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Calixarene-supported Pd-NHC complexes as efficient catalysts for scalable Suzuki-Miyaura cross-couplings

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Benzyloxycalix[8]arene is reported as a suitable macrocyclic support for Pd-NHC complexes, which catalyses C-C cross-coupling reactions with high efficiency. Resulting PEPPSI-derived complexes, issued from a scalable synthetic procedure avoiding any tedious purification, are indeed used as heterogeneous catalysts in ethanol to promote the Suzuki-Miyaura coupling between various aryl halides and arylboronic acids (or esters). Optimisation of the reaction conditions allowed the use of only a slight excess of base (K_3PO_4 , 1.2 equivalents) and boronic acid (1.1 equivalents), and these conditions were also successfully applied to a large scale benchmark reaction (1 mole of substrate) using a low palladium loading (0.001 mol %). Furthermore, target products were easily isolated after simple filtration procedures with low residual Pd traces (down to 3 ppm) thanks to the insoluble nature of the macrocyclic catalyst in ethanol, thus proving the usefulness of this support to promote coupling reactions relevant to the fine chemical industry.

Introduction

The fine chemical industry is continuously looking for the most direct and economically viable methods to obtain highly functionalised valuable compounds. Catalytic processes are particularly desirable because they generally allow to lower the temperature and to reduce the reaction time, for an overall decrease in both production cost and impact on the environment.¹ The huge success of organometallic catalysis is well established because it meets these criteria, provided that the procedures in place prevent the contamination of the target products by metal traces.² Indeed, only very low metal content are tolerated inside ended pharmaceutical, agrochemical or cosmetic products, due to their toxicity. Furthermore, beyond these health and regulatory concerns, the whole chemical industry is impacted by metal contamination as the final composition of a reaction may dramatically be changed while using waste reagents.³ Lowering the catalytic charge, which necessitates the use of increasingly reactive metal complexes, is therefore highly desirable.⁴ Another solution relates to the development of innovative procedures, allowing easy removal of the catalyst from the reaction mixture. Obviously, nothing prevents the combination of these two solutions. This has led to the

emergence of numerous studies describing the immobilisation of various types of homogeneous catalysts, leading to their elimination by simple filtration.⁵

As a prerequisite for the use of a supported catalyst in the pharmaceutical industry, it must afford, in an immutable manner, the desired product with constant characteristics in terms of purity and yield. In this context, we addressed the immobilisation of transition metal complexes, our goal being the development of catalysts attractive for the fine chemical industry.

To this aim, preparation of *N*-heterocyclic carbene-based Pd-complexes led to easy-to-handle and stable precatalysts for highly active species, particularly the PEPPSI type structures.⁶ Some efforts were already devoted to anchor such complexes on various supports, some of them displaying an organic structure.⁷

We have previously reported a practical and low-cost synthesis of a benzyloxycalix[8]arene intermediate and its transformation via a chromatography-free procedure into a support bearing eight well-defined PEPPSI-type Pd-NHC complexes.⁸ Advantageously, Suzuki-Miyaura cross-couplings⁹ occurred in heterogeneous conditions, with the catalysts suspended in ethanol. They showed high TON and TOF for a large panel of functionalised aryl bromides, with low metal contamination after simple filtration.¹⁰

We report here our efforts to optimise the amount of introduced material without increasing the reaction time, in order to develop reaction conditions more suitable for large scale transformations. A special emphasis is placed on the filtration processes to allow very low release amounts of palladium into the target products, while maintaining simple and cost-efficient procedures. The catalysts are also used for

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the preparation of some key precursors dedicated to the synthesis of valuable pharmaceutical compounds, to show their facile and broad applicability.

Results and discussion

We recently described a synthetic procedure allowing easy preparation of calix[8]arene-supported PEPPSI complexes.¹⁰ Catalysts **1** and **2** (**cat1** and **cat2**, Figure 1) were obtained in high global yield without the need for any tedious purification. In this work, the synthesis of both catalysts was upscaled. They are indeed easily prepared from palladium chloride or palladium bromide, resulting in more than 7 g of palladium catalysts per batch (see supporting information). Their purification could be achieved by avoiding the use of silica gel chromatography, and by favouring precipitation and washing in various common organic solvents. Pure compounds were isolated on this large scale in 50 and 73 % yield, respectively. Throughout their whole synthesis, the calixarene-based catalysts remained soluble in the solvents used, allowing an easy control of the functionalisation steps, and leading to their precise characterisation.

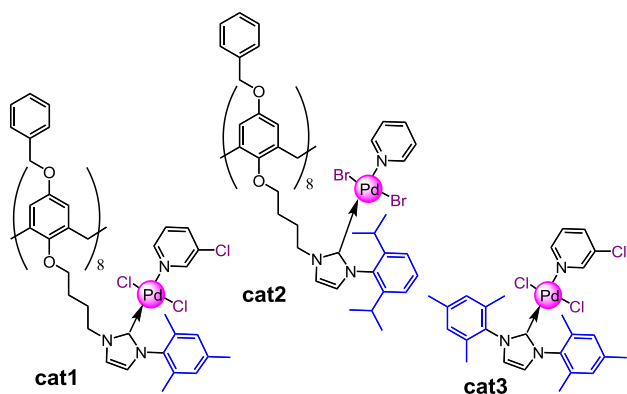
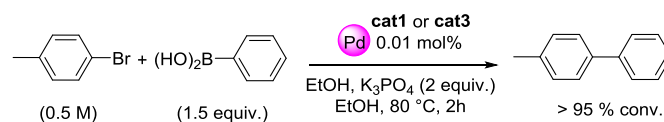


Figure 1. Calixarene-supported palladium PEPPSI catalysts and a PEPPSI analogue

Perfectly reproducible analytical data was obtained for this procedure, delivering supported catalysts with a w/w metal content close to 15 %. Suitable crystals for X-ray analysis were obtained by vapour diffusion of diethyl ether into a dichloromethane/acetonitrile solution of **cat1**.¹⁰ This catalyst resulting from the use of PdCl₂ was chosen to carry out most of the optimization tests reported here because of its advantageous preparation, allowing both cost and atom savings.

We have reported that both catalysts were particularly efficient to promote the Suzuki-Miyaura cross-coupling of a wide range of aryl bromides with arylboronic acids.¹⁰ Interestingly, the best reaction rates and yields were obtained in ethanol as solvent, in which the catalysts were not soluble. It should also be noted that the use of pure water as solvent led to a very slow reaction, which nevertheless reached a suitable conversion after 24h stirring at room temperature.

Furthermore, ethyl acetate was also tested, as recommended solvent for use in sustainable chemistry,¹¹ in which **cat1** was insoluble. A very low activity was recorded (14 % conversion in 2h) which could however be greatly accelerated by addition of a small amount of water (EtOAc/H₂O 7/1; 60 % after 2h, 75 % after 24h), with this accelerating role of additional water being commonly observed in numerous Suzuki-Miyaura cross-couplings.¹² Albeit not well understood, a significant effect of the calixarene macrocyclic structure on the reactivity of the anchored PEPPSI catalytic sites is particularly noticeable, depending on the solvent used. The screening of various bases demonstrated the efficiency of the low cost and easy-to-handle K₃PO₄ as base. Thus, in a comparison experiment under these conditions, **cat1** and its homogeneous analogue (see **cat3** in Figure 1) were engaged in a benchmark Suzuki-Miyaura coupling reaction with a 0.01 mol % loading in palladium (scheme 1), for a better evaluation of their initial activity in ethanol.



Scheme 1. Suzuki-Miyaura benchmark reaction performed with **cat1** or **cat3**

Tests were performed under these conditions for which > 95 % conversion was reached in both cases, after 2h at 80 °C in ethanol. GC sampling at the very beginning of the reaction proved however that a high conversion was indeed reached after only 2 minutes when the homogeneous PEPPSI catalyst **cat3** was used. For **cat1**, 4 minutes were necessary for the same efficiency, highlighting nevertheless the very high activity of this insoluble catalyst, which remained comparable to that of its homogeneous counterpart.

Of major importance for industrial application is the evaluation of the palladium leaching after use of these supported systems. This was easily achieved due to the heterogeneous nature of the transformation in ethanol. The final product was indeed recovered after elimination of the insoluble species by simple paper filtration. ICP-MS analyses of the crude residue were performed to compare the leaching levels of **cat1**, **cat2** and the homogeneous PEPPSI analogue of **cat1** (see Figure 2 and supporting information).¹⁰

	[Pd] traces (ppm)
cat1	10.6
cat2	50.8
cat3	516.5

Figure 2. Residual palladium content determined by ICP-MS

The palladium content inside 4-phenyltoluene reached only 10.6 ppm when **cat1** was used. A five times higher amount of palladium was measured using **cat2**, while **cat3** led to a much

higher Pd content (516.5 ppm) detected in the final biaryl product.

Based on these promising results, further tests were conducted attempting to reach lower Pd contamination, while focusing on keeping simple purification procedures. The tests were performed on the reaction between 2-bromobenzonitrile and phenylboronic acid at a quarter-mole scale in the presence of **cat1** (0.1 mol % Pd) in ethanol. After two hours at 80 °C, 95 % conversion was achieved. Purification of a one-gram sample by flash column chromatography allowed to isolate [1,1'-biphenyl]-2-carbonitrile in 90 % yield. After a short prefiltration to remove most of the insoluble material, the filtrate was divided into equal parts, each of them undergoing an additional filtration before preparation of the ICP-MS samples (Figure 3).

		[Pd] traces (ppm)	Pd eliminated (%)
cat1 0.1 mol% EtOH, K ₃ PO ₄ 80 °C, 2h 95 % conv.	simple prefiltration	54	90.9
	prefiltration combined with subsequent filtration on:		
	sintered glass filter (porosity 5)	33	94.4
	Whatman® paper (2.5 μm)	28.5	95.2
	polypropylene filter (0.5 μm)	22	96.3
	Dicalite™	16.5	97.2
	carbon filter	3	99.5

Figure 3. Comparison of various types of filter media for very low palladium leaching content

With the short prefiltration, a moderate amount of Pd (54 ppm) was detected in the target functionalised cross-coupling product. Additional filtration on filters with different porosities (sintered glass filter, Whatman® paper, polypropylene) led to a decrease of this value (down to 22 ppm), but the limits authorised by the legislation could not be reached. Nevertheless, purification through Dicalite™ permitted the removal of 97.2 % of the introduced amount of palladium; this value reached 99.5 % via the use of a carbon filter, allowing recovery of the crude product containing only 3 ppm of Pd. Thus, immobilisation of PEPPSI-type Pd-catalysts on calixarenic structures led to the preparation of products almost rid of any palladium traces, after combining a short prefiltration step and a simple carbon filtration.








Both supported-catalysts **cat1** and **cat2** showed a similar reactivity which we already highlighted in our previous article, although **cat2**, with the bulkier diisopropyl-phenyl substituent on the NHC, proved to be more efficient for the transformation of demanding and sterically hindered substrates.^{10,13} Table 1 gives additional examples of Suzuki-Miyaura cross-couplings, varying first the aryl halide coupling partner.¹⁴ To ensure high conversion while maintaining a short reaction time, tests were performed at a 0.5 M concentration, with 1.5 equivalents of phenylboronic acid and 2 equivalents of base. Typical trends in terms of reactivity were observed in

the presence of aryl bromide derivatives bearing electron donating or withdrawing groups. For each example, the catalyst amount was adjusted, leading to the target products in excellent isolated yields within two hours (table 1, entries 1-2). The coupling of 1-bromo-2-chlorobenzene using **cat2** occurred with complete conversion of the starting material (entry 3). Using only 1.1 equivalent of the boronic acid derivative led to the formation of 2-chlorobiphenyl in 91 % isolated yield, together with a small amount of the bis-coupling product (See GC traces in the SI). Transformation of 1-bromo-2-fluorobenzene led to 2-fluorobiphenyl in only 62 % yield, since the cross-coupling reaction was accompanied with non-negligible debromination (entry 4).

Table 1. Scope of the reaction with phenylboronic acid

$$\text{Ar-X} + (\text{HO})_2\text{B-C}_6\text{H}_5 \xrightarrow[\text{EtOH, K}_3\text{PO}_4, 80^\circ\text{C, 2h}]{\text{cat1 or cat2}} \text{Ar-C}_6\text{H}_5$$

X = Br, Cl

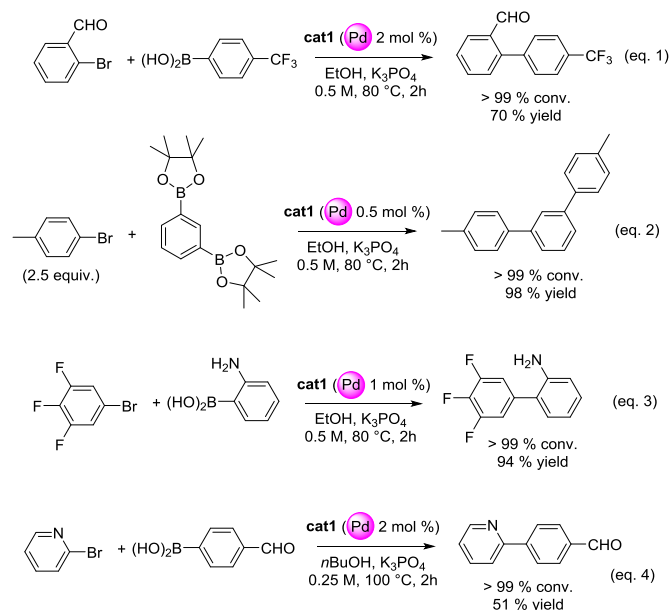
Entry	Ar-X	Cat	Pd (mol%)	Conv (%) ^[a,b]	Yield (%)
1		1	0.5	> 99	96
2		1	0.05	> 99	88
3		2	0.5	> 99	91 ^[c]
4		2	2	> 99	62
5		1		51	n.d.
		2	2	74	58
6		2	2	69	56
7		2	2	63	38 ^[d]

^[a] Aryl bromide (1 equiv., 0.50 M), phenylboronic acid (1.5 equiv.), K₃PO₄ (2 equiv.), under argon atmosphere. ^[b] Conversion determined by GC and GC/MS analyses. ^[c] Use of 1.1 equiv. of phenylboronic acid. ^[d] Use of (2-methoxyphenyl)boronic acid (1.5 equiv.) as coupling partner.

The reaction of a very hindered substrate (entry 5) required a higher catalyst loading to reach a moderate conversion. **Cat2** was more efficient than **cat1** and allowed the coupling of pentamethylbromobenzene, albeit complemented with some debromination of the reactant. Use of **cat2** nevertheless afforded the desired coupling product in 58 % yield (see SI). As already reported, aryl chlorides were less reactive substrates, but some success (56 % yield) was met in the case of an electron-deficient derivative (entry 6). However, 1,2-dichlorobenzene reacted only hardly with 2-(methoxyphenyl)boronic acid, whose structure has been chosen to facilitate the purification procedure. In the presence of **cat2**, a moderate conversion was observed and 2-chloro-4'-methoxy-1,1'-biphenyl was isolated in only 38 % yield due to

protodeborylation and formation of some bis-coupling product (entry 7, and SI).

The synthetic utility of **cat1** was further demonstrated by coupling various functionalised boronic derivatives with different aryl halides, thus widening the scope of the procedure compatibility. All the tests were performed on a 1 mmol scale (0.5 M or 0.25 M) in the presence of 2 equivalents of base and 1.5 equivalents of the boronic partner (scheme 2). This additional screening showed that the cross-coupling reaction can also be conducted efficiently with an electron-poor boronic acid derivative bearing a CF₃ group (eq. 1). Bis-coupling occurred satisfyingly with a bis-pinacol phenyl boronate, provided that an excess of 4-bromotoluene is used (2.5 equiv., eq. 2).



Scheme 2. Synthetic applications of **cat1**.

Furthermore, inspired by a recent report on the synthesis of a key intermediate for the preparation of Fluxapyroxad, a synthetic carboxamide with antifungal properties,¹⁵ the cross-coupling between 5-bromo-1,2,3-trifluorobenzene and (2-aminophenyl) boronic acid was evaluated. The reaction implied the use of **cat1** with a 1 mol % loading in palladium, and allowed isolation of the target product (eq. 3) in 94 % yield. Reversing the coupling previously described in the literature by the direct use of the boronic acid holding an amine function has made it possible to reduce the number of steps for a simple access to this compound of interest. Harsher conditions were needed for the complete conversion of 2-bromopyridine with (4-formylphenyl)boronic acid (eq. 4), since the reaction was performed in *n*-BuOH at 100 °C. The desired pyridinyl benzaldehyde coupling product, already used in the synthesis of Atazanavir, a HIV protease inhibitor,¹⁶ was unfortunately isolated in only 51 % yield, because of the presence of unavoidable degradation compounds.

The standard conditions were further optimised with the constant aim of driving the reaction under optimal conditions in terms of atom economy. The amount of both boronic acid and base, together with the concentration of the substrate, were modified for the reaction at the mmole scale promoted by **cat1** (see table 2). The volume of the solvent was therefore reduced (entries 1 to 4) affording high conversion in short reaction times. A 2 M concentration of aryl halide (entries 4 and 5) also proved to be successful, although the solubility limit of the reagents was reached under these conditions. Furthermore, the amount of phenylboronic acid could be adjusted to 1.1 equivalents, leading however to a slower reaction, which yielded full conversion in 6.5 hours (entries 6 and 7). Finally, the amount of base was also decreased down to 1.2 equivalents, and high conversion was still reached albeit reaction time had to be slightly increased (entries 8 and 9). By merging all optimised conditions to minimise the amount of reagents and reduce waste, we were pleased to obtain 80 % conversion for the room temperature transformation of 4-bromotoluene at a 2 M concentration in EtOH with only 1.2 equiv. K₃PO₄ and 1.1 equiv. phenylboronic acid in the presence of 0.5 mol % **cat1** (see entry 10).

Worth mentioning is the sluggish aspect of the reaction mixture under these conditions, due to the reduced amount of solvent. Therefore, the reaction temperature was raised up to 80 °C to enhance mass transfer, together with a great reduction of the catalyst loading by a factor of 500, down to 0.001 mol % Pd. After two hours, the conversion reached 90 %.

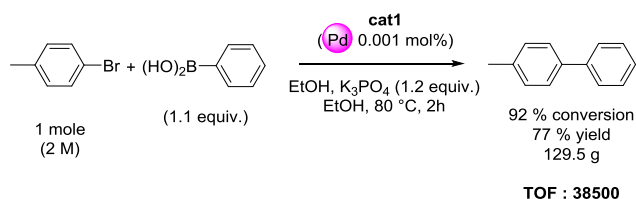
Table 2. Optimisation of the reaction conditions

Entry	K ₃ PO ₄ (equiv.)	PhB(OH) ₂ (equiv.)	[4-Bromotoluene] (mol.L ⁻¹)	Time (h)	Conv. (%) ^[a,b]
1	2	1.5	0.17	2	93
2	2	1.5	0.25	2	98
3	2	1.5	0.5	2	99 (93) ^[c]
4	2	1.5	2	2	93
5	2	1.5	2	24	98
6	2	1.1	0.5	2	85
7	2	1.1	0.5	6.5	99
8	1.2	1.5	0.25	2	94
9	1.2	1.5	0.25	6	96
10	1.2	1.1	2	2	80

^[a] 4-Bromotoluene (1 mmol, 1 equiv.), PhB(OH)₂ (x equiv.), K₃PO₄ (x equiv.), under argon atmosphere. ^[b] Conversion determined by GC analysis. ^[c] Isolated yield.

Accordingly, a reaction was conducted on the mole scale in the presence of 0.001 mol % of palladium from **cat1** at 80 °C, and fixing the concentration of the substrate at 2 M. It is noteworthy that a very low amount of catalytic species, which only features 6 ppm of palladium, is engaged in this transformation. This large-scale reaction behaved gratifyingly, and after two hours, 92 % conversion could be obtained, and the desired coupling product was further isolated in 77 % yield. Adjustment of the conditions thus allowed to obtain a very

high TOF of 38500 for this Suzuki-Miyaura coupling, clearly demonstrating the valuable use of benzyloxycalix[8]arene-supported Pd-NHC complexes for the high yielded preparation of nearly metal-free coupling products.



Scheme 3. Suzuki-Miyaura reaction performed on the mole scale

The heterogeneous nature of the benzyloxycalix[8]arene-supported palladium catalysts was previously demonstrated by the absence of catalytic activity of the hot-filtered solution.¹⁰ Additional tests were further performed to evaluate the recyclability of **cat1**. First, 4-bromotoluene was coupled with phenylboronic acid with full GC conversion (**cat1**, 0.5 mol % Pd, room temperature, 2 h in EtOH). Then, a new batch of substrates and base (same amount as used in the first run) was directly added in the reaction mixture without further treatment. Pleasingly, this second run afforded the desired product with the same GC conversion after 2 h reaction time.

To further prove the recyclability of the calixarene-supported catalyst under these reaction conditions, another crude mixture from the same benchmark reaction (4-bromotoluene and phenylboronic, **cat1**, 0.5 mol % Pd, room temperature, 2 h in EtOH) was filtered after completion through a DicaliteTM pad, which was further washed with ethanol to ensure removal of the reaction product and the residual boronic salts. The catalyst was then recovered from the pad by washings with dichloromethane as solubilising solvent. The dichloromethane catalyst solution was evaporated, dried and then engaged in a new catalytic run, by adding ethanol and a new set of reagents. After 2 h reaction, a complete conversion was delightfully recorded, which proves that the recycled catalyst still exhibits high catalytic activity. Moreover, we should underline that this recycling procedure is easy and straightforward, which makes it suitable for large scale applications.

Conclusions

To conclude, we report here a detailed study for the optimised use of benzyloxycalix[8]arene-supported PEPSI-type NHC-based palladium complexes in Suzuki-Miyaura cross-coupling reactions. We also describe here an upscaled synthesis of these calixarene-supported catalysts in high yields and without any fastidious purification procedure. These syntheses are perfectly reproducible, as is the Pd loading inside these catalysts. The coupling reactions were performed in ethanol, an industrially relevant solvent, in which the supported catalysts were insoluble. The extent of application of these catalysts is here demonstrated for the coupling of various substrates, for which the reaction conditions (in particular the

temperature and the catalytic amount) have been optimised. The amount of base and boronic acid partner was also lowered to match at best the concept of atom economy, a key parameter for industrial applications. Some precursors for valuable pharmaceuticals were straightforwardly obtained via this procedure. The reaction was furthermore performed on the mole scale using a very low catalyst loading, without altering the efficiency of the process. Simple filtrations through a sintered glass filter followed by a carbon filter led to the product recovery with very low amount of residual palladium (3 ppm) as revealed by ICP-MS analyses. All in one, this work highlights a range of catalysts in line with a set of experimental conditions that combine all features needed for industrial applications in a green route. Further work is currently in progress to widen the structure of the easily accessible, well-defined and structurally-modular benzyloxycalix[8]arene macrocycle, for its use as support in various heterogeneous catalytic reactions involving other ligands and/or metallic salts, by taking advantage of its simple functionalisation.

Conflicts of interest

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

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