1944 *Organometallics* **2008,** *27,* 1944–1947

Facile Synthesis of Bis(isoindolinone) through Carbonylative Cyclization and Dimerization of Phenylimine with Nickel(0) Complexes

Ruixia Cao, Hongjian Sun, and Xiaoyan Li*

School of Chemistry and Chemical Engineering, Shandong University, Shanda Nanlu 27,
Jinan 250100, People's Republic of China

Received January 17, 2008

A simple and convenient synthetic method for obtaining the novel bis(isoindolinones) **2a−d** starting from aryl chlorides is described, using phenylimines with stoichiometric amounts of tetrakis(trimethylphosphine)nickel(0) as starting materials under a CO atmosphere (1 bar) at room temperature. The formation mechanism was proposed and discussed. The intermediate chelate arylnickel(II) complex **5d** was also isolated and structurally characterized.

Introduction

The chemistry of the isoindolinone ring system has been widely investigated from both a physiological activity and an industrial point of view.[1] The development of new and general methods for their preparation is of significant interest.[2] It was recognized that 3-substituted isoindolinones of the general structure I[3] possess anxiolytic activity and are of interest as sedatives, hypnotics, and muscle relaxants,[4] including the anxiolytic pazinaclon II[5] and the 5-HT antagonist III (Figure 1).[6] Lactams are of considerable importance in a variety of pharmaceuticals, such as piracetam oxiracetam, rhynchophylline dolastin 15, glimepiride, and so on. It was also reported that lactams are frequently used to control many diseases such as age-related cognitive disorders,[7] hypotensive vasodilators,[8] cancer,[9] and so on.

Cho reported the palladium-catalyzed synthesis of 3-(alkylamino)isoindolin-1-ones by carbonylative cyclization of 2-bromobenzaldehyde with primary amines.[10] This process was realized at elevated temperature (100 °C) and under high CO pressure (13 atm). In this paper, a simple and convenient synthetic method for some novel bis(benzolactams) (**2a–d**) starting from aryl chlorides is described by reaction of phenylimines with stoichiometric amounts of tetrakis(trimethylphosphine)nickel(0) as a starting material under 1 bar of CO and at room temperature. Although this is a stoichiometric reaction, it is synthetically useful, because the cost of nickel is lower than that of noble metals and the crystallization workup is simple and convenient. The products in the crystalline state are very pure. A mechanism is proposed and discussed. The intermediate arylnickel(II) complex **5d** was also isolated and structurally characterized.

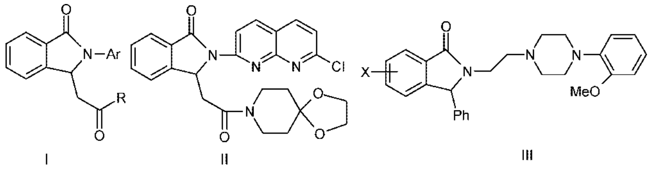
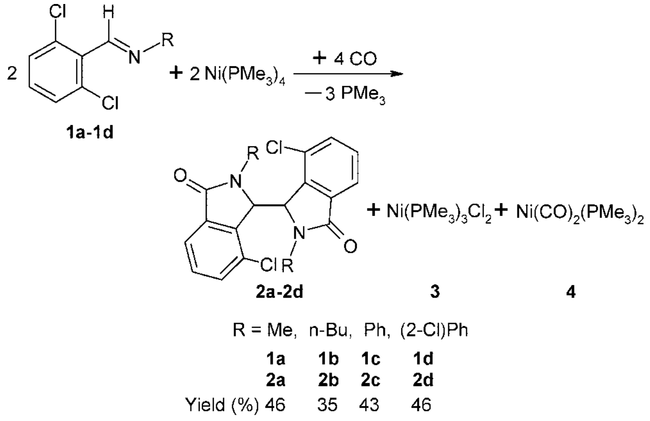


Figure 1. Structures of I−III.

Results and Discussion

The reaction of $Ni(PMe_3)_4$ with a molar equivalent amount of the phenylimines $(2,6\text{-}C_6H_3Cl_2)CH{=}NR$ (**1a−d**) under CO gives rise to the coupling products **2a−d** according to eq 1.



(1)

The white solids of **2a−d** were purified by precipitation from CH_2Cl_2, giving white microcrystals in 35–46% yield. In the infrared spectra of complexes **2a−d**, the characteristic $\nu(C{=}O)$ bands are found between 1683 and 1712 cm^{-1}. The proton resonances of the bridging C−H groups in complexes **2a−d**

---

* To whom correspondence should be addressed. Fax: +86-531-88564464. E-mail: xli63@sdu.edu.cn.

(1) (a) Feliu, L.; Vera-Luque, P.; Albericio, F.; Alvarez, M. *J. Comb. Chem.* **2007**, *9*, 521–565. (b) Gelalcha, F. G. *Chem. Rev.* **2007**, *107*, 3338–3361. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4464–4680.

(2) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432–1437.

(3) Hiraga, K.; Saji, Y. PCT Int. Appl. WO 8303 410, 1984; *Chem. Abstr.* 1984, *100,* 51451p.

(4) Rang, H. P.; Dale, M. M.; Ritter, J. M. *Pharmacology*, 3rd ed.; Churchill-Livingstone: London, 1995.

(5) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353–355.

(6) Zhuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157–166.

(7) Angelucci, L.; Calvisi, P.; Catini, R.; Cosentino, U.; Cozzolino, R. *J. Med. Chem.* **1993**, *36*, 1511–1519.

(8) Zhang, W.; Chen, C.; Sim, S.; Kwan, C. *Naunyn-Schmiedebergs Arch. Pharmacol.* **2004**, *369*, 232–238.

(9) Mross, K.; Herbst, K.; Berdel, W.; Korfel, A.; von Broen, I.; Bankmann, Y.; Hossfeld, D. *Onkologie* **1996**, *19*, 490–495.

(10) Cho, C. S.; Jiang, L. H. *J. Heterocycl. Chem.* **1997**, *34*, 1371.

10.1021/om800049m CCC: $40.75

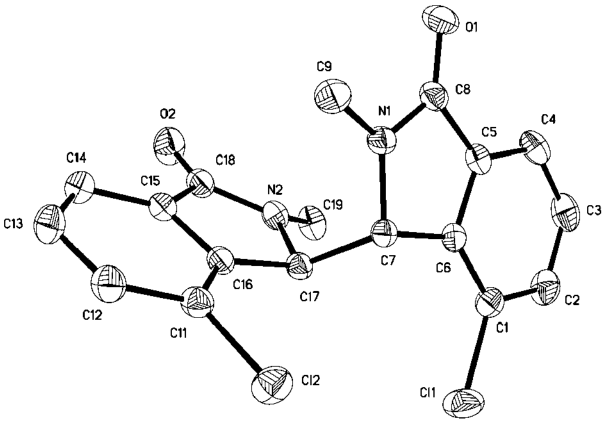


Figure 2. Molecular structure of **2a**.

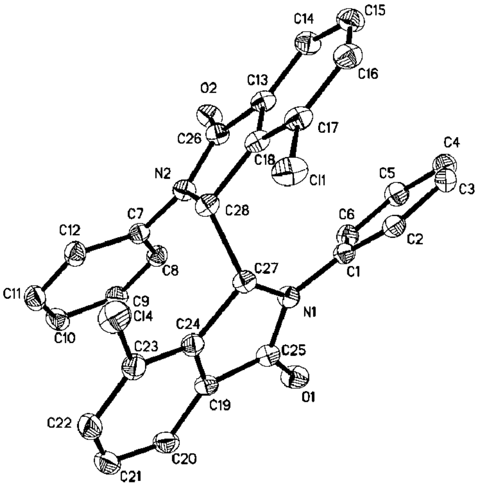


Figure 3. Molecular structure of **2c**.

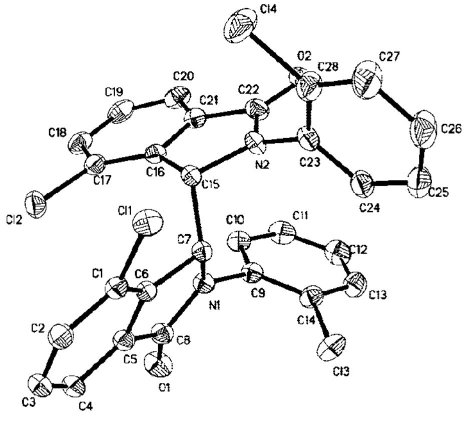
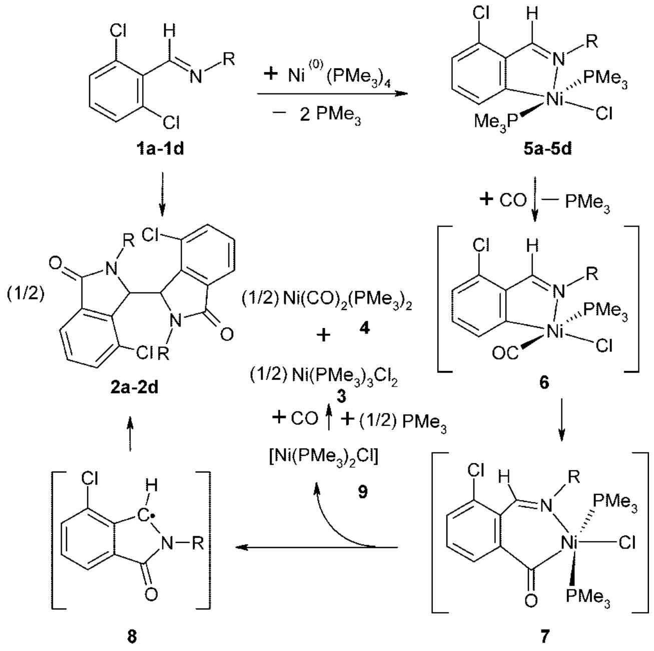


Figure 4. Molecular structure of **2d**.

Scheme 1

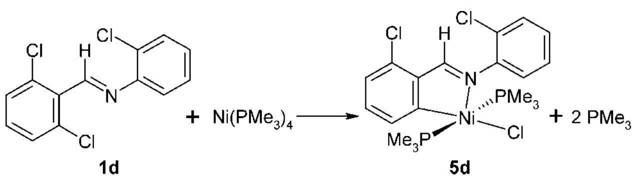


are recorded as singlets at 5.74–6.47 ppm. Only in the spectrum of **2d** is this signal split into two singlets at 6.56 and 6.57 ppm, indicating the presence of two rotamers in solution which arise from the bulky 2-chlorophenyl substituent. Accordingly, in the molecular structure of **2d** the isoindolinone plane forms an angle of 78.2° with the 2-chlorophenyl substituents, which is much larger than that in the structure of **2a** or **2c** (Figures 2−4). Spectroscopic data are otherwise in accordance with expected molecular configurations and are comparable with those in the literature.[10]

Tris(trimethylphosphine)nickel(II) chloride **3** (eq 1) was spectroscopically and structurally characterized.[11] The dicarbonylnickel(0) complex **4** was identified by its ν(CO) bands at 1999 and 1939 cm^{-1}.[12] It was experimentally verified that complex **4** does not participate in the reaction.

A reaction sequence is proposed in Scheme 1. The first step is the formation of a Ni(II) chelate intermediate (**5a**−**d**) through oxidative addition of a C−Cl function. Carbonylation give rise to intermediates **6** and **7**. By reductive elimination and cyclization the radical **8** is formed with the release of an unstable Ni(I) species (**9**), which disproportionates to form **3** and **4**. Radical coupling of **8** generates the isoindolinones **2a**−**d** as final products. The strong nucleophilicity of the imine nitrogen stabilizes the radical intermediates. This is the decisive step in the mechanism, as is the case in similar metal-catalyzed C−C coupling reactions.[3,13–15]

In order to verify this mechanism, a stoichiometric reaction was carried out with $(2,6\text{-}C_6H_3Cl_2)CH{=}N(2\text{-}ClPh)$ (**1d**) and $Ni(PMe_3)_4$ in the absence of CO (eq 2). Brown-yellow crystals of **5d** as the sole product arising from an oxidative substitution reaction could be isolated in 56% yield.



(2)

Solid samples are stable in air for at least 3 h, but they rapidly decompose in solution at room temperature. In the infrared

---

(11) (a) Cao, R.; Wang, Q.; Sun, H. *Acta Crystallogr.* **2008**, *E64*, m335. (b) Dawson, J. W.; McLennan, T. J.; Robinson, W.; Merle, A.; Dartiguenave, M.; Dartiguenave, Y.; Gray, H. B. *J. Am. Chem. Soc.* **1974**, *96*, 4428–4435.

(12) Klein, H.-F.; Petermann, A. *Inorg. Chim. Acta* **1997**, *261*, 187–195.

(13) Cho, C. S.; Jiang, L. H.; Lee, D. Y.; Shim, S. C. *Bull. Korean Chem. Soc.* **1996**, *17*, 1095–1096.

(14) Shim, S. C.; Lee, D. Y.; Jiang, L. H.; Kim, T. J.; Cho, S. D. *J. Heterocycl. Chem.* **1995**, *32*, 363–366.

(15) Marchal, J.; Bodiguel, J.; Fort, Y.; Caubere, P. *J. Org. Chem.* **1995**, *60*, 8336–8340.

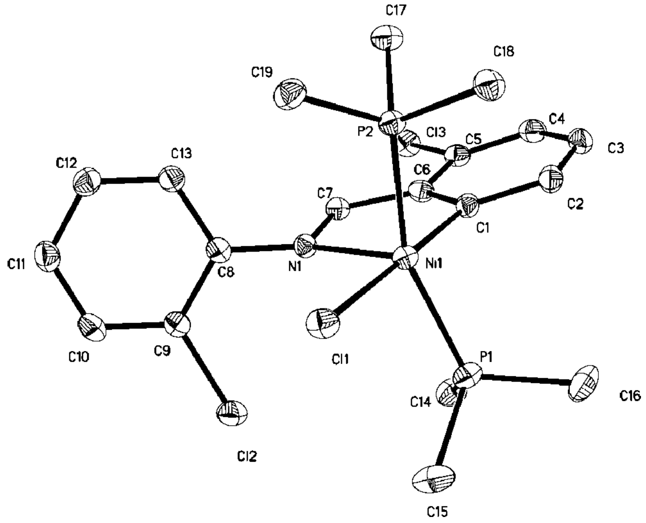


Figure 5. Molecular structure of **5d**.

spectrum of complex **5d**, the characteristic ν(C=N) band is found at 1602 cm^{-1} showing a bathochromic coordination shift by 53 cm^{-1}. Other spectroscopic data are in accordance with square-pyramidal configurations of nickel complexes,[16] as exemplified by the molecular structure of complex **5d** (Figure 5).

Current efforts are being directed toward investigating the scope of application and optimizing the reaction.

Conclusion

Novel bis(isoindolinones) **2a**−**d** were synthesized through carbonylative cyclization and dimerization of phenylimine with an equivalent amount of tetrakis(trimethylphosphine)nickel(0) under a CO atmosphere (1 bar) at room temperature. The formation mechanism was proposed and discussed. The intermediate chelate arylnickel(II) complex **5d** was also isolated and structurally characterized.

Experimental Section

General Procedures and Materials. Standard vacuum techniques were used in manipulations of volatile and air-sensitive material. Infrared spectra (4000–400 cm^{-1}), as obtained from Nujol mulls between KBr disks, were recorded on a Nicolet 5700 instrument. ^{1}H, ^{13}C, and ^{31}P NMR (300, 75, and 121 MHz, respectively) spectra were recorded on a Bruker Avance 300 spectrometer. Melting points and decomposition temperatures were obtained from sealed capillaries and are uncorrected. Literature procedures were followed in the preparation of tetrakis(trimethylphosphine)nickel(0).[17] Schiff bases were obtained by the condensation of 2,6-dichlorobenzaldehyde with amines. Other chemicals were used as purchased.

Synthesis of 2a. A solution of **1a** (0.78 g, 4.1 mmol) in 30 mL of pentane was combined with a solution of Ni(PMe$_3$)$_4$ (1.5 g, 4.1 mmol) in pentane (20 mL) at −78 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 h. During this period the pale yellow mixture turned red-brown. Then the red-brown mixture was stirred under 1 bar of CO for 16 h. The solution slowly turned blue, and a white powder precipitated. At this point the solution was filtered; freezing at 4 °C afforded 0.49 g of blue crystals of **3** (66.2%). The white powder was purified by recrystallization from CH$_2$Cl$_2$, giving white cubic crystals of **2a** suitable for X-ray diffraction analysis (yield 0.34 g, 46%). Mp: >200 °C. IR (Nujol mull, cm^{-1}): 1702, ν(C=O). ^{1}H NMR (300 MHz, CDCl$_3$, 297 K): δ 5.76 (s, 2H, C*H*N), 2.27 (s, 6H, C*H*$_3$), 7.45–7.76 (m, 6H, C*H*$_{\rm arom}$). ^{13}C NMR (75 MHz, CDCl$_3$, 297 K): δ 29.9 (s, *C*H$_3$), 60.5 (s, *C*H), 167.6 (s, *C*=O), 122.8–139.8 (s, *C*$_{\rm arom}$).

Synthesis of 2b. A solution of **1b** (0.95 g, 4.1 mmol) in 30 mL of diethyl ether was combined with a solution of Ni(PMe$_3$)$_4$ (1.5 g, 4.1 mmol) in diethyl ether (20 mL) at −78 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 h. During this period the pale yellow mixture turned red-brown. Then the red-brown mixture was stirred under 1 bar of CO for 16 h. The solution slowly turned blue and then was filtered. Crystallization at 4 °C afforded 0.51 g of blue crystals of **3** (68.9%) and white crystals of **2b** (yield 0.32 g, 35%). Mp: >136 °C. IR (Nujol mull, cm^{-1}): 1683, ν(C=O). ^{1}H NMR (300 MHz, CDCl$_3$, 297 K): δ 5.74 (br, 2H, C*H*N), 3.42 (t, 2H, NC*H*$_2$), 1.76 (m, 2H, NCC*H*$_2$), 1.33 (m, 2H, NCCC*H*$_2$), 1.14 (t, 3H, C*H*$_3$), 7.42–7.70 (m, 6H, C*H*$_{\rm arom}$).

Synthesis of 2c. A solution of **1c** (0.85 g, 3.4 mmol) in 30 mL of pentane was combined with a solution of Ni(PMe$_3$)$_4$ (1.24 g, 3.4 mmol) in pentane (20 mL) at −78 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 h. During this period the pale yellow mixture turned brown-yellow. Then the brown-yellow mixture was stirred under 1 bar of CO for 16 h. The solution slowly turned blue, and a great deal of white powder was obtained. At this point the solution was filtered; freezing at 4 °C afforded 0.42 g of blue crystals of **3** (69.1%). The white powder was purified by recrystallization from CH$_2$Cl$_2$, giving white cubic crystals of **2c** (yield 0.35 g, 43%). Mp: >200 °C. IR (Nujol mull, cm^{-1}): 1705, ν(C=O). ^{1}H NMR (300 MHz, CDCl$_3$, 297 K): δ 6.47 (s, 2H, C*H*N), 6.81–7.72 (m, 16H, C*H*$_{\rm arom}$). ^{13}C NMR (75 MHz, CDCl$_3$, 297 K): δ 59.0 (s, *C*H), 165.8 (s, *C*=O), 122.7–138.8 (s, *C*$_{\rm arom}$).

Synthesis of 2d. A solution of **1d** (0.76 g, 2.7 mmol) in 30 mL of diethyl ether was combined with a solution of Ni(PMe$_3$)$_4$ (0.97 g, 2.7 mmol) in diethyl ether (20 mL) at −78 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 h. During this period the pale yellow mixture turned brown-yellow. Then the brown-yellow mixture was stirred under 1 bar of CO for 16 h. The solution slowly turned blue, and a great deal of white powder was obtained. At this point the solution was filtered; freezing at 4 °C afforded 0.34 g of blue crystals of **3** (70.4%). The white powder was purified by recrystallization from THF, giving white cubic crystals of **2d** (yield 0.35 g, 46%). Mp: >200 °C. IR (Nujol mull, cm^{-1}): 1712, ν(C=O). ^{1}H NMR (300 MHz, CDCl$_3$, 297 K): δ 6.56 (s, 1H, C*H*N), 5.57 (s, 1H, C*H*N), 6.03–7.54 (m, 14H, C*H*$_{\rm arom}$). ^{13}C NMR (75 MHz, CDCl$_3$, 297 K): δ 60.4 (s, *C*H), 61.7 (s, *C*H), 168 (s, *C*=O), 122.9–140.4 (s, *C*$_{\rm arom}$).

Preparation of 5d. A sample of Ni(PMe$_3$)$_4$ (0.97 g, 2.67 mmol) in 30 mL of diethyl ether was combined with a solution of **1d** (0.76 g, 2.67 mmol) in diethyl ether (20 mL) at −80 °C. The reaction mixture was warmed to ambient temperature and stirred for 18 h to form a brown-yellow solution. The volatiles were removed in vacuo, and the resulting solid was extracted with pentane (60 mL). Crystallization at 4 °C afforded brown-yellow crystals of **5d** suitable for X-ray diffraction analysis (yield 0.75 g, 56%), Mp: 125 °C. IR (Nujol mull, cm^{-1}): 1602, ν(C=N). ^{1}H NMR (300 MHz, C$_6$D$_6$, 297 K): δ 0.80 (br, 18H, PC*H*$_3$), 9.41 (s, 1H, C*H*=N), 6.59–7.71 (m, 8H, C*H*$_{\rm arom}$). ^{13}C NMR (75 MHz, C$_6$D$_6$, 297 K): δ 13.25 (d, $|^1J(\mathrm{PC}) + {}^3J(\mathrm{PC})| = 11.3$ Hz, P*C*H$_3$), 166.3 (s, *C*H=N), 120.1–148.8 (s, *C*$_{\rm arom}$). ^{31}P NMR (121 MHz, C$_6$D$_6$, 295 K): δ −21 (s, *P*CH$_3$).

Crystal Data. Data for **2a**: C$_{18}$H$_{14}$Cl$_2$N$_2$O$_2$, $M_r = 361.21$, crystal dimensions 0.36 × 0.30 × 0.18 mm, monoclinic, space group $P2_1/c$, $a = 9.780(3)$ Å, $b = 11.512(3)$ Å, $c = 14.451(4)$ Å, $\beta = 100.518(4)°$, $V = 1599.6(8)$ Å^3, $T = 273(2)$ K, $Z = 4$, $D_c = 1.500$ g cm^{-3}, $\mu = 0.419$ mm^{-1}, Bruker AXS SMART APEX. A total of 9957 reflections were collected; 4095 were unique ($R_{\rm int}$ =

---

(16) Klein, H.-F.; Dal, A.; Jung, T.; Flörke, U.; Haupt, H-J. *Eur. J. Inorg. Chem.* **1998**, 2027–2032.

(17) Klein, H.-F.; Karsch, H. H. *Chem. Ber.* **1972**, *105*, 2628–2636.

0.0217), with $\theta_{\max} = 29.19°$ and semiempirical correction. R1 = 0.0416 (for 4095 reflections with $I > 2\sigma(I)$); wR2 = 0.1097. The structure was solved by direct methods and refined with full-matrix least squares on all F^2 (SHELXL-97) with non-hydrogen atoms anisotropic. Data for **2c**: $C_{56}H_{36}C_{l4}N_4O_4$, M_r = 970.69, crystal dimensions 0.58 × 0.52 × 0.32 mm, triclinic, space group $P\bar{1}$, a = 7.7780(16) Å, b = 15.393(3) Å, c = 18.333(4) Å, α = 90.09(3)°, β = 90.05(3)°, γ = 92.15(3)°, V = 2193.4(8) Å^3, T = 293(2) K, Z = 2, D_c = 1.470 g cm^{-3}, μ = 0.327 mm^{-1}, Bruker AXS SMART APEX. A total of 11 451 reflections were collected; 8056 were unique (R_{int} = 0.0310), with $\theta_{\max}$ = 27.07° and semiempirical correction. R1 = 0.0536 (for 8056 reflections with $I > 2\sigma(I)$); wR2 = 0.1671. The structure was solved by direct methods and refined with full-matrix least squares on all F^2 (SHELXL-97) with non-hydrogen atoms anisotropic. Data for **2d**: $C_{28}H_{16}Cl_4N_2O_2$, M_r = 554.23, crystal dimensions 0.38 × 0.29 × 0.42 mm, monoclinic, space group $P2_1/n$, a = 10.919(2) Å, b = 15.313(3) Å, c = 15.812(3) Å, β = 109.94(3)°, V = 2485.4(9) Å^3, T = 293(2) K, Z = 4, D_c = 1.481 g cm^{-3}, μ = 0.507 mm^{-1}, Bruker AXS SMART APEX. A total of 19 241 reflections were collected,; 5387 were unique (R_{int} = 0.0270), with $\theta_{\max}$ = 27.07° and semiempirical correction. R1 = 0.0339 (for 5387 reflections with $I > 2\sigma(I)$); wR2 = 0.0892. The structure was solved by direct methods and refined with full-matrix least squares on all F^2 (SHELXL-97) with non-hydrogen atoms anisotropic. Data for **5d**: $C_{19}H_{26}Cl_3NNiP_2$, M_r = 495.41, crystal dimensions 0.36 × 0.25 × 0.15 mm, triclinic, space group $P\bar{1}$, a = 10.482(2) Å, b = 13.832(3) Å, c = 16.276(3) Å, α = 77.70(3)°, β = 82.19(3)°, γ = 89.95(3)°, V = 2283.3(8) Å^3, T = 273(2) K, Z = 4, D_c = 1.441 g cm^{-3}, μ = 1.345 mm^{-1}, Bruker AXS SMART APEX. A total of 14 669 reflections were collected; 9038 were unique (R_{int} = 0.0421), with $\theta_{\max}$ = 27.04° and semiempirical correction. R1 = 0.0347 (for 9038 reflections with $I > 2\sigma(I)$); wR2 = 0.1054. The structure was solved by direct methods and refined with full-matrix least squares on all F^2 (SHELXL-97) with non-hydrogen atoms anisotropic. CCDC-666539 (**2a**), CCDC-666538 (**2c**), CCDC-666535 (**2d**), and CCDC-666534 (**5d**) contain the supplementary crystallographic data for these compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgment. We gratefully acknowledge the support by the NSFC China Grant Nos. 20772072 and 20572062 and kind assistance from Prof. Dieter Fenske (TU Karlsruhe, Karlsruhe, Germany) for the X-ray diffraction analysis.

Supporting Information Available: Tables giving crystal data and figures giving NMR spectra for compounds **2a**,**c**,**d** and **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800049M