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FACILE SYNTHESIS OF DIARYLMETHYLPYRIDINES/DIARYLMETHYLQUINOLINES THROUGH SUPERELECTROPHILIC ACTIVATION OF PYRIDINECARBOXALDEHYDES/QUINOLINECARBOXALDEHYDES WITH BORON TRIFLUORIDE MONOHYDRATE

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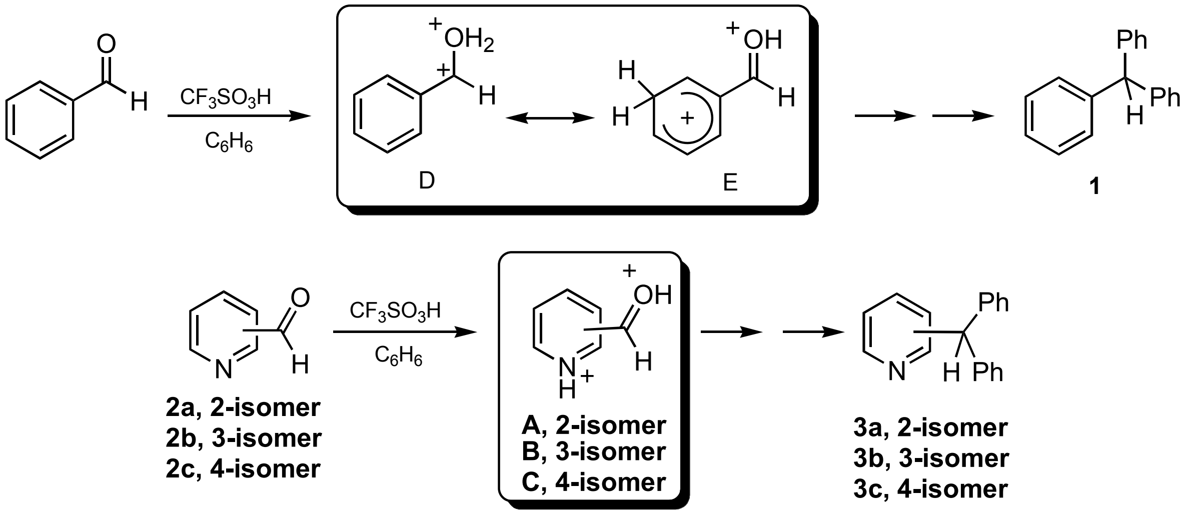
Dedicated with friendship and admiration to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract – Synthesis of diarylmethylpyridines and diarylmethylquinolines has been achieved by Friedel-Crafts hydroxyalkylation reactions of pyridinecarboxaldehydes and quinolinecarboxaldehydes with aromatic compounds under superelectrophilic activation using boron trifluoride monohydrate system (BF_3-H_2O). Since BF_3-H_2O is more economic, easy to prepare and offers high acidity ($H_0 \approx -12$), this method using BF_3-H_2O is found to be more convenient and useful compared to the methods reported earlier. The reaction is very simple and clean, eliminating the use of organic solvents and other expensive acid systems. Products are obtained in high yields and purity in most cases.

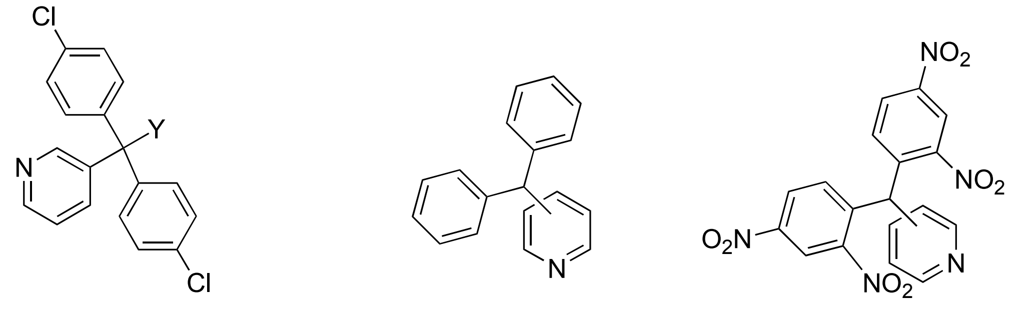
INTRODUCTION

The acid catalyzed condensation of ketones and aldehydes with aromatic compounds is described in the literature as the hydroxyalkylation reaction.[1] Previous studies show that benzaldehyde reacts with benzene under highly acidic conditions (Lewis as well as Brønsted) at elevated temperatures (excess $AlCl_3$, 60 °C) leading to a number of products such as triphenylmethane, diphenylmethane, triphenylmethanol and anthracene in 30-60%.[2] These reactions are generally feasible with activated arenes. With less reactive aromatic compounds, activated ketones or aldehydes bearing strong electron withdrawing groups are quite often required. However, it has been found that under superacidic conditions, benzaldehyde reacts with benzene at ambient temperatures to afford triphenylmethane in high yields.[2] Recently, there has been significant interest in the chemistry of superelectrophilic reactive intermediates. The concept of superelectrophilic activation was first proposed by Olah.[3] Superelectrophilic activation may occur in superacidic solution by protosolvation of electrophiles to give highly reactive superelectrophilic species. Superelectrophilic activation has been studied extensively in the Friedel-Crafts reaction of 1,2-dicarbonyl compounds,[4] aldehydes,[2,5] nitriles[6] etc. with arenes, Friedel-Crafts cyclodehydration of 1,3-diphenyl-1-propanones[7] and cycli-acyalkylation with unsaturated carboxylic acids[8] in superacidic solutions. Klumpp and Lau[9] have recently studied superacid catalyzed condensation of pyridinecarboxaldehydes with arenes in trifluoromethanesulfonic acid. Involvement of diprotonated pyridinecarboxaldehydes (A, B, C) was proposed similar to the superelectrophilic systems observed for diprotonated benzaldehyde (D↔E) (Scheme 1).[2,9]



Scheme 1. Superelectrophilic activation of benzaldehyde and pyridinecarboxaldehydes in superacid medium

The diarylmethylpyridines have been recently studied as a new class of highly potent dopamine transporter inhibitors and it was proposed that these compounds may have therapeutic values in the treatment of cocaine addiction and abuse.[10] Aromatase inhibitory activities of bis(4-chlorophenyl)methylpyridines have also been described *in vitro*.[11] Bis(4-*tert*-butylphenyl)methyl-2-pyridine has been used to the ligand synthesis for the $Mo^{IV}O_2$ complexes used in oxygen atom transfer reactions.[12] Furthermore, bis(2,4-dinitrophenyl)methylpyridinium compounds have also been used as pH indicators for test paper strips for determination of urea in blood or blood serum.[13]

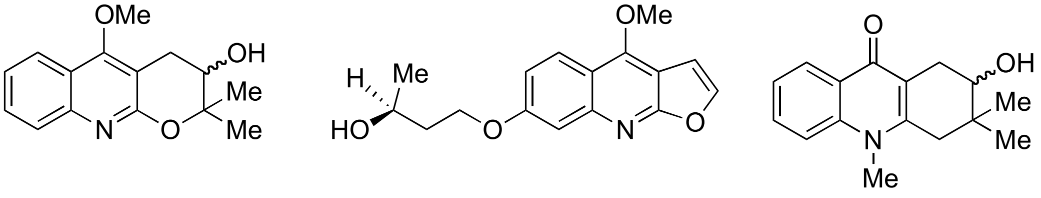


Y = Cl, F, H, Me, OMe

Estrogen Synthetase Inhibitors Dopoamine Transport Inhibitors pH Indicators

Figure 1: Biologically important compounds with diarylmethylpyridine framework

Quinoline and its derivatives are found to be very important in pharmaceutical industry. Quinoline moiety is very prominent in antimalarial agents, fungicides, antibacterial agents, the HIV-1 Protease inhibitor and potential HIV-1 integrase inhibitors.[14] A number of alkaloids such as geibalasine, ribalinine contain pyranoquinoline as the basic framework.[15] Their use in synthesizing materials having non linear optical properties has been widely explored.[16] Quinoline compounds are found to have antiasthmatic, anti-inflammatory and antihypertensive properties. Certain bioorganic and bioorganometallic processes are studied using quinoline derivatives.[17]



geibalansine roxamine ribaline

Figure 2: Biologically significant alkaloids based on quinoline framework

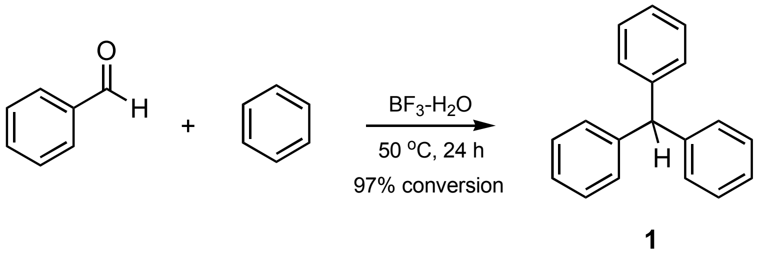
During our study of Friedel-Crafts reactions and acid catalyzed synthetic transformations in various superacidic conditions, we found that boron trifluoride monohydrate (BF_3-H_2O) is a very effective catalyst and activating agent for many organic transformations such as the Fries rearrangement of phenolic esters to provide corresponding hydroxyketones,[18] preparation of sufides from carbonyl compounds,[19] nitration of aromatics and preparation of alkyl nitrates using metal nitrate,[20] halogenation of deactivated arenes using N-halosuccinimides,[21] etc., under relatively mild conditions. Now, we have explored the Friedel-Crafts hydroxyalkylation of aromatics using pyridine- and quinolinecarboxaldehydes in nonoxidizing, less expensive boron trifluoride monohydrate acid system.

RESULTS AND DISCUSSION

Friedel-Crafts hydroxyalkylation of aromatics with pyridinecarboxaldehydes in borontrifluoride monohydrate

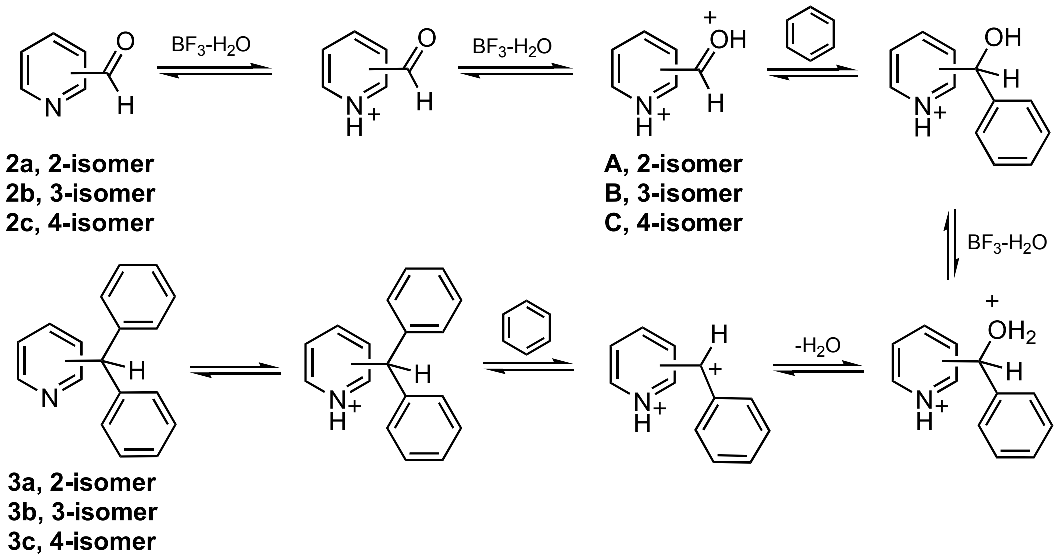
Mathes et al. reported in the 60's that pyridinecarboxaldehydes react with benzene in H_2SO_4 at elevated temperatures.[22] Later on, Klumpp and Lau described condensation of pyridinecarboxaldehydes with benzene and deactivated arenes in CF_3SO_3H (triflic acid,TfOH) at ambient temperatures. These studies suggested the formation of diprotonated pyridinecarboxaldehydes in superacidic solution.[9a] The reaction proceeds through the formation of dicationic intermediates by the protonation at the nitrogen atom in the heterocyclic ring as well as the protonation of the carbonyl group. The dications were directly observed using low temperature ^{13}C NMR spectroscopy. Diprotonated pyridinecarboxaldehydes were also studied using *ab initio* computational methods, supporting the proposed mechanism.[9b]

Since BF_3-H_2O is more economic than triflic acid, easier to prepare, and offers high and optimum acidity, the hydroxyalkylation reaction of pyridinecarboxaldehydes **(2a-c)** with aromatics was carried out in the acid system. BF_3-H_2O complex is a colorless fuming liquid with a density of 1.8 g/mL and melting point of 6.2 °C.[23a,b] In aqueous solution, BF_3-H_2O behaves as a strong Brønsted acid and is extensively converted to the ionic form of dihydrate $(H_3O)^+(BF_3OH)^-$.[23c] To compare the electrophilic reactivities of the pyridinecarboxaldehydes **(2a-c)** with benzaldehyde, the hydroxyalkylation reactions were carried out with both aldehydes. Benzaldehyde was found to condense slowly with benzene in BF_3-H_2O acid system (Scheme 2).



Scheme 2. BF_3-H_2O catalyzed hydroxyalkylation of benzene with benzaldehyde

Condensation of benzaldehyde with benzene at room temperature for 24 h led to only 15% conversion of benzaldehyde to triphenylmethane. When the reaction temperature was varied to 50 °C over 24 h, conversion was found to be 97% (Scheme 2). However, reaction of pyridinecarboxaldehydes (**2a-c**) with benzene at room temperature was complete in one hour giving diphenylmethylpyridines in excellent yields (Table 1, 2, 3). Therefore, pyridinecarboxaldehydes (**2a-c**) are more reactive than benzaldehyde, suggesting the formation of more reactive superelectrophilic species (**A**, **B**, **C**) in hydroxyalkylation reaction with benzene. Pyridinecarboxaldehydes (**2a-c**) form the dicationic intermediates (**A**, **B**, **C**) more readily due to relatively strong Lewis nitrogen base site (Scheme 3).

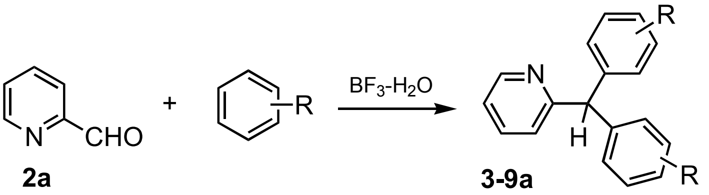


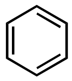
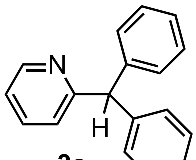
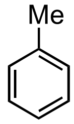
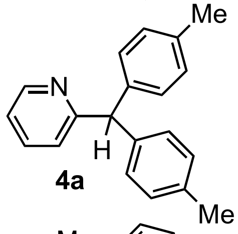
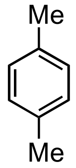
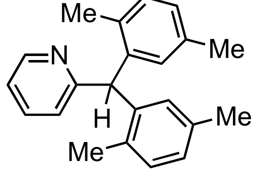
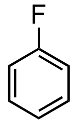
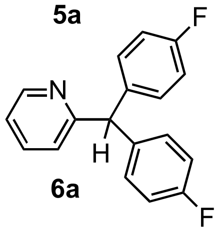
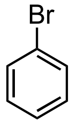
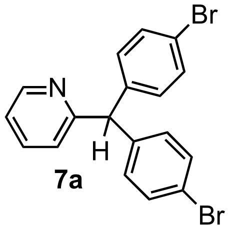
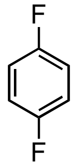
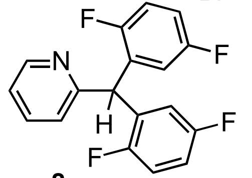
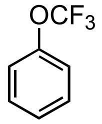
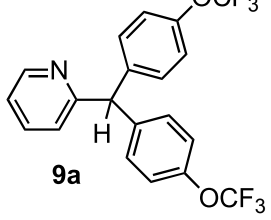
Scheme 3. BF_3-H_2O catalyzed hydroxyalkylation of benzene with pyridinecarboxaldehydes

The condensation reactions of pyridinecarboxaldehydes with benzene in concentrated sulfuric acid requires elevated temperatures (80 °C) and long reaction times (15-20 h),[22] indicating BF_3-H_2O is more effective and a stronger acid.

A wide variety of new diarylmethylpyridine derivatives was synthesized through Friedel-Crafts hydroxyalkylation reaction of pyridinecarboxaldehydes (**2a-c**) with different arenes in BF_3-H_2O acid system. As expected, hydroxyalkylation is much faster with activated aromatics. Therefore, the reactions with benzene and toluene were carried out at room temperature for a short period of time leading to diarylmethylpyridines (**3a-c**) and (**4a-c**) in excellent yields (Table 1, 2, 3). However, reactions with *p*-xylene leading to (**5a-c**) was completed over a longer period of time (3 h) probably due to steric effects imposed from methyl group at the *ortho* position. Reaction of fluorobenzene with pyridinecarboxaldehydes (**2a-c**) at room temperature gave rise to the corresponding products (**6a-c**) as well. However, higher temperature and larger amount of BF_3-H_2O were needed for highly deactivated arenes. Condensation of 2- and 4-pyridinecarboxaldehydes **2a**, **2c** with difluorobenzene was carried out at 85 °C for 24 h, resulting in the final products **8a, 8c** in 72-83% yields. Reaction of 3-pyridinecarboxaldehydes **2b** with difluorobenzene needed higher temperature and longer reaction time (100 °C, 72 h) for completion. These results indicate that 2- and 4- pyridinecarboxaldehydes **2a**, **2c** are more reactive than 3- pyridinecarboxaldehydes **2b**. It appears that in diprotonated intermediates the presence of protonated nitrogen in 2- or 4- position to carboxonium moeity increases the electrophilic reactivity of the protonated carbonyl carbon significantly. Condensation of mono-substituted arenes with pyridinecarboxaldehydes (**2a-c**) gave rise to *para-para'* substituted diarylmethylpyridines dervatives as major products along with other regioisomers. Trifluoromethoxybenzene undergoes condensation reaction with very high regioselectivity (96-97%) for *para-para'* derivatives (**9a**, **9c**).

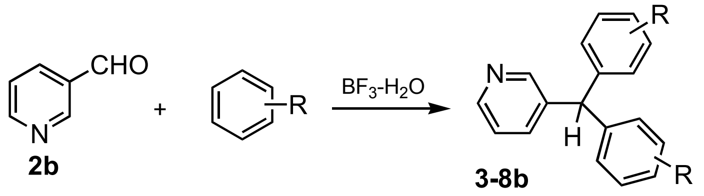
Table 1. Reaction of 2-pyridinecarboxaldehyde (**2a**) with arenes in presence of BF_3-H_2O

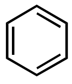
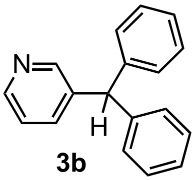
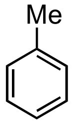
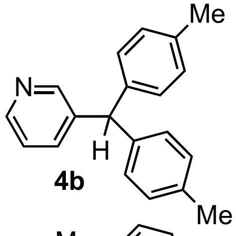
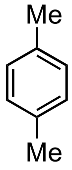
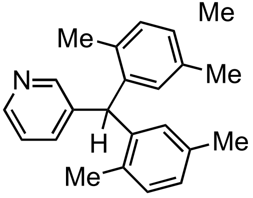
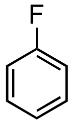
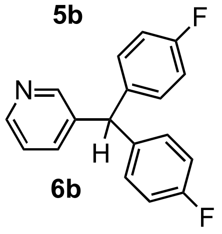
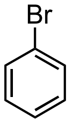
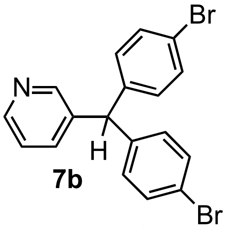
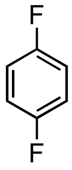
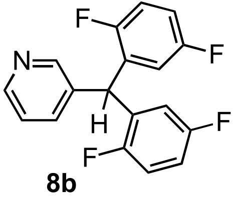


Entry	Substrate	Temp (°C)	Time (h)	Major products (*p*-*p'*)	*p*-*p'*/other isomers	Yield (%)*
1		RT	1	 **3a**	-	95
2		RT	0.5	 **4a**	91/9	98
3		RT	3	 **5a**	-	98
4		RT	1.5	 **6a**	93/7	95
5		50	2	 **7a**	87/13	90
6		85	24	 **8a**	-	72
7		30	4	 **9a**	97/3	90

* isolated yield

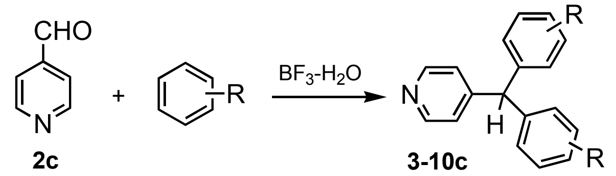
Table 2. Reaction of 3-pyridinecarboxaldehyde (**2b**) with arenes in presence of BF_3-H_2O



Entry	Substrate	Temp (^{o}C)	Time (h)	Major products (*p,p'*)	*p-p'*/other isomers	Yield (%)*
1		RT	1	 **3b**	-	92
2		RT	0.5	 **4b**	90/10	96
3		RT	3	 **5b**	-	85
4		RT	2	 **6b**	92/8	92
5		60	3	 **7b**	86/14	68
6		100	72	 **8b**	-	70

* Isolated yield

Table 3. Reaction of 4-pyridinecarboxaldehyde (**2c**) with arenes in presence of BF_3-H_2O



2c **3-10c**

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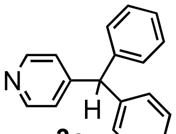
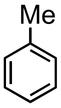
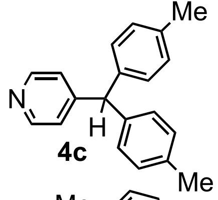
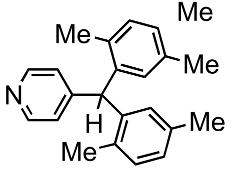
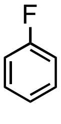
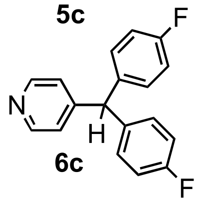
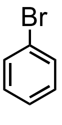
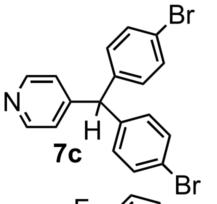
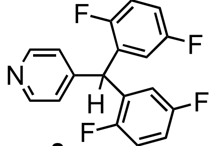
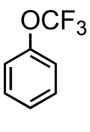
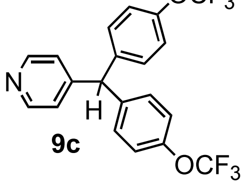
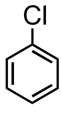
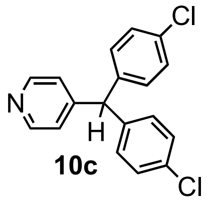
1		RT	1	 **3c**	-	97
2	 Me	RT	0.5	 **4c**	89/11	98
3		RT	3	 **5c**	-	98
4		RT	1.5	 **6c**	93/7	95
5		50	2	 **7c**	85/15	90
6		85	24	 **8c**	-	83
7		30	5	 **9c**	96/4	85
8		RT	6	 **10c**	84/16	76

* Isolated yield

Friedel-Crafts hydroxyalkylation of aromatics with quinolinecarboxaldehydes (11a-c) in borontrifluoride monohydrate

Klumpp and coworkers reported the use of triflic acid for the hydroxyalkylation reaction of quinolinecarboxaldehyes and acetyl substituted heteroarenes.[24] We found that BF_3-H_2O also facilitates this reaction at room temperature giving the products in high yields in few hours. Similar to pyridinecarboxaldehyes **2a-c**, quinolinecarboxaldehydes **11a-c** also form the diprotonated species, which helps the reaction to complete faster at milder conditions through superelectrophilic activation.[3] It has been shown that these dicationic intermediates are sufficiently electrophilic to carry out hydroxyalkylation on arenes such as benzene, chlorobenzene and even dichlorobenzene.[24]

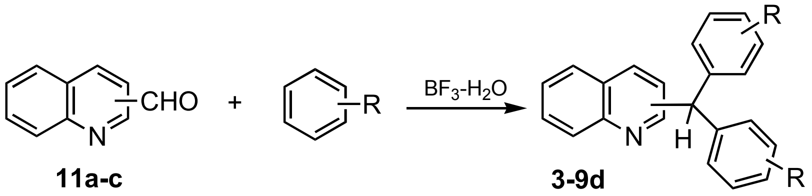
In the case of monosubstituted arenes as the starting material, the major product was the *para-para'* substituted diarylmethylquinolines. In the case of *p*-xylene, the reaction time was 3 hours, three times that required for benzene (Table 4), probably due to the steric crowding at the *ortho* positions as anticipated. We explored the reactions of 2-, 3- and 4-quinolinecarboxaldehydes (**11a-c**) and found that the reaction time did not change significantly. The results are summarized in Table 4.

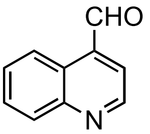
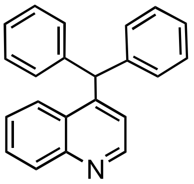
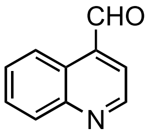
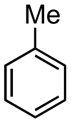
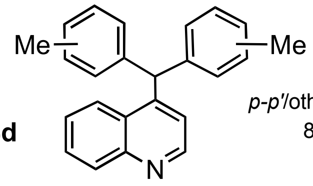
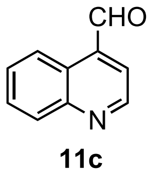
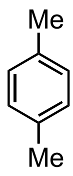
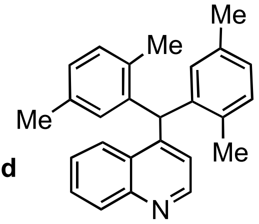
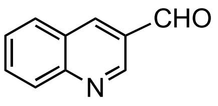
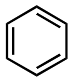
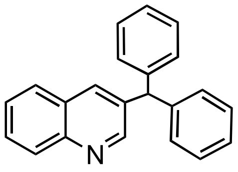
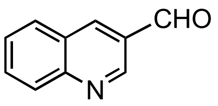
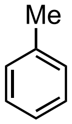
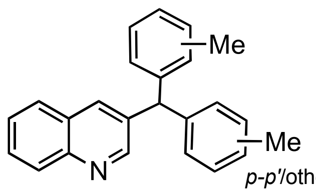
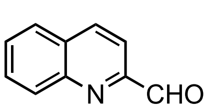
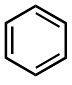
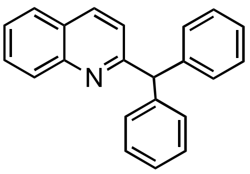
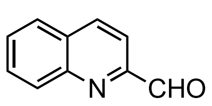
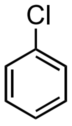
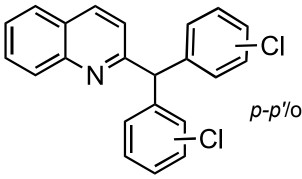
In summary, we have found that Friedel-Crafts hydroxyalkylation of 2-, 3-, and 4-pyridinecarboxaldehydes with arenes in BF_3-H_2O system gives rise to a variety of diarylmethylpyridine derivatives in high yields and purity. This chemistry has also been extended to quinolinecarboxaldehydes. BF_3-H_2O catalyzes these condensation reactions through the formation of superelectrophilic dicationic intermediates by diprotonation of pyridinecarboxaldehydes or quinolinecarboxaldehydes. As already mentioned, BF_3-H_2O plays a dual role, as an acid catalyst and an effective protosolvating medium (solvent) eliminating the use of expensive acids and organic solvents. This method gives easy access to biologically active diarylmethylpyridines and diarylmethylquinolines, respectively.

EXPERIMENTAL

Unless otherwise mentioned, all chemicals were purchased from commercial sources. BF_3-H_2O was prepared by the method described below. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on varian NMR at 400 MHz. ^1H NMR chemical shifts were determined relative to internal tetramethylsilane at δ 0.0 ppm, ^{13}C NMR chemical shifts were determined relative to ^{13}C signal of $CDCl_3$ at δ 77.0 ppm. ^{19}F NMR chemical shifts were determined relative to internal $CFCl_3$ at δ 0.0 ppm. GC-MS spectra were recorded on a ThermoFinnigan Mass (EI) spectrometer. HRMS data were obtained from a high resolution Micromass GCT (GC-MS TOF) spectrometer at Mass Spectrometry Facility, Department of Chemistry, University of Arizona.

Table 4. Reactions of quinolinecarboxaldehydes with arenes in presence of BF_3-H_2O



Entry[a]	Quinolinecarboxaldehyde	Arene	Time (h)	Product	Yield[b]
1	 **11c**		1	**3d** 	92
2	 **11c**		1	**4d**  *p-p'*/other isomers 85/15	90
3	 **11c**		3	**5d** 	94
4	 **11b**		1	**6d** 	91
5	 **11b**		1	**7d**  *p-p'*/other isomers 85/15	94
6	 **11a**		1	**8d** 	90
7	 **11a**		5	**9d**  *p-p'*/other isomers 80/20	80

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[a] Reactions were carried out at room temperature for 1-5 hours, [b] Isolated Yield.

(a) Typical procedure for the preparation of BF_3-H_2O (1:1) complex

BF_3 was passed carefully into a Nalgene bottle containing a weighed amount of distilled water (36 g, 2 mol) with frequent cooling (-78 °C) until a desired weight increase was observed. The amount of BF_3 needed is 134 g, which corresponds to a ratio of 1:1.

(b) General procedures for BF_3-H_2O catalyzed reactions of pyridinecarboxaldehydes (2a-c) or quinolinecarboxaldehydes (11a-c) with arenes

The pyridinecarboxaldehyde (0.248 g, 2.5 mmol) or quinolinecarboxaldehyde (0.392 g, 2.5 mmol) was mixed with excess of arene (10 mmol) in a pressure tube. The mixture was cooled to 0 ºC and BF_3-H_2O (5 g, 58 mmol) was added slowly. For bromobenzene and difluorobenzene 10 g and 15 g of BF_3-H_2O were used, respectively. The mixture was stirred for the required period of time (Table 1-4) at rt or higher temperatures depending on the substrate (Table 1, 2, 3). Progress of the reaction was monitored by TLC (4:1 hexane/EtOAc) and GC-MS. After the completion of reaction the mixture was poured over ice, neutralized with sodium bicarbonate and extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. The solvent was removed by vacuum evaporation and crude products were purified with column chromatography on silica gel (70-230 mesh) using hexane/EtOAc as eluent. The products were characterized by spectral analysis- NMR, GC-MS and HRMS. The characterization data of **3d**, **6d**, and **8d** are consistent with those reported earlier.[24]

Diphenylmethyl-2-pyridine (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (s, 1H), 7.06-7.07 (m, 1H), 7.11 (ddd, *J* = 7.55 Hz, *J* = 4.89 Hz, *J* = 1.14 Hz, 1H), 7.15-7.23 (m, 6H), 7.26-7.31 (m, 4H), 7.58 (ddd, *J* = 7.69 Hz, *J* = 7.69 Hz, *J* = 1.95 Hz, 1H), 8.59 (ddd, *J* = 4.85 Hz, *J* = 1.93 Hz, *J* = 0.91 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 59.28, 121.35, 123.69, 126.46, 128.36, 129.3, 136.36, 142.64, 149.49, 163.13; GC-MS (EI), m/z 245.8 (M^+), HRMS (FAB), m/z calcd for $C_{18}H_{16}N$ (M+1) 246.1283, observed 246.1286.

Bis(*p*-tolyl)methyl-2-pyridine (4a)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.3 (s, 6H), 5.63 (s, 1H), 7.03-7.10 (m, 10H), 7.55 (ddd, *J* = 7.69 Hz, *J* = 7.69 Hz, *J* = 1.83 Hz, 1 H), 8.57 (ddd, *J* = 4.76 Hz, *J* = 1.83 Hz, *J* = 0.91 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 20.95, 58.54, 121.19, 123.56, 129.02, 129.11, 135.88, 136.27, 139.86, 149.4, 163.57; GC-MS (EI), m/z 273.8 (M^+), HRMS (FAB), m/z calcd for $C_{20}H_{20}N$ (M+1) 274.1596, observed 274.1608.

Bis(2,5-dimethylphenyl)methyl-2-pyridine (5a)

^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.11 (s, 6H) 2.17 (s, 6H), 5.81 (s, 1H), 6.47 (d, *J* = 0.91 Hz, 2H) , 6.87-6.94 (m, 3H), 7.02 (d, , *J* = 7.51 Hz, 2H), 7.11 (ddd, *J* = 7.5 Hz, *J* = 4.89 Hz, *J* = 1.05 Hz, 1H), 7.55 (ddd, *J* = 7.69 Hz, *J* = 7.69 Hz, *J* = 1.83 Hz, 1H), 8.58 (ddd, *J* = 4.76 Hz, *J* = 1.83 Hz, *J* = 0.91 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 19.24, 21.22, 53.27, 121.15, 123.93, 127.15, 129.6, 130.28, 133.6, 135.04, 136.23, 140.59, 149.57, 162.94; GC-MS (EI), m/z, 300.6 (M$^+$), HRMS (FAB), m/z calcd for $C_{22}H_{24}N$ (M+1) 302.1909, observed 302.1907.

Bis(4-fluorophenyl)methyl-2-pyridine (6a)

^{1}H NMR (400 MHz, $CDCl_3$): 5.64 (s, 1H), 6.95-7.00 (m, 4H), 7.06 (ddd, J = 7.87 Hz, J = 0.82 Hz, J = 0.82 Hz, 1H), 7.09-7.15 (m, 5H), 7.60 (ddd, J = 7.69 Hz, J = 7.69 Hz, J = 1.83 Hz, 1H), 8.59 (ddd, J = 4.94 Hz, J = 1.83 Hz, J = 0.91 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 57.52, 115.22 (d, $^2J_{(C,F)}$ = 21.36 Hz), 121.61, 123.55, 130.64 (d, $^3J_{(C,F)}$ = 7.63 Hz), 136.62, 138.25 (d, $^4J_{(C,F)}$ = 3.05 Hz), 149.55, 161.5 (d, $^1J_{(C,F)}$ = 244.90 Hz), 162.57; ^{19}F NMR (376 MHz, $CDCl_3$): δ -116.71(m); GC-MS (EI), m/z, 281.6 (M$^+$), HRMS (EI) m/z calcd for $C_{18}H_{13}F_2N$ 281.1016, observed 281.1007.

Bis(4-bromophenyl)methyl-2-pyridine (7a)

^{1}H NMR (400 MHz, $CDCl_3$) : δ 5.56 (s, 1H), 7.00-7.07 (m, 5H), 7.15 (ddd, J = 7.51 Hz, J = 4.76 Hz, J = 1.1 Hz, 1H), 7.40-7.43 (m, 4H), 7.61(ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.83 Hz, 1H), 8.59 (ddd, J = 4.85 Hz, J = 1.81 Hz, J = 0.82 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 57.92, 120.7, 121.74, 123.57, 130.89, 131.52,136.63, 141.16, 149.67, 161.78; GC-MS (EI), m/z 403.9 (M$^+$), HRMS (FAB), m/z calcd for $C_{18}H_{14}Br_2N$ (M+1) 403.9473, observed 401.9480.

Bis(2,5-difluorophenyl)methyl-2-pyridine (8a)

^{1}H NMR (400 MHz, $CDCl_3$) : 6.09 (s, 1H), 6.79 (ddd, $J_{(ortho)\ H\text{-}F}$ = 9.02 Hz, $J_{(meta)\ H\text{-}F}$ = 5.81 Hz, $J_{(meta)\ H\text{-}H}$ = 3.11 Hz, 2H), 6.91-6.97 (m, 2 H), 7.02 (ddd, $J_{(ortho)\ H\text{-}F}$ = 9.02 Hz, $J_{ortho\ (H\text{-}H)}$ = 9.02 Hz, $J_{(meta)\ H\text{-}F}$ = 4.85 Hz, 2H), 7.14 (d, J = 7.87 Hz, 1H), 7.2 (ddd, J = 7.6 Hz, J = 4.85 Hz, J = 1.1 Hz,1H), 7.65 (ddd, J = 7.69 Hz, J = 7.69 Hz, J = 1.83 Hz,1 H), 8.62 (ddd, J = 4.81 Hz, J = 1.81 Hz, J = 0.91 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 44.67, 115.17 (dd, $^2J_{(C,F)}$ = 24.03 Hz, $^3J_{(C,F)}$ = 8.77 Hz), 116.44 (dd, $^2J_{(C,F)}$ = 25.17 Hz, $^3J_{(C,F)}$ = 8.39 Hz), 117.1 (dd, $^2J_{(C,F)}$ = 25.17 Hz, $^3J_{(C,F)}$ = 3.81 Hz), 122.16, 123.37, 129.82 (dd, $^2J_{(C,F)}$ = 16.78 Hz, $^3J_{(C,F)}$ = 7.63 Hz), 136.89, 149.81, 156.5 (dd, $^1J_{(C,F)}$ = 243.00 Hz, $^4J_{(C,F)}$ = 2.67 Hz), 158.59 (dd, $^1J_{(C,F)}$ = 242.23 Hz, $^4J_{(C,F)}$ = 2.29 Hz), 159.31; ^{19}F NMR (376 MHz, $CDCl_3$): δ -122.52 (m), –118.63 (m); GC-MS (EI), m/z 316.5 (M$^+$), HRMS (FAB), m/z calcd for $C_{18}H_{12}F_4N$ (M+1) 318.0906, observed 318.0912.

Bis(4-trifluoromethoxyphenyl)methyl-2-pyridine (9a)

^{1}H NMR (400 MHz, $CDCl_3$): 5.68 (s, 1H), 7.08 (d, , J = 7.87 Hz, 1H), 7.14-7.21 (m, 9 H), 7.62 (ddd, J = 7.69 Hz, J = 7.69 Hz, J = 1.83 Hz, 1H), 8.61 (dd, J = 4.85 Hz, J = 0.91 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 57.78, 120.95, 120.43 (q, $^1J_{(C,F)}$ = 257.11 Hz), 121.85, 123.66, 130.55, 136.77, 140.93, 147.94, 149.75, 161.90; ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.30, GC-MS (EI), m/z 413.7 (M$^+$).

Diphenylmethyl-3-pyridine (3b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (s, 1H), 7.07-7.09 (m, 4H), 7.17-7.23 (m, 3H), 7.26-7.30 (m, 4H), 7.38 (dddd, J = 7.87, J = 2.38 Hz, J = 1.65 Hz, J = 0.73 Hz, 1H), 8.41 (ddd, J = 2.2 Hz, J = 0.73 Hz, J = 0.73 Hz, 1H), 8.45 (dd, J = 4.76 Hz, J = 1.65 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 54.31, 123.2, 126.68, 128.52, 129.24, 136.66, 139.32, 142.63, 147.7, 150.79; GC-MS (EI), m/z 245.6 (M^+); HRMS (FAB), m/z calcd for $C_{18}H_{16}N$ (M+1) 246.1283, observed 246.1281.

Bis(p-tolyl)methyl-3-pyridine (4b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 6H), 5.46 (s, 1H), 6.97 (d, *J* = 8.24 Hz, 4H), 7.09 (d, *J* = 7.87 Hz, 4H), 7.18 (ddd, *J* = 7.87 Hz, *J* = 4.76 Hz, *J* = 0.73 Hz, 1H), 7.39 (dddd, *J* = 7.87, *J* = 2.33 Hz, *J* = 1.69 Hz, *J* = 0.6 Hz, 1H), 8.41 (d, *J* = 2.38 Hz, 1H), 8.44 (dd, *J* = 4.76 Hz, *J* = 1.65 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 21.24, 53.81, 123.44, 129.33, 129.44, 136.45, 136.93, 140.0, 140.13, 147.75, 150.96; GC-MS (EI), m/z 273.8 (M^+); HRMS (FAB), m/z calcd for $C_{20}H_{20}N$ (M+1) 274.1596, observed 274.1588.

Bis(2,5-dimethylphenyl)methyl-3-pyridine (5b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 6H), 2.19 (s, 6H), 5.64 (s, 1H), 6.51 (d, *J* = 0.91 Hz, 2H), 6.96 (dd, *J* = 7.69 Hz, *J* = 1.28, 2H), 7.05 (d, *J* = 7.69 Hz, 2H), 7.19 (ddd, *J* = 7.87 Hz, *J* = 4.76 Hz, *J* = 0.73 Hz, 1H), 7.3 (dddd, *J* = 7.87, *J* = 2.38 Hz, *J* = 1.65 Hz, *J* = 0.55 Hz, 1H), 8.35 (d, *J* = 2.2 Hz, 1H), 8.47 (dd, *J* = 4.85 Hz, *J* = 1.56 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 19.05, 21.15, 47.85, 123.15, 127.29, 129.65, 130.38, 133.16, 135.22, 137.05, 138.35, 140.44, 147.49 151.24; GC-MS (EI), m/z 300.9 (M^+); HRMS (FAB), m/z calcd for $C_{22}H_{24}N$ (M+1) 302.1909, observed 302.1901.

Bis(4-fluorophenyl)methyl-3-pyridine (6b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (s, 1H), 6.95-7.00 (m, 4H), 7.02-7.06 (m, 4H), 7.21 (ddd, *J* = 7.89 Hz, *J* = 4.73 Hz, *J* = 0.76 Hz, 1H), 7.36-7.38 (m, 1H), 8.41 (d, *J* = 2.44 Hz, 1H), 8.48 (dd, *J* = 4.73 Hz, *J* = 1.68 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 52.61, 115.32 (d, $^2J_{(C,F)}$ = 21.97 Hz), 123.2, 130.49, (d, $^3J_{(C,F)}$ = 7.93 Hz), 136.31, 138.11 (d, $^4J_{(C,F)}$ = 3.11 Hz), 138.84, 147.84, 150.46, 161.46 (d, $^1J_{(C,F)}$ = 245.96 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -116.19 (m); GC-MS (EI), m/z 281.7 (M^+); HRMS (FAB), m/z calcd for $C_{18}H_{14}F_2N$ (M+1) 282.1094, observed 282.1108.

Bis(4-bromophenyl)methyl-3-pyridine (7b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 1H), 6.93-6.97 (m, 4H), 7.23 (ddd, *J* = 7.87 Hz, *J* = 4.76 Hz, *J* = 0.55 Hz, 1H), 7.35 (dddd, *J* = 7.87, *J* = 2.28 Hz, *J* = 1.65 Hz, *J* = 0.62 Hz, 1H), 7.42-7.45 (m, 4H), 8.39 (s, 1H), 8.5 (d, *J* = 3.85 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 53.09, 120.90, 123.34, 130.75, 131.70, 136.38, 138.10, 141.04, 148.07, 150.45; GC-MS (EI), m/z 404.1 (M^+); HRMS (FAB), m/z calcd for $C_{18}H_{14}Br_2N$ (M+1) 403.9473, observed 401.9492.

Bis(2,5-difluorophenyl)methyl-3-pyridine (8b)

^{1}H NMR (400 MHz, $CDCl_3$) : 5.95 (s, 1H), 6.56 (ddd, $J_{\text{(ortho) H-F}}$ = 8.88 Hz, $J_{\text{(meta) H-F}}$ = 5.77 Hz, $J_{\text{(meta) H-H}}$ = 3.11 Hz, 2H) 6.91-6.96 (m, 2H), 7.00 (ddd, $J_{\text{(ortho) H-F}}$ = 8.97 Hz, $J_{\text{ortho (H-H)}}$ = 8.97 Hz, $J_{\text{(meta) H-F}}$ = 4.58 Hz, 2H), 7.23 (ddd, *J* = 7.87 Hz, *J* = 4.76 Hz, *J* = 0.73 Hz, 1H) 7.35-7.37 (m, 1H), 8.38 (d, *J* = 2.38 Hz, 1H), 8.51 (dd, *J* = 4.8 Hz, *J* = 1.56 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 40.55, 115.46 (dd, $^2J_{(C,F)}$ = 24.03 Hz, $^3J_{(C,F)}$ = 8.77 Hz), 116.54-116.92 (2C, *two dd merging*), 123.44, 129.63 (dd, $^2J_{(C,F)}$ = 16.80 Hz,

$^3J_{(C,F)}$ = 6.87 Hz), 135.36, 136.05, 148.55, 150.14, 156.29 (dd, $^1J_{(C,F)}$ = 244.14 Hz, $^4J_{(C,F)}$ = 2.29 Hz), 158.64 (dd, $^1J_{(C,F)}$ = 243.38 Hz, $^4J_{(C,F)}$ = 2.29 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ -122.04 (m), –118.13 (m); GC-MS (EI), m/z 316.4 (M$^+$); HRMS (FAB), m/z calcd for $C_{18}H_{12}F_4N$ (M+1) 318.0906, observed 318.0912.

Diphenylmethyl-4-pyridine (3c)

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.50 (s, 1H), 7.04 (ddd, *J* = 4.4 Hz, *J* = 1.65 Hz, *J* = 0.73 Hz, 2H), 7.08-7.11 (m, 4H), 7.22-7.27 (m, 2H), 7.28-7.33 (m, 4H), 8.5 (dd, *J* = 4.39 Hz, *J* = 1.65 Hz, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$): δ 56.14, 124.55, 126.80, 128.52, 129.26, 142.01, 149.75, 152.67; GC-MS (EI), m/z 245.8 (M$^+$); HRMS (FAB), m/z calcd for $C_{18}H_{16}N$ (M+1) 246.1283, observed 246.1288.

Bis(*p*-tolyl)methyl-4-pyridine (4c)

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.3 (s, 6H), 5.40 (s, 1H), 6.96 (d, *J* = 8.06 Hz, 4H), 7.01 (ddd, *J* = 4.39 Hz, *J* = 1.56 Hz, *J* = 0.64 Hz, 2H), 7.08 (d, *J* = 7.87 Hz, 4H), 8.47 (dd, *J* = 4.39 Hz, *J* = 1.65 Hz, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$): δ 20.98, 55.5, 124.57, 129.10, 129.21, 136.36, 139.26, 149.59, 153.2; GC-MS (EI), m/z 273.8 (M$^+$); HRMS (FAB), m/z calcd for $C_{20}H_{20}N$ (M+1) 274.1596, observed 274.1593.

Bis(2,5-dimethylphenyl)methyl-4-pyridine (5c)

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.11(s, 6H), 2.2 (s, 6H), 5.6 (s, 1H), 6.49 (d, *J* = 0.91 Hz, 2H), 6.95-6.99 (m,4H), 7.06 (d, *J* = 7.51 Hz, 2H), 8.50 (dd, *J* = 4.58 Hz, *J* = 1.65 Hz, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$): δ 19.17, 21.23, 49.83, 125.12, 127.53, 129.76, 130.46, 133.40, 135.38, 140.00, 149.83, 152.36; GC-MS (EI), m/z 273.8 (M$^+$); HRMS (FAB), m/z calcd for $C_{22}H_{24}N$ (M+1) 302.1909, observed 302.1923.

Bis(4-fluorophenyl)methyl-4-pyridine (6c)

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.47 (s, 1H), 6.98-7.06 (m, 10H), 8.52 (dd, *J* = 4.39 Hz, *J* = 1.65 Hz, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$): δ 54.56, 115.50 (d, $^2J_{(C,F)}$ = 21.36 Hz), 124.32, 130.66 (d, $^3J_{(C,F)}$ = 7.63 Hz), 137.60 (d, $^4J_{(C,F)}$ = 3.05 Hz), 149.91,152.30, 161.66 (d, $^1J_{(C,F)}$ = 247.20 Hz); ^{19}F NMR (376 MHz, CDCl$_3$): δ -115.97 (m); HRMS (EI), m/z 281.1010, calculated for $C_{18}H_{13}F_2N$ 281.1016.

Bis(4-bromophenyl)methyl-4-pyridine (7c)

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.41 (s, 1H), 6.92-6.96 (m, 4H), 6.99 (dd, *J* = 4.48 Hz, *J* = 1.56 Hz, 2H), 7.42-7.46 (m, 4H), 8.53 (dd, *J* = 4.58 Hz , *J* = 1.46 Hz, 2H); ^{13} C NMR (100.5 MHz, CDCl$_3$): δ 54.94, 121.11, 124.28, 130.84, 131.79, 140.47, 149.99, 151.42; GC-MS (EI), m/z 403.9 (M$^+$); HRMS (FAB), m/z calcd for $C_{18}H_{14}Br_2N$ (M+1) 403.9473, observed 401.9474.

Bis(2,5-difluorophenyl)methyl-4-pyridine (8c)

^{1}H NMR (400 MHz, CDCl$_3$) : 5.95 (s, 1H), 6.60 (ddd, $J_{(ortho)\ H\text{-}F}$ = 8.79 Hz, $J_{(meta)\ H\text{-}F}$ = 5.68 Hz, $J_{(meta)\ H\text{-}H}$ = 3.11 Hz, 2H), 6.96-7.09 (m, 6H), 8.59 (dd, *J* = 4.49 Hz, *J* = 1.56 Hz, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$):

δ 42.17, 115.68 (dd, $^2J_{(C,F)}$ = 24.41 Hz, $^3J_{(C,F)}$ = 8.39 Hz), 116.61-116.97 (2C, *two dd merging*), 123.79, 129.06 (dd, $^2J_{(C,F)}$ = 17.17 Hz, $^3J_{(C,F)}$ = 7.25 Hz), 148.72, 150.21, 156.39 (dd, $^1J_{(C,F)}$ = 244.14 Hz, $^4J_{(C,F)}$ = 2.29 Hz), 158.6 (dd, $^1J_{(C,F)}$ = 243.38 Hz, $^4J_{(C,F)}$ = 2.29 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ-121.95 (m), –117.96 (m); GC-MS (EI), m/z 316.4 (M^+); HRMS (FAB), m/z calcd for $C_{18}H_{12}F_4N$ (M+1) 318.0906, observed 318.0905.

Bis(4-trifluoromethoxyphenyl)methyl-4-pyridine (9c)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (s, 1H), 7.02 (ddd, *J* = 4.58 Hz, *J* = 1.60 Hz, *J* = 0.55 Hz, 2H), 7.1-7.13 (m, 4H), 7.16-7.20 (m, 4H), 8.55 (dd, *J* = 4.57 Hz , *J* = 1.65 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 54.71, 120.34 (q, $^1J_{(C,F)}$ = 257.11 Hz), 121.07, 124.24, 130.49, 140.16, 148.10, 150.2, 151.47; ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.28; GC-MS (EI), m/z 413.4 (M^+).

Bis(4-chlorophenyl)methyl-4-pyridine (10c)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (s, 1H), 6.98-7.02 (m, 6H), 7.28-7.31 (m, 4H), 8.53 (dd, *J* = 4.58 Hz , *J* = 1.65 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 54.86, 124.39, 128.88, 130.50, 133.05, 140.01, 149.78, 152.01; GC-MS (EI), m/z 314.8 (M^+); HRMS (FAB), m/z calcd for $C_{18}H_{14}Cl_2N$ (M+1) 314.0503, observed 314.0494.

Triphenylmethane (1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.55 (s, 1H), 7.10-7.29 (m, 15H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 56.78, 126.27, 128.27, 129.43, 143.86; GC-MS (EI), m/z 244.8 (M^+).

Bis(*p*-tolyl)methyl-4-quinoline (4d)

^{1}H NMR (400 MHz, $CDCl_3$): 2.34 (s, 6H), 6.32 (s, 1H), 6.95 (4H, d, J=7 Hz), 7.15(d, 4H, *J* = 7 Hz), 7.43 (1H, d, *J* = 6.0 Hz), 7.76 (1H, m), 7.99 (1H, m), 8.24 (1H, d, *J* = 8.0 Hz), 8.62 (1H, d, *J* = 8.0 Hz), 9.00 (1H, d, *J* = 6.0 Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 21.0, 53.0, 122.2, 122.4, 125.2, 127.7, 128.2, 128.9, 129.0, 129.9, 134.2, 136.9, 137.6, 137.8, 143.0, 163.0; HRMS (FAB), m/z calcd for $C_{24}H_{22}N$ (M+1) 324.1754, found 324.1743.

Bis(2,5-dimethylphenyl)methyl-4-quinoline (5d)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 6H), 2.18 (s, 6H), 6.41(s, 3H), 7.06 (2H, d, *J* = 6.0 Hz), 7.16 (2H, d, *J* = 6Hz), 7.33 (1H, d, *J* = 6.0 Hz), 7.77(1H, m), 7.98 (m, 3H), 8.65 (1H, d, *J* = 7.0 Hz), 8.97 (1H, d, *J* = 6.0 Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 19.1, 21.1, 47.4, 122.1, 122.8, 124.7, 127.9, 128.7, 130.5, 131.1, 132.7, 136.3, 137.7, 138.0, 143.2, 163.1; HRMS (FAB), m/z calcd for $C_{26}H_{26}N$ (M+1) 352.2067, found 352.2062.

Bis(*p*-tolyl)methyl-3-quinoline (7d)

^{1}H NMR (400 MHz, $CDCl_3$): 2.35 (s, 6H), 5.80 (s, 1H), 7.01 (4H, d, *J* = 7.0 Hz), 7.16 (d, 4H, *J* = 7.0 Hz), 7.43 (1H, d, *J* = 6.0 Hz), 7.76 (1H, m), 7.99 (1H, m), 8.24 (1H, d, *J* = 8.0 Hz), 8.62 (1H, d, *J* = 8Hz), 9.00 (1H, d, *J* = 6.0 Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 21.0, 53.0, 122.2, 125.2, 127.7, 128.2, 128.9, 129.0, 129.9, 134.2, 136.9, 137.6, 137.8, 143.0, 163.0; HRMS (FAB), m/z calcd for $C_{24}H_{22}N$ (M+1) 324.1754, found 324.1750.

Bis(4-cholorophenyl)methyl-2-quinoline (9d)

^{1}H NMR (400 MHz, $CDCl_3$): 6.42 (s, 1H), 6.92 (4H, d, *J* = 6.0 Hz), 6.97 (d, 4H, *J* = 6.8 Hz), 7.38 (m, 1H), 7.50 (1H, m), 7.71 (1H, m), 7.80 (1H, m), 8.38 (1H, d, *J* = 7.2 Hz), 8.60 (1H, d, *J* = 7.0 Hz); ^{13} C NMR (100.5 MHz, $CDCl_3$): δ 52.7, 121.5, 121.8, 127.4, 128.3, 128.6, 129.3, 132.8, 134.2, 135.0, 136.4, 146.1, 160.0. HRMS (FAB), m/z calcd for $C_{22}H_{16}Cl_2N$ (M+1) 364.0662, found 364.0602.

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