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Direct arylation of azine *N*-oxides with aryl triflates

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ABSTRACT

Palladium catalyzed direct arylation of azine *N*-oxides using aryl triflates to afford the corresponding 2-aryl azine *N*-oxides is described. The reaction is carried out with a range of both *N*-oxides and aryl triflates. The arylation can be carried out in sequence to yield differentially diarylated products. The regioselectivity and scope of 3-substituted azine *N*-oxides are investigated. The method is applied to the synthesis of a compound that exhibits antimalarial and antimicrobial activities.

1. Introduction

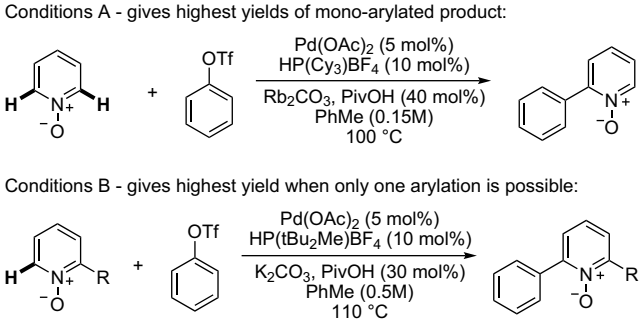
Biaryl compounds represent an important class of molecule.[1] Specifically, the 2-aryl azine motif features prominently in ligand, medicinal, and materials chemistry.[2] Transition metal catalyzed cross coupling reactions of aryl halides with aryl organometallics such as Suzuki, Stille, and Negishi reactions represent some of the most important methods for synthesizing biaryl compounds.[1] However, the requirement for substrate pre-activation renders the overall process inefficient and uneconomical. An emerging alternative to these methods, which has received increased attention in recent years is direct arylation, in which one of the pre-activated components, usually the organometallic, is replaced by a simple arene.[3] Although direct arylation reactions have been investigated thoroughly with use of halides, there are few reports employing the use of aryl triflates.[4] Triflates are an important class of electrophile because they can be easily synthesized from phenols and consequently can be revealed at a late stage in a synthetic sequence.

We previously reported the palladium catalyzed direct arylation of pyridine and diazine *N*-oxides using a wide range of aryl halides.[5] In this account we report (1) an operationally simple catalyst system for the direct arylation of azine *N*-oxide substrates employing aryl triflates, (2) a sequential arylation to yield deferentially diarylated products that takes advantage of the increased propensity of aryl triflates to induce diarylation, (3) the scope and regioselectivity of arylation on a range of 3-substituted azine *N*-oxides, and (4) the application of this method to the synthesis of an antimalarial and antimicrobial compounds.

2. Results

An optimization study commenced with previously reported conditions using pyridine *N*-oxide and *p*-tolyl trifluoromethanesulfonate.

These studies revealed that, unlike reactions employing aryl bromide substrates, diarylation of the *N*-oxide substrate was a significant challenge with aryl triflates leading to diminished yields. An evaluation of the various reaction variables leads to two optimized reaction conditions (Scheme 1). The first set of conditions was found to minimize diarylation side products thus maximizing the yield of the monoarylation product. This method employs the use of tricyclohexylphosphine as the ligand, Rb_2CO_3 as the base, and 40 mol % pivalic acid in toluene (0.15 M) at 100 °C for 15 h (conditions A). The second set of conditions, which result in increased reactivity, were developed to maximize yields with substrates for which diarylation is not problematic. This method makes use of di-*tert*-butylmethylphosphine as the ligand, K_2CO_3 as the base, with 30 mol % pivalic acid in toluene (0.5 M) at 110 °C for 15 h (conditions B). The increased reactivity of this system could be partially due to the less sterically demanding nature of the



Scheme 1. Optimized arylation conditions.

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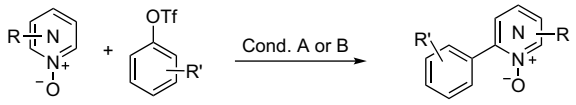
Table 1
Azine arylation scope



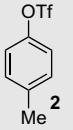
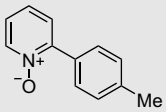
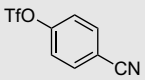
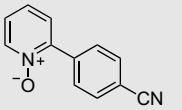
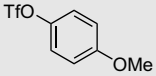
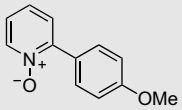
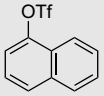
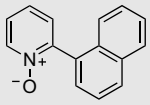
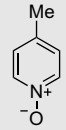
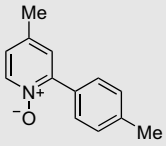
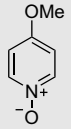
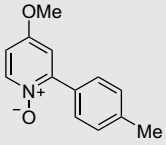
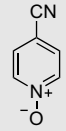
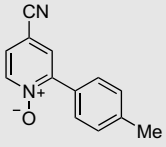
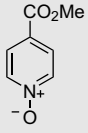
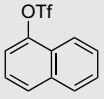
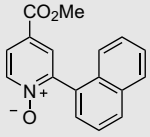
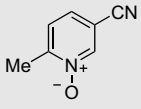
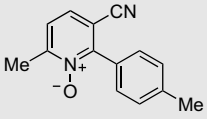
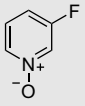
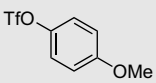
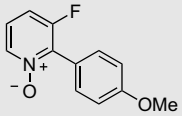
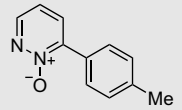
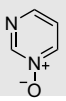
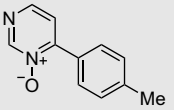
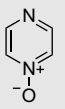
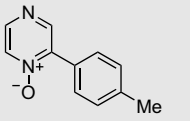
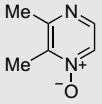
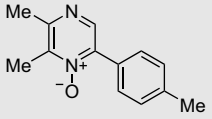
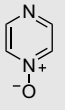
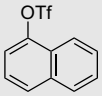
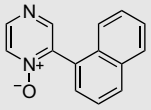
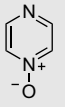
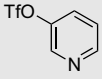
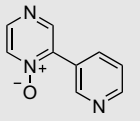
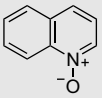
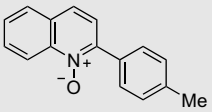
Entry	*N*-Oxide	Aryl triflate	Product	Cond.[a]	Yield[b]
1				A	51%[c]
2				A	65%[d]
3				A	89%
4				A	91%[e]
5	**1**			A	49%
6	**1**			A	75%
7	**1**			A	75%
8		**2**		A	71%
9		**2**		A	39%
10		**2**		A	38%
11				A	59%
12		**2**		B	74%
13				A	90%
14		**2**		A	51%
15				B	99%
16		**2**		A	0%
17				B	20%[f]

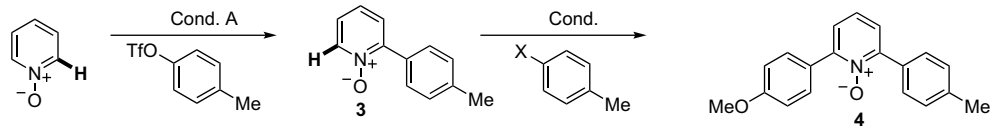
Table 1 (*continued*)

Entry	*N*-Oxide	Aryl triflate	Product	Cond.[a]	Yield[b]
18		**2**		A	80%
19		**2**		B	99%[g]
20				A	60%
21				A	43%
22		**2**		A	68%
23				B	81%
24		**2**		A	82%
25				A	27%
26				B	85%[g]

[a] Conditions A: *N*-oxide (2 equiv), Triflate (1 equiv), $Pd(OAc)_2$ (0.05 equiv), $HP(Cy_3)BF_4$ (0.10 equiv), Rb_2CO_3 (2 equiv), PivOH (0.4 equiv), PhMe (0.15 M), 100 °C, 15 h. Conditions B: *N*-oxide (2 equiv), Triflate (1 equiv), $Pd(OAc)_2$ (0.05 equiv), $HP(^tBu_2)MeBF_4$ (0.10 equiv), K_2CO_3 (2 equiv), PivOH (0.3 equiv), PhMe (0.5 M), 110 °C, 15 h.
[b] Isolated yields.
[c] Using 1.0 equiv of *N*-oxide.
[d] Using 1.5 equiv of *N*-oxide.
[e] Using 2.5 equiv of *N*-oxide.
[f] CuCN (10 mol %) added.
[g] Using 1.1 equiv of *N*-oxide.

$P(^tBu_2)Me$ compared to that of the PCy_3 ligand. Illustrative examples for reaction with aryl triflates under the two different reaction conditions are outlined in Table 1. The arylation proceeds with 89–91% yield with 2–2.5 equiv of pyridine *N*-oxide, respectively (Table 1, entries 3 and 4). If less pyridine *N*-oxide is used diminished yields of 51–65% are noted (Table 1, entries 1 and 2). Lower yields of 38–59% are obtained with substitution of electron-donating or electron-withdrawing groups at the 4-position (Table 1, entries 9–11), although low solubility of these substrates could explain diminished yields. The reaction proceeds well with electron rich aryl triflates (Table 1, entries 6, 13, and 26).

Diazine *N*-oxides are also compatible with the arylation. Pyridazine *N*-oxide is arylated in 99% when using conditions B (Table 1, entry 15). Pyrazine *N*-oxide is also a competent substrate (Table 1, entries 18–21). Pyrimidine *N*-oxide is less suitable, resulting in 20%



Conditions	Equiv. of 3	X	Yield
Cond. B	2	OTf	84%
Ref 5e	4	Br	50%

Scheme 2. Differential diarylation.

yield when employing conditions B and a 10% CuCN additive (Table 1, entry 17).[5] Quinoline (Table 1, entry 23) and isoquinoline (Table 1, entry 24) substrates are also suitable for the arylation.

The more active nature of conditions B compared to conditions A is illustrated by two examples. Pyridazine *N*-oxide, which may undergo reaction at only one position, is arylated in 51% yield under conditions A (Table 1, entry 14), but the yield increases to 99% when using conditions B (Table 1, entry 15). Also, quinoline *N*-oxide is arylated in 68% yield under conditions A (Table 1, entry 22) but in 81% yield under conditions B (Table 1, entry 23). High yields can be obtained even when using 1 equiv of *N*-oxide by utilizing conditions B in conjunction with an *N*-oxide substrate where diarylation is not problematic as exemplified by the arylation of phthalazine *N*-oxide (Table 1, entry 26).

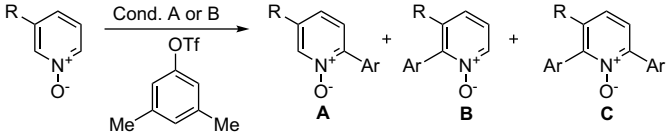
The arylation proceeds with a range of aryl triflates. Electron deficient aryl triflates result in somewhat diminished yields (Table 1, entries 5 and 21). Sterically demanding aryl triflates undergo reaction in 59–75% yield (Table 1, entries 7, 11, and 20); however, lower yields are obtained when used in combination with a sterically demanding *N*-oxide (Table 1, entry 25). Heterocyclic aryl triflates can also be employed as illustrated by the use of 3-pyridyl trifluoromethanesulfonate (Table 1, entry 21).

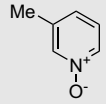
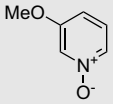
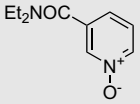
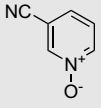
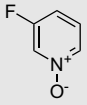
Differentially diarylated products can be obtained by carrying out the arylation reactions in sequence as shown in Scheme 2. Pyridine *N*-oxide is arylated with *p*-tolyl trifluoromethanesulfonate in 89% yield under conditions A.

This product can then be resubmitted to arylation conditions with 4-methoxyphenyl trifluoromethanesulfonate under the more active conditions B to generate the differentially diarylated compound **4** in 84% yield. Previously reported conditions for the arylation of pyridine *N*-oxide with aryl bromides resulted in 50% yield of the desired product.[5e] These conditions also require 4 equiv of the *N*-oxide to obtain satisfactory yields. Conditions B, which employs aryl triflates, results in not only higher yield than the previously reported conditions but also requires less equivalents of intermediate **3**. Therefore, it can be advantageous to employ aryl triflates when low yields are obtained with aryl bromides or when *N*-oxide substrates are precious.

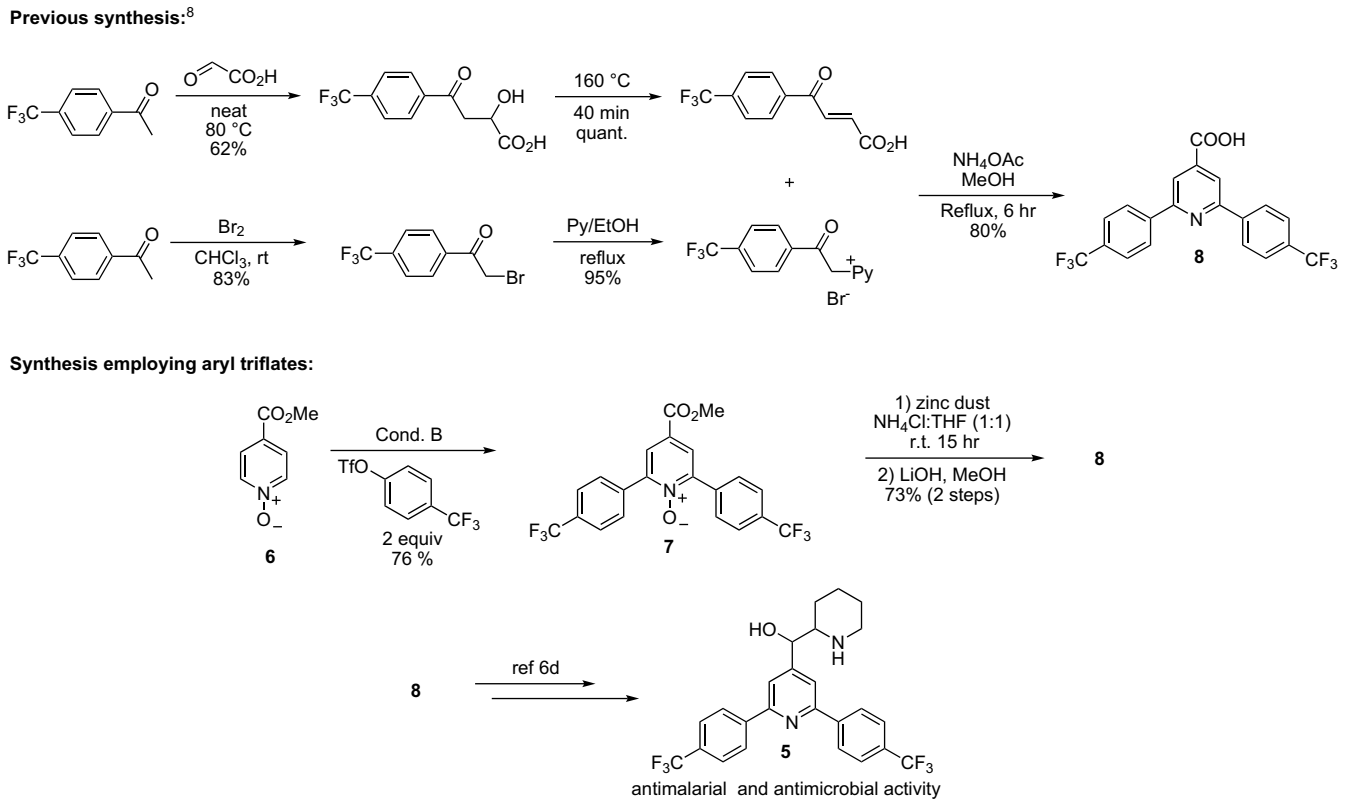
To further investigate the reactivity and selectivity for reaction with aryl triflates, the arylation was carried out on a series of 3-substituted azine *N*-oxides (Table 2), affording a mixture of 2-, 6- and disubstituted products. Alkyl substitution favors arylation at the 2-position, but diarylation is a significant by-product (Table 2,

Table 2
3-Substituted azine *N*-oxides



Entry	*N*-Oxide	Cond.[a]	Yield (A:B:C)[b]
1		Conditions A[c]	94 (28:55:11)
2		Conditions B	92 (16:32:44)
3		Conditions A	85 (11:67:7)
4		Conditions B	81 (9:64:8)
5		Conditions A[c]	97 (73:14:10)
6		Conditions B	68 (trace:61:7)
7		Conditions A	90 (trace:90:trace)

[a] Conditions A: *N*-oxide (2 equiv), Triflate (1 equiv), $Pd(OAc)_2$ (0.05 equiv), $HP(Cy_3)BF_4$ (0.10 equiv), Rb_2CO_3 (2 equiv), PivOH (0.4 equiv), PhMe (0.15 M), 100 °C, 15 h. Conditions B: *N*-oxide (2 equiv), Triflate (1 equiv), $Pd(OAc)_2$ (0.05 equiv), $HP(^tBu_2)MeBF_4$ (0.10 equiv), K_2CO_3 (2 equiv), PivOH (0.3 equiv), PhMe (0.5 M), 110 °C, 15 h.
[b] Isolated yields.
[c] Using 4 equiv of *N*-oxide.



Scheme 3. Formal synthesis of **5**.

entries 1 and 2). Electron-donating groups give more favorable selectivities for the 2-position and diarylation is not as problematic (Table 2, entries 3 and 4). Electron-withdrawing substituents are the most selective substituents for the 2-position as only trace amounts of the 6-arylated product are observed (Table 2, entries 6 and 7). The only substitution that results in preferential arylation at the 6-postion is a diethylamide substituent, which gives the 6-arylated product as the major regioisomer, which is possibly due to the increased steric requirements of this group (Table 2, entry 5).

The methodology for the direct arylation of azine *N*-oxides using aryl triflates was also evaluated in the context of the synthesis of key intermediate **8** in the synthesis of diarylpyridine **5**,[6d] which exhibits both antimalarial[6] and antimicrobial[7] activities. A previous synthesis of **8**, shown in Scheme 3, involves the assembly of the pyridine core with aryl groups already attached.[8] We envisioned that, given that **8** is symmetrically bis-arylated, the greater propensity of aryl triflates to undergo bis-arylation compared to aryl halides may be capitalized upon. Consequently, methyl isonicotinate *N*-oxide was subjected to conditions B with two equivalents of 4-(trifluoromethyl)phenyl trifluoromethanesulfonate to yield 76% of the bis-arylated product **7**. Compound **7** was then subsequently reduced and saponified to give **8** in 73% yield over two steps. Compared to the previous synthesis of **7**, the direct arylation approach saves several chemical steps and is more amenable to the synthesis of derivatives.

3. Conclusion

In conclusion, we have developed a method for the arylation of azine *N*-oxides with aryl triflates. The reaction is broadly applicable to a wide range of both azine *N*-oxides and aryl triflates. The arylation can be carried out in sequence to afford diarylated products. The method was applied to the formal synthesis of a medicinally relevant compound.

4. Experimental

4.1. General

Pyridine *N*-oxide was purchased from Aldrich and used without further purification. Reagent grade dichloromethane and degassed HPLC grade toluene were used without further purification. Palladium sources and ligands were purchased from Strem, stored in a desiccator and weighed out to air unless otherwise specified. All other reagents and solvents were used as is from commercial sources. Unless noted below, all other compounds have been reported in the literature or are commercially available. Unless otherwise notes, all reactions were performed in oven-dried glassware under an argon atmosphere. Coupling reactions were performed with regard for exclusion of ambient air. Analysis of crude reaction mixtures was done using TLC or NMR. Reactions were purified by flash chromatography on silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer in the specified solvent at ambient temperature and chemical shifts are reported relative to tetramethylsilane (TMS). Fourier-transform infra-red (FTIR) spectra were obtained as thin films on sodium chloride plates. High resolution mass spectra were obtained with a Kratos Concept IIH mass spectrometer. Melting points and are reported uncorrected.

4.2. Direct arylation

4.2.1. Procedure A

All reactions were performed on 0.5 mmol scale. A test tube is charged with $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), Rb_2CO_3 (2 equiv), PivOH (0.4 equiv), and azine *N*-oxide (1.1–2 equiv.). The tube is then sealed and purged with Argon. In a solution of toluene (0.15 M), the aryl triflate (1 equiv) is then added. The reaction is stirred at 100 °C for 15–18 h, and then allowed to cool, diluted with

CH_2Cl_2, and filtered over Celite. The residues are then purified using silica gel chromatography.

4.2.2. Procedure B

All reactions were performed on 0.5 mmol scale. A test tube is charged with $Pd(OAc)_2$ (5 mol %), $P^tBu_2Me\cdot HBF_4$ (10 mol %), K_2CO_3 (2 equiv), PivOH (0.3 equiv), and azine *N*-oxide (1.1–2 equiv). The tube is then sealed and purged with Argon. In a solution of toluene (0.5 M), the aryl triflate (1 equiv) is then added. The reaction is stirred at 110 °C for 15–18 h, and then allowed to cool, diluted with CH_2Cl_2, and filtered over Celite. The residues are then purified using silica gel chromatography.

4.2.3. 2-(4-Cyanophenyl)pyridine 1-oxide (Table 1, entry 5)

Obtained in 49% yield as a white solid by following direct arylation procedure A. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 7.30–7.34 (1H, m), 7.36 (1H, td, *J*=7.6 and 1.4 Hz), 7.45 (1H, dd, *J*=7.7 and 2.2 Hz), 7.78 (2H, d, *J*=8.4 Hz), 7.96 (2H, d, *J*=8.4 Hz), 8.35 (1H, dd, *J*=6.4 and 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 113.2, 118.4, 125.7, 125.8, 127.3, 130.0, 132.1, 136.9, 140.7; IR (ν_{max}/cm^{-1}): 2950, 2217, 1481, 1246, 835; HRMS calculated for $C_{12}H_8N_2O$ (M^+) 196.0637, found: 196.0659; mp: 162–168 °C (CH_2Cl_2); *Rf*: 0.32 (3:10:87 MeOH/acetone/CH_2Cl_2).

4.2.4. 4-Methyl-2-p-tolylpyridine 1-oxide (Table 1, entry 8)

This compound was obtained in 71% yield as a light green oil by following direct arylation procedure A. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.35 (3H, s), 2.39 (3H, s), 7.00 (1H, dd, *J*=6.6 and 2.1 Hz), 7.20 (1H, d, *J*=2.5 Hz), 7.26 (2H, d, *J*=7.9 Hz), 7.70 (2H, d, *J*=8.2 Hz), 8.20 (1H, d, *J*=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 20.3, 21.4, 125.1, 127.8, 128.9, 129.2, 129.8, 137.6, 139.6, 139.7, 148.5; IR (ν_{max}/cm^{-1}): 2922, 1623, 1480, 1224, 784; HRMS calculated for $C_{13}H_{13}NO$ (M^+) 199.0997, found: 199.1012; *Rf*: 0.35 (4:6:90, MeOH/acetone/CH_2Cl_2).

4.2.5. 4-Cyano-2-p-tolylpyridine 1-oxide (Table 1, entry 10)

This compound was obtained in 38% yield as a light green solid by following direct arylation procedure A. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.42 (3H, s), 7.30 (2H, d, *J*=8.0 Hz), 7.41 (1H, dd, *J*=6.8 and 2.5 Hz), 7.66 (3H, dd, *J*=5.5 and 2.7 Hz), 8.31 (1H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 21.5, 107.6, 116.1, 126.3, 127.7, 129.0, 129.3, 129.8, 141.0, 141.4, 150.6; IR (ν_{max}/cm^{-1}): 3050, 2217, 1272, 896, 828; HRMS calculated for $C_{13}H_{10}N_2O$ (M^+) 210.0793, found: 210.0790; mp: 192–194 °C (CH_2Cl_2); *Rf*: 0.42 (5:95 acetone/CH_2Cl_2).

4.2.6. 4-(Methoxycarbonyl)-2-(naphthalen-1-yl)pyridine 1-oxide (Table 1, entry 11)

This compound was obtained in 59% yield as a yellow solid by following direct arylation procedure A. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 3.91 (3H, s), 7.42–7.58 (5H, m), 7.90–7.98 (3H, m), 8.06 (1H, d, *J*=2.5 Hz), 8.40 (1H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 52.7, 125.0, 125.3, 125.3, 125.8, 126.4, 127.0, 127.9, 128.6, 129.0, 130.2, 130.5, 130.7, 133.4, 140.4, 149.9, 164.1; IR (ν_{max}/cm^{-1}): 2950, 1722, 1271, 1241, 770; HRMS calculated for $C_{17}H_{13}NO_3$ (M^+) 279.0895, found: 279.0895; mp: 138–140 °C (CH_2Cl_2); *Rf*: 0.32 (5:95 acetone/CH_2Cl_2).

4.2.7. 3-Fluoro-2-(4-methoxyphenyl)pyridine 1-oxide (Table 1, entry 13)

This compound was obtained in 90% yield as a tan solid by following direct arylation procedure A. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 3.84 (3H, s), 7.02 (2H, dd, *J*=6.9 and 2.0 Hz), 7.08–7.17 (2H, m), 7.61 (2H, dt, *J*=7.4 and 2.1 Hz), 8.19 (1H, d, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 55.3, 113.4 (d, *J*=23.0 Hz), 113.8, 118.4 (d, *J*=1.8 Hz), 123.1 (d, *J*=10.5 Hz), 131.7 (d, *J*=2.4 Hz), 136.7 (d, *J*=3.6 Hz), 140.4 (d, *J*=24.5 Hz), 158.3 (d, *J*=250.5 Hz), 160.7; IR (ν_{max}/cm^{-1}): 2966, 1432, 1227, 1024, 842; HRMS calculated for $C_{12}H_{10}FNO_2$ (M^+) 219.0696, found: 219.0700; mp: 132–134 °C (CH_2Cl_2); *Rf*: 0.32 (2:6:92 MeOH/acetone/CH_2Cl_2).

4.2.8. 2-(Pyridin-3-yl)pyrazine 1-oxide (Table 1, entry 21)

This compound was obtained in 43% yield as a white solid by following direct arylation procedure A. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 7.47 (1H, ddd, *J*=8.0, 4.9, and 0.8 Hz), 8.24 (1H, dd, *J*=4.1 and 0.6 Hz), 8.30 (1H, dt, *J*=8.0 and 2.0 Hz), 8.46 (1H, d, *J*=4.1 Hz), 8.68 (1H, s), 8.74 (1H, dd, *J*=4.8 and 1.6 Hz), 9.0 (1H, dd, *J*=2.3 and 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 123.2, 125.4, 134.5, 136.8, 142.0, 146.6, 148.0, 149.4, 151.3; IR (ν_{max}/cm^{-1}): 3175, 1287, 1005, 813, 703; HRMS calculated for $C_9H_7N_3O$ (M^+) 173.0589, found: 173.0574; mp: 188–189 °C (CH_2Cl_2); *Rf*: 0.23 (3:15:82 MeOH/acetone/CH_2Cl_2).

4.2.9. 1-(Naphthalen-1-yl)isoquinoline 2-oxide (Table 1, entry 25)

This compound was obtained in 27% yield as a beige solid by following direct arylation procedure A. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 7.20 (1H, d, *J*=8.5 Hz), 7.27 (1H, d, *J*=8.4 Hz), 7.38 (2H, t, *J*=7.5 Hz), 7.48–7.55 (3H, m), 7.66 (1H, t, *J*=7.6 Hz), 7.77 (1H, d, *J*=7.2 Hz), 7.84 (1H, d, *J*=8.2 Hz), 7.96 (1H, d, *J*=8.2 Hz), 8.04 (1H, d, *J*=8.3 Hz), 8.36 (1H, d, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 123.7, 125.1, 125.5, 125.6, 126.4, 126.8, 127.0, 128.3, 128.4, 128.7, 128.8, 128.9, 129.2, 130.0, 130.3, 131.3, 133.8, 137.5, 145.5; IR (ν_{max}/cm^{-1}): 3058, 1320, 1224, 945, 777; HRMS calculated for $C_{19}H_{13}NO$ (M^+) 271.0997, found: 271.0992; mp: 160–162 °C (CH_2Cl_2); *Rf*: 0.30 (2:6:92 MeOH/acetone/CH_2Cl_2).

4.2.10. 1-(4-Methoxyphenyl)phthalazine 2-oxide (Table 1, entry 26)

This compound was obtained in 85% yield as a tan solid by following direct arylation procedure B. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 3.91 (3H, s), 7.11 (2H, dd, *J*=6.7 and 2.1 Hz), 7.53–7.57 (3H, m), 7.63–7.67 (1H, m), 7.69–7.74 (1H, m), 7.93 (1H, d, *J*=7.7 Hz), 9.07 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 55.4, 114.4, 121.3, 121.6, 124.6, 127.2, 128.7, 131.7, 132.9, 133.5, 151.5, 160.6, one overlapping signal as one peak is missing even with prolonged scans; IR (ν_{max}/cm^{-1}): 3428, 1609, 1352, 1249, 829; HRMS calculated for $C_{15}H_{12}N_2O_2$ (M^+) 252.0899, found: 252.0905; mp: 216 °C (decomp.) (CH_2Cl_2); *Rf*: 0.37 (2:10:88 MeOH/acetone/CH_2Cl_2).

4.2.11. 2-(4-Methoxyphenyl)-6-p-tolylpyridine 1-oxide (Scheme 2)

This compound was obtained in 84% yield as a tan solid by following direct arylation procedure B. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.40 (3H, s), 3.85 (3H, s), 6.98 (2H, dd, *J*=6.8 and 2.1 Hz), 7.26–7.30 (3H, m), 7.33–7.38 (2H, m), 7.74 (2H, dd, *J*=6.5 and 1.7 Hz), 7.84 (2H, dd, *J*=6.8 and 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 21.4, 55.3, 113.4, 124.9, 125.4, 125.5, 125.6, 128.7, 129.4, 130.6, 131.1, 139.3, 149.5, 149.9, 160.3; IR (ν_{max}/cm^{-1}): 2933, 1609, 1476, 1180, 782; HRMS calculated for $C_{19}H_{17}NO_2$ (M^+) 291.1259, found: 291.1286; mp: 170–173 °C (CH_2Cl_2); *Rf*: 0.45 (10:90 EtOAc/CH_2Cl_2).

4.2.12. 2-(3,5-Dimethylphenyl)-3-methylpyridine 1-oxide (Table 2, entry 1, B)

This compound was obtained in 55% yield as an off-white solid by following conditions A with the exception of using 4 equiv of the *N*-oxide and in 32% yield following conditions B. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K, TMS): 2.09 (3H, s), 2.36 (6H, d, *J*=0.5 Hz), 6.96–6.92 (2H, m), 7.09–7.05 (1H, m), 7.15–7.10 (1H, m), 7.18–7.14 (1H, m), 8.22 (1H, ddd, *J*=6.1, 1.5, and 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 19.9, 21.4, 123.6, 126.4, 127.3, 130.7, 132.2, 136.0, 137.7, 138.4, 150.2; IR (ν_{max}/cm^{-1}): 2911, 1601, 1413, 1268. 1237, 1196, 1076, 784; HRMS calculated for $C_{14}H_{15}NO$ (M^+) 213.1154, found: 213.1151; mp: 149–151 °C ($CHCl_3$); *Rf*: 0.39 (2% MeOH, 10% Me_2CO, $CHCl_3$).

4.2.13. 2,6-Bis(3,5-dimethylphenyl)-3-methylpyridine 1-oxide (Table 2, entries 1 and 2, C)

This compound was obtained in 11% yield as a yellow oil by following conditions A with the exception of using 4 equiv of the *N*-oxide and in 44% yield following conditions B. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K, TMS): 2.14 (3H, s), 2.33 (6H, d, *J*=0.5 Hz), 2.34 (6H, d, *J*=0.5 Hz), 6.99–6.96 (2H, m), 7.03–7.01 (1H, m), 7.05–7.03 (1H, m), 7.18 (1H, dd, *J*=8.1 and 0.5 Hz), 7.33 (1H, d, *J*=8.1 Hz), 7.48–7.45 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 19.9, 21.3, 21.4, 124.9, 126.7, 126.8, 127.3, 130.3, 132.9, 133.1, 134.0, 137.4, 138.2, 147.3, 150.5; IR (ν_{max}/cm^{-1}): 2920, 2863, 1603, 1346, 1275, 1219, 850, 729; HRMS calculated for $C_{22}H_{23}NO$ (M^+) 317.1780, found: 317.1786; R_f: 0.92 (2% MeOH, 10% Me_2CO, $CHCl_3$).

4.2.14. 2-(3,5-Dimethylphenyl)-5-methoxypyridine 1-oxide (Table 2, entries 3 and 4, A)

This compound was obtained in 11% yield as a pale yellow oil by following conditions A and in 9% yield following conditions B. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K, TMS): 2.36 (6H, s), 3.87 (3H, s), 6.91 (1H, dd, *J*=8.9 and 2.4 Hz), 7.08–7.02 (1H, m), 7.27 (1H, d, *J*=8.7 Hz), 7.36–7.31 (2H, m), 8.08 (1H, d, *J*=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 21.6, 56.2, 113.7, 126.87, 126.93, 127.8, 130.8, 132.5, 137.8, 143.1, 156.6; IR (ν_{max}/cm^{-1}): 2918, 2849, 1598, 1512, 1375, 1308, 1198, 1172, 1024; HRMS calculated for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found: 229.1098; R_f: 0.20 (1% MeOH, 10% Me_2CO, $CHCl_3$).

4.2.15. 2,6-Bis(3,5-dimethylphenyl)-3-methoxypyridine 1-oxide (Table 2, entries 3 and 4, C)

This compound was obtained in 7% yield as a yellow oil by following conditions A and in 8% yield following conditions B. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K, TMS): 2.33 (6H, d, *J*=0.5 Hz), 2.34 (6H, d, *J*=0.5 Hz), 3.82 (3H, s), 6.98 (1H, d, *J*=9.0 Hz), 7.03–7.00 (1H, m), 7.05–7.03 (1H, m), 7.13–7.10 (2H, m), 7.35 (1H, d, *J*=8.9 Hz), 7.42–7.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 21.3, 21.4, 56.4, 108.7, 124.7, 127.4, 127.8, 129.8, 130.4, 130.7, 133.0, 137.4, 137.6, 141.4, 143.4, 154.6; IR (ν_{max}/cm^{-1}): 3008, 2924, 1605, 1563, 1498, 1459, 1345, 1293, 1235, 1086, 852; HRMS calculated for $C_{22}H_{23}NO_2$ (M^+) 333.1729, found: 333.1734; R_f: 0.86 (1% MeOH, 10% Me_2CO, $CHCl_3$).

4.2.16. 3-(Diethylcarbamoyl)-2-(3,5-dimethylphenyl)pyridine 1-oxide (Table 2, entry 5, B)

This compound was obtained in 14% yield as a pale yellow oil by following conditions A with the exception of using 4 equivalents of the *N*-oxide. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K, TMS): 0.73 (3H, t, *J*=7.1 Hz), 0.90 (3H, t, *J*=7.1 Hz), 2.88–2.68 (2H, m), 3.13–3.00 (1H, m), 3.82–3.69 (1H, m), 7.05 (1H, br s), 7.15 (2H, br s), 7.21 (1H, dd, *J*=7.8 and 1.3 Hz), 7.29–7.24 (1H, m), 8.35 (1H, dd, *J*=6.3 and 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 11.5, 13.7, 21.3, 38.5, 42.6, 123.2, 124.6, 127.2, 129.8, 131.5, 136.8, 137.8, 140.1, 146.7, 165.8; IR (ν_{max}/cm^{-1}): 2977, 2929, 1633, 1433, 1406, 1289, 1258, 1196, 859; HRMS calculated for $C_{18}H_{22}N_2O_2$ (M^+) 298.1681, found: 298.1688; R_f: 0.15 (2% MeOH, 10% Me_2CO, $CHCl_3$).

4.2.17. 3-(Diethylcarbamoyl)-2,6-bis(3,5-dimethylphenyl)pyridine 1-oxide (Table 2, entry 5, C)

This compound was obtained in 10% yield as a pale yellow oil by following conditions A with the exception of using 4 equiv of the *N*-oxide. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K, TMS): 0.75 (3H, t, *J*=7.1 Hz), 0.94 (3H, t, *J*=7.1 Hz), 2.30 (6H, s), 2.35 (6H, s), 2.92–2.72 (2H, m), 3.25–3.10 (1H, m), 3.85–3.72 (1H, m), 7.02 (1H, s), 7.06 (1H, s), 7.20 (2H, br s), 7.24 (1H, d, *J*=8.1 Hz), 7.44 (1H, d, *J*=8.2 Hz), 7.46 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 11.5, 13.7, 21.3, 38.5, 42.6, 122.6, 126.0, 127.2, 127.4, 130.4, 131.1, 131.2, 132.6, 134.9, 137.5, 137.6, 147.0, 149.9, 166.1; IR (ν_{max}/cm^{-1}): 2973, 2919, 1636, 1451, 1427, 1286, 846; HRMS calculated for $C_{26}H_{30}N_2O_2$ (M^+) 402.2307, found: 402.2301; R_f: 0.80 (2% MeOH, 10% Me_2CO, $CHCl_3$).

4.2.18. 3-Cyano-2,6-bis(3,5-dimethylphenyl)pyridine 1-oxide (Table 2, entry 6, C)

This compound was obtained in 7% yield as a yellow oil by following conditions B. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K, TMS): 2.35 (6H, d, *J*=0.5 Hz), 2.38 (6H, d, *J*=0.5 Hz), 7.13–7.10 (1H, m), 7.15–7.13 (1H, m), 7.25–7.23 (2H, m), 7.47–7.45 (2H, m), 7.49 (1H, d, *J*=8.3 Hz), 7.56 (1H, d, *J*=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 21.31, 21.34, 111.5, 115.3, 125.9, 127.1, 127.2, 127.6, 129.6, 131.5, 132.2, 132.4, 138.0, 138.3, 153.8, 153.9; IR (ν_{max}/cm^{-1}): 2924, 2866, 2363, 2223, 1592, 1541, 1342, 848; HRMS calculated for $C_{22}H_{20}N_2O$ (M^+) 328.1576, found: 328.1565; R_f: 0.89 (2% MeOH, 10% Me_2CO, $CHCl_3$).

4.2.19. 4-(Methoxycarbonyl)-2,6-bis(4-(trifluoromethyl)-phenyl)pyridine 1-oxide (Scheme 3)

This compound was obtained in 76% yield as a yellow solid by following conditions B with the exception of using 2 equiv of the triflate and 1 equiv of the *N*-oxide. ^{1}H NMR (400 MHz, $CDCl_3$, 296 K, TMS): 3.98 (3H, s), 7.76 (4H, d, *J*=8.2 Hz), 7.95 (4H, d, *J*=8.1 Hz), 8.08 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K, TMS): 53.0, 123.8 (q, *J*=272.4 Hz), 125.4 (q, *J*=3.7 Hz), 125.9, 130.0, 131.8 (q, *J*=32.7 Hz), 135.7, 149.1, 164.0; IR (ν_{max}/cm^{-1}): 2957, 1726, 1620, 1562, 1325, 1251, 1169, 1125, 1067, 846, 818, 764; HRMS calculated for $C_{21}H_{13}F_6NO_3$ (M^+) 441.0800, found: 441.0776; mp: 152–153 °C ($CHCl_3$); R_f: 0.66 (CH_2Cl_2).

4.2.20. Methyl 2,6-bis(4-(trifluoromethyl)phenyl)isonicotinate (Scheme 3)

A solution of 4-(methoxycarbonyl)-2,6-bis(4-(trifluoromethyl)-phenyl)pyridine 1-oxide (148 mg, 0.335 mmol, 1 equiv) and zinc dust (99 mg, 1.509 mmol, 4.5 equiv) in THF:NH_4Cl satd 1:1 (3.5 ml) is stirred at room temperature overnight. The reaction is diluted with ether, dried over $MgSO_4$, and filtered over Celite. The crude product is purified by column chromatography (10–15% ether/pet. ether) to give a white solid in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 296 K, TMS): 4.05 (3H, s), 7.79 (4H, d, *J*=8.2 Hz), 8.31 (4H, d, *J*=8.1 Hz), 8.34 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 297 K, TMS): 53.0, 119.0, 124.10 (q, *J*=272.2 Hz), 125.83 (q, *J*=3.7 Hz), 131.51 (q, *J*=32.6 Hz), 139.7, 141.5, 156.6, 165.4; IR (ν_{max}/cm^{-1}): 2957, 1730, 1563, 1325, 1254, 1123, 1067, 847; HRMS calculated for $C_{21}H_{13}F_6NO_2$ (M^+) 425.0850, found: 425.0835; mp: 143–145 °C ($CHCl_3$); R_f: 0.33 (10% ether/pet. ether).

4.2.21. 2,6-Bis(4-(trifluoromethyl)phenyl)isonicotinic acid (Scheme 3)

A solution of methyl 2,6-bis(4-(trifluoromethyl)phenyl)isonicotinate (75 mg, 0.176 mmol, 1 equiv) and lithium hydroxide (37 mg, 0.882 mmol, 5 equiv) in MeOH (1 ml) is stirred at room temperature overnight. The reaction is diluted with water and the methanol is removed under reduced pressure. The solution is acidified with 10% HCl and extracted with EtOAc (3×20 ml). The combined organic extracts were dried over $MgSO_4$. The crude product is purified by flash chromatography (5% MeOH, 7% acetone, $CHCl_3$) to afford a white solid in 84% yield. ^{1}H NMR (400 MHz, $(CD_3)_2CO$, 296 K): 7.84 (4H, d, *J*=7.3 Hz), 8.45 (4H, d, *J*=7.3 Hz), 8.46 (2H, s); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, 297 K): 119.4, 124.5 (q, *J*=271.4 Hz), 125.7 (q, *J*=7.3 Hz), 127.7, 130.7 (q, *J*=32.1 Hz), 142.0, 156.0, 165.9; IR (ν_{max}/cm^{-1}): 3088, 2940, 1709, 1327, 1167, 1123, 1068, 1017, 847; HRMS calculated for $C_{20}H_{11}F_6NO_2$ (M^+) 411.0694, found: 411.0683; mp: 274–277 °C ($CHCl_3$); R_f: 0.53 (5% MeOH, 7% Me_2CO, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.077.

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