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Synthesis, Catalytic Activity and Comparative Leaching Studies of Calix[8]arene-Supported Pd-NHC Complexes for Suzuki-Miyaura Cross-Couplings

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Dedicated to Professor Rinaldo Poli on the occasion of his 65th birthday

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Abstract: A rapid and scalable synthesis of supported NHC–Pd(II)-pyridine complexes on a benzyloxycalix[8]arene macrocycle is reported. Their subsequent use in Suzuki-Miyaura benchmark reactions led to the optimisation of the nature of the ligands around the metal centre, delivering two very active precatalysts. They both promote the cross-coupling of challenging API precursors at low catalytic loadings, when used as insoluble species in EtOH as a green reaction solvent. Moreover, their activity has been shown to be comparable or even superior to that of more conventional homogeneous catalysts. Of main importance, a simple filtration of the insoluble supported catalysts after reaction afforded the lowest Pd contamination values in the target products, in some cases directly approaching the levels authorised by the industrial regulations. Offering furthermore the possibility of easy palladium recovery in the current context of its overconsumption, we are convinced that these calixarene-supported NHC-PEPPSI Pd complexes are valuable tools for the fine chemical industry, to prepare metal-free functionalised biaryl compounds in high yields, ranging from 76 to 94%.

Keywords: Calixarenes; Catalysis; C–C coupling; *N*-Heterocyclic carbene; Palladium; Leaching

Introduction

The Suzuki-Miyaura cross-coupling is considered as an ubiquitous reaction for the formation of C–C bonds between a broad variety of aromatic compounds.[1] This catalytic transformation, conventionally promoted by palladium complexes, has aroused the interest of many researchers and has reached a very high level of maturity.[2] This catalytic reaction has now become a prevalent tool in fine chemical industry.[3] In this context, the active catalytic species have to be used at low loadings, to both minimise the cost of the process and facilitate the purification of the target products. These features are also expected when using heterogeneous organometallic catalysts, but for the latter obtaining minimal residual palladium traces in the

coupling products is another important objective.[4] Most of the transition metals are indeed toxic species, and their presence in valuable chemicals is regulated accurately, according to their mode of administration.[5] Furthermore, residual amounts of metals can interfere with the subsequent synthetic steps of the process.

This cross-coupling reaction has been performed very efficiently with palladium complexes coordinated to phosphine-based ligands, and also with the bench-stable *N*-heterocyclic carbene (NHC) PEPPSI (pyridine-enhanced precatalyst preparation stabilization and initiation) catalysts.[6] The corresponding supported species with different features have been reported in the literature, affording variable results depending on the nature of the support.[7] Although interesting catalytic activity values have been obtained, their main drawback is probably their synthesis. Indeed, for large-scale production purposes, the preparation of the supported active metal species must be simple, robust and reproducible, in order to fulfil cost and regulation constraints.[4] For industrial applications, their precise and reliable characterisation is mandatory, notably concerning their metallic content. Moreover, a high metal/support mass ratio is desirable, to avoid the use of large quantities of material which would result in major mass transfer and ecological problems. We have proposed a solution fitting these requirements. Indeed, our macrocycle-supported precatalysts are easy to handle and can be removed by simple filtration, leading to low metal leaching. Benzyloxycalix[8]arenes-NHC palladium catalysts[8] were prepared according to a scalable synthetic procedure avoiding tedious purification by silica gel chromatography. Intermediates and catalysts were fully characterised, allowing a fine control of their structure. They promoted Suzuki-Miyaura couplings through a large panel of functionalised aryl bromides, along with low metal contamination after simple filtration.[9] While this first generation of catalysts proved unfit to convert efficiently more difficult aryl chlorides, we disclosed a new strategy to prepare more sterically hindered calixarene-supported catalysts.[10] Inspired by the procedure reported by Organ *et al.* for the immobilisation of Pd-PEPPSI complexes on silica,[11] we were able to anchor the Pd-NHC moiety onto the macrocycle via a copper catalysed click-reaction between a functionalised aryl-alkyne imidazolium moiety and a benzyloxycalix[8]octa-azide. Despite a synthetic route that lacks simplicity, this supported catalyst demonstrated a much higher reactivity for the cross-coupling of numerous aryl chlorides.

Inspired by the work of César and Lavigne,[12] we recently reported a faster and easier access to calix[8]arene supported catalysts which respects all the expectations of industrial synthesis. Crowded Pd–NHC complexes supported on benzyloxycalix[8]arene were indeed obtained through immobilisation of sterically hindered 4-hydroxyimidazolium bromides.[13] The corresponding Pd cinnamyl complexes are very active for Buchwald–Hartwig cross-coupling reactions, allowing the coupling between numerous aryl halides and a wide variety of alkyl and aryl amines using low catalytic loadings. In addition, these catalysts led to low Pd leaching measured in the final products.[14]

We describe here our efforts towards the synthesis of the corresponding PEPPSI-type catalysts and their evaluation to promote challenging Suzuki-Miyaura reactions, with sterically hindered substrates and electron rich aryl chlorides. Furthermore, these new supported catalysts have been used for the synthesis of functionalised biaryl precursors for active pharmaceutical scaffolds. Their efficiency, determined both in terms of activity and palladium release in the target products, is compared with other common homogeneous Pd-catalysts.[15]

Results and Discussion

Our first results concerning the Suzuki-Miyaura cross-couplings have been reported with the first generation of benzyloxycalix[8]arene-supported catalysts. Among them, **Cat. 1** is the most crowded complex, with an aromatic group bearing two *i*Pr substituents in *ortho* position of the NHC moiety (see Figure 1). Although the use of this macrocyclic complex led to a low palladium leaching, its activity remained insufficient to promote couplings with challenging substrates.[9] We

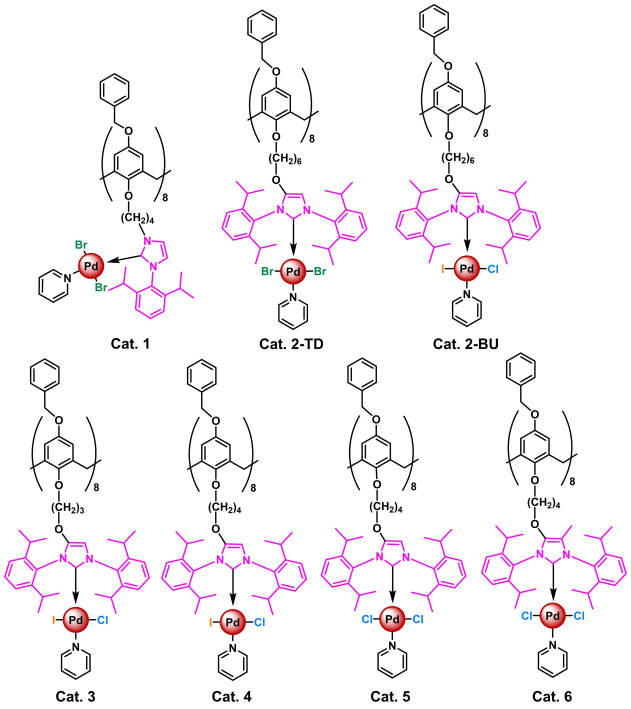


Figure 1. Calixarene-supported palladium NHC catalysts used in this study.

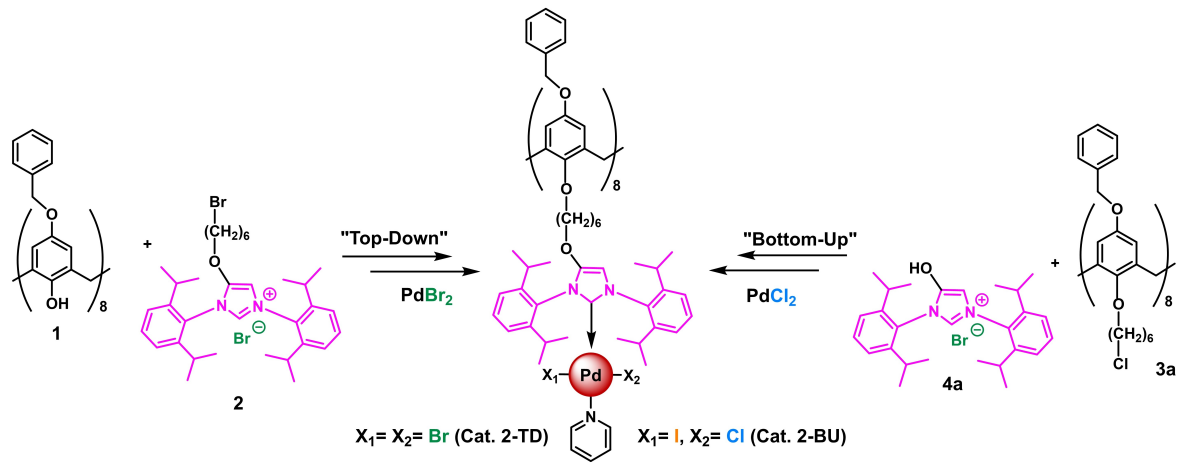
therefore aimed at the preparation of bulkier PEPPSI-type catalysts, expecting an activity improvement.

With the 4-hydroxyimidazolium bromide **4 a** as key intermediate (see Scheme 1), we explored two synthetic routes which differ by the introduction order of the linker between the NHC ligand and the calixarene-based support. The first route starts with the mono-condensation of **4 a** on 1,6-dibromohexane, leading to the imidazolium bromide **2** functionalised with a six-methylene spacer (see Scheme 1).[13] Alkylation of the phenols of benzyloxycalix[8]arene **1** then occurred in good yield with K_2CO_3 in refluxing acetonitrile for 18 h.

The supported imidazolium salt thus obtained was purified by filtration and trituration, and was directly engaged with $PdBr_2$, pyridine and K_2CO_3 to yield **Cat. 2-TD** (**TD**: "Top-Down" strategy, see Scheme 1). The second route involved a strategy we already described, *i. e.* prior chloroalkylation of the macrocyclic phenols,[9a] here with 1-bromo-6-chlorohexane in DMF, with NaH as base. The subsequent condensation of crowded imidazolium **4 a** on the linker alkyl chain of the calixarene requires the presence of NaI in large excess. The supported imidazolium was reacted with $PdCl_2$ to afford **Cat. 2-BU** (**BU**: "Bottom-Up" strategy), the structure of which is very similar to the one of **Cat. 2-TD**.

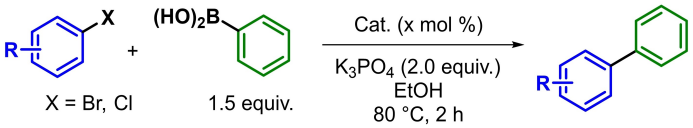
The structure of the two catalysts obtained via the approaches **TD** and **BU** should therefore differ only by the halogen atoms linked to the Pd. Nevertheless, first investigations by NMR spectroscopy showed a marked difference between the two species. Indeed, the superposition of the ^{1}H NMR spectra of **Cat. 2-BU** and **Cat. 2-TD** (see SI) reveals that **Cat. 2-BU**'s spectrum displays a much better resolution. Indeed, for **Cat. 2-BU**, the characteristic broad signals of the macrocycle (and particularly those representing the aromatic and methylene protons of the calixarene structure) are clearly defined and characteristic for a symmetrical molecule. We assume that such defined NMR signals indicate that all monomers of the macrocycle are similar, *i. e.* that the functionalisation occurred identically on each calixarene subunit. Furthermore, the integration for each signal is conform to the one expected for one repeating unit of **Cat. 2-BU**. These conclusions are in clear discrepancy with **Cat. 2-TD** which displays an ill-defined spectrum (see SI). Unfortunately, this complex has remained difficult to characterise, regardless of the analytical technique used. For instance, XPS analysis, which gives the relative content of the atoms in these complexes, revealed the presence of Pd in **Cat. 2-TD** in a too low amount. We thus considered that the access to the target catalysts via the "Top-Down" strategy is delicate and risky, and not suitable for further development on a larger scale.

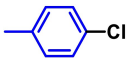
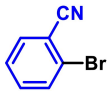
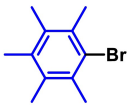
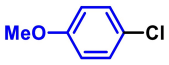
Nevertheless, preliminary catalytic tests were performed to evaluate the efficiency of both macrocyclic complexes, to promote the cross-couplings of challenging substrates via the Suzuki-Miyaura reaction (Table 1). The experimental conditions are those optimised during our previous studies.[9] They imply the use of a slight excess of boronic acid (1.5 equiv.) and K_3PO_4 as base (2 equiv.). Conventional conditions involve heating for 2 hours at 80 °C in ethanol as green solvent, in which the pre-catalysts are insoluble. Results reported in Table 1 clearly show that **Cat. 2-TD**, despite its unknown precise structure, is an efficient catalyst for such cross-couplings. The conversion of 1-chloro-4-methylbenzene is indeed much higher at a lower catalyst loading compared to the results obtained with the first generation catalyst, **Cat. 1** (entries 1 and 2). Although this higher activity is not obvious for the coupling of a more reactive aryl



Scheme 1. Synthetic strategies ("Top-down", **TD** and "Bottom-Up", **BU**) to prepare PEPPSI-type Calixarene-supported palladium-NHC catalysts.

Table 1. Comparison of the catalysts activity for Suzuki-Miyaura benchmark reactions.

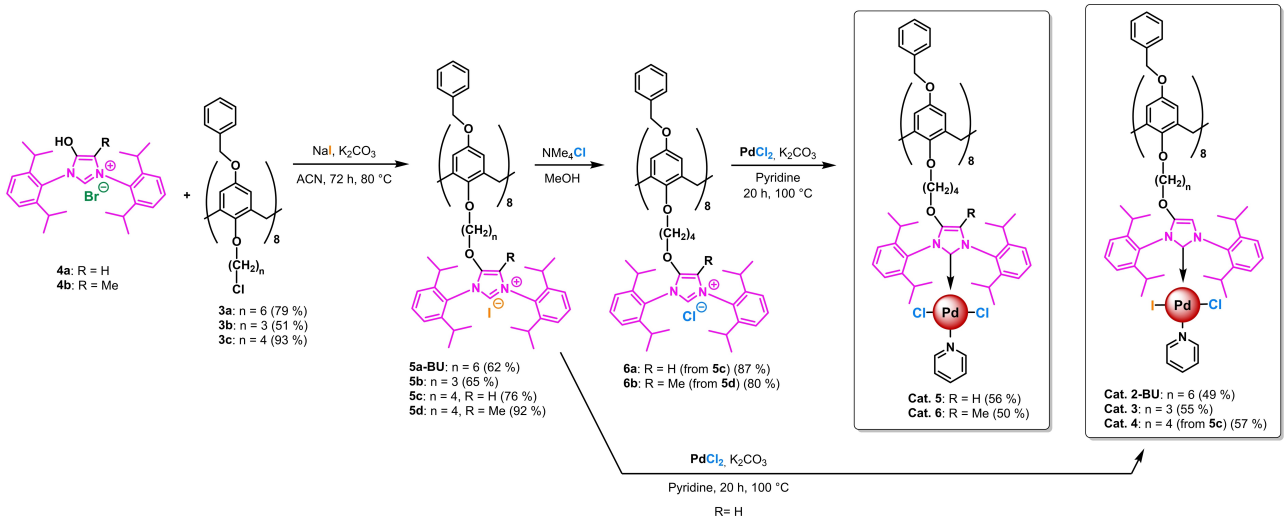


Entry	ArX	Pd (x mol %)	Cat.	Conv. (%)[a]	Product
1		2	**Cat. 1**	38	**7a**
2		0.5	**Cat. 2-TD**	87	
3		0.1	**Cat. 1**	>99	
4		0.1	**Cat. 2-TD**	82	**7b**
5		2	**Cat. 1**	74	
6		0.5	**Cat. 2-TD**	>99[b]	
7		0.5	**Cat. 2-BU**	68	
8		0.5	**Cat. 3**	86	**7c**
9		0.5	**Cat. 4**	>99	
10		0.5	**Cat. 5**	>99	
11		1	**Cat. 6**	71	
12		2	**Cat. 1**	30	
13		2	**Cat. 2-TD**	>99	
14		2	**Cat. 2-BU**	43	
15		2	**Cat. 3**	39	**7d**
16		2	**Cat. 4**	50	
17		1	**Cat. 5**	91	
18		1	**Cat. 6**	72	

[a] Conversion determined by GC analysis.
[b] Reaction performed at 60 °C.

bromide such as 2-bromobenzonitrile (entries 3 and 4), it is restored for the transformation of more challenging substrates, namely 1-bromo-2,3,4,5,6-pentamethylbenzene (entries 5 and 6), and 1-chloro-4-methoxybenzene (entries 12 and 13). The preparation of **7c** was also conducted in the presence of the well-defined species **Cat. 2-BU**, which revealed also more active than **Cat. 1**. Indeed, we reached similar conversion with a 4-times lower catalytic loading (entries 5 and 7), confirming the importance of the steric hindrance and electron richness on the NHC backbone. This conclusion remains true for the preparation of **7d** from less reactive 1-chloro-4-methoxybenzene, although the difference is less marked (entries 12 and 14). Nevertheless, and albeit **Cat. 2-TD** turned out to be the best catalyst (entries 6 and 7, 13 and 14), its uncertain structure led us to abandon its use. We then decided to optimise the structure of **Cat. 2-BU** following the "Bottom-Up" synthetic route.

The detail of the synthetic strategy we selected is reported in Scheme 2. The choice of the structure for the new catalysts was driven by the ambition to control overall steric constraints and halide ligands on the active palladium site. The spacer length between the calixarene-based support and the NHC moiety has been varied through the preparation of two supplementary macrocycles. The chloroalkylation with 1-bromo-3-chloropropane and 1-bromo-4-chlorobutane led respectively to **3b** and **3c** (see Scheme 2 and SI). With the aim of creating a bulkier catalyst, **4b** (the methylated analogue of **4a**) was also engaged in the subsequent substitution of the macrocycle **3c**. Thus, by following the "Bottom-up" procedure, supported imidazolium iodides **5b** to **5d** were isolated in good yields after precipitation steps, without the use of any column chromatography. These compounds have been fully characterised by NMR, HR-MS and infra-red analyses (see SI), unambiguously proving their structure. Further metalation of **5b** and **5c** with $PdCl_2$ in pyridine afforded **Cat. 3** and **Cat. 4**, analogues of **Cat. 2-BU** bearing a shorter spacer. Once again, NMR analyses confirm the expected symmetrical structure for all compounds and reveal that, on average, the palladium centres bear one chlorine and one iodine atom. The catalytic activity of **Cat. 2-BU**, **Cat. 3** and **Cat. 4** was then compared for the synthesis of the coupling products **7c** and **7d** (see Table 1, entries 7 to 9 and 14 to 16, respectively). In both cases, using the same catalytic loading, **Cat. 4** possessing a four-methylene long spacer led to the highest conversion.



Scheme 2. "Bottom-Up" strategy for the synthesis of benzyloxycalixarene-supported PEPPSI-type catalysts with spacers of different lengths.

We therefore decided to focus on the precursors carrying this 4-chain link (**5c** and **5d**), and to continue the study by determining the influence of the halide ligand on the reactivity.

The chlorinated imidazolium salts **6a** and **6b** were prepared respectively from **5c** and **5d** by simple halide exchange with an excess of tetramethylammonium chloride in methanol. The successful halide exchange has been proven by comparative NMR, by HR-MS and by XPS analyses, revealing the presence of only residual traces of iodide anions in the imidazoliums (less than 0.1%). Metalation then occurred with $PdCl_2$ to deliver **Cat. 5** and **Cat. 6**, PEPPSI-type Pd(II)-NHC catalysts with two chlorine ligands, in good yields and high purity. The influence of the halide anions can be highlighted by comparing entries 9–10 and 16–17 in Table 1. Albeit both catalysts behaved identically for the synthesis of **7c**, a higher catalytic activity of the "NHC-Pd**Cl$_2$**Py" complex could be observed for the cross-coupling between 1-chloro-4-methoxybenzene and phenylboronic acid. On the other hand, the bulkier catalyst **Cat. 6** which bears an additional methyl group did not allow to further increase the reactivity of the chlorinated precatalyst. In fact, **Cat. 6** has led to lower conversions than its analogue **Cat. 5** (entry 11 *vs* 10 and entry 18 *vs* 17). We should mention that this trend is the opposite of the one we observed with Buchwald-Hartwig couplings with analogous catalyst structures.[14] In conclusion, all these results led us to choose both complexes **Cat. 4** and **Cat. 5** for the rest of this study.

Our next task was to evaluate their efficiency for the synthesis of valuable products of interest, while investigating further the influence of the halide ligand of the palladium centre. In parallel, we also decided to compare their activity to the one of more conventional catalytic systems. Worthy of note, a special attention was devoted to the determination of Pd leaching values in the target biaryl compounds. As previously mentioned, precatalysts **Cat. 4** and **Cat. 5** are insoluble in ethanol. At the end of the reaction, the crude is simply filtered on a Dicalite® pad and extracted with water to remove the base. Vacuum heating and subsequent mineralisation in nitric acid afforded the aqueous solutions for ICP-MS measurements. The same procedure was used for all the catalysts used, whether soluble or insoluble, in order to make an unbiased comparison of the subsequent contamination of Pd in the recovered products. We have estimated that a precise determination of the palladium release in the reaction product is only valid if the reaction yield is equal or higher than 90%. In each case, optimisation was therefore conducted to reach the highest conversion at the lowest catalyst loading, (see SI for the detailed optimisation tables). The first test concerns the synthesis of 3-phenylpyridine (see Tables 2 and SI-1). The coupling was performed using a low 0.1 mol% Pd loading of either **Cat. 4** or **Cat. 5** in ethanol at 80 °C for 2 hours, and the target product **8** was obtained in high yield in both cases. We should underline that at the end of the catalytic reaction with **Cat. 4**, a simple treatment of the solution (filtration and water extraction) leads to a very low amount of Pd (10 ppm) measured in product **8**, already matching the authorised limits for parenteral drugs administration. A similar leaching value was obtained when using the homogeneous analogue PEPPSI-IPr, albeit introduced in a smaller amount (entries 1–3). In our hands, other classical catalytic systems were also very active for this coupling at a low Pd loading. Reaction conditions

Table 2. Catalysts activity and Pd contamination for the Suzuki-Miyaura reaction between 3-bromopyridine and phenylboronic acid.

Entry	Cat.	Pd (x mol %)	Solvent	Yield (%)[a]	Pd content (ppm)
1	**Cat. 4**	0.1	EtOH	89	10
2	**Cat. 5**	0.1	EtOH	86 (84)[b]	22
3	PEPPSI-IPr	0.05	EtOH	92	12
4	$Pd(OAc)_2/PPh_3$ (1:2)	0.1	$EtOH/H_2O$ (4:1)	96	176
5	$Pd(PPh_3)_4$	0.1	$dioxane/H_2O$ (4:1)	90	513

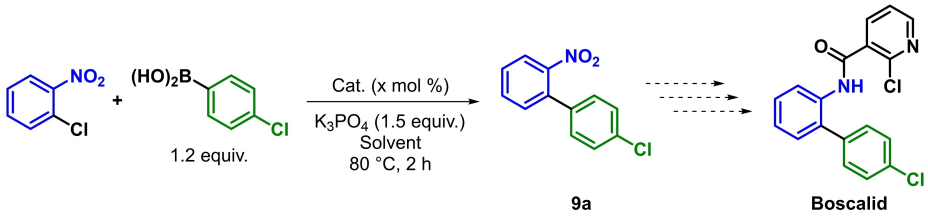
[a] GC yield using hexadecane as internal standard;
[b] Isolated yield.

inspired from the literature mentioned the usefulness of water addition in the reaction media, in particular to promote the transmetalation step (entries 4 and 5).[16] When using conventional catalysts, however, a very high palladium contamination was measured in the coupling product, which would then require additional purification steps to comply with the legislation.

The synthesis of 4′-chloro-2-nitro-1,1′-biphenyl **9a** was next investigated via the coupling of 2-chloronitrobenzene and 4-chlorophenylboronic acid (Tables 3 and SI-2). The biaryl compound **9a** is a precursor for the synthesis of Boscalid, a widely used fungicide.[17] When we compared **Cat. 4** and **Cat. 5** for the preparation of **9a**, we observed a similar trend than for **8**. Indeed, both catalysts promoted the coupling at a 0.5 mol% Pd loading. In this case, the Pd leaching arising from the use of **Cat. 4** was much lower than with its chlorinated analogue **Cat. 5** (entries 1 and 2). Worthy of note, the classical homogeneous catalytic system $Pd(OAc)_2$/XPhos led to a leaching value almost 50 times higher than the one obtained with **Cat. 4** (entries 1 and 3).

We then engaged **Cat. 4** and **Cat. 5** for the preparation of 5-phenylpyrazin-2-amine **10**, a synthetic intermediate of a NPY-5 receptor antagonist, drug candidate for the prevention and treatment of diabetes and obesity.[18] The presence of the aminopyrazine moiety, as potential palladium scavenger, imposes the use of a relatively high catalytic loading (1 mol% Pd), thus affording the product in a good yield. Furthermore, the addition of water to the reaction medium led to a drastic yield increase (Tables 4 and SI-3), highlighting **Cat. 5** as the most active complex among the Pd-NHC catalysts tested. Concerning the leaching, the superiority of both supported catalysts is obvious in this case. Indeed, while the release of Pd in the target compound is similar for **Cat. 4** and **Cat. 5** (about 100 ppm, entries 1 and 2), the use of the homogeneous PEPPSI-IPr catalyst leads to a much higher Pd leaching value which cannot be decreased by the

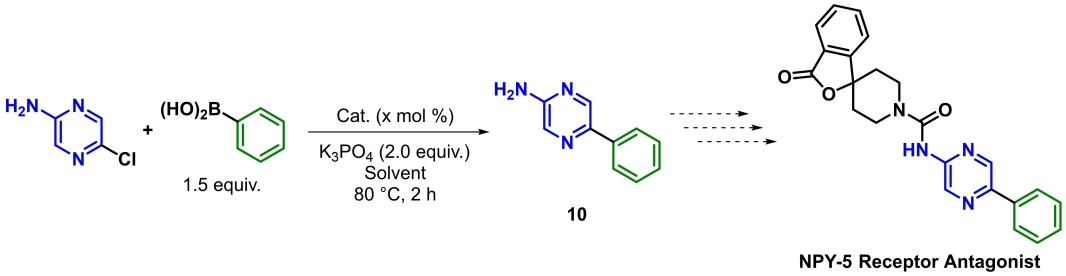
Table 3. Catalysts activity and Pd contamination for the Suzuki-Miyaura reaction between 2-chloronitrobenzene and 4-chlorophenylboronic acid.



Entry	Cat.	Pd (x mol %)	Solvent	Yield (%)[a]	Pd content (ppm)
1	**Cat. 4**	0.5	EtOH	88	31
2	**Cat. 5**	0.5	EtOH	93 (87)[b]	121
3	$Pd(OAc)_2$/XPhos (1:2)	0.5	$EtOH/H_2O$ (4:1)	88	1450

[a] GC yield using hexadecane as internal standard;
[b] Isolated yield.

Table 4. Catalysts activity and Pd contamination for the Suzuki-Miyaura reaction between 2-amino-5-chloropyrazine and phenylboronic acid.



Entry	Cat.	Pd (x mol%)	Solvent	Yield (%)[a]	Pd content (ppm)
1	**Cat. 4**	1	EtOH/H_2O (9:1)	87	119
2	**Cat. 5**	1	EtOH/H_2O (9:1)	94 (93)[b]	103
3	PEPPSI-IPr	1	EtOH/H_2O (4:1)	92	1430
4	$Pd(OAc)_2$/XPhos (1:2)	0.5	EtOH/H_2O (4:1)	91	2410

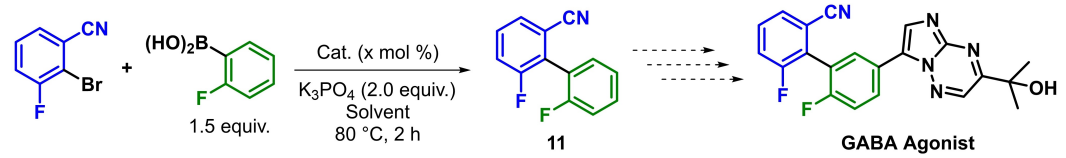
[a] GC yield using hexadecane as internal standard;
[b] Isolated yield.

filtration protocol (entry 3). The same conclusion can be drawn when using $Pd(OAc)_2$/XPhos; despite this system requires a lower Pd amount to reach similar yield, the palladium release is 25 times greater (entry 4 *vs* entries 1 and 2). It seems that the use of this catalytic system does not allow to retain the Pd, which is preferentially trapped by the reaction product.

We then investigated the synthesis of 2′,6-difluoro-[1,1′-biphenyl]-2-carbonitrile **11**, precursor for the synthesis of a $GABA_A$ $\alpha_{2/3}$ selective agonist involved in the treatment of central nervous system disorders (Tables 5 and SI-4).[19] The efficiency of "NHC-$PdCl_2$Py" catalyst **Cat. 5**. was evaluated in the presence of two different bases, KF or K_3PO_4. While the use of the first one led to almost completion at a low catalytic ratio (0.5 mol%), K_3PO_4 required a slightly larger amount of catalyst, but it afforded the target compound contaminated by only 15 ppm of Pd (entries 1 and 2, Table 5). The classical homogeneous catalytic systems were also very efficient, but their use resulted in relatively high Pd release levels (entries 3 and 4).[19]

The coupling between 1,2,3-trifluoro-5-bromobenzene and 2-aminophenylboronic acid leads to the formation of **12**, an advanced synthon towards the antifungal drug Fluxapyroxad.[20] This reaction was also performed successfully with both calixarene-supported NHC catalysts (Tables 6 and SI-5). Delightfully in this case, **Cat. 4**. and **Cat. 5**. were proven to be the most active species for this coupling, while

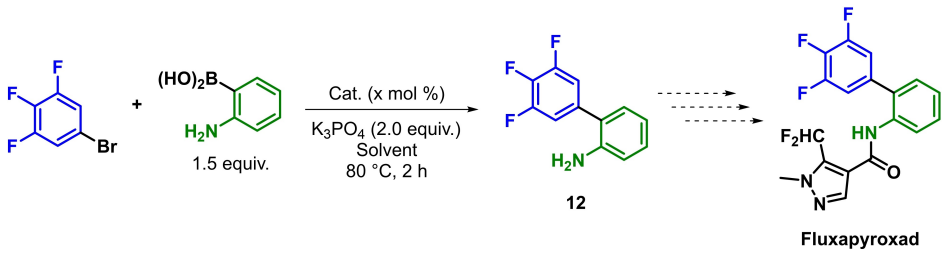
Table 5. Catalysts activity and Pd contamination for the Suzuki-Miyaura reaction between 2-bromo-3-fluorobenzonitrile and 2-fluorophenylboronic acid.



Entry	Cat.	Pd (x mol%)	Solvent	Yield (%)[a]	Pd content (ppm)
1[b]	**Cat. 5**	0.5	EtOH	95 (92)[c]	300
2	**Cat. 5**	1	EtOH	81 (76)[c]	15
3	PEPPSI-IPr	0.5	EtOH	96	714
4[d]	$[Pd(allyl)Cl]_2$/P(*t*Bu)$_3$ (1:2)	1.2	THF/ACN/H_2O	97	7780

[a] GC yield using hexadecane as internal standard;
[b] 2.5 equiv. of KF instead of K_3PO_4;
[c] Isolated yield;
[d] 1.26 equiv. of 2-fluorophenylboronic acid, 1.1 equiv. of K_3PO_4, THF/ACN/H_2O (1:0.7:0.3), 50 °C, 2 h.

Table 6. Catalysts activity and Pd contamination for the Suzuki-Miyaura reaction between 1,2,3-trifluoro-5-bromobenzene and 2-aminophenylboronic acid.



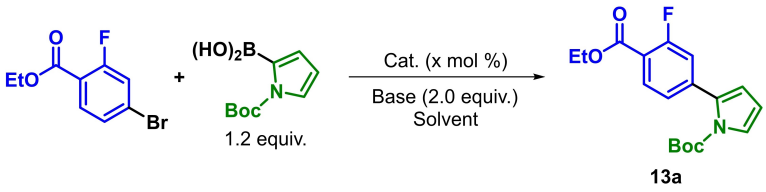
Entry	Cat.	Pd (x mol%)	Solvent	Yield (%)[a]	Pd content (ppm)
1	**Cat. 4.**	0.2	EtOH	>99	59
2	**Cat. 5.**	0.2	EtOH	>99 (94)[b]	65
3	PEPPSI-IPr	0.2	EtOH	>99	776
4	$Pd(OAc)_2/PPh_3$ (1:2)	0.5	$EtOH/H_2O$ (4:1)	>99	54
5	$Pd(OAc)_2$/XPhos (1:2)	0.5	$EtOH/H_2O$ (4:1)	>99	110
6	$Pd(PPh_3)_4$	1	$Dioxane/H_2O$ (4:1)	>99	2426

[a] GC yield using hexadecane as internal standard;
[b] Isolated yield.

leading to the lowest Pd release amount in the target compound (entries 1 and 2 *vs* entries 3 to 6).

Finally, the catalysts were engaged in an even more challenging coupling reaction between ethyl 2-fluoro-4-bromobenzoate and *N*-Boc-2-pyrrolylboronic acid (Tables 7 and SI-6).[21] The nature of the base had to be adjusted to respect the integrity of the functional groups on both substrates. Thus, the use of K_2CO_3 afforded the best results allowing the use of **Cat. 4**. or **Cat. 5**. at a low catalytic loading. The product **13 a** was indeed delivered in high yield along with a low Pd contamination (entries 1 and 2). This coupling has been described in the presence of a 1:1 mixture of K_3PO_4/K_2HPO_4 with other homogeneous catalytic systems.[21] Although these reaction conditions led to isolation of the target product in high yield, the Pd leaching was very high, a result we also obtained when using **Cat. 5**. in the same conditions (Table 7, entry 3). An attempt to reuse **Cat. 5** was made when coupling 4-chloroanisole and phenylboronic acid at a 1 mol% Pd loading (table 1, entry 17). After 2 h at 80 °C, the crude was filtered through a Whatman® filter paper, which was washed with ethanol and diethylether. The recovered solid pad, containing the catalyst and the salts coming from the first run was then re-engaged with new substrates and base at the same temperature.

Table 7. Catalysts activity and Pd contamination for the Suzuki-Miyaura reaction between ethyl 2-fluoro-4-bromobenzoate and *N*-Boc-2-pyrrolylboronic acid.



Entry	Cat.	Pd (x mol%)	Base	Yield (%)[a]	Pd content (ppm)
1[b]	**Cat. 4**	0.5	K_2CO_3	86	23
2[b]	**Cat. 5**	0.5	K_2CO_3	89	14
3[c]	**Cat. 5**	1	K_3PO_4/K_2HPO_4	86	931
4[c]	PEPPSI-IPr	0.5	K_2CO_3	89	83
5[c]	$Pd(OAc)_2$/XPhos (1:2)	0.5	K_3PO_4/K_2HPO_4	91	476
6[c]	$Pd(dtbpf)Cl_2$	0.5	K_3PO_4/K_2HPO_4	96	459

[a] Isolated yield;
[b] EtOH, 80 °C, 2 h;
[c] DME/H_2O/EtOH (51:37:12), 25 °C, 4 h.

However, the formation of the desired product could not be observed, which indicates that the catalytic species is unfortunately not recyclable under these experimental conditions.

Conclusion

To conclude, new supported PEPPSI-type Pd-NHC precatalysts have been synthesised and their anchoring onto a benzyloxycalix[8]arene core has been precisely optimised. Their best access involves pre-functionalisation of the macrocycle with a long methylene spacer. Subsequent nucleophilic substitutions with hydroxyimidazolium salts afforded perfectly defined precursors, ensuring the grafting of eight sterically hindered imidazolium units assembled close to each other. This synthetic route was used to prepare six palladium catalysts, differing in the spacer length between the macrocyclic support and the active site, in the halide ligands around the Pd metal centre and in the steric hindrance of the NHC moiety. Importantly, these macrocyclic species were precisely characterised, thanks to their solubility in some polar solvents. In addition, their preparation is simple, scalable and does not require the need of long and expensive column chromatography purifications. Their activity and metal leaching have been evaluated and compared to other popular Pd-catalysts on benchmark reactions. Results clearly highlighted that **Cat. 4**. and **Cat. 5**. are very active species at low catalytic loadings for the transformation of challenging substrates, such as sterically hindered aryl halides and electron rich aryl chlorides. Delightfully, they are equally or more active than homogeneous catalytic systems in which common phosphine derivatives were used as ligands. Of main importance, a simple filtration of these macrocyclic-supported catalysts over a Dicalite® pad afforded the lowest Pd contamination values for each example studied, even directly approaching the levels authorised by the regulations in some cases. **Cat. 4**. and **Cat. 5**. are undoubtedly very active, easily accessible, and low-polluting precatalysts that can serve as powerful tools for the fine chemical industry to prepare valuable biaryl products. They also offer the possibility of a facile recovery of the palladium, in a context of overconsumption on a global scale.

Experimental Section

General Procedure for the Catalysts Synthesis

In a Schlenk-tube equipped with a magnetic stirring bar were introduced the supported imidazolium precursor (1 equiv.), palladium bromide or chloride (10 equiv.) and dry potassium carbonate (40 equiv.). The solids were dried under vacuum for 10 minutes, and the Schlenk-tube was backfilled with argon, then evacuated and backfilled with argon 2 more times. Anhydrous pyridine (C = 0.024 M) was added under argon, and the mixture was briefly degassed before stirring the solution at 100 °C for 20 hours. The reaction was then allowed to cool down to room temperature under argon, and DCM was added. The mixture was centrifuged (20 min, 20 °C, 9000 rpm) and the supernatant was filtered on a Dicalite® pad and rinsed with DCM. The solution was evaporated, and the residue was dissolved in a minimum of DCM and then poured slowly in a flask containing a large volume of diethyl ether under vigorous stirring. The heterogeneous solution was stirred under argon 15 min at room temperature, then filtered on a fritted glass filter and washed with Et_2O two times. The resulting solid was stirred in EtOH overnight under argon at room temperature. The solid was filtered on a fritted glass filter, washed with diethyl ether and dried under vacuum overnight to afford the desired catalyst as a dry powder.

General Procedure for the Palladium-Catalysed Suzuki-Miyaura Cross-Couplings

In a Schlenk-tube equipped with a magnetic stirring bar were introduced the catalyst (x mol % Pd), the base (1.5 or 2.0 equiv.) the aryl halide (1 equiv., if solid) and the boronic acid (1.2 or 1.5 equiv.). The solids were dried under vacuum for 10 minutes, and the Schlenk-tube was backfilled with argon, then evacuated and backfilled with argon 2 more times. Then the aryl halide (1 equiv., if liquid) and the solvent (0.5 M) were introduced under argon. The reaction mixture was stirred for 2 hours at 80 °C using a pre-heated oil bath. Then the reaction was allowed to cool down to room temperature under argon, and the internal standard (hexadecane, 1 equiv.) was added, before diluting the reaction mixture with ethyl acetate. A sample was collected, filtered on a small Dicalite® pad (rinsed with ethyl acetate) and the filtrate was analysed by GC to determine the conversion and the yield. The reaction mixture was then filtered on a Dicalite® pad, rinsed with ethyl acetate, and the solvents were evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel, to afford the expected biaryl derivatives as pure products.

General Procedure for the Preparation of Samples for ICP-MS Analyses (Leaching Tests)

Caution: all the glassware used for the reaction, the storage of solutions and the filtration operations were thoroughly washed with aqua regia, rinsed with distilled water and oven-dried before their use in the residual palladium content determination tests.

In a Schlenk-tube equipped with a magnetic stirring bar were introduced the catalyst (x mol % Pd), the base (1.5 or 2.0 equiv.) the aryl halide (1 mmol, 1 equiv., if solid) and the boronic acid (1.2 or 1.5 equiv.). The solids were dried under vacuum for 10 minutes, and the Schlenk-tube was backfilled with argon, then evacuated and backfilled with argon 2 more times. Then the aryl halide (1 mmol, 1 equiv., if liquid) and the solvent (0.5 M) were introduced under argon. The reaction mixture was stirred for 2 hours at 80 °C using a pre-heated oil bath. The solution was then allowed to cool down to room temperature under argon for 30 minutes, the crude was filtered

on a Dicalite® pad, rinsed with diethyl ether or ethyl acetate, then a liquid/liquid extraction was performed using distilled water. The solvents of the organic phase were evaporated under reduced pressure and the crude residue was heated under high vacuum (10^{-1} mmHg) with a heat-gun for 10 to 15 minutes. The remaining solid was mineralised in nitric acid (69%, TraceMetal grade, V = 3 mL) at 140 °C for 2 or 3 h until obtaining a homogeneous light-yellow solution, which was used to perform the ICP-MS analyses.

3-Phenylpyridine (8): The reaction mixture was filtered on a Dicalite® pad using Et_2O and the filtrate was concentrated under reduced pressure. Then, the crude was purified by silica gel column chromatography (pentane/Et_2O = 5:5 to 7:3) to afford 130.4 mg (84%) of the pure desired compound as a colorless oil; TLC: Rf = 0.21 (pentane/Et_2O = 5:5, SiO_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 8.81 (d, J = 2.2 Hz, 1H), 8.54 (dd, J = 5.0 Hz and 1.4 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.44–7.39 (m, 2H), 7.36–7.32 (m, 1H), 7.28 (dd, J = 7.9 Hz and 4.1 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 148.2, 148.0, 137.4, 136.2, 133.9, 128.8 (2 C), 127.8, 126.8 (2 C), 123.2; HR-MS [ESI(+)]: *m/z* $[M+H]^+$ calculated for $[C_{11}H_{10}N]^+$: 156.0808, found: 156.0815.

4′-Chloro-2-nitro-1,1′-biphenyle (9 a): The reaction mixture was filtered on a Dicalite® pad with EtOAc and the filtrate was concentrated under reduced pressure. Then, the crude was purified by silica gel column chromatography (petroleum ether/THF = 98:2 to 95:5) to afford 203.3 mg (87%) of the pure desired compound as a yellow solid; TLC: Rf = 0.23 (petroleum ether/THF = 95:5, SiO_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 8.10 (dd, J = 8.3 Hz and 0.9 Hz, 1H), 7.84 (td, J = 7.6 Hz and 0.9 Hz, 1H), 7.72 (td, J = 7.6 Hz and 0.9 Hz, 1H), 7.64–7.61 (m, 3H), 7.48 (d, J = 8.6, Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 148.9, 136.0, 135.0, 134.3, 132.6, 131.8, 129.3 (2 C), 128.8 (2 C), 128.6, 124.2; HR-MS [ESI(+)]: *m/z* $[M+H]^+$ calculated for $[C_{12}H_8ClNNaO_2]^+$: 256.0136, found: 256.0129.

2-Amino-5-phenylpyrazine (10): The reaction mixture was filtered on a Dicalite® pad with EtOAc and the filtrate was concentrated under reduced pressure. Then, the crude was purified by silica gel column chromatography (DCM/ACN = 98:2 to 75:25) to afford 158.7 mg (93%) of the pure desired compound as a yellow solid; TLC: Rf = 0.16 (DCM/ACN = 95:5, SiO_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 8.43 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.43 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 4.71 (br. s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 153.3, 143.1, 139.2, 137.1, 131.8, 129.0 (2 C), 128.3, 125.8 (2 C); HR-MS [ESI(+)]: *m/z* $[M+H]^+$ calculated for $[C_{10}H_{10}N_3]^+$: 172.0869, found: 172.0869.

2′,6-Difluoro-[1,1′-biphenyl]-2-carbonitrile (11): The reaction mixture was filtered on a Dicalite® pad with EtOAc and the filtrate was concentrated under reduced pressure. Then, the crude was purified by silica gel column chromatography (pentane/Et_2O = 99:1 to 95:5) to afford 198.0 mg (92%, Table 5, entry 1) or 164.4 mg (76%, Table 5, entry 2) of the pure desired compound as a white solid; TLC: Rf = 0.40 (pentane/Et_2O = 95:5, SiO_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.61 (d, J = 7.9 Hz, 1H), 7.53–7.40 (m, 4H), 7.31 (t, J = 7.2 Hz, 1H), 7.25 (t, J = 8.6 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 159.7 (d, J = 248.1 Hz, 2 C), 131.6, 131.5, 130.5 (d, J = 7.9 Hz), 129.0 (d, J = 3.9 Hz), 127.1 (d, J = 19.6 Hz), 124.3 (d, J = 2.6 Hz), 120.5 (d, J = 22.3 Hz), 119.3 (d, J = 15.8 Hz), 116.8 (d, J = 4.0 Hz), 115.9 (d, J = 22.3 Hz), 114.8 (d, J = 5.3 Hz); ^{19}F NMR (235 MHz, $CDCl_3$): δ −110.4 (d, J = 10.6 Hz), −113.3 (d, J = 10.8 Hz); HR-MS [ESI(+)]: *m/z* $[M+H]^+$ calculated for $[C_{13}H_8F_2N]^+$: 216.0619, found: 216.0615.

3′,4′,5′-Trifluoro-[1,1′-biphenyl]-2-amine (12): The reaction mixture was filtered on a Dicalite® pad with EtOAc and the filtrate was concentrated under reduced pressure. Then, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc/triethylamine = 80:17:3) to afford 209.8 mg (94%) of the pure desired compound as a brown solid; TLC: Rf = 0.70 (petroleum ether /EtOAc/triethylamine = 80:17:3, SiO_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.17 (td, J = 7.9 Hz and 1.4 Hz, 1H), 7.13–7.07 (m, 2H), 7.05 (dd, J = 7.9 Hz and 1.1 Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 3.72 (br. s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 151.5 (ddd, J = 248.2 Hz, 9.2 Hz and 3.4 Hz, 2 C), 143.5, 139.0 (dt, J = 249.5 Hz and 14.5 Hz), 135.7 (dd, J = 7.9 Hz and 5.2 Hz), 130.3, 129.6, 124.5, 119.0, 116.1, 113.4 (dd, J = 14.4 Hz and 6.6 Hz, 2 C); ^{19}F NMR (235 MHz, $CDCl_3$): δ −133.9 (d, J = 17.9 Hz, 2F), −162.3 (t, J = 17.9 Hz); HR-MS [ESI(+)]: *m/z* $[M+H]^+$ calculated for $[C_{12}H_9F_3N]^+$: 224.0682, found: 224.0681.

Ethyl 4-(*N*-Boc-pyrrolyl)-2-fluorobenzoate (13 a): The reaction mixture was filtered on a Dicalite® pad with EtOAc and the filtrate was concentrated under reduced pressure. Then, the crude was purified by silica gel column chromatography (petroleum ether/acetone = 97:3 to 95:5) to afford 296.7 mg (89%) of the pure desired compound as a colorless oil (which became pink red after 1 day of storage); TLC: Rf = 0.45 (petroleum ether/acetone = 95:5, SiO_2); IR (ATR-GE): $\tilde{\nu}$ (cm^{-1}) = 3339, 2958, 2853, 2362, 2337, 1698, 1618, 1583, 1559,1540, 1506, 1459, 1419, 1391, 1368, 1353, 1317, 1278, 1256, 1210, 1168, 1140, 1122, 1102, 1042, 1019 ; ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.88 (t, J = 8.3 Hz, 1H), 7.35 (dd, J = 3.2 Hz and 1.8 Hz, 1H), 7.15 (dd, J = 9.1 Hz and 1.4 Hz, 1H), 7.09 (dd, J = 11.9 Hz and 1.4 Hz, 1H), 6.24 (dd, J = 3.2 Hz and 1.8 Hz, 1H), 6.20 (t, J = 3.4 Hz, 1H), 4.36 (q, J = 7.5 Hz, 2H), 1.39 (s, 9H), 1.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 164.3 (d, J = 4.0 Hz), 161.4 (d, J = 257.3 Hz), 149.0, 140.7 (d, J = 10.5 Hz), 132.7, 131.3, 124.5 (d, J = 3.9 Hz), 124.1, 117.3 (d, J = 32.8 Hz), 117.2, 116.1, 111.0, 84.4, 61.3, 27.7 (3 C), 14.4; ^{19}F NMR (235 MHz, $CDCl_3$): δ −110.6 (s); HR-MS [ESI(+)]: *m/z* $[M+H]^+$ calculated for $[C_{18}H_{21}FNO_4]^+$: 334.1449, found: 334.1444.

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