Tetrahedron Letters 52 (2011) 5995–5999

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

5,5-Diaryldipyrromethanes: syntheses and anion binding properties

K. C. Gowri Sreedevi [a], Ajesh P. Thomas [d], P. S. Salini [a], S. Ramakrishnan [a], K. S. Anju [a], M. G. Derry Holaday [a], M. L. P. Reddy [b,*], C. H. Suresh [c,*], A. Srinivasan [d,*]

[a] *Photosciences and Photonics Section, National Institute for Interdisciplinary Science and Technology (NIIST-CSIR), Thiruvananthapuram 695 019, Kerala, India*
[b] *Inorganic Chemistry Section, Chemical Sciences and Technology Division, National Institute for Interdisciplinary Science and Technology (NIIST-CSIR), Thiruvananthapuram 695 019, Kerala, India*
[c] *Computational Modeling Simulation Section, Process Engineering and Environmental Technology Division, National Institute for Interdisciplinary Science and Technology (NIIST-CSIR), Thiruvananthapuram 695 019, Kerala, India*
[d] *School of Chemical Sciences, National Institute of Science Education and Research (NISER), Bhubaneswar 751 005, Orissa, India*

ARTICLE INFO

Article history:
Received 2 August 2011
Revised 26 August 2011
Accepted 29 August 2011
Available online 2 September 2011

Keywords:
Dipyrromethane
Pyrrole-2-carbinol
Grignard reagent
Anion binding

ABSTRACT

A two-step synthesis of 5,5-diaryldipyrromethanes in good yields is described. The adopted synthetic strategy can be used to tune the substituent at the *meso*-carbon very easily by choosing the Grignard reagent of interest. Further, the influence of the incorporation of various diaryl units at the *meso*-carbon atom in the inherent anion binding affinities of the dipyrromethanes through hydrogen bonding was discussed.

meso-Aryldipyrromethanes are frequently synthesized as precursors to *normal*, *expanded*, *contracted*, and *hybrid* porphyrins.[1] Also, the boron difluoride complexes of dipyrromethenes, which is the oxidized form of dipyrromethane, known as BODIPY dyes, have found importance as fluorescent dyes for biological samples.[2] Compared to the *meso*-aryldipyrromethanes[1] and *meso*-dialkyldipyrromethanes,[3] the chemistry of *meso*-diaryldipyrromethanes are not well established due to the presence of *meso*-H in the former and steric stability involved in the latter. However, the title compounds were found to have potential application in the *normal* and *expanded* calixpyrrole synthesis.[4] The dianionic form of these compounds are widely used to stabilize the highly reactive low valent lanthanide metals and increase the reactivity of the metal center.[5] The similar chemistry is further extended to the transition metals.[6]

The synthesis of this molecule was initiated in 1998, when Eichen and co-workers reported a general methodology to synthesize such dipyrromethanes where pyrrole and the ketone (benzophenone/di-(2-pyridyl) ketone/9-fluorenone) are mixed in the ethanol medium in 2:1 ratio and allowed to react in the presence of $BF_3{\cdot}OEt_2$ as an acid-catalyst for a week to afford the respective dipyrromethanes in 39% yield.[7] Later, the same group modified the procedure by reducing the reaction time from a week to 5 days, under similar conditions with overall yield of 50%.[4a]

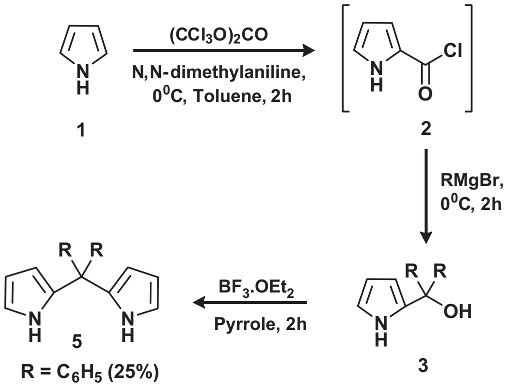
These two reaction conditions were recently further modified by Gambarotta and co-workers, where 1:1 ratio of pyrrole and benzophenone were mixed in 99% ethanol solution, in the presence of methanesulphonic acid as catalyst and allowed to reflux at 60–70 °C for 4 h resulting in 13% yield.[5c] Overall, depending on the reaction time and the acid-catalyst used, the observed yield is from 13% to maximum 50% only. Herein, we wish to report a two-step synthesis for *meso*-diaryldipyrromethanes, which offers promising yield in a comparatively very short reaction time. Further, we examined the influence of the incorporation of various diaryl units at the *meso*-carbon in the inherent anion binding properties of the dipyrromethanes.

Our initial synthetic strategy to obtain **5** is shown in Scheme 1, which starts with the synthesis of diaryl pyrrole-2-carbinol (**3**). Even though, the mono aryl pyrrole carbinols[8] are well known precursors for the porphyrin synthesis, the synthesis of diaryl substituted pyrrole-2-carbinols are quite rare in the literature.[9] We achieved this through nucleophilic addition of the Grignard reagent to pyrrole-2-acid chloride. Pyrrole (**1**) reacts with triphosgene in the presence of *N*,*N*-dimethylaniline afforded the corresponding acid chloride **2**. Excess amount (5 equiv) of freshly prepared phenylmagnesium bromide is added in situ at 0 °C to generate **3** in 15% yield. Without further purification, **3** was treated with excess amount (25 equiv) of pyrrole in the presence of

---

* Corresponding authors. Tel.: +91 674 230 4077; fax: +91 674 230 2436 (A.S.).
E-mail address: srini@niser.ac.in (A. Srinivasan).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.08.163



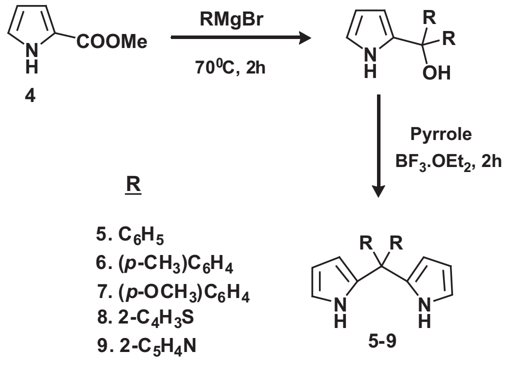
Scheme 1. Synthesis of diphenyldipyrromethane.

$BF_3{\cdot}OEt_2$ as an acid-catalyst, followed by column chromatographic purification afforded the target molecule in 25% yield.

Although Scheme 1 provides a strategic route toward the synthesis of **5**, where we were able to decrease the reaction time interval from 5 days to 6 h, but, without much improvement in the yield as reported earlier. Alternative attempt to increase the yield was successful, which is summarized in Scheme 2.

In the modified synthetic methodology, the precursor **3** was achieved from the readily available and stable pyrrole derivative, pyrrole-2-ester (**4**) which reacts with phenylmagnesium bromide to afford **3** in a quantitative yield. The precursor **3** was further subjected to the acid-catalyzed condensation with pyrrole. Interestingly, the addition of the acid-catalyst, $BF_3{\cdot}OEt_2$, resulted in immediate precipitation. The precipitate was collected, washed with 0.1 N NaOH, and then water successfully afforded the *meso*-diphenyldipyrromethane (**5**) in 82% yield. Generalization of this synthetic methodology was tested by incorporating other diaryl groups at the *meso*-carbon such as tolyl, anisoyl, 2-thienyl, and 2-pyridyl just by using the appropriate Grignard reagent of interest as shown in Scheme 2. The yields of **5**–**9** are mentioned in Table 1. In the case of **8** and **9**, the reaction was completed after 2 h and also, the final compounds did not precipitate out; hence, the column chromatography was required to purify the compounds. However, the generality of the reaction depends on, how feasible the formation of particular Grignard reagent, hence introduction of electron withdrawing group like nitrobenzene at the *meso*-carbon was not successful due to the difficulty in making the corresponding Grignard reagent.

All the compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and FAB mass spectrometry. The final confirmation has come from the single crystal X-ray analysis of **7**, which is shown in the Figure 1.[10] The good quality single crystals were grown by slow evaporation of *n*-hexane into CH_2Cl_2 solution of **7**. As predicted from the spectral analyses, two pyrrole and two anisoyl units are connected through the *meso*-carbon atom where the NH proton of the pyrrole rings are pointing toward opposite direction. The angles between α-carbon of the pyrrole ring and the aryl carbon atom which are connected through the *meso*-sp^3 carbon atom are: 112.9° and 108.2° (Fig. 1b), respectively, with the mean value of 110.6° suggests that the geometry around the *meso*-sp^3 carbon atom is slightly deviated from the regular tetrahedral environment. The difference in the deviation may be due to the steric factor that arose from the bulky anisole groups at the *meso*-carbon. In addition to the self-assembled dimer,[11] the pyrrolic NHs are in intermolecular hydrogen bonding interaction with phenylic π-clouds of the adjacent molecule to generate the one-dimensional supramolecular array in the solid state with the distance 2.94 Å and angle of 144° as shown in Figure 1c.



Scheme 2. Syntheses of 5,5-diaryldipyrromethanes.

Table 1
Yields of **5**–**9**

Compound	R	Yield (%)	Lit. yield (%)	Mp (°C)
5	C_6H_5	82	50[4a]	263
6	$(p\text{-}CH_3)C_6H_4$	80	–	220
7	$(p\text{-}OMe)C_6H_4$	65	–	175
8	$2\text{-}C_4H_3S$	38	–	154
9	$2\text{-}C_5H_4N$	32	35[7]	165

The anion recognition properties of diaryldipyrromethanes with a wide variety of anions such as halides, oxoanions, etc. were investigated by means of ^{1}H NMR titration technique in CD_3CN at room temperature.[11] In all cases, binding affinities were monitored by the complexation induced shifts of the NH resonance of pyrrole upon addition of anions as their tetrabutylammonium salts.

As a representative example, Figure 2 summarizes the changes in the chemical shift values of NH proton of **7** with various anions. Addition of one equivalent of fluoride ion showed a remarkable downfield shift of NH signal ($\Delta\delta = 4.53$ ppm), while the addition of benzoate and dihydrogen phosphate anions also caused downfield shift of the NH protons ($\Delta\delta = 1.52$ ppm and $\Delta\delta = 0.83$ ppm, respectively), but only to a much smaller extent as compared to fluoride ion. The other anions offered a very weak or almost no interactions.

The titration profile showed in Figure 3, explains the pronounced changes observed in the NMR spectrum of **6** by the addition of fluoride ion. The signals correspond to the pyrrolic NH protons originally appeared at 8.69 ppm were deshielded to 13.37 ppm by the addition of 1 equiv of F^- anion with a difference of 4.68 ppm which indicates a strong interaction of F^- ion with NH proton through hydrogen bonding. Further addition of anion does not make much change in the chemical shift value of NH proton, giving an impression of 1:1 binding mode with the anion. The α-CH proton of pyrrole near to the binding site, at first, experienced an upfield shift up to 0.5 equiv of anion from 6.72 to 6.65 ppm, and then shifted back to 6.72 ppm, finally merging with the phenyl protons. At the same time, the two β-CH protons and the phenyl CH protons underwent a reasonable upfield shift (0.19 and 0.35 ppm for pyrrolic CH; 0.05 and 0.21 ppm for phenyl CH) which, possibly due to the electronic perturbation experienced by the system due to the anion moiety through bond and space, respectively.

Further, the binding affinities of compounds **5–9** toward F^- ion along with $C_6H_5COO^-$ and $H_2PO_4^-$ ions are investigated. The presence of two basic pyridyl groups enhances the deprotonation of NH proton during the addition of F^- ion eventually restricts any binding studies with compound **9**.[11] Even though the NMR titration experiments supports 1:1 binding, continuous downfield shift of the NH protons with increase in the F^- concentration eliminates

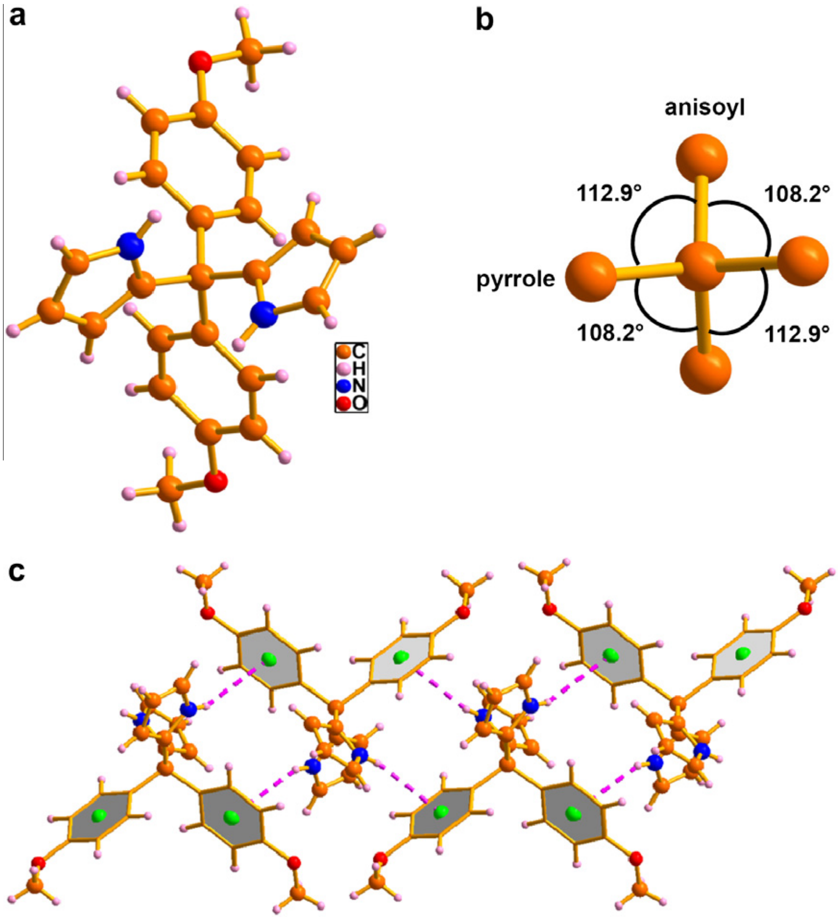


Figure 1. Single crystal X- ray structure of **7** with one-dimensional array.

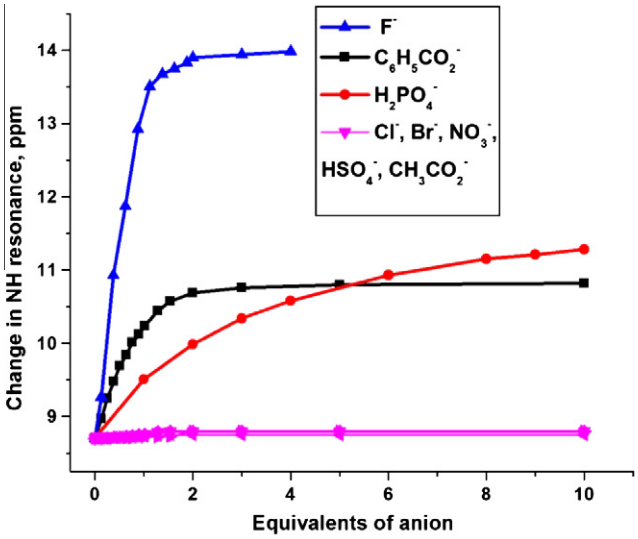


Figure 2. Variation of NH resonance for **7** with different anions in CD_3CN at 298 K.

the chance to determine the exact ratio of binding through the Job plot as shown by the representative example **7**.[11] This continuous shift in the NH resonance may indicate the presence of multiple equilibria with higher F^- ion concentration.[12]

To clarify the binding mode of **7** with F^-, density functional theory (DFT) calculations have been done using *Gaussian 03*[13] at the MPWB1K/6-31+G (d,p) level[14] for the possible modes of complexation of **5–8** with fluoride anion like 1:1, 1:2, and 2:1.[11] Polarizable continuum model[15] was incorporated in the DFT calculation to provide solvation effect of the acetonitrile.

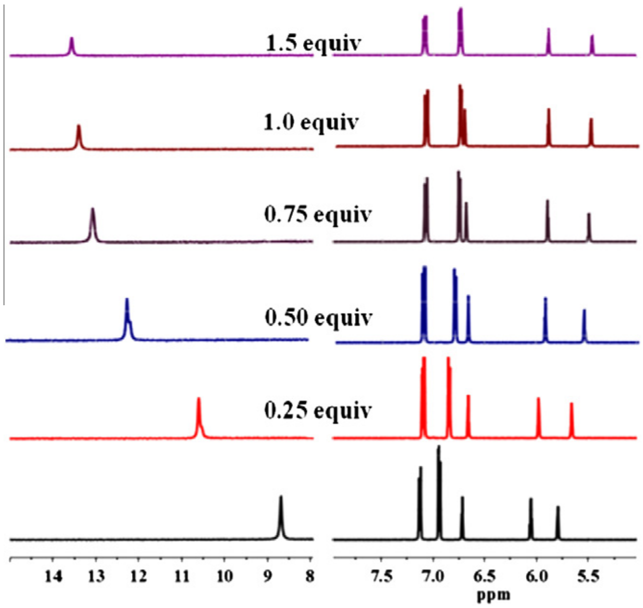


Figure 3. ^1H NMR spectra of 6 with addition of fluoride ions.

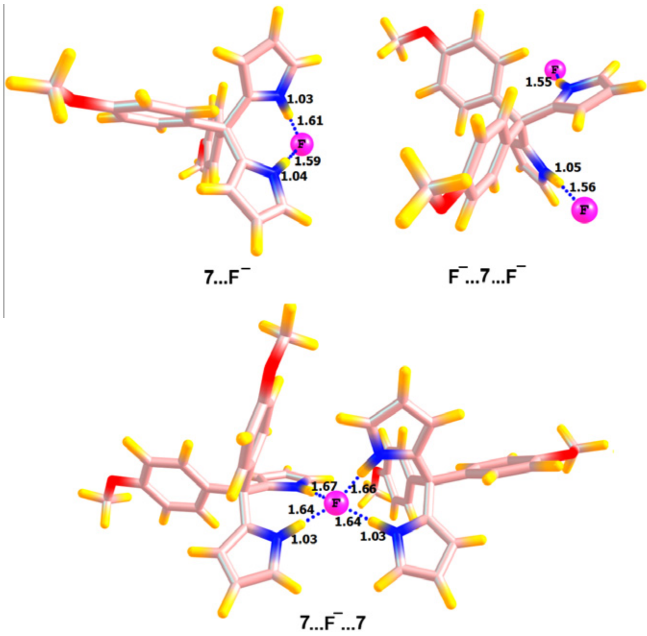


Figure 4. Optimized geometry for 1:1, 1:2 and 2:1 complexes of **7** and F⁻. All bond lengths are given in Å.

Table 2
The binding constants [M^{-1}] of **5–9** in CD_3CN at 298 K

Compound	F⁻	$C_6H_5COO^-$	$H_2PO_4^-$
5	61	16	13
6	37	12	10
7	17	<10	<10
8	36	14	12
9	—[a]	—[b]	—[b]

[a] Could not be obtained due to deprotonation.
[b] No binding. Errors estimated to be within ±5%.

The binding energy for the different modes are calculated by taking **7** as a model compound and the value obtained is 15.3, 12.3, and 9.9 kcal/mol for 1:1, 1:2, and 2:1 modes of binding, respectively. Even though the values obtained for 1:1 and 1:2 complexes are comparable, calculation of binding energy per fluoride in 1:2 complex is only 6.15 kcal/mol which is less than half of the 1:1 complex. Further, entropy will favor more the formation of 1:1 complex than three component 1:2 or 2:1 complexes. Optimized structures of 1:1, 1:2, and 2:1 modes are given in Figure 4. The association constants were calculated for all the 1:1 complexes using Benesi Hildebrand equation and summarized in Table 2.

The binding constants calculated for compound **5–8** with F⁻ ion are lower compared to the dialkyl and monoaryldipyrromethanes (170 M^{-1}),[16] and is expected by considering the stronger repulsive interaction between the anion and the two aryl rings, where as the binding constants with the oxoanions are found to be too low. The observed decrease in the binding constants from **5–7** with F⁻ can be correlated with the increased positive inductive effect from phenyl to anisoyl group, which strongly affects the π-cloud of the system with an increase in the electron density, thereby destabilizing the hydrogen bond formed by F⁻ with NH of pyrrole.

In conclusion, we have demonstrated a two-step synthesis of *meso*-diaryldipyrromethanes by using easily available and stable precursor in comparatively shorter reaction time with high yield. The synthetic methodology adopted here is simple and straightforward due to the absence of side products and hence easier for purification. Also, we could tune the functional groups at the *meso*-carbon just by altering the Grignard reagent of interest. Further, the anion binding abilities of these compounds were evaluated, which shows relatively high binding affinity toward fluoride ions with respect to the other anions analyzed. The role of diaryl functionality at the *meso*-position of the dipyrromethane in the binding process is discussed, which can influence the design of novel macrocycles and supramolecular systems in future. Work is currently underway in this direction in our group.

Acknowledgments

Dr. A.S. thanks DST, New Delhi and NWP-23 for the financial support. K.C.G.S. thanks CSIR for the fellowship. We thank Dr. C. S. Purohit, Faculty, SCS, NISER-Bhubaneswar for solving the crystal structure of **7**. We gratefully acknowledge Viji and Adarsh, NIIST-CSIR, for recording the FAB and NMR spectra.

Supplementary data

Supplementary data (experimental procedures, ^1H, ^{13}C and FAB mass spectra for all the new compounds, crystal data for **7** in CIF format, Anion Binding studies of **5–8**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.163.

References and notes

1. (a) Kadish, K. M.; Smith, K. M.; Guilard, R. *The Porphyrin Handbook. Vol. 1: Synthesis and Organic Chemistry and Vol. 2: Heteroporphyrins, Expanded Porphyrins and Related Macrocycles*; Academic Press: New York, 2000; (b) Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427–11440; (c) Sessler, J. L.; Tomat, E. *Acc. Chem. Res.* **2007**, *40*, 371–379.
2. (a) Zeng, L.; Miller, E. W.; Pralle, A.; Isacoff, E. Y.; Chang, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 10–11; (b) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891–4932; (c) Ulrich, G.; Ziessel, R.; Harriman, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1184–1201; (d) Miao, Q.; Shin, J.-Y.; Patrick, B. O.; Dolphin, D. *Chem. Commun.* **2009**, 2541–2543.
3. (a) Sobral, A. J. F. N.; Rebanda, N. G. C. L.; da Silva, M.; Lampreia, S. H.; Silva, M. R.; Beja, A. M.; Paixão, J. A.; Gonsalves, A. M. R. *Tetrahedron Lett.* **2003**, *44*, 3971–3973; (b) Gao, G. H.; Lu, L.; Gao, J. B.; Zhou, W. J.; Yang, J. G.; Yu, X. Y.; He, M. Y. *Chin. Chem. Lett.* **2005**, *16*, 900–902; (c) Sobral, A. J. F. N. *J. Chem. Educ.* **2006**, *83*, 1665–1666; (d) Zhang, Y.; Liang, J.; Shang, Z. *Chin. J. Chem.* **2010**, *28*, 259–262.
4. (a) Turner, B.; Shterenberg, A.; Kapon, M.; Suwinska, K.; Eichen, Y. *Chem. Commun.* **2001**, 13–14; (b) Turner, B.; Shterenberg, A.; Kapon, M.; Suwinska, K.; Eichen, Y. *Chem. Commun.* **2002**, 404–405.
5. (a) Dubé, T.; Gambarotta, S.; Yap, G. P. A.; Conoci, S. *Organometallics* **2000**, *19*, 115–117; (b) Ganesan, M.; Gambarotta, S.; Yap, G. P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 766–769; (c) Freckmann, D. M. M.; Dubé, T.; Bérubé, C. D.; Gambarotta, S.; Yap, G. P. A. *Organometallics* **2002**, *21*, 1240–1246; (d) Arunachalampillai, A.; Crewdson, P.; Korobkov, I.; Gambarotta, S. *Organometallics* **2006**, *25*, 3856–3866.
6. (a) Novak, A.; Blake, A. J.; Wilson, C.; Love, J. B. *Chem. Commun.* **2002**, 2796–2797; (b) Gao, G.; Korobkov, I.; Gambarotta, S. *Inorg. Chem.* **2004**, *43*, 1108–1115; (c) Nikiforov, G. B.; Crewdson, P.; Gambarotta, S.; Korobkov, I.; Budzelaar, P. H. M. *Organometallics* **2007**, *26*, 48–55; (d) Vidyaratne, I.; Crewdson, P.; Lefebvre, E.; Gambarotta, S. *Inorg. Chem.* **2007**, *46*, 8836–8842.
7. Turner, B.; Botoshansky, M.; Eichen, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2475–2478.
8. (a) Volz, H.; Schäffer, H. *Chem. Zeit.* **1985**, *109*, 308; (b) Volz, H.; Hassler, M.; Schäffer, H. *Z. Naturforsch.* **1986**, *41b*, 1265–1272; (c) Volz, H.; Hassler, M. *Z. Naturforsch.* **1988**, *43b*, 1043–1052.
9. Hafner, K.; Pfeiffer, K. *Tetrahedron Lett.* **1968**, *9*, 4311–4314.
10. Crystal data for **7** (from CH_2Cl_2/hexane): $C_{23}H_{22}N_2O_2$, M_w = 358.43, monoclinic, a = 15.328, b = 11.964, c = 12.157 Å, α = 90.00, β = 122.03, γ = 90.00°, V = 1890.0 $Å^3$, T = 293 (2) K, space group C12/C1, Z = 4, D_c = 1.260 mg/m^3, μ(Mo-Kα) = 0.081 mm^{-1}, 17159 reflections collected, 2340 unique (R_{int} = 0.0312), R_1 = 0.0523, wR_2 = 0.1363, GOF = 1.093 {$I > 2\sigma(I)$}.
11. See the Supplementary data.
12. Coles, S. J.; Frey, J. G.; Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Navakhun, K.; Thomas, G. L. *Chem. Commun.* **2003**, 568–569.
13. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, J. T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.;

Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision E.01; Gaussian Inc.: Wallingford CT, 2004.

14. Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908–6918.
15. Mennucci, B.; Cammi, R.; Tomasi, J. *J. Chem. Phys.* **1999**, *110*, 6858–6870.
16. Alešković, M.; Basarić, N.; Majerski, K. M.; Molćanov, K.; Prodić, B. K.; Kesharwani, M. K.; Ganguly, B. *Tetrahedron* **2010**, *66*, 1689–1698.