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Journal of Organometallic Chemistry 690 (2005) 6247–6251
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Communication

Sterically controlled formation of monodentate versus chelating carbene ligands from phenylhydrazine

Adriana I. Moncada [a], Joseph M. Tanski [b], LeGrande M. Slaughter [a,*]

[a] Department of Chemistry, Oklahoma State University, 107 Physical Science I, Stillwater, OK 74078, USA
[b] Department of Chemistry, Vassar College, 124 Raymond Avenue, Poughkeepsie, NY 12604, USA

Received 31 May 2005; accepted 4 July 2005
Available online 10 August 2005

Abstract

Palladium-templated addition of phenylhydrazine to methylisocyanide led to a Chugaev-type chelating dicarbene–palladium complex that is an effective catalyst for Suzuki-Miyaura cross-coupling reactions of aryl bromides and activated aryl chlorides. In contrast, the use of isopropylisocyanide resulted in an unprecedented complex containing aminohydrazinocarbene ligands, which was characterized by X-ray crystallography. The latter complex represents a possible intermediate in the formation of chelating carbene ligands.

Keywords: Carbene ligands; Chelating ligands; Palladium; Suzuki

1. Introduction

Since the first report of a metal–carbene complex by Fischer and Maasböl in 1964 [1], heteroatom-stabilized carbene ligands have become ubiquitous in organometallic chemistry. Diaminocarbenes possess particularly favorable ancillary ligand properties, acting as powerful σ-donors without the electrophilic reactivity of Fischer-type carbenes [2]. This is exemplified by the imidazole-derived N-heterocyclic carbenes (NHCs) [3], which have received increasing attention following their isolation as free carbenes by Arduengo and co-workers [4]. The strong σ-donation of these ligands combined with their increased oxidative and thermal stability relative to phosphines have placed NHC's at the forefront of ligand design for organometallic catalysis [5]. Significant advances in catalytic activity for olefin metathesis [6] and cross-coupling reactions [7,8] have already been achieved using NHC ligands, and opportunities exist for their application in a range of other synthetically useful reactions. Because each catalytic reaction has unique requirements for ligand steric and electronic properties, the search for new carbene ligand types that permit systematic tuning of these parameters is an important goal.

An overlooked but historically interesting class of bidentate diaminocarbene ligands is the "Chugaev-type" carbenes, which are formed by nucleophilic addition of hydrazines or diamines to metal-bound isocyanide ligands [9,10]. Platinum complexes of these ligands were reported as early as 1915 (**a**, Fig. 1), [9] though they were not recognized as carbenes until their structural characterization by Burke, Balch and Enemark in 1970 [11]. These chelating carbenes are intriguing candidates for catalyst development due to their similiarity to acyclic diaminocarbenes [12], which have been reported to be stronger σ-donors than imidazole-based NHCs [13] but have not been substantially

* Corresponding author. Tel.: +1 405 744 5941; fax: +1 405 744 6007.
E-mail address: lms@chem.okstate.edu (LeGrande M. Slaughter).

0022-328X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2005.07.019

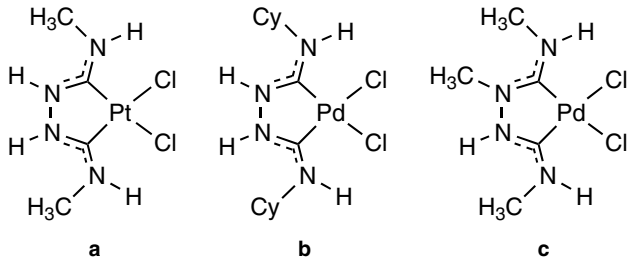


Fig. 1. Chugaev-type carbene complexes.

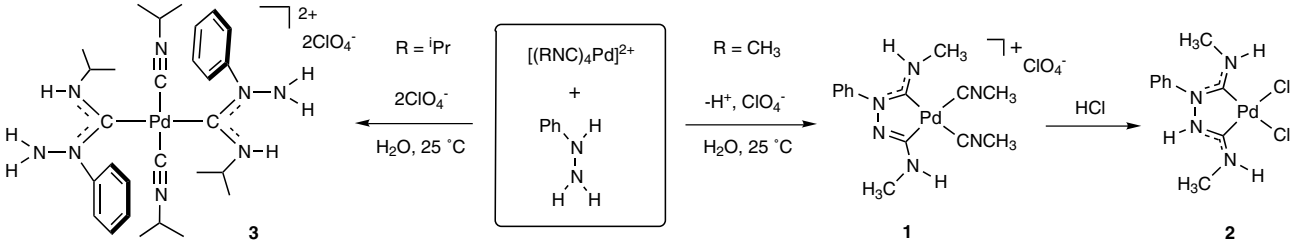
explored in catalysis. In addition, they have potential for systematic steric and electronic "tuning" by variation of the isocyanide and diamine backbone. Our initial studies showed that palladium–dicarbene complex **b** (Fig. 1) is a stable and active catalyst for Suzuki-Miyaura coupling of aryl bromides and electron-poor aryl chlorides, even under aerobic conditions [14]. Subsequently, systematic variation of ligand substituents and screening of the resulting catalyst "library" allowed identification of complex **c** as a more active catalyst with improved substrate scope [15]. This ability to optimize catalyst activity via systematic ligand modification is promising for the further development of Chugaev-type diaminocarbenes as ancillary ligands.

We have sought Chugaev-type diaminocarbene ligands with steric bulk directed toward the metal center through the use of substituted hydrazines and bulky alkylisocyanides. This is important because increased bulk is thought to expedite product-forming reductive elimination steps in cross-coupling reactions [8]. Herein we report that palladium-templated addition of phenylhydrazine to isopropylisocyanide results in an unprecedented monodentate aminohydrazinocarbene ligand instead of the expected chelating dicarbene. The resulting carbene complex is mechanistically interesting, as it represents a likely intermediate in the formation of Chugaev-type carbenes that has not previously been observed. In contrast, the use of methylisocyanide gives rise to a chelating dicarbene complex that is an active precatalyst for Suzuki-Miyaura cross-coupling reactions. This effect of sterics on the type of carbene formed provides valuable insights for future ligand design efforts.

2. Results and discussion

Sequential addition of methylisocyanide (4 equiv.) and phenylhydrazine (1 equiv.) to an aqueous solution of K_2PdCl_4 resulted in formation of a yellow solution, and a yellow precipitate was collected upon addition of excess $LiClO_4$ [16]. The ^1H NMR spectrum (CD_3CN) of this compound contains two NH resonances (δ 5.98, 4.82) and three CH_3 peaks (one unresolved) in addition to the phenyl resonances [16], diagnostic for a cationic complex containing two isocyanides and a deprotonated form of a Chugaev carbene ligand (**1**, Scheme 1). Such complexes are often the first products obtained in Chugaev carbene syntheses [11,14]. Complex **1** was readily converted into neutral (dicarbene)$PdCl_2$ **2** by dissolution in hot 3 M aqueous HCl [17]. Dicarbene complex **2** is characterized by three NH resonances (δ 11.32, 8.26, 7.95) and two CH_3 peaks in the ^1H NMR spectrum (DMSO-d_6) as well as the absence of isocyanide C≡N stretches in the IR spectrum [17]. No crystals of **1** or **2** suitable for X-ray diffraction could be obtained. Thus, the differing stereochemistries of the terminal CH_3 groups nearest the phenyl group in **1** and **2** are assigned based on the reported structures of methylhydrazine-derived analogues [15,18], with a *trans* configuration for **1** and a *cis* configuration for **2**. However, the presence of two sets of phenyl and CH_3 peaks in the ^{13}C spectra of **1** and **2** suggests that both isomers of these compounds are in equilibrium in solution.

An identical procedure to that used to prepare **1**, but with isopropylisocyanide replacing methylisocyanide, afforded a colorless compound with different spectral signatures from **1** [19]. The ^1H NMR spectrum (CD_3CN) exhibited two NH resonances in a 1:2 ratio (δ 7.93, 4.66) as well as two distinct isopropyl groups, and only one carbene resonance was observed in the ^{13}C NMR (δ 182.1) [19]. An X-ray crystallographic analysis[20] revealed this complex to be a dication containing two *monodentate* carbene ligands and two isocyanides in a *trans* configuration (**3**, Scheme 1, Fig. 2). To the best of our knowledge, **3** is the first reported complex of an aminohydrazinocarbene ligand. A few examples of hydrazinocarbene ligands have been published, but these have alkynyl [21], alkenyl [22], or alkyl[23] groups as the second carbene substituent and more than one



Scheme 1. Synthesis of chelating versus monodentate carbene complexes from phenylhydrazine.

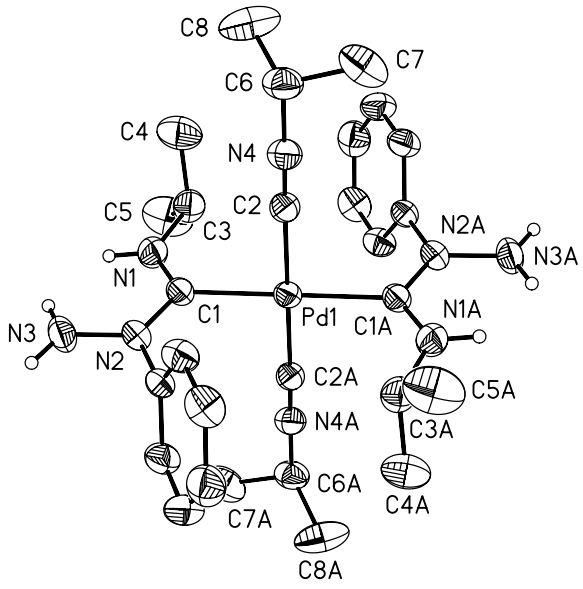


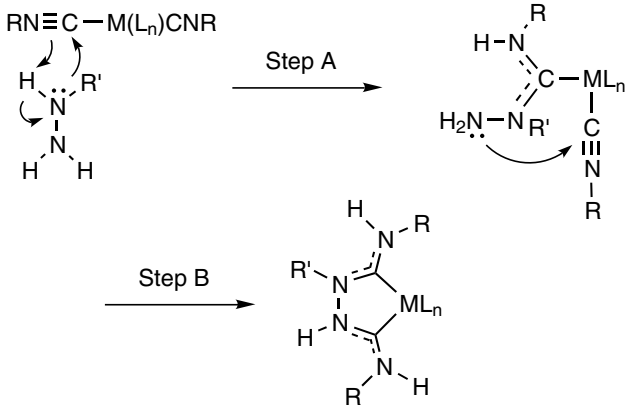
Fig. 2. Molecular structure of **3**, with 30% probability ellipsoids and ClO_4^- anions omitted for clarity. Selected distances (Å) and angles (°): Pd(1)–C(1) = 2.055(5), Pd(1)–C(2) = 1.983(6), C(1)–N(1) = 1.311(7), C(1)–N(2) = 1.333(7), N(2)–N(3) = 1.421(6), C(2)–N(4) = 1.140(7), N(1)–C(1)–N(2) = 117.8(5), C(1)–Pd(1)–C(2) = 91.6(2), C(2)–Pd(1)–C(1)–N(1) = 84.2(5).

substituent on the hydrazino group. Of note is the recently reported synthesis by Lassaletta et al. of a stable 1,3-bis(*N*,*N*-dialkylamino)imidazolin-2-ylidene, which can be formally regarded as a dihydrazinocarbene [24]. Intriguingly, Bertrand and co-workers [25] recently reported syntheses of two *free* aminohydrazinocarbenes, and they observed that these species degrade over minutes to hours via N–N bond cleavage. The isolation of **3** clearly demonstrates that metal complexation can stabilize this type of carbene.

The structural asymmetric unit of **3** consists of two halves of two distinct molecules, with each Pd atom occupying a crystallographic inversion center. The two molecules have no significant structural differences, and this discussion focuses on only one of them. The carbene NCN units are oriented nearly perpendicular to the square coordination plane, with a torsion angle of 84.2(5)°. The Pd–$C_{carbene}$ distances of 2.055(5) Å are slightly longer than the typical 1.99–2.01 Å range for Pd(II)–NHC complexes. By contrast, *cis*-chelating Chugaev carbene ligands exhibit Pd–$C_{carbene}$ bond lengths slightly below this range [14]. This Pd–$C_{carbene}$ bond lengthening may be partly due to the *trans*-influence of the two opposing carbene ligands, and the Pd–$C_{carbene}$ distances of **3** can be compared with the corresponding distances in Pd(II) complexes with two *trans* NHC ligands (2.00–2.03 Å).[26] However, sterics may also affect the Pd–$C_{carbene}$ distances, and we do not believe that meaningful assessments of the σ-donor ability of aminohydrazinocarbene ligands relative to NHC's can be made from this data given the small differences in bond lengths.

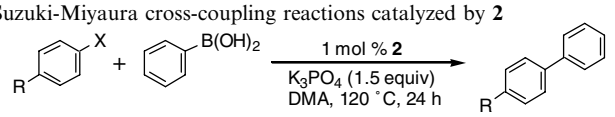
The isolation of **3** has interesting mechanistic implications, because its monodentate aminohydrazinocarbene ligands represent likely intermediates in the formation of chelating Chugaev carbenes. Nucleophilic attack of one end of a hydrazine on an isocyanide ligand would result in a hydrazinocarbene ligand like those of **3** (Step A, Scheme 2), and subsequent intramolecular attack of the second nitrogen on a *cis* isocyanide would complete the cyclization (Step B, Scheme 2). Such a mechanism has been assumed in kinetic studies of Chugaev carbene formation by addition of hydrazine to Fe-isocyanide complexes [27]. However, no spectroscopic evidence for monodentate intermediates was obtained, and the cyclization step (B) was assumed to be rapid following rate-determining step A. The isolation of **3** in comparison to **1** demonstrates that a change in isocyanide substituent from CH_3 to ^{i}Pr is sufficient to sterically prevent the normally rapid cyclization step in this case. No conversion of the hydrazinocarbenes into chelating dicarbenes was observed upon heating a CD_3CN solution of **3**, with no change in the ^{1}H NMR spectrum at 65 °C and gradual decomposition observed at 100 °C. In addition, attempts to prepare a complex with only one hydrazinocarbene were unsuccessful, and **3** was obtained whether 1 or 2 equiv. of phenylhydrazine were employed.

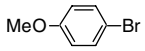
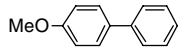
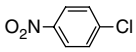
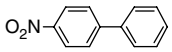
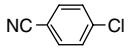
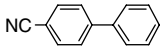
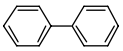
Given the similarity of (dicarbene)$PdCl_2$ **2** to complex **c** (Fig. 1), which was found to be the most active catalyst for Suzuki-Miyaura cross-coupling reactions among a series of Pd–dicarbene complexes [15], we tested the effectiveness of **2** in catalyzing challenging examples of this reaction (Table 1). With 1 mol% **2** at 120 °C, excellent yields were obtained for Suzuki couplings of a deactivated aryl bromide (entry 1) and activated aryl chlorides (entries 2 and 3), but the catalyst was not effective for unactivated aryl chlorides (entry 4). Precatalyst **2** gave similar or higher yields in these reactions



Scheme 2. Proposed mechanism for chelating carbene ligand formation.

Table 1
Suzuki-Miyaura cross-coupling reactions catalyzed by **2**



Entry	ArX	Product	Yield[a] (^{1}H NMR)
1			92%
2			95%
3			98%
4			10%

[a] Reaction conditions: 1 mol% **2**, 1.7 mmol ArX, 2.6 mmol $PhB(OH)_2$, 2.6 mmol K_3PO_4, DMA, 120 °C, 24 h under N_2; reaction times not optimized. See [14] for further experimental details.

compared with complex **c**, supporting our hypothesis that backbone substituents on the dicarbene provide favorable ligand electronic properties for the development of cross-coupling catalysts.

In conclusion, we have found that simple replacement of an isocyanide CH_3 substituent with ^{i}Pr in the Pd-templated nucleophilic addition of phenylhydrazine to isocyanides changes the favored product from a chelating dicarbene complex to a monodentate carbene complex. This strong steric influence on carbene formation suggests that more reactive nucleophiles, such as deprotonated amines, may be required to attain sterically hindered dicarbene ligands by this synthetic route.

Acknowledgment

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

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[16] Preparation and characterization of **1**: Methylisocyanide (100 mg, 2.45 mmol) was added to a stirred solution of K_2PdCl_4, prepared in situ from $PdCl_2$ (108 mg, 0.61 mmol) and KCl (190 mg, 2.54 mmol) in 20 mL of H_2O at 25 °C. Phenylhydrazine (60 μL, 1 equiv.) was then introduced to give a yellow solution. Excess $LiClO_4$ (130 mg, 2 equiv.) was added to precipitate a yellow solid, which was filtered, washed with cold H_2O, and dried in vacuo over P_2O_5. The compound was recrystallized by slow addition of ether to a concentrated CH_3CN solution (132 mg, 45%). **CAUTION:** Perchlorates are potentially explosive and should be handled carefully. ^{1}H NMR (300 MHz, CD_3CN): δ 7.55–7.40 (m, 3H, Ph), 7.33–7.27 (m, 2H, Ph), 5.98 (br s, 1H, N*H*), 4.82 (br s, 1H, N*H*), 3.47 (2s unresolved, 6H, CNCH_3), 2.82 (br s, 3H, HNCH_3), 2.63 (d, 3H, $^3J_{HH} = 5.1$ Hz, HNCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 192.5 (carbene), 172.5 (imidoyl), 139.2 (unresolved, Ph *ipso*), 129.7, 129.2, 128.3, 127.8, 127.1, 126.6 (Ph), 36.2 (CN*C*H_3, unresolved), 30.3 (unresolved, HN*C*H_3), 29.9, 29.5 (HNCH_3); *C*NCH_3 not observed. IR (Nujol, cm^{-1}): *v* 3464 (m, NH), 3340 (w, NH), 3180 (br, Ph CH), 2260, 2248 (m, C≡N), 1623 (w, Ph), 1556, 1508 (m, C=N). Anal. Calc. for $C_{14}H_{19}N_6ClO_4Pd$: C, 35.24; H, 4.01; N, 17.61. Found: C, 35.32; H, 4.30; N, 16.74.
[17] Preparation and characterization of **2**: Compound **1** (128 mg, 0.27 mmol) was dissolved in a minimal amount of hot 3M aqueous HCl. The solution was cooled with stirring until a white precipitate formed, which was filtered, washed with H_2O and dried in vacuo over P_2O_5(84 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.32 (s, 1H, N*H*), 8.26 (br s, 1H, N*H*), 7.95 (br s, 1H, N*H*), 7.65–7.50 (m, 5H, Ph), 2.79 (d, 3H, $^3J_{HH} = 5.2$ Hz, CH_3), 2.25 (d, 3H, $^3J_{HH} = 5.2$ Hz, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 180.3, 176.1 (carbenes), 137.8 (unresolved, Ph *ipso*), 130.9, 130.4, 129.8, 129.5, 129.4, 129.1 (Ph), 33.2, 33.0 , 30.8, 30.4 (*C*H_3). IR (Nujol, cm^{-1}): *v* 3294, 3279 (m, NH), 3151 (br, Ph CH), 1607 (w, Ph), 1594, 1570 (m, C=N). Anal. Calc. for $C_{10}H_{14}N_4Cl_2Pd$: C, 32.67; H, 3.84; N, 15.24. Found: C, 32.27; H, 3.59; N, 14.97.
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[19] Preparation and characterization of **3**: Isopropylisocyanide (169 mg, 2.45 mmol) was added to a stirred solution of in situ prepared K_2PdCl_4 (0.61 mmol) in 20 mL H_2O at 25 °C. Phenylhydrazine (121 μL, 1.22 mmol) was introduced, and then excess $LiClO_4$ (260 mg, 4 equiv.) was added to precipitate the product, which was filtered, washed with H_2O, and dried in vacuo over P_2O_5. The colorless compound was recrystallized by slow diffusion of ether into a CH_3CN solution (317 mg, 65%). ^{1}H NMR (300 MHz, CD_3CN): δ 7.93 (m, 2H, ^{i}PrN*H*), 7.62–7.50 (m, 6H, Ph), 7.35–7.30 (m, 4H, Ph), 4.66 (s, 4H, NH_2), 4.33 (sept, 2H, $^3J_{HH} = 6.7$ Hz, CN^{i}Pr C*H*), 2.60 (m, 2H, HN^{i}Pr C*H*), 1.49 (dd, 12H, $^3J_{HH} = 6.8$ Hz, $^4J_{HH} = 1.4$ Hz, HN^{i}Pr CH_3), 0.95 (d, 12H, $^3J_{HH} = 7.2$ Hz, CN^{i}Pr CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 182.1 (carbene), 145.9 (*C*N^{i}Pr), 129.8, 128.9, 127.4, 121.8 (Ph), 50.4 (2 unresolved, *C*H), 22.6, 21.9 (*C*H_3). IR (Nujol, cm^{-1}): *v* 3364, 3340, 3283 (br w, NH), 2240 (m, C≡N), 1626 (m, Ph), 1551, 1492 (m, C=N). Anal.

Calc. for $C_{27}H_{44}N_8Cl_2O_8Pd$: C, 42.14; H, 5.50; N, 14.04. Found: C, 42.02; H, 5.26; N, 13.95.

[20] Crystal data for **3**: $C_{28}H_{44}N_8Pd \cdot 2ClO_4$, $M_r = 798.01$, triclinic, space group $P\bar{1}$, $a = 10.749(2)$ Å, $b = 11.049(2)$ Å, $c = 16.551(3)$ Å, $\alpha = 84.14(3)°$, $\beta = 82.51(3)°$, $\gamma = 76.50(3)°$, $U = 1889.8(6)$ Å^3, $T = 293(2)$ K, $Z = 2$, μ(Mo Kα) = 0.686 mm^{-1}, 8978 total reflections, 8978 independent. Final $R1(2\sigma) = 0.0626$, w$R2$ (all data) = 0.1854. Crystal: colorless block, $0.3 \times 0.3 \times 0.3$ mm. Diffractometer: Syntex P21. No absorption correction. Crystallographic data for compound **3** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 273156. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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