Journal of Fluorine Chemistry 131 (2010) 1182–1186

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Substitution of hydroxide by fluoride at the boron center of a BODIPY dye

Todd W. Hudnall, Tzu-Pin Lin, François P. Gabbaï *

Department of Chemistry, Texas A&M University, College Station, TX 77843, United States

ARTICLE INFO

Article history:
Received 9 April 2010
Received in revised form 15 June 2010
Accepted 15 June 2010
Available online 23 June 2010

This paper is dedicated to Russ Hughes in honor of his ACS Award for Creative Work in Fluorine Chemistry.

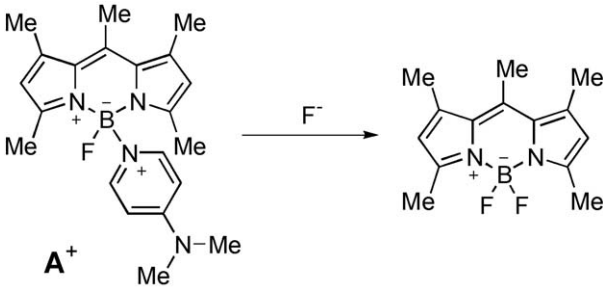
Keywords:
Fluoride
BODIPY
Fluorination
Fluorescence
Sensing
Dye

ABSTRACT

4-Chloro-4-phenyl-1,3,5,7,8-pentamethyl-3a,4a-diaza-4-bora-s-indacene (**2**) has been synthesized, structurally characterized and converted into the corresponding hydroxide derivative 4-hydroxo-4-phenyl-1,3,5,7,8-pentamethyl-3a,4a-diaza-4-bora-s-indacene (**3**). This boron hydroxide derivative reacts with fluoride anions under acidic conditions to afford the corresponding fluoride derivative 4-fluoro-4-phenyl-1,3,5,7,8-pentamethyl-3a,4a-diaza-4-bora-s-indacene (**4**). This simple reaction may become useful for the incorporation of [^{18}F]-fluoride and may serve for the preparation of radiolabeled BODIPY derivatives.

1. Introduction

The coordination of fluoride anions to boron compounds has attracted a great deal of interest because of its implication in the field of anion sensing [1–5] and molecular imaging by [^{18}F]-positron emission tomography [6–8]. As part of our contribution to the general area of fluoride ion coordination to boron compounds, we have recently reported that cationic BODIPY compounds [9,10] such as $\mathbf{A}^+$ react with fluoride anions in $CHCl_3$ to afford the corresponding BODIPY difluoride species [11]. Presumably, this reaction is facilitated by the lability of the DMAP ligand as well as the overall positive charge of $\mathbf{A}^+$. We have now decided to determine if similar fluorination reactions could also be observed starting from a neutral BODIPY bearing a labile group. In this paper we report on a fluoride for hydroxide substitution reaction at the boron center of a neutral BODIPY derivative.

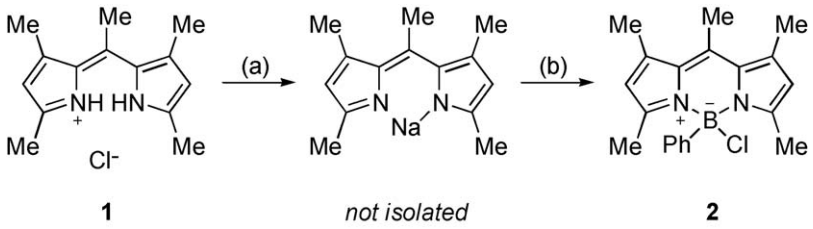


2. Results and discussion

To make our study of hydroxide for fluoride substitution reactions more straight forward, we decided to synthesize a BODIPY compound containing a single substitution site. With this in mind, we chose to investigate monoarylated BODIPY derivatives, a class of compounds that have been recently reported by Ziessel [12–14] as well as by Piers [9,10]. By adaptation of the work of Cowley on the synthesis of on β-diketiminate boron species [15], we allowed 3,5,3′,5′,6-pentamethyldipyrrin hydrochloride (**1**) [16] to react with sodium hydride (NaH) in diethyl ether/hexanes (1:1; v:v). The resulting sodium salt (generated *in situ*) was treated with

* Corresponding author at: Chemistry Department, Texas A&M, University, TAMU 3255, College Station, TX 77843-3255, United States. Tel.: +1 979 862 2070; fax: +1 979 845 4719.
E-mail address: francois@tamu.edu (F.P. Gabbaï).

0022-1139/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2010.06.012



Scheme 1. Synthesis of compound **2**. (a) NaH, Et_2O/hexanes 1:1 (v/v), RT; (b) $PhBCl_2$, toluene, RT.

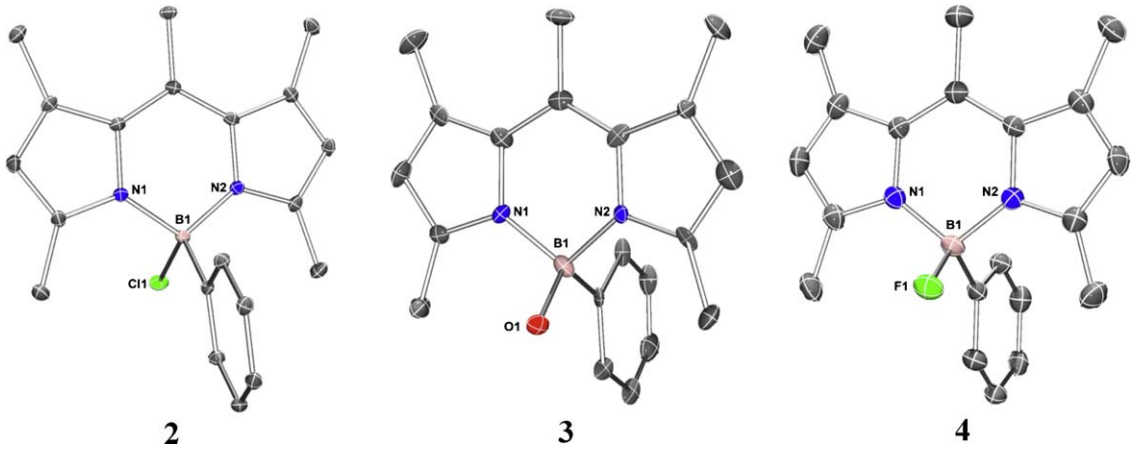
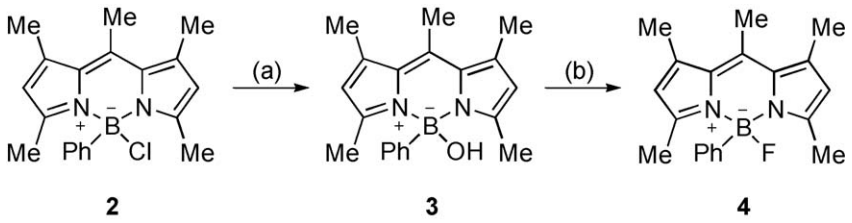


Fig. 1. ORTEP view of **2**–**4** (50% ellipsoids, H-atoms omitted for clarity). Selected bond lengths and angles are given in units of Å and deg respectively. For **2**: N1–B1 1.538(3), N2–B1 1.543(3), B1–Cl1 1.921(3), N1–B1–N2 107.12(18), N1–B1–C15 112.41(18), N2–B1–C15 111.59(18), N1–B1–Cl1 107.08(15), N2–B1–Cl1 106.92(15). For **3** (the metrical parameters of the second independent molecule are given in brackets): N1–B1 1.563(10) [1.558(10)], N2–B1 1.574(10) [1.582(9)], B1–O1 1.443(9) [1.432(9)], N1–B1–N2 104.6(6) [102.7(6)], N1–B1–C15 109.4(6) [109.1(6)], N2–B1–C15 110.6(6) [109.7(6)], N1–B1–O1 111.5(6) [111.9(6)], N2–B1–O1 112.2(6) [110.3(6)]. For 4: N1–B1 1.553(4), N2–B1 1.555(4), B1–F1 1.410(3), N1–B1–N2 105.6(2), N1–B1–C15 110.9(2), N2–B1–C15 111.4(2), N1–B1–F1 108.6(2), N2–B1–F1 108.5(2).

Table 1
Crystal data, data collection, and structure refinement for **2**–**4**.

	2	**3**	**4**
Crystal data			
Formula	$C_{20}H_{22}BClN_2$	$C_{20}H_{23}BON_2$	$C_{20}H_{22}BFN_2$
M_r	336.66	318.21	320.21
Crystal size (mm^3)	$0.15 \times 0.14 \times 0.09$	$0.21 \times 0.17 \times 0.14$	$0.16 \times 0.13 \times 0.09$
Crystal system	Triclinic	Monoclinic	Triclinic
Space group	*PI*	$P2_1$	*PI*
a (Å)	7.667(2)	10.158(3)	7.561(3)
b (Å)	10.529(4)	14.479(5)	10.331(4)
c (Å)	11.808(3)	11.622(4)	11.652(4)
α (°)	92.059(4)		80.457(6)
β (°)	102.968(3)	98.302(7)	78.295(6)
γ (°)	111.319(3)		72.473(6)
V ($Å^3$)	858.0(4)	1691.4(9)	844.6(5)
Z	2	4	2
ρ_{calc} ($g\,cm^{-3}$)	1.303	1.250	1.259
μ (mm^{-1})	0.226	0.076	0.081
F(000)	356	680	340
Data collection			
T (K)	110(2)	110(2)	110(2)
Scan mode	ω	ω	ω
hkl range	$-10 \rightarrow +10$, $-13 \rightarrow +13$, $-15 \rightarrow +15$	$-8 \rightarrow +12$, $-17 \rightarrow +17$, $-13 \rightarrow +13$	$-8 \rightarrow +8$, $-11 \rightarrow +11$, $-13 \rightarrow +13$
Measd reflns	10015	8499	7567
Unique reflns [R_{int}]	4010 [0.0315]	5833 [0.0754]	2658 [0.0352]
Reflns used for refinement	4010	5833	2658
Refinement			
Refined parameters	217	425	217
GOF on F^2	1.008	1.032	1.004
*R*1,[a] *wR2*[b] all data	0.0653, 0.1807	0.1563, 0.1554	0.0745, 0.1847
ρ_{fin} (max/min) ($e\,Å^{-3}$)	0.641 −0.669	0.446, −0.277	0.428, −0.328

[a] $R1 = \sum||Fo| - |Fc||/\sum|Fo|$.
[b] $wR2 = \{[\sum w(Fo^2 - Fc^2)^2]/[\sum w(Fo^2)^2]\}^{1/2}$.



Scheme 2. Synthesis of compounds **3** and **4**; (a) eluted over SiO_2 (eluent: toluene); (b) KHF_2, THF, 25 °C, 24 h.

phenylborondichloride to afford the monoarylated boron chloride BODIPY species, **2**, as a dark red microcrystalline solid (Scheme 1).

Compound **2** is sensitive to moisture. Attempts to form a borenium species by abstraction of the chloride anion with $AlCl_3$ in d_8-toluene resulted in the formation of a complex and intractable mixture of compounds. A clean conversion of **2** into the corresponding hydroxide derivative (**3**) was, however, observed by simply passing a freshly prepared solution of **2** in toluene over a short plug of silica. The hydroxide derivative **3** is air and water stable but reacts with fluoride under acidic conditions. Thus, treatment of **3** with potassium bifluoride (KHF_2) in THF afforded the monoarylated BODIPY-phenylboron fluoride species **4** as an orange powder in high yield (Scheme 2).

Salient spectroscopic features of compounds **2**–**4** included: (i) four sharp singlets in the ^{1}H NMR spectrum characteristic of the pentamethylated BODIPY scaffold resonating at ca. 2.0, 2.4, 2.7 and 6.0 ppm; (ii) and ^{11}B NMR chemical shifts at 2.53, 0.97 and 2.51 ppm for **2**, **3** and **4** respectively, consistent with four-coordinate sp^3-hybridized boron nuclei. Evidence for boron-fluorine coupling was not observed in the ^{11}B NMR spectra of **4**, possibly because of quadrupolar broadening. In agreement with what has been typically observed for fluoroborate moieties, the fluoride complex **4** exhibited a broad signal centered at −174.2 ppm in the ^{19}F NMR spectrum, corresponding to the boron-bound fluorine atom.

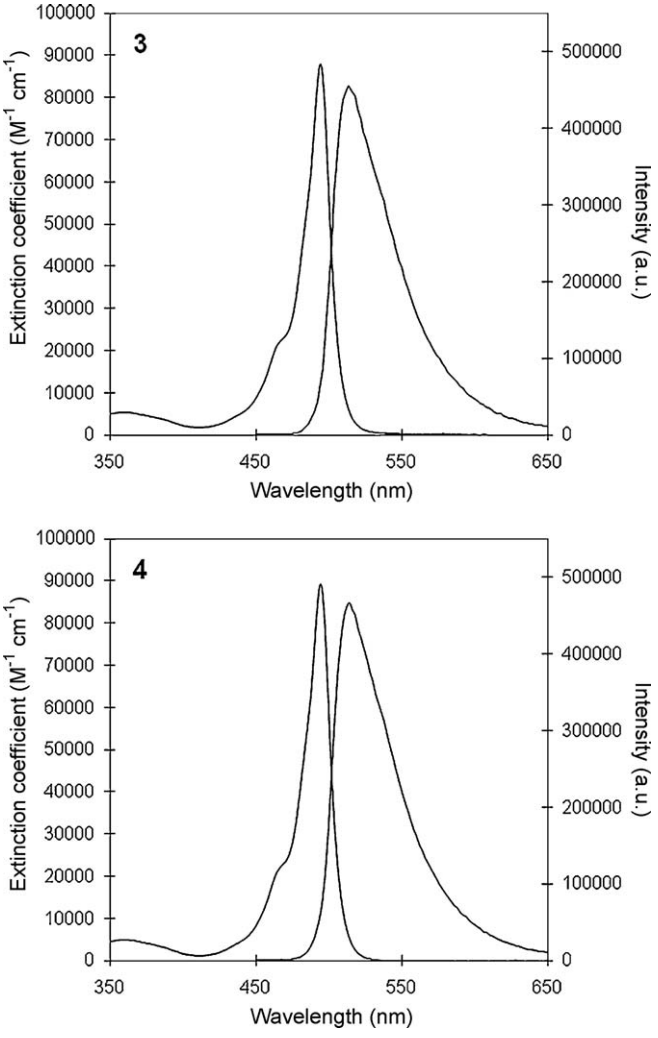


Fig. 2. Absorption and emission spectra of **3** and **4** in MeOH.

Compounds **2**–**4** are all highly crystalline solids which facilitated their solid state characterization (Fig. 1 and Table 1). In all three cases, the boron atom adopts a nearly ideal tetrahedral geometry, a structural feature which corroborates the high field ^{11}B NMR resonance observed for these three compounds. All of the bond lengths and angles for the BODIPY core are in good agreement with what has been observed for other pentamethylated BODIPY derivatives [17]. The B(1)–Cl(1) bond length of 1.921(3) Å in **2** is slightly longer than those observed in four-coordinate boron chlorides (ca. 1.86–1.89 Å) [18,19]. This elongation may be caused by the tight coordination of the two dipyrrin nitrogen atoms to the boron center. In **3**, which crystallizes with two independent molecules in the asymmetric unit, the average B–O distance of 1.43 Å can be compared to the value of 1.40 Å observed in another BODIPY hydroxide derivative [20]. The B(1)–F(1) distance of 1.410(3) Å can be compared to the B–F bond distance of 1.394(3) measured in 4,4-difluoro-1,3,5,7,8-pentamethyl-3a,4a-diaza-4-bora-s-indacene [17].

The fluorescence properties of **3** and **4** have been investigated. Both derivatives give rise to a bright green emission characteristic of such BODIPY derivatives [21]. The emission spectra of both compounds in MeOH are virtually identical and show a fluorescence emission band with a maximum at λ_{fluo} = 512 nm (Fig. 2). The similarity of these emission spectra is noteworthy and indicates that the emissive state is insensitive to the small electronic difference existing between a fluoro or hydroxo group [22,23]. The λ_{fluo} measured for **3** and **4** is slightly red shifted when compared to that of the parent 4,4-difluoro-1,3,5,7,8-pentamethyl-3a,4a-diaza-4-bora-s-indacene (λ_{fluo} = 504 nm, MeOH) which may be assigned to the presence of a phenyl group **3** and **4**. Although the emission spectra of **3** and **4** are virtually identical, the quantum yield of the fluoride derivative **4** (Φ = 77%) is higher than that of **3** (Φ = 69%). The hydroxo group, or its ability to hydrogen bond with solvent molecules, may be responsible for this small disparity.

3. Conclusion

In this paper, we show that a BODIPY hydroxide species can be easily converted into the corresponding fluoride derivative under acidic condition. This reaction may become useful for the incorporation of [^{18}F]-fluoride and may serve for the preparation of radiolabeled BODIPY derivatives.

4. Experimental

4.1. General considerations

3,5,3′,5′,6-Pentamethyldipyrrin hydrochloride (**1**) was prepared according to a literature procedure [16]. Sodium hydride

and dichlorophenyl borane were purchased from Aldrich and used without further purification. Potassium hydrogen difluoride (KHF_2) was purchased from Alfa Aesar. Et_2O and THF were dried by reflux over Na/K. Toluene, hexane and dichloromethane were dried by passing through a column charged with activated alumina. Air-sensitive compounds were handled under a N_2 atmosphere using standard Schlenk and glovebox techniques. Elemental analyses were performed at Atlantic Microlab (Norcross, GA). NMR spectra were recorded on a Varian Unity Inova 400 FT NMR (399.59 MHz for ^{1}H, 375.99 MHz for ^{19}F, 128.19 MHz for ^{11}B, 100.45 MHz for ^{13}C) spectrometer at ambient temperature. Chemical shifts δ are given in ppm, and are referenced against external Me_4Si (^{1}H, ^{13}C), $BF_3{\cdot}Et_2O$ (^{11}B) and $CFCl_3$ (^{19}F).

4.2. Crystallographic measurements

The crystallographic measurement of **2** was performed using a Bruker APEX-II CCD area detector diffractometer, with a graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å); and compounds **3** and **4** were measured using a Bruker SMART-97 CCD instrument. Single crystals of **2** were obtained by slow evaporation of a concentrated toluene solution under an atmosphere of N_2. Single crystals of **3** and **4** were grown from ethyl acetate at −40 °C. In each case, a specimen of suitable size and quality was selected and mounted onto glass fiber with apiezon grease. The structure was solved by direct methods, which successfully located most of the non-hydrogen atoms. Subsequent refinement on F^2 using the SHELXTL/PC package (version 5.1) allowed location of the remaining non-hydrogen atoms.

4.3. UV–vis and fluorescence measurements

UV–vis spectra were recorded on an Ocean Optics USB4000 spectrometer with a Ocean Optics ISS light source. Steady state emission spectra were collected at room temperature using a PTI QuantaMaster 4 fluorescence spectrophotometer equipped with a Model 810 PMT detector. The spectra of **3** and **4** were measured in MeOH with a substrate concentration of 10.5 μM. The quantum yields were measured using fluorescein in a 0.1 M NaOH solution.

4.4. Synthesis

4.4.1. Synthesis of 2

Compound **1** (100 mg, 0.40 mmol) was dissolved in 5 mL of a Et_2O/hexanes (1:1, v:v) solvent mixture. To this solution, NaH (20 mg, 0.83 mmol) was added slowly at room temperature in a drybox. The suspension was stirred overnight in the drybox then the solvent was removed *in vacuo*. The resulting residue was extracted with hexanes, filtered, and the solvent was again removed *in vacuo*. The sodium salt of **1** was then taken into a drybox, dissolved in toluene (10 mL) and $PhBCl_2$ (380 mg, 2.4 mmol) was added slowly which resulted in the appearance of a green fluorescence. The solution was stirred in the drybox overnight then filtered over Celite. Slow evaporation of the toluene produced a crop of dark red crystals of **2** (75 mg, 56% yield, *not optimized*). ^{1}H NMR (399.59 MHz, $CDCl_3$): δ 1.93 (s, 6H, dipyrrin-CH_3), 2.44 (s, 6H, dipyrrin-CH_3), 2.67 (s, 3H, dipyrrin-CH_3), 5.97 (s, 2H, dipyrrin-C*H*), 7.17–7.22 (m, 3H, phenyl-C*H*), 7.55 (d, 2H, ^2J = 8.0 Hz, phenyl-C*H*). ^{13}C NMR (100.48 MHz, $CDCl_3$): δ 16.36, 16.73, 17.74, 122.60, 126.47, 126.93, 131.45, 133.29, 140.24, 141.38, 154.73. B–*C* peak not observed. ^{11}B NMR (128.20 MHz, $CDCl_3$): δ 2.53. Satisfactory elemental analysis could not be obtained for this compound.

4.4.2. Synthesis of 3

A freshly prepared solution of **2** (prepared using 100 mg of **1**) in toluene (10 mL) was quickly eluted over a short plug of silica gel. The solvent was removed under reduced pressure to afford an orange-red residue which was recrystallized at −40 °C in EtOAc (5 mL). The resulting red-orange microcrystalline solid was collected by filtration and dried *in vacuo* to give **3** (69 mg, 97% yield). ^{1}H NMR (399.59 MHz, $CDCl_3$): δ 2.18 (s, 6H, dipyrrin-CH_3), 2.43 (s, 6H, dipyrrin-CH_3), 2.65 (s, 3H, dipyrrin-CH_3), 5.93 (s, 2H, dipyrrin-C*H*), 7.07(m, 1H, phenyl-C*H*), 7.13 (t, 2H, ^2J = 6.0 Hz, phenyl-C*H*), 7.31 (d, 2H, ^2J = 7.0 Hz, phenyl-C*H*), O*H* signal not observed. . ^{13}C NMR (100. 48 MHz, $CDCl_3$): δ 16.47, 16.81, 17.77, 122.54, 126.51, 126.90, 131.65, 133.49, 140.54, 141.41, 154.34. B–*C* peak not observed. ^{11}B NMR (128.20 MHz, $CDCl_3$): δ 0.97. λ_{fluo} = 512 nm (MeOH, Φ = 69%). Anal. Calcd for $C_{20}H_{24}BO_{1.5}N_2$ (**3**·0.5H_2O): C, 73.41; H, 7.39. Found: C, 73.77; H, 7.41.

4.4.3. Synthesis of 4

A THF (5 mL) solution of **3** (50 mg, 0.157 mmol) was treated with KHF_2 (74 mg, 0.943 mmol) and stirred for 24 h. The reaction mixture was then quenched with water (10 mL) and extracted with dichloromethane (3× 5 mL). The organic layers were combined, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the residue was recrystallized at −40 °C from EtOAc (5 mL) to afford **4** as a bright orange crystalline solid (46 mg, 91% yield). ^{1}H NMR (399.59 MHz, $CDCl_3$): δ 2.15 (s, 6H, dipyrrin-CH_3), 2.42 (s, 6H, dipyrrin-CH_3), 2.66 (s, 3H, dipyrrin-CH_3), 5.94 (s, 2H, dipyrrin-C*H*), 7.10(t, 1H, ^2J = 4.5 Hz, phenyl-C*H*), 7.15 (t, 2H, ^2J = 7.0 Hz, phenyl-C*H*), 7.31 (d, 2H, ^2J = 7.0 Hz, phenyl-C*H*). ^{13}C NMR (100. 48 MHz, $CDCl_3$): δ 16.50, 16.81, 17.79, 122.49, 126.53, 126.92, 131.61, 133.51, 140.52, 141.44, 154.38. B–*C* peak not observed. ^{19}F NMR (375.97 MHz, $CDCl_3$): δ −174.2 ^{11}B NMR (128.20 MHz, $CDCl_3$): δ 2.51 (bs). λ_{fluo} = 512 nm (MeOH, Φ = 77%). Anal. Calcd for $C_{20}H_{22}BFN_2$: C, 75.02; H, 6.93. Found: C, 74.95; H, 6.96.

5. Supplementary data

Crystallographic data (as cif files) for **2**, **3** and **4** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 770591, 770592 and 770593 respectively). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgments

Support by the National Science Foundation (CHE-0646916 and CHE-0952912), the Welch Foundation (A-1423), Texas A&M University (Davidson Professorship) and the Laboratory for Molecular Simulation at Texas A&M University (software and computation resources) is gratefully acknowledged.

References

[1] F.P. Gabbaï, Angew. Chem. Int. Ed. 42 (2003) 2218.
[2] T.W. Hudnall, C.-W. Chiu, F.P. Gabbaï, Acc. Chem. Res. 42 (2009) 388.
[3] Z.M. Hudson, S. Wang, Acc. Chem. Res. 42 (2009) 1584.
[4] S. Yamaguchi, A. Wakamiya, Pure Appl. Chem. 78 (2006) 1413.
[5] S. Yamaguchi, S. Akiyama, K. Tamao, J. Organomet. Chem. 652 (2002) 3.
[6] R. Ting, C. Harwig, U. auf dem Keller, S. McCormick, P. Austin, C.M. Overall, M.J. Adam, T.J. Ruth, D.M. Perrin, J. Am. Chem. Soc. 130 (2008) 12045.
[7] R. Ting, M.J. Adam, T.J. Ruth, D.M. Perrin, J. Am. Chem. Soc. 127 (2005) 13094.
[8] Y. Li, A. Asadi, D.M. Perrin, J. Fluorine Chem. 130 (2009) 377.
[9] C. Bonnier, W.E. Piers, M. Parvez, T.S. Sorensen, Chem. Commun. (2008) 4593.
[10] C. Bonnier, W.E. Piers, A. Al-Sheikh Ali, A. Thompson, M. Parvez, Organometallics 28 (2009) 4845.
[11] T.W. Hudnall, F.P. Gabbaï, Chem. Commun. (2008) 4596.
[12] G. Ulrich, R. Ziessel, A. Harriman, Angew. Chem. Int. Ed 47 (2008) 1184.

[13] G. Ulrich, C. Goze, S. Goeb, P. Retailleau, R. Ziessel, New J. Chem. 30 (2006) 982.
[14] C. Goze, G. Ulrich, L.J. Mallon, B.D. Allen, A. Harriman, R. Ziessel, J. Am. Chem. Soc. 128 (2006) 10231.
[15] A.H. Cowley, Z. Lu, J.N. Jones, J.A. Moore, J. Organomet. Chem. 689 (2004) 2562.
[16] M. Shah, K. Thangaraj, M.L. Soong, L. Wolford, J.H. Boyer, I.R. Politzer, T.G. Pavlopoulos, Heteroat. Chem. 1 (1990) 389.
[17] C.L. Picou, E.D. Stevens, M. Shah, J.H. Boyer, Acta Crystallogr. Sect. C: Cryst. Struct. Commun. C46 (1990) 1148.
[18] M. Enders, G. Ludwig, H. Pritzkow, Organometallics 21 (2002) 3856.
[19] N.J. Hill, J.A. Moore, M. Findlater, A.H. Cowley, Chem. Commun. (2005) 5462.
[20] Y. Takeuchi, A. Matsuda, N. Kobayashi, J. Am. Chem. Soc. 129 (2007) 8271.
[21] T.L. Arbeloa, F.L. Arbeloa, I.L. Arbeloa, I. Garcia-Moreno, A. Costela, R. Sastre, F. Amat-Guerri, Chem. Phys. Lett. 299 (1999) 315.
[22] Y. Gabe, T. Ueno, Y. Urano, H. Kojima, T. Nagano, Anal. Bioanal. Chem. 386 (2006) 621.
[23] A. Loudet, K. Burgess, Chem. Rev. 107 (2007) 4891.