Tetrahedron Letters 53 (2012) 6961–6964

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis and characterization of original N-*meso* chiral substituted diarylporphyrins

Zahra Abada [a,b], Laurent Ferrié [b], Bernardin Akagah [a], Anh Tuan Lormier [a], Bruno Figadère [b,*]

[a] Alpha-Chimica, 5 rue Jean-Baptiste Clément, F-92296 Châtenay-Malabry, France
[b] UMR CNRS 8076, University Paris-Sud, Laboratoire de Pharmacognosie, UFR de Pharmacie, Châtenay-Malabry F-92296, France

ARTICLE INFO

Article history:
Received 23 July 2012
Revised 5 October 2012
Accepted 9 October 2012
Available online 17 October 2012

Keywords:
Porphyrin
Cross coupling amination
Palladium
Atropisomers

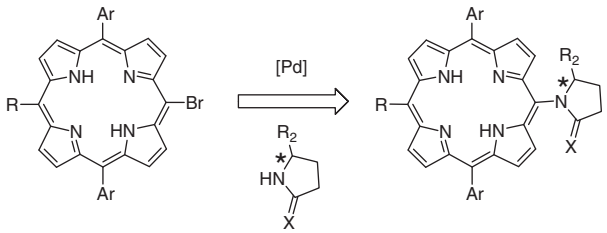
ABSTRACT

A first palladium catalyzed cross-coupling amination with chiral auxiliaries at the two *meso* positions of diarylporphyrins was reported. We noticed that, the non-metallation of porphyrins and steric hinderance of the chiral auxiliary play an essential role to the effectiveness of this cross coupling-reaction. Here, when two methyl pyroglutamates were added, the reaction leads to atropisomers and their behaviors were investigated by NMR spectroscopy. Finally, functionalizations of these chiral porphyrins were performed onto the pyrroglutamate moiety to give new original chiral porphyrins.

The ability of cytochromes to perform diverse oxidations of organic compounds with incomparable chemoselectivities, regioselectivity, and enantioselectivity attracted numerous organic chemists to mimic the activity of these biomolecules in asymmetric oxidations.[1–3] In analogy with the environment of these proteins, many porphyrins were synthesized, for decades, comprising a chain of amino and bulky substituents. This steric hindrance is intended to induce regio- and enantioselectivities and also to avoid deactivation of the catalyst. All of these structures include aromatic groups substituted with carbon–carbon bond at *meso* positions.[4] To the best of our knowledge, no chiral porphyrins containing a heteroatom at *meso* positions were reported. In particular, N-meso substituted porphyrins seem to be an interesting alternative to C-*meso* porphyrins as lot of chiral, notably heterocyclic, nitrogen building blocks are available. Furthermore physical and chemical properties of these *meso*-heterocyclic substituted porphyrins could differ from the classical C-*meso* substituted macrocycles (e.g. aqueous solubility, log *P*, etc.). Recently, we reported a general method for the synthesis of diarylporphyrins from 5-aryldipyrromethanes and orthoesters under trifluoroacetic acid catalysis,[5] and from these building blocks we are showing herein the synthesis of diverse *N*-heterocyclic-*meso* diarylporphyrins. Our initial plan as shown in Scheme 1 was to couple *N*-chiral heterocyclic building blocks with mono or di-brominated diarylporphyrins using a palladium catalyzed C–N cross coupling reaction which is the most convergent strategy.

In order to achieve such a transformation, we needed to prepare mono-bromo and dibromodiarylporphyrins. Bromination of the free *meso* positions was performed with NBS in dichloromethane/methanol system at room temperature as already reported.[6] Bromination of triphenylporphyrin **1** was achieved cleanly in 90% yield by using slightly more than one equivalent of NBS.

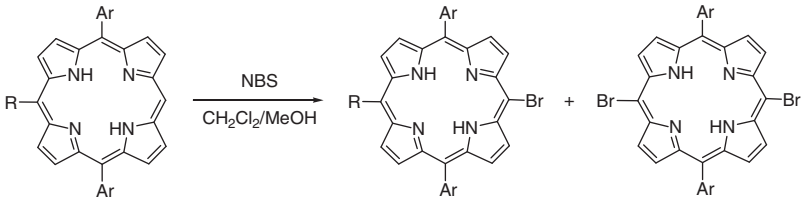
Diarylporphyrins were generally harder to brominate selectively: by using 1.01 equiv of NBS, diarylporphyrin **2** afforded in 58% yield mono-bromide **5**, along with some dibromide **7** and some starting material. With 2.01 equivalents of NBS, diarylporphyrin **2** was transformed more selectively into **7** with 71% yield, along with some traces of mono-bromide **5** whereas diarylporphyrin **3** was more difficult to brominate, affording dibromide **8** in 40% yield along with mono-bromide **6** in 10% yield and starting material under the same conditions. It is important to stress that using an excess of NBS decreases generally the yield as non-selective oxidations can then occur on β-pyrrolic positions and further lead to



Scheme 1. General retrosynthetic analysis.

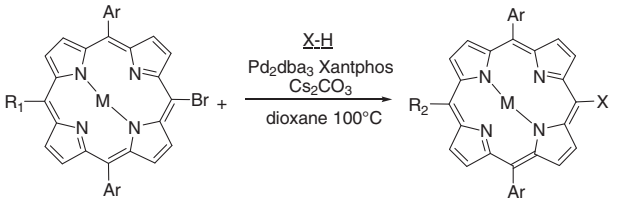
* Corresponding author.
E-mail address: bruno.figadere@u-psud.fr (B. Figadère).

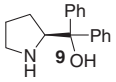
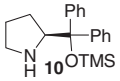
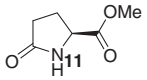
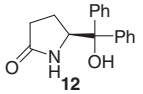
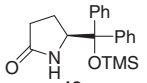
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.041



Scheme 2. Selective bromination of diarylporphyrins.

Table 1
Cross coupling reaction of chiral amines or amides **9**–**13** with *meso*-bomoporphyrins (M = H_2 or Zn, Ni)



Entry	Starting material	X	R_1	M	Ar	Product	Yield
1	**Zn-5**	 **9**	H	Zn	Ph	**Zn-14a**	x
2	**Zn-5**	 **10**	Br	Ni	Ph	**Ni-15b**	x
3	**Ni-7**	**10**	H	Zn	Ph	**Zn-14a**	x
4	**Zn-5**	 **11**	H	Zn	Ph	**Zn-14b**	x
5	**5**	**11**	H	H_2	Ph	**14c**	75%
6	**7**	**11**	Br	H_2	Ph	**15c**	85%
7	**4**	**11**	Ph	H_2	Ph	**16c**	72%
8	**8**	**11**	H	H_2	3,4,5-OMe-phenyl	**17c**	73%
9	**6**	**11**	Br	H_2	3,4,5-OMe-phenyl	**18c**	63%
10	**7**	 **12**	Br	H_2	Ph	**15d**	x
11	**7**	 **13**	Br	H_2	Ph	**15e**	x
12[a]	**7**	**11**	Br	H_2	Ph	**15c**	94%[a]

[a] Reaction was run in a sealed tube in THF at 100 °C.

porphyrin ring-opening (scheme 2).[6] From mono-brominated or di-brominated porphyrins, Buchwald–Hartwig type palladium-catalyzed coupling reactions were performed in order to achieve linkage with some chiral amines or amides. We first decided to use conditions already reported to perform a reaction between achiral amides or amines with brominated diarylporphyrins.[7–9] Using similar conditions (Pd_2dba_3, Xantphos, Cs_2CO_3, dioxane, 100 °C), several cross-coupling reactions were reported in Table 1. When metallated porphyrins **Zn-5** and **Ni-7** were treated as described above with amine **9** or **10**,[10] no coupling reaction was observed (entries 1–3).[11] With methyl pyrroglutamate **11** no coupling product was neither obtained under the same conditions from Zn-5 (entry 4).

Many other methods have been tested to achieve the coupling with diphenylprolinol **9** but no one allowed us to obtain the desired compound.[12,13] It is interesting to note that, in the literature,

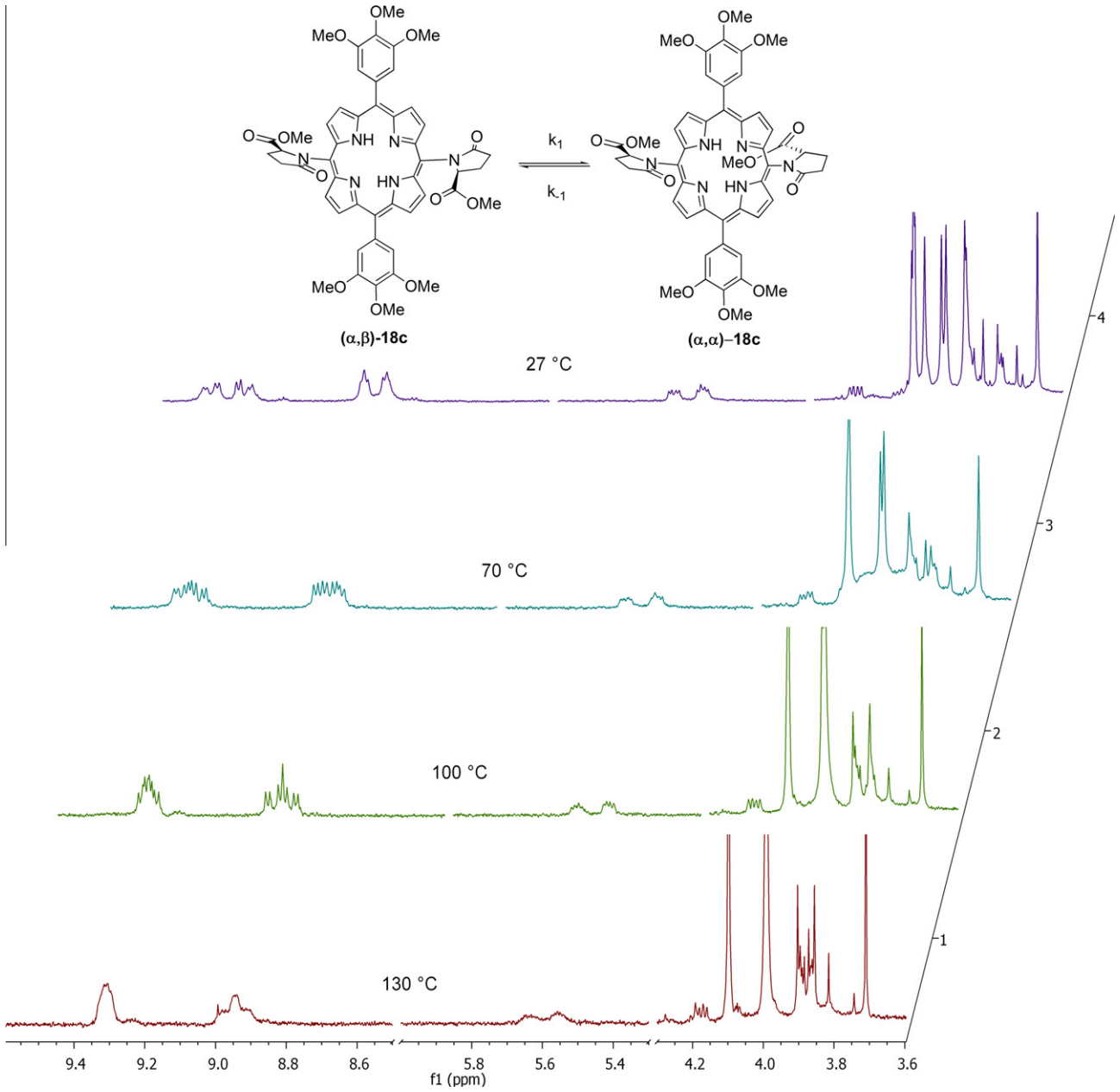
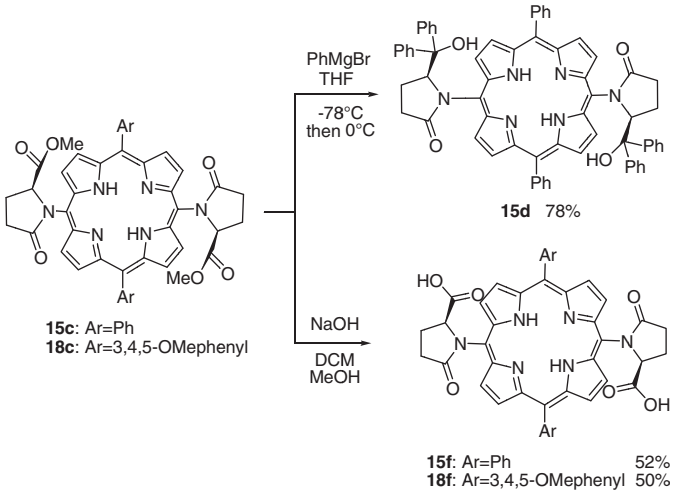


Figure 1. Evolution of **18c** ^{1}H NMR depending on the temperature in DMSO-d_6: observation of reversible atropisomerization.

only simple amines and amides were already studied for the same reaction. Indeed, Zhang and co-workers[9a] were able to couple simple amines with *meso*-bromoporphyrins as well as Zn-metallated porphyrins. We can therefore explain the lack of reactivity for our system by a steric hindrance directly in the α-position of amine or amide groups (vide infra).

Fortunately, the cross coupling between our less hindered chiral auxiliary **11** and non-metallated porphyrin **5** afforded finally the expected product **14c** in 75% yield (entry 5) whereas triphenylporphyrin **4** afforded the cross product **16c** in 72% yield (entry 7). Non-metallation seems indeed to play a critical role in this cross coupling reaction. To continue under these reaction conditions, 5,15-dibromo-10,20-diphenylporphyrin **7** afforded the corresponding double coupled compound **15c** in excellent yield (85%, entry 6). It is important to notice that the coupling reaction worked best in sealed tubes in THF at 100 °C where **15c** was then isolated in an improved yield (94%, entry 12 vs entry 6, 85%). Cross coupling reaction with other porphyrins was studied and gave similar results from bromo-10,20-(3,4,5-trimethoxyphenyl)porphyrins **6** and **8** (entries 8 and 9, **17c**: 73% and **18c**: 63%). However attempts to couple porphyrin **7** with more bulky pyroglutamates **12** and **13** were still unsuccessful (entries 10–11) due to steric hindrance provided by aromatic groups in the α position of the amide function.

A ^{1}H NMR analysis of compounds **15c** and **18c** was then performed and revealed the presence of two atropisomers α,α and α,β. In porphyrin family, atropisomers are derived from the free rotation around the C–N bond at *meso* positions and were already extensively studied in particular for tetraarylporphyrins with *ortho*-substituted groups on *meso* aromatics.[14,15] However, this is the first time this type of atropisomers, with chiral heterocyclic moiety due to ester moiety on pyroglutamates, is obtained and studied. Some chromatographic conditions allowed us to see clearly two distinct spots on TLC, but only with the CH_2Cl_2/MeOH (99:1) solvent system. Many attempts to separate atropisomers



Scheme 3. Synthesis of diverse functionalized chiral porphyrins.

remained unsuccessful. Indeed, the kinetic of equilibration between the α,α and α,β isomers seems to be slow enough to allow us to separate them by TLC (2–4 min duration) whereas using a column chromatography (>30 min) is long enough to able the equilibration of the two atropisomers. A temperature NMR study was achieved in order to confirm this hypothesis (Fig. 1). Proton NMR spectrum simplifies nicely at higher temperature and β-pyrrolic, aromatic, and methoxy proton signals are clearly coalescing while increasing the temperature. Only N–CH signals of the amide moiety at 5.6 ppm still remain separated at 130 °C although they are closer than at room temperature.

It is important to note that pyrroglutamate moiety in diarylporphyrins **14c–18c** can be further functionalized by many readily available compounds allowing access to more complex porphyrins with original structures. Therefore, phenyl magnesium bromide was added selectively on the ester moiety to give porphyrin **15d** in 78% yield (Scheme 3).[16] This protocol is an alternative to the failing cross-coupling between **7** and **12** or **13**. Thus, methyl ester can be cleaved by saponification, affording diacides **15f** and **18f** in 52% and 50%, respectively.[17] Further functionalization into amide or ester function could be then envisioned.

In conclusion, we synthesized new chiral porphyrins including C–N-*meso* substituted ones. Methyl pyrroglutamate appeared to be the best candidate for Buchwald–Hartwig type cross coupling reaction affording the expected adduct in 94% yield. More bulky substrates did not react under these reaction conditions. For porphyrins containing two chiral moieties, a mixture of α,β and α,α atropisomers was obtained, nevertheless the kinetic of equilibration is sufficiently high to unable their physical separation for characterization. Ester function of pyrroglutamate can be further transformed to give new chiral porphyrins. Utilization of these new chiral porphyrins will be reported in due course.

Acknowledgments

Thanks are due to K. Leblanc for her help in chromatography analyses, and for mass spectrometry analyses. We wish to thank J.C. Jullian (Châtenay-Malabry) for NMR experiments.

Supplementary data

Supplementary data (^{1}H NMR spectra and experimental data of compounds **1–8**, **14c**, **15c**, **16c**, **17c**, **15d**, **15f**, and **18f**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.041.

References and notes

1. (a) Groves, J. T.; Han, Y.-Z.. In *Cytochrome P-450 Structure Mechanism and Biochemistry*; de Montellano, R. R. Ortiz, Ed.; Plenum Press: New York, 1995; (b) Meunier, B.; De Visser, S. P.; Shaik, S. *Chem. Rev.* **2004**, *104*, 3947.
2. Rose, E.; Quelquejeu, M.; Pandian, R. P.; Lecas-Nawrocka, A.; Vilar, A.; Ricart, G.; Collman, J. P.; Wang, Z.; Straumanis, A. *Polyhedron* **2000**, *19*, 581.
3. Akagah, B.; Lormier, A. T.; Alain Fournet, A.; Figadère, B. *Org. Biomol. Chem.* **2008**, *6*, 4494–4497.
4. Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu, M. *Chem. Soc. Rev.* **2005**, *34*, 573–583.
5. Abada, Z.; Ferrié, L.; Akagah, B.; Lormier, A. T.; Figadère, B. *Tetrahedron Lett.* **2011**, *52*, 3175–3178.
6. Shen, D. M.; Liu, C.; Chen, Q. Y. *J. Org. Chem.* **2006**, *71*, 6508.
7. (a) Gao, G.-Y.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2004**, *6*(11), 1837–1840; (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*(25), 7421–7428; (c) Audisio, D.; Messaoudi, S.; Alami, M. *Tetrahedron Lett.* **2007**, *48*, 6928–6932.
8. (a) Liu, C.; Shen, D. M.; Chen, Q. Y. *Eur. J. Org. Chem.* **2006**, 2703; (b) Liu, C.; Chen, Q. Y. *Synlett* **2005**, *8*, 1306; (c) Liu, C.; Chen, Q. Y. *Eur. J. Org. Chem.* **2005**, 3680; (d) Gao, G. Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2004**, *69*, 8886; (e) Gao, G. Y.; Chen, Y.; Zhang, X. P. *Org. Lett.* **1837**, *2004*, 6; (f) Gao, G. Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 3261; (g) Gao, G. Y.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 6215; (h) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432.
9. (a)*Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley: Weinheim, 2004; (b) Montgomery, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908; (c) Li, Z.; Fu, Y.; Liu, L.; Guo, Q.-X. *Chin. J. Org. Chem.* **2005**, *25*, 1508–1529; d) Prim, D.; Campagne, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075.D.
10. (a) Mathre, D. J.; Johnes, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751; b) Kanth, J. V. B.; Peryasamy, M. *Tetrahedron* **1993**, *49*, 5127–5132.D.
11. A mixture of starting material and debrominated compound was recovered.
12. It is important to stress that alternative conditions to palladium (Ni or Cu catalysis) did not produce expected products either: Liu, C.; Shen, D. M.; Chen, Q.-Y. *J. Org. Chem.* **2007**, *72*, 2732–2736.
13. Balaban, M. C.; Chappaz-Gillot, C.; Canard, G.; Fuhr, O.; Roussel, C.; Balaban, T. S. *Tetrahedron* **2009**, *65*, 3733–3739.
14. (a) Freitag, R. A.; Mercer-Smith, J. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 1226; (b) Crossley, M. J.; Field, L. D.; Forster, A. J.; Harding, M. M.; Sternhell, S. *J. Am. Chem. Soc.* **1987**, *109*, 341; (c) Hatano, K.; Azai, K.; Kobu, T.; Tamai, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3518; (d) Miyamoto, T. K.; Hasegawa, T.; Takagi, S.; Sasaki, Y. *Chem. Lett.* **1983**, 1181; (e) Hanato, K.; Kowasaki, K.; Munakata, S.; Iitaka, Y. *Bull. Chem. Soc. Jpn.* **1985**, *60*, 1985; (f) Freitag, R. A.; Whitten, D. G. *J. Phys. Chem.* **1983**, *87*, 3918.
15. (a) Rose, E.; Quelquejeu, M.; Pochet, C.; Julien, N.; Kossanyi, A.; Hamon, L. *J. Org. Chem.* **1993**, *58*, 5030–5031; (b) Rose, E.; Cardon-Pilotaz, A.; Quelquejeu, M.; Bernard, N.; Kossanyi, A. *J. Org. Chem.* **1995**, *60*, 3919–3920.
16. Deskus, J.; Fan, D.; Smith, M. B. *Synth. Commun.* **1998**, *28*, 1649–1660.
17. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*, Third edition; John Wiley & Sons: New York, 1999.