Synthesis and Characterization of Novel PEPPSI type Pd–BICAAC Complexes

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This paper is dedicated to the memory of a cherished colleague, Prof. István Pálinkó

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ABSTRACT: A series of bicyclic alkylamino carbenes (BICAAC) (where N-aryl = dipp, mes, 2,6-dimethyl-4-(dimethylamino)phenyl, 5a-d) and their novel air- and moisture-resistant pyridine (pyridine, 4-dimethylaminopyridine) containing palladium PEPPSI-type Pd(II) complexes (6a-e) were synthetized and characterized. The new palladium complexes have shown high activity in Mizoroki–Heck coupling reaction even at as low as 100 ppm loading (TON up to 10000). Kinetic studies revealed that reactions carried out in the presence of elemental mercury resulted in decrease in activity. It indicates that the coupling reaction may have both molecular and Pd(0)-mediated catalytic paths.

KEYWORDS: Pd-PEPPSI • BICAAC • Mizoroki–Heck reaction • PEPPSI complex • Palladium carbene complex •
1. Introduction

Designing robust sustainable homogenous catalyst systems rely on several driving forces such as high activity at low catalyst loading, broad functional group tolerance and low moisture and oxygen sensitivity.

Palladium-carbene catalyst systems are excellent tools for cross-coupling reactions. A wide range of catalysts including in situ generated species (e.g. Pd(II)-salt and phosphine ligand), palladacycles and bis-carbene (mostly N-heterocyclic carbene, NHC) structures are recently reviewed.\textsuperscript{1–3} A special type of Pd(II) halogenide-based, one pyridine- and one carbene-containing (so-called PEPPSI-type) complexes were reported first by Organ \textit{et al.} in 2006.\textsuperscript{4} The PEPPSI is originating from the abbreviation of the \textit{“pyridine enhanced precatalyst preparation stabilization and initiation”} concept. In PEPPSI complexes, the pyridine acts as a \textit{“throw-away ligand”}: meaning that the active palladium species forms upon dissociation of the pyridine. On the other hand, the carbene ensures the stability of the palladium species. Since their discovery, numerous PEPPSI-complexes were reported as highly efficient catalyst of coupling reactions.\textsuperscript{5,6} The combination of carbenes (NHC) and pyridines having a wide range of functionalities enable the fine-tuning of the steric and electronic properties of the catalysts. Some representative examples including the modification of NHC carbene ligands,\textsuperscript{7} dimetallic \textit{bis}-carbene-based,\textsuperscript{8} trimetallic \textit{tris}-carbene-derived,\textsuperscript{9} solid phase-supported,\textsuperscript{10} benzimidazole-derived amide,\textsuperscript{11} bulky arly-substituted,\textsuperscript{12} ring-expanded,\textsuperscript{13} tetraaryl-functionalized (sterically encumbered)\textsuperscript{14} andacenaphthyl-derived\textsuperscript{15} species have been reported. Even microwave-assisted flow processes were published using PEPPSI catalysts.\textsuperscript{16} However, the impact of different type of carbene ligands on the catalytic activity of the PEPPSI-complexes is less investigated so far. A few examples includes MIC (mesoionic carbene)\textsuperscript{17} and triazole-based NHC\textsuperscript{18} systems. Complexes similar to PEPPSI bearing azide or $\eta^3$-allyl moieties instead of pyridine – as throw-away ligand – were also reported containing tetrazole-based\textsuperscript{19} or cyclic alkylamino carbene (CAAC)\textsuperscript{20} ligands.

An interesting trend can be observed in the selection of suitable ligands for transition metal catalysts: phosphine- or amine/imine-based ligands were first replaced by NHC and then CAAC ligands due to their better steric and electronic properties.\textsuperscript{21} At palladium complexes, NHC-,\textsuperscript{22} MIC-\textsuperscript{23} and CAAC-based\textsuperscript{24} systems were also investigated. One of the emerging carbene ligands
is the bicyclic modification of the CAAC structure bearing a 2-azabicyclo[2.2.2]octan-3-ylidene structure.25 Inspired by the progressive trend observed for Grubbs-type olefin metathesis catalyst systems, we became interested in the synthesis and catalytic investigation of bicyclic alkylamino carbene- (BICAAC)-based Pd-PEPPSI complexes (Scheme 1).

Scheme 1. Evolution of carbene ligands and their Pd-complexes (selected examples)

Although the literature of BICAAC-complexes are still limited, some transition metal BICAAC complexes have already been reported: copper-group metals (Cu, Ag, and Au) were complexed with BICAAC ligands,25–27 and bis-BICAAC complexes were prepared giving zinc(0)28 and palladium(II)29 complexes; the latter was found to be an effective catalyst in cross-coupling reactions.
2. Experimental

2.1. General

Unless stated otherwise, all reactions were conducted under nitrogen atmosphere using Schlenk-technique or under argon using a glovebox. Some catalytic reactions were carried out under nitrogen and as well as under air atmosphere for comparison. The reagents (Merck, Fluorochem) and deuterated solvents (such as CDCl$_3$, CD$_2$Cl$_2$, acetone-d$_6$ from Eurisotop) – were used as received. Dry solvents and palladium(II) chloride were purchased from Merck and stored in the glovebox. Aldehyde 1 (Trivertal, Fluorochem) and anilines 2a, 2c (Merck) are commercially available. Compound 2b was synthetized following the procedure described in a paper published by our group recently.$^{30}$

GC-MS analyses were carried out using a Shimadzu GC-MS-QP2010 instrument fitted with an Rxi-5Sil MS column coupled with a quadrupole mass filter with pre-rods.

NMR spectra were recorded on Varian Unity INOVA and Varian INOVA spectrometers operating at an equivalent $^1$H frequency of 499.64 and 299.96 MHz, respectively. The chemical shifts are referred to the chemical shifts of the non-deuterated content in NMR solvents from the chart of Cambridge Isotope Laboratories, Inc. or to TMS as internal standard.

For the high-resolution mass spectrometric measurements (HRMS) a Maxis II type Qq-TOF MS instrument (Bruker Daltonics, Bremen, Germany) equipped with an electrospray ion-source were applied. The spray voltage was maintained at 3.5 kV and N$_2$ was used as the drying (200 °C, 4.0 L/min) and nebulizer gas (0.5 bar). The mass spectra were recorded by a digitizer at a sampling rate of 2 GHz. The mass accuracy of the instrument is < 600 ppb (internal calibration), the resolution is 40000 at m/z 400 (fwhm). The ESI-QTOF MS spectra were calibrated internally with sodium formate clusters formed in situ under electrospray conditions and evaluated using the Compass DataAnalysis 4.4 software from Bruker Daltonics (Bremen, Germany). The samples were dissolved in dichloromethane (DCM) and then diluted with methanol (MeOH) (MeOH/DCM: 9/1 V/V) to obtain sample concentrations of 0.01-0.04 mg/mL.

Some MS and collision induced dissociation (CID) MS/MS experiments were also performed using a MicroTOF-Q instrument (Bruker Daltonics, Bremen, Germany) with similar source parameters as those set for Maxis II. The collision gas was nitrogen. The precursor ions for CID-MS/MS were selected with an isolation width of 4 m/z units and the collision energies were varied in the range of 5-25 eV.
2.2. Crystal structure determinations

X-ray-quality crystals of 6a and 6b were grown by slow evaporation or cooling of hexane solution. A crystal well-looking in polarized light microscope was fixed under a microscope onto a Mitegen loop using high-density oil. Diffraction intensity data were collected at room temperature (295-300 K) using a Bruker-D8 Venture diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) equipped with INCOATEC IμS 3.0 (Incoatec GmbH, Geesthacht, Germany) dual (Cu and Mo) sealed tube micro sources and a Photon II Charge-Integrating Pixel Array detector (Bruker AXS GmbH, Karlsruhe, Germany) using Mo Kα (λ = 0.71073 Å) radiation. High multiplicity data collection and integration were performed using APEX3 (version 2017.3-0, Bruker AXS Inc., 2017, Madison, USA) software. Data reduction and multiscan absorption correction were performed using SAINT (version 8.38A, Bruker AXS Inc., 2017, Madison, USA). The structure was solved using direct methods and refined on F² using the SHELXL program incorporated into the APEX3 suite. Refinement was performed anisotropically for all non-hydrogen atoms. Hydrogen atoms were placed into geometric positions except the proton of solvent OH in 6b which could be found at the difference electron density map and O-H distance should be constrained. The CIF file was manually edited using Publicif software, while graphics were prepared using the Mercury program. The results for the X-ray diffraction structure determinations were very good according to the Checkcif functionality of PLATON software (Utrecht University, Utrecht, The Netherlands). The A and B level alerts in 6b can be explained by liberation of the CAAC ligand as short C(sp3)-C(sp3) bond of C7 - C9 by 1.216(18) Å was found. Moreover, the orientation of the solvent ethanol results the hydroxyl group in hydrophobic environment, but these errors do not influence the overall correctness of structure determination. Structural parameters such as bond length and angle data were in the expected range (for selected data, see the caption for Figure 1 and Supplementary material (SI) Table S3 and Table S4 for 6a and 6b, respectively).
2.3. Synthesis of new BICAAC precursors

As representative example, the intermediates of the dimethylamino group functionalized ligand 5b (MeBICAACNMe2) is described here. For other compounds, see the SI.

2.3.1. Synthesis of imine 3b: 2,4-Dimethylcyclohex-3-en-1-carbaldehyde (Trivertal, 1, 33.83 mmol, 5.00 mL) and aniline 2b, (33.83 mmol, 5.54 g) were mixed in a Schlenk-flask in equimolar ratio, then the flask was put on vacuum, finally, dry nitrogen gas was introduced to the flask. To the formed emulsion, 40 mL of dry dichloromethane and 20 g of dry molecular sieves (3 Å) were added. The mixture was let to stay overnight (16 hours) at room temperature without stirring. The formed yellow supernatant was analyzed by GCMS and NMR. The mixture was filtered and concentrated at reduced pressure. The crude oil was dried under high vacuum using a 90 °C oil bath affording the imine 3b as yellow oil in 98% yield (9.40 g). In 1H NMR, two diastereomers were observed. 1H NMR (300 MHz, CDCl3) δ: 7.67 (d, J = 5.8 Hz, 0.53 × 1H, CH=N, major isomer), 7.55 (d, J = 5.8 Hz, 0.47 × 1H, CH=N, minor isomer), 6.85 (s, 2H, ArC), 5.36 (s, 0.53 × 1H, olefinic C=CH, major isomer), 5.29 (s, 0.47 × 1H, C=CH, minor isomer), 2.83 – 2.71 (m, 1H), 2.66 – 2.56 (m, 1H), 2.46 – 2.33 (m, 1H), 2.27 (s, 3H, Ar4-Me), 2.08 (s, 6H, Ar2,6-Me2), 2.06 – 1.95 (m, 3H), 1.71 (s, 0.47 × 3H, C-Me, minor isomer), 1.67 (s, 0.53 × 3H, C-Me, major isomer), 1.12 (d, J = 6.9 Hz, 0.47 × 3H, CH-Me, major isomer), 1.04 (d, J = 7.2 Hz, 0.53 × 3H, CH-Me, major isomer). 13C NMR (75 MHz, CDCl3) δ: 171.84, 171.28, 149.18, 148.89, 133.66, 133.31, 132.68, 132.66, 128.94, 128.73, 128.70, 126.87, 126.46, 48.10, 44.33, 32.76, 32.15, 29.15, 28.40, 26.11, 24.09, 23.65, 23.60, 20.79, 18.35, 18.22. HRMS: [C19H28N2+H]+: measured/calculated m/z: 285.2323/285.2325.

2.3.2. Synthesis of alkylated imine 4b: In a Schlenk-flask, imine 3b (30 mmol, 8.08 g) was dissolved in 15 mL of dry diethyl ether. LDA solution (2 M in THF-ethylbenzene, 60 mmol, 30 mL) was diluted with dry diethyl ether (15 mL), than it was cooled to 0 °C using an ice-bath. To the stirred LDA solution diethyl ether solution of imine was added dropwise. The resulted reddish-brown mixture was allowed to warm up to room temperature (25 °C). The mixture was stirred for additional 4 hours. Then, the solution was cooled to 0 °C, and alkyl iodide was added dropwise resulting in a yellow suspension. After overnight (16 h) reaction the conversion was monitored by GCMS. As workup, distilled water (40 mL) and tech. hexane (40 mL) were added to the suspension, until the precipitated inorganic salts dissolved. The organic layer was washed three times with water (40 mL) and once with diluted (10%) sodium bisulfite solution (20 mL).
Finally, it was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated at reduced pressure affording 4b as brown oil in 96% yield (8.60 g). **1H NMR** (300 MHz, CDCl₃) δ: 7.69 (s, 1H, CH=N), 6.48 (s, 2H ArCH), 5.24 (s, 1H, C=CH), 2.89 (s, 6H, NMe₂), 2.73 – 2.59 (m, 1H), 2.32 – 2.11 (m, 2H), 2.08 (s, 6H, Ar2,6-Me₂), 2.06 – 1.93 (m, 2H), 1.80 – 1.70 (m, 2H), 1.66 (s, 3H, C-Me), 1.27 (s, 3H, C-Me), 1.02 (d, J = 7.3 Hz, 3H, CH-Me). **13C NMR** (75 MHz, CDCl₃) δ: 173.37, 147.29, 142.79, 133.29, 127.72, 126.26, 113.33, 113.27, 41.57, 41.44, 39.01, 32.79, 28.08, 23.68, 23.36, 18.93, 17.28. HRMS: [C₂₀H₃₀N₂⁺]+: measured/calculated m/z: 299.2479/299.2482.

### 2.3.3. Synthesis of MeBICAACNMe₂ precursor 5b:

In a Schlenk-flask, imine 4b (25.00 mmol, 7.46 g) was dissolved in 15 mL of dry 1,4-dioxane. Then 1,4-dioxane solution of hydrochloric acid (HCl, 4 M, 250.00 mmol, 83.33 mL) was added dropwise at room temperature at continuous stirring. The flask was sealed and stirred at 80 °C for 48 hours. The formed solution was allowed to cool down to room temperature, then concentrated sodium bicarbonate solution (30 mL) and dichloromethane (50 mL) were added. The organic phase was separated and concentrated at reduced pressure. Then concentrated aqueous solution of ammonium tetrafluoroborate (5.24 g, 50 mmol) was added. The resulted mixture was stirred for two hours, then separated, and the organic phase was evaporated affording the mixture of the unreacted starting material (4b) and the product. The solid residue was washed with diethyl ether and the crude BICAAC salt was recrystallized from hot hexane, giving 5b in 14% yield as brown solid (1.35 g). **1H NMR** (500 MHz, CDCl₃) δ: 9.06 (s, 1H, CH=N⁺), 6.37 (s, 2H, ArCH), 2.96 (s, 6H, NMe₂), 2.44 (dd, J = 14.0, 10.1 Hz, 1H), 2.30 – 2.21 (m, 1H), 2.20 (s, 3H), 2.14 (s, 3H), 2.12 – 2.01 (m, 2H), 2.00 – 1.91 (m, 1H), 1.89 – 1.81 (m, 1H), 1.63 (s, 3H), 1.62 – 1.56 (m, 1H), 1.24 (s, 3H), 1.07 (d, J = 7.2 Hz, 3H, CH-Me). **13C NMR** (75 MHz, CDCl₃) δ: 193.76, 150.85, 133.57, 132.88, 127.72, 112.03, 111.95, 69.37, 44.92, 43.82, 40.13, 38.46, 33.32, 33.17, 21.42, 20.61, 20.56, 19.21, 18.80. **19F NMR** (282 MHz, CDCl₃) δ: -152.32, -152.37. **HRMS**: C₁₉H₃₁N₂⁺: measured/calculated m/z: 299.2481/299.2482.
2.4. Preparation of bis-pyridine complexes A-C

Paladium(II)-chloride (1.69 mmol, 300 mg) was measured into a 30 mL screw-cap vial, then 20 mL techn. methanol and three equivalent of the pyridine ligand [pyridine (5.06 mmol, 409 μL), 4-dimethylaminopyridine (5.06 mmol, 620 mg) or 3-chloropyridine (5.06 mmol, 383 μL)] was added. Yellow precipitate formed in 30 minutes. The resulted suspension was sealed and stirred vigorously overnight. Then the precipitate was filtered and washed with methanol (50 mL)-diethyl-ether (20 mL) mixture. The products were isolated as yellow solids: complex A 497 mg, yield: 88%; complex B 302 mg, yield: 53%, complex C 638 mg, yield: 92%. Full characterization was only possible for complex A, as others showed poor solubility. Compound A: $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.85 (m, 4H, orto-pyr), 7.78 (tt, 2H, para-pyr), 7.35 (m, 4H, meta-pyr). $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 153.51 (4C, orto-pyr), 138.73 (2C, para-pyr), 125.12 (4C, meta-pyr).

2.5. Synthesis of Pd-BICAAC-PEPPSI complexes

Representative example for complex 6b: In a glovebox palladium(II)-chloride-bis-pyridine complex A (129 μmol, 43.4 mg) and the HBF$_4$-salt of the MeBICAAC$^{NMe2}$ precursor (5b, 129 μmol, 50.0 mg) were measured into two separate vials. Using a syringe, 1-1 mL of dry dioxane was added to both compounds meanwhile a suspension formed. The LiHMDS (1 M in THF, 129 μmol, 129 μL) was added to the stirred suspension of BICAAC precursor (5b) at room temperature, resulting in a clear, brown solution indicating the formation of the free carbene. This solution was transferred to the stirred suspension of the palladium(II)-chloride-bis-pyridine complex (A) giving a yellowish-brown suspension. This mixture was sealed with a cap, and warmed up to 80 °C for 2 hours, then stirred overnight (additional 14 hours) at room temperature. Workup was performed on air using technical solvents. The resulted suspension was conentrated to 1 mL with nitrogen gas flow, 15 mL hexane was added, and the mixture was filtered on a cotton plug. The resulted solution was subjected to column chromatography using hexane/ethyl acetate (0–30 V%) eluent. The yellow fractions were collected and concentrated, affording the products as yellow solid in 46% yield (27.1 mg). The complex is soluble polar in organic solvents like DMF, THF, acetone, dichloromethane, chloroform, and they found to be insoluble in apolar solvents like hexane, toluene and DEE. $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.55 (d, $J = 4.9$ Hz, 2H, 2-pyr), 7.57 (tt, $J = 7.6$, 1.6 Hz, 1H, 4-pyr), 7.14 (dd, $J = 7.5$, 6.5 Hz, 2H,
$3\text{-pyr}$, 6.51 (s, 1H, $\text{CHN-}^{\text{Ar}}$), 2.98 (s, 6H, Ar$\text{NMe}_2$), 2.91 – 2.77 (m, 1H, $\text{CH/CH}_2\text{BICAAC}$), 2.45 (s, 3H, Ar$\text{2/6-Me}_2$), 2.44 (s, 3H, Ar$\text{2/6-Me}_2$), 2.24 (s, 3H, MeBICAAC), 2.12 – 2.05 (m, 1H, $\text{CH/CH}_2\text{BICAAC}$), 2.02 – 1.95 (m, 1H, $\text{CH/CH}_2\text{BICAAC}$), 1.94 – 1.82 (m, 2H, $\text{CH/CH}_2\text{BICAAC}$), 1.69 – 1.54 (m, 2H, $\text{CH/CH}_2\text{BICAAC}$), 1.23 (d, $J = 7.1$ Hz, 3H, CH-MeBICAAC), 1.09 (s, 3H, MeBICAAC).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 238.63 (carbene), 151.14, 149.98, 137.27, 136.57, 136.46, 132.53, 124.08, 112.78, 112.61, 68.23, 67.23, 52.91, 44.83, 40.47, 38.30, 33.65, 33.04, 24.89, 22.96, 22.92, 22.01, 20.33. HRMS: [C$_{25}$H$_{35}$Cl$_2$N$_3$-Cl]$^+$ [M-Cl]$^+$: measured/calculated m/z: 520.1549/520.1548.

2.6. General procedure for catalytic reactions

Tetra-$n$-butylammonium bromide (TBAB) and potassium carbonate (K$_2$CO$_3$) were placed to a Schlenk-tube equipped with a magnetic stirrer. The powders were dried in vacuum, then dry nitrogen was introduced to the tube. The solvent and the substrates were added by syringes through a septum. Finally, a crop of catalyst stock solution was added. The resulted suspension was heated for 8 hours, until the end of the reaction which was monitored by GCMS. Bromobenzene and styrene model compounds were used for reaction condition optimization (Table 1). The optimized parameters were found as follows: DMF solvent, 140 °C, 0.1 mol% catalyst and 1.0 equivalent of TBAB (rel. to the bromobenzene).
3. Results and discussion

3.1. Synthesis of BICAAC ligands

Following the method described by the Bertrand group, 2,6-dialkyl-substituted anilines (2a-c) were used as N-aryl group variables. Followed by the imine formation of 2,4-dimethyl-3-cycloexene-1-carboxaldehyde (commercially available as Trivertal, 1), 3a-c was alkylated in its alfa-position. The ring-closing reaction was carried out using HCl 1,4-dioxane solution (Scheme 4), followed by an ion exchange with ammonium tetrafluoroborate giving the precursor salt of the BICAAC-ligand (5a-d) (Scheme 2) in poor overall yields (5-14%).

Scheme 2. Synthesis of BiCAAC ligand precursors (5a-d). Conditions: (i) DCM, room temperature, molecular sieves (3 Å); (ii) 2 eq. LDA, dry THF, 2 eq. alkyl iodide (R–I), 0 °C, (iii) 3-6 eq. HCl in dioxane (3 M), 80 °C, NH₄BF₄.

At the second reaction step (ii) various alkylating agents (alkyl iodides, R–I) can be used. As described previously, this alkyl group has significant influence on complexation abilities of carbenes. While the imine formation and the alfa-alkylation steps (i) and (ii) are almost quantitative, the ring-closing reaction (iii) step works only in poor yield. In particular, while precursors 5a-b have been synthetized in mediocre (15%), 5c-d could be synthetized only in as low as 5% yield. The same trend was observed for their crystallization ability: 5a-b could be purified easily via recrystallization (using diethyl ether or hexane), 5c-d showed poor crystallization ability (for additional synthetic details, see SI).
3.2. Synthesis of Pd-BICAAC-PEPPSI complexes

The conventional method for preparing PEPPSI complexes is the heating the NHC-precursor salt together with palladium(II) chloride in pyridine affording the desired complex with excellent yield. Due to the higher pK<sub>a</sub> value of the BICAAC ligand (comparing to those of NHC) precursor salts the pyridine is not strong enough for their deprotonation. Keeping in mind, that carbenes show higher affinity to the metals than tertiary amines, the bis-BICAAC complexes are not suitable precursors for the PEPPSI complex synthesis. Considering the complexation affinities of the reported carbenes<sup>35</sup> new synthetic paths to mono-carbene-mono-pyridine (PEPPSI) complex system have been developed (Scheme 3).

Scheme 3. Synthetic plan for the PEPPSI complexes.
According to literature procedures,\textsuperscript{36} three bis-pyridine complexes have been synthesized bearing pyridine (A), 4-dimethylaminopyridine (B) and 3-chloropyridine (C) ligands. Based on the preliminary tests, it was found that the solubility of the bis-pyridine complex has significant influence on the formation of PEPPSI complexes. Complexes B and C hardly reacted with the \textit{in situ} generated BICAAC carbene due to their poor solubility. Only the 4-dimethylaminopyridine complex 6e could be synthesized and fully characterized. Regarding the R alkyl substituent next to the carbene atom in the BICAAC ligands it was found that both methyl (5a-c) and isopropyl (5d) groups were suitable for complexation (Scheme 4). The formed PEPPSI complexes (Scheme 5) render low air- and moisture sensitivity.

**Scheme 4.** Synthesis of bis-pyridine and PEPPSI complexes 6a-e
Scheme 5. Overview of the prepared novel PEPPSI complexes 6a-e
3.3. X-ray crystallography

The structures show the expected bond length and bond angle data. However, search of the Cambridge Structural Database (version 5.42 Updates September 2021)\(^3\) revealed 202 hits for PdCl\(_2\)py(NHC) complexes, while 6a and 6b are the first complexes with BICAAC ligands (Figure 1). The most interesting feature of the structures is the relative configuration of the stereogenic centers which turned to be C2R*, C5S*, C7S*. As the synthetic route is achiral, the complex crystallizes as racemate, and the enantiomer pair is also present in the lattice as well as the spacegroup is centrosymmetric in each of our structures. The same was observed for the analogous \(\text{bis}\)-BICAAC palladium complex.\(^2\)

![Figure 1](image)

**Figure 1.** ORTEP view of 6a and 6b at 30% probability level for better visibility with partial numbering scheme. Hydrogen is omitted for clarity. Selected bond lengths [Å] and angles [°] for 6a are Pd1-N41 2.148(3), Pd1-C1 1.955(4), Pd1-Cl1 2.2976(13), Pd1-Cl2 2.3055(13), C1-C2 1.516(6), N1-C1 1.302(5); Cl1-Pd1-Cl2 170.6(6), C1-Pd1-N41 178.6(16), C1-Pd1-Cl1 90.8(13).), N41-Pd1-Cl1 90.48(11) (For additional information see SI).
Figure 2. Overlay of complexes in structure 6a and 6b. Hydrogen atoms and solvent molecule in 6b are omitted for clarity.

Figure 2 shows that the coordination of Pd(II) is the expected square planar the palladium ion being 0.07 Å and 0.057 Å above the Cl1-Cl2-N41-C1 plane while the Cl1-Pd1-Cl2 angle is 170.59(6) and 175.41(10) degree for 6a and 6b, respectively. This small deviation from linearity can be attributed to the repulsion of the sterically demanding BICAAC ligand. In the analogous structure (CCDC Deposition Number, 2003312), the palladium is in inversion center and the angle is exactly 180 degree, probably this is an additional effect of the balanced repulsion of both large ligands. The very rigid BICAAC ligand has also the same conformation in both complexes. Some difference in the bending of the di-isopropylphenyl and 4-dimethylaminophenyl rings relative to the coordination square or the BICAAC ligand is also visible. The angle of the pyridine ring to the coordination plane is 39.5 and 34.3 degrees. In the packing diagram of 6a stacking of the pyridine rings is observed (Figure S18) with distances of the side carbon atoms of 3.38 Å. In 6b the solvent ethanol is also stabilizing the structure with weak C-H..Cl hydrogen bonds (Table S4).
3.4. HRMS measurements

For the HRMS measurements ESI-MS were used to observe the intact, unfragmented molecules allowing the unambiguous determination of the composition of target molecules. Since the compounds contained basic nitrogen atoms with no oxygen atoms to which alkali metal ion can attach, thus, as expected, mostly protonated molecules, i.e., [M+H]^+ were formed from compounds 3b (Figure S1) and 4b (Figure S3) under electrospray conditions. However, in the case of 5b (Figure S5), the organic cation formed (M^+) by the loss of its counter ion can be observed in the ESI-MS spectra. The resolution power and the mass accuracy for all target ions were better than 50000 and 1 ppm, respectively, allowing the determination of the composition of compounds below m/z 500. For example, for an organic ion consisting of C, H, N, O with even electrons (EE^+) at m/z 299.2481 only a composition of C_{20}H_{31}N was found within 1 ppm mass accuracy, which is line with the composition of 5b.

The most abundant isotopic peak of complex 6b appeared at m/z 520.1548 (calculated m/z: 520.1549). The m/z value and the isotopic distribution support the presence of [M-Cl]^+ ions corresponding to a composition of C_{25}H_{35}ClN_{3} (Figure S9). Furthermore, the [M-Cl]^+ ions were subjected to collision induced dissociation (CID) experiments to support the presence of pyridine and ligand 5b in the complex 6b. Indeed, CID experiments showed the loss of a neutral moiety with a mass of 79.0371 (C_{5}H_{5}N) corresponding to the mass of a pyridine molecule (Figure S10). In addition, the presence of [5b-2H]^+ (297.2054, C_{25}H_{33}ClN_{3}^+) in the CID-MS/MS spectra could also be recognized (Figure S11). These findings unambiguously confirm the elementary composition of complex 6b and the presence of ligands of palladium.
3.5. NMR investigation

The complexation reactions were monitored by NMR measurements: the most characteristic indication of the reaction’s progress is the ortho-positioned protons’ signal of the pyridine ligand. It was observed that this signal upshifts upon pyridine-BICAAC exchange (Figure 3).

![Figure 3. Signals of ortho-positioned hydrogen at the pyridine or DMAP ligands (A, B, 6a-e). Solvent: CDCl₃.](image)

A two-dimensional NOESY measurement of complex 6a revealed a clear correlation between the ortho-positioned protons’ signal of the pyridine ligand and the closest methyl groups on the BICAAC ligand (see Figures S15 and S16 in SI).

In $^{13}$C NMR, the signal of the carbene is the most characteristic indication of the complexation. All the carbene signals were detected between 238 and 242 ppm (see Figure S14 in SI). As comparison, recently reported complexes containing the $^{Me}$BICAAC$^{dip}$ ligand (derived from 5a) are bearing different chemical shifts (Table 1). It can be concluded, that the $^{13}$C NMR chemical shift of the carbene carbon certainly is driven rather by the central transition metal basic characteristics than by the steric and electronic feature of the BICAAC ligands (Table 1).
### Table 1. $^{13}$C NMR shifts of recently reported MeBICAAC$^{dipp}$ carbene complexes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Complex type</th>
<th>Chem. shift in $^{13}$C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu</td>
<td>(BICAAC$<em>{2}$-Cu)$^{+}$CuBr$</em>{2}$</td>
<td>258.4/258.7</td>
<td>Bertrand gr. $^{25}$</td>
</tr>
<tr>
<td>2</td>
<td>Rh</td>
<td>BICAAC-RhCl(COD)</td>
<td>276.6</td>
<td>Bertrand gr. $^{25}$</td>
</tr>
<tr>
<td>3</td>
<td>(Se)</td>
<td>BICAAC=Se</td>
<td>214.8</td>
<td>Bertrand gr. $^{25}$</td>
</tr>
<tr>
<td>4</td>
<td>Au</td>
<td>BICAAC-AuPh</td>
<td>268.4</td>
<td>Bertrand gr. $^{25}$</td>
</tr>
<tr>
<td>5</td>
<td>(–)</td>
<td>(free carbene)</td>
<td>336.0</td>
<td>Bertrand gr. $^{25}$</td>
</tr>
<tr>
<td>6</td>
<td>Au</td>
<td>BICAAC-AuCl</td>
<td>241.6</td>
<td>Bertrand gr. $^{26}$</td>
</tr>
<tr>
<td>7</td>
<td>Au</td>
<td>(BICAAC$<em>{2}$-Au)$^{+}$BF$</em>{4}$</td>
<td>235.7</td>
<td>Bertrand gr. $^{26}$</td>
</tr>
<tr>
<td>8</td>
<td>Au</td>
<td>(BICAAC$<em>{2}$-Au)$^{+}$AuBr$</em>{2}$</td>
<td>279.1</td>
<td>Singh gr. $^{27}$</td>
</tr>
<tr>
<td>9</td>
<td>Cu</td>
<td>(BICAAC$<em>{2}$-Cu)$^{+}$CuI$</em>{2}$</td>
<td>258.3</td>
<td>Singh gr. $^{27}$</td>
</tr>
<tr>
<td>10</td>
<td>Pd</td>
<td>BICAAC$<em>{2}$-PdCl$</em>{2}$</td>
<td>262.9</td>
<td>Singh gr. $^{29}$</td>
</tr>
<tr>
<td>12</td>
<td>Zn</td>
<td>BICAAC$_{2}$-Zn(0)</td>
<td>177</td>
<td>Mandal gr. $^{28}$</td>
</tr>
<tr>
<td>13</td>
<td>(CO$_{2}$)</td>
<td>BICAAC$^{+}$-COO$^{-}$</td>
<td>193</td>
<td>Mandal gr. $^{28}$</td>
</tr>
<tr>
<td>14</td>
<td>Pd</td>
<td>BICAAC-PdCl$_{2}$-pyr</td>
<td>240.7</td>
<td>This work</td>
</tr>
</tbody>
</table>

### 3.6. Catalytic investigation

The catalytic activity of the new Pd-PEPPSI-BICAAC complexes have been investigated in the Mizoroki–Heck coupling reaction. The model coupling reaction of bromobenzene, and styrene was selected giving stilbene as product (Scheme 6). In accordance with literature data, it was found that the reaction requires elevated temperature (at least 60 °C) and the addition of a quaternary ammonium salt, tetra-n-butyllammonium bromide (TBAB). The latter has important role avoiding the precipitation of catalytically inactive palladium clusters and facilitating the stability of Pd-species in the catalytic cycle.$^{38-40}$

![Scheme 6. Model catalytic coupling reaction using 6a catalyst](image-url)
Table 2. Optimization of the Mizoroki–Heck coupling reaction using catalyst 6a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. load [mol%]</th>
<th>TBAB [eq.]*</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Conversion [%]</th>
<th>Reaction setup</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.500</td>
<td>1.0</td>
<td>ethanol</td>
<td>80</td>
<td>7</td>
<td>on air</td>
</tr>
<tr>
<td>2</td>
<td>0.500</td>
<td>1.0</td>
<td>DMF-water (1-1)</td>
<td>80</td>
<td>6</td>
<td>on air</td>
</tr>
<tr>
<td>3</td>
<td>0.500</td>
<td>1.0</td>
<td>DMF-water (1-1)</td>
<td>100</td>
<td>52</td>
<td>on air</td>
</tr>
<tr>
<td>4</td>
<td>1.000</td>
<td>1.0</td>
<td>DMF-water (1-1)</td>
<td>100</td>
<td>23</td>
<td>on air</td>
</tr>
<tr>
<td>5</td>
<td>1.000</td>
<td>1.0</td>
<td>DMF</td>
<td>140</td>
<td>67</td>
<td>on air</td>
</tr>
<tr>
<td>6</td>
<td>0.500</td>
<td>1.0</td>
<td>DMF</td>
<td>140</td>
<td>68</td>
<td>on air</td>
</tr>
<tr>
<td>7</td>
<td>0.100</td>
<td>1.0</td>
<td>DMF</td>
<td>140</td>
<td>100</td>
<td>on air</td>
</tr>
<tr>
<td>8</td>
<td>0.010</td>
<td>1.0</td>
<td>DMF</td>
<td>140</td>
<td>0</td>
<td>on air</td>
</tr>
<tr>
<td>9</td>
<td>0.010</td>
<td>1.0</td>
<td>DMF</td>
<td>140</td>
<td>99</td>
<td>inert</td>
</tr>
<tr>
<td>10</td>
<td>0.001</td>
<td>1.0</td>
<td>DMF</td>
<td>140</td>
<td>0</td>
<td>inert</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>1.0</td>
<td>DMF</td>
<td>140</td>
<td>0</td>
<td>inert</td>
</tr>
<tr>
<td>12</td>
<td>0.100</td>
<td>0.5</td>
<td>DMF</td>
<td>140</td>
<td>90</td>
<td>on air</td>
</tr>
<tr>
<td>13</td>
<td>0.100</td>
<td>0.1</td>
<td>DMF</td>
<td>140</td>
<td>80</td>
<td>on air</td>
</tr>
</tbody>
</table>

Conditions: 1.00 mmol bromobenzene, 1.30 mmol styrene, 1.50 mmol potassium carbonate (K₂CO₃), 2 mL solvent, catalyst 6a, reaction time: 8 hours. Remarks: a) relative to the bromobenzene.

Investigations have revealed that all new PEPPSI complexes showed catalytic activity. However, it was found that 6a catalyzed reaction has shown some decrease of activity in the presence of elemental mercury, suggesting that the coupling reaction may have both molecular and Pd(0)-mediated catalytic paths. All complexes showed similar catalytic performance, except 6d – having isopropyl group right next to the carbene carbon atom –, which has rendered lower activity. It could be concluded, that neither the type of pyridine ligand (6c vs. 6e) nor the N-aryl (6a–e) substituent has significant impact on the catalytic performance. The detailed investigation is reported in SI, chapter 4.
The catalytic activity of complexes using 6a have been demonstrated on additional substrates at the optimized conditions (0.1 mol% catalyst loading, 140°C, 1.0 eq. TBAB) (Scheme 7, Table 3).

\[
\text{Scheme 7. Catalytic Mizoroki–Heck coupling reactions}
\]

**Table 3. Substrate scope of the examined coupling reaction.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halogenide</th>
<th>Olefin</th>
<th>Conversion [%] (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bromobenzene</td>
<td>Styrene</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>bromobenzene</td>
<td>1-dodecene</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>bromobenzene</td>
<td>1-octadecene</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>bromobenzene</td>
<td>beta-pinene</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>bromobenzene</td>
<td>hepta-1,6-dien-4-ol(^b)</td>
<td>100(^c)</td>
</tr>
<tr>
<td>6</td>
<td>bromobenzene</td>
<td>9-decene-1-ol</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>bromobenzene</td>
<td>diethyl-diallyl-malonate(^b)</td>
<td>63(^c)</td>
</tr>
<tr>
<td>8</td>
<td>2-bromoanisole</td>
<td>styrene</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>4-bromoanisole</td>
<td>styrene</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>4-bromoacetanilide</td>
<td>styrene</td>
<td>51</td>
</tr>
</tbody>
</table>

Conditions: 1.00 mmol aryl halogenide, 1.30 mmol olefin, 1.50 mmol potassium carbonate (K\(_2\)CO\(_3\)), 2 mL DMF, 0.1 mol% (0.0001 mmol) catalyst 6a, reaction time: 8 hours. Remarks: a) relative to the aryl halogenide; b) 0.65 mmol was used due to the two olefinic double bonds; c) only mono-arylation was detected on the olefin.

Longer chain olefins showed isomerization products, as the hydride intermediate (Pd-H) inducts the isomerization of olefinic double bonds. Bi- or oligo-arylation as well as germinal arylation (e.g. 1,1-diphenylethylene) of olefins was also detected as side reaction, but only below 5% ratio relative of the expected mono-coupled product. Although the efficiency of the
catalysis drops in the presence of air (Table 2), hydroxyl groups do not decrease the reaction’s progress (entries 5, 6). Sterically hindered substrates (entries 4, 7, 8 in Table 3) are harder to convert to coupled products. This aligns with the kinetic observations regarding the sterically bulkier thus less effective ligand iPrBICAACmes at complex 6d.

**Conclusion**

The first examples of the synthesis of BICAAC ligands and their novel Pd-PEPPSI-complexes have been demonstrated. The molecules were characterized with NMR, XRD and HRMS. Preliminary catalytic investigations revealed, that the new Pd-PEPPSI-BICAAC complexes work as exceptional precatalysts for Mizoroki-Heck cross-coupling reactions. It was found that the variation of the BICAAC ligands rendering different electronical properties has no significant impact on the catalytic activity. Meanwhile, the steric hindrance may decrease the catalytic efficiency (complex 6d, bulky substrate).

**Declaration of Competing Interest**

There is no competing interest to declare.

**CRediT authorship contribution statement**


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**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:
Appendix A. Supplementary data

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 2124190 for 6a and 2124191 for 6b.

References


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2015, 34 (11), 2463–2470.

https://doi.org/10.1021/OM5012038/SUPPL_FILE/OM5012038_SI_003.PDF.