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Catalytic deoxygenation of pyridine N-oxides with N-fused porphyrin rhenium complexes

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Abstract

Deoxygenation reactions of pyridine N-oxide derivatives catalyzed by N-fused porphyrin rhenium(VII) trioxo complexes are developed, affording the corresponding pyridine derivatives in quantitative yields with excellent turnover numbers up to 340,000.

In recent years, transition-metal-catalyzed site-selective atom transfer reactions have gained considerable attention.[1,2] Among atom transfer reactions, deoxygenation reactions of heteroaromatic N-oxides are particularly important in the preparation of heterocyclic compounds, which are indispensable in the field of pharmacology and coordination chemistry.[3–5] While various equimolar deoxygenation reactions have been reported,[6–12] the number of metal-catalyzed deoxygenation reactions is quite small and they still have some limitation for the substrates or efficiency.[13–16] Hence, the development of alternative methods is awaited.

We have recently been interested in N-fused porphyrinato (NFP) ligands, which are isoelectronic with cyclopentadienyl ligands.[17] The rhenium complexes bearing various NFP ligands were successfully synthesized and their excellent stability as well as electronic flexibility was illustrated, which implies promising application to catalysts.[18] This time we have developed new catalysts, rhenium(VII) trioxo complexes bearing NFP ligands [Re(NFP)O_3],[18b] for the deoxygenation reactions of pyridine N-oxides, which afford the parent pyridine derivatives in good to excellent yields. The catalysts can be synthesized in only three steps from pyrrole and aryl aldehyde, and turnover numbers (TONs) reached up to 340,000. Notably, this is the first example of catalytic reactions by NFP metal complexes.[19]

The reaction procedures were simple. To a solution of a mixture of pyridine N-oxide and a catalyst, PPh_3 was added at room temperature in air. After stirring for several hours, the reaction mixture was directly subjected to silica gel column chromatography, affording the deoxygenated product in pure form. An inert atmosphere was not required at all. Reagent grade solvent could be used as received; it did not cause the decomposition of the catalyst. When 4-phenylpyridine N-oxide was treated with 1 equiv of PPh_3 in the presence of 1 mol % of N-fused tetraphenylporphyrin rhenium(VII) trioxide (Re(NFTPP)O_3) at 23 °C, the reaction proceeded smoothly to give 4-phenylpyridine in quantitative yield (Scheme 1). Practically all of PPh_3 was consumed to afford $O{=}PPh_3$ after the reaction. Essentially the same results were obtained with or without protection from air and sunlight. In both cases, a considerable portion of the catalyst remained unchanged after the reaction.

The substituent effect of the catalysts was examined (Table 1). The catalysts were prepared according to the reported procedures.[18b] Introduction of the electron-donating group (entries 2, 5, and 7), the electron-withdrawing group (entries 3 and 8), or the bulky group (entry 4) into the *meso*-aryl positions did not cause considerable refinement of the catalytic activity. This incomprehensible tendency would be explained by the antagonism between

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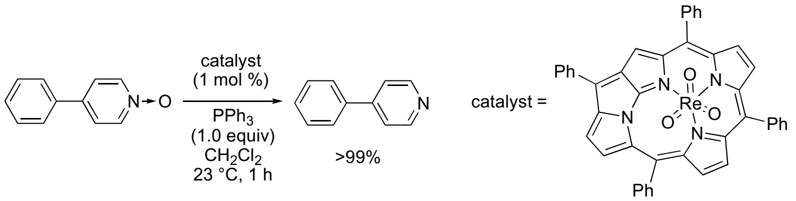
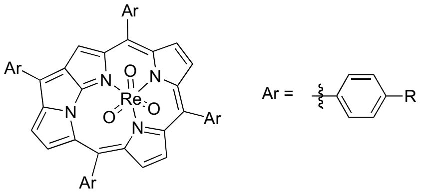


Scheme 1. Re(NFTPP)O_3-catalyzed deoxygenation reaction of 4-phenylpyridine N-oxide.

Table 1
Deoxygenation reactions of 4-phenylpyridine N-oxide with PPh_3 catalyzed by the various Re(VII) complexes



Entry	R	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)
1	H	0.1	23	1	53
2	OMe	0.1	23	1	38
3	CF_3	0.1	23	1	37
4	^{t}Bu	0.1	23	1	44
5	Me	0.1	23	1	35
6	H	0.01	40	16	67
7	OMe	0.01	40	16	70
8	CF_3	0.01	40	16	60

stability and activity of the catalysts. Thus, for further investigations, intact Re(NFTPP)O_3 was used as the catalyst.

The solvent effect was examined and the results are listed in Table 2. The reactions were achieved with 4-phenylpyridine N-oxide at 23 °C in the presence of 0.1 mol % of Re(NFTPP)O_3. While the excellent yields were obtained after prolonged reaction time, the yields were determined after 1 h for comparison. The good results were obtained in less polar solvents such as benzene (entry 1, 62% yield) and toluene (entry 2, 65% yield). In polar solvents, the reactions proceeded more slowly with less yields (entries 4 and 5). In hexane, the reaction was very slow because of the poor solubility of 4-phenylpyridine N-oxide (entry 6). Under the same conditions with entry 2, PEt_3, $P(OEt)_3$, and $P(OPh)_3$ were tried in place of PPh_3. Whereas the reactions proceeded in all of the cases, PPh_3 so far gave the best result (PEt_3: 10%, $P(OEt)_3$: 28%, and $P(OPh)_3$: 41%).

Table 2
Oxygen atom transfer reactions of 4-phenylpyridine N-oxide with PPh_3 in various solvents

Entry	Solvent	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)
1	Benzene	0.1	23	1	63
2	Toluene	0.1	23	1	65
3	CH_2Cl_2	0.1	23	1	53
4	PhCl	0.1	23	1	46
5	THF	0.1	23	1	44
6	Hexane[a]	0.1	23	1	18

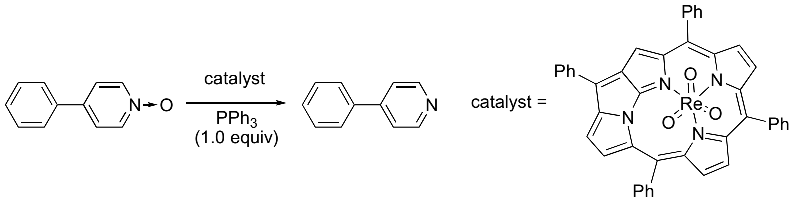
[a] Pyridine oxide was sparsely soluble.

To verify the catalytic activity of Re(NFTPP)O_3, the reactions were performed with decreasing amounts of the catalyst. The results are summarized in Table 3. All the reactions were carried out with 200 mg of 4-phenylpyridine N-oxide without protection from air and sunlight, and the yields were determined based on the amounts of the isolated product. First, 0.1 mol % of the catalyst was used. The reaction was completed after 9 h and the product was obtained in quantitative yield (entry 3). Then the amount of the catalyst was decreased to 0.01 mol % (entry 4). While the reaction was not completed under these conditions, the product was isolated in 64% yield after 72 h and the TON reached 6400. Slight modification of the yield (67%) and the TON (6700) was observed under refluxing conditions in CH_2Cl_2 (entry 5). Meanwhile, significant refinement of the TON was observed when PPh_3 was added very slowly. Namely, to a CH_2Cl_2 solution of 4-phenylpyridine N-oxide and the catalyst, a CH_2Cl_2 solution of PPh_3 was added dropwise. With this method, the TON reached 7800 (entry 6). Further refinement of the TON was observed in reactions at elevated temperature in toluene. As shown in entries 7–9, the TON finally reached 340,000 (21,000 h^{-1}). Note that the reaction did not proceed at all in the absence of catalyst (entry 10).[20]

The generality and limitations of the rhenium-catalyzed oxygen atom transfer reactions were investigated (Table 4). All the reactions were achieved with 0.5 mol % of Re(NFTPP)O_3. Because pyridine N-oxides usually show poor solubility in toluene or benzene at ambient temperature, dichloromethane was used for the reactions at ambient temperature despite less efficiency than toluene (Method A).[21] For less reactive substrates, the reactions were achieved in toluene at 80 °C where pyridine N-oxides show practical solubility. In all cases, the corresponding pyridine derivatives were obtained in good to excellent yields. For example, the reactions proceeded smoothly in the presence of the methoxy (entry 3), cyano (entry 4), and nitro (entry 5) groups. The reactions also proceeded efficiently even in the presence of the hydroxy groups (entries 6–8). The reactions were essentially site-selective, and functional groups applied here did not disrupt the reactions. While the reaction was slow, quinoline was also obtained in a quantitative yield (entry 9).

Several experiments gave significant information on the mechanism of the deoxygenation reactions catalyzed by

Table 3
Deoxygenation reactions of 4-phenylpyridine N-oxide with PPh_3 catalyzed by decreasing amounts of $Re(NFTPP)O_3$

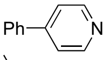
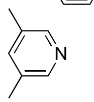
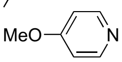
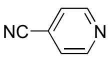
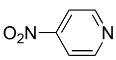
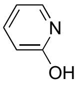
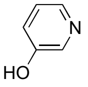
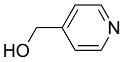
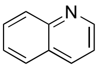


Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)	TON (TON/h)
1	1	CH_2Cl_2	23	1	99	99 (99)
2	0.1	CH_2Cl_2	23	1	53	530 (530)
3	0.1	CH_2Cl_2	23	9	99	990 (110)
4	0.01	CH_2Cl_2	23	72	64	6400 (89)
5	0.01	CH_2Cl_2	40	16	67	6700 (420)
6[a]	0.01	CH_2Cl_2	23	40	78	7800 (200)
7[b]	0.01	Toluene	80	16	91	9100 (570)
8[b]	0.001	Toluene	80	16	91	91,000 (5700)
9[b]	0.0001	Toluene	80	16	34	340,000 (21,000)
10	—	Toluene	80	16	0	0

[a] A CH_2Cl_2 solution of PPh_3 was added dropwise with a syringe pump over 30 h.

[b] A toluene solution of PPh_3 was added dropwise with a syringe pump over 10 h.

Table 4
Deoxygenation reactions of the pyridine N-oxide derivatives with PPh_3

Entry	Product	Method	Time (h)	Yield (%)
1	 Ph N	A	1	99
2[a]	 N	A	6	88
3[a]	 MeO N	B	3	99
4	 NC N	A	3	92
5[b]	 O2N N	B	2	91
6	 N OH	A	3	99
7	 N HO	B	4.5	98
8[c]	 HO N	A	6	90
9[a]	 N	B	67	98

Method A: CH_2Cl_2, 23 °C, Method B: toluene, 80 °C.

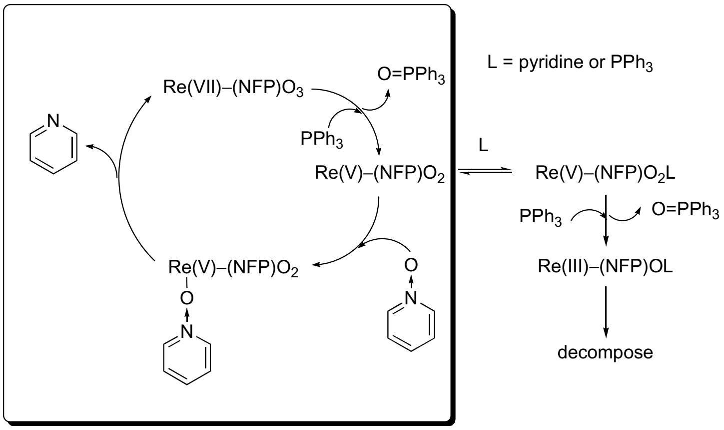
[a] The yields were determined by ^1H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard.

[b] A solution of PPh_3 was added dropwise.

[c] MeOH (5%) was added to dissolve the starting material.

Re(VII)–(NFP)O_3. When Re(NFTPP)O_3 was treated with a stoichiometric amount of PPh_3, almost no reaction proceeded over 1 h. Reduction of Re(NFTPP)O_3 with PPh_3, which should be required for the generation of an active species, proceeded slowly. When treated with excess PPh_3, on the other hand, Re(NFTPP)O_3 decomposed immediately. While excess amounts of PPh_3 were always present during the catalytic reactions, considerable amounts of the catalyst were recovered after the completion of the reactions. These facts imply that the active species was temporarily stabilized under the reaction conditions and went back to the starting Re(VII)–(NFP)O_3 after the catalytic cycle. Furthermore, the parent ion peaks corresponding to Re(NFTPP)O_2(PhCN) were observed in the MALDI-TOF mass analysis of the mixture of Re(NFTPP)O_3 and PPh_3 in PhCN.[22] Consequently, we have postulated that Re(V)–(NFP)O_2 was the active species. The transient Re(V)–(NFP)O_2 would be stabilized temporarily through coordination by pyridine or PPh_3 until it was coordinated by pyridine N-oxide. The π-electrons of the NFP ligand would also contribute to stabilize the active Re(V) species without losing the activity through a fine tuning of the electron density of the metal center. Subsequent cleavage of the N–O bond in the coordinating pyridine N-oxide afforded the product and the starting Re(VII) complex. Further reduction of the Re(V) complex to a Re(III) species might cause the decomposition of the catalyst and a loss of catalytic activity. This deactivation process would be inhibited by the slow addition of PPh_3. Thus, the mechanism of the rhenium-catalyzed oxygen atom transfer reactions can be described as shown in Scheme 2. This type of mechanism was often suggested in the rhenium(VII) trioxo complex-catalyzed reactions.[23–25]

In summary, efficient Re(NFP)O_3-catalyzed deoxygenation reactions of pyridine N-oxides were developed. The reactions exhibited excellent site-selectivity, and quantitative yields were obtained for a variety of substrates. Re(NFP)O_3 was stable under the reaction conditions and,



Scheme 2. A plausible mechanism of Re(VII)–(NFP)O_3-catalyzed oxygen atom transfer reactions.

in the case of Re(NFTPP)O_3, TON reached 340,000. On the basis of recent advances in the chemistry of the rhenium oxo complexes[26] and the rich heritage of porphyrinoid chemistry, further development in the field of catalysis as well as coordination chemistry will be expected.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.117.

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