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Catalytic α-Arylation of Imines Leading to N-Unprotected Indoles and Azaindoles

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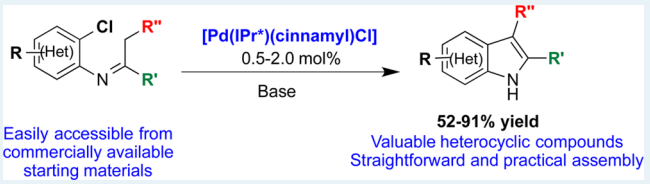
Supporting Information

ABSTRACT: A palladium N-heterocyclic carbene catalyzed methodology for the synthesis of substituted, N-unprotected indoles and azaindoles is reported. The protocol permits access to various, highly substituted members of these classes of compounds. Although two possible reaction pathways (deprotonative and Heck-like) can be proposed, control experiments, supported by computational studies, point toward a deprotonative mechanism being operative.



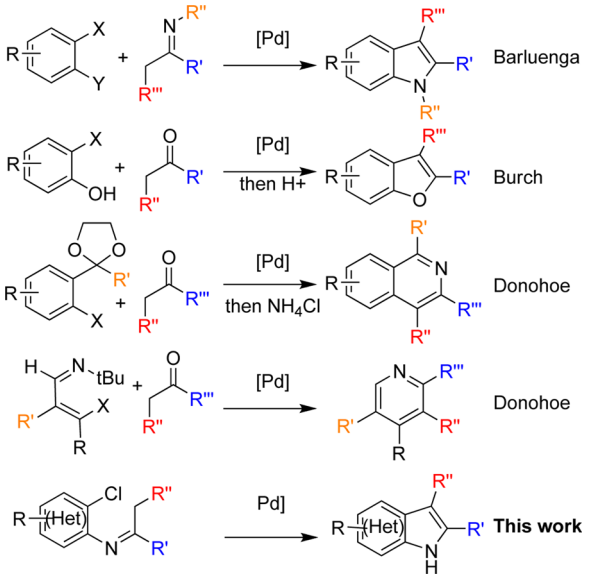
KEYWORDS: *cross-coupling, NHC, indole, heterocyclic compounds, ketone arylation, ligand effect*

INTRODUCTION

Heterocyclic architectures comprise the core of countless biologically active compounds[1] and functional materials.[2] The development of methodologies enabling their synthesis began in the late 19th century[3] and remains a field of high activity. Since the report of early examples by Hegedus,[4] Larock,[5] and Cacchi,[6] palladium catalysis has provided a number of entries into the synthesis and functionalization of heterocyclic compounds.[7] The Pd-catalyzed α-arylation of carbonyl compounds belongs to the class of deprotonative cross-coupling processes,[8] in which the nucleophile is generated by deprotonation of acidic compounds, affording the reactive anionic nucleophilic coupling partner. Discovered concomitantly by Hartwig, Buchwald, and Miura,[9] this process has rapidly evolved and can currently be performed on a wide range of coupling partners in a very efficient manner.[10] The well-known chemistry of carbonyl compounds makes these protocols particularly suitable for further functionalization toward complex molecules:[11] indeed, during the past decade, the application of the α-arylation (or vinylation) of carbonyl derivatives has provided a number of protocols achieving highly substituted heterocyclic moieties such as indole derivatives,[12] benzofurans,[13] isoquinolines,[14] and pyridines[15] (see Scheme 1).

Despite their relatively recent development, these approaches have already proven useful in the synthesis of medicinal compounds and natural products,[16] as recently demonstrated by Donohoe and co-workers in the preparation of various members of the protoberberine class of alkaloids.[17] As for most of the cross-coupling protocols reported to date, the efficiency of the α-arylation of carbonyls (AAC) is profoundly influenced by the steric and electronic properties of the ancillary ligand(s) bound to the Pd center:[8] bulky, electron-rich phosphines as

Scheme 1. Selected Synthetic Approaches Leading to Highly Substituted Heterocycles by α-Arylation or Vinylation Reactions



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well as N-heterocyclic carbenes (NHCs) generally provide a state-of-the-art level of reactivity in cross-coupling processes.[18]

Although rare examples of ligand-free protocols exist,[19] our recent work has demonstrated that bulky yet flexible, "new generation" NHC ligands are ideally suited for this palladium catalysis, rendering transformations more facile and less demanding of precious metals.[20] Following this initial study, we envisaged the possibility of preparing unprotected *N*-indole derivatives by a sequential ketone arylation/condensation reaction between a ketone and an *o*-chloroaniline derivative. Such an approach would potentially give access to a wide variety of indole scaffolds, which is considered the most widespread heterocyclic motif found in industrially relevant compounds.[21] Disappointingly, the intermolecular one-pot approach did not afford clean reaction crudes, as competition between α-arylation and N-arylation at the aniline moiety occurs.[22]

In order to overcome this problem, we prepared the imine **1a** by condensation of the two coupling partners (see Figure 1),

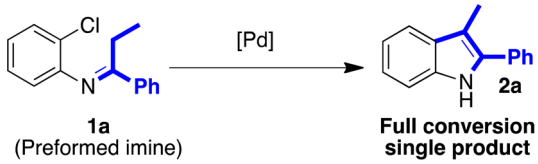


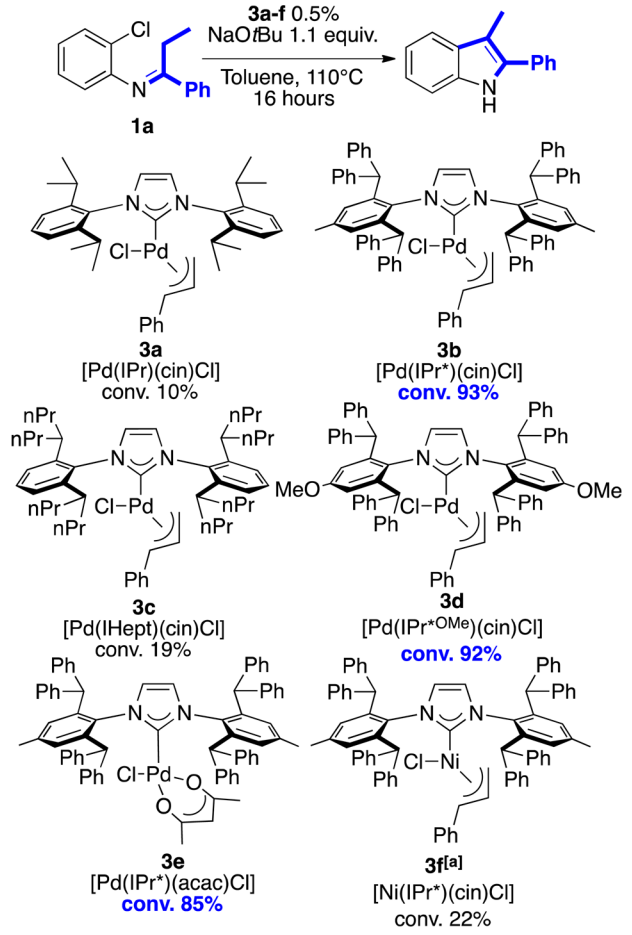
Figure 1. Intramolecular approach toward the unprotected *N*-indole scaffold.

followed by a distinct cyclization step. A strategy involving the cyclization of *o*-haloimines has been previously developed by Lachance and co-workers,[23] although their protocol suffers many drawbacks (high temperatures, high catalyst loadings, only moderate yields when chloroarenes are used). Moreover, the reaction conditions used by this group, namely $[Pd(PPh_3)_4]$ as catalyst and an amine base, suggest that a Heck mechanism, rather than ACC, was active. The present work is therefore aimed at the development of an intrinsically different, and ideally more efficient, catalytic method affording indole scaffolds.

RESULTS AND DISCUSSION

Selection of the Precatalyst. Our initial attempts at the cyclization of **1a** were carried out employing the conditions we previously developed for the intramolecular ketone arylation using different precatalysts.[20] We found that the bulky IPr* ligand (IPr* = 1,3-bis(2,6-dibenzhydryl-4-methylphenyl)-2-methylene-2,3-dihydro-1*H*-imidazol-2-ylidene) gave full conversion to a single product at 1 mol % catalyst loading. We therefore lowered the catalyst loading to 0.5 mol % and screened a library of precatalysts, varying the bulkiness of the ancillary ligand, the throw-away ligand, and the metal (see Scheme 2). Surprisingly, both IPr- and IHept-based precatalysts (**3a**,**c**), which proved active in the α-arylation of ketones,[20,24] gave low conversion. Ni-based precatalyst **3f** also gave poor conversions even at relatively high catalyst loading. We found, however, that the (flexible) bulkiness of the ligand was crucial when Pd was the metal: precatalysts **3b**,**d**, bearing IPr* and IPr*^{OMe} ligands, respectively, afforded nearly quantitative conversions to the desired product **2a** even at 0.5 mol % catalyst loading; various other ligands gave unsatisfactory conversion (for the complete screening list, see the Supporting Information). Complex **3e**, in which the cinnamyl sacrificial

Scheme 2. Selection of the Precatalyst[b]



[a]Catalyst loading 5 mol %. [b]Conversion determined by GC analysis. Conditions unless specified otherwise: 0.25 mmol of **1a**, 1.1 equiv of NaO*t*Bu, 0.5 mol % of catalyst, 0.125 M in toluene, 110 °C, 16 h.

ligand was substituted with the acetylacetonate moiety, showed slightly inferior results. The role of the very bulky IPr*-derived ligands clearly appears critical in promoting this reaction efficiently at low catalyst loading. These results further highlight the colossal effect that exceedingly bulky, monodentate ligands have on the catalytic properties of monoligated Pd species.[25] Similar performance-enhancing effects have also been observed under Ni catalysis, both in cross-coupling processes[26] and in other transformation types.[27] The steric shielding provided by such ligands has also been used in the study of highly unstable complexes of coinage metals.[28]

Optimization of the Base/Solvent System. Once the commercially available[29] complex **3b** was selected as the optimal precatalyst for this transformation, we performed a screening of base/solvent combinations (selected results are summarized in Table 1). These experiments showed the profound influence of the base counterion, especially in relation to the solvent employed: when *tert*-butoxide bases were used, switching from sodium to lithium to potassium cations completely changed the reactivity. While NaO*t*Bu gave good results in both toluene and dioxane, with no detection of starting material in the latter case (entries 4 and 5), it gave lower conversion in DME (entry 6). KO*t*Bu gave high conversion only in toluene, while it performed very poorly in ethers (entries 7−9); LiO*t*Bu, in contrast, gave almost no

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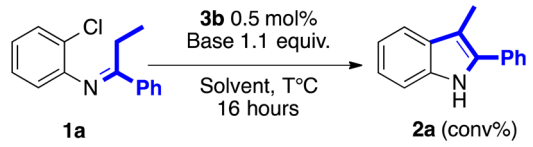
Table 1. Optimization of the Base/Solvent System[a]



entry	*T*, °C	base	solvent	conversion, %[b]
1	110	LiO*t*Bu	toluene	3
2	110	LiO*t*Bu	dioxane	81
3	110	LiO*t*Bu	DME	95
4	110	NaO*t*Bu	toluene	93
5	**110**	**NaO*t*Bu**	**dioxane**	**>99**
6	110	NaO*t*Bu	DME	68
7	110	KO*t*Bu	toluene	96
8	110	KO*t*Bu	dioxane	16
9	110	KO*t*Bu	DME	33
10	80	NaO*t*Bu	toluene	20
11	**80**	**NaO*t*Bu**	**dioxane**	**67**
12	80	LiO*t*Bu	DME	33
13	80	KO*t*Bu	toluene	10
14	110	NaO*t*Bu	dioxane	95[c]
15	**110**	**NaO*t*Bu**	**dioxane**	**>99**[d]
16	110	NaO*t*Bu	dioxane	17[e]

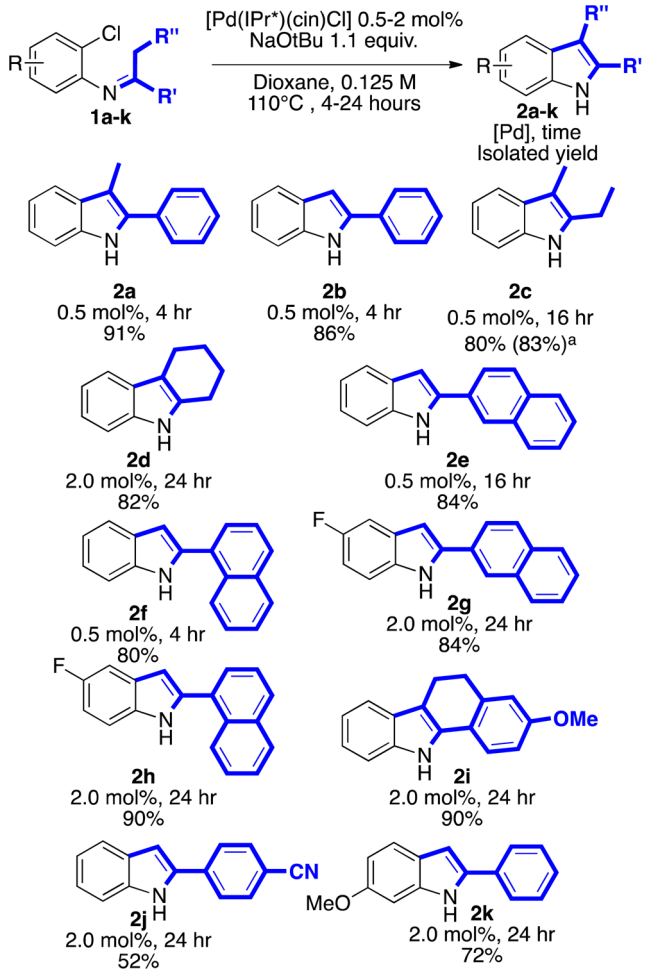
[a]Conditions unless specified otherwise: 0.25 mmol of **1a**, 1.1 equiv of base, 0.5 mol % of **3b**, 0.125 M in solvent, 80 or 110 °C, 16 h. [b]Calculated by GC analysis. [c]Concentration 0.250 M. [d]Reaction time 4 h. [e]Catalyst loading 0.1 mol %.

conversion in toluene but high conversion in ethers, particularly in DME (entries 1−3). Such an influence of the base counterion is typically observed in deprotonative couplings, such as the AAC class of reactions.[10b,20,26c] The complete base/solvent optimization can be found in the Supporting Information.

The reactions presented in Table 1, entries 3−5 and 7, were repeated at lower temperature to identify the best base/solvent system (entry 11). Further optimization of the reaction time showed that the conversion was complete after 4 h (entry 15), and an increase in concentration only slightly lowered the efficiency of this intramolecular process (entry 14). However, a further decrease of the catalyst loading from 0.5 to 0.1 mol % resulted in a dramatic decrease in conversion (entry 16). The conditions summarized in entry 15 were therefore adopted for the study of the scope of the cyclization reaction.

Scope of the Reaction. The protocol proved suitable for the synthesis of differently substituted indoles (see Scheme 3): the propiophenone-derived imine **1a** was fully converted to the respective 3-methyl-2-phenylindole and isolated in 91% yield. The acetophenone-derived indole **2b** was also obtained in good yield under the same conditions. 3-Pentanone-derived indole **2c** was also obtained at 0.5 mol % catalyst loading by prolonging the reaction time to overnight, while tricyclic product **2d** required higher catalyst loading and 24 h under these reaction conditions to afford good yields. Substitution with 1- and 2-naphthyl at the 2-position was well tolerated. It is interesting to notice the difference in reactivity observed between regioisomers **2e** and **2f**, which only differ in the position of the indole−naphthalene bond: the former bears the less sterically crowded 2-naphthalene moiety and requires longer reaction times in comparison to the bulkier 1-naphthalene derivative **2f**, clearly showing a positive effect of the steric pressure on the overall catalytic efficiency. This

Scheme 3. Scope of the Reaction: Synthesis of Indoles[b]



[a]Reaction performed on a 10 mmol scale: 10 mmol of **1c**, 1.2 equiv of NaO*t*Bu, 0.5 mol % of **3b**, 0.125 M in dioxane, 110 °C, 24 h. [b]Conditions unless specified otherwise: 0.25 mmol of **1**, 1.1 equiv of NaO*t*Bu, 0.5 mol % or 2.0% of **3b**, 0.125 M in dioxane, 110 °C, 4−24 h. Yields are the average of two runs.

methodology was also able to afford tetracyclic cores such as **2i**. Basee-sensitive functional groups, such as the nitrile moiety, were tolerated, although in this case the yield was lower (entry **2j**). The presence of a deactivating electron-donating group on the A ring was also accepted, as exemplified in compound **2k**. The protocol was found suitable for scale-up, as illustrated by a 10 mmol scale (ca. 2 g) synthesis of **2c**, affording slightly improved yield.

Of note, some of the compounds shown in Scheme 3 are industrially significant: compound **2g** is a key intermediate in the synthesis of antidiabetic drugs,[30] while **2i** is an intermediate in the synthesis of organic electronic materials[31] and **2k** is used in the synthesis of drugs for lower urinary tract dysfunction.[32]

As it does not require drybox technique and relies on a bench-stable, single-component precatalyst, this protocol is of remarkable practicality, especially considering the wide variety of *o*-chloroanilines and ketones that are commercially available. The results obtained in the synthesis of indoles encouraged us to extend this methodology to even more challenging targets, namely 4- and 6-azaindole cores, which are of great interest in medicinal chemistry (see Scheme 4).[32]

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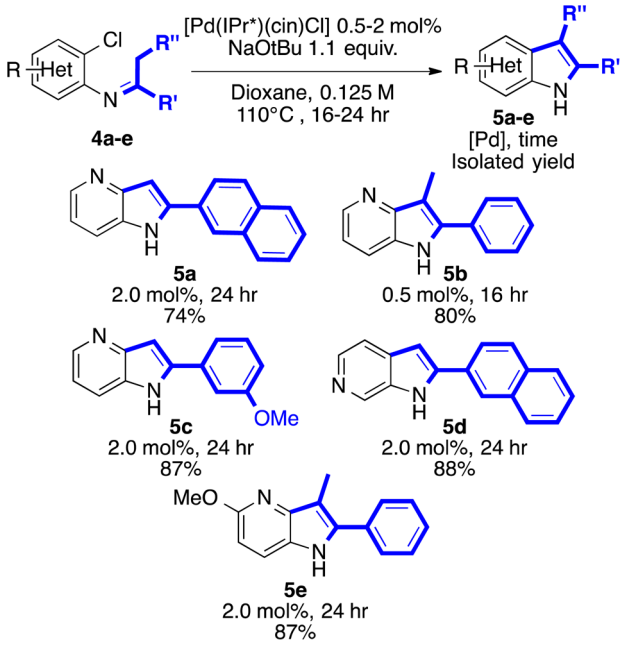
Scheme 4. Synthesis of Azaindoles[a]



[a]Conditions: 0.25 mmol of **1a**, 1.1 equiv of NaO*t*Bu, 0.5 or 2.0 mol % of **3b**, 0.125 M in dioxane, 110 °C, 16−24 h. Yields are the average of two runs.

Four differently substituted 4-azaindole derivatives were prepared: compound **5a**, bearing the bulky 2-naphthyl substituent at the 2-position, was obtained in good yield. The propiophenone derivative **5b** was obtained in 80% yield with only 0.5 mol % catalyst loading. Substitution on both starting materials was well tolerated (**5c**,**e**), and the 6-azaindole core was also accessible by this methodology (entry **5d**). Attempts to expand the scope to 2,3-diphenyl-substituted indoles, as well as the extension of this methodology to the 5- and 7-azaindole cores, were unsuccessful: in both cases, the synthesis of the imine could not be achieved in significant yield.

Mechanistic Study. *Computational Studies.* The proposed mechanisms for the catalytic transformation of **1** into **2** (or **2′**) are given in Scheme 5. The following notation is introduced in the scheme: if the substrate is in the enamine form, the compound or complex is designated with a prime (′): e.g., **1′**. Since coordination of one 1,4-dioxane molecule to [Pd^0(NHC)] species was found to be exergonic by 2.7 kcal/mol, we believe the reaction begins from a complex of [Pd^0(NHC)] with 1,4-dioxane, denoted as **6**. The relative free energy of **6** plus the substrate was taken as 0 kcal/mol. At the first step of the mechanism, reaction of the organic substrate **A** with **6** occurs via C−Cl bond scission and formation of complex **7** and release of dioxane. This transformation was found to be endergonic by only 1.3 kcal/mol. The following conversion of **7** to **7′** occurs with hydrogen migration to the nitrogen atom and simultaneous coordination of the olefin to the Pd center. This process is exergonic by 13.3 kcal/mol. The direct transformation **6** → **7′** is exergonic by 12 kcal/mol and thus possible if **1** undergoes isomerization to **1′**, which is only 4.3 kcal/mol less stable.

Starting from species **7′**, there are three different pathways leding to product **2** (or **2′**) and regeneration of the catalyst. First, we propose a pathway involving imine deprotonation followed by reductive elimination (path A in Scheme 5). In this mechanism, **7′** reacts with NaO*t*Bu and forms **8′** and NaCl. This step was found to be endergonic by 11.6 kcal/mol. The following transformation of **8′** into **10′** and *t*BuOH was calculated to be thermodynamically favorable by 22.6 kcal/mol and occurs via transition state **TSA1**. The associated Gibbs free energy barrier is 21.1 kcal/mol. **10′** can then eliminate **2′**, giving back the catalytic species **6**. This process is exergonic by almost 40 kcal/mol and is apparently irreversible. Kinetically this is a very fast conversion, since the associated transition state (**TSA2**) is only 4.3 kcal/mol above **10′**. Alternatively, **10′** can isomerize into **10**. This process is thermodynamically favorable by 2.7 kcal/mol. Then, **10** can form the initial species **1** and eliminate **2** via transition state **TSA3**. The process is favorable thermodynamically by 37.2 kcal/mol, and the associated Gibbs free energy barrier is only 3.5 kcal/mol. Afterward, **2** converts into **2′**, since this process is thermodynamically favorable by 10.8 kcal/mol because of the aromatization of the heterocycle. The rate-limiting barrier in path A is between **TSA1** and **7′** and amounts to 32.7 kcal/mol. Overall the **1** → **2′** conversion is exergonic by 62.9 kcal/mol. In addition, direct amine deprotonation of **7′** with NaO*t*Bu to form the negatively charged ion **5** with *t*BuOH and Na^+ species was studied (path C). As expected in 1,4-dioxane solvent, this transformation is thermodynamically prohibited, being endergonic by 40.8 kcal/mol, and can therefore be discarded. The second proposed mechanism is a "Heck type" (carbopalladation followed by hydride elimination, path B) and was postulated for a similar transformation, which occurs under different conditions with respect to the precatalyst, the base, and the temperature used.[23] In this mechanism **7′** converts into **11′** via a carbopalladation transition state (**TSB1**). Despite the fact that this process is thermodynamically favorable by 11.9 kcal/mol, it requires 32.2 kcal/mol of activation energy, which makes it the rate-determining step in path B. Further transformation of **11′** into **12** is exergonic by 16 kcal/mol and occurs with elimination of **2′**. This step is almost barrierless, since the associated *β*-hydride elimination transition state (**TSB2**) was found to be energetically equal to **11′** (in fact even slightly more stable, which is an artifact of calculations, due to different basis sets for geometry optimizations and SP energy evaluations). The subsequent reaction of **12** with NaO*t*Bu to form **13** and NaCl was found to be exergonic by 4.7 kcal/mol. The subsequent transformation of **13** into the initial catalyst **6** is thermodynamically favorable by 18.3 kcal/mol and occurs with the release of *t*BuOH.

On the basis of DFT calculations, the catalytic conversion of **1** into **2′** can occur via two highly competitive mechanisms, paths A and B. Both mechanisms possess an estimated overall activation barrier of some 33 kcal/mol, which is in good agreement with the experimental conditions (4 h at 110 °C in 1,4-dioxane).

Further Mechanistic Studies: Ruling out the Heck Pathway. To shed further light on the mechanism, we designed an additional set of experiments involving the use of triethylamine (TEA) as a base for this reaction. Our hypothesis relies on the intrinsically different role of the base in the two mechanistic pathways (A and B) proposed: in path A, the base is necessary to form the imine enolate by deprotonation at the *α*-position, while in path B it acts as a proton sponge, facilitating the reduction of the Pd(II)−hydride species. In the former case, the pK_a of the base chosen, as well as its counterion, should play a central role in dictating the catalytic efficiency; in the latter case, the reactivity should not significantly be affected by

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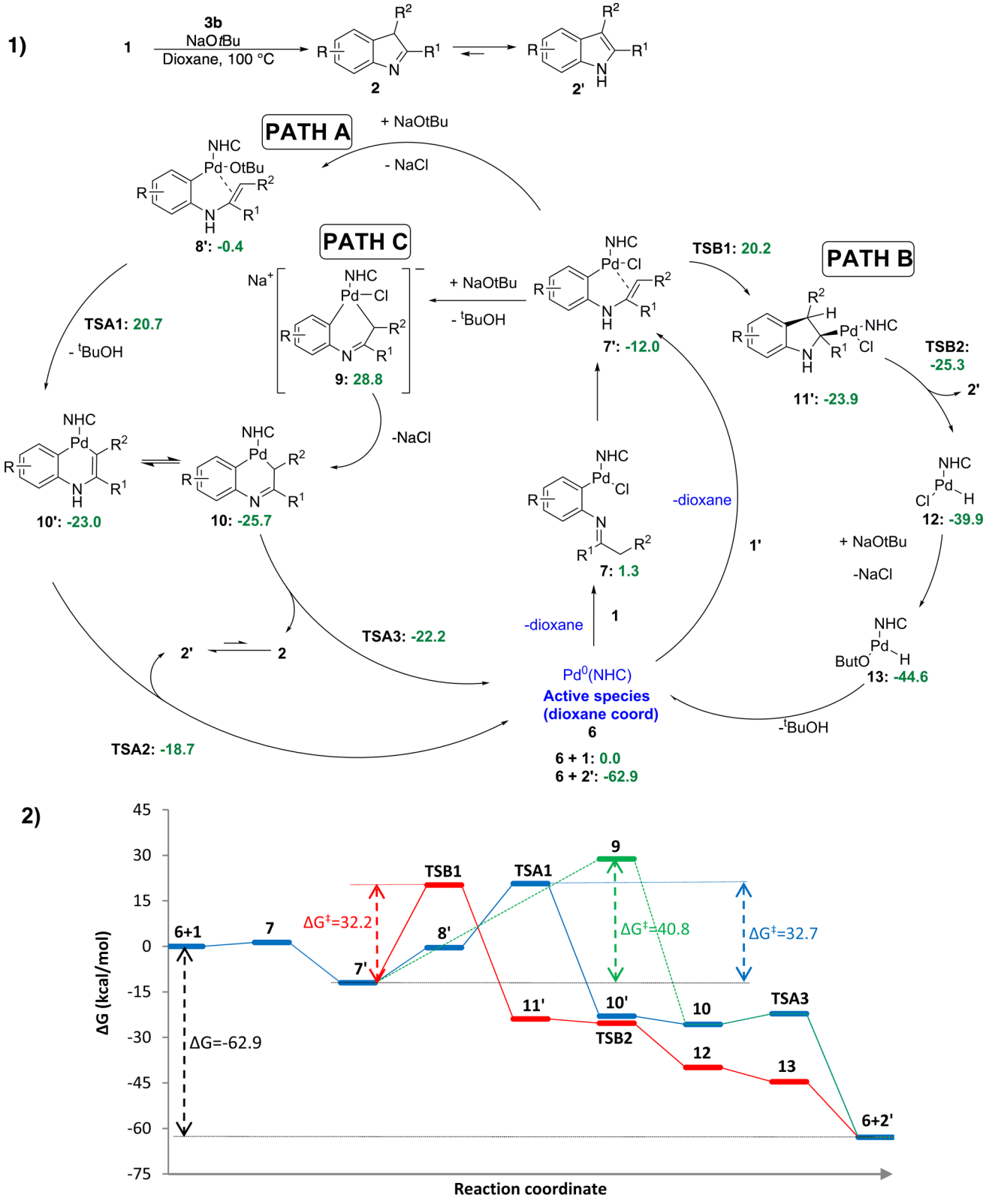
Scheme 5. (1) Possible Reaction Pathways Involved in This Approach and (2) Their Representation on the Reaction Coordinates



the pK_a of the base. This hypothesis is based on typical conditions for the Heck reaction in comparison to those employed for the AAC.[33] The use of TEA would therefore be disadvantageous if the reaction proceeds through path A, in which the deprotonation step is rate-determining, while it would not affect the reaction outcome in path B, as in that case the base is not involved in the rate-limiting step. The catalytic experiments performed are shown in Scheme 6. The reaction summarized in eq 1 was performed under the conditions previously applied for the transformation (see Scheme 3, entry

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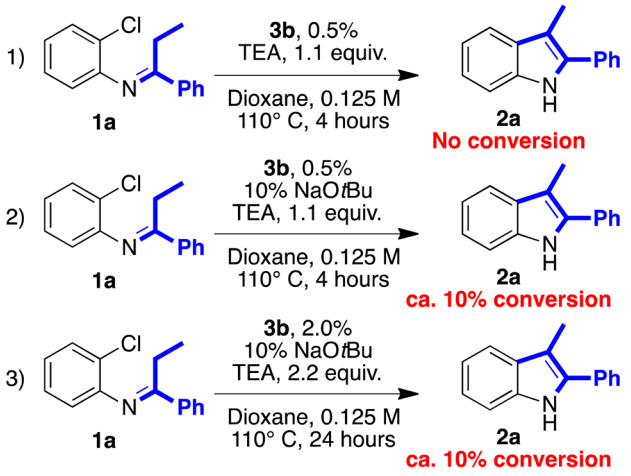
Scheme 6. Further Mechanistic Studies

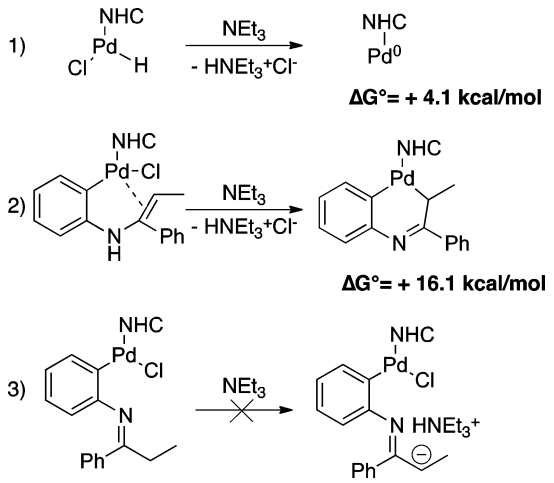


2a), substituting the *tert*-butoxide base with TEA, and afforded no detectable product.

To rule out the possibility that this could be due to the inability of such a weak base to promote the activation of the cinnamyl-based precatalyst,[34] we performed a reaction under the same conditions, adding 10 mol % of NaO*t*Bu. In this case, only 10% conversion was observed (Scheme 6, eq 2). We finally tested the feasibility of such a reaction under more forcing conditions, increasing the catalyst loading to 2.0 mol % and the reaction time to 24 h, obtaining again only 10% conversion (Scheme 6, eq 3). These results point toward an AAC-like mechanism (path A) rather than a Heck mechanism. To further confirm these data, additional computational experiments were performed, examining the thermodynamic feasibility of the catalytic steps involving the base in both paths A and B.

The reaction depicted in eq 1 of Scheme 7 was found to be thermodynamically unfavorable by 4.1 kcal/mol. Clearly, with

Scheme 7. Three Additional Reactions Used To Discriminate between Paths A and B



standard 1 M conditions the reactants are more preferable than the products. However, this equilibrium can be shifted to the left by the concentration factor and is therefore theoretically possible. The second reaction (Scheme 7, eq 2) is thermodynamically forbidden, since the associated Gibbs free energy change is 16.1 kcal/mol: this equilibrium cannot be shifted by the concentration factor. Finally, the direct α-deprotonation show in eq 3 of Scheme 7 cannot take place under the computed conditions, as the products are immediately converted to the starting materials. Comparing these computed results with the experiments performed using TEA as a base (Scheme 6), we can conclude that the Heck-like mechanism, which would be theoretically active in the presence of a weak base, can be excluded as a viable reaction route. Therefore, we propose that the reaction proceeds via a deprotonative mechanism, related to that of the α-arylation of carbonyls, when [Pd(IPr*)(cinnamyl)Cl] (**3b**) is used as a precatalyst.

CONCLUSIONS

The present work disclosed an efficient synthesis of N-unprotected indole derivatives starting from *o*-chloroarylimines. This transformation highlights the remarkable effects of the steric properties of the ligand employed and allows for the synthesis of a wide variety of functionalized compounds also on a gram scale. This protocol represents an improvement over existing methods in terms of reaction temperature, catalyst loading, average yields, and reaction scope. Other catalytic protocols leading to the synthesis and functionalization of heterocycles are currently being developed in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

Synthesis of Imines 1 and 4. *Method A.* The ketone (2.0 mmol, 1.0 equiv), 2-chloroaniline (2.4 mmol, 1.2 equiv), $NaHCO_3$ (840 mg, 10 mmol, 5 equiv), a magnetic bar, and activated molecular sieves were charged with 8 mL of toluene into a 50 mL Schlenk flask under anaerobic/anhydrous conditions. The reaction was then stirred for 16 h at 90 °C. After this time the mixture was cooled to room temperature and filtered though Celite; the solvent and the excess aniline were evaporated under reduced pressure. The imine isolated was used without further purification.

Method B. The ketone (2.0 mmol, 1.0 equiv), 2-chloroaniline (2.4 mmol, 1.2 equiv), *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol, 10%), a magnetic stirring bar, and activated molecular sieves were charged with 10 mL of toluene into a 50 mL Schlenk flask under anhydrous conditions. The reaction mixture was then stirred for 16 h at 110 °C. After this time the mixture was warmed to room temperature and was then quenched with sodium carbonate and filtered though Celite; the solvent and the excess aniline were evaporated under reduced pressure. The imine was used without further purification.

Large-Scale Synthesis of ***1c.*** A flame-dried 100 mL round-bottom flask, equipped with a stirring bar and a condenser, was charged with 30 g of activated 3 Å molecular sieves, 21.2 mL of 3-pentanone (17.3 g, 0.2 mol, 10 equiv), and 2.1 mL of 2-chloroaniline (2.51 g, 20 mmol). The mixture was heated to reflux for 48 h and then cooled to room temperature, filtered through $MgSO_4$, and washed with EtOAc; then the excess pentanone was evaporated using a rotaevaporator and the traces of 2-chloroaniline were removed. This mixture was dried at the pump for 2 days at 35 °C with stirring. The desired product was obtained as a yellow liquid (2.5 g, 64%).

Optimized Protocol for the Cyclization of Imines into Indoles. *Method Cy-A.* The precatalyst **3b** ([Pd(IPr*)-

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(cinnamyl)Cl]; 1.5 mg, 0.5 mol %), the imine (0.25 mmol, 1 equiv), and NaO*t*Bu (26.4 mg, 0.28 mmol, 1.1 equiv) were weighed and charged into a screw-cap vial equipped with a magnetic stirring bar. The vial was closed with a septum cap and purged with three vacuum/nitrogen cycles. Dry dioxane (2 mL) was added with a syringe, and the reaction mixture was then stirred at 110 °C for 4 h. The vessel was then cooled to room temperature, and the reaction was quenched with 3 drops of water; the organic phase was filtered through magnesium sulfate, washing with ethyl acetate. The two reaction duplicates were purified together via flash chromatography to afford the pure product.

Method Cy-B. The precatalyst **3b** ([Pd(IPr*)(cinnamyl)Cl]; 1.6 mg, 0.5 mol %), the imine (0.25 mmol, 1 equiv), and NaO*t*Bu (26.4 mg, 0.28 mmol, 1.1 equiv) were weighed into a screw-cap vial equipped with a magnetic stirring bar. The vial was closed with a septum cap and purged with three vacuum/nitrogen cycles. Dry dioxane (2 mL) was added by syringe, and the reaction mixture was then stirred at 110 °C for 16 h. The vessel was then cooled to room temperature and the reaction quenched with 3 drops of water; the organic phase was filtered through magnesium sulfate, washing with ethyl acetate. The two reaction duplicates were purified together via flash chromatography to afford the desired product.

Method Cy-C. The precatalysts **3b** [Pd(IPr*)(cinnamyl)Cl] (5.9 mg, 2.0%), the imine (0.25 mmol, 1 equiv), and NaO*t*Bu (26.4 mg, 0.28 mmol, 1.1 equiv) were weighed into a screw-cap vial equipped with a magnetic stirring bar. The vial was closed with a septum cap and purged with three vacuum/nitrogen cycles. Dry dioxane (2 mL) was added with a syringe, and the reaction mixture was then stirred at 110 °C for 24 h. The vessel was then cooled to room temperature, and the reaction was quenched with 3 drops of water; the organic phase was filtered through magnesium sulfate, washing with ethyl acetate. The two reaction duplicates were purified together via flash chromatography to afford the desired product.

Large-Scale Cyclization. A flame-dried 250 mL Schlenk flask containing a stirring bar was charged with NaOtBu (1.15 g, 12 mmol, 1.2 equiv) and filled with argon, and then 60 mL of dry, degassed dioxane was added via syringe. The imine (1.95 g, 10 mmol) was weighed into a vial and added via syringe, washing both vial and syringe with dioxane (2 × 5 mL). [Pd(IPr*)(cinnamyl)Cl] (**3b**; 55 mg, 0.5 mol %) was dissolved in 5 mL of dioxane and added to the reaction mixture with a syringe, washing with 5 mL of dioxane. The flask was then immerged in a preheated oil bath at 110 °C, stirring at 300 rpm for 24 h. The reactor was then cooled to room temperature and the reaction mixture quenched with 20 mL of water and extracted with diethyl ether (4 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was left under high vacuum for 2 h, after which time NMR analysis revealed the pure product to be present (>95%). Isolated yield: 1.31 g, 83%.

Computational Details. *Geometry Optimizations and Calculations of Thermochemical Corrections.* All geometry optimizations were performed using the PBE GGA[35] functional as implemented in the PRIRODA 13 DFT code.[36] All-electron basis sets (λ1)[37] comparable in quality to the correlation consistent valence double-ζ plus polarization (cc-PVDZ) basis sets of Dunning were used. All stationary geometries were characterized by an analytically calculated Hessian matrix. Scalar relativistic effects (for Pd and Br) were taken into account via the Dyall Hamiltonian.[38] The default, adaptively generated PRIRODA grid, corresponding to an accuracy of the exchange-correlation energy per atom (1×10^{-8} hartree) was decreased by a factor of 100 for more accurate evaluation of the exchange-correlation energy. Default values were used for the self-consistent-field (SCF) convergence and the maximum gradient for geometry optimization criterion (1×10^{-4} au), whereas the maximum displacement geometry convergence criterion was decreased to 0.0018 au. Translational, rotational, and vibrational partition functions for thermal corrections to arrive at total Gibbs free energies were computed within the ideal-gas, rigid-rotor, and harmonic oscillator approximations. The temperature used in the calculations of thermochemical corrections was set to 298.15 K in all cases.

Single-Ooint (SP) Energy Evaluations. The energies were re-evaluated at optimized geometries by means of the M06[39] functional as implemented in the Gaussian 09 code.[40] All-electron def2-tzvpp basis sets of the Ahlrichs group were used with corresponding density-fitting basis sets.[41] The default value for the SP SCF convergence was adopted. The "Integral (grid = ultrafine)" option was used for evaluation of the exchange-correlation term.

Solvent Effects. Electrostatic and nonelectrostatic solvent effects were estimated by means of the SMD[42,43] solvation model as implemented in the Gaussian 09 code. The internal program values for 1,4-dioxane (dielectric constant etc.) were adopted.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00040.

Experimental procedures, computational details, and characterization of the products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (c) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (d) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627−646.
(2) Hughes, G.; Bryce, M. R. *J. Mater. Chem.* **2005**, *15*, 94−107.
(3) (a) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635−1642. (b) Fischer, E.; Hutz, H. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 585−587.

DOI: 10.1021/acscatal.6b00040
ACS Catal. 2016, 6, 2930−2938

(4) Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4282−4288.
(5) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690.
(6) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915−3918.
(7) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644−4680. (b) D'Souza, D. M.; Muller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095−1108. (c) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929−3968. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1−35.
(8) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676−707.
(9) (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1742. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (c) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383.
(10) For selected reports on the arylation of carbonyl compounds, see: (a) Martín, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236−7239. (b) Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489−5492. (c) Grasa, G. A.; Colacot, T. J. *Org. Process Res. Dev.* **2008**, *12*, 522−529. (d) Biscoe, M. R.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 1773−1775. (e) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194−5197. (f) Johansson Seechurn, C. C. C.; Parisel, S. L.; Colacot, T. J. *J. Org. Chem.* **2011**, *76*, 7918−7932. (g) Crawford, S. M.; Alsabeh, P. G.; Stradiotto, M. *Eur. J. Org. Chem.* **2012**, *2012*, 6042−6050. (h) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 4190−4193. (i) Raders, S. M.; Jones, J. M.; Semmes, J. G.; Kelley, S. P.; Rogers, R. D.; Shaughnessy, K. H. *Eur. J. Org. Chem.* **2014**, *2014*, 7395−7404. (j) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. *J. Org. Chem.* **2015**, *80*, 6794−6813.
(11) Potukuchi, H. K.; Spork, A. P.; Donohoe, T. J. *Org. Biomol. Chem.* **2015**, *13*, 4367−4373.
(12) (a) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168−15169. (b) Barluenga, J.; Jiménez-Aquino, A.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1529−1532. (c) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031−4041. (d) Hellal, M.; Singh, S.; Cuny, G. D. *J. Org. Chem.* **2012**, *77*, 4123−4130. (e) Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10588−10591. (f) Rotta-Loria, N. L.; Borzenko, A.; Alsabeh, P. G.; Lavery, C. B.; Stradiotto, M. *Adv. Synth. Catal.* **2015**, *357*, 100−106. (g) Pham, N. N.; Dang, T. T.; Ngo, N. T.; Villinger, A.; Ehlers, P.; Langer, P. *Org. Biomol. Chem.* **2015**, *13*, 6047−6058.
(13) (a) Eidamshaus, C.; Burch, J. D. *Org. Lett.* **2008**, *10*, 4211−4214. (b) Lee, J. H.; Kim, M.; Kim, I. *J. Org. Chem.* **2014**, *79*, 6153−6163.
(14) (a) Donohoe, T. J.; Pilgrim, B. S.; Jones, G. R.; Bassuto, J. a. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 11605−11608. (b) Pilgrim, B. S.; Gatland, A. E.; McTernan, C. T.; Procopiou, P. A.; Donohoe, T. J. *Org. Lett.* **2013**, *15*, 6190−6193.
(15) Hardegger, L. A.; Habegger, J.; Donohoe, T. J. *Org. Lett.* **2015**, *17*, 3222−3225.
(16) Sivanandan, S. T.; Shaji, A.; Ibnusaud, I.; Seechurn, C. C. C. J.; Colacot, T. J. *Eur. J. Org. Chem.* **2015**, *2015*, 38−49.
(17) Gatland, A. E.; Pilgrim, B. S.; Procopiou, P. A.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 14555−14558.
(18) (a) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440−1449. (b) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151−5169. (c) Lundgren, R. J.; Stradiotto, M. *Chem. - Eur. J.* **2012**, *18*, 9758−9769.
(19) (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370. (b) Carole, W. A.; Bradley, J.; Sarwar, M.; Colacot, T. J. *Org. Lett.* **2015**, *17*, 5472−5475.
(20) Marelli, E.; Corpet, M.; Davies, S. R.; Nolan, S. P. *Chem. - Eur. J.* **2014**, *20*, 17272−17276.
(21) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920. (b) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J. C. *Chem. Soc. Rev.* **2012**, *41*, 3929−3968.
(22) This approach has been successfully used by Spergel and co-workers, although their protocol has major drawbacks regarding substrate scope (only electron-poor aniline derivatives) and efficiency (20% loading of a well-defined Pd-NHC complex was necessary to reach generally moderate yields): (a) Spergel, S. H.; Okoro, D. R.; Pitts, W. *J. Org. Chem.* **2010**, *75*, 5316−5319. A complementary method for the synthesis of 2-vinyl, N-unprotected indoles and carbazoles has been recently reported by Kapur and co-workers: (b) Kale, A. P.; Kumar, G. S.; Mangadan, A. R. K.; Kapur, M. *Org. Lett.* **2015**, *17*, 1324−1327.
(23) Lachance, N.; April, M.; Joly, M.-A. *Synthesis* **2005**, 2571−2577. Together with the works in ref 22, this is the only Pd-catalyzed protocol affording N-unprotected indoles to our knowledge.
(24) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816−3821.
(25) (a) Szilvási, T.; Veszprémi, T. *ACS Catal.* **2013**, *3*, 1984−1991. (b) Izquierdo, F.; Manzini, S.; Nolan, S. P. *Chem. Commun.* **2014**, *50*, 14926−14937.
(26) (a) Martin, A. R.; Makida, Y.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2013**, *32*, 6265−6270. (b) Martin, A. R.; Nelson, D. J.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. *Eur. J. Org. Chem.* **2014**, *2014*, 3127−3131. (c) Fernández-Salas, J. A.; Marelli, E.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P. *Chem. - Eur. J.* **2015**, *21*, 3906−3909. (d) Marelli, E.; Fernández Salas, J. A.; Nolan, S. P. *Synthesis* **2015**, *47*, 2032−2037.
(27) (a) Makida, Y.; Marelli, E.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2014**, *50*, 8010−8013. (b) Schramm, Y.; Takeuchi, M.; Semba, K.; Nakao, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 12215−12218.
(28) (a) Hussong, M. W.; Rominger, F.; Krämer, P.; Straub, B. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 9372−9375. (b) Hussong, M. W.; Hoffmeister, W. T.; Rominger, F.; Straub, B. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10331−10335.
(29) Complex **3b** can be purchased on a larger scale from Umicore and in research quantities from Strem (Cat. No. 46-0298) .
(30) Nadelson, J. (Sandoz, Inc.) U.S. Patent 4,582,848, 1986.
(31) Bae, J.; Kim, J. (LG Chem, Ltd.) Eur. Patent EP2332911A2, 2011.
(32) Kondo, T.; Kondo, A.; Tatani, K.; Kawamura, N. (Kissei Pharmaceutical Co. Ltd.) U.S. Patent US2012/122931 A1, 2012.
(33) (a) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120−1132. (b) Saab, F.; Bénéteau, V.; Schoentgen, F.; Mérour, J.-Y.; Routier, S. *Tetrahedron* **2010**, *66*, 102−110. (c) Mérour, J.-Y.; Routier, S.; Suzenet, F.; Joseph, B. *Tetrahedron* **2013**, *69*, 4767−4834.
(34) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. See also conditions reported in ref 22.
(35) (a) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111. (b) Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M. *J. Am. Chem. Soc.* **2014**, *136*, 7300−7316. (c) Takeda, Y.; Ikeda, Y.; Kuroda, A.; Tanaka, S.; Minakata, S. *J. Am. Chem. Soc.* **2014**, *136*, 8544−8547.
(36) (a) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1997**, *78*, 1396−1396. (b) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865−3868.
(37) Laikov, D. N.; Ustynyuk, Y. A. *Russ. Chem. Bull.* **2005**, *54*, 820−826.
(38) Laikov, D. N. *Chem. Phys. Lett.* **2005**, *416*, 116−120.
(39) Dyall, K. G. *Chem. Phys. Lett.* **1994**, *224*, 186−194.
(40) Zhao, Y.; Truhlar, D. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(41) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, T.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.;

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ACS Catal. 2016, 6, 2930−2938

Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, R.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision D.01*; Gaussian, Inc., Wallingford, CT, 2009.

(42) (a) Weigend, F. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057−1065. (b) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.

(43) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.

DOI: 10.1021/acscatal.6b00040
ACS Catal. 2016, 6, 2930−2938