Supporting Information

Room Temparature, Open-flask C-H Arylation of Electron-deficient Heteroarenes with Aryl Triazenes: Rapid Synthesis of Heterobiaryls

Rui Wang* and John R. Falck

Division of Chemistry, Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9038, United States

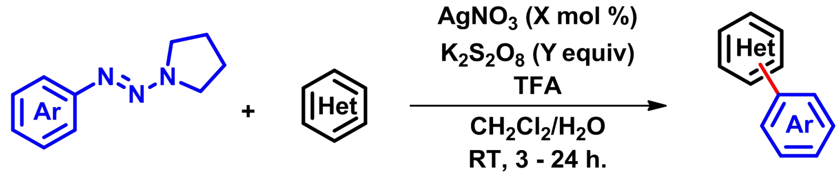
E-mail: rwang9@albany.edu; shairwang@gmail.com

Table of Contents

I. Introduction

All reactions were conducted open to air atomphosphere unless otherwise stated. All solvents (CH_2Cl_2, CH_3CN and water) were purchased from Fisher Scientific Company and used without further purification. Flash chromatography (FC) was performed using E. Merck silica gel 60 (240-400 mesh). Thin layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on spectrometers at operating frequencies of 400 MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum. Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ = 7.26 for ^{1}H NMR or δ = 77.3 for proton decoupled ^{13}C NMR) and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet. Low resolution LC-MS spectrum were obtained with an Agilent 1200 series API-LC/MSD spectrometer. High resolution mass spectral analyses were kindly provided by Professor Kevin A. Schug at Department of Chemistry & Biochemistry, The University of Texas at Arlington.
All starting material compounds were purchased from Sigma-Aldrich or TCI America.

II. General experiment procedure



To a stirred solution of heteroarenes (0.4 mmol) in CH_2Cl_2 (1.5 mL) at ambient temperature under open-flask was added TFA (0.32 mL) and the triazenes (0.6 mmol), the mixture was then stirred vigorously for 5 minutes. H_2O (1.5 mL) and $AgNO_3$ solution (20 mol % in 1.0 mL water) and $K_2S_2O_8$ (0.32 g) was added successively. Reaction was monitored by TLC plate. If the starting material was not completely consumed, 3 hours later, additional $AgNO_3$ solution (20 mol % in 1.0 mL water) and $K_2S_2O_8$ (0.32 g) was added and the mixture was stirred vigorously for overnight. 2N NaOH was added to quench excess TFA, extracted with CH_2Cl_2 (5 X 20 mL), dried over Na_2SO_4. Solvent was evaporated under reduced pressure and the crude residue was purified by silica gel flash chromatography using fluent (10% MeOH in CH_2Cl_2) to provide corresponding products.

III. Screening of the reaction conditions

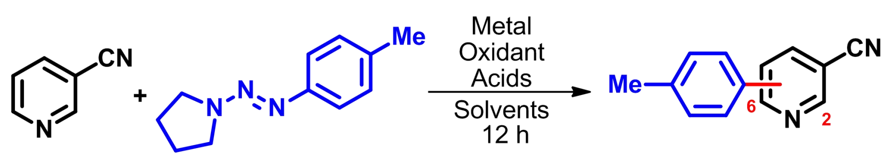


Table 1

Entry	Solvents (2 mL)	Metals	Oxidant	Acids	Temp.	Time	Conv.(%)	Yield(%)
1	CF_3CH_2OH	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.16 mL)	RT	12	0	0
2	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	60-70	43
3	Et_2O/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>95	<5
4	THF/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	40-50	30
5	Toluene/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	70	40
6	PhCl/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.16 mL)	RT	12	90	67
7	**$PhCF_3/H_2O$ 3/4**	**$AgNO_3$ (20 mol %)**	**$K_2S_2O_8$ (3.0 equiv)**	**TFA (0.16 mL)**	**RT**	**12**	**90**	**70**
8	DME/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>95	trace
9	CH_3CN/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>95	messy
10	DMF/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>95	messy
11	DMSO/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>95	10
12	MeOH/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>90	messy
13	CH_3NO_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>90	messy

14	$(ClCH_2)_2/H_2O$ 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>90	messy
15	$(ClCH_2)_2/H_2O$ 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>90	messy
16	$CHCl_3/H_2O$ 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>80	40
17	1,4-dioxane/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>30	messy
18	Acetone/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	>80	messy
19	CH_3NO_2	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	30	trace
20	DMSO	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	30	trace
21	Acetone	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	20	trace
22	CH_2Cl_2	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.02 mL)	RT	12	30	trace
23	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (1.0 equiv)	RT	12	60	40
24	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (3.0 equiv)	RT	12	70	52
25	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (6.0 equiv)	RT	12	75	55
26	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (9.0 equiv)	RT	12	80	60
27	**CH_2Cl_2/H_2O 3/4**	**$AgNO_3$ (20 mol %)**	**$K_2S_2O_8$ (3.0 equiv)**	**TFA (10.5 equiv)**	**RT**	**12**	**100**	**80**
28	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	36% HCl (2 equiv)	RT	12	0	0
29	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	48% HBr (2 equiv)	RT	12	0	0
30	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	AcOH (2 equiv)	RT	12	70	50
31	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	65% $HClO_4$ (2 equiv)	RT	12	95	73
32	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	$MeSO_3H$ (2 equiv)	RT	12	100	trace
33	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	85% H_3PO_4 (2 equiv)	RT	12	60	40
34	CH_2Cl_2	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	$BF_3{\cdot}OEt_2$ (2 equiv)	RT	12	100	trace
35	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	$TsOH{\cdot}H_2O$ (2 equiv)	RT	12	0	0
36	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	CSA (2 equiv)	RT	12	0	0
37	CH_2Cl_2/H_2O 3/4	Ag_2O (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	81	67
38	CH_2Cl_2/H_2O 3/4	AgF_2 (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	90	72
39	CH_2Cl_2/H_2O 3/4	Ag_2O (2equiv), $AgSF_6$ (30 mol%)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	65	48
40	CH_2Cl_2/H_2O 3/4	$Cu(OAc)_2{\cdot}H_2O$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
41	CH_2Cl_2	$Cu(OAc)_2{\cdot}H_2O$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
42	CH_2Cl_2/H_2O 3/4	AgF (30 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0

43	CH_2Cl_2/H_2O 3/4	Ag_2CrO_4 (30 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	70	50
44	CH_2Cl_2/H_2O 3/4	Ag_2CO_3 (30 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	80	72
45	**CH_2Cl_2/H_2O 3/4**	**none**	**$K_2S_2O_8$ (3.0 equiv)**	**TFA (10.5 equiv)**	**RT**	**12**	**0**	**0**
46	CH_2Cl_2/H_2O 3/4	BQ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
47	CH_2Cl_2/H_2O 3/4	DDQ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
48	CH_2Cl_2/H_2O 3/4	TBHP (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
49	CH_2Cl_2/H_2O 3/4	^{t}BuOOBz (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
50	CH_2Cl_2/H_2O 3/4	$PhI(OAc)_2$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
51	CH_2Cl_2/H_2O 3/4	Oxane (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
52	CH_2Cl_2/H_2O 3/4	CuCl (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
53	CH_2Cl_2/H_2O 3/4	CuBr (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
54	CH_2Cl_2/H_2O 3/4	Cu_2O (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
55	CH_2Cl_2/H_2O 3/4	$Mn(OAc)_3$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	60 ^oC	12	10	5
56	CH_2Cl_2	$Mn(OAc)_3$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	60 ^oC	12	0	0
57	CH_2Cl_2/H_2O 3/4	$Fe(acac)_3$ (20 mol%)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	30	10
58	CH_2Cl_2/H_2O 3/4	$FeSO_4$ (20 mol%)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
59	**CH_2Cl_2/H_2O 3/4**	**$AgNO_3$ (20 mol %)**	**$K_2S_2O_8$ (3.0 equiv)**	**none**	**60 ^oC**	**12**	**0**	**0**
60	CH_2Cl_2/H_2O 3/4	Ag(TFA)(20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
61	CH_2Cl_2/H_2O 3/4	$HgCl_2$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	95	trace
62	CH_2Cl_2/H_2O 3/4	$HgBr_2$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
63	CH_2Cl_2/H_2O 3/4	HgO (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
64	CH_2Cl_2/H_2O 3/4	$Hg(CF_3CO_2)_2$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
65	CH_2Cl_2/H_2O 3/4	$HgCl_4$ (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
66	CH_2Cl_2/H_2O 3/4	HgO, Ag_2O (2 equiv)	$K_2S_2O_8$ (3.0 equiv)	TFA (10.5 equiv)	RT	12	0	0
67	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$(NH_4)_2S_2O_8$	TFA (10.5 equiv)	RT	12	95	70

Additional more strict control experiments were employed, which was suggested by one of the reviewer, see following table 2,

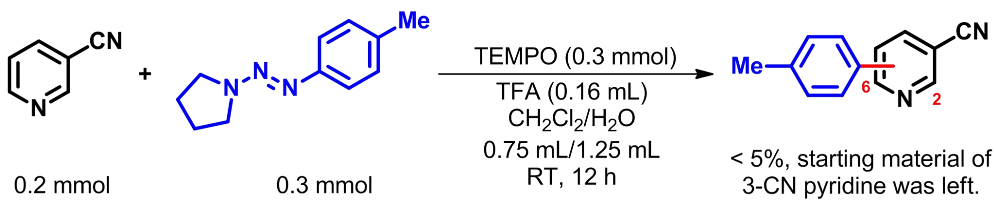
Table 2

Entry	Solvents (2 mL)	**Metals**	**Oxidant**	Acids	Temp.	Time	Conv.(%)	Yield(%)
1	CH_2Cl_2/H_2O 3/4	**none**	**none**	TFA (0.16 mL)	Air, RT	24	< 5%	< 5 %

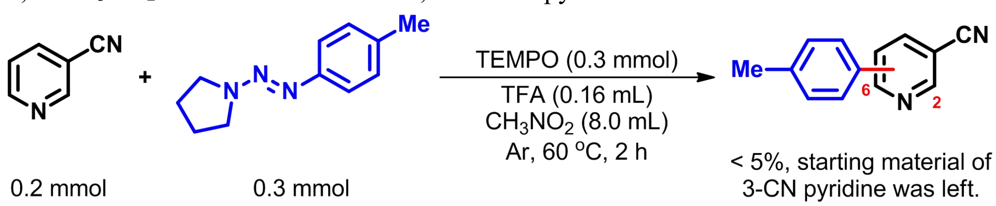
2	CH_2Cl_2/H_2O 3/4	**none**	**$K_2S_2O_8$ (3.0 equiv)**	TFA (0.16 mL)	Air, RT	24	< 5%	< 5%
3	CH_2Cl_2/H_2O 3/4	**$AgNO_3$ (20 mol %)**	**none**	TFA (0.16 mL)	Air, RT	24	< 5%	< 5%
4	CH_2Cl_2/H_2O 3/4	**$AgNO_3$ (20 mol %)**	**$K_2S_2O_8$ (3.0 equiv)**	TFA (0.16 mL)	Air, RT	24	**100 %**	**80 %**
5	CH_2Cl_2/H_2O 3/4	$AgNO_3$ (20 mol %)	$K_2S_2O_8$ (3.0 equiv)	TFA (0.16 mL)	Ar, RT	24	98 %	78 %

Note: Under standard reaction condition, if no $AgNO_3$ and $K_2S_2O_8$, all the 3-CN pyridine was left (entry 1, table 2); if no $AgNO_3$, we can detect trace mount of arylated product, almost all the 3-CN pyridine was left (entry 2); if no $K_2S_2O_8$, the 3-CN pyridine was almost left (entry 3); interestingly, there is no difference between the two reactions that were conducted under air or Ar atomosphere.

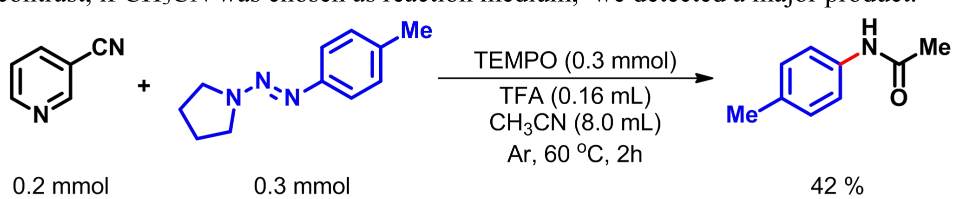
Also, a referred experiment was conducted, TEMPO was selected as initial reagent instead of $AgNO_3/K_2S_2O_8$, open to air under room temperture for 12 hours, only trace mount of arylated pyridine was detected, most of 3-CN pyridine was left.



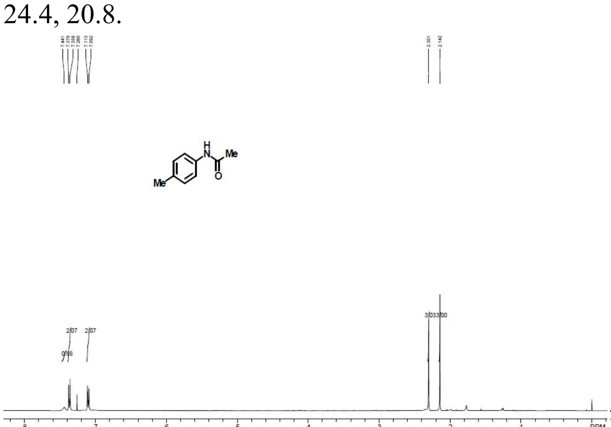
However, if CH_3NO_2 was selected as solvent, the 3-CN pyridine was almost left.

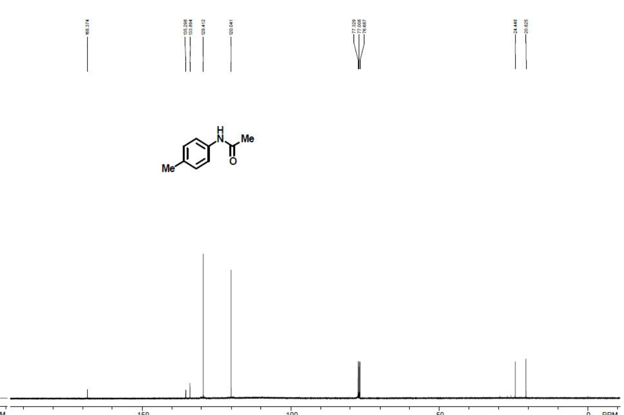


In sharp contrast, if CH_3CN was chosen as reaction medium, we detected a major product.

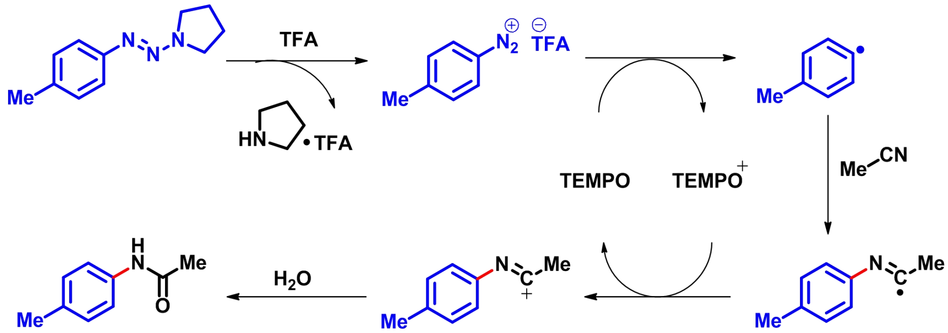


Using 2N NaOH to quench the reaction, we found that most of 3-CN pyridine was consumed, but desired arylated product was < 5% yield. The major product of the reaction under current reaction condition is *N*-(p-tolyl)acetamide. Pale-yellow solid: $[M+H]^+$ 150.1698, $[M-H]^+$ 148.0761; ^1H NMR 7.43 (br s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 2.30 (s, 3H), 2.15 (s, 3H); ^{13}C NMR 168.3, 135.2, 133.9, 129.4, 119.9, 24.4, 20.8.





Possible mechanistic pathway:

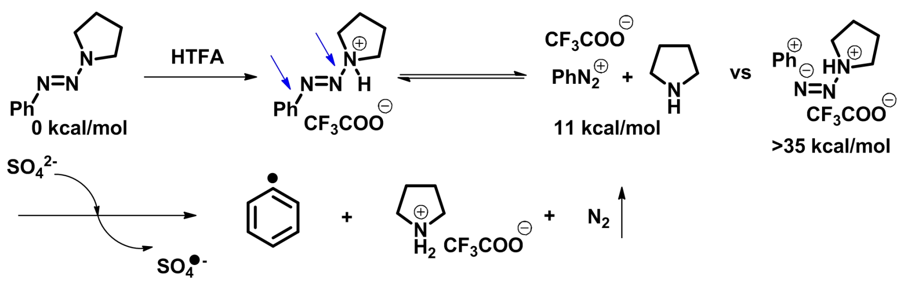


IV. Calculated, elucidated and plausible mechanism pathway

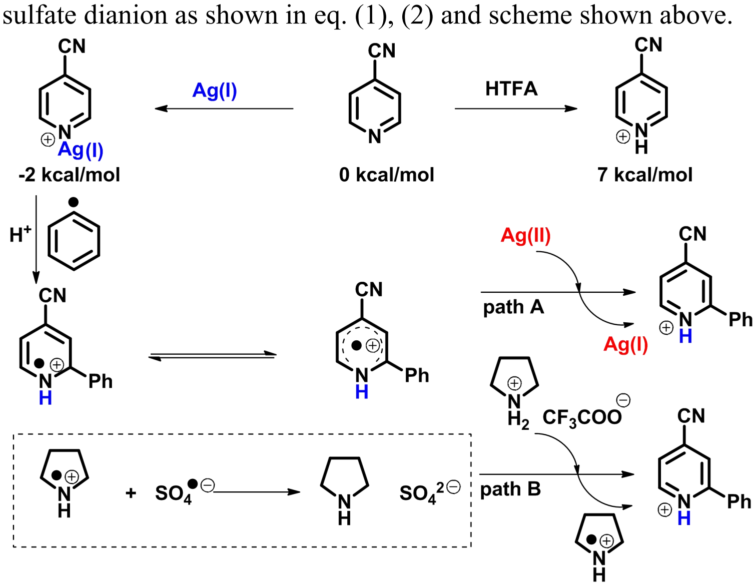
$$Ag(I) + S_2O_8^{2-} \longrightarrow Ag(II) + SO_4^{2-} + SO_4^{\bullet -} \quad (1)$$

$$Ag(I) + SO_4^{\bullet -} \longrightarrow Ag(II) + SO_4^{2-} \quad (2)$$

The possible transformation of intermediates Ag(I)/ Ag(II) and $K_2S_2O_8$.

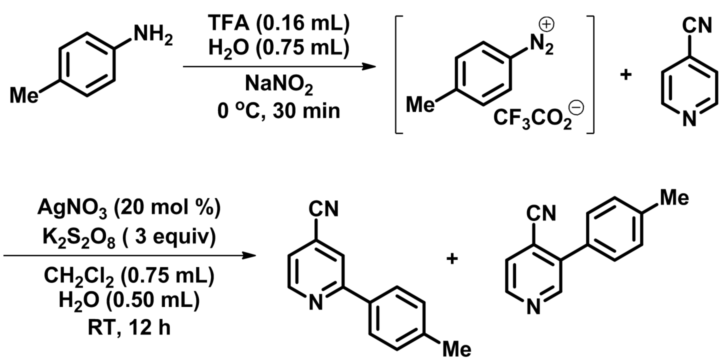


The possible pathway to obtain aromatic radicals from triazenes. The triazenes are firstly protonated; Secondly, the activated forms are transformed to C-N/N-N cleavage species, N-N cleavages are preferred; Finally, aromatic diazonium intermediate are transferred to phenyl radicals and the a sulfate radical anion is regenerated by the sulfate dianion as shown in eq. (1), (2) and scheme shown above.



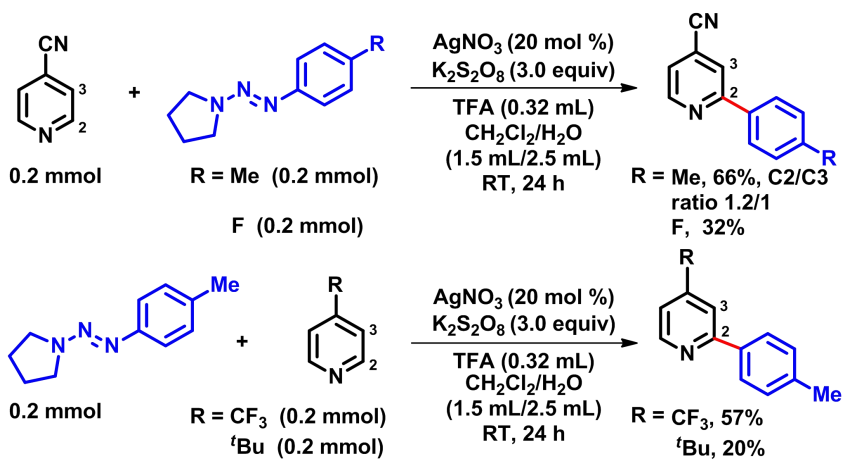
Mechanistic hypothesis: heterocycles are activated firstly by Ag(I), aromatic radical intermediates attack the activated heterocycles; the corresponding radical intermediates lose one electron to provide the arylated products and either the Ag(I)/ Ag(II) circles or tetrahedyopyrrole transformations are involved.

Consequently, we run a control experiment using 4-methoxyaniline. In situ generated phenyl dizonium salt was conducted in standard reaction condition,



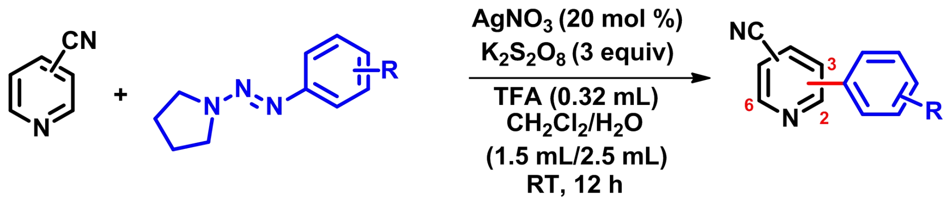
We still isolated C2/C3 arylated products in 60% yield with ratio 1.1/1. This result indicated that without the tetrahydropyrrole group, the reaction still proceeded in moderate yield. This exclude the reduction function of tetrahydropyrrole group in such transformation.

Intermolecular Competition Experiment

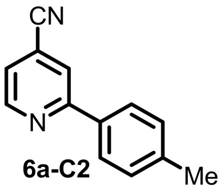


Given the rapid and efficient arylation of heteroaromatics, we tried to elucidate its mode of action. Firstly, we conducted intermolecular competition studies with differently substituted triazenes (Me and F), which indicated the electron-rich methyl-substituted triazene to react preferentially. Secondly, another competition experiments between heterocycles (CF_3 and ^{t}Bu) revealed that the electron-deficient heterocycle (CF_3-substituted) dominated the corresponding arylated products. These results can be rationalized with the so-called polar effect which is thought to involve a charge transfer process, in which the aromatic radicals (initiated from triazenes, electron donor) to pyridinium ion (originated from heterocycles, electron acceptor).

V. Part I-Key compounds characterization data



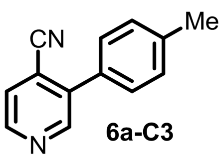
2-(p-tolyl)isonicotinonitrile (6a-C2):[1]



6a-C2

White solid, 54% yield, 41.9 mg, m.p. 83-84 °C; R_f 0.5 (25% EtOAc in n-Hexane); ^{1}H NMR ($CDCl_3$, 400MHz) δ 2.42 (s, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.91-7.90 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.3, 116.8, 121.1, 121.7, 122.8, 126.8, 129.8, 134.5, 140.5, 150.5, 158.7; ESI-HRMS *m/z* Calcd for $C_{13}H_{10}N_2$ $[M+H]^+$: 195.0917, Found: 195.0912.

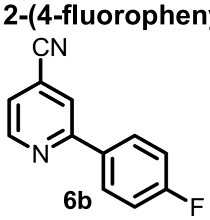
3-(p-tolyl)isonicotinonitrile (6a-C3):[1,2]



6a-C3

Colorless solid, 45% yield, 35.3 mg, m.p. 98-100 °C; R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR ($CDCl_3$, 400MHz) δ 2.44 (s, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 4.0 Hz, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.4, 116.5, 118.7, 126.0, 128.6, 129.9, 131.5, 138.7, 139.8, 148.4, 150.9; ESI-HRMS *m/z* Calcd for $C_{13}H_{10}N_2$ $[M+H]^+$: 195.0917, Found: 195.0910.

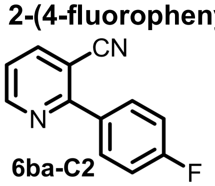
2-(4-fluorophenyl)isonicotinonitrile (6b):[3]



6b

Yellow solid, 100% yield, 79.2 mg, m.p. 143-145 °C; R_f 0.3 (25% EtOAC in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 4.0 Hz, 1H), 7.90 (s, 1H), 8.02-7.98 (dd, *J* = 8.0, 4.0 Hz, 2H), 8.84 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.0 (d, $J_{C\text{-}F}$ = 21.0 Hz), 116.6, 121.3, 121.7, 123.1, 129.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 133.5 (d, $J_{C\text{-}F}$ = 3.0 Hz), 150.6, 157.6, 164.2 (d, $J_{C\text{-}F}$ = 249.5 Hz); ESI-HRMS *m/z* Calcd for $C_{12}H_7FN_2$ $[M+H]^+$: 199.0666, Found: 199.0660.

2-(4-fluorophenyl)nicotinonitrile (6ba-C2):

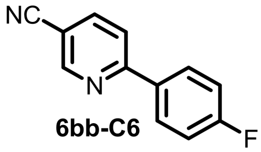


6ba-C2

Brown solid, 35% yield, 190 mg (5 mmol scale, unoptimized), m.p. 145-147 °C; R_f 0.3 (50% EtOAc in n-Hexane)**;** Major, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.0 Hz, 1H), 8.05 (d, *J* = 4.0 Hz, 1H), 7.94 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 4.0 Hz, 8.0Hz, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 164.0 (d, $J_{C\text{-}F}$ = 250.0 Hz), 159.9, 152.7, 141.9, 133.3 (d, $J_{C\text{-}F}$ = 5.0 Hz), 131.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 121.6, 117.6, 115.8 (d, $J_{C\text{-}F}$ = 22.0 Hz), 107.3; ESI-HRMS *m/z* Calcd for $C_{12}H_7FN_2$ $[M+H]^+$: 199.0666, Found: 199.0664.

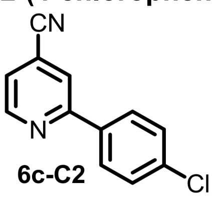
6-(4-fluorophenyl)nicotinonitrile (6bb-C6):[4]



6bb-C6

Gray solid, 35% yield, 190 mg (5 mmol scale, unoptimized), m.p. 140-141 ºC; R_f 0.1 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.0 Hz, 1H), 8.05 (d, *J* = 4.0 Hz, 1H), 7.94 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 4.0 Hz, 1H), 7.23 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (d, $J_{C\text{-}F}$ = 250.0 Hz), 154.0, 152.9, 151.2, 131.5 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.5 (d, $J_{C\text{-}F}$ = 9.0 Hz), 123.6, 116.6, 116.4 (d, $J_{C\text{-}F}$ = 22.0 Hz), 108.5; ESI-HRMS *m/z* Calcd for $C_{12}H_7FN_2$ $[M+H]^+$: 199.0666, Found: 199.0658.

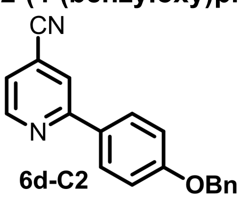
2-(4-chlorophenyl)isonicotinonitrile (6c-C2):[3]



6c-C2

White solid, 94% yield, 80.5 mg, m.p. 161-162 ºC; R_f 0.6 (25% EtOAC in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.43 (m, 3H), 7.91 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.85 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.6, 121.4, 121.8, 123.4, 128.2, 129.3, 135.7, 136.5, 150.7, 157.5; ESI-HRMS *m/z* Calcd for $C_{12}H_7ClN_2$ $[M+H]^+$: 215.0371, Found: 215.0360.

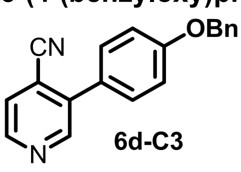
2-(4-(benzyloxy)phenyl)isonicotinonitrile (6d-C2):



6d-C2

Red-solid, 18% yield, 18.3 mg, m.p. 143-144 ºC; R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.47-7.33 (m, 6H), 7.87 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 8.80 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.1, 115.3, 116.9, 121.1, 121.3, 122.3, 127.5, 128.1, 128.4, 128.7, 130.1, 136.5, 150.5, 158.3, 160.6; ESI-HRMS *m/z* Calcd for $C_{19}H_{14}N_2O$ $[M+H]^+$: 287.1179, Found: 287.1165.

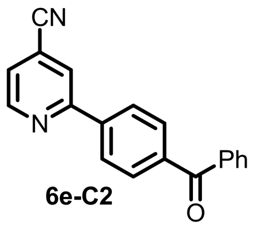
3-(4-(benzyloxy)phenyl)isonicotinonitrile (6d-C3):



6d-C3

White-solid, 24% yield, 27.2 mg, m.p. 113-114 ºC; R_f 0.1 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.47-7.35 (m, 5H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 8.70 (d, *J* = 4.0 Hz, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.2, 115.5, 116.6, 118.4, 126.0, 126.9, 127.5, 128.2, 128.7, 130.2, 136.4, 138.4, 148.1, 150.9, 159.9; ESI-HRMS *m/z* Calcd for $C_{19}H_{14}N_2O$ $[M+H]^+$: 287.1179, Found: 287.1167.

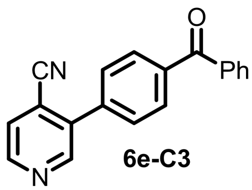
2-(4-benzoylphenyl)isonicotinonitrile (6e-C2):



6e-C2

Red solid, 27% yield, 31.1 mg, m.p. 130-132 ºC; R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.49 (m, 3H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H), 8.02 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 8.91 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.5, 121.5, 122.4, 123.9, 126.9, 128.4, 130.1, 130.7, 132.7, 137.3, 138.8, 140.7, 150.9, 157.6, 196.1; ESI-HRMS *m/z* Calcd for $C_{19}H_{12}N_2O$ $[M+H]^+$: 285.1022, Found: 285.1028.

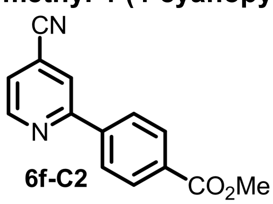
3-(4-benzoylphenyl)isonicotinonitrile (6e-C3):



6e-C3

White solid, 36% yield, 40.2 mg, m.p. 160-162 ºC; R_f 0.1 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 8.83 (d, *J* = 4.0 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.0, 118.9, 126.2, 128.5, 128.8, 130.1, 130.7, 132.8, 137.1, 138.1, 138.4, 149.4, 150.4, 150.8, 195.9; ESI-HRMS *m/z* Calcd for $C_{19}H_{12}N_2O$ $[M+H]^+$: 285.1022, Found: 285.1007.

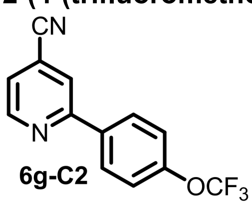
methyl 4-(4-cyanopyridin-2-yl)benzoate (6f-C2):



6f-C2

Light-red solid, 61% yield, 41.5 mg, m.p. 99-100 ºC; R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.51 (d, *J* = 4.0 Hz, 1H), 8.00 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 8.0 Hz, 2H), 8.90 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 116.5, 121.4, 122.4, 123.9, 126.9, 130.3, 131.5, 141.2, 150.8, 157.5, 166.5; ESI-MS $[M+MeOH+H]^+$: 271.3.

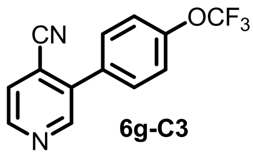
2-(4-(trifluoromethoxy)phenyl)isonicotinonitrile (6g-C2):[5]



6g-C2

Light-yellow solid, 54% yield, 45.9 mg, m.p. 64-65 ºC; R_f 0.5 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 4.0 Hz, 1H), 7.92 (s, 1H), 8.04 (d, *J* = 4.0 Hz, 2H), 8.86 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.5, 120.4 (q, $J_{C\text{-}F}$ = 257.0 Hz), 121.3, 121.4, 121.9, 123.5, 124.2, 128.5, 135.8, 150.7, 157.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.7; ESI-HRMS *m/z* Calcd for $C_{13}H_7F_3N_2O$ $[M+H]^+$: 265.0583, Found: 265.0578.

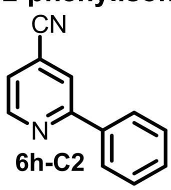
3-(4-(trifluoromethoxy)phenyl)isonicotinonitrile (6g-C3):



6g-C3

White solid, 18% yield, 15.3 mg, m.p. 71-72 °C; R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.64-7.61 (m, 3H), 8.79 (d, *J* = 4.0 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.1, 118.8, 120.4 (q, $J_{C\text{-}F}$ = 257.2 Hz), 121.5, 126.1, 130.4, 132.9, 137.3, 149.2, 150.2, 150.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.8; ESI-HRMS *m/z* Calcd for $C_{13}H_7F_3N_2O$ $[M+H]^+$: 265.0583, Found: 265.0578.

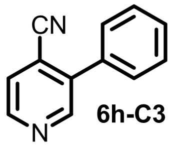
2-phenylisonicotinonitrile (6h-C2):



6h-C2

Colorless solid, 71% yield, 51.1 mg, m.p. 75-76 °C; R_f 0.5 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 1H), 7.54-7.48 (m, 3H), 7.95 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.86 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.7, 121.2, 122.0, 123.1, 127.0, 129.1, 130.2, 137.3, 150.6, 158.8; ESI-HRMS *m/z* Calcd for $C_{12}H_8N_2$ $[M+H]^+$: 181.0760, Found: 181.0758.

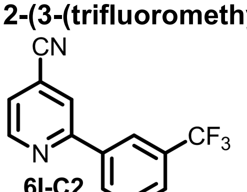
3-phenylisonicotinonitrile (6h-C3):[6]



6h-C3

Colorless oil, 7% yield, 5.1 mg, m.p. 92-93 °C, R_f 0.2 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.51 (m, 5H), 7.63 (d, *J* = 8.0 Hz, 1H), 8.76 (d, *J* = 4.0 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3, 118.8, 126.0, 128.8, 129.2, 129.6, 134.4, 138.7, 148.7, 151.0; ESI-HRMS *m/z* Calcd for $C_{12}H_8N_2$ $[M+H]^+$: 181.0760, Found: 181.0752.

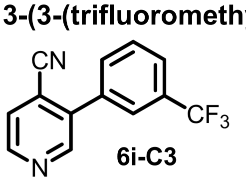
2-(3-(trifluoromethyl)phenyl)isonicotinonitrile (6i-C2):



6I-C2

Light-yellow solid, 41% yield, 41.1 mg, m.p. 73-74 °C; R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 4.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 8.31 (s, 1H), 8.90 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 150.9, 138.0, 131.7 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.0, 129.6, 126.8 (q, $J_{C\text{-}F}$ = 3.0 Hz), 124.0, 123.9 (q, $J_{C\text{-}F}$ = 4.0 Hz), 123.9 (q, $J_{C\text{-}F}$ = 271.0 Hz), 122.0, 121.6, 116.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8; ESI-HRMS *m/z* Calcd for $C_{13}H_7F_3N_2$ $[M+H]^+$: 249.0634, Found: 249.0632.

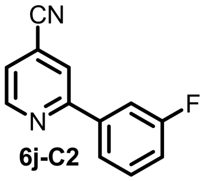
3-(3-(trifluoromethyl)phenyl)isonicotinonitrile (6i-C3):



6i-C3

Colorless solid, 32% yield, 30.8 mg, m.p. 59-60 °C; R_f 0.1 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.82 (d, *J* = 4.0 Hz, 2H), 8.83 (d, *J* = 4.0 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 149.6, 135.2, 132.2, 131.8 (q, $J_{C\text{-}F}$ = 33.0 Hz), 129.7, 129.6, 126.4 (q, $J_{C\text{-}F}$ = 4.0 Hz), 126.4 (q, $J_{C\text{-}F}$ = 271.0 Hz), 126.1, 125.7 (q, $J_{C\text{-}F}$ = 4.0 Hz), 119.1, 115.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8; ESI-HRMS *m/z* Calcd for $C_{13}H_7F_3N_2$ $[M+H]^+$: 249.0634, Found: 249.0631.

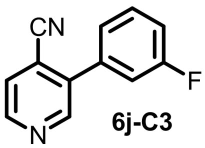
2-(3-fluorophenyl)isonicotinonitrile (6j-C2):



6j-C2

Colorless solid, 52% yield, 41.4 mg, m.p. 133-134 °C; R_f 0.5 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (dt, *J* = 8.0, 4.0 Hz, 1H), 7.51 (dd, *J* = 12.0, 8.0 Hz, 1H), 7.65 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.85 (td, *J* = 10.4, 2.0 Hz, 1H), 7.88 (ddd, *J* = 7.2, 1.6, 0.8 Hz, 1H), 8.24 (s, 1H), 8.84 (dd, *J* = 5.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 113.4 (d, $J_{C\text{-}F}$ = 23.0 Hz), 116.2, 116.4 (d, $J_{C\text{-}F}$ = 22.0 Hz), 121.5, 122.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 122.5 (d, $J_{C\text{-}F}$ = 3.0 Hz), 124.1, 130.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 139.7 (d, $J_{C\text{-}F}$ = 7.7 Hz), 150.4, 156.9 (d, $J_{C\text{-}F}$ = 2.8 Hz), 163.3 (d, $J_{C\text{-}F}$ = 243.0 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ -114.0; ESI-HRMS *m/z* Calcd for $C_{12}H_7FN_2$ $[M+H]^+$: 199.0666, Found: 199.0658.

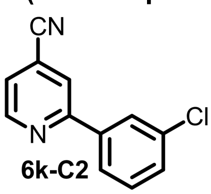
3-(3-fluorophenyl)isonicotinonitrile (6j-C3):



6j-C3

Light-yellow solid, 33% yield, 25.9 mg, m.p. 96-97 °C; R_f 0.1 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, CD_3OD) δ 7.30 (dt, *J* = 8.0, 4.0 Hz, 1H), 7.47-7.41 (m, 2H), 7.65 (dd, *J* = 16.0, 8.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 4.0 Hz, 1H), 8.78 (d, *J* = 4.0, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 115.5 (d, $J_{C\text{-}F}$ = 5.0 Hz), 115.7, 116.0 (d, $J_{C\text{-}F}$ = 21.0 Hz), 119.3, 124.7 (d, $J_{C\text{-}F}$ = 5.0 Hz), 126.4, 130.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 136.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 137.5 (d, $J_{C\text{-}F}$ = 2.0 Hz), 148.9, 150.1, 162.8 (d, $J_{C\text{-}F}$ = 245.0 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ -114.0; ESI-HRMS *m/z* Calcd for $C_{12}H_7FN_2$ $[M+H]^+$: 199.0666, Found: 199.0659.

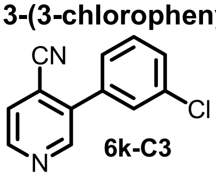
2-(3-chlorophenyl)isonicotinonitrile (6k-C2):



6k-C2

White solid, 44% yield, 37.7 mg, m.p. 113-114 °C; R_f 0.7 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 3H), 7.86 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.92 (s, 1H), 8.03 (s, 1H), 8.87 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.5, 121.4, 122.0, 123.8, 125.0, 127.2, 130.2, 130.3, 135.3, 139.0, 150.7, 157.2; ESI-HRMS *m/z* Calcd for $C_{12}H_7ClN_2$ $[M+H]^+$: 215.0371, Found: 215.0373.

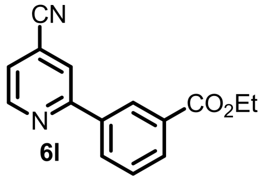
3-(3-chlorophenyl)isonicotinonitrile (6k-C3):



6k-C3

White solid, 40% yield, 34.2 mg, m.p. 145-147 °C; R_f 0.5 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 3H), 7.56 (d, *J* = 4.0 Hz, 1H), 7.65 (d, *J* = 4.0 Hz, 1H), 8.80 (d, *J* = 4.0 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.9, 118.9, 126.1, 127.1, 128.8, 129.7, 130.4, 135.2, 136.1, 137.3, 149.3, 150.7; ESI-HRMS *m/z* Calcd for $C_{12}H_7ClN_2$ $[M+H]^+$: 215.0371, Found: 215.0369.

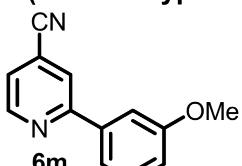
ethyl 3-(4-cyanopyridin-2-yl)benzoate (6l):



6l

Light-yellow oil, 80% yield, 80.6 mg, R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, *J* = 8.0 Hz, 3H), 4.44 (q, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 4.0 Hz, 1H), 8.01 (s, 1H), 8.16 (d, *J* = 4.0 Hz, 1H), 8.22 (d, *J* = 4.0 Hz, 1H), 8.64 (d, *J* = 4.0 Hz, 1H), 8.89 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 61.5, 116.6, 121.4, 122.1, 123.6, 128.0, 129.2, 131.1, 131.2, 131.4, 137.6, 150.8, 157.7, 166.1; ESI-HRMS *m/z* Calcd for $C_{15}H_{12}N_2O_2$ $[M+H]^+$: 253.0972, Found: 253.0968.

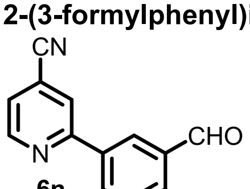
2-(3-methoxyphenyl)isonicotinonitrile (6m):



6m

Yellow solid, 31% yield, 26.0 mg, m.p. 87-89 ^oC; R_f 0.6 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.04 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.46-7.40 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.94 (s, 1H), 8.86 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 95.0, 112.1, 116.3, 116.7, 119.3, 121.2, 122.2, 123.3, 130.1, 138.7, 150.5, 160.3; ESI-HRMS *m/z* Calcd for $C_{13}H_{10}N_2O$ $[M+H]^+$: 211.0866, Found: 211.0869.

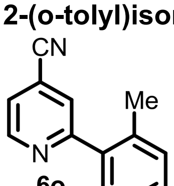
2-(3-formylphenyl)isonicotinonitrile (6n):



6n

White solid, 25% yield, 20.8 mg, m.p. 158-160 ^oC; R_f 0.3 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 8.03-8.00 (m, 2H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.53 (s, 1H), 8.91(d, *J* = 4.0 Hz, 1H), 10.1 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.4, 121.6, 122.0, 123.9, 128.2, 129.9, 131.0, 132.6, 137.1, 138.3, 150.9, 157.2, 191.7; ESI-HRMS *m/z* Calcd for $C_{13}H_8N_2O$ $[M+H]^+$: 209.0709, Found: 209.0713.

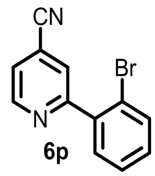
2-(o-tolyl)isonicotinonitrile (6o):



6o

Colorless oil, 18% yield, 14.0 mg, R_f 0.6 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.35-7.31 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 8.88 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 116.6, 120.6, 122.9, 125.6, 126.2, 129.3, 129.6, 131.1, 135.9, 138.3, 150.2, 161.5; ESI-HRMS *m/z* Calcd for $C_{13}H_{10}N_2$ $[M+H]^+$: 195.0917, Found: 195.0913.

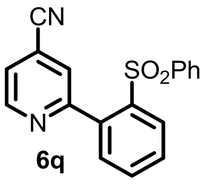
2-(2-bromophenyl)isonicotinonitrile (6p):



6p

Colorless oil, 25% yield, 25.8 mg, R_f 0.3 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.55-7.52 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 8.90 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.5, 120.3, 121.5, 123.7, 126.5, 127.8, 130.7, 131.4, 133.6, 139.2, 150.4, 159.6; ESI-HRMS *m/z* Calcd for $C_{12}H_7BrN_2$ $[M+H]^+$: 258.9865, Found: 258.9852.

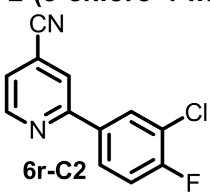
2-(2-(phenylsulfonyl)phenyl)isonicotinonitrile (6q):



6q

Yellow solid, 24% yield, 30.7 mg, m.p. 145-147 ^oC; R_f 0.9 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.54-7.49 (m, 4H), 7.62-7.57 (m, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.25 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.9, 124.8, 127.7, 128.3, 128.5, 128.8, 129.3, 129.4, 130.4, 131.1, 133.2, 133.3, 134.9, 139.0, 140.8, 141.6； ESI-HRMS *m/z* $[H+MeOH+H]^+$ = 353.1

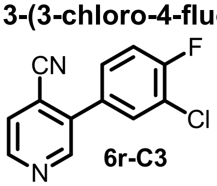
2-(3-chloro-4-fluorophenyl)isonicotinonitrile (6r-C2):



6r-C2

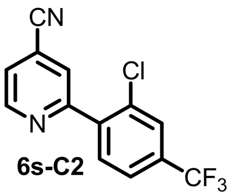
Yellow solid, 36% yield, 33.3 mg, m.p. 109-110 ^oC; R_f 0.6 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 4.0 Hz, 1H), 7.95- 7.92 (m, 1H), 8.16 (t, *J* = 8.0 Hz, 1H), 8.24 (s, 1H), 8.82 (d, *J* = 8.0 Hz, 1H); * impurities 4.00 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.9 (d, J_{C-F} = 21.0 Hz), 119.4, 121.6, 121.8 (d, J_{C-F} = 18.0 Hz), 126.7 (d, J_{C-F} = 8.0 Hz), 129.4, 135.7 (d, J_{C-F} = 4.0 Hz), 138.4, 150.6, 156.1, 159.0 (d, J_{C-F} = 251.0 Hz), 165.5; * impurities 52.9; ^{19}F NMR (376 Mhz, $CDCl_3$) δ -114.5; ESI-HRMS *m/z* Calcd for $C_{12}H_6ClFN_2$ $[M+H]^+$: 233.0276, Found: 233.0265.

3-(3-chloro-4-fluorophenyl)isonicotinonitrile (6r-C3):



6r-C3

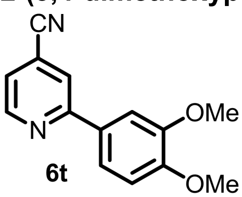
Colorless solid, 18% yield, 17.1 mg, m.p. 148-151 ^oC; R_f 0.2 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 8.0 Hz, 1H), 7.48 (q, *J* = 4.0 Hz, 1H), 7.65-7.61 (m, 2H), 8.80 (d, *J* = 4.0 Hz, 1H), 8.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.8, 117.5 (d, J_{C-F} = 21.0 Hz), 118.9, 122.2 (d, J_{C-F} = 19.0 Hz), 126.0, 128.9 (d, J_{C-F} = 7.0 Hz), 131.1, 131.5 (d, J_{C-F} = 4.0 Hz), 136.4, 149.4, 150.6, 159.0 (d, J_{C-F} = 252.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.3; ESI-HRMS *m/z* Calcd for $C_{12}H_6ClFN_2$ $[M+H]^+$: 233.0276, Found: 233.0265.



6s-C2

2-(2-chloro-4-(trifluoromethyl)phenyl)isonicotinonitrile (6s-C2):
Yellow solid, 35% yield, 39.5 mg, m.p. 125-127 °C; R_f 0.4 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 4.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.5, 121.5, 121.7, 123.4 (q, J_{C-F} = 34.0 Hz), 123.4 (q, J_{C-F} = 271.0 Hz), 124.7, 125.2 (q, J_{C-F} = 4.0 Hz), 126.9 (q, J_{C-F} = 3.0 Hz), 132.2, 133.9, 138.8, 142.3, 143.6; * impurities 176.2, 138.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ - 62.0. * impurities -75.5, -63.0, -62.6, -62.2, -61.4; ESI-MS *m/z* 283.2

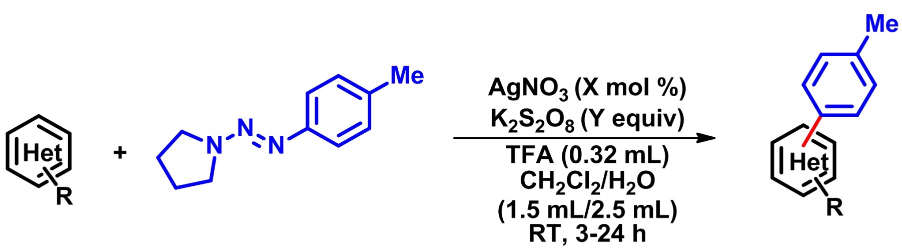
2-(3,4-dimethoxyphenyl)isonicotinonitrile (6t):



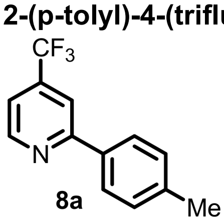
6t

Colorless solid, 10% yield, 9.6 mg, m.p. 86-88 °C; R_f 0.6 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 6H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 7.93 (s, 1H), 8.86 (d, *J* = 4.0 Hz, 1H); * impurities 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 112.1, 116.3, 116.7, 119.3, 121.2, 122.2, 123.3, 130.1, 138.7, 150.5, 158.5, 160.3; * impurities 30.9, 50.9; ESI-HRMS *m/z* Calcd for $C_{14}H_{12}N_2O_2$ $[M-OMe+H]^+$: 211.1.

VI. Part II-Key compounds characterization data



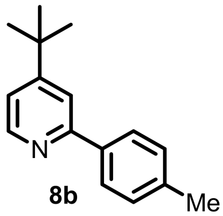
2-(p-tolyl)-4-(trifluoromethyl)pyridine (8a):*[1]*



8a

Colorless oil, 80% yield brsm, 75.8 mg, R_f 0.7 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 4.0 Hz, 1H), 7.90 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 8.84 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 115.6 (q, J_{C-F} = 4.0 Hz), 117.2 (q, J_{C-F} = 4.0 Hz), 123.0 (q, J_{C-F} = 273.0 Hz), 126.9, 129.7, 135.2, 139.1 (q, J_{C-F} = 34.0 Hz), 140.1, 150.5, 158.8; ESI-HRMS *m/z* Calcd for $C_{13}H_{10}F_3N$ $[M+H]^+$: 238.0838, Found: 238.0831.

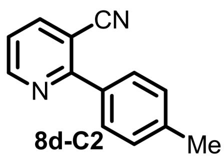
4-(tert-butyl)-2-(p-tolyl)pyridine (8b):*[1]*



8b

Yellow oil, 54% yield brsm, 31.2 mg, R_f 0.8 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.41 (s, 3H), 7.21 (d, *J* = 4.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.68 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 8.58 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 30.6, 34.8, 117.5, 119.0, 126.9, 129.4, 137.2, 138.7, 149.4, 157.5, 160.6; ESI-HRMS *m/z* Calcd for $C_{16}H_{19}N$ $[M+H]^+$: 226.1590, Found: 226.1582.

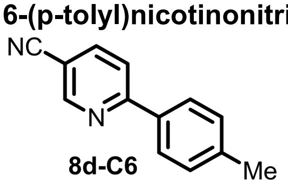
2-(p-tolyl)nicotinonitrile (8d-C2):[7]



8d-C2

White solid, 42% yield brsm, 32.5 mg, m.p. 83-84 °C; R_f 0.5 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.0 Hz, 1H), 8.05 (t, *J* = 4.0 Hz, 1H), 7.83 (s, 2H), 7.36-7.33 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 152.6, 141.8, 140.5, 134.4, 129.4, 128.8, 121.2, 117.8, 107.2, 21.4; ESI-HRMS *m/z* Calcd for $C_{13}H_{11}N_2$ $[M+H]^+$: 195.0917, Found: 195.0915.

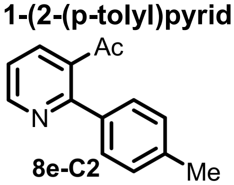
6-(p-tolyl)nicotinonitrile (8d-C6):[8]



8d-C6

Yellow solid, 38% yield brsm, 29.6 mg, m.p. 100-102 °C; R_f 0.4 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.78 (d, *J* = 4.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 4.0 Hz, 1H), 7.34 (d, *J* = 4.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 152.7, 152.3, 140.7, 132.5, 129.9, 128.3, 123.6, 116.9, 108.4, 21.4; ESI-HRMS *m/z* Calcd for $C_{13}H_{11}N_2$ $[M+H]^+$: 195.0917, Found: 195.0911.

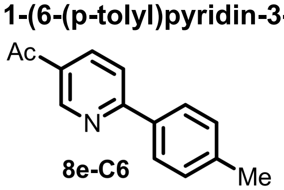
1-(2-(p-tolyl)pyridin-3-yl)ethanone (8e-C2):[1]



8e-C2

Yellow solid, 44% yield brsm, 37.4 mg, m.p. 101-102 °C; R_f 0.7 (10% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.41 (s, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 30.3, 121.6, 129.0, 129.5, 136.1, 136.2, 136.8, 139.5, 150.8, 157.2, 203.9; ESI-HRMS *m/z* Calcd for $C_{14}H_{13}NO$ $[M+H]^+$: 212.1070, Found: 212.1071.

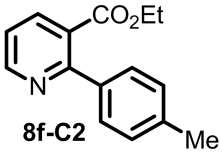
1-(6-(p-tolyl)pyridin-3-yl)ethanone (8e-C6):[1]



8e-C6

Colorless oil, 32% yield brsm, 26.7 mg, R_f 0.9 (10% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.65 (s, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 8.27 (d, *J* = 12.0 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.7, 119.8, 127.2, 129.7, 130.3, 135.3, 136.3, 140.4, 150.1, 160.9, 196.5; ESI-HRMS *m/z* Calcd for $C_{14}H_{13}NO$ $[M+H]^+$: 212.1061, Found: 212.1066.

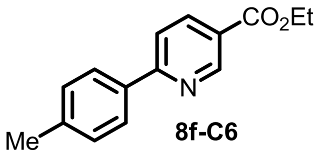
ethyl 2-(p-tolyl)nicotinate (8f-C2):



8f-C2

Colorless oil, 40% yield brsm, 23.2 mg, R_f 0.6 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, *J* = 8.0 Hz, 3H), 2.40 (s, 3H), 4.18 (q, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 4.0 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 21.3, 61.5, 121.2, 127.3, 128.5, 128.8, 137.2, 137.7, 138.6, 151.1, 158.8, 168.3; ESI-HRMS *m/z* Calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.1176, Found: 242.1189.

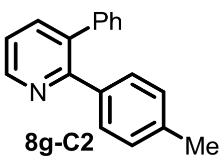
ethyl 6-(p-tolyl)nicotinate (8f-C6):



8f-C6

Yellow solid, 27% yield brsm, 15.8 mg, m.p. 79-80 ^{o}C; R_f 0.8 (50% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 8.0 Hz, 3H), 2.42 (s, 3H), 4.42 (q, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 8.32 (d, *J* = 12.0 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.4, 61.3, 119.4, 124.1, 127.2, 129.6, 135.5, 137.7, 140.2, 150.9, 160.8, 165.5; ESI-HRMS *m/z* Calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.1176, Found: 242.1168.

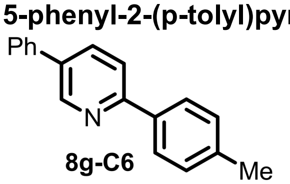
3-phenyl-2-(p-tolyl)pyridine (8g-C2):[9]



8g-C2

Colorless oil, 28% yield brsm, 27.1 mg, R_f 0.6 (10% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 7.04 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 4.0 Hz, 2H), 7.32-7.24 (m, 6H), 7.70 (d, *J* = 8.0 Hz, 1H), 8.68 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 121.8, 127.1, 128.3, 128.6, 129.5, 129.8, 135.9, 137.2, 137.5, 138.5, 140.2, 148.3, 157.1; ESI-HRMS *m/z* Calcd for $C_{18}H_{15}N$ $[M+H]^+$: 246.1277, Found: 246.1274.

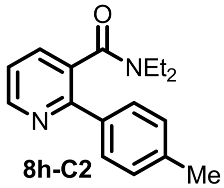
5-phenyl-2-(p-tolyl)pyridine (8g-C6):



8g-C6

Yellow solid, 17% yield brsm, 17.0 mg, m.p. 80-81 ^{o}C; R_f 0.8 (10% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.42 (q, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.79 (q, *J* = 8.0 Hz, 1H), 7.95 (m, 3H), 8.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 120.0, 126.7, 127.0, 128.0, 129.1, 129.5, 134.6, 135.0, 136.2, 137.7, 139.0, 148.0, 156.2; ESI-HRMS *m/z* Calcd for $C_{18}H_{15}N$ $[M+H]^+$: 246.1277, Found: 246.1283.

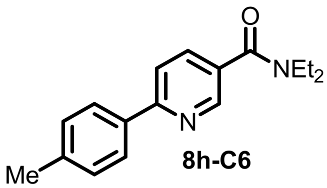
N,N-diethyl-2-(p-tolyl)nicotinamide (8h-C2):



8h-C2

Colorless solid, 17% yield brsm, 18.0 mg, m.p. 71-72 ^{o}C; R_f 0.3 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (t, *J* = 4.0 Hz, 3H), 1.03 (t, *J* = 4.0 Hz, 3H), 2.37 (s, 3H), 2.72-2.65 (m, 1H), 2.95-2.86 (m, 1H), 3.16-3.08 (m, 1H), 3.97-3.70 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 8.71 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 13.3, 21.3, 38.8, 42.5, 121.7, 128.7, 129.1, 131.6, 135.7, 136.1, 139.0, 149.8, 154.6, 169.3; ESI-HRMS *m/z* Calcd for $C_{17}H_{20}N_2O$ $[M+H]^+$: 269.1648, Found: 269.1641.

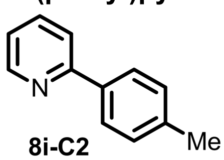
N,N-diethyl-6-(p-tolyl)nicotinamide (8h-C6):



8h-C6

Yellow oil, 35% yield brsm, 37.8 mg, R_f 0.4 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (br s, 3H), 1.25 (br s, 3H), 2.41 (s, 3H), 3.34 (br s, 2H), 3.57 (br s, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.4, 21.3, 39.6, 43.5, 119.8, 126.9, 129.6, 130.8, 135.3, 135.5, 139.6, 147.1, 158.0, 168.8; ESI-HRMS *m/z* Calcd for $C_{17}H_{20}N_2O$ $[M+H]^+$: 269.1648, Found: 269.1640.

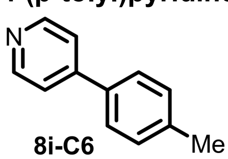
2-(p-tolyl)pyridine (8i-C2):[1]



8i-C2

Colorless oil, 38% yield brsm, 25.4 mg, R_f 0.7 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.75-7.69 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.22-7.18 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 120.4, 122.0, 126.7, 129.7, 136.6, 136.8, 139.1, 149.7, 157.6; ESI-HRMS *m/z* Calcd for $C_{12}H_{11}N$ $[M+H]^+$: 170.0964, Found: 170.0957.

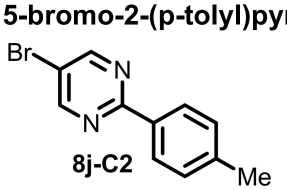
4-(p-tolyl)pyridine (8i-C6):[1]



8i-C6

White solid, 23% yield brsm, 15.9 mg, m.p. 86-87 ^{o}C; R_f 0.1 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 8.64 (d, *J* = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 121.4, 126.8, 129.8, 135.2, 139.2, 148.2, 150.2; ESI-HRMS *m/z* Calcd for $C_{12}H_{11}N$ $[M+H]^+$: 170.0964, Found: 170.0957.

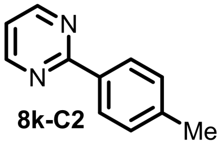
5-bromo-2-(p-tolyl)pyrimidine (8j-C2):[10]



8j-C2

White solid, 62% yield brsm, 61.7 mg, m.p. 79-80 ºC; R_f 0.7 (10% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 8.90 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 119.0, 129.0, 129.3, 133.9, 140.7, 156.8, 160.1, 164.2; ESI-HRMS *m/z* Calcd for $C_{11}H_9BrN_2$ $[M+H]^+$: 249.0022, Found: 249.0014.

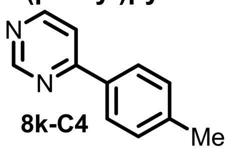
2-(p-tolyl)pyrimidine (8k-C2):*[1]*



8k-C2

Colorless solid, 52% yield brsm, 35.5 mg, m.p. 93-94 ºC; R_f 0.6 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.16 (t, *J* = 4.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 8.33 (d, *J* = 8.0 Hz, 2H), 8.79 (d, *J* = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 118.8, 128.1, 129.4, 134.8, 141.0, 157.2, 164.8; ESI-HRMS *m/z* Calcd for $C_{11}H_{10}N_2$ $[M+H]^+$: 171.0917, Found: 171.0908.

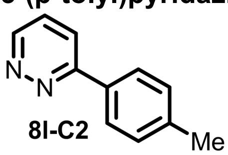
4-(p-tolyl)pyrimidine (8k-C4):*[1]*



8k-C4

White solid, 25% yield brsm, 16.9 mg, m.p. 71-72 ºC; R_f 0.4 (50% EtOAc in n-Hexane);^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 4.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 2H), 8.73 (d, *J* = 4.0 Hz, 1H), 9.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 116.7, 127.0, 129.8, 133.6, 141.6, 157.3, 159.0, 163.9; ESI-HRMS *m/z* Calcd for $C_{11}H_{10}N_2$ $[M+H]^+$: 171.0917, Found: 171.0908.

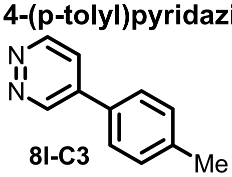
3-(p-tolyl)pyridazine (8l-C2):*[1]*



8l-C2

Colorless solid, 20% yield brsm, 13.9 mg, m.p. 90-92 ºC; R_f 0.3 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, CD_3OD) δ 2.42 (s, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.76 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 1H), 9.11 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 19.9, 125.0, 126.7, 128.0, 129.4, 133.1, 140.5, 149.6, 159.9; ESI-HRMS *m/z* Calcd for $C_{11}H_{10}N_2$ $[M+H]^+$: 171.0917, Found: 171.0900.

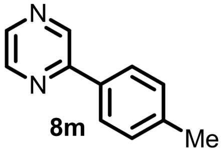
4-(p-tolyl)pyridazine (8l-C3):*[1]*



8l-C3

Colorless solid, 33% yield brsm, 22.2 mg, m.p. 49-50 ºC; R_f 0.2 (50% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, CD_3OD) δ 2.38 (s, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 4.0 Hz, 1H), 9.13 (d, *J* = 4.0 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 19.9, 123.7, 126.7, 129.9, 130.8, 139.4, 140.8, 149.3, 151.2; ESI-HRMS *m/z* Calcd for $C_{11}H_{10}N_2$ $[M+H]^+$: 171.0917, Found: 171.0904.

2-(p-tolyl)pyrazine (8m):*[1]*

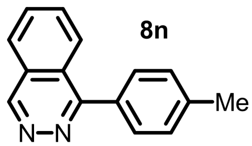


8m

Yellow solid, 46% yield brsm, 31.3 mg, m.p. 126-127 ºC; R_f 0.4 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 8.48 (d, *J* = 4.0

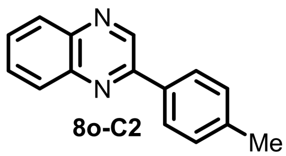
Hz, 1H), 8.61 (d, *J* = 4.0 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 126.8, 129.8, 133.5, 140.1, 142.0, 142.5, 144.1, 152.9; ESI-HRMS *m/z* Calcd for $C_{11}H_{10}N_2$ $[M+H]^+$: 171.0917, Found: 171.0910.

1-(p-tolyl)phthalazine (8n):[1]



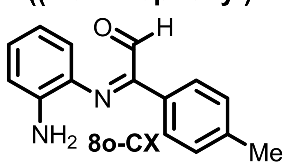
Colorless oil, 52% yield brsm, 45.8 mg, R_f 0.3 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.92-7.83 (m, 2H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 125.5, 126.3, 126.6, 127.1, 129.3, 130.3, 132.1, 132.5, 133.2, 139.5, 150.4, 159.9; ESI-HRMS *m/z* Calcd for $C_{15}H_{12}N_2$ $[M+H]^+$: 221.1073, Found: 221.1064.

2-(p-tolyl)quinoxaline (8o-C2):[11]



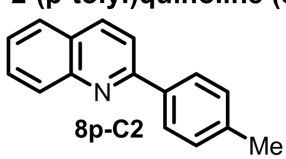
Yellow solid, 67% yield brsm, 28.5 mg, m.p. 84-86 ^{o}C; R_f 0.5 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.77-7.73 (m, 2H), 8.15-8.10 (m, 4H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 127.4, 129.1, 129.3, 129.5, 129.9, 130.2, 134.0, 140.5, 141.4, 142.3, 143.3, 151.8; ESI-HRMS *m/z* Calcd for $C_{15}H_{12}N_2$ $[M+H]^+$: 221.1073, Found: 221.1063.

2-((2-aminophenyl)imino)-2-(p-tolyl)acetaldehyde (8o-CX):



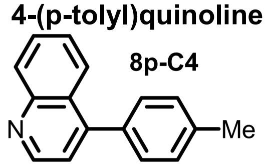
Colorless oil, 20% yield brsm, 8.5 mg, R_f 0.7 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.45-7.42 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 10.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 124.5, 127.7, 128.1, 128.9, 129.2, 129.7, 130.2, 135.1, 138.7, 139.7, 147.4, 192.0; ESI-MS *m/z* 239.1.

2-(p-tolyl)quinoline (8p-C2):[1]



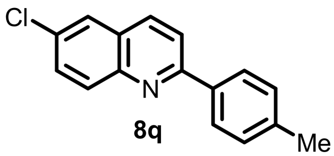
White solid, 12% yield, 10.2 mg, m.p. 81-82 ^{o}C; R_f 0.6 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 118.9, 126.1, 127.1, 127.4, 127.5, 129.5, 129.6, 136.7, 136.8, 139.4, 148.2, 157.3; ESI-HRMS *m/z* Calcd for $C_{16}H_{13}N$ $[M+H]^+$: 220.1121, Found: 220.1119.

4-(p-tolyl)quinoline (8p-C4):[1]



Yellow oil, 39% yield brsm, 34.5 mg, R_f 0.2 (25% EtOAc in n-Hexane), Major one; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.34-7.32 (m, 2H), 7.42-7.38 (m, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.19-8.11 (m, 2H), 8.93 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 121.3 (121.1), 125.9, 126.5 (126.6), 126.9, 127.8 (128.3), 129.3, 129.5 (129.4), 129.7, 135.0, 136.1, 138.4, 148.2 (148.6), 149.9 (150.4); ESI-HRMS *m/z* Calcd for $C_{16}H_{13}N$ $[M+H]^+$: 220.1121, Found: 220.1129.

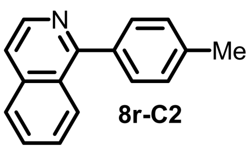
6-chloro-2-(p-tolyl)quinoline (8q):



8q

White solid, 68% yield brsm, 30.2 mg, m.p. 160-161 °C; R_f 0.6 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.34 (d, *J* = 4.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 8.12-8.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 119.6, 126.1, 127.4, 127.6, 129.6, 130.5, 131.2, 131.6, 135.7, 136.4, 139.7, 146.7, 157.6; ESI-HRMS *m/z* Calcd for $C_{16}H_{12}ClN$ $[M+H]^+$: 254.0371, Found: 254.0723.

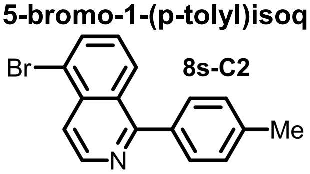
1-(p-tolyl)isoquinoline (8r-C2):*[1]*



8r-C2

Colorless oil, 29% yield brsm, 25.0 mg, R_f 0.4 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.66-7.59 (m, 3H), 7.69 (t, *J* = 4.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.61 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 119.7, 126.7, 126.9, 127.1, 127.7, 129.0, 129.9, 130.0, 136.6, 136.9, 138.5, 142.1, 160.8; ESI-HRMS *m/z* Calcd for $C_{16}H_{13}N$ $[M+H]^+$: 220.1121, Found: 220.1133.

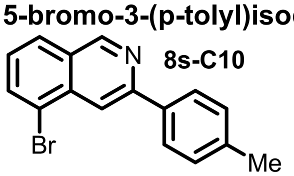
5-bromo-1-(p-tolyl)isoquinoline (8s-C2):



8s-C2

White solid, 31% yield brsm, 20.2 mg, m.p. 83-84 °C; R_f 0.5 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.39-7.33 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 4.0 Hz, 1H), 8.01 (d, *J* = 4.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.70 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 118.5, 121.9, 127.2, 127.6, 127.9, 129.1, 129.9, 133.7, 135.9, 136.3, 138.7, 143.5, 161.3; ESI-HRMS *m/z* Calcd for $C_{16}H_{12}BrN$ $[M+H]^+$: 298.0226, Found: 298.0225.

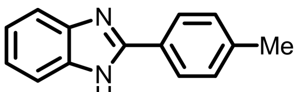
5-bromo-3-(p-tolyl)isoquinoline (8s-C10):



8s-C10

White solid, 8% yield brsm, 5.3 mg, m.p. 99-101 °C; R_f 0.2 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.39-7.32 (m, 5H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.66 (d, *J* = 4.0 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 119.4, 120.5, 128.6, 129.3, 129.9, 133.5, 134.9, 135.2, 138.1, 141.1, 144.2, 146.1, 151.6; ESI-HRMS *m/z* Calcd for $C_{16}H_{12}BrN$ $[M+H]^+$: 298.0226, Found: 298.0211.

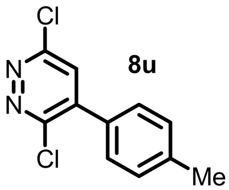
2-(p-tolyl)-1H-benzo[d]imidazole (8t):*[12]*



8t

Light-yellow solid, 17% yield, 14.1 mg, m.p. 265-266 ºC; R_f 0.5 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, CD_3OD) δ 2.42 (s, 3H), 7.26-7.22 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.59 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.97 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 124.5, 127.7, 128.1, 128.9, 129.2, 130.2, 135.1, 138.7, 139.7, 147.4, 191.9; ESI-HRMS *m/z* Calcd for $C_{14}H_{12}N_2$ $[M+H]^+$: 209.1073, Found: 209.1065.

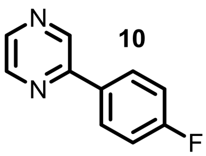
3,6-dichloro-4-(p-tolyl)pyridazine (8u):[13]



8u

Colorless solid, 5% yield, 4.8 mg, m.p. 95-96 ºC; R_f 0.7 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 128.8, 129.4, 129.6, 130.2, 140.8, 142.8, 154.9, 156.0; ESI-HRMS *m/z* Calcd for $C_{11}H_8Cl_2N_2$ $[M+H]^+$: 239.0137, Found: 239.0148.

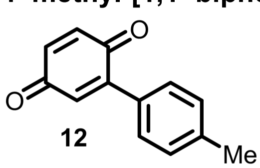
2-(4-fluorophenyl)pyrazine (10):



10

Yellow solid, 56% yield, 1.23 g, m.p. 96-97 ºC; R_f 0.7 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (app t, *J* = 8.0 Hz, 2H), 8.02 (app t, *J* = 8.0 Hz, 2H), 8.50 (br s, 1H), 8.61 (br s, 1H), 9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.1 (d, $J_{C\text{-}F}$ = 22.0 Hz), 128.9 (d, $J_{C\text{-}F}$ = 8.0 Hz), 132.5 (d, $J_{C\text{-}F}$ = 4.0 Hz), 141.9, 142.9, 144.1, 151.8, 164.0 (d, $J_{C\text{-}F}$ = 249.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2; ESI-HRMS *m/z* Calcd for $C_{10}H_7FN_2$ $[M+H]^+$: 175.0666, Found: 175.0652.

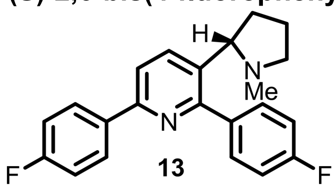
4'-methyl-[1,1'-biphenyl]-2,5-dione (12):[14]



12

Yellow solid, 71% yield, 56.3 mg, m.p. 134-135 ºC; R_f 0.5 (25% EtOAc in n-Hexane)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 6.87-6.80 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 129.2, 129.3, 129.8, 132.0, 136.2, 137.0, 140.6, 145.8, 186.8, 187.6; ESI-HRMS *m/z* Calcd for $C_{13}H_{10}O_2$ $[M-H]^-$: 197.0608, Found: 197.0611.

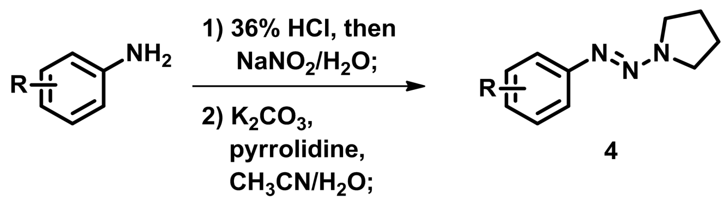
(S)-2,6-bis(4-fluorophenyl)-3-(1-methylpyrrolidin-2-yl)pyridine (13):



13

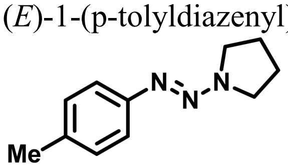
Colorless oil, 38% yield, 26.6 mg, R_f 0.5 (25% EtOAc in n-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82-1.71 (m, 2H), 2.05-1.90 (m, 1H), 2.06 (s, 3H), 2.23-2.12 (m, 2H), 3.25-3.17 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 4.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 8.04 (dd, *J* = 8.0, 4.0 Hz, 2H), 8.09 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 35.4, 40.2, 56.8, 66.1, 115.0 (d, $J_{C\text{-}F}$ = 21.0 Hz), 115.5 (d, $J_{C\text{-}F}$ = 21.0 Hz), 119.4, 128.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 131.0 (d, $J_{C\text{-}F}$ = 8.0 Hz), 135.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 135.5, 136.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 136.8, 154.0, 157.7, 162.6 (d, $J_{C\text{-}F}$ = 245.0 Hz), 163.4 (d, $J_{C\text{-}F}$ = 247.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.4, -113.4; ESI-HRMS *m/z* Calcd for $C_{22}H_{20}F_2N_2$ $[M+H]^+$: 351.1667, Found: 351.1659.

VII. Triazenes general synthesis[15]



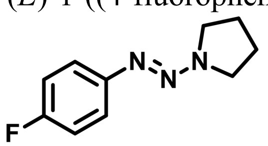
General procedure: In a 100 mL RBF was weighted aniline (10 mmol), conc. hydrochloric acid (4.0 mL) was added under ice-water bath. Sodium sulfate (850 mg) in ice-water (20 mL) was poured into the mixture for 30 minutes. In another 250 mL RBF, in a mixture of acetonitrile (40 mL) and water (20 mL) was added potassium carbonate (13.8 g) and pyrrolidine (4.0 mL). After 5 minutes, the previous diazonium mixtures were poured into the 250 mL flask under 0 ^{o}C over 10 minitues, the reaction was warm to ambient temperature for 12 hours. The mixture was extracted with EtOAc (5 x 40 mL), washed with brine, dried over Na_2SO_4. Solvents were removed under vacuum and the residue was purified by silica-gel flash chromatography using fluent (25% EtOAc in hexane) to provide corresponding products.

(*E*)-1-(p-tolyldiazenyl)pyrrolidine **(4a)**



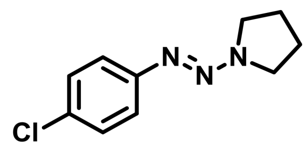
Red solid, m.p. 79-81 °C, 90%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03-1.99 (br s, 4H), 2.33 (s, 3H), 3.78 (br s, 4H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 23.8, 120.1, 129.4, 134.7, 149.1.

(*E*)-1-((4-fluorophenyl)diazenyl)pyrrolidine **(4b)**



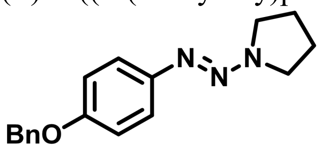
Yellow solid, m.p. 58-59 °C, 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03-2.00 (br s, 4H), 3.77 (br s, 4H), 7.03-6.97 (m, 2H), 7.39-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 110.2 (d, $J_{C\text{-}F}$ = 22.0 Hz), 116.3 (d, $J_{C\text{-}F}$ = 22.0 Hz), 142.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 155.4 (d, $J_{C\text{-}F}$ = 242.0 Hz).

(*E*)-1-((4-chlorophenyl)diazenyl)pyrrolidine **(4c)**



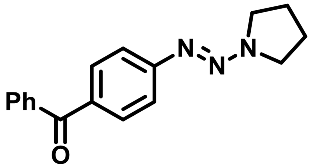
Yellow solid, m.p. 62 ºC, 56%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (br s, 4H), 3.77 (br s, 4H), 7.27 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 121.5, 128.8, 130.1, 150.0.

(*E*)-1-((4-(benzyloxy)phenyl)diazenyl)pyrrolidine **(4d)**



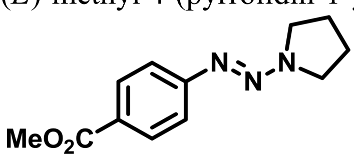
Yellow solid, m.p. 122-124 ºC, 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02-1.99 (m, 4H), 3.76 (br s, 4H), 5.06 (s, 2H), 6.96-6.92 (m, 2H), 7.45-7.30 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 70.2, 115.1, 121.2, 127.5, 127.9, 128.5, 137.2, 145.5, 156.6.

(*E*)-phenyl(4-(pyrrolidin-1-yldiazenyl)phenyl)methanone **(4e)**



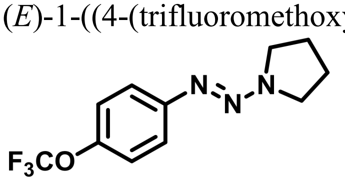
Orange solid, m.p. 105-106 ºC, 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (br s, 4H), 3.70 (br s, 2H), 3.95 (br s, 2H), 7.47 (m, 5H), 7.83-7.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 46.6, 51.3, 120.0, 128.2, 129.8, 131.5, 131.9, 133.7, 138.3, 154.9, 196.1.

(*E*)-methyl 4-(pyrrolidin-1-yldiazenyl)benzoate (**4f)**



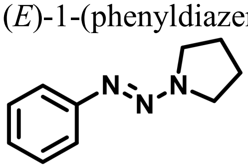
White solid, m.p. 113-114 °C, 82%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (br s, 4H), 3.69 (br s, 2H), 3.89 (s, 3H), 3.95 (br s, 2H), 7.43 (d, J = 12.0 Hz, 2H), 8.00 (d, J = 12.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 46.5, 51.8, 51.9, 120.0, 126.2, 130.6, 155.1, 167.2.

(*E*)-1-((4-(trifluoromethoxy)phenyl)diazenyl)pyrrolidine (**4g)**



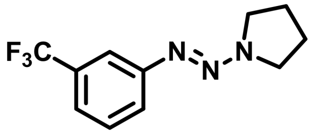
Yellow solid, m.p. 42 ºC, 87%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (br s, 4H), 3.77 (br s, 4H), 7.16 (d, J = 8.0 Hz, 2H), 7.4 (d, J = 4.0 Hz, 1H), 7.43 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 46.2, 51.0, 120.5 (q, $J_{C\text{-}F}$ = 255.0 Hz), 121.2, 121.4, 146.4, 150.1.

(*E*)-1-(phenyldiazenyl)pyrrolidine **(4h)**

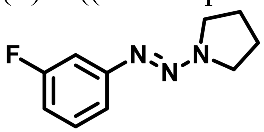


Light yellow solid, m.p. 51-53 °C, 87%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (br s, 4H), 3.80 (br s, 4H), 7.13 (t, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 2H), 7.42 (d, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,

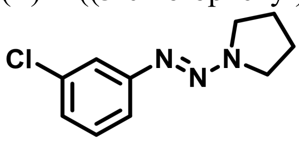
100 MHz) δ 23.8, 120.3, 125.1, 128.8, 151.4.
(*E*)-1-((3-(trifluoromethyl)phenyl)diazenyl)pyrrolidine **(4i)**



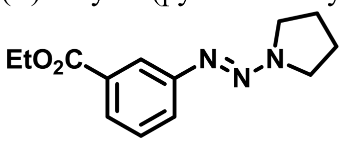
Yellow oil, 91%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (br s, 4H), 3.93-3.68 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 46.4, 51.2, 117.1 (q, $J_{C\text{-}F}$ = 4.0 Hz), 121.3 (q, $J_{C\text{-}F}$ = 4.0 Hz), 123.6, 124.3 (q, $J_{C\text{-}F}$ = 271.0 Hz), 129.2, 131.2 (q, $J_{C\text{-}F}$ = 32.0 Hz), 151.8.
(*E*)-1-((3-fluorophenyl)diazenyl)pyrrolidine **(4j)**



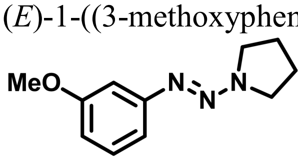
Yellow oil, 73%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (br s, 4H), 3.87-3.80 (m, 4H), 6.82-6.80 (m, 1H), 7.29-7.12 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 106.5 (d, $J_{C\text{-}F}$ = 23.0 Hz), 111.5, 116.8 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.8 (d, $J_{C\text{-}F}$ = 3.0 Hz), 153.4 (d, $J_{C\text{-}F}$ = 8.0 Hz), 163.4 (d, $J_{C\text{-}F}$ = 243.0 Hz).
(*E*)-1-((3-chlorophenyl)diazenyl)pyrrolidine **(4k)**



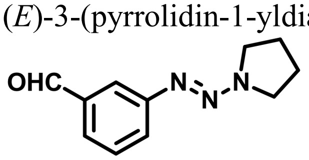
Yellow solid, m.p. 52 °C, 70%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (br s, 4H), 3.67 (br s, 2H), 3.88 (br s, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 46.4, 51.2, 119.2, 119.9, 124.8, 129.8, 134.5, 152.7.
(*E*)-ethyl 3-(pyrrolidin-1-yldiazenyl)benzoate **(4l)**



Yellow oil, 75%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, *J* = 8.0 Hz, 3H), 2.02 (br s, 4H), 3.74 (br s, 2H), 3.85 (br s, 2H), 4.37 (dd, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 23.8, 46.3, 51.0, 60.9, 121.4, 124.7, 126.0, 128.7, 131.2, 151.6, 166.8.
(*E*)-1-((3-methoxyphenyl)diazenyl)pyrrolidine **(4m)**

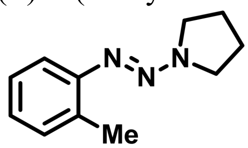


Red oil, 89%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97 (br s, 4H), 3.77 (br s, 4H), 3.82 (s, 3H), 6.71 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.06-7.03 (m, 2H), 7.24 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 55.2, 105.1, 111.4, 113.2, 129.5, 152.9, 160.3.
(*E*)-3-(pyrrolidin-1-yldiazenyl)benzaldehyde **(4n)**



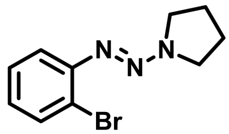
Yellow oil, 18% (2 steps from 3-nitrobenzaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (br s, 4H), 3.68 (br s, 2H), 3.91 (br s, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.66-7.61 (m, 2H), 7.90 (s, 1H), 10.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 30.8, 46.4, 51.2, 121.3, 125.8, 126.7, 129.4, 137.2, 152.2, 192.6.

(*E*)-1-(o-tolyldiazenyl)pyrrolidine **(4o)**



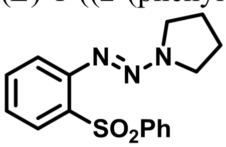
Red oil, 67%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05-2.01 (m, 4H), 2.46 (s, 3H), 3.81 (br s, 4H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.22-7.15 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6, 23.8, 48.8, 116.5, 125.0, 126.2, 130.5, 132.3, 149.3.

(*E*)-1-((2-bromophenyl)diazenyl)pyrrolidine **(4p)**



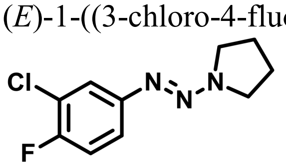
Yellow solid, m.p. 63-64 ^{o}C, 79%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (br s, 4H), 3.74 (br s, 2H), 3.94 (br s, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 23.8, 46.8, 51.2, 118.6, 119.4, 126.0, 127.8, 133.0, 148.7.

(*E*)-1-((2-(phenylsulfonyl)phenyl)diazenyl)pyrrolidine **(4q)**



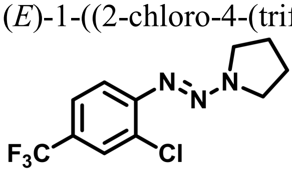
Brown solid, m.p. 198 ^{o}C, 60%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04-1.93 (m, 4H), 3.45 (t, *J* = 8.0 Hz, 2H), 3.86 (t, *J* = 8.0 Hz, 2H), 7.28-7.25 (m, 1H), 7.45-7.41(m, 2H), 7.51-7.48 (m, 3H), 7.92 (d, *J* = 8.0 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5, 23.9, 47.5, 51.2, 117.8, 124.4, 127.6, 128.2, 129.4, 132.1, 132.6, 134.3, 142.9, 148.9.

(*E*)-1-((3-chloro-4-fluorophenyl)diazenyl)pyrrolidine **(4r)**



Light-yellow solid, m.p. 77-78 ^{o}C, 86%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (br s, 4H), 3.87-3.64 (m, 4H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.23 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 25.0, 46.2, 51.1, 116.3 (d, $J_{C\text{-}F}$ = 22.0 Hz), 120.2 (d, $J_{C\text{-}F}$ = 4.0 Hz), 121.0 (d, $J_{C\text{-}F}$ = 19.0 Hz), 121.4, 148.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 155.7 (d, $J_{C\text{-}F}$ = 245.0 Hz).

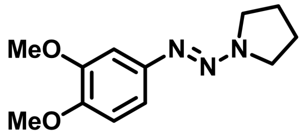
(*E*)-1-((2-chloro-4-(trifluoromethyl)phenyl)diazenyl)pyrrolidine **(4s)**



Red solid, m.p. 57-58 ^{o}C, 46%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10-2.03 (m, 4H), 3.75 (t, *J* = 8.0 Hz, 2H), 3.98 (t, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H); ^{13}C NMR($CDCl_3$, 100 MHz) δ 23.5, 23.9, 47.1, 51.4, 118.5, 123.8 (q, $J_{C\text{-}F}$ = 271.0 Hz), 124.0 (q, $J_{C\text{-}F}$ = 4.0 Hz), 127.1 (q, $J_{C\text{-}F}$ = 33.0 Hz), 127.2 (q, $J_{C\text{-}F}$ = 4.0 Hz), 129.0, 150.4 (q, *J* C-

$_F$ = 2.0 Hz).

(*E*)-1-((3,4-dimethoxyphenyl)diazenyl)pyrrolidine **(4t)**



Yellow solid, m.p. 68 °C, 89%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02-1.99 (m, 4H), 3.77 (br s, 4H), 3.88 (s, 3H), 3.91 (s, 3H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 55.8, 56.0, 103.0, 111.1, 112.9, 145.5, 146.9, 149.2;

VIII. References

(1) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.
(2) Fleckenstein, C. A.; Plenio, H. *Chem. Eur. J.* **2008**, *14*, 4267.
(3) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X.-Q. *Chem. Comm*. **2012**, *48*, 11769.
(4) Walford, G. L.; Jones, H.; Shan, T.-Y. *J. Med. Chem*. **1971**, *14*, 339.
(5) Berthelot, D. J. C.; Gijsen, H. J. M.; Zaja, M.; Rech, J.; Lebsack, A.; Xiao, W.; Breitenbucher, J. G.; Branstetter, B. Heterocyclic Amides as Modulators as TRPA1. PCT Int. Appl. 2010141805, 09 Dec 2010.
(6) Guo, P.-F.; Joo, J.-M.; Rakshit, S.; Sames, D.; *J. Am. Chem. Soc.* **2011**, *133*, 16338.
(7) Cappelli, A.; Mohr, G. P.; Gallelli, A.; Rizzo, M.; Anzini, M.; Vomero, S.; Mennuni, L.; Ferrari, F.; Makovec, F.; Menziani, M. C.; De Benedetti, P. G.; Giorgi, G. *J. Med. Chem.* **2004**, *47*, 2574.
(8) Zhang, N.; Thomas, L.; Wu, B.-Q. *J. Org Chem*. **2001**, *66*, 1500.
(9) Kagabu, S.; Naruse, S.; Tagami, Y.; Watanabe, Y. *J. Org. Chem*. **1989**, *54*, 4275.
(10) Kuribayashi, T.; Kubota, H.; Fukuda, T.; Takano, R.; Tsuji, T.; Sasaki, H.; Tanaka, N. Jpn. Kokai. Tokkyo Koho JP, 2011105708 A 20110602, 2011.
(11) Kang, F.-A.; Sui, Z.-H.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300.
(12) Peng, J.-S.; Ye, M.; Zong, C.-J.; Hu, F.-Y.; Feng, L.-T.; Wang, X.-Y.; Wang, Y.-F.; Chen, C.-X. *J. Org. Chem*. **2011**, *76*, 716.
(13) Augustin, M.; Reinemann, P. *Zeitschrift fuer Chemie* **1973**, *13*, 12.
(14) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292.
(15) For the synthesis of triazenes, see: (a) Goeminne, A.; Scammells, P. J.; Devine, S. M.; Flynn, B. L. *Tetrahedron Lett.* **2010**, *51*, 6882. (b) Hafner, A.; Bräse, S. *Angew. Chem.* **2012**, *124*, 3773. *Angew. Chem. Int. Ed.* **2012**, *51*, 3713.