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## ARTICLE

## Benzyloxycalix[8]arene supported Pd-NHC cinnamyl complexes for Buchwald-Hartwig C-N cross-couplings

Sandra Abi Fayssal,<sup>a,b</sup> Timothée Naret,<sup>a</sup> Vincent Huc,<sup>a</sup> Julien Buendia,<sup>\*b</sup> Cyril Martini<sup>\*b</sup> and Emmanuelle Schulz<sup>\*a</sup>

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A scalable synthesis of Pd-NHC cinnamyl complexes supported on a benzyloxycalix[8]arene is reported. These catalysts are very active for Buchwald-Hartwig cross-coupling reactions, allowing the coupling of aryl chlorides and bromides with a wide variety of alkyl and aryl amines using low catalytic loadings. The supported complexes also successfully afforded attractive unsymmetrical triaryl amines, and in one case promoted the synthesis of an unprecedented Pd-catalyzed C-H activation product. Thanks to the calixarenic support, the target products could be isolated with low levels of residual palladium, in some cases even below the restrictive toxic metal standards applied by pharmaceutical industry. Through an easy to implement procedure, these perfectly characterised catalysts thus combine the best of homogeneous and heterogeneous catalysis: high efficiency (similar or even better than the corresponding homogeneous complexes), and low Pd leaching levels expected from heterogeneous catalysts.

### Introduction

The formation of C-N bonds is ubiquitous in synthetic methodology. In this context, the palladium-catalysed procedure disclosed by Buchwald and Hartwig in the mid-1990s has become part of the toolbox of synthetic chemists, mainly due to its efficiency and its broad substrate scope.<sup>1</sup> During the last three decades, this palladium-catalysed cross-coupling was continuously improved, most of the studies focusing on the development of new phosphine ligands to reach higher catalytic performance.<sup>2</sup> As a valuable alternative to the Pd/phosphine systems, Pd-NHC (*N*-Heterocyclic Carbene) complexes, initially generated *in situ*, also demonstrated their high efficiency for C-N cross-coupling reactions.<sup>3</sup> Thanks to major advances from Organ<sup>4</sup> and Nolan groups,<sup>5</sup> readily prepared and air-stable NHC-based catalysts are currently considered as one of the most versatile systems to perform such transformations.

Searching for more active metal species to convert challenging substrates and to reduce the consumption of precious metal is probably the main goal in catalysis. Moreover, decreasing the amount of catalyst is also essential in order to minimise Pd release in the target product, thus allowing to comply with

industrial regulations concerning metal toxicity.<sup>6</sup> Flow chemistry represents an interesting solution to decrease the amount of catalyst required. This has been highlighted by researchers from Astrazeneca in an elegant preparation of a pharmaceutical precursor, performed by Buchwald-Hartwig coupling in flow conditions.<sup>7</sup> Also of relevance, the use of supported catalysts is a good alternative to homogeneous catalysis since it highly limits metal leaching. On an industrial scale, this greatly simplifies later purification of intermediates and final products, leading to important savings in terms of energy, raw materials and solvents. Furthermore, their simple removal from the reaction mixture allows easy recycling of the precious metal and offers the opportunity to reuse the catalyst.<sup>8</sup> It should be mentioned that many metals essential to the fine chemical industry (namely platinoids like palladium) suffer from overconsumption from automotive industry. Recycling has thus become one of the main challenges that green chemistry needs to address.

Only few studies report Buchwald-Hartwig reactions promoted by heterogeneous supported catalysts, most of them focusing on phosphine ligands.<sup>9</sup> Furthermore, only a handful number of Pd-NHC catalysts immobilised for C-N cross-couplings have been described. Hence, polyvinylpyridine<sup>10</sup> or polyisobutylene<sup>11</sup> were found as suitable polymers to coordinate PEPPSI-type (Pyridine-Enhanced Precatalyst Preparation Stabilisation and Initiation) Pd-NHC complexes to promote aminations. A very recent example reports the immobilisation of a Pd-NHC-cinnamyl complex on a Wang resin via a silyl linker. This leads to an efficient supported catalyst

<sup>a</sup> Université Paris-Saclay, CNRS, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bâtiment 420, 91405 Orsay, France. E-mail : emmanuelle.schulz@universite-paris-saclay.fr.

<sup>b</sup> NOVECAL, [www.novecal.com](http://www.novecal.com). E-mail : [julien.buendia@novecal.com](mailto:julien.buendia@novecal.com); [cyril.martini@novecal.com](mailto:cyril.martini@novecal.com)

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for the preparation of tertiary amines at low Pd loading (0.2 mol %).<sup>12</sup>

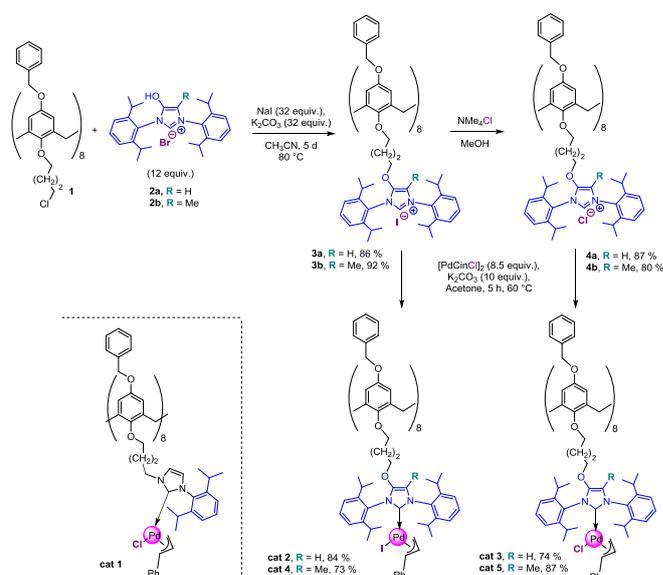
Encouraged by recent results obtained with sterically hindered Pd-NHC-cinnamyl complexes,<sup>13</sup> we decided to immobilise this type of catalysts on a support to prevent metal contamination while maintaining their high efficiency. Thus, we report herein the synthesis and the catalytic activity evaluation of Pd-NHC complexes covalently grafted on calix[8]arene supports for the C-N bond formation between aryl halides and a variety of amine partners. These filterable supported catalysts are expected to perform efficient cross-coupling reactions using simplified synthesis and purification processes, with a reduction in both the ecological footprint and the cost, while allowing the recovery of precious metal.

## Results and discussion

Calixarene derivatives are well-defined cyclic compounds straightforwardly available from phenols and aldehydes, whose size strongly depends on the conditions applied for their synthesis (temperature, amount and nature of the base).<sup>14</sup> Worthy of note, calixarenes are particularly known to form inclusion complexes by cations coordination. Furthermore, functionalisation of the rims was already described to anchor organometallic complexes for their use in supported catalysis, more particularly in the case of calix[4]- and calix[6]arenes.<sup>15</sup> The use of a calix[8]arene as catalytic support has been rarely described,<sup>16</sup> however this highly flexible macrocycle allows proximal assembly of many active sites and easier characterisation by NMR (no conformational locking). The choice of this organic support is further motivated by the fact that, after catalyst deactivation, the palladium can be easily recovered by combustion of the support.

We previously reported a practical, scalable and low cost synthesis of benzyloxycalix[8]arenes,<sup>17</sup> and their modification for the grafting of PEPSI-type Pd-NHC complexes as active species for Suzuki-Miyaura couplings.<sup>18</sup> This procedure was used here to prepare **Cat 1**: after quaternarisation of (2,6-diisopropylphenyl)-imidazole with **1** followed by an anion exchange, metalation of the intermediate with [Pd( $\pi$ -cinnamyl)Cl]<sub>2</sub> in acetone in the presence of K<sub>2</sub>CO<sub>3</sub><sup>19</sup> finally afforded **Cat 1** in 56 % yield (see structure in Scheme 1 and SI for more details). Inspired by the work of César and Lavigne,<sup>20</sup> our search for more crowded catalytic species led to the preparation of other imidazolium derivatives. Therefore, two sterically hindered 4-hydroxyimidazolium bromides<sup>21</sup> (see **2a** and **2b** in Scheme 1) were reacted with **1** in the presence of sodium iodide and potassium carbonate, delivering the supported imidazolium iodides **3a** and **3b** in excellent yields. Then, deprotonation of the imidazolium followed by complexation on the Pd-cinnamyl moiety afforded **Cat 2** and **Cat 4** in high yields. These reaction conditions lead to Pd-I active sites (as proved by XPS analysis), the iodine atom originating from the imidazolium salt. In order to further study the influence of the halide counterion on the catalysts activity, we decided to prepare the corresponding Pd-Cl complexes.

Thus, anion exchanges were performed by simple treatment of the iodide salts **3a** and **3b** with NMe<sub>4</sub>Cl in methanol. The corresponding imidazolium chlorides **4a** and **4b** were isolated, and absence of iodide counterions was proven by ESI mass spectrometry and XPS analyses. **Cat 3** and **Cat 5** catalysts, Pd-Cl complexes analogous to **Cat 2** and **Cat 4**, were then prepared using the same procedure. During their synthesis, the calixarene-based catalysts remained soluble in the solvent used, allowing an easy control of the functionalisation steps and their precise characterisation. Importantly, isolation of each intermediate and of the final catalysts did not require purification by chromatography on silica. They were rather simply obtained with high purity by precipitation and washing steps in specific solvents (see SI).

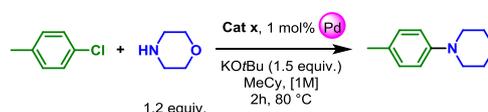


**Scheme 1.** Synthetic procedure for the preparation of **Cat 1-5**.

This procedure was successfully scaled up, as demonstrated by the preparation of a 8 g batch of **Cat 5**. Each catalyst is thus composed of a benzyloxycalix[8]arene crown which carries eight Pd-NHC (I or Cl)-cinnamyl complexes, making them densely functionalised catalysts. Thanks to the ideal length of the four methylene groups used as linkers to the macrocycle, all active sites are in the immediate vicinity of the crown while still being easily accessible.

In order to evaluate the influence of their particular structure in terms of efficiency, selectivity and palladium release, **Cat 1-5** were compared in a benchmark Buchwald-Hartwig cross-coupling reaction between 4-chlorotoluene and morpholine (Table 1).

**Table 1.** Comparison of **Cat 1 - Cat 5** activity for the Buchwald-Hartwig coupling between 4-chlorotoluene and morpholine



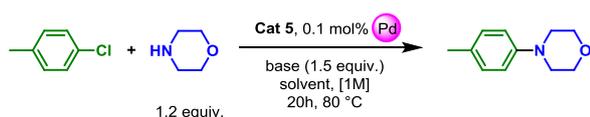
Cat x	GC conv. (%) <sup>a</sup>	GC yield (%) <sup>a</sup>
Cat 1	12	7
Cat 2	50	41
Cat 3	62	59
Cat 4	> 99	> 99
Cat 5	> 99	> 99

<sup>a</sup> Determined using hexadecane as internal standard.

The experiments were all performed at a relatively high metal loading (1 mol% Pd), in methylcyclohexane (MeCy) at 80 °C in the presence of KOtBu as base. For each catalyst, conversion and yield were recorded after 2h reaction, revealing significant differences. Under these experimental conditions, **Cat 1** led to a very poor conversion, clearly highlighting that catalysts activity is highly dependent on the steric hindrance around the palladium. As expected, **Cat 2** and **Cat 3** bearing two bulky aryl groups on their NHC moieties provided the desired *N*-(4-tolyl)morpholine in modest to good yields. Nevertheless, the best results were obtained with **Cat 4** and **Cat 5**, thanks to the additional steric hindrance induced by the methyl substituent on the imidazole core.

The reaction conditions (solvent and base) were then optimised in the presence of **Cat 5** at a lower catalyst loading (0.1 mol% Pd, Table 2). The efficiency of KOtBu as base was observed in various solvents with different polarities, the best results being obtained in ethers, *i.e.* cyclopentyl-methylether (CPME), methyl-THF (MeTHF) and 1,4-dioxane (entries 1-4). Interestingly, addition of a small amount of water<sup>22</sup> in MeCy also led to complete conversion when using 0.2 mol% Pd catalytic loading. In this case, water probably favours dissociation and dissolution of the base (entries 5-7).<sup>23</sup> Performing the reaction in toluene also required a slightly higher amount of catalyst in order to obtain the coupling product in quantitative yield (entry 9).

**Table 2.** Evaluation of the activity of **Cat 5**: solvent and base screening



Entry	Solvent	Base	GC conv. (%) <sup>a</sup>	GC yield (%) <sup>a</sup>	Leaching (ppm Pd) <sup>b</sup>
1	CPME	KOtBu	> 99	93	38
2	MeTHF	KOtBu	> 99	> 99	24
3	Dioxane	KOtBu	> 99	> 99	25
4	Dioxane <sup>c</sup>	KOtBu	97	97	8.7
5	MeCy	KOtBu	38	30	-
6	MeCy + 1% H <sub>2</sub> O	KOtBu	74	73	-
7	MeCy + 1% H <sub>2</sub> O <sup>d</sup>	KOtBu	> 99	97	9.5
8	Toluene	KOtBu	85	82	-
9	Toluene <sup>d</sup>	KOtBu	> 99	> 99	43
10	Dioxane	NaOtBu	14	< 5	-
11	Dioxane	K <sub>3</sub> PO <sub>4</sub>	12	< 5	-

12	Dioxane	Cs <sub>2</sub> CO <sub>3</sub>	10	0	-
13	THF <sup>e</sup>	LiHMDS	16	13	-

<sup>a</sup> Determined using hexadecane as internal standard. <sup>b</sup> Determined by ICP-MS analyses. <sup>c</sup> 0.05 mol% Pd, 100 °C. <sup>d</sup> 0.2 mol% Pd, 100 °C. <sup>e</sup> LiHMDS, 1M in THF.

Pleasingly, the use of 1,4-dioxane allowed to lower this amount to 0.05 mol% Pd while maintaining an excellent yield of 97 % (entry 4).

Traces of palladium in the coupling products were determined for each test leading to full conversion. ICP-MS measurements were performed on the crude products after a simple filtration of the reaction solution, carried out to remove most of the insoluble material. It is interesting to note that low leaching values were obtained in all solvents evaluated for these experiments, underlining the broad solvent compatibility of this procedure. This is a real asset for future potential use on industrial processes, in which specific solvents are often needed to meet particular requirements. Despite the use of a higher catalytic loading, a very low Pd release was measured in MeCy with additional water (9.5 ppm, entry 7). This corresponds to removal by filtration of more than 99% of the amount of palladium introduced at the beginning of the reaction. These conditions can be very useful for large scale procedures, when the use of alkane solvents displaying high calorific power may be preferred.<sup>24,25</sup> The use of 1,4-dioxane is also attractive, leading to a palladium release which is lower than the legal recommendations for oral administration (entry 4).<sup>6</sup> Consequently, and also because of its ability to solubilise a large scope of substrates, 1,4-dioxane was chosen as the preferred solvent for the rest of the study. The nature of the base was then investigated since this parameter is known to have a significant influence on the efficiency of the coupling (entries 3 and 10-13).<sup>26</sup> Attempts involving common inorganic bases such as Cs<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub> or NaOtBu led to poor conversion. The reaction employing LiHMDS (entry 13), although somehow more selective, afforded the target product in only 13 % yield. Among the bases tested, the best result was clearly obtained when using KOtBu (entry 3), this base was thus selected for the rest of the study.

To confirm these preliminary results, the reactivity of **Cat 2-Cat 5** was studied more deeply through the coupling of three primary amines. These more challenging substrates were reacted with 4-chlorotoluene in 1,4-dioxane using KOtBu as base. Anilines are less nucleophilic than dialkylamines, and often require higher reaction temperature to obtain satisfactory results. Indeed, for each of our catalysts, increasing the temperature to 100 °C allowed the coupling of aniline with only 0.1 mol% Pd in good to excellent yields (Table 3, entries 1-6). In particular, very high conversions were reached with the most sterically hindered **Cat 4** and **Cat 5**. Moreover, comparison of these two experiments after 2h showed that the chloride containing precursor (entry 4) leads to a much faster conversion than its iodide analogue (entry 6). Pleasingly, in all cases the transformation is particularly selective, since no trace of triarylamine could be detected. It should be mentioned that our results are comparable with

those described with hindered homogeneous catalysts, such as the Pd-NHC cinnamyl complex prepared from IPr\*,<sup>5e</sup> or with the long-chain containing NHC-ligands.<sup>24</sup> Indeed, our procedure displays lower Pd amount, shorter reaction time or more convenient reaction conditions (no need for use of glovebox or degassed solvents).

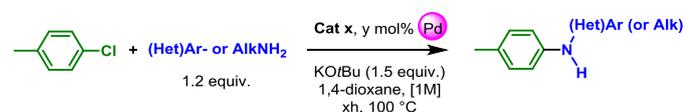
Next, the coupling between 4-chlorotoluene and 3-aminopyridine was evaluated. This amine is particularly challenging, due to unfavourable electronics effects, associated with its ability to complex the palladium leading to reaction inhibition.<sup>24,27</sup> In this case, the steric hindrance generated by the methyl group on the imidazolium moiety demonstrated its particular importance since **Cat 2** and **Cat 3** failed to afford complete substrate conversion, even at a high palladium loading of 1 mol% (Table 3, entries 7 and 8). On the contrary, **Cat 4** and **Cat 5** were more active and selective, even when using lower catalyst amounts (0.5 and 0.3 mol% Pd respectively). Once again, the beneficial role of chloride as Pd counterion was highlighted in this case, allowing a significant decrease of the catalyst amount (entry 10 versus entry 9).

Finally, bulky *tert*-butylamine was engaged in this coupling reaction, for which each pair of catalysts displayed very similar activity and selectivity. **Cat 2** and **Cat 3** selectively afforded the targeted secondary amine, although with modest conversion (entries 11 and 12). Pleasingly, the use of **Cat 4** and **Cat 5** at a palladium loading of 1 mol% led to complete conversion along with an excellent yield (entries 13 and 14).

as base. Various products were synthesised (see Scheme 2) by coupling simple or functionalised (het)aryl bromides or chlorides with a wide range of amines. For instance, the mono-arylation of non-hindered *n*-butylamine required the use of a hindered aryl halide (2-chloro-1,3-dimethylbenzene) in order to reach good selectivity. Thus, using a low catalyst loading of 0.3 mol% Pd, **5** was obtained in a good 70 % isolated yield. Under our conditions, secondary alkyl amines were also efficient coupling partners, leading to the expected arylamines in high yields using very low amounts of **Cat 5** (see **6-9**, down to 0.03 mol% for the preparation of **8**). It is interesting to note that this procedure tolerates the presence of various functional groups such as esters, amides, carbamates, ketals and aryl ketones (**6** to **20**), affording the corresponding secondary and tertiary amines in excellent yields.

Pd leaching was then evaluated for some of these experiments. At first glance, the preparation of tertiary amines led to significantly lower values compared to secondary amines (see **6**, **12** and **17**). This is coherent with the leaching value obtained for the secondary aniline described Table 3 entry 10 (see note b). Indeed, under the same reaction conditions, this analogue of **17** affords 56 ppm Pd leaching value, while only 27 ppm are detected in the recovered **17**. It seems reasonable to assume that Pd coordination by the coupling product is favoured in the case of secondary amines, thus leading to a higher palladium contamination.

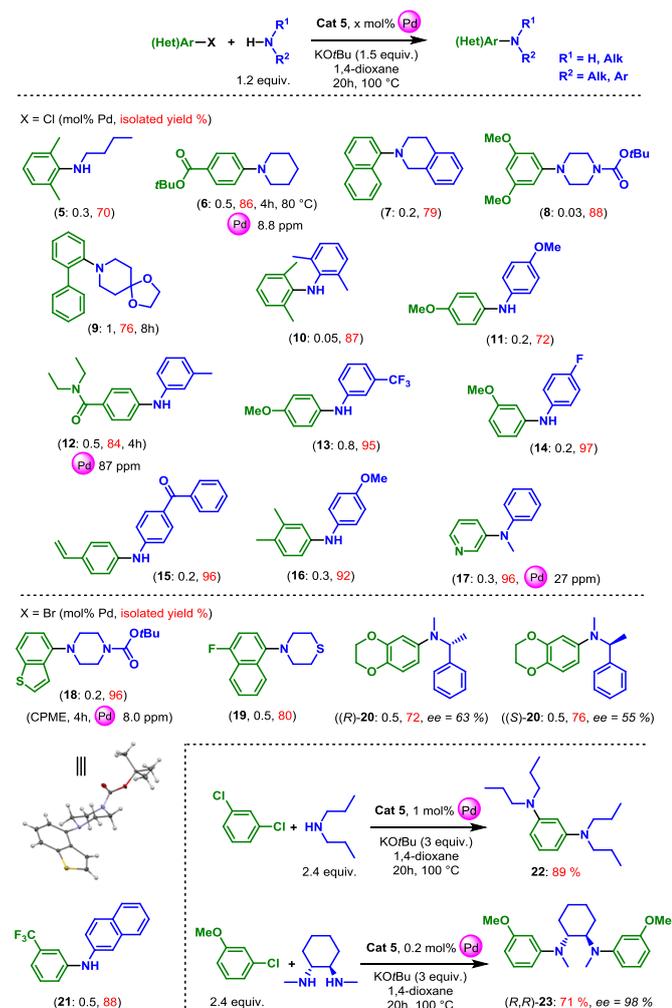
**Table 3.** Evaluation of the catalysts activity for the Buchwald-Hartwig coupling of primary amines



Entry	(Het)ArNH <sub>2</sub> or AlkNH <sub>2</sub>	Cat x	Pd (mol %)	Time (h)	GC conv (%) <sup>a</sup>	GC yield (%) <sup>a</sup>
1		<b>Cat 2</b>	0.1	20	82	72
2		<b>Cat 3</b>	0.1	20	74	70
3		<b>Cat 4</b>	0.1	20	95	90
4		<b>Cat 4</b>	0.1	2	67	63
5		<b>Cat 5</b>	0.1	20	> 99	95
6		<b>Cat 5</b>	0.1	2	97	93
7		<b>Cat 2</b>	1	20	83	62
8		<b>Cat 3</b>	1	20	55	45
9		<b>Cat 4</b>	0.5	5	> 99	98
10 <sup>b</sup>		<b>Cat 5</b>	0.3	5	97	93
11		<b>Cat 2</b>	1	20	54	48
12		<b>Cat 3</b>	1	20	56	44
13		<b>Cat 4</b>	1	20	93	88
14		<b>Cat 5</b>	1	20	96	88

<sup>a</sup> Determined using hexadecane as internal standard. <sup>b</sup> Pd content of 56 ppm was measured inside this product.

The scope of this Buchwald-Hartwig coupling procedure was next investigated under optimised conditions, *i.e.* with **Cat 5** as the most active catalyst, in 1,4-dioxane at 100 °C using KOtBu



**Scheme 2.** Scope of the Buchwald-Hartwig coupling with **Cat 5**.

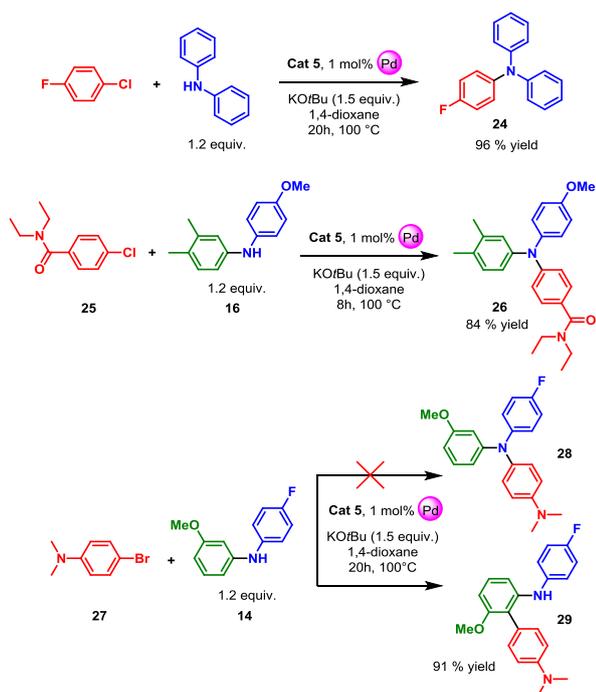
Very satisfactory results have also been obtained from aryl bromides (**18** to **21**). Preparation of **18** is of particular interest, since this product is a key intermediate in the synthesis of Brexpiprazole, a modulator of the serotonin-dopamine activity.<sup>28</sup> The reaction was performed in CPME with a low catalyst amount of 0.2 mol% Pd, and **18** was isolated in almost quantitative yield after 4h. Single crystals of **18** were obtained by slow evaporation from diethyl ether, and its structure was confirmed by X-ray analysis (see Scheme 2 and SI for details). This experiment was then performed again, and at the end of the reaction the solution was simply filtered over a Dicalite<sup>TM</sup> plug, and the residue analysed by ICP-MS. Only 8 ppm of palladium were detected in the crude product, which means that more than 98.8% of the palladium introduced have been easily removed. By consequent, the synthesis of this product on a large scale would not require any further purification by chromatography on silica, recrystallization or treatment by complex and expensive scavengers to respect the industrial constraints concerning metal content. To establish a direct comparison, this coupling was performed under the same experimental conditions (including the filtration step), except for the use of homogeneous PEPPSI<sup>TM</sup>-IPr as catalyst (0.2 mol%). The reaction also went to completion, but in this case

the palladium leaching reached a much higher value of 212 ppm. These results perfectly highlight the impact of the calixarene support for the preparation of valuable intermediates almost rid of palladium traces. In other terms, it clearly underlines the environmental benefits brought by our catalyst, which stands as an attractive candidate for the development of greener processes.

Enantiopure secondary alkylamines were also engaged in the coupling with a bromoaryl derivative, and the coupling products were isolated in good yields using **Cat 5** at a 0.5 mol% Pd loading (see (*R*)-**20** and (*S*)-**20**). Unfortunately, under these conditions partial racemisation occurred in both cases, as determined by chiral HPLC investigations. In order to soften the reaction conditions,<sup>29</sup> the same experiment was repeated in toluene instead of 1,4-dioxane, but unfortunately the targeted product could not be obtained with complete retention of configuration.

The efficiency of our procedure was also confirmed in the case of bis-couplings, starting either from an aryl bishalide or a diamine (Scheme 2, **22** and **23**). The reactions proceeded successfully in both cases, provided that 3 equivalents of base are employed. When using 1 mol% Pd of **Cat 5**, the coupling between 1,3-dichlorobenzene and dipropylamine led to isolation of *N,N,N',N'*-tetrapropyl-benzene-1,3-diamine **22** in high yield, whereas the bis-coupling of (*1R,2R*)-*N,N'*-dimethylcyclohexane-1,2-diamine could be achieved with a lower loading of 0.2 mol%. Delightfully, in this case chiral HPLC analyses of (*R,R*)-**23** showed that the reaction occurred with complete retention of the optical purity of the stereogenic carbon atoms. This could be explained by the lower acidity of the protons attached to the chiral carbons of **23**, compared to the benzylic protons of **20**. This preservation of the chiral information opens attractive synthetic opportunities towards a very large number of enantiopure ligands with optimal structures for metal coordination, and would be very useful in asymmetric catalysis.

Unsymmetrical triaryl amines play an important role in the field of optoelectroactive materials,<sup>30</sup> as well as for the synthesis of pharmacologically relevant products.<sup>31</sup> This finally prompted us to tackle the preparation of these challenging molecules with help of **Cat 5**.



**Scheme 3.** Preparation of unsymmetrical triaryl amines.

As a first attempt, 1-chloro-4-fluorobenzene was engaged in the coupling with diphenylamine under our standard conditions. Pleasingly, the corresponding fluoro-substituted triarylamine **24** was easily isolated in almost quantitative yield. Consequently, attempts to synthesise triaryl amines bearing three different aromatic groups have been carried out. Triarylamine **26** was thus obtained successfully from the coupling between **16** and **25** in 84 % yield. It is worthy of note that **16** was previously prepared in high yield, and that the formation of the diarylation product was not observed when using 0.3 mol% Pd. Indeed, the coupling of less reactive diarylamines requires higher catalyst amount (1 mol% Pd), allowing the two-step synthesis of **25** to be greatly selective. The reaction between compound **14** and 4-bromo-*N,N*-dimethylaniline **27** was then studied, expecting the formation of **28** bearing substituents with electron donating or withdrawing effects on the aromatic rings. However, reaction led to an unexpected outcome, since no trace of the desired product could be detected and compound **29** was instead isolated in an excellent 91 % yield. This original product results from a metal insertion in the C-H bond placed in  $\alpha$ -position of both the methoxy and amine groups. This reactivity is not yet clearly understood, but is probably due to the electronic effects resulting from the substituents involved and their specific positioning. It should be mentioned that the intermolecular non-directed  $C(sp^2)$ -H activation of arenes by Pd-NHC complexes is extremely rare<sup>32</sup> and mainly concerns the arylation of pentafluorobenzene.<sup>33</sup> Thus, formation of the C-H arylated compound **29** paves the way for an even wider extension of the applicability of **Cat 5**, which is currently under investigation by our group.

## Conclusions

A facile and scalable immobilisation of Pd-NHC-cinnamyl complexes on a benzyloxycalix[8]arene through methylene spacers is described, leading to very active catalysts which are particularly suitable for industrial applications. The synthetic preparation allowed to obtain iodinated or chlorinated precatalysts, the latter revealing a slightly higher activity for various Buchwald-Hartwig couplings. Best results were recorded with the use of **Cat 5**, for which the NHC-ring attached to the benzyloxycalix[8]arene is substituted by an additional methyl group, generating an increased steric hindrance. These couplings were carried out successfully in various solvents in the presence of KOtBu as base. The application scope of this catalyst is very broad, leading to efficient and selective couplings from aryl chlorides and bromides, in the presence of various types of alkyl and aryl amines. Interestingly, both partners can bear various functional groups well tolerated by this coupling procedure. As a general trend, low to very low catalyst loadings (down to 0.03 mol% Pd) were sufficient to obtain full conversion and high yields. **Cat 5** also afforded bis-coupling products and challenging unsymmetrical triaryl amines in satisfactory yields. Moreover, we were able to isolate an original compound arising from an unprecedented C-H activation, thus underlining the vast potential of these catalysts. More generally, immobilisation of the *i*Pr-NHC on the calixarenic structure did not alter the activity described for the corresponding homogeneous Pd-cinnamyl catalysts.<sup>5b,5e,11,13,24</sup> Furthermore, special attention has been devoted to the search of palladium traces inside the coupling products. The presence of the calixarene support allowed, after a simple filtration, to recover the desired products with very low levels of residual palladium, some of them directly matching the industrial restrictive norms concerning toxic metals. To conclude, benzyloxycalix[8]arene is shown to be a suitable support for hindered Pd-NHC complexes, providing highly efficient catalysts to perform the renowned Buchwald-Hartwig reaction. These perfectly characterised catalysts, which contain a rarely reported high metal content ( $\approx 11$  % w/w), have combined both the performances of similar homogeneous metallic catalysts (or even exceeded them) and the advantages of heterogeneous catalysts, for which simple filtration allows efficient metal removal. Further work is currently in progress to widen the scope of such supports to various metal-catalysed reactions, involving other kinds of ligands and metallic salts.

## Conflicts of interest

VH, CM and ES are co-founders of Novecal.

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## Notes and references

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