than an electrophilic aromatic substitution pathway (S_EAr) (Figure S72, see SI for detailed calculations). The Heck-type mechanism represents here a new pathway since previously proposed pathways for catalytic indole C-H arylation reactions were of S_EAr type.^{11,25} Noteworthy, the selectivity of the S_EAr reaction in the Mg(HMDS)₂ catalyzed indole arylation was explained so far only by steric effects. The use of a bulky counter ion such as HMDS⁻ was supposed to hinder the required C-3 to C-2 migration of palladium, thus increasing the amount of C-3 arylated indole.

Here, in the Heck-type insertion-elimination mechanism, the overall energy barriers are very similar for both the C-2 and C-3 arylation pathways. However, two key intermediates, both implying the second LiHMDS molecule, favorably drive the arylation to the C-3 position, namely **D3** and **D3'** (Figure 1). First, in the insertion step, the **D3** species is stabilized by 19.3 kcal/mol compared to the analogous **D2** species due to the interaction between one lithium atom and the bromide of the palladium complex.

This stabilizing effect of LiHMDS is already present in the coordination of Pd to C-2=C-3 as illustrated by the larger stability of **C3** compared to **C2**. The energy barrier to achieve the base-assisted elimination at C-3 is composed of two individual events: decoordination of LiHMDS from **D3** to reach a configuration (**D3'**) prone to effectively deprotonate the C-3 position, and actual base-assisted elimination through **TS-D3**. Even though the transition state from **D3** to **D3'** could not be located, the first step has an energy barrier of approximately 18.8 kcal/mol, whereas the second one has an energy barrier of 15.5 kcal/mol. In comparison, base-assisted elimination in the C-2 pathway shows a direct transition from **D2** to reach the corresponding **TS-D2** having a much higher energy barrier of 33.9 kcal/mol.

The calculations highlight that the transition between **D3** and **D3'** with the highest energy barrier (approximately 18.8 kcal/mol) should be the rate-determining step. This supports the absence of a KIE observed experimentally, in line with

the “no KIE” scenario reported by Simmons and Hartwig.⁵⁵ Here the rate-determining step has to occur before the cleavage of the C-H bond, *e.g.* the formation of a complex undergoing subsequent deprotonation at the functionalized carbon.

Moreover, the computed structures confirm the experimental evidence that the [indolide·Li₂·HMDS], denoted **B** in Figure 1, is the most stable species in a system of one molecule of 1*H*-indole and two molecules of LiHMDS.

Based on experimental and computational findings, we demonstrate herein for the first time the direct *C*-3 arylation of indoles proceeding *via* a Heck-type mechanism. In this insertion-elimination pathway LiHMDS acts not only as a base but also as a unique transient directing group driving the regioselectivity of the reaction towards the *C*-3 position.

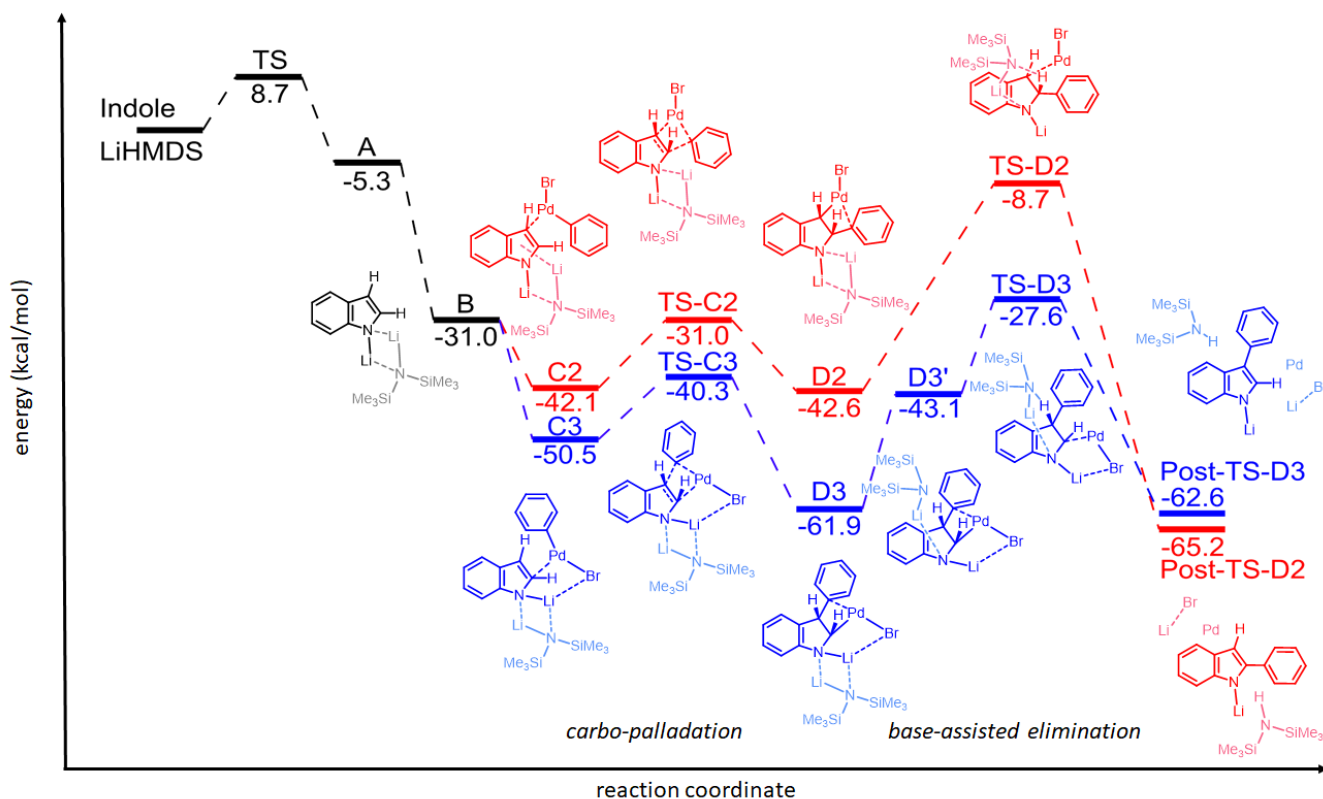


Figure 1. Schematic relative free energy profile for the reported reaction calculated at the DFT (PBE0-D3) level. Pathways towards *C*-2 or *C*-3 arylated indole are shown in red and blue, respectively. Structures of calculated intermediates and transition states are represented.

In summary, we have uncovered a catalytic system able to achieve the arylation of free (NH)-indoles with 100% selectivity for the *C*-3 arylated product and remarkable turnover numbers at the same time. Experimental findings combined with DFT calculations highlight the key relevance of a bis-lithium indolide hexamethyldisilazide [indolide·Li₂·HMDS] species as activated indole substrate. For the first time in indole C-H arylation, the observed selectivity is explained by a Heck-type mechanism in which LiHMDS uniquely plays the role of both a base and transient directing group. In light of these results, the use of LiHMDS opens new perspectives for the transition metal catalyzed regioselective C-H arylation of heteroarenes.

AUTHOR INFORMATION

Corresponding Author

*jerome.canivet@ircelyon.univ-lyon1.fr

*thieuleux@cpe.fr

Author Contributions

All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

ACKNOWLEDGMENT

This work has been carried out within the H-CCAT project that has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement No 720996. F.M.W. gratefully acknowledges financial support from the Deutsche Forschungsgemeinschaft (DFG, Postdoctoral Research Fellowship, grant number WI 4721/1-1) and from CNRS through Momentum 2018 excellence grant. The authors are very grateful to P. Mascunan for ICP-OES analysis, and to C. Lorentz for solid-state NMR spectroscopy.

REFERENCES

- (1) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845–5859.
- (2) Sravanthi, T. V.; Manju, S. L. Indoles — A Promising Scaffold for Drug Development. *Eur. J. Pharm. Sci.* **2016**, *91*, 1–10.

- (3) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. Biomedical Importance of Indoles. *Molecules* **2013**, *18*, 6620–6662.
- (4) King, A. O.; Yasuda, N. Palladium-Catalyzed Cross-Coupling Reactions in the Synthesis of Pharmaceuticals. In *Organometallics in Process Chemistry*; Larsen, R., Ed.; Topics in Organometallic Chemistry; Springer-Verlag: Berlin, Heidelberg, 2004; Vol. 6, pp 205–245.
- (5) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. Efficient Activation of Aromatic C-H Bonds for Addition to C-C Multiple Bonds. *Science* **2000**, *287*, 1992–1995.
- (6) Daugulis, O.; Zaitsev, V. G. Anilide Ortho-Arylation by Using C-H Activation Methodology. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046–4048.
- (7) Yu, D. G.; Gensch, T.; De Azambuja, F.; Vázquez-Céspedes, S.; Glorius, F. Co(III)-Catalyzed C-H Activation/Formal SN-Type Reactions: Selective and Efficient Cyanation, Halogenation, and Allylation. *J. Am. Chem. Soc.* **2014**, *136*, 17722–17725.
- (8) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. Weakly Coordinating Directing Groups for Ruthenium(II)-Catalyzed C-H Activation. *Adv. Synth. Catal.* **2014**, *356*, 1461–1479.
- (9) Schranck, J.; Tlili, A.; Beller, M. Functionalization of Remote C-H Bonds: Expanding the Frontier. *Angew. Chem. Int. Ed.* **2014**, *53*, 9426–9428.
- (10) Segawa, Y.; Maekawa, T.; Itami, K. Synthesis of Extended π -Systems through C-H Activation. *Angew. Chem. Int. Ed.* **2015**, *54*, 66–81.
- (11) Kurokhtina, A. A.; Larina, E. V.; Yarosh, E. V.; Lagoda, N. A.; Schmidt, A. F. Mechanistic Study of Direct Arylation of Indole Using Differential Selectivity Measurements: Shedding Light on the Active Species and Revealing the Key Role of Electrophilic Substitution in the Catalytic Cycle. *Organometallics* **2018**, *37*, 2054–2063.
- (12) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation across a Broad Range of Aromatic Substrates. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.
- (13) Guihaumé, J.; Clot, E.; Eisenstein, O.; Perutz, R. N. Importance of Palladium–Carbon Bond Energies in Direct Arylation of Polyfluorinated Benzenes. *Dalt. Trans.* **2010**, *39*, 10510.
- (14) García-Melchor, M.; Gorelsky, S. I.; Woo, T. K. Mechanistic Analysis of Iridium(III) Catalyzed Direct C-H Arylations: A DFT Study. *Chem. Eur. J.* **2011**, *17*, 13847–13853.
- (15) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. Analysis of the Palladium-Catalyzed (Aromatic)C-H Bond Metalation-Deprotonation Mechanism Spanning the Entire Spectrum of Arenes. *J. Org. Chem.* **2012**, *77*, 658–668.
- (16) Santoro, S.; Himo, F. Mechanism and Selectivity of Rhodium-Catalyzed C-H Bond Arylation of Indoles. *Int. J. Quantum Chem.* **2018**, *118*, e25526.
- (17) Steinmetz, M.; Ueda, K.; Grimme, S.; Yamaguchi, J.; Kirchberg, S.; Itami, K.; Studer, A. Mechanistic Studies on the Pd-Catalyzed Direct C-H Arylation of 2-Substituted Thiophene Derivatives with Arylpalladium Bipyridyl Complexes. *Chem. Asian J.* **2012**, *7*, 1256–1260.
- (18) Colletto, C.; Islam, S.; Juliá-Hernández, F.; Larrosa, I. Room-Temperature Direct β -Arylation of Thiophenes and Benzo[b]Thiophenes and Kinetic Evidence for a Heck-Type Pathway. *J. Am. Chem. Soc.* **2016**, *138*, 1677–1683.
- (19) Tang, S. Y.; Guo, Q. X.; Fu, Y. Mechanistic Origin of Ligand-Controlled Regioselectivity in Pd-Catalyzed C-H Activation/Arylation of Thiophenes. *Chem. Eur. J.* **2011**, *17*, 13866–13876.
- (20) Yamamoto, K.; Kimura, S.; Murahashi, T. σ - π Continuum in Indole-Palladium(II) Complexes. *Angew. Chem. Int. Ed.* **2016**, *55*, 5322–5326.
- (21) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. Modulating Reactivity and Diverting Selectivity in Palladium-Catalyzed Heteroaromatic Direct Arylation through the Use of a Chloride Activating/Blocking Group. *J. Org. Chem.* **2010**, *75*, 1047–1060.
- (22) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C-H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936.
- (23) Sambiagio, C.; Schönbauer, D.; Blicke, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A Comprehensive Overview of Directing Groups Applied in Metal-Catalyzed C-H Functionalisation Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.
- (24) Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem* **2018**, *4*, 199–222.
- (25) Lane, B. S.; Brown, M. A.; Sames, D. Direct Palladium-Catalyzed C-2 and C-3 Arylation of Indoles: A Mechanistic Rationale for Regioselectivity. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.
- (26) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. Direct Palladium-Catalyzed C-3 Arylation of Indoles. *Tetrahedron Lett.* **2007**, *48*, 2415–2419.
- (27) Bellina, F.; Benelli, F.; Rossi, R. Direct Palladium-Catalyzed C-3 Arylation of Free (NH)-Indoles with Aryl Bromides under Ligandless Conditions. *J. Org. Chem.* **2008**, *73*, 5529–5535.
- (28) Cusati, G.; Djakovitch, L. First Heterogeneously Palladium-Catalyzed Fully Selective C3-Arylation of Free NH-Indoles. *Tetrahedron Lett.* **2008**, *49*, 2499–2502.
- (29) Join, B.; Yamamoto, T.; Itami, K. Iridium Catalysis for C-H Bond Arylation of Heteroarenes with Iodoarenes. *Angew. Chem. Int. Ed.* **2009**, *48*, 3644–3647.
- (30) Perato, S.; Large, B.; Lu, Q.; Gaucher, A.; Prim, D. Pyridylmethylamine–Palladium Catalytic Systems: A Selective Alternative in the C–H Arylation of Indole. *ChemCatChem* **2017**, *9*, 389–392.
- (31) Yamaguchi, M.; Suzuki, K.; Sato, Y.; Manabe, K. Palladium-Catalyzed Direct C3-Selective Arylation of n-Unsubstituted Indoles with Aryl Chlorides and Triflates. *Org. Lett.* **2017**, *19*, 5388–5391.
- (32) Vaidya, G. N.; Fiske, S.; Verma, H.; Lokhande, S. K.; Kumar, D. A Micellar Catalysis Strategy Applied to the Pd-Catalyzed C-H Arylation of Indoles in Water. *Green Chem.* **2019**, *21*, 1448–1454.
- (33) Chen, J.; Wu, J. Transition-Metal-Free C3 Arylation of Indoles with Aryl Halides. *Angew. Chem. Int. Ed.* **2017**, *56*, 3951–3955.
- (34) Ackermann, L.; Dellacqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. Metal-Free Direct Arylations of Indoles and Pyrroles with Diaryliodonium Salts. *Org. Lett.* **2011**, *13*, 2358–2360.
- (35) Dekker, W. H.; Selling, H. A.; Overeem, J. C. Structure-Activity Relations of Some Antifungal Indoles. *J. Agric. Food Chem.* **1975**, *23*, 785–791.
- (36) Wu, T. S.; Liou, M. J.; Lee, C. J.; Jong, T. T.; McPhail, A. T.; McPhail, D. R.; Lee, K. H. Structure and Synthesis of Murrapanine, a Novel Skeletal Indole-Naphthoquinone Alkaloid and Cytotoxic Principal from *Murraya paniculata* Var. *Omphalocarpa*. *Tetrahedron Lett.* **1989**, *30*, 6649–6652.
- (37) Pedras, M. S. C.; Hossain, M. Design, Synthesis, and Evaluation of Potential Inhibitors of Brassinin Glucosyltransferase, a Phytoalexin Detoxifying Enzyme from *Sclerotinia sclerotiorum*. *Bioorg. Med. Chem.* **2007**, *15*, 5981–5996.
- (38) Leboho, T. C.; Michael, J. P.; van Otterlo, W. A. L.; van Vuuren, S. F.; de Koning, C. B. The Synthesis of 2- and 3-Aryl Indoles and 1,3,4,5-Tetrahydropyrano[4,3-b]Indoles and Their Antibacterial and Antifungal Activity. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4948–4951.
- (39) Richardson, T. I.; Clarke, C. A.; Yu, K. L.; Yee, Y. K.; Bleisch, T. J.; Lopez, J. E.; Jones, S. A.; Hughes, N. E.; Muehl, B. S.; Lugar, C. W.; Moore, T. L.; Shetler, P. K.; Zink, R. W.; Osborne, J. J.; Montrose-Rafizadeh, C.; Patel, N.; Geiser, A. G.; Galvin, R. J. S.; Dodge, J. A. Novel 3-Aryl Indoles as Progesterone Receptor Antagonists for Uterine Fibroids. *ACS Med. Chem. Lett.* **2011**, *2*, 148–153.
- (40) Patel, P. A.; Kvaratskhelia, N.; Mansour, Y.; Antwi, J.; Feng, L.; Koneru, P.; Kobe, M. J.; Jena, N.; Shi, G.; Mohamed, M. S.; Li, C.; Kessler, J. J.; Fuchs, J. R. Indole-Based Allosteric Inhibitors of HIV-1 Integrase. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4748–4752.
- (41) Browne, C. M.; Jiang, B.; Ficarro, S. B.; Doctor, Z. M.; Johnson, J. L.; Card, J. D.; Sivakumaren, S. C.; Alexander, W. M.; Yaron, T. M.; Murphy, C. J.; Kwiatkowski, N. P.; Zhang, T.; Cantley, L. C.; Gray, N. S.; Marto, J. A. A Chemoproteomic Strategy for Direct and Proteome-Wide Covalent Inhibitor Target-Site Identification. *J. Am. Chem. Soc.* **2019**, *141*, 191–203.

- (42) Beletskaya, I. P.; Cheprakov, A. V. Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009–3066.
- (43) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. Homeopathic Ligand-Free Palladium as a Catalyst in the Heck Reaction. A Comparison with a Palladacycle. *Org. Lett.* **2003**, *5*, 3285–3288.
- (44) Alimardanov, A.; Schmieder-Van De Vondervoort, L.; De Vries, A. H. M.; De Vries, J. G. Use of “Homeopathic” Ligand-Free Palladium as Catalyst for Aryl-Aryl Coupling Reactions. *Adv. Synth. Catal.* **2004**, *346*, 1812–1817.
- (45) Larhed, M.; Moberg, C.; Hallberg, A. Microwave-Accelerated Homogeneous Catalysis in Organic Chemistry. *Acc. Chem. Res.* **2002**, *35*, 717–727.
- (46) Gawande, M. B.; Shelke, S. N.; Zboril, R.; Varma, R. S. Microwave-Assisted Chemistry: Synthetic Applications for Rapid Assembly of Nanomaterials and Organics. *Acc. Chem. Res.* **2014**, *47*, 1338–1348.
- (47) Kokel, A.; Schäfer, C.; Török, B. Application of Microwave-Assisted Heterogeneous Catalysis in Sustainable Synthesis Design. *Green Chem.* **2017**, *19*, 3729–3751.
- (48) Roger, J.; Požgan, F.; Doucet, H. Ligand-Free Palladium-Catalyzed Direct Arylation of Thiazoles at Low Catalyst Loadings. *J. Org. Chem.* **2009**, *74*, 1179–1186.
- (49) Gensch, T.; James, M. J.; Dalton, T.; Glorius, F. Increasing Catalyst Efficiency in C–H Activation Catalysis. *Angew. Chem. Int. Ed.* **2018**, *57*, 2296–2306.
- (50) Wannagat, U. The Chemistry of Silicon-Nitrogen Compounds. In *Adv. Inorg. Chem. Radiochem.*; Emelius, H. J., Sharpe, A. G., Eds.; Academic Press, 1964; Vol. 6, pp 225–278.
- (51) Popenova, S.; Mawhinney, R. C.; Schreckenbach, G. Density Functional Study of Lithium Hexamethyldisilazide (LiHMDS) Complexes: Effects of Solvation and Aggregation. *Inorg. Chem.* **2007**, *46*, 3856–3864.
- (52) Neufeld, R.; Michel, R.; Herbst-Irmer, R.; Schöne, R.; Stalke, D. Introducing a Hydrogen-Bond Donor into a Weakly Nucleophilic Brønsted Base: Alkali Metal Hexamethyldisilazides (MHMDS, M=Li, Na, K, Rb and Cs) with Ammonia. *Chem. Eur. J.* **2016**, *22*, 12340–12346.
- (53) Nicholas, H. M.; Goodwin, C. A. P.; Kragoskow, J. G. C.; Lockyer, S. J.; Mills, D. P. Structural Characterization of Lithium and Sodium Bulky Bis(Silyl)Amide Complexes. *Molecules* **2018**, *23*, 1138.
- (54) Reich, H. J. Role of Organolithium Aggregates and Mixed Aggregates in Organolithium Mechanisms. *Chem. Rev.* **2013**, *113*, 7130–7178.
- (55) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.
- (56) Lapointe, D.; Fagnou, K. Overview of the Mechanistic Work on the Concerted Metallation–Deprotonation Pathway. *Chem. Lett.* **2010**, *39*, 1118–1126.

