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Synthesis of 1,8-bis(cyclam) and 1,8-bis(azacrown) substituted anthracenes by palladium-catalyzed arylation of cyclam

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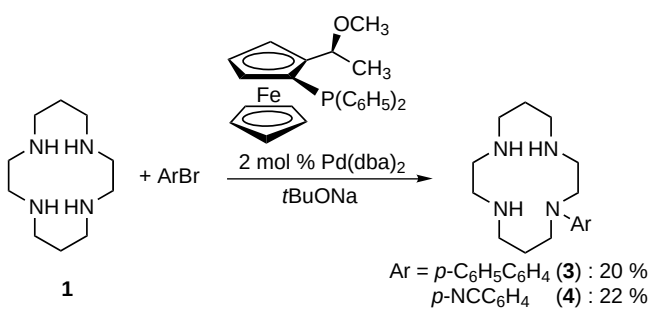
Abstract—The Pd-catalyzed arylation of cyclam, cyclen, and azacrown ethers by aryl halides was studied. Cofacial biscyclam and bisazacrown were synthesized by direct bonding of the anthracenyl spacer to a nitrogen atom of macrocycles.

The synthesis of cofacial metallodiporphyrins has played a significant role in the investigation of electron transfer and of the activation of small molecules (such as dihydrogen, dioxygen, dinitrogen, water, or ammonia) and has also enabled us to understand the mechanism of photosynthesis.[1,2] Pacman A and B porphyrins were also used to prepare various binuclear catalysts which can be employed for dioxygen reduction.[3,4] Other types of face-to-face porphyrins have also been investigated and interesting applications have been found, for instance, for molecular recognition.[2,5,6] The distance between the two porphyrin rings as well as the rigidity of the spacer group play a crucial role in the chemical properties of cofacial diporphyrins.[7] Over the last decade, the use of saturated bismacrocyclic ligands instead of porphyrins has been studied because of their easier synthesis.[8] They contain two polyazamacrocycles which are linked, either through aliphatic (or aromatic) spacers bonded to nitrogen atoms or through two covalently bonded carbon atoms.[9,10] Recently, the synthesis of a variety of bismacrocycles bound through aryl spacers has been described by our group.[11] However, so far, only aliphatic or benzyl-type linkers have been used to prepare these models; direct bonding of two polyazamacrocycles to an aryl spacer can hardly be achieved with known synthetic procedures, and this fact strictly limits any progress in this area.

Here we show that the Pd-catalyzed amination reaction of aryl halides can be a useful tool to synthesize new model compounds which are saturated analogues of cofacial porphyrins containing a rigid spacer group. Over the past 5 years the Pd-catalyzed carbon–nitrogen bond formation became a remarkable method in organic chemistry.[12] However, the Pd-catalyzed arylation of polyazamacrocycles might pose several problems, given that the secondary amines are known to be the most reluctant substrates in Pd-catalyzed arylation. Indeed, the formation of stable palladium complexes with polyamines and polyazamacrocycles can also be observed, thus hindering the catalytic reaction.[13] For this reason, we have already studied the catalytic arylation of cyclam **1** and cyclen **2**, which are typical representatives of saturated tetraazamacrocycles. The reaction of cyclam with aryl halides (chloro-, bromo-, iodosubstituted benzenes, 1-bromonaphthalene, 4-bromobiphenyl, and 9-bromoanthracene) was tested using various combinations of a palladium source with sup-



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Scheme 1.

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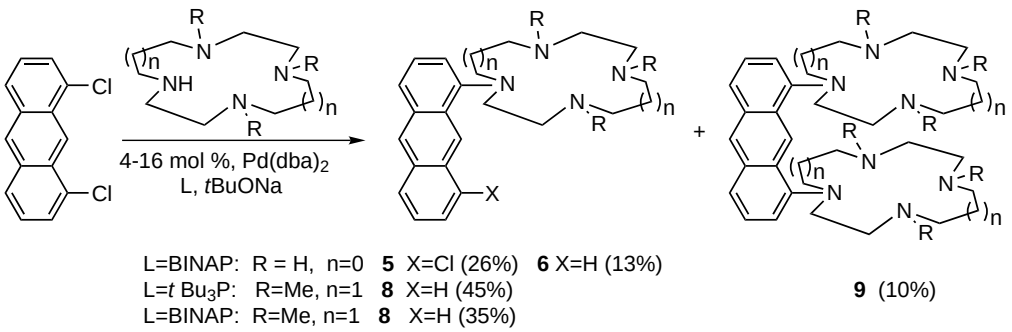
porting ligands: $Pd(dba)_2$, $Pd(OAc)_2$, $PdCl_2$, dppf, BINAP, tBu$_3$P, P(o-Tol)$_3$, P(Cy)$_3$ but none of them proved to be suitable for our purpose. We have only noted the full or partial reduction of aryl halides into the corresponding hydrocarbons. Yet, the reaction of cyclam with 4-bromobiphenyl and 4-bromobenzonitrile using PPF-OMe,[14] afforded *N*-arylated cyclams **3** and **4** in 20–22% yields (Scheme 1). It is remarkable to note that among numerous derivatives of cyclam,[15] only the *N*-arylated molecules containing electron-withdrawing groups on the aromatic substituents were obtained by aromatic nucleophilic substitution. Thus, the Pd-catalyzed arylation of cyclam leads to a wider range of tetraazamacrocycles possessing aromatic substituents directly bonded to the nitrogen atom.

The possible Pd-catalyzed arylation of cyclam led us to study the synthesis of saturated analogues of cofacial diporphyrins. The 1,8-disubstituted anthracene was chosen as a spacer since we had carried out the amination of 1,8-dichloroanthracene with primary and secondary amines.[16] During the first experiments, we used the catalytic system $Pd(dba)_2$/BINAP instead of the expensive PPF-OMe. The reaction of 1,8-dichloroanthracene with cyclam in the presence of 4–8 mol% of $Pd(dba)_2$/BINAP and tBuONa only led to the formation of anthracene, which is the reduction product of the starting dichloride. The same reaction starting from the less basic cyclen **2** in the presence of 5 mol% $Pd(dba)_2$/BINAP has been more successful, yielding a mixture of monocyclen substituted anthracenes **5**, **6** together with the free anthracene (Scheme 2). Nevertheless, a prolonged heating of the reaction mixture and the use of a greater amount of the catalyst precursor did not produce biscyclen substituted anthracene. Besides, the use of the very promising tri-*tert*-butylphosphine as a supporting ligand in this reaction also failed.[17]

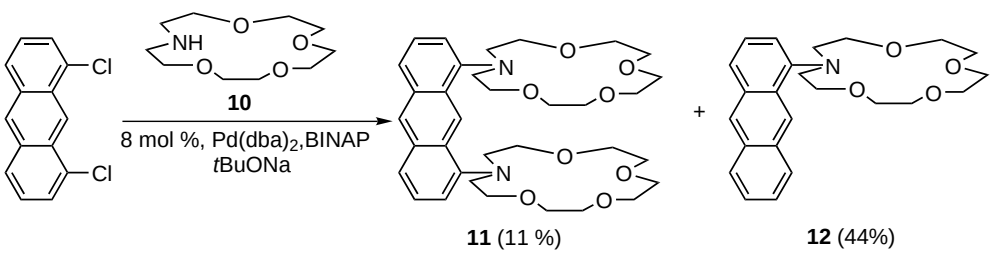
In order to avoid an undesirable reduction of the dichloride derivative, *N*,*N*′,*N*″-trisubstituted derivatives of cyclam should be used: indeed, they seem more suitable than the free cyclam which contains four secondary amino groups capable of participating in the reduction of dichloroanthracene. The reactions of *N*,*N*′,*N*″-trimethylcyclam **7** promoted by the Pd complex ($Pd(dba)_2$, 16 mol%) with tBu$_3$P generated a monocyclam derivative of anthracene **8** in 45% yield. Only traces of the aimed biscyclam product **9** were detected in the mass spectrum. Further attempts to use $Pd(dba)_2$/BINAP as a catalytic system (16 mol%), resulted in the formation of the target compound **9** in 10% yield together with the monosubstituted anthracene **8** (35%) (Scheme 2).

This preparation of the aimed cofacial biscyclam led us to demonstrate the applicability of such a methodology regarding the synthesis of biscrown substituted anthracene. Previously, only a few aryl substituted azacrown ethers were known.[18] The reaction of 1-aza-4,7,10,13-tetraoxacyclopentadecane **10** with 1,8-dichloroanthracene in the presence of $Pd(dba)_2$/BINAP gave the target face-to-face bisazacrown **11** in 11% yield (Scheme 3).

In conclusion, we have shown that the Pd-catalyzed amination reaction is a convenient tool for the preparation of aryl substituted tetraazamacrocycles and azacrown ethers including saturated analogues of face-to-face porphyrins. Despite the fact that up to now



Scheme 2.



Scheme 3.

yields have been low, this is a unique methodology for the one-pot synthesis of such demanded molecules which uses commercially available materials as starting compounds. Moreover, these compounds are important ligands for the complexation of a great variety of metal ions and for the study of their reactivity towards oxygen and other small molecules. This work is in progress in our group.

Synthesis of 1,8-*N*,*N*′-bis(4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecyl-1) anthracene 9: A two-necked flask filled with argon was charged with 1,8-dichloroanthracene (247 mg, 1 mmol), *N*,*N*′,*N*″-trimethylcyclam (484 mg, 2 mmol), $Pd(dba)_2$ (92 mg, 0.16 mmol), BINAP (110 mg, 0.178 mmol), *t*BuONa (400 mg, 4 mmol) and 10 ml of dioxane. The reaction mixture was refluxed for ca. 100 h, then dioxane was evaporated in vacuum, and the solid residue was taken in dichloromethane (30 ml), washed three times with 10 ml of water, dried over Na_2SO_4, evaporated in vacuum and chromatographed on silica (CH_2Cl_2/MeOH/NH_3(aq) = 10:3:1). Yield of **9** after chromatography 67 mg (10%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H ppm (J_{HH}, Hz): 1.71 q (4H, 6.4), 1.75 q (4H, 6.4), 2.17 s (6H), 2.20 s (6H), 2.30 s (6H), 2.34–2.68 m (24H), 3.38 t (4H, 6.6), 3.48 t (4H, 6.8), 7.11 d (2H, 7.0), 7.35 t (2H, 7.7), 7.65 d (2H, 8.3), 8.33 s (1H), 9.26 s (1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C, ppm: 24.0 (4C), 43.6 (4C), 43.8 (2C), 50.5 (2C), 51.9 (2C), 53.3 (2C), 53.4 (2C), 53.7 (2C), 54.8 (2C), 55.0 (2C), 55.5 (2C), 116.5 (2C), 119.4 (1C), 123.1 (2C), 125.2 (2C), 126.6 (1C), 128.1 (2C), 133.0 (2C), 149.6 (2C). [M^+] 658.7.

Synthesis of 1,8-*N*,*N*′-bis(1-aza-4,7,10,13-tetraoxacyclopentadecyl-1)anthracene 11: 1,8-Dichloroanthracene (123 mg, 0.5 mmol), 1-aza-4,7,10,13-tetraoxapentadecane **10** (264 mg, 1.0 mmol), *t*BuONa (200 mg, 2.1 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol) and BINAP (62 mg, 0.1 mmol) were dissolved in dioxane (40 ml) in a Schlenk flask under argon. The reaction mixture was refluxed for 48 h. The reaction mixture was cooled down to room temperature and concentrated in vacuum. The residue was taken in dichloromethane (30 ml), washed with water, dried over Na_2SO_4 and evaporated in vacuum. The residue was chromatographed on silica using CH_2Cl_2/MeOH (100:3). Yield of **11** 36 mg (11%). ^{1}H NMR (200 MHz, $CDCl_3$) δ_H, ppm (J_{HH}, Hz): 3.60–3.80 m (40H), 7.23 d (2H, 7.2), 7.35 t (2H, 4.2), 7.67 d (2H, 8.6), 8.33 s (1H), 9.15 s (1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C, ppm: 54.3 (4C), 70.3 (4C), 70.6 (4C), 70.8 (4C), 71.0 (4C), 117.0 (2C), 119.6 (1C), 123.4 (2C), 125.4 (2C), 126.9 (1C), 128.4 (2C), 133.2 (2C), 148.7 (2C).

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References

1. (a) Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435; (b) Osuka, A.; Kobayashi, F.; Nakajima, S.; Maruyama, K.; Yamazaki, I.; Nishimura, Y. *Chem. Lett.* **1993**, 161; (c) Arnold, D. P.; Nitschinsk, L. J. *Tetrahedron Lett.* **1993**, *34*, 693; (d) Lin, V. S. Y.; DiMango, S. G.; Therein, M. J. *Science* **1994**, *264*, 1105; (e) Senge, M. O.; Vicente, M. G. H.; Gerzevske, K. R.; Forsyth, T. P.; Smith, K. M. *Inorg. Chem.* **1994**, *33*, 5625.
2. Collman, J. P.; Wagenknecht, P. S.; Hutchison, J. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1537.
3. (a) Chang, C. K.; Abdalmuhdi, I. *J. Org. Chem.* **1983**, *48*, 5388; (b) Guilard, R.; Lopez, M. A.; Tabard, A.; Richard, P.; Lecomte, C.; Brandès, S.; Hutchison, J. E.; Collman, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 9877; (c) Chang, C. K.; Abdalmuhdi, I. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 164; (d) Collman, J. P.; Hutchison, J. E.; Lopez, M. A.; Tabard, A.; Guilard, R.; Seok, W. K.; Ibers, J. A.; L'Her, M. *J. Am. Chem. Soc.* **1992**, *114*, 9869.
4. (a) Guilard, R.; Brandès, S.; Tardieux, C.; Tabard, A.; L'Her, M.; Miry, C.; Gouerec, P.; Knop, Y.; Collman, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11721; (b) Lachkar, M.; Tabard, A.; Brandès, S.; Guilard, R.; Atmani, A.; De Cian, A.; Fischer, J.; Weiss, R. *Inorg. Chem.* **1997**, *36*, 4141.
5. Risch, N.; Gauler, R.; Keuper, R. *Tetrahedron Lett.* **1999**, *40*, 2925.
6. Hayashi, T.; Nonoguchi, M.; Aya, T.; Ogoshi, H. *Tetrahedron Lett.* **1997**, *38*, 1603.
7. Kadish, K. M.; Smith, K. M.; Guilard, R. *The Porphyrin Handbook*; Academic Press: New York, 2000; Vol. 3, p. 235.
8. (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Aza-Crown Macrocycles*; Wiley: New York, 1993; 51; (b) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, 1989; 122.
9. (a) Schneider, R.; Riesen, A.; Kaden, T. A. *Helv. Chim. Acta* **1985**, *68*, 53; (b) Ciampolini, M.; Fabbrizzi, L.; Perotti, A.; Poggi, A.; Seghi, B.; Zanobini, F. *Inorg. Chem.* **1987**, *26*, 3527; (c) Urfer, A.; Kaden, T. A. *Helv. Chim. Acta* **1994**, *77*, 23; (d) Bridger, G. J.; Skerlj, R. T.; Thornton, D.; Padmanabhan, S.; Martellucci, S. A.; Henson, G. W.; Abrams, M. J.; Yamamoto, N.; De Vreese, K.; Pauwels, R.; De Clercq, E. *J. Med. Chem.* **1995**, *38*, 366.
10. (a) Buttafava, A.; Fabbrizzi, L.; Perotti, A.; Seghi, B. *J. Chem. Soc., Chem. Commun.* **1982**, 1166; (b) Fabbrizzi, L.; Montagna, L.; Poggi, A.; Kaden, T. A.; Siegfried, L. C. *Inorg. Chem.* **1986**, *25*, 2672; (c) Buttafava, A.; Fabbrizzi, L.; Perotti, A.; Poggi, A.; Seghi, B. *Inorg. Chem.* **1984**, *23*, 3917; (d) Kajiwara, T.; Yamaguchi, T.; Kido, H.; Kawabata, S.; Kuroda, R.; Ito, T. *Inorg. Chem.* **1993**, *32*, 4990.
11. Brandès, S.; Gros, C.; Denat, F.; Pullumbi, P.; Guilard, R. *Bull. Soc. Chim. Fr.* **1996**, *133*, 65.
12. (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125; (b) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2047; (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144; (d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

13. (a) Zhang, D.; Busch, D. H. *Inorg. Chem.* **1994**, *33*, 5138; (b) Bazzicalupi, C.; Bencini, A.; Cohen, H.; Giorgi, C.; Golub, G.; Meyerstein, D.; Navon, N.; Paoletti, P.; Valtancoli, B. *J. Chem. Soc., Dalton Trans.* **1998**, 1625.
14. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
15. Beletskaya, I. P.; Artamkina, G. A.; Ivushkin, V. A.; Guilard, R. *Tetrahedron Lett.* **2000**, *41*, 313.
16. (a) Beletskaya, I. P.; Averin, A. D.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **2001**, *42*, 4983; (b) Beletskaya, I. P.; Averin, A. D.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **2001**, *42*, 4987.
17. Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.
18. (a) Matsumoto, K.; Hashimoto, M.; Toda, M.; Tsukube, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2497; (b) Tsukube, H.; Minatogawa, H.; Munakata, M.; Toda, M.; Matsumoto, K. *J. Org. Chem.* **1992**, *57*, 542; Pd-catalyzed approach; (c) Witulski, B. *Synlett* **1999**, 1223; (d) Witulski, B.; Zimmermann, Y.; Darcos, V.; Desvergne, J.-P.; Bassani, D. M.; Bouas-Laurent, H. *Tetrahedron Lett.* **1998**, *39*, 4807 when this manuscript was in preparation a study of azacrown arylation was published by Buchwald and Witulski; (e) Zhang, X. X.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 8027; (f) Witulski, B.; Weber, M.; Bergstraesser, U.; Desvergne, J.-P.; Bassani, D. M.; Bouas-Laurent, H. *Org. Lett.* **2001**, *3*, 1467.