# Selective Deoxygenation of Heteroaromatic *N*-Oxides with Olefins Catalyzed by Ruthenium Porphyrin

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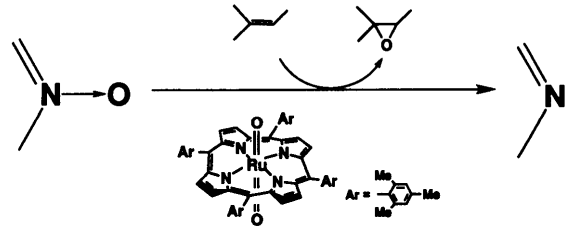
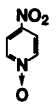
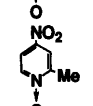
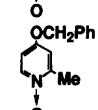
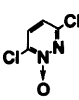
**A new convenient method of deoxygenation of heteroaromatic *N*-oxides is described. Ruthenium porphyrin was used as a catalyst and this method expressed high yields for *o*-substituted pyridine *N*-oxides, quinoline *N*-oxide derivatives, acridine *N*-oxide, *etc.* under mild conditions. Moreover, nitro-, benzyloxy-, and ketone carbonyl groups, which can be affected by the usual deoxygenation methods such as catalytic hydrogenation or borane reduction, were retained.**

**Key word** deoxygenation; heteroaromatic *N*-oxide; ruthenium porphyrin

Deoxygenation of heteroaromatic *N*-oxides is often necessary in syntheses involving an electrophilic substitution process at the nitrogen-containing heteroaromatic ring.[1] $CrCl_2$, $TiCl_3$, borane, or catalytic hydrogenation over palladium is generally used for this purpose.[2] However, acidic or strongly reductive conditions limit the applicable range of substrates, due to acid hydrolysis or overreduction. Stoichiometric use of heavy metal salts makes it difficult to discard or recover metal-containing byproducts. Therefore the catalytic use of metal and mild reaction conditions are desirable for the deoxygenation method. We have developed the ruthenium (Ru) porphyrin-2,6-disubstituted pyridine *N*-oxide system, a robust catalytic system that oxidizes olefins, unactivated alkanes, and aromatic rings to afford epoxides, alco-

Table 1. Ruthenium Porphyrin-catalyzed Deoxygenation of Heteroaromatic *N*-Oxides




| Run | Substrate | Conditions | Isolated Yield | Run | Substrate | Conditions | Isolated Yield |
|---|---|---|---|---|---|---|---|
| 1 |  | 30°C, 15 h[1] |  94 % | 8 |  | 80°C, 15 h[2] |  20 % |
| 2 |  | 30°C, 15 h[1] |  99 % | 9 |  | 80°C, 15 h[2] |  21 % |
| 3 |  | 30°C, 15 h[1] |  94 % | 10 |  | 80°C, 15 h[1] |  99 % |
| 4 |  | 80°C, 15 h[2] |  96 % | 11 |  | 30°C, 15 h[1] |  98 % |
| 5 |  | 30°C, 15 h[1] |  87 % | 12 |  | 30°C, 15 h[1] |  99 % |
| 6 |  | 80°C, 15 h[2] |  99 % | 13 |  | 30°C, 15 h[1] |  97 % |
| 7 |  | 80°C, 15 h[2] |  99 % | 14 |  | 80°C, 1.5 d[2] |  95 % |

These reactions were carried out in benzene (15 ml) under Ar. Products were purified by silica gel column chromatography. [heteroaromatic *N*-oxide]: 0.5 mmol; [olefin]: 5 equiv. 1) 2-methyl-2-butene, 2) *cis*-cyclooctene [$Ru(TMP)(O)_2$]: 1.1 mol%

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hols/ketones, and quinones, respectively, together with the corresponding 2,6-disubstituted pyridine in high yields.[3] Thus Ru porphyrin effectively catalyzes the oxygen transfer reaction from an *N*-oxide to a substrate such as an olefin. Here we report the deoxygenation of various heteroaromatic *N*-oxides with olefins catalyzed by Ru porphyrin under very mild conditions.

**Experimental Procedure**

The preparation of 3-nitroquinoline involves a typical procedure: A solution of 3-nitroquinoline *N*-oxide (purified by alumina column chromatography) (95 mg, 0.50 mmol), 2-methyl-2-butene (175 mg, 2.5 mmol) and Ru(TMP)$(O)_2$ (5 mg, 5.5 $\mu$mol) in benzene (15 ml) was stirred overnight (for 15 h) at 30 °C under argon. The reaction mixture was chromatographed on silica gel to afford 3-nitroquinoline (86 mg, yield 99%). In the case of volatile amines, the eluent was carefully evaporated at low temperature.

## Results and Discussion

Volatile 2-methyl-2-butene or *cis*-cyclooctene was chosen as an oxygen acceptor since both the olefins and the resulting epoxides are easily removable by evaporation. Ruthenium (VI) *meso*-tetramesitylporphyrin dioxo complex (abbreviated as Ru(TMP)$(O)_2$[4] was used as the catalyst (*ca.* 1 mol%). The system reduced 2,6-disubstituted pyridine *N*-oxides most effectively (Table, runs 1—3). *o*-Monosubstituted pyridine *N*-oxides were also deoxygenated in high yields but less efficiently (runs 4—7). The reduction of pyridine *N*-oxides without any substituent at the 2 and 6 positions resulted in low conversion (runs 8, 9), and pyridine *N*-oxides were recovered in high yields (run 8: 77%; run 9: 70%). This difference in reactivity is considered to be due to the coordination ability of the formed pyridine, because the reaction was completely inhibited by the addition of a small amount of pyridine,[3d] and not at all by the addition of 2,6-dichloropyridine. Heteroaromatic *N*-oxides other than pyridine *N*-oxide also gave the corresponding heteroarene in high yields (runs 10—14).

The electron-withdrawing group accelerated deoxygenation. 4-Nitropicoline *N*-oxide (run 5) and 3-nitroquinoline *N*-oxide (run 12) were deoxygenated more effectively than picoline *N*-oxide (18% at 30 °C) and quinoline *N*-oxide (74% at 30 °C), respectively. The benzyloxy group, which is labile in catalytic hydrogenation, was unaffected under these reaction conditions (run 6). Catalytic hydrogenation, $CrCl_2$, and $TiCl_3$ readily reduces the nitro group, but the present system retained the nitro moiety (runs 5, 9, 13). The ketone carbonyl group, which is reduced by borane, was not reduced in the deoxygenation (run 7). This selective deoxygenation system would be highly advantageous for application to multifunctionalized substrates. Further, the products can be readily purified since the olefins, epoxides, and catalyst are easily removable. This reduction system is effective for the selective deoxygenation of heteroaromatic *N*-oxides in which the neighboring positions of the nitrogen atom have any substituent(s).

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**References and Notes**

1) *a*) Ochiai E. (ed.), "Aromatic Amine Oxides," Elsevier, Amsterdam, 1967; *b*) Katritzky A. R., Lagowski J. M., "Chemistry of the Heterocyclic *N*-oxides," Academic Press, London, New York, 1971.
2) Hudlicky M., "Reductions in Organic Chemistry," Ellis Horwood Ltd., West Sussex, 1984, and references cited therein.
3) *a*) Higuchi T., Ohtake H., Hirobe M., *Tetrahedron Lett.*, **30**, 6545—6548 (1989); *b*) *Idem*, *ibid.*, **32**, 7435—7438 (1991); *c*) Ohtake H., Higuchi T., Hirobe M., *J. Am. Chem. Soc.*, **114**, 10660—10662 (1992); *d*) Ohtake H., Higuchi T., Hirobe M., *Heterocycles*, **40**, 867—903 (1995); *e*) Higuchi T., Satake C., Hirobe M., *J. Am. Chem. Soc.*, **117**, 8879—8880 (1995); *f*) Higuchi T., *J. Synth. Org. Chem. Jpn.*, **53**, 633—644 (1995); *g*) Shingaki T., Miura K., Higuchi T., Hirobe M., Nagano T., *Chem. Commun.*, 861—862 (1997).
4) Groves J. T., Quin R., *Inorg. Chem.*, **23**, 3844—3846 (1984).

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