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VIP C-H Functionalization Very Important Paper

Palladium-Catalyzed *para*-C–H Arylation of Anilines with Aromatic Halides

Dominik Lichte, Nico Pirkl, Gregor Heinrich, Sayan Dutta, Jonas F. Goebel, Debasis Koley, and Lukas J. Gooßen**

Abstract: Controlling regioselectivity in C–H functionalizations is a key challenge in chemical method development. In arenes, functionalizations are most difficult to direct towards the C–H group furthest away from a substituent, in its *para* position. We herein demonstrate how the *para*-C–H arylation of anilines with non-activated aryl halides, elusive to date, is achieved by a base-assisted "metalla-tautomerism" approach. A proton is abstracted from the aniline substrate and replaced by an arylpalladium species, generated from the aryl halide coupling partner. In this step, the palladium is directed away from the *N*- to the tautomeric *para*-C–H position by a large phosphine ligand combined with a triphenylmethyl shielding group. The triphenylmethyl group is easily installed and removed, and can be recycled.

The biaryl substructure is a central motif in pharmaceuticals, agrochemicals, and functional materials.[1] Traditional methods for its synthesis, such as the Suzuki reaction, are based on the cross-coupling of prefunctionalized aryl electrophiles and aryl nucleophiles, and produce salt waste.[2] Electrophilic C–H arylations draw on simple arenes as the nucleophilic reaction partner and do not require pre-forming organometallic reagents (Figure 1, A). However, these advantages are often offset by the necessity to use highly reactive aryl electrophiles (Ar^+) such as aryliodonium salts, or elaborate photocatalytic activation.[3] Moreover, if the position of C–H arylation is determined solely by electronic and steric factors, the products are usually obtained as mixtures of isomers.

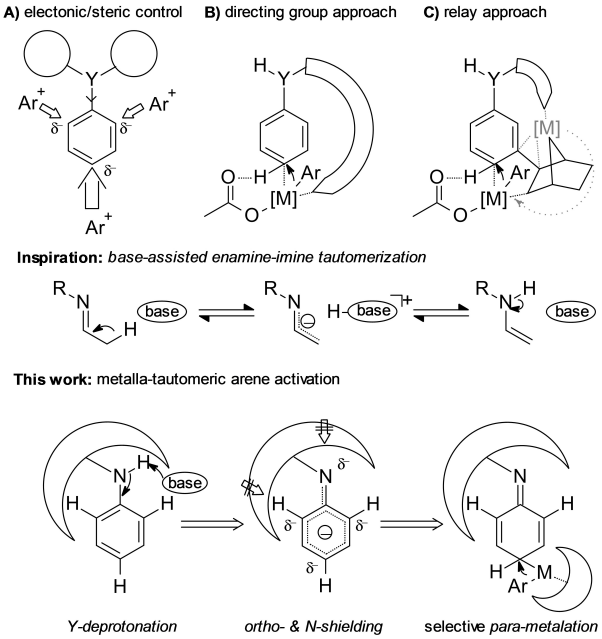

Figure 1. Strategies towards selective *para*-C–H-arylations and C–H functionalization directed by metalla-tautomerism.

A common strategy to achieve regioselectivity in C–H arylation employs a pre-installed directing group to steer a catalyst towards a specific position.[4] The catalyst activates the aryl electrophile by oxidative insertion, and the C–H bond is usually broken via concerted metalation-deprotonation (CMD). This strategy is well established for *ortho*-[5] and *meta*-,[6] but reaches its limits for *para*-functionalizations.[7] Only few, elaborate directing groups can steer electrophiles all the way to the *para* position, e.g. in the work by Maiti[6a,7a] or Li,[7c] but for aryl electrophiles, this approach has not been shown to work (Figure 1, B).[8] A workaround uses primary, pre-installed directing groups to promote the introduction of a secondary, transient directing group into their *meta* position (Figure 1, C). The transient group then relays an aryl group into the *para* position. However, this Catellani-type approach is limited to elaborate substrate combinations.[9]

Anilines are particularly common aromatic molecules. Their arylation via Friedel–Crafts, aryne, or radical mechanisms usually leads to mixtures of *ortho* and *para* isomers.[10] Non-directed reactions of activated substrates, e.g. via radical pathways, permit the introduction of difluorometh-

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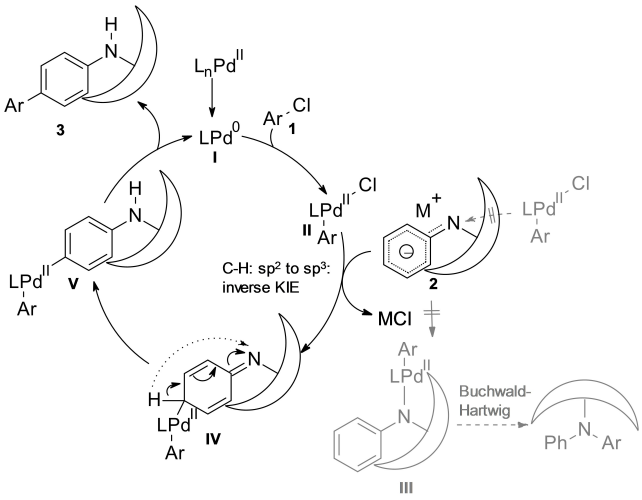
yl,[11] sulfonyl,[12] alkyl,[13] halo groups,[14] or thianthrenes[15] in the *para* position of the amino group. *Para*-selective catalytic olefinations[16,17] and Friedel–Crafts type silylations[18] or borylations[19] of anilines have also been reported. To this date, no directing groups are known that would steer catalytic arylations selectively into the aniline *para* position. Only certain specialized C–C couplings, such as benzidine rearrangements[20] or oxidative dimerizations,[21] produce *para*-arylated aniline derivatives.[22] The current selectivity record in aniline C–H arylations is held by Gaunt et al., who achieved high *para*-selectivity in a copper-catalyzed coupling of doubly benzylated anilines with highly reactive diaryliodonium salts, however along with *ortho*/*para*-diarylated byproducts.[23] This reaction type had been implemented by Kita for anisole derivatives.[24] Buchwald et al. also obtained *para*-selectivity for the dehydrogenative coupling of anisole with anilides.[5d]

Alternative directing concepts are needed to achieve *para*-specific C–H arylations of abundant aromatic substrates based on simple, non-activated aryl electrophiles. In response to this long-standing challenge, we herein present a straightforward protocol for the C–H arylation of anilines with aryl halides. It is enabled by a readily installed and cleaved trityl shielding group combined with a bulky palladium/phosphine catalyst system.

Our concept for *para*-selective C–H arylation is based on the consideration that the enamine/imine tautomerism should relay the reactivity of the NH group to CH groups within the aromatic ring. In tautomerizations, catalytic base temporarily removes a proton from an enolizable substrate, yielding a resonance-stabilized anion. This can be reprotonated at either the hetero- or the carbon atom, giving rise to two tautomeric products (Figure 1, middle). In anilines, deprotonation of the NH group leads to a resonance-stabilized anilide anion that is activated towards electrophilic attack at the nitrogen, the two *ortho*-, and the *para*-carbon atoms. Its reprotonation should, in principle, give all four possible tautomers. However, the "trienamine" tautomer (aniline) predominates to an extent that other tautomers are not observable. An electrophilic metal complex should react with anilide anions just like a proton, but due to its size, it should be more sensitive towards steric hindrance. We reasoned that by shielding the nitrogen and the *ortho*-C–H positions with a bulky protecting group, a transition metal catalyst carrying an electrophile might be steered towards the *para*-C–H position, initially yielding a "metalla-dienimine" rather than the "metalla-trienamine" tautomer (Figure 1, bottom).

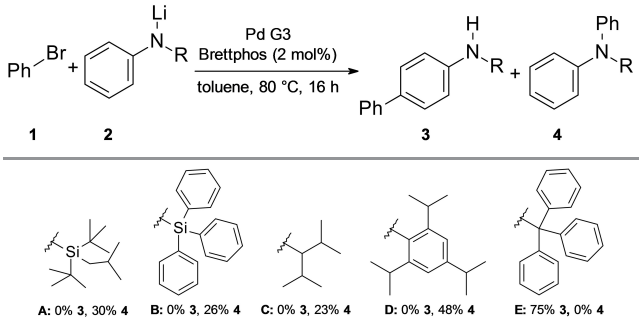
Our mechanistic blueprint for a catalytic *para*-arylation based on this directing concept is depicted in scheme 1. An aryl chloride **1** oxidatively adds to a reactive Pd^0 species **I** with formation of the electrophilic Pd^{II} complex **II**. A bulky substituent shields the amino group of its reaction partner, the anilide salt **2**. This impedes the formation of aryl-Pd anilide **III**, which would lead to a Buchwald–Hartwig type *N*-arylation. Instead, complex **I** binds to the *para* position of **2** and forms the pallada-cyclohexadiene-imine tautomer **IV**. This should rapidly tautomerize to the aromatic enamine intermediate **V** via an electronically favorable, sterically insensitive suprafacial [1,5]-H shift. Reductive elimination of the aminobiphenyl product **3** from complex **V** should regenerate the catalyst, closing the cycle. Notably, the overall C–H activation process is likely to be limited by the loss of aromatic resonance involving sp^2–sp^3 rehybridization rather than by the actual C–H bond cleavage. Thus, in contrast to CMD processes, one would expect an inverse rather than a normal kinetic isotope effect. In order to probe the viability of this mechanism, we investigated the coupling of various *N*-shielded lithium anilides with phenyl bromide in the presence of an *ortho*-biphenylamine-stabilized palladium precatalyst (Pd G3)[25] bearing the bulky ligand BrettPhos[26] (Table 1).



Scheme 1. Mechanistic blueprint for a Pd-catalyzed *para*-arylation of anilines.

Even for sterically crowded derivatives bearing e.g. 1-isopropyl-2-methylpropyl,[27] triisopropylsilyl,[27] di-*tert*-butylisobutylsilyl,[28] or 1,3,5-tris-isopropylphenyl groups, the arylation still occurred exclusively at the N-terminus (Table 1, **A–D**, see also Table S2 in the Supporting Information). However, the selectivity was fully inverted when introducing a trityl substituent (Table 1, **E**). Starting from

Table 1: Comparison of *N*-shielding groups for the *para*-arylation of anilines.[a]



[a] Reaction conditions: 0.25 mmol **1**, 0.25 mmol **2**, 2 mol% Pd G3 Brettphos, 0.5 mL toluene, 80 °C, 16 h. Yields were determined using GC analysis with *n*-tetradecane as an internal standard.

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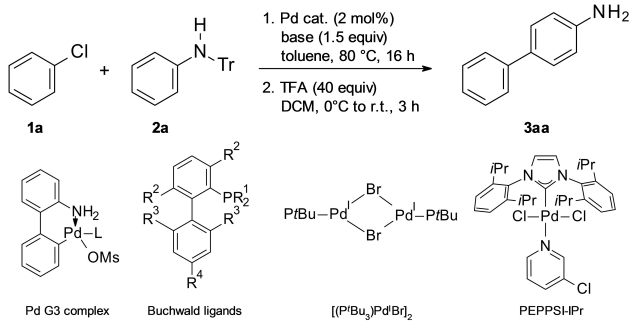
trityl aniline, the desired *para*-C–H-arylation product formed exclusively without traces of *ipso*- or *ortho*-arylation byproducts. The trityl group has the added benefit that it is easily installed by treating anilines with trityl chloride and NEt_3,[29] and cleaved quantitatively by stirring the product mixture with trifluoroacetic acid.[30] The crystal structure of lithiated tritylaniline shows that the small Li ion is located at the nitrogen, despite steric hindrance by the trityl group that completely engulfs the nitrogen atom (see the crystal structure in the Supporting Information).[31]

After achieving the required regioselectivity in the arylation of lithium anilides, we set out to develop a synthetic protocol using the coupling of *N*-tritylaniline with chlorobenzene as the model (Table 2, see also Table S1 in the Supporting Information). The aniline was now deprotonated in situ, with the non-nucleophilic base LiHMDS[32] giving the best results (entries 1–3).

Compared to other state-of-the-art catalysts, such as the "Yale" system $[(t\mathrm{Bu_3P})\mathrm{PdBr}]_2$[33] or Organ's pyridine-ligated *N*-heterocyclic carbene-palladium complex PEPPSI-IPr,[34] Pd G3 precatalysts bearing bulky monodentate ligands, particularly 2- di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*t*BuXPhos), were most effective (Table 2, entries 4–7). The reaction works best in non-polar solvents (see Table S1 in the Supporting Information) at a temperature of 80 °C (Table 2, entries 5, 8, 9). A catalyst loading of 1 mol % is sufficient (Table 2, entry 10), a slight excess of the tritylaniline and base is beneficial (Table 2, entry 11). A control experiment revealed that the omission of Pd completely shut down the reaction (Table 2, entry 12). We have tried to use milder organic bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO), pyridine or triphenylamine together with catalytic amounts of LiHMDS, however only traces of the product were detected (Table 2, entry 13 and Table S2). Besides unreacted aniline, triphenylmethane, dehalogenated aryl chloride and arylated hexamethylsilamides were the only detectable side products. Not even traces of *ortho*- or *N*-arylated aniline were formed under the optimized conditions.

Table 2: *Para*-arylation of *N*-triphenylmethylaniline with chlorobenzene.[a]



entry	catalyst	base	T [°C]	ratio **1a**:**2a** [equiv]	**3aa** [%][b]
1	Pd G3 Brettphos	KO^{t}Bu	80	1:1	4
2	"	LDA	"	"	8
3	"	LiHMDS	"	"	24
4	Pd G3 RuPhos	"	"	"	0
5	Pd G3 *t*BuXPhos	"	"	"	77
6	$[(t\mathrm{Bu_3P})\mathrm{PdBr}]_2$	"	"	"	11
7	PEPPSI-IPr	"	"	"	0
8	Pd G3 *t*BuXPhos	"	r.t.	"	29
9	"	"	60	"	74
10	" (1 mol%)	"	80	"	80
11[c]	"	"	"	1:1.5	84
12[c]	none	"	"	1:1.5	0
13[d]	Pd G3 *t*BuXPhos	DABCO	"	"	3

[a] Reaction conditions: 0.50 mmol **1a**, 1.0 equiv **2a**, 2 mol% [Pd], 1.5 equiv base, 1.2 mL toluene, 16 h. Cleavage via addition of 40.0 equiv TFA and 1.2 mL DCM. Yields were determined using GC analysis with *n*-tetradecane as an internal standard. Tr = trityl. [b] Incomplete conversion of **1a** and **2a**, no traces of *ortho*- or *N*-arylated aniline were observed. Protodehalogenated **1a** was observed as byproduct. [c] 1.75 equiv LiHMDS. [d] 1.75 equiv 1,4-diazabicyclo-[2.2.2]octane (DABCO) and 10 mol% LiHMDS as base.

The examples in Table 3 demonstrate the applicability of this synthetic transformation. Various anilines were converted into the corresponding tritylanilines, then subjected to *para*-arylation by reaction with diverse aryl electrophiles, and deprotected in situ to give biphenylamine products (Table 3). In test reactions with trityl aniline **2a**, phenyl chloride, bromide, iodide and triflate reacted similarly well (**3aa**). Further couplings were performed with aryl chlorides as the most available, least expensive but also least reactive aryl source. *Ortho*-, *meta*- and *para*-substituted, electron rich and electron deficient aryl chlorides all gave high yields in the coupling with **2a**. Benzannulated aryl halides (**3ma** and **3na**) and heterocycles (**3oa**–**3ra**) were also successfully converted. The broad scope with regard to the aniline was demonstrated in couplings with phenyl chloride (**3ab**–**3ai**). Various functional groups including ester, amide, dimethylamino and fluoro are tolerated in this transformation. Expectedly, acidic functionalities such as alcohols, acids and enolizable carbonyl compounds are outside its scope. All reactions gave exclusively the *para* isomers, NH- or *ortho*-C–H-coupling products were not detected.

For the example of **3aa**, it was demonstrated that installation of the trityl group, C–H-arylation and the removal of the protection group can all be performed in one pot, giving the desired **3aa** in a high overall yield of 80 %. After cleaving the trityl group, the triphenylmethanol byproduct was recovered, converted back to the trityl chloride reagent by reaction with acetyl chloride (95 % yield), and reused. This demonstrates a level of practicality and atom economy that goes far beyond that of most directing group approaches (see the Supporting Information).

A series of experiments was performed to elucidate the reaction mechanism. Reaction of **Li-2a** with perdeuterated methanol yields mostly *N*- and *ortho*-C-deuterated products, demonstrating that the steric bulk of the Pd-catalyst is decisive to achieve *para*-selectivity (see the Supporting Information, Figure S1). In a parallel coupling experiment of tritylaniline **2a** and $\mathbf{d_5}$**-2a** with phenyl chloride **1a**, an inverse kinetic isotope effect of $k_H/k_D = 0.88$ was observed. This speaks against a concerted metalation deprotonation pathway for which the KIE is usually in the range of 2.0–7.0,[35,36] and is in agreement with an electrophilic substitution, for which KIEs < 1[37] have been reported.

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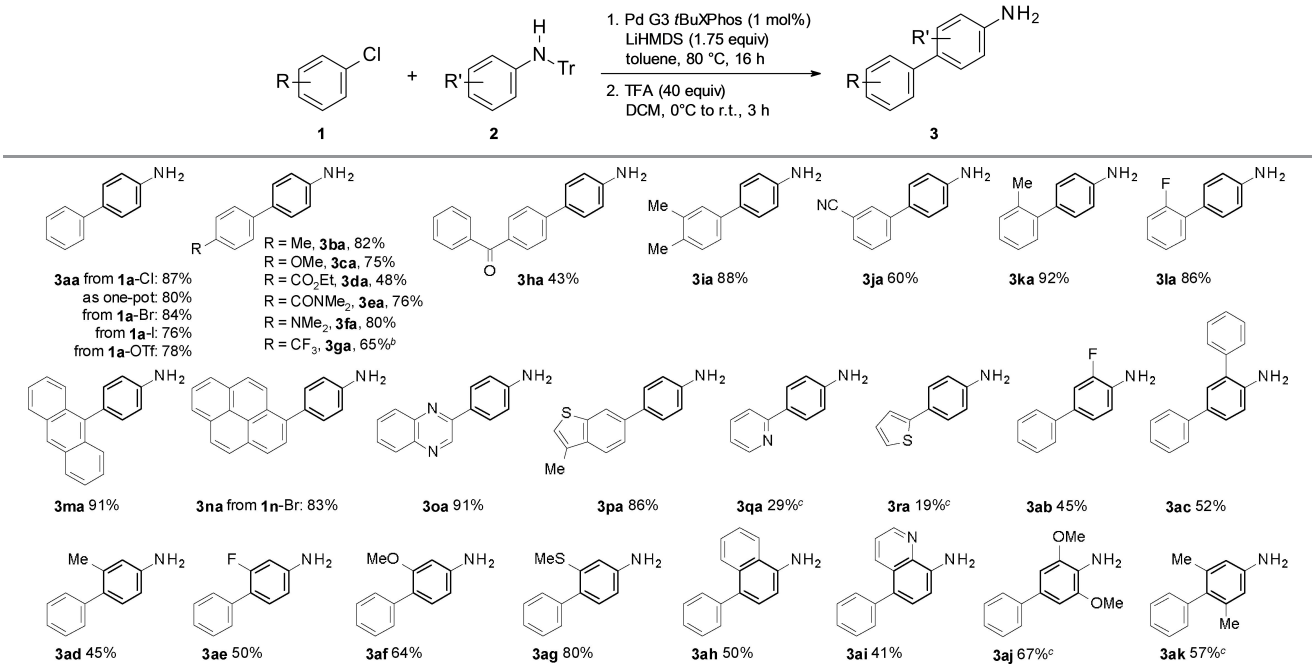
Table 3: Scope of the *para*-arylation of anilines.[a]



[a] Reaction conditions: 1.00 mmol **1**, 1.50 mmol. **2**, 1.75 mmol. LiHMDS, 1 mol% Pd G3 *t*BuXPhos, 2.4 mL toluene, 80 °C, 16 h. Cleavage of the trityl group using 40.0 equiv TFA in 3.2 mL DCM, r.t., 3 h. Isolated yields. [b] Starting from 1.50 mmol lithiated tritylaniline without LiHMDS. [c] 0.50 mmol scale. Tr = trityl.

The catalytic cycle was modelled by DFT calculations. The active catalyst (**INT-1**) was predicted to be a monoligated Pd-complex, formed from Pd G3 *t*BuXPhos by reductive elimination of the carbazole (see the Supporting Information, Figure S2).[25,38] It is stabilized by Pd–P and Pd-arene interactions. The oxidative addition of the aryl chloride to **INT-1** proceeds via a small barrier of only 12.2 kcal mol^{-1} (see the Supporting Information, Figure S3). Coordination of the lithium amide **Li-2** is strongly exergonic (Figure 2, **INT-4**). A barrier of well above 40 kcal mol^{-1} for the transition state **TS-3** blocks the access to the Buchwald-Hartwig *N*-arylation pathway. In contrast, coordination of the palladium to the *para*-carbon with formation of the cyclohexadiene imine tautomer has only a low barrier of approximately 22.8 kcal mol^{-1} (see the Supporting Information, Figure S4). In a comparative calculation for triphenylsi-

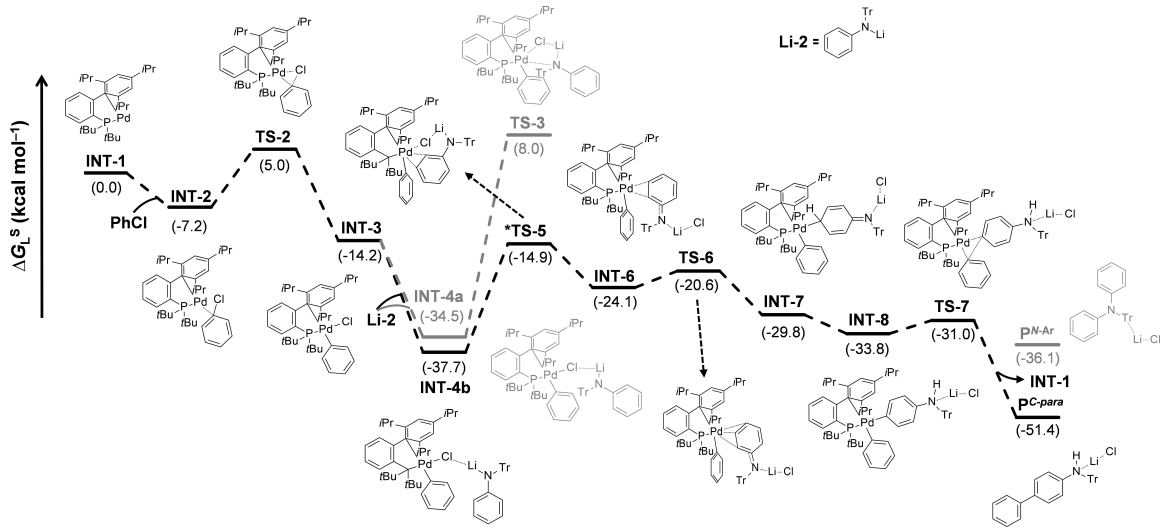


Figure 2. Energy profile diagram (ΔG_L^S kcal mol^{-1}) for the potential mechanistic pathway of the *para*-arylation. The inhibited *N*-arylation is indicated by the grey pathway (for detailed computational data see the Supporting Information, Figures S2–S5).

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lylated aniline (Table 1, protecting group B), the barrier to *N*-arylation is much lower, which is in agreement with the experimental finding that this group does not efficiently shield the nitrogen (see Figure S6 in the Supporting Information).

The strong attraction between the lithium cation and the chloride aids the addition of Pd to the aromatic ring with formation of the cyclohexadiene-imine tautomer **INT-7** under sp^2–sp^3 C–H rehybridization. The decoordination of the Lewis acidic LiCl requires an extra 7 kcal mol^{-1}. For maximal consistency within the catalytic cycle, LiCl was left coordinated to the nitrogen for all following steps. Regeneration of the aromatic system via [1,5]-H-shift was confirmed to be energetically favorable, the reductive elimination of the product proceeds smoothly. The rate-determining step is **INT-4b**→**TS-5**. Calculating this barrier for deuterated and non-deuterated substrate predicts a kinetic isotope effect of 0.89 for $\mathbf{d_5}$**-2a** and 0.90 for ***p*-$\mathbf{d_1}$-2a**, which is in excellent agreement with the experiment (see Figures S10 and S11 in the Supporting Information). Comparative calculations confirm that the efficient and selective *para*-arylation concept is mechanistically distinct from established C–H functionalization approaches.

In an attempt to provide a simplified model for predicting the selectivity of protecting groups, the relative stabilities of intermediates **INT-9** and **INT-9^{Si}** were compared to the *ortho*- and *para*-C–H arylated species (Figures S6–S9 in the Supporting Information). However, the values do not align with the experimental data, so that a calculation of transition states cannot be avoided.

Relaying the reactivity of an NH group into the aromatic ring via Pd-enamine/imine tautomerism proved viable as a concept for promoting the so far elusive *para*-arylation of anilines. The metalla-tautomerism concept is expected to extend beyond the conversion of aniline substrates or arylation reactions with palladium catalysts. It offers opportunities for the *para*-functionalization of various arenes bearing substituents that can be deprotonated. It should also be applicable to a wide range of electrophilic reaction partners including vinyl, allyl, (fluoro)alkyl, halo and many other groups.

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Conflict of Interest

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.

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