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Graphical Abstract

Synthesis of porphyryl boronates with (un)saturated side–chains

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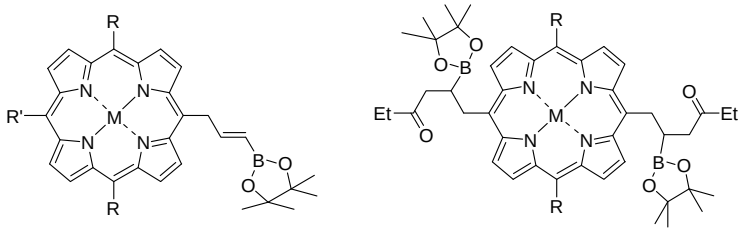

Note

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Abstract

Porphyrins with (un)saturated side–chains containing boron residues were developed as synthons for porphyrin functionalization. Porphyrins with mono and bis-substituted unsaturated boronyl residues were prepared in good yields (52–66 %) using a cross–metathesis approach in the presence of Grubbs I-generation catalysts. In all cases complete *E*–stereoselectivity (100 %) was observed. Furthermore, formal cross–metathesis products with α,β–unsaturated chains smoothly underwent addition with bis(pinacolato)diboron [$(Me_4C_2O_2)B–B(O_2C_2Me_4)$] to yield the corresponding saturated boron compounds in 60−70 % yields.

Key words: boron, porphyrin, cross-metathesis, Ru-catalyst

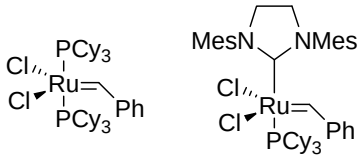
1. Introduction

Applications of metal-catalysed coupling reactions continue to grow rapidly and require easy access to novel heteroatomic building blocks. The continuing development of new catalysts with widespread activities expands the variety of functionalities to be introduced into the substrates and allows the preparation of more elaborate and multifunctional synthons. Ones of the best and powerful examples known are boron containing compounds, which serve as excellent precursors in many areas of synthetic chemistry.[1] Moreover, new strategies accessing molecules of choice have being developed in order to extent the scope of the available boron compounds.

The many possible applications of porphyrins require the development of new and more efficient reactions to introduce functional groups into the macrocycle.[2] So far, only few strategies for the synthesis of porphyrin building blocks containing boronyl residues either directly attached at the meso/β-positions or via aromatic linkers have been described.[3]

2. Results and discussion

Here, we present results aimed at a novel strategy for the synthesis of alkenyl **2** and saturated **5** boronyl porphyrins, which were not previously accessible. Recently, we reported on the preparation of allyl porphyrins **1** via standard Suzuki reactions.[4] This prompted us to investigate their utility as versatile precursors for the synthesis of boronyl porphyrins using a cross-metathesis approach. Nevertheless, it is known CM to be limited by its lack of predictability and stereoselectivity of the final products and empirical models for selective CM have not yet been developed.[5,6]



Ru-I **Ru-II**

Fig.1. Type I and II generations of Ru–catalysts used in this study.

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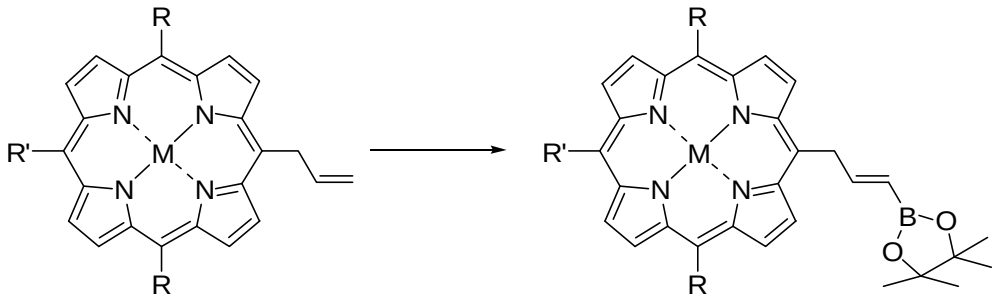


1a R: 4-MeC_6H_4; R': allyl; M: 2H
1b R: 3-$MeOC_6H_4$; R': allyl; M: 2H
1c R: 3-$MeOC_6H_4$; R': allyl; M: Zn(II)
1d R, R': Ph; M: 2H

2a R': $CH_2CH{=}CHB(OCH(CH_3)_2)_2$ 52 %
2b R': $CH_2CH{=}CHB(OCH(CH_3)_2)_2$ 50 %
2c R': $CH_2CH{=}CHB(OCH(CH_3)_2)_2$ 65 %
2d R': Ph 66 %

Scheme 1. Synthesis of compound **2** via cross–metathesis of allyl porphyrin **1**.

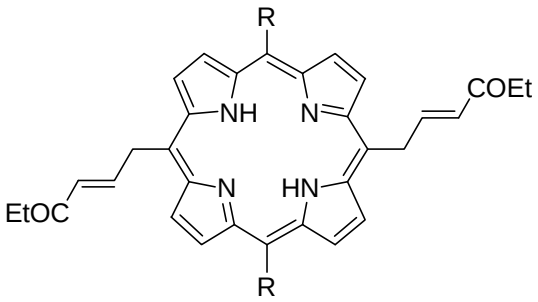
Reaction conditions: porphyrin (1 eq), vinyl boronic acid pinacol ester (10–20 eq) and **Ru–I** (0.1-0.2 eq), CH_2Cl_2, reflux 12–24 h under argon.

First attempts to use "second generation" Grubbs catalyst **Ru-II** were unsuccessful, no reaction occurred. Modification of the reaction conditions such as solvents, catalysts and temperature, finally resulted in the formation of the boronyl porphyrins **2** in good yields (Scheme 1). The allyl-porphyrins **1a-d** could be easily converted under heating to reflux in CH_2Cl_2 into the corresponding boronyl compounds **2** in the presence of **Ru-I** (0.1-0.2 eq) only.

In contrast to reports in the literature, modification of β–vinyl chlorins and β–vinyl porphyrins catalysed by a "second generation" Grubbs' catalyst[7] involving β-substituents was successfully accomplished. However, meso-vinyl porphyrins did not participate in CM reactions with vinyl boronates either, in the presence of **Ru-I** or **Ru-II** catalysts. This fact strongly underlines the differences in the nature of the meso and β positions of the macrocycle in the catalytic cycle, where electronic effects play a significant role in promoting the reaction. Noteworthy, more reactive allyl boronates, did not undergo CM reaction with the corresponding allyl or/and vinyl porphyrins. Similarly, self-dimerization of the vinyl-porphyrins did not take place with either catalyst. This is contrasted by the reaction of β-allyl porphyrins, which could be utilised for the preparation of benzoporphyrins via olefin ring–closure metathesis as described by Liu et al.[8]

Significantly, the CM products **2** obtained here were all formed exclusively as the *E*–isomers. This was easily confirmed by ^{1}H NMR spectroscopy. The *J* coupling constants calculated were in the range of 15.8–17.8 Hz and strongly indicate a *trans* stereochemistry for all compounds in this series.

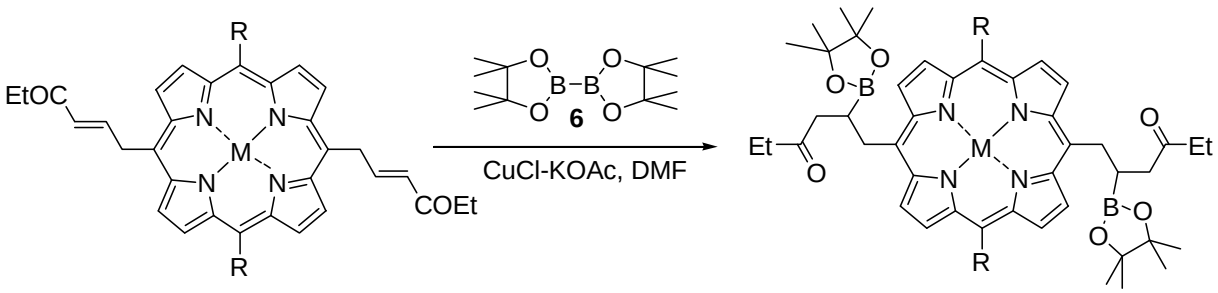
It is well known that α,β-unsaturated compounds can undergo 1,4-addition reactions with reagents such as cuprates or boronates. For example, Takahashi *et al.* reported that α,β-unsaturated compounds undergo boronation with (pinacolato)diboron [$(Me_4C_2O_2)B–B(O_2C_2Me_4)$].[9] This strategy offers the possibility to prepare saturated boronyl porphyrins from the corresponding α,β-unsaturated porphyrins. We found that α,β-unsaturated porphyrins can also be prepared using a CM-approach. Porphyrins **1b** and 5,15-diallyl-10,20-diphenylporphyrin **1e**[4] reacted smoothly with ethyl vinyl ketone in the presence of Grubbs II **Ru-II**, forming the corresponding compounds **3a** and **3b** in excellent yields of 94 %, each.



3a R: Ph 94 %
3b R: 3-$MeOC_6H_4$ 94 %

Attempts to use these porphyrins for 1,4-addition reactions to α,β-unsaturated compounds showed that the free base porphyrins **3** were very sensitive to the reaction conditions ([$(Me_4C_2O_2)B–B(O_2C_2Me_4)$]) and fast decomposition of the boronated complexes took place.

However, the novel metallated CM products **4** were easily transformed into the boronates via 1,4–addition reactions (Scheme 2). For example, compounds **4a** and **4b** reacted with (pinacolato)diboron [$(Me_4C_2O_2)B–B(O_2C_2Me_4)$] in the presence of CuCl/KOAc to yield the corresponding bisboronated adducts **5** in up to 70 % yield. Interestingly, these transformations are very susceptible to the reaction temperature. While compound **5b** was easily prepared at 55°C a further increase in temperature resulted in rapid decomposition. An even higher sensitivity was observed in for the zinc complex **5a**. A reaction temperature of 45°C caused rapid decomposition of the products formed, while the reaction at room temperature proceeded smoothly to give **5a** in 70 % yield.



Scheme 2. Boronation of CM compounds **4**. *Reaction conditions*: porphyrin (1 eq, ~30 mg), (pinacolato)diboron **6** (4–6 eq.), CuCl (0.1 eq.), KOAc (0.1 eq.), DMF (3–5 mL), rt (for **5a**), 55°C (for **5b**), argon.

The syntheses described offer a convenient approach to the novel boronyl functionalised porphyrins **2** and **5** and expand the repertoire of reagents to be utilised in metal-catalyzed coupling reactions for the functionalisation of the porphyrin periphery. Based on the rich chemistry of boron derivatives of aromatic compounds,[1] the porphyrylboronates presented can serve as versatile precursor molecules for the facile introduction of carbonheteroatom bonds in to a macrocycle. The boronated porphyryl species constitute a new class of synthons for porphyrin-based materials via metal-catalyzed C–C bond-forming reactions or hydroboration polymerization. Compounds of type **5** with saturated chains are an intriguing new class of porphyrins for transformation into porphyrin bioconjugates, e.g., amino and hydroxy acid derivatives, esp. for medicinal applications.

3. Experimental

General experimental conditions were as described earlier.[10,11] Grubbs catalysts **Ru-I** and **Ru-II** were purchased from Sigma-Aldrich.

*3.1 Synthesis of compounds **1** via Suzuki reaction.*[4]
Compounds **1a-c,e** were prepared as reported elsewhere.[4]

3.1.1 *Compound* (**1d**)
Yield: 89 %. M.p. >250°C. UV/vis (CH_3CO_2Et): λ_{max}(lg ε) 415 (5.5), 513 (4.3), 548 (4.1), 593 (4.0), 648 (4.0) nm. ^{1}H NMR (400 MHz, $CDCl_3$): -2.69 (s, 2H), 5.22 (dd, *J* = 10.5 Hz, 16.9 Hz, 2H), 5.82 (d, *J* = 5.2 Hz, 2H), 6.89 (m, 1H), 7.78 (m, 9H), 8.25 (m, 6H), 8.84 (br, 4H), 8.95 (d, *J* = 4.7 Hz, 2H), 9.51 (d, *J* = 4.7 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 38.6, 115.8, 119.3, 119.4, 126.2, 126.3, 127.3, 127.8 (br), 130.8 (br), 134.1, 141.1, 141.6, 141.9. HRMS (ES+): $C_{41}H_{30}N_4$ calcd for [M+H$^+$] 579.2543 found 579.2536.

*3.2 General procedure for the synthesis of compounds **2** and **3** via cross-metathesis.*
A solution of porphyrin **1** (0.1 mmol) and Ru–catalysts (0.2 mmol) in 30 mL of CH_2Cl_2 was flushed with argon and an appropriate olefin (1–2 mmol) was added. The reaction mixture was flushed with argon again and refluxed under argon for 12–24 hours (TLC–control). The mixture was filtered through silica gel and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on Silica with CH_2Cl_2/hexanes and recrystallised from MeOH–CH_2Cl_2 to yield the corresponding product **2**. For the synthesis of compound **2** **Ru-I** and for the compound **3** and **4**, **Ru II** have been used.

3.2.1 *Compound* (**2a**)
Yield: 52 %. M.p. >250°C. UV/vis (CH_3CO_2Et): λ_{max}(lg ε) 420 (5.5), 519 (4.7) nm. ^{1}H NMR (400 MHz, $CDCl_3$): -2.67 (s, 2H), 1.15 (s, 24H), 2.75 (s, 6H), 5.66 (d, *J* = 17.6 Hz, 1H), 5.85 (d, *J* = 5.9 Hz, 2H), 7.58, (m, 4H), 7.59 (dt, *J* = 5.9 Hz, 17.6 Hz, 2H), 8.09 (m, 4H), 8.90 (d, *J* = 4.7 Hz, 4H), 9.41 (d, *J* = 4.7 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.1, 24.8, 40.5, 82.6, 114.4, 118.9, 126.8, 126.3, 126.8, 133.9, 136.8, 139.1, 154.9. HRMS (ES+): $C_{52}H_{56}B_2N_4O_4$ calcd for [M+H$^+$] 823.4560 found 823.4552.

3.2.2 *Compound* (**2b**)
Yield: 50 %. M.p. >250°C. ^{1}H NMR (400 MHz, $CDCl_3$): -2.68 (br, 2H), 1.16 (s, 24H), 4.00 (s, 6H), 5.65 (d, *J* = 18.1 Hz, 2H), 5.85 (d, *J* = 4.7 Hz, 4H), 7.37 (m, 2H), 7.62 (dt, *J* = 4.7 Hz, 18.1 Hz, 2H), 7.68 (m, 2H), 7.82 (m, 4H), 8.91 (d, *J* = 4.7 Hz, 4H), 9.41 (d, *J* = 4.7 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 24.3, 40.4, 55.1, 82.7, 113.3, 114.1, 118.6, 119.7, 126.3, 127.1, 127.6, 131.5, 143.4, 154.9, 157.4.

3.2.4 *Compound* (**2c**)
Yield: 65 %. M.p. 195°C. UV/vis (CH_2Cl_2): λ_{max}(lg ε) 421 (6.0), 550 (4.8) nm. ^{1}H NMR (400 MHz, $CDCl_3$): 1.16 (s, 24H), 4.01 (s, 6H), 5.65 (d, *J* = 17.6 Hz, 2H), 5.88 (d, *J* = 4.9 Hz, 4H), 7.36 (m, 2H), 7.71 (m, 8H), 9.01 (d, *J* = 4.0 Hz, 4H), 9.52 (d, *J* = 4.0 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 24.7, 41.2, 55.5, 83.1, 113.6, 116.1, 120.0, 120.1, 127.3, 127.5, 129.5, 132.5, 144.2, 149.5, 150.6, 155.7, 157.8. MS (ES+): $C_{52}H_{54}B_2N_4O_6Zn$ calcd for [M+H_3O^+] 935.4 found 935.5.

3.2.5 *Compound* (**2d**)
Yield: 66 %. M.p. >250°C. UV/vis (CH_3CO_2Et): λ_{max}(lg ε) 415 (5.6), 513 (4.4), 548 (4.3), 593 (4.2), 650 (4.2) nm. ^{1}H NMR (400 MHz, $CDCl_3$): -2.72 (s, 2H), 1.16 (s, 12H), 5.66 (d, *J* = 17.8 Hz, 1H), 5.91 (d, *J* = 5.8 Hz, 2H), 7.64 (d, *J* = 5.8 Hz, 17.8 Hz, 1H), 7.78 (m, 9H), 8.24 (m, 6H), 8.82 (br, 4H), 8.92 (d, *J* = 5.0 Hz, 2H), 9.51 (d, *J* = 5.0 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 24.2, 40.6, 82.7, 115.0, 119.2, 119.3, 126.2, 126.3, 127.2, 130.5 (br), 134.0, 134.1, 141.6, 141.9, 154.9. HRMS (ES+): $C_{47}H_{41}BN_4O_4$ calcd for [M+H$^+$] 705.3395 found 705.3371.

3.2.6 *Compound* (**3a**)

Yield: 94 %. M.p. 193°C. UV/vis (CH_3CO_2Et): λ_{max}(lg ε) 416 (5.3), 516 (4.3), 548 (4.2), 593 (4.2), 656 (4.2) nm. ^{1}H NMR (400 MHz, $CDCl_3$): -2.67 (br, 2H), 0.91 (t, *J* = 7.6 Hz, 6H), 2.32 (q, *J* = 7.6 Hz, 4H), 5.92 (d, *J* = 5.2 Hz, 4H), 6.07 (d, *J* = 15.8 Hz, 2H), 7.79 (m, 8H), 8.21 (m, 4H), 8.91 (d, *J* = 4.6 Hz, 4H), 9.37 (d, *J* = 4.6 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 7.3, 33.1, 37.0, 113.1, 119.4, 126.1, 126.2, 127.3, 127.4, 130.9, 132.0, 134.0, 140.8, 141.6, 146.4, 147.4, 200.5. HRMS (ES+): $C_{44}H_{38}N_4O_2$ calcd for [M+H] 655.3073 found 655.3082.

3.2.7 *Compound* (**3b**)

Yield: 94 %. M.p. 220°C. UV/vis (ethyl acetate): λ_{max}(lg ε) 421 (5.4), 517 (4.3), 558 (4.1), 592 (4.1), 652 (4.0) nm. ^{1}H NMR (400 MHz, $CDCl_3$): 2.68 (br, 2H), 0.93 (t, *J* = 7.3 Hz, 6H), 2.34 (q, *J* = 7.3 Hz, 4H), 4.04 (s, 6H), 5.89 (d, *J* = 5.8 Hz, 4H). 6.07 (d, *J* = 15.8 Hz, 2H), 7.40 (m, 2H), 7.69 (m, 2H), 7.80 (m, 6H), 8.97 (d, *J* = 4.7 Hz, 4H), 9.35 (d, *J* = 4.7 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 7.3, 33.1, 36.9, 55.1, 113.1 (m), 119.1, 120.0, 1270, 127.1, 127.4, 130.9, 131.9, 142.9, 147.4, 157.5, 200.5. HRMS (ES+): $C_{46}H_{42}N_4O_4$ calcd for [M+H] 715.3284 found 715.3286.

3.2.8 *Compound* (**4a**)

4a was obtained by metallaion of **3a** with $Zn(OAc)_2{\cdot}2H_2O$ in CH_2Cl_2-MeOH according with standard procedure.[2]

Yield: 87 %. M.p. >250°C. UV/vis (CH_2Cl_2): λ_{max}(lg ε) 421 (6.0), 551 (4.7) nm. ^{1}H NMR (400 MHz, $CDCl_3$): 0.86 (t, *J* = 7.0 Hz, 6H), 2.31 (q, *J* = 7.0 Hz, 4H), 5.74 (d, *J* = 5.8 Hz, 4H), 6.02 (d, *J* = 15.8 Hz, 2H), 7.40 (dt, *J* = 5.8 Hz, 15.8 Hz, 2H), 7.80 (m, 6H), 8.18 (m, 4H), 8.94 (d, *J* = 4.7 Hz, 4H), 9.32 (d, *J* = 4.7 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 7.4, 32.8, 37.4, 114.1, 120.3, 126.2, 127.2, 128.4, 130.6, 132.6, 133.9, 142.1, 147.8, 149.4, 149.8, 200.6.

3.2.9 *Compound* (**4b**)

4b was obtained by metallaion of **3b** with $Ni(acac)_2$ in toluene according with standard procedure.[2]

Yield: 73 %. M.p. 250°C. UV/vis (CH_2Cl_2): λ_{max}(lg ε) 417 (5.5), 533 (4.5) nm. ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (t, *J* = 4.8 Hz, 6H), 2.42 (q, *J* = 4.8 Hz, 4H), 3.97 (s, 6H), 5.46 (d, *J* = 4.0 Hz, 4H). 6.19 (d, *J* = 10.6 Hz, 2H), 7.31 (m, 2H), 7.55 (m, 2H), 7.61 (m, 4H), 7.65 (dt, *J* = 4.0 Hz, 10.6 Hz, 2H), 8.84 (d, *J* = 3.0 Hz, 4H), 9.18 (d, *J* = 3.0 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 7.7, 33.3, 36.4, 55.3, 112.0, 113.4, 118.2, 119.5, 126.5, 127.7, 129.2, 131.0, 133.1, 141.6, 141.8, 142.3, 147.2, 158.0, 200.8.

3.3 General procedure for the synthesis of compounds ***5*** *via 1,4-addition.*

A solution of KOAc (1 mg), CuCl (1 mg) and (pinacolato)diboron **6** (0.2335 mmol, 59.3 mg) in 2 mL of anhydrous DMF was stirred for 10-15 min (color change to green-blue). Porphyrin **4** (0.0584 mmol) was added as a solid and the reaction was stirred for 20 min (TLC-control). For **5a** the reaction was stirred at rt. For **5b** the mixture was warmed up to 55 °C. The final solution was washed with water and NH_4Cl (sat), extracted with CH_2Cl_2 and dried with Na_2SO_4. The crude product was purified by column chromatography (CH_3CO_2Et:hexane=1:2) to give **5**.

3.3.1 *Compound* (**5a**)

Yield: 70 %. M.p. >250°C. UV/vis (CH_2Cl_2): λ_{max}(lg ε) 421 (6.2), 552 (5.0) nm. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.91 (m, 6H), 1.28 (m, 12H), 1.39 (m, 12H), 1.49 (m, 2H), 2.09 (m, 2H), 2.41 (m, 4H), 2.55 (m, 2H), 4.93 (m, 2H), 5.45 (m, 2H), 7.80 (m, 6H), 8.22 (m, 4H), 8.96 (d, *J* = 4.5 Hz, 4H), 9.56 (br, 4H). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 7.7, 24.7, 28.0, 34.1 (d), 35.3, 43.0 (d), 83.2, 119.8, 120.0 (d), 126.3, 127.2, 129.2, 132.0, 134.1, 134.2, 134.3, 134.4, 143.0, 149.2, 150.5, 211.7. MS (ES): $C_{56}H_{62}B_2N_4O_8Zn$ calcd for [M+OH^-] 989.2, found 989.4.

3.3.2 *Compound* (**5b**)

Yield: 60 %. M.p. 255°C. UV/vis (CH_2Cl_2): λ_{max}(lg ε) 418 (6.3), 533 (5.3) nm. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.83 (m, 6H), 1.30 (br, 24H), 1.93 (m, 10H), 3.97 (s, 6H), 4.54 (m, 2H), 5.16 (m, 2H), 7.29 (m, 2H), 7.57 (m, 6H), 8.80 (d, *J* = 4.1 Hz, 4H), 9.29 (br, 4H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 7.6, 24.7, 25.4, 32.3 (d), 35.1, 42.3 (d), 55.3, 83.2, 113.3, 117.2, 117.4, 119.5, 126.5, 127.6, 130.0, 132.4, 141.2, 142.0, 142.5, 158.0, 211.5. MS (ES): $C_{58}H_{66}B_2N_4NiO_8$ calcd for [M+H^+] 1027.5, found 1027.9.

Acknowledgments

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[11] Note: MS spectra for **2b**, **4a,b** could not be measured due to low stability.