Configurationally Stable Biaryl Analogues of 4-(Dimethylamino)pyridine: A Novel Class of Chiral Nucleophilic Catalysts

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A short synthetic approach toward a novel class of chiral nucleophilic catalysts, the dissymmetry of which stems from restricted rotation about an Ar−Ar bond, has been developed. The key steps of the synthesis include preparation of a nucleophilic 1-methyl-2-pyrrolino[3,2-*c*]pyridine core **16** by *ortho*-lithiation and creation of the biaryl axes via Suzuki cross-coupling reactions. Comparative HPLC studies of racemization for configurationally labile biaryls **31**, **38**, and **43** containing 1-methyl-2-pyrrolino[3,2-*c*]pyridine, 4-(dimethylamino)pyridine, and 4-(1-pyrrolidino)pyridine cores, respectively, have demonstrated that a pyrrolidino substituent *ortho* to the biaryl axis is optimal for slowing Ar−Ar rotation. Biaryls containing all three cores have been shown to retain DMAP-like catalytic activity in the acylation of a hindered alcohol. Biaryls **55** and **56**, which are configurationally stable at ambient temperature, have also been prepared via modification of configurationally labile derivatives. Compounds **55** and **56** in optically pure form should provide a useful starting point for studies on catalytic asymmetric acyl transfer using atropisomeric analogues of DMAP.

Introduction

The development of chiral catalysts capable of mediating asymmetric organic transformations is one of the most challenging and rewarding areas of organic synthesis. Although the design and synthesis of chiral ligands for metal-based catalytic systems has commanded particular attention in recent years, there has also been considerable interest in the development of small, purely organic catalysts.[1] Much of the inspiration behind the development of synthetic chiral catalysts can be attributed to the desire of chemists to develop systems that mimic enzymes. In view of the importance of nucleophilic catalysis in many enzyme-mediated transformations[2] it is, therefore, rather surprising that asymmetric nucleophilic catalysis by small organic compounds has, until very recently, scarcely been addressed.[3] However, the last three years have witnessed an explosion of interest in this area[4] and, in particular, highly effective nucleophilic catalysts based around 4-(dimethylamino)pyridine (DMAP) have been discovered.[5]

The high nucleophilicity of DMAP was first noted over 30 years ago, when it was found to be an excellent catalyst for the acylation of hindered alcohols.[6] Subsequently, DMAP has been employed as a nucleophilic catalyst in a wide range of related transformations.[7] The first *chiral* DMAP-based acyl transfer reagent was reported by Vedejs and Chen in 1996.[8] Although their reagent was noncatalytic, high levels of chiral discrimination were obtained in the acylative kinetic resolution of various secondary alcohols, especially when combined with the elegant concept of parallel kinetic resolution.[9] Shortly thereafter, Fu and Ruble[10] reported on the synthesis and catalytic activity of a novel class of planar-chiral analogues of DMAP. The MIT group have subsequently utilized one of their enantiomerically pure catalysts in a wide range of asymmetric transformations, achieving impressive levels of enantioselectivity.[11] Fuji and coworkers have also described a chiral derivative of DMAP, which proved highly effective for the acylative kinetic resolution of a specific series of secondary alcohols.[12]

Here we report on the synthesis of a novel family of chiral DMAP-based nucleophilic catalysts, the dissymmetry of which stems from restricted rotation about an aryl−aryl bond.[13]

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† Single-crystal X-ray analyses.

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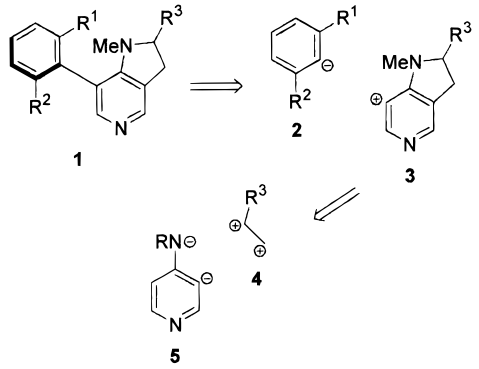
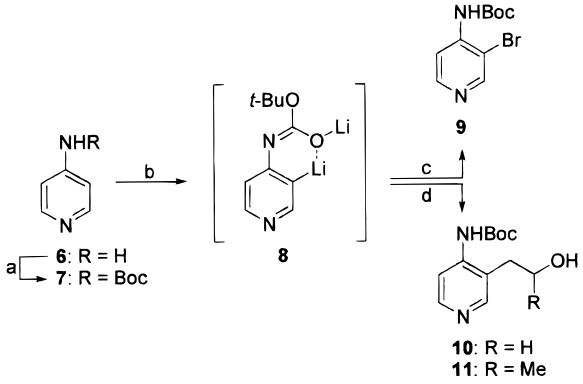
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) Boc_2O, DCM, rt, 45 min; >99%; (b) *t*-BuLi, THF, −78 °C → −15 °C, 3.5 h; (c) $Br(CH_2)_2Br$, −78 °C → rt, 2 h; 85%; (d) ethylene oxide, −78 °C → rt, 2 h; 75% of **10**, or $Br(CH_2)_2OLi$, −78 °C → rt, 2 h; 66% of **10**, or propylene oxide, −78 °C → rt, 2 h; 81% of **11**.

Results and Discussion

A synthetic strategy for the preparation of atropisomeric analogues of DMAP **1** (Scheme 1) involves formation of the Ar−Ar bond via direct coupling of an appropriately substituted organometallic partner **2** with an electrophilic equivalent of bicyclic heterocyle **3**. By varying substituents R^1 and R^2, satisfactory levels of both the internal rotational barrier and dissymmetry of the molecular systems **1** were anticipated to be achieved. In our initial studies, a substituent R^3 was incorporated as a chiral marker, to enable straightforward observation of atropisomerism by both ^1H and ^{13}C NMR, although in the synthesis of catalyst candidates, formation of racemates (R^3 = H) rather than diastereoisomeric mixtures would be preferred.

Instead of using DMAP itself as a catalytically active subunit in biaryls **1**, we opted for 1-methyl-2-pyrrolino-[3,2-*c*]pyridine **16**, as it was anticipated that stopping rotation about the C_{Ar}−N bond would enhance the barrier to internal rotation about the central biaryl axis. Moreover, it has been recently reported[14] that amine **16** shows catalytic activity comparable to DMAP itself, although no detail regarding its synthesis was given. Since the previously reported synthetic routes leading to amine **16** are both multistep and low-yielding,[15] it was planned to prepare bicyclic amine **16** via alkylation of a pyridyl dianion **5** with a vicinal dielectrophile **4**. The choice of R = Boc would allow the preparation of the dianion **5** using directed *ortho*-metalation methodology[16] and subsequent utilization of the carbamate as a latent methyl group.

The synthesis commenced with the conversion of 4-aminopyridine **6** to the known carbamate **7**[17] (Scheme 2). Although amine **6** is not highly soluble in CH_2Cl_2, treatment of a suspension thereof with Boc_2O resulted in rapid and quantitative conversion to carbamate **7**. The *ortho*-lithiation of carbamate **7** to its dianion **8** was performed as previously reported using *t*-BuLi in THF.[17a,18] Unfortunately, attempts to bis-alkylate dianion **8** in one step failed. While both 1,2-dibromoethane and 1-bromo-2-chloroethane reacted with dianion **8** to give a high yield of aryl bromide **9**, the product of halophilic attack, 1,2-dichloroethane, for which the halophilic attack was not expected, proved not reactive enough for alkylation to proceed. In contrast, dianion **8** reacted smoothly with lithium 2-bromoethanoate to give primary alcohol **10**. For large-scale preparations, it was more convenient to synthesize alcohol **10** by the alkylation of dianion **8** with ethylene oxide. Analogously, alkylation of dianion **8** with propylene oxide gave secondary alcohol **11** as the only isomer. No product of epoxide ring opening on the more substituted carbon atom was noted. The expected mode of epoxide ring opening leading to secondary alcohol **11** was confirmed by single-crystal X-ray analysis of biaryl **22**.

Amino alcohols **10** and **11** were cyclized (Scheme 3) by conversion to the corresponding methanosulfonates **12** and **13**, respectively, on treatment with $MsCl/Et_3N$. While the primary mesylate **12** underwent in situ cyclization to bicyclic carbamate **14**, the intramolecular alkylation of mesylate **13** leading to carbamate **15** was sluggish. However, isolation of mesylate **13** and treatment with LHMDS furnished the cyclized product **15** in high yield. Subsequent reduction of carbamates **14** and **15** to *N*-methylamines **16** and **17**, respectively, was accomplished in moderate yield using either $LiAlH_4$ or DIBAL. Reductions with $LiAlH_4$ provided substantial amounts of *N*-demethylated side-products, although the overall recovery of the material was high.[19,20] In contrast, DIBAL gave almost exclusively (~ 10:1) the product of the carbamate reduction without the C−N bond cleavage, although in

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(19) When the TFA-mediated removal of the Boc group from carbamate **14** was attempted, only traces of the desired product were obtained and the overall material recovery was low. Presumably, *tert*-butylation of the highly nucleophilic product on the pyridyl nitrogen interferes. Performing the cleavage in the presence of Et_3SiH (ref 20), however, allowed for a high yield of the deprotected product to be isolated.

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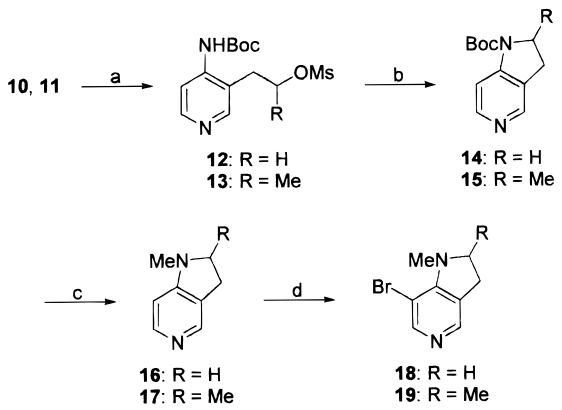
Scheme 3[a]

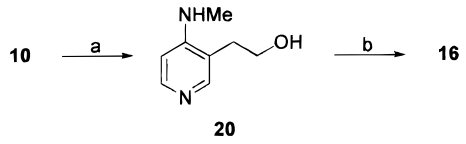


[a] Reagents and conditions: (a) MsCl, Et_3N, DCM, −10 °C → rt, 2 h for **12** and −20 °C → rt, 80 min for **13**; (b) as (a); >99% of **14** or LHMDS, THF, −78 °C → reflux, overnight; 95% of **15**; (c) DIBAL, DCM, 0 °C → reflux, 20 h; 55% of **16** or $LiAlH_4$, THF, 0 °C → reflux, 4 h; 38% of **17**; (d) NBS, DMF, 0 °C, 90 min; 81% of **18** or 62% of **19**.

this case the material recovery was lower. Bromination of amines **16** and **17** under mild conditions using NBS/DMF[21] gave aryl bromides **18** and **19**, respectively. The structure of aryl bromide **18** was confirmed by single-crystal X-ray analysis.

In contrast to moderate yields observed for reduction of carbamates **14** and **15** (Scheme 3), reduction of carbamate **10** with $LiAlH_4$ gave amino alcohol **20** in excellent yield (99%, Scheme 4). In this case, however,

Scheme 4[a]

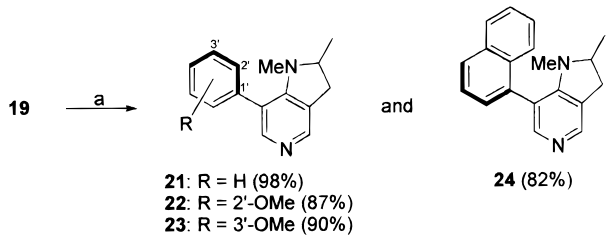


[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C → reflux, 4 h; 99%; (b) NaH, PhN(Me)$PIPh_3$, DMF, 80 °C, 2 h; 63%.

conversion to amine **16** proved difficult. Attempted cyclization of alcohol **20** via its mesylate to amine **16**, the method successfully applied to cyclization of carbamates **10** and **11**, gave only a small amount (<20%) of the desired product **16** with a significant loss of material during workup. Presumably, the increased nucleophilicity of the pyridyl nitrogen in amine **20**, as compared to its Boc-deactivated analogues **10** and **11**, makes quaternization of the substrate/product a significant side-reaction. Since intermolecular alkylations of 4-monoalkylaminopyridine anions are known to proceed selectively on the exocyclic nitrogen,[22] it was anticipated that conversion of the hydroxyl group in amino alcohol **20** to a good leaving group with concomitant deprotonation of the amine would improve the yield of the process. Indeed, treatment of the alkoxide of aminol **20** with (*N*-methylphenylamino)triphenylphosphonium iodide (Murahashi's reagent),[23] gave the desired product in good yield. The high cost of the reagent, however, prevented us from using this route in large-scale preparations of amine **16**.

With efficient syntheses of aryl bromides **18** and **19** in hand, the key biaryl cross-coupling step was investigated. Gratifyingly, treatment of aryl bromide **19** with a series of unhindered arylboronic acids under standard Suzuki cross-coupling conditions [$Pd(PPh_3)_4$, Na_2CO_3 in PhMe/H_2O/EtOH],[24] furnished biaryls **21**−**24** in excellent yield (Scheme 5). Neither the ^1H nor the ^{13}C NMR spectra of

Scheme 5[a]

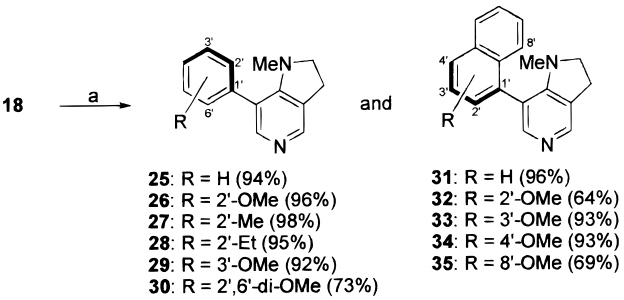


[a] Reagents and conditions: (a) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, PhMe, H_2O, EtOH, reflux, 2−24 h.

biaryls **22** and **23** showed any evidence of diasteroisomerism due to slow rotation about the biaryl axis (on the NMR time-scale). By comparison with low-temperature NMR experiments of closely related compounds (vide infra), it appears that the similarity in the NMR behavior between fully symmetrical biaryl **21** and biaryls **22** and **23** reflects the low level of dissymmetry exerted by the methoxy substituent. In contrast, the naphthyl analogue **24** could be observed as a ∼1:1 mixture of atropisomers (in $CDCl_3$ at room temperature).

To explore the formation of racemic biaryls, the Suzuki cross-coupling of a series of arylboronic acids with aryl bromide **18** was performed (Scheme 6). As previously,

Scheme 6[a]



[a] Reagents and conditions: (a) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, PhMe, H_2O, EtOH, reflux, 2−24 h.

high yields of biaryls were obtained when unhindered arylboronic acids were used (**25**−**29**, **31**, **33**, and **34**). In more difficult cases (**30**, **32**, and **35**[25]), the yields of the cross-coupling were lower and required increased amounts of both catalyst (5 mol % vs 3 mol %) and arylboronic acids (2.0 equiv vs 1.2 equiv).

As the result of axial dissymmetry, the protons of each of the two methylene groups, at C-2 and C-3, in biaryls **26**−**29** and **31**−**35** are diastereotopic. ^1H NMR studies

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(25) The ability of biaryl **35** to induce α-elimination of HCl from dichloromethane was noted during the growth of a single crystal from an ether/dichloromethane solution. The crystal grown was demonstrated to be hydrochloride of biaryl **35** by single-crystal X-ray analysis.

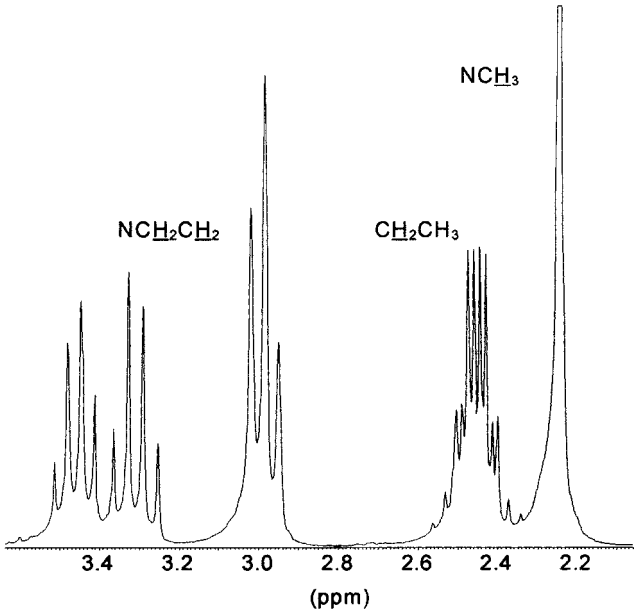


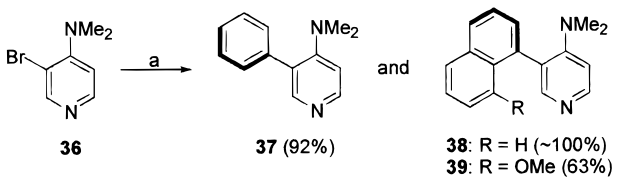
Figure 1. High-field fragment of the ^{1}H NMR spectrum of axially chiral biaryl **28** in $CDCl_3$ (250 MHz).

(250 MHz, $CDCl_3$, rt) showed that in biaryls **26**, **29**, and **35** these protons are isochronous, i.e., appear as a pair of triplets, as in symmetrical biaryls **25** and **30**.[26,27] In contrast, the methylene protons in biaryls **27**, **28**, and **31**−**34** are anisochronous and show more complex splitting patterns (Figure 1), which unequivocally confirms slow internal rotation about the central biaryl axis due to steric hindrance. For naphthyl derivative **31**, no coalescence was observed even at 100 °C. Its racemization, however, could be conveniently studied using chiral HPLC (Figure 2).[28] Computer simulation of the plateau-shaped elution profiles[29] allowed calculation of the rotational energy barrier for biaryl **31** which was found to be 85.9 ± 0.3 kJ/mol (20 °C). This corresponds to a half-life for racemization of ∼1.9 min at 20 °C which is significantly shorter than the arbitrarily set threshold of 1000 s considered the minimum requirement for chemical separation of optical antipodes.[30] Similar HPLC analysis of methoxynaphthalene biaryls **32**−**35** enabled us to study both stereoelectronic (conjugation across the biaryl system) and steric effects of varying substitution patterns on the barrier to Ar−Ar rotation.[31]

Although the studies described herein focus on configurationally stable naphthyl-based biaryls (vide infra), symmetrically substituted 2′6′-dimethoxy biaryl **30** could be envisaged to constitute an attractive starting material (via its 2′,6′-ditriflate) for the asymmetric synthesis of configurationally stable phenyl-based biaryls by enantioposition-selective couplings.[32]

At this juncture, having developed an efficient methodology for the preparation of relatively unhindered and configurationally labile biaryls, the racemization of which could be conveniently followed by chiral HPLC, we embarked on the preparation of an analogous set of compounds containing DMAP itself as a nucleophilic component. This would enable us to assess the effect of freezing the rotation about the C−N bond on the barrier to rotation about the biaryl axis. As in previous cases, Suzuki cross-coupling of the known aryl bromide **36**[33] with selected arylboronic acids proceeded uneventfully (Scheme 7) yielding biaryls **37**−**39**.

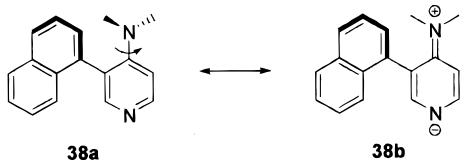
Scheme 7[a]



[a] Reagents and conditions: (a) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, PhMe, H_2O, EtOH, reflux, 2−24 h.

Here, atropisomerism could not be observed by NMR, but the rotational behavior of the DMAP analogues **38** and **39** was easily followed by chiral HPLC. Contrary to our expectations, the barriers to internal rotation observed for naphthyl-substituted biaryls **31** (Figure 2) and **38** (Figure 3) were not significantly different. It could, therefore, be concluded that the increased conformational rigidity of the nucleophilic component has no significant effect on the configurational stability of the biaryls. This presumably reflects the importance of conjugation across the 4-aminopyridyl system, for which coplanarity is optimal, thus restricting rotation about the C−N bond (Scheme 8).[34] In the case of biaryl **31**, for which the

Scheme 8



coplanarity is enforced, the *N*-methyl group is pulled away from the biaryl axis due to Baeyer strain imposed by the five-membered ring. As a result, the *N*-methyl group in biaryl **31** plays a lesser role in slowing the Ar−Ar rotation than the proximal *N*-methyl group in conjugated resonance form **38**(**b**). This effect becomes more

(26) For biaryl **26**, the broad ^{1}H NMR signals for methylene protons gave a more complex splitting pattern at 243 K (similar to that of biaryl **28**). For biaryl **29** no decoalescence was observed even at 223 K.

(27) The *N*-methyl groups in 7-aryl derivatives of azaindoline **16** show a significant ring current upfield shift in ^{1}H NMR ($CDCl_3$). The effect is more pronounced for naphthyl derivatives **31** and **55** (−0.69 and −0.70 ppm, respectively, relative to **16**) than for phenyl analogue **25** (−0.34 ppm).

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(34) X-ray single-crystal structures of biaryl **38** and its *N*-oxide are almost superimposable, suggesting a high level of across-ring conjugation in the parent molecule **38**.

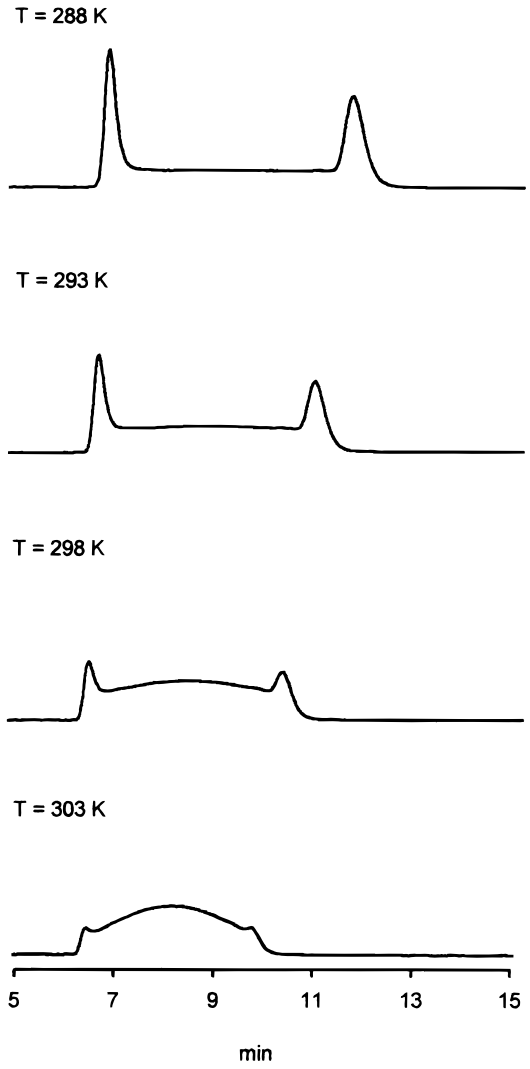


Figure 2. Interconversion of enantiomers on chiral HPLC (Chiralcel OD column, 4.6 mm × 25 cm; hexanes/2-propanol/diethylamine, 79/20/1, 1 mL min^{-1}) for biaryl **31** (7 μg).

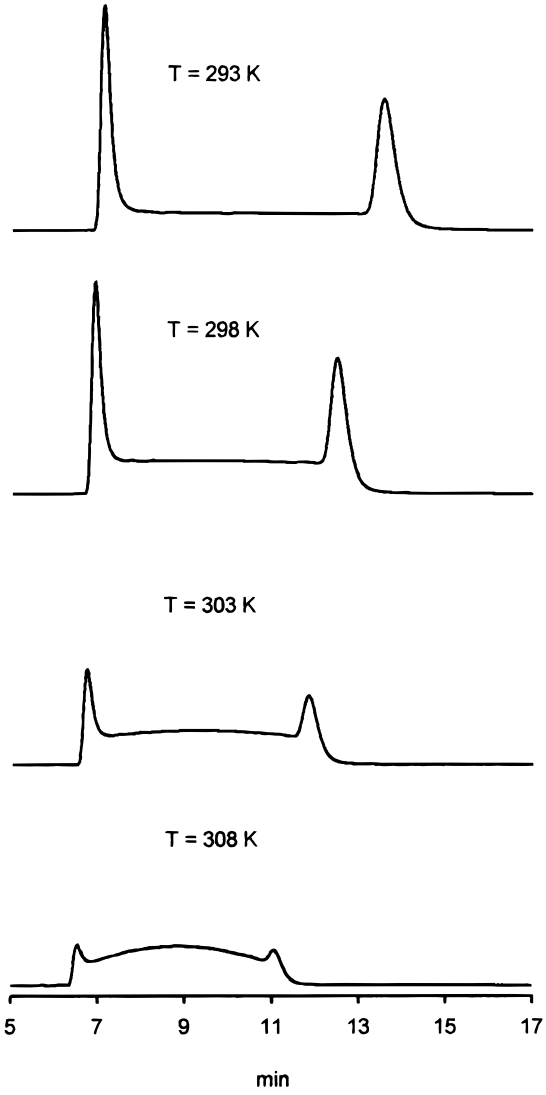
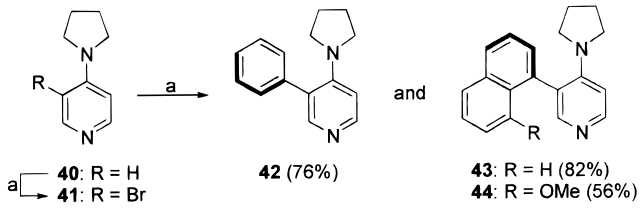


Figure 3. Interconversion of enantiomers on chiral HPLC (Chiralcel OD column, 4.6 mm × 25 cm; hexanes/2-propanol/triethylamine, 79/20/1, 1 mL min^{-1}) for biaryl **38** (5.5 μg).

pronounced for tri-*ortho*-substituted biaryls for which DMAP-based analogues seem rotationally much more restricted than the corresponding analogues of azaindoline **16** (vide infra).

If the above reasoning is correct, analogous biaryl derivatives of yet another highly nucleophilic catalyst, 4-(1-pyrrolidino)pyridine (4-PPY) **40**, should show even higher barriers to Ar−Ar rotation due to prevented rotation about the N−CH_2 bonds. Thus (Scheme 9),

Scheme 9[a]



[a] Reagents and conditions: (a) Br_2, K_2CO_3, Bu_4NOH, CH_2Cl_2, rt, 3 h; 47%; (b) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, PhMe, H_2O, EtOH, reflux, 2−24 h.

bromination of 4-PPY **40** with Br_2 gave aryl bromide **41**, which was subsequently coupled with a series of arylboronic acids under standard Suzuki conditions[24] to give biaryls **42**−**44** in good yields. For biaryls **43** and **44**, atropisomerism could be observed by ^1H NMR owing to more complex splitting patterns for the methylene groups as compared with symmetrical phenyl derivative **42**. As anticipated, chiral HPLC studies revealed that the barrier to Ar−Ar rotation in biaryl **43** is significantly higher than for its closely related analogues **31** and **38** and can be compared to the levels of steric hindrance observed in *peri*-methoxy-substituted naphthalene **35** (Figure 4). Since aryl bromides **36** and **41** are far more readily available than aryl bromide **18**, their use as templates on which configurationally stable atropisomeric nucleophilic catalysts can be constructed is an attractive option. Moreover, the use of DMAP and 4-PPY as nucleophilic components should allow the preparation of their 3,5-bis(aryl) derivatives possessing C_2-symmetry, a feature that may enhance chiral recognition in acyl transfer as compared to the corresponding monoaryl analogues. In our initial studies, however, we utilized aryl bromide **18** as the nucleophilic template.

It was anticipated that the attachment of a sterically more demanding group at the 2′-position in biaryl **31** would be sufficient to increase the barrier to internal

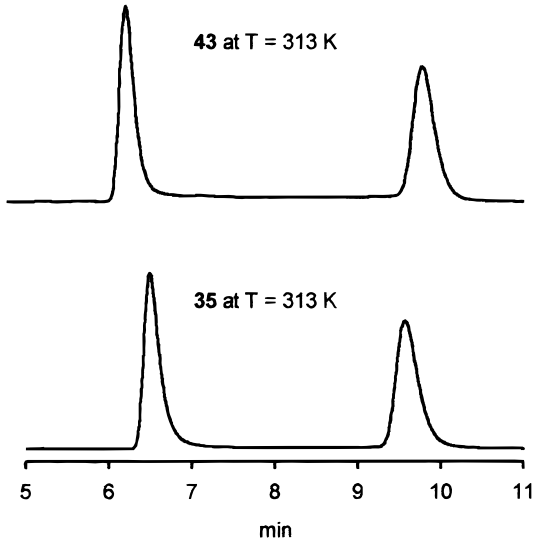
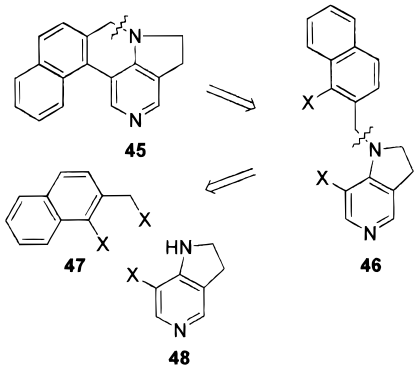


Figure 4. Interconversion of enantiomers on chiral HPLC (Chiralcel OD column, 4.6 mm × 25 cm; 2-propanol/hexanes/diethylamine, 78/20/2, 1 mL min^{-1}) for biaryls **43** (2.5 μg) and **35** (4.0 μg).

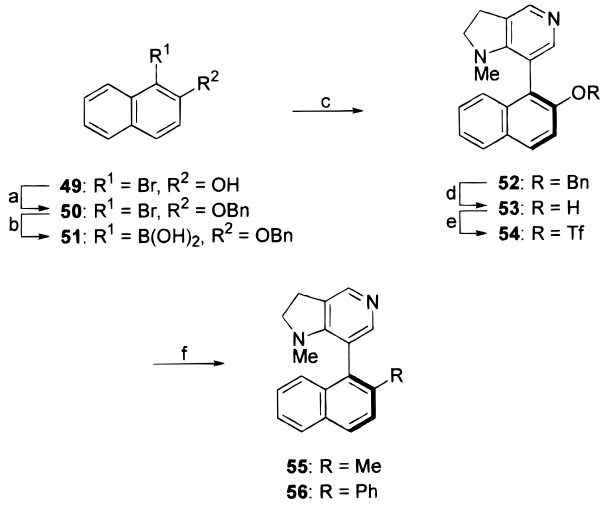
rotation to such a degree that racemization of the corresponding biaryls would become negligible at room temperature. Unfortunately, all attempts to perform direct Suzuki cross-coupling of 2-methyl-1-naphthaleneboronic acid/di-*n*-butyl ester or Kharasch-type cross-coupling of the corresponding Grignard reagent failed and, at best, only small amounts of biaryl **55** (<5%) could be detected by ^{1}H NMR/HPLC. One way to circumvent this problem would be to carry out the crucial biaryl coupling in *intramolecular* fashion using an auxiliary bridge (Scheme 10), a strategy successfully applied to the

Scheme 10



preparation of a broad range of highly substituted biaryls.[35] Thus, alkylation of amine **48** with naphthalene derivative **47** would lead to amine **46**. A subsequent intramolecular biaryl coupling would create the central biaryl axis to give **45**, which after benzylamine cleavage and *N*-methylation would furnish the desired highly substituted biaryl **55**. Initially, however, we decided to use a more direct approach. As such, it was anticipated that 2′-methoxy-substituted biaryl **32** could be conveniently converted to the desired 2′-methyl analogue. Since demethylation of methyl ether **32** proved rather difficult (at best, a yield of ∼35% could be achieved using EtSH/$AlCl_3$[36]), the synthesis was modified using benzyl as an easily removable protecting group (Scheme 11). Thus, benzylation of phenol **49** with $BnBr/K_2CO_3$ furnished benzyl ether **50** which was converted in a high overall yield to arylboronic acid **51** upon lithiation with *n*-BuLi in Et_2O at 0 °C, followed by quenching with $B(OMe)_3$. The Suzuki cross-coupling of arylboronic acid **51** with aryl bromide **18** gave biaryl **52** in high yield. Catalytic hydrogenation of benzyl ether **52** furnished phenol **53**, which was subsequently converted to triflate **54** on treatment with Tf_2O/pyridine. The triflate group in biaryl **54** was substituted by the methyl group using either Stille cross-coupling[37] with Me_4Sn or, preferably, Kumada−Corriu cross-coupling with MeMgBr[38] to give biaryl **55** in good yield. A similar Kharasch-type cross-coupling[39] with PhMgBr gave 2′-phenyl derivative **56**. The structure of biaryl **56** was confirmed by single-crystal X-ray analysis (Figure 5).

Scheme 11[a]



[a] Reagents and conditions: (a) BnBr, K_2CO_3, DMF, 60 °C, 5 h; 93%; (b) *n*-BuLi, Et_2O, −78 °C → 0 °C, 1 h followed by $B(OMe)_3$, −78 °C → rt, overnight; 83%; (c) 18, Na_2CO_3, $Pd(PPh_3)_4$, PhMe, H_2O, EtOH, reflux, 24 h; 82% (based on **18**); (d) H_2 (1 atm), Pd/C, EtOH, rt, 5 h; (e) Tf_2O, pyridine, 0 °C, 90 min; 93% over two steps; (f) MeMgBr, $NiBr_2(PPh_3)_2$, Et_2O, reflux, 15 h; 85% of **55** or Me_4Sn, $Pd(PPh_3)_2Cl_2$, PPh_3, LiCl, 2,6-di-*tert*-butyl-4-methylphenol, DMF, 120 °C, 20 h; 73% of **55** or PhMgBr, $PdCl_2$(dppp), Et_2O, reflux, 24 h; 85% of **56**.

At this stage, several of these molecules were tested as acyl transfer catalysts using Ac_2O and 1-methylcyclohexanol **57** (Table 1), the standard test used previously by others to assess the catalytic activity of DMAP and its analogues.[6b] As anticipated, the introduction of the aryl substituents into either **16** or DMAP does cause a drop in catalytic activity, but the effect is not dramatic, especially when compared with the background acylation level observed in the absence of the catalyst (Table 1, entry 1).

The barriers to internal rotation for biaryls **55** and **56**, which were to be used as chiral nucleophilic catalysts, were then evaluated. Thus, samples of racemic biaryls

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(36) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275−4277.

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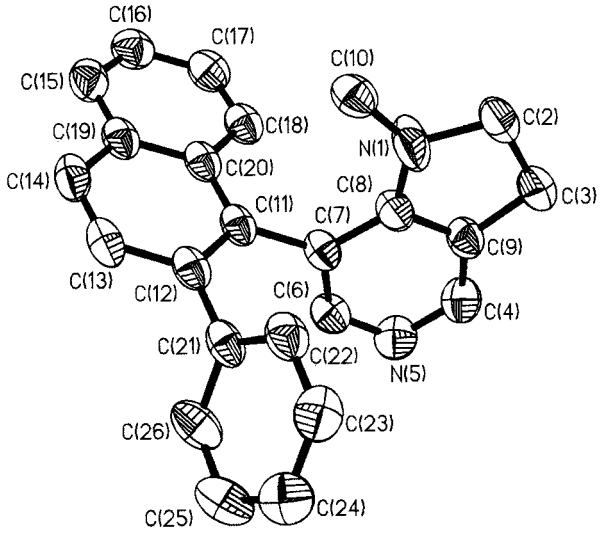
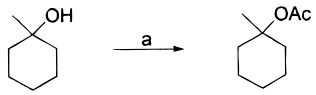


Figure 5. An ORTEP plot of the molecular structure of biaryl **56**. H atoms and a molecule of water are omitted for clarity. Torsion angle C20−C11−C7−C8 = 78.7°, torsion angle C11−C12−C21−C6 = 74.1°. The bond lengths of the biaryl axes: C11−C7 = 1.50 Å and C12−C21 = 1.49 Å.

Table 1. Acylation of Alcohol 57[a]



57 **58**

		57:**58** ratios[b]	
entry	catalyst	after 10 h	after 24 h
1	no catalyst	99:1	98:2
2	DMAP	13:87	5:95
3	**16**	21:79	10:90
4	**18**	96:4	90:10
5	**31**	36:64	18:82
6	**38**	63:37	45:55
7	**55**	22:78	13:87
8	**56**	30:70	14:86

[a] Key: (a) Ac_2O (2.1 equiv), Et_3N (1.5 equiv), catalyst (4 mol %); rt. [b] Established by GC on a DB1701 ISM capillary column (70 °C).

Table 2. Racemization Kinetics of Biaryls 55, 56, and 59 in Benzene[a]

	55	**56**	**59**
T/K	$10^7 k_{racem}/s^{-1}$	$10^6 k_{racem}/s^{-1}$	$10^7 k_{racem}/s^{-1}$
373	−	1.14 (0.01)	−
383	−	3.35 (0.06)	−
393	8.93 (0.22)	7.32 (0.18)	7.6 (0.3)
403	−	16.2 (0.3)	18.0 (1.2)
413	45.4 (2.0)	39.5 (0.4)	45.0 (0.6)
423	−	83.7 (2.8)	114 (7)
433	185 (3)	153 (28)	235 (27)
443	−	−	551 (11)
453	682 (16)	−	−

[a] Separation of enantiomers and monitoring of racemization were performed on chiral HPLC [Chiralcel OD column, 4.6 mm × 25 cm; hexanes/2-propanol, 96/4; 1 mL min^{-1}; 0 °C (for **55**) or hexanes/EtOAc/Et_2NH, 75/24/1; 1 mL min^{-1}; 25 °C (for **56** and **59**)].

55 and **56** were separated into enantiomers using analytical chiral HPLC and the atropisomerization of the individual enantiomers studied in benzene over a wide temperature range (sealed-tube experiments, Table 2). Kinetic parameters for the racemization (Table 3) were obtained from Arrhenius and Eyring plots.[40] Extrapolation of the Eyring plots (Figure 6) indicated that an enantiomerically homogeneous sample of biaryl **55** would lose less than 1% of its optical purity over 1 year in solution at room temperature (298 K). Although, biaryl **56** ($t_{1/2(racem)}$ = ∼125 years at 298 K) is configurationally less stable than the methyl analogue **55**, its racemization at room temperature is slow enough for its practical use.

Table 3. Arrhenius Parameters and Transition-State Functions for Racemization of Biaryls 55, 56, and 59 in Benzene

	55	**56**	**59**
E_a/kJ mol^{-1}	107 (3)	110 (5)	124 (5)
$\ln(A/s^{-1})$	18.8 (1.0)	21.7 (1.4)	23.9 (1.3)
$\Delta H^{\ddagger}$/kJ mol^{-1}	103 (4)	106 (5)	121 (5)
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	−100 (8)	−75 (12)	−57 (11)

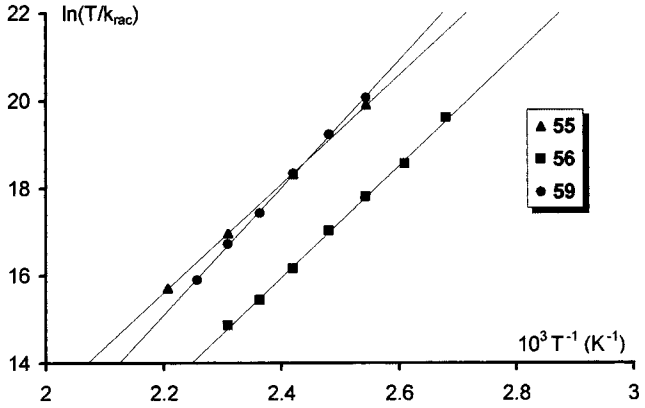
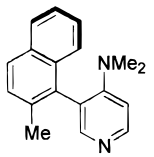


Figure 6. Eyring plots for the racemization of biaryls **55**, **56**, and **59** in benzene.

Since barriers to internal rotation in biaryls **31** and **38** had been demonstrated to be similar, it was expected that the levels of steric hindrance in biaryl **59**[41] would



59

be at least comparable to these observed for biaryl **55**. Indeed, racemization studies for the individual enantiomers of biaryl **59** (Tables 2 and 3 and Figure 6) showed that its configurational stability is far superior (at ambient temperature) to either biaryl **55** or **56**. Extrapolation of the corresponding Eyring plot indicates that the half-life for racemization for biaryl **59** at 298 K exceeds 5000 years. Interestingly, the racemization of biaryl **55** is slower than the racemization of biaryl **59** at temperatures exceeding ∼410 K. This is due to the larger absolute value of $\Delta S^{\ddagger}$ for biaryl **55** relative to biaryl **59**, which is indicative of a more highly ordered transition state for rotation (relative to the ground state) for the former.

Optical resolution of racemic biaryls **55** and **56** was performed using semipreparative chiral HPLC. The

(40) (a) Cagle, F. W., Jr.; Eyring, H. *J. Am. Chem. Soc.* **1951**, *73*, 5628−5630. (b) Cooke, A. S.; Harris, M. M. *J. Chem. Soc. C* **1967**, 988−992.

(41) Prepared by an analogous route to that described for the preparation of biaryl **55** via low-yielding (13%) Suzuki cross-coupling of aryl bromide **36** with arylboronic acid **51**. Various attempts to accomplish a similar coupling with aryl bromide **41** failed.

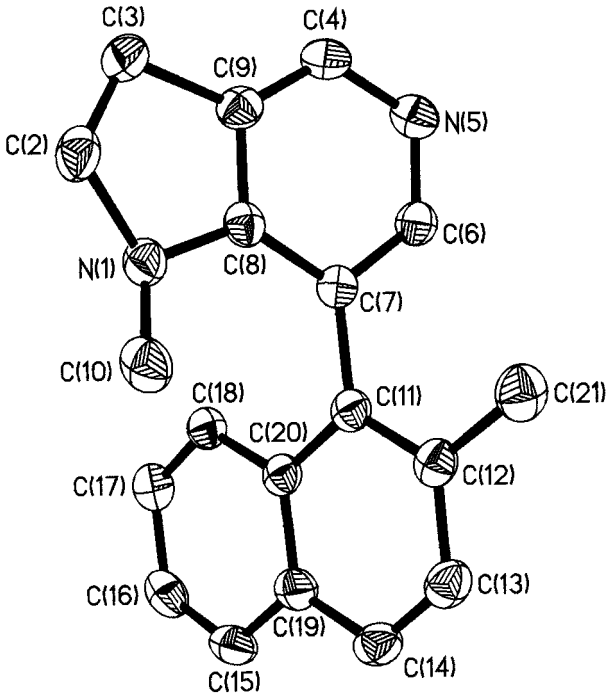


Figure 7. An ORTEP plot of the molecular structure of biaryl (+)-**55**. H atoms are omitted for clarity. Torsion angle C20−C11−C7−C8 = 71.9°. The bond length of the biaryl axis: C11−C7 = 1.49 Å.

structure of biaryl **55** was confirmed by single-crystal X-ray analysis of the dextrorotatory enantiomer (+)-**55** {$[\alpha]^{25}_D$ +107 (*c* 0.43 in $CHCl_3$)} (Figure 7).

Conclusions

In summary, a concise synthetic approach toward axially chiral biaryls incorporating a structural motif of 4-(dimethylamino)pyridine has been developed. This novel family of chiral DMAP's have been shown to retain the high catalytic activity of the parent compound toward acylation of a hindered alcohol. Biaryls **55**, **56**, and **59**, for which internal rotation about the chiral axis has been shown to be sufficiently slow at ambient temperature to allow for their chiral separation and easy handling without racemization, are of potential use as chiral catalysts for resolution of secondary alcohols and for other asymmetric transformations. Studies in this area are ongoing, and results will be reported shortly.

Experimental Section

General Methods. All reactions were performed under anhydrous conditions and an inert atmosphere of argon in the flame-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to known procedures.[42] Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230−400 mesh) silica gel. Only distilled solvents were used as eluents. Thin-layer chromatography (TLC) was performed on Merck DC−Alufolien or glass plates precoated with silica gel 60 F_{254} which were visualized either by quenching of ultraviolet fluorescence (λ_{max} = 254 nm) or by charring with 5% w/v phosphomolybdic acid in 95% EtOH, 10% w/v ammonium molybdate in 1 M H_2SO_4, or 10% $KMnO_4$ in 1 M H_2SO_4. Observed retention factors (R_f) are quoted to the nearest 0.05. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over calcium. Anhydrous THF and Et_2O were obtained by distillation, immediately before use, from sodium/benzophenone ketyl under an inert atmosphere of nitrogen. Anhydrous DMF was obtained by distillation from calcium hydride under reduced pressure. Petroleum ether refers to the fraction of light petroleum boiling between 40 and 60 °C. High-resolution mass spectrometry (HRMS) measurements are valid to ±5 ppm (±10 ppm for biaryl **54**).

(*tert*-Butoxy)-*N*-(4-pyridyl)carboxamide (7). A solution of Boc_2O (43.6 g, 0.20 mol) in CH_2Cl_2 (100 mL, not anhydrous) was added over 20 min to a stirred suspension of 4-aminopyridine **6** (18.8 g, 0.20 mol) in CH_2Cl_2 (200 mL). The resulting pale yellow solution was stirred at room temperature for 25 min (TLC) and acidified with 1 M HCl (230 mL, 0.23 mol). The phases were separated, and the aqueous layer was washed with CH_2Cl_2. The aqueous layer was mixed with a fresh portion of CH_2Cl_2 (200 mL) and treated during vigorous stirring with solid K_2CO_3 (21.1 g, 0.16 mol). The phases were separated, and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the title compound **7** as a white solid (38.6 g, >99%) which was used in the next step without further purification. For analytical purposes, a small amount of the product was recrystallized from EtOAc/petroleum ether: R_f = 0.30 (EtOAc); mp 151.0−151.5 °C (EtOAc/petroleum ether) (lit.[17c] 144−145 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (s, 9H), 7.37 (d, J = 5.5 Hz, 2H), 8.38 (d, J = 5.5 Hz, 2H), and 8.52 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.22, 81.28, 112.5, 146.6, 150.0, and 152.5; IR ($CHCl_3$) ν_{max} 1724, 1598, 1507, and 1260 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 194 (25%, M^+), 138 (5), 121 (10), 94 (15), and 57 (100). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.94; H, 7.27; N, 14.20.

The General Method for the Lithiation of Carbamate (7). (*tert*-Butoxy)-*N*-[3-(2-hydroxyethyl)(4-pyridyl)]carboxamide (10). The first method: To a solution of carbamate **7** (38.8 g, 200 mmol) in THF (500 mL) at −78 °C was added *t*-BuLi (282 mL, 1.7 M, 480 mmol) in pentane over 70 min. The resulting bright yellow suspension was stirred at −78 °C for 20 min and at −15 °C for 2 h. After recooling to −78 °C, the pale yellow suspension was treated via cannula with ethylene oxide (15 mL, 300 mmol) at −78 °C. The reaction mixture was allowed to warm to room temperature over 2 h and quenched after cooling to −78 °C with water (80 mL). The solvents were evaporated in vacuo, and the residue was partitioned between water (250 mL) and CH_2Cl_2 (350 mL). The phases were separated, and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give a pale yellow solid. The crude product was dissolved in a small amount of CH_2Cl_2 and passed through a short plug of flash silica eluting with EtOAc. Fractions containing the product were concentrated, and the title compound **10** as a white crystalline precipitate was removed by filtration (32.1 g, 67%). The mother liquor was concentrated and purified by flash chromatography (EtOAc) to afford an additional amount of the product **10** (3.5 g, 7%; total yield: 75%) along with the starting material **7** (2.5 g, 7%).

The second method: To a solution of 2-bromoethanol (3.2 mL, 45 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (21.6 mL, 2.5 M, 54 mmol) in hexanes. After 10 min, the mixture was transferred via cannula to a flask containing the lithiated species **8** prepared from carbamate **7** (5.82 g, 30.0 mmol) according to the general procedure. The reaction and purification were carried out as in the first method to afford the title compound **10** (4.73 g, 66%) and the starting material **7** (999 mg, 17%). Alcohol **10**: R_f = 0.15 (EtOAc); mp 138.5−139.0 °C (EtOAc/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.73 (t, J = 5.0 Hz, 2H), 3.88 (t, J = 5.0 Hz, 2H), 4.82 (br s, 1H), 7.89 (d, J = 6.0 Hz, 1H), 8.03 (s, 1H), 8.16 (d, J = 6.0 Hz, 1H), and 8.96 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.25, 32.88, 63.34, 80.92, 114.0, 125.1, 146.2, 148.1, 150.5,

(42) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

and 152.8; IR ($CHCl_3$) ν_{max} 1730, 1583, and 1509 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 238 (15%, M^+), 182 (10), 152 (15), 107 (15), and 57 (100). Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.41; H, 7.57; N, 11.59.

(*tert*-Butoxy)-*N*-(3-bromo(4-pyridyl))carboxamide (9). The lithiated species **8** prepared from carbamate **7** (469 mg, 2.00 mmol) according to the general procedure was reacted with 1,2-dibromoethane (250 mL, 2.90 mmol). The reaction was carried out as described for the preparation of alcohol **10**, and purification by flash chromatography (EtOAc) furnished the title product **9** (559 mg, 85%) as a white solid, along with the starting material **7** (40 mg, 9%): Aryl bromide **9**: $R_f = 0.60$ (CH_2Cl_2/EtOAc, 3/1); ^1H NMR (250 MHz, $CDCl_3$) δ 1.47 (s, 9H), 7.17 (s, 1H), 8.07 (d, $J = 5.5$ Hz, 1H), 8.29 (d, $J = 5.5$ Hz, 1H), and 8.50 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.15, 82.41, 109.6, 113.1, 143.2, 149.4, 151.4, and 151.5; IR ($CHCl_3$) ν_{max} 1739, 1583, 1569, 1505, 1450, and 1407 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 272 (10%, M^+), 172 (10), and 57 (100); HRMS calcd for $C_{10}H_{13}BrN_2O_2$ (M^+) 272.0160, found 272.0167.

(*tert*-Butoxy)-*N*-[3-(2-hydroxypropyl)(4-pyridyl)]carboxamide (11). The lithiated species **8** prepared from carbamate **7** (9.70 g, 50.0 mmol) according to the general procedure was reacted with propylene oxide (3.8 mL, 55 mmol). The reaction was carried out as described for the preparation of alcohol **10**, and purification by flash chromatography (EtOAc) furnished the title product **11** (10.2 g, 81%) as a white crystalline solid: $R_f = 0.25$ (EtOAc); mp 128.5−129.5 °C (EtOAc/petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 1.21 (d, $J = 6.0$ Hz, 3H), 1.46 (s, 9H), 2.64 (dd, $J = 7.0$, 14.5 Hz, 1H), 2.75 (dd, $J = 2.5$, 14.5 Hz, 1H), 4.12 (ddq, $J = 2.5$, 6.0, 7.0 Hz, 1H), 5.24 (br s, 1H), 7.90 (d, $J = 5.5$ Hz, 1H), 8.02 (s, 1H), 8.17 (d, $J = 5.5$ Hz, 1H), and 9.28 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.54, 28.28, 38.62, 69.01, 80.83, 114.2, 123.5, 146.2, 148.2, 151.2, and 152.8; IR ($CHCl_3$) ν_{max} 1728, 1583, 1512, 1249, and 1157 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 252 (15%, M^+), 208 (10), 152 (55), 108 (35), and 57 (100). Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.86; H, 8.01; N, 10.98.

***tert*-Butyl 2-Pyrrolino[3,2-*c*]pyridinecarboxylate (14).** To a stirred solution of alcohol **10** (35.6 g, 150 mmol) and triethylamine (46.0 mL, 330 mmol) in CH_2Cl_2 (400 mL) was added methanesulfonyl chloride (12.8 mL, 165 mmol) over 80 min, while the temperature was maintained between −10 and −5 °C. After 1 h at room temperature, the reaction mixture was washed sequentially with satd $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a brown oil which was purified by flash chromatography (EtOAc) to afford the title compound **14** (32.8 g, ∼100%) as a white solid: $R_f = 0.15$ (EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.96 (t, $J = 9.0$ Hz, 2H), 3.84 (t, $J = 9.0$ Hz, 2H), 7.47 (br s, 1H), 8.13 (s, 1H), and 8.17 (d, $J = 5.5$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.80, 28.19, 47.63, 81.71, 109.3, 126.8, 145.5, 149.1, and 152.0 (one C not detected); IR ($CHCl_3$) ν_{max} 1703, 1600, 1494, 1389, and 1160 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 220 (35%, M^+), 164 (55), 120 (30), and 57 (100); HRMS calcd for $C_{12}H_{16}N_2O_2$ (M^+) 220.1212, found 220.1204.

***tert*-Butyl 2-Methyl-2-pyrrolino[3,2-*c*]pyridinecarboxylate (15).** To a solution of alcohol **11** (10.2 g, 40.4 mmol) and triethylamine (7.3 mL, 53 mmol) in CH_2Cl_2 (150 mL) was added methanesulfonyl chloride (3.4 mL, 44 mmol) over 80 min at −20 °C. The reaction mixture was warmed to room temperature, washed with satd $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo to give crude mesylate **13** (13.4 g, ∼100%) as a white solid.

2-{4-[(*tert*-Butoxy)carbonylamino](3-pyridyl)}isopropyl methylsulfonate (13): ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (d, $J = 6.0$ Hz, 3H), 1.51 (s, 9H), 2.86 (s, 3H), 2.89 (dd, $J = 6.5$, 15.0 Hz, 1H), 3.04 (dd, $J = 6.0$, 15.0 Hz, 1H), 4.86 (ddq, $J = 6.0$, 6.0, 6.5 Hz, 1H), 7.23 (br s, 1H), 8.02 (d, $J = 5.5$ Hz, 1H), 8.24 (s, 1H), and 8.37 (d, $J = 5.5$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.62, 28.16, 36.27, 38.18, 78.51, 81.07, 113.6, 119.1, 144.6, 149.8, 151.9, and 152.2.

To a solution of mesylate **13** (13.4 g, 40.4 mmol) in THF (150 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (44.4 mL, 1.0 M, 44.4 mmol) in THF. After 1 h, the reaction mixture was allowed to warm to room temperature and was then refluxed overnight. After cooling to 0 °C, the mixture was quenched with water (50 mL) and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a yellow oil which was purified by flash chromatography (EtOAc) to afford the title compound **15** (9.00 g, 95%) as a pale yellow solid: $R_f = 0.30$ (EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (d, $J = 6.5$ Hz, 3H), 1.38 (s, 9H), 2.47 (dd, $J = 2.5$, 16.0 Hz, 1H), 3.15 (dd, $J = 10.0$, 16.0 Hz, 1H), 4.33 (ddq, $J = 2.5$, 6.5, 10.0 Hz, 1H), 7.33 (br s, 1H), 8.10 (s, 1H), and 8.14 (d, $J = 5.5$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.00, 28.16, 33.26, 55.72, 81.59, 109.8, 125.6, 145.8, 148.6, 149.1, and 151.6; IR ($CHCl_3$) ν_{max} 1702, 1522, 1485, 1428, 1385, and 1226 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 234 (25%, M^+), 178 (45), 119 (35), and 57 (100); HRMS calcd for $C_{13}H_{18}N_2O_2$ (M^+) 234.1368, found 234.1369.

1-Methyl-2-pyrrolino[3,2-*c*]pyridine (16). The first method: To a solution of carbamate **14** (32.8 g, 149 mmol) in CH_2Cl_2 (400 mL) at 0 °C was added diisobutylaluminum hydride (100 g, 700 mmol) in CH_2Cl_2 (400 mL) over 1 h. The resulting yellow solution was refluxed for 20 h, recooled to 0 °C, and treated sequentially with solid NaF (118 g, 2.81 mol) in portions over 30 min and water (39 mL, 2.2 mol) over 90 min. The resulting thick suspension was warmed to room temperature over 3 h, filtered through a thin pad of Celite, and evaporated in vacuo to give a brown oil, which was found to be a ∼10:1 mixture of amine **16** and its *N*-demethylated analogue by ^1H NMR. The oil was dissolved in CH_2Cl_2 (200 mL) and treated with Boc_2O (6.0 g, 28 mmol). After 3 h at room temperature, the mixture was concentrated in vacuo and purified by flash chromatography (EtOAc → EtOAc/Et_3N, 95/5) to give the starting material **14** (1.75 g, 5%) and the title compound **16** (11.0 g, 55%) as a white solid.

The second method: A suspension of aminol **20** (76 mg, 0.50 mmol) and NaH (12 mg, 0.50 mmol) in DMF (2 mL) was heated at 80 °C until a clear solution resulted (∼40 min). After cooling to 0 °C, the mixture was treated with (*N*-methylphenylamino)triphenylphosphonium iodide (248 mg, 0.50 mmol) and heated at 80 °C for 2 h. The mixture was cooled to room temperature and partitioned between water (5 mL) and CH_2Cl_2 (5 mL). The phases were separated, and extraction was completed with additional portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc → EtOAc/Et_3N, 95/5) to give the title compound **16** (42 mg, 63%) as a white solid: $R_f = 0.15$ (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.74 (s, 3H), 2.94 (t, $J = 8.5$ Hz, 2H), 3.40 (t, $J = 8.5$ Hz, 2H), 6.21 (d, $J = 5.5$ Hz, 1H), 7.99 (s, 1H), and 8.07 (d, $J = 5.5$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 26.03, 33.64, 54.53, 101.3, 125.4, 143.6, 149.1, and 158.4; IR ($CHCl_3$) ν_{max} 2958, 1605, 1510, and 1305 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 134 (75%, M^+), 133 (100), and 118 (20); HRMS calcd for $C_8H_{10}N_2$ (M^+) 134.0844, found 134.0841.

1,2-Dimethyl-2-pyrrolino[3,2-*c*]pyridine (17). To a solution of carbamate **15** (8.89 g, 38.0 mmol) in THF (150 mL) at 0 °C was added lithium aluminum hydride (5.78 g, 152 mmol) over 30 min, and the reaction mixture was refluxed for 4 h. After recooling to 0 °C, the mixture was quenched sequentially with water (5.8 mL), 15% NaOH (5.8 mL), and water (17.4 mL) to give a thick suspension which was filtered through Celite. The filtrate was evaporated in vacuo to give a white solid, which was found to be a ∼1:1 mixture of amine **17** and its *N*-demethylated analogue by ^1H NMR. The solid was dissolved in THF (100 mL) and treated with Boc_2O (5.0 g, 23 mmol). After 24 h at room temperature, the solvent was evaporated in vacuo and the residue purified by flash chromatography (EtOAc → EtOAc/Et_3N, 95/5) to give the starting material **15** (3.48 g, 39%) and the title compound **17** (2.14 g, 38%) as a pale yellow solid. Amine **17**: $R_f = 0.15$ (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, $J = 6.0$ Hz, 3H), 2.52 (dd, $J = 8.5$, 15.5 Hz, 1H), 2.68 (s, 3H), 3.08 (dd, $J = 9.0$, 15.5 Hz, 1H), 3.59 (ddq, $J = 6.0$, 8.5, 9.0 Hz, 1H), 6.15 (d, $J = 5.5$ Hz, 1H), 7.93 (s, 1H), and 8.04 (d, $J = 5.5$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.01, 31.19, 43.43, 61.46, 101.2,

124.4, 142.5, 148.6, and 158.3; IR ($CHCl_3$) ν_{max} 2971, 1606, 1504, and 1296 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 148 (55%, M^+), 133 (100), and 118 (20); HRMS calcd for $C_9H_{12}N_2$ (M^+) 148.1000, found 148.1000.

7-Bromo-1-methyl-2-pyrrolino[3,2-*c*]pyridine (18). To a solution of amine **16** (7.73 g, 57.7 mmol) in DMF (100 mL) at 0 °C was added a solution of *N*-bromosuccinimide (11.3 g, 63.5 mmol) in DMF (100 mL). After 90 min (TLC) the solvent was evaporated in vacuo, and the residue partitioned between water (100 mL) and CH_2Cl_2 (100 mL). The phases were separated, and the extraction completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc) to give the title compound **18** (9.97 g, 81%) as a white solid: $R_f = 0.15$ (EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 2.92 (t, $J = 9.0$ Hz, 2H), 3.16 (s, 3H), 3.46 (t, $J = 9.0$ Hz, 2H), 7.85 (s, 1H), and 8.09 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.31, 35.97, 55.91, 97.98, 127.9, 142.3, 152.1, and 153.8; IR ($CHCl_3$) ν_{max} 2960, 1602, 1496, 1416, and 1314 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 214/212 (100%, M^+), 132 (70), 118 (20), 105 (20), and 63 (30); HRMS calcd for $C_8H_9BrN_2$ (M^+) 211.9949, found 211.9943.

7-Bromo-1,2-dimethyl-2-pyrrolino[3,2-*c*]pyridine (19). As described for the preparation of aryl bromide **18**, amine **17** (2.10 g, 14.1 mmol) was reacted with *N*-bromosuccinimide (2.65 g, 14.9 mmol) to give, after purification by flash chromatography (EtOAc), the title compound **19** (1.99 g, 62%) as a pale yellow solid: $R_f = 0.20-0.45$ (EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (d, $J = 6.0$ Hz, 3H), 2.36 (dd, $J = 8.0$, 16.0 Hz, 1H), 2.98 (s, 3H), 2.98 (dd, $J = 10.0$, 16.0 Hz, 1H), 3.48 (ddq, $J = 6.0$, 8.0, 10.0 Hz, 1H), 7.69 (s, 1H), and 7.96 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.27, 33.75, 33.81, 62.41, 97.94, 126.7, 142.1, 152.2, and 153.5; IR ($CHCl_3$) ν_{max} 2972, 1601, 1488, 1415, and 1305 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 228/226 (70%, M^+), 211/213 (100), and 132 (80); HRMS calcd for $C_9H_{11}BrN_2$ (M^+) 226.0106, found 226.0101.

2-[4-(Methylamino)-3-pyridyl]ethan-1-ol (20). To a solution of carbamate **10** (2.38 g, 10.0 mmol) in THF (50 mL) at 0 °C was added lithium aluminum hydride (1.98 g, 52.0 mmol) over 20 min, and the resulting mixture was refluxed for 4 h. After recooling to 0 °C, the reaction mixture was quenched sequentially with water (2.0 mL), 15% NaOH (2 mL), and water (6.0 mL). The resulting thick suspension was diluted with EtOH (30 mL) and filtered through a thin pad of Celite. Evaporation in vacuo gave a crude product, which was purified by flash chromatography ($EtOH/H_2O/NH_4OH$, 95/3/2) to give the title compound **20** (1.50 g, 99%) as a white solid: $R_f = 0.50$ ($EtOH/Et_3N$, 10/1); mp 155.0−156.0 °C (MeOH/EtOAc); ^1H NMR (250 MHz, d_4-MeOH) δ 2.73 (t, $J = 6.5$ Hz, 2H), 2.89 (s, 3H), 3.76 (t, $J = 6.5$ Hz, 2H), 6.55 (d, $J = 6.0$ Hz, 1H), 7.91 (s, 1H), and 8.03 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (63 MHz, d_4-MeOH) δ 29.52, 32.86, 61.75, 105.3, 120.0, 148.7, 149.1, and 155.2; IR ($CHCl_3$) ν_{max} 2976 and 1600 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 152 (45%, M^+), 121 (100), 92 (15), and 65 (15); HRMS calcd for $C_8H_{12}N_2O$ (M^+) 152.0950, found 152.0946. Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.04; H, 7.92; N, 18.23.

The General Procedure for the Suzuki Cross-Coupling Involving Sterically Unhindered Arylboronic Acids. 1-Methyl-7-naphthyl-2-pyrrolino[3,2-*c*]pyridine (31). To a solution of aryl bromide **18** (213 mg, 1.00 mmol) in toluene (2 mL) and ethanol (0.5 mL) was added 2 M Na_2CO_3 (2 mL) followed by $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) and 1-naphthaleneboronic acid (206 mg, 1.2 mmol). The mixture was refluxed for 6 h (TLC), cooled to room temperature, and partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The phases were separated, and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc → $EtOAc/Et_3N$, 98/2) to give the title compound **31** (249 mg, 96%) as a white crystalline solid: $R_f = 0.30$ ($EtOAc/Et_3N$, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.08 (t, $J = 8.5$ Hz, 2H), 3.31−3.54 (m, 2H), 7.41−7.63 (m, 5H), 7.85−7.90 (m, 2H), 8.01 (s, 1H), and 8.13 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.79, 35.77, 55.77, 116.1, 125.2, 125.7, 126.0, 126.3, 126.4, 128.1 (2C?), 128.3, 133.1, 133.2, 135.0, 143.2, 151.3, and 155.9; IR ($CHCl_3$) ν_{max} 2956, 1597, 1497, and 1413 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 260 (100%, M^+); HRMS calcd for $C_{18}H_{16}N_2$ (M^+) 260.1313, found 260.1303.

1,2-Dimethyl-7-phenyl-2-pyrrolino[3,2-*c*]pyridine (21). Following the general procedure, aryl bromide **19** (114 mg, 0.50 mmol) was reacted with phenylboronic acid (73 mg, 0.60 mmol) to give, after purification by flash chromatography (EtOAc → $EtOAc/Et_3N$, 98/2), the title compound **21** (110 mg, 98%) as a pale yellow oil: $R_f = 0.35$ ($EtOAc/Et_3N$, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (d, $J = 6.0$ Hz, 3H), 2.36 (s, 3H), 2.59 (dd, $J = 9.0$, 16.0 Hz, 1H), 3.19 (dd, $J = 9.0$, 16.0 Hz, 1H), 3.54 (ddq, $J = 6.0$, 9.0, 9.0 Hz, 1H), 7.34 (s, 5H), 7.98 (s, 1H), and 7.99 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.58, 34.19, 35.48, 62.91, 118.4, 124.9, 127.1, 128.0, 129.6, 137.5, 142.6, 150.8, and 155.3; IR ($CHCl_3$) ν_{max} 2971, 1598, 1482, and 1412 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 224 (70%, M^+) and 209 (100); HRMS calcd for $C_{15}H_{16}N_2$ (M^+) 224.1313, found 224.1317.

1-(1,2-Dimethyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))-2-methoxybenzene (22). Following the general procedure, aryl bromide **19** (227 mg, 1.00 mmol) was reacted with 2-methoxybenzeneboronic acid (182 mg, 1.20 mmol) to give, after purification by flash chromatography (EtOAc → $EtOAc/Et_3N$, 98/2), the title compound **22** (222 mg, 87%) as a white solid: $R_f = 0.35$ ($EtOAc/Et_3N$, 99/5); mp 154.0−155.0 °C (EtOAc/petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (d, $J = 5.5$ Hz, 3H), 2.35 (s, 3H), 2.60 (dd, $J = 8.0$, 15.5 Hz, 1H), 3.20 (dd, $J = 9.0$, 15.5 Hz, 1H), 3.64 (ddq, $J = 5.5$, 8.0, 9.0 Hz, 1H), 3.76 (s, 3H), 6.90 (d, $J = 8.0$ Hz, 1H), 6.97 (t, $J = 7.5$ Hz, 1H), 7.22 (br s, 1H), 7.31 (ddt, $J = 1.5$, 7.5, 8.0 Hz, 1H), 7.91 (s, 1H), and 7.97 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.44, 33.10, 34.08, 55.31, 62.11, 110.3, 114.1, 120.3, 124.2, 126.6, 129.0, 131.7, 142.6, 151.2, 155.2, and 157.5; IR ($CHCl_3$) ν_{max} 2968, 1599, 1494, 1412, and 1206 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 254 (100%, M^+), 239 (100), 223 (15), and 207 (25); HRMS calcd for $C_{16}H_{18}N_2O$ (M^+) 254.1419, found 254.1423. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.45; H, 7.11; N, 10.86.

1-(1,2-Dimethyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))-3-methoxybenzene (23). Following the general procedure, aryl bromide **19** (241 mg, 1.06 mmol) was reacted with 3-methoxybenzeneboronic acid (193 mg, 1.27 mmol) to give, after purification by flash chromatography (EtOAc → $EtOAc/Et_3N$, 98/2), the title compound **23** (242 mg, 90%) as a clear oil: $R_f = 0.35$ ($EtOAc/Et_3N$, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (d, $J = 6.5$ Hz, 3H), 2.40 (s, 3H), 2.59 (dd, $J = 9.0$, 16.0 Hz, 1H), 3.20 (dd, $J = 9.0$, 16.0 Hz, 1H), 3.55 (ddq, $J = 6.5$, 9.0, 9.0 Hz, 1H), 3.80 (s, 3H), 6.83−6.93 (m, 3H), 7.27 (ddd, $J = 1.0$, 7.5, 7.5 Hz, 1H), and 7.99 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.68, 34.31, 35.47, 55.36, 63.01, 112.7, 115.4, 118.3, 122.4, 125.0, 129.1, 139.0, 142.8, 150.9, 155.3, and 159.4; IR ($CHCl_3$) ν_{max} 2969, 1598, 1486, and 1410 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 254 (60%, M^+), 239 (100), and 195 (35); HRMS calcd for $C_{16}H_{18}N_2O$ (M^+) 254.1419, found 254.1430.

1,2-Dimethyl-7-naphthyl-2-pyrrolino[3,2-*c*]pyridine (24). Following the general procedure, aryl bromide **19** (227 mg, 1.00 mmol) was reacted with 1-naphthaleneboronic acid (206 mg, 1.20 mmol) to give, after purification by flash chromatography (EtOAc → $EtOAc/Et_3N$, 98/2), the title compound **24** (225 mg, 82%) as a white solid: $R_f = 0.30$ ($EtOAc/Et_3N$, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 1.21−1.25 (m, 3H), 1.99 [s, 3H (major atropisomer)], 2.06 [s, 3H (minor atropisomer)], 2.61−2.73 (m, 1H), 3.26 (dd, $J = 9.0$, 16.0 Hz, 1H), 3.50−3.69 (m, 1H), and 7.38−8.10 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.14, 19.61, 33.25, 33.52, 34.21, 62.02, 62.35, 115.5, 116.0, 124.2, 124.7, 125.1, 125.3, 126.0, 126.2, 126.3, 126.5, 128.0, 128.1, 128.2, 128.3, 132.8, 133.1, 133.4, 133.5, 135.0, 143.0, 143.1, 151.4, 151.5, 155.6, and 155.7; IR ($CHCl_3$) ν_{max} 2970, 1597, 1485, and 1412 cm^{-1}; MS (EI^+) *m/z* (rel intensity) 274 (35%, M^+) and 259 (100); HRMS calcd for $C_{19}H_{18}N_2$ (M^+) 274.1470, found 274.1484.

1-Methyl-7-phenyl-2-pyrrolino[3,2-*c*]pyridine (25). Following the general procedure, aryl bromide **18** (213 mg, 1.00 mmol) was reacted with phenylboronic acid (146 mg, 1.20 mmol) to give, after purification by flash chromatography

(EtOAc → EtOAc/Et_3N, 98/2), the title compound **25** (197 mg, 94%) as a pale yellow oil: R_f = 0.30 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.00 (t, J = 8.5 Hz, 2H), 3.43 (t, J = 8.5 Hz, 2H), 7.28−7.40 (m, 5H), 7.98 (s, 1H), and 8.03 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.72, 37.42, 56.12, 118.7, 126.0, 127.2, 128.1, 129.6, 137.3, 142.8, 150.7, and 155.4; IR ($CHCl_3$) ν_{max} 2957, 1597, 1495, and 1412 cm^{-1}; MS (EI^+) m/z (rel intensity) 210 (90%, M^+) and 209 (100); HRMS calcd for $C_{14}H_{14}N_2$ (M^+) 210.1157, found 210.1155.

2-Methoxy-1-(1-methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))benzene (26). Following the general procedure, aryl bromide **18** (213 mg, 1.00 mmol) was reacted with 2-methoxybenzeneboronic acid (182 mg, 1.20 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **26** (230 mg, 96%) as a white solid: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.99 (t, J = 8.5 Hz, 2H), 3.43 (br s, 2H), 3.75 (s, 3H), 6.90 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.19 (dd, J = 1.5, 7.5 Hz, 1H), 7.29 (dt, J = 1.5, 8.0 Hz, 1H), 7.90 (s, 1H), and 8.00 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.64, 35.44, 55.46, 55.77, 110.4, 114.4, 120.3, 125.5, 126.4, 129.1, 131.8, 142.8, 151.1, 155.5, and 157.6; IR ($CHCl_3$) ν_{max} 3028, 1598, 1494, and 1413 cm^{-1}; MS (EI^+) m/z (rel intensity) 240 (100%, M^+), 224 (15), and 209 (20); HRMS calcd for $C_{15}H_{16}N_2O$ (M^+) 240.1263, found 240.1258.

1-Methyl-7-(2-methylphenyl)-2-pyrrolino[3,2-*c*]pyridine (27). Following the general procedure, aryl bromide **18** (213 mg, 1.00 mmol) was reacted with 2-methylbenzeneboronic acid (163 mg, 1.2 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **27** (219 mg, 98%) as a white solid: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.23 (s, 3H), 2.97 (t, J = 8.5 Hz, 2H), 3.22−3.51 (m, 2H), 7.10−7.21 (m, 4H), 7.86 (s, 1H), and 8.01 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.07, 25.72, 35.78, 55.84, 117.8, 125.5, 127.8, 129.5, 130.6, 136.8, 137.6 (2C?), 142.9, 150.5, and 155.1; IR ($CHCl_3$) ν_{max} 2955, 1597, 1494, 1467, 1413, and 1318 cm^{-1}; MS (EI^+) m/z (rel intensity) 224 (100%, M^+); HRMS calcd for $C_{15}H_{16}N_2$ (M^+) 224.1313, found 224.1308.

7-(2-Ethylphenyl)-1-methyl-2-pyrrolino[3,2-*c*]pyridine (28). Following the general procedure, aryl bromide **18** (213 mg, 1.00 mmol) was reacted with 2-ethylbenzeneboronic acid[43] (180 mg, 1.20 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **28** (227 mg, 95%) as a white solid: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (t, J = 7.5 Hz, 3H), 2.24 (s, 3H), 2.37−2.53 (m, 2H), 2.98 (t, J = 8.5 Hz, 2H), 3.25−3.51 (m, 2H), 7.15−7.30 (m, 4H), 7.88 (s, 1H), and 8.02 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.72, 25.69, 26.31, 35.91, 55.76, 117.4, 125.4, 125.5, 127.8, 128.0, 130.9, 136.1, 142.9, 143.5, 150.7, and 155.1; IR ($CHCl_3$) ν_{max} 2968, 1597, 1496, 1466, 1412, and 1207 cm^{-1}; MS (EI^+) m/z (rel intensity) 238 (100%, M^+), 224 (40), 207 (30), and 194 (30); HRMS calcd for $C_{16}H_{18}N_2$ (M^+) 238.1470, found 238.1480.

3-Methoxy-1-(1-methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))benzene (29). Following the general procedure, aryl bromide **18** (213 mg, 1.00 mmol) was reacted with 3-methoxybenzeneboronic acid (182 mg, 1.20 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **29** (221 mg, 92%) as a clear oil: R_f = 0.30 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.01 (t, J = 8.5 Hz, 2H), 3.44 (t, J = 8.5 Hz, 2H), 3.81 (s, 3H), 6.84−6.93 (m, 3H), 7.26−7.32 (m, 1H), 7.99 (s, 1H), and 8.03 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.41, 37.01, 55.24, 56.02, 113.1, 115.2, 122.1, 129.2, 137.9, 140.6, 148.8, 155.8, and 159.3; IR ($CHCl_3$) ν_{max} 2959, 1597, 1488, 1466, 1410, and 1286 cm^{-1}; MS (EI^+) m/z (rel intensity) 240 (100%, M^+) and 195 (25); HRMS calcd for $C_{15}H_{16}N_2O$ (M^+) 240.1263, found 240.1258.

3-Methoxy-1-(1-methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))naphthalene (33). Following the general procedure, aryl bromide **18** (107 mg, 0.50 mmol) was reacted with 3-methoxy-1-naphthaleneboronic acid[44,45] (121 mg, 0.60 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **33** (135 mg, 93%) as a white crystalline solid: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.03 (t, J = 8.5 Hz, 2H), 3.26−3.51 (m, 2H), 3.89 (s, 3H), 7.10−7.14 (m, 2H), 7.22−7.75 (m, 4H), 7.98 (s, 1H), and 8.09 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.75, 35.71, 55.33, 55.72, 106.0, 115.5, 120.7, 124.0, 125.7, 126.2, 126.6, 127.2, 128.9, 134.5, 136.8, 143.2, 151.1, 155.8, and 156.7; IR ($CHCl_3$) ν_{max} 2959, 1599, 1412, and 1225 cm^{-1}; MS (EI^+) m/z (rel intensity) 290 (100%, M^+) and 257 (25); HRMS calcd for $C_{19}H_{18}N_2O$ (M^+) 290.1419, found 290.1407.

4-Methoxy-1-(1-methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))naphthalene (34). Following the general procedure, aryl bromide **18** (107 mg, 0.50 mmol) was reacted with 4-methoxy-1-naphthaleneboronic acid[46] (121 mg, 0.60 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **34** (135 mg, 93%) as a white crystalline solid: R_f = 0.20 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.03 (t, J = 8.5 Hz, 2H), 3.26−3.50 (m, 2H), 4.00 (s, 3H), 6.82 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.40−7.55 (m, 3H), 7.99 (s, 1H), 8.10 (s, 1H), and 8.28−8.32 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.76, 35.72, 55.54, 55.76, 103.2, 116.2, 122.2, 125.2, 125.3, 125.6, 126.1, 126.8, 127.0, 128.0, 134.0, 143.0, 151.7, 155.3, and 156.2; IR ($CHCl_3$) ν_{max} 1597, 1465, 1413, and 1293 cm^{-1}; MS (EI^+) m/z (rel intensity) 290 (100%, M^+); HRMS calcd for $C_{19}H_{18}N_2O$ (M^+) 290.1419, found 290.1425.

Dimethyl(3-phenyl(4-pyridyl))amine (37). Following the general procedure, aryl bromide **36** (1.21 g, 6.00 mmol) was reacted with phenylboronic acid (878 mg, 7.20 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **37** (1.09 g, 92%) as a clear oil: R_f = 0.30 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.55 (s, 6H), 6.65 (d, J = 6.0 Hz, 1H), 7.19−7.38 (m, 5H), 8.13 (s, 1H), and 8.21 (d, J = 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 41.95, 110.5, 126.1, 127.0, 128.5, 128.6, 139.4, 149.1, 151.9, and 155.8; IR ($CHCl_3$) ν_{max} 2954, 1588, 1506, and 1402 cm^{-1}; MS (EI^+) m/z (rel intensity) 198 (100%, M^+); HRMS calcd for $C_{13}H_{14}N_2$ (M^+) 198.1157, found 198.1158.

Dimethyl(3-naphthyl(4-pyridyl))amine (38). Following the general procedure, aryl bromide **36** (1.01 g, 5.00 mmol) was reacted with 1-naphthaleneboronic acid (1.03 g, 6.00 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **38** (1.24 g, ∼100%) as a white crystalline solid: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 2.46 (s, 6H), 6.71 (d, J = 6.0 Hz, 1H), 7.33−7.84 (m, 7H), 8.19 (s, 1H), and 8.33 (d, J = 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 41.26, 109.6, 123.11, 125.5, 125.9, 126.1, 127.3, 127.8, 128.2, 131.9, 133.5, 137.5, 149.2, 152.7, and 155.6; IR ($CHCl_3$) ν_{max} 1586 and 1506 cm^{-1}; MS (EI^+) m/z (rel intensity) 248 (100%, M^+) and 233 (75); HRMS calcd for $C_{17}H_{16}N_2$ (M^+) 248.1313, found 248.1305. Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 81.99; H, 6.47; N, 11.09.

3-Phenyl-4-pyrrolidinylpyridine (42). Following the general procedure, aryl bromide **41** (114 mg, 0.50 mmol) was reacted with phenylboronic acid (73 mg, 0.60 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **42** (85 mg, 76%) as a clear oil: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^1H NMR (250 MHz, $CDCl_3$) δ 1.73−1.79 (m, 4H), 2.94−2.99 (m, 4H), 6.55 (d, J = 6.0 Hz, 1H), 7.26−7.38 (m, 5H), 8.10 (s, 1H), and 8.19 (d, J = 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.60, 50.49, 108.2, 123.2, 126.8, 127.8, 129.8, 140.1, 148.4, 151.4, and 152.0; IR ($CHCl_3$) ν_{max} 2952, 1587, 1501, 1481, 1414, and 1369 cm^{-1}; MS (EI^+) m/z (rel intensity) 290 (100%, M^+) and 195 (20); HRMS calcd for $C_{15}H_{16}N_2$ (M^+) 224.1313, found 224.1302.

(43) Dale, W. J.; Rush, J. E. *J. Org. Chem.* **1962**, *27*, 2598−2603.

(44) Prepared from 1-bromo-3-methoxynaphthalene (ref 45) according to the procedure described for the preparation of arylboronic acid **51**.

(45) Newman, M. S.; Sankaran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237−3242.

(46) Snyder, H. R.; Wyman, F. W. *J. Am. Chem. Soc.* **1948**, *70*, 234−237.

3-Naphthyl-4-pyrrolidinylpyridine (43). Following the general procedure, aryl bromide **41** (41 mg, 0.18 mmol) was reacted with 1-naphthaleneboronic acid (37 mg, 0.22 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **43** (40 mg, 82%) as a clear oil: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.56−1.64 (m, 4H), 2.60−2.73 (m, 2H), 2.92−3.01 (m, 2H), 6.59 (d, J = 6.0 Hz, 1H), 7.38−7.51 (m, 4H), 7.54 (d, J = 8.5 Hz, 1H); 7.83−7.89 (m, 2H), 8.10 (s, 1H), and 8.27 (d, J = 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.41, 49.42, 108.0, 120.5, 125.0, 125.9, 126.2, 126.4, 127.8, 128.2 (2C?), 133.1, 133.2, 137.7, 148.7, 151.7, and 152.4; IR ($CHCl_3$) ν_{max} 2976, 1587, and 1500 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 274 (100%, M$^+$); HRMS calcd for $C_{19}H_{18}N_2$ (M$^+$) 274.1470, found 274.1459.

3-Bromo-4-pyrrolidinylpyridine (41). To a solution of 4-(1-pyrrolidino)pyridine **40** (2.20 g, 14.9 mmol) in CH_2Cl_2 (20 mL) were added satd K_2CO_3 solution (20 mL) and a drop tetrabutylammonium hydroxide (40% w/w in water). During vigorous stirring, bromine (1.15 mL, 22.3 mmol) was added, and after 3 h (TLC) the reaction mixture was diluted with water (50 mL). The phases were separated, and the extraction was completed with additional portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a brown oil. Purification by flash chromatography (EtOAc) furnished the title compound **41** (1.60 g, 47%) as a low-melting white solid: R_f = 0.30 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.78−1.82 (m, 4H), 3.40−3.45 (m, 4H), 6.30 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 6.0 Hz, 1H), and 8.22 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.60, 50.74, 104.8, 110.4, 147.8, 151.3, and 153.6; IR ($CHCl_3$) ν_{max} 2977, 1584, 1501, 1482, and 1414 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 227 (100%, M$^+$) and 147 (25); HRMS calcd for $C_9H_{11}BrN_2$ (M$^+$) 226.0106, found 226.0098.

The General Procedure for the Suzuki Cross-Coupling Involving Sterically Hindered Arylboronic Acids. 1-(1-Methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))-2-(phenylmethoxy)naphthalene (52). To a solution of aryl bromide **18** (1.49 g, 7.00 mmol) in toluene (28 mL) and ethanol (5 mL) was added 2 M Na_2CO_3 (28 mL) followed by $Pd(PPh_3)_4$ (243 mg, 0.210 mmol) and arylboronic acid **51** (2.53 g, 9.1 mmol). The mixture was refluxed for 24 h while additional portions of arylboronic acid **51** [(680 mg, 2.44 mmol) after both 90 min and 4.5 h] and $Pd(PPh_3)_4$ [(81 mg, 0.070 mmol) after both 90 min and 4.5 h] were added. The phases were separated, and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2) to give the title compound **52** (2.09 g, 82%) as a white crystalline solid: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.14 (s, 3H), 3.09 (t, J = 8.5 Hz, 2H), 3.43 (t, J = 8.5 Hz, 2H), 5.18 (s, 2H), 7.23−7.56 (m, 9H), 7.80−7.88 (m, 2H), 7.96 (s, 1H), and 8.15 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) d 25.77, 34.87, 55.62, 71.15, 111.4, 115.2, 121.0, 124.0, 125.6, 125.7, 126.8, 127.0, 127.7, 128.0, 128.4, 129.0, 129.6, 134.5, 137.3, 143.0, 151.9, 154.1, and 156.5; IR ($CHCl_3$) ν_{max} 2958, 1597, and 1226 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 366 (90%, M$^+$), 349 (100), 275 (90), 257 (40), and 91 (30); HRMS calcd for $C_{25}H_{22}N_2O$ (M$^+$) 366.1732, found 366.1726.

1,3-Dimethoxy-2-(1-methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))benzene (30). Following the general procedure, aryl bromide **18** (107 mg, 0.50 mmol) was reacted with 2,6-dimethoxy-1-benzeneboronic acid[47] (182 mg, 1.00 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **30** (99 mg, 73%) as a white solid: R_f = 0.20 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.97 (t, J = 8.5 Hz, 2H), 3.40 (t, J = 8.5 Hz, 2H), 3.70 (s, 6H), 6.57 (d, J = 8.5 Hz, 2H), 7.27 (t, J = 8.5 Hz, 1H), 7.80 (s, 1H), and 7.97 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.61, 34.63, 55.62, 55.84, 103.6, 109.4, 114.5, 125.6, 129.3, 142.5, 151.7, 155.9, and 158.7; IR ($CHCl_3$) ν_{max} 2939, 1597, 1472, 1250, and 1114 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 270 (100%, M$^+$) 237 (10), and 223 (15); HRMS calcd for $C_{16}H_{18}N_2O_2$ (M$^+$) 270.1368, found 270.1369.

2-Methoxy-1-(1-methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))naphthalene (32). Following the general procedure, aryl bromide **18** (213 mg, 1.00 mmol) was reacted with 2-methoxy-1-naphthaleneboronic acid[48] (404 mg, 2.00 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **32** (200 mg, 69%) as a white solid: R_f = 0.30 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.05 (t, J = 8.5 Hz, 2H), 3.41 (t, J = 8.5 Hz, 2H), 3.85 (s, 3H), 7.29−7.46 (m, 4H), 7.76−7.90 (m, 2H), 7.90 (s, 1H), and 8.10 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.72, 34.76, 55.65, 56.58, 111.3, 113.3, 119.8, 123.7, 125.4, 125.8, 126.8, 127.9, 128.7, 129.8, 134.5, 142.9, 151.9, 155.0, and 156.4; IR ($CHCl_3$) ν_{max} 2940, 1597, 1508, 1467, 1413, 1312, and 1261 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 290 (100%, M$^+$) and 257 (20); HRMS calcd for $C_{19}H_{18}N_2O$ (M$^+$) 290.1419, found 290.1410.

8-Methoxy-1-(1-methyl(2-pyrrolino[2,3-*d*]pyridin-7-yl))naphthalene (35). Following the general procedure, aryl bromide **18** (107 mg, 0.50 mmol) was reacted with 8-methoxy-1-naphthaleneboronic acid[49] (202 mg, 1.00 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **35** (131 mg, 90%) as a white solid: R_f = 0.20 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.94 (t, J = 8.5 Hz, 2H), 3.30 (t, J = 8.5 Hz, 2H), 3.44 (s, 3H), 6.69 (d, J = 7.5 Hz, 1H), 7.16 (dd, J = 1.0, 7.0 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.35−7.39 (m, 2H), 7.70 (dd, J = 1.0, 8.0 Hz, 1H), 7.79 (s, 1H), and 7.97 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.88, 35.78, 55.53, 55.80, 106.6, 121.1, 121.7, 124.5, 125.4, 125.6, 126.2, 128.1, 129.9, 133.2, 135.4, 142.1, 149.3, 155.0, and 156.9; IR ($CHCl_3$) ν_{max} 2958, 1594, 1498, 1464, 1413, and 1257 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 290 (100%, M$^+$), 259 (30), and 244 (85); HRMS calcd for $C_{19}H_{18}N_2O$ (M$^+$) 290.1419, found 290.1410.

[3-(8-Methoxynaphthyl)(4-pyridyl)]dimethylamine (39). Following the general procedure, aryl bromide **36** (101 mg, 0.50 mmol) was reacted with 8-methoxy-1-naphthaleneboronic acid[49] (202 mg, 1.00 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **39** (87 mg, 63%) as a white solid: R_f = 0.35 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.56 (s, 6H), 3.51 (s, 3H), 6.66 (d, J = 6.0 Hz, 1H), 6.76 (dd, J = 1.0, 7.0 Hz, 1H), 7.25 (dd, J = 1.0, 7.0 Hz, 1H), 7.38 (dd, J = 8.0, 8.0 Hz, 1H), 7.44 (dd, J = 7.0, 7.0 Hz, 1H), 7.46 (dd, J = 1.0, 8.0 Hz, 1H), 7.78 (dd, J = 1.0, 8.0 Hz, 1H), 8.01 (s, 1H), and 8.25 (d, J = 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 41.57, 55.22, 106.0, 109.2, 121.1, 124.4, 125.6, 126.1, 127.8, 128.8, 129.2, 135.5, 135.8, 147.8, 150.6, 154.7, and 156.7; IR ($CHCl_3$) ν_{max} 1586, 1507, 1463, and 1253 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 278 (100%, M$^+$), 263 (30), 247 (55), 232 (80), and 219 (40); HRMS calcd for $C_{18}H_{18}N_2O$ (M$^+$) 278.1419, found 278.1425.

8-Methoxy-1-(4-pyrrolidinyl(3-pyridyl))naphthalene (44). Following the general procedure, aryl bromide **41** (114 mg, 0.50 mmol) was reacted with 8-methoxy-1-naphthaleneboronic acid[49] (202 mg, 1.00 mmol) to give, after purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2), the title compound **44** (85 mg, 56%) as a white solid: R_f = 0.20 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.61−1.66 (m, 4H), 2.83−3.00 (m, 4H), 3.50 (s, 3H), 6.47 (d, J = 6.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 7.25 (~d, J = 7.0 Hz, 1H), 7.37 (dd, J = 8.0, 8.0 Hz, 1H), 7.40 (dd, J = 7.0, 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), and 8.16 (d, J = 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.58, 49.36, 55.47, 106.5, 107.2, 121.2, 125.1, 125.9, 126.0, 126.2, 127.8, 130.1, 135.3, 136.1, 147.7, 150.3, 150.8, and 157.0; IR ($CHCl_3$) ν_{max} 2974, 1588, 1505, 1483, 1463, and 1253 cm^{-1}; MS (EI$^+$) m/z (rel intensity) 304 (90%, M$^+$), 273 (100), 219 (20), and 83 (90); HRMS calcd for $C_{20}H_{20}N_2O$ (M$^+$) 304.1576, found 304.1575.

1-Bromo-2-(phenylmethoxy)naphthalene (50). To a suspension of 1-bromo-2-naphthol **49** (15.0 g, 67.3 mmol) and K_2-

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CO_3 (18.6 g, 135 mmol) in DMF (100 mL) was added benzyl bromide (9.6 mL, 81 mmol), and the mixture was stirred at 60 °C for 5 h. After cooling to room temperature, the solvent was evaporated in vacuo and the residue, dissolved in a small amount of CH_2Cl_2, passed through a thin pad of flash silica. Fractions containing the product were evaporated in vacuo to give an off-white solid. Crystallization from CH_2Cl_2/petroleum ether gave the title compound **50** as a white crystalline solid (16.0 g, 76%). The mother liquor was concentrated and purified by flash chromatography (petroleum ether/CH_2Cl_2, 2/1) to give an additional amount of the product **50** (3.7 g, 17%; total yield: 93%). Benzyl ether **50**: $R_f = 0.50$ (petroleum ether/CH_2Cl_2, 2/1); mp 104−106 °C (CH_2Cl_2/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.35 (s, 2H), 7.32 (d, $J = 9.0$ Hz, 1H), 7.38−7.50 (m, 4H), 7.57−7.66 (m, 2H), 7.79−7.86 (m, 3H), and 8.31 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 71.81, 110.0, 115.6, 124.6, 126.3, 127.2, 127.8, 128.1 (2C), 128.7, 128.9, 130.1, 133.2, 136.7, and 153.0; IR ($CHCl_3$) ν_{max} 1626, 1596, 1502, 1350, and 1268 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 314/312 (25%, M$^+$) and 91 (100); HRMS calcd for $C_{17}H_{13}BrO$ (M$^+$) 312.0150, found 312.0150. Anal. Calcd for $C_{17}H_{13}BrO$: C, 65.19; H, 4.18; Br, 25.51. Found: C, 64.94; H, 4.12; Br, 25.71.

2-(Phenylmethoxy)-1-naphthaleneboronic Acid (51). To a suspension of aryl bromide **50** (6.26 g, 20.0 mmol) in Et_2O (75 mL) at −78 °C was added *n*-BuLi (8.0 mL, 2.5 M, 20 mmol) in hexanes, and the mixture was stirred at 0 °C for 1 h. After recooling to −78 °C, the mixture was treated with trimethyl borate (2.5 mL, 22 mmol) and allowed to warm to room-temperature overnight. The resulting mixture was quenched with 1 M HCl (50 mL) and stirred at room temperature for 45 min. The phases were separated, and the extraction was completed with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the title compound **51** as a white powder (4.62 g, 83%), which was used in the next step without further purification. For analytical purposes, a small amount of the product was recrystallized from MeOH/H_2O: mp 133.0−135.0 °C (MeOH/H_2O); ^{1}H NMR (250 MHz, d_4-MeOH) δ 5.20 (s, 2H), 7.28−7.60 (m, 9H), and 7.56−7.88 (m, 2H); ^{13}C NMR (63 MHz, d_4-MeOH) δ 71.95, 115.4, 124.8, 127.7 (2C), 128.4, 128.9, 129.5, 129.6, 130.7 (2C?), 131.8, 137.2, 139.0, and 159.7;[50] IR ($CHCl_3$) ν_{max} 3609, 3490, 1592, 1509, 1386, and 1332 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 278 (10%, M$^+$), 234 (10), and 91 (100); HRMS calcd for $C_{17}H_{15}BO_3$ (M$^+$) 277.1151, found 277.1163. Anal. Calcd for $C_{17}H_{15}BO_3$: C, 73.42; H, 5.44. Found: C, 73.07; H, 5.33.

1-(1-Methyl-2-pyrrolino[2,3-*d*]pyridin-7-yl)-2-naphthyl (Trifluoromethyl)sulfonate (54). A suspension of benzyl ether **52** (1.83 g, 5.0 mmol) in EtOH (80 mL) was hydrogenated under normal pressure in the presence of 10% Pd/C (700 mg) for 5 h (TLC). The reaction mixture was filtered through a thin pad of Celite and evaporated in vacuo to give a crude phenol **53** (1.38 g, 5.0 mmol) as a white solid, which was used in the next step without further purification. Thus, to a solution of phenol **53** (1.38 g, 5.0 mmol) in pyridine (15 mL) at 0 °C was added trifluoromethanesulfonic anhydride (925 mL, 5.5 mmol). After 70 min, the solvent was evaporated in vacuo and the residue partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The phases were separated, and the extraction was completed with additional portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a red oil. Purification by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2) afforded the title compound **54** (1.90 g, 93%) as a pale orange solid: $R_f = 0.40$ (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.09 (s, 3H), 3.06 (t, $J =$ 8.5 Hz, 2H), 3.46 (t, $J = 8.5$ Hz, 2H), 7.43−7.68 (m, 4H), 7.88−7.95 (m, 3H), and 8.11 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.56, 34.66, 55.48, 107.4, 118.3 (q, $J = 320$ Hz), 119.4, 126.0, 129.6, 127.2, 127.8, 127.9, 128.3, 130.6, 132.1, 134.1, 143.7, 145.4, 151.5, and 156.0; IR ($CHCl_3$) ν_{max} 2957, 1600, 1507, 1419, 1314, 1218, and 1140 cm^{-1}; MS (FAB$^+$) *m*/*z* (rel intensity) 409 (100%, MH$^+$), 275 (15), and 259 (15); HRMS calcd for $C_{19}H_{16}F_3N_2O_3S$ (MH$^+$) 409.0834, found 409.0805.

(±)-1-Methyl-7-(2-methylnaphthyl)-2-pyrrolino[3,2-*c*]pyridine (55). The first method: To a vial charged with triflate **54** (57 mg, 0.14 mmol), LiCl (18 mg, 0.42 mmol), PPh_3 (22 mg, 0.084 mmol), $Pd(PPh_3)_2Cl_2$ (12 mg, 0.017 mmol), and a crystal of 2,6-di-*tert*-butyl-4-methylphenol was added DMF (1 mL) followed by tetramethyltin (25 μL, 0.18 mmol). The vial was tightly sealed and kept at 120 °C for 20 h. After recooling to room temperature, the mixture was diluted with EtOAc and washed with 10% NH_4OH. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2) to give the title compound **55** as a white solid (28 mg, 73%).

The second method: To a solution of triflate **54** (1.08 g, 2.65 mmol) in Et_2O (17 mL) was added $NiBr_2(PPh_3)_2$ (59 mg, 0.080 mmol) followed by MeMgBr (2.2 mL, 3.0 M, 6.6 mmol) in Et_2O. The mixture was refluxed for 24 h, quenched with water (30 mL), and diluted with CH_2Cl_2 (30 mL). The phases were separated, and the extraction was completed with additional portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2) to give the title compound **55** (618 mg, 85%) as a white solid: $R_f =$ 0.30 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.27 (s, 3H), 3.07 (t, $J = 9.0$ Hz, 2H), 3.33−3.51 (m, 2H), 7.33−3.50 (m, 4H), 7.76−7.84 (m, 2H), 7.87 (s, 1H), and 8.13 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.95, 25.77, 34.79, 55.65, 114.5, 125.0, 125.8 (2C?), 126.2, 127.9 (2C?), 128.3, 131.8, 132.5, 133.8, 135.3, 143.1, 151.2, and 155.9; IR ($CHCl_3$) ν_{max} 2955, 1598, 1497, 1468, 1413, and 1311 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 274 (100%, M$^+$); HRMS calcd for $C_{19}H_{18}N_2$ (M$^+$) 274.1470, found 274.1463.

(±)-1-Methyl-7-(2-phenylnaphthyl)-2-pyrrolino[3,2-*c*]pyridine (56). To a solution of triflate **54** (652 mg, 1.60 mmol) in Et_2O (10 mL) was added $PdCl_2$(dppp) (47 mg, 0.08 mmol) followed by PhMgBr (1.1 mL, 3.0 M, 3.3 mmol) in Et_2O. The mixture was refluxed for 24 h, quenched with water (10 mL), and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2) to give the title compound **56** (457 mg, 85%) as a white solid: $R_f =$ 0.30 (EtOAc/Et_3N, 99/5); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.82−3.10 (m, 2H), 3.35 (t, $J = 9.0$ Hz, 2H), 7.13−7.30 (m, 5H), 7.43−3.64 (m, 4H), 7.79 (s, 1H), and 7.89−7.97 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.60, 34.85, 55.35, 114.0, 125.3, 126.0, 126.6, 126.7, 127.0, 127.8, 128.0, 128.1, 129.7, 132.1, 132.4, 133.8, 140.0, 141.6, 142.6, 151.9, and 156.1; IR ($CHCl_3$) ν_{max} 2955, 1599, 1497, 1413, and 1310 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 336 (5%, M$^+$), 203 (85), 185 (75), and 82 (100); HRMS calcd for $C_{19}H_{18}N_2O$ (M$^+$) 290.1419, found 290.1410.

X-ray Crystal Structure Analyses. The structures were solved by direct methods (SHELXTL[51]). For further details of the crystal structure determination, see: Supporting Information.

X-ray Crystal Structure Analysis of Aryl Bromide 18. $C_8H_9BrN_2$ (213.08); from $CHCl_3$ as colorless blocks; crystal dimensions: 0.50 × 0.48 × 0.45 mm; monoclinic; space group: $P2_1/c$ (C_{2h}^5, No. 14); unit cell dimensions: $a = 7.7576(15)$, $b =$ 13.231(3), $c = 8.2134(16)$ Å; $\beta = 110.010(4)°$; $U = 792.1(3)$ Å^3, $Z = 4$, $D_c = 1.787$ mg m^{-3}; Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 5.119 mm^{-1}, $F(000) = 424$. Cell parameters were refined from the setting angles of 46 reflections (θ range 2.79 < 28.26°); total number of reflections: 4053; number of independent reflections: 1407 (exceeding the significance level $|F|/\sigma(|F|) > 4.0$); $R = 0.0491$ ($wR_{2all} = 0.1270$).

X-ray Crystal Structure Analysis of Biaryl 22. $C_{16}H_{18}N_2O$ (254.32); from EtOAc as colorless blocks; crystal dimensions: 0.40 × 0.21 × 0.21 mm; orthorhombic; space group: $P2_12_12_1$ (D_2^4, No. 19); unit cell dimensions: $a = 7.461(6)$, $b = 8.350(8)$, $c = 21.315(18)$ Å; $U = 1328(2)$ Å^3, $Z = 4$, $D_c = 1.272$ mg m^{-3}; Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 0.080 mm^{-1},

(50) Another set of weak signals could be observed in ^{13}C NMR, which can be attributed to a small amount of the anhydride formed.

(51) *An Integrated System for Solving and Refining Crystal Structures from Diffraction Data (Revision 5.1)*; Bruker AXS Ltd.

$F(000) = 544$. Cell parameters were refined from the setting angles of 45 reflections (θ range 1.91 < 28.72°); total number of reflections: 8858; number of independent reflections: 1505 (exceeding the significance level $|F|/\sigma(|F|) > 4.0$); $R = 0.1018$ ($wR_{2all} = 0.2882$).

X-ray Crystal Structure Analysis of Biaryl 35. $C_{19}H_{18}N_2O{\cdot}HCl$ (326.31); from petroleum ether/CH_2Cl_2 as colorless blocks; crystal dimensions: 0.32 × 0.16 × 0.15 mm; monoclinic; space group: $P2_1/n$ (a nonstandard setting of $P2_1/c$ $C_{2h'}^5$, No. 14); unit cell dimensions: $a = 7.194(3)$, $b = 23.993(7)$, $c = 9.667(3)$ Å; $\beta = 106.41(4)°$; $U = 1600.5(9)$ Å^3, $Z = 4$, $D_c = 1.356$ mg m^{-3}; Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 0.245 mm^{-1}, $F(000) = 688$. Cell parameters were refined from the setting angles of 45 reflections (θ range 1.70 < 28.31°); total number of reflections: 10487; number of independent reflections: 2157 (exceeding the significance level $|F|/\sigma(|F|) > 4.0$); $R = 0.0832$ ($wR_{2all} = 0.2675$).

X-ray Crystal Structure Analysis of Biaryl 38. $C_{17}H_{16}N_2$ (248.32); from petroleum ether/CH_2Cl_2 as colorless blocks; crystal dimensions: 0.40 × 0.32 × 0.32 mm; monoclinic; space group: $P2_1$ (C_2^2, No. 4); unit cell dimensions: $a = 7.1351(12)$, $b = 7.1394(12)$, $c = 13.279(2)$ Å; $\beta = 104.452(3)°$; $U = 655.03(19)$ Å^3, $Z = 2$, $D_c = 1.259$ mg m^{-3}; Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 0.075 mm^{-1}, $F(000) = 264$. Cell parameters were refined from the setting angles of 48 reflections (θ range 1.58 < 28.30°); total number of reflections: 4356; number of independent reflections: 2403 (exceeding the significance level $|F|/\sigma(|F|) > 4.0$); $R = 0.0651$ ($wR_{2all} = 0.2159$).

X-ray Crystal Structure Analysis of *N*-Oxide of Biaryl 38. $C_{17}H_{16}N_2O{\cdot}H_2O$ (282.33); from CH_2Cl_2/EtOAc as colorless blocks; crystal dimensions: 0.37 × 0.22 × 0.22 mm; monoclinic; space group: $P2_1/c$ ($C_{2h'}^5$, No. 14); unit cell dimensions: $a = 6.8156(9)$, $b = 7.6023(10)$, $c = 27.838(4)$ Å; $\beta = 96.509(2)°$; $U = 1433.1(3)$ Å^3, $Z = 4$, $D_c = 1.309$ mg m^{-3}; Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 0.087 mm^{-1}, $F(000) = 600$. Cell parameters were refined from the setting angles of 66 reflections (θ range 2.78 < 28.34°); total number of reflections: 9146; number of independent reflections: 2491 (exceeding the significance level $|F|/\sigma(|F|) > 4.0$); $R = 0.0542$ ($wR_{2all} = 0.1716$).

X-ray Crystal Structure Analysis of Biaryl (+)-55. $C_{19}H_{18}N_2$ (274.35); from EtOAc as colorless blocks; crystal dimensions: 0.34 × 0.31 × 0.31 mm; orthorhombic; space group: $P2_12_12_1$ (D_2^4, No. 19); unit cell dimensions: $a = 7.8911(16)$, $b = 12.503(3)$, $c = 14.477(3)$ Å; $U = 1428.4(5)$ Å^3, $Z = 4$, $D_c = 1.276$ mg m^{-3}; Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 0.075 mm^{-1}, $F(000) = 584$. Cell parameters were refined from the setting angles of 45 reflections (θ range 2.15 < 28.36°); total number of reflections: 9470; number of independent reflections: 1715 (exceeding the significance level $|F|/\sigma(|F|) > 4.0$); $R = 0.0472$ ($wR_{2all} = 0.1326$).

X-ray Crystal Structure Analysis of Biaryl (±)-56. $C_{24}H_{20}N_2{\cdot}H_2O$ (354.44); from EtOAc as colorless blocks; crystal dimensions: 0.24 × 0.12 × 0.12 mm; triclinic; space group: $P\bar{1}$ (C_i^1, No. 2); unit cell dimensions: $a = 9.977(3)$, $b = 9.993(3)$, $c = 10.769(3)$ Å; $\alpha = 107.865(5)°$, $\beta = 113.068(5)°$, $\gamma = 93.022(5)°$; $U = 921.6(4)$ Å^3, $Z = 2$, $D_c = 1.277$ mg m^{-3}; Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 0.078 mm^{-1}, $F(000) = 376$. Cell parameters were refined from the setting angles of 26 reflections (θ range 2.18 < 28.30°); total number of reflections: 6108; number of independent reflections: 2424 (exceeding the significance level $|F|/\sigma(|F|) > 4.0$); $R = 0.0564$ ($wR_{2all} = 0.1694$).

Optical Resolution of the Racemic Biaryl (±)-55. The enantiomers of the biaryl **55** were separated using semipreparative HPLC (Chiralcel OD column, 1 cm × 25 cm; hexanes/EtOAc/Et_2NH, 75/24/1; 3 mL min^{-1}; 25 °C). UV detection was performed at 250 nm. Injections of ~3.5 mg of the racemate in 100 mL of dichloromethane were made every 13 min. Enantiomer (+)-**55** was collected from 15.6 to 17.4 min, and the enantiomer (−)-**55** was collected from 19.5 to 21.9 min. The enantiomers were further purified by flash chromatography (EtOAc) to give final products as white crystalline solids. Analytical HPLC revealed the enantiomeric purity of 99.9% {$[\alpha]^{25}_D$ +107 (*c* 0.43 in $CHCl_3$)} and 99.7% {$[\alpha]^{25}_D$ −107 (*c* 0.45 in $CHCl_3$)} for the two enantiomers, respectively.

Optical Resolution of the Racemic Biaryl (±)-56. The enantiomers of the biaryl **56** were separated using semipreparative HPLC (Chiralcel OD column, 1 cm × 25 cm; hexanes/EtOAc/Et_2NH, 75/24/1; 4 mL min^{-1}; 35 °C). UV detection was performed at 250 nm. Injections of ~8 mg of the racemate in 35 mL of dichloromethane were made every 14 min. Enantiomer (−)-**56** was collected from 9.7 to 12.4 min, and the enantiomer (+)-**56** was collected from 14.9 to 19.1 min. The enantiomers were further purified by flash chromatography (EtOAc → EtOAc/Et_3N, 98/2) to give final products as white foams. Analytical HPLC revealed the enantiomeric purity of >99.9% for both the levorotatory {$[\alpha]^{25}_D$ −144 (*c* 1.9 in $CHCl_3$)} and the dextrorotatory {$[\alpha]^{25}_D$ +151 (*c* 1.9 in $CHCl_3$)} enantiomer.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all compounds and single-crystal X-ray data for compounds **18**, **22**, **35**, **38**, *N*-oxide of **38**, (+)-**55**, and **56**. This material is available free of charge via the Internet at http://pubs.acs.org.

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