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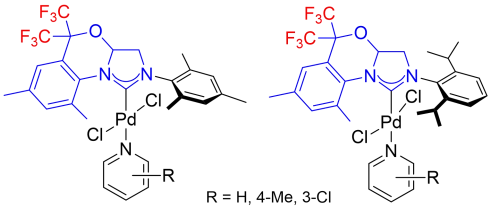
New Pd-PEPPSI complexes with fluorinated tricyclic NHC ligands: synthesis and catalytic activity

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New Pd-PEPPSI complexes with bulky fluorinated NHC ligands were synthesized and fully characterized. Their catalytic activity was tested in model Suzuki cross-coupling reaction of 1-bromo-4-methylbenzene and bromobenzene with (4-methoxyphenyl) boronic acid demonstrating from good to excellent activities under standard conditions.



Keywords: N-Heterocyclic carbenes, palladium-PEPPSI complexes, synthesis, catalysis, Suzuki-Miyaura coupling, transmetallation.

Palladium-catalyzed cross-coupling reactions are the most commonly used synthetic methods for the construction of various molecular frameworks.[1] Among the diversity of catalysts developed to date, NHC-based complexes are particularly frequently applied in a wide range of C-C and C-N bonds forming processes, exhibiting exceptional stability and remarkable catalytic activity. In this context, the search for new, more efficient and robust catalysts is of great interest.[2]

In 2006, Organ and co-workers reported air- and moisture-stable Pd(II)-NHC complexes, [Pd(NHC)(3-Cl-py)Cl_2], with 3-chloro-pyridine as a labile ancillary ligand on palladium, and called them PEPPSI (Pyridine-Enhanced Precatalyst Preparation, Stabilization, and Initiation).[3] These complexes bearing two anionic ligands (usually Cl^-), one NHC and a stabilizing "throw-away" pyridine ligand exhibited the unique ability to both fast dissociation of the electron-deficient 3-chloropyridine ligand and its slow rebinding, which has resulted in an explosion of interest in this class of Pd(II)-NHC complexes in cross-coupling reactions such as Suzuki-Miyaura,[4,5] Negishi,[6-8] Stille-Migita,[9] Kumada-Tamao-Corriu[10] as well as Buchwald-Hartwig.[11-15] In addition, Pd-PEPPSI pre-catalysts have been shown to be highly stable in air allowing for easy storage and handling.

We have recently synthesized a series of novel Ru-, Cu- and Au-complexes with trifluoromethyl-containing tricyclic NHC ligands, which exhibited high catalytic activity in different types of alkene metathesis,[16,17] 1,3-dipolar cycloaddition reactions,[18] acetylene hydroamination[19] and intermolecular allenyne annulation[20] as well. Now we want to disclose a convenient synthesis of six novel Pd-PEPPSI-NHC complexes containing these NHC ligands (Figure 1) and our initial study of their catalytic activity.

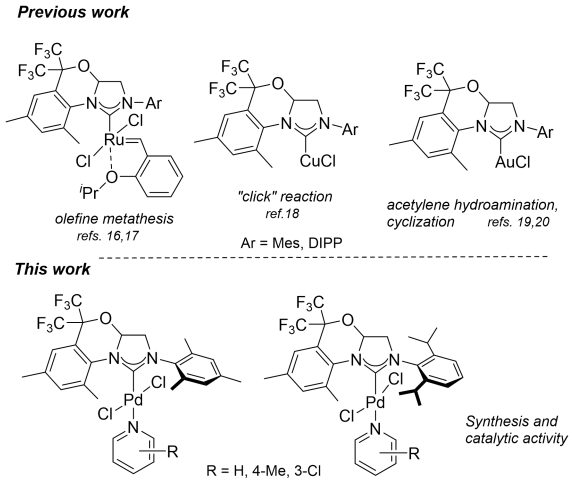


Figure 1 Previous results and this work.

Among a variety of synthetic methods to NHC-Pd-PEPPSI complexes one of the most common ones includes the heating of the corresponding NHC·HCl salt with $PdCl_2$ in pyridine as a solvent[2] or with previously synthesized bipyridine adduct [$PdCl_2(Py)_2$][21] in the presence of K_2CO_3 affording the desired products even on multigram scale. However, the both of these approaches did not allow us to obtain the target complexes.

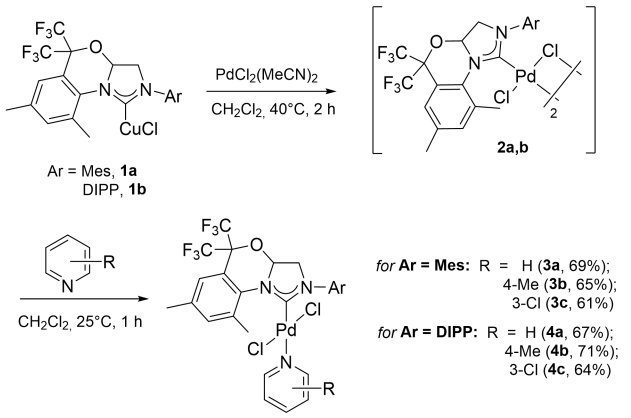
Another access to NHC-Pd-PEPPSI complexes was developed by Organ *et al.* in 2016. This method involves transmetallation of NHC-CuCl with [$PdCl_2$(3-Cl-Py)$_2$] as palladium source under heating at 110 °C in toluene for 48 h.[22] Unfortunately, we have revealed that the application of above conditions results in low yield (25%) of the desired PEPPSI-complex.

At the same time, in 2017 Goldsmith *et al.* found that some NHC·HCl salts can be metallated with $Pd(OAc)_2$ to form the chloro-bridged dimeric species [Pd(μ-Cl)Cl(NHC)]$_2$ *via* carbene-transfer reaction, which were then cleaved by 4-

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picoline to afford the corresponding Pd-PEPPSI complexes.[23] It was also shown that similar palladium dimers can be obtained through transmetallation of NHC-CuCl c $PdCl_2(CH_3CN)_2$ under mild conditions.[24]

Given the above precedents we decided to combine the transmetallation approach to dimeric Pd-complexes with their ability to desymmetrization by the treatment with pyridine derivatives. As a result, it was revealed that readily available copper complexes **1a,b**[18] with tricyclic NHC ligand can be successfully used for the preparation of the corresponding Pd-PEPPSI complexes *via* one pot two steps procedure, involving initial transmetallation with $PdCl_2(CH_3CN)_2$ to form intermediate dimers **2a,b** followed by reaction with different pyridines to give the desired products **3a-c** and **4a-c** in good yields (Scheme 1).



Scheme 1

The complexes obtained **3a-c** and **4a-c** were isolated in pure form as white powder *via* column chromatography on silica gel and fully characterized by standard physicochemical methods. The ^{13}C NMR spectra of the NHCs display the corresponding resonances at 188.3-190.2 ppm for the carbene center (see Supplementary Materials). In addition, single crystals of good quality for X-ray analysis from complexes **3a** and **4b** (Figure 2) were obtained by slow diffusion of hexane into concentrated solution of **3a**, **4b** in $CHCl_3$.

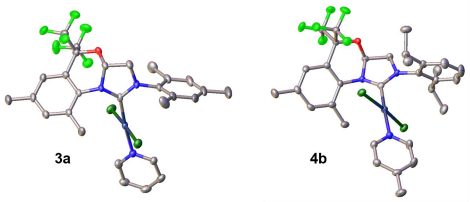
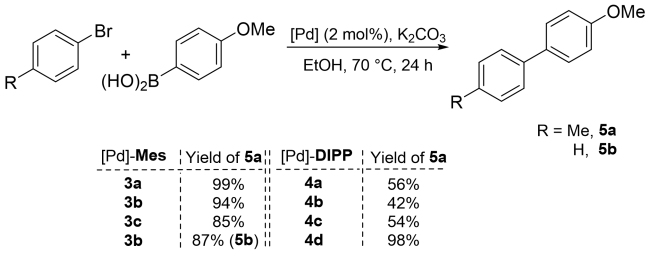


Figure 2 Molecular structure of complexes **3a** and **4b** showing thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. [=]

A preliminary study of the catalytic activity of the new complexes **3** and **4** was conducted using a model reaction of 1-bromo-4-methylbenzene and bromobenzene with (4-methoxyphenyl) boronic acid to yield the cross-coupling product **5a** and **5b** under standard Suzuki-Miyaura reaction conditions. As a result, it was found that complexes **3a-c** with a Mes-containing ligand exhibit noticeably higher activity compared to complexes **4a-c**, which contain the bulkier DIPP group (Scheme 2). Then commercially available complex Pd-PEPPSI-IPr (**4d**) was tested as a benchmark catalyst under the same condition. As a result, it exhibited almost identical activity compared to new Pd-complex **3a**. For all studied cases TON values did not exceed 50.



[Pd]-**Mes**	Yield of **5a**	[Pd]-**DIPP**	Yield of **5a**
3a	99%	**4a**	56%
3b	94%	**4b**	42%
3c	85%	**4c**	54%
3b	87% (**5b**)	**4d**	98%

Scheme 2

In conclusion, have elaborated an efficient one pot two steps synthesis of six new Pd(II)-PEPPSI complexes bearing fluorinated tricyclic NHC ligands. The method is based on transmetallation of the corresponding NHC-Cu(I) complexes with $PdCl_2(CH_3CN)_2$ to form the intermediate Pd-dimers followed by their cleavage with different pyridines. The compounds obtained were fully characterized by standard physicochemical methods including X-ray analysis. The initial investigation of catalytic activity of new NHC-Pd-PEPPSI complexes was accomplished on typical Suzuki-Miyaura cross-coupling reaction indicating higher catalytic activity of the complexes with N-mesityl group in NHC ligand.

To commemorate Prof. Sergey E. Nefedov

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:

[=] Crystal data for **3a**. $C_{28}H_{27}N_3F_6Cl_2PdO$, monoclinic, space group $P2_1/c$, a = 13.1545(4) Å, b = 16.6054(4) Å, c = 14.1819(3) Å, α = γ = 90°, β = 111.3381(9)°, V = 2885.47(13) Å^3, Z = 4, T = 150.15 K, μ(MoKα) = 0.895 mm^{-1}, *Dcalc* = 1.641 g/cm^3, 35530 reflections measured (4.372° ≤ 2Θ ≤ 59.996°), 8413 unique (R_{int} = 0.0596, R_{sigma} = 0.0610) which were used in all calculations. The final R_1 was 0.0512 (I > 2σ(I)) and wR_2 was 0.1029 (all data).

Crystal data for **4b**·$CHCl_3$. $C_{33}H_{36}Cl_5F_6N_3OPd$, monoclinic, space group $P2_1/c$, a = 9.9446(3) Å, b = 23.6774(7) Å, c = 16.0893(5) Å, α = γ = 90°, β = 98.5300(10)°, V = 3746.5(2) Å^3, Z = 4, T = 120 K, μ(MoKα) = 0.913 mm^{-1}, *Dcalc* = 1.575 g/cm^3, 40693 reflections measured (3.44° ≤ 2Θ ≤ 51.996°), 7353 unique (R_{int} = 0.0445, R_{sigma} = 0.0404) which were used in all calculations. The final R_1 was 0.0306 (I > 2σ(I)) and wR_2 was 0.0774 (all data).

CCDC 2582198 and 2582199 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk.

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