

(CAAC)Pd(py) Catalysts Disproportionate to Pd(CAAC)₂

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Cite This: <https://doi.org/10.1021/acs.organomet.3c00150>

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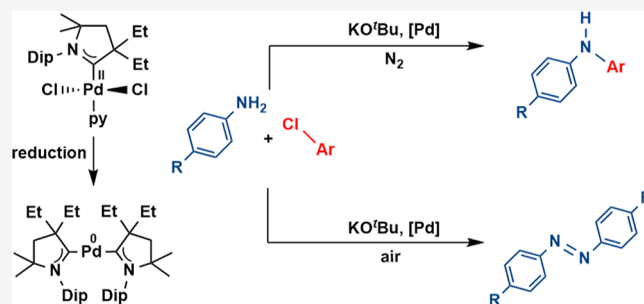
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ABSTRACT: Palladium complexes with one *N*-heterocyclic carbene (NHC) and a pyridine ancillary ligand are powerful cross-coupling precatalysts. Herein, we report such complexes with a cyclic (alkyl)(amino)carbene (CAAC) ligand replacing the NHC. We find that the alleged reduced form, (CAAC)Pd(py), disproportionates to the (CAAC)₂Pd⁰ complex and palladium nanoparticles. This notwithstanding, they are potent catalysts in the Buchwald–Hartwig amination with aryl chlorides under mild conditions (60 °C). In the presence of dioxigen, these complexes catalyze the formation of diazenes from anilines. The catalytic activities of the NHC- and CAAC-supported palladium(0) and palladium(II) complexes are similar in the cross-coupling reaction,



yet the CAAC complexes are superior for diazene formation.

Palladium complexes with *N*-heterocyclic carbene (NHC)¹ ligands are popular cross-coupling catalysts.² Organ's PEPPSI (pyridine-enhanced precatalyst preparation stabilization and initiation) complexes rank among the most powerful catalysts in the field.³ These air-stable precatalysts (Figure 1, 1;

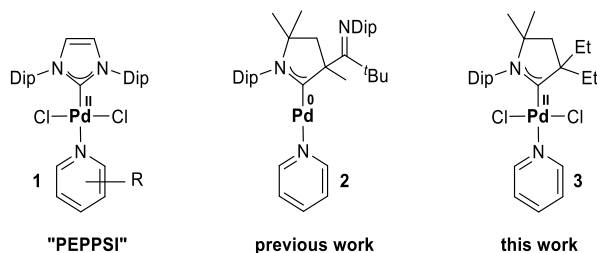


Figure 1. PEPPSI Pd^{II} precatalyst 1, CAAC Pd⁰ congener 2, and PEPPSI-CAAC Pd^{II} complex 3; Dip, 2,6-diisopropylphenyl.

NHC = IPr) allow for mild reaction conditions in, inter alia, the Buchwald–Hartwig-, Negishi-, Suzuki-, and Kumada-coupling reactions⁴ and are particularly active with bulky NHCs.⁵ Whereas their activation is slower than for allyl-coordinating or μ -chloro-bridged NHC-based precatalysts, they excel with their facile synthesis and robustness.⁶ The sacrificial pyridine donor ligand allegedly allows to access transient 12-valence electron palladium(0) intermediates,⁷ which aid the oxidative addition of strong bonds as is the case for aryl chlorides. However, the zero-valent intermediate (NHC)Pd⁰(py) has not been isolated so far. Based on isotopic labeling, MS spectrometry, nuclear magnetic resonance (NMR), and FE-SEM analysis, Ananikov and colleagues reported the formation of Pd⁰ nanoparticles in combination with (NHC)₂Pd⁸ and referred to this mixture as “catalytic

cocktail”.⁹ They concluded that the presence of strong bases induces the reduction of the PEPPSI precursor complex, with the formation of Pd⁰ nanoparticles and O–NHC coupling with urea formation in case of oxygen-derived bases.^{8a}

A similar mechanism has been proposed for the pre-activation of phosphine-based palladium catalysts.¹⁰ Furthermore, Ananikov et al. showed that the dissociation of the NHC does not compromise the activity of the catalyst and that the presence of ureas might even boost turnover.^{8,9} Cyclic (alkyl)(amino) carbenes (CAACs) stabilize low-valent compounds and radicals due to their π -acidity.¹¹ Although not yet quantified, they are also expected to show a strong trans-effect. Thus, they are emerging as ancillary ligands in late transition metal catalysis complementing conventional NHCs. So far, examples for zerovalent group 10 metals are rare.¹² We reported a 14-electron palladium(0) complex with a bidentate CAAC ligand¹³ in combination with a pyridino ligand,¹⁴ thus paralleling the elusive reduced form of the PEPPSI catalyst (Figure 1, 2). The pyridino ligand is only weakly bound due to the hard/soft mismatch with the low-valent metal. Dissociation provides access to the 12-electron palladium intermediate,¹⁵ which is extraordinarily reactive and oxidatively adds not only phenyl chloride but also amines, anilines, alcohols, and water at room temperature.¹⁴ This low-coordinate intermediate also provides the driving force to synthesize terminal nitrene complexes.¹⁶ However, the hemilabile imino-functionality

Received: March 21, 2023

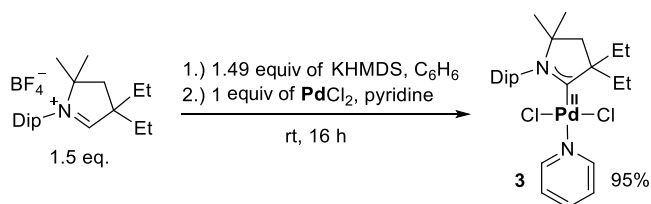
disfavors reductive elimination from palladium(II). We turned hence our attention toward conventional monodentate CAAC ligands.

Herein, we report the palladium PEPPSI-CAAC congener **3**. We show that its reduced form, (CAAC)Pd(py), is only transient in nature and disproportionates even in pyridine instantaneously to the (CAAC)₂Pd complex. Similarly, we reinvestigate complex **1** and find that it also disproportionates upon reduction. All NHC and CAAC complexes show similar catalytic activity in the Buchwald–Hartwig cross-coupling reaction with aryl chlorides under mild reaction conditions. CAACs are however superior to NHCs for the oxidative coupling of anilines to diazenes by dioxygen, which is unprecedented for palladium.

RESULTS AND DISCUSSION

PEPPSI complexes may be prepared by heating the NHC-precursor salt together with palladium chloride in pyridine. Due to the higher pK_a value of the CAAC ligand salt compared to NHC precursor salts, pyridine is not suitable for their deprotonation. Adopting a similar synthetic strategy to that used for a related biCAAC complex,¹⁷ **3** was conveniently prepared through treating palladium dichloride in pyridine with an excess (1.5 equiv) of the free carbene generated in benzene (Scheme 1), which affords a near-quantitative yield (95%). Complex **3** is remarkably stable under ambient conditions with a melting point of 210 °C.

Scheme 1. Synthesis of (Et^tCAAC)PdCl₂(py)



The solid-state structure of **3** was determined by single-crystal X-ray spectroscopy (Figure 2). All structural parameters are in the expected range, including the Pd–pyridine bond length of 2.1193(11) Å, which is similar to 2.122(3) Å found in **1**.¹⁸ The CAAC–Pd bond in **3** is 1.9577(13) Å,

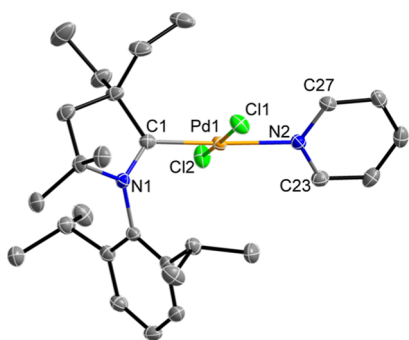
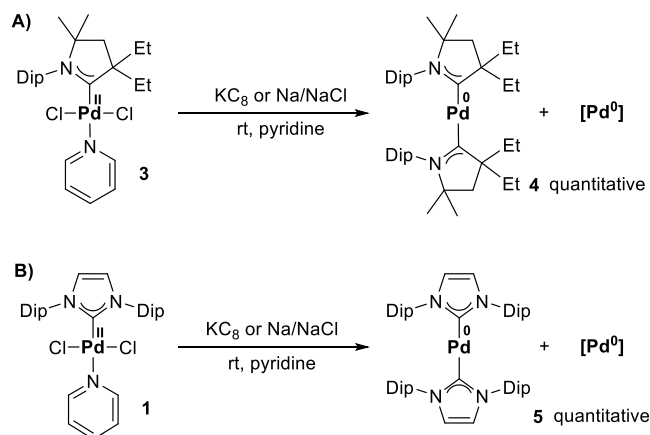


Figure 2. Solid-state structure of **3**. Ellipsoids are shown at the 50% probability level; hydrogen atoms are omitted for clarity. Selected bond lengths [Å], angles, and dihedral angles [°]: Pd1–C1, 1.9577(13); Pd1–N2, 2.1193(11); Pd1–Cl1 2.3254(5); Pd1–Cl2, 2.2914(5); C1–Pd1–N2, 174.98(5); N1–C1–Pd1 124.70(9); N1–C1–N2–C23, 50.30°(13); N1–C1–N2–C27, –131.17°(13).

considerably shorter than the one found for the Pd(0) bis^{Cy}CAAC complex (≈2.01 Å).^{12b}

Following our procedure for the imino-functionalized CAAC palladium(0) complex **2**,^{16a} **3** was reduced by potassium on graphite (Attention!: pyrophoric agent on air and explosive agent in water) in pyridine (Scheme 2, A). To our surprise, we

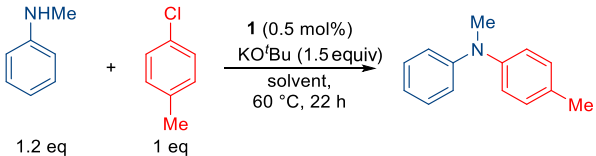
Scheme 2. Reduction of **3** (A) and **1** (B) by KC₈ (3 h) or Na/NaCl (16 h)



isolated the dark-green bisCAAC palladium(0) complex **4** in quantitative yield. This was authenticated through comparison of the ¹H and ¹³C NMR spectra with a separately synthesized batch of **4** obtained by the reduction of (Et^tCAAC)₂PdCl₂.^{12a} The attempt to avoid disproportionation by using sodium on sodium chloride (Na/NaCl) as a milder reductant¹⁹ gave **4** likewise in quantitative yield. In the latter case, the formation of palladium black was evident after 2 h reaction time, which relates to approximately 40% conversion. Reduction attempts in other solvents such as toluene or tetrahydrofuran afforded **4** as well. Eventually, also reduction by KO^tBu in isopropanol²⁰ gave **4** cleanly (Figure S5). We conclude that the isolation of (imino^oCAAC)Pd(py) **2** is likely due to the sterically encumbering imino substituent involving bulky *tert*-butyl- and Dip-substituents.²¹ In sight of the enhanced steric demand of IPr regarding Et^tCAAC due to the second Dip substituent, and in the context of Ananikov's findings outlined in the Introduction, we evaluated subsequently the reduction of **1** under the same reaction conditions (Scheme 2, B). Also here, the reduction with either KC₈ or Na/NaCl afforded the bis(NHC) complex **5** in quantitative yield.

Having established the formation of palladium(0) bis-(carbene) complexes pending reduction of their palladium(II) precursors, the catalytic properties in palladium cross-coupling catalysis were examined. We chose the Buchwald–Hartwig amination since it (i) represents a hallmark in palladium catalysis, (ii) it may be conducted under comparatively mild conditions, and (iii) because zerovalent palladium CAAC complexes oxidatively add the N–H bonds of anilines.²² Following state-of-the-art catalytic systems²³ using *para*-chlorotoluene and *N*-methylaniline as coupling partners, KO^tBu as the base, and 0.5 mol % catalyst loading, we obtained 40% crude yield in toluene at room temperature (Table 1, a). Quantitative conversion and spectroscopic yield was obtained after heating to 60 °C overnight in either toluene or benzene (Table 1, b).

Table 1. Optimization of Buchwald–Hartwig Coupling



entry	solvent	yield [%]
a	toluene (rt)	40
b	toluene/benzene	>99
c	THF	80
d	1,4-dioxane	75
e	DME	73
f	DMF	<1
g	pyridine	<1
h	toluene (0.1 mol %)	40

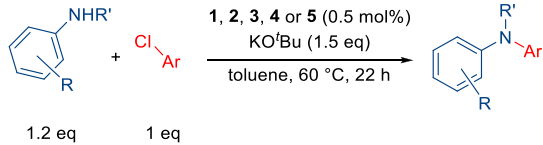
Since weakly coordinating, soft solvents could stabilize potential transient mono-NHC (mono-CAAC, respectively), palladium(0) species, solvent effects were evaluated in more detail. The *O*-donor solvents THF (Table 1, c; 80%), 1,4-dioxane (Table 1, d; 75%) and dimethoxyethane (DME, Table 1, e; 73%) afforded significantly lower yields.²⁴ Neither DMF nor pyridine (Table 1, f, g) led to conversion. Lowering the catalyst loading to 0.1 mol % reduced the yield to 40% (Table 1, h). For further optimization details, see Tables S1–S3.

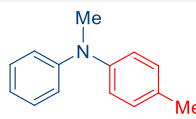
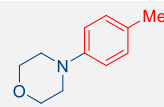
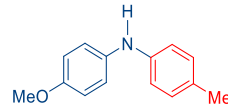
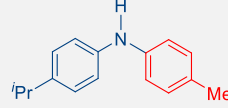
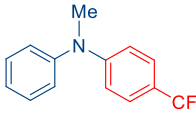
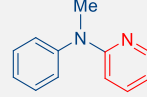
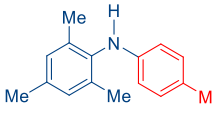
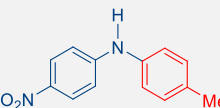
Using the optimized reaction condition, the catalytic activity of complexes 1–5 was assessed (Table 2). Both complexes 1 and 5 gave quantitative spectroscopic yields (Table S4) and near-quantitative isolated yields (1, 95%; 5, 94%) for the coupling reaction between *para*-chlorotoluene and *N*-methylaniline (Table 2, a). Likewise high yields were observed with morpholine (Table 2, b) and *para*-anisidine (Table 2, c) as well as *para*-isopropyl aniline for catalysts 1 and 5 (Table 2, d). Under the rigorous exclusion of air (*vide infra*), the CAAC complexes 3 and 4 afforded 54% (53%, respectively). High isolated yields were also obtained for electron-deficient aryl halides such as *para*-(trifluoromethyl)benzene chloride (Table 2, e; 1, 94%; 5, 93%) and 2-chloropyridine (Table 2, f; 1, 92%; 5, 92%). The sterically more demanding 2,4,6-trimethylaniline still gave 91% yield in the reaction with *para*-chlorotoluene, albeit raising the temperature to 90 °C was required (Table 2, g). No conversion was observed with a nitro- (NO₂) substituent in the *para*-position of the aniline (Table 2, h), even at 110 °C. The same was found for the nitrile-²⁵ and trifluoromethyl-(CF₃) groups. As expected in sight of a difficult reductive elimination step, no turnover was obtained with the imino-functionalized iminoCAAC complex 2 (Table 2, a). The yields obtained with the CAAC complexes 3 and 4 are very similar with the NHC-PEPSI system, but tend to be marginally lower (e.g., a, 95% yield for 1 *vs.* 92% for 3).

The coupling reaction between *para*-isopropyl aniline and *para*-chlorotoluene turned out to be peculiar (Scheme 3). Whereas 1 and 5 gave the expected cross-coupling product in quantitative yields in crimp-cap vials (*cf.* Table 2, d), catalysts 3 and 4 afforded the diazene instead (3, 81%; 4, 79%).

If running this reaction under the rigorous exclusion of air in the glovebox, 54% (53%, respectively) yield of the secondary aniline was obtained (*cf.* Table 2, d), thus corroborating that dioxygen serves as an oxidant. Further control reactions confirmed that both the palladium complexes and KO^tBu are

Table 2. Buchwald–Hartwig Coupling with Various Substrates and Catalysts



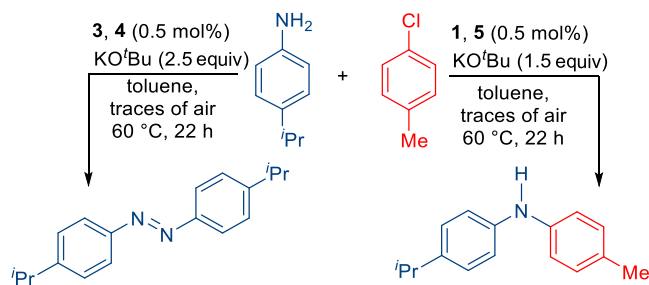
Entry	Product	Cat.	Yield [%]
a		1	95
		2	0
		3	92
		4	92
		5	94
b		1	96
		3	95
		4	96
		5	95
		c	
3	92		
4	91		
5	93		
d			
		3	0 (54%) ^a
		4	0 (53%) ^a
		5	95
		e	
3	93		
4	94		
5	93		
f			
		3	88
		4	87
		5	92
		g	
3	81 (90 °C)		
4	80 (90 °C)		
5	90 (90 °C)		
h			
		3	0
		4	0
		5	0

^aPerformed in a dinitrogen-filled glovebox; all other reactions were performed in aluminum Pharmafix PTFE-coated crimp-cap butyl rubber vials.

required for this transformation, while the presence of aryl halides does not affect turnover (Tables S5–S8).

It is known that KO^tBu mediates diazene formation from hydrazobenzenes,²⁶ yet diazenes are typically synthesized by diazo-coupling or dehydrogenation of hydrazines.²⁷ Catalytic approaches are rare and typically rely on transient nitrenes

Scheme 3. Diazenes Form in the Presence of Dioxygen



derived from azides.²⁸ Besides Pd-catalyzed cross-coupling of silicon-masked diazenyl anions,²⁹ it has been shown that oxidative coupling under 1 atm of dioxygen in the presence of 6 mol % of copper catalyst and 18 mol % of pyridine additive allows to directly synthesize diazenes from anilines at 60 °C.³⁰ Consequently, we sought to demonstrate that also other anilines may be selectively converted to diazenes under palladium catalysis. Indeed, running these reactions in the absence of aryl halide under air confirmed the formation of the diazene also for parent aniline and anisidine in yields between 64 and 83% (Table 3, entries b, c); for spectroscopic yields, see

Table 3. Catalytic Diazene Formation

Entry	Product	Cat.	Yield [%]
a		1	80
		3	81
		4	79
		5	79
b		1	65
		3	67
		4	65
		5	64
c		1	82
		3	83
		4	80
		5	80
d		1	0
		3	0
		4	0
		5	0

Table S9. In agreement with Scheme 3, the yields obtained with the CAAC complexes 3, 4 tentatively seem to be higher than that with the NHC complexes 1, 5 (e.g., Table 3, entry b: 65% for 1; 67% for 3).

In the case of *para*-nitroaniline, the starting material was isolated upon workup, even if running the reaction at 100 °C. Nevertheless, we conclude that palladium complexes 1, 3, 4, and 5 catalyze the diazene formation from anilines in the

presence of dioxygen under milder conditions compared to that of copper.³⁰

CONCLUSION

The synthesis of a CAAC-analogue of the PEPPSI-family of palladium precatalysts was presented. Opposed to bidentate CAAC ligands, these complexes disproportionate upon reduction to the bisCAAC complexes. Reinvestigating the PEPPSI system revealed that (IPr)Pd(py) disproportionates as well and is thus neither isolable. Both CAAC- and NHC catalysts show good performance in the Buchwald–Hartwig amination of chloroarenes under mild reaction conditions. The catalytic activity of the CAAC- and NHC-palladium(II) precatalysts is similar to each other and also to that of the biscarbene palladium(0) compounds. In the presence of air, the unprecedented formation of diazenes was observed for parent aniline, anisidine, and *para*-isopropyl aniline. This transformation is more favorable with the CAAC- than with the NHC-based catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.organomet.3c00150>.

Synthetic procedures, optimization studies, spectroscopic data, and crystallographic details (PDF)

Accession Codes

CCDC 2217204 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 Research and Innovation Program (grant no. 948185). Instrumentation and technical assistance for this work were

provided by the Service Center X-ray Diffraction, with financial support from Saarland University and the German Science Foundation (project number INST 256/506-1). N.M. gratefully acknowledges support by the Erasmus+ Program.

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