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Catalyst and base controlled site-selective sp^2 and sp^3 direct arylation of azine *N*-oxides

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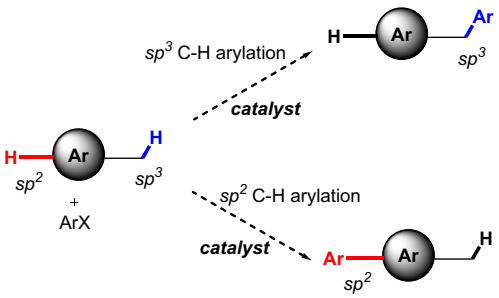
ABSTRACT

Site-selective direct arylation of both sp^2 and sp^3 sites on azine *N*-oxide substrates is described. The arylation reactions are carried out in either a divergent manner or a sequential manner. The sp^3 arylation reaction is applied to the synthesis of the natural products, papaverine and crykonisine, and a rationale for low reactivity of electron-deficient aryl halides is provided. Mechanistic investigations point toward the intimate involvement of the base in the mechanism of these reactions.

1. Introduction

While rare even just a decade ago, direct arylation of heterocycles has become a valuable tool in the transformation of otherwise chemically inert C–H bonds into a number of functional groups.[1] A particularly appealing and frequently discussed aspect of this chemistry involves the ubiquity of the C–H bond as a 'functional group' and the potential to strategically transform these with high site selectivity.[2] In practice, the challenge associated with achieving a high yielding reaction at even just one position makes the realization of controlled multi-site selectivity rare. Important advances have been made with some classes of electron-rich heteroaromatics.[3] For example, the inherent bias of azoles to undergo C5 direct arylation can be overridden through the use of copper additives, which induce reaction at C2.[4] 3-Carboxy furan and thiophene can be selectively arylated at either the C2 or C5 position.[5] Sames et al. have also reported examples of C2/C3 site selectivity in indole arylations.[6] Gaunt et al. have demonstrated that regiocontrol can be achieved in indole and pyrrole alkenylation and arylation reactions through the choice of the solvent and the azole *N*-substituent.[7] We have recently demonstrated that the choice of oxidant as well as the nature of the *N*-acyl substituent can reverse the site selectivity of the oxidative coupling of benzene with indole.[8] Significantly, these reactions all involve selectivity at aromatic sp^2 C–H bonds. As a greater appreciation of the possible mechanisms of C–H bond cleavage/functionalization is gained, and particularly as transformations and mechanisms, which exhibit complimentary and orthogonal reactivity are discovered, this long-term goal of chemo- and site-selective direct functionalization should become increasingly achievable.

We have previously reported the site-selective direct arylation of 2-methyl azine and diazine *N*-oxides, where reaction may be induced to occur at either a benzylic sp^3 C–H bond or an aromatic sp^2 C–H bond (Scheme 1).[9] In this account, we report (1) operationally simple catalyst systems for the site-selective direct arylation of sp^2 and sp^3 carbons of azine *N*-oxide substrates and several new examples, exhibiting broad scope for aryl chlorides, bromides, and iodides; (2) that the arylation reactions can be carried out in either a divergent manner or a sequential manner in which either the sp^2 or the sp^3 arylation can be carried out first; (3) the application of the novel sp^3 arylation process to the synthesis of the natural products, papaverine and crykonisine, in three steps from simple starting materials; (4) insight into catalyst poisoning with electron-deficient aryl halides leading to new mechanistic insights;



Scheme 1. Catalyst controlled site-selective sp^2/sp^3 arylation.

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(5) mechanistic studies pointing toward the intimate involvement of the base in the mechanism of the reactions.

2. Results and discussion

As part of a research program targeted at the development of new direct arylation reactions, we sought to develop catalyst systems that would enable selective arylation at both sp^2 and sp^3 centers on the same substrate. We have previously reported that treatment of 2-picoline *N*-oxide and 4-bromotoluene with a Pd/X-Phos catalyst using NaO^{t}Bu as the base and toluene as the solvent resulted in high yield and selectivity of the sp^3 arylated product (Fig. 1).[9]

Subsequent re-optimization studies revealed that any deviations from these reaction conditions resulted in lower yields.

An expanded scope of the sp^3 arylation reaction is outlined in Table 1. Different aryl halides are tolerated including cheap and readily available chlorides (Table 1, entries 1, 10, and 12) as well as more commonly used bromides (Table 1, entries 2–5, 7–9, 11, and 13–14 and Table 2 entries 1–7) and iodides (Table 1, entry 6). Arylation can be carried out using catalyst loadings as low as 1 mol % Pd (Table 1, entry 3). Also near equimolar amounts of the *N*-oxide and aryl halide can be employed (Table 1, entry 4). Thermal heating conditions were also developed utilizing Ru-Phos as the ligand although this method results in slightly diminished yields (Table 1, entry 5 and Table 2, entry 3).

A variety of substitution patterns including *ortho*, *meta*, and *para* are tolerated on the aryl halide (Table 1). Very sterically demanding substrates require the use of S-Phos as the ligand (Table 1, entries 10 and 11). While electron-rich aryl halides are broadly applicable (Table 1, entry 13 and Table 2, entry 1), electron-poor aryl halides are not compatible with this catalyst system (Table 1, entry 15). Heterocyclic aryl halides can also be employed as illustrated by the use of an indole halide (Table 1, entry 12).

We have determined that a broad range of *N*-oxide substrates can be used in sp^3 arylation reactions (Table 2). *meta* and *para* Methyl substituted aryl bromides participate in high yield and complete selectivity (Table 2, entries 1–3). Quinoline (Table 2, entry 4) and isoquinoline (Table 2, entry 5) *N*-oxides are also competent substrates, although 3 equiv of 2-methyl quinoline *N*-oxide must be used due to increased amounts of diarylation. Diazine *N*-oxides can be employed in the reaction as illustrated by the use of 2,3-dimethyl diazine *N*-oxide (Table 2, entry 6). Other alkyl groups can also be arylated under the reaction conditions with no products arising from a potentially competitive β-hydride elimination (Table 2, entry 7).

The scope of the sp^2 arylation of 2-methyl azine *N*-oxides is outlined in Table 3. We have previously described the use of *N*-oxides in direct arylation reactions as a means of avoiding the use of problematic organometallics in the formation of biaryl molecules and the selective arylation of the sp^2 position in the presence of a 2-methyl substituent.[9] The sp^2 arylation reaction is compatible with electron-neutral (Table 3, entries 1–6), electron-rich (Table 3, entries 7 and 9), and electron-poor (Table 3, entry 8) aryl bromides. A range of *N*-oxides, including substituted pyridines (Table 3, entries 1–4, 8, and 9), isoquinoline (Table 3, entry 6), and diazines (Table 3, entries 5 and 7) are suitable to be employed in the sp^2 arylation reaction.

To further demonstrate the utility of these methods for the functionalization of heterocycles, we have established that the sp^2/sp^3 arylations can be carried out in both a divergent and a sequential manner (Scheme 2). Reaction of 2-picoline *N*-oxide (**1**) with bromotoluene was chosen as a model reaction. 2-Picoline *N*-oxide is arylated with 4-bromotoluene (**2**) under the sp^2 arylation conditions to give a 56% yield of product **3**. *N*-Oxide **3** is then subjected to the sp^3 arylation conditions with 2-bromotoluene to

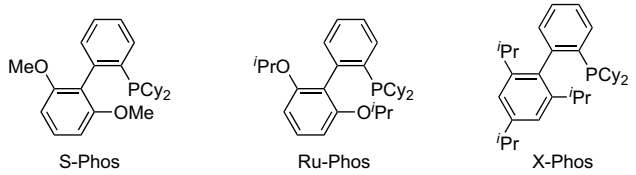
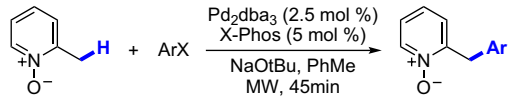


Figure 1.

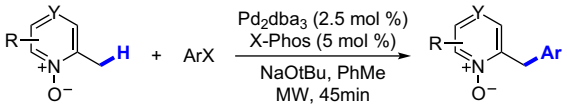
Table 1
sp^3 Arylation of picoline *N*-oxide[a]

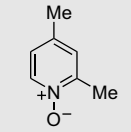
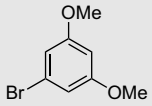
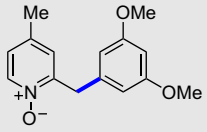
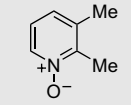
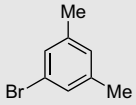
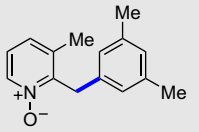
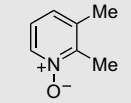
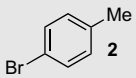
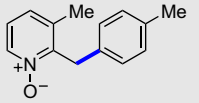
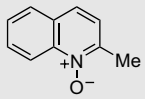
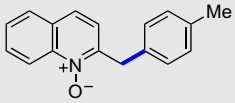
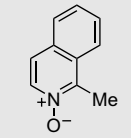
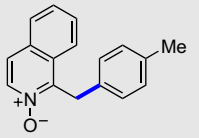
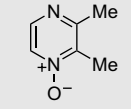
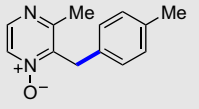
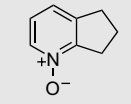
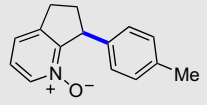


Entry	*N*-Oxide	Aryl halide	Product	Yield[b]
1		X=Cl		91
2		X=Br		89
3		X=Br		84[c]
4		X=Br		77[d]
5		X=Br		78[e]
6		X=I		85
7	**1**			92
8	**1**			93
9	**1**			72
10	**1**	X=Cl		84[f]
11		X=Br		90[f]
12	**1**			90
13	**1**			72
14	**1**			72
15	**1**	R=CN, CO_2Et, COPh, NO_2		Trace

[a] Conditions: picoline *N*-oxide (1.5 equiv), aryl halide (1 equiv), Pd_2dba_3 (0.025 equiv), X-Phos (0.05 equiv), and NaO^{t}Bu (3 equiv) in PhMe (0.5–1 M), MW, 110 °C for 45 min.
[b] Isolated yield.
[c] Using 1 mol % Pd.
[d] Using 1.1 equiv *N*-oxide.
[e] Using picoline *N*-oxide (2 equiv), aryl halide (1 equiv), Pd_2dba_3 (0.025 equiv), Ru-Phos (0.1 equiv), and NaO^{t}Bu (3 equiv) in PhMe (0.3 M), thermal heating, 70 °C overnight.
[f] Using S-Phos.

Table 2
sp^3 Arylation of azine *N*-oxides[a]



Entry	*N*-Oxide	Aryl halide	Product	Yield[b]
1				70
2				90
3				76[c]
4		**2**		73[d]
5		**2**		60
6		**2**		79
7		**2**		64[d,e]

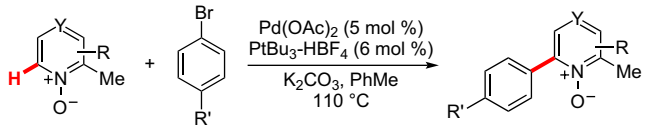
[a] Conditions: picoline *N*-oxide (1.5 equiv), aryl halide (1 equiv), Pd_2dba_3 (0.025 equiv), X-Phos (0.05 equiv), and NaO^{t}Bu (3 equiv) in PhMe (0.5–1 M), MW, 110 °C for 45 min.
[b] Isolated yield.
[c] Using picoline *N*-oxide (2 equiv), aryl halide (1 equiv), Pd_2dba_3 (0.025 equiv), Ru-Phos (0.1 equiv), and NaO^{t}Bu (3 equiv) in PhMe (0.3 M), thermal heating, 70 °C overnight.
[d] Using 3 equiv *N*-oxide.
[e] Using S-Phos.

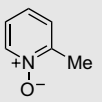
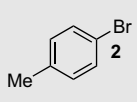
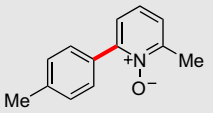
give a 77% yield of the differentially diarylated product **5**. Alternatively, **1** could be first subjected to the sp^3 arylation conditions with 2-bromotoluene to give a 92% yield of product **4**, demonstrating the divergent reactivity of a single substrate under different catalytic conditions. Compound **4** can then be arylated under the sp^2 conditions with 4-bromotoluene to give the same differentially diarylated product as the previous route in 59% yield.

The methodology for the sp^3 direct arylation of 2-methyl pyridine *N*-oxides was further validated in an efficient synthesis of natural products, papaverine (**11**) and crykonisine (**9**). Papaverine is one of the four major components of opium and is used as a non-narcotic antispasmodic agent.[10] Crykonisine is a natural product isolated from the plant *Papaver Triniifolium* and the stem bark of *Cryptocarya Chinensis Hemsl.*[11] Compound **6** is oxidized to the *N*-oxide (**7**) by treatment with methyltrioxorhenium and aqueous hydrogen peroxide in DCM.[12] Compound **7** is then subjected to sp^3 arylation conditions with 4-benzyloxybromobenzene, which affords the arylated product **8**. Simultaneous removal of the benzyl group and reduction of the *N*-oxide take place under hydrogenation conditions with Pd/C in methanol to yield the natural product cykonisine in three steps and 34% overall yield from commercially available starting materials (Scheme 3).

The common intermediate **7** is again subjected to sp^3 arylation conditions with 4-bromoveratrole to yield **10**. The *N*-oxide (**10**) is subsequently reduced with zinc in saturated NH_4Cl/THF to yield the natural product papaverine in three steps and 30% overall yield.[13] The syntheses of these two natural products from a common intermediate demonstrate the potential utility of this method for the

Table 3
sp^2 Arylation azine *N*-oxides[a]



Entry	*N*-Oxide	Aryl halide	Product	Yield[b]
1				21[c]
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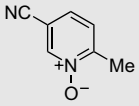
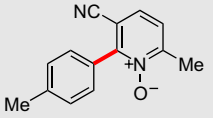
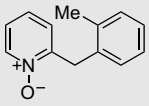
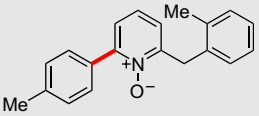
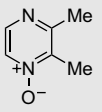
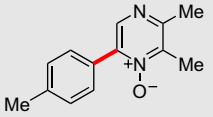
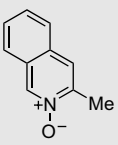
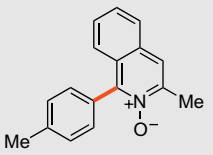
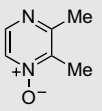
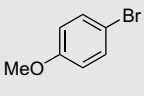
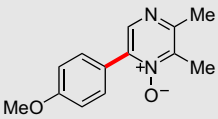
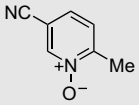
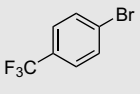
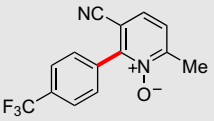
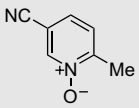
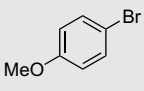
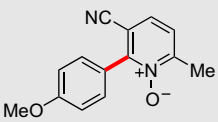
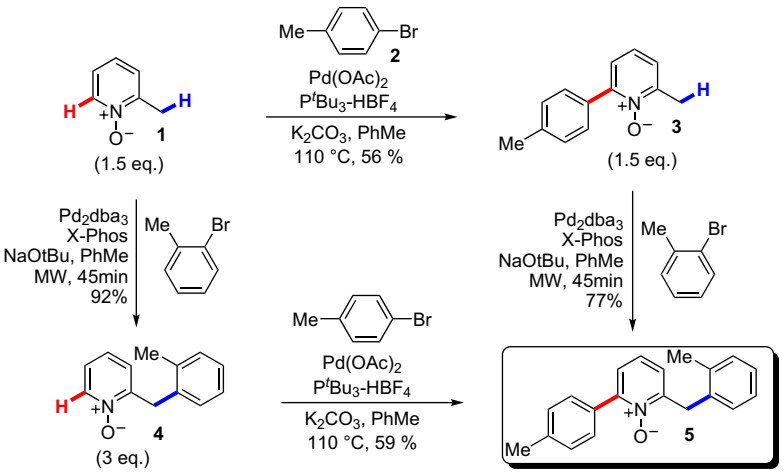
3		**2**		74
4		**2**		59[d]
5		**2**		89
6		**2**		90[e]
7				86
8				48
9				73

[a] Conditions: *N*-oxide (2 equiv), aryl halide (1 equiv), $Pd(OAc)_2$ (0.05 equiv), P^{t}Bu$_3$–HBF_4 (0.06 equiv), and K_2CO_3 (1.5 equiv) in PhMe (0.15 M), 110 °C overnight.
[b] Isolated yield.
[c] Previously reported conditions.
[d] Using 3 equiv *N*-oxide.
[e] Using 1.1 equiv *N*-oxide.

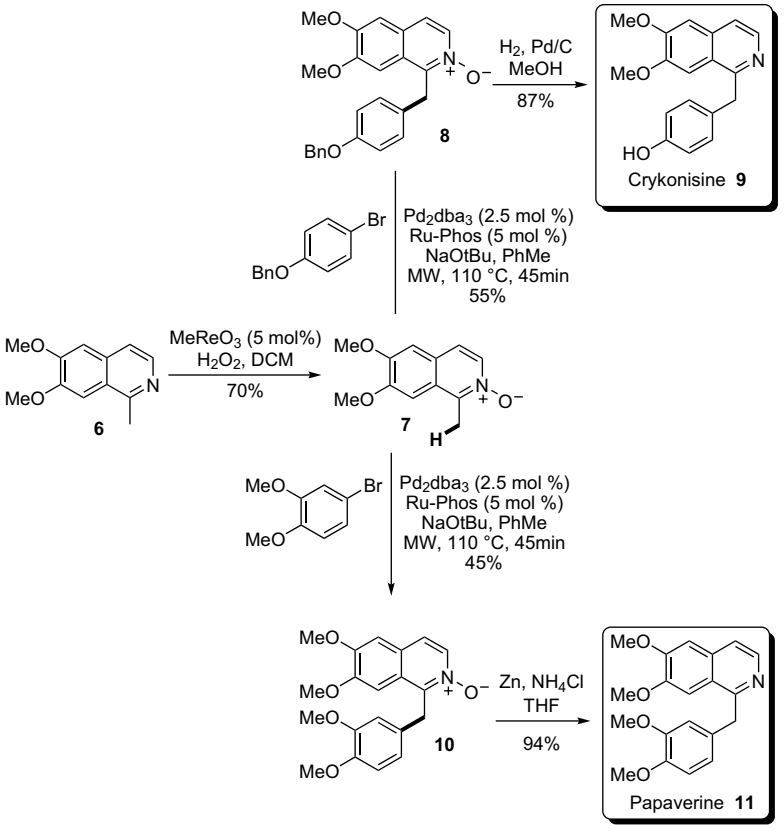


Scheme 2. Divergent and sequential sp^2/sp^3 arylation.

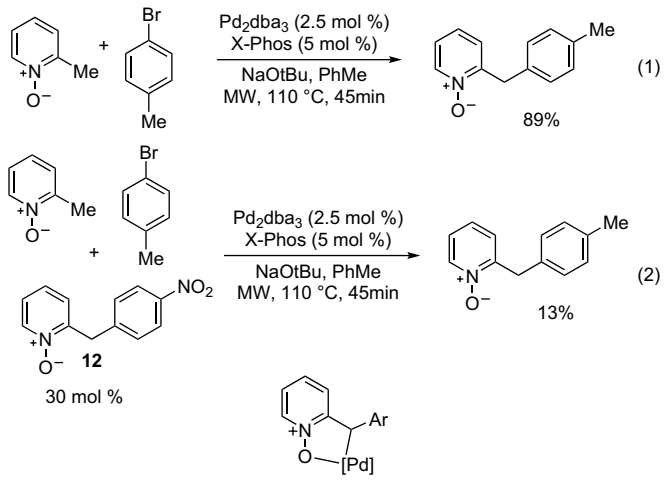
generation of a large family of related compounds rapidly from common intermediates.

While evaluating the scope of sp^3 arylation, it was noticed that severely reduced yields were obtained for most electron-poor aryl halides (Table 1, entry 15). Since electron-deficient aryl halides undergo oxidative addition more readily than electron-rich aryl halides, we hypothesized that the attenuated reactivity of electron-poor aryl halides might be explained by product inhibition of the catalyst. Upon arylation of the sp^3 position with an electron-deficient arene the benzylic protons become more acidic, which may lead to the formation of a stable palladacycle that is unable to participate in the reaction (Scheme 4). To test this hypothesis, a poisoning experiment was carried out in which two reactions were performed, one without additive (Scheme 4, Eq. 1) and one with 30 mol % **12** (Scheme 4, Eq. 2). The reaction with no additive resulted in an 89% yield of the desired product, while the reaction with 30 mol % **12** added resulted in only 13% yield of the desired product. These results imply product inhibition may account for the diminished yields associated with electron-deficient aryl halides.

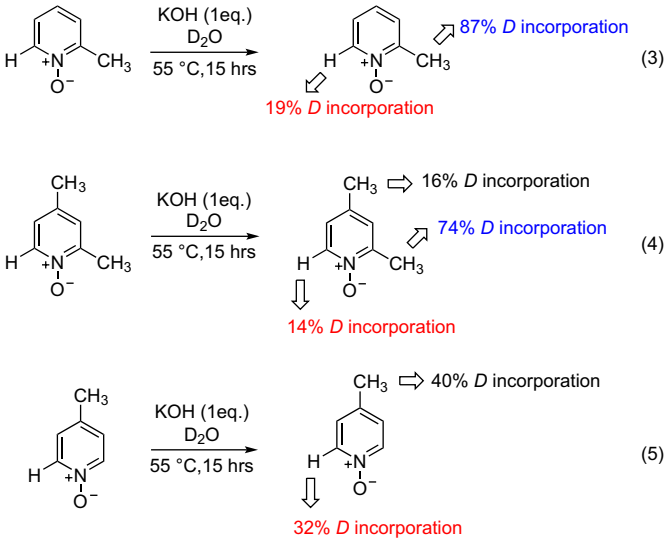
To investigate the role C–H bond acidity plays in the site selectivity of these reactions, deuterium incorporation experiments were carried out (Scheme 5). Deuterium exchange of 2-picoline *N*-oxide by treatment with KOH in D_2O reveals that the methyl sp^3 site exchanges at a significantly faster rate than the sp^2 site adjacent to the nitrogen (Eq. 3). Exchange on 2,4-lutidine *N*-oxide shows that the 2-methyl position undergoes exchange faster than the



Scheme 3. Synthesis of crykonisine and papaverine.



Scheme 4. Poisoning experiment.



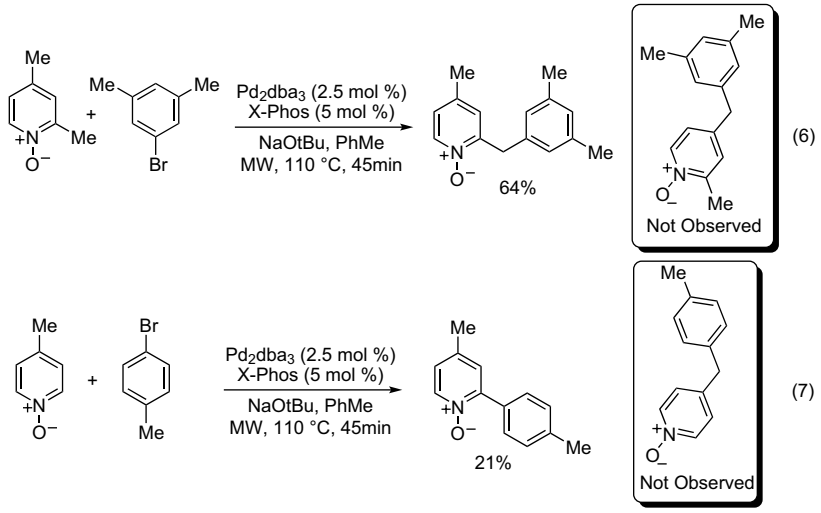
Scheme 5.

4-methyl position and that the sp^2 position undergoes exchange at the slowest rate of the three positions (Eq. 4). Exchange on 4-picoline *N*-oxide shows that in the absence of a 2-methyl substituent the 4-methyl position undergoes exchange faster than the sp^2 positions (Eq. 5).

A series of experiments were also performed to determine if the *N*-oxide moiety influences regioselectivity (Scheme 6). Arylation of 2,4-lutidine *N*-oxide under the sp^3 arylation conditions results in exclusive reaction at the 2-methyl position (Eq. 6). Arylation of 4-picoline *N*-oxide under the sp^3 arylation protocol results in exclusive arylation of the sp^2 center adjacent to the *N*-oxide (Eq. 7). No product arising from arylation of the sp^3 center is observed (even though the sp^2 and sp^3 positions undergo deuterium exchange at a similar rate) (Eq. 5). Given that arylation only occurs adjacent to the *N*-oxide, it is plausible that *N*-oxide interactions with the palladium catalyst could play an important role in governing the selectivity of these reactions.

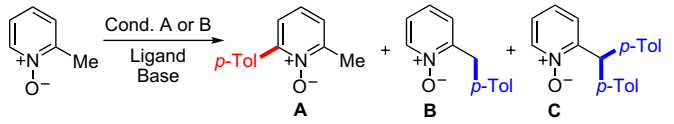
A series of experiments were also carried out to determine the role of the base in site selectivity (Table 4). Arylation of 2-picoline *N*-oxide with 4-bromotoluene under conditions similar to those used for sp^2 arylation (condition A) using K_2CO_3 as the base yields 56% of the sp^2 arylated product with complete sp^2 selectivity (entry 1). Under identical conditions, but with NaO^{t}Bu instead of K_2CO_3, a complete inversion of the sp^2/sp^3 selectivity is observed (entry 2). Similarly, under conditions analogous to those employed for sp^3 arylation (condition B) using NaO^{t}Bu as the base, a 94% yield of sp^3 arylated product is obtained with complete selectivity for the sp^3 position (entry 3). Again if the base is changed under otherwise identical conditions from NaO^{t}Bu to K_2CO_3, a complete inversion of the sp^2/sp^3 selectivity is observed (entry 4). These results indicate that it is the nature of the base that is of primary importance in determining sp^2/sp^3 site selectivity pointing toward its intimate involvement in the catalytic cycle.

A catalytic cycle for these transformations is proposed in Scheme 7. The active Pd(0) catalyst oxidatively inserts into the aryl halide bond to generate intermediate **13**. The next step, palladation of the *N*-oxide, determines site selectivity and is base dependant. With the strong base, NaO^{t}Bu, the most acidic sp^3 2-methyl position may be deprotonated and proceeds through a pathway similar to α-arylation of carbonyls to yield **15**.[14] K_2CO_3 is not a strong enough base to deprotonate the 2-methyl position, but it does allow for the six-membered transition state of a concerted metalation–deprotonation (CMD) pathway to activate the sp^2 position as depicted in Scheme 7, which gives rise to **14**. We and others have evaluated this



Scheme 6.

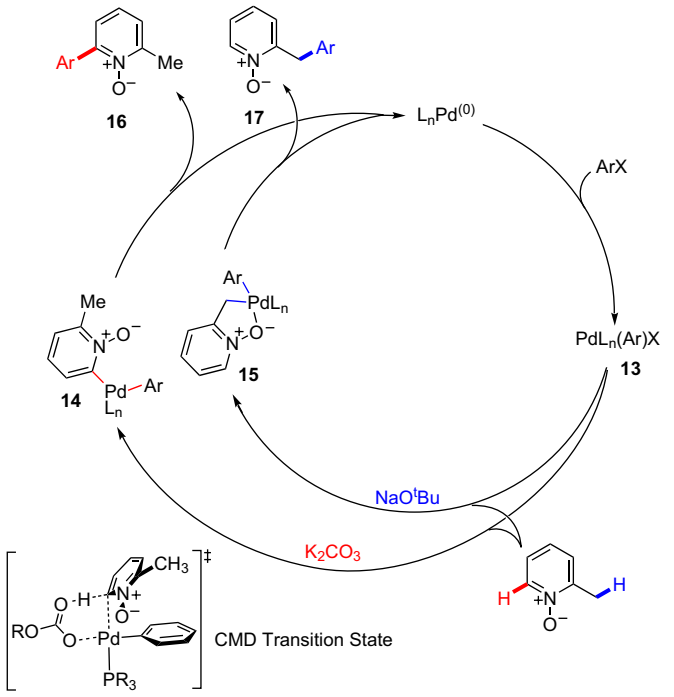
Table 4
Origin of site selectivity



Entry	Condition[a,b]	Base	Ratio A/B/C	Yield[c] (%)
1	A	K_2CO_3	1:0:0	56
2	A	NaO^{t}Bu	0:1:1.5	45
3	B	NaO^{t}Bu	0:20:1	94
4	B	K_2CO_3	1:0:0	2

[a] Condition A: 2-picoline *N*-oxide (2 equiv), 4-bromotoluene (1 equiv), $Pd(OAc)_2$ (0.05 equiv), P^{t}BuHBF$_4$ (0.06 equiv), base (1.5 equiv) in PhMe (0.15 M), 110 °C overnight.
[b] Condition B: 2-picoline *N*-oxide (1.5 equiv), 4-bromotoluene (1 equiv), Pd_2dba_3 (0.025 equiv), X-Phos (0.05 equiv), base (3 equiv) in PhMe (1 M), MW, 110 °C for 45 min.
[c] NMR yield using 1,3,5-trimethoxybenzene as standard.

pathway for the C–H activation of arenes.[15] Both intermediates **14** and **15** then undergo reductive elimination to form products **16** and **17**, respectively.



Scheme 7. Catalytic cycle for sp^2/sp^3 arylation.

3. Conclusion

In conclusion, we have developed completely site-selective arylation reactions on both sp^2 and sp^3 positions compatible with a broad range of azine *N*-oxides and aryl halides. The reactions are carried out in both a divergent and a sequential manner. The efficacy of sp^3 arylation is demonstrated by the rapid synthesis of the natural products papaverine and crykonisine in three steps. Mechanistic studies reveal the importance of the nature of the base for catalyst controlled site selectivity. These reactions should find use for the rapid functionalization of azine derivatives and the mechanistic insights should lead to investigations of similar reactivity to other substrate classes.

4. Experimental

4.1. General

Picoline *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 and stored in a dessicator and were 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. All reactions were performed in air-dried glassware. Coupling reactions were performed with regard for exclusion of ambient air. Microwave heating was performed using a CEM Discover Microwave (specific reaction conditions are described below). Analysis of crude reaction mixture 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 or Varian INOVA 500 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 were recorded using a Gallenkamp Melting Point Apparatus and are reported uncorrected.

4.2. sp^3 Direct arylation (Tables 1 and 2)

4.2.1. Procedure A: using microwave irradiation

All reactions were performed on 0.6 mmol scale: Pd_2dba_3 (0.025 equiv), X-Phos (0.05 equiv), NaO^{t}Bu (3 equiv), and azine *N*-oxide (1.5 equiv) are weighed to air and placed in a microwave tube with a magnetic stir bar (if the aryl halide is a solid, it is also added). The flask is capped with a rubber septum and purged with argon. The aryl halide (1 equiv) is then added via syringe followed by degassed (with argon) ACS grade toluene (0.5–1.0 M). The rubber septum is then replace by a microwave tube cap and the mixture is then placed in a CEM Discover microwave reactor at 110 °C for 30–45 min (conditions: max power: 200 W; T^o: 110 °C; max pressure: 250 psi). The reaction mixture is then diluted with 50 mL of DCM and filtered through Celite and then evaporated under reduced pressure. The residue is then loaded onto a silica gel column for chromatography typically using DCM/acetone/MeOH mixtures.

4.2.2. Procedure B: using conventional heating

All reactions were performed on 0.6 mmol scale: Pd_2dba_3 (0.025 equiv), Ru-Phos (0.1 equiv), NaO^{t}Bu (3 equiv), and azine *N*-oxide (2 equiv) are weighed to air and placed in a test tube with a magnetic stir bar (if the aryl halide is a solid, it is also added). The flask is capped with a rubber septum and purged with argon. The aryl halide (1 equiv) is then added via syringe followed by degassed (with argon) ACS grade toluene (0.3 M). The mixture is then placed in an oil bath and the heat source is set to 70 °C. Reaction mixture was left stirring at this temperature for 12–15 h (overnight, reaction times were not optimized). The reaction mixture is then diluted with 50 mL of DCM and filtered through Celite and then evaporated under reduced pressure. The residue is then loaded onto a silica gel column for chromatography typically using DCM/acetone/MeOH mixtures.

4.2.3. 2-(4-Methylbenzyl)pyridine 1-oxide (Table 1, entries 1–6)

Obtained in 89% yield as a yellow oil by following sp^3 direct arylation procedure A or B. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.35 (3H, s), 4.22 (2H, s), 6.92–6.95 (1H, m), 7.10–7.17 (6H, m), 8.28–8.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 21.1, 36.1,

123.4, 125.5, 125.7, 129.6, 129.6, 133.1, 136.7, 139.4, 152.3; IR (ν_{max}/cm^{-1}): 2922, 1436, 1245, 766; HRMS calculated for $C_{13}H_{13}NO$ (M^+) 199.0997, found: 199.1010; mp: 47–49 °C (Chloroform) R_f: 0.18 (1%MeOH, 15% Me_2CO, DCM).

4.2.4. 2-(2-Methylbenzyl)pyridine 1-oxide (Table 1, entry 7)

Obtained in 92% yield as a yellow oil by following sp^3 direct arylation procedure A. ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.20 (3H, s), 4.25 (2H, s), 6.71 (1H,d, J=7.5 Hz), 7.10–7.25 (6H, m), 8.33 (1H, d, J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 19.3, 34.4, 123.4, 125.0, 125.6, 126.5, 127.5, 130.6, 134.4, 137.2, 139.4, 151.3. There is a missing peak even with prolonged scans. IR (ν_{max}/cm^{-1}): 3019, 1489, 1435, 1244, 745; HRMS calculated for $C_{13}H_{13}NO$ (M^+) 199.0997, Found: 199.0987; R_f: 0.22 (1% MeOH, 20% Me_2CO, DCM).

4.2.5. 2-(3,5-Dimethylbenzyl)pyridine 1-oxide (Table 1, entry 8)

Obtained in 93% yield as a yellow oil by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.30 (6H, s), 4.20 (2H, s), 6.88–7.14 (6H, m), 8.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 21.3, 36.3, 123.4, 125.8, 127.5, 128.7, 136.1, 138.4, 139.5, 152.4. There is a missing peak even with prolonged scans. IR (ν_{max}/cm^{-1}): 2923, 1604, 1487, 1435, 1239, 848; HRMS calculated for $C_{14}H_{15}NO$ (M^+) 213.1154, found: 213.1175; R_f: 0.17 (1% MeOH, 20% Me_2CO, DCM).

4.2.6. 2-(Naphthalen-2-ylmethyl)pyridine 1-oxide (Table 1, entry 9)

Obtained in 72% yield as a yellow oil by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 4.44 (2H, s), 6.95 (1H, d, J=7.1 Hz), 7.05–7.17 (2H, m), 7.38 (1H, d, J=8.4 Hz), 7.44–7.50 (2H, m), 7.74 (1H, s), 7.79–7.84 (3H, m), 8.30 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 123.5, 125.6, 125.9, 126.3, 127.6, 127.7, 127.8, 128.4, 128.6, 128.8, 132.5, 133.6, 133.8, 139.5. There is a missing peak even with prolonged scans. IR (ν_{max}/cm^{-1}): 3054, 2927, 1487, 1434, 1241; HRMS calculated for $C_{16}H_{13}NO$ (M^+) 235.0997, found: 235.0987; R_f: 0.18 (1% MeOH, 20% Me_2CO, DCM).

4.2.7. 2-(2,6-Dimethylbenzyl)pyridine 1-oxide (Table 1, entries 10 and 11)

Obtained in 90% yield as a yellow oil by following sp^3 direct arylation procedure A except S-Phos was used instead of X-Phos. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.18 (6H, s), 4.26 (2H, s), 6.56 (1H, d, J=7.7 Hz), 7.07–7.18 (5H, m), 8.36 (1H, d, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS):20.0, 30.6, 123.3, 123.9, 125.7, 127.2, 128.4, 133.0, 137.5, 139.4, 150.5; IR (ν_{max}/cm^{-1}): 3072, 2921, 1488, 1433, 1242; HRMS calculated for $C_{14}H_{15}NO$ (M^+) 213.1154, found: 213.1155; R_f: 0.21 (1% MeOH, 20% Me_2CO, DCM).

4.2.8. 2-((1-Methyl-1H-indol-5-yl)methyl)pyridine 1-oxide (Table 1, entry 12)

Obtained in 90% yield as a yellow oil by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 3.79 (3H, s), 4.36 (2H, s), 6.45 (1H, d, J=2.9 Hz), 6.88 (1H, d, J=7.4 Hz), 7.04–7.12 (4H, m), 7.31 (1H, d, J=8.3 Hz), 7.52 (1H, s), 8.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 32.9, 36.5, 100.7, 109.6, 121.9, 123.1, 123.4, 125.6, 125.8, 126.8, 128.9, 129.4, 135.9, 139.2, 153.4; IR (ν_{max}/cm^{-1}): 3091, 1488, 1435, 1245, 763; HRMS calculated for $C_{15}H_{14}N_2O$ (M^+) 238.1106, found: 238.1116; R_f: 0.17 (1% MeOH, 20% Me_2CO, DCM).

4.2.9. 2-(4-Methoxybenzyl)pyridine 1-oxide (Table 1, entry 13)

Obtained in 72% yield as a white solid by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 3.81 (3H, s), 4.20 (2H, s), 6.88–6.91 (2H, m), 6.93–6.96 (1H, m), 7.10–7.16 (2H, m), 7.18–7.22 (2H, m), 8.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 35.7, 55.3, 114.3, 123.4, 125.5, 125.7, 128.2, 130.8, 139.4, 152.4, 158.7; IR (ν_{max}/cm^{-1}): 2931, 1512, 1436, 1247, 1031; HRMS calculated for $C_{13}H_{13}NO_2$ (M^+) 215.0946, found: 215.0948; mp: 94–96 °C (chloroform) R_f: 0.16 (1% MeOH, 20% Me_2CO, DCM).

4.2.10. 2-(4-Fluorobenzyl)pyridine 1-oxide (Table 1, entry 14)

Obtained in 72% yield as a yellow solid by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 4.24 (2H, s), 6.95–7.00 (1H, m), 7.01–7.06 (2H, m), 7.14–7.19 (2H, m), 7.23–7.28 (2H, m), 8.27–8.31 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 35.8, 115.7 (d, J=21.3 Hz), 123.8, 125.5, 125.7, 131.2 (d, J=8.1 Hz), 132.0 (d, J=3.3 Hz), 139.5, 151.7, 162.0 (d, J=245.4 Hz); IR (ν_{max}/cm^{-1}): 3075, 2928, 1508, 1222, 770; HRMS calculated for $C_{12}H_{10}FNO$ (M^+) 203.0746, found: 203.0753; mp: 79–81 °C (chloroform) R_f: 0.17 (1% MeOH, 20% Me_2CO, DCM).

4.2.11. 2-(3,5-Dimethoxybenzyl)-4-methylpyridine 1-oxide (Table 2, entry 1)

Obtained in 70% yield as a yellow solid by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.24 (3H, s), 3.75 (6H, s), 4.10 (2H, s), 6.38 (1H, t, J=2.3 Hz), 6.55 (2H, d, J=2.3 Hz), 7.02–7.09 (2H, m), 8.09 (1H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 20.1, 36.7, 55.5, 99.2, 108.3, 125.6, 127.4, 136.3, 139.2, 140.7, 150.9, 162.0; IR (ν_{max}/cm^{-1}): 2938, 1595. 1495, 1205, 1064; HRMS calculated for $C_{15}H_{17}NO_3$ (M^+) 259.1208, found: 259.1195; mp: 109–111 °C ($CHCl_3$); R_f: 0.21 (3% MeOH, 15% Me_2CO, DCM).

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

Obtained in 90% yield as a orange solid by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.24 (6H, s), 2.32 (3H, s), 4.36 (2H, s), 6.82 (1H, br s), 6.86 (2H, br s), 7.05 (2H, d, J=4.1 Hz), 8.19 (1H, d, J=3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 19.3, 21.3, 32.5, 122.8, 126.1, 127.4, 128.2, 135.9, 136.6, 137.5, 138.0, 150.4; IR (ν_{max}/cm^{-1}): 2915, 1603, 1422, 1248, 822; HRMS calculated for $C_{15}H_{17}NO$ (M^+) 227.1310, found: 227.1297; mp: 108–110 °C ($CHCl_3$); R_f: 0.16 (1.5% MeOH, 15% Me_2CO, DCM).

4.2.13. 3-Methyl-2-(4-methylbenzyl)pyridine 1-oxide (Table 2, entry 3)

Obtained in 90% yield as a yellow solid by following sp^3 direct arylation procedure B. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.28 (3H, s), 2.32 (3H, s), 4.38 (2H, s), 7.04–7.07 (4H, m), 7.17 (2H, d, J=7.84 Hz), 8.18 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 19.3, 21.0, 32.3, 122.8, 127.7, 128.3, 129.2, 133.7, 135.7, 136.0, 137.5, 150.6; IR (ν_{max}/cm^{-1}): 3049, 1429, 1250, 809; HRMS calculated for $C_{14}H_{15}NO$ (M^+) 213.1154, found: 213.1143; mp: 100–102 °C ($CHCl_3$); R_f: 0.18 (1.5% MeOH, 15% Me_2CO, DCM).

4.2.14. 2-(4-Methylbenzyl)quinoline 1-oxide (Table 2, entry 4)

Obtained in 73% yield as a yellow oil by following sp^3 direct arylation procedure A except 3 equiv of the *N*-oxide was used. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.35 (3H, s), 4.44 (2H, s), 7.06 (1H, d, J=8.7 Hz), 7.16 (2H, d, J=7.9 Hz), 7.22 (2H, d, J=8.0 Hz), 7.57–7.61 (2H, m), 7.75 (1H, ddd, J=7.2, 7.0, and 1.18 Hz), 7.80 (1H, d, J=8.1 Hz), 8.81 (1H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 21.1, 37.0, 119.8, 121.9, 125.1, 127.9, 128.0, 129.1, 129.6, 129.6, 130.4, 133.4, 136.6, 141.6. There is a missing peak even with prolonged scans. IR (ν_{max}/cm^{-1}): 2922, 1513, 1349, 1240, 807; HRMS calculated for $C_{17}H_{15}NO$ (M^+) 249.1154, found: 249.1151; R_f: 0.19 (1% MeOH, 1% Me_2CO, DCM).

4.2.15. 1-(4-Methylbenzyl)isoquinoline 2-oxide (Table 2, entry 5)

Obtained in 60% yield as a light yellow solid by following sp^3 direct arylation procedure A. ^1H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.26 (3H, s), 4.77 (2H, s), 7.05 (2H, d, J=7.8 Hz), 7.24 (2H, d,

J=8.0 Hz), 7.51–7.56 (2H, m), 7.59 (1H, ddd, J=7.0, 7.0, and 1.3 Hz), 7.75 (1H, d, J=7.9 Hz), 8.00 (1H, d, J=8.0 Hz), 8.22 (1H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 21.0, 31.3, 122.5, 124.0, 127.4, 128.1, 128.5, 128.9, 128.9, 129.3, 133.9, 136.1, 136.9 (br), 147.1; 1 overlapping signal as one peak is missing even with prolonged scans. IR (ν_{max}/cm^{-1}): 3051, 1513, 1336, 1219, 749; HRMS calculated for $C_{17}H_{15}NO$ (M^+) 249.1154, found: 249.1133; mp: 170–172 °C ($CHCl_3$); R_f: 0.20 (1% MeOH, 15% Me_2CO, DCM).

4.2.16. 3-Methyl-2-(4-methylbenzyl)pyrazine 1-oxide (Table 2, entry 6)

Obtained in 79% yield as a yellow oil by following sp^3 direct arylation procedure A. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.30 (3H, s), 2.60 (3H, s), 4.31 (2H, s), 7.08 (2H, d, J=8.1 Hz), 7.14 (2H, d, J=8.1 Hz), 8.04 (1H, d, J=4.3 Hz), 8.21 (1H, d, J=4.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.0, 22.4, 31.4, 128.2, 129.4, 132.0, 132.6, 136.6, 143.6, 145.2, 157.0; IR (ν_{max}/cm^{-1}): 2923, 1513, 1423, 1251, 791; HRMS calculated for $C_{15}H_{17}NO$ (M^+) 214.1166, found: 214.1166; mp: 95–97 °C ($CHCl_3$); R_f: 0.20 (2% MeOH, 10% Me_2CO, DCM).

4.2.17. 7-p-Tolyl-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide (Table 2, entry 7)

This compound was obtained in 64% yield as a light yellow oil by following sp^3 direct arylation procedure A except S-Phos and 3 equiv of the N-oxide was used. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.14–2.22 (1H, m), 2.28 (3H, s), 2.59–2.69 (1H, m), 2.99 (1H, ddd, J=16.4, 9.2, and 2.1 Hz), 3.15–3.24 (1H, m), 4.71 (1H, dd, J=9.2 and 1.3 Hz), 6.69–7.19 (6H, m), 8.01 (1H, d, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 21.0, 30.3, 32.9, 47.0, 122.2, 124.5, 127.0, 129.3, 136.2, 138.0, 138.4, 142.5, 154.1; IR (ν_{max}/cm^{-1}): 3083, 2843, 1603, 1444, 1257, 1013; HRMS calculated for $C_{15}H_{15}NO$ (M^+) 225.1159, found: 225.1140; R_f: 0.10 (1% MeOH, 10% Me_2CO, DCM).

4.3. sp^2 Direct arylation (Table 3)

$Pd(OAc)_2$ (5 mol %), $P^tBu_3 \cdot HBF_4$ (6 mol %), potassium carbonate powder (K_2CO_3, 1.5 equiv), aryl halide (1 equiv), and azine N-oxide (1.1-4 equiv) are weighed to air and placed inside the flask. The flask is then fitted with a reflux condenser, which is capped with a rubber septum. The whole setup is then evacuated under vacuum and refilled with argon four times. Toluene (0.15 M) is then added under a steady flow of argon. After addition, the reaction mixture is immersed in the oil bath. Stirring is commenced and the heating source is turned on (set to 125 °C). The reaction mixture is left stirring for 12–18 h (overnight), then allowed to cool, diluted with DCM, and filtered over Celite. The residues are then purified using silica gel chromatography.

4.3.1. 2-Methyl-6-p-tolylpyridine 1-oxide (Table 3, entries 1 and 2)

Obtained in 54% yield as a tan solid by following the general sp^2 direct arylation procedure. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K, TMS): 2.41 (3H, s), 2.57 (3H, s), 7.18 (1H, t, J=7.8 Hz), 7.22 (1H, dd, J=7.8 and 1.9 Hz), 7.26–7.31 (3H, m), 7.70 (2H, d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 18.7, 21.4, 124.6, 124.8 (br), 128.8, 129.3, 130.5, 139.3, 149.5, 149.8; 1 overlapping signal as one peak is missing even with prolonged scans. IR (ν_{max}/cm^{-1}): 3040, 1729, 1374, 1225, 757; HRMS calculated for $C_{13}H_{13}NO$ (M^+) 199.0997, found: 199.0982; mp: 102–104 °C ($CHCl_3$) R_f: 0.21 (2% MeOH, 10% Me_2CO, DCM).

4.3.2. 3-Cyano-6-methyl-2-p-tolylpyridine 1-oxide (Table 3, entry 3)

Obtained in 74% yield as a white solid by following the general sp^2 direct arylation procedure. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K, TMS): 2.42 (3H, s), 2.59 (3H, s), 7.33–7.36 (3H, m), 7.47 (1H, d, J=8.1 Hz), 7.53 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 19.0, 21.6, 110.9, 115.4, 125.1, 126.7, 127.4, 129.3, 129.6, 141.0, 152.5, 154.6; IR (ν_{max}/cm^{-1}): 2919, 2231, 1348, 1269, 815; HRMS calculated for $C_{14}H_{12}N_2O$ (M^+) 224.0950, found: 224.0943; mp: 137–139 °C (CH_2Cl_2); R_f: 0.20 (1% MeOH, 5% Me_2CO, DCM).

4.3.3. 2-(2-Methylbenzyl)-6-p-tolylpyridine 1-oxide (Table 3, entry 4 and Scheme 2)

Obtained in 77% yield as a yellow solid by following the general sp^2 direct arylation procedure except using 3 equiv of the N-oxide. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.23 (3H, s), 2.41 (3H, s), 4.29 (2H, s), 6.63 (1H, dd, J=7.1 and 2.1 Hz), 7.10 (1H, t, J=7.8 Hz), 7.19–7.26 (4H, m), 7.27–7.31 (3H, m), 7.73 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 19.4, 21.4, 35.0, 123.4, 124.6, 124.7, 126.5, 127.4, 128.8, 129.4, 130.4, 130.6, 130.7, 135.1, 137.3, 139.4, 149.4, 151.9; IR (ν_{max}/cm^{-1}): 3019, 2921, 1479, 1378, 1254, 770; HRMS calculated for $C_{20}H_{19}NO$ (M^+) 289.1467, found: 289.1445; mp: 99–100 °C ($CHCl_3$) R_f: 0.2 (20% EtOAc, petroleum ether).

4.3.4. 2,3-Dimethyl-6-p-tolylpyrazine 1-oxide (Table 3, entry 5)

Obtained in 89% yield as a light yellow solid by following the general sp^2 direct arylation procedure. Spectral data correspond to that previously described in the literature.[16]

4.3.5. 3-Methyl-1-p-tolylisoquinoline 2-oxide (Table 3, entry 6)

Obtained in 98% yield as a white solid by following the general sp^2 direct arylation procedure except using 1.1 equiv of the N-oxide. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K, TMS): 2.47 (3H, s), 2.68 (3H, s), 7.37–7.41 (5H, m), 7.44 (1H, d, J=8.3 Hz), 7.50 (1H, td, J=7.3 and 1.2 Hz), 7.67 (1H, s), 7.72 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 18.3, 21.5, 122.2, 125.6, 126.0, 127.7, 127.9, 128.5, 128.7, 128.9, 129.4, 130.0, 139.0, 146.2, 146.4; IR (ν_{max}/cm^{-1}): 3050, 1329, 1292, 1212, 1109, 811; HRMS calculated for $C_{17}H_{15}NO$ (M^+) 249.1154, found: 249.1146; mp: 168–170 °C ($CHCl_3$); R_f: 0.20 (1.5% MeOH, 8.5% Me_2CO, DCM).

4.3.6. 6-(4-Methoxyphenyl)-2,3-dimethylpyrazine 1-oxide (Table 3, entry 7)

This compound was obtained in 86% yield as a light yellow solid by following the general sp^2 direct arylation procedure. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.53 (3H, s), 2.61 (3H, s), 3.86 (3H, s), 7.01 (2H, d, J=8.6 Hz), 7.75 (2H, d, J=8.7 Hz), 8.36 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 13.5, 22.5, 55.4, 113.9, 122.2, 130.8, 141.7, 142.8, 143.1, 153.2, 160.8; IR (ν_{max}/cm^{-1}): 3004, 2873, 1610, 1467, 1302, 1251, 832; HRMS calculated for $C_{13}H_{14}N_2O_2$ (M^+) 230.1055, found: 230.1042; mp: 104–106 °C (CH_2Cl_2); R_f: 0.51 (2% MeOH, 8% Me_2CO, DCM).

4.3.7. 3-Cyano-6-methyl-2-(4-(trifluoromethyl)phenyl)pyridine 1-oxide (Table 3, entry 8)

This compound was obtained in 48% yield as a clear oil by following the general sp^2 direct arylation procedure. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.61 (3H, s), 7.43 (1H, d, J=8.1 Hz), 7.53 (1H, d, J=8.1 Hz), 7.77 (2H, d, J=8.4 Hz), 7.82 (2H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 18.9, 111.0, 114.8, 125.7 (q, J=3.7 Hz), 126.0, 127.5, 130.4, 132.4, 132.7, 133.2, 150.8, 155.0; IR (ν_{max}/cm^{-1}): 3038, 2921, 1353, 1325, 1169, 1135, 1065, 839; HRMS calculated for $C_{14}H_9N_2O_1F_3$ (M^+) 278.0667, found: 278.0672; R_f: 0.61 (30% Me_2CO, DCM).

4.3.8. 3-Cyano-2-(4-methoxyphenyl)-6-methylpyridine 1-oxide (Table 3, entry 9)

This compound was obtained in 73% yield as a light yellow solid by following the general sp^2 direct arylation procedure. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.59 (3H, s), 3.88 (3H, s), 7.04 (2H, d, J=8.9 Hz), 7.33 (1H, d, J=8.1 Hz), 7.47 (1H, d, J=8.1 Hz), 7.63 (2H, d,

J=8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 19.2, 55.5, 110.8, 114.1, 115.7, 121.7, 124.9, 127.7, 131.6, 152.3, 154.7, 161.5; IR (ν_{max}/cm^{-1}): 2912, 2235, 1614, 1272, 1260, 1017; HRMS calculated for $C_{14}H_{12}N_2O_2$ (M^+) 240.0899, found: 240.08825; mp: 193–195 °C (CH_2Cl_2); R_f: 0.14 (1% MeOH, 3% Me_2CO, DCM).

4.4. Natural product synthesis (Scheme 3)

4.4.1. 6,7-Dimethoxy-1-methylisoquinoline 2-oxide (**7**)

Prepared by a method adopted from Sharpless et al.[12] A mixture of 6,7-dimethoxy-1-methylisoquinoline (1 g, 4.9 mmol) and $MeReO_3$ (60 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was treated with 4 mL of 50% aqueous H_2O_2 and stirred for 15 h at 24 °C. The biphasic reaction mixture was then treated with a catalytic amount of MnO_2 and stirred until oxygen evolution ceased. Following phase separation, the water layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and flashed over silica gel using 5% MeOH/10% Me_2CO/CH_2Cl_2 to give 753 mg (70%) of a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 2.87 (3H, s), 4.02 (3H, s), 4.05 (3H, s), 7.04 (1H, s), 7.13 (1H, s), 7.39 (1H, d, J=7.0 Hz), 8.13 (1H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 13.2, 56.1, 56.2, 102.8, 106.0, 120.3 124.7, 125.2, 135.0, 143.8, 151.2, 151.5; IR (ν_{max}/cm^{-1}): 2842, 1619, 1517, 1433, 1270, 1201, 1058, 805; HRMS calculated for $C_{12}H_{13}NO_3$ (M^+) 219.0895, found: 219.0876; mp: 84–86 °C (CH_2Cl_2) R_f: 0.18 (5% MeOH, 10% Me_2CO, DCM).

4.4.2. 1-(4-(Benzyloxy)benzyl)-6,7-dimethoxyisoquinoline 2-oxide (**8**)

This compound was obtained in 55% yield as a brown solid using the general sp^3 arylation procedure except Ru-Phos was used in place of X-Phos as the ligand. ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 3.93 (3H, s), 3.98 (3H, s), 4.73 (2H, s), 4.99 (2H, s), 6.87 (2H, d, J=8.6 Hz), 7.02 (1H, s), 7.18 (1H, s), 7.26–7.41 (8H, m), 8.15 (1H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 31.3, 56.0, 56.1, 70.0, 103.0, 106.0, 115.1, 120.9, 124.7, 125.5, 127.4, 127.9, 128.5, 129.6, 129.7, 135.2, 137.0, 145.8, 151.1, 151.6, 157.5; IR (ν_{max}/cm^{-1}): 3036, 2932, 1612, 1267, 1235, 803; HRMS calculated for $C_{25}H_{23}NO_4$ (M^+) 401.1627, found: 401.1643; mp: 74–77 °C; R_f: 0.31 (5% MeOH, 10% Me_2CO, DCM).

4.4.3. 4-((6,7-Dimethoxyisoquinolin-1-yl)methyl)phenol (**9**)

A mixture of **8** (60 mg, 0.15 mmol) and Pd/C (10%, 2 mg) was stirred in MeOH (1 mL) under a hydrogen atmosphere (1 atm) for 72 h at 24 °C. The reaction mixture was then filtered, concentrated, and flashed over silica gel using 20–30% Me_2CO/CH_2Cl_2 to give 38 mg (87%) of a light yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6, 293 K, TMS): 3.86 (3H, s), 3.89 (3H, s), 4.42 (2H, s), 6.63 (2H, d, J=8.5 Hz), 7.11 (2H, d, J=8.5 Hz), 7.31 (1H, s), 7.47 (1H, s), 7.52 (1H, d, J=5.6 Hz), 8.24 (1H, d, J=5.6 Hz), 9.16 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6, 293 K, TMS): 40.3, 55.5, 55.6, 104.2, 105.5, 115.0, 118.2, 121.9, 129.4, 129.8, 132.7, 140.4, 149.4, 152.0, 155.4, 158.1; IR (ν_{max}/cm^{-1}): 2923, 1595, 1233, 1157, 835; HRMS calculated for $C_{18}H_{17}NO_3$ (M^+) 295.1208, found: 295.1181; R_f: 0.38 (30% Me_2CO, DCM).

4.4.4. 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline 2-oxide (**10**)

This compound was obtained in 45% yield as a brown solid using the general sp^3 arylation procedure except Ru-Phos was used in place of X-Phos as the ligand. ^{1}H NMR (400 MHz, DMSO-d_6, 293 K): 3.66 (3H, s), 3.68 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 4.66 (2H, s), 6.79 (1H, d, J=8.2 Hz), 6.84 (1H, dd, J=8.2, 1.5 Hz), 7.15 (1H, d, J=1.5 Hz), 7.37 (1H, s), 7.39 (1H, s), 7.66 (1H, d, J=7.0 Hz), 8.12 (1H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 293 K): 30.2, 55.3, 55.4, 55.7, 55.8, 102.9, 106.5, 111.9, 112.7, 115.1, 120.3, 121.2, 124.0, 124.5, 130.6, 134.7, 147.3, 148.5, 150.4, 151.2; IR (ν_{max}/cm^{-1}): 2933, 1517, 1265, 1026, 806; HRMS calculated for $C_{20}H_{21}NO_5$ (M^+) 355.1420, found: 355.1415; R_f: 0.33 (5% MeOH, 10% Me_2CO, DCM).

4.4.5. 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (**11**)

N-Oxide reduction was carried out using a procedure described by Ohta et al.[17] The *N*-oxide (30 mg, 0.084 mmol) is dissolved in THF (1.3 mL). To this mixture is then added saturated NH_4Cl solution (1.3 mL) and zinc dust (55.2 mg, 0.844 mmol). This mixture is then stirred for 1 h. The deposit is then collected by filtration on Celite and washed with Et_2O. The organic layer is then separated and the aqueous layer is extracted with Et_2O. The organics are combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel column chromatography using 3% MeOH/7% Me_2CO/DCM gave papaverine in 94% yield. Spectral data corresponds to that previously described in the literature.[13a]

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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.2008.12.004.

References and notes

1. For general reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35; (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173; (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200; (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.
2. For reviews on C–H activation, see: (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483; (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507; (c) Ritleng, V.; Silin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731; (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633; (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67; (f) Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979; (g) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987.
3. For reviews, see Refs. 1c and 1d. For recent examples, see: (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897; (b) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835; (c) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700; (d) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996; (e) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449; (f) Turner, G. L.; Morris, J. A.; Greany, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996; (g) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543; (h) Požgan, F.; Rogerm, J.; Doucet, H. *ChemSusChem* **2008**, *1*, 404.
4. (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467; (b) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111.
5. Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301.
6. Lane, B. S.; Brown, M. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.
7. (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125; (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528; (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.
8. (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *317*, 1172; (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.
9. Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.
10. (a) Bentley, K. W. In *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic: Amsterdam, 1998; pp 107–122; (b) Bentley, K. W. *Nat. Prod. Rep.* **2005**, *22*, 249; (c) Isolation of papaverine: Merck, G. *Ann.* **1848**, *66*, 125.
11. (a) Sar, A.; Saryar, G. *Pharmazie* **2000**, *55*, 471; (b) Lin, F. W.; Wang, J. J.; Wu, T. S. *Chem. Pharm. Bull.* **2002**, *50*, 157.
12. Coperet, C.; Adolfsson, H.; Khovong, T. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.
13. For previous syntheses of papaverine, see: (a) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558; (b) Pictet, A.; Finkelstein, M. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 1979; (c) Rosenmund, K. W.; Nothnagel, M.; Riesenfeldt, H. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 392; (d) Mannich, C.; Walther, O. *Arch. Pharm.*

1927, *265*, 1; (e) Galat, A. *J. Am. Chem. Soc.* **1951**, *73*, 3654; (f) Wahl, H. *Bull. Soc. Chim. Fr.* **1950**, *17*, 680; (g) Popp, F. D.; McEwen, W. E. *J. Am. Chem. Soc.* **1957**, *79*, 3773; (h) Hirsenkorn, R. *Tetrahedron Lett.* **1991**, *32*, 1775.
14. (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360; (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
15. (a) Ozdemir, I.; Demir, S.; Cetinkaya, B.; Gourlauoen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156; (b) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299; (c) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Polleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210; (d) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880; (e) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754; (f) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066; (g) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848; (h) Pascual, S.; Mendoza, P.; dBraga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021.
16. Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781.
17. Aoyagi, Y.; Tomomitsu, A.; Ohta, A. *Synthesis* **1997**, *8*, 891.