ORGANIC LETTERS

2013
Vol. 15, No. 14
3798–3801

Hydrogen Bond Templated 1:1 Macrocyclization through an Olefin Metathesis/Hydrogenation Sequence

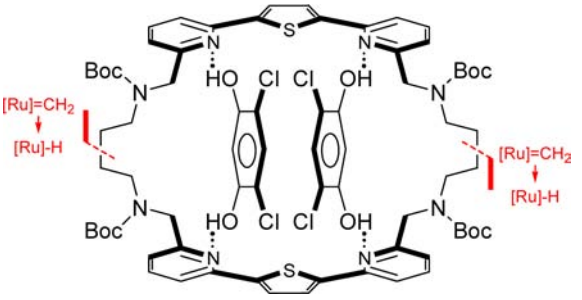
Andrada Stefania Trita,[†] Thierry Roisnel,[‡] Florence Mongin,[†] and Floris Chevallier*,[†]

Chimie et Photonique Moléculaires, Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS - Université de Rennes 1, Campus de Beaulieu, CS 74205, 35042 Rennes Cedex, France, and Centre de DIFfractométrie X, Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS - Université de Rennes 1, Campus de Beaulieu, CS 74205, 35042 Rennes Cedex, France

floris.chevallier@univ-rennes1.fr

Received June 26, 2013

ABSTRACT



The construction of pyridine-containing macrocyclic architectures using a nonmetallic template is described. 4,6-Dichlororesorcinol was used as an exotemplate to self-organize two aza-heterocyclic units by OH···N hydrogen bonds. Subsequent sequential double olefin metathesis/hydrogenation reactions employing a single ruthenium−alkylidene precatalyst open access to macrocyclic molecules.

Macrocycles are important structural elements in many fields, including natural products,[1] pharmaceuticals,[2] and nanotechnologies.[3] Templation strategies for macrocyclic molecule synthesis by ring closure involve covalent, including dipolar bonds, and noncovalent bonding forces.[4] The latter rely on supramolecular recognition motifs such as π-interactions, van der Waals forces, and hydrogen bonds. These reversible electrostatic interactions have been elegantly employed in guanidinium-,[5] ammonium-,[6] chloride-,[7] barbiturate-,[8] or dicarbonyl-directed[9] elaborations of macrocyclic and interlocking structures.

Here we report the construction of pyridine-containing macrocycles using a nonmetallic template. For this purpose, we focused on ditopic hydrogen-bond donors as exotemplate and especially on resorcinol (Figure 1).

[†] CPM.
[‡] CDIFX.

(1) (a) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012. (b) Nor, S. M. M.; Xu, Z.; Ye, T. In *Heterocyclic Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; p 569.

(2) (a) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608. (b) Mallinson, J.; Collins, I. *Future Med. Chem.* **2012**, *4*, 1409.

(3) (a) Iyoda, M.; Yamakawa, J.; Rahman, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10522. (b) Davis, F.; Higson, S. *Macrocycles: Construction, Chemistry and Nanotechnology Applications*; John Wiley & Sons Ltd: Chichester, 2011.

(4) (a) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*; VCH: Weinheim, 1993. (b) Gerbeleu, N. V.; Arion, V. B.; Burgess, J. *Template Synthesis of Macrocyclic Compounds*; Wiley-VCH: Weinheim, 1999. (c) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210. (d) Vilar, R. *Struct. Bonding (Berlin)* **2004**, *111*, 85. (e) Laughrey, Z. R.; Gibb, B. C. *Top. Curr. Chem.* **2005**, *249*, 67. (f) Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4808.

(5) Madan, K.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1975**, 427.

(6) Ashton, P. R.; Campbell, P. J.; Chrystal, E. J. T.; Glinke, P. T.; Menzer, S.; Philp, D.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1865.

(7) Alcalde, E.; Alvarez-Rúa, C.; García-Granda, S.; García-Rodriguez, E.; Mesquida, N.; Pérez-García, L. *Chem. Commun.* **1999**, 295.

(8) Cardullo, F.; Calama, M. C.; Snellink-Ruël, B. H. M.; Weidmann, J. L.; Bielejewska, A.; Timmerman, P.; Reinhoudt, D. N.; Fokkens, R.; Nibbering, N. M. M. *Chem. Commun.* **2000**, 367.

(9) Gatti, F. G.; Leigh, D. A.; Nepogodiev, S. A.; Slawin, A. M. Z.; Teat, S. J.; Wong, J. K. Y. *J. Am. Chem. Soc.* **2001**, *123*, 5983.

10.1021/ol401803t
Published on Web 07/05/2013

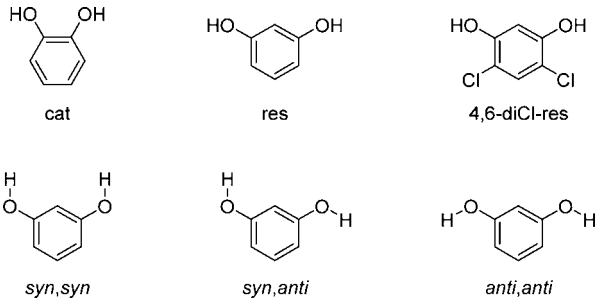
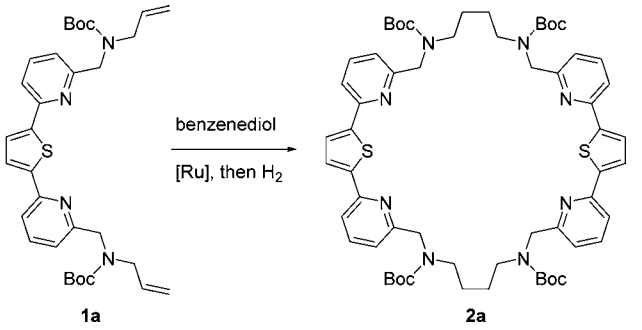


Figure 1. Catechol (cat), resorcinol (res), 4,6-dichlororesorcinol (4,6-diCl-res), and three conformations of resorcinol.

This neutral organic molecule has demonstrated its ability to self-organize two aza-heterocyclic units[10] and has been efficiently used as a linear template to direct intermolecular [2 + 2] photodimerization in the solid state.[11] Due to the compatibility of ring-closing, ring-opening/ring-closing and cross metathesis with hydrogen-bonded assemblies,[12] we opted for the olefin metathesis approach to achieve the construction of the macrocyclic architecture under mild conditions. Moreover, ruthenium alkylidene metathesis catalysts being effective precatalysts for alkene reduction,[13] the sequential metathesis/hydrogenation process was found to be suitable to study the macrocyclization step while avoiding diastereomeric mixture of *cis*/*trans* olefin products and thus facilitate the analysis.

In a first set of experiments, we studied the 1:1 macrocyclization of the aromatic triheterocycle **1a** which contains two carbamate-protected allylamine functions. The reactions were attempted with commercially available first-generation, $[(PCy_3)_2Cl_2Ru{=}CHPh]$, and second-generation, $[(H_2IMes)(PCy_3)Cl_2Ru{=}CHPh]$, Grubbs catalysts (10 mol %) in 1,2-dichloroethane[14] under an atmospheric pressure of argon and dihydrogen, successively (Table 1). In the absence of any template molecule and whatever the catalyst selected, the desired macrocycle **2a**

Table 1. Evaluation of Reaction Parameters for Two-Component Macrocyclization[a]



entry	benzenediol	yield (%)
1		14, 6[b]
2[c]		17, 10[b]
3	catechol (1.0 equiv)	7
4	resorcinol (1.0 equiv)	61
5	4,6-diCl-res (1.0 equiv)	82, 66[b]
6	4,6-diCl-res (1.5 equiv)	71
7	4,6-diCl-res (0.5 equiv)	75
8	4,6-diCl-res (0.1 equiv)	41

[a] Reaction conditions: $[\mathbf{1a}]_{t=0} = 10^{-2}$ M in $(ClCH_2)_2$, benzenediol, $[(H_2IMes)(PCy_3)Cl_2Ru{=}CHPh]$ (10 mol %), 50 °C, 2 h, then H_2 (1 atm), 70 °C, 24 h. [b] Reaction performed with $[(PCy_3)_2Cl_2Ru{=}CHPh]$. [c] Reaction performed with $[\mathbf{1a}]_{t=0} = 10^{-4}$ M.

was obtained in low yields, and linear oligomers were formed as side products by an acyclic diene metathesis (ADMET)/hydrogenation pathway (entry 1). A similar conclusion was made after performing the reaction in a hundred times less concentrated solution without significant increasing of the selectivity (entry 2). Repeating the reaction with the second generation Grubbs carbene complex in the presence of 1 equivalent of catechol (Figure 1) resulted in the formation of **2a** in 7% yield together with ADMET products (entry 3). In order to examine the templating effect of 1,3-diols, a similar reaction procedure was carried out using resorcinol (1 equiv). In this case, the expected cyclized and reduced product **2a** was isolated in a 61% yield (entry 4). Higher yields of 82% with second, and 66% with first generation Grubbs catalysts, were observed when using 1 equivalent of 4,6-dichlororesorcinol (Figure 1) as template (entry 5). In addition, on the basis of entries 5–8, this type of reaction appears to require 1 equiv of 4,6-diCl-res to afford the desired adduct in good yield.

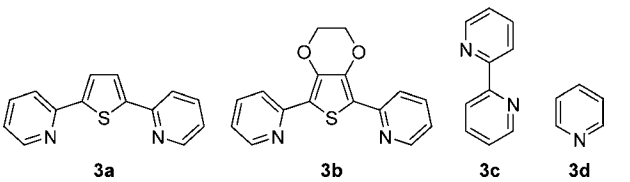


Figure 2. Nonsubstituted pyridine-containing substrates **3a**–**d**.

(10) (a) Watson, W. H.; Galloy, J.; Vögtle, F.; Müller, W. M. *Acta Crystallogr., Sect. C Cryst. Struct. Commun.* **1984**, *C40*, 200. (b) Aoyama, Y.; Endo, K.; Anzai, T.; Yamaguchi, Y.; Sawaki, T.; Kobayashi, K.; Kanehisa, N.; Hashimoto, H.; Kai, Y.; Masuda, H. *J. Am. Chem. Soc.* **1996**, *118*, 5562. (c) Nagasato, S.; Sunatsuki, Y.; Ohsato, S.; Kido, T.; Matsumoto, N.; Kojima, M. *Chem. Commun.* **2002**, 14.

(11) (a) MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 7817. (b) Gao, X.; Friščić, T.; MacGillivray, L. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 232. (c) Dutta, S.; Bučar, D.-K.; MacGillivray, L. R. *Org. Lett.* **2011**, *13*, 2260.

(12) (a) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364. (b) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599. (c) Yang, X.; Gong, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 1352. (d) Zeng, J.; Wang, W.; Deng, P.; Feng, W.; Zhou, J.; Yang, Y.; Yuan, L.; Yamato, K.; Gong, B. *Org. Lett.* **2011**, *13*, 3798.

(13) (a) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (b) Drouin, S. D.; Zamanian, F.; Fogg, D. E. *Organometallics* **2001**, *20*, 5495. (c) Børsting, P.; Nielsen, P. *Chem. Commun.* **2002**, 2140. (d) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (e) Schmidt, B.; Pohler, M. *Org. Biomol. Chem.* **2003**, *1*, 2512. (f) Menozzi, C.; Dalko, P. I.; Cossy, J. *Synlett* **2005**, 2449. (g) Miao, X.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *ChemSusChem* **2009**, *2*, 542.

(14) The primary studies have shown that the use of dichloromethane as solvent leads to a mixture of cyclized and isomerized olefin products, without hydrogen transfer.

The low yield of **2a** observed with catechol can be explained by the inability of this 1,2-diol to properly assemble two pyridine substrates in solution. This was supported by the X-ray diffraction study of single crystals, obtained by slow evaporation of a dichloromethane solution containing an equimolar mixture of catechol and a nonsubstituted triheterocyclic compound **3a** (Figure 2), structurally similar to **1a** (Figure 3a). In contrast, resorcinol and, above all, 4,6-diCl-res induced a positive effect on the selectivity of the reaction. The difference between the results obtained using resorcinol and 4,6-diCl-res is due to not only the fact that 4,6-diCl-res is a better H-bond donor than resorcinol but also in relation with the conformation adopted by the hydroxyl groups of the resorcinols (Figure 1). Indeed, in order to assemble the components in a discrete structure, the *syn-syn* conformation of resorcinols is required.[15] The introduction of chlorine substituents

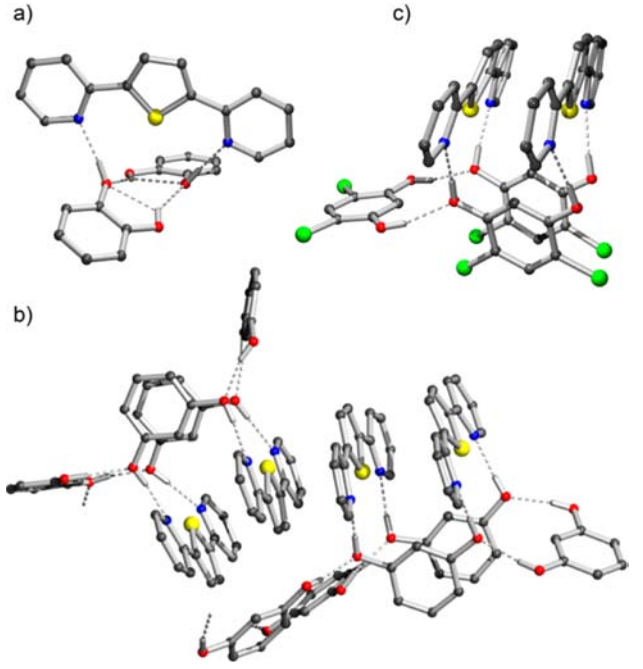


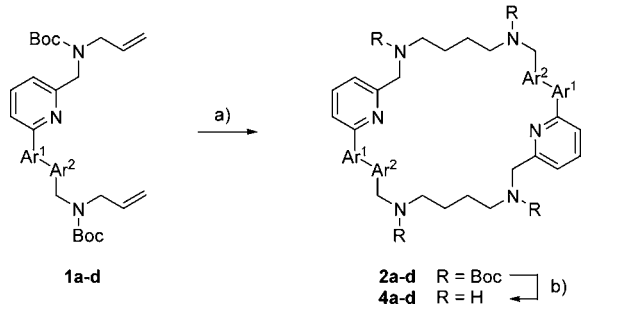
Figure 3. Crystal structures of (a) $(cat)_2\cdot(\mathbf{3a})$, (b) $(res)_{8.5}\cdot(\mathbf{3a})_4$, and (c) $(4,6\text{-diCl-res})_3\cdot(\mathbf{3a})_2$. Key: C, dark gray; H, light gray; Cl, green; N, blue; O, red; S, yellow. Hydrogen atoms bound to carbon atoms are omitted for clarity.

in the 4- and 6-position of resorcinol can constrain, by steric interactions, the diol to adopt a convergent conformation,[16] and consequently, 4,6-diCl-res can promote more efficiently the macrocyclization step.

In order to obtain additional information about the assembly of these hydrogen-bond acceptors and donors, the cocrystallization of **3a** with an equimolar amount of resorcinol and 4,6-diCl-res has been investigated, affording $(res)_{8.5}\cdot(\mathbf{3a})_4$ (Figure 3b) and $(4,6\text{-diCl-res})_3\cdot(\mathbf{3a})_2$ (Figure 3c). In both cases, X-ray structures reveal that two bis-pyridyl units **3a** are preorganized by two 1,3-diols in a stacked arrangement by way of four OH···N hydrogen bonds (O···N interatomic distances from 2.6777(19) to 2.832(2) Å). It has to be noted that one additional 4,6-diCl-res molecule, and more than four additional resorcinol units, stabilized by hydrogen-bonding interactions with oxygen atoms, were also identified in the crystal structures. The additional *ortho*-disubstituted resorcinol adopts the *syn*,*syn* conformation while the additional nonsubstituted resorcinols adopt the *syn*,*syn*, *syn*,*anti*, and *anti*,*anti* conformations.

With the reaction conditions established, the macrocyclization/hydrogenation sequential reaction of a variety of pyridine-containing derivatives has been examined (Table 2). In the presence of a stoichiometric amount of 4,6-diCl-res, the cyclized and reduced products **2a**–**d** were obtained in 42 to 85% yield. The replacement of the thiophene ring with the electron-donating 3,4-ethylenedioxythiophene building

Table 2. Two-Component Macrocyclization Using Various Pyridine-Containing Terminal Dienes



entry	Ar^1	Ar^2	**2** (yield, %)	**4** (yield, %)
1			**2a** (82)	**4a** (97)
2			**2b** (85)	**4b** (95)
3		-	**2c** (79)	**4c** (90)
4	-	-	**2d** (42, 72[c])	**4d** (95)

[a] Reaction conditions: 4,6-diCl-res (1.0 equiv), $[\mathbf{1a}-\mathbf{d}]_{t=0} = 10^{-2}$ M in $(ClCH_2)_2$, $[(H_2IMes)(PCy_3)Cl_2Ru{=}CHPh]$ (10 mol %), 50 °C, 2 h, then H_2 (1 atm), 70 °C, 24 h. [b] Reaction conditions: TFA, CH_2Cl_2, rt, 3 h. [c] Reaction performed with 0.5 equiv of 4,6-diCl-res.

block[17] resulted in the product being isolated in similar yield (entry 2). This observation was not significantly affected by the use of a bipyridine derivative **1c** as a reactant (entry 3). As shown in entry 4, the moderate 42% yield obtained by employing **1d** in the same process can be attributed to the excess of ditopic template (1 equiv) relative to the monotopic substrate. Indeed, the decrease of 4,6-diCl-res amount to 0.5

(15) Friščić, T.; MacGillivray, L. R. *Mol. Cryst. Liq. Cryst.* **2006**, *456*, 155.

(16) Papaefstathiou, G. S.; MacGillivray, L. R. *Org. Lett.* **2001**, *3*, 3835.

(17) Chevallier, F.; Charlot, M.; Katan, C.; Mongin, F.; Blanchard-Desce, M. *Chem. Commun.* **2009**, 692.

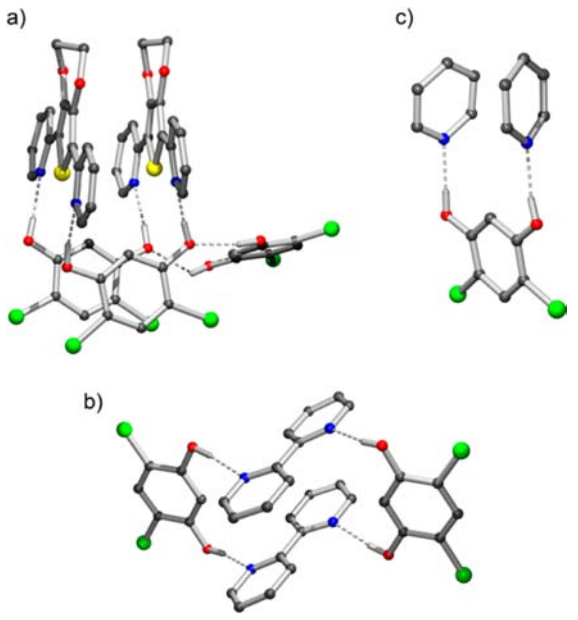


Figure 4. Crystal structures of (a) (4,6-diCl-res)$_3$·(**3b**)$_2$, (b) (4,6-diCl-res)$_2$·(**3c**)$_2$, and (c) (4,6-diCl-res)·(**3d**)$_2$. Key: C, dark gray; H, light gray; Cl green; N, blue; O, red; S, yellow. Hydrogen atoms bound to carbon atoms are omitted for clarity.

equiv led to the expected product **2d** in 72% yield. Lastly, the treatment with trifluoroacetic acid cleaved the *tert*-butyl carbamates to furnish the deprotected cyclic tetrasecondary amines **4a**–**d** in high yields.

The behavior of **1a**–**d** and 4,6-diCl-res in solution was studied by means of NMR spectroscopy in deuterated chloroform.[18] In addition to the variations of the ^{1}H and ^{13}C chemical shift values of individual and combined compounds, the meaningful nuclear Overhauser effects observed allowed us to establish proximities between the proton at C-2 of 4,6-diCl-res and the methylene protons adjacent to the pyridine ring of **1a**–**d**.[18] Complementary IR spectroscopy measurements revealed the shift to lower energy of the hydroxyl-stretching vibrations of 4,6-diCl-res after addition of **1a**–**d**, which is consistent with the presence of hydrogen-bonding networks.[18] Finally, cocrystallization of 4,6-diCl-res with the nonsubstituted heterocyclic components **3b**–**d** (Figure 2) produced discrete assemblies similar to that observed with **3a**. In these hydrogen-bonded structures, two ditopic pyridine substrates were organized parallel by two orthogonal 4,6-diCl-res (Figure 4a,b), while monotopic substrates were assembled by one 4,6-diCl-res molecule (Figure 4c).

In conclusion, we have demonstrated that 4,6-diCl-res can be efficiently used as a ditopic template in solution. The template-mediated cyclization by sequential double olefin metathesis/hydrogenation, using a single ruthenium-alkylidene precatalyst, requires 0.5 equiv of 4,6-diCl-res per substrate binding site to afford pyridine-containing macrocycles.

Acknowledgment. We gratefully acknowledge Pauline Grijol and François Loyer (Université de Rennes 1) for their contributions to this study.

Supporting Information Available. Experimental procedures, characterization data, X-ray crystallographic information (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(18) For details, see the Supporting Information.

The authors declare no competing financial interest.