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Naphthyridine-Based Helical Foldamers and Macrocycles: Synthesis, Cation Binding, and Supramolecular Assemblies

Anne Petitjean,[†,‡] Louis A. Cuccia,[†,§] Marc Schmutz,[||] and Jean-Marie Lehn*[,†]

Laboratoire de Chimie Supramoléculaire, Institut de Science et d'Ingénierie Supramoléculaires, Université Louis Pasteur, 8 Allée Gaspard Monge, BP 70028, 67083 Strasbourg Cedex, France, and Institut Charles Sadron, BP 40016, 6 rue Boussingault, 67083 Strasbourg Cedex, France

lehn@isis.u-strasbg.fr

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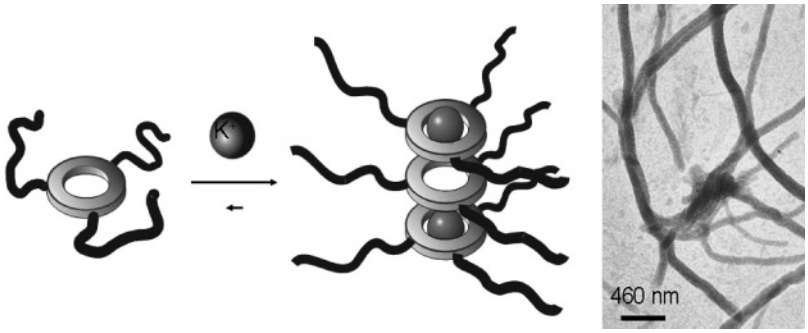

Unraveling the factors that control the conformation of molecular chains is of great interest both for understanding the shape of biological molecular strands and for designing artificial ones that adopt desired forms. Thus, a variety of artificial folding codons have been identified that enforce the formation, among others, of helices, strands, and loops, the major emphasis being on the shape of the foldamer. We report herein the synthesis and study of a family of foldamers and macrocycles based on the 1,8-naphthyridine and pyrimidine units, whose internal cavity is large enough to accommodate ionic substrates, and focus on the impact of guest binding within a cylindrical environment. Interestingly, the binding event within these large oligomers is translated to the outside of the receptors and affects the interaction of the overall complexes with the outside world. For instance, alkali cations bind to the one-turn helices and macrocycles to promote fibril formation and aggregation. Also, polyammonium substrates are able to tune the length of the overall helix assemblies and the rigidity of long oligomers. The reported data on one-turn, two-turn helices and macrocycles not only allows one to devise a model for the ion-controlled supramolecular assembly of such systems but also provides evidence that such controlled scaffolds bear promise in the design of complex systems.

Introduction

Developing systems of controlled conformational properties (foldamers[1]) and understanding their relation to function is of basic interest both for unraveling the factors determining the shapes of biological molecular strands and for designing artificial ones that fold in a desired fashion. In more general terms, the behavior of such entities implements *molecular self-organization* processes that result from geometric and conformational features

[†] Université Louis Pasteur.
[‡] Present address: Department of Chemistry, Queen's University, 90 Bader Lane, Kingston ON, Canada K7L3N6.
[§] Present address: Department of Chemistry & Biochemistry, Concordia University, 7141 Sherbrooke St. W., Montreal QC, Canada H4B 1R6.
[||] Institut Charles Sadron.

(1) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011. (c) Sanford, A.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649−1659.

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introduced by covalent bonds as well as from nonbonded intramolecular interactions. It corresponds, on the molecular level, to the supramolecular self-organization processes that generate specific complex architectures resulting from the operation of noncovalent interactions.[2]

Helical conformations have been the subject of great interest, in view of both their extensive presence in biomolecules and their attractive structural features. They result from the intrinsic conformational preference of *folding codons* based on hydrogen bonding,[3] dipolar[4] and steric[5] effects and from interactions with the environment.[6] Interest in molecular helices is also triggered by their inherent chirality which can be encoded in a molecular strand either by its components[7] or by interactions with the environment.[8,4g] In line with the active development of research on molecular machines,[9] the focus has evolved from the mere control of the conformation of helical foldamers to the induced properties, such as the control of the folding/unfolding processes by ionic,[10] organic[11,6e] and coordination[12] effectors and light,[13] the optical[14a] and stereochemical[14b] properties, as well as by the effect of the conformation on the interactions with the environment.[6,15] These features may involve not only the outside of the helix but notably its inside cavity. In this context, we have been interested in extending the helical foldamers based on a pyridine (py)-pyrimidine (pym) helicity codon, studied in our laboratory, to systems whose cavity would be large enough to accommodate substrates.

Design and Synthesis of Naphthyridine-Pyrimidine Foldamers

In solution as well as in the solid state, sequences of alternating pyridine (py) and pyrimidine (pym) heterocycles fold into helices because of the transoid conformational preference of the 2,2′-bipyridine motif.[16] Seven such heterocycles are required to complete a one-turn helix, whose external and internal diameters are of the order of 13 and 2.6 Å, respectively.[4a] The latter dimension being too small to incorporate substrates other than protons, larger helical structures were anticipated to be formed if one could "stretch the pyridines". Using the 1,8-naphthyridine (napy) groups as two fused pyridines instead of one, would be expected to yield helices presenting external and internal diameters in the order of 15 and 3.8 Å, respectively, large enough to accommodate small ions. In addition to enlarging the internal cavity, the introduction of such napy units, whose electric dipole is nearly twice that of pyridine,[17] was also anticipated to affect the electrostatic features of the oligomer. This should affect (i) the conformational bias of the oligomer as well as (ii) its electrostatic interactions with cations. The *preferred transoid* conformation of the 2,2′-bipyridine motif, which can be extended to any α,α′-connected heterocyclic diad, results, in part, from the stabilizing antiparallel dipole/dipole interaction between the two heterocyclic units. When exchanging a pyridine for a napy, the increase in the dipole moment should lead to an enhanced *transoid* preference, as quantified by DFT calculations reported in Table 1.[4e,18]

From the point of view of cation binding, the larger naphthyridine dipole was also anticipated to be favorable since, in the preferred helical conformation, the negative pole of the napy dipole should point toward the center of the cavity.

Results and Discussion

Synthesis of the Polyheterocyclic napy-pym Strands. Aside from their advantageous electrostatic properties, napy units are particularly attractive in view of their facile synthesis by ring-formation via the Friedländer condensation of an aminoaldehyde with a ketone. Scheme 1 illustrates how a "seven subunit" oligomer may be constructed by two consecutive Friedländer condensations to form the "external" and "internal" napy cycles.

Three families of napy-based oligomers were synthesized: (i) an open seven subunit oligomer (anticipated to form a one turn-helix), (ii) an open eleven subunit oligomer (anticipated to form a two turn helix), and (iii) a closed six subunit macrocycle. In the seven subunit family, three individual

(2) (a) Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763−4768 and references therein. (b) Atwood, J. L., Davies, J. F. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Eds. *Comprehensive Supramolecular Chemistry*; Pergamon Press: Oxford, 1996; Vol. 9. (c) Lehn, J.-M. *Supramolecular Chemistry−Concepts and Perspectives*; VCH: Weinheim, 1995; Chapter 9.

(3) (a) Berl, V.; Huc, I.; Khoury, R. G.; Krische, M.; Lehn, J.-M. *Chem. Eur. J.* **2001**, *7*, 2798−2809. (b) Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol*. **2001**, *5*, 650−653. (c) Sanford, A. R.; Yamato, K.; Yang, X.; Yuan, L.; Han, Y.; Gong, B. *Eur. J. Biochem*. **2004**, *271*, 1416−1425. (d) Sinkeldam, R. W.; van Houtem, M. H. C. J.; Koechelberghs, G.; Vekemans, J. A. J. M.; Meijer, E. W. *Org. Lett.* **2006**, *8*, 383−385.

(4) (a) Hanan, G.; Lehn, J.-M.; Kyritsakas, N.; Fisher, J. *Chem. Soc., Chem. Commun*. **1995** 757−766. (b) Okhita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J*. **1999**, *5*, 3471−3481. (c) Cuccia, L. A.; Lehn, J.-M.; Homo, J.-C.; Schmutz, M. *Angew. Chem., Int. Ed*. **2000**, *39*, 239−243. (d) Gardinier, K. M.; Khoury, R. G.; Lehn, J.-M. *Chem. Eur. J*. **2000**, *6*, 4124−4131. (e) Cuccia, L. A.; Ruiz, E.; Lehn, J.-M.; Homo, J.-C.; Schmutz, M. *Chem. Eur. J*. **2002**, *8*, 3448−3457. (f) Petitjean, A.; Cuccia, L. A.; Lehn, J.-M.; Nierengarten, H.; Schmutz, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1195−1198. (g) Petitjean, A.; Nierengarten, H.; Van Dorsselaer, A.; Lehn, J.-M. *Angew. Chem., Int. Ed*. **2004**, *43*, 3695−3695. (h) Schmitt, J.-L.; Stadler, A. M.; Kyritsakas, N.; Lehn, J. M. *Helv. Chim. Acta* **2003**, *86*, 1598−1624. (i) Stadler, A. M.; Kyritsakas, N.; Lehn, J.-M. *Chem. Commun*. **2004**, 2024−2025. (j) Petitjean, A.; Lehn, J.-M. *Inorg. Chim. Acta* **2007**, *360*, 849−856.

(5) Huck, B. R.; Fisk, J. D.; Guzei, I. A.; Carlson, H. A.; Gellman, S. H. *J. Am. Chem. Soc*. **2003**, *125*, 9035−9037.

(6) (a) Prince, R. B.; Saven, J. G.; Wolynes, P. G.; Moore, J. S. *J. Am. Chem. Soc*. **1999**, *121*, 3114−3121. (b) Prince, R. B.; Okada, T.; Moore, J. *Angew. Chem., Int. Ed*. **1999**, *38*, 233−236. (c) Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 2758−2762. (d) Hill, D. J.; Moore, J. S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5053−5057. (e) Inouye, M.; Waki, M.; Abe, H. *J. Am. Chem. Soc*. **2004**, *126*, 2022−2027.

(7) (a) Gin. M. S.; Tsutomu, Y.; Prince, R. B.; Moore, J. S. *J. Am. Chem. Soc*. **1999**, *121*, 2643−2644. (b) Prince, R. B.; Brunsveld, L.; Meijer, E. W.; Moore, J. S. *Angew. Chem., Int. Ed*. **2000**, *39*, 228−230. (c) Sinkeldam, R. W.; van Houten, M. H. C. J.; Pieterse, K.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem. Eur. J*. **2006**, *12*, 6129−6137.;

(8) (a) Tanatani, A.; Mio, M. J.; Moore, J. S. *J. Am. Chem. Soc*. **2001**, *123*, 1792−1793. (b) Wilson, A. J.; Masuda, M.; Sijbesma, R. P.; Meijer, E. W. *Angew. Chem., Int. Ed*. **2005**, *44*, 2275−2279.

(9) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72−191.

(10) (a) Barboiu, M.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5201−5206. (b) Kolomiets, E.; Berl, V.; Odriozola, I.; Stadler, A.-M.; Kyritsakas, N.; Lehn J.-M. *Chem. Commun*. **2003**, 2868−2869.

(11) Maeda, K.; Mochizuki, H.; Watanabe, M.; Yashima, E. *J. Am. Chem. Soc*. **2006**, *128*, 7639−7650.

(12) Tashiro, S.; Masahide, T.; Yamaguchi, Y.; Kato, K.; Fujita, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 241−244.

(13) Khan, A.; Kaiser, C.; Hecht, S. *Angew. Chem., Int. Ed*. **2006**, *45*, 1878−1881.

(14) (a) Jiang, X.; Bollinger, J. C.; Lee, D. *J. Am. Chem. Soc*. **2006**, *128*, 11732−11733. (b) Clayden, J.; Vassiliou, N. *Org. Biomolec. Chem*. **2006**, *4*, 2667−2678.

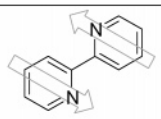
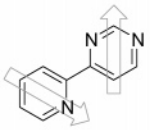
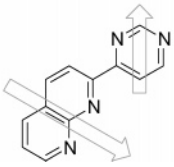
(15) (a) Cornell, R. B.; Taneva, S. G. *Curr. Prot. Pept. Science* **2006**, *7*, 539−552. (b) DeGrado, W.; Woolfson, D. N. *Curr. Opin. Struct. Biol*. **2006**, *16*, 505−507.

(16) Howard, S. T. *J. Am. Chem. Soc*. **1996**, *118*, 10269−10274.

(17) (a) Lide, D. R. *Handbook of Chemistry and Physics*; CRC Press, Inc.: Boca Raton, 1994. (b) Markgraf, J. H.; Skinner, J. F.; Marshall, G. T. *J. Chem. Eng. Data* **1988**, *33*, 9−10.

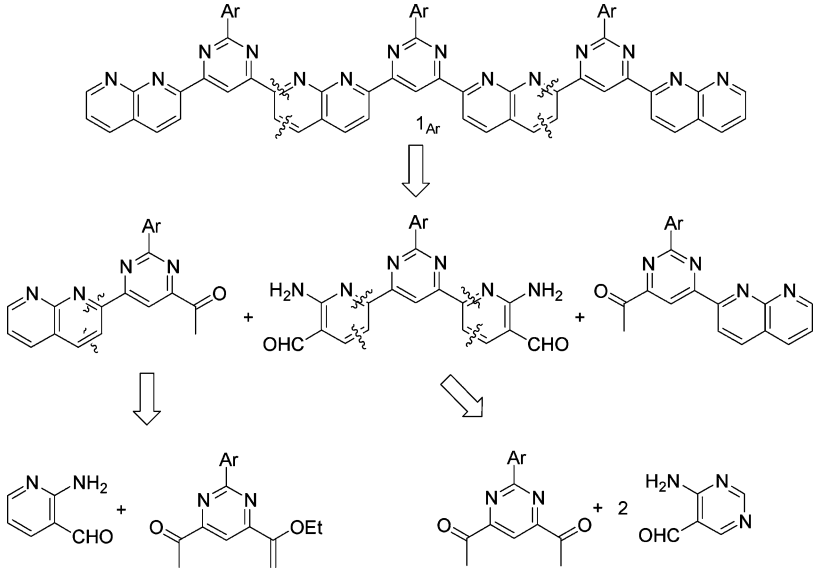
(18) Ruiz, E.; Lehn, J.-M. Unpublished results.

TABLE 1. Energies of Cis Conformers of Several Diads Relative to Their Trans Counterparts[a]

motif	abbreviation	E(*cis* in plane)	E(*cis* out of plane)
	**py-py**	8.3 kcal/mol	6.5 kcal/mol
	**py-pym**	8.0 kcal/mol	6.6 kcal/mol
	**napy-pym**	9.7 kcal/mol	7.6 kcal/mol

[a] Group dipole orientations are indicated by the arrows.

SCHEME 1. Retrosynthetic Analysis for the Synthesis of a Seven Heterocyclic Subunit Sequence



members differing by their peripheral substituents (*tert*-butyl, *n*-butyl, *p*-benzyloxyphenyl) were synthesized, for reasons discussed below. In the eleven subunit family, two members possessing five identical *n*-butylphenyl or mixed *n*-butylphenyl and benzyloxyphenyl substituents were synthesized.

Synthesis of the Pyrimidine Synthons. 2-, 4-, and 6-substituted pyrimidines were synthesized starting from substituted benzonitrile as shown in Scheme 2. Noncommercially available nitriles were derived from the corresponding bromide by a CuCN-mediated Sandmeier reaction[19] or by functionalization of the corresponding phenols. The nitriles were converted to benzamidines by consecutive reaction with ethanolic HCl and ammonia. Base-mediated condensation with diethyl malonate and chlorination using phosphoryl oxychloride yielded the 4-substituted 2,4-dichlorosubstituted pyrimidines. Stille cross-coupling with 1-ethoxyvinyltris(*n*-butyl)stannane allowed the introduction of the keto groups according to the stoechiometry.[4e]

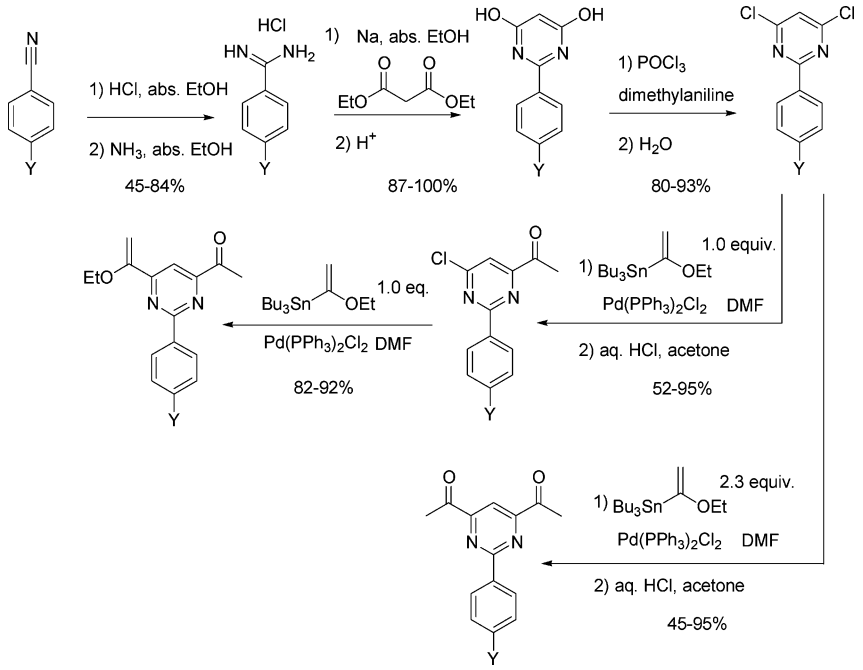
Synthesis of the Heterocyclic napy-py Strands. Seven Subunit Oligomers $\mathbf{1_Y}$. The seven subunit oligomers were synthesized by condensation of a central bis(aminoaldehyde) $\mathbf{3_Y}$ with 2 equiv of monoketone $\mathbf{4_Y}$ (Scheme 3). The bis(aminoaldehyde) $\mathbf{3_Y}$ was obtained by base-catalyzed Friedländer condensation of the corresponding bisketone with 4-aminopyrimidine-5-carboxaldehyde,[20] followed by acidic hydrolysis. Moderate yields were obtained for $\mathbf{3_{OBz}}$ as partial debenzylation occurred under these conditions. However, the deprotected phenol derivative $\mathbf{3_{OH}}$ was also isolated by column chromatography giving an overall condensation yield of 55%. The monoketones $\mathbf{4_Y}$ are also products of base-catalyzed Friedländer condensation of the corresponding ketovinyl ether with 2-aminonicotinaldehyde,[21] followed by mild acidic hydrolysis. The final Friedländer condensation proceeded smoothly using a

(19) Von Schubert, H.; Zachke, H. *J. Prakt. Chem.* **1970**, *312*, 494−506.

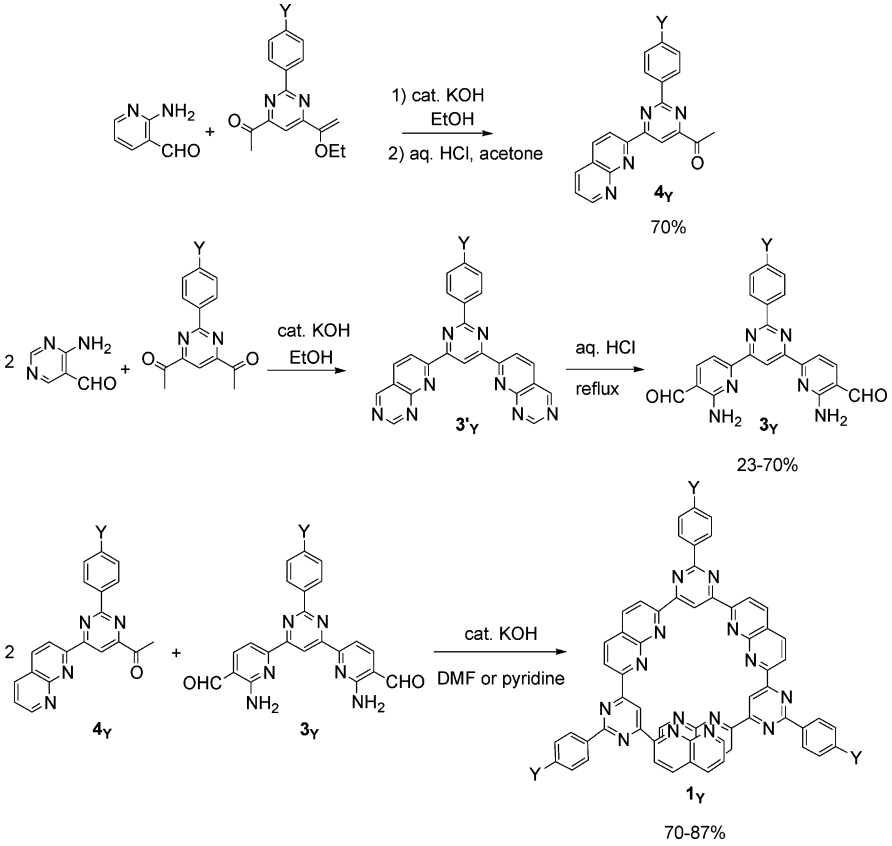
(20) Bredereck, H.; Simchen, G.; Traut, H. *Chem. Ber*. **1967**, *100*, 3664−3670.

(21) (a) Osselaere, J. P.; Dejardin, J. V.; Dejardin-Duchêne, M. *Bull. Soc. Chim. Belg.* **1969**, *78*, 289−298. (b) Majewicz, T. G.; Caluwe, P. *J. Org. Chem.* **1974**, *39*, 720−721.

SCHEME 2. Synthetic Scheme for the Generation of the Methyl Ketone Functionalized Pyrimidine Intermediates (Y = nBu, tBu, OBz, $OC_{12}H_{25}$)



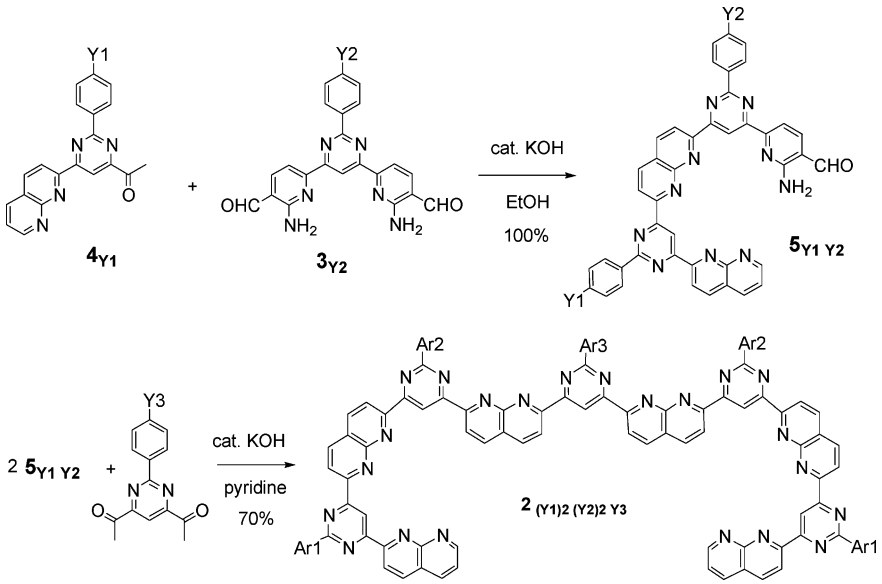
SCHEME 3. Synthetic Scheme for the Generation of the Seven Subunit Napy-py Sequences (Y = nBu, tBu, OBz)



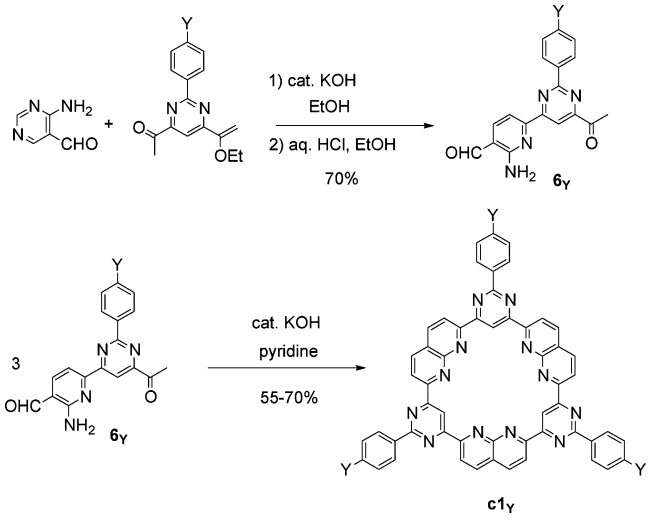
catalytic amount of potassium hydroxide in DMF or pyridine (ethanol was not appropriate as indicated below).

Eleven Subunit Oligomers 2_Y. The eleven subunit oligomers, anticipated to form two-turn helices, were synthesized in a similar modular manner (Scheme 4). When ethanol was used as a solvent, the monoaminoaldehyde $\mathbf{5_{Y1Y2}}$ was produced quantitatively by base-catalyzed condensation of the Y1-substituted arylpyrimidine ketone $\mathbf{4_{Y1}}$ and the Y2-substituted bis(aminoaldehyde) $\mathbf{3_{Y2}}$, as the monocondensed product precipitated from the reaction mixture. Thus, ethanol was not an appropriate solvent for the synthesis of the seven subunit oligomer. Two equivalents of $\mathbf{5_{Y1Y2}}$ was then condensed with

SCHEME 4. Synthetic Scheme for the Generation of the 11 Subunit Napy-py Sequences (Y1 = nBu, OBz; Y2 = Y3 = nBu)



SCHEME 5. Synthetic Scheme for the Generation of the Napy-py Macrocycles $c1_Y$ (Y = nBu, $OC_{12}H_{25}$)



1 equiv of Y3 substituted bisketone in pyridine to yield the desired Y1-, Y2-, Y3-substituted eleven subunit oligomer $\mathbf{2_{(Y1)2(Y2)2Y3}}$. Although this strategy may be used to produce a library of oligomers with a variety of Y groups, we describe herein the synthesis of all *n*Bu (Y1 = Y2 = Y3 = *n*Bu) and mixed (OBz)(nBu)$_2$ (Y1 = OBz, Y2 = Y3 = *n*Bu) oligomers only for characterization purposes.

Synthesis of Cyclic Sequences. Six Subunit Macrocycles $\mathbf{c1_Y}$. Because of the transoid orientation, closure into a C_3-symmetric macrocycle is likely to be favored. The appropriate self-compatible bisfunctional fragment was easily synthesized (Scheme 5). The ketoamino aldehyde $\mathbf{6_Y}$ was obtained by condensation of the corresponding ketovinyl ether with 4-aminopyrimidine-5-carboxaldehyde, followed by acidic hydrolysis (which releases both keto and amino aldehyde functions). The bisfunctional fragment was then self-condensed to form the cyclic $\mathbf{c1_Y}$ product in high yields (essentially limited by the isolation and washing procedure) without requiring high dilution conditions. The conformational preorganization of the intermediates due to the transoid preference of the consecutive heterocycles, together with entropic factors, may be expected to favor the formation of cyclic products.

Conformational Features of the napy-py Strands. In line with the helical features of py-pym heterocyclic strands, the helical conformation of open-ended sequences $\mathbf{1_Y}$ and $\mathbf{2_Y}$ oligomers was confirmed in solution by NMR spectroscopy and in the solid state by powder X-ray diffraction. The comparison of ^{1}H NMR spectra of seven subunit oligomers, anticipated to form one-turn helices, and of very short sequences, such as the napy-pym-napy triad,[22] provides preliminary information regarding the particular electronic environment within the longer sequences (Figure 1). Although the central fragment of each compound shows very similar chemical shifts (e.g., protons 1, Ha and Hb of napy-pym-napy and 1′, Ha′ and Hb′ of $\mathbf{1_{tBu}}$), a marked shielding is observed for the protons at the extremities of $\mathbf{1_{tBu}}$ (e.g., 1, Ha, Hb, and most noticeably 5, 6, and 7 with $\Delta\delta$s of −0.51, −0.71, and −0.8 ppm respectively), suggesting that the two extremities of the long oligomers do overlap in solution as a result of helical folding.[23] Similar upfield shifts are observed for py-pym-py-based oligomers which fold into helical architectures.[4a,b,h]

The longer eleven subunit oligomers $\mathbf{2_Y}$ also show a similar shielding effect, although the ^{1}H NMR spectrum is complicated by temperature effects. Indeed, at room temperature, all $\mathbf{2_Y}$ species show broad signals (top of Figure 2). Variable-temperature ^{1}H NMR spectroscopy studies were conducted on $\mathbf{2_{(OBz)2(nBu)4}}$ (Figure 2c) in order to understand this behavior (Figure 2).[24] As the temperature is lowered, resolved peaks

(22) The napy-pym-napy sequence was synthesized by base-catalyzed condensation of 2 equiv of 2-amino-3-carboxaldehydepyridine and 1 equiv of *tert*-butylphenyl-susbtituted bis ketopyrimidine; see: Petitjean, A.; Puntoriero, F.; Campagna, S.; Juris, A.; Lehn, J.-M. *Eur. J. Inorg. Chem.* **2006**, 3878−3892.

(23) These chemical shifts do not change much upon dilution, suggesting that intermolecular processes do not contribute significantly to this effect.

(24) $\mathbf{2_{(nBu)5}}$ shows a similar behaviour (broad signals at room temperature, better resolved at low temperature). Since the investigation of helical chirality was our first focus, high temperature studies have not been conducted yet. The large number of signals at low temperature may due to aggregation/binding/formation of double helices. For instance protonated dimers are very often observed by mass spectrometry for this family of molecules, but their structure has not been investigated.

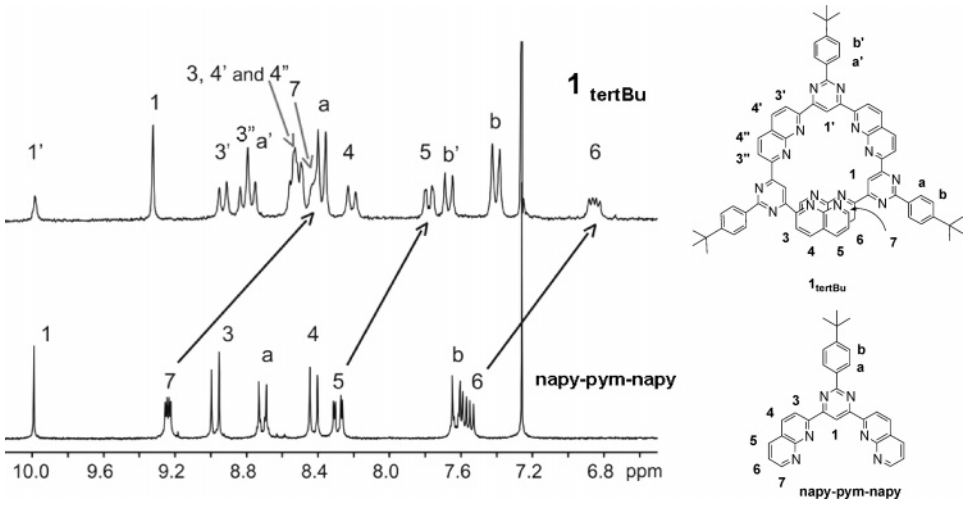


FIGURE 1. Comparison of the ^{1}H NMR spectra of the short (**napy-pym-napy**) and long ($\mathbf{1_{tertBu}}$) oligomers, highlighting the ring overlap due to the helical folding ($CDCl_3$, 200 MHz).

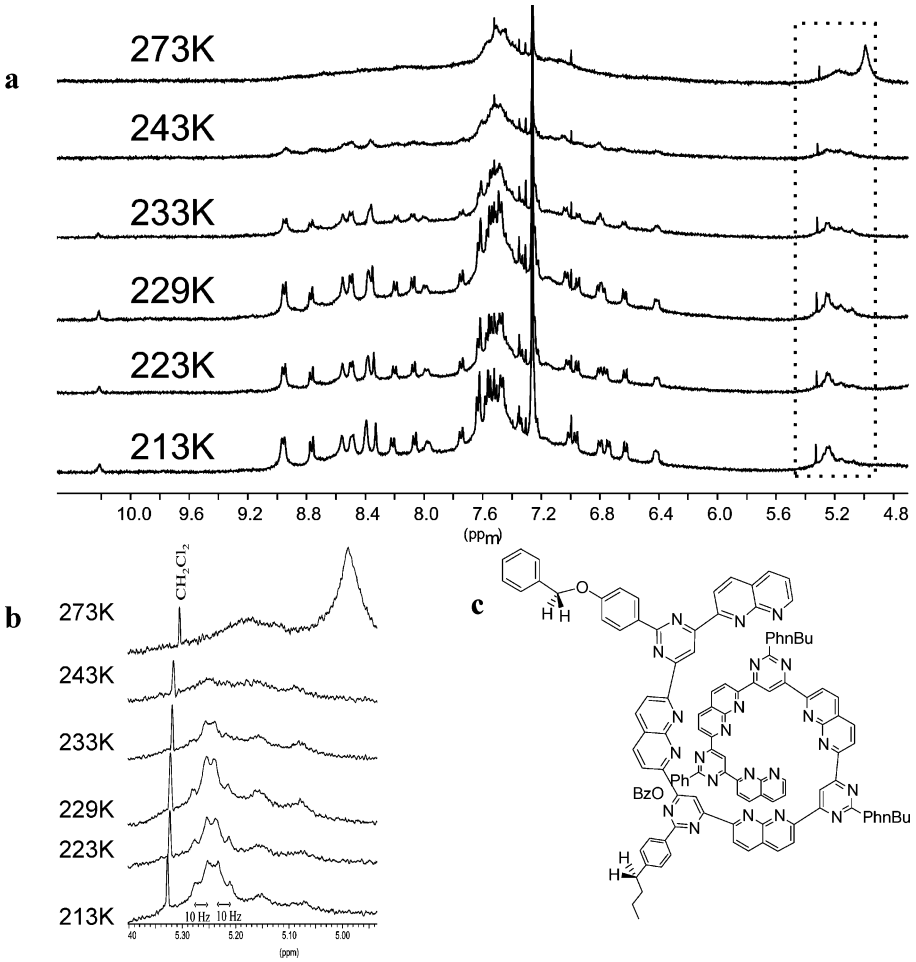


FIGURE 2. Variable-temperature ^{1}H NMR spectra of $\mathbf{2_{(OBz)2\ (nBu)4}}$ ($CDCl_3$, 400 MHz): (a) 11−4.8 ppm range, (b) benzylic protons region, (c) $\mathbf{2_{(OBz)2\ (nBu)4}}$ formula highlighting the terminal OBz protons.

appear and support a helical conformation. First, in the aromatic region, the terminal naphthyridine protons appear shielded (cf. H6 type proton at 6.4 ppm), which relates to the chemical shift of protons borne by the terminal pyridine in the py-(py-pym)$_5$-py-py oligomers, which have been shown to form two-turn helices in solution and in the solid state.[25] Second, in the region of the benzylic CH_2 protons (Figure 2b), an AB system is present at low temperature with a coupling constant of 10 Hz. This is consistent with two diastereotopic protons as a consequence of

(25) Bassani, D. M.; Lehn, J.-M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 897−906.

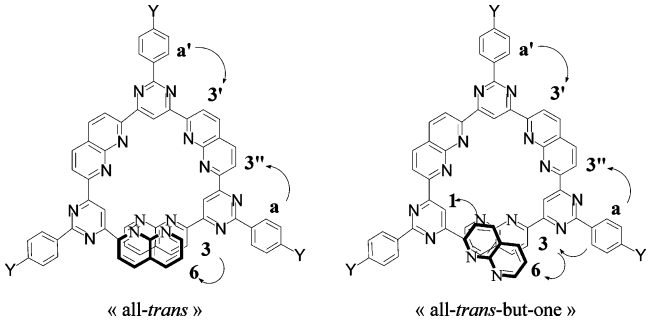


FIGURE 3. NOE cross-peaks observed for $\mathbf{1}_{\mathbf{tertBu}}$ and $\mathbf{1}_{\mathbf{OBz}}$ (^{1}H NMR at 400 MHz in $CDCl_3$) and proposed conformations.

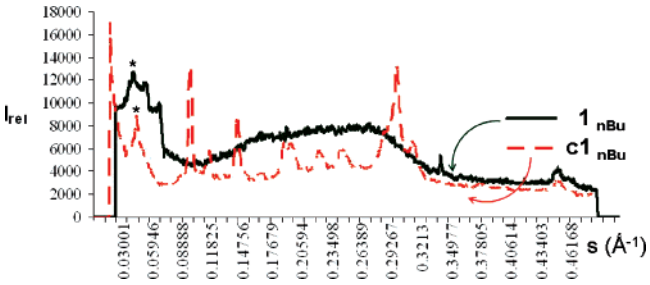


FIGURE 4. Superimposed X-ray powder diffraction spectra for $\mathbf{1}_{\mathbf{nBu}}$ and $\mathbf{c1}_{\mathbf{nBu}}$.

the M/P chirality of the helix, and is, once again, a behavior similar to that of the py-(py-pym)$_5$-py-py oligomers.[25]

2D ^{1}H NMR ROESY spectroscopy also supports the preference for helical conformers in solution (Figure 3). $\mathbf{1}_{\mathbf{OBz}}$ and $\mathbf{1}_{\mathbf{tBu}}$ both show NOE signals (i) between protons at the periphery of the helix, such as the cross-peaks between Ha′ and 3′ and those between Ha and 3″, and (ii) between the helix extremities, such as the cross-peak between protons 3 and 6. Additionally, the NOE signal between protons 1 and 3 suggests at least a partial occupation of the "all-trans-but-one" conformer. Such a terminal cisoid orientation might be favored, considering the energetic cost of maintaining two parallel terminal naphthyridine dipoles in a one turn helix for which very little compensating stacking stabilization exists.

Overall, 1D and 2D ^{1}H NMR data confirms the helical conformation of napy-pym oligomers in solution, in a very similar fashion as their py-pym parents.

Although single crystals amenable to X-ray analysis could not be obtained for this family of compounds, powder diffraction did give some indication of a helical conformation in the solid state. Figure 4 displays the diffraction patterns of open-ended $\mathbf{1}_{\mathbf{nBu}}$ and macrocyclic $\mathbf{c1}_{\mathbf{nBu}}$. $\mathbf{1}_{\mathbf{nBu}}$ does not show a pronounced organization at large angles (for distances between 2 and 11 Å), and $\mathbf{c1}_{\mathbf{nBu}}$ is far more organized (see discussion below). However, one notes a repeat distance in the powder of $\mathbf{1}_{\mathbf{nBu}}$ (∗ in Figure 4) of 25 Å, consistent with the overall diameter of a one-turn helix (twice the distance from the center of the helix to the end of the extended *n*-butyl chain). This observation is echoed by the similar distance (23 Å) observed for the macrocycle (∗ in Figure 4). It therefore appears that the helical conformation of the napy-pym oligomers is (at least mainly) retained in the solid state.

Overall, the solution and solid-state studies confirm the preference for a helical conformation for napy-pym oligomers.

Aggregation Propensity of the Macrocycles and Helices. The marked solubility difference between the macrocyclic and

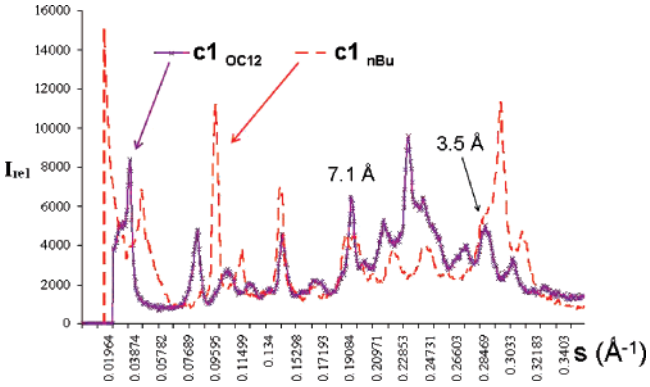


FIGURE 5. Comparison of the powder X-ray diffraction spectra for two macrocycles ($\mathbf{c1}_{\mathbf{nBu}}$ and $\mathbf{c1}_{\mathbf{OC12H25}}$).

open-ended oligomers (e.g., $\mathbf{1}_{\mathbf{nBu}}$ is far more soluble in chlorinated solvents than $\mathbf{c1}_{\mathbf{nBu}}$) highlights a favorable interaction between these flat macrocycles, which is hardly compensated for by solvation. This qualitative observation correlates well with the powder diffraction data (Figure 4), which shows a much richer diffraction pattern for $\mathbf{c1}_{\mathbf{nBu}}$ than for $\mathbf{1}_{\mathbf{nBu}}$, an indication for the propensity of the macrocycle to undergo aggregation. When comparing the diffraction pattern of two differently functionalized macrocycles (Figure 5), common reflections are observed at 3.5 and 7.1 Å, which may be a sign of $\pi-\pi$ stacking of macrocycles in columns.[26]

The helical oligomers also appear to aggregate to an extent that is limited by the steric hindrance of their peripheral substituents. Indeed, the line width of the ^{1}H NMR signals increases from *tert*-butyl to *O*-benzyl and to *n*-butyl-substituted one-turn helices, which seems to indicate that self-association is facilitated by linear substituents compared to the bulkier *tert*-butyl groups, for which a very well-resolved spectrum is obtained (Figure 6a). Dilution experiments on $\mathbf{1}_{\mathbf{nBu}}$ confirm the concentration dependence of its signals, in particular the signals of the protons at the extremities of the helix (e.g., protons 1, 5, and 6, each deshielded by 0.25 ppm upon 4-fold dilution), which would undergo a stronger compaction effect.

Hence, macrocyclic as well as open-ended sequences show an intrinsic bias toward self-association, a common feature of large flat heterocyclic oligomers.[4c,e]

Cation-Promoted Aggregation of napy-pym-Based Helices and Macrocycles. As reported previously,[4f] titration of alkali cationic salts such as potassium and cesium, in a mixture of $CDCl_3$ and CD_3CN, into a solution of one turn helices such as $\mathbf{1}_{\mathbf{nBu}}$ leads to a significant NMR line broadening and shielding of the signals, which may be interpreted as an ion-induced aggregation of the helices. Electrospray mass spectrometry confirms the existence of fragments of oligomers in the gas phase (up to five helices combined with two cations), although the primary signal comes from the 1:1 complex. Finally, very long fibers were observed from solution by transmission electron microscopy.[4f] Organic ions such as guanidinium of C_3-symmetry also lead to the same observations: NMR line broadening, aggregate fragments in the gas phase and long fibers of varying rigidity depending on the solvent by TEM (Figure 7). In a mixture of acetonitrile and a chlorinated solvent, very small

(26) This is a very primitive interpretation, and more experimental work should be done in order to fully understand the diffraction pattern.

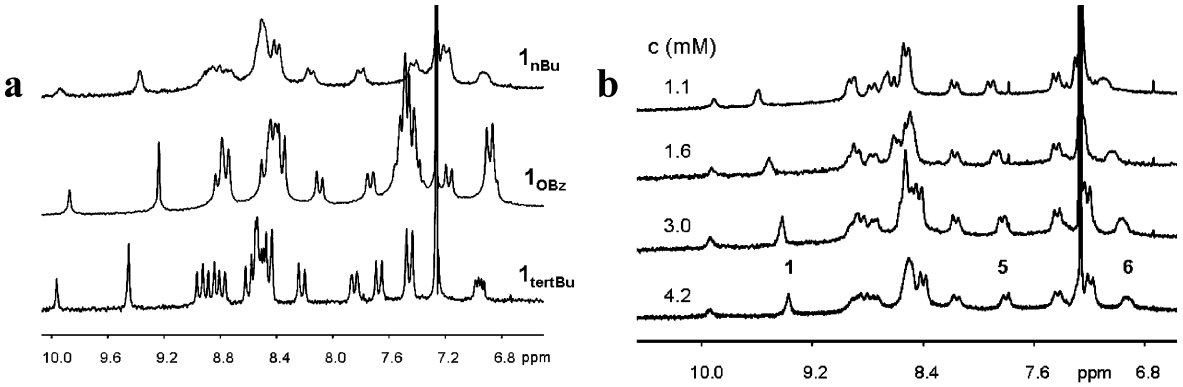


FIGURE 6. (a) Comparison of the ^{1}H NMR spectra of $\mathbf{1}_{\mathbf{tertBu}}$, $\mathbf{1}_{\mathbf{OBz}}$, and $\mathbf{1}_{\mathbf{nBu}}$ under the same conditions ($CDCl_3$, 200 MHz, 298 K). (b) Dilution experiments on $\mathbf{1}_{\mathbf{nBu}}$ ($CDCl_3$, 200 MHz, 298 K); see Figure 1 for proton numbering.

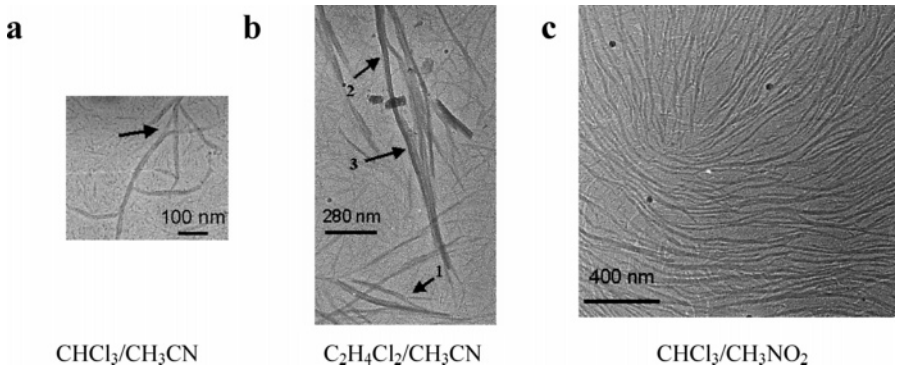


FIGURE 7. TEM images of guanidinium $\mathbf{1}_{\mathbf{nBu}}$ (1 mM) in different solvent mixtures (arrows highlight merging fibrils).

fibrils merge into larger and larger fibers through lateral interactions leading to very long and rigid filaments (Figure 7b).

The binding of all these ions shares common features, which are consistent with the stacking of the helices following an initial electrostatic interaction of the ion with a polar helical central cavity. Yet, with flexible ligands such as helices, opening and unwrapping must also to be probed, especially since accurate structural data could not be abstracted from the NMR spectra. Several pieces of evidence contradict the helix opening interpretation. First, powder diffraction shows very similar features for $\mathbf{1}_{\mathbf{nBu}}$ and Cs$\mathbf{1}_{\mathbf{nBu}}$, Pic (for instance), with conservation of the peak at 26 Å, which we assign to the helix diameter. Second, the ^{1}H NMR spectra of short fragments such as the napy-pym-napy triad (Figure 1) were followed on titration with potassium ions to probe for bond rotation and nitrogen binding in the conditions used for helix binding. The signals of napy-pym-napy were not influenced at all by the salt addition, indicating that potassium ions do not promote bond rotation and that cation binding requires the synergistic electronic effects of the dipoles of more than two naphthyridines to occur. Cation binding is an effect of the conformational control generating a helical ligand and results in the convergence of strong dipoles which subsequently stabilize the complexation of the ionic guest.

Even more informative is the study of the macrocycle complexation to ions. In this case, conformational change through bond rotation is precluded; hence, the electrostatics of the cavity is directly probed. Titration of the more soluble $\mathbf{c1}_{\mathbf{(OC12H25)}}$ with potassium picrate once again led to (i) broadening and (ii) shielding of all the proton NMR signals (Figure 8; solvent and temperature were dictated by the limited solubility of the macrocycle) in a manner very similar to the behavior of $\mathbf{1}_{\mathbf{nBu}}$ in the presence of potassium picrate. Electron microscopy once again confirmed solvent-dependent aggregation (Figure 8b,c). Globular aggregates with a diameter of about 50 nm were observed when acetonitrile was used as a cosolvent, whereas very long "liana"-like fibers formed in the presence of nitromethane by lateral fusion of thinner fibrils (the thinnest detected had a diameter of roughly 50 nm).

Cation-promoted macrocycle aggregation[27a,b] and its solvent-dependent nature[27c] have been observed with similar aromatic systems.

Substrate-Induced Regulation of Helix Assembly. Since small cations promote the aggregation of the helices, we reasoned that molecules containing a "string" of cationic sites might be appropriate substrates for helical wrapping and assembly control. Such is the case for oligoammonium cations; they are conveniently synthesized, and their charge may be controlled by pH. Scheme 6 indicates the list of cations that were synthesized and tested for binding. The achiral amines **CmNn** (Scheme 6a) were obtained by reductive amination of 2-naphthaldehyde with primary diamines using sodium borohydride as a reductant. The naphthyl groups behave as stoppers at the end of the cationic chain and facilitate the mass spectrometry analysis. The chiral amines **ProCmNn** (Scheme 6b) are derived from enantiomerically pure *N*-benzylproline

(27) (a) Gallant, A. J.; MacLachlan, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5307−5310. (b) Margadonna, S.; Prassides, K.; Iwasa, Y.; Taguchi, Y.; Craciun, M. F.; Rogge, S.; Morpurgo, A. F. *Inorg. Chem.* **2006**, *45*, 10472−10478. (c) Ma, C. T. L.; MacLachlan, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 4178−4182.

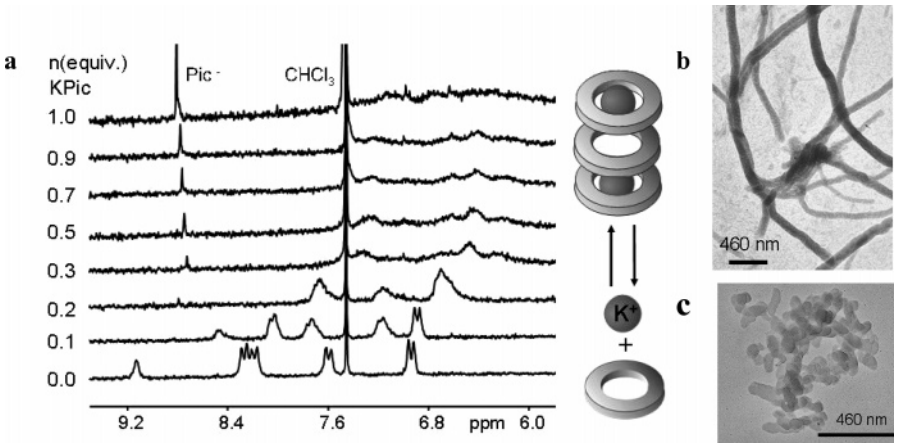
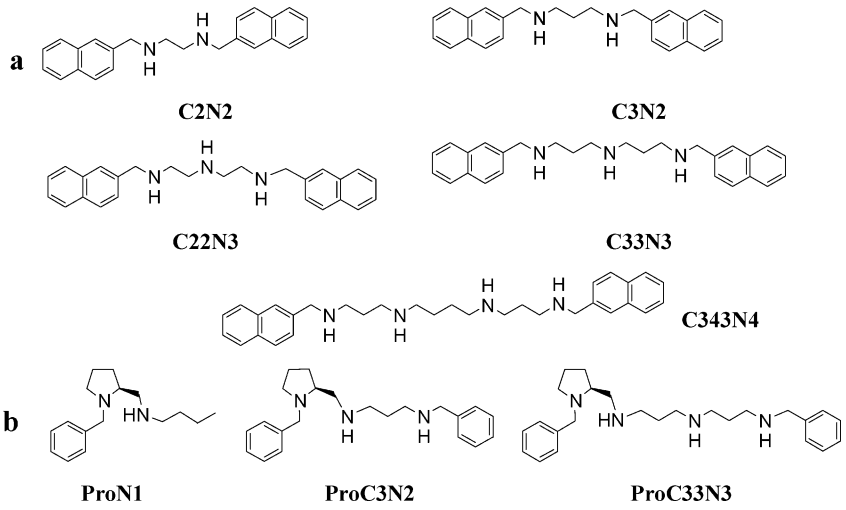


FIGURE 8. (a) ^{1}H NMR spectra observed on titration of **c1**$_{(OC12H25)}$ with potassium picrate ($CDCl_3/CD_3OD$ 2.0:1.0, 318 K, 200 MHz) and cartoon representing the presumed aggregation process. (b) TEM image of [**Kc1**$_{(OC12H25)}$, Pic], 1 mM in $CHCl_3/CH_3NO_2$; TEM image of [**Kc1**$_{(OC12H25)}$, Pic], 1 mM in $CHCl_3/CH_3CN$.

SCHEME 6. Oligoamines Used as Substrates[a]



[a] Key: (a) achiral **CmNn,** where *n* is the total number of nitrogen atoms and *m* the number of carbon atoms between two consecutive nitrogen atoms; (b) chiral amines derived from proline.

methyl ester via trimethylaluminum-promoted acylation followed by amide reduction using lithium aluminum hydride.

We have previously reported the formation of specific assemblies, induced by a given substrate as graphically summarized in Figure 9. Briefly, when 2 equiv of helices were combined with 1 equiv of diamine **C2N2** or **C3N3** in the presence of 2 equiv of trifluoroacetic acid, the only product detected by ESMS was the 2:1 complex for both bridge lengths (C2 and C3). In the triamine case, an excess of helices (>5 equiv) allowed the formation of the fully saturated complex with **C33N3** (Figure 9, right). When the spacer between the positive charges was shorter than the van der Waals width of the oligomer (**C22N3**), only the 2:1 complex formed regardless of the helix excess (Figure 9, left). This observation was consistent with the proposed architectures. This behavior can be generalized to longer substrates, such as the spermine derivative **C343N4,** which contains oligomethylene spacers between the cationic sites appropriate for the stacking of helices; it also formed the fully saturated assembly as the only ESMS detected

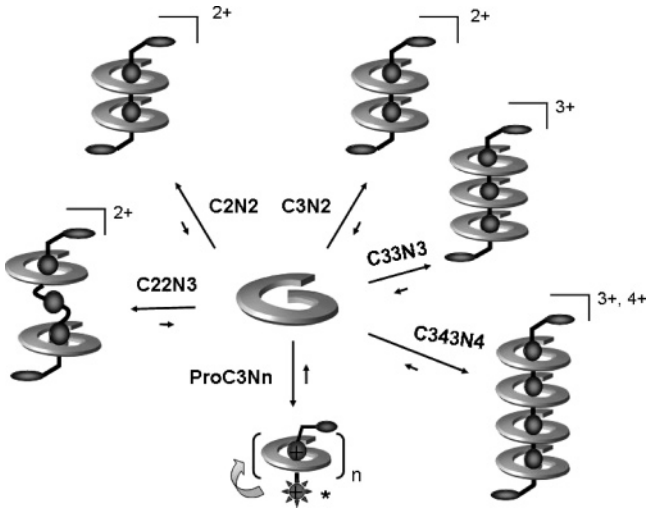


FIGURE 9. Cartoon representation for the formation of the oligoammonium controlled supramolecular assemblies of helical ligands in chloroform (∗ highlights the chirality of the proline-derived substrates).

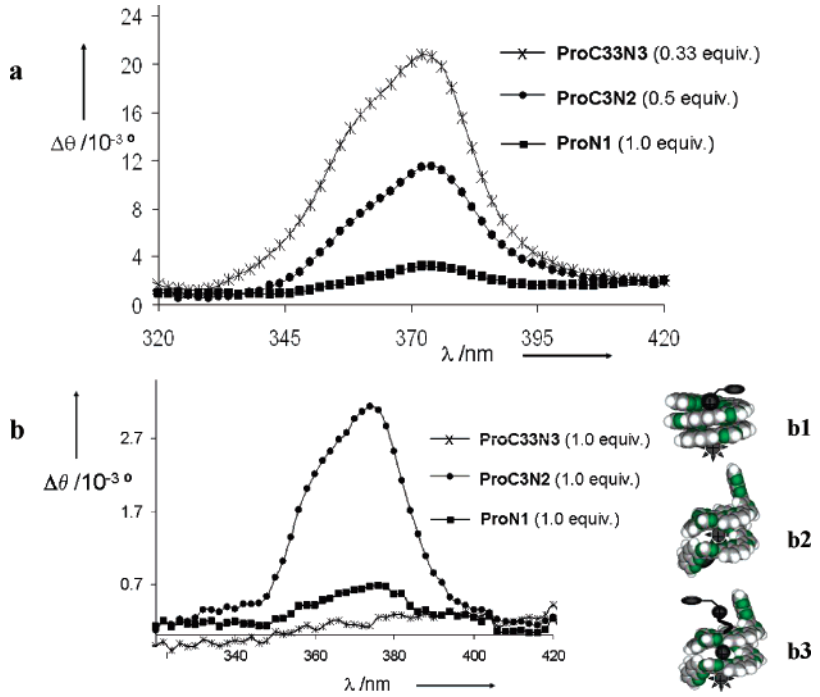


FIGURE 10. Circular dichroism induced by chiral substrates in the absorption region of the naphthyridine units of the oligomers: (a) $\mathbf{1}_{\mathbf{nBu}}$ (10^{-3} M in $CHCl_3$) combined with **ProC3Nn** (1/n equivalent) and TFA (1.0 equiv); (b) (left) CD signal for $\mathbf{2}_{\mathbf{nBu}}$ (10^{-4} M in $CHCl_3$) combined with **ProC3mNn** (1/*n* equivalent) and TFA (1.0 equiv); (right) model for the 1:1 complexes between the oligoammoniums and the two turn-helix (b1: model for $\mathbf{2}_{\mathbf{nBu}}$ + **ProC3N2**, b2: model for $\mathbf{2}_{\mathbf{nBu}}$ + **ProN1**; b3: model for $\mathbf{2}_{\mathbf{nBu}}$ + **ProC33N2**).

supramolecular assembly (7 equiv of helices were used). These assemblies also represent rotaxane-type architectures involving helical subunits, rather than macrocyclic rings, as in the usual rotaxanes.[28]

Additionally, competition, solvent, and counteranion effects were investigated. In order to probe for relative stability, the oligoammonium chains were subjected to competitive binding to a limited amount of helix binder. Thus, a mixture of $\mathbf{1}_{\mathbf{nBu}}$ with **C2N2** (0.5 equiv), **C3N2** (0.5 equiv), **C22N3** (0.33 equiv), **C33N3** (0.5 equiv), and trifluoracetic acid (1.0 equiv) can virtually form all combinations mentioned above, in addition to nonsaturated ones. The species detected (in order of decreasing relative abundance) were $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C3N2}]^{2+}$, $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3}]^{2+}$, $[(\mathbf{1}_{\mathbf{nBu}})_3, \mathbf{C33N3}]^{3+}$, $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C22N3}]^{2+}$. The competition process deserves two comments. Substrates with short intercationic bridges $[(\mathbf{1}_{\mathbf{nBu}})_3, \mathbf{C22N3}]^{3+}$ and $[(\mathbf{1}_{\mathbf{nBu}})_3, \mathbf{C2N2}]^{2+}$ were completely excluded in the competition process showing that steric hindrance disfavors their formation. Conversely, the significant proportion of the fully saturated 3:1 complex $[(\mathbf{1}_{\mathbf{nBu}})_3, \mathbf{C33N3}]^{3+}$, despite the limited amount of available $\mathbf{1}_{\mathbf{nBu}}$ ligand, is a sign of its marked stability.

As anticipated, the environment plays a major role in the control of these assemblies. Chloroform was an appropriate solvent to yield the saturated assemblies such as **C33N3**. Addition of acetonitrile to a 3:1 $\mathbf{1}_{\mathbf{nBu}}$/$\mathbf{C33N3}^{3+}$mixture which, in chloroform, yielded $[(\mathbf{1}_{\mathbf{nBu}})_3, \mathbf{C33N3}]^{3+}$ and $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3}]^{2+}$ as major and minor products, respectively, led to a mixture of all combinations $\mathbf{C33N3}H^+$, $\mathbf{1}_{\mathbf{nBu}}H^+$, $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3}]^{2+}$, $[(\mathbf{1}_{\mathbf{nBu}})_3, \mathbf{C33N3}]^{3+}$, $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3}]^{3+}$, $[\mathbf{1}_{\mathbf{nBu}}, \mathbf{C33N3}]^{2+}$, in decreasing order of abundance. Hence, dissociation was induced by the competitive solvation of the ammonium ions by acetonitrile and the helix cavity. Similarly, the ammonium/helix association depends on the counteranion. The ionic attraction between triflates and ammoniums in chloroform did not prevent the dipole/ion interaction between the helices and the ammonium sites. When trifluoroacetic acid was replaced by picric acid, which combines the potential for both ion/ion and stacking interactions, the $[(\mathbf{1}_{\mathbf{nBu}})_3, \mathbf{C33N3}]^{3+}$ and $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3}]^{2+}$ mixture was replaced by 2:1 complexes such as $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3}]^{2+}$, $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3, Pic}]^{2+}$, $[(\mathbf{1}_{\mathbf{nBu}})_2, \mathbf{C33N3}]^{3+}$ accompanied by $\mathbf{1}_{\mathbf{nBu}}H^+$. The stacking potential of the picrate counterion may also play a role in the titration of potassium picrate with the $\mathbf{c1}_{(\mathbf{OC12H25})}$ macrocycle (the chemical shift of the picrate anion varies slightly in the course of the titration, cf. Figure 8). The most stable architecture could indeed involve the picrate anion close to the cationic sites and stacked between the organic receptors.

Circular dichroism data are also consistent with the proposed assembly of one-turn helices around their substrate: the proline-based oligoamines transfer their chirality to their helical binder to a greater extent as their charge increases, which correlates with supramolecular assemblies where increasing numbers of naphthyridine dipoles adopt an organized orientation around their substrate and amplify the substrate chiral information (Figure 10a). Preliminary observations on dilute solutions of the two turn helix $\mathbf{2}_{\mathbf{nBu}}$ seem to confirm this rationale. The monoamine **ProN1** leads to a slight chiral induction with a very weak signal; indeed, the monoammonium substrate is too short to force a strong organization of the whole strand (Figure 10b2).

(28) (a) Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1959−1976. (b) Ashton, P. R.; Baxter, I.; Fyfe, M. C. T.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; White, A.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 2297−2307. (c) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643−1663. (d) Wentz, G.; Han, B.-H.; Müeller, A. *Chem. Rev.* **2006**, *106*, 782−817.

The longer **ProC33N3** does not lead to a significant chiral induction either, which might be surprising at first glance; it looks as if the three cationic sites of the substrate can be stabilized by a variety of states of the two-turn helix, with the naphthyridine-based oligomer being more or less extended, leading to a poorly defined orientation of the napy-pym oligomer along the substrate (Figure 10b3). In contrast, **ProC3N2** leads to a strong CD signal, which can be interpretated as arising from the fit between the dicationic substrate and the binding sites of the two turns of the helix (Figure 10b1). The substrate may indeed be best stabilized when the two turn-helix is constrained to a well-stacked conformation, which would lead to a high degree of organization of the naphthyridine dipoles and, consequently, to significant chiral transfer and expression.

Conclusion

The spectrometric (NMR, CD, mass spectrometry) and microscopy data reported herein all support the conclusion that the control of conformation provided by the py-pym codon can be generalized to larger, fused heterocycles such as 1,8-naphthyridines in napy-pym oligomers, allowing the facile synthesis of one- and two-turn helices with a larger cavity. In addition to the enlarged cavity size, the converging napy units confer a strong polarity to the inner cavity where small cations are well accommodated. Cation binding then promotes helix association. Macrocycles are also easily synthesized in high yields without requiring high-dilution conditions, probably due a "self-templating" pre-organization of the macrocycle precursors. Similar cation binding behaviors are observed for both the helices and the macrocycles (e.g., NMR, electron microscopy data), which indicates the importance of the converging napy dipoles in both types of receptors. The outcome of the ion-induced self-assembly of the helices can be controlled through the introduction of oligoammonium cations inside the cavity, with a transfer of the substrate information such as chain length and chirality to the (assembly of the) helical receptors. One may note that this substrate controlled self-assembly teaches much about these systems: in the case of the one-turn helices, the substrate must present a good fit with the helix pitch in order to be fully bound (e.g., the oligoammonium species with short N to N bridges do not lead to the saturation of the ammonium sites by the helices). In the case of the two-turn helices, 1:1 binding of an oligoammonium substrate of appropriate bridge length leads to the rigidification of the helix and, hence, chirality transfer, only for the bis-ammonium which fits the length of the helix. Once again, this is an indication for a conserved helical conformation in these complexes.

The resulting self-assembled pseudo-rotaxanes have significant potential for the elaboration of nanosystems: (i) Friedländer condensation allows for facile synthesis of large systems and for the introduction of a variety of side-chains protruding from the helix (cf. Yi substituents on the two-turn helices), (ii) as a result of conformational control, the distribution of the substituents is well-determined, as in natural systems such as amphipatic helices[15] and (iii) larger systems are accessible through substrate-controlled self-assembly. Although the detailed geometry of the "stringed" helical complexes remains to be determined, their formation and dynamic nature reported herein represent a step forward toward higher complexity and should lead to interesting applications as functional nanostructures.

Experimental Section

4-Dodecyloxybenzonitrile. Commercially available 4-hydroxybenzonitrile (4.00 g, 33.6 mmol) and potassium carbonate (5.61 g) were suspended in a mixture of iododododecane (11 mL, 47 mmol, 1.4 equiv) and DMF (30 mL) and brought to 50 °C for 14 h. The reaction mixture was then diluted with diethyl ether and water. The water layer was further extracted with diethyl ether, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/CH_2Cl_2 2.0:1.0 to 3.5:2.0, $R_f = 0.36$) to yield 7.75 g of a colorless oil which crystallized slowly and is a mixture (probably the desired nitrile and the corresponding amide). It was used in the next step without further purification.

4-*n*-Butylbenzamidine Hydrochloride.[19] In a solution of 15.94 g of 4-*n*-butylbenzonitrile[19] (0.10 mol) in benzene (75 mL) and absolute ethanol (20 mL) was bubbled gaseous HCl until saturation. The solution was stirred for 1 h and allowed to stand at room temperature for 3 days. The volume was reduced to a third until white crystals appeared; the flask was cooled in ice, and diethyl ether was added. The solid was filtered, washed with diethyl ether, and dried in vacuo. It was subsequently suspended in ammonia-saturated absolute ethanol (60 mL). The white precipitate which formed immediately was stirred for 1 day and allowed to stand for 4 days. The fine suspension was then filtered and the filtrate concentrated. The white solid that formed from the filtrate was filtered, washed with diethyl ether, and dried in vacuo to yield 16.71 g (78%) of a white solid. ^{1}H NMR (DMSO-d_6): 9.0 (br s, 1.5H), 7.76 (d, $^3J = 8.3$ Hz, 2H), 7.44 (d, $^3J = 8.3$ Hz, 2H), 2.68 (t, $^3J = 7.5$ Hz, 2H), 1.58 (quint, $^3J = 7.5$ Hz, 2H), 1.30 (sext, $^3J = 7.5$ Hz, 2H), 0.93 (t, $^3J = 7.3$ Hz, 3H).

2-(4-*n*-Butylphenyl)-4,6-dihydroxypyrimidine.[29] To 4-*n*-butylbenzamidine hydrochloride (16.71 g, 79 mmol) suspended in diethyl malonate (12.8 mL, 84 mmol, 1.07 equiv) and absolute ethanol (150 mL) was added dropwise a freshly prepared solution of sodium methoxide (6.6 g, 0.28 mol, 3.5 equiv, of sodium in 75 mL of absolute methanol). The mixture was refluxed under an inert N_2 atmosphere for 7 h. After evaporation of the solvent, the pink wax was taken up in water (120 mL) and the solution acidified (pH 3−4) with concentrated HCl (∼20 mL). The fine light yellow precipitate was filtered and washed with water, air dried, and dried in vacuo to yield 20 g of 2-(4-*n*-butylphenyl)-4,6-dihydroxypyrimidine (100%). ^{1}H NMR (DMSO-d_6): 8.8 (br s, 1H), 8.01 (d, $^3J = 8.3$ Hz, 2H), 7.33 (d, $^3J = 8.4$ Hz, 2H), 5.38 (s, 1H), 2.63 (t, $^3J = 7.8$ Hz, 2H), 1.59 (quint, $^3J = 7.8$ Hz, 2H), 1.31 (sext, $^3J = 7.5$ Hz, 2H), 0.89 (t, $^3J = 7.2$ Hz, 3H). ^{13}C NMR (DMSO-d_6): 167.4, 157.3, 146.5, 129.5, 128.4, 127.6, 88.2, 34.5, 32.6, 21.6, 13.6. Mp >260 °C dec. FAB+: 245.2 (MH^+). Anal. Calcd for $C_{14}H_{16}N_2O_2 \cdot 2.26$ HCl (244.29): C, 51.44; H, 5.63; N, 8.57. Found: C, 51.45; H, 5.20; N, 8.54.

2-(4-*n*-Butylphenyl)-4,6-dichloropyrimidine.[29] To *N*,*N*-dimethylaniline (9.2 mmol, 73 mmol, 1.7 equiv) were added 21 mL of phosphoryl chloride (0.23 mol, 5.3 equiv) dropwise, at room temperature. Solid 2-(4-*n*-butylphenyl)-4,6-dihydroxypyrimidine (10.34 g, 42.3 mmol) was then added portionwise (the reaction is exothermic and the brown mixture turns reddish). The mixture was refluxed for 1.25 h, cooled to room temperature, and poured cautiously into ice (80 g, caution: induction period). The pinkish solid was filtered, washed with water until the filtrate was transparent, dried in vacuo, and chromatographed on silica gel (hexane/CH_2Cl_2 80:6 to 40:7) to yield 20.45 g of a white crystalline solid (87%). ^{1}H NMR ($CDCl_3$): 8.33 (d, $^3J = 8.3$ Hz, 2H), 7.29 (d, $^3J = 8.3$ Hz, 2H), 7.23 (s, 1H), 2.68 (t, $^3J = 7.8$ Hz, 2H), 1.60 (quint, $^3J = 7.8$ Hz, 2H), 1.37 (sext, $^3J = 7.5$ Hz, 2H), 0.94 (t, $^3J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): 165.9, 161.9, 147.9, 132.5, 128.9, 118.3, 35.7, 33.3, 22.4, 14.0. R_f (SiO_2, hexane/CH_2Cl_2 2.0:

(29) Burdeska, v. K.; Fuhrer, H.; Kabas, G.; Siegrist, A. E. *Helv. Chim. Acta*. **1981**, *64*, 113−152.

0.2) = 0.36. Mp = 71 °C. FAB+: 281.2 (MH^+). Anal. Calcd for $C_{14}H_{14}N_2Cl_2$ (281.18): C, 59.99; H, 5.04; N, 10.00; Cl, 25.31. Found: C, 59.96; H, 5.04; N, 10.05.

1-[2-(4-*n*-Butylphenyl)-6-chloropyrimidin-4-yl]ethyl Ketone. A solution of (1-ethoxyvinyl)tris(*n*-butyl)stannane (4.16 g, 11.5 mmol, 1.08 equiv)[4e] and 2-(4-*n*-butylphenyl)-4,6-dichloropyrimidine (2.99 g, 10.3 mmol) in DMF (38 mL) was degassed with argon. Dichlorobistriphenylphosphinepalladium(II) (0.15 g, 2.4 mmol, 0.02 equiv) was added and the solution degassed once more with argon and heated at 80 °C for 14 h under argon, protected from light. After the crude mixture was cooled to room temperature, it was poured into an aqueous solution of potassium fluoride (9 g in 90 mL water). Diethyl ether (130 mL) was added and the white precipitate filtered and washed three times with diethyl ether. The two layers were separated; the organic layer was washed twice with water, dried with sodium sulfate, filtered, concentrated, and filtered through silica gel (hexane/diethyl ether 95:5) to yield 3.55 g of an 80:20 mixture of mono- and bisfunctionalized enol ethers which were directly submitted to acidic hydrolysis.

A 3.55 g portion of the 80:20 mixture was solubilized in acetone (54 mL), and 2 N aqueous hydrochloric acid (8 mL) was added. After the mixture was stirred at room temperature for 6 h, the solvent was evaporated and the white residue taken up in dichloromethane (100 mL) and washed with a saturated solution sodium hydrogenocarbonate (30 mL, pH 7−8). The aqueous layer was extracted three times with dichloromethane, the combined organic layers were dried on sodium sulfate, filtered, and concentrated, and the crude product was purified by flash chromatography on silica gel (hexane/CH_2Cl_2 3.0:2.0) to yield 1.93 g of the monoacylated arylchloropyrimidine (65%). ^{1}H NMR ($CDCl_3$): 8.40 (d, ^3J = 8.4 Hz, 2H), 7.72 (s, 1H), 7.32 (d, ^3J = 8.4 Hz, 2H), 2.80 (s, 3H), 2.70 (t, ^3J = 7.5 Hz, 2H), 1.66 (quint, ^3J = 7.8 Hz, 2H), 1.38 (sext, ^3J = 8.0 Hz, 2H), 0.94 (t, ^3J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 198.5, 166.2, 163.7, 160.8, 147.9, 133.4, 129.3, 129.0, 115.4, 36.1, 33.7, 26.1, 22.7, 14.2. R_f (SiO_2, hexane/CH_2Cl_2 1.5:1.0) = 0.29. Mp = 80 °C. FAB+: 289.2 (MH^+). Anal. Calcd for $C_{16}H_{17}N_2OCl$ (288.77): C, 66.64; H, 5.95; N, 9.72; O, 5.55; Cl, 12.14. Found: C, 66.65; H, 5.88; N, 9.72.

1-[2-(4-*n*-Butylphenyl)-6-(1-ethoxyvinyl)pyrimidin-4-yl]ethyl Ketone. To 1-[2-(4-*n*-butylphenyl)-6-chloropyrimidin-4-yl]ethyl ketone (1.92 g, 6.65 mmol) and (1-ethoxyvinyl)tris(*n*-butyl)-stannane[4e] (2.90 g, 8.0 mmol, 1.2 equiv) solubilized in anhydrous DMF (24 mL) and degassed with argon were 94 mg of dichlorobistriphenylphosphinepalladium (II). The solution was purged with argon and heated at 80 °C under argon for 12 h. After being cooled to room temperature, the black solution was poured into an aqueous solution of potassium fluoride (6 g of potassium fluoride in 60 mL of water). The brown precipitate was filtered and washed with copious amounts of diethyl ether. The ether layer was washed with a saturated solution of sodium chloride, dried on sodium sulfate, filtered, concentrated, and purified by flash chromatography on silica gel (hexane/CH_2Cl_2 4.0:1.0 to 4.0:2.0) to yield 1.99 g of a pale yellow solid (92%). ^{1}H NMR ($CDCl_3$): 8.47 (d, ^3J = 8.6 Hz, 2H), 8.02 (s, 1H), 7.32 (d, ^3J = 8.6 Hz, 2H), 5.89 (d, ^2J = 1.9 Hz, 1H), 4.57 (d, ^2J = 1.9 Hz, 1H), 4.00 (quadr, ^3J = 7.0 Hz, 2H), 2.82 (s, 3H), 2.71 (t, ^3J = 7.5 Hz, 2H), 1.66 (quint, ^3J = 7.5 Hz, 2H), 1.48 (t, ^3J = 7.0 Hz, 3H), 1.39 (sext, ^3J = 7.5 Hz, 2H), 0.96 (t, ^3J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 200.4, 164.1, 162.8, 160.4, 157.0, 146.4, 134.7, 128.8, 128.4, 109.1, 88.2, 64.0, 35.7, 33.5, 25.9, 22.4, 14.6, 14.1. R_f (SiO_2, hexane/CH_2Cl_2 2.0:1.0) = 0.43. Mp = 63 °C. FAB+: 325.3 (MH^+). Anal. Calcd for $C_{20}H_{24}N_2O_2 \cdot 0.06CH_2Cl_2$ (324.42): C, 73.12; H, 7.38; N, 8.50; O, 9.70. Found: C, 73.08; H, 7.37; N, 8.44.

1-[6-Acetyl-2-(4-*n*-butylphenyl)pyrimidin-4-yl]ethyl Ketone. To a degassed solution containing 2-(4-*n*-butylphenyl)-4,6-dichloropyrimidine (6.0 g, 21.3 mmol) and (1-ethoxyvinyl)tris(*n*-butyl)-stannane[4e] (17.68 g, 49 mmol, 2.3 equiv) in dry DMF (90 mL) was added dichlorobistriphenylphosphinepalladium(II) (450 mg, 0.39 mmol, 0.16 equiv); the solution was degassed once more with argon and heated at 80 °C under argon for 12 h. After being cooled to room temperature, the black solution was poured in a solution of aqueous potassium fluoride (20 g of KF in 200 mL of water), and the brown precipitate was filtered and washed with diethyl ether (300 mL, then 4 × 80 mL). The ether layer was then washed with brine, dried with sodium sulfate, filtered, and concentrated. The resulting light brown crude was purified by flash chromatography on silica gel (hexane/diethyl ether 95:5) to yield 7.22 g of the desired bis-vinyl ether as a white solid (97%).

To a solution of the bisvinyl ether (5.11 g, 14.5 mmol) solubilized in acetone (80 mL) were added 15 mL of 2 N aqueous HCl. After the solution was stirred for 6 h at room temperature, the white residue was taken up in dichloromethane (200 mL) and washed with a saturated solution of sodium hydrogenocarbonate (60 mL, pH 7−8). The aqueous layer was extracted three times with dichloromethane and the combined organic layers dried on Na_2SO_4, filtered, and concentrated. The crude white solid was purified by flash chromatography on silica gel (hexane/CH_2Cl_2 1.0:2.0) to yield 4.28 g of bis-acetylpyrimidine (100%). ^{1}H NMR ($CDCl_3$): 8.50 (d, ^3J = 8.2 Hz, 2H), 8.26 (s, 1H), 7.37 (d, ^3J = 8.2 Hz, 2H), 2.84 (s, 3H), 2.73 (t, ^3J = 7.6 Hz, 2H), 1.68 (quint, ^3J = 7.6 Hz, 2H), 1.40 (sext, ^3J = 7.5 Hz, 2H), 0.96 (t, ^3J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 199.2, 165.3, 161.2, 147.2, 133.7, 129.0, 128.4, 110.3, 35.6, 33.4, 25.7, 22.3, 13.9. R_f (SiO_2, hexane/CH_2Cl_2 1.0:2.0) = 0.30. Mp = 84 °C. FAB+: 297.3 (MH^+). Anal. Calcd for $C_{18}H_{20}N_2O_2$ (296.36): C, 72.94; H, 6.81; N, 9.46; O, 10.8. Found: C, 72.92; H, 6.75; N, 9.41.

1-[6-Acetyl-2-(4-dodecyloxyphenyl)pyrimidin-4-yl]ethyl Ketone. The hydrolysis of the bis-vinyl ether (4,6-bis(1-ethoxyvinyl)-2-(4-dodecyloxyphenyl)pyrimidine; 8.36 mmol) was performed as above except that a THF (5 mL)/acetone (5 mL) mixture to which 6 N aqueous hydrochloric acid was added was used and the yellow solution heated at 60 °C overnight. After evaporation of the solvents, the aqueous residue was taken up in dichloromethane and washed with a saturated solution of sodium carbonate, the aqueous layer was extracted with dichloromethane, and the combined organic layers dried (Na_2SO_4), filtered, and concentrated. The light yellow solid was then purified by flash chromatography (silica gel, hexane/CH_2Cl_2 1.0:1.0 to 0.5:2.0) to yield 324 mg of diketone (91%). ^{1}H NMR ($CDCl_3$): 8.53 (d, ^3J = 8.5 Hz, 2H), 8.20 (s, 1H), 7.04 (d, ^3J = 8.9 Hz, 2H), 4.07 (t, ^3J = 6.5 Hz, 2H), 2.82 (s, 6H), 1.84 (quint, ^3J = 7.4 Hz, 2H), 1.2−1.6 (m, 20H), 0.88 (t, ^3J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 199.2, 165.1, 162.3, 161.3, 130.2, 128.6, 114.7, 109.8,68.3, 32.0, 29.7, 29.4, 29.2, 26.0, 25.7, 22.7, 14.1. R_f (SiO_2, hexane/CH_2Cl_2 0.5:2.0) = 0.29. Mp = 95 °C. EI: 424.4 (M^-), 256.2 ($(M - C_{12}H_{25})^-$). Anal. Calcd for $C_{26}H_{36}N_2O_3 \cdot 0.5 C_3H_6O$ (424.58): C, 72.81; H, 8.67; N, 6.18; O, 12.65. Found: C, 72.70; H, 9.03; N, 6.08.

4,6-Bis(2-amino-3-formylpyridyl)-2-(4-*n*-butylphenyl)pyrimidine (3_{nBu}).[30] To a solution of 1-[6-acetyl-2-(4-*n*-butylphenyl)-pyrimidin-4-yl]ethyl ketone diketone (1.00 g, 3.41 mmol) and 4-aminopyrimidine-5-carboxaldehyde[20] (890 mg, 7.23 mmol, 2.1 equiv) in absolute ethanol (100 mL) brought to reflux under argon were added five drops of 10% solution of potassium hydroxide in methanol. The solution turned brown and a light orange precipitate appeared. The mixture was allowed to stir at room temperature for a few hours and refluxed overnight. After the mixture was cooled to room temperature, the precipitate was centrifuged and dried in vacuo. The solid was then suspended in 2 N aqueous hydrochloric acid (340 mL) and refluxed under vigorous stirring for 5 h. After being cooled to room temperature, the mixture was neutralized with concentrated aqueous ammonia. The orange suspension was filtered and washed with distilled water, dried in vacuo, and chromatographed (silica gel, CH_2Cl_2/EtOAc 400:15 to 400:40) to yield 1.01 g (65%) of a yellow solid which was recrystallized from dichloromethane/hexane. ^{1}H NMR (DMSO-d_6): 9.98 (s, 2H), 8.92 (s, 1H), 8.52 (d, ^3J = 8.2 Hz, 2H), 8.28 (d, ^3J = 7.9 Hz, 2H), 8.01 (d,

(30) Evens, G.; Caluwe, P. *J. Org. Chem.* **1975**, *40*, 1438−1439.

^3J = 7.6 Hz, 2H), 7.73 (br s), 7.39 (d, ^3J = 8.2 Hz, 2H), 2.68 (t, ^3J = 7.5 Hz, 2H), 1.62 (quint, ^3J = 7.9 Hz, 2H), 1.34 (sext, ^3J = 7.0 Hz, 2H), 0.92 (t, ^3J = 7.2 Hz, 2H). ^{13}C NMR (DMSO-d_6): 193.3, 163.3, 163.0, 157.8, 157.2, 145.9, 145.8, 145.7, 145.5, 128.5, 128.0, 114.4, 110.0, 34.7, 32.7, 21.7, 13.7. R_f (SiO_2, CH_2Cl_2/EtOAc 2.0:0.2) = 0.34. Mp = 209 °C. FAB+: 453.1 (MH^+). Anal. Calcd for $C_{26}H_{24}N_6O_2$·0.045 CH_2Cl_2 (452.20): C, 68.55; H, 5.32; N, 18.42; O, 7.01. Found: C, 68.53; H, 5.33; N, 18.49.

1-[2-(4-*n*-Butylphenyl)-6-[1,8]naphthyridin-2-ylpyrimidin-4-yl]ethyl Ketone (4_{nBu}).[31] General protocol: To a solution containing 1.89 g of 1-[2-(4-*n*-butylphenyl)-6-(1-ethoxyvinyl)pyrimidin-4-yl]-ethyl ketone (5.82 mmol) and 742 mg of 2-aminonicotinaldehyde[21] (6.97 mmol, 1.04 equiv) in absolute ethanol (170 mL) at reflux under argon were added 20 drops of 10% potassium hydroxide in methanol, and the dark yellow solution was refluxed overnight. After the solution was cooled to room temperature, the solvent was evaporated and the residual solid taken up in acetone (100 mL). Aqueous 2 N hydrochloric acid (35 mL) was added, and the mixture was stirred at room temperature overnight. After evaporation of the acetone, the residue was taken up in dichloromethane (300 mL) and neutralized with K_2CO_3 (s) (up to pH 8) and the aqueous layer extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc 40:8 to 40:12) to yield 1.5 g of a white solid (69%) which was recrystallized from dichloromethane/hexane. ^{1}H NMR ($CDCl_3$): 9.22 (dd, ^3J = 4.2 Hz, ^4J= 1.9 Hz, 1H), 9.15 (s, 1H), 8.92 (d, ^3J = 8.9 Hz, 1H), 8.57 (d, ^3J = 8.2 Hz, 2H), 8.41 (d, ^3J = 8.5 Hz, 1H), 8.28 (dd, ^3J = 8.1 Hz, ^4J = 2.0 Hz, 1H), 7.56 (dd, ^3J = 8.2 Hz, ^3J = 4.3 Hz, 1H), 7.37 (d, ^3J = 8.5 Hz, 2H), 2.85 (s, 3H), 2.73 (t, ^3J = 7.6 Hz, 2H), 1.69 (quint, ^3J = 7.6 Hz, 2H), 1.41 (sext, ^3J = 7.3 Hz, 2H), 0.96 (t, ^3J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): 199.5, 164.8, 164.7, 160.9, 157.3, 155.8, 154.5, 146.7, 138.4, 137.1, 134.6, 128.9, 128.5, 124.0, 123.1, 120.2, 112.2, 35.7, 33.5, 26.0, 22.4, 14.0. R_f (SiO_2, CH_2Cl_2/EtOAc 2.0:0.5) = 0.31. mp = 229 °C. FAB+: 383.1 (MH^+). Anal. Calcd for $C_{24}H_{22}N_4O$·0.105 CH_2Cl_2 (382.46): C, 73.98; H, 5.72; N, 14.31; O, 4.09. Found: C, 73.95; H, 5.57; N, 14.30.

7-[2-(4-Dodecyloxyphenyl)-6-(1-ethoxyvinyl)pyrimidin-4-yl]-pyrido[2,3-*d*]pyrimidine ($6'_{OC12H25}$). To a solution containing 254 mg of 1-[2-(4-dodecyloxyphenyl)-6-(1-ethoxyvinyl)pyrimidin-4-yl]-ethyl ketone (5.61 mmol) and 76 mg of 4-aminopyrimidine-5-carboxaldehyde[20] (6.17 mmol, 1.1 equiv) in warm absolute ethanol (10 mL) under argon were added 10 drops of 10% potassium hydroxide. After 1 h of reflux, the solvent was evaporated and the mixture taken up in minimal amount of ethanol, filtered, and dried. ^{1}H NMR ($CDCl_3$): 9.62 (s, 1H), 9.56 (s, 1H), 9.08 (d, ^3J = 8.5 Hz, 1H), 8.83 (s, 1H), 8.60 (d, ^3J = 8.9 Hz, 2H), 8.51 (d, ^3J = 8.5 Hz, 1H), 7.04 (d, ^3J = 8.9 Hz, 2H), 5.91 (d, ^2J = 1.8 Hz, 1H), 4.59 (d, ^2J = 1.7 Hz, 1H), 4.0−4.2 (m, 4H), 1.84 (quint, ^3J = 7.7 Hz, 2H), 1.53 (t, ^3J = 7.0 Hz, 3H), 1.2−1.5 (m, 20H), 0.88 (t, ^3J = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): 163.5, 163.0, 162.6, 162.2, 161.7, 159.0, 157.8, 157.4, 137.3, 130.0, 122.1, 120.3, 114.4, 110.6, 87.9, 68.2, 64.0, 31.9, 29.7, 29.4, 29.3, 22.7, 26.1, 14.6, 14.1. Mp = 140 °C. EI: 539.5 (M^-), 524.5 ($(M - CH_3)^-$), 340.1 ($(M - C_2H_5 - C_{12}H_{25})^-$). Anal. Calcd for $C_{33}H_{41}N_5O_2$·0.15CH_2Cl_2 (539.71): C, 72.07; H, 7.54; N, 12.68; O, 5.79. Found: C, 72.05; H, 7.48; N, 12.74.

7-[2-(4-*n*-Butylphenyl)-6-(1-ethoxyvinyl)pyrimidin-4-yl]pyrido-[2,3-*d*]pyrimidine ($6'_{nBu}$). Same protocol as for the C_{12} chain (mp = 173 °C); the crude product is hydrolyzed (see below) without further purification.

6-[6-Acetyl-2-(4-dodecyloxyphenyl)pyrimidin-4-yl]-2-aminopyridine-3-carboxaldehyde ($6_{OC12H25}$). Vinyl ether ($6'_{OC12H25}$) (200 mg, 3.71 mmol) suspended in 3 N aqueous hydrochloric acid (100 mL) was refluxed with vigorous stirring for 24 h under a nitrogen atmosphere. After being cooled to room temperature, the mixture was further cooled in ice and neutralized with concentrated aqueous ammonia (pH 7−8). The light brown precipitate was filtered, washed with water, and dried in vacuo. ^{1}H NMR analysis of the crude product indicated that the reaction was not complete, probably due to the low solubility of the starting material in acidic water. The precipitate was therefore solubilized in 70 mL of ethanol, 10 mL of concentrated hydrochloric acid were added, and the solution was refluxed overnight. After being cooled in ice, the yellow mixture was neutralized by addition of concentrated aqueous ammonia (pH 8), filtered, dried in vacuo, and purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc 200:5) to yield a yellow solid (70%). ^{1}H NMR ($CDCl_3$): 9.97 (s, 1H), 8.65 (s, 1H), 8.58 (d, ^3J = 8.8 Hz, 2H), 8.12 (d, ^3J = 7.7 Hz, 1H), 8.01 (d, ^3J = 8.0 Hz, 1H), 7.04 (d, ^3J = 9.0 Hz, 2H), 6.8 (br s), 4.07 (t, ^3J = 6.6 Hz, 2H), 2.85 (s, 3H), 1.84 (quint, ^3J = 6.9 Hz, 2H), 1.2−1.5 (m, 20H), 0.88 (t, ^3J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): 200.4, 192.7, 164.8, 164.4, 162.3, 160.9, 158.2, 145.5, 130.4, 129.7, 115.4, 114.9,-111.3, 68.6, 32.3, 29.9, 29.8, 29.7, 29.6, 26.4, 26.2, 23.0, 14.5. R_f (SiO_2, CH_2Cl_2/EtOAc 200:5) = 0.50. Mp = 131 °C. EI: 502.4 (M^-), 334.2 ($(M - C_{12}H_{25})^-$), 306.1 ($(M - C_{12}H_{25} - CO)^-$), 292 ($(M - C_{12}H_{25} - COCH_3)^-$). Anal. Calcd for $C_{30}H_{38}N_4O_3$·0.04 CH_2Cl_2 (502.65): C, 71.30; H, 7.58; N, 11.07; O, 9.48. Found: C, 71.32; H, 7.64; N, 11.01.

6-[6-Acetyl-2-(4-*n*-butylphenyl)pyrimidin-4-yl]-2-aminopyridine-3-carboxaldehyde (6_{nBu}). To ($6'_{nBu}$) (114 mg, 277 μmol) solubilized in 25 mL of warm ethanol were added 10 mL of water and 7 mL of concentrated aqueous hydrochloric acid. The brown solution was refluxed for 1 h. Another 15 mL of water and 5 mL of concentrated hydrochloric acid were added, and the yellow solution was refluxed for an additional 2 h. After being cooled in ice, the mixture was neutralized with concentrated aquous ammonia and the mixture extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography on silica gel (CH_2Cl_2) to yield 54 mg of a yellow solid (52% for two steps). ^{1}H NMR ($CDCl_3$): 9.94 (s, 1H), 8.66 (s, 1H), 8.51 (d, ^3J = 7.0 Hz, 2H), 8.10 (d, ^3J = 7.9 Hz, 1H), 7.99 (d, ^3J = 7.9 Hz, 1H), 7.35 (d, ^3J = 7.0 Hz, 2H), 6.8 (br s), 2.84 (s, 3H), 2.72 (t, ^3J = 7.5 Hz, 2H), 1.67 (quint, ^3J = 7.5 Hz, 2H), 1.38 (sext, ^3J = 7.3 Hz, 2H), 0.96 (t, ^3J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 200.0, 192.4, 164.7, 164.2, 160.6, 157.8, 157.7, 146.7,145.2, 134.5, 128.8, 128.4, 115.0, 111.5, 111.0, 35.7, 33.5, 26.5, 22.4, 14.0. R_f (SiO_2, CH_2Cl_2) = 0.39. Mp = 167 °C. FAB+: 375.2 (MH^+). Anal. Calcd for $C_{22}H_{22}N_4O_2$·0.025 CH_2Cl_2 (374.44): C, 70.25; H, 5.90; N, 14.88; O, 8.50. Found: C, 70.24; H, 6.05; N, 14.72.

1_{OBz}. Diaminodialdehyde 3_{OBz} (50.3 mg, 1.00 × 10^{-4} mol) and ketone (4_{OBz}) (88 mg, 2.03 × 10^{-4} mol, 2.03 equiv) were solubilized in DMF (10 mL) and heated at 50 °C. Two drops of 10% KOH in methanol were added, and the red solution was stirred at 50 °C for 5 h. The reaction mixture was diluted with 30 mL of water, centrifuged, and washed with water and the precipitate recrystallized from dichloromethane and acetone to yield 113 mg of an off-white solid (87%). ^{1}H NMR ($CDCl_3$): 9.87 (s, 1H), 9.23 (s, 2H), 8.7−8.9 (m, 6H), 8.2−8.6 (m, 12H), 8.10 (d, ^3J = 8.5 Hz, 2H), 7.73 (d, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 2H), 7.4−7.6 (m, 15H), 7.18 (d, ^3J = 8.8 Hz, 2H), 6.8−6.9 (m, 6H), 5.20 (s, 2H), 5.05 (s, 4H). ^{13}C NMR ($CDCl_3$): not soluble enough. Mp = 255 °C dec. FAB+: 1296.5 (MH^+), 1205.5 [$(M - CH_2Ph)H^+$], 1113.4 [$(M - 2CH_2Ph)\ H^+$], 1023.4 [$(M - 3CH_2Ph)H^+$], 1317.5 (MNa^+), 1333.5 (MK^+). Anal. Calcd for $C_{83}H_{54}N_{14}O_3$·0.49 CH_2Cl_2: C, 75.00; H, 4.14; N, 14.67; O, 3.59. Found: C, 75.08; H, 4.37; N, 14.94.

2-Amino-6-(2-(4-*n*-butylphenyl)-6-{7-[2-(4-*n*-butylphenyl)-6-[1,8]naphthyridin-2-ylpyrimidin-4-yl][1,8]naphthyridin-2-yl}-pyrimidin-4-yl)pyridine-3-carboxaldehyde $5_{(nBu)2}$. To bisaminoaldehyde $3_{(nBu)}$ (99 mg, 2.2 × 10^{-4} mol) and ketone $4_{(nBu)}$ (85.3 mg, 2.2 × 10^{-4} mol, 1.0 equiv) solubilized in warm absolute ethanol (55 mL) were added three drops of 10% potassium hydroxide in methanol, and the solution was refluxed for 6 h. After being cooled to room temperature, the yellow precipitate was centrifuged, washed

(31) (a) Caluwe, P.; Majewicz, T. G. *J. Org. Chem.* **1975**, *40*, 2566−2567. (b) Caluwe, P. *Tetrahedron* **1980**, *36*, 2359−2407.

with ethanol, and dried in vacuo to yield 175 mg (100%) of the desired monoaminoaldehyde which was recrystallized by diffusion of ethanol in a solution in dichloromethane. ^{1}H NMR ($CDCl_3$): 10.0 (s, 1H), 9.97 (s, 1H), 9.67 (s, 1H), 9.26 (dd, ^3J = 4.1 Hz, ^4J = 1.7 Hz, 1H), 8.9−9.1 (m, 3H), 8.71 (d, ^3J = 8.1 Hz, 2H), 8.67 (d, ^3J = 8.3 Hz, 2H), 8.4−8.6 (m, 3H), 8.31 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1H), 8.18 (d, ^3J = 7.9 Hz, 1H), 8.01 (d, ^3J = 7.9 Hz, 1H), 7.58 (dd, ^3J = 8.1 Hz, ^3J = 4.1 Hz, 1H), 7.41 (d, ^3J = 8.0 Hz, 2H), 7.39 (d, ^3J = 8.2 Hz, 2H), 7.0 (br s, 2H), 2.76 (br t, ^3J = 6.9 Hz, 4H), 1.71 (br quint, ^3J = 6.9 Hz, 4H), 1.44 (br sext, ^3J = 7 Hz, 4H), 0.99 (br t, ^3J = 7 Hz, 6H). ^{13}C NMR ($CDCl_3$): not soluble enough. R_f (Al_2O_3, CH_2Cl_2/CH_3OH 2.0:0.1) = 0.67. Mp > 260 °C. FAB+: 799.3 (MH^+), 1597.6 ($2MH^+$), 1619.5 ($2MNa^+$), 1636.6 ($2MK^+$). Anal. Calcd for $C_{50}H_{42}N_{10}O$·0.825 CH_2Cl_2: C, 71.56; H, 5.16; N, 16.58; O, 1.84. Found: C, 71.55; H, 5.42; N, 16.58.

2-Amino-6[6-{7-[2-(4-benzyloxyphenyl)-6-[1,8]naphthyridin-2-ylpyrimidin-4-yl][1,8]naphthyridin-2-yl}-2-(4-*n*-butylphenyl)-pyrimidin-4-yl]pyridine-3-carboxaldehyde $\mathbf{5_{(OBz)(nBu)}}$. To bisaminoaldehyde $\mathbf{3_{(nBu)}}$ (53 mg, 1.2 × 10^{-4} mol) and ketone $\mathbf{4_{(OBz)}}$ (51 mg, 1.2 ×10^{-4} mol, 1.0 equiv) solubilized in warm absolute ethanol (35 mL) were added four drops of a 10% potassium hydroxide solution in methanol, and the solution was refluxed for 3 h. After the solution was cooled to room temperature, the precipitate was centrifuged, washed with ethanol, and dried in vacuo to yield 100 mg (100%) of the desired monoaminoaldehyde which was recrystallized by diffusion of ethanol into dichloromethane. ^{1}H NMR ($CDCl_3$): 9.98 (s, 1H), 9.96 (s, 1H), 9.66 (s, 1H), 9.23 (dd, ^3J = 4.3 Hz, ^4J = 1.9 Hz, 1H), 8.9−9.1 (m, 3H), 8.75 (d, ^3J = 8.1 Hz, 2H), 8.65 (d, ^3J = 8.3 Hz, 2H), 8.4−8.6 (m, 3H), 8.30 (dd, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 1H), 8.19 (d, ^3J = 7.9 Hz, 1H), 8.02 (d, ^3J = 7.9 Hz, 1H), 7.57 (dd, ^3J = 8.1 Hz, ^3J = 4.1 Hz, 1H), 7.36−7.53 (m, 7H), 7.18 (d, ^3J = 8.8 Hz, 2H), 7.1 (br s, 2H), 5.21 (s, 2H), 2.75 (t, ^3J = 7.6 Hz, 2H), 1.71 (br quint, ^3J = 6.9 Hz, 2H), 1.43 (sext, ^3J = 7.6 Hz, 6H), 0.98 (t, ^3J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): not soluble enough. R_f (Al_2O_3, CH_2Cl_2/CH_3OH 2.0:0.1) = 0.67. Mp > 260 °C. FAB+: 849.5 (MH^+), 1697.8 ($2MH^+$), 1720.8 ($2MNa^+$). Anal. Calcd for $C_{53}H_{40}N_{10}O_2$·0.725 CH_2Cl_2: C, 70.88; H, 4.59; N, 15.26; O, 3.51. Found: C, 70.88; H, 4.69; N, 15.38.

$\mathbf{2_{(nBu)5}}$. To a suspension of aminoaldehyde $\mathbf{5_{(nBu)2}}$ (51 mg, 6.4 × 10^{-5} mol, 2.0 equiv) and diketone (1-[6-acetyl-2-(4-*n*-butylphenyl)-pyrimidin-4-yl]ethyl ketone, 9.4 mg, 3.2 × 10^{-5} mol) in DMF (10 mL) at 60 °C was added one drop of 10% potassium hydroxide in methanol under argon. The dark solution was stirred at 60 °C for 12 h. After being cooled to room temperature, the DMF was distilled under vacuum and the residue taken up in chloroform, washed with distilled water, dried (Na_2SO_4), filtered, and concentrated. The crude solid was solubilized in minimal dichloromethane and toluene was diffused in. The light brown precipitate was isolated by filtration (40 mg, 70%). ^{1}H NMR ($CDCl_3$): broad signals. ^{13}C NMR ($CDCl_3$): not soluble enough. Mp > 260 °C. HR-MALDI-TOF+: $C_{118}H_{96}N_{22}$. K^+: calcd 1859.78199 (MK^+), obsd 1859.78353.

$\mathbf{2_{(OBz)2(nBu)2(nBu)2}}$. To a solution of aminoaldehyde $\mathbf{5_{(OBz)(nBu)}}$ (50 mg, 6.0 × 10^{-5} mol, 2.0 equiv) and diketone ((1-[6-acetyl-2-(4-*n*-butylphenyl)pyrimidin-4-yl]ethyl ketone, 8.7 mg, 2.9 × 10^{-5} mol) in pyridine (10 mL) at 60 °C under argon was added one drop of 10% potassium hydroxide in methanol, and the dark solution was heated at 68−70 °C for 4 h. After the solution was cooled to room temperature, the solvent was evaporated and the residue taken up in dichloromethane and washed with water. The organic layer was coevaporated with toluene, dried in vacuo, and recrystallized from dichloromethane and acetone. ^{1}H NMR ($CDCl_3$, −50 °C, 400 MHz): 8.95 (d, ^3J = 8.0 Hz, 4H), 8.77 (d, ^3J = 8.2 Hz, 2H), 8.56 (s, 1H), 8.49 (d, ^3J = 7 Hz, 2H), 8.37 (s, 4H), 8.20 (d, ^3J = 8.2 Hz, 2H), 8.07 (d, ^3J = 8.2 Hz, 2H), 7.98 (d, ^3J = 8.5 Hz, 2H), 7.74 (d, ^3J = 8.0 Hz, 2H), 7.4−7.6 (m), 7.01 (d, ^3J = 8.0 Hz, 2H), 6.95 (d, ^3J = 8.0 Hz, 2H), 6.80 (d, ^3J = 8.2 Hz, 2H), 6.76 (d, ^3J = 7.7 Hz, 2H), 6.63 (d, ^3J = 8.6 Hz, 2H), 6.41 (dd, ^3J = 8 Hz, ^3J = 3 Hz, 2H), 5.26 (d, ^3J = 9 Hz, 2H), 5.22 (d, ^3J = 10 Hz, 2H), 2.6−3.0 (m), 0.7−1.7 (m). ^{13}C NMR ($CDCl_3$): not soluble enough. Mp >260 °C. HR-MALDI-TOF+: $C_{124}H_{92}N_{22}O_2H^+$ calcd 1921.7846 (MH^+), obsd 1921.8095.

$\mathbf{c1_{OC12H25}}$. To a solution of $\mathbf{6_{OC12H25}}$ (77 mg, 1.53 × 10^{-4} mol) in pyridine (40 mL) at 60 °C were added two drops of 10% potassium hydroxide in methanol. The brown solution was stirred at 60 °C under argon for 10 h. After evaporation of the solvent, the solid residue was taken up in chloroform and washed with water. The organic layer was coevaporated with toluene and washed with 1:1 CH_2Cl_2/acetone mixture to yield 50 mg of an off-white solid (70%). ^{1}H NMR ($CDCl_3$/CD_3OD 2.0:1.0, internal calibration with TMS, 318 K): 9.13 (s, 1H), 8.27 (d, ^3J = 8.0 Hz, 2H), 8.19 (d, ^3J = 8.8 Hz, 1H), 7.60 (d, ^3J = 7.7 Hz, 1H), 6.94 (d, ^3J = 8.8 Hz, 2H), 4.07 (t, ^3J = 6.4 Hz, 2H), 1.93 (quint, ^3J = 7.3 Hz, 2H), 1.2−1.5 (m, 20H), 0.95 (t, ^3J = 6.9 Hz, 3H). ^{13}C NMR: not soluble enough. R_f (SiO_2, CH_2Cl_2/EtOAc 200:5) = 0.50. Mp > 260 °C. HR-MALDI-TOF+: $C_{90}H_{102}N_{12}O_3H^+$ calcd 1399.8271 (MH^+), obsd 1399.8366, 1421.9 (MNa^+), 1438.0 (MK^+).

$\mathbf{c1_{nBu}}$. To a solution containing 47 mg of $\mathbf{6_{nBu}}$ (1.24 × 10^{-4} mol) in 25 mL of pyridine at 60 °C was added one drop of 10% potassium hydroxide in methanol. The solution was stirred at 60 °C for 1.5 h under argon. After evaporation of the solvent, the solid residue was taken up in 1:1 CH_2Cl_2/acetone, centrifuged, and washed with acetone to yield 23 mg of an off-white solid (55%). ^{1}H and ^{13}C NMR ($CDCl_3$): not soluble enough. Mp > 260 °C. HR-FAB+: $C_{66}H_{54}N_{12}H^+$ calcd 1015.4673 (MH^+), obsd 1015.4675.

Bisnaphthyloligoamines (CmNn).[32a] **General Protocol.** A mixture of commercially available 2-naphthaldehyde (2.23 g, 14.3 mmol, 2.2 equiv) and primary diamine (6.5 mmol) was refluxed with 8 g of activated 3 Å molecular sieves in anhydrous dichloromethane (100 mL) for 12 h under nitrogen. After the mixture was cooled to room temperature, the molecular sieves were filtered, and the evaporated yellow residue was taken up in methanol (150 mL) and cooled in ice under nitrogen. Sodium borohydride (1.63 g, 43 mmol, 6.6 equiv) was added portionwise and the mixture refluxed under nitrogen for 2.5 h. The solvent was concentrated in vacuo and the residue taken up in dichloromethane (150 mL) and 1 M aqueous sodium hydroxide (100 mL). The organic layer was washed once again with 1 M aqueous sodium hydroxide (50 mL) and 1 mL concentrated hydrochloric acid was added. The solvent was evaporated, water was added, the precipitate filtered, washed with ethanol, and dried in vacuo (P_2O_5) to yield 85% of the anticipated hydrochloride salt. The desired amine was isolated by treating the hydrochloride salt (typically 400 mg) with 2 M aqueous sodium hydroxide (10 mL for 360 mg of hydrochloride salt) and dichloromethane (20 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated and the oily residue chromatographed (basic alumina) to yield the desired amine as a colorless oil (75% yield). **C2N2**: ^{1}H NMR ($CDCl_3$): 7.7−7.9 (m, 8H), 7.4−7.5 (m, 6H), 3.95 (s, 4H), 2.83 (s, 4H). ^{13}C NMR ($CDCl_3$): 137.9, 133.5, 132.7, 128.1, 127.7, 126.6, 126.5, 126.0, 125.5, 54.0, 48.7. R_f (Al_2O_3, CH_2Cl_2/CH_3OH 2.0:0.1) = 0.25. Mp = 71 °C (white solid). FAB+: 341.3 (MH^+). Anal. Calcd for $C_{24}H_{24}N_2$·0.12 CH_2Cl_2. C, 82.62; H, 6.97; N, 7.99. Found: C, 82.58; H, 6.72; N, 8.12.

Chiral Oligoamines (ProCmNn). *N*-Benzylpropylenediamine (BzCmNn).[32] To a warm solution of 1,3-diaminopropane (2.0 mL, 24 mmol) in 20 mL of dichloromethane (20 mL) was added a solution of benzaldehyde (2.4 mL, 24 mmol, 1.0 equiv) in anhydrous dichloromethane (10 mL). The solution was refluxed for 8 h, the solvent evaporated, and the oily residue taken up in methanol (25 mL). After the mixture was cooled on ice, sodium borohydride (1.85 g, 49 mmol, 2.0 equiv) was added and the mixture refluxed for 8 h under nitrogen. After being cooled to room temperature, the mixture was acidified with concentrated hydro-

(32) (a) Sclafani, J.; Maranto, M. T.; Sisk, T. S.; Van Arman, S. A. *J. Org. Chem.* **1996**, *61*, 3221−3222. (b) Yagyu, T.; Iwatsuki, S.; Aizawa, S.; Funahashi, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1857−1862.

chloric acid (pH 1), the methanol was evaporated, and the pasty residue was taken up in water and basified using 2 M aqueous sodium hydroxide. The suspension was filtered, washed with chloroform, and the aqueous layer was extracted with chloroform. The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and chromatographed (SiO_2). The collected fractions were evaporated, taken up in dichloromethane (100 mL) and washed with 2 M aqueous sodium hydroxide (30 mL). The aqueous layer was extracted with some more dichloromethane. The combined organic layers were filtered onto Celite and concentrated to yield the monoalkylated amine as a light yellow oil (**BzC3N2**, 32%; **BzC33N3**, 26%).

BzC3N2. Eluent for chromatography: $CHCl_3/CH_3OH/Et_3N$ 40:16:8, then $CHCl_3/CH_3OH$/cc aq NH_3 40:16:4. ^1H NMR ($CDCl_3$): 7.2−7.4 (m, 5H), 3.78 (s, 2H), 2.77 (t, ^3J = 7.1 Hz, 2H), 2.70 (t, ^3J = 7.0 Hz, 2H), 1.65 (quint, ^3J = 7.0 Hz, 2H), 1.49 (br s). R_f (SiO_2, $CHCl_3/CH_3OH/NH_3$ 40:16:4) = 0.41.

BzC33N3. Eluent for chromatography: $CHCl_3/CH_3OH$/cc aq NH_3 40:16:4. R_f (SiO_2, $CHCl_3/CH_3OH$/cc aq NH_3 2.0:0.8:0.2) = 0.20. ^1H NMR ($CDCl_3$): 7.1−7.4 (m, 5H), 3.74 (s, 2H), 2.70 (t, ^3J = 6.7 Hz, 2H), 2.65 (t, ^3J = 7.0 Hz, 2H), 2.63 (t, ^3J = 6.7 Hz, 2H), 2.62 (t, ^3J = 7.0 Hz, 2H), 1.66 (quint, ^3J = 6.7 Hz, 2H), 1.58 (quint, ^3J = 7.0 Hz, 2H), 1.3 (br s, 4H). ^{13}C NMR ($CDCl_3$): 140.8, 128.6, 128.3, 127.0, 54.3, 48.8, 48.2, 40.8, 34.0, 30.5.

***N*-Benzylproline-*n*-butylamide (ProAN1).**[33a] In a flame-dried two-neck flask were added 6.9 mL of 2.0 M trimethylaluminum in hexane (14 mmol, 1.5 equiv vs ester group) to 1.4 mL of freshly distilled commercially available *n*-butylamine (14 mmol, 1.5 equiv) solubilized in anhydrous dichloromethane (20 mL) at 25 °C under argon. After being stirred for 20 min, 2.0 g of *N*-benzylproline methyl ester[34] (9.1 mmol) were added neat and the weighing vial rinsed with anhydrous dichloromethane (2 mL followed by 1 mL). The solution was heated at 35 °C for 12h, the mixture was acidified (∼ 5 mL of 0.6 M aqueous hydrochloric acid) and basified with a saturated aqueous solution of sodium hydrogenocarbonate. The aqueous layer was extracted with dichloromethane. The aqueous layer was basified once more with 2 M aqueous sodium hydroxide (4 mL) and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to yield a light yellow oil (2.3 g, 97%). ^1H NMR ($CDCl_3$): 7.2−7.5 (m, 5H), 3.86 (d, ^2J = 13.1 Hz, 1H), 3.48 (d, ^2J = 13.1 Hz, 1H), 3.1−3.3 (m, 3H), 2.95−3.1 (m, 1H), 2.1−2.2 (m, 2H), 1.6−1.95 (m, 3H), 1.2−1.5 (m, 4H), 0.91 (t, ^3J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): 174.7, 139.0, 128.9, 128.7, 127.5, 67.8, 60.2, 54.3, 38.8, 32.0, 31.0, 24.4, 20.4, 14.0. EI: 260.1 (M^-), 160.2 ((M − CONHBu)$^-$). Anal. Calcd for $C_{16}H_{24}N_2O$·0.4 CH_2Cl_2: C, 70.94; H, 9.00; N, 10.09. Found: C, 70.93; H, 9.07; N, 10.76.

***N*-Benzylprolinebutylamine (ProN1).**[33b] **ProAN1** (2.0 g, 7.7 mmol) dried over P_2O_5 in vacuo solubilized in THF (10 mL) under nitrogen was cooled in ice, 20 mL of 1 M lithium aluminum hydride (20 mmol, 2.6 equiv) was added dropwise, and the solution was refluxed under nitrogen for 4 h. After the solution was cooled in ice, 3 mL of 20% aqueous potassium hydroxide was slowly added and the mixture was refluxed for 3.5 h. After the mixture was cooled to room temperature, the white solids were filtered and washed with copious amounts of THF, suspended in water (2 mL), and refluxed for 2 h. After filtration and washing with THF, the combined filtrates were dried (Na_2SO_4), filtered, concentrated, and chromatographed on silica gel (CH_2Cl_2/hexane/Et_3N 1.0:2.0:0.1) to yield a light yellow oil (1.53 g, 81%). ^1H NMR ($CDCl_3$): 7.1−7.4 (m, 5H), 3.98 (d, ^2J = 13.1 Hz, 1H), 3.33 (d, ^2J = 13.1 Hz, 1H), 2.85−3.0 (m, 1H), 2.5−2.8 (m, 5H), 2.20 (quadr, ^3J = 8.2 Hz, 1H), 1.6−2.0 (m, 3H), 1.2−1.6 (m, 5H), 0.92 (t,^3J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): 140.3, 128.9, 128.4, 127.0, 64.1, 59.7, 54.9, 53.5, 50.5, 32.6, 29.5, 23.2, 20.8, 14.3. R_f (SiO_2, CH_2Cl_2/hexane/Et_3N 1.0:2.0:0.1) = 0.31. EI: 245.0 (M^-), 160.1 ((M − $CH_2NHC_4H_9$)$^-$). Anal. Calcd for $C_{16}H_{26}N_2$·0.14 CH_2Cl_2: C, 75.06; H, 10.26; N, 10.85. Found: C, 75.03; H, 10.44; N, 10.47.

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Supporting Information Available: ^1H and ^{13}C spectra of newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171−4174. (b) Ishihara, K.; Karumi, Y.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 5692−5695.

(34) Bucher, C. B.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 935−946.