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Synthesis and Deprotonation of 2-(Halophenyl)pyridines and 1-(Halophenyl)isoquinolines

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The ability of the 2-pyridyl and 1-isoquinolyl groups to direct metalation was studied in the benzene series. For this purpose, 2-(halophenyl)pyridines and 1-(halophenyl)isoquinolines were prepared. Interestingly, nucleophilic addition reactions on the azine ring were not observed under kinetic control using butyllithium, and the substrates were cleanly deprotonated on the benzene ring: the azine ring acidifies the adjacent hydrogen $H_{2'}$ ($N-H_{2'}$ interaction through space and/or inductive electron-withdrawing effect) and probably favors the approach of butyllithium (chelation). Under thermodynamic conditions using lithium dialkylamides, the presence of the azine group makes the lithio derivative at C2′ more stable (chelation and/or inductive electron-withdrawing effect). This was evidenced in two ways: (1) syntheses of 2-halophenyllithiums (F, Cl, Br) substituted at C6 by a 2-pyridyl or 1-isoquinolyl group without elimination of lithium halide and (2) iodine migration from C2′ to C4′ when treating 2-(3-halo-2-iodophenyl)pyridines or 1-(3-fluoro-2-iodophenyl)isoquinoline with LTMP. Comparisons between the 2-pyridyl and fluoro units showed the latter was the stronger directing group for deprotonation.

Introduction

The directed ortho-metalation plays an important role in the modern organic synthesis.[1,2] Despite the maturity gained by the method since its creation, the way a substituent acts in its vicinity remains somewhat misunderstood.

A heteroatom-containing unit (known as the directed metalation group, DMG) makes the deprotonation process easier by coordinating the base; it also stabilizes the lithio derivative by chelation. In addition, an electron-withdrawing DMG favors the deprotonation in its environment (mostly at the ortho position) and reinforces the stabilization of the lithio derivative.

The 2-pyridyl group has been shown to direct ortho-lithiation in a few examples. Its effect on aromatic deprotonation was evidenced in the course of the reaction of 2-(2-thienyl)pyridine (Chart 1): whereas the hydrogen at the 3′ position is abstracted using butyllithium in THF at 0 °C, the deprotonation occurs at the 5′ position using *tert*-butyllithium in diethyl ether at −70 °C (a); the latter result can be attributed to a coordination between the ring nitrogen and the base lithium before deprotonation.[3] The lithiation of 2-(3-thienyl)pyridine at the 2′ position using butyllithium in diethyl ether was reported in 1990 (b); in this case, both chelation before deprotonation and the acidifying effect of the 2-pyridyl group could be responsible for the result observed.[4] In 1996, the 2-pyridyl group was exploited in the reactions of 2,2′- and 2,4′-bipyridines using LTMP in THF at −40 or −70 °C (c).[5] The medium to good yields obtained could be due to the nature of the electrophiles used, which prefer to trap the aryllithium before the lithium amide (note the presence of disubstituted products at C3 and C3′ starting from 2,2′-bipyridine), allowing the lithiation equilibrium to be displaced toward the deprotonated product. Nevertheless, the 2-pyridyl group favors the deprotonation since bare pyridine can hardly be deprotonated at C3.[2] Selective deprotonation of 2-chloro-6-phenylpyridine at the 2′ position using *tert*-butyllithium in a mixture of diethyl ether and cumene at −75 °C was published recently (d),[6] a result due to interactions between the 6-chloro-2-pyridyl unit and the lithium of the base before deproto-

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(1) The concept emerged from the systematic studies of Gilman, Wittig and Hauser, and found numerous disciples, notably Gschwend, Beak, and Snieckus: (a) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109−112. (b) Wittig, G.; Fuhrmann, G. *Chem. Ber.* **1940**, *73*, 3B, 1197−1218. (c) Hauser, C. R.; Puterbaugh, W. H. *J. Org. Chem.* **1964**, *29*, 853−856. (d) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1−360. (e) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (f) Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553−7558.

(2) In the π-deficient azaaromatics series, see: (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−304. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059−4090. (c) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489−4505.

(3) Kauffmann, T.; Mitschker, A.; Woltermann, A. *Chem. Ber.* **1983**, *116*, 992−1000.

(4) Kumar Das, V. G.; Mun, L. K.; Wei, C.; Mak, T. C. W. *Organometallics* **1987**, *6*, 10−14.

(5) Zoltewicz, J. A.; Dill, C. D. *Tetrahedron* **1996**, *52*, 14469−14474.

(6) Fort, Y.; Rodriguez, A. L. *J. Org. Chem.* **2003**, *68*, 4918−4922.

10.1021/jo049454v CCC: $27.50

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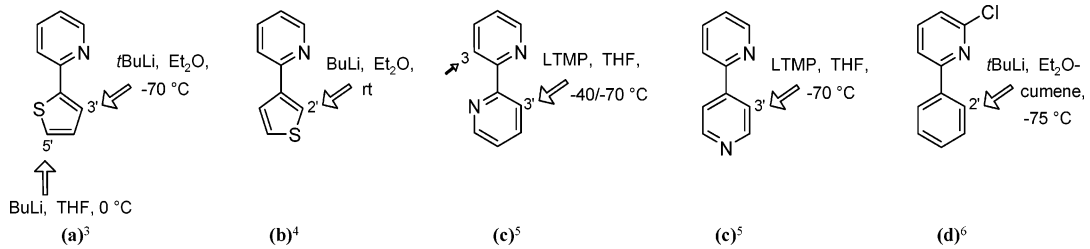
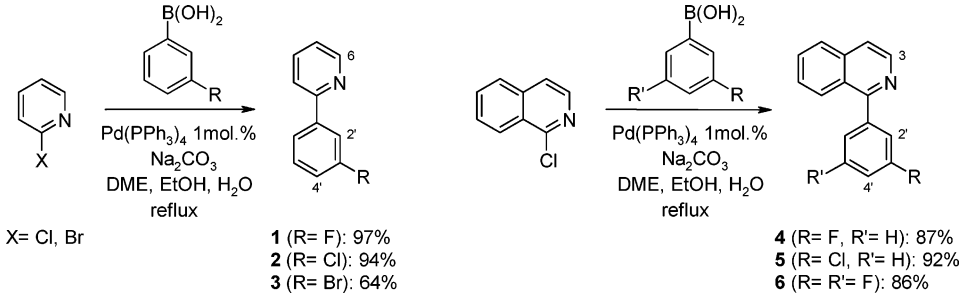
CHART 1



(a)[3] **(b)**[4] **(c)**[5] **(c)**[5] **(d)**[6]

SCHEME 1



nation. It represents the only example of benzene ortho-lithiation directed by a 2-pyridyl group.

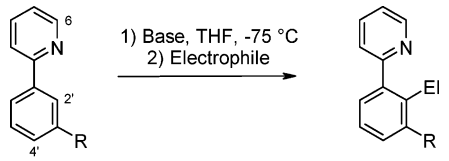
Results and Discussion

Since biphenyl is ortho-metalated in high proportions,[7] one can wonder what the changes will be if one phenyl is replaced by a 2-pyridyl (or 1-isoquinolyl). The total atomic charges of biphenyl, 2-phenylpyridine, and 1-phenylisoquinoline were determined by ab initio calculations using Gaussian 94 at the HF/6-31G(d) level after energy minimization using cvff-300-1.01 (Cerius2 4.9).[8] Values of 0.245 or 0.222 for the hydrogens at the position 2′- of 2-phenylpyridine or 1-phenylisoquinoline, respectively, were determined. This shows the nitrogenous groups exhibit an acidifying effect, since 0.208 was found for the hydrogen at C2 in biphenyl. Partly because it is out of the plane of the phenyl ring,[9] the 1-isoquinolyl group effect on the acidity of $H_{2'}$ is weaker.

Deprotonation of 2-phenylpyridine was attempted by Gros and Fort under various conditions (lithium dialkylamides or alkyllithiums, with or without additive, in ethereal or hydrocarbon solutions):[10] the substrate either undergoes 1,2-addition of alkyllithiums in ethereal solvents, or deprotonation at C2 using the BuLi−LiDMAE superbase in hexane. To promote deprotonation at the phenyl group, we introduced a second ortho-directing group, in this case a halo group, at the 3′ position of 2-phenylpyridine or 1-phenylisoquinoline.

The starting biaryl substrates **1**−**6** were synthesized by Suzuki cross-coupling reactions between the required 2-halopyridine, or 1-chloroisoquinoline, and halophenylboronic acid, using standard conditions[11] (Scheme 1).

TABLE 1. Deprotonation of 2-(3-Halophenyl)pyridines 1−3



1-3 **7-9**

entry	substrate	product	yield (%)
1[a]	**1** (R = F)	**7a** (El = D)[b]	88
2[a]	**1** (R = F)	**7b** (El = I)[c]	66
3[a]	**2** (R = Cl)	**8a** (El = D)[b]	76
4[a]	**2** (R = Cl)	**8b** (El = I)[c]	62
5[d]	**2** (R = Cl)	**8a** (El = D)[b]	42
6[d]	**3** (R = Br)	**9** (El = D)[b]	29

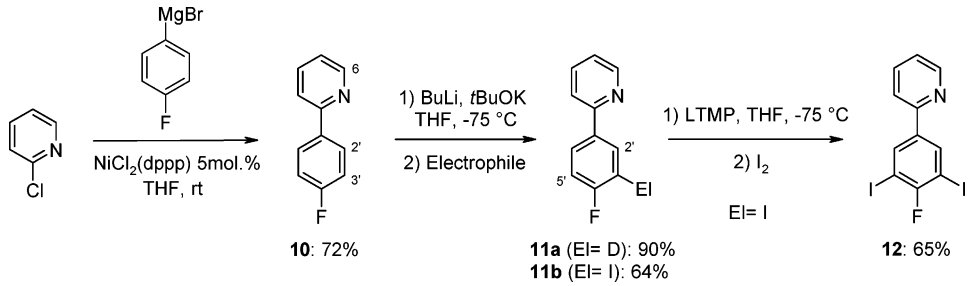
[a] The base is BuLi (1 equiv). [b] The electrophile is D_2O. [c] The electrophile is I_2. [d] The base is LTMP (2 equiv).

Deprotonation of the 2-(3-halophenyl)pyridines **1**−**3** was first considered. Even if alkyllithiums are renowned for facile nucleophilic additions to the C=N bond of pyridines,[2] their use was attempted to deprotonate the fluoride **1** and the chloride **2**. Indeed, the metalations of fluorobenzene and chlorobenzene have been reported using such bases.[12,13]

The fluoride **1** was easily deprotonated at C2′ using 1 equiv of butyllithium in THF at −75 °C, and the lithio intermediate was intercepted with D_2O or iodine to give the compounds **7a**,**b** in good yields (Table 1, entries 1 and 2). Note that a mixture of butyllithium and potassium *tert*-butoxide also furnished **7a** (75% yield) together with a little amount of degradation compounds. When compared with the metalation of fluorobenzene, which requires a 7 h contact with butyllithium in THF at −50

(7) Neugebauer, W.; Kos, A. J.; Schleyer, P. V. R. *J. Organomet. Chem.* **1982**, *228*, 107−118.
(8) Note that the data probe ground states rather than transition states, but even the use of more extended basis sets would not have guaranteed meaningful results.
(9) Energy minimization using cvff-300-1.01 (Cerius2 4.9) shows the more stable conformation of 1-phenylisoquinoline has a dihedral angle of 45°; the energy increases by about 1000 kcal·mol^{-1} when the 1-isoquinolyl ring is kept in the phenyl plane. On the other hand, the more stable conformation of 2-phenylpyridine is planar.
(10) Gros, P.; Fort, Y. *J. Org. Chem.* **2003**, *68*, 2028−2029.
(11) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743−756.
(12) Gilman, H.; Soddy, T. S. *J. Org. Chem.* **1957**, *22*, 1715−1716.
(13) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622−3627.

SCHEME 2



°C,[12] the reaction involving the fluoride **1** is particularly facile. Both the ability of the 2-pyridyl group to coordinate the lithiating agent and the acidifying effect of the nitrogenous DMG may be suggested to explain the regioselectivities observed.

Similarly, the chloride **2** furnished the compounds **8a**,**b** in good yields (Table 1, entries 3 and 4). Other bases such as *sec*-butyllithium or a mixture of butyllithium and potassium *tert*-butoxide (LICKOR) were less effective or/and gave nucleophilic addition compounds at C6. Whereas 2-chloro-1-lithiobenzene already provides benzyne at −75 °C,[13] the reaction involving the chloride **2** was easily conducted at this temperature. Stabilization of the lithio derivative by chelation of the metal with the pyridine nitrogen and/or inductive electron-withdrawing effect of the 2-pyridyl group could in our case prevent the elimination of lithium chloride giving the aryne.[14]

Since alkyllithiums cannot be used in the presence of bromine atoms, the deprotonation of the bromide **3** was attempted using LTMP (pK_a of 2,2,6,6-tetramethylpiperidine: 37.3),[15] a lithium amide more basic than LDA (pK_a of diisopropylamine: 35.7).[15] Interestingly, the bromide **3** was deprotonated on exposure to 2 equiv of LTMP in THF at −75 °C, as demonstrated by deuteriolysis to afford **9** (Table 1, entry 6). The yield of 29% is low, certainly, but the result is unprecedented since deprotonation of bromobenzene has never been achieved before, probably due to decomposition giving benzyne under metalation conditions. Indeed, whereas 2-fluoro- and 2-chlorophenyllithium are stable at −75 and −90 °C, respectively, 2-bromophenyllithium (all are generated through bromine−lithium exchange) already decomposes at −100 °C.[16] Elimination of lithium bromide is prevented here, a consequence of the stabilizing effect the nitrogen exerts. Note that under the same conditions, the chloride **2** furnished the deuterated compound **8a** in 42% yield, showing only a little difference between both halogens[17] (Table 1, entry 5).

To compare the 2-pyridyl and fluoro groups, the fluoride **10** was prepared by cross-coupling reaction between 4-fluorophenylmagnesium bromide and 2-chloropyridine under nickel catalysis[18] and submitted to the deprotonation procedure. The reaction was first attempted using various butyllithiums (with or without TMEDA) without success: the starting substrate was recovered when the reaction was conducted at −75 °C, and nucleophilic addition compounds at C6 were obtained at higher temperatures. Having recourse to the superbasic mixture of butyllithium and potassium *tert*-butoxide (LICKOR),[19] under the conditions reported for deprotonating fluorobenzene,[20] finally ensured a clean metalation of **10** at the 3′ position. As intramolecular competition of ortho-directing groups sometimes gives treacherous results, the 2-pyridyl and fluoro groups were better compared using an intermolecular competition experiment.[21] Under the conditions used for the deprotonation of the fluoride **10**, an equimolar mixture of 2-phenylpyridine and fluorobenzene afforded 2-fluorobenzoic acid in 60% yield (deprotonation of 2-phenylpyridine was not observed), showing the 2-pyridyl group is not strong enough to compete with a fluoro group.

Deprotonation occurred next to the fluoro group too when the dihalide **11b** was treated with LTMP at low temperature,[22] giving the trihalide **12** after trapping with iodine (Scheme 2). In a recent publication, Schlosser documented an iodine migration on 2-fluoro-1,3-diiodobenzene using LTMP, giving after the quenching step with an electrophile 2-substituted 3-fluoro-1,4-diiodobenzenes.[23] Nevertheless, the attempts to conduct such a reaction with **12** failed: the latter either remained unchanged or underwent deiodination reactions on exposure to LTMP. A plausible assumption to explain deiodination is SET from the base to the trihalide. The radical anion thus generated eliminates lithium iodide to produce an aryl radical. The latter may either abstract a hydrogen atom from the solvent or absorb another unpaired electron to give an aryllithium species to be quenched by the free amine or to survive until electro-

(14) The good stabilities of lithium 2-lithio-3-chlorobenzoate and lithium 2-lithio-3-bromobenzoate toward elimination of lithium halide were similarly attributed to the chelation of lithium with the adjacent group, in this case the carboxylate moiety: Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, *68*, 2030−2033.

(15) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442−3443.

(16) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217−2222.

(17) Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997**, *38*, 1559−1562.

(18) Concerning Kharasch cross-coupling reactions between arylmagnesium halides and aryl chlorides under nickel catalysis, see: (a) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066−4068. (b) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602−1604. (c) Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, 1008−1010.

(19) (a) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9−16. (b) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, *7*, 1115−1126.

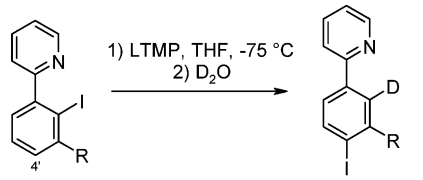
(20) Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett* **1990**, 747−748.

(21) Schlosser, M., Ed. In *Organometallics in Synthesis: A Manual*; Wiley: Chichester, 1994 (1st ed.) and 2002 (2nd ed.).

(22) 1-Fluoro-2-iodobenzene was also deprotonated next to the fluoro group using LDA: Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7499−7502.

(23) Rausis, T.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 3351−3358.

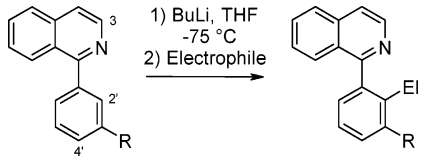
SCHEME 3



7b (R= F)
8b (R= Cl)

13 (R= F): 50%
14 (R= Cl): 24%

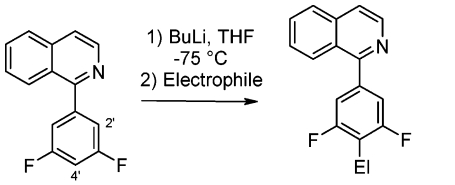
SCHEME 4



4 (R= F)
5 (R= Cl)

15a (R= F, El= D): 86%
15b (R= F, El= I): 70%
16a (R= Cl, El= D): 66%
16b (R= Cl, El= I): 67%

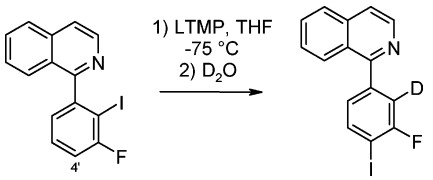
SCHEME 5



6

17a (El= I): 73%
17b (El= $SiMe_3$): 72%

SCHEME 6



15b

18: 55%

philic trapping.[24] Iodine being less acidifying than bromine, deprotonation in its immediate vicinity occurs even more slowly and is not detected.

On the other hand, leading the reaction on the dihalides **7b** and **8b** resulted in the compounds **13** and **14** after deuteriolysis. Deprotonation at C4′ generates first a lithio derivative, which is next converted into a thermodynamically more stable isomer through iodine migration (Scheme 3). The halogen migration mechanism has been the subject of several studies considering halogen-rich species as intermediates.[2] The halogen transfer could be carried out via a hypervalent halogen (ate) complex.[25]

The lower yield obtained for **14** can be partially explained by competitive iodine loss.

Deprotonation of the 1-(3-halophenyl)isoquinolines **4** and **5** was next considered. As previously described for the pyridine derivatives **1**, the fluoride **4** was easily deprotonated using 1 equiv of butyllithium in THF at −75 °C, and the lithio intermediates were intercepted with D_2O or iodine to give the compounds **15a**,**b** in good yields. The reaction is still regioselective at C2′. The compounds **16a**,**b** were similarly generated, starting from the chloride **5** (Scheme 4). Metalation of the latter was additionally conducted using 2 equiv of LTMP in THF at −75 °C; subsequent deuteriolysis afforded **16a** (31% yield), a result comparable to that obtained with **2**.

With the difluoride **6**, a comparison between the fluoro and 1-isoquinolyl units is possible: the former exhibits a stronger directing power, as demonstrated by trapping with iodine or chlorotrimethylsilane to afford **17a**,**b** in good yields (Scheme 5). All the attempts to make the iodine of **17a** migrate using LTMP were unsuccessful.

As described above in the pyridine series, metalation of the dihalide **15b** with LTMP promoted iodine migration to afford after quenching the deuterated product **18** (Scheme 6).

Conclusions

The ability of the 2-pyridyl and 1-isoquinolyl groups to direct metalation was studied in the benzene series. For this purpose, 2-(halophenyl)pyridines and 1-(halophenyl)isoquinolines were prepared. Interestingly, nucleophilic addition reactions on the azine ring were not observed under kinetic control using butyllithium, and the substrates were cleanly deprotonated on the benzene ring: the azine ring acidifies the adjacent hydrogen $H_{2'}$ ($N-H_{2'}$ interaction through space and/or inductive electron-withdrawing effect) and probably favors the approach of butyllithium (chelation). Under thermodynamic conditions using lithium dialkylamides,[26] the presence of the azine group makes the lithio derivative at C2′ more stable (chelation and/or inductive electron-withdrawing effect). This was evidenced in two ways: (1) syntheses of 2-halophenyllithiums (F, Cl, Br) substituted at C6 by a 2-pyridyl or 1-isoquinolyl group without elimination of lithium halide and (2) iodine migration from C2′ to C4′ when treating 2-(3-halo-2-iodophenyl)pyridines or 1-(3-fluoro-2-iodophenyl)isoquinoline with LTMP. Comparisons between the 2-pyridyl and fluoro units showed the latter was the stronger directing group for deprotonation.

Further investigations to extend the scope of this reaction to the syntheses of chiral ligands are currently in progress.

Experimental Section

General Procedures. The NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75 MHz). Deuterium incorporation was determined from the ^1H NMR integration values. The main IR absorptions of the IR spectra are given. THF was distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[27] Metalation and cross-coupling reactions were carried out under dry N_2. Petrol refers to petroleum ether (bp 40−60 °C). After the reaction, hydrolysis, and neutralization, the aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, the solvents were evaporated under reduced pressure, and

(24) Mongin, F.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2771−2777.

(25) Concerning the iodine transfer from iodobenzene to 2-lithioaromatics, see: Tripathy, S.; LeBlanc, R.; Durst, T. *Org. Lett.* **1999**, *1*, 1973−1975.

(26) Note that lithium dialkylamides sometimes give products from kinetic control when used in the presence of an electrophile using Barbier-type conditions.

(27) Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, 151.

unless otherwise noted, the crude compound was chromatographed on a silica gel (Geduran Si 60, 0.063−0.200 mm) column (the eluent is given in the product description). Pd(PPh$_3$)$_4$ was synthesized by a literature method.[28] 2-(3-Fluorophenyl)pyridine (**1**),[29] 2-(3-chlorophenyl)pyridine (**2**),[30] and 2-(4-fluorophenyl)pyridine (**10**)[31] were previously described.

2-(3-Bromophenyl)pyridine (3). A degassed mixture of 2-bromopyridine (0.96 mL, 10 mmol), Na_2CO_3 (2.3 g, 22 mmol), water (11 mL), EtOH (8 mL), dimethoxyethane (25 mL), 3-bromophenylboronic acid (2.0 g, 10 mmol), and Pd(PPh$_3$)$_4$ (115 mg, 0.10 mmol) was heated at reflux for 18 h to afford 1.5 g (64%) of **3** (eluent: CH_2Cl_2): colorless oil; ^{1}H and ^{13}C NMR data are in agreement with literature values;[32] IR (KBr) ν 3064, 3008, 1586, 1559, 1458, 1441, 1432, 1404, 1277, 785, 765, 673. Anal. Calcd for $C_{11}H_8BrN$ (234.10): C, 56.44; H, 3.44; N, 5.98. Found: C, 56.32; H, 3.51; N, 5.81.

1-(3-Fluorophenyl)isoquinoline (4). A degassed mixture of 1-chloroisoquinoline (1.6 g, 10 mmol), Na_2CO_3 (2.3 g, 22 mmol), water (11 mL), EtOH (8 mL), dimethoxyethane (25 mL), 3-fluorophenylboronic acid (1.4 g, 10 mmol), and Pd(PPh$_3$)$_4$ (115 mg, 0.10 mmol) was heated at reflux for 18 h to afford 1.9 g (87%) of **4** (eluent: petrol/AcOEt 80:20): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 1H), 7.43 (d, 1H, J = 10 Hz), 7.5 (m, 3H), 7.7 (m, 2H), 7.91 (d, 1H, J = 8.2 Hz), 8.09 (d, 1H, J = 8.5 Hz), 8.61 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 115.5 (d, J = 21 Hz), 116.9 (d, J = 22 Hz), 120.3, 125.6 (d, J = 2.9 Hz), 126.4, 127.0, 127.0, 127.4, 129.8 (d, J = 8.2 Hz), 130.1, 136.7, 141.6 (d, J = 7.5 Hz), 142.1, 159.1, 162.6 (d, J = 246 Hz); IR (KBr) ν 3052, 1582, 1556, 1443, 1385, 1354, 1191, 899, 827, 799, 785, 752, 703. Anal. Calcd for $C_{15}H_{10}FN$ (223.25): C, 80.70; H, 4.51; N, 6.27. Found: C, 80.68; H, 4.55; N, 6.25.

1-(3-Chlorophenyl)isoquinoline (5). A degassed mixture of 1-chloroisoquinoline (1.6 g, 10 mmol), Na_2CO_3 (2.3 g, 22 mmol), water (11 mL), EtOH (8 mL), dimethoxyethane (25 mL), 3-chlorophenylboronic acid (1.6 g, 10 mmol), and Pd(PPh$_3$)$_4$ (115 mg, 0.10 mmol) was heated at reflux for 18 h to afford 2.2 g (92%) of **5** (eluent: petrol/AcOEt 80:20): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 2H), 7.6 (m, 2H), 7.7 (m, 3H), 7.90 (d, 1H, J = 8.2 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.61 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 120.2, 126.3, 126.8, 126.9, 127.3, 127.9, 128.5, 129.4, 129.8, 130.0, 134.2, 136.6, 141.1, 142.0, 158.8; IR (KBr) ν 3050, 1551, 1382, 1350, 881, 824, 804, 784, 752, 695, 668. Anal. Calcd for $C_{15}H_{10}ClN$ (239.71): C, 75.16; H, 4.21; N, 5.84. Found: C, 75.19; H, 4.35; N, 5.62.

1-(3,5-Difluorophenyl)isoquinoline (6). A degassed mixture of 1-chloroisoquinoline (1.6 g, 10 mmol), Na_2CO_3 (2.3 g, 22 mmol), water (11 mL), EtOH (8 mL), dimethoxyethane (25 mL), 3,5-difluorophenylboronic acid (1.6 g, 10 mmol), and Pd(PPh$_3$)$_4$ (115 mg, 0.10 mmol) was heated at reflux for 18 h to afford 2.1 g (86%) of **6** (eluent: CH_2Cl_2/AcOEt 97.5:2.5): mp 100−102 °C; ^{1}H NMR ($CDCl_3$) δ 6.95 (t, 1H, J = 8.8 Hz), 7.24 (m, 2H), 7.59 (t, 1H, J = 7.6 Hz), 7.7 (m, 2H), 7.91 (d, 1H, J = 8.2 Hz), 8.06 (d, 1H, J = 8.5 Hz), 8.60 (d, 1H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 104.0 (t, J = 25 Hz), 113.1 (d, J = 26 Hz), 120.8, 126.3, 126.7, 127.2, 127.7, 130.3, 136.9, 142.1, 142.7 (t, J = 10 Hz), 158.0, 162.8 (dd, J = 249, 13 Hz); IR (KBr) ν 3096, 3060, 1626, 1599, 1583, 1431, 1392, 1356, 1118, 985, 822, 694. Anal. Calcd for $C_{15}H_9F_2N$ (241.24): C, 74.68; H, 3.76; N, 5.81. Found: C, 74.52; H, 3.86; N, 5.82.

2-(2-[2*H*]-3-fluorophenyl)pyridine (7a). A solution of the fluoride **1** (0.17 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, D_2O (0.1 mL) to afford 0.16 g (96%, 92% *d*) of **7a** (eluent: CH_2Cl_2). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 2′-H by 2′-D and 2′-CH by 2′-CD, respectively.

2-(3-Fluoro-2-iodophenyl)pyridine (7b). A solution of the fluoride **1** (0.17 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, a solution of iodine (0.25 g, 1.0 mmol) in THF (3 mL) to afford 0.20 g (66%) of **7b** (eluent: CH_2Cl_2): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.11 (td, 1H, J = 8.0, 1.4 Hz), 7.25 (dd, 1H, J = 7.9, 1.2 Hz), 7.34 (ddd, 1H, J = 7.5, 4.9, 1.0 Hz), 7.39 (td, 1H, J = 7.9, 5.5 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.80 (td, 1H, J = 7.8, 1.8 Hz), 8.72 (d, 1H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ 84.9 (d, J = 26 Hz), 114.9 (d, J = 25 Hz), 122.7, 124.3, 125.8 (d, J = 2.9 Hz), 129.7 (d, J = 8.5 Hz), 136.1, 147.1, 149.2, 159.6, 161.6 (d, J = 245 Hz); IR (KBr) ν 3392, 3063, 3008, 1584, 1563, 1455, 1436, 1416, 1242, 891, 775, 749. Anal. Calcd for $C_{11}H_7FIN$ (299.09): C, 44.18; H, 2.36; N, 4.68. Found: C, 44.28; H, 2.57; N, 4.48.

2-(2-[2*H*]-3-chlorophenyl)pyridine (8a). A solution of the chloride **2** (0.19 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, D_2O (0.1 mL) to afford 0.18 g (95%, 80% *d*) of **8a** (eluent: CH_2Cl_2/AcOEt 95:5). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 2′-H by 2′-D and 2′-CH by 2′-CD, respectively.

2-(3-Chloro-2-iodophenyl)pyridine (8b). A solution of the chloride **2** (0.19 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, a solution of iodine (0.25 g, 1.0 mmol) in THF (3 mL) to afford 0.20 g (62%) of **8b** (eluent: CH_2Cl_2/AcOEt 95:5): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.26 (dd, 1H, J = 4.0, 1.8 Hz), 7.4 (m, 2H), 7.45 (d, 1H, J = 7.8 Hz), 7.50 (dd, 1H, J = 7.9, 1.6 Hz), 7.79 (td, 1H, J = 7.7, 1.7 Hz), 8.71 (d, 1H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ 101.6, 122.7, 124.2, 127.7, 128.8, 129.0, 136.1, 139.5, 148.3, 149.1, 161.2; IR (KBr) ν 3400, 3058, 3004, 1588, 1567, 1474, 1444, 1426, 1391, 774, 748, 712. Anal. Calcd for $C_{11}H_7ClIN$ (315.54): C, 41.87; H, 2.24; N, 4.44. Found: C, 41.68; H, 2.27; N, 4.38.

2-(2-[2*H*]-3-bromophenyl)pyridine (9). A solution of the bromide **3** (0.23 g, 1.0 mmol) in THF (2 mL) was added to a solution of LTMP [obtained by adding BuLi (2.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.35 mL, 2.1 mmol) in THF (2 mL) at 0 °C] at −75 °C. After 1 h at −75 °C, deuteriolysis with D_2O (0.2 mL) afforded 0.19 g (82%, 35% *d*) of **9** (eluent: CH_2Cl_2). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 2′-H by 2′-D and 2′-CH by 2′-CD, respectively.

2-(3-[2*H*]-4-fluorophenyl)pyridine (11a). A solution of the fluoride **10** (0.17 g, 1.0 mmol) and potassium *tert*-butoxide (0.11 g, 1.0 mmol) in THF (3 mL) was treated with BuLi (1.0 mmol) at −75 °C. After 1 h at −75 °C, deuteriolysis with D_2O (0.2 mL) afforded 0.15 g (90%, 100% *d*) of **11a** (eluent: CH_2Cl_2/hexane 50:50). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 3′-H by 3′-D and 3′-CH by 3′-CD, respectively.

2-(4-Fluoro-3-iodophenyl)pyridine (11b). A solution of the fluoride **10** (0.17 g, 1.0 mmol) and potassium *tert*-butoxide (0.11 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, a solution of iodine (0.25 g, 1.0 mmol) in THF (3 mL) to afford 0.19 g (64%) of **11b** (eluent: petrol/CH_2Cl_2 80:20): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.14 (t, 1H, J = 8.1 Hz), 7.25 (ddd, 1H, J = 7.9, 4.8, 1.0 Hz), 7.66 (d, 2H, J = 8.0 Hz), 7.75 (td, 1H, J = 7.9, 1.7 Hz), 7.93 (ddd, 1H, J = 8.5, 4.8, 2.2 Hz), 8.41 (dd, 1H, J = 6.1, 2.2 Hz), 8.67 (d, 1H, J = 4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 81.7 (d, J = 25 Hz), 115.6 (d, J = 24 Hz), 120.2, 122.4, 122.3, 128.5 (d, J = 7.2 Hz), 136.9, 137.9, 149.7, 157.2 (d, J = 249 Hz), 164.6; IR (KBr) ν 3064, 3006, 1590, 1563, 1494, 1462, 1433, 1261, 778. Anal. Calcd for $C_{11}H_7FIN$ (299.09): C, 44.18; H, 2.36; N, 4.68. Found: C, 44.28; H, 2.07; N, 4.98.

2-(4-Fluoro-3,5-diiodophenyl)pyridine (12). A solution of the dihalide **11b** (0.30 g, 1.0 mmol) in THF (2 mL) was added

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to a solution of LTMP [obtained by adding BuLi (1.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol) in THF (2 mL) at 0 °C] at −75 °C. After 1 h at −75 °C, quenching with a solution of iodine (0.25 g, 1.0 mmol) in THF (3 mL) afforded 0.28 g (65%) of **12** (eluent: CH_2Cl_2): white powder; mp 160−161 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (ddd, 1H, J = 7.4, 4.8, 1.0 Hz), 7.66 (d, 1H, J = 7.9 Hz), 7.78 (td, 1H, J = 8.0, 1.7 Hz), 8.37 (d, 2H, J = 5.4 Hz), 8.68 (d, 1H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ 80.7 (d, J = 29 Hz), 120.4, 122.9, 137.1, 138.0, 138.7, 149.9, 153.4, 160.7 (d, J = 245 Hz); IR (KBr) ν 3086, 3005, 1584, 1449, 1429, 1287, 1246, 1154, 780, 739, 602. Anal. Calcd for $C_{11}H_6FI_2N$ (424.98): C, 31.09; H, 1.42; N, 3.30. Found: C, 31.33; H, 1.02; N, 3.27.

2-(2-[2*H*]-3-fluoro-4-iodophenyl)pyridine (13). A solution of the dihalide **7b** (0.30 g, 1.0 mmol) in THF (2 mL) was treated with a solution of LTMP [obtained by adding BuLi (1.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol) in THF (2 mL) at 0 °C] at −75 °C. After 1 h at −75 °C, deuteriolysis with D_2O (0.1 mL) afforded 0.21 g (69%, 72% *d*) of **13** (eluent: CH_2Cl_2/AcOEt 95:5): pale yellow powder; mp 67−68 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (ddd, 1H, J = 7.9, 4.8, 1.3 Hz), 7.54 (d, 1H, J = 8.3 Hz), 7.70 (d, 1H, J = 7.9 Hz), 7.77 (td, 1H, J = 8.0, 1.8 Hz), 7.83 (dd, 1H, J = 8.2, 1.8 Hz), 8.68 (d, 1H, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 81.2 (d, J = 26 Hz), 113.2 (m), 119.7, 122.5, 123.3 (d, J = 2.6 Hz), 136.4, 139.0, 141.4 (d, J = 6.9 Hz), 149.3, 154.3, 161.7 (d, J = 245 Hz); IR (KBr) ν 3006, 1589, 1548, 1456, 1434, 1383, 1221, 993, 776, 757, 741, 722. Anal. Calcd for $C_{11}H_6FIND$ (300.09): C, 44.03; "H",[33] 2.39; N, 4.67. Found: C, 44.18; "H", 2.45; N, 4.42.

2-(2-[2*H*]-3-chloro-4-iodophenyl)pyridine (14). A solution of the dihalide **8b** (0.32 g, 1.0 mmol) in THF (2 mL) was treated with a solution of LTMP [obtained by adding BuLi (1.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol) in THF (2 mL) at 0 °C] at −75 °C. After 1 h at −75 °C, deuteriolysis with D_2O (0.1 mL) afforded 0.10 g (30%, 80% *d*) of **14** (eluent: CH_2Cl_2): colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.28 (ddd, 1H, J = 7.2, 4.8, 1.2 Hz), 7.57 (d, 1H, J = 8.3 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.77 (td, 1H, J = 7.7, 1.8 Hz), 7.94 (d, 1H, J = 8.3 Hz), 8.69 (d, 1H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ 98.7, 120.2, 122.9, 126.0, 127.5, 136.8, 139.0, 140.3, 141.1, 149.6, 155.7; IR (KBr) ν 3055, 3004, 1507, 1471, 1452, 1427, 1353, 1000, 787, 778, 753, 692. Anal. Calcd for $C_{11}H_6ClIND$ (316.55): C, 41.74; "H",[33] 2.26; N, 4.42. Found: C, 41.68; "H", 2.37; N, 4.48.

1-(2-[2*H*]-3-fluorophenyl)isoquinoline (15a). A solution of the fluoride **4** (0.22 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, D_2O (0.1 mL) to afford 0.21 g (94%, 91% *d*) of **15a** (eluent: petrol/AcOEt 80:20). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 2′-H by 2′-D, and 2′-CH by 2′-CD, respectively.

1-(3-Fluoro-2-iodophenyl)isoquinoline (15b). A solution of the fluoride **4** (0.22 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, a solution of iodine (0.25 g, 1.0 mmol) in THF (3 mL) to afford 0.21 g (70%) of **15b** (eluent: CH_2Cl_2/AcOEt 95:5): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 2H), 7.5 (m, 3H), 7.8 (m, 2H), 7.93 (d, 1H, J = 8.3 Hz), 8.63 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 85.8 (d, J = 26 Hz), 114.9 (d, J = 24 Hz), 120.6, 125.7 (d, J = 3.0 Hz), 126.7, 126.8, 127.1, 127.3, 129.6 (d, J = 8.4 Hz), 130.2, 136.1, 141.7, 146.1, 160.8, 161.5 (d, J = 246 Hz); IR (KBr) ν 3054, 1583, 1558, 1424, 1386, 1359, 1241, 902, 828, 818, 798, 786, 750. Anal. Calcd for $C_{15}H_9FIN$ (349.15): C, 51.60; H, 2.60; N, 4.01. Found: C, 51.48; H, 2.47; N, 4.02.

1-(2-[2*H*]-3-Chlorophenyl)isoquinoline (16a). A solution of the chloride **5** (0.24 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, D_2O (0.1 mL) to afford 0.22 g (91%, 72% *d*) of **16a** (eluent: petrol/AcOEt 80:20). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 2′-H by 2′-D, and 2′-CH by 2′-CD, respectively.

1-(3-Chloro-2-iodophenyl)isoquinoline (16b). A solution of the chloride **5** (0.24 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, a solution of iodine (0.25 g, 1.0 mmol) in THF (3 mL) to afford 0.24 g (67%) of **16b** (eluent: CH_2Cl_2/AcOEt 95:5): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.27 (dd, 1H, J = 7.5, 1.5 Hz), 7.44 (t, 1H, J = 7.7 Hz), 7.6 (m, 3H), 7.7 (m, 2H), 7.92 (d, 1H, J = 8.3 Hz), 8.63 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 102.4, 120.8, 126.4, 126.9, 126.9, 127.5, 127.8, 128.9, 129.1, 130.3, 136.4, 139.5, 141.9, 147.0, 162.3; IR (KBr) ν 3052, 1621, 1583, 1557, 1396, 1386, 1356, 827, 787, 752. Anal. Calcd for $C_{15}H_9ClIN$ (365.60): C, 49.28; H, 2.48; N, 3.83. Found: C, 49.26; H, 2.57; N, 3.78.

1-(3,5-Difluoro-4-iodophenyl)isoquinoline (17a). A solution of the difluoride **6** (0.24 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, a solution of iodine (0.25 g, 1.0 mmol) in THF (3 mL) to afford 0.27 g (73%) of **17a** (eluent: CH_2Cl_2/AcOEt 98:2): mp 164 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 2H, J = 6.9 Hz), 7.60 (t, 1H, J = 7.7 Hz), 7.72 (m, 2H), 7.92 (d, 1H, J = 8.2 Hz), 8.06 (d, 1H, J = 8.5 Hz), 8.60 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 71.4 (t, J = 29 Hz), 112.9 (d, J = 26 Hz), 120.9, 126.3, 126.4, 127.2, 127.8, 130.3, 136.3, 142.1, 142.6 (t, J = 8.9 Hz), 157.0, 162.4 (dd, J = 248, 6.3 Hz); IR (KBr) ν 3064, 1551, 1409, 1389, 1360, 1019, 1012, 866, 856, 819, 752, 686, 658. Anal. Calcd for $C_{15}H_8F_2IN$ (367.14): C, 49.07; H, 2.20; N, 3.82. Found: C, 49.17; H, 2.34; N, 3.56.

1-(3,5-Difluoro-4-(trimethylsilyl)phenyl)isoquinoline (17b). A solution of the difluoride **6** (0.24 g, 1.0 mmol) in THF (3 mL) was successively treated with BuLi (1.0 mmol) at −75 °C and, 1 h later, chlorotrimethylsilane (0.13 mL, 1.0 mmol) to afford 0.23 g (72%) of **17b** (eluent: cyclohexane/AcOEt 90:10): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.66 (s, 9H), 7.38 (d, 2H, J = 7.5 Hz), 7.75 (t, 1H, J = 7.7 Hz), 7.85 (m, 2H), 8.06 (d, 1H, J = 8.3 Hz), 8.31 (d, 1H, J = 8.7 Hz), 8.79 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 112.5 (d, J = 31 Hz), 113.8 (t, J = 35 Hz), 120.5, 126.1, 126.6, 127.0, 127.5, 130.2, 136.7, 141.9, 143.4 (t, J = 10 Hz), 157.9, 166.7 (dd, J = 245, 17 Hz); IR (KBr) ν 3054, 2958, 2901, 1621, 1538, 1398, 1252, 1186, 1001, 906, 847, 827, 659. Anal. Calcd for $C_{18}H_{17}F_2NSi$ (313.43): C, 68.98; H, 5.47; N, 4.47. Found: C, 69.03; H, 5.65; N, 4.42.

1-(2-[2*H*]-3-Fluoro-4-iodophenyl)isoquinoline (18). A solution of the dihalide **15b** (0.35 g, 1.0 mmol) in THF (2 mL) was treated with a solution of LTMP [obtained by adding BuLi (1.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol) in THF (2 mL) at 0 °C] at −75 °C. After 1 h at −75 °C, deuteriolysis with D_2O (0.1 mL) afforded 0.26 g (74%, 74% *d*) of **18** (eluent: CH_2Cl_2/AcOEt 95:5): pale yellow powder; mp 125 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 1H, J = 7.6 Hz), 7.58 (td, 1H, J = 7.6, 1.0 Hz), 7.69 (d, 1H, J = 5.7 Hz), 7.72 (td, 1H, J = 7.0, 0.9 Hz), 7.91 (d, 1H, J = 8.0 Hz), 7.93 (d, 1H, J = 8.0 Hz), 8.06 (d, 1H, J = 8.5 Hz), 8.60 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 81.6 (d, J = 25 Hz), 116.9 (d, J = 25 Hz), 120.3, 125.9, 126.4, 126.9, 127.0 (d, J = 3.2 Hz), 127.4, 130.0, 136.5, 138.9 (d, J = 1.4 Hz), 141.6 (d, J = 6.7 Hz), 141.9, 157.8, 161.3 (d, J = 246 Hz); IR (KBr) ν 3046, 1405, 1392, 1352, 1224, 870, 837, 828, 808, 746, 678. Anal. Calcd for $C_{15}H_8FIND$ (350.15): C, 51.45; "H",[33] 2.62; N, 4.00. Found: C, 51.58; "H", 2.77; N, 4.08.

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