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Synthesis of carbo- and heterobiaryls by intermolecular radical addition of aryl bromides onto aromatic solvents

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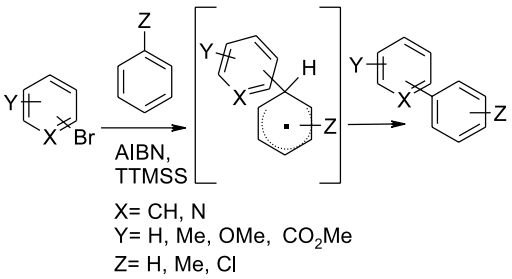
Abstract—Tris(trimethylsilyl)silane (TTMSS) and azabisisobutyronitrile (AIBN) promoted the intermolecular arylation of aryl and heteroaryl bromides onto aromatic solvents under thermal conditions via a radical pathway.

1. Introduction

Biaryls (Ar^1-Ar^2) and related systems, such as heterobiaryls and arylheterocyclic compounds have found numerous applications in several fields: as advanced materials, biologically active molecules, chelating agents or metal ligands.[1–3] Consequently, a wide variety of synthetic methods have been developed for their preparation, with palladium cross-coupling reactions currently being the most popular choice.[1,4] Additional methods reported for the preparation of biaryls include some examples involving arylation of arenes through radical mechanisms. Intramolecular radical additions, of aryl radicals to benzene[5] or heterocyclic rings,[6] under reductive conditions, followed by rearomatisation, have been reported. In this context, intramolecular arylations, by *ipso* substitution of suitable sulfonyl,[7] phosphinate,[8] silyl[9] or benzylic ether[10] derivatives, also under reductive conditions, have been widely reported for the preparation of both biaryls and arylheterocyclic derivatives. On the other hand, the intermolecular version of the radical arylation has been scarcely explored. At the start of the present project, only radical approaches based on photochemical arylation of arenes, among other oxidative conditions, have been described.[11] Our group recently reported a simple method for the preparation of aryl compounds,[12] based on thermal intermolecular radical addition of aryl or heteroaryl radicals onto benzene (Scheme 1). The process takes place under reductive conditions, using the corresponding aryl bromides as starting material and AIBN/TTMSS (azobis-isobutyronitrile/tris(trimethylsilyl)silane) as initiator for the radical process. The intermolecular radical addition of *ortho*-functionalized aryl iodides to benzene has recently been applied by Crich and Sannigrahi in an elegant approach to functionalised tetrahydrobenzofuranes.[13]



Scheme 1.

In this paper, the results on the intermolecular addition of aryl (and heteroaryl) radicals onto arenes and heteroarenes are described. During the study, scope and limitations of the process were evaluated, by varying the radical acceptor (usually the solvent) and the aryl radical donor.

2. Results and discussion

2.1. Variations on the radical acceptor

In a preceding communication[12] we reported phenylation of 2-bromopyridine **1a** (Scheme 2, Z=H; Table 1, entry 1). The best results were obtained by slow addition (8 h) of a solution of TTMSS (2 equiv.), AIBN (2 equiv.) and 2-bromopyridine (1 equiv.) in 5 mL of benzene, into an additional 10 mL of benzene (Method A), to supply 2-phenylpyridine **2a** in 41% yield. Similar results were obtained from 3-bromopyridine **1b**, which gave

Keywords: Aryl bromides; Arylation; Biaryls; Radicals and radical reaction; Tris(trimethylsilyl)silane (TTMSS).
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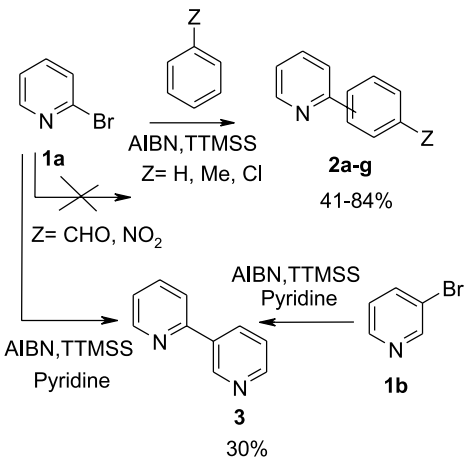
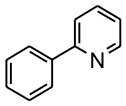
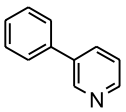
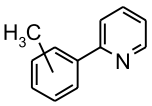
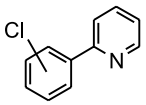
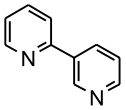
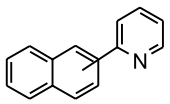
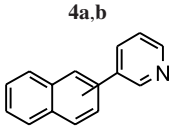


Scheme 2.

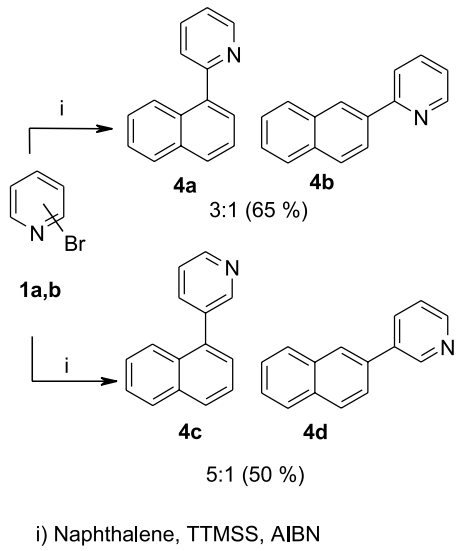
3-phenylpyridine **2b** in 74% yield (Table 1, entry 2). Attempts to extend the scope of the process were carried out using toluene (Scheme 2, Z=Me; Table 1, entry 3) and chlorobenzene (Scheme 2, Z=Cl; Table 1, entry 4) as aromatic solvents. In these cases, the best results were obtained using chlorobenzene, an electron-poor substrate, which produced a mixture of the 2-phenylpyridines (13:0:1 of the *o*/*m*/*p* isomers) with an overall yield of 84%. The use of toluene led to a mixture of the corresponding 2-tolylpyridines (2:1:1 of the *o*/*m*/*p* isomers) in 61% overall yield. As the best results were obtained using chlorobenzene, other electron-deficient solvents were also tested, such as benzaldehyde (Scheme 2, Z=CHO; Table 1, entry 5) or nitrobenzene (Scheme 2, Z=NO_2; Table 1, entry 6): but no arylated products were detected.

Pyridine, another electron-deficient substrate was also tested. Thus, when the process was carried out using 2-bromopyridine **1a** as a source of the 2-pyridyl radical, and pyridine as the solvent, 2,3′-bipyridine **3**, was isolated, in a

Table 1. Variations of the (radical acceptor) solvent

Entry	Starting material	Solvent	Biaryl comp.	Ratio	Yield (%)[a]	Method
1	**1a**	Ph-H	 **2a**	—	41	A
2	**1b**	Ph-H	 **2b**	—	74	A
3	**1a**	Ph-Me	 **2c–e**	*o*/*m*/*p* 2:1:1	61	A
4	**1a**	Ph-Cl	 **2f**,**g**	*o*/*m*/*p* 13:0:1	84	A
5	**1a**	Ph-CHO	—	—	—	A
6	**1a**	Ph-NO_2	—	—	—	A
7	**1a**	Pyr	 **3**	—	30	A
8	**1b**	Pyr	**3**	—	30	A
9	**1a**	$C_{10}H_8$	 **4a**,**b**	α:β 3:1	61	B
10	**1b**	$C_{10}H_8$	 **4c**,**d**	α:β 5:1	50	B

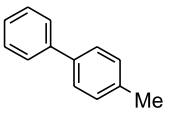
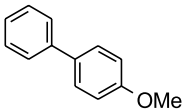
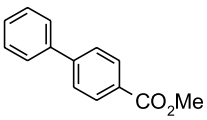
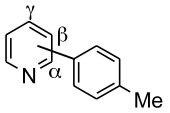
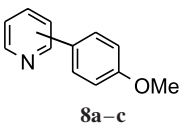
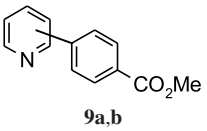
[a] Yields refer to isolated pure product. All the compounds were identified by spectroscopic and literature data. Method A: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding pyridyl bromide **1** (1 equiv.) in the solvent (5 mL) added into an additional 10 mL of the corresponding solvent during 8 h, 80 °C, 24 h. Method B: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding pyridyl bromide **1** in MeCN (5 mL) added over naphthalene (55 equiv.) during 4 h, 80 °C, 24 h.



Scheme 3.

30% yield (Scheme 2; Table 1, entry 7). Surprisingly, the same process using 3-bromopyridine **1b** as the starting material, also yielded 2,3′-bipyridine **3**, again in 30% yield, and only traces of the alternative isomeric compound (Scheme 2; Table 1, entry 8). In general, one would expect that the regioselectivity of the process mainly depends on the electrophilicity or nucleophilicity of both, radical and acceptor, as well as on polar effects and orbital control. As far as the character of attacking radicals is concerned, it is now recognized that heteroaryl species with a carbon radical adjacent to the heteroatom behave as electrophiles, with the electrophilicity interpreted in terms of the inductive effect of the ring heteroatom.[11a,b] In all examples discussed, the 2-pyridyl radical would act as an electrophile, thus attacking either substituted benzenes or pyridine when they are both acceptor and solvent. Almost all substituents stabilize radicals, and so, substituted benzenes, including toluene and chlorobenzene, usually react faster than benzene itself. Furthermore, most substituted benzenes show some preference for *ortho*/*para* attack, because attack at these sites gives the more stable intermediates.[14] Moreover, in the case of chlorobenzene, the mesomeric π-donor character of the chloro-substituent must be taken into consideration. In a

Table 2. Variations on the radical

Entry	Starting material	Biaryl compound	Ratio α:β:γ	Yield (%)[a]	Method
1	**5a**	 **6a**	—	51	A
2	**5b**	 **6b**	—	50	A
3	**5c**	 **6c**	—	52	A
4	**5a**	 **2e**,**7**	—	—	A
5	**5a**	**2e**,**7**	4:1:0	10	C
6	**5b**	 **8a**–**c**	4:1:1	30	A
7	**5b**	**8a**–**c**	10:1:4	72	C
8	**5c**	 **9a**,**b**	2:1:0	15	A
9	**5c**	**9a**–**c**	2:1:0.1	20	C

[a] Yields refer to isolated pure product. All the compounds were identified by spectroscopic and literature data. Method A: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding aryl bromide **5** (1 equiv.) in the solvent (5 mL) added into an additional 10 mL of solvent during 8 h, 80 °C, 24 h. Method C: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding pyridyl bromide **5** (1 equiv.) in pyridine (5 mL) added over additional 10 mL of pyridine and 2.5 mL of acetic acid during 8 h, 80 °C, 24 h.

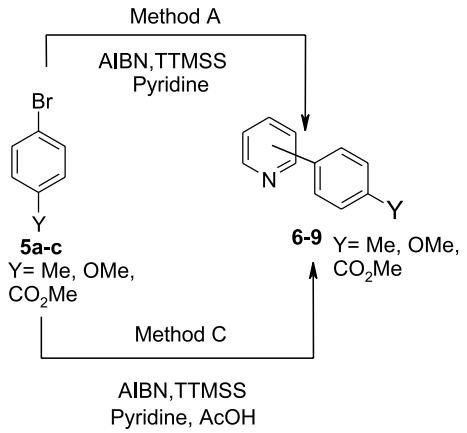
similar way, when the solvent is pyridine, the 2-pyridyl radical would behave as an electrophile, thus attacking at the 3-position, a situation in agreement with other photochemical arylations described previously.[11a] In contrast, the 3-pyridyl radical, which is comparatively nucleophilic, would attack preferentially at the 2-position of the pyridine acceptor.

Several attempts were undertaken to make the radical more π-deficient (e.g., using 2-bromopyridine-*N*-oxide instead of 2-bromopyridine) or to increase the electrophilicity of the solvent (e.g., using thiophene instead of pyridine). However, these approaches did not generate any satisfactory results.

Other aromatic solvents were also tested. Reaction of the 2-pyridyl radical, obtained from 2-bromopyridine **1a** on naphthalene, using a modified experimental method (Method B) (see Table 1 and Section 4) produced a 3:1 mixture of α/β naphthyl derivatives **4a**,**b** in 61% yield (Scheme 3; Table 1, entry 9). Similarly, 3-bromopyridine **1b**, produced a 5:1 mixture of α/β 3-(naphthyl)pyridines **4c**,**d** (Scheme 3; Table 1, entry 10). The regioselectivity of the radical attack is clearly as one would expect, considering orbital control, because of the symmetry of the system and in agreement with the regioselectivity reported for other radical arylations.[14,15]

2.2. Variations on the aryl radical

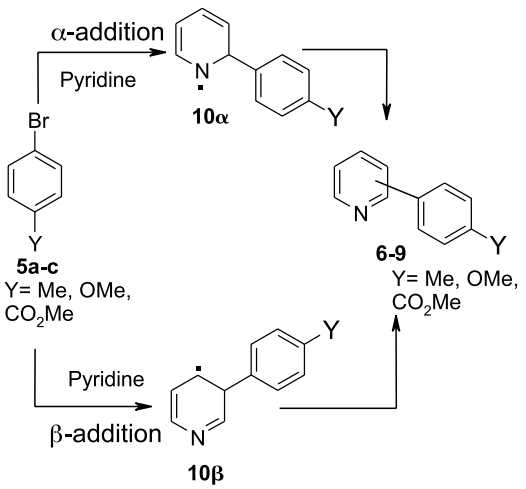
It is an axiom in radical chemistry that the π-system in an aryl radical should have little or no effect on its reactivity, since the unpaired electron would be placed on the σ-skeleton.[16,17] On this assumption, additional experiments were carried out using 4-methylphenyl, 4-methoxyphenyl, and 4-methoxycarbonylphenylbromides **5a**–**c** as sources of aryl radicals. In a previous communication[12] we reported these arylations using benzene as solvent, which yielded compounds **6a**–**c** (50–52%) essentially yielding the same results for both, heterocyclic and carbocyclic radicals. The experimental results are summarized in Table 2 (Entries 1–3) and in Section 4. The same process, but using pyridine as solvent, is outlined in Scheme 4 and Table 2. The slow addition (8 h) of a solution of TTMSS (2 equiv.), AIBN (2 equiv.) and 1-bromo-4-methyl benzene **5a** (1 equiv.) in pyridine to an additional 10 mL of pyridine at 80 °C, with the mixture kept at 80 °C for a further 16 h, did not generate any detectable biaryl (Table 2, entry 4). When the same conditions were applied to 1-bromo-4-methoxy-benzene **5b** as the starting material, biaryls **8a**–**c** were isolated in 30% yield (4:1:1 of the α:β:γ isomers) (Table 2, entry 6). The same process, when applied from 4-bromo benzoic acid methyl ester **5c**, yielded 15% of biaryls **9a**,**b** (2:1:0 of the α:β:γ isomers) (Table 2, entry 8). The experimental results seem to suggest that all radical species used in this particular type of reaction behave as relatively nucleophilic, with the ring substituents, however, exerting some effect on the reactivity of such radicals. The lack of reactivity for compound **5a** and the higher percentage of α-substitution on pyridine in the other cases could, tentatively, be explained by considering the following two classes of factors:



Scheme 4.

(a) A relatively nucleophilic radical has a higher energy SOMO and will react faster with molecules having a low-energy LUMO.[14,18,19]

(b) For unprotonated pyridines, the reactivity and selectivity on the homolytic phenylation appears to be mainly governed by the stability of the intermediate radical adduct **10**[20] (Scheme 5), with regioselectivity being α>β for both the more and the less nucleophilic radical (i.e., radicals derived from **5b** and **5c**, respectively). Since there is no radical π-stabilizing effect by aryl substituents, a relatively weak inductive effect could be exerted by the relatively π-excessive or π-deficient aryl substrate (intermediate **10α**,**β**, where Y=OMe or CO_2Me, respectively),[19] whereas the absence of such effect in **5a** should prevent the progress of the reaction.



Scheme 5.

Presumably, the radical arylation on protonated heteroaromatic bases will be more important, where the dominant SOMO/LUMO interaction may well be stronger. So in the case of unsubstituted pyridinium cation, reaction at the α- and at the γ-positions is predicted according to theory.[19,20] Bearing these factors in mind, and in accordance with the work of Minisci[20–22] and Togo,[23,24] the reaction was performed in an acidic medium. Thus, in protonated pyridines, in which polarity is strongly increased, the polar effect would play a significant role in determining both

reactivity and regioselectivity (Table 2).[20] Protonated heteroarenes are π-deficient substrates, which react with nucleophilic radicals with high regioselectivity, and the rate of radical addition correlated with nucleophilicity of the attacking radical (derived from **5a** and **5b**, entries 5 and 7, respectively), whereas the reaction with the less nucleophilic radical (derived from **5c**, entry 9) is scarcely affected with regard to reactivity and regioselectivity.

3. Conclusion

As a conclusion, a simple method of synthesis of biaryl compounds has been developed, based on the intermolecular radical addition of aryl or heteroaryl radicals onto an aromatic solvent. The method is very efficient when the aromatic solvent is benzene, but in general, occurs in low yields on other arenes. Experimental results seem to suggest that most aryl radicals, are nucleophilic to some extent, with aryl substituents modulating the reactivity through their electronic effect on the π-aryl system.

4. Experimental

4.1. General

All experiments were carried out under dry argon atmosphere. Toluene and benzene were distilled from sodium under dry argon. Chlorobenzene was distilled from calcium chloride, under dry argon. Pyridine was distilled from potassium hydroxide pellets under dry argon. Acetonitrile was distilled from phosphorus pentoxide under dry argon. Naphthalene was crystallized from ethanol. All chemicals were purchased from Aldrich Chemical company and were used without purification. ^{1}H and ^{13}C were recorded on a Varian UNITY 300 MHz or a VARIAN UNITY PLUS 500 MHz spectrometers. Mass spectra were recorded on a VG AutoSec (Micromass Instrument).

4.2. General procedure. Method A

A solution of TTMSS (498 mg, 2 mmol), AIBN (328 mg, 2 mmol), and the corresponding bromide **1a**,**b** or **5a**–**c** (1 mmol) in 5 mL of the suitable solvent, was dropwise added with a syringe pump along 8 h, to 10 mL of the same solvent, stirred at 80 °C (bath temperature). Stirring was maintained at the same temperature for 24 h, and full consumption of starting material was observed (TLC analysis). The pale yellow solution was concentrated in vacuo, providing a crude mixture that was purified using flash chromatography to yield the corresponding biaryl compound.

4.3. Method B

A solution of TTMSS (498 mg, 2 mmol), AIBN (328 mg, 2 mmol) and the corresponding bromide **1a**,**b** (1 mmol, 158 mg) in 5 mL of MeCN, was dropwise added with a syringe pump over 4 h, to 7 g (55 mmol) of naphthalene, stirred at 80 °C (bath temperature). Stirring was maintained at the same temperature for 24 h, and full consumption of **1** was observed (TLC analysis). The solution was concentrated, providing a crude mixture, which was separated by flash chromatography (silicagel, hexanes/ethyl acetate (80:20)), yielding the pure compounds.

4.4. Method C

A solution of TTMSS (498 mg, 2 mmol), AIBN (328 mg, 2 mmol), and the corresponding bromide **5a**–**c** (1 mmol) in 5 mL of pyridine, was dropwise added with a syringe pump over 8 h, to 10 mL of pyridine and 5 mL of acetic acid, stirred at 80 °C (bath temperature). Stirring was maintained at the same temperature for 24 h, then the solution was made basic with potassium carbonate and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and evaporated to dryness. The residue was purified using flash chromatography to yield the corresponding compounds **7**–**9**.

4.5. Preparation of arylpyridines 2a–g and bipyridine 3

4.5.1. 2-Phenylpyridine 2a.[25] The general procedure (Method A) using **1a** (158 mg) as bromide and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (90/10)), a colorless liquid (63.5 mg, 41%). This product was identical to an authentic sample obtained from Aldrich. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (td, 1H, J=4.7, 1.4 Hz), 8.01 (dd, 2H, J=8.4, 1.6 Hz), 7.69 (m, 2H), 7.45 (m, 3H), 7.19 (dd, 1H, J=8.8, 4.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 149.4, 139.2, 136.5, 128.8, 128.5, 126.7, 121.8, 120.3.

4.5.2. 3-Phenylpyridine 2b.[25,26] The general procedure (Method A) using **1b** as bromide (158 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (80:20)), a colorless liquid (115 mg, 74%). The product was identical to an authentic sample obtained from Aldrich. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (dd, 1H, J=2.6, 0.9 Hz), 8.57 (dd, 1H, J=4.9, 1.6 Hz), 7.85 (ddd, 1H, J=7.7, 2.6, 1.6 Hz), 7.56 (dd, 2H, J=8.2, 1.4 Hz), 7.45 (m, 3H), 7.34 (ddd, 1H, J=7.7, 4.9, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 148.2, 137.7, 136.4, 134.2, 128.9, 127.9, 127.0, 123.3.

4.5.3. 2-(2′-Methylphenyl)pyridine 2c,[27,28] **2-(3′-methylphenyl)pyridine 2d**[27,28] **and 2-(4′-methylphenyl)pyridine 2e.**[11a,27,29] The general procedure (Method A) using **1a** as bromide (158 mg) and toluene as solvent, gave a mixture of products (*o*/*m*/*p*, 2:1:1). After separation by flash chromatography (silicagel, dichloromethane/ethyl acetate (100:2.5)), pure compounds **2c**, **2d** and **2e** were obtained. Yield 61% (50.5 mg of **2c** (R_f=0.35), 27 mg of **2d** (R_f=0.41) and 25.5 mg of **2e** (R_f=0.40)). **2c** Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, 1H, J=4.8, 1.8, 1.0 Hz), 7.72 (dt, 1H, J=7.7, 1.8 Hz), 7.37 (td, 1H, J=7.7, 1.0 Hz), 7.36 (m, 1H), 7.27 (m, 3H), 7.22 (ddd, 1H, J=7.7, 4.8, 1.0 Hz), 2.34 (s, 3H). **2d** Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, 1H, J=4.8, 1.5, 1.0 Hz), 7.82 (bs, 1H), 7.73 (dt, 1H, J=8.0, 1.5 Hz), 7.70 (m, 2H), 7.34 (t, 1H, J=7.6 Hz), 7.21 (m, 1H), 7.20 (ddd, 1H, J=8.0, 4.8, 1.9 Hz) 2.42 (s, 3H). **2e** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H, J=4.4 Hz), 7.86 (d, 2H, J=8.1 Hz), 7.70 (m, 2H), 7.26 (d, 2H, J=8.1 Hz), 7.20 (m,

1H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 149.3, 138.6, 136.4, 136.3, 129.2, 126.5, 121.5, 120.0, 21.0.

4.5.4. 2-(2′-Chlorophenyl)pyridine 2f[27,28] and 2-(4′-chlorophenyl)pyridine 2g.[27] The general procedure (Method A) using **1a** as bromide (158 mg) and chlorobenzene as solvent, gave a mixture of products (*o*/*m*/*p*, 13:0:1). After separation by flash chromatography (silicagel, hexanes/ethyl acetate (90:10)), pure compounds **2f** and **2g** were obtained. Yield 84% (148 mg of **2f** (R_f=0.35) and 11.5 mg of **2g** (R_f=0.45)). **2f** Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (ddd, 1H, *J*=5.0, 1.7, 1.1 Hz), 7.75 (dt, 1H, *J*=8.7, 1.7 Hz), 7.63 (td, 1H, *J*=7.7, 1.1 Hz), 7.57 (m, 1H), 7.46 (m, 1H), 7.33 (m, 2H), 7.27 (ddd, 1H, *J*=7.7, 5.0, 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.5, 139.2, 135.8, 132.1, 131.5, 130.0, 129.4, 127.0, 124.8, 122.3. **2g** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H, *J*=4.5 Hz), 7.93 (d, 2H, *J*=8.6 Hz), 7.75 (dt, 1H, *J*=7.2, 1.6 Hz), 7.69 (bd, 1H, *J*=7.2 Hz), 7.44 (d, 2H, *J*=8.6 Hz), 7.24 (ddd, 1H, *J*=7.2, 4.5, 1.6 Hz).

4.5.5. 2,3′-Bipyridinyl 3.[25,30] The general procedure (Method A) using **1a** (158 mg) as bromide and pyridine as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (30:70), R_f=0.21) 47 mg, 30% yield of bipyridine **3** as a colorless oil. Identical results were obtained from **1b** (158 mg) and only traces were detected of other isomeric bipyridines. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (dd, 1H, *J*=2.2, 0.7 Hz), 8.71 (d, 1H, *J*=4.6 Hz), 8.64 (dd, 1H, *J*=4.7, 1.7 Hz), 8.31 (ddd, 1H, *J*=8.2, 2.2, 1.7 Hz), 7.77 (m, 2H), 7.40 (ddd, 1H, *J*=8.2, 4.7, 0.7 Hz), 7.26 (ddd, 1H, *J*=7.8, 4.6, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 150.1, 149.9, 148.2, 137.1, 134.4, 123.7, 122.9, 120.7; MS (EI, 70 eV) *m*/*z* (relative intensity) 156 (M^+, 100), 155 (M^+-1, 72), 130 (22), 78 (14).

4.6. Preparation of naphthylpyridines 4a–d

4.6.1. 2-Naphthalen-1-yl-pyridine 4a[31] and 2-naphthalen-2-yl-pyridine 4b.[31] The general procedure (Method B) using **1a** (158 mg) as starting bromide gave, after flash chromatography, 61% yield (α/β 3:1) of 2-naphthalenyl-pyridines **4a**,**b**, (94 mg of **4a** (R_f=0.56) and 30 mg of **4b** (R_f=0.58). **4a**: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (dd, 1H, *J*=4.8, 1.7 Hz), 8.08 (dd, 1H, *J*=7.1, 2.9 Hz), 7.91 (d, 2H, *J*=8.1), 7.82 (dt, 1H, *J*=7.7, 1.7 Hz), 7.56 (m, 5H), 7.33 (ddd, 1H, *J*=7.7, 4.8, 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 149.7, 138.7, 136.5, 134.2, 131.4, 129.0, 128.5, 127.6, 126.6, 126.0, 125.8, 125.4, 125.2, 122.1. MS (EI, 70 eV) *m*/*z* (relative intensity) 205 (M+, 39), 204 (100), 176 (9), 126 (2). **4b**: yellow solid; mp 77–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 1H, *J*=4.2 Hz), 8.49 (s, 1H), 8.14 (dd, 1H, *J*=8.6, 1.5 Hz), 7.90 (m, 4H), 7.80 (td, 1H, *J*=7.5, 1.8 Hz), 7.50 (m, 2H), 7.26 (dd, 1H, *J*=7.5, 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 149.7, 136.7, 133.5, 133.4, 128.6, 128.3, 127.6, 126.4, 126.2, 124.5, 122.1, 120.7; MS (EI, 70 eV) *m*/*z* (relative intensity) 205 (M^+, 100), 204 (66), 176 (16), 126 (8).

4.6.2. 3-Naphthalen-1-yl-pyridine 4c[32] and 3-naphthalen-2-yl-pyridine 4d.[31] The general procedure (Method B) using **1b** (158 mg) as starting bromide gave, after flash chromatography 50% (α/β 5:1) of 3-Naphthalenyl-pyridines **4c**,**d**, (85.5 mg of **4c** (R_f=0.35) and 17 mg of **4d** (R_f=0.23). **4c**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 1H, *J*=2.2 Hz), 8.67 (dd, 1H, *J*=4.9, 1.6 Hz), 7.92 (m, 2H), 7.82 (m, 2H), 7.54 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 148.4, 137.4, 136.2, 133.8, 131.5, 128.5, 128.4, 127.4, 126.5, 126.1, 125.3, 125.2, 123.1; HPLC-MS (CI) [M^++1]=206.1. **4d**: white solid, mp 101–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, 1H, *J*=1.6 Hz), 8.60 (dd, 1H, *J*=4.8, 1.6 Hz), 8.06 (s, 1H), 8.03 (td, 1H, *J*=8.1, 1.6 Hz), 7.90 (m, 3H), 7.71 (dd, 1H, *J*=8.5, 2.0 Hz), 7.53 (m, 2H), 7.40 (dd, 1H, *J*=8.1, 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 148.4, 135.0, 134.5, 133.5, 132.8, 128.8. 128.1, 127.6, 126.5, 126.3, 126.1, 124.9, 123.5; MS (CI, 70 eV) *m*/*z* (relative intensity) 206 (M^++1, 100), 159 (5).

4.7. Preparation of biphenyl compounds 6a–c and arylpyridines 7–9

4.7.1. 4-Methylbiphenyl 6a.[33,34] The general procedure (Method A) using **5a** as bromide (171 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (95:5)), a white solid, mp 46–47 °C (85.5 mg, 51%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (dd, 2H, *J*=8.3, 1.2 Hz), 7.50 (d, 2H, *J*=8.1 Hz), 7.42 (t, 2H, *J*=8.3 Hz), 7.31 (td, 1H, *J*=8.3, 1.2 Hz) 7.25 (d, 2H, *J*=8.1 Hz), 2.39 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 142.4, 139.6, 138.1, 130.4, 129.7, 127.9, 127.8, 127.7, 21.1.

4.7.2. 4-Methoxybiphenyl 6b.[33,35] The general procedure (Method A) using **5b** as bromide (187 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (95:5)), a white solid, mp 86–87 °C (92 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 4H), 7.43 (t, 2H, *J*=7.5 Hz), 7.32 (tt, 1H, *J*=7.5, 1.2 Hz) 6.99 (d, 2H, *J*=8.8 Hz), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.3.

4.7.3. Biphenyl 4-carboxylic acid methyl ester 6c.[34,36] The general procedure (Method A) using **5c** as bromide (215 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (95:5)), a white solid, mp 116–117 °C (110 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2H, *J*=8.4 Hz), 7.59 (d, 2H, *J*=8.4 Hz), 7.56 (dd, 2H, *J*=7.4, 1.3 Hz); 7.44 (dd, 2H, *J*=7.4, 7.2 Hz), 7.33 (tt, 1H, *J*=7.2, 1.3 Hz) 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 145.5, 139.9, 130.0, 128.8, 128.6, 128.1, 127.2, 126.9, 52.0.

4.7.4. 2-(4′-Methylphenyl)pyridine 2e[11a,27,29] and 3-(4′-methylphenyl)pyridine 7.[11a] The general procedure (Method A) using **5a** (171 mg) as starting bromide and pyridine as solvent did not generate any biaryl compound. The same process, using Method C gave, after separation by flash chromatography (silicagel, hexanes/ethyl acetate (80:20)), 10% yield of 4′-methylphenyl)pyridines (α/β/γ 4:1:0). **2e** (13.5 mg, R_f=0.80) colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H, *J*=4.4 Hz), 7.86 (d, 2H, *J*=8.1 Hz), 7.70 (m, 2H), 7.26 (d, 2H, *J*=8.1 Hz), 7.20 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 149.3, 138.6, 136.4, 136.3, 129.2, 126.5, 121.5, 120.0, 21.0; MS (EI, 70 eV) *m*/*z* (relative intensity) 169 (M^+, 100), 168 (59, M^++1), 154 (9), 51 (20). **7** (4 mg, R_f=0.53) colorless

oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, 1H, J=2.3 Hz), 8.55 (dd, 1H, J=4.6, 1.5 Hz), 7.85 (ddd, 1H, J=7.81, 2.3, 1.5 Hz), 7.48 (d, 2H, J=8.2 Hz), 7.35 (m, 1H), 7.30 (d, 2H, J=8.2 Hz), 2.42 (s, 3H); MS (EI, 70 eV) m/z (relative intensity) 169 (M^+, 83), 110 (100), 80 (30).

4.7.5. 2-(4′-Methoxyphenyl)pyridine 8a,[11a,27] 3-(4′-methoxyphenyl)pyridine 8b[11a] and 4-(4′-methoxyphenyl)pyridine 8c.[37] The general procedure (Method A) using **5b** (187 mg) as starting bromide and pyridine as solvent gave, after separation by flash chromatography (silicagel, hexanes/ethyl acetate (70:30)), 30% yield of methoxyphenylpyridines **8a–c** (α/β/γ 4:1:1). The same process, using Method C gave 72% yield of methoxyphenylpyridines **8a–c** (α/β/γ 10:1:4). **8a** (37 mg from Method A or 92.5 mg from Method B) (R_f=0.80) colorless plates, mp 53–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (dd, 1H, J=4.7, 1.8 Hz), 7.95 (d, 2H, J=7.9 Hz), 7.72 (ddd, 1H, J=8.0, 6.9, 1.8 Hz), 7.66 (dd, 1H, J=8.0, 1.5 Hz), 7.16 (ddd, 1H, J=6.9, 4.7, 1.5 Hz), 6.98 (d, 2H, J=7.9 Hz), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 156.9, 149.3, 136.7, 131.7, 128.1, 121.3, 119.9, 114.0, 55.3; MS (EI, 70 eV) m/z (relative intensity) 185 (M^+, 100), 170 (36), 142 (45), 141 (31), 84 (14). **8b** (9 mg from Method A or 9 mg from Method C) (R_f=0.35) colorless plates, mp 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H, J=1.8 Hz), 8.53 (dd, 1H, J=4.7, 1.4 Hz), 7.83 (ddd, 1H, J=8.1, 1.8, 1.4 Hz), 7.51 (d, 2H, J=8.8 Hz), 7.33 (ddd, 1H, J=8.1, 4.7, 0.7 Hz), 7.01 (d, 2H, J=8.8 Hz), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 148.0, 147.9, 136.2, 133.8, 130.2, 128.2, 123.4, 114.5, 55.3; MS (EI, 70 eV) m/z (relative intensity) 185 (M^+, 100), 170 (54), 142 (52), 115 (30). **8c** (9 mg from Method A or 30 mg from Method C) (R_f=0.22), white solid, mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (dd, 2H, J=4.6, 1.6 Hz), 7.60 (d, 2H, J=9 Hz), 7.51 (dd, 2H, J=4.6, 1.6 Hz), 7.01 (d, 2H, J=9 Hz), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 150.3, 148.1, 130.5, 128.3, 121.3, 114.8, 55.6; MS (EI, 70 eV) m/z (relative intensity) 185 (M^+, 100), 170 (34), 142 (42),115 (32), 86 (51), 84 (75).

4.7.6. 4-Pyridin-2-yl-benzoic acid methyl ester 9a,[11a,27] 4-pyridin-3-yl-benzoic acid methyl ester 9b[11a] and 4-pyridin-4-yl-benzoic acid methyl ester 9c.[38] The general procedure (Method A) using **5c** (215 mg) as starting bromide and pyridine as solvent gave, after separation by flash chromatography (silicagel, hexanes/ethyl acetate (70:30)), 15% yield of **9a**,**b** (α/β/γ 2:1:0). The same process, using Method B gave 20% yield of 4-pyridin benzoic acid methyl esters **9a–c** (α/β/γ 2:1:0.1). **9a** (21 mg from Method A or 29 mg from Method C) (R_f=0.60) colorless plates, mp 97–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, 1H, J=4.7, 1.3 Hz), 8.13 (d, 2H, J=8.7 Hz), 8.11 (d, 2H, J=8.7 Hz), 7.77 (m, 2H), 7.27 (dd, 1H, J=8.9, 4.7 Hz), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 156.1, 149.8, 143.4, 136.9, 130.3, 129.9, 126.7, 122.8, 120.9, 52.1; MS (EI, 70 eV) m/z (relative intensity) 213 (M^+, 58), 182 (100), 154 (47), 127 (24). **9b** (11 mg from Method A or 15 mg from Method C) (R_f=0.40), white solid, mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, 1H, J=1.7 Hz), 8.63 (dd, 1H, J=4.8, 1.7 Hz), 8.14 (d, 2H, J=8.4 Hz), 7.91 (td, 1H, J=7.8, 1.7 Hz), 7.65 (d, 2H, J=8.4 Hz), 7.40 (dd, 1H, J=7.8, 4.8 Hz), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 149.1, 148.2, 142.1, 135.5, 134.4, 130.3, 129.7, 127.0, 123.6, 52.1; MS (EI, 70 eV) m/z (relative intensity) 213 (M^+, 68), 182 (100), 154 (27), 127 (21).

9c (1 mg from Method C) (R_f=0.15) white solid, mp 103–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, 2H, J=4.2 Hz), 8.15 (d, 2H, J=8.4 Hz, 7.70 (d, 2H, J=8.4 Hz), 7.54 (d, 2H, J=4.2 Hz), 3.94 (s, 3H); MS (EI, 70 eV) m/z (relative intensity) 213 (M^+, 95), 182 (100), 154 (56), 127 (66), 80 (48).

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