Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 1399–1403

Tetrahedron Letters

A palladium Chugaev carbene complex as a modular, air-stable catalyst for Suzuki–Miyaura cross-coupling reactions

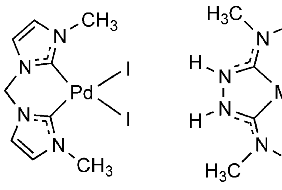
Adriana I. Moncada,[a] Masood A. Khan[b] and LeGrande M. Slaughter[a,*]

[a]*Department of Chemistry, Oklahoma State University, 107 Physical Science I, Stillwater, OK 74078, USA*
[b]*Department of Chemistry and Biochemistry, University of Oklahoma, 620 Parrington Oval, Norman, OK 73019, USA*

Received 6 January 2005; accepted 10 January 2005
Available online 25 January 2005

Abstract—A new Chugaev-type palladium carbene complex was prepared via a convenient metal-templated route and fully characterized by X-ray crystallography, NMR, and IR. This complex proved effective as a precatalyst for Suzuki–Miyaura cross-coupling reactions of a range of aryl bromides, even under aerobic conditions, and its modular synthesis should allow for further catalyst fine-tuning.

Recent advances in ligand design have dramatically improved the scope and utility of metal-catalyzed cross-coupling reactions.[1] This is exemplified by the palladium-catalyzed Suzuki–Miyaura coupling of aryl halides with arylboron reagents,[2] a reaction that has attracted growing interest due to its high functional group tolerance as well as the prevalence of biaryl moieties in natural products, organic materials, and new ligands.[3] A guiding theme has been the combination of strong σ-donor ligands, which are thought to facilitate aryl halide oxidative addition, with steric bulk, which promotes biaryl reductive elimination.[4] Littke and Fu[5] and Buchwald and co-workers[6] first demonstrated that electron-rich, sterically hindered phosphine ligands facilitate Suzuki–Miyaura couplings of electron-rich aryl chlorides, a substrate class that had previously been inaccessible. Rational modification of bulky phosphines by Buchwald and co-workers has led to a general catalyst system that shows high coupling activity for a wide range of aryl bromides and chlorides, in many cases at room temperature.[7]



a **b**

Figure 1. Chelating NHC (**a**, Ref. 11) and Chugaev carbene (**b**) ligands.

Parallel to the development of phosphines, N-heterocyclic carbene (NHC) ligands (e.g., **a**, Fig. 1)[8] have been pursued in cross-coupling catalysis primarily due to their potentially stronger σ-donating ability[9] and enhanced stability to air and high temperature.[10] Following Herrmann's initial report of Suzuki coupling with a palladium–NHC catalyst,[11] Nolan and co-workers developed catalyst systems based on palladium precursors combined with imidazolium salts that allowed practical Suzuki–Miyaura coupling of deactivated aryl chlorides.[4,12] Palladium complexes of bulky NHC's were reported by Herrmann and co-workers to catalyze Suzuki–Miyaura coupling of unhindered aryl chlorides at room temperature.[13] Subsequently, Glorius and co-workers achieved the formation of di- and tri-*ortho*-substituted biaryls at room temperature from aryl chlorides using an NHC ligand containing 'flexible steric bulk',[14] and systematic variation of ligand sterics by these authors recently resulted in the unprecedented Suzuki–Miyaura synthesis of a range of tetra-*ortho*-substituted biaryls from aryl chlorides.[15]

Given the recent successes in tuning cross-coupling catalyst activity through ligand modification, a ligand design that combines strong σ-donor groups with a

---

Keywords: Carbene ligands; Palladium; Suzuki; Air-stable.

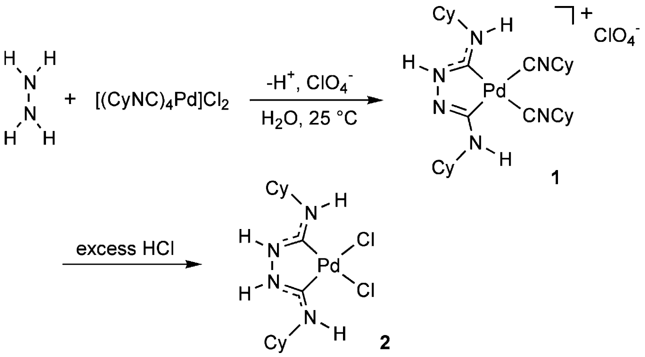
[*] Corresponding author. Tel.: +1 405 744 5941; fax: +1 405 744 6007; e-mail: lms@chem.okstate.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.033

readily altered structural framework would clearly be advantageous. While investigating synthetically flexible routes to chelating carbenes that possess these attributes, we became intrigued by 'Chugaev-type' carbenes (**b**, Fig. 1),[16] a relatively unexplored class of chelate ligands that are formed via the metal-templated addition of hydrazines or other bifunctional nucleophiles to *cis*-coordinated isocyanides. Platinum complexes of these ligands were prepared as early as 1915,[16] but their structures were unknown until spectroscopic studies by Rouschias and Shaw[17] and crystallographic studies by Balch and co-workers[18] in 1970 revealed their chelating nature. These ligands contain nitrogen-stabilized carbene donors analogous to NHC's, but they have never been investigated in catalysis. Additionally, reports of similar chelate ligands synthesized from diamines such as 2,6-diaminopyridine[19] and 1,2-ethylenediamine[20] suggest that the metal-templated synthetic strategy could be extended to a wide range of structures, potentially including sterically hindered or chiral examples.

As a starting point to explore the scope of Chugaev carbene synthesis, we targeted palladium dicarbene complexes derived from hydrazine and bulky isocyanides. Palladium complexes of methylisocyanide-derived Chugaev carbenes are known,[18] but the only reported example synthesized from a sterically encumbered isocyanide is a platinum dicarbene complex prepared from *tert*-butylisocyanide.[21] Herein we report a new Chugaev carbene complex of palladium and its use as an air-stable catalyst for Suzuki–Miyaura cross-coupling reactions. The convenient synthesis of this complex opens new opportunities for the modular design of novel chelating carbene ligands.

Addition of excess hydrazine hydrate to a stirred solution of $[Pd(CNCy)_4]Cl_2$,[22] generated in situ from $PdCl_2$ and cyclohexylisocyanide, provided a yellow precipitate, which was washed with aqueous $LiClO_4$ and water and then dried in vacuo.[23] Consistent with the original reports of methylisocyanide-derived Chugaev carbene complexes,[17,18] this product is assigned as $[Pd(C_{14}H_{25}N_4)(CNCy)_2][ClO_4]$ (**1**, Scheme 1), containing a deprotonated form of the chelating dicarbene ligand. Treatment of an acetonitrile solution of **1** with 3 M HCl followed by addition of Et_2O afforded neutral $Pd(C_{14}H_{26}N_4)Cl_2$ **2** in 65% yield.[24] Characteristic spectroscopic changes accompanied the conversion of **1** into **2**, including replacement of three NH peaks in the ^1H NMR (DMSO-d_6) of **1** (δ 4.49, 6.79, 10.09) with two NH peaks for **2** (δ 7.71, 11.15), as well as disappearance of the isocyanide stretches of **1** ($\nu(C{\equiv}N)$ 2220, 2210 cm^{-1}) in the IR spectrum.



Scheme 1. Synthesis of palladium Chugaev carbene complexes.

X-ray crystallographic analysis of **2**[25] revealed the expected chelating carbene ligand with a planar NCNNCN backbone (Fig. 2). The coordination about palladium is almost perfectly planar (sum of angles 359.96(9)°), but the five-membered chelate ring of the dicarbene constrains the C–Pd–C angle to a small value of 79.91(6)°. The N–$C_{carbene}$ distances of the ligand (average 1.326 Å) are slightly smaller than the normal range of 1.34–1.37 Å for imidazolium-based NHC ligands, indicating substantial π-interaction within the dicarbene unit. In addition, the Pd–$C_{carbene}$ distances (1.9583(15), 1.9638(15) Å) are slightly shorter than those in comparable Pd–NHC complexes (typically 1.99–2.00 Å),[8,11] suggesting possibly stronger binding to the metal. The steric bulk of the cyclohexyl groups is directed away from the palladium coordination sphere and does not substantially perturb the ligand backbone. Thus, the use of even larger isocyanides appears feasible. An intriguing feature is hydrogen bonding of the backbone NH units with DMSO solvent molecules. Interestingly, X-ray quality crystals could only be grown from DMSO.

In view of the similarity of Chugaev carbene ligands to NHC's, we have tested the catalytic activity of **2** in Suzuki–Miyaura cross-coupling reactions. Complex **2** is stable to air and moisture, and therefore we regarded it as potentially useful under aerobic conditions. The ability to operate under air would greatly increase the practicality of the reaction. However, only a few palladium Suzuki catalysts have been reported to function under air,[26] primarily involving nitrogen ligands,[27] with only one example of an aerobic Suzuki reaction reported using a Pd–NHC catalyst.[28]

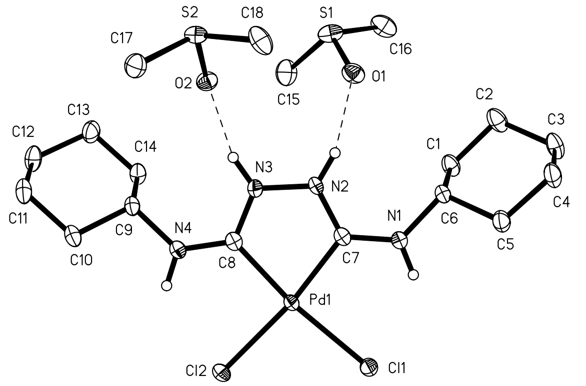
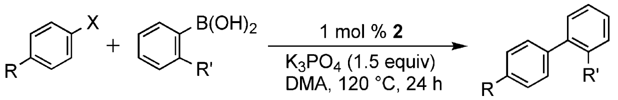
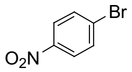
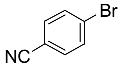
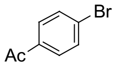
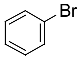
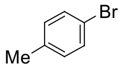
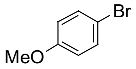
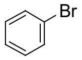
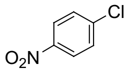
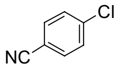
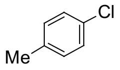


Figure 2. ORTEP diagram of **2** (50% probability ellipsoids). Selected distances (Å) and angles (°): Pd(1)–C(7) = 1.9583(15), Pd(1)–C(8) = 1.9638(15), C(7)–N(1) = 1.3205(19), C(7)–N(2) = 1.332(2), C(8)–N(3) = 1.3311(19), C(8)–N(4) = 1.3191(19), C(7)–Pd(1)–C(8) = 79.91(6), C(7)–Pd(1)–Cl(1) = 93.26(5), C(8)–Pd(1)–Cl(2) = 92.97(4), Cl(1)–Pd(1)–Cl(2) = 93.818(14).

Table 1. Suzuki–Miyaura cross-coupling reactions catalyzed by Chugaev carbene complex **2**[a]



Entry	ArX	R′	Conditions	Yield (%)[b]	Homocoupling product (TON)[c]
1a		H	N_2	99 (99)	0.025
1b			Air	98	0.25
2a		H	N_2	99 (95)	nd[d]
2b			Air	99	0.21
3a		H	N_2	97	0.004
3b			Air	93	0.25
4a		H	N_2	99	—
4b			Air	93	—
5a		H	N_2	93	nd[d]
5b			Air	67	0.72
6a		H	N_2	87	0.010
6b			Air	59	0.70
7a		Me	N_2	89	nd[d]
7b			Air	79	nd[d]
8		H	N_2	79	nd[d]
9		H	N_2	25	nd[d]
10		H	N_2	3	0.071

[a] Reactions conditions: 1 mol % **2**, 1.7 mmol ArX, 2.6 mmol $Ar'B(OH)_2$, 2.6 mmol K_3PO_4, DMA, 120 °C, 24 h; reaction times not optimized.
[b] Yields determined by ^1H NMR; isolated yields in parentheses.
[c] TON = moles biphenyl/moles catalyst; determined by GC.
[d] None detected.

The results of Suzuki–Miyaura cross-coupling reactions using 1 mol % of **2** as a precatalyst are presented in Table 1.[29] With DMA as solvent and K_3PO_4 as a mild base additive, this system catalyzes couplings of phenylboronic acid with a range of aryl bromides having both electron-donating and electron-withdrawing substituents (entries 1–6) in high yield, though a temperature of 120 °C is necessary to obtain >90% yields. In addition, *ortho*-methyl substituents on the arylboron reagent are well tolerated (entry 7). Suzuki–Miyaura reactions of electron-poor and electron-neutral aryl bromides were performed *open to air* in wet DMA solvent with only minimal loss of yield (entries 1–4). Electron-rich aryl bromides (entries 5 and 6) gave poorer yields under aerobic conditions, possibly due to oxidation of the substrate or product methyl groups at the high temperatures used. Reasonable yields were obtained for 4-chloronitrobenzene (entry 8), but this catalyst system did not prove effective for less 'activated' aryl chlorides (entries 9 and 10).

To assess whether aerobic reaction conditions affect the product distribution, we measured the amount of biphenyl homocoupling product produced in each reaction. Homocoupling can result from 'double transmetalation' by the arylboron reagent followed by biaryl reductive elimination,[30] and this side pathway could become more important if the key Pd(0) intermediate of the Suzuki catalytic cycle[2] is depleted by aerobic oxidation to Pd(II). While larger amounts of homocoupling products were observed under air compared with reactions under nitrogen, the largest quantities produced still amounted to less than one catalytic turnover and ~1% of the total product (entries 5 and 6). Thus, precatalyst **2** is capable of sustaining the catalytic Suzuki–Miyaura reaction under air without substantial byproduct formation.

In summary, we have developed a convenient synthetic route to a novel palladium Chugaev carbene complex and found it to be a promising precatalyst for aerobic Suzuki–Miyaura cross-coupling reactions. While this system lacks the low-temperature activity and ability to couple aryl chlorides displayed by the best catalysts,[7] the potentially modular synthetic procedure should allow substantial tuning of catalyst activity through systematic modification of ligand electronic and steric properties. Further efforts to design highly active cross-coupling catalysts by modular variation of the Chugaev carbene structure, as well as to develop chiral variants of these ligands from optically active diamines, will be reported in due course.

Acknowledgements

Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund (#40196-G1) for support of this research.

References and notes

1. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley: New York, 2004.
2. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
3. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
4. Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873.
5. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387–3388.
6. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723; (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
7. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1871–1876.
8. Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1290–1309.
9. Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370–2375.
10. Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201–202.
11. Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93–96.
12. Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805.
13. Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1363–1365.
14. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3690–3693.
15. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.
16. (a) Chugaev, L.; Skanavy-Grigorieva, M. *J. Russ. Chem. Soc.* **1915**, *47*, 776; (b) Chugaev, L.; Skanavy-Grigorieva, M.; Posniak, A. *Z. Anorg. Allg. Chem.* **1925**, *148*, 37.
17. Rouschias, G.; Shaw, B. L. *Chem. Commun.* **1970**, 183.
18. Burke, A.; Balch, A. L.; Enemark, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 2555–2557.
19. Balch, A. L.; Parks, J. E. *J. Am. Chem. Soc.* **1974**, *96*, 4114–4121.
20. Fehlhammer, W. P.; Bliss, T.; Sperber, W.; Fuchs, J. *Z. Naturforsch. B* **1994**, *49*, 494–500.
21. Lai, S.-W.; Chan, M. C. W.; Wang, Y.; Lam, H.-W.; Peng, S.-M.; Che, C.-M. *J. Organomet. Chem.* **1999**, *617–618*, 133–140.
22. Miller, J. S.; Balch, A. L. *Inorg. Chem.* **1972**, *11*, 2069–2074.
23. Preparation and characterization of **1**: cyclohexylisocyanide (0.40 g, 3.7 mmol) was added at 25 °C to a stirred aqueous solution of K_2PdCl_4, prepared in situ from $PdCl_2$ (163 mg, 0.92 mmol) and KCl (274 mg, 3.68 mmol) in 30 mL of H_2O. Excess hydrazine hydrate (1.5 mL, 26 equiv) was added to the resulting colorless solution to give a yellow precipitate of **1**, which was collected by filtration, washed with aqueous $LiClO_4$ and water, and dried in vacuo over P_2O_5 (455 mg, 73%). **CAUTION**: perchlorates are potentially explosive and should be handled carefully and in small amounts. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.09 (s, 1H, N*H*), 6.79 (s, 1H, N*H*), 4.49 (s, 1H, N*H*), 4.04 (s, 2H, CyNH *ipso* C*H*), 3.32 (s, 2H, CyNC *ipso* C*H*), 1.0–2.2 (unresolved m, 40H, Cy). ^{13}C NMR (101 MHz, CD_3CN): δ 188.2 (Pd–*C*), 53.0 (Cy *ipso*), 51.2 (Cy *ipso*), 31.9 (Cy), 31.1 (Cy), 25.1 (Cy), 24.3 (Cy, 2 unresolved), 22.0 (Cy). IR (Nujol, cm^{-1}): ν 3381, 3157 (br, NH), 2220, 2210 (m, C≡N), 1572, 1539 (m, C=N). Anal. Calcd for $C_{28}H_{47}N_6ClO_4Pd$: C, 49.96; H, 7.03; N, 12.48. Found: C, 50.32; H, 6.65; N, 12.48.
24. Preparation and characterization of **2**: aqueous 3 M HCl was added dropwise to an acetonitrile solution (15 mL) of **1** (201 mg, 0.298 mmol) until a pale yellow solution was formed. The solution volume was reduced and Et_2O was added dropwise to give a white precipitate of **2**, which was filtered, washed with Et_2O, and dried in vacuo (83 mg, 65%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.15 (s, 2H, N*H*), 7.71 (d, 2H, $^3J_{HH} = 8$ Hz, CyN*H*), 3.53 (s, 2H, Cy *ipso* C*H*), 1.0–2.2 (unresolved, 20H, Cy). ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.7 (Pd–*C*), 51.3 (Cy *ipso*), 31.3 (Cy), 24.7 (Cy), 23.5 (Cy). IR (Nujol, cm^{-1}): ν 3320 (m, NH), 3177 (w, NH), 3115 (w, NH), 3074 (m, NH), 1592, 1501 (m, C=N). Anal. Calcd for $C_{14}H_{26}N_4Cl_2Pd$: C, 39.33; H, 6.13; N, 13.13. Found: C, 39.72; H, 6.11; N, 13.14.
25. Crystal data for **2**: $C_{14}H_{26}N_4Cl_2Pd{\cdot}2C_2H_6SO$, $M_r = 583.94$, monoclinic, space group $P2_1/c$, $a = 11.9954(6)$ Å, $b = 11.1195(6)$ Å, $c = 19.6281(11)$ Å, $\beta = 99.3080(10)°$, $U = 2583.6(2)$ Å^3, $T = 103(2)$ K, $Z = 4$, $D_c = 1.501$ g cm^{-3}, μ (Mo Kα) = 1.108 mm^{-1}, 30772 total reflections, 6230 independent ($R_{int} = 0.019$). Final $R1(2\sigma) = 0.0208$, $wR2$ (all data) = 0.0544. CCDC 258981 contains the supplementary crystallographic data for **2**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
26. Xiong, Z.; Wang, N.; Dai, M.; Li, A.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3337–3340.
27. (a) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077–1080; (b) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540–1541; (c) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588–5594; (d) Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330–4335; (e) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809–2811; (f) Gossage, R. A.; Jenkins, H. A.; Yadav, P. N. *Tetrahedron Lett.* **2004**, *45*, 7689–7691.
28. Loch, J. A.; Albrecht, M.; Peris, E.; Mata, J.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 700–706.
29. Suzuki–Miyaura coupling procedure: aryl halide (1.7 mmol), arylboronic acid (2.55 mmol, 1.5 equiv), and K_3PO_4 (anhydrous, 2.55 mmol, 1.5 equiv) were placed in a flask, and a solution of **2** (7.3 mg, 17 μmol) in DMA (5 mL) was added. For reactions under N_2, all manipulations were done in a dry box, anhydrous DMA (Acros) was used, and the flask was sealed with a Teflon stopcock. For aerobic reactions, wet unpurified DMA was employed and the flask was attached to a reflux condenser open to

air. The flask was placed in a preheated oil bath at 120 °C and stirred for 24 h. After cooling, 100 μL of diethylene glycol dibutyl ether (NMR/GC standard) was added to the flask. A 200 μL aliquot of the reaction mixture was added to 10 mL of CH_2Cl_2, and the resulting mixture was extracted with 4 × 10 mL H_2O and then dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was analyzed by ^1H NMR. Product peak assignments were based on authentic samples or published data (Ref. 6b). In some reactions, the product was isolated by extraction of the entire reaction mixture with CH_2Cl_2 followed by silica flash chromatography (4:1 hexanes/EtOAc).

30. Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525–2528.