Deoxygenation of Pyridine *N*-Oxides by Palladium-Catalysed Transfer Oxidation of Trialkylamines

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Abstract: A convenient and chemoselective method for deoxygenation of pyridine *N*-oxide derivatives by transfer oxidation of triethylamine-catalysed by [$Pd(OAc)_2$]/dppf is described.

Key words: deoxygenation, homogeneous catalysis, palladium, pyridine *N*-oxides, ligand effects

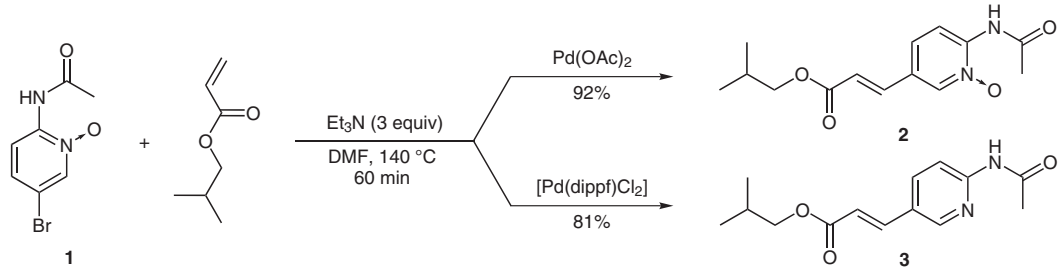
The reduction of pyridine *N*-oxides to the parent pyridines is an extensively used process due to the special reactivity of pyridine *N*-oxides that is utilised in the synthesis of functionalised pyridine derivatives. There has been a considerable amount of research devoted to developing improved procedures for deoxygenation.[1] The majority of the more recent methods do show some chemoselectivity but use stoichiometric amounts of transition-metal or main-group reagents to effect the process. A well-established catalytic method is the Pd/C catalysed deoxygenation using hydrogen or a formate salt as the reductant. While this is an important method, the Pd/H_2 system can result in reduction or cleavage of other functional groups such as alkenes, carbonyl, nitro, and benzyl-protected species.[2] In the course of our work on designing libraries of complementary additives to tune the behaviour of asymmetric catalysts, we made use of a Pd-catalysed cross-coupling of bromo-pyridine *N*-oxides **1** in order to prepare a family of pyridinone additives.[3] Using typical Heck catalysts based on palladacycles or $Pd(OAc)_2$, good yields of Heck products were readily obtained after 30–60 minutes of microwave heating. However, when the catalyst system was changed to [$Pd(dippf)Cl_2$] (dippf = 1,1′-bis(diisopropylphosphino)ferrocene), a surprising tandem Heck–deoxygenation reaction occurred (Scheme 1).[4]

The deoxygenation utilised catalytic quantities of palladium, and presumably involved transfer of oxygen to the triethylamine used as base. A process using only triethylamine as reagent seemed to hold potential as a catalytic and genuinely chemoselective reduction process. In this letter, we report our investigations into this novel palladium-catalysed reaction.

To establish optimum conditions for the new deoxygenation reaction, we chose acetamido-pyridine *N*-oxide **4** as a model substrate, and initially carried out the reaction using microwave heating in acetonitrile. The results are shown in Table 1.[5] It can be seen that triethylamine (3 equiv) seems the most appropriate amine reagent (no conversion was observed without amine present), and that the presence of a ligand, palladium, and base are all required for the reaction to proceed (entries 9–11). Polar solvents, such acetonitrile or DMF are preferred, but the reactions also proceed in less polar solvents such as toluene, but at a slower rate (entry 14).

Palladium(II) acetate provided almost full conversion to the parent pyridine when used with dppf (1,1′-bis(diphenylphosphino)ferrocene) as ligand (Table 1, entry 8). Other Pd precursors such as palladium(II) trifluoroacetate and palladium(0) dibenzylidenacetone also proved to be effective (entries 20 and 21), but slightly lower conversions were obtained.

Using $Pd(OAc)_2$ as catalyst precursor, the deoxygenation of **4** was then studied in the presence of a series of phosphines. A striking ligand effect was observed, only diphosphinoferrocene-derived ligands (dppf and dippf) were active in the reaction. Monophosphines such as



Scheme 1 Tandem Heck coupling–deoxygenation of bromide **1** with isobutyl acrylate

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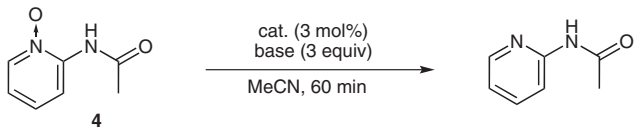
Table 1 Optimisation Study for the Palladium-Catalysed Deoxygenation Reaction



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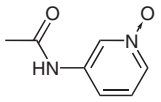
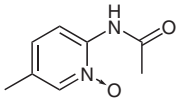
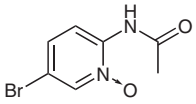
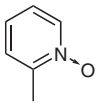
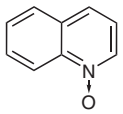
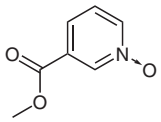
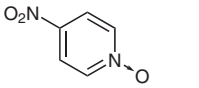
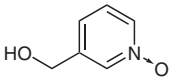
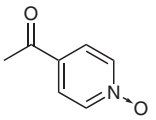
Entry	Catalyst	Base	Temp (°C)	Yield (%)[a]
1	[Pd(dippf)Cl_2]	Et_3N	140	34
2	[Pd(dippf)Cl_2]	Et_3N	150	52
3	[Pd(dippf)Cl_2]	Et_3N	160	95 (88)
4	[Pd(dippf)Cl_2]	DABCO	160	41
5	[Pd(dippf)Cl_2]	pyrrolidine	150	43
6	$Pd(OAc)_2$, dippf	Et_3N	150	91 (79)
7	$Pd(OAc)_2$, dippf	DABCO	160	94 (84)
8	$Pd(OAc)_2$, dppf	Et_3N	150	96 (89)
9	None	Et_3N	150	0
10	$Pd(OAc)_2$	Et_3N	140	0
11	dppf	Et_3N	140	0
12[b]	$Pd(OAc)_2$, dppf	Et_3N	150	96
13	$Pd(OAc)_2$, dppf	Et_3N	140	77
14[c]	$Pd(OAc)_2$, dppf	Et_3N	140	31
15	$Pd(OAc)_2$, Ph_3P	Et_3N	150	0
16	$Pd(OAc)_2$, MeCgPPh	Et_3N	150	0
17	$Pd(OAc)_2$, dppe	Et_3N	150	0
18	$Pd(OAc)_2$, BINAP	Et_3N	150	0
19	$Pd(OAc)_2$, Xantphos	Et_3N	150	0
20	$Pd(TFAc)_2$, dppf	Et_3N	150	75
21	$Pd(dba)_2$, dppf	Et_3N	150	88
22[d]	$Pd(OAc)_2$, dppf	Et_3N	140	96 (88)
23[d]	$Pd(OAc)_2$, dppf	Et_3N	110	96
24[d]	$Pd(OAc)_2$, dppf	Et_3N	85	39

[a] Determined by ^{1}H NMR analysis, (yields of pyridines after chromatographic purification are in parentheses). Reactions were carried out using microwave heating unless indicated.
[b] Reaction time: 45 min.
[c] Toluene.
[d] Reactions carried out in a sealed tube heating in an oil bath for 17 h.

Ph_3P, or phenylphosphatrioxaadamantane (Table 1, entries 15 and 16) or diphosphines with different electronic and steric properties: dppe, BINAP, and Xantphos (entries 17–19) were all ineffective ligands for the reaction. The reaction also readily takes place using conventional heating in a sealed tube at the lower temperature of 110 °C (entry 23) but when the reaction was carried out at 85 °C (entry 24), only 39% of product was obtained. These results show that although the high temperatures used in the microwave process are not required, the temperature does need to be above 85 °C to get good conversion within a reasonable reaction time.

Table 2 Generality and Functional Group Tolerance of the Palladium-Catalysed Transfer Oxidation Process

Entry	Substrate	Catalyst	Temp (°C)	Yield (%)[a]
1		$Pd(OAc)_2$, dppf	150	80 (64)
2		[Pd(dippf)Cl_2]	150	96 (95)
3		[Pd(dippf)Cl_2]	140	96 (87)
4		$Pd(OAc)_2$, dppf	160	94
5		$Pd(OAc)_2$, dppf	160	99 (88)
6[b]		$Pd(OAc)_2$, dppf	160	99 (91)
7		[Pd(dippf)Cl_2]	160	86 (70)
8		$Pd(OAc)_2$, dppf	150	80[c] (66)
9		$Pd(OAc)_2$, dppf	150	70 (64)

[a] Determined by ^{1}H NMR analysis, (yields of pure pyridines obtained after chromatography are in parentheses). Reactions were carried out using catalyst (3 mol%; and ligand), Et_3N (3 equiv) in MeCN for 60 min using microwave heating
[b] A similar yield was obtained (99% conversion, 93% yield) when the reaction was carried out in a sealed-tube heating in an oil bath at 110 °C for 17 h.
[c] Nicotinaldehyde (20%) formed as a separable byproduct.

The generality and functional group tolerance of this palladium-catalysed transfer oxidation process was then investigated. The reactions were carried out using the optimum conditions found for substrate **4**: $Pd(OAc)_2$, dppf, acetonitrile, and Et_3N as transfer oxidation reagent. The results are summarised in Table 2. In all cases, the parent pyridine derivatives were obtained in good to ex-

cellent yields without reduction or cleavage of other functional groups. The reactions proceeded smoothly in the presence of amido (entries 1–3), nitro (entry 7), ester (entry 6), hydroxy (entry 8), carbonyl (entry 9), and Br (entry 3) groups, and the position in the pyridine ring of the substituent does not seem to have any influence in the process. When 3-pyridylcarbinol *N*-oxide was deoxygenated under the reaction conditions (entry 8), the parent pyridine was obtained together with (readily separated) nicotinaldehyde as a byproduct. This is probably due to a similar process as the one recently described in the literature for deoxygenation of *N*-heteroarene *N*-oxides using 1-phenylethanol as solvent.[1j] 4-Acetyl pyridine *N*-oxide (entry 9) also proved to be stable under the reaction conditions affording the corresponding deoxygenated pyridine.

Overall high yields using microwave heating in just 60 minutes were obtained. Reactivity for difficult substrates was improved by increasing the reaction temperature from 140 to 160 °C, and both preformed Pd-phosphinoferrocene complex and in situ formed catalyst can effectively perform in the reaction.

In summary, the fortuitous observation of an unexpected product in the Pd/dippf-catalysed Heck coupling of a pyridine *N*-oxide has led to a convenient procedure for deoxygenation of pyridine *N*-oxides that is characterised by being catalytic in palladium and being highly tolerant of sensitive functional groups.

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(4) **Synthesis of Pyridine *N*-Oxide 2 (Scheme 1)**
Aryl bromide **1** (67 mg, 0.29 mmol), $Pd(OAc)_2$ (1.9 mg, 3 mol%), and a stirring bead were placed in a 5 mL microwave process vial that was placed under a nitrogen atmosphere before the addition of dry DMF (4 mL), Et_3N (0.12 mL, 0.87 mmol), and isobutyl acrylate (0.13 mL, 0.87 mmol). The reaction mixture was heated by microwave irradiation at 140 °C for 60 min. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The crude mixture was purified by chromatography on a SiO_2 column using EtOAc–MeOH (8:1) as eluent to give the corresponding coupling product **2** (74 mg, 0.27 mmol, 92%) as a yellow solid; mp 149–151 °C. IR (KBr): 3065, 2959, 2876, 1718, 1692, 1639, 1605, 1569, 1525, 1399 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.7 Hz, 6 H, CH_3), 1.94 (m, 1 H, CH), 2.26 (s, 3 H, CH_3), 3.94 (d, *J* = 6.7 Hz, 2 H, CH_2), 6.38 (d, *J* = 16.0 Hz, 1 H, =CH), 7.41 (d, *J* = 16.0 Hz, 1 H, =CH), 7.43 (d, *J* = 8.8 Hz, 1 H, ArCH), 8.33 (s, 1 H, ArCH), 8.39 (d, *J* = 8.8 Hz, 1 H, ArCH), 9.98 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 25.4, 28.2, 71.5, 114.7, 121.6, 126.8, 127.0, 136.6, 138.5, 144.9, 166.3, 169.3. MS (TOF-ES): *m/z* (%) = 301.1 (100) $[M + Na]^+$. HRMS (TOF-ES): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O_4Na$: 301.1164; found: 301.1173.
Synthesis of Compound 3 (Scheme 1)
To aryl bromide **1** (134 mg, 0.58 mmol) and $[Pd(dippf)Cl_2]$ (10.4 mg, 3 mol%) in a 5 mL microwave process vial were added dry DMF (4 mL), Et_3N (0.24 mL, 1.74 mmol), and isobutyl acrylate (0.35 mL, 1.74 mmol). The reaction mixture was heated by microwave irradiation at 140 °C for 60 min. After being cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. The crude mixture was purified by chromatography on a SiO_2 column using EtOAc–hexane (3:1) as eluent to give the corresponding coupling product **3** (130 mg, 0.47 mmol, 81%) as a white solid; mp 112–114 °C. IR (KBr): 3245, 3095, 2959, 2876, 1720, 1687, 1641, 1604, 1586, 1542, 1369 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.7 Hz, 6 H, CH_3), 1.94 (m, 1 H, CH), 2.17 (s, 3 H, CH_3), 3.93 (d, *J* = 6.7 Hz, 2 H, CH_2), 6.38 (d, *J* = 16.0 Hz, 1 H, =CH), 7.56 (d, *J* = 16.0 Hz, 1 H, =CH), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1 H, ArCH), 8.19 (d, *J* = 8.7 Hz, 1 H, ArCH), 8.31 (d, *J* = 2.3 Hz, 1 H, ArCH), 8.58 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 24.8, 27.8, 70.8, 113.9, 118.7, 126.5, 136.6, 140.3, 148.2, 152.5, 166.7, 168.9. MS (TOF-ES): *m/z* (%) = 263.1 (14) $[M + H]^+$, 285.0(100) $[M + Na]^+$. HRMS (TOF-ES): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O_3Na$: 285.1215; found: 285.1206.

(5) **General Procedure for the Deoxygenation of Pyridine *N*-Oxides**

Pyridine *N*-oxide (0.29 mmol), $Pd(OAc)_2$ (1.9 mg, 3 mol%), dppf (4.8 mg, 3 mol%), and a stirring bead were placed in a 5 mL microwave process vial that was then put under a nitrogen atmosphere. Dry MeCN (2.5 mL) and Et_3N (0.12 mL, 0.87 mmol) were then added by syringe. The reaction mixture was heated by microwave irradiation at the temperature and time indicated in Tables 1 and 2. After NMR analysis, the solvent was concentrated under reduced pressure. The crude mixture was purified by chromatography on SiO_2 using EtOAc as eluent to afford the corresponding deoxygenated products. The spectral data for the isolated material was in accord with the literature data, and authentic samples.