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Chiral Hexahalogenated 4,4′-Bipyridines

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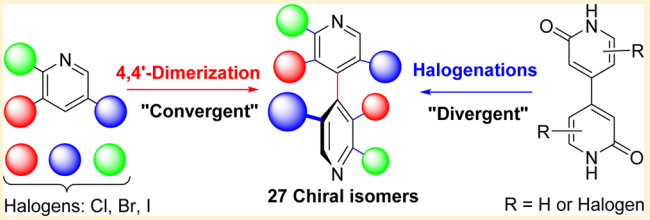
Supporting Information

ABSTRACT: The preparation of 27 isomers of chiral hexahalogeno-4,4′-bipyridines by means of two complementary methods is described. The first one is convergent and based on the LDA-induced 4,4′-dimerization of trihalopyridines, whereas the second method is divergent and achieved through regioselective halogenation reactions of 4,4′-bipyridine-2,2′-diones. Iodine in 2,2′-positions of the 4,4′-bipyridines was introduced by a copper-catalyzed Finkelstein reaction (Buchwald procedure) performed on 2,2′-dibromo derivatives. Selected compounds of this new family of atropisomeric 4,4′-bipyridines were enantioseparated by high performance liquid chromatography on chiral stationary phases, and the absolute configurations of the separated enantiomers were assigned by using X-ray diffraction analysis. The latter revealed that various halogen bond types are responsible for crystal cohesion.



INTRODUCTION

Pyridine derivatives are well-known ligands for transition metals.[1] In contrast, the dimeric 4,4′-bipyridyl system is far less common, although quite used as connector between metal atoms to build macrocyclic complexes,[2] coordination polymers,[3] and more recently to construct metal−organic frameworks (MOFs).[4]

Functionalized 4,4′-bipyridines, especially polyhalogenated 4,4′-bipyridines, constitute valuable atropisomeric ligands for the preparation and development of new homochiral complexes, including MOFs, for applications in asymmetric catalysis,[5] and enantioseparations.[6] Indeed, halogen substituents offer the possibility of further functionalization via palladium-catalyzed cross-coupling reactions and aromatic nucleophilic substitutions. Halogens can also form specific intermolecular interactions with Lewis bases, known as halogen bonds,[7] which are recognized in many fields such as biology, medicinal chemistry,[8] and crystal engineering[9] and are now leading to new emerging applications. In particular, our groups have recently shown that the halogen bond can drive enantiodiscrimination processes in a high performance liquid chromatography (HPLC) environment.[10] Furthermore, the availability of iodine-enriched fragment libraries has been recently recognized as an important tool for lead discovery in medicinal chemistry.[11] In another, but related medicinal application, polyiodo-4,4′-bipyridines could represent an interesting alternative to the well-known iodo-containing molecules used as contrast media for X-ray diagnostics, for which the opacifying ability is related to the iodine content.[12] It is worth noting in this context that polyiodinated biaryl compounds have, for example, been developed (Figure 1).[13]

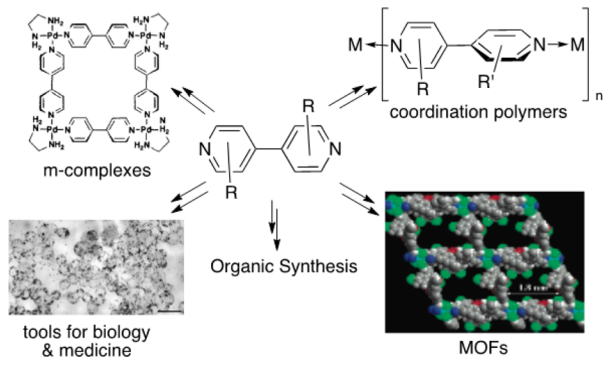


Figure 1. 4,4′-Bipyridines and some applications.

All of these applications require convenient access to polyhalogenated 4,4′-bipyridines. However, such derivatives have been scarcely described in the literature. The reported procedures for the formation of the 4,4′-bipyridine scaffold from substituted pyridines supported only fluorine and chlorine substitution,[14] whereas bromine and iodine were not considered. Except for our recent reports on chiral tetra- and pentahalogenated 4,4′-bipyridines (Figure 2a),[15] only three

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examples of chiral polyhalogenated 4,4′-bipyridines containing bromine or iodine were described (Figure 2b).[16]

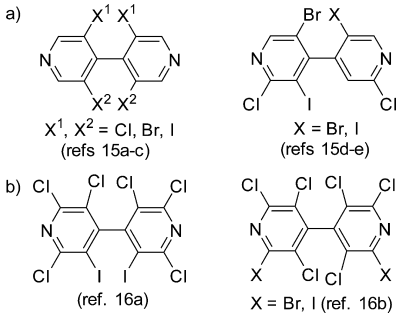


Figure 2. Polyhalogenated 4,4′-bipyridines described in the literature.

In this paper, we focus on the synthesis of chiral symmetrical hexahalo-4,4′-bipyridines. Two complementary chemical routes are described for the preparation of these compounds: the LDA-induced 4,4′-dimerization of trihalopyridines (route 1, 8 derivatives) and the halogenation of 4,4′-bipyridine-2,2′-diones (route 2, 10 derivatives). In particular, the compounds bearing an iodo substituent at the 2-position were obtained through a copper-catalyzed Finkelstein Br/I exchange (9 derivatives) (Figure 3).

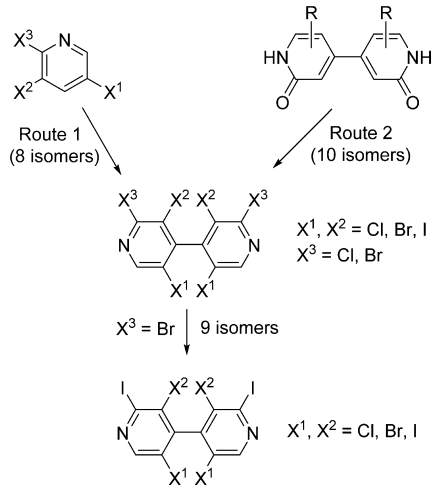


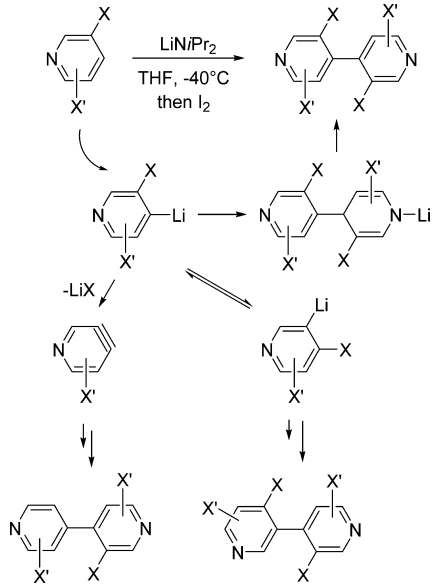
Figure 3. Strategies for the preparation of the 27 examples of symmetrical hexahalo-4,4′-bipyridines.

RESULTS AND DISCUSSION

Route 1: Dimerization of Trihalopyridines. The dimerization route is based on a method, which was originally disclosed for the dimerization of dihalopyridines (Scheme 1, top).[17] During this study, we noticed that 2,5-dihalopyridines were good substrates, whereas 2,3-dihalopyridines were prone to halogen dance[18] in the presence of LDA, thus giving a mixture of 4,4′- and 3,4′-bipyridines in poor yields (Scheme 1, bottom right). For some 2,5- and 2,3-dihalopyridines, arynes[19] were formed, leading finally to trihalobipyridines (Scheme 1, bottom left).

Since the 2,3,5-substitution pattern represents a mixed situation of the 2,3- and 2,5-substitutions, it was worth trying the LDA-mediated dimerization procedure. We decided to start

Scheme 1. Dimerization Reaction Leading to Polyhalogenated 4,4′-Bipyridines: Mechanism and Side Reactions



looking at this reaction with the commercially available 3,5-dibromo-2-chloropyridine **1a** (Table 1).

Full conversion was observed upon treatment of **1a** with 1 equiv of LDA at −40 °C, followed by a temperature rise to −5 °C during 1 h. After quenching at −78 °C through the addition of 1 equiv of I_2 as oxidizing agent, **5** was obtained with a good yield of 72% (entry 1). Other commercially available or readily prepared trihalopyridines **1**−**4** (see the Experimental Section) were dimerized under these optimized conditions (Table 1). Pyridines bearing chlorine, bromine, or iodine reacted smoothly to give the expected bipyridines **5**−**12** with moderate to good yields. With some pyridine substrates (**1a**, **2a**−**b**, **4a**, and **4b**), the reactions were clean with no noticeable degradation products (entries 1, 3, 4, 7, and 8). In contrast, for other pyridines (**1b**, **3a**, and **3b**), mixtures of products were obtained, thus explaining the lower yields (entries 2, 5, and 6). In these cases, the degradation products could originate from the variable stability of the lithiated halopyridine intermediates, which could suffer from aryne formation and/or halogen dance (Scheme 1).

Route 2: Halogenation of Bipyridones. Although the preceding dimerization route proved useful, its convergence could be a problem to obtain a series of compounds, as for any convergent strategy, usually designed for a specific compound. When several compounds of a series are needed, a divergent approach can be more advantageous. Such reasoning led us to envisage an alternative and divergent strategy to the required hexahalobipyridines. Furthermore, during our precedent study on the dimerization of dihalopyridines,[17] it has been noted that 3,5-diodopyridine was a poor substrate for the dimerization process, which in this case led to the corresponding 3,3′,5,5′-tetraiodo-4,4′-bipyridine only with low yield (9%). Therefore, a new methodology was required to introduce iodine atoms at positions 3,3′ and 5,5′. This observation also led us to look for a divergent method allowing the access to a library of hexahalobipyridines from the same starting material.

A retrosynthetic analysis (Figure 4) suggests to get hexahalobipyridines **16**−**25** through a Vilsmeier-type halogen-

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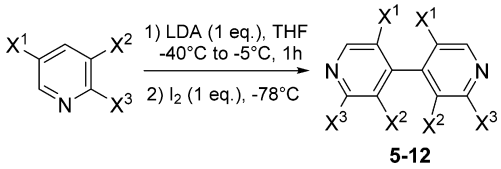
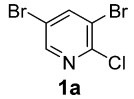
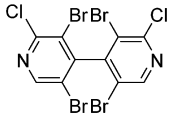
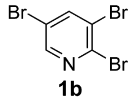
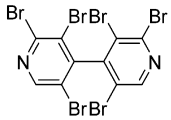
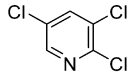
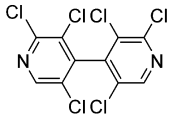
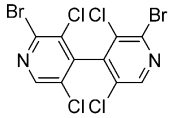
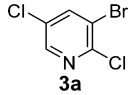
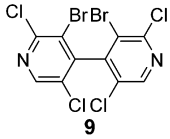
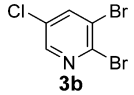
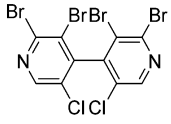
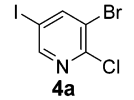
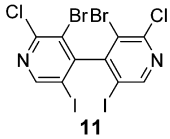
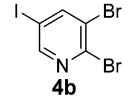
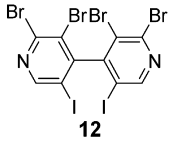
Table 1. Synthesis of Bipyridines 5−12 by LDA-Induced Dimerization of Trihalopyridines[a]



5-12

Entry	Substrate	Product	Yield (%)
1	 **1a**	 **5**	72
2	 **1b**	 **6**	35
3	 **2a**	 **7**	70
4	 **2b**	 **8**	59
5	 **3a**	 **9**	47
6	 **3b**	 **10**	23
7	 **4a**	 **11**	73
8	 **4b**	 **12**	74

[a]Reaction conditions: (i) Pyridine **1**−**4** (1 mmol), LDA (1 mmol), THF, −40 to −5 °C, 1 h. (ii) I_2 (1 mmol), −78 °C, 10 min then rt.

ation of 4,4′-bipyridine-2,2′-diones **13**, by analogy with the synthesis of 2,3,5-trihalopyridines.[20] Compounds **13** could be available upon electrophilic halogenation of the corresponding 4,4′-bipyridine-2,2′-diones **14**, which can be obtained through hydrolysis of the 2,2′-C−Cl bonds of the readily available tetrahalo-4,4′-bipyridines **15**.[21]

Indeed, bipyridines **15a**−**d** have been already described in our previous works[17] and compound **15e** was obtained by dimerization of 2-chloro-5-iodopyridine or from **15d** by double

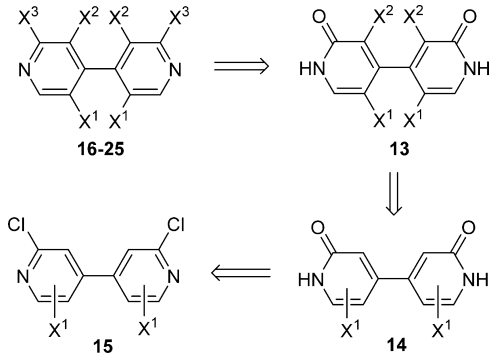
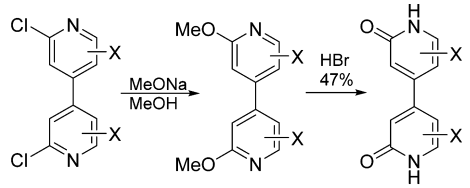


Figure 4. Retrosynthetic analysis for the synthesis of bipyridines **16**−**25** (route 2).

Br/I exchange using *n*-BuLi and I_2 (see the Experimental Section). Although **14a** was reported,[22] we found that the best route to 4,4′-bipyridine-2,2′-diones **14a**−**e** was the exchange of the 2,2′-chlorine atoms by a methoxy group in an addition−elimination process, followed by hydrolysis of the so-formed imidate using aqueous HBr (Scheme 2).

Scheme 2. Synthesis of 4,4′-Bipyridine-2-ones 14a−e



15a (X = H)
15b (X = 5-Cl)
15c (X = 5-Br)
15d (X = 5-I)
15e (X = 3-Cl)

26a
26b
26c
26d
26e

14a (82%)
14b (85%)
14c (97%)
14d (74%)
14e (70%)

4,4′-Bipyridine-2,2′-diones **14a**−**e** were thus obtained in good to excellent yields, but they need to be further halogenated. The iodination of **14a** and **14d** was first considered. *N*-Iodosuccinimide (NIS) proved to be the best reagent to efficiently perform this reaction. Starting from **14a** or **14d** and various amounts of NIS, the reaction was not complete at room temperature. With an excess of NIS (5 equiv for **14a** and 3 equiv for **14d**) and high temperature, complete reactions were finally achieved, leading to bipyridone **13a** in 57% and 43% yield, respectively. Applied to bipyridones **14b**−**c** and **14e**, these conditions allowed the formation of bipyridones **13b**−**c** with 65% (91% purity) and 70% yield (85% purity), whereas **13d** was not sufficiently pure to go further in the synthesis. Consequently, *N*-chlorosuccinimide (NCS) was used to obtain pure bipyridone **13d** by chlorination of **14d** with 35% yield. Analogously, dichlorination of bipyridone **14d** allowed the formation of compound **13e** with 68% yield (Scheme 3).

Interestingly, dibromination of **14d** with 6 equiv of Br_2 delivered the unexpected tetrabrominated bipyridone **13f** where the iodine atoms were replaced by bromines. Bipyridone **13f** could alternatively be obtained by dibromination of **14c**. The desired bipyridone **13g** could be observed in the reaction mixture by reducing the amount of Br_2 to 2.5 equiv. Nevertheless, it was obtained as an inseparable mixture with bipyridone **13h** where only one iodine atom was exchanged (Scheme 4).[23]

It is worth noting that, for solubility reasons, compounds **13** could not be purified by chromatography. In most cases, full

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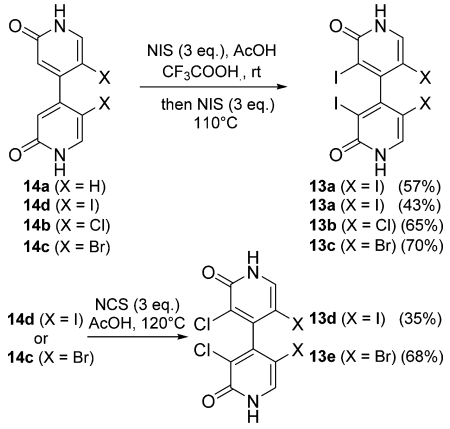
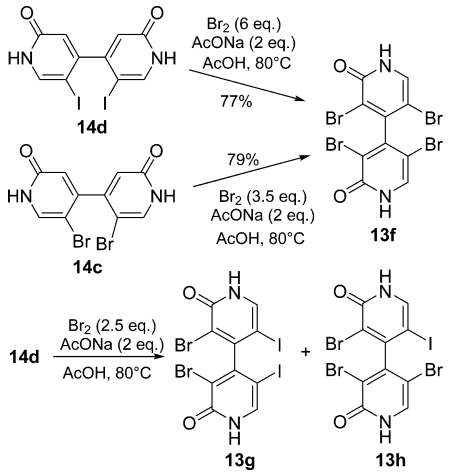
Scheme 3. Synthesis of Chiral Tetrahalo-4,4′-bipyridine-2,2′-diones 13a−e



Scheme 4. Br_2-Induced Iodine/Bromine Exchange during Bromination of Bipyridone 14d

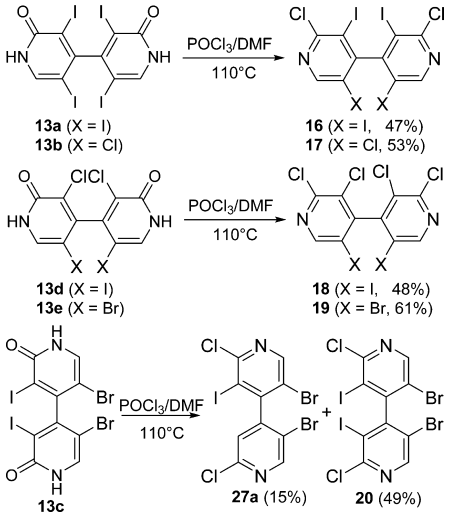


conversions were achieved, leading to pure **13**. When the reactions were not complete, the purity of **13** was determined by ^{1}H NMR. In these cases, compounds **13** were used as mixtures in the next 2,2′-halogenation step.

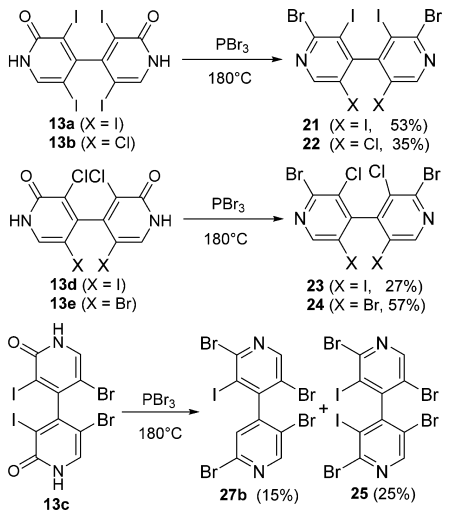
This last step of the sequence was based on a Vilsmeier-type halogenation of the 4,4′-bipyridine-2,2′-diones **13**. For the formation of the 2,2′-chlorinated bipyridines **16−20**, the classical method using $POCl_3$/DMF was first examined and was found efficient for the transformation of all bipyridones **13**.[24] Under these conditions, compounds **16−20** were obtained with moderate to good yields from the corresponding bipyridones **13a,b** and **13d,e**. It is worth noting that bipyridone **13c** (85% purity) delivered pentahalobipyridine **27a**[15d] along with the expected bipyridine **20** with 15% and 49% yields, respectively (Scheme 5).

To get the analogue 2,2′-brominated bipyridines from bipyridones **13**, a similar reaction, but with PBr_3, was attempted. However, this reaction required heating at 180 °C and the solubility of the bipyridones in PBr_3 represented an important limitation. Therefore, these conditions resulted in low to moderate yields of the expected products (Scheme 6). The best results were achieved for the tetrahalogenated 4,4′-bipyridines **21** and **24**, which were isolated with yields of 53% and 57%, respectively. Similarly, bipyridines **22** and **23** were obtained with 35% and 27% yields from **13b** and **13d**,

Scheme 5. Synthesis of Hexahalobipyridines 16−20



Scheme 6. Synthesis of Hexahalobipyridines 21−25



respectively. Under the same conditions, bipyridone **13c** delivered the expected bipyridine **25** but the pentahalobipyridine **27b** was also formed. The yield of bipyridine **25** was thus lower (25%).

Despite the harsh conditions required for this Vilsmeier-type 2,2′-bromination, this route provided better results than the dimerization route. The tetrabrominated bipyridone **13f** was thus transformed to bipyridine **6** in 53% yield, while the dimerization route provided a lower yield (35%; Table 1, entry 2). After dibromination in 3,3′-positions using Br_2, the 5,5′-dichlorobipyridone **14b** was transformed to the bipyridone **13i**, which, after 2,2′-dibromination with PBr_3, furnished bipyridine **10** in excellent yield (Scheme 7). The latter was previously obtained in poor yield (23%; Table 1, entry 6).

For iodination reaction in the 2-position, we first examined the method described by Maloney and co-workers.[25] On this basis, bipyridone **13f** was first reacted with triflic anhydride to generate the bis-triflate intermediate, which was subjected *in situ* to NaI. Unfortunately, the expected bipyridine **28** could not be observed in the reaction mixture. Attempts to isolate the bis-triflate intermediate failed probably because of the very low solubility of the bipyridone starting material. We then considered the copper-catalyzed Finkelstein reaction described

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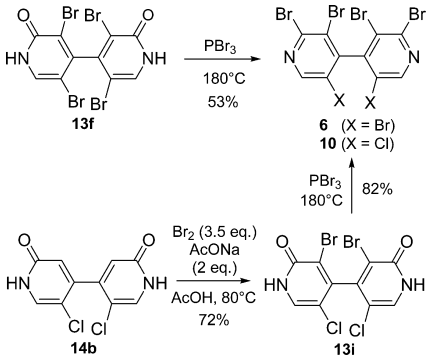
Scheme 7. Improved Synthesis of Bipyridines 6 and 10



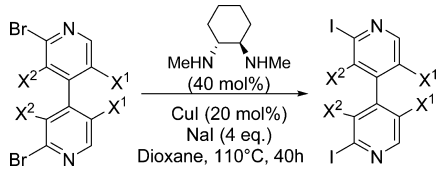
by Buchwald and Klapars[26] for Br/I exchange of aryl, heteroaryl, and vinyl bromides, and recently employed by Lützen and co-workers with 2-bromopyridines.[27] Selected as a model, the hexabrominated bipyridine **6** was mixed with 4 equiv of NaI, 20 mol % of CuI, and 40 mol % of *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine in dioxane at 110 °C. Although the reaction was slow, we observed that the starting material was entirely consumed after 40 h. After purification, bipyridine **28** was isolated with a good 58% yield. Therefore, the Buchwald method was applied to the synthesis of all the other 2,2′-diiodo-3,3′,5,5′-tetrahalo-4,4′-bipyridines through Br/I exchange of the corresponding hexahalo-4,4′-bipyridines. No modification of the reaction conditions was necessary, and after 40 h, bipyridines **29**–**36** were obtained with good to excellent yields (53–87%) (Table 2). Moreover, the possible halogen/iodine exchange at other positions (3, 3′, 5, and 5′) was never observed, probably because of the high steric hindrance around the chiral axis. It is worth noting that the hexaiodo-4,4′-bipyridine **32** having a very high iodine content is a very stable molecule.[28]

Enantioseparation of Chiral Hexahalo-4,4′-bipyridines. Fourteen selected chiral racemic, atropisomeric bipyridines **5**, **6**, **12**, **20**–**23**, **25**, **28**, **31**–**34**, and **36** among the 27 hexahalobipyridine derivatives prepared in this work were enantioseparated by HPLC on chiral stationary phases (Table 3), and the absolute configurations of the recovered pure enantiomers (≥95.6% ee) were assigned by X-ray diffraction (XRD) using an anomalous dispersion signal (for ORTEP plots, see Figures S16–S29 in the Supporting Information). Interestingly, the (*M*) enantiomers were recovered with a very high ee (>98.5–99%) except for two cases (**21** and **34**, ee 95.7% and 95.6%, respectively). The (*P*) enantiomers were recovered with very high ee, but overall slightly lower than the (*M*) enantiomers (97.2–99%).

These 14 bipyridines crystallize in the same $P2_12_12_1$ space group with one molecule in the asymmetric unit, with similar unit cell parameters and volumes (see the Supporting Information, Table S3). They are thus isostructural, as evidenced in Figure 5. The main difference affects bipyridine **22**, which presents a similar structure compared to the others but with a significantly different orientation of the bipyridine molecules.

The intermolecular interactions common to the 13 isostructures are depicted in Figure 6, with interatomic distances reported in Table S4 and the corresponding penetration parameters in Table 4. When comparing interatomic distances to the sum of the corresponding van der Waals radii,[29] the two halogen–Lewis base contacts (Hal_2···N and Hal_3···N) emerge as the most important interactions, with the largest penetration of the van der Waals atomic spheres (Table 4). These interactions arise from the polarization of the halogen atom due to the covalent C_{sp2}–Hal bond, creating the so-called sigma hole[30] which points toward the electron-rich nitrogen atom of the bipyridine rings. These interactions lead to almost linear C_{sp2}–Hal···N contacts (Table S4). The extent of the penetration follows the known halogen bond strength,[31] decreasing in the order I > Br > Cl (I: from

Table 2. Synthesis of Bipyridines 28–36 by Copper-Catalyzed Finkelstein Reaction



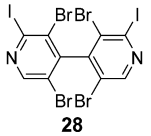
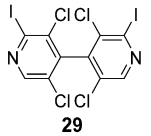
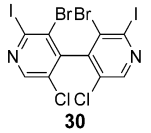
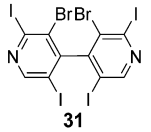
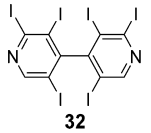
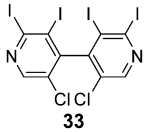
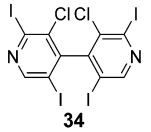
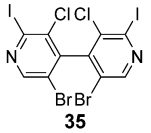
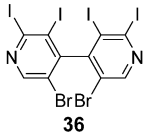
Entry	Substrate	Product	Yield (%)
1	**6**	 **28**	58
2	**8**	 **29**	76
3	**10**	 **30**	68
4	**12**	 **31**	53
5	**21**	 **32**	58
6	**22**	 **33**	75
7	**23**	 **34**	62
8	**24**	 **35**	75
8	**25**	 **36**	87

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Table 3. Enantioseparation of Selected Hexahalogeno-4,4′-bipyridines[a]

4,4′-Bipy	conditions[b]	absolute configuration (ee[c] %)	
		1st eluted	2nd eluted
5	A	*M* (>99)	*P* (>99)
6	B	*M* (98.9)	*P* (>99)
12	C	*M* (99.0)	*P* (98.0)
20	D	*M* (>99)	*P* (>99)
21	C	*M* (95.7)	*P* (98.2)
22	D	*M* (>99)	*P* (98.3)
23	E	*M* (98.5)	*P* (97.7)
25	D	*M* (>99)	*P* (>99)
28	F	*M* (>99)	*P* (97.2)
31	F	*M* (98.6)	*P* (98.6)
32	A	*M* (>99)	*P* (>99)
33	G	*M* (>99)	*P* (>99)
34	E	*M* (95.6)	*P* (>99)
36	H	*M* (>99)	*P* (>99)

[a]All the compounds were separated on Chiralpak IA except **6**, which was separated on Chiralcel OD-H. [b]Conditions of enantioseparation: mobile phase and flow rate (IPA = isopropanol). A: *n*-Heptane/IPA 90:10, 1.0 mL/min; B: *n*-Hexane/IPA 90:10, 0.8 mL/min; C: MeOH/IPA 1:1, 0.4 mL/min; D: *n*-Heptane/EtOH/MeOH 90:05:05, 0.8 mL/min; E: *n*-Heptane/IPA 95:05, 1.0 mL/min; F: *n*-Hexane/IPA 90:10, 1.0 mL/min; G: *n*-Hexane/EtOH 90:10, 1.0 mL/min; H: *n*-Hexane/IPA/MeOH 90:05:05, 0.8 mL/min. All other data (retention times, retention factors, and separation factors) as well as HPLC traces can be found in the Supporting Information (Tables S1−S2 and Figures S1−S14). [c]ee: Enantiomeric excess.

−11.5% to −15.1%; Br: from −3.4% to −9.8%; Cl: from −2.8% to −4.3%). Besides these interactions, a weak hydrogen bond (Hal_2···H, Table 4) and a type-II halogen bond[32] (Hal_5···$Hal_{3'}$, Table 4) are also present in most of the structures, although, in some of them, the interatomic distances are longer than the corresponding sum of van der Waals radii (compounds **23**, **28**, and **33**).

In sharp contrast and surprisingly, the structure of the bipyridine **22** does not exhibit such halogen−nitrogen interaction ($Hal_{2,3}$···N; see the Supporting Information, Figure S15) despite the presence of two good halogen bond donors (Br, I). Furthermore, Cl atoms in structures of **5**, **20**, **23**, and **34** exhibit such interaction, but none exists in **22**. Only two

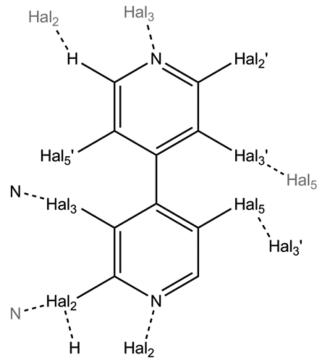

Figure 6. Interaction scheme common to the 13 isostructural bipyridine structures (excluding **22**).

characteristic type-II halogen−halogen interactions can be observed in that particular structure, namely, C−Br···I (3.749 Å, 157.3°) and C−Br···Br (3.565 Å, 165.3°).

CONCLUSION

We have disclosed the synthesis of 27 new atropisomeric 2,2′,3,3′,5,5′-hexahalo-4,4′-bipyridines through two complementary methods by means of convergent and divergent strategies. Based on LDA-mediated 4,4′-dimerization of 2,3,5-trihalopyridines, the convergent synthesis delivered the expected bipyridines generally in good yields. Another, but divergent, synthesis was developed starting from the readily available 4,4′-bipyridine-2,2′-dione scaffold. Hexahalogenated 4,4′-bipyridines were thus obtained, generally in good yields, by means of successive regioselective halogenation reactions. For the synthesis of the 2,2′-diiodo derivatives, a Br/I exchange in the 2,2′-dibromo-3,3′,5,5′-tetrahalo-4,4′-bipyridines was achieved through a copper-catalyzed Finkelstein reaction.

Fourteen of these new atropisomeric 4,4′-bipyridines were enantioseparated by HPLC on chiral stationary phases, and the absolute configurations of the pure enantiomers were assigned by using XRD. Various halogen bonds (Hal···N and Hal···Hal) were observed in almost all the hexahalobipyridines studied by XRD.

These racemic and enantiopure polyhalogenated 4,4′-bipyridines represent valuable synthetic intermediates, which could be further functionalized at the different C−halogen

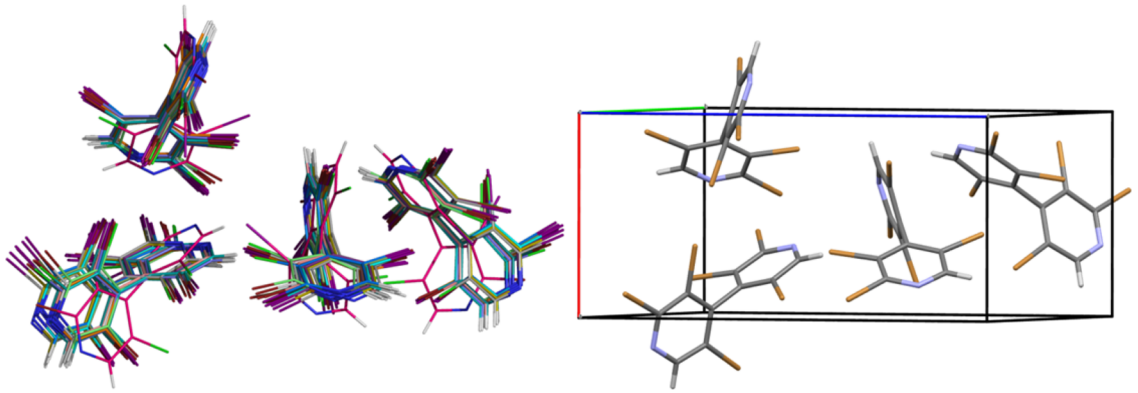

Figure 5. Left: superposition of the 14 bipyridine structures, all converted to (*M*) enantiomers. The fitting of the structures was performed by minimizing the N···N distances between each bipyridine molecule included within one unit cell, with the structure of **6** as reference. The particular bipyridine **22** which deviates from the general trend is displayed with its carbon atoms drawn in pink. Right: reference structure **6** displayed together with its unit cell (color axis scheme: *a*: red; *b*: green; *c*: blue).

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Table 4. Penetration Parameters in Interatomic Contacts $At_1 \cdots At_2$ (Defined as $100 \times \{(d_{At1 \cdots At2})/(r_{vdWAt1} + r_{vdWAt2}) - 1\}$), Where $d_{At1 \cdots At2}$ is the Interatomic Distance and $r_{vdWAt1,2}$ the Corresponding van der Waals Radii)[a]

bipyridine	Hal_2	Hal_3	Hal_5	$N \cdots Hal_2$ (%)	$Hal_2 \cdots H$ (%)	$Hal_3 \cdots N$ (%)	$Hal_5 \cdots Hal_{3'}$ (%)	$Hal_3 \cdots Hal_5$ (%)
5	Cl	Br	Br	−4.3	−7.9	−9.3	−2.7	
6	Br	Br	Br	−9.2	−6.9	−9.8	−1.7	
12	Br	Br	I	−6.3	−8.1	−8.6	−2.7	
25	Br	I	Br	−7.3	−5.1	−12.4	−2.5	
28	I	Br	Br	−14.9	−2.0	−9.3	1.2	
20	Cl	I	Br	−2.8	−5.7	−11.5	−3.6	−2.3
23	Br	Cl	I	−6.7	−8.3	−4.3	0.1	
21	Br	I	I	−3.4	−8.6	−11.7	−3.6	−2.7
36	I	I	Br	−15.1	0.2	−14.3	−0.4	
31	I	Br	I	−13.8	−2.8	−8.8	−3.0	
32	I	I	I	−13.9	−1.8	−14.2	−4.0	
33	I	I	Cl	−14.1	1.8	−13.2	7.7	
34	I	Cl	I	−13.5	−2.9	−2.9	−0.4	

[a]Bipyridines are arranged in families of identical atomic chemical composition.

bonds toward a multitude of new structures. Further work is in progress in our groups for such selective modifications and for various applications, including building MOFs.

EXPERIMENTAL SECTION

General Information. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on the following 300, 400, or 500 MHz instruments. The chemical shifts are given in parts per million (ppm) on the delta scale. The solvent peak was used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.26 ppm. For ^{13}C NMR: $CDCl_3$ = 77.16 ppm. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, b = broad), integration, and coupling constants (J/Hz). High-resolution mass spectra (HRMS) data were recorded on a micrOTOF spectrometer equipped with an orthogonal electrospray interface (ESI). X-ray crystallographic data were collected at low temperature on CCD diffractometers using Cu(Kα) or Mo(Kα) radiations. In each case, anomalous dispersion effects were strong enough in order to unambiguously attribute the chirality of the compounds (see the Supporting Information) Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates with visualization by ultraviolet light. Reagents and solvents were purified using standard means. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone and stored under an argon atmosphere. Anhydrous reactions were carried out in flame-dried glassware and under an argon atmosphere. All other chemicals were used as received. 3,5-Dibromopyridin-2-amine[33] and 3-bromo-5-iodopyridin-2-amine[34] were prepared according to literature procedures. 3,5-Dichloropyridin-2-amine and 3-bromo-5-chloropyridin-2-amine were purchased and used as received.

For HPLC analyses, a high-pressure binary gradient system equipped with a diode-array detector operating at 220 (254, 280) nm and a 20 μL sample loop was employed. Chiralcel OD-H (cellulose tris-3,5-dimethylphenylcarbamate) and Chiralpak IA (amylose tris-3,5-dimethylphenylcarbamate) were used as chiral columns (250 × 4.6 mm) (5 μm). HPLC-grade n-hexane (Hex), n-heptane, ethanol (EtOH), methanol (MeOH), and 2-propanol (IPA) were purchased and used as received.

General Procedure for the Synthesis of 2-Chloro-3,5-dihalopyridines 1a−4a.[35] 3,5-Dihalo-2-aminopyridine (2 mmol) was dissolved in conc. HCl (6 mL), and the solution was cooled to −20 °C. $NaNO_2$ (4 mmol, 276 mg) was added by portions. After the end of the addition, the temperature was raised to room temperature and the mixture was stirred for 4 h. NaOH (10 M) was added until pH 11, and the mixture was extracted with ethyl acetate (2 × 30 mL). The organic phases were combined, washed with brine (40 mL), and dried over anhydrous $MgSO_4$. After concentration, the crude was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5).

Analytical data of *3,5-dibromo-2-chloropyridine* (***1a***)[36] and *2,3,5-trichloropyridine* (***2a***)[37] are identical to those reported in the literature.

3-Bromo-2,5-dichloropyridine (***3a***). m = 268 mg; yield = 59%. Mp: 42−44 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 2.5 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 148.1, 141.0, 131.4, 118.8. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_5H_3Cl_2BrN$ 225.8820; Found 225.8811.

3-Bromo-2-chloro-5-iodopyridine (***4a***). m = 401 mg; yield = 63%. Mp: 66−68 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 2 Hz, 1H), 8.21 (d, J = 2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 150.5, 149.3, 121.4, 90.4. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_5H_3ClBrIN$ 317.8177; Found 317.8207.

General Procedure for the Synthesis of 2-Bromo-3,5-dihalopyridines 1b−4b. These compounds were prepared in two steps starting from 2-amino-dihalopyridines.

Step 1: Transformation of 2-Amino-dihalopyridines to Dihalopyrid-2-ones. 3,5-Dihalo-2-aminopyridine (4 mmol) was added to H_2SO_4 (20%, 24 mL) at −5 °C. A solution of $NaNO_2$ (8 mmol, 552 mg) in H_2O (4 mL) was slowly added, and the reaction was stirred at −5 °C for 2 h. The precipitate was filtered, washed with H_2O (3 × 20 mL), and dried under vacuum.

Analytical data of *3,5-dibromopyridin-2(1H)-one*[22] and *3,5-dichloropyridin-2(1H)-one*[38] are identical to those reported in the literature.

3-Bromo-5-chloropyridin-2(1H)-one. m = 359 mg; yield = 43%. Mp: 152−154 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.06 (d, J = 2.5 Hz, 1H), 7.72 (d, J = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 157.6, 142.6, 134.1, 115.3, 110.9. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_5H_4ClBrNO$ 207.9159; Found 207.9172.

3-Bromo-5-iodopyridin-2(1H)-one.[39] m = 1.14 g; yield = 95%. Mp: 249−251 °C. ^{1}H NMR (300 MHz, DMSO) δ 12.31 (broad s, 1H), 8.09 (s, 1H), 7.71 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 158.0, 149.3, 141.2, 116.9, 64.7.

Step 2: Transformation of Dihalopyrid-2-ones to 2-Bromo-3,5-dihalopyridines ***1b−4b***. Pyridone (2 mmol) was added to PBr_3 (8 mL), and the mixture was heated at 180 °C and stirred for 4 h. After cooling to room temperature, the mixture was dropped over ice-water (100 mL), basified with NaOH (10 M) and extracted with dichloromethane (2 × 50 mL). The organic phases were combined, washed with brine (50 mL), and dried over anhydrous $MgSO_4$. After concentration, the crude was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5).

Analytical data of *2,3,5-tribromopyridine* (***1b***),[40] *2-bromo-3,5-dichloropyridine* (***2b***),[41] and *2,3-dibromo-5-chloropyridine* (***3b***)[20c] are identical to those reported in the literature.

2,3-Dibromo-5-iodopyridine (***4b***). m = 537 mg; yield = 74%. Mp: 76−78 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 1.2 Hz, 1H), 8.17 (d, J = 1.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 148.8, 143.2, 124.8, 91.2. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_5H_3Br_2IN$ 361.7671; Found 361.7666.

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General Procedure for the Dimerization Reaction. To a solution of freshly prepared LDA (1 mmol) in THF (4 mL) at −40 °C was added a solution of trihalopyridine **1**−**4** (1 mmol) in THF (6 mL) during 20 min while maintaining the temperature close to −40 °C. After the end of the addition, the temperature was slowly raised to −5 °C (during 1 h). The temperature was lowered to −78 °C; then a solution of I_2 (280 mg, 1.1 mmol) in THF (1 mL) was slowly added. After 10 min at −78 °C, the temperature was raised to room temperature and the reaction was quenched by the addition of an aqueous saturated solution of $Na_2S_2O_3$ (2 mL). Water was added (5 mL), and the mixture was extracted twice with ethyl acetate (2 × 10 mL). The organic phases were combined, washed with brine (10 mL), and dried over anhydrous $MgSO_4$. After concentration, the crude was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5) to give bipyridines **5**−**12**.

*3,3′,5,5′-Tetrabromo-2,2′-dichloro-4,4′-bipyridine (**5**).* *m* = 390 mg; yield = 72%. Mp: 83−85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 150.1, 150.05, 121.0, 118.7. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_4Cl_2N_2$ 536.6401; Found 536.6425.

*2,2′,3,3′,5,5′-Hexabromo-4,4′-bipyridine (**6**).* *m* = 220 mg; yield = 35%. Mp: 150−152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 149.9, 143.9, 124.2, 119.3. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_6N_2$ 624.5391; Found 624.5405.

*2,2′,3,3′,5,5′-Hexachloro-4,4′-bipyridine (**7**).* *m* = 254 mg; yield = 70%. Mp: 101−103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 146.9, 142.7, 129.9, 129.8. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Cl_6N_2$ 360.8422; Found 360.8457.

*2,2′-Dibromo-,3,3′,5,5′-tetrachloro-4,4′-bipyridine (**8**).* *m* = 266 mg; yield = 59%. Mp: 155−157 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 142.4, 140.8, 132.6, 130.3. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_2Cl_4N_2$ 448.7412; Found 448.7371.

*3,3′-Dibromo-2,2′,5,5′-tetrachloro-4,4′-bipyridine (**9**).* *m* = 212 mg: yield = 47%. Mp: 95−97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.6, 146.9, 129.3, 120.9. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_2Cl_4N_2$ 448.7412; Found 448.7432.

*2,2′,3,3′-Tetrabromo-5,5′-dichloro-4,4′-bipyridine (**10**).* *m* = 124 mg; yield = 23%. Mp: 132−134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 146.6, 143.0, 129.8, 124.2. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_4Cl_2N_2$ 536.6401; Found 536.6400.

*3,3′-Dibromo-2,2′-dichloro-5,5′-diiodo-4,4′-bipyridine (**11**).* *m* = 463 mg; yield = 73%. Mp: 177−179 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 155.4, 152.5, 120.9, 93.9. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_2Cl_2I_2N_2$ 632.6124; Found 632.6124.

*2,2′,3,3′-Tetrabromo-5,5′-diiodo-4,4′-bipyridine (**12**).* *m* = 535 mg; yield = 74%. Mp: 206−208 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 155.6, 145.2, 123.8, 94.7. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_4I_2N_2$ 720.5114; Found 720.5117.

*Improved Synthesis of 2,2′,5,5′-Tetrachloro-4,4′-bipyridine (**15b**) and 2,2′,3,3′-Tetrachloro-4,4′-bipyridine (**15e**).*[17] To a solution of freshly prepared LDA (11 mmol) in THF (70 mL) at −40 °C was added a solution of 2,5-dichloropyridine or 2,3-dichloropyridine (2.9 g, 20 mmol) in THF (120 mL) during 1 h while maintaining the temperature close to −40 °C. After the end of the addition, the temperature was slowly raised to −15 °C (during 1 h). The temperature was lowered to −78 °C; then a solution of a precooled solution of I_2 (2.8 g, 11 mmol) in THF (10 mL) was added at once. After 10 min at −78 °C, the temperature was raised to room temperature and the reaction was quenched by the addition of an aqueous saturated solution of $Na_2S_2O_3$ (20 mL). Water was added (50 mL), and the mixture was extracted twice with ethyl acetate (2 × 100 mL). The organic phases were combined, washed with brine (100 mL), and dried over anhydrous $MgSO_4$. After concentration, the crude was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5) to give **15b** (1.75 g, 61%) or **15e** (1.66 g, 57%).

Improved Synthesis of 5,5′-Dibromo-2,2′-dichloro-4,4′-bipyridine[13] *(**15c**).* To a solution of freshly prepared LDA (11 mmol) in THF (70 mL) at −40 °C was added a solution of 5-bromo-2-chloropyridine (3.85 g, 20 mmol) in THF (120 mL) during 1 h while maintaining the temperature close to −40 °C. After the end of the addition, the mixture was stirred at −40 °C for 1 h. The temperature was lowered to −78 °C; then a solution of a precooled solution of I_2 (2.8 g, 11 mmol) in THF (10 mL) was added at once. After 10 min at −78 °C, the temperature was raised to room temperature and the reaction was quenched by the addition of an aqueous saturated solution of $Na_2S_2O_3$ (20 mL). Water was added (50 mL), and the mixture was extracted twice with ethyl acetate (2 × 100 mL). The organic phases were combined, washed with brine (100 mL), and dried over anhydrous $MgSO_4$. After concentration, the crude was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5) to give **15c** (2.5 g, 65%).

*2,2′-Dichloro-5,5′-diiodo-4,4′-bipyridine (**15d**).* It was prepared by two different routes:

From 2-chloro-5-iodopyridine: the same procedure as that for **15c** was employed. LDA (3.3 mmol), 2-chloro-5-iodopyridine (1.44 g, 6 mmol), I_2 (3.3 mmol, 840 mg). **15d** was obtained with 37% yield (530 mg).

From bipyridine **15c**: *n*-BuLi (1.43 M, 6.3 mmol, 4.4 mL) in THF (7.5 mL) was cooled at −78 °C. A solution of bipyridine **15c** (1.15 g, 3 mmol) in THF (30 mL) was slowly added, and the mixture was stirred at −78 °C for 15 min. A precooled solution of I_2 (1.6 g, 6.3 mmol) in THF (7.5 mL) was added at once; then the mixture was stirred for 10 min −78 °C. The temperature was raised to room temperature, and the reaction was quenched by the addition of an aqueous saturated solution of $Na_2S_2O_3$ (10 mL). Water was added (25 mL), and the mixture was extracted twice with ethyl acetate (2 × 500 mL). The organic phases were combined, washed with brine (50 mL), and dried over anhydrous $MgSO_4$. After concentration, the crude was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5) to give **15d** (1.0 g, 70%). Mp: 215−217 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, *J* = 3 Hz, 2H), 7.17 (d, *J* = 3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 154.8, 152.0, 124.6, 94.2. HRMS calcd for $C_{10}H_5Cl_2I_2N_2$ (M + H) 476.7914, found 476.7952.

General Procedure for the Preparation of Bipyridones 14. Sodium (10 equiv, 20 mmol, 460 mg) was added to MeOH (20 mL) at room temperature. After complete dissolution of Na, bipyridine **15** (2 mmol) was added and the mixture was heated at 65 °C for 10 h. After cooling to room temperature, the mixture was added over a cold aqueous solution of $NaHCO_3$ (5%, 20 mL) and extracted with ethyl acetate (50 mL), dried over anhydrous $MgSO_4$, and concentrated to give **26**, which was used without further purification in the next step. To **26** was added HBr (47%, 8 mL) and the mixture was heated at 110 °C for 4 h. After cooling to room temperature, the mixture was slowly poured on a saturated aqueous solution of $NaHCO_3$ (300 mL). The mixture was filtered and washed with water (20 mL), isopropanol (5 mL), and diethyl ether (10 mL) to give compounds **14** as white powders.

*5,5′-Dichloro-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**14b**).* *m* = 218 mg; yield = 85%. Mp > 300 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.93 (broad s, 2H), 7.82 (s, 2H), 6.42 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 161.2, 147.5, 137.0, 118.1, 111.6. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_7Cl_2N_2O_2$ 256.9879; Found 256.9874.

*5,5′-Dibromo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**14c**).* *m* = 335 mg; yield = 97%. Mp > 300 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.00 (broad s, 2H), 7.88 (s, 2H), 6.37 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 161.4, 150.5, 139.1, 118.3, 99.3. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_7Br_2N_2O_2$ 344.8869; Found 344.8836.

*5,5′-Diiodo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**14d**).* *m* = 326 mg; yield = 74%. Mp > 300 °C. ^{1}H NMR (300 MHz, DMSO) δ 11.86 (broad s, 2H), 7.88 (s, 2H), 6.26 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 161.6, 156.1, 143.3, 118.2, 70.7. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_7I_2N_2O_2$ 440.8591; Found 440.8572.

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*3,3′-Dichloro-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**14e**).* *m* = 180 mg; yield = 70%. Mp > 300 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.35 (s, 2H), 7.51 (d, *J* = 6.7 Hz, 2H), 6.17 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 158.3, 146.7, 134.2, 121.9, 105.1. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_7Cl_2N_2O_2$ 256.9879; Found 256.9879.

General Procedure for 5,5′-Diiodination of Bipyridones 14. To bipyridone **14a−d** (0.5 mmol) in acetic acid (3 mL) were added NIS (428 mg, 1.5 mmol; 713 mg, 2.5 mmol for iodination of **14a**) and trifluoroacetic acid (0.3 mL), and the mixture was stirred for 10 h at room temperature. More NIS (428 mg, 1.5 mmol; 713 mg, 2.5 mmol for iodination of **14a**) and trifluoroacetic acid (0.3 mL) were added, and the reaction mixture was heated to 110 °C and stirred for 5 h. After cooling to room temperature, the mixture was poured on H_2O (10 mL) and made basic by addition of NH_4OH. After filtration and washing with H_2O (2 × 10 mL) and acetonitrile (2 × 5 mL), the solid was dried under vacuum.

*3,3′,5,5′-Tetraiodo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**13a**).* *m* = 197 mg; yield = 57%. Yellow solid. Mp > 300 °C. ^{1}H NMR (300 MHz, DMSO) δ 11.08 (Broad s, 2H), 7.94 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 161.4, 159.7, 142.2, 96.9, 66.9. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_5I_4N_2O_2$ 692.6524; Found 692.6547.

*5,5′-Dichloro-3,3′-diiodo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**13b**).* *m* = 165 mg; yield = 65%. ^{1}H NMR (300 MHz, DMSO) δ 12.43 (s, 2H), 7.94 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 159.6, 154.7, 135.5, 108.7, 97.1.

*5,5′-Dibromo-3,3′-diiodo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**13c**).* *m* = 209 mg; yield = 70%. ^{1}H NMR (300 MHz, DMSO) δ 12.43 (s, 2H), 7.99 (s, 2H).

*5,5′-Dichlorination of Bipyridones **14**.* To a suspension of bipyridone **14c−d** (0.34 mmol) in acetic acid (1 mL) was added NCS (197.4 mg, 1.02 mmol), and the mixture was heated at 120 °C for 2 h. After cooling to room temperature, H_2O (2 mL) was added; then the precipitate was washed with H_2O (2 × 5 mL), acetonitrile (3 × 2 mL), and diethyl ether (5 mL). After drying under vacuum, compounds **13d−e** were recovered as white powders.

*3,3′-Dichloro-5,5′-diiodo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**13d**).* *m* = 61 mg; yield = 35%. Mp > 300 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.69 (s, 2H), 7.97 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 157.5, 151.1, 147.4, 140.9, 122.4. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_5Cl_2I_2N_2O_2$ 508.7812; Found 508.7788.

*3,3′-Dichloro-5,5′-dibromo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**13e**).* *m* = 96 mg; yield = 68%. Mp > 300 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.86 (s, 2H), 8.02 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 157.3, 146.0, 136.6, 123.0, 96.3. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_5Br_2Cl_2N_2O_2$ 412.8089; Found 412.8125.

General Procedure for 5,5′-Dibromination of Bipyridones 14. To a suspension of bipyridone **14b**, **14c**, or **14d** (0.289 mmol) in acetic acid (1 mL) was added AcONa (47.4 mg, 0.578 mmol). Bromine (2.5, 3.5, or 6 equiv) was slowly added, and the mixture was heated at 80 °C for 12 h. After cooling to room temperature, the precipitate was filtered and washed with H_2O (3 × 5 mL), isopropanol (2 × 2 mL), and diethyl ether (5 mL). The white powder was finally dried under vacuum.

*3,3′,5,5′-Tetrabromo-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**13f**).* *m* = 105 mg; yield = 72%. Mp > 300 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.71 (s, 2H), 8.03 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 157.9, 150.1, 137.3, 115.3, 96.4. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_5Br_4N_2O_2$ 500.7079; Found 500.7098.

*3,3′-Dibromo-5,5′-dichloro-[4,4′-bipyridine]-2,2′(1H,1′H)-dione (**13i**).* *m* = 95 mg; yield = 79%. Mp > 300 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.75 (s, 2H), 8.00 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 157.7, 147.5, 135.1, 115.3, 109.3. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_5Br_2Cl_2N_2O_2$ 412.8089; Found 412.8112.

General Procedure for 2,2′-Dichlorination of Bipyridones 13. Bipyridone **13a−e** (0.1 mmol) was dissolved in DMF (1 mL). $POCl_3$ (0.12 mL, 1.2 mmol) was added, and the mixture was heated at 110 °C for 1 h 30 min. After cooling to room temperature, H_2O (2 mL) was added and the mixture was extracted with ethyl acetate (2 × 10 mL). The organic phase was washed with sat. $NaHCO_3$ and dried over $MgSO_4$. After filtration and concentration, the product was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5), and hexahalobipyridines **16−20** were obtained.

*2,2′-Dichloro-3,3′,5,5′-tetraiodo-4,4′-bipyridine (**16**).* *m* = 34 mg; yield = 47%. Mp: 240−242 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 92.9, 99.1, 156.60, 156.65, 162.2. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Cl_2I_4N_2$ 728.5847; Found 728.5844.

*2,2′,5,5′-Tetrachloro-3,3′-diiodo-4,4′-bipyridine (**17**).* *m* = 28.9 mg; yield = 53%. Mp: 135−137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.0, 148.6, 128.1, 99.3. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Cl_4I_2N_2$ 544.7134; Found 544.7160.

*2,2′,3,3′-Tetrachloro-5,5′-diiodo-4,4′-bipyridine (**18**).* *m* = 26.2 mg; yield = 48%. Mp: 151−153 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 152.2, 150.6, 129.4, 94.1. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Cl_4I_2N_2$ 544.7134; Found 544.7160.

*5,5′-Dibromo-2,2′,3,3′-tetrachloro-4,4′-bipyridine (**19**).* *m* = 27.6 mg; yield = 61%. Mp: 93−95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.6, 146.9, 129.3, 120.9. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_2Cl_4N_2$ 448.7412; Found 448.7371.

*5,5′-Dibromo-2,2′-dichloro-3,3′-diiodo-4,4′-bipyridine (**20**).* *m* = 26 mg; yield = 41%. Mp: 135−137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 155.4, 151.1, 117.6, 99.4. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_2Cl_2I_2N_2$ 632.6124; Found 632.6108.

General Procedure for 2,2′-Dibromination of Bipyridones 13. A suspension of bipyridone **13a−e** (0.2 mmol) in PBr_3 (1 mL) was heated at 180 °C for 6 h. After cooling to room temperature, the mixture was dropped over ice-water (50 mL) and treated with NaOH (10 M) until pH 12. The mixture was extracted with dichloromethane (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated. After chromatography on silica gel (cyclohexane/ethyl acetate 95/5), hexahalobipyridines **21−25** were obtained.

*2,2′-Dibromo-3,3′,5,5′-tetraiodo-4,4′-bipyridine (**21**).* *m* = 76.7 mg; yield = 53%. Mp: 208−210 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 156.6, 150.0, 103.5, 93.6. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_2I_4N_2$ 816.4836; Found 816.4808.

*2,2′-Dibromo-5,5′-dichloro-3,3′-diiodo-4,4′-bipyridine (**22**).* *m* = 44.4 mg; yield = 35%. Mp: 160−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 148.8, 148.0, 128.6, 103.7. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Cl_2Br_2I_2N_2$ 632.6124; Found 632.6125.

*2,2′-Dibromo-3,3′-dichloro-5,5′-diiodo-4,4′-bipyridine (**23**).* *m* = 34.3 mg; yield = 27%. Mp: 152−154 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 151.7, 142.8, 131.9, 94.8. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Cl_2Br_2I_2N_2$ 632.6124; Found 632.6162.

*2,2′,5,5′-Tetrabromo-3,3′-dichloro-4,4′-bipyridine (**24**).* *m* = 61.6 mg; yield = 57%. Mp: 168−170 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 145.7, 141.6, 132.5, 119.8. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_4Cl_2N_2$ 536.6401; Found 536.6393.

*2,2′,5,5′-Tetrabromo-3,3′-diiodo-4,4′-bipyridine (**25**).* *m* = 36.2 mg; yield = 25%. Mp: 188−190 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 151.3, 148.8, 118.2, 103.8. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_3Br_4I_2N_2$ 720.5114; Found 720.5116.

*2,2′,5,5′-Tetrabromo-3-iodo-4,4′-bipyridine (**27b**).* *m* = 17.9 mg; yield = 15%. Mp: 170−172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.56 (s, 1H), 7.24 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 152.9, 152.85, 150.8, 148.7, 141.1, 128.0, 119.4, 118.3, 104.2. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{10}H_4Br_4IN_2$ 594.6147; Found 594.6144.

General Procedure for 2,2′-Diiodination of 2,2′-Dibromo-3,3′,5,5′-tetrahalo-4,4′-bipyridines: Synthesis of Bipyridines 28−36. In a dry Schlenk tube were placed 2,2′-dibromo-tetrahalo-

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4,4′-bipyridine (0.1 mmol), NaI (60 mg, 0.4 mmol), CuI (3.8 mg, 0.02 mmol), and diamine ligand (5.68 mg, 0.04 mmol). The flask was evacuated and filled with argon before addition of degassed dioxane (1 mL). The mixture was heated at 120 °C for 40 h. After cooling to room temperature, NH_4OH (2 mL) and H_2O (4 mL) were added; then the product was extracted with dichloromethane (3 × 10 mL). After drying over $MgSO_4$, filtration, and concentration, the product was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95/5).

*3,3′,5,5′-Tetrabromo-2,2′-diiodo-4,4′-bipyridine (**28**).* m = 42 mg; yield = 58%. Mp: 200−202 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 148.4, 129.8, 123.3, 120.1. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_4I_2N_2$ 720.5114; Found 720.5104.

*3,3′,5,5′-Tetrachloro-2,2′-diiodo-4,4′-bipyridine (**29**).* m = 41.5 mg; yield = 76%. Mp: 128−130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 140.8, 137.0, 130.8, 119.5. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Cl_4I_2N_2$ 544.7134; Found 544.7129.

*3,3′-Dibromo-5,5′-dichloro-2,2′-diiodo-4,4′-bipyridine (**30**).* m = 43.2 mg; yield = 68%. Mp: 195−197 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 145.2, 130.4, 129.8, 122.4. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_2Cl_2I_2N_2$ 632.6124; Found 632.6121.

*3,3′-Dibromo-2,2′,5,5′-tetraiodo-4,4′-bipyridine (**31**).* m = 43.3 mg; yield = 53%. Mp: 233−235 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 154.2, 129.3, 124.7, 95.6. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_2I_4N_2$ 816.4836; Found 816.4832.

*2,2′,3,3′,5,5′-Hexaiodo-4,4′-bipyridine (**32**).* m = 52.9 mg; yield = 58%. Mp: 220 °C (degradation). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 156.9, 131.5, 111.5, 94.8. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3I_6N_2$ 912.4559; Found 912.4595.

*5,5′-Dichloro-2,2′,3,3′-tetraiodo-4,4′-bipyridine (**33**).* m = 54.6 mg; yield = 75%. Mp: 182−184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 149.0, 129.2, 129.1, 111.7. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Cl_2I_4N_2$ 728.5847; Found 728.5847.

*3,3′-Dichloro-2,2′,5,5′-tetraiodo-4,4′-bipyridine (**34**).* m = 45.2 mg; yield = 62%. Mp: 181−183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 150.1, 136.2, 121.7, 95.7. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Cl_2I_4N_2$ 728.5847; Found 728.5860.

*5,5′-Dibromo-3,3′-dichloro-2,2′-diiodo-4,4′-bipyridine (**35**).* m = 47.6 mg; yield = 75%. Mp: 216−218 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 144.2, 136.9, 120.45, 120.4. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_2Cl_2I_2N_2$ 632.6124; Found 632.6142.

*5,5′-Dibromo-2,2′,3,3′-tetraiodo-4,4′-bipyridine (**36**).* m = 71.1 mg; yield = 87%. Mp: 225−227 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 151.4, 130.1, 119.0, 111.8. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_2I_4N_2$ 816.4836; Found 816.4850.

*3,3′,5-Tribromo-2,2′-dichloro-5′-iodo-4,4′-bipyridine (**37**).* By analogy to the synthesis of **16**−**20**, the mixture of **13g** and **13h** (150 mg, ca. 0.34 mmol) was treated with $POCl_3$/DMF to give **37** (48 mg, ca. 30% yield) along with **11** (37 mg, ca. 23% yield) after chromatography on silica gel (cyclohexane/ethyl acetate 95/5).

Mp: 138−140 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.63 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 153.6, 152.6, 152.4, 151.4, 150.2, 121.0, 120.5, 118.8, 93.6. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_3Cl_2IN_2$ 584.6263; Found 584.6308.

*2,2′,3,3′,5-Pentabromo-5′-iodo-4,4′-bipyridine (**38**).* By analogy to the synthesis of **21**−**25**, the mixture of **13g** and **13h** (350 mg, ca. 0.59 mmol) was treated with PBr_3 to give **38** (34 mg, ca. 9% yield) along with **12** (13 mg, ca. 3% yield) after chromatography on silica gel (cyclohexane/ethyl acetate 95/5).

Mp: 129−131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.61 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 153.3, 152.3, 150.4, 145.0, 143.9, 124.2, 123.7, 119.4, 94.4. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_5IN_2$ 672.5232; Found 672.5251.

*3,3′,5-Tribromo-2,2′,5′-triodo-4,4′-bipyridine (**39**).* It was obtained following the general procedure of the copper-catalyzed Br/I exchange from **38** (20 mg, 0.03 mmol). Bipyridine **39** was obtained in 55% yield (12.7 mg) after chromatography on silica gel (cyclohexane/ethyl acetate 95/5).

Mp: 218−220 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.59 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 151.8, 150.9, 150.85, 129.8, 129.3, 124.6, 123.4, 120.1, 95.4. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_3Br_3I_3N_2$ 768.4975; Found 768.4964.

*2,2′-Dichloro-3,5,5′-triiodo-4,4′-bipyridine (**40**).* To bipyridone **14d** (40 mg, 0.091 mmol) in acetic acid (1 mL) were added NIS (28.5 mg, 0.1 mmol) and trifluoroacetic acid (50 μL), and the mixture was stirred for 10 h at room temperature. The mixture was poured on H_2O (5 mL) and made basic by addition of NH_4OH. After filtration, washing with H_2O (2 × 2 mL) and acetonitrile (2 × 1 mL), the solid was dried under vacuum. The crude product was treated with $POCl_3$ (70 μL, 0.636 mmol) in DMF (0.5 mL) at 110 °C for 1 h 30 min. After treatment and purification by chromatography on silica gel (cyclohexane/ethyl acetate 95/5), 9 mg of bipyridine **40** was obtained (16% yield for the two steps). Mp: 210−212 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.74 (s, 1H), 7.07 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 158.7, 158.1, 156.4, 156.2, 152.3, 124.2, 99.2, 94.1, 92.9. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_4Cl_2I_3N_2$ 602.6880; Found 602.6852.

Crystal Data for 5. $C_{10}H_2Br_4Cl_2N_2$, M = 540.68, orthorhombic, a = 7.659(4) Å, b = 11.921(6) Å, c = 15.999(11) Å, V = 1460.9(14) Å^3, T = 110(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 11.366 mm^{-1}, 45 174 reflections measured, 7010 independent reflections (R_{int} = 0.0558). Flack parameter = 0.005(5). The final R_1 values were 0.0236 ($I > 2\sigma(I)$) and 0.0265 (all data). The final $wR(F^2)$ values were 0.0521 ($I > 2\sigma(I)$) and 0.0532 (all data). The goodness of fit on F^2 was 1.042. CCDC no. 1455704.

Crystal Data for 6. $C_{10}H_2Br_6N_2$, M = 629.60, orthorhombic, a = 7.64440(10) Å, b = 11.7708(2) Å, c = 16.6604(3) Å, V = 1499.11(4) Å^3, T = 100(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 19.224 mm^{-1}, 11 688 reflections measured, 3150 independent reflections (R_{int} = 0.0340). Flack parameter = −0.01(3). The final R_1 values were 0.0287 ($I > 2\sigma(I)$) and 0.0290 (all data). The final $wR(F^2)$ values were 0.0754 ($I > 2\sigma(I)$) and 0.0754 (all data). The goodness of fit on F^2 was 1.159. CCDC no. 1455705.

Crystal Data for 12. $C_{10}H_2Br_4I_2N_2$, M = 723.58, orthorhombic, a = 7.888(4) Å, b = 12.138(5) Å, c = 16.364(8) Å, V = 1566.7(13) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 14.199 mm^{-1}, 29 605 reflections measured, 5545 independent reflections (R_{int} = 0.0523). Flack parameter = 0.100(9). The final R_1 values were 0.0296 ($I > 2\sigma(I)$) and 0.0330 (all data). The final $wR(F^2)$ values were 0.0679 ($I > 2\sigma(I)$) and 0.0695 (all data). The goodness of fit on F^2 was 1.070. CCDC no. 1455706.

Crystal Data for 20. $C_{10}H_2Br_2Cl_2I_2N_2$, M = 634.66, orthorhombic, a = 8.034(2) Å, b = 11.838(2) Å, c = 16.278(3) Å, V = 1548.1(5) Å^3, T = 102(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 9.553 mm^{-1}, 57 166 reflections measured, 6621 independent reflections (R_{int} = 0.0434). Flack parameter = 0.009(4). The final R_1 values were 0.0152 ($I > 2\sigma(I)$) and 0.0163 (all data). The final $wR(F^2)$ values were 0.0331 ($I > 2\sigma(I)$) and 0.0333 (all data). The goodness of fit on F^2 was 1.081. CCDC no. 1455707.

Crystal Data for 21. $C_{10}H_2Br_2I_4N_2$, M = 817.56, orthorhombic, a = 8.177(6) Å, b = 12.152(8) Å, c = 16.434(10) Å, V = 1633.0(18) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 12.511 mm^{-1}, 40 413 reflections measured, 7819 independent reflections (R_{int} = 0.0381). Flack parameter = 0.019(5). The final R_1 values were 0.0191 ($I > 2\sigma(I)$) and 0.0213 (all data). The final $wR(F^2)$ values were 0.0382 ($I > 2\sigma(I)$) and 0.0389 (all data). The goodness of fit on F^2 was 1.082. CCDC no. 1455708.

Crystal Data for 22. $C_{10}H_2Br_2Cl_2I_2N_2$, M = 634.66, orthorhombic, a = 7.913(5) Å, b = 11.911(9) Å, c = 15.781(12) Å, V = 1487.4(19) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 9.943 mm^{-1}, 48 541 reflections measured, 5248 independent reflections (R_{int}

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= 0.0376). Flack parameter = 0.001(8). The final R_1 values were 0.0243 ($I > 2\sigma(I)$) and 0.0271 (all data). The final $wR(F^2)$ values were 0.0515 ($I > 2\sigma(I)$) and 0.0523 (all data). The goodness of fit on F^2 was 1.041. CCDC no. 1455709.

Crystal Data for 23. $C_{10}H_2Br_2Cl_2I_2N_2$, M = 634.66, orthorhombic, a = 7.779(4) Å, b = 12.148(5) Å, c = 16.057(7) Å, V = 1517.3(12) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 9.747 mm^{-1}, 48 074 reflections measured, 7257 independent reflections (R_{int} = 0.0403). Flack parameter = 0.010(5). The final R_1 values were 0.0197 ($I > 2\sigma(I)$) and 0.0213 (all data). The final $wR(F^2)$ values were 0.0426 ($I > 2\sigma(I)$) and 0.0431 (all data). The goodness of fit on F^2 was 1.069. CCDC no. 1455710.

Crystal Data for 25. $C_{10}H_2Br_4I_2N_2$, M = 723.58, orthorhombic, a = 7.997(2) Å, b = 11.722(2) Å, c = 16.948(3) Å, V = 1588.6(6) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 14.003 mm^{-1}, 48 146 reflections measured, 6807 independent reflections (R_{int} = 0.0573). Flack parameter = 0.016(5). The final R_1 values were 0.0231 ($I > 2\sigma(I)$) and 0.0249 (all data). The final $wR(F^2)$ values were 0.0543 ($I > 2\sigma(I)$) and 0.0551 (all data). The goodness of fit on F^2 was 1.086. CCDC no. 1455711.

Crystal Data for 28. $C_{10}H_2Br_4I_2N_2$, M = 723.58, orthorhombic, a = 7.800(3) Å, b = 11.334(5) Å, c = 18.031(7) Å, V = 1594.1(11) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 13.955 mm^{-1}, 36 984 reflections measured, 7610 independent reflections (R_{int} = 0.0718). Flack parameter = 0.018(7). The final R_1 values were 0.0316 ($I > 2\sigma(I)$) and 0.0339 (all data). The final $wR(F^2)$ values were 0.0740 ($I > 2\sigma(I)$) and 0.0756 (all data). The goodness of fit on F^2 was 1.096. CCDC no. 1455712.

Crystal Data for 31. $C_{10}H_2Br_2I_4N_2$, M = 817.56, orthorhombic, a = 7.985(3) Å, b = 11.766(4) Å, c = 17.716(7) Å, V = 1664.3(11) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 12.275 mm^{-1}, 50 710 reflections measured, 7978 independent reflections (R_{int} = 0.0641). Flack parameter = 0.027(9). The final R_1 values were 0.0287 ($I > 2\sigma(I)$) and 0.0291 (all data). The final $wR(F^2)$ values were 0.0753 ($I > 2\sigma(I)$) and 0.0755 (all data). The goodness of fit on F^2 was 1.105. CCDC no. 1455713.

Crystal Data for 32. $C_{10}H_2I_6N_2$, M = 911.54, orthorhombic, a = 8.219(3) Å, b = 11.493(5) Å, c = 18.059(7) Å, V = 1706.0(11) Å^3, T = 102(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 10.911 mm^{-1}, 54 826 reflections measured, 7324 independent reflections (R_{int} = 0.0512). Flack parameter = 0.00(3). The final R_1 values were 0.0200 ($I > 2\sigma(I)$) and 0.0204 (all data). The final $wR(F^2)$ values were 0.0486 ($I > 2\sigma(I)$) and 0.0488 (all data). The goodness of fit on F^2 was 1.220. CCDC no. 1455714.

Crystal Data for 33. $C_{10}H_2Cl_2I_4N_2$, M = 728.64, orthorhombic, a = 7.957(3) Å, b = 10.910(4) Å, c = 18.607(7) Å, V = 1615.3(10) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 8.031 mm^{-1}, 45 227 reflections measured, 6929 independent reflections (R_{int} = 0.0411). Flack parameter = −0.014(13). The final R_1 values were 0.0163 ($I > 2\sigma(I)$) and 0.0167 (all data). The final $wR(F^2)$ values were 0.0389 ($I > 2\sigma(I)$) and 0.0393 (all data). The goodness of fit on F^2 was 1.122. CCDC no. 1455715.

Crystal Data for 34. $C_{10}H_2Cl_2I_4N_2$, M = 728.64, orthorhombic, a = 7.906(3) Å, b = 11.780(5) Å, c = 17.605(7) Å, V = 1639.6(11) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 7.912 mm^{-1}, 43 791 reflections measured, 7833 independent reflections (R_{int} = 0.0459). Flack parameter = 0.001(16). The final R_1 values were 0.0217 ($I > 2\sigma(I)$) and 0.0220 (all data). The final $wR(F^2)$ values were 0.0519 ($I > 2\sigma(I)$) and 0.0520 (all data). The goodness of fit on F^2 was 1.187. CCDC no. 1455716.

Crystal Data for 36. $C_{10}H_2Br_2I_4N_2$, M = 817.56, orthorhombic, a = 8.028(2) Å, b = 11.128(2) Å, c = 18.411(4) Å, V = 1644.9(6) Å^3, T = 105(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 12.420 mm^{-1}, 40 559 reflections measured, 7035 independent reflections (R_{int} = 0.0492). Flack parameter = 0.022(6). The final R_1 values were 0.0196 ($I > 2\sigma(I)$) and 0.0201 (all data). The final $wR(F^2)$ values were 0.0469 ($I > 2\sigma(I)$) and 0.0471 (all data). The goodness of fit on F^2 was 1.150. CCDC no. 1455717.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00413.

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds; details concerning the multimilligram enantioseparation by HPLC on chiral stationary phases and structure characteristics of hexahalobipyridines **5**−**6**, **12**, **20**−**23**, **25**, **28**, **31**−**34**, and **36**; and X-ray structures of the corresponding enantiomers (*M* or *P*) (PDF)

Crystallographic data for **5** (CIF)

Crystallographic data for **6** (CIF)

Crystallographic data for **12** (CIF)

Crystallographic data for **20** (CIF)

Crystallographic data for **21** (CIF)

Crystallographic data for **22** (CIF)

Crystallographic data for **23** (CIF)

Crystallographic data for **25** (CIF)

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Crystallographic data for **32** (CIF)

Crystallographic data for **33** (CIF)

Crystallographic data for **34** (CIF)

Crystallographic data for **36** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Tomasik, P.; Ratajewicz, Z. *Pyridine-Metal Complexes*; Newkome, G. R., Strekowski, L., Eds.; The Chemistry of Heterocyclic Compounds; J. Wiley & Sons: New York, 1985; Vol. *14*. (b) Zafar, M. N.; Atif, A. H.; Nazar, M. F.; Sumrra, S. H.; Gul-E-Saba; Paracha, R. *Russ. J. Coord. Chem.* **2016**, *42*, 1−18. For a recent example, see: (c) Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 1760−1763.

(2) Fujita, M.; Ogura, K. *Coord. Chem. Rev.* **1996**, *148*, 249−264.

(3) Birada, K.; Sarkar, M.; Rajput, L. *Chem. Commun.* **2006**, 4169−4179.

(4) For reviews on MOF, see: (a) Furukawa, H.; Cordova, K. E.; O'Keeffe, M.; Yaghi, O. M. *Science* **2013**, *341*, 974−985. (b) Leong, W. L.; Vittal, J. J. *Chem. Rev.* **2011**, *111*, 688−764. (c) Tranchemontagne, D. J.; Mendoza-Cortés, J. L.; O'Keeffe, M.; Yaghi, O. M. *Chem. Soc. Rev.* **2009**, *38*, 1257−1283. For specific examples based on 4,4′-bipyridines, see: (d) Pal, T. K.; Chatterjee, N.; Bharadwaj, P. K. *Inorg. Chem.* **2016**, *55*, 1741−1747. (e) Lee, S. J.; Doussot, C.; Baux, A.; Liu, L.; Jameson, G. B.; Richardson, C.; Pak, J. J.; Trousselet, F.; Coudert, F.-X.; Telfer, S. G. *Chem. Mater.* **2016**, *28*, 368−375. (f) Aulakh, D.; Varghese, J. R.; Wriedt, M. *Inorg. Chem.* **2015**, *54*, 1756−1764.

(5) Yoon, M.; Srirambalaji, R.; Kim, K. *Chem. Rev.* **2012**, *112*, 1196−1231.

(6) Peluso, P.; Mamane, V.; Cossu, S. *J. Chromatogr. A* **2014**, *1363*, 11−26.

DOI: 10.1021/acs.joc.6b00413
J. Org. Chem. 2016, 81, 4576−4587

(7) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. *Chem. Rev.* **2016**, *116*, 2478−2601.
(8) Lu, Y.; Wang, Y.; Zhu, W. *Phys. Chem. Chem. Phys.* **2010**, *12*, 4543−4551.
(9) Mukherjee, A.; Tothadi, S.; Desiraju, G. R. *Acc. Chem. Res.* **2014**, *47*, 2514−2524.
(10) (a) Peluso, P.; Mamane, V.; Aubert, E.; Cossu, S. *J. Chromatogr. A* **2014**, *1345*, 182−192. For a review, see: (b) Peluso, P.; Mamane, V.; Cossu, S. *Chirality* **2015**, *27*, 667−684.
(11) Wilcken, R.; Liu, X.; Zimmermann, M. O.; Rutherford, T. J.; Fersht, A. R.; Joerger, A. C.; Boeckler, F. M. *J. Am. Chem. Soc.* **2012**, *134*, 6810−6818.
(12) Lusic, H.; Grinstaff, M. W. *Chem. Rev.* **2013**, *113*, 1641−1666.
(13) (a) Anelli, P. L.; Brocchetta, M.; Maffezzoni, C.; Paoli, P.; Rossi, P.; Uggeri, F.; Visigalli, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1175−1181. (b) Mirk, D.; Willner, A.; Frohlich, R.; Waldvogel, S. R. *Adv. Synth. Catal.* **2004**, *346*, 675−681.
(14) (a) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200−1203. (b) Gutov, A. V.; Rusanov, E. B.; Ryabitskii, A. B.; Chernega, A. N. *J. Fluorine Chem.* **2010**, *131*, 278−281. (c) Miller, A. O.; Krasnov, V. I.; Peters, D.; Platonov, V. E.; Miethchen, R. *Tetrahedron Lett.* **2000**, *41*, 3817−3819. (d) Chambers, R. D.; Musgrave, W. K. R.; Sargent, C. R.; Drakesmith, F. G. *Tetrahedron* **1981**, *37*, 591−595. (e) Mack, A. G.; Suschitzky, H.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1682−1687. (f) Banks, R. E.; Haszeldine, R. N.; Phillips, E. *J. Fluorine Chem.* **1977**, *9*, 243−246. (g) Foulger, N. J.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 871−875. (h) Cook, J. D.; Foulger, N. J.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 995−996.
(15) (a) Mamane, V.; Aubert, E.; Peluso, P.; Cossu, S. *J. Org. Chem.* **2012**, *77*, 2579−2583. (b) Peluso, P.; Mamane, V.; Aubert, E.; Cossu, S. *J. Chromatogr. A* **2012**, *1251*, 91−100. (c) Peluso, P.; Mamane, V.; Aubert, E.; Cossu, S. *J. Sep. Sci.* **2013**, *36*, 2993−3003. (d) Mamane, V.; Aubert, E.; Peluso, P.; Cossu, S. *J. Org. Chem.* **2013**, *78*, 7683−7689. (e) Peluso, P.; Mamane, V.; Aubert, E.; Cossu, S. *J. Sep. Sci.* **2014**, *37*, 2481−2489.
(16) (a) Bratt, J.; Iddon, B.; Mack, A. G.; Suschitzky, H.; Taylor, J. A.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 648−656. (b) Wakefield, B. J. *J. Organomet. Chem.* **1975**, *99*, 191−197.
(17) Abboud, M.; Mamane, V.; Aubert, E.; Lecomte, C.; Fort, Y. *J. Org. Chem.* **2010**, *75*, 3224−3231 and references cited therein.
(18) (a) Mallet, M.; Quéguiner, G. *Tetrahedron* **1985**, *41*, 3433−3440. For a general review, see: (b) Schnuerch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046−1057.
(19) (a) Jamart-Gregoire, B.; Leger, C.; Caubère, P. *Tetrahedron Lett.* **1990**, *31*, 7599−7602. (b) Connon, S. J.; Hegarty, A. F. *J. Chem. Soc., Perkin 1* **2000**, 1245−1249.
(20) (a) Koseki, Y.; Sugimura, T.; Ogawa, K.; Suzuki, R.; Yamada, H.; Suzuki, N.; Masuyama, Y.; Lin, Y. Y.; Usuki, T. *Eur. J. Org. Chem.* **2015**, *2015*, 4024−4032. (b) Gloaguen, C.; Voisin-Chiret, A. S.; Sopkova-de Oliveira Santos, J.; Fogha, J.; Gautier, F.; De Giorgi, M.; Burzicki, G.; Perato, S.; Petigny-Lechartier, C.; Simonin-Le Jeune, K.; et al. *J. Med. Chem.* **2015**, *58*, 1644−1668. (c) Quallich, G. J.; Fox, D. E.; Friedmann, R. C.; Murtiashaw, C. W. *J. Org. Chem.* **1992**, *57*, 761−764.
(21) (a) **15a** was prepared according to ref 15c. (b) **15b**−**15e** were obtained after improvement of the reported procedure of ref 17 (see the Experimental Section for details).
(22) Kelly, T. R.; Lee, Y.-J.; Mears, R. J. *J. Org. Chem.* **1997**, *62*, 2774−2781.
(23) The mixture of **13g** and **13h** was treated with $POCl_3$/DMF to give bipyridines **11** and **37**, and with PBr_3 to give bipyridines **12** and **38**. This last compound was transformed to bipyridine **39** through the copper-catalyzed Br/I exchange (see the Experimental Section for details).
(24) When $POCl_3$/DMF was applied to bipyridone **14d** initially treated with 1.1 equiv of NIS at room temperature, the pentahalobipyridine **40** with only 3 iodine atoms was the major product (16% yield after 2 steps) (see the Experimental Section for details).
(25) Maloney, K. M.; Nwakpuda, E.; Kuethe, J. T.; Yin, J. *J. Org. Chem.* **2009**, *74*, 5111−5114.
(26) (a) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844−14845. (b) Chen, M.; Ichikawa, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 263−266.
(27) Meyer-Eppler, G.; Küchler, L.; Tenten, C.; Benkhäuser, C.; Brück, S.; Lützen, A. *Synthesis* **2014**, *46*, 1085−1090.
(28) During the melting point measurement, bipyridine **32** became dark violet around 220 °C, probably due to iodine loss induced by high temperature. The dark violet solid then melted at 264−266 °C.
(29) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441−451.
(30) (a) Awwadi, F. F.; Willett, R. D.; Peterson, K. A.; Twamley, B. *Chem.—Eur. J.* **2006**, *12*, 8952−8960. (b) Bui, T. T. T.; Dahaoui, S.; Lecomte, C.; Desiraju, G. R.; Espinosa, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3838−3841. (c) Aubert, E.; Lebègue, S.; Marsman, M.; Bui, T. T. T.; Jelsch, C.; Dahaoui, S.; Espinosa, E.; Ángyán, J. G. *J. Phys. Chem. A* **2011**, *115*, 14484−14494.
(31) Politzer, P.; Lane, P.; Concha, M. C.; Ma, Y.; Murray, J. S. *J. Mol. Model.* **2007**, *13*, 305−311.
(32) Desiraju, G. R.; Parthasarathy, R. *J. Am. Chem. Soc.* **1989**, *111*, 8725−8726.
(33) Canibano, V.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; Carreno, M. C.; Gonzalez, G.; Garcia-Ruano, J. L. *Synthesis* **2001**, *2001*, 2175−2179.
(34) Younis, Y.; Douelle, F.; Feng, T.-S.; Cabrera, D. G.; Le Manach, C.; Nchinda, A. T.; Duffy, S.; White, K. L.; Shackleford, D. M.; Morizzi, J.; et al. *J. Med. Chem.* **2012**, *55*, 3479−3487.
(35) Chamas, Z.; Marchi, E.; Presson, B.; Aubert, E.; Fort, Y.; Ceroni, P.; Mamane, V. *RSC Adv.* **2015**, *5*, 2715−2723.
(36) Wang, H.; Wen, K.; Wang, L.; Xiang, Y.; Xu, X.; Shen, Y.; Sun, Z. *Molecules* **2012**, *17*, 4533−4544.
(37) Steiner, E.; Martin, P.; Bellus, D. *Helv. Chim. Acta* **1982**, *65*, 983−985.
(38) Katritzky, A. R.; Khan, G. R.; Leahy, D. E.; De Rosa, M. *J. Org. Chem.* **1984**, *49*, 4784−4786.
(39) Meana, A. M.; Rodríguez, J. F.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *Synlett* **2003**, 1678−1682.
(40) Burzicki, G.; Voisin-Chiret, A. S.; Sopková-de Oliveira Santos, J.; Rault, S. *Synthesis* **2010**, *2010*, 2804−2810.
(41) Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, *2001*, 1371−1376.

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