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Computed CH Acidity of Biaryl Compounds and Their Deprotonative Metalation by Using a Mixed Lithium/Zinc-TMP Base**

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Abstract: With the aim of synthesizing biaryl compounds, several aromatic iodides were prepared by the deprotonative metalation of methoxybenzenes, 3-substituted naphthalenes, isoquinoline, and methoxypyridines by using a mixed lithium/zinc-TMP (TMP = 2,2,6,6-tetramethylpiperidino) base and subsequent iodolysis. The halides thus obtained, as well as commercial compounds, were cross-coupled under palladium catalysis (e.g., Suzuki coupling with 2,4-dimethoxy-5-pyrimidylboronic acid) to afford various representative biaryl compounds. Deprotometalation of the latter compounds was performed by using the lithium/zinc-TMP base and evaluated by subsequent iodolysis. The outcome of these reactions has been discussed in light of the CH acidities of these substrates, as determined in THF solution by using the DFT B3LYP method. Except for in the presence of decidedly lower pK_a values, the regioselectivities of the deprotometalation reactions tend to be governed by nearby coordinating atoms rather than by site acidities. In particular, azine and diazine nitrogen atoms have been shown to be efficient in inducing the reactions with the lithium/zinc-TMP base at adjacent sites (e.g., by using 1-(2-methoxyphenyl)isoquinoline, 4-(2,5-dimethoxyphenyl)-3-methoxypyridine, or 5-(2,5-dimethoxyphenyl)-2,4-dimethoxypyrimidine as the substrate), a behavior that has already been observed upon treatment with lithium amides under kinetic conditions. Finally, the iodinated biaryl derivatives were involved in palladium-catalyzed reactions.

Keywords: acidity · basicity · biaryls · density functional calculations · metalation

Introduction

Biaryl skeletons bind to numerous biological receptors and, thus, molecules that contain them are frequently used in medicinal chemistry. Among them, biphenyl compounds are, for example, endowed with antifungal, anti-inflammatory, antirheumatic, anti-infective, antitumor, antihypertensive, and analgesic properties.[1] Biaryl compounds are also prospective organic semiconductors and liquid crystals,[2] as well as materials for nonlinear optics.[3] Thus, it is of interest to develop synthetic methods to access elaborate biaryl derivatives. The development of new ligands for transition metals is also a field in which new synthetic approaches to afford biaryl scaffolds are appreciated.[4] If the main synthetic

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[**] TMP = 2,2,6,6-tetramethylpiperidino.

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route to afford biaryl compounds involves the formation of the aryl–aryl bond,[5] it is also possible to functionalize already formed biaryl compounds.[6]

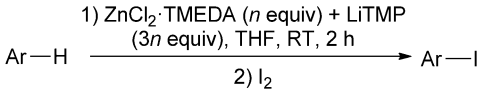
The deprotonative metalation of biaryl compounds has great synthetic potential. Methods that use alkyl lithium compounds and lithium amides have largely been used to achieve the deprotonative metalation of aromatic compounds.[7] Nevertheless, owing to the low tolerance of functionalized or heterocyclic substrates toward organolithium species, organic chemists have developed more-compatible substitutes. In particular, $(R)_n(R')_{n'}MLi$-type bases, in which the metal (M) is not an alkali metal, have been reported by different research groups for their ability to deprotonate sensitive substrates.[8]

Our group contributed to this area, notably with the development of a room-temperature-operating lithium/zinc combination, which was prepared in situ from $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and Li(TMP) (TMP = 2,2,6,6-tetramethylpiperidino, 3 equiv), and taken to be Li(TMP)/$Zn(TMP)_2$ (1:1).[9] Herein, we report our efforts to functionalize biaryl compounds, including heterocycles, by deprotonative metalation by using this base. In addition, the pK_a values of the biaryl compounds that were involved in these reactions were calculated within the density functional theory (DFT) framework for their solutions in THF to evaluate the CH-acidity/regioselectivity relationship.

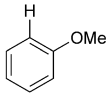
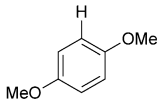
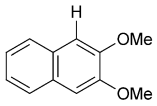
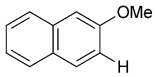
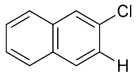
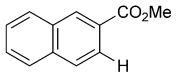
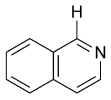
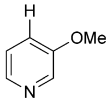
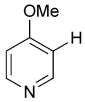
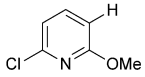
Results and Discussion

To access a series of biaryl compounds, various aromatic iodides were prepared for palladium-catalyzed coupling reactions with arylmetals or related compounds (Table 1). For this purpose, a previously reported method was employed by using anisole as a substrate (product **1a**; Table 1, entry 1).[9e] Similarly, the use of the base that was generated in situ from $ZnCl_2$·TMEDA (0.5 equiv) and Li(TMP) (1.5 equiv) in THF with 1,4-dimethoxybenzene for 2 h led, after subsequent trapping with iodine, to product **1b** in 82% yield (Table 1, entry 2). In the naphthalene series, iodides **1c**–**1f** were furnished in satisfying yields by using $ZnCl_2$·TMEDA (1 equiv) and Li(TMP) (3 equiv) under the same reaction conditions. Whereas 2,3-dimethoxynaphthalene is logically functionalized at its free 1-position (Table 1, entry 3), two different sites next to the substituent can be attacked in the case of 2-substituted naphthalenes.[10] By using methoxy, chloro, and methyl ester substituents, regioselective deprotometalation was observed in favor of the 3-position (Table 1, entries 4–6). 1-Iodoisoquinoline, which has previously been synthesized from isoquinoline by using Li(TMP)/$Zn(tBu)_2$,[11] was isolated herein in a similar 92% yield (Table 1, entry 7). The reactions of 3- and 4-methoxypyridine regioselectively afforded the corresponding 4- and 3-iodo derivatives, respectively (Table 1, entries 8, 9), as previously observed by using Li(TMP)/$Zn(tBu)_2$.[12] Finally, 2-chloro-6-methoxypyridine was functionalized next to the methoxy group when treated in a similar manner (Table 1, entry 10).

Table 1. Synthesis of aryl iodides **1a**–**1j** through a deprotometalation/iodination sequence.



1

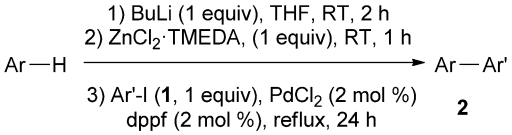
Entry	Ar–H	*n* Equiv	Product	Yield [%][a]
1		0.5	**1a**	84[e]
2		0.5	**1b**	82
3		1	**1c**	79
4		1	**1d**	92
5		1	**1e**	78[b]
6		1	**1f**	51[c]
7		1	**1g**	92
8		2	**1h**	61[d]
9		1	**1i**	60
10		1	**1j**	71

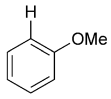
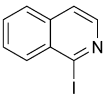
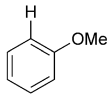
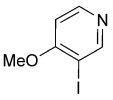
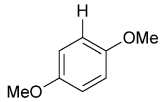
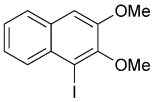
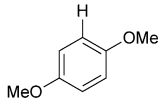
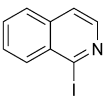
[a] After purification by column chromatography on silica gel. [b] From 1-chloronaphthalene, a mixture was obtained under the same reaction conditions. [c] From 2-cyanonaphthalene, a mixture was obtained under the same reaction conditions. [d] 2,4-Diiodo-3-methoxypyridine was also isolated in 29% yield. [e] Ref. [9e].

Next, we turned to the coupling of these iodides with arylmetals and related compounds under palladium catalysis. For this purpose, we first considered the Negishi coupling[13] of arylzinc chlorides that were prepared from their corresponding lithiated compounds. In 2008, we showed the benefit of a sequential deprotolithiation/transmetalation-coupling reaction sequence by using $ZnCl_2$·TMEDA as a transmetalation agent and activated chlorides as the coupling part-

ners.[14] Transposition to iodides **1g**, **1i**, **1c**, and **1g** was attempted by using arylzinc chlorides that were generated from anisole and 1,4-dimethoxybenzene (Table 2). The use of catalytic amounts of palladium(II) chloride and 1,1′-bis-(diphenylphosphino)ferrocene (dppf) provided the expected coupling products (**2a**–**2d**), but in low yields (9–36%).

Table 2. Synthesis of biaryl compounds **2a**–**2d** through a deprotometalation/coupling sequence.

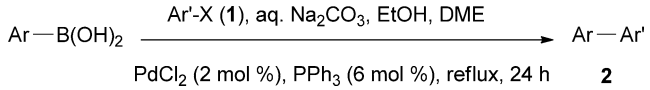


Entry	Ar–H	Ar′–I	Product	Yield [%][a]
1		**1g** 	**2a**	36[b]
2		**1i** 	**2b**	44
3		**1c** 	**2c**	9
4		**1g** 	**2d**	23

[a] After purification by column chromatography on silica gel. [b] The deprotometalation of isoquinoline (Table 1, entry 7), followed by treatment with 4-iodoanisole in the presence of $PdCl_2$ (2 mol.%) and dppf (2 mol.%) in THF at reflux for 24 h, led to a complex mixture; similarly, the deprotometalation of anisole (Table 1, entry 1), followed by treatment with 1-iodoisoquinoline in the presence of $PdCl_2$ (2 mol.%) and dppf (2 mol.%) in THF at reflux for 24 h, did not afford compound **2a** but instead afforded a complex mixture.

These disappointing results led us to consider Suzuki coupling[15] of the synthesized iodides, as well as commercial bromides, with commercially available arylboronic acids. Under previously described conditions,[16] most of the attempted reactions led to the expected coupling products (Table 3). Products **2c** and **2d**, which had already been prepared according to the method described in Table 2, entries 3 and 4 in 9 and 23% yield, respectively, were isolated by using 2,5-dimethoxyphenylboronic acid in 40 and 80% yield, respectively (Table 3, entries 1 and 2). The same boronic acid was also successfully used with 4-bromoisoquinoline (Table 3, entry 3), 4-iodo-3-methoxypyridine (**1h**; Table 3, entry 4), 3-iodo-4-methoxypyridine (**1i**; Table 3, entry 5), and 2,3-dibromopyridine (Table 3, entry 6); in the latter reaction, a major coupling product was noted in favor of the 2-position. 3-Thienylboronic acid and 3-pyridylboronic acid reacted with 1-iodo-2,3-dimethoxynaphthalene (**1c**) to afford compounds **2i** and **2j** in moderate yields (Table 3,

Table 3. Synthesis of biaryl compounds **2c**–**2x** through a Suzuki-type coupling reaction.



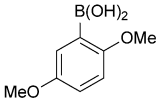
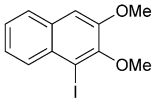
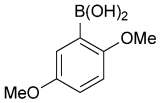
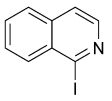
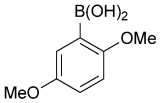
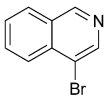
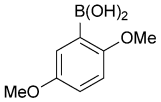
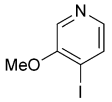
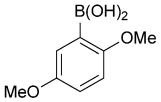
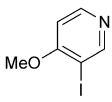
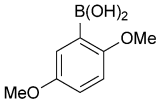
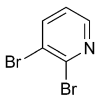
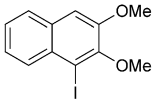
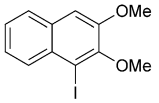
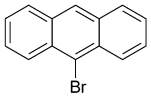
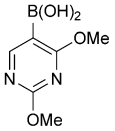
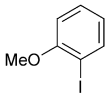
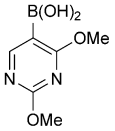
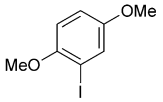
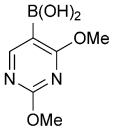
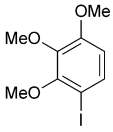
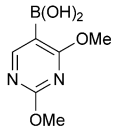
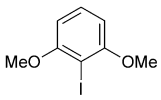
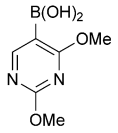
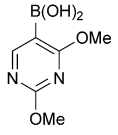
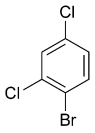
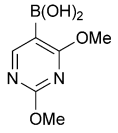
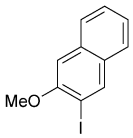
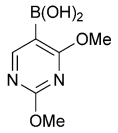
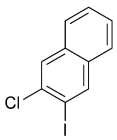
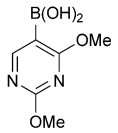
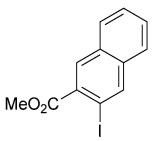
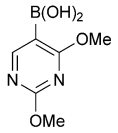
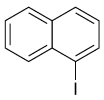
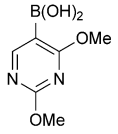
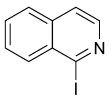
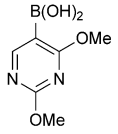
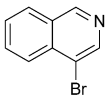
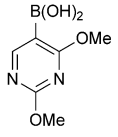
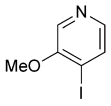
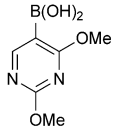
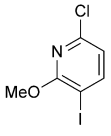
Entry	Ar–$B(OH)_2$	Ar′–X	Product	Yield [%][a]
1		**1c** 	**2c**	40
2		**1g** 	**2d**	80
3			**2e**	71
4		**1h** 	**2f**	81
5		**1i** 	**2g**	65
6			**2h**	50[b]
7		**1c** 	**2i**	39
8		**1c** 	**2j**	42
9			–	–
10		**1a** 	**2k**	90
11		**1b** 	**2l**	88
12			**2m**	81

Table 3. (Continued)

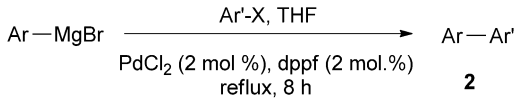
Entry	Ar–B(OH)$_2$	Ar′–X	Product	Yield [%][a]
13			**2n**	37
14			**2o**	78
15			**2p**	71
16		**1d** 	**2q**	82
17		**1e** 	**2r**	84
18		**1f** 	**2s**	91
19			**2t**	90
20		**1g** 	**2u**	68
21			**2v**	80
22		**1h** 	**2w**	38
23		**1j** 	**2x**	75

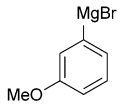
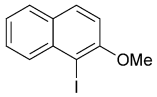
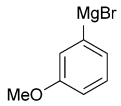
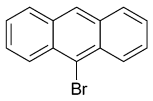
[a] After purification by column chromatography on silica gel. [b] Major coupling was with Br at the 2-position; competitive coupling with Br at the 3-position was observed, but only gave the corresponding product in a low (10%) yield.

entries 7 and 8), possibly owing to more-important steric hindrance (which could rationalize the 40% yield in Table 3, entry 1) and no coupled product was obtained from 5-pyrimidylboronic acid and 9-bromoanthracene (Table 3, entry 9). The use of 2,4-dimethoxy-5-pyrimidylboronic acid with methoxy-substituted iodobenzenes (Table 3, entries 10–13), chloro-substituted iodo- and bromobenzenes (Table 3, entries 14 and 15), 3-substituted 2-iodonaphthalenes (Table 3, entries 16–18), 1-iodonaphthalene (Table 3, entry 19), 1-iodo- and 4-bromoisoquinolines (Table 3, entries 20 and 21), and substituted iodopyridines (Table 3, entries 22 and 23) led to a large range of biaryl compounds in moderate-to-good yields (**2k**–**2x**).

To afford 3-methoxyphenyl-substituted compounds **2y** and **2z**, Kumada coupling[17] was preferred (Table 4). The application of catalytic amounts of palladium(II) chloride and dppf[18] allowed us to isolate the corresponding coupling products in moderate yields. Finally, 2,2′,5,5′-tetramethoxybiphenyl (**2aa**) was prepared in 64% yield through the homocoupling of 2-iodo-1,4-dimethoxybenzene (**1b**) in the presence of activated copper, according to a literature procedure.[19]

Table 4. Synthesis of biaryl compounds **2y** and **2z** through a Kumada-type coupling reaction.



Entry	Ar–MgBr	Ar′–X	Product	Yield [%][a]
1			**2y**	50
2			**2z**	52

[a] After purification by column chromatography on silica gel.

With these biaryl compounds in hands, next, we considered their deprotometalation by using the base that was generated in situ from $ZnCl_2$·TMEDA (1 equiv) and Li(TMP) (3 equiv) in THF. Because the number of substances that we investigated was rather large, we decided to present some general trends in their computed CH acidity first. Then, the experimental results for particular derivatives are discussed in connection with their acidities and literature data.

Computational aspects: Unfortunately, both experimental and simulation data on CH acidity in biaryl compounds are scarce. The main reasons for this lack of data are the necessity of using very strong bases at low temperatures and the possible side reactions of the generated carbanions. A brief review of reports that were devoted to the experimental and theoretical investigation of CH acidity in azines was presented in our previous publication.[20] These works typically con-

cerned aromatic compounds for which side-group CH acidity was of interest; notable among these reported experimental studies are CH-acidity measurements on alkylated pyridines in THF.[21]

Herein, the CH-acidity values for the biaryls were calculated within the DFT framework by using the same approach as that previously employed for substituted azoles,[22] including arylpyrazoles[9f] and aryltriazoles,[9h] as well as azines.[20] The gas-phase acidity of a compound was associated with its Gibbs energy ($\Delta_{acid}G$) of deprotonation, according to Equations (1) and (2).

$$R{-}H_{(g)} \rightarrow R^-_{(g)}{+}H^+_{(g)} \quad (1)$$

$$\Delta_{acid}G = G^0_{298}(R^-){+}G^0_{298}(H^+){-}G^0_{298}(RH) \quad (2)$$

All of the calculations were carried out by using the DFT B3LYP method. The geometries were optimized by using the 6-31G(d) basis set. No symmetry constraints were imposed. Because the biaryls included rotatable fragments, the most-stable conformers were specified by using different initial values of the corresponding dihedral angles. To perform stationary-point characterization and to calculate the zero-point vibrational energies (ZPVE) and the thermal corrections to the Gibbs free energy, vibrational frequencies were calculated at the same level of theory. The single-point energy calculations were performed by using the 6-311+G(d,p) basis set. The gas-phase Gibbs energies (G^0_{298}) were calculated for each species according to Equation (3) (no scaling factors were applied).

$$G^0_{298} = E{+}ZPVE{+}H_{0\rightarrow298}{-}TS^0_{298} \quad (3)$$

The solvent effects were evaluated by using the polarized continuum model (PCM) with the default parameters for THF.[23] The PCM energies were also calculated at the B3LYP/6-311+G(d,p) level of theory by using geometries that were optimized for isolated structures. The cavity was built up by using a united atom (UA) model that was applied on the atomic radii of the UFF force field. The Gibbs energies in solution (G_s) were calculated for each species according to Equation (4).

$$G_s = G^0_{298}{+}E_{PCM}{-}E \quad (4)$$

To cancel out any possible errors, the pK_a values were calculated by means of the isodesmic reaction method. We considered the homodesmic reaction shown in Equation (5), where Het–H is an appropriate six-membered heterocycle with a known pK_a value.

$$R{-}H_{(s)}{+}Het^-_{(s)} \rightarrow R^-_{(s)}{+}Het{-}H_{(s)} \quad (5)$$

We chose bare pyridine as a reference compound (pK_a (THF) = 40.2), owing to its structural and pK_a-range similarities. Then, the pK_a values were calculated from the Gibbs energy for the homodesmic reaction by using Equation (6).

$$pK_a(R-H) = 40.2 + \frac{\Delta_r G_s}{RT}\frac{1}{\ln 10} \quad (6)$$

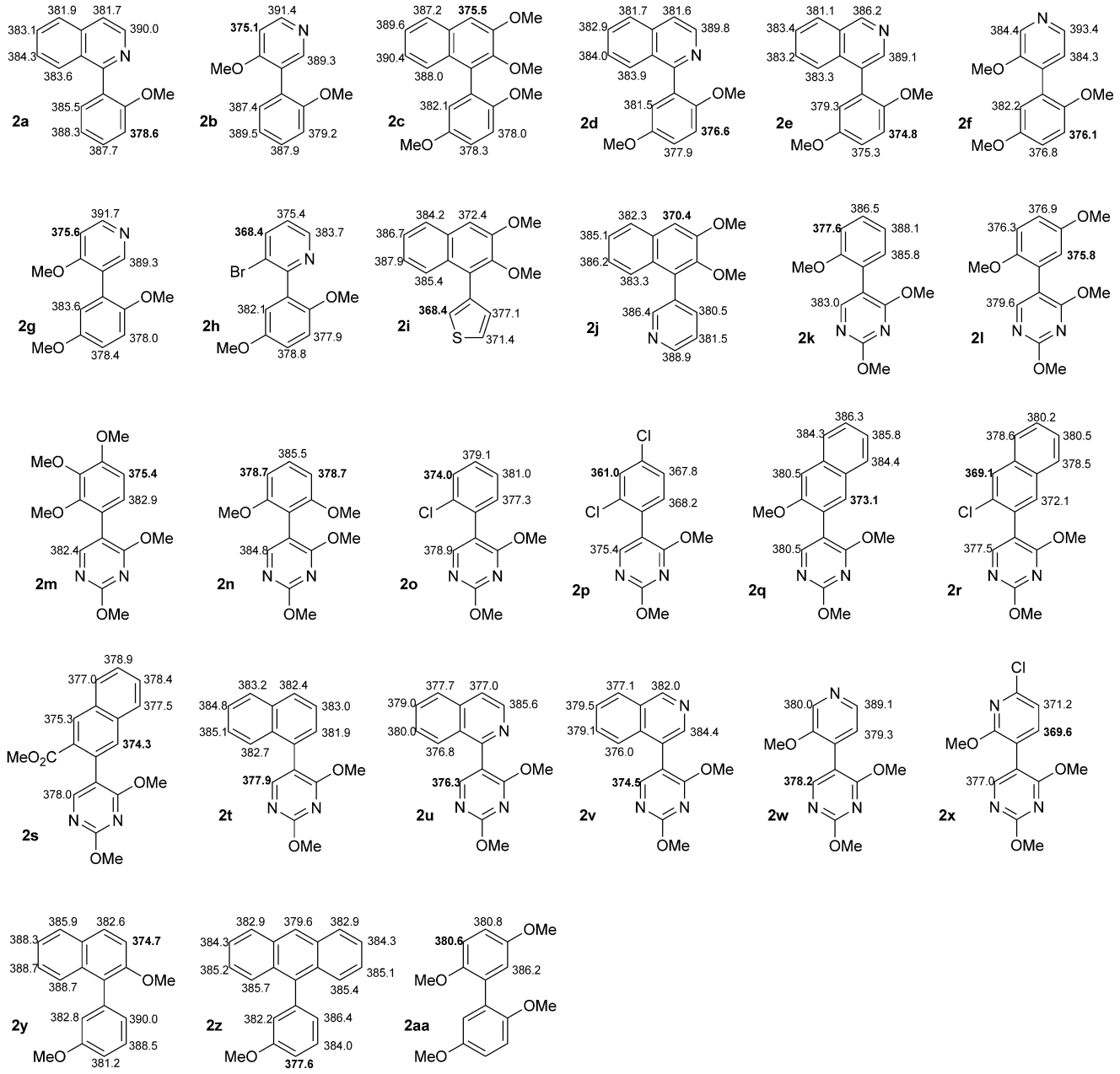
The CH acidity of the (methoxy) side groups was not taken into consideration because it was expected to be lower and because these groups remained intact under the employed synthetic conditions.

An investigation of gas-phase CH acidity is worthwhile for the development of an acidity scale that is free of solvent effects. The calculated $\Delta_{acid}G$ values of the investigated compounds range from 361 to 393 kcal mol^{-1} (Scheme 1), which are typical for weak CH acids. The corresponding pK_a(THF) values are given in Table 5 and Table 6, together with the deprotometalation results, and are within the range 29–49. Both series of data refer to the most-stable rotamers.

According to Alkorta and Elguero, biphenyls and biaryls usually possess two rotational barriers, that is, planar (steric) and perpendicular barriers (electronic).[24] In our case, the available conformational space is limited, owing to the physical demands of bulky substituents; thus, global and local minima could be easily found.

The global trends in the $\Delta_{acid}G$ and pK_a values, which could be deduced by comparing compounds that contained common 2,6-dimethoxypyrimidyl or mono/dimethoxyphenyl moieties, are the same and can be summarized as follows. First, the CH acidities of the corresponding positions correlate with the electron-donating or electron-withdrawing effect of the aryl substituent. The most-prominent acidifying effect was obtained by halogen insertion. On the contrary, the protons α to the azine nitrogen atoms appeared to be less prone to abstraction through an overriding base-promoted mechanism.[25] Next, by considering the aromatic rings, one can see that, in the remote parts of the systems, the CH acidities are closer and suffer less from the influence of substituents. Moreover, the pK_a values at sites that are adjacent to interaryl bonds are hampered, maybe by steric factors.

Deprotometalation results: By using the base that was generated in situ from $ZnCl_2$·TMEDA (1 equiv) and Li(TMP) (3 equiv) in THF to perform the reaction with methoxy-substituted substrate **2aa**, we found that, following subsequent trapping with iodine, the abstraction of the most-acidic hydrogen atom occurred at the 4-position. This result is not surprising, because all of the possible deprotonation sites are adjacent to a methoxy group (Table 5, entry 1). In the case of compound **2c**, functionalization also took place at the 4-position of the 2,5-dimethoxyphenyl group. The reason why the most-acidic hydrogen atom next to the methoxy group on the naphthyl ring is not attacked could be due to steric hindrance (peri position), but it is difficult to understand why the reaction does not take place at the most-acidic 3-position of the 2,5-dimethoxyphenyl group (Table 5, entry 2). Unfortunately, attempts to functionalize compounds **2y** and **2z** led to complex mixtures (Table 5, entries 3 and 4).

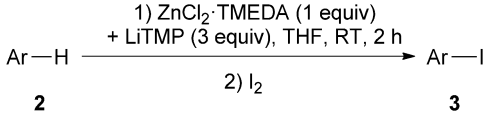


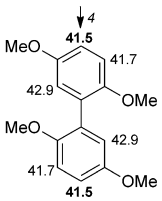
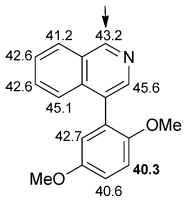
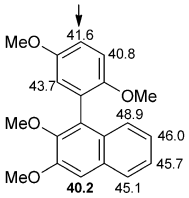
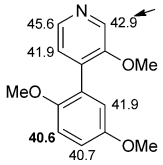
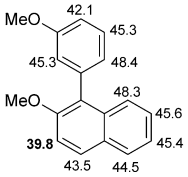
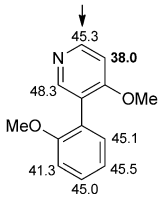
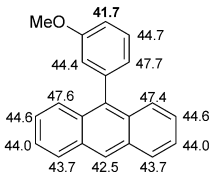
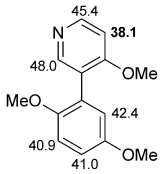
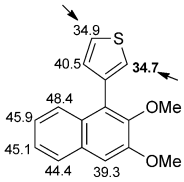
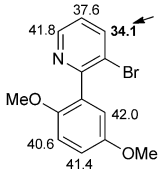
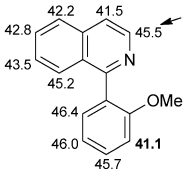
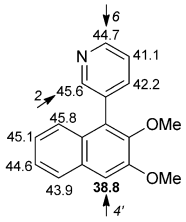
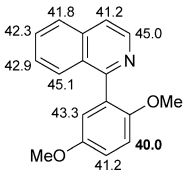
Scheme 1. Calculated values of the Gibbs energies ($\Delta_{acid}G$) [kcal mol^{-1}] for deprotonation of the investigated biaryl compounds at their corresponding positions (the lowest value for each compound is given in bold).

Starting from 3-substituted thiophene **2i**, double deprotonation at its most-acidic 2 and 5-positions was observed under the same reaction conditions (Table 5, entry 5). This result is not surprising, because such a base has previously led to the double deprotonation of doubly activated five-membered aromatic heterocycles.[9f,h,26]

Starting from the 1-substituted quinoline **2a**, an attack on a hydrogen atom that was far from being the most acidic was noted (Table 5, entry 6), which led us to attempt to rationalize this result. In 2011, García-Álvarez, Mulvey, and Parkinson published a study by using DOSY NMR spectroscopy about the nature of the base that was generated from $ZnCl_2$•TMEDA and Li(TMP) (3 equiv) in THF. The authors suggested a mixture that contained $Zn(TMP)_2$ (as a spectator species) and a Li(TMP)/LiCl (1:2) complex with the possible (reversible) coordination of TMEDA (as a possible active lithiating base) as being the nature of the base.[9k] Thus, it seems reasonable to consider a pathway that involves an initial lithiation step; subsequent transmetalation through $Zn(TMP)_2$ could then take place, thereby leading to more-stabilized derivatives. It is well-established that azines can be deprotolithiated at positions that are adjacent to

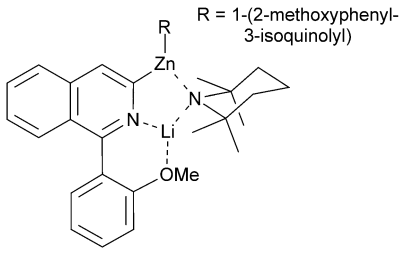
Table 5. Calculated pK_a(THF) values for biaryl compounds **2aa**, **2a**–**2j**, **2y**, and **2z** and the results of the deprotometalation/iodination sequence.



Entry		Ar–H[a]	Product	Yield [%][b]	Entry		Ar–H[a]	Product	Yield [%][b]
1	**2aa**		**3aa**	48	8	**2e**		**3e**	63
2	**2c**		**3c**	45	9	**2f**		**3f**	71
3	**2y**		–[c]	–	10	**2b**		–[d]	–
4	**2z**		–[c]	–	11	**2g**		–[c]	–
5	**2i**		**3i**	59	12	**2h**		**3h**	38
6	**2a**		**3a**	39	13	**2j**		–[e]	–
7	**2d**		–[c]	–					

[a] The arrows that point toward the formula of the biaryl compounds indicate the observed deprotometalation/iodination sites, whilst the numbers are the calculated pK_a values for deprotonation at the corresponding positions (the lowest value for each compound is given in bold). [b] After purification by column chromatography on silica gel. [c] A complex mixture was obtained. [d] Obtained in low (10%) yield, owing to degradation. [e] A mixture of the 6-iodo- (20% yield), 2-iodo- (15% yield), and 6,4′-diiodo derivatives (12% yield) was obtained.

their nitrogen atoms (as atoms that are able to coordinate the metal of the base) upon treatment under kinetic conditions. It is also known that, when possible (for example, in reversible reactions with Li(TMP)), the lithiated compounds thus formed can be converted into more-stable isomers that contain lithium atoms at positions that are remote from the ring nitrogen atoms (with decreased charge repulsion).[27] In this example, a direct attack of Li(TMP) next to the azine nitrogen atom is likely. The reason why there is no isomerization of the thus-formed lithiated compound in this case could be due to the absence of more-stable isomers (notably for steric reasons). In addition, if transmetalation through $Zn(TMP)_2$ rapidly takes place, a structure may be formed in which both the lithium and zinc species synergistically contribute to the stabilization. Previously, we isolated crystals several weeks at −18 °C after the deprotonative metalation of anisole[9e] and *N*-phenylpyrrole[9a] by using the same base and X-ray diffraction analysis showed TMEDA-chelated diarylzincs as the corresponding structures. The latter species were supposed to come from the corresponding TMP-containing lithium zincates[28] through the loss of Li(TMP) with time. Such a lithium zincate, if formed in the case of compound **2a**, could be particularly stabilized through coordination of both the azine nitrogen atom and the methoxy group to the lithium atom (Scheme 2).



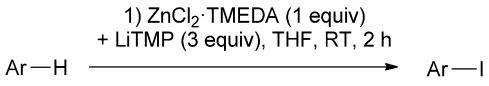
Scheme 2. Proposed structure of the deprotometalated species that is obtained from compound **2a**.

Introducing a second methoxy group onto the phenyl substituent led to a complex mixture (Table 5, entry 7). When the 2,5-dimethoxyphenyl group was moved from the 1-position of isoquinoline to the 4-position, the reaction occurred at the 1-position (Table 5, entry 8), as previously observed in the case of unsubstituted isoquinoline by using Li(TMP)Zn-(tBu)$_2$.[11] Both the 1 and 3-positions next to the isoquinoline nitrogen atom could be attacked and abstraction of the hydrogen atom at the 1-position, which was more acidic than that at the 3-position, was observed.

With 3-methoxypyridine **2f**, which was 4-substituted by a 2,5-dimethoxyphenyl group, the reaction also took place next to the heterocyclic nitrogen atom; in addition, the more-acidic 2-position was favored over the 6-position (Table 5, entry 9). Again, coordination by the nitrogen atom overcomes its acidity and the methoxy substituents are not capable of competing in directing the reaction. With 4-methoxypyridine **2b**, which was 3-substituted by a 2-methoxyphenyl group, deprotometalation took place in a similar manner next to the nitrogen atom, thus keeping the 5-position, which corresponded to the most-acidic hydrogen atom, intact. Nevertheless, degradation was also observed in this case and the iodide was formed in low yield (Table 5, entry 10). When the 2-methoxyphenyl group was replaced by a 2,5-dimethoxyphenyl group (substrate **2g**), a mixture was obtained from which it was not possible to unambiguously identify the components (Table 5, entry 11). When the 2,5-dimethoxyphenyl group was connected to the 2-position of 3-bromopyridine, deprotometalation occurred at the 4-position, that is, the adjacent position to the halogen atom. The 6-position, that is, next to the nitrogen atom, is not attacked in this case, possibly owing to the decidedly lower pK_a value at the 4-position (Table 5, entry 12). The reaction of pyridine **2j**, which was 3-substituted by a 2,3-dimethoxy-1-naphthyl group, was more complex. Indeed, under the same reaction conditions, a mixture that contained at least the 6-iodo- (20% yield), 2-iodo- (15% yield), and 6,4′-diiodo derivatives (12% yield) was obtained (Table 5, entry 13). These compounds show a nonregioselective deprotometalation at both positions next to the pyridine nitrogen atom, which could be related to the similar acidities of the hydrogen atoms at the 2- and 6-positions.

We then turned our attention to the deprotometalation of 5-substituted 2,4-dimethoxypyrimidines (Table 6). With a methoxyphenyl group as the substituent (substrates **2k**–**2n**), the reaction regioselectively took place at the free position

Table 6. Calculated pK_a(THF) values for biaryl compounds **2k**–**2x** and the results of the deprotometalation/iodination sequence.



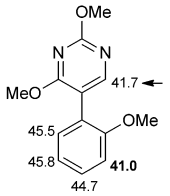
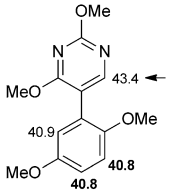
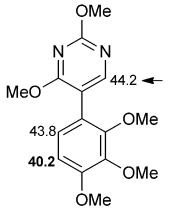
Entry	Ar–H[a]	Product	Yield [%][b]
1	**2k** 	**3k**	97
2	**2l** 	**3l**	94
3	**2m** 	**3m**	89

Table 6. (Continued)

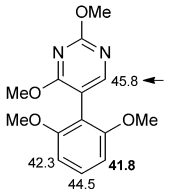
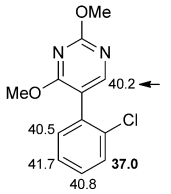
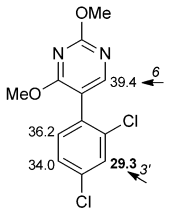
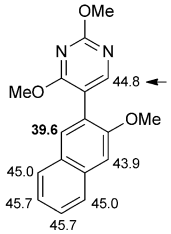
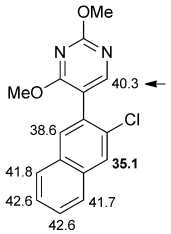
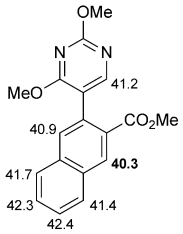
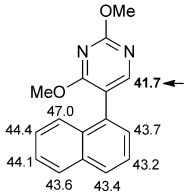
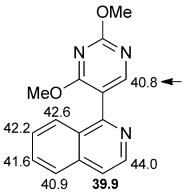
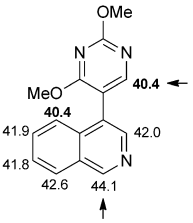
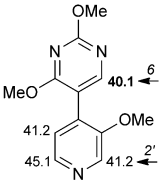
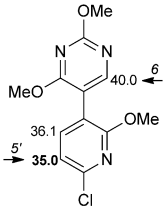
Entry		Ar–H[a]	Product	Yield [%][b]
4	**2n**		**3n**	82
5	**2o**		**3o**	78
6	**2p**		**3p** **3p′**	70[d] 15[e]
7	**2q**		**3q**	82
8	**2r**		**3r**	83
9	**2s**		–[c]	–
10	**2t**		**3t**	67

Table 6. (Continued)

Entry		Ar–H[a]	Product	Yield [%][b]
11	**2u**		**3u**	85
12	**2v**		**3v**	60[f]
13	**2w**		–[g]	–
14	**2x**		**3x** **3x′**	66[h] 26[i]

[a] The arrows that point toward the formula of the biaryl compounds indicate the observed deprotometalation/iodination sites, whilst the numbers are the calculated pK_a values for deprotonation at the corresponding positions (the lowest value for each compound is given in bold). [b] After purification by column chromatography on silica gel. [c] Either compound **2s** was recovered or degradation was observed, depending on the reaction temperature. [d] I at the 6-position. [e] I at the 6- and 3′-position. [f] Diiodide. [g] A 1:1 mixture of the 6-iodo- and 2′-iodo derivatives was obtained. [h] I at the 6-position. [i] I at 6- and 5′-position.

on the pyrimidine ring (Table 6, entries 1–4). This result was confirmed in the case of compounds **3l**–**3n** (Table 6, entries 2–4) by X-ray diffraction from suitable crystals (see the Supporting Information). Once again, this result demonstrates that coordination by the nitrogen atom overcomes the acidity issue, because the methoxy substituent(s) on the phenyl ring make(s), in all cases, the adjacent hydrogen atom(s) more acidic than the pyrimidine hydrogen atom.

The chloro group is a strong acidifying substituent and, even if steric hindrance makes reaction at adjacent positions difficult, deprotonation of the ring on which it is connected should be favored through long-range effects.[29] Nevertheless, in spite of the relatively low pK_a values on the chlorophenyl rings, 5-substituted 2,4-dimethoxypyrimidines **2o** and **2p** were attacked at their free pyrimidine position to afford the corresponding monoiodides (**3o** and **3p**) in 70–78% yield (Table 6, entries 5 and 6). In the case of compound **2p**,

diiodide **3p′**, which resulted from deprotonation at both the pyrimidine and benzene groups, was also isolated in 15% yield (Table 6, entry 6).

The use of Li(TMP) (1 equiv) in THF at −70°C with substrate **2p** led to the formation of different iodides, depending on the reaction time. When quenching was performed with iodine after 30 min, compound **3p** was also isolated, but in a moderate 28% yield, owing to competitive degradation. Extending the reaction time to 2 h led to the formation of many iodides and more degradation. Iodide **3p** was no longer detected among the different products, but diiodide **3p′** (about 10% yield), as well as the monoiodide that resulted from deprotonation at the 3′-position (10% yield), were observed. Even if they were distorted owing to degradation, these results with Li(TMP) suggested the preliminary formation of a kinetic lithiated compound on the diazine ring (at its free position, next to the nitrogen atom, as previously observed in the pyridine series)[27d] and its subsequent isomerization into more-stable derivatives. By using the lithium/zinc reagent at room temperature (reaction time: 2 h), the diazinylmetal is formed in a more chemoselective way and isolated compounds **3p** and **3p′** are both iodinated at the 6-position, thus showing preference for species that are metalated next to the nitrogen atom.

With 3-methoxy-2-naphthyl or 3-chloro-2-naphthyl substituents, 5-substituted 2,4-dimethoxypyrimidines **2q** and **2r** were only functionalized at their free pyrimidine position (Table 6, entries 7 and 8). However, we could not react the corresponding 3-methoxycarbonyl-2-naphthyl analogue (**2s**), owing to its degradation under the required conditions for deprotometalation (Table 6, entry 9). With a 1-naphthyl substituent (**2t**), the reaction logically took place next to the nitrogen atom, thus furnishing iodide **3t** in 67% yield (Table 6, entry 10). Next, we turned to 5-isoquinolyl-2,4-dimethoxypyrimidine substrates **2u** and **2v**. With 1-isoquinolyl as the substituent, the reaction occurred at the most-acidic site next to the nitrogen atom and monoiodide **3u** was isolated in 85% yield (Table 6, entry 11). In contrast, with the 4-isoquinolyl analogue as the substituent, dimetalation took place at two sites next to nitrogen atoms, thus giving, after trapping, diiodide **3v** in 60% yield (Table 6, entry 12). Finally, we studied the behavior of 5-pyridyl-2,4-dimethoxypyrimidine substrates **2w** and **2x**. With the 3-methoxy-4-pyridyl substrate, the deprotonation was not regioselective and a 1:1 mixture of the 6-iodo- and 2′-iodo derivatives (owing to reactions at the most-acidic sites next to the pyrimidine and pyridine nitrogen atoms, respectively) was obtained (Table 6, entry 13). In the case of 6-chloro-2-methoxy-3-pyridyl analogue, the reaction took place at the only free position next to the nitrogen atom, thus affording compound **3x** in 66% yield. As already observed from compound **2p**, diiodide **3x′**, which resulted from deprotonation of both the pyrimidine and pyridine rings (next to the chloro group) was also isolated in 26% yield (Table 6, entry 14). The structures of compounds **3o**, **3q**, **3t**–**3v**, and **3x′** were unambiguously identified by X-ray diffraction (see the Supporting Information).

Here we should briefly account for the observed results, because, at first glance, they are at variance with what has been reported previously in other series.[9f,20] The formation of a particular product could be rationalized if two opposing tendencies are taken into account, namely: 1) the most-acidic position attracts the deprotometalation/iodination sequence when its pK_a(THF) value is low enough (less than about 35), and 2) in the presence of an atom that is able to coordinate a metal (methoxy oxygen atoms or, above all, azine nitrogen atoms), the reaction is directed to a nearby position. Similar diiodination reactions have previously been reported for pyridylpyrazoles,[9f] but the pyrazole′s nitrogen atom was less influenced with respect to the α orientation in comparison with the nitrogen atoms in the pyrimidine or pyridine groups reported herein. These results can be explained in terms of the higher pK_b value of pyrazole (11.5) as compared with pyridine (8.7), thus leading to a weakening of the metal–ligand σ interaction.[30]

To show the value of such iodinated biaryl compounds, we considered their further functionalization through palladium-catalyzed reactions. For this purpose, we selected 5-substituted 6-iodo-2,4-dimethoxypyrimidines **3l**, **3q**, **3o**, and **3r** and converted them through Suzuki cross-coupling[15] with 2-chloro- or 2-aminophenylboronic acid under previously reported conditions[9i] into derivatives **4l**, **4q**, **4o**, and **4r** in high yields (Table 7).

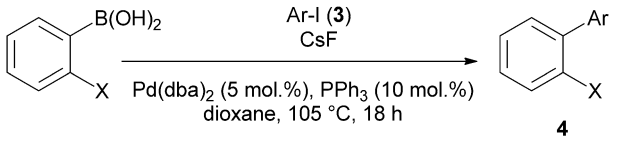
Intramolecular C–H arylation[31] of chlorides **4l** and **4q** was considered to afford the corresponding tetracycle and pentacycle, respectively. From compound **4q**, by using different ligands, such as tri(cyclohexyl)phosphine, tri(*tert*-butyl)-phosphine, and Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), in the presence of palladium(II) acetate as a transition-metal source and cesium carbonate as a base led to degradation together with starting material after stirring for 18 h in 1,4-dioxane at 105°C or *o*-xylene at 150°C. In contrast, in the case of compound **4l**, tri(cyclohexyl)phosphine was efficiently employed, thereby affording dibenzo-[*f*,*h*]quinazoline **5l** after purification in 68% yield (Scheme 3).

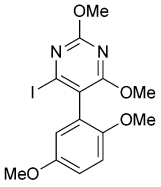
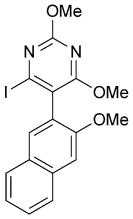
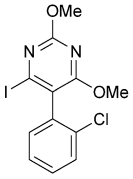
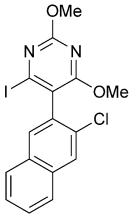
The intramolecular N-arylation[5,32] of chlorides **4o** and **4r** was attempted under various reaction conditions with recourse to nickel-, copper-, and palladium-based catalysts. Unfortunately, either degradation or recovery of the starting material was obtained from both substrates. The reaction of 4-(2-aminophenyl)-3-bromo-2-(2,5-dimethoxyphenyl)pyridine was easier; indeed, under the same conditions that were used to prepare it from the corresponding 4-iodo substrate (**3h**), both Suzuki coupling and subsequent cyclization took place, thus furnishing azacarbazole **5h** in 70% yield (Scheme 4).

Conclusion

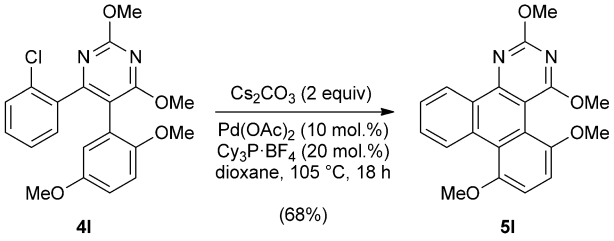
The results obtained herein show that the "all-TMP" mixed lithium/zinc base is a powerful reagent for the room-temperature deprotonative metalation of biaryl compounds, includ-

Table 7. Synthesis of biaryl compounds **4l**, **4q**, **4o**, and **4r** through a Suzuki-type coupling reaction.



Entry	X	Ar–I (**3**)	Product	Yield [%][a]
1	Cl	**3l** 	**4l**	92
2	Cl	**3q** 	**4q**	91
3	NH_2	**3o** 	**4o**	94
4	NH_2	**3r** 	**4r**	91

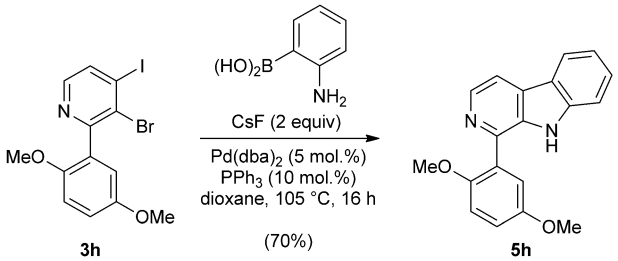
[a] After purification by column chromatography on silica gel.



Scheme 3. Palladium-catalyzed cyclization of compound **4l** (Cy = cyclohexyl).

ing sensitive heterocycles, for which lithium bases are inappropriate. The regioselectivities obtained during this study are relevant because they provide information on the possible role of both the CH acidities and the substituent coordinating abilities in determining the course of these reactions.

From the literature, it is known that lithium amides, when employed in polar solvents (e.g., THF) and at moderately



Scheme 4. Palladium-catalyzed coupling/cyclization sequence from compound **3h**.

low temperatures, favor deprotometalation at the most-acidic sites through thermodynamic control. In particular, deprotonation in the position α to the azine nitrogen atom is thermodynamically unlikely, owing to destabilization of the formed carbanion by repulsion with neighboring electron lone pairs.[22a]

On the contrary, in the majority of cases, employing the "all-TMP" mixed lithium/zinc base drives the substitution at the position α to the azine nitrogen atom, which is also the favored position when using lithium amides under kinetic control and is supposed to result from the coordination of the nitrogen atom to lithium (Table 5, entries 1 and 2 and Table 6). If no azine nitrogen atom is present, the reaction can either be directed by stronger CH acidities (Table 5, entries 1, 5, and 12) or by adjacent methoxy groups, which are also able to coordinate metal atoms (Table 5, entries 1 and 2).

Experimental Section

Unless otherwise noted, the reactions were performed under an argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatographic separations were performed on silica gel (40–63 μm). Melting points were measured on a Kofler apparatus. IR spectra were recorded on a Perkin–Elmer Spectrum 100 spectrometer. ^1H and ^{13}C nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively. ^1H chemical shifts (δ) are reported in ppm relative to the residual solvent peak, ^{13}C chemical shifts are reported relative to the central peak of the solvent signal,[33] and coupling constants (J) are given in Hz. High-resolution mass spectroscopy (HRMS) was performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) in Rennes on either a Waters Q-TOF 2 or a Bruker micrOTOF Q II instrument in positive electrospray CI mode.

2,3-Dimethoxynaphthalene[34] and methyl-2-naphthoate[35] were prepared according to literature procedures. 1-Iodo-2,3,4-trimethoxybenzene[36] and 2-iodo-1,3-dimethoxybenzene[37] were synthesized as described previously. 1-Iodo-2-methoxynaphthalene was prepared in 93% yield by adapting a reported procedure.[38] $ZnCl_2$·TMEDA was prepared as described previously.[39]

General procedure A for the synthesis of aryl iodides 1:[9e] To a stirring, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.82 mL, 3.0 mmol) in THF (3 mL) were successively added BuLi (3.0 mmol, about 1.6 M in hexanes) and $ZnCl_2$·TMEDA (0.30 g, 1.0 mmol). The mixture was stirred for 10 min at 0 °C before the introduction of the appropriate substrate (1.0 mmol). After 2 h at RT, a solution of I_2 (1.0 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before the addition of a saturated aqueous solution of $Na_2S_2O_3$ (10 mL)

and extraction with Et_2O (20 mL) and EtOAc (2×20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

General procedure B for the synthesis of biaryls 2a–2d through a deprotonation/coupling sequence:[14] To a stirring, cooled (−78 °C) solution of the appropriate substrate (4.0 mmol) in THF (5 mL) were added BuLi (4.0 mmol, about 1.6 M in hexanes) and, after 2 h at RT, $ZnCl_2$·TMEDA (1.2 g, 4.0 mmol). After a further 1 h at RT, the aryl halide (4.0 mmol), $PdCl_2$ (14 mg, 80 μmol, 2 mol %), and dppf (44 mg, 80 μmol, 2 mol %) were added and the mixture was heated at reflux for 24 h. Then, the reaction mixture was diluted with water and extracted with Et_2O and EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

General procedure C for the synthesis of biaryls 2c–2x through a Suzuki-type coupling reaction:[16] A degassed solution of the aryl halide (10 mmol), the boronic acid (10 mmol), Na_2CO_3 (2.3 g, 22 mmol), $PdCl_2$ (35 mg, 0.2 mmol, 2 mol %), and PPh_3 (0.16 g, 0.6 mmol, 6 mol %) in water (11 mL), EtOH (8 mL), and 1,2-dimethoxyethane (25 mL) was heated at reflux for 24 h. Then, the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3×40 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

General procedure D for the synthesis of biaryls 2y and 2z through a Kumada-type coupling reaction:[18] A solution of the aryl halide (3.0 mmol), the aryl Grignard reagent (3.6 mmol, about 1.0 M in THF), $PdCl_2$ (10 mg, 60 μmol, 2 mol %), and dppf (33 mg, 60 μmol, 2 mol %) in THF (5 mL) was heated at reflux for 8 h. Then, the reaction mixture was diluted with water (20 mL) and extracted with Et_2O (20 mL) and CH_2Cl_2 (2×20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

General procedure E for the synthesis of biaryl iodides 3:[9e] To a stirring, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.82 mL, 3.0 mmol) in THF (3 mL) were successively added BuLi (3.0 mmol, about 1.6 M in hexanes) and $ZnCl_2$·TMEDA (0.30 g, 1.0 mmol). The mixture was stirred for 10 min at 0 °C before the introduction of the appropriate biaryl substrate (1.0 mmol). After 2 h at RT, a solution of I_2 (1.0 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before the addition of a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and extraction with Et_2O (20 mL) and EtOAc (2×20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

General procedure F for the synthesis of biaryls 4:[9i] To a degassed solution of the aryl iodide (1.0 mmol), the boronic acid (4.0 mmol), and CsF (0.30 g, 2.0 mmol) in 1,4-dioxane (10 mL) were added $[Pd(dba)_2]$ (28 mg, 50 μmol, 5 mol %, dba = dibenzylideneacetone) and PPh_3 (52 mg, 0.20 mmol, 10 mol %). The resulting mixture was heated for 18 h at 105 °C before cooling and diluting with Et_2O (50 mL), washing with water (20 mL), and extracting with CH_2Cl_2 (3×30 mL). After drying over Na_2SO_4, the solvent was evaporated under reduced pressure and the coupled compound was isolated by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane).

1-Iodo-2,3-dimethoxynaphthalene (1c): General procedure A was employed by using 2,3-dimethoxynaphthalene. Purification by flash chromatography on silica gel (14:86 EtOAc/*n*-heptane) gave compound **1c** (79% yield) as a white powder: M.p. 51 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.93 (s, 3H), 3.99 (s, 3H), 7.17 (s, 1H), 7.39–7.44 (m, 2H), 7.64–7.68 (m, 1H), 8.04–8.08 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.8, 60.5, 96.0, 108.1, 125.5, 125.9, 126.9, 130.1, 131.6, 131.7, 150.1, 151.6 ppm; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{11}IO_2Na$: 336.9701 $[M+Na]^+$; found: 336.9703.

2-Chloro-3-iodonaphthalene (1e): General procedure A was employed by using 2-chloronaphthalene. Purification by flash chromatography on silica gel (5:95 EtOAc/*n*-heptane) gave compound **1e** (78% yield) as a white powder: M.p. 101–102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.44–7.54 (m, 2H), 7.65–7.74 (m, 2H), 7.88 (s, 1H), 8.35 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 95.5, 126.5, 126.8, 126.8, 127.1, 127.3, 133.1, 133.4, 134.5, 139.6 ppm; HRMS (ESI/ASAP): *m*/*z* calcd for $C_{10}H_6{}^{35}ClI$: 287.9203 $[M]^+$; found: 287.9203.

6-Chloro-3-iodo-2-methoxypyridine (1j): General procedure A was employed by using 2-chloro-6-methoxypyridine. Purification by flash chromatography on silica gel (2:98 EtOAc/*n*-heptane) gave compound **1j** (71% yield) as a yellow powder: M.p. 64 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.97 (s, 3H), 6.66 (d, J = 7.8 Hz, 1H), 7.88 ppm (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.4, 76.8, 118.1, 148.7, 149.6, 161.7 ppm; HRMS (ESI): *m*/*z* calcd for $C_6H_6{}^{35}ClINO$: 269.9183 $[M+H]^+$; found: 269.9182.

1-(2-Methoxyphenyl)isoquinoline (2a): General procedure B was employed by using anisole and 1-iodoisoquinoline. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **2a** (36% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.69 (s, 3H), 7.06 (d, J = 8.3 Hz, 1H), 7.12 (td, J = 7.4, 0.9 Hz, 1H), 7.39 (dd, J = 7.4, 1.7 Hz, 1H), 7.47 (m, 2H), 7.66 (m, 2H), 7.71 (br d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 8.62 ppm (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.6, 111.2, 120.2, 120.9, 126.8, 126.9, 127.9, 128.0, 128.8, 130.0, 130.1, 131.3, 136.3, 142.4, 157.2, 159.2 ppm; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{13}NO$: 235.0997 $[M+Na]^+$; found: 423.0068.

4-Methoxy-3-(2-methoxyphenyl)pyridine (2b): General procedure B was employed by using anisole and 3-iodo-4-methoxypyridine. Purification by flash chromatography on silica gel (40:60 EtOAc/*n*-heptane) gave compound **2b** (44% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.77 (s, 3H), 3.83 (s, 3H), 6.88 (d, J = 5.7 Hz, 1H), 6.98–7.06 (m, 2H), 7.24 (dd, J = 7.5, 1.8 Hz, 1H), 7.34–7.41 (m, 2H), 8.36 (s, 1H), 8.48 ppm (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.5, 55.7, 106.9, 111.1, 120.4, 128.0, 124.3, 129.7, 131.3, 149.9, 150.7, 157.0, 164.0 ppm; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{14}NO_2$: 216.1024 $[M+H]^+$; found: 216.1021.

1-(2,5-Dimethoxyphenyl)-2,3-dimethoxynaphthalene (2c): General procedure C was employed by using 2,5-dimethoxyphenylboronic acid and 1-iodo-2,3-dimethoxynaphthalene. Purification by flash chromatography on silica gel (17:83 EtOAc/*n*-heptane) gave compound **2c** (40% yield) as a white solid: M.p. 89 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.65 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 4.02 (s, 3H), 6.81–7.00 (m, 3H), 7.19–7.25 (m, 2H), 7.30–7.37 (m, 2H), 7.74 ppm (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.7, 55.8, 56.4, 60.9, 107.0, 112.4, 114.0, 117.6, 123.9, 125.2, 125.7, 126.1, 126.7, 128.5, 128.7, 131.2, 146.9, 152.0, 152.3, 153.5 ppm; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}O_4Na$: 347.1259 $[M+Na]^+$; found: 347.1257.

1-(2,5-Dimethoxyphenyl)isoquinoline (2d): General procedure C was employed by using 2,5-dimethoxyphenylboronic acid and 1-iodoisoquinoline. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **2d** (80% yield) as a brown solid: M.p. 128–129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.64 (s, 3H), 3.81 (s, 3H), 6.98 (m, 3H), 7.49 (m, 1H), 7.67 (m, 2H), 7.74 (dd, J = 8.4, 0.9 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 8.62 ppm (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 56.0, 56.5, 112.8, 115.6, 116.5, 120.4, 126.8, 127.1, 127.8, 128.1, 129.5, 130.1, 126.3, 142.3, 151.5, 153.9, 158.9 ppm; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}NO_2Na$: 288.1000 $[M+Na]^+$; found: 288.0999.

4-(2,5-Dimethoxyphenyl)isoquinoline (2e): General procedure C was employed by using 2,5-dimethoxyphenylboronic acid and 4-bromoisoquinoline. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **2e** (71% yield) as a white solid: M.p. 110–111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.64 (s, 3H), 3.80 (s, 3H), 6.89 (t, J = 1.7 Hz, 1H), 6.99 (d, J = 1.7 Hz, 2H), 7.61 (m, 3H), 8.01 (m, 1H), 8.47 (s, 1H), 9.26 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.9, 56.3, 112.4, 114.4, 117.8, 125.6, 126.8, 127.1, 127.8, 128.3, 130.2, 130.3, 134.8, 143.3, 151.7, 152.1, 153.7 ppm; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}NO_2Na$: 288.1000 $[M+Na]^+$; found: 288.1002.

4-(2,5-Dimethoxyphenyl)-3-methoxypyridine (2f): General procedure C was employed by using 2,5-dimethoxyphenylboronic acid and 4-iodo-3-methoxypyridine. Purification by flash chromatography on silica gel (40:60 EtOAc/*n*-heptane) gave compound **2f** (81% yield) as a yellow solid: M.p. 103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.69 (s, 3H), 3.75 (s, 3H), 3.84 (s, 3H), 6.80 (m, 1H), 6.88 (m, 2H), 7.17 (br d, J = 4.7 Hz, 1H), 8.26 (br d, J = 4.7 Hz, 1H), 8.34 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.6, 56.2, 56.3, 112.4, 114.2, 116.6, 125.6, 125.7, 134.0, 135.2,

142.2, 150.8, 153.1, 153.3 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}NO_3Na$: 268.0950 $[M+Na]^+$; found: 268.0946.

3-(2,5-Dimethoxyphenyl)-4-methoxypyridine (2g): General procedure C was employed by using 2,5-dimethoxyphenylboronic acid and 3-iodo-4-methoxypyridine. Purification by flash chromatography on silica gel (40:60 EtOAc/*n*-heptane) gave compound **2g** (65% yield) as a white solid: M.p. 103–104°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.72$ (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 6.82 (dd, $J=2.6$, 0.9 Hz, 1H), 6.91 (m, 2H), 8.36 (s, 1H), 8.48 ppm (d, $J=5.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=55.4$, 55.8, 56.4, 106.4, 112.5, 113.9, 117.4, 123.6, 124.9, 150.5, 151.4, 151.5, 153.4, 163.0 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}NO_3Na$: 268.0950 $[M+Na]^+$; found: 268.0951.

3-Bromo-2-(2,5-dimethoxyphenyl)pyridine (2h): General procedure C was employed by using 2,5-dimethoxyphenylboronic acid and 2,3-dibromopyridine. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **2h** (60% yield) as a yellow solid: M.p. 111°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.75$ (s, 3H), 3.79 (s, 3H), 6.85 (dd, $J=2.8$, 0.4 Hz, 1H), 6.92 (d, $J=0.4$ Hz, 1H), 6.94 (d, $J=2.8$ Hz, 1H), 7.15 (dd, $J=8.1$, 4.7 Hz, 1H), 7.95 (dd, $J=8.1$, 1.4 Hz, 1H), 8.61 ppm (dd, $J=4.7$, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=55.9$, 56.3, 112.4, 115.5, 115.6, 122.2, 123.5, 129.9, 140.3, 147.9, 150.9, 153.5, 157.1 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}{}^{79}BrNO_2Na$: $[M+Na]^+$ 315.9949; found: 315.9951.

3-(2,3-Dimethoxy-1-naphthyl)thiophene (2i): General procedure C was employed by using thiophene-3-boronic acid and 1-iodo-2,3-dimethoxynaphthalene. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **2i** (39% yield) as a white solid: M.p. 116°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.63$ (s, 3H), 4.02 (s, 3H), 7.21 (m, 2H), 7.27 (m, 1H), 7.36 (dd, $J=3.0$, 1.2 Hz, 1H), 7.40 (m, 1H), 7.47 (dd, $J=4.9$, 3.0 Hz, 1H), 7.62 (br d, $J=8.4$ Hz, 1H), 7.74 ppm (br d, $J=8.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=55.8$, 61.1, 107.0, 124.1, 124.7, 124.8, 125.4, 125.7, 126.7, 127.1, 128.9, 130.3, 131.3, 135.4, 147.2, 152.3 ppm; HRMS (ESI): *m/z* calcd for $C_{16}H_{14}O_2SNa$: 293.0612 $[M+Na]^+$; found: 293.0611.

3-(2,3-Dimethoxy-1-naphthyl)pyridine (2j): General procedure C was employed by using pyridine-3-boronic acid and 1-iodo-2,3-dimethoxynaphthalene. Purification by flash chromatography on silica gel (25:75 EtOAc/*n*-heptane) gave compound **2j** (42% yield) as a yellow solid: M.p. 104–105°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.64$ (s, 3H), 4.03 (s, 3H), 7.24–7.30 (m, 2H), 7.37–7.47 (m, 3H), 7.73–7.79 (m, 2H), 8.66–8.70 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=55.7$, 61.0, 107.7, 123.2, 124.4, 125.1, 125.5, 126.8, 128.1, 128.2, 131.3, 131.9, 138.3, 147.0, 148.5, 151.1, 152.1 ppm; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}NO_2Na$: 288.1000 $[M+Na]^+$; found: 288.1003.

2,4-Dimethoxy-5-(2-methoxyphenyl)pyrimidine (2k): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 2-iodoanisole. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **2k** (90% yield) as a brown solid: M.p. 96°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.77$ (s, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 6.99 (m, 2H), 7.23 (dd, $J=7.5$, 1.7 Hz, 1H), 7.35 (m, 1H), 8.18 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.1$, 54.8, 55.6, 111.2, 113.1, 120.5, 122.4, 129.5, 131.4, 157.2, 158.6, 164.6, 168.6 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{14}N_2O_3Na$: 269.0902 $[M+Na]^+$; found: 269.0904.

5-(2,5-Dimethoxyphenyl)-2,4-dimethoxypyrimidine (2l): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 2-iodo-1,4-dimethoxybenzene. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **2l** (88% yield) as a yellow solid: M.p. 74–76°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.73$ (s, 3H), 3.78 (s, 3H), 3.96 (s, 3H), 4.03 (s, 3H), 6.85 (m, 3H), 8.19 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.2$, 54.9, 55.9, 56.4, 112.4, 113.0, 113.9, 117.5, 123.3, 151.5, 153.5, 158.6, 164.7, 168.6 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N_2O_4Na$: 299.1008 $[M+Na]^+$; found: 299.1009.

2,4-Dimethoxy-5-(2,3,4-trimethoxyphenyl)pyrimidine (2m): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 1-iodo-2,3,4-trimethoxybenzene. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **2m** (81% yield) as a yellow solid: M.p. 140°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.77$ (s, 3H), 3.89 (s, 6H), 3.97 (s, 3H), 4.03 (s, 3H), 6.71 (d, $J=8.5$ Hz, 1H), 6.92 (d, $J=8.5$ Hz, 1H), 8.14 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.2$, 54.9, 56.1, 60.9, 61.0, 107.1, 113.1, 120.0, 125.5, 142.3, 152.0, 154.0, 158.2, 164.6, 168.8 ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{18}N_2O_5Na$: 329.1113 $[M+Na]^+$; found: 329.1112.

5-(2,6-Dimethoxyphenyl)-2,4-dimethoxy-pyrimidine (2n): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 2-iodo-1,3-dimethoxybenzene. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **2n** (37% yield) as a white solid: M.p. 124°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.74$ (s, 6H), 3.93 (s, 3H), 4.03 (s, 3H), 6.63 (d, $J=8.4$ Hz, 2H), 7.31 (t, $J=8.4$ Hz, 1H), 8.08 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.1$, 54.8, 56.0 (2C), 104.1 (2C), 109.0, 110.8, 129.8, 158.4, 159.3 (2C), 164.7, 169.1 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N_2O_4Na$: 299.1008 $[M+Na]^+$; found: 299.1019.

5-(2-Chlorophenyl)-2,4-dimethoxypyrimidine (2o): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 1-chloro-2-iodobenzene. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **2o** (78% yield) as a white solid: M.p. 98°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.97$ (s, 3H), 4.04 (s, 3H), 7.30 (m, 3H), 4.46 (m, 1H), 8.14 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.2$, 55.0, 114.4, 126.8, 129.6, 129.8, 131.9, 132.6, 134.5, 158.3, 165.2, 168.4 ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{11}{}^{35}ClN_2O_2Na$: 273.0407 $[M+Na]^+$; found: 273.0405.

5-(2,4-Dichlorophenyl)-2,4-dimethoxypyrimidine (2p): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 1-bromo-2,4-dichlorobenzene. Purification by flash chromatography on silica gel (5:95 EtOAc/*n*-heptane) gave compound **2p** (71% yield) as a white solid: M.p. 114°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.94$ (s, 3H), 4.01 (s, 3H), 7.18 (d, $J=8.2$ Hz, 1H), 7.27 (dd, $J=2.0$, 8.2 Hz, 1H), 7.45 (d, $J=2.0$ Hz, 1H), 8.10 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.2$, 55.0, 113.3, 127.1, 129.6, 131.1, 132.6, 134.7, 135.1, 158.4, 165.3, 168.3 ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{10}{}^{35}Cl_2N_2O_2Na$: 307.0017 $[M+Na]^+$; found: 307.0019.

2,4-Dimethoxy-5-(3-methoxy-2-naphthyl)pyrimidine (2q): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 2-iodo-3-methoxynaphthalene. Purification by flash chromatography on silica gel (15:85 EtOAc/*n*-heptane) gave compound **2q** (82% yield) as a white solid: M.p. 108–109°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.89$ (s, 3H), 3.97 (s, 3H), 4.06 (s, 3H), 7.21 (s, 1H), 7.33–7.49 (m, 2H), 7.69 (s, 1H), 7.77 (m, 2H), 8.25 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.2$, 54.9, 55.7, 105.7, 113.3, 124.1, 124.3, 126.6, 126.8, 127.8, 128.5, 130.8, 134.6, 155.7, 158.4, 164.8, 169.0; ppm HRMS (ESI): *m/z* calcd for $C_{17}H_{16}N_2O_3Na$: 319.1059 $[M+Na]^+$; found: 319.1056.

5-(3-Chloro-2-naphthyl)-2,4-dimethoxypyrimidine (2r): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 2-chloro-3-iodonaphthalene. Purification by flash chromatography on silica gel (7:93 EtOAc/*n*-heptane) gave compound **2r** (84% yield) as a yellow solid: M.p. 108–110°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.98$ (s, 3H), 4.07 (s, 3H), 7.51 (m, 2H), 7.55–7.83 (m, 3H), 7.95 (s, 1H), 8.21 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.2$, 55.1, 114.7, 126.7, 126.9, 127.3, 127.8, 127.9, 130.6, 131.0, 131.8, 132.1, 133.7, 158.3, 165.3, 168.8 ppm; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}{}^{35}ClN_2O_2Na$: 323.0563 $[M+Na]^+$; found: 323.0560.

Methyl-3-(2,4-dimethoxy-5-pyrimidyl)-2-naphthoate (2s): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and methyl-3-iodonaphthalene-2-carboxylate. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **2s** (91% yield) as a yellow solid: M.p. 130–132°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.79$ (s, 3H), 3.92 (s, 3H), 4.06 (s, 3H), 7.58 (m, 2H), 7.73 (br s, 1H), 7.87 (br d, $J=7.5$ Hz, 1H), 7.94 (dd, $J=7.9$, 1.4 Hz, 1H), 8.27 (br s, 1H), 8.51 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=52.2$, 54.0, 55.1, 117.2, 127.2, 127.9, 128.6, 128.7, 128.9, 130.3, 130.5, 131.7, 132.1, 134.8, 156.2, 164.9, 167.9, 168.5 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}N_2O_4Na$: 347.1008 $[M+Na]^+$; found: 347.1010.

2,4-Dimethoxy-5-(1-naphthyl)pyrimidine (2t): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 1-iodonaphthalene. Purification by flash chromatography on silica gel (5:95 EtOAc/*n*-heptane) gave compound **2t** (90% yield) as a white solid: M.p.

96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.92 (s, 3H), 4.10 (s, 3H), 7.37–7.59 (m, 5H), 7.89 (d, J = 8.2 Hz, 2H), 8.26 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.0, 54.9, 115.0, 125.3, 125.5, 125.9, 126.2, 128.0, 128.4, 128.7, 131.2, 132.1, 133.6, 158.8, 165.1, 168.9 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{14}N_2O_2Na$: 289.0953 $[M+Na]^+$; found: 289.0952.

1-(2,4-Dimethoxy-5-pyrimidyl)isoquinoline (2u): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 1-iodoisoquinoline. Purification by flash chromatography on silica gel (40:60 EtOAc/*n*-heptane) gave compound **2u** (68% yield) as a white solid: M.p. 132–134 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.92 (s, 3H), 4.08 (s, 3H), 7.52 (m, 1H), 7.69 (m, 3H), 7.87 (m, 1H), 8.38 (s, 1H), 8.61 ppm (d, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.3, 55.2, 114.8, 120.9, 126.9, 127.1, 127.5, 127.9, 130.4, 136.5, 142.5, 154.2, 159.6, 165.6, 168.9 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{13}N_3O_2Na$: 290.0905 $[M+Na]^+$; found: 290.0904.

2,4-Dimethoxy-5-(3-methoxy-4-pyridyl)pyrimidine (2w): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 4-iodo-3-methoxypyridine. Purification by flash chromatography on silica gel (70:30 EtOAc/*n*-heptane) gave compound **2w** (38% yield) as a yellow solid: M.p. 170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.88 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 7.21 (d, J = 4.5 Hz, 1H), 8.25 (s, 1H), 8.29 (d, J = 4.8 Hz, 1H), 8.36 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.3, 55.1, 56.4, 110.5, 125.4, 130.2, 134.2, 142.6, 153.1, 158.9, 165.3, 168.3 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{13}N_3O_3Na$: 270.0855 $[M+Na]^+$; found: 270.0870.

5-(6-Chloro-2-methoxy-3-pyridyl)-2,4-dimethoxypyrimidine (2x): General procedure C was employed by using 2,4-dimethoxypyrimidine-5-boronic acid and 6-chloro-3-iodo-2-methoxypyridine. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **2x** (75% yield) as a white solid: M.p. 166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.93 (s, 3H), 3.97 (s, 3H), 4.04 (s, 3H), 6.97 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 8.23 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.3, 54.5, 55.1, 110.4, 114.9, 116.4, 141.9, 148.0, 158.7, 161.0, 164.9, 168.5 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{12}{}^{35}ClN_3O_3Na$: 304.0465 $[M+Na]^+$; found: 304.0466.

2-Methoxy-1-(3-methoxyphenyl)naphthalene (2y): General procedure D was employed by using 3-methoxyphenylmagnesium bromide and 1-iodo-2-methoxynaphthalene. Purification by flash chromatography on silica gel (*n*-heptane) gave compound **2y** (50% yield) as a white solid: M.p. 112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.86 (s, 3H), 3.87 (s, 3H), 6.98 (m, 3H), 7.34–7.47 (m, 4H), 7.55 (m, 1H), 7.84 (m, 1H), 7.90 ppm (br d, J = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.3, 56.9, 112.9, 113.9, 116.5, 123.5, 123.6, 125.3, 125.4, 126.5, 127.9, 129.1, 129.2, 129.3, 133.7, 137.9, 153.8, 159.5 ppm; HRMS (ESI): m/z calcd for $C_{18}H_{16}O_2Na$: 287.1048 $[M+Na]^+$; found: 287.1049.

9-(3-Methoxyphenyl)anthracene (2z): General procedure D was employed by using 3-methoxyphenylmagnesium bromide and 9-iodoanthracene. Purification by flash chromatography on silica gel (*n*-heptane) gave compound **2z** (52% yield) as a yellow solid: M.p. 110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.88 (s, 3H), 7.10 (m, 3H), 7.41 (m, 2H), 7.53 (m, 3H), 7.80 (d, J = 8.7 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 8.53 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.3, 113.4, 116.7, 123.8, 125.2 (2C), 125.5 (2C), 126.7, 127.0 (2C), 128.4 (2C), 129.5 (2C), 130.2, 131.5 (2C), 137.0, 140.3, 159.7 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{16}ONa$: 307.1099 $[M+Na]^+$; found: 307.1099.

4-Iodo-2,2′,5,5′-tetramethoxybiphenyl (3aa): General procedure E was employed by using **2aa**. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **3aa** (48% yield) as a white solid: M.p. 112–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.73 (s, 6H), 3.79 (s, 3H), 3.83 (s, 3H), 6.76 (s, 1H), 6.81–6.93 (m, 3H), 7.36 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.9, 56.6, 56.8, 57.1, 84.6, 112.6, 113.6, 114.3, 117.3, 122.8, 128.1, 128.8, 151.3, 151.8, 152.5, 153.5 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{17}IO_4Na$: 423.0069 $[M+Na]^+$; found: 423.0068.

3-Iodo-1-(2-methoxyphenyl)isoquinoline (3a): General procedure E was employed by using **2a**. Purification by flash chromatography on silica gel (15:85 EtOAc/*n*-heptane) gave compound **3a** (39% yield) as a brown solid: M.p. 120–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.69 (s, 3H), 7.03 (d, J = 8.3 Hz, 1H), 7.10 (td, J = 7.4, 0.9 Hz, 1H), 7.38 (dd, J = 7.4,1.7 Hz, 1H), 7.47 (m, 2H), 7.65 (m, 2H), 7.73 (br d, J = 8.3 Hz, 1H), 8.16 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.6, 109.5, 111.2, 121.0, 125.5, 127.0, 127.5, 128.3, 128.4, 130.6, 130.7, 130.8, 131.5, 137.9, 157.2, 160.2 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{13}INO$: 362.0042 $[M+H]^+$; found: 362.0042.

1-(4-Iodo-2,5-dimethoxyphenyl)-2,3-dimethoxynaphthalene (3c): General procedure E was employed by using compound **2c**. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **3c** (45% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.65 (s, 3H), 3.69 (s, 3H), 3.79 (s, 3H), 4.02 (s, 3H), 6.73 (s, 1H), 7.23–7.31 (m, 3H), 7.38 (m, 1H), 7.46 (s, 1H), 7.74 ppm (br d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.8, 56.5, 57.1, 61.0, 84.9, 107.2, 114.9, 122.6, 124.1, 125.3, 125.5, 126.3, 126.8, 127.9, 128.4, 131.2, 146.9, 152.3, 152.4, 152.6 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{19}IO_4Na$: 473.0226 $[M+Na]^+$; found: 473.0230.

4-(2,5-Dimethoxyphenyl)-1-iodoisoquinoline (3e): General procedure E was employed by using compound **2e**. Purification by flash chromatography on silica gel (5:95 EtOAc/*n*-heptane) gave compound **3e** (63% yield) as a white solid: M.p. 121 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.63 (s, 3H), 3.80 (s, 3H), 6.85 (dd, J = 2.3, 1.2 Hz, 1H), 6.99 (m, 2H), 7.53 (m, 1H), 7.64 (m, 2H), 8.16 (m, 1H), 8.19 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.9, 56.2, 112.4, 114.6, 117.7, 125.6, 126.4, 127.0, 128.9, 131.0, 131.2, 131.3, 133.0, 135.4, 143.3, 151.6, 153.7 ppm; HRMS (ESI): m/z calcd for $C_{17}H_{14}INO_2$: 413.9967 $[M+Na]^+$; found: 413.9965.

4-(2,5-Dimethoxyphenyl)-2-iodo-3-methoxypyridine (3f): General procedure E was employed by using compound **2f**. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **3f** (71% yield) as a yellow solid: M.p. 110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.49 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 6.87 (m, 1H), 6.94 (m, 2H), 7.19 (d, J = 4.8 Hz, 1H), 8.15 ppm (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 56.0, 56.4, 61.0, 112.6, 115.6, 116.0, 117.4, 124.9, 126.7, 139.6, 145.4, 150.6, 153.6, 154.6 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{14}INO_3Na$: 393.9916 $[M+Na]^+$; found: 393.9918.

3-Bromo-2-(2,5-dimethoxyphenyl)-4-iodopyridine (3h): General procedure E was employed by using compound **2h**. Purification by flash chromatography on silica gel (15:85 EtOAc/*n*-heptane) gave compound **3h** (38% yield) as a yellow solid: M.p. 168–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.75 (s, 3H), 3.78 (s, 3H), 6.80 (d, J = 2.5 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 6.95 (dd, J = 9.0, 2.5 Hz, 1H), 7.78 (br d, J = 4.0 Hz, 1H), 8.18 ppm (br d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.9, 56.3, 112.4, 114.1, 115.1, 115.7, 130.0, 131.2, 134.2, 147.4, 150.6, 153.5, 158.0 ppm; HRMS (ESI): m/z calcd for $C_{13}H_{11}{}^{79}BrINO_2Na$: 441.8916 $[M+Na]^+$; found: 441.8914.

3-(2,3-Dimethoxy-1-naphthyl)-2,5-diiodothiophene (3i): General procedure E was employed by using compound **2i**. Purification by flash chromatography on silica gel (15:85 EtOAc/*n*-heptane) gave compound **3i** (59% yield) as a yellow solid: M.p. 130–132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.73 (s, 3H), 4.02 (s, 3H), 7.04 (s, 1H), 7.30 (m, 3H), 7.41 (m, 1H), 7.76 ppm (br d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.8, 61.3, 76.4, 81.2, 108.0, 124.5, 125.2, 125.6, 125.7, 126.8, 127.8, 131.1, 139.8, 144.9, 147.5, 152.0 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{12}I_2O_2SNa$: 544.8545 $[M+Na]^+$; found: 544.8549.

5-(2,3-Dimethoxy-1-naphthyl)-2-iodopyridine: General procedure E was employed to afford the product (20% yield), which was identified by its NMR data: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.66 (s, 3H), 4.03 (s, 3H), 7.26–7.31 (m, 2H), 7.35–7.44 (m, 3H), 7.77 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 8.42 ppm (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.7, 61.1, 108.0, 116.0, 124.6, 124.7, 125.6, 126.6, 126.9, 127.7, 131.3, 131.7, 134.5, 140.3, 146.9, 151.8, 151.9 ppm.

3-(2,3-Dimethoxy-1-naphthyl)-2-iodopyridine: General procedure E was employed to afford the product (15% yield), which was identified by its NMR data: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.77 (s, 3H), 4.05 (s, 3H), 7.12 (d, J = 8.4 Hz, 1H), 7.32 (m, 1H), 7.43 (m, 2H), 7.56 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 8.48 ppm (m, 1H).

2-Iodo-5-(4-iodo-2,3-dimethoxy-1-naphthyl)pyridine: General procedure E was employed to afford the product (12% yield), which was identified

by its NMR data: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.72 (s, 3H), 4.00 (s, 3H), 7.36–7.40 (m, 3H), 7.52 (ddd, J = 8.2, 4.8, 3.4 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 8.20 (dt, J = 8.5, 0.8 Hz, 1H), 8.40 ppm (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 60.8, 61.4, 97.3, 117.0, 125.6, 126.6, 127.3, 128.2, 130.5, 131.2, 132.5, 132.6, 134.6, 140.0, 149.4, 152.1, 153.2 ppm.

4-Iodo-2,6-dimethoxy-5-(2-methoxyphenyl)pyrimidine (3k): General procedure E was employed by using compound **2k**. Purification by flash chromatography on silica gel (15:85 EtOAc/*n*-heptane) gave compound **3k** (97% yield) as a brown solid: M.p. 130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.77 (s, 3H), 3.88 (s, 3H), 4.02 (s, 3H), 7.03 (m, 3H), 7.42 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.8, 55.4, 55.8, 111.3, 119.7, 120.6, 125.7, 130.3, 131.7, 134.7, 157.1, 163.0, 167.5 ppm; HRMS (ESI): m/z calcd for $C_{13}H_{13}IN_2O_3Na$: 394.9869 $[M+Na]^+$; found: 394.9869.

5-(2,5-Dimethoxyphenyl)-4-iodo-2,6-dimethoxypyrimidine (3l): General procedure E was employed by using compound **2l**. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **3l** (94% yield) as a white solid: M.p. 132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.72 (s, 3H), 3.78 (s, 3H), 3.87 (s, 3H), 4.01 (s, 3H), 6.65 (d, J = 2.8 Hz, 1H), 6.91 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.8, 55.4, 55.8, 56.4, 112.5, 114.7, 117.5, 119.5, 126.4, 134.5, 151.3, 153.4, 162.9, 167.3 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{15}IN_2O_4Na$: 424.9974 $[M+Na]^+$; found: 424.9977.

4-Iodo-2,6-dimethoxy-5-(2,3,4-trimethoxyphenyl)pyrimidine (3m): General procedure E was employed by using compound **2m**. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **3m** (89% yield) as a yellow solid: M.p. 110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.77 (s, 3H), 3.89 (s, 3H), 3.90 (s, 6H), 4.02 (s, 3H), 6.73 (s, J = 8.5 Hz, 1H), 6.77 ppm (s, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.8, 55.4, 56.0, 61.0, 61.1, 107.1, 119.6, 123.6, 125.8, 135.1, 142.2, 151.8, 154.4, 163.0, 167.5 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{17}IN_2O_5Na$: 455.0080 $[M+Na]^+$; found: 455.0073.

5-(2,6-Dimethoxyphenyl)-4-iodo-2,6-dimethoxypyrimidine (3n): General procedure E was employed by using compound **2n**. Purification by flash chromatography on silica gel (15:85 EtOAc/*n*-heptane) gave compound **3n** (82% yield) as a white solid: M.p. 166–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.75 (s, 6H), 3.87 (s, 3H), 4.02 (s, 3H), 6.63 (d, J = 8.4 Hz, 2H), 7.38 ppm (t, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.7, 55.3, 56.1 (2C), 104.2 (2C), 114.5, 116.5, 130.5, 135.7, 158.1 (2C), 163.0, 167.8 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{15}IN_2O_4Na$: 424.9974 $[M+Na]^+$; found: 424.9971.

5-(2-Chlorophenyl)-4-iodo-2,6-dimethoxypyrimidine (3o): General procedure E was employed by using compound **2o**. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **3o** (78% yield) as a white solid: M.p. 152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.89 (s, 3H), 4.04 (s, 3H), 7.18 (m, 1H), 7.37 (m, 2H), 7.48 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.9, 55.6, 120.6, 127.0, 129.7, 130.1, 132.2, 133.9, 134.6, 135.7, 163.3, 163.2 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{10}{}^{35}ClIN_2O_2Na$: 398.9373 $[M+Na]^+$; found: 398.9374.

5-(2,4-Dichlorophenyl)-4-iodo-2,6-dimethoxypyrimidine (3p): General procedure E was employed by using compound **2p**. Purification by flash chromatography on silica gel (5:95 EtOAc/*n*-heptane) gave compound **3p** (70% yield) as a white solid: M.p. 124–126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.89 (s, 3H), 4.03 (s, 3H), 7.12 (d, J = 8.2 Hz, 1H), 7.33 (dd, J = 8.2, 2.1 Hz, 1H), 7.50 ppm (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.0, 55.6, 119.6, 127.5, 129.7, 133.0, 133.9, 134.3, 135.4, 135.5, 163.5, 167.2 ppm; HRMS (ESI): m/z calcd for $C_{12}H_9{}^{35}Cl_2IN_2O_2Na$: 432.8983 $[M+Na]^+$; found: 432.8983. 5-(2,4-Dichloro-3-iodophenyl)-4-iodo-2,6-dimethoxypyrimidine (**3p′**) was also isolated (15% yield) as a white solid: M.p. 179–180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.90 (s, 3H), 4.04 (s, 3H), 7.12 (d, J = 8.2 Hz, 1H), 7.45 ppm (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.0, 55.7, 104.9, 120.8, 127.6, 132.3, 133.6, 134.7, 141.1, 147.6, 163.5, 167.0 ppm; HRMS (ESI): m/z calcd for $C_{12}H_8{}^{35}Cl_2I_2N_2O_2Na$: 558.7950 $[M+Na]^+$; found: 558.7949.

5-(2,4-Dichloro-3-iodophenyl)-2,6-dimethoxypyrimidine: The product was identified by its NMR data: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.97 (s, 3H), 4.05 (s, 3H), 7.19 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 8.08 ppm (s, 1H).

4-Iodo-2,6-dimethoxy-5-(3-methoxy-2-naphthyl)pyrimidine (3q): General procedure E was employed by using compound **2q**. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **3q** (82% yield) as a white solid: M.p. 194 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.88 (s, 6H), 4.05 (s, 3H), 7.22 (s, 1H), 7.64–7.51 (m, 2H), 7.59 (s, 1H), 7.79 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.8, 55.4, 55.8, 105.9, 119.5, 124.0, 126.7, 126.9, 127.3, 128.0, 128.6, 131.4, 134.6, 134.9, 155.3, 163.0, 167.6 ppm; HRMS (ESI): m/z calcd for $C_{17}H_{15}IN_2O_3Na$: 445.0025 $[M+Na]^+$; found: 445.0027.

5-(3-Chloro-2-naphthyl)-4-iodo-2,6-dimethoxypyrimidine (3r): General procedure E was employed by using compound **2r**. Purification by flash chromatography on silica gel (5:95 EtOAc/*n*-heptane) gave compound **3r** (83% yield) as a white solid: M.p. 188–190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.90 (s, 3H), 4.07 (s, 3H), 7.53 (m, 2H), 7.70 (s, 1H), 7.83 (m, 2H), 7.99 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.9, 55.6, 120.7, 126.6, 127.1, 127.6, 127.8, 128.1, 131.7, 131.8, 131.9, 133.6, 134.0, 134.4, 163.4, 167.5 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{12}{}^{35}ClIN_2O_2Na$: 448.9530 $[M+Na]^+$; found: 448.9532.

4-Iodo-2,6-dimethoxy-5-(1-naphthyl)pyrimidine (3t): General procedure E was employed by using compound **2t**. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **3t** (67% yield) as a white solid: M.p. 96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.83 (s, 3H), 4.09 (s, 3H), 7.33 (dd, J = 7.1, 1.1 Hz, 1H), 7.43–7.58 (m, 4H), 7.94 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.9, 55.6, 120.9, 124.9, 125.6, 126.2, 126.6, 128.5, 128.6, 129.1, 131.7, 133.7, 134.4, 135.1, 163.4, 167.8 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{13}IN_2O_2Na$: 414.9919 $[M+Na]^+$; found: 414.9917.

1-(4-Iodo-2,6-dimethoxy-5-pyrimidyl)isoquinoline (3u): General procedure E was employed by using compound **2u**. Purification by flash chromatography on silica gel (30:70 EtOAc/*n*-heptane) gave compound **3u** (85% yield) as a white solid: M.p. 179–180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.84 (s, 3H), 4.08 (s, 3H), 7.58 (m, 2H), 7.73 (m, 2H), 7.92 (d, J = 8.3 Hz, 1H), 8.66 ppm (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.9, 55.6, 120.2, 121.3, 126.1, 127.3, 127.6, 127.8, 130.5, 132.7, 136.5, 142.6, 156.3, 163.5, 168.0 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{12}IN_3O_2Na$: 415.9872 $[M+Na]^+$; found: 415.9868.

1-Iodo-4-(4-iodo-2,6-dimethoxy-5-pyrimidyl)isoquinoline (3v): General procedure E was employed by using compound **2v**. Purification by flash chromatography on silica gel (20:80 EtOAc/*n*-heptane) gave compound **3v** (60% yield) as a white solid: M.p. 248 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.82 (s, 3H), 4.07 (s, 3H), 7.34 (m, 1H), 7.70 (m, 2H), 8.10 (s, 1H), 8.20 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.0, 55.8, 116.7, 124.8, 128.3, 129.2, 129.4, 131.6, 131.7, 133.6, 134.8, 135.1, 144.4, 163.9, 168.0 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{11}I_2N_3O_2Na$: 541.8838 $[M+Na]^+$; found: 541.8837.

5-(6-Chloro-2-methoxy-3-pyridyl)-4-iodo-2,6-dimethoxypyrimidine (3x): General procedure E was employed by using compound **2x**. Purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) gave compound **3x** (66% yield) as a white solid: M.p. 132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.87 (s, 3H), 3.90 (s, 3H), 4.01 (s, 3H), 6.98 (d, J = 7.7 Hz, 1H), 7.35 ppm (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.5, 54.9, 55.6, 116.4, 117.0, 118.3, 134.4, 142.6, 148.8, 160.8, 163.3, 167.4 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{11}{}^{35}ClIN_3O_3Na$: $[M+Na]^+$ 429.9431; found: 429.9433. 5-(6-Chloro-5-iodo-2-methoxy-3-pyridyl)-4-iodo-2,6-dimethoxypyrimidine (**3x′**) was also isolated (26% yield) as a white solid: M.p. 176–178 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.88 (s, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 7.75 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.7, 54.9, 55.6, 82.2, 115.7, 120.3, 134.3, 151.4, 151.7, 160.6, 163.4, 167.3 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{10}{}^{35}ClI_2N_3O_3Na$: 555.8398 $[M+Na]^+$; found: 555.8405.

4-(2-Chlorophenyl)-2,6-dimethoxy-5-(2,5-dimethoxyphenyl)pyrimidine (4l): General procedure F was employed by using compound **3l** and 2-chlorophenylboronic acid, gave compound **4l** (92% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.57 (s, 3H), 3.64 (s, 3H), 3.98 (s, 3H), 4.04 (s, 3H), 6.63 (d, J = 3.0 Hz, 1H), 6.66 (d, J = 9.0 Hz, 1H), 6.72 (dd, J = 9.0, 3.0 Hz, 1H), 7.04–7.17 (m, 3H), 7.29 ppm (dd, J = 7.8, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.5, 55.0, 55.7, 55.8, 111.6, 112.1, 114.4, 117.4, 122.8, 125.9, 129.4, 129.5, 130.4, 132.6, 137.7, 151.4, 153.0,

164.0, 165.3, 169.7 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}{}^{35}ClN_2O_4Na$: 409.0931 $[M+Na]^+$; found: 409.0929; *m/z* calcd for $C_{20}H_{20}{}^{35}ClN_2O_4$: 387.1112 $[M+H]^+$; found: 387.1115.

4-(2-Chlorophenyl)-2,6-dimethoxy-5-(3-methoxy-2-naphthyl)pyrimidine (4q): General procedure F was employed by using compound **3q** and 2-chlorophenylboronic acid, gave compound **4q** (91% yield) as a white powder: M.p. 225°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.75$ (s, 3H), 3.97 (s, 3H), 4.08 (s, 3H), 6.96–7.14 (m, 4H), 7.22–7.30 (m, 2H), 7.38 (ddd, $J=8.4$, 6.9, 1.2 Hz, 1H), 7.53 (s, 1H), 7.65 ppm (dd, $J=8.1$, 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.5$, 55.1, 55.4, 105.3, 112.1, 123.7, 124.0, 126.0, 126.4, 126.5, 127.8, 128.4, 129.4, 129.6, 130.3, 131.4, 132.5, 134.4, 137.7, 155.7, 164.1, 165.4, 170.0 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}{}^{35}ClN_2O_3Na$: 429.0982 $[M+Na]^+$; found: 429.0979; *m/z* calcd for $C_{23}H_{20}{}^{35}ClN_2O_3$: 407.1162 $[M+H]^+$; found: 407.1177.

4-(2-Aminophenyl)-5-(2-chlorophenyl)-2,6-dimethoxypyrimidine (4o): General procedure F, employed by using **3o** and 2-aminophenylboronic acid, gave compound **4o** (94% yield) as a whitish powder: M.p. 90°C (deg.); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.99$ (s, 3H), 4.06 (s, 3H), 4.26 (br s, 2H), 6.42 (td, $J=7.5$, 0.9 Hz, 1H), 6.70 (dd, $J=8.1$, 0.9 Hz, 1H), 6.71 (dd, $J=7.5$, 1.5 Hz, 1H), 6.97–7.03 (s, 2H), 7.10 (td, $J=7.5$, 1.5 Hz, 1H), 7.19 (td, $J=7.7$, 1.8 Hz, 1H), 7.38 ppm (dd, $J=8.1$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.6$, 55.1, 112.9, 117.3, 118.3, 122.8, 126.7, 129.1, 129.3, 130.1, 130.7, 132.6, 133.4, 135.2, 144.3, 164.2, 165.7, 170.3 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}{}^{35}ClN_3O_2$: 342.1009 $[M+H]^+$; found: 342.1008; *m/z* calcd for $C_{18}H_{16}{}^{35}ClN_3O_2Na$: 364.0829 $[M+Na]^+$; found: 364.0829.

4-(2-Aminophenyl)-5-(3-chloro-2-naphthyl)-2,6-dimethoxypyrimidine (4r): General procedure F was employed by using compound **3r** and 2-aminophenylboronic acid, gave compound **4r** (91% yield) as a white powder: M.p. 180°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.97$ (s, 3H), 4.08 (s, 3H), 4.50 (br s, 2H), 6.31 (td, $J=7.5$, 0.9 Hz, 1H), 6.64 (dd, $J=8.1$, 0.9 Hz, 1H), 6.77 (dd, $J=7.8$, 1.5 Hz, 1H), 6.92 (ddd, $J=7.7$, 7.2, 1.5 Hz, 1H), 7.36–7.48 (m, 2H), 7.50 (s, 1H), 7.64 (d, $J=8.1$ Hz, 1H), 7.73 (d, $J=8.1$ Hz, 1H), 7.90 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.6$, 55.0, 112.9, 117.1, 118.1, 122.5, 126.2, 126.8, 127.0, 127.4, 128.0, 130.0, 130.7, 131.4, 131.7, 131.8, 132.9, 133.4, 145.0, 164.2, 166.0, 170.7; ppm HRMS (ESI): *m/z* calcd for $C_{22}H_{19}{}^{35}ClN_3O_2$: 392.1166 $[M+H]^+$; found: 392.1165; *m/z* calcd for $C_{22}H_{18}{}^{35}ClN_3O_2Na$: 414.0985 $[M+Na]^+$; found: 414.0981.

2,4,5,8-Tetramethoxydibenzo[*f,h*]quinazoline (5l): To a degassed solution of compound **4l** (0.19 g, 0.50 mmol) and Cs_2CO_3 (0.32 g, 1.0 mmol) in 1,4-dioxane (5 mL) were added $Pd(OAc)_2$ (10 mg, 50 μmol, 10 mol%) and $Cy_3P{\cdot}BF_4$ (17 mg, 0.10 mmol, 20 mol%). The resulting mixture was heated for 18 h at 105°C before cooling and diluting with Et_2O (10 mL), washing with water (10 mL), and extracting with CH_2Cl_2 (3×20 mL). After drying over Na_2SO_4, the solvent was evaporated under reduced pressure and cyclized compound **5l** was isolated (68% yield) by purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.99$ (s, 3H), 4.06 (s, 3H), 4.15 (s, 3H), 4.22 (s, 3H), 7.11 (d, $J=9.0$ Hz, 1H), 7.14 (d, $J=9.0$ Hz, 1H), 7.65 (ddd, $J=8.1$, 6.9, 1.2 Hz, 1H), 7.73 (ddd, $J=8.7$, 6.9, 1.8 Hz, 1H), 9.15 (dd, $J=7.8$, 1.5 Hz, 1H), 9.54 ppm (dd, $J=8.4$, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=54.6$, 55.0, 56.4, 56.7, 104.4, 110.0, 110.4, 119.0, 121.0, 125.4, 127.0, 128.3, 129.5, 130.2, 133.0, 151.0, 152.6, 154.5, 162.3, 169.2 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}N_2O_4$: 351.1345 $[M+H]^+$; found: 351.1344; *m/z* calcd $C_{20}H_{18}N_2O_4Na$: 373.1164 $[M+Na]^+$; found: 373.1164.

1-(2,5-Dimethoxyphenyl)-9*H*-pyrido[3,4-*b*]indole (5h): was prepared by following a previously reported procedure.[9j] To a degassed solution of compound **3h** (0.21 g, 0.50 mmol), 2-aminophenylboronic acid (0.27 g, 2 mmol), and CsF (0.15 g, 1.0 mmol) in 1,4-dioxane (5 mL) were added $[Pd(dba)_2]$ (14 mg, 25 μmol, 5 mol%) and PPh_3 (13 mg, 50 μmol, 10 mol%). The resulting mixture was heated for 16 h at 105°C before cooling and diluting with Et_2O (10 mL), washing with water (10 mL), and extracting with CH_2Cl_2 (3×20 mL). After drying over Na_2SO_4, the solvent was evaporated under reduced pressure and cyclized compound **5h** was isolated (70% yield) by purification by flash chromatography on silica gel (10:90 EtOAc/*n*-heptane) as a beige powder: M.p. 110°C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.80$ (s, 3H), 3.88 (s, 3H), 7.05 (dd, $J=9.0$, 3.0 Hz, 1H), 7.10 (d, $J=9.0$ Hz, 1H), 7.34 (t, $J=7.3$ Hz, 1H), 7.39 (d, $J=3.0$ Hz, 1H), 7.52–7.62 (m, 2H), 8.06 (d, $J=5.4$ Hz, 1H), 8.19 (d, $J=8.1$ Hz, 1H), 8.62 ppm (d, $J=5.4$ Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz): $\delta=56.3$, 56.6, 113.3, 114.2, 115.9, 117.6, 118.0, 121.6, 121.9, 123.2, 125.0, 130.9, 132.6, 134.9, 135.7, 140.3, 143.9, 152.9, 155.3 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_2$: 305.1290 $[M+H]^+$; found: 305.1292.

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