

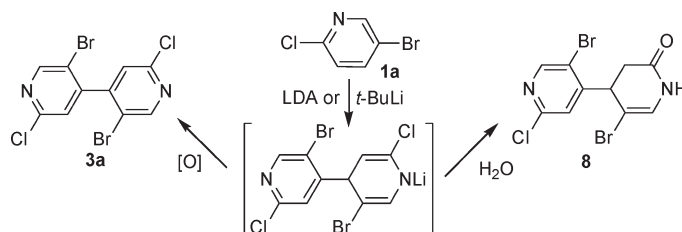
Synthesis of Polyhalogenated 4,4'-Bipyridines via a Simple Dimerization Procedure

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Polyhalogenated 4,4'-bipyridines were conveniently synthesized in a single step starting from dihalopyridines. A mechanism was proposed on the basis of experiments performed with 2-chloro-5-bromopyridine **1a**. 2-Chloro-4-lithio-5-bromopyridine **A1** was produced via ortholithiation of **1a** by using either LDA or *t*-BuLi bases. When LDA was used, dimer **3a** containing two chlorines and two bromine atoms was formed predominantly accompanied by several byproducts whose structure and mechanism of formation are discussed. In the case of *t*-BuLi, although the major product was 2-chloropyridine **7**, a new pyridone product **8** was formed that is probably the result of the dihydropyridine intermediate hydrolysis. The dimerization procedure involving LDA was employed to prepare a large number of halogenated 4,4'-bipyridines in moderate to good yields. In some specific cases, halogenated 3,4' and 2,4'-bipyridines were obtained in lower yields and their structures were unambiguously assigned by X-ray diffraction analysis.

Introduction

The 4,4'-bipyridine skeleton represents an excellent building block in supramolecular chemistry¹ and biology² and is

an important intermediate in the synthesis of viologens.³ Thus much effort has been made in the preparation of functionalized 4,4'-bipyridine derivatives. Different methods were described in the literature particularly involving metal-catalyzed reactions and sodium metal-induced dimerization. Cross-coupling reactions⁴ often have been used but required long reaction sequences for the preparation of the two coupling partners. For the rapid synthesis of symmetrical bipyridines bearing reactive functions, homocoupling reactions represent an excellent alternative.⁵ The use of sodium metal in order to induce 4,4'-dimerization of pyridine has been known for a long time but only simple alkyl-substituted pyridines tolerated the use of the highly reducing conditions.⁶ It was

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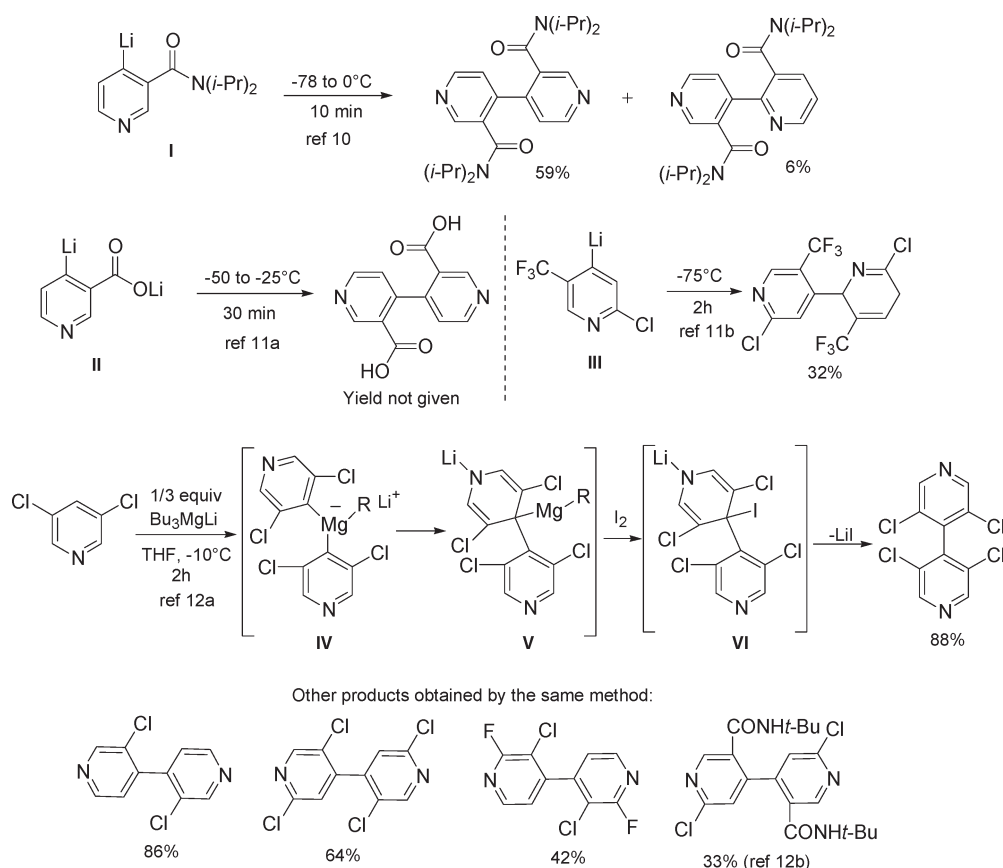


FIGURE 1. Reactivity of metalated pyridines in the 4-position.

shown that radical anions of pyridine were formed in this reaction with subsequent dimerization and aromatization to yield 4,4'-bipyridine. Interestingly, a similar dimerization of pyridine giving 2,2'-bipyridine was described in the presence of lithium diisopropylamide (LDA).⁷ It was shown that the reaction probably occurred via a radical-anion intermediate initiated by one-electron transfer from LDA.⁸ The same results were found when reacting pyridine with the superbasic system *n*BuLi-LiDMAE (lithium dimethylaminoethanolate).⁹ Other unusual dimerizations of pyridine derivatives in the presence of lithium bases have been reported in the last years (Figure 1). Although the radical-anion mechanism was not excluded in the dimerization of **I**,¹⁰ the addition of the 4-lithio pyridine derivative to the starting material was proposed in cases of **II**^{11a} and **III**.^{11b} Lithium–magnesium mixed bases were also shown to induce the 4,4'-dimerization of pyridine derivatives but only when I₂ was used as the electrophile.¹² This result was explained by the formation of intermediate **IV**,

which after 1,2-migration of the 4-pyridyl group delivered **V**. Reaction of intermediate **V** with I₂ furnished the iodo-derivative **VI**, which suffered LiI elimination (Figure 1).^{12a} This paper reports results concerning the synthesis of new functionalized 4,4'-bipyridines starting from the relatively unstable 4-lithio-dihalopyridines. In light of the isolation and characterization of several byproducts from this reaction a mechanism involving exclusively anionic intermediates is proposed.

Results and Discussion

During the study on the synthesis of ferroceno- and benzo-(iso)quinolines,¹³ some 2-chloropyridines bearing a bromine and a methyl group¹⁴ in vicinal positions were necessary. For this purpose the directed ortholithiation was the method of choice.¹⁵ Thus, 2-chloro-5-bromopyridine **1a** was reacted in the presence of LDA in THF to form the 4-lithio derivative followed by trapping with methyl iodide. Along with the expected product **2**, a small amount of a dimeric material **3a** was isolated and its structure obtained by X-ray diffraction

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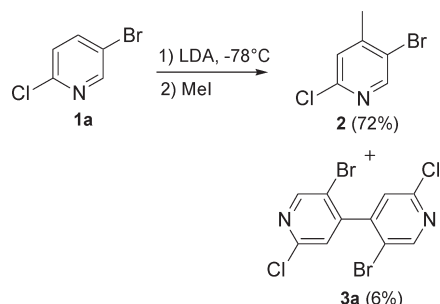
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SCHEME 1. Initial Observation of Dimer 3a



indicated a 4,4' connectivity (see the Supporting Information for details) (Scheme 1).

In view of the importance of this new highly functionalized 4,4'-bipyridine building block, experiments were conducted in order to increase the yield of 3a and to have some insight about the mechanism of its formation (Table 1).

When the reaction depicted in Scheme 1 was repeated without electrophile, several products were obtained after purification including the desired dimer 3a in 11% yield (entry 1). All other compounds were isolated and their structure was assigned on the basis of mass spectra and NMR analyses. The structure of 6 was supported by X-ray diffraction (see the Supporting Information for details). It appeared that raising the temperature to rt overnight caused the degradation of the lithio intermediates A1 and A2 to arynes B1 and B2.¹⁶ Thus, reaction of B1 with LDA and A1 afforded respectively compounds 5b¹⁷ and 4 while reaction of B2 with A1 delivered 6 (Scheme 2).¹⁸

A clean reaction was observed by performing the metalation at -40 °C with 1.05 equiv of LDA. Under these conditions, compounds 5a, 5b, and 6 were not observed but the formation of 4 was still effective keeping the yield of 3a very low (13%) (entry 2). A plausible mechanism for the formation of 3a could be the direct attack of 1a by A1 in the 4-position to give the dihydropyridine intermediate A3¹⁹ followed by hydrolysis to A4 and air oxidation (Scheme 3).²⁰ Use of MnO₂ in order to accelerate the rearomatization step resulted in the formation of dimer 3a in 52% yield while the formation of 4 was considerably decreased (entry 3). Another

method observed to induce rearomatization involved use of I₂ as the electrophile and resulted in the formation of 3a in a good yield of 69% (entry 4).^{21,22}

The remaining question concerned the higher formation of 4 in entry 2 compared to that in entries 3 and 4. Equilibrium between A1 and A3 cannot be considered due to the fact that all the reactions were performed under the same conditions (1.05 equiv of LDA, -40 °C, 1 h); they differ only in the rearomatization step. Considering these observations, another pathway involving intermediate A3 is proposed to explain the formation of 4. After hydrolysis, A3 can be regenerated through a ⁻OH-mediated deprotonation of dihydropyridine A4. After a 1,3-lithium shift leading to A5, LiBr elimination would produce carbene A6, which after 1,2-hydride shift would give dimer 4 (through intermediate A7).²³

It was shown recently in our laboratory that stoichiometric *t*-BuLi could produce cleanly and rapidly A1 from 1a at -78 °C while the lithium-bromine exchange was not observed.²⁴ Half equivalent of *t*-BuLi was then used at -78 °C in order to obtain an equimolar amount of 1a and A1 in the reaction mixture (entry 5). Since the coupling was not effective at -78 °C, the temperature was raised to -30 °C and unexpectedly 2-chloropyridine 7 was formed as the major compound accompanied by the desired dimer 3a as well as 4 in low yields. Furthermore, pyridone 8 was formed in low yield and its structure assigned based on X-ray single crystal diffraction. The formation of 8 was explained by the partial hydrolysis of intermediate A3. A similar pyridone formation was recently observed by Collum and co-workers during their study on the 3-picoline dimerization process.²⁵ It is worth noting that compound 8 was never observed when using LDA as the base. This is probably due to the presence of *i*Pr₂NH in the reaction mixture, but the way it could avoid the formation of 8 is still unclear. The low yield of 3a and the high formation of 7 in the reaction of 1a with *t*-BuLi can be interpreted by the fact that above -78 °C the lithium-bromine exchange is the preferred process over the ortholithiation. The use of I₂ did increase the yield of 3a with complete disappearance of 8 but we noticed that the amount of 7 was again very high (entry 6). The absence of 2-chloro-5-iodopyridine in the reaction mixture indicated that

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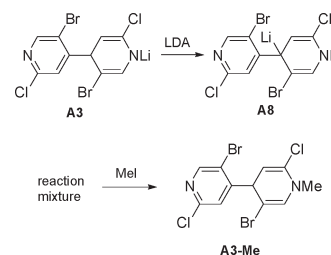
(17) Compound 5a was not isolated in this reaction but it is probably formed (see ref 16a). For an unambiguous characterization of 5a and 5b, the reaction of 1a with 2.1 equiv of LDA at -40 °C was performed followed by raising the temperature to rt. Under these conditions, 5a and 5b were both formed and isolated respectively in 31% and 25% yields.

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(19) The observed selective addition of A1 to 1a in the 4-position over the 2-position was, however, unexpected in comparison with the dimerization product obtained by lithiation of 2-chloro-5-trifluoromethylpyridine III (ref 11b, Figure 1). Calculations (see the Supporting Information for details) have shown the same charge distribution in 1a and III with the higher positive charge in the 2-position. Presumably, the bromine atom in the 5-position of 1a participated in the approach of A1 by coordination to the lithium.

(20) One referee suggested the possible formation of the double anion A8 generated from the reaction of A3 with the remaining LDA. However, when the reaction mixture was quenched with iodomethane instead of I₂, only the *N*-methylated compound A3-Me was observed (see the ¹H NMR spectrum of the crude mixture in the Supporting Information) indicating that A8 was probably not formed in the dimerization reaction of 1a.

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(22) For the full optimization study with I₂ as the electrophile, see Figure S1 in the Supporting Information.

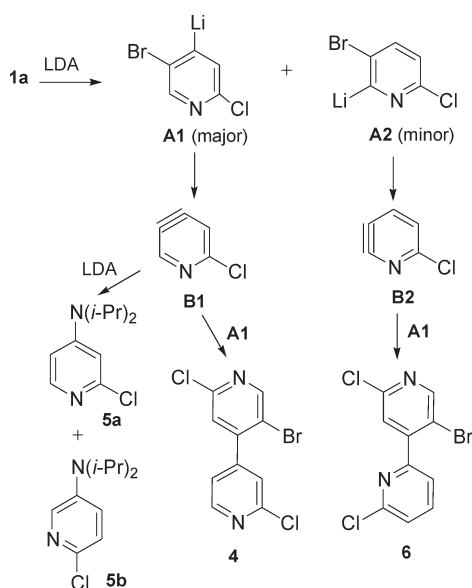
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TABLE 1. Lithiation of 1a: Optimization of 3a Formation

entry	base (<i>n</i> equiv)	conditions (<i>T</i> , time)	treatment	conversion (%)	products	GC (%)	isolated yield (%)
1	LDA (1.2)	−78 to rt, 12 h	H ₂ O	88	3a	35	11
					4	46	17
					5b	2	0.5
					6	5	2
2	LDA (1.05)	−40 °C, 1 h	H ₂ O	86	3a	33	13
					4	53	21
3	LDA (1.05)	−40 °C, 1 h	MnO ₂ then H ₂ O	86	3a	70	52
					4	16	9
4	LDA (1.05)	−40 °C, 1 h	I ₂ then H ₂ O	90	3a	75	69
					4	15	9
5	<i>t</i> -BuLi (0.5)	−78 to −30 °C, 30 min then −30 °C, 2 h	H ₂ O	78	3a	8	
					4	4	
					7	47	
					8	19	15
6	<i>t</i> -BuLi (0.5)	−78 to −30 °C, 30 min then −30 °C, 2 h	I ₂ then H ₂ O	77	3a	44	38
					7	33	

SCHEME 2. Formation and Reactivity of Arynes A1 and A2

2-chloropyridine **7** was probably formed in situ through the reaction of the lithiated species with 2-bromo-2-methylpropane (Scheme 4).

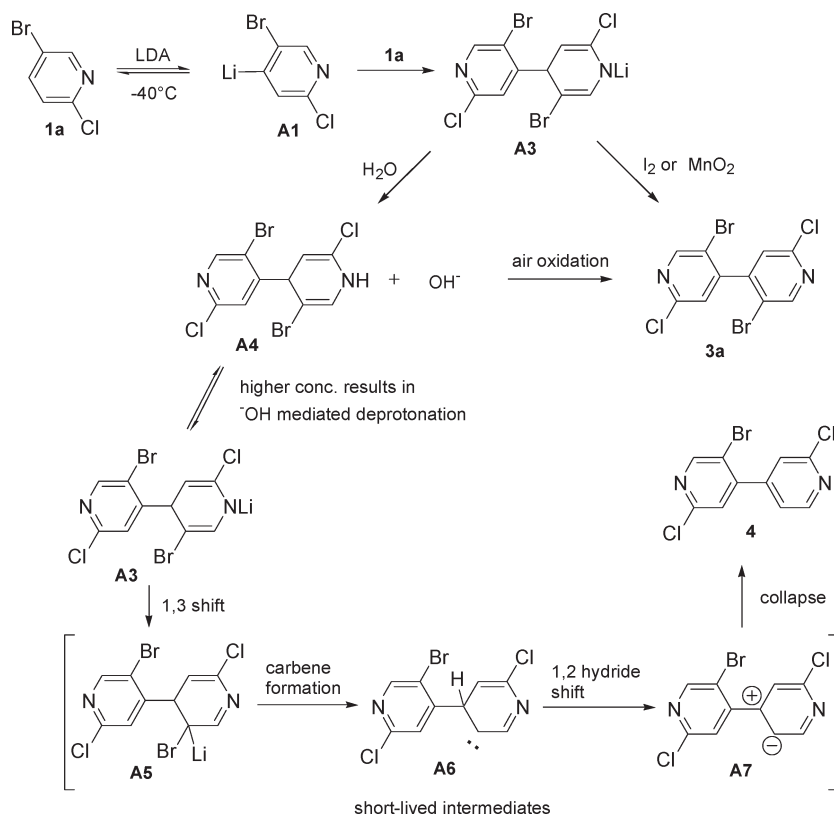
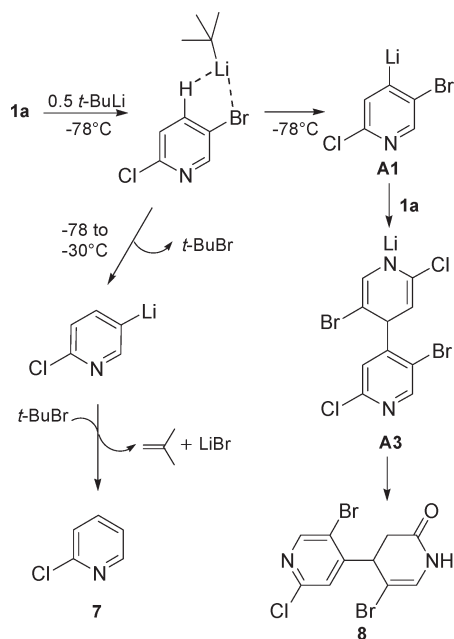
Synthesis of Halogenated Bipyridines. Under the optimized conditions for the formation of **3a**, several new bipyridines with 4,4' (and 3,4') connectivity were prepared (Table 2). The presence of the chlorine in the 2-position was found crucial since no dimeric product **3b** was formed with 3-bromopyridine **1b** as the substrate (entry 1). 2,5-Dihalopyridines were first evaluated in the dimerization process (entries 2–4). The dimeric product **3c** was not observed during the lithiation of 2,5-dichloropyridine **1c** at −40 °C. However, upon raising the temperature to 0 °C the reaction occurred accompanied by some degradation products thus explaining the low yield for compound **3c** (entry 2). As shown by entries 3 and 4, the reaction performed better with bromide substitution on the pyridine. Indeed, the reaction of 2-bromo-5-chloropyridine **1d** and 2,5-dibromopyridine **1e** performed smoothly at −40 °C to furnish respectively compounds **3d** in a moderate yield (entry 3) and **3e** in a good yield (entry 4). It should be noted that even the

iodinated pyridine **1f** could be dimerized in the presence of LDA to give compound **3f** in a moderate yield of 44% (entry 5). However, compound **3f** was found to be unstable and should be stored at low temperature. The dimerization of 2,3-dihalopyridines **1g–i** was more problematic, particularly **1h** and **1i** in which halogen dance²⁶ was the major process during the lithiation step (entries 6–8). The expected tetrachlorinated compound **3g** could be isolated in a moderate yield from 2,3-dichloropyridine **1g** (entry 6). Under the same conditions, 2-chloro-3-bromopyridine **1h** gave a complex mixture with several products resulting from halogen dance and iodine trapping as indicated by GC-MS analysis. To suppress the iodinated products, the direct hydrolysis after the metalation step was performed and compound **3h** was isolated from the complex mixture. Its structure was supported by X-ray diffraction analysis. Since this compound was not observed in the presence of I₂, its formation was explained analogously to **4** (Scheme 5). Starting from 2,3-dibromopyridine **1i** and under the optimized conditions, the dimeric material **3i** with a 3,4' connectivity was isolated in low yield. Probably, the lithiation occurred, followed by the 3,4-bromine displacement to form a new lithiated species that finally adds to the starting pyridine **1i** (Scheme 5). Another way to prepare a polyhalogenated 3,4'-bipyridine was to use 2,6-dibromopyridine **1j** as the substrate (entry 9). Indeed, **1j** can simultaneously suffer lithiation in the 3-position and addition in the 4-position thus producing the 3,4'-connectivity. The isolation of compound **3j** in 15% yield is encouraging and optimization is necessary to achieve better yields. Finally, the dimerization of 3,5-dihalopyridines **1k–m** was considered (entries 10–12). As depicted in Figure 1, compound **3k** was obtained in an excellent yield by dimerization of **1k** in the presence of Bu₃MgLi followed by quenching with iodine.^{12a,27} Under our conditions, the yield of **3k** was moderate (entry 10) but the analogous compound **3l** bearing four bromine atoms was obtained in a good yield of 72% (entry 11). The lithiation of pyridine **1m** was performed in

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(27) During the preparation of this paper, Do and Daugulis have reported the oxidative dimerization of pyridine **1k** to the tetrachlorinated 2,2'-bipyridine by using the basic system *i*PrMgCl*LiCl + ZnCl₂ (1:0.25) in the presence of oxygen and a catalytic amount of CuCl₂, see: Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052–17053.

SCHEME 3. Proposed Pathways for the LDA-Mediated Dimerization of 1a

SCHEME 4. Proposed Pathways for the *t*-BuLi-Mediated Dimerization of 1a

a THF/DMPU 4/1 mixture for solubility reasons.²⁸ However, the tetraiodo pyridine compound **3m** was isolated in low yield (entry 12).

(28) DMPU = 1,3-Dimethyltetrahydropyrimidin-2(1H)-one or *N,N'*-dimethylpropyleneurea. For its first use as cosolvent for highly reactive bases, see: Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385–391.

X-ray Diffraction Analysis

Crystal structures were determined by single crystal X-ray diffraction for bipyridines with 4,4' (**3a**, **3h**), 3,4' (**3i**, **3j**), and 2,4' (**6**) connectivity and also for the new pyridone **8** (see the Supporting Information for full details). As expected from the chemical content of these compounds, these structures are characterized by a variety of intermolecular interactions competing with each other, namely π - π stacking, halogen (including halogen... halogen, halogen...N,O) and hydrogen (C-H... π , C-H...N, C-H...O, C-H...halogen, N-H...N) bonds.

Among the most remarkable interactions in these structures are short Br...N and Br...O intermolecular contacts in **3a** and **8**, respectively. The interatomic distances in these contacts (3.006(2) Å for Br...N and 2.998(1) Å for Br...O) are respectively 0.39 and 0.37 Å shorter than the sum of the corresponding van der Waals radii and lie within the short-distance shoulder observed in the distance density function plots obtained from a recent Cambridge Structural Database analysis performed on Br...O,N contacts, revealing these contacts as specific interactions.²⁹ The intermolecular C-Br...N,O angles are close to linearity (162.4(1)° and 164.41(5)°, respectively; Figure 2), in coherence with the electrostatic model of halogen bonding where a positive σ hole opposite to the covalent carbon-halogen bond is surrounded by a negative crown,³⁰ as recently shown by high-resolution X-ray diffraction on hexachlorobenzene crystal.³¹ A recent

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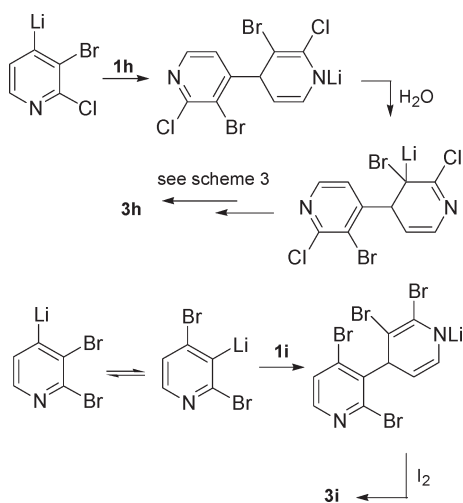
(31) Bui, T. T. T.; Dhaoui, S.; Lecomte, C.; Desiraju, G. R.; Espinosa, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3838–3841.

TABLE 2. Scope of the Reaction^a

entry	pyridine 1	product 3	yield (%)	entry	pyridine 1	product 3	yield (%)
1			0	7			12 ^c
2 ^b			24	8			15
3			44	9			15
4			67	10			44
5			44	11			72
6			42	12			9 ^d

^aReaction conditions: (i) **1** (1 mmol), LDA (1.05 mmol), THF, -40°C , 1 h. (ii) I_2 (1.05 mmol), -78°C to rt, 1 h. ^bThe metalation was conducted at 0°C for 30 min. ^cDirect hydrolysis was performed (no iodine added). ^dThe metalation was performed in THF/DMPU 4/1 at -40°C .

SCHEME 5. Proposed Mechanisms for the Formation of **1h** and **1i**



theoretical study showed that substitution on aromatic rings bearing bromine influences the strength of halogen bonding with acetone, with interaction energies up to

ca. $-7 \text{ kcal}\cdot\text{mol}^{-1}$,³² and competitive cocrystallization experiments showed that halogen bonding could overwhelm hydrogen bonding in some specific systems.³³

Halogen-halogen interactions are also present in these structures, mostly of type-II. In this geometric arrangement, the positive electron density hole on a first halogen atom should be directed toward the negative crown of a second halogen atom.³¹ These interactions are isolated (for example in **3j** with $\text{Br}\cdots\text{Br} = 3.5614(4) \text{ \AA}$) or form infinite chains in **8** where cooperativity may thus be present to stabilize the structure, as demonstrated by theoretical calculations on model clusters of diatomic interhalogen molecules.³⁴

Conclusion

We have developed a simple procedure for the synthesis of halogenated 4,4'-bipyridines based on the lithiation of halopyridines. The mechanism of the reaction has been studied by isolation and characterization of several byproducts.

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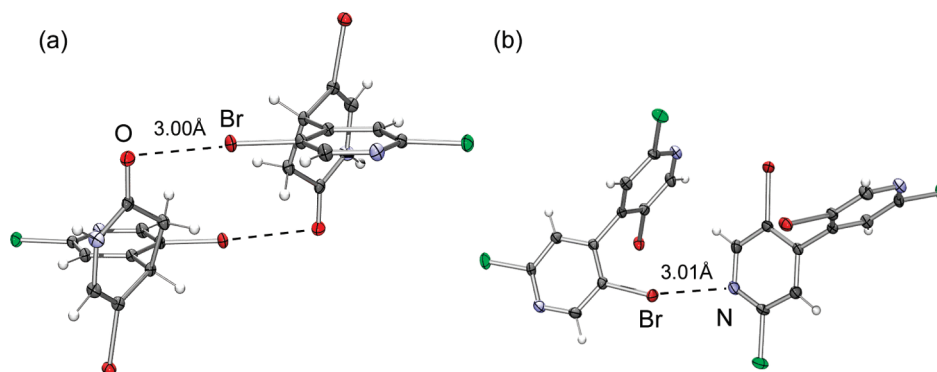


FIGURE 2. Short (a) Br...O interactions in **8** and (b) Br...N in **3a** are shown as broken lines (bromine atoms in brown, chlorine in green, oxygen in red).

Different parameters have to be respected for success of the reaction: (i) two halogens are necessary in order to increase the electrophilicity of the pyridine ring, (ii) one of these two halogens has to be in the 3-position in order to induce the ortho-lithiation in the 4-position, (iii) working at low temperature is necessary to avoid aryne formation, and (iv) the oxidant has to be added at the end of the reaction in order to accelerate the rearomatization step and then to avoid the loss of one halogen. The methodology was then applied to the formation of several 4,4'-bipyridines bearing chlorine, bromine, and even iodine. In some cases we could isolate bipyridines having 3,4' and 2,4' connectivity. Most representative products were characterized by X-ray diffraction and showed specific halogen interactions which will be examined in a dedicated work, motivated by the importance these interactions have, for example, in biological systems.³⁵ Knowing the importance of the 4,4'-bipyridine unit in coordination chemistry and in crystal design, we are also currently preparing new metal complexes in order to study by X-ray diffraction analysis the different modes of coordination of the halogenated bipyridines as well as other functionalized bipyridines obtained by cross-coupling reactions.

Experimental Section

Representative Procedure for the Dimerization of Halopyridines with LDA: Preparation of 5,5'-Dibromo-2,2'-dichloro-[4,4']bipyridinyl (3a**) (Table 1, entry 4).** Freshly distilled diisopropylamine (0.15 mL, 1.05 mmol) was added to dry THF (6 mL) and the solution was cooled to -40°C . A solution of *n*-butyllithium (1.6 M in hexanes, 0.66 mL, 1.05 mmol) was added dropwise under argon atmosphere. After the solution was stirred for 5 min at -40°C , 5-bromo-2-chloropyridine **1a** (192 mg, 1 mmol) solubilized in dry THF (4 mL) was added. The mixture was then stirred at -40°C for 1 h and cooled to -78°C then I_2 (254 mg, 1 mmol) in THF (4 mL) was added dropwise. After the solution was warmed to rt, the reaction was quenched with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and the mixture was extracted with ethyl acetate, dried over MgSO_4 , and concentrated. The crude product was purified by chromatography on silica gel to give **3a** (132 mg, white powder, 69% yield). Mp $163\text{--}165^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.24 (s, 2H), 8.66 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 119.0, 125.0, 148.2, 150.7, 152.2; MS (EI) m/z 382 (M^+ , 70), 303 (100), 222 (55); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{N}_2\text{Br}_2\text{Cl}_2$ 384.8145, found 384.8147 [MH] $^+$.

(35) Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16789–16794.

2,5,2',5'-Tetrachloro-[4,4']bipyridinyl (3c**):** mp $117\text{--}119^{\circ}\text{C}$; ^1H NMR (250 MHz, CDCl_3) δ 7.27 (s, H), 8.53 (s, 2H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 125.0, 129.4, 144.7, 149.8, 150.0; MS (EI) m/z 294 (M^+ , 100), 257 (45), 221 (20), 186 (20); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{N}_2\text{Cl}_4$ 294.9172, found 294.9185 [MH] $^+$.

2,2'-Dibromo-5,5'-dichloro-[4,4']bipyridinyl (3d**):** mp $110\text{--}112^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.41 (s, 2H), 8.52 (s, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 128.6, 130.1, 140.0, 144.3, 150.2; MS (EI) m/z 382 (M^+ , 100), 303 (65), 222 (40), 187 (35); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{Br}_2\text{Cl}_2\text{N}_2$ 382.8169, found 382.8174 [MH] $^+$.

2,5,2',5'-Tetrabromo-[4,4']bipyridinyl (3e**):** mp $188\text{--}189^{\circ}\text{C}$; ^1H NMR (200 MHz, CDCl_3) δ 7.37 (s, 2H), 8.64 (s, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ 119.8, 128.7, 140.9, 147.9, 152.6; MS (EI) m/z 472 (M^+ , 100), 391 (55), 312 (45), 231 (35), 152 (50); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{Br}_4\text{N}_2$ 472.7140, found 472.7142 [MH] $^+$.

2,2'-Dibromo-5,5'-diiodo-[4,4']bipyridinyl (3f**):** 75°C dec; ^1H NMR (250 MHz, DMSO) δ 7.76 (s, 2H), 8.90 (s, 2H); ^{13}C NMR (62.5 MHz, DMSO) δ 97.4, 128.1, 141.0, 154.7, 157.3; MS (EI) m/z 566 (M^+ , 40), 439 (100), 312 (10), 233 (20), 152 (60); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{Br}_2\text{I}_2\text{N}_2$ 566.6883, found 566.6899 [MH] $^+$.

2,3,2',3'-Tetrachloro-[4,4']bipyridinyl (3g**):** mp $200\text{--}201^{\circ}\text{C}$; ^1H NMR (200 MHz, CDCl_3) δ 7.16 (d, $J = 4.8$ Hz, 2H), 8.43 (d, $J = 5$ Hz, 2H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 123.4, 129.1, 146.1, 147.2, 150.8; MS (EI) m/z 294 (M^+ , 100), 259 (80), 222 (30), 186 (20); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{Cl}_4\text{N}_2$ 294.9172, found 294.9204 [MH] $^+$.

3-Bromo-2,2'-dichloro-[4,4']bipyridinyl (3h**):** mp $153\text{--}155^{\circ}\text{C}$; ^1H NMR (250 MHz, CDCl_3) δ 7.16 (d, $J = 4.6$ Hz, 1H), 7.27 (d, $J = 4.4$ Hz, 1H), 7.37 (s, 1H), 8.42 (d, $J = 4.6$ Hz, 1H), 8.53 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 120.0, 122.1, 123.5, 123.9, 147.9, 149.1, 149.7, 150.1, 152.0, 152.8; MS (EI) m/z 304 (M^+ , 100), 269 (25), 188 (15), 223 (10), 152 (15); HRMS m/z calcd for $\text{C}_{10}\text{H}_6\text{N}_2\text{BrCl}_2$ 303.9062, found 304.9079 [MH] $^+$.

2,4,2',3'-Tetrabromo-[3,4']bipyridinyl (3i**):** mp $106\text{--}108^{\circ}\text{C}$; ^1H NMR (200 MHz, CDCl_3) δ 7.14 (d, $J = 4.4$ Hz, 1H), 7.65 (d, $J = 4.8$ Hz, 1H), 8.28 (d, $J = 5.0$ Hz, 1H), 8.47 (d, $J = 4.6$ Hz, 1H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 124.2, 124.9, 127.4, 134.2, 137.9, 142.0, 145.4, 148.6, 149.9, 150.5; MS (EI) m/z 472 (M^+ , 50), 393 (100), 312 (50), 231 (35), 152 (30); HRMS m/z calcd for $\text{C}_{10}\text{H}_4\text{Br}_4\text{N}_2\text{Na}$ 494.6960, found 494.6950 [MNa] $^+$.

2,6,2',6'-Tetrabromo-[3,4']bipyridinyl (3j**):** mp $208\text{--}209^{\circ}\text{C}$; ^1H NMR (200 MHz, CDCl_3) δ 7.46 (d, $J = 8$ Hz, 1H), 7.52 (s, 2H), 7.61 (d, $J = 8$ Hz, 1H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 125, 127.3, 127.7, 133.7, 139.9, 140.2, 141.1, 141.6, 149.9; MS (EI) m/z 472 (M^+ , 100), 391 (20), 312 (40), 231 (25), 152 (25); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{Br}_4\text{N}_2$ 472.7140, found 472.7133 [MH] $^+$.

3,5,3',5'-Tetrachloro-[4,4']bipyridinyl (3k**):** mp $102\text{--}104^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 4H); ^{13}C NMR (100 MHz,

CDCl_3) δ 131.3, 140.0, 147.9; MS (EI) m/z 294 (M^+ , 100), 257 (30), 222 (20); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{Cl}_4\text{N}_2$ 294.9172, found 294.9200 $[\text{MH}]^+$.

3,5,3',5'-Tetrabromo-[4,4']bipyridinyl (3f); mp 148–150 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.82 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 120.8, 146.7, 150.8; MS (EI) m/z 472 (M^+ , 100), 391 (25), 312 (40); HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{Br}_4\text{N}_2$ 472.7140, found 472.7180 $[\text{MH}]^+$.

3,5,3',5'-Tetraiodo-[4,4']bipyridinyl (3m); mp 230 °C dec; ^1H NMR (400 MHz, CDCl_3) δ 8.99 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 156.9, 96.2; HRMS m/z calcd for $\text{C}_{10}\text{H}_5\text{I}_4\text{N}_2$ 660.6637, found 660.6626 $[\text{MH}]^+$.

Reaction of 1a with *t*-BuLi: Formation of 5,5'-Dibromo-2'-chloro-3,4-dihydro-1*H*-[4,4']bipyridinyl-2-one (8) (Table 1, entry 5). To a solution of 5-bromo-2-chloropyridine **1a** (192 mg, 1 mmol) in THF (4 mL) cooled at -78 °C, under argon atmosphere, was added dropwise *t*-BuLi (0.3 mL, 0.5 mmol). After addition, the temperature was raised to -30 °C during 30 min, and the mixture was stirred at -30 °C for 2 h. The reaction was quenched by addition of water and the solution was warmed to rt. The reaction mixture was extracted with ethyl acetate, dried over MgSO_4 , and concentrated. The crude product was dried under vacuum overnight to remove 2-chloropyridine **7** and then purified by

chromatography on silica gel to give pyridone **8** (27 mg, white powder, 15% yield). Mp 205–207 °C; ^1H NMR (400 MHz, DMSO) δ 2.47 (dd, $J = 4.4$ Hz, 1H), 3.22 (dd, $J = 16.8, 8.9$ Hz, 1H), 4.24 (dd, $J = 8.8, 4.2$ Hz, 1H), 6.84 (d, $J = 5.2$ Hz, 1H), 7.31 (s, 1H), 8.67 (s, 1H), 9.66 (d, $J = 4.6$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 36.4, 44.8, 96.6, 121.0, 123.4, 129.7, 150.1, 151.4, 152.4, 166.1; MS (EI) m/z 287 (M^+ , 100), 366 (80), 178 (45); HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{OBr}_2\text{Cl}$ 366.8691, found 366.8676 $(\text{MH})^+$.

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Supporting Information Available: Experimental procedures of Table 1, spectroscopic data of compounds **4**, **5a**, **5b**, and **6**, NMR spectra of all compounds, crystallographic data, and CIF files of compounds **3a**, **3h**, **3i**, **3j**, **6**, and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.