Extending the NHC Concept: C–C Coupling Catalysis by a Pd^{II} Carbene (*r*NHC) Complex with Remote Heteroatoms

Sabine K. Schneider,[a] Patric Roembke,[b] Gerrit R. Julius,[b] Christoph Loschen,[c] Helgard G. Raubenheimer,*[b] Gernot Frenking,*[c] and Wolfgang A. Herrmann*[a]

Keywords: Carbene ligands / C–C Coupling / Density functional calculations / Homogeneous catalysis

A palladium complex, *trans*-Cl(PPh$_3$)$_2$Pd{C^a-*cyclo*-C$_6$H$_4$-*o*-N(Me)C=C^{b}H}(C^a–C^b), that contains a carbene ligand with remote heteroatoms (*r*NHC) is much more active in certain C–C coupling reactions than comparably simple NHC- and phosphane-containing precatalysts. The *r*NHC ligand binds strongly by electrostatic as well as orbital interaction to the metal.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2005)

Carbon–carbon bond formation with palladium complexes as catalysts is a key step in the synthesis of organic chemicals, natural products as well as in a variety of industrial processes.[1–3] Important examples of such catalysis are found in the Suzuki and Heck reaction types.[4,5] Activity in this area is presently characterized by a search for new ligands and, not independent thereof, the collection of mechanistic information.[6] Phosphanes have been the ligands of choice and are still further investigated.[1,7] However, numerous studies have been undertaken in the recent past to overcome their limitations and replace them by ligands that afford stable compounds while avoiding unwanted side reactions and aiming at even increased activities.[8] Recent successes include the use of N-heterocyclic carbenes (NHC's) as ligands in the precursor complexes.[9–11]

Very few N-heterocyclic-coordinated carbene ligands with remote heteroatoms (*r*NHC's) are known[12] (related, but without remote heteroatoms are α-N carbenes derived from pyridine[13] or azoles[14]). The recent discovery of the exceptional stability and complex dynamics of such Pd^{II} and Pt^{II} compounds[15] encouraged a study to establish their potential use as precatalysts in coupling reactions. Herein we report on a series of comparative Mizoroki–Heck (M–H) and Suzuki–Miyaura (S–M) couplings that involve a number of phosphane and NHC complexes, and the cationic complex chloro(2-methoxy-*N*-methylquinolin-4-yl)-bis(triphenylphosphane)palladium(II) (**1**), that has been described in detail before.[15] A more meaningful comparison of competitive activities with the most effective systems in the literature, will only be possible after steric effects have been incorporated into **1** and other *r*NHC ligands. In this preliminary report we show that such ligand types certainly have potential as precatalysts and also describe a quantum mechanical comparison between NHC and *r*NHC model ligands and complexes. Descriptions of the ligand electronic structures as well as the metal–ligand bonding in NHC and the "newcomer" *r*NHC complex types are extracted from DFT calculations at the RI-BP86/SVP level.[16]

The catalyst precursors, all prepared according to standard procedures and screened for their activity and efficiency in well-known M–H and S–M reactions, are shown in Figure 1 and the results obtained in Table 1 and Table 2. These reactions do not represent troublesome couplings but

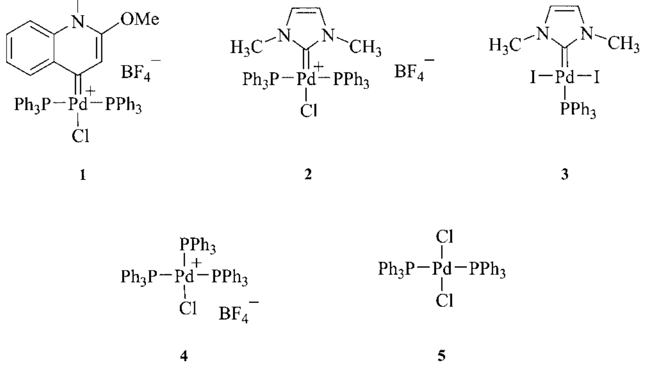


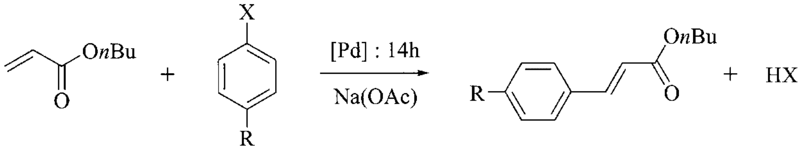
Figure 1. Precatalysts employed in C–C coupling reactions.

---

[a] Department of Chemistry, Technische Universität München,
Lichtenbergstr. 4, 85747 Garching, Germany
E-mail: wolfgang.herrmann@ch.tum.de
Fax: +49-89-289-13473
[b] Department of Chemistry and Polymer Science,
Private Bag X1, Matieland, Stellenbosch, South Africa
E-mail: hgr@sun.ac.za
Fax: +27-21-808-3849
[c] Fachbereich Chemie, Philips-Universität,
Hans-Meerweinstr, 35043 Marburg, Germany
E-mail: frenking@chemie.uni-marburg.de
Fax: +49-6421-282 5566

Supporting information for this article is available on the WWW under http://www.eurjic.org or from the author.

Table 1. Mizoroki–Heck reaction.



Entry[a]	R	mol-% Pd	Temp. [°C]	Catalyst	Conversion [%][b]	Yield [%][b]	TON [mol product (mol cat)$^{-1}$]
1	$C(O)CH_3$	0.01	130	**1**	>99.99	94	9400
2	$C(O)CH_3$	0.01	130	**3**	45	41	4100
3	$C(O)CH_3$	0.001	145	**1**	>99.99	94	94000
4	$C(O)CH_3$	0.0001	145	**1**	92	91	910000
5	$C(O)CH_3$	0.0001	145	**3**	8	6	60000
6	$C(O)CH_3$	0.5[c]	150	**1**	85	81	162
7	OCH_3	0.5	145	**1**	84	80	160
8[d]	H	0.1	145	**1**	>99.99	95	950
9	H	0.1	145	**2**	68	66	660
10	H	0.1	145	**3**	20	17	170
11	H	0.1	145	**4**	38	34	340
12	H	0.1	145	**5**	39	37	370
13	H	0.5[c]	150	**1**	64	55	110

[a] X = Br, except for **6** and **13**; ratio of aryl halide/olefin/NaOAc = 1:1.5:1.5; solvent: DMAc (dimethylacetamide). [b] GC yield and conversion using diethylene glycol/di-*n*-butyl ether as internal standard. [c] X = Cl; 0.2 mol-equiv. of $[R_4N]Br$ added to the reaction mixture. [d] For Entries 8–12 compare also Figure 2.

simple ones using relatively simple catalytic systems to allow a comparison on an electronic (and not steric) basis and to show that *r*NHC ligands deserve further attention. The data indicate clearly the superiority of the stable *r*NHC complex which gives relatively high conversions even at low concentration. Under the reported conditions TON's of 9.1×10^5 in the M–H and 3.2×10^6 in the S–M coupling are reached. Catalyst loading in the latter situation, however, is too low and affects the efficiency of the process. Arylchlorides couple successfully at 0.5% loading level of the *r*NHC complex according to M–H, and at 1.0% in the S–M reaction without any evidence of palladium black formation, even after stirring for 24 hours.

An even better picture of the relative catalyst activities emerged from the time-conversion curves in Figure 2 and Figure 3 determined under similar conditions for the two types of C–C coupling respectively.

The two sets of curves are remarkably similar,[10] and the *r*NHC complex, which requires no induction period, comes out on top of the chosen series again. Cationic charge (or alternatively, the number of phosphane ligands present) on the complex is not an important parameter for the halophosphane compounds **4** and **5**, but differentiate clearly between NHC complexes **2** and **3**.

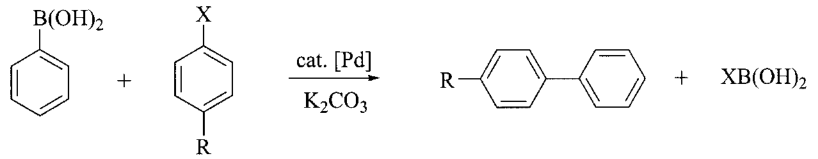
To better understand from a chemical viewpoint the reasons behind the relatively high activity of the *r*NHC complex in comparison with a simple cationic NHC complex, we theoretically analyzed their metal–carbene bonds. First, the geometries of the model compounds **1M** and **2M** with phenyl (on P) and methyl (on N and O) substituents replaced by hydrogen atoms, were optimized at the RI-BP86/SVP level.[16]

For this study the crystal and molecular structures of **2** – prepared similarly to **1**[15] (compare also ref.[17]) – were determined. Crystal data and calculated geometries are given as Supporting Information (for details see also the footnote on the first page of this article). The agreement between calculated and experimental bond lengths is quite good. Both methods indicate similar Pd–C(carbene) bond lengths, but a significantly larger *trans* influence is exhibited by the *r*NHC ligand (experimental Pd–Cl bond length 0.044 Å longer in **1** than in **2**)

We used different methods for extracting chemical bonding information in **1M** and **2M**. Figure 4 shows the most important frontier orbitals of the two simplified free carbene ligands *r*NHC and NHC. The σ-donor HOMO orbital in *r*NHC is 1.28 eV higher in energy than in NHC. HOMO-1, the highest-lying occupied π-orbital, has a much larger coefficient at the carbene C-atom in NHC than in *r*NHC affording a higher electron population at the C(carbene) p(π) AO in NHC (0.66) than in *r*NHC (0.53) which is disadvantageous for M–L π back donation in the former complex. The LUMO of NHC (not shown) is a π* orbital of the C=C double bond which has a node at the C(carbene) atom. The next low-lying π-acceptor orbital, LUMO+1, has a large coefficient at the C(carbene) p(π) AO. The π-acceptor LUMO of *r*NHC is lower in energy than the LUMO+1 of NHC but it is much more delocalized. The increase in the p(π) AO population on the carbene carbon atom of *r*NHC after formation of the complex **1M** ($\Delta q\pi$ = 0.28 e) is larger than in NHC ($\Delta q\pi$ = 0.20 e) and suggests that this ligand may also be a somewhat stronger π-acceptor than the latter species.

A deeper insight into the metal–carbene bonding situation results from an energy decomposition analysis (EDA)[17,19] of **1M** and **2M** (Table 3). The metal–carbene interactions in the *r*NHC carbene complex, **1M**, are significantly stronger (ΔE_{int} = –107.6 kcal/mol) than in **2M** (ΔE_{int} =

Table 2. Suzuki–Miyaura coupling.



Entry[a]	R	X	mol-% Pd	Catalyst	Time	Yield (%)[b]	TON [mol product. mol cat^{-1}]
1	$C(O)CH_3$	Br	0.0001	**1**	13 h	>99.99	1000000
2	$C(O)CH_3$	Br	10^{-5}	**1**	13 h	32	3200000
3	$C(O)CH_3$	Cl	1.0[c]	**1**	14 h	46	460
4	H	Br	0.01	**1**	13 h	>99.99	10000
5	H	Br	0.001	**1**	13 h	98	98000
6	H	Br	0.1	**1**	10 min	95	950
7	H	Br	0.1	**3**	10 min	16	160
8[d]	OCH_3	Br	0.1	**1**	13 h	>99.99	1000
9	OCH_3	Br	0.1	**2**	13 h	85	850
10	OCH_3	Br	0.1	**3**	13 h	32	320
11	OCH_3	Br	0.1	**4**	13 h	72	720
12	OCH_3	Br	0.1	**5**	13 h	77	770
13	OCH_3	Br	0.01	**1**	13 h	54	5400

[a] Ratio of aryl halide/phenylboronic acid/K_2CO_3 = 1:1.2:1.5; solvent: xylene; T = 130 °C. [b] GC yield using diethylene glycol/di-*n*-butyl ether as internal standard. [c] Cs_2CO_3 was used as base. [d] For Entries 8–12 compare also Figure 3.

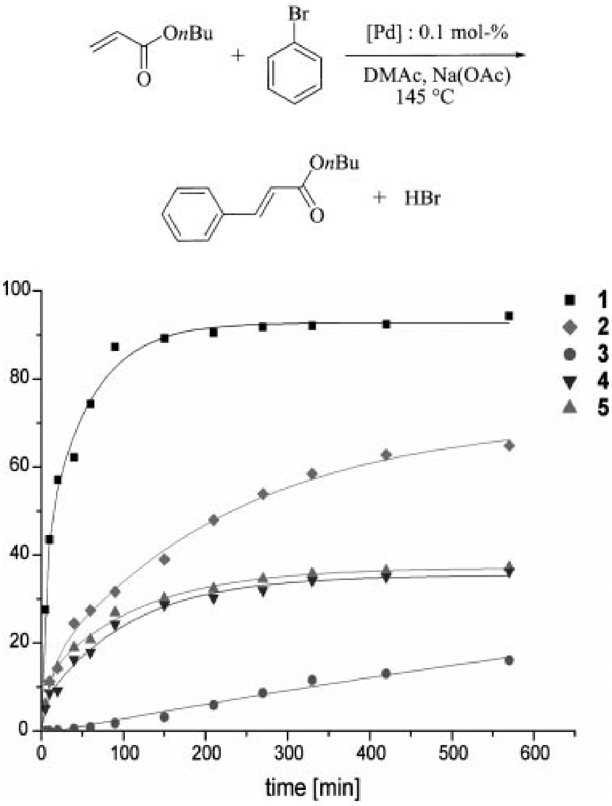


Figure 2. Time-conversion-curves: Mizoroki–Heck reaction.

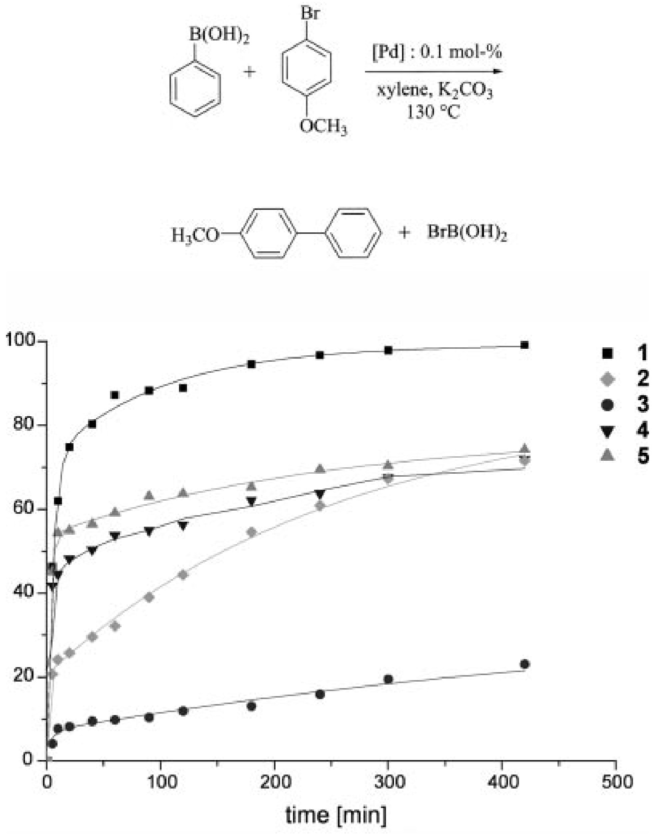


Figure 3. Time-conversion-curves: Suzuki–Miyaura reaction.

–85.5 kcal/mol). The rather small calculated geometry relaxation of the fragments (ΔE_{prep}) indicates that the former complex also has a bond dissociation energy of ca. 20 kcal/mol higher than the latter (also compare a related discussion involving other carbene complexes by one of us[20]).

The metal–carbene bonding in both complexes comes mainly from classical electrostatic interactions, ΔE_{elstat}, which contribute ca. 70% to the attractive forces.

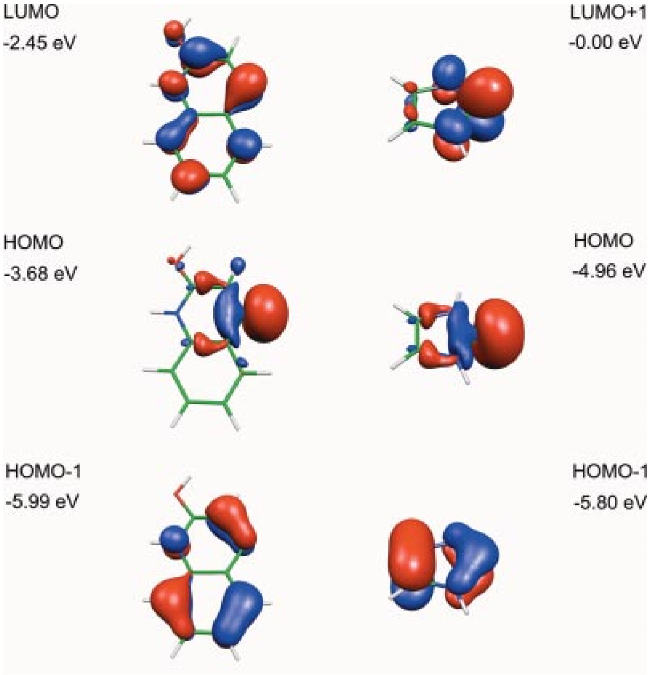


Figure 4. Frontier orbitals of the free model carbenes *r*NHC (left) and NHC (right).

Table 3. Energy decomposition analyses of **1M** and **2M**.[a]

	1M		**2M**	
ΔE_{int}	–107.6		–85.5	
ΔE_{Pauli}	184.9		157.9	
ΔE_{elstat}	–204.6	(69.9%)	–171.8	(70.6%)
ΔE_{orb}	–87.9	(30.1%)	–71.5	(29.4%)
a′	–72.8	(82.8%)	–60.4	(84.5%)
a′′	–15.1	(17.2%)	–11.1	(15.5%)
ΔE_{prep}	3.6		2.4	
$\Delta E = -D_e$	–104.0		–83.1	

[a] Energy given in kcal mol^{-1}.

The most interesting part of the EDA is the breakdown of the total orbital interaction term, ΔE_{orb}, into orbital contributions of different symmetry (Table 3). The EDA calculations of complexes **1M** and **2M** were carried out with C_s symmetry, which means that the strength of the σ-bonding is given by the a′ orbitals while π-bonding is given by the a′′ orbitals. The former contribution is clearly more important [72.8 kcal/mol (82.8%) in **1M** and 60.4 kcal/mol (84.5%) in **2M**] than π-bonding [15.1 kcal/mol (17.2%) in **1M** and 11.1 kcal/mol (15.5%) in **2M**].

In conclusion, this study, using palladium as central metal, has shown that a carbene-type ligand with no heteroatom in the immediate vicinity of the carbon donor atom activates the metal centre significantly more than comparable simple N-heterocyclic carbenes. No serious dichotomy arises when Heck- and Suzuki-type conversions are compared. The exceptionally strong metal–carbene bond in such a complex – as determined by quantum chemical DFT calculations – is mainly due to very strong metal–ligand electrostatic attraction as well as an energetically higher-lying σ-HOMO on the ligand that overlaps well and donates electrons readily.

All our results are in accordance with an *r*NHC ligand that remains attached to the central metal during the catalytic cycle and indicate that catalytic activity could be increased by further ligand tailoring, especially an increase in steric bulk.[11,21] Finally we anticipate that this work will provide an impetus for further study and that the new class of ligands will find application in other important catalytic processes and should, individually, be considered as useful alternatives to NHC′s as we shall show in future reports.

Experimental Section

The preparation of the catalyst precursor complex **2** is described in the Supporting Information, **3**[11a] as well as **4**[22] were prepared according to literature procedures and **5** is commercially available.

Heck Reaction: A constant ratio of sodium acetate (3.00 mmol, 246 mg) and aryl halide (2.00 mmol, e. g. 315 mg bromobenzene) as well as 100 mg diethylene glycol/di-*n*-butyl ether were placed in a Schlenk tube equipped with a stirring bar under argon. Then 3.00 mmol of *n*-butyl acrylate (0.43 mL) and 2 mL degassed DMAc were added. After 10 min at the desired temperature, the catalyst solution was added against a positive stream of argon. To terminate the reaction the mixture was allowed to cool to room temperature and 3 mL of aqueous HCl added. The water phase was extracted thrice with 2 mL of dichloromethane and the organic fraction dried with $MgSO_4$. Conversions and yields were determined by GC-MS using diethylene glycol/di-*n*-butyl ether as internal standard.

Suzuki Reaction: Phenylboronic acid (2.40 mmol, 293 mg) and potassium carbonate (3.00 mmol, 415 mg) were placed in a Schlenk tube equipped with a stirring bar under argon. Aryl halide (2.00 mmol; e. g. 374 mg bromoanisole), 100 mg diethylene glycol/di-*n*-butyl ether and 2 mL degassed xylene were added. After thermostating at 130 °C for 10 min, the catalyst solution was added against a positive stream of argon. To end the reaction, the mixture was cooled to room temperature and 3 mL of water added. The water phase was extracted three times with 2 mL of diethyl ether and the organic phases dried with $MgSO_4$.

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie (SKS), the NRF (PR) and Sasol Technologies (GRJ).

---

[1] W. A. Herrmann, in: *Applied Homogenous Catalysis with Organometallic Compounds*, (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1996**, vol. 1 and 2, p. 712.

[2] a) H. Geisler, in *Transition Metals for Organic Synthesis*, vol. 1 (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, vol. 1, p. 158; b) F. Diederich, P. J. Stang (Eds.), *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.

[3] a) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **1995**; b) L. Brandsma, S. F. Vasilevsky, H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer, Berlin, **1998**.

[4] a) N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866; b) N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; d) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[5] a) T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; b) R. F. Heck, J. P. Nolley Jr., *J. Org. Chem.* **1972**, *37*,

2320; c) A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2473; d) M. Shibasaki, E. M. Vogl, *J. Organomet. Chem.* **1999**, *576*, 1.

[6] U. Christmann, R. Vilar, *Angew. Chem. Int. Ed.* **2005**, *44*, 366 and references cited therein.

[7] a) F. Ozawa, in: S. Komiya (Ed.), *Synthesis of Organometallic Compounds*, Wiley, Sussex, **1997**, p. 249; b) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

[8] V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553.

[9] a) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889; b) L. Xu, W. Chen, J. Xiao, *Organometallics* **2000**, *19*, 1123; c) W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290 and references therein; d) W. A. Herrmann, K. Öfele, D. v. Preysing, S. K. Schneider, *J. Organomet. Chem.* **2003**, *687*, 229 and references cited therein.

[10] a) I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178; b) P. W. N. van Leeuwen, *Homogenous Catalysis Understanding the Art*, Kluwer Academic Publishers, Dordrecht, **2004**, p. 271 and references cited therein.

[11] a) W. A. Herrmann, V. P. W. Böhm, C. W. K. Gstöttmayr, M. Grosche, C.-P. Reisinger, T. Weskamp, *J. Organomet. Chem.* **2001**, *617*, 616; b) H. Palencia, F. Garcia-Jimenez, J. M. Takacs, *Tetrahedron Lett.* **2004**, *45*, 3849.

[12] H. G. Raubenheimer, M. Desmet, P. J. Olivier, G. J. Kruger, *J. Chem. Soc. Dalton Trans.* **1996**, 4431.

[13] a) H. G. Raubenheimer, J. G. Toerien, G. J. Kruger, R. Otte, W. van Zyl, P. Olivier, *J. Organomet. Chem.* **1994**, *466*, 291; b) J. S. Owen, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **2004**, *126*, 8247.

[14] X. Li, L. N. Appelhans, J. W. Faller, R. H. Crabtree, *Organometallics* **2004**, *23*, 3378.

[15] a) W. H. Meyer, M. Deetlefs, M. Pohlmann, R. Scholz, M. W. Esterhuysen, G. R. Julius, H. G. Raubenheimer, *Dalton Trans.* **2004**, 413.

[16] The calculations were carried out using the program package TURBOMOLE: a) R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165; b) O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346; c) Becke–Perdew (BP86) exchange-correlation functional and Resolution-of-the-Identity-Approximation (RI): S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200; d) J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822; e) D. Becke, *Phys. Rev. A* **1988**, *38*, 3098; Erratum:J. P. Perdew, *Phys. Rev. B* **1986**, *34*, 7406; f) K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Lett.* **1995**, *242*, 652; g) For the calculations an SVP basis set was used:A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571.

[17] A. Fürstner, G. Seidel, D. Kremzow, C. W. Lehmann, *Organometallics* **2003**, *22*, 907.

[18] The EDA calculations have been performed using the program package ADF: a) F. M. Bickelhaupt, E. J. Baerends, *Rev. Comput. Chem.* (Eds.: K. B. Lipkowitz, D. B. Boyd), Wiley-VCH, New York, **2000,** vol. 15, p. 1; b) G. te Velde, F. M. Bickelhaupt, E. J. Baerends, S. J. A. van Gisbergen, C. Fonseca Guerra, J. G. Snijders, T. Ziegler, *J. Comput. Chem.* **2001**, *22*, 931. The calculations have been carried out at the BP86 level [16c–e] using uncontracted Slater-type orbitals (STOs) as basis functions: c) J. G. Snijders, E. J. Baerends, P. Vernooijs, *At. Nucl. Data Tables* **1982**, *26*, 483; The basis sets have TZP quality. An auxiliary set of s, p, d, f and g STOs was used to fit the molecular densities and to represent the Coulomb and exchange potentials accurately in each SCF cycle; d) J. Krijn, E.J. Baerends, *Fit Functions in the HFS-Method*, Internal Report (in Dutch), Vrije Universiteit Amsterdam, The Netherlands, **1984**.

[19] For a review of EDA results on bonding in transition metal complexes see: G. Frenking, K. Wichmann, N. Fröhlich, C. Loschen, M. Lein, J. Frunzke, V. M. Rayón, *Coord. Chem. Rev.* **2003**, *238*, 55.

[20] M. Lein, A. Szabó, A. Kovács, G. Frenking, *Faraday Discuss.* **2003**, 365.

[21] a) T. Weskamp, V. P. W. Böhm, W. A. Herrmann, *J. Organomet. Chem.* **1999**, *585*, 348; b) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **1999**, *38*, 2411; c) J. P. Wolfe, S. L. Buchwald, *Angew. Chem. Int. Ed. Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2413; d) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020; e) T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Org. Lett.* **2000**, *2*, 1729.

[22] E. P. Urriolabeita, *J. Chem. Educ.* **1997**, *74*, 325.

Received: April 14, 2005

Published Online: June 28, 2005

© 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim