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C(sp^3)–H Arylation Promoted by a Heterogeneous Palladium-N-Heterocyclic Carbene Complex in Batch and Continuous Flow

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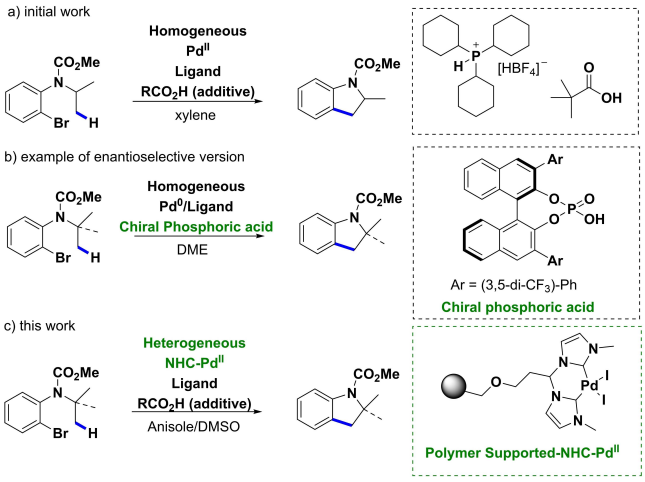
A heterogeneous reusable palladium(II)-bis(N-heterocyclic carbene) catalyst was prepared and shown to catalyze the intramolecular C(sp^3)–H activation/cyclization of *N*-alkyl-2-bromoanilines furnishing indolines. This new catalytic system was based on a bis-imidazolium ligand immobilized on a spaced cross-linked polystyrene support. The iodide ligands on the catalyst played a central role in the efficiency of the process occurring through a "release and catch" mechanism. The heterogeneous nature of the catalyst was further exploited in the design of a continuous-flow protocol that allowed a more efficient recovery and reuse of the catalyst, as well as a very fast and safe procedure.

Introduction

In the past years, the synthesis of natural products and biologically active compounds promoted by transition-metal-catalyzed C–H bond activation has raised a growing interest.[1] Whereas C(sp^2)–H activation is facilitated by a higher acidity and more favorable reactant–catalyst interactions, the activation of C(sp^3)–H bonds for the formation of carbon–carbon or carbon–heteroatom bonds is still a significant and stimulating challenge.[2]

In this context, the palladium(0)-catalyzed activation of unactivated methyl or methylene C–H bonds has been an effective strategy for the construction of carbo- and heterocycles, and has attracted a great deal of attention in the past years.[3,4] In particular, Ohno and co-workers reported an interesting methodology allowing the intramolecular coupling of *N*-aryl-*N*-alkyl carbamates to access indolines, molecules of broad interest for the synthesis of bioactive compounds and natural products. Since the initial work by Ohno and co-workers (Scheme 1a),[3j] several groups developed enantioselective versions of this reaction using either chiral phosphine or N-heterocyclic carbene (NHC) ligands.[5] In particular, Baudoin and co-workers reported a very efficient asymmetric Pd^0-catalyzed C(sp^3)–H activation/cyclization using a catalytic chiral base and an achiral phosphine ligand,[6] exploiting the presence of the coordinated chiral base during the C–H bond cleavage (Scheme 1b).

C–H activation processes are showing an increasingly larger scope of applications in various areas of organic synthesis. However, they mostly rely on the use of homogeneous catalytic systems, which, although very efficient, are usually very difficult to recover and recycle. This usually leads to the need for additional purification steps to completely remove metal traces from the products. Nowadays, the attention of the scientific community is shifting towards more environmentally favorable



Scheme 1. Indolines by Pd^0-catalyzed C(sp^3)–H arylation: precedents and current work. For a) see Ref. [3j]; for b) see Ref. [6].

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solutions that involve the use of recoverable and reusable heterogeneous catalytic systems.[7] Besides the use of inorganic supports,[8] our research group's attention has been directed towards the development of organic polystyrene-based supports featuring ionic heterocyclic pincer-type ligands (POLymeric Ionic Tag, POLITAG) to develop effective recoverable transition-metal catalysts.[9]

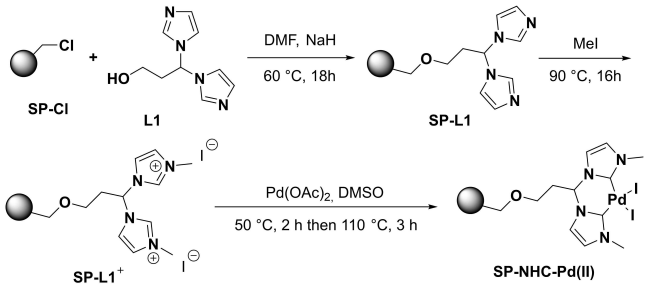
In particular, heterogeneous POLITAG–Pd catalysts have been successfully employed to promote the selective C2–H alkenylation of quinoline *N*-oxides,[10] showing a complete recoverability and minimal leaching of the metal via a purely heterogeneous mechanism. Besides, the use of reusable NHC-based complexes in organometallic catalysis has provided effective and more sustainable chemical procedures.[11] Bidentate methylene-bridged bis(NHC) systems have proven their versatility in anchoring a wide range of metals, leading to several catalytic applications.[12] In this study, as an extension of our ongoing efforts to develop recoverable catalytic systems, we report a new polystyrene-supported heterogeneous palladium catalyst based on a bis(NHC) ligand which enables the sustainable and effective synthesis of indolines via C(sp^3)–H arylation (Scheme 1c). The utility of this heterogeneous system is further demonstrated through the development of a reactor that allows to perform this reaction in continuous flow on a larger scale.

In the last two decades, continuous-flow processes have proven their utility and advantages over typical batch processes. Efficient heat transfer, improvement in mixing, ease of scale-up, precise control of the reaction conditions, and ability to operate at high temperature and pressure, thus reducing reaction time, are some of the promising features that make protocols conducted in continuous flow attractive.[13] In addition, flow chemistry has proven to be very effective when using heterogeneous catalysts as their stability and durability is preserved while the production of waste is minimized.[14] A number of C–H activation protocols have been developed in flow under homogeneous or heterogeneous conditions. However, there are very few examples of flow processes for catalytic C(sp^3)–H activation especially under heterogeneous flow conditions.[15,16] The current work presents, to the best of our knowledge, the first example of heterogeneous palladium(0)-catalyzed C(sp^3)–H activation in continuous flow.

Results and Discussion

The synthesis of the heterogeneous catalyst was performed by anchoring a bis-imidazole derivative (**L1**) onto our gel-type spaced cross-linked polystyrene (SPACER) resin[17] followed by quaternization using MeI as previously described (Scheme 2).[10] Finally, the Pd catalyst was prepared by stirring the resulting polystyrene supported bis-imidazolium iodide in a solution of $Pd(OAc)_2$ in DMSO. The amount of palladium was determined by microwave plasma-atomic emission spectroscopy (MP-AES) measurement, showing a 2.8 wt% loading of palladium.

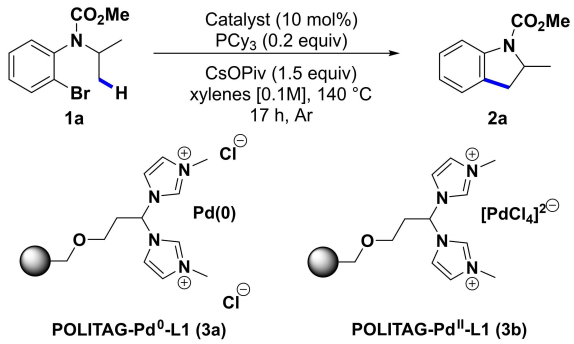
We then tested the efficiency of SP-NHC-Pd^{II} on the Pd-catalyzed C(sp^3)–H arylation of model substrate **1 a** leading to



Scheme 2. Synthesis of SP-NHC-Pd^{II} complex.

indoline **2 a**, using stoichiometric cesium pivalate as the active base (Table 1). The latter is preferable to the combination of catalytic pivalic acid and stoichiometric cesium carbonate, which is usually employed under homogeneous conditions,[18] for solubility reasons. The immobilized palladium complex SP-NHC-Pd^{II} proved to be an excellent alternative to homogeneous $Pd(OAc)_2$, providing a comparable conversion and yield (entries 1 and 2; see the Supporting Information for the detailed optimization of the reaction conditions). While the two commercially available microencapsulated Pd^{II} heterogeneous catalysts Pd-EnCat 30 and Pd-EnCat 40 were less effective leading to the desired product with lower conversions (entries 5 and 6), Pd/C showed a very good catalytic activity, with a full

Table 1. Tests of catalytic efficiency for the intramolecular C(sp3)–H arylation of **1 a**.[a]



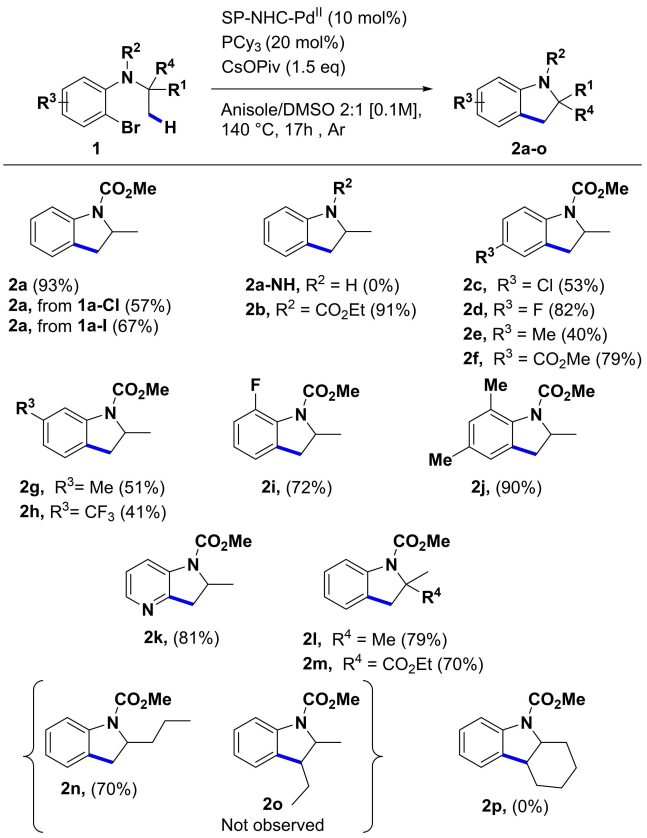
Entry	Catalyst	Yield[b] [%]
1	SP-NHC-Pd^{II}	95
2[c]	$Pd(OAc)_2$	96
3	Pd/C	92
4	Pd/C	NR (2nd run)[h]
5	Pd-EnCat 30[d]	70
6	Pd-EnCat 40[d]	65
7	POLITAG-Pd^0-L1 (**3 a**)[e]	20
8	POLITAG-Pd^{II}-L1 (**3 b**)[e]	25
9[f]	SP-NHC-Pd^{II}	NR
10[g]	SP-NHC-Pd^{II}	95
11	SP-NHC-Pd^{II}	95 (2nd run)[h]

[a] Reaction conditions: **1 a** (0.2 mmol), PCy_3 (20 mol%), CsOPiv (1.5 equiv.), xylenes [0.1 M], 140 °C, 17 h. [b] NMR yield using trichloroethylene as internal standard. [c] Using 5 mol% of catalyst. [d] Palladium acetate, microencapsulated in polyurea matrix. [e] For synthesis and characterization see ref. [10]. [f] Without PCy_3. [g] A 2:1 mixture of anisole and DMSO was used instead of xylenes. [h] Reaction conditions for the 2nd run are equal to the reaction conditions for the 1st run.

conversion to the indoline product **2a** (entry 3). However, a crucial difference between SP-NHC-Pd^{II} and Pd/C was found in recovery and reuse tests. Indeed, Pd/C completely lost its catalytic activity already at the second run (entry 4) whereas the activity was maintained with SP-NHC-Pd^{II} (entry 11).

Stimulated by the efficiency of Pd/C, ionic catalysts (POLITAG) containing either Pd^{0} or Pd^{II} (**3a** and **3b**), which provided interesting results in a previously reported C(sp^2)–H alkenylation,[10] were examined. However, these POLITAG catalysts gave incomplete conversions of the starting material in otherwise identical conditions (entries 7 and 8). It is worth noting that in the reaction catalyzed by SP-NHC-Pd^{II}, no conversion to **2a** occurred in the absence of phosphine ligand (entry 9), and among the tested monodentate phosphines, PCy_3 furnished the best results (Table S1). Several other variations of reaction conditions were also tested (Table S2). In particular, since the reagents are partially insoluble in xylenes, and keeping in mind the goal of achieving this reaction in flow, we tested various alternative reaction media. Among these, a mixture of anisole and dimethyl sulfoxide (DMSO) in a 2:1 ratio provided the best balance between solubility of the different reagents and reactivity, while preserving a good miscibility (entry 10). In particular, the presence of DMSO had a positive influence to minimize the formation of the proto-dehalogenated side-product, which was observed in minimal amounts (2%).

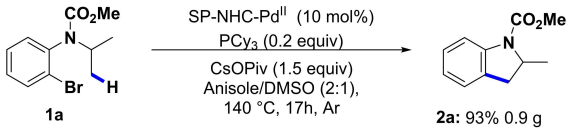
With the optimized conditions in hand, the scope and limitations of the indoline synthesis were examined with various 2-haloaniline derivatives (Scheme 3). The influence of the halide was first investigated. While the chloride **1a-Cl** provided a lower reactivity and gave **2a** along with the proto-dehalogenated starting material (30%), the iodide **1a-I** led to indoline **2a** with a slightly higher yield but still accompanied by proto-dehalogenated starting material (12%). The bromide **1a** showed the best reactivity, furnishing the desired product **2a** with a very good isolated yield (93%) and only 2% of the proto-dehalogenated **1a**. The presence of the *N*-carbamate protecting group was found to be crucial. Indeed, the reaction of the free aniline **1a-NH** did not provide any product and 92% of the starting material were recovered. Methyl or ethyl carbamates were found to be optimal substrates, providing the indoline products **2a** and **2b** in high yields. The reaction of variously substituted bromoanilines was then investigated, giving rise to products **2c-k** with satisfactory results. A good tolerance of substituents possessing various electronic characteristics at different positions on the aromatic ring was observed. Moreover, an azaindoline derivative (**2k**) was also obtained in good yield, hence demonstrating further the applicability of this C–H activation process. Substrates **1l** and **1m** containing a tetrasubstituted carbon were also investigated,[6] and furnished the corresponding indoline products (**2l**, **2m**), featuring a valuable α-quaternary amino acid moiety, with good yields. We finally examined the palladium-catalyzed C(sp^3)–H arylation of other branched alkyl substrates to compare the reactivity of methyl and methylene groups. Using the optimized conditions, the reaction proceeded smoothly towards the formation of product **2n** in good yield, whereas product **2o** was not observed. The



Scheme 3. Substrate scope of the reaction. Reaction conditions: **1** (0.2 mmol), SP-NHC-Pd^{II} (10 mol% Pd), PCy_3 (20 mol%), CsOPiv (1.5 equiv.), anisole/DMSO 2:1 [0.1 M], 140 °C, 17 h.

inability of the current catalytic system to activate secondary C–H bonds was further demonstrated with *N*-cyclohexyl substrate **1p**, which failed to deliver tricyclic product **2p**. Finally, a gram-scale reaction of the model substrate **1a** (5.0 mmol) using the SP-NHC-Pd^{II} heterogeneous catalyst was performed without any detrimental effect on the reactivity and provided product **2a** in 93% yield (Scheme 4).

Transmission electron microscopy (TEM) analyses of the SP-NHC-Pd^{II} catalyst, performed before and after its use, showed the formation of Pd nanoparticles (≈4 nm) in small quantities (Figure S1). Investigations were hence conducted to elucidate the nature of the active catalyst and its mode of action. Since different anions are present in the reaction mixture (iodide from the starting catalyst, bromide from the substrate and pivalate from the base), the role of the anionic ligand in the NHC catalyst was investigated. To this aim, homogeneous bis(NHC) catalysts possessing iodide, bromide or pivalate as anionic

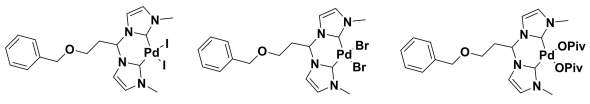


Scheme 4. Gram-scale batch reaction of **1a**.

ligand were synthesized (see the Supporting Information) and their catalytic activity examined (Table 2). A significantly lower activity was observed for the bromide- (NHC–Pd_Br_2, entries 3 and 4) and pivalate-based (NHC–Pd_$PivO_2$, entry 5) catalysts compared to the iodide-based catalyst (NHC–Pd_I_2, entries 1 and 2), thereby indicating the pivotal role of the initial iodide in maximizing the efficiency of the heterogeneous catalyst. In line with this result, we found that the catalytic activity of SP-NHC-Pd^{II} could be maintained over 3 runs upon regeneration via stirring in a saturated KI solution in DMSO.

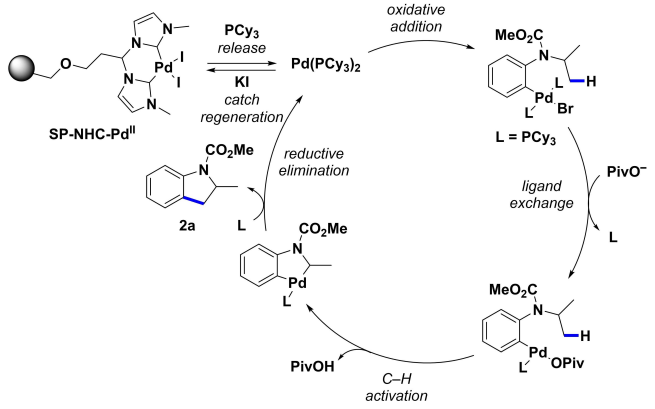
Further investigations on the nature of the active catalyst were conducted via Hg poisoning and hot filtration tests (Table S5). First, we observed that the reaction still occurred and led to comparable results to the standard experiment after filtrating the hot reaction mixture or after adding an excess of Hg. These results indicate that a homogeneous Pd complex rather than Pd nanoparticles is responsible for the catalytic activity. In an attempt to identity this homogeneous species, the supernatant of the mixture of SP-NHC-Pd^{II} and PCy_3 at room temperature was analyzed by ^{31}P NMR spectroscopy (Figure S2). This analysis revealed the formation of [$Pd(PCy_3)_2$], which is the active complex in homogeneous C(sp^3)–H arylation reactions catalyzed by Pd^0/PCy_3,[19] together with O=PCy_3. The latter presumably arises from the hydrolysis of the initially formed $PCy_3{\cdot}I_2$ salt[20] with traces of water. Finally, a relatively low palladium leaching (≈17 ppm) was observed in solution during the catalytic process (Table S6). Taken together, these results indicate that a "release and catch" mechanism is operative, with the homogeneous [$Pd(PCy_3)_2$] complex as the catalytically active species.[21]

Table 2. Catalytic test of homogeneous complexes with different anionic ligands.[a]



Entry	catalyst	Yield[b] [%]	*t* [h]	TON[c]	TOF[d] [h^{-1}]
1	NHC-Pd^{II}_I_2 (**4a**)	>99	3	10	3.3
2	NHC-Pd^{II}_I_2 (**4a**)	35	1	10	3.5
3	NHC-Pd^{II}_Br_2 (**4b**)	56	3	5.6	1.8
4	NHC-Pd^{II}_Br_2 (**4b**)	20	1	5.6	2
5	NHC-Pd^{II}_Piv_2 (**4c**)	21	3	2.1	0.7

[a] Reaction conditions: **1a** (0.1 mmol), Pd^{II} catalyst (10 mol%), PCy_3 (20 mol%), CsOPiv (1.5 equiv.), anisole/DMSO = 2:1 [0.1 M], 140 °C. [b] NMR yield using trichloroethylene as internal standard. [c] Turnover number. [d] Turnover frequency.



Scheme 5. Proposed mechanism.

Based on these data, a plausible reaction mechanism is depicted in Scheme 5. After an initial induction period during which [$Pd(PCy_3)_2$] is released into solution by reduction and coordination with PCy_3, oxidative addition of the aryl bromide substrate and subsequent ligand exchange with pivalate[19] set the stage for the C–H activation event. After reductive elimination from the palladacycle intermediate, product **2a** is formed together with the active Pd^0 catalyst. After the reaction, Pd is recaptured by the supported bis-NHC ligand and SP-NHC-Pd^{II} is regenerated. The exact mechanism of this regeneration, which must involve oxidation of Pd^0 to Pd^{II} and coordination of iodide anions, is unknown at this stage and will be the subject of future investigations.

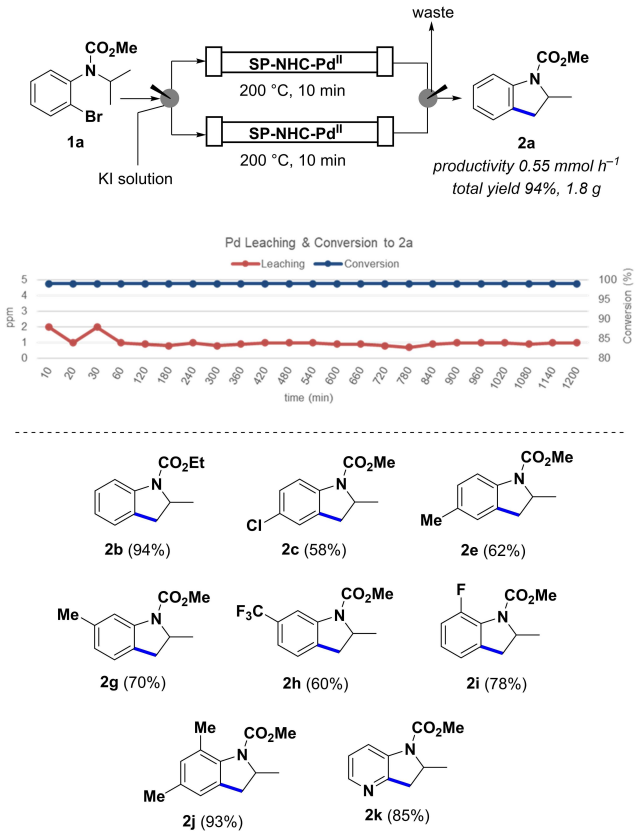
In order to conduct the indoline synthesis using an automated protocol on larger scale while simplifying the catalyst recovery, regeneration, and reuse, we directed our attention towards the development of a continuous flow process. To this purpose, a stainless-steel column was filled with SP-NHC-Pd^{II} (47 mg, 2.8 wt%, 0.012 mmol of Pd) and glass powder to disperse the catalyst. After an initial optimization of the flow parameters (Table 3), the correct residence time, temperature and back pressure unit were established (entry 4). The reaction was left to flow through the column charged with the catalyst and kept at 200 °C. An impressive increase in the reactivity was observed, furnishing product **2a** in 93% yield with only 10 min of residence time. These conditions allowed a dramatic reduction of the reaction time, while operating under safe conditions and completely preserving the morphology of the solid catalyst despite the high temperature (as confirmed by thermogravimetric analysis). Indeed, under flow conditions the catalyst is maintained in the sealed packed reactor and is not damaged by mechanical stirring, making its recovery and reuse facile and reproducible[22] without requiring a manual filtration.

To optimize the regeneration procedure, we installed two parallel catalyst columns and an automated valve able to easily switch from the reagent line to a solution of KI (Scheme 6, top). This continuous-flow procedure was tested for 20 h using a

Table 3. Flow parameters optimization.

Entry	*T* [°C]	Flow rate [mL min^{-1}]	BPR [psi]	Residence time [min]	Yield[b] [%]
1	140	0.2	20	120	22
2	160	0.5	40	110	54
3	200	1	20	5	46
4	200	0.1	20	10	93[c]

[a] Reaction conditions: **1a** (0.2 mmol), SP-NHC-Pd^{II} (10 mol%), PCy3 (20 mol%), CsOPiv (1.5 equiv.), anisole/DMSO 2:1 [0.1 M], [b] NMR yield using trichloroethylene as internal standard. [c] Isolated yield.



Scheme 6. Development of a continuous-flow procedure.

total of 10 mmol of **1 a**. The achievement of the steady state of the flow reactor was observed by crossing the obtained conversion and leaching values over the time, and was reached after both column reactors were switched once. Notably, a reduced palladium leaching was observed compared to batch conditions (Scheme 4, middle), with a minimal average palladium leaching over the course of a 20 h-long operating flow procedure. Indeed, compared to batch conditions in which around 17 ppm of Pd was leached (Table S6), under flow conditions the periodical measurement never exceeded the value of 2 ppm, and was always around 1 ppm after reaching the steady state (Scheme 6, middle). This manifold allowed to achieve an indoline productivity of around 0.5 mmol h^{-1} and to obtain 1.8 g of **2 a** with a total yield of 94%. The scope of the flow procedure was further tested for representative substrates, leading in all cases to higher yields compared to the equivalent batch conditions (Scheme 6, bottom), and thus offering a practical and fast access to these indoline products.

Conclusion

We developed the first Pd^0-catalyzed C(sp^3)–H functionalization process promoted by a heterogeneous and reusable palladium(II)-bis[N-heterocyclic carbene (NHC)] catalyst. This catalyst proved efficient to synthesize a range of indoline products containing both α-tertiary and -quaternary carbons. Mechanistic investigations indicated that this system proceeds via a "release and catch" mode of action, with release of the catalytically active homogeneous [$Pd(PCy_3)_2$] complex and recapture of Pd by the supported bis-NHC ligand. These investigations also led to the development of an innovative continuous-flow procedure, hence setting the stage for the use of such C–H activation methodologies in an industrial setting.

Experimental Section

Unless otherwise stated, all solvents and reagents were used as obtained from commercial sources without further purification. Anhydrous solvents were obtained by distillation over calcium hydride (anisole and xylenes). Anhydrous DMSO was obtained by storage of the solvent over activated 3 Å molecular sieves for at least 72 h. The solvents were degassed by three cycles of freeze–pump–thaw. GC analyses were performed by using a Hewlett-Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm), a flame-ionization detector (FID), and helium as gas carrier. GC-EIMS analyses were carried out using a Hewlett-Packard HP 6890 N Network GC system/5975 Mass Selective Detector equipped with an electron impact ionizer at 70 eV. NMR spectra were recorded on a Bruker DRX-ADVANCE 400 MHz (1H at 400 MHz, 13 C at 100.6 MHz and 19F at 376 MHz) using $CDCl_3$ or DMSO-d6 as solvents and tetramethyl silane (TMS) as the internal standard. Chemical shifts are reported in ppm with multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants in Hertz. Elemental analysis (EA) was conducted on Elementar UNICUBE® elemental analyzer. Palladium content was measured by using an Agilent 4210 MP AES instrument.

General procedure for the synthesis of indolines in batch

N-alkyl-o-haloarylamine derivative (0.2 mmol, 1.0 equiv.), catalyst (0.1 equiv.), cesium pivalate (1.5 equiv.), and PCy_3 (0.2 equiv.) were successfully weighted and placed into a 4 mL screw capped vial equipped with a magnetic stirrer under argon. Degassed dry anisole/DMSO = 2:1 (2 mL) was added under argon. The resulting mixture was sealed with a Teflon-lined cap and vigorously stirred at 140 °C for 17 h using a preheated metal round block. After that time, the reaction mixture was cooled down to room temperature and the catalyst was recovered by centrifugation (3 × 2 mL, 6000 rpm, 15 min at 5 °C). The supernatant was concentrated under reduced pressure, and the crude was directly purified by flash column chromatography on silica gel using EtOAc/petroleum ether mixture as an eluent to afford the desired indoline.

Catalyst regeneration

The recovered catalyst was stirred in a saturated solution on KI in DMSO (2 mL) at 25 °C for 1 h. After centrifugation, the supernatant liquid was removed, and the catalyst as washed with DMSO (2 mL) and acetone (1 mL) and dried under vacuum at 120 °C overnight. The dried catalyst was reused for the model reaction.

Leaching studies

Following separation and regeneration of the catalyst, the crude reaction mixture was dried under reduced pressure and digested in 2 mL of aqua regia for 1 h. Subsequently, the digested material was

diluted in milli-Q water to a final volume of 10 mL. The residual organic solid was filtered off and the amount of palladium leached in solution was measured with a microwave plasma-atomic emission spectrometer (MP-AES 4210), and the results are reported in the Table 3.

General flow procedure for the synthesis of indolines

N-alkyl-o-haloarylamine derivative (1.0 equiv.), cesium pivalate (1.5 equiv.), and PCy_3 (0.2 equiv.) were successfully weighted and placed into a 4 mL screw-capped vial equipped with a magnetic stirrer under argon and capped with a septum. Degassed dry anisole/DMSO = 2 : 1 [0.1 M] were added to the vial and continuously stirred for 10 min until all the solids were dissolved. The resulting homogeneous mixture was pumped through the flow reactor filled with SP-NHC-Pd^{II} and installed into a thermostated aluminum block at 200 °C. The flow rate was set at 0.1 mL min^{-1}. At a periodically constant time of 10 min the solvent valve was switched and the reaction mixture was directed to the second reactor column, while in the first column a premixed solution of KI was passed through. The final crude mixture was concentrated under reduced pressure and the crude solid was directly purified by flash column chromatography on silica gel using EtOAc/petroleum ether mixture as an eluent to afford the desired indoline

Acknowledgements

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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 from the corresponding author upon reasonable request.

Keywords: C–H activation · flow technologies · heterocycles · heterogeneous catalysis · palladium

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