

Aerobic oxidative *N*-dealkylation of tertiary amines in aqueous solution catalyzed by rhodium porphyrins†‡

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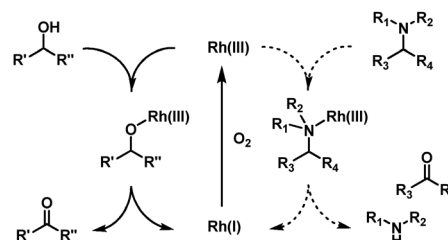
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Aerobic oxidative *N*-dealkylation of a variety of aliphatic tertiary amines and anilines catalyzed by rhodium(III) tetra (*p*-sulfonato-phenyl) porphyrin ((TSPP)Rh^{III}) is achieved in aqueous solution using dioxygen as the sole oxidant.

Rhodium porphyrin complexes demonstrate a wide range of important substrate reactions.¹ Our focus of interest is in exploring the scope of useful catalytic processes for rhodium(III) and related Group 9 Co(III) and Ir(III) porphyrins.² Water promoted rapid quantitative aerobic oxidation of (TSPP)Rh^I to (TSPP)Rh^{III} provides this system the capability to undergo catalytic aerobic oxidation reactions in aqueous solution.³ Previous work from our lab accomplished stoichiometric aerobic oxidation of olefins and catalytic oxidation of primary and secondary alcohols by (TSPP)Rh^{III}.⁴ The mechanistic investigation in aqueous solution indicated that βC–H elimination was the rate determining step for alcohol oxidation.^{4b} With an interest in extending the substrate scope of the aerobic oxidation process, we turned to study the oxidative *N*-dealkylation of amines which might be mechanistically germane to the mode of oxidation of alcohols (Scheme 1).

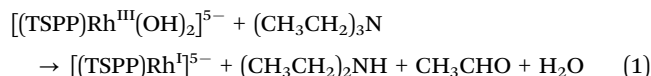
The oxidative *N*-dealkylation of tertiary amines represents an important type of biochemical reaction and functions as the major process of detoxification of xenobiotics.⁵ There are two generally used strategies for the cleavage of the C–N bond of tertiary amines: (1) by oxometal (M=O) complexes⁶ and (2) by low-valence transition metal complexes.⁷ However, in most cases the substrate scope is limited to *N,N*-dialkylaniline or tetrahydroisoquinoline motifs. In addition, high-valence transition metal complexes (non-oxo) are rarely reported to catalyze this process probably because the secondary aliphatic amine product coordinates to the electrophilic metal center and thus poisons the metal. Herein, we describe a general method for



Scheme 1 (TSPP)Rh^{III} catalyzed aerobic oxidation of alcohols and amines.

aerobic oxidative *N*-dealkylation of tertiary amines including aliphatic amines and anilines catalyzed by high-valence metal complex (TSPP)Rh^{III} in aqueous solution.

The reaction of (TSPP)Rh^{III} with triethylamine in the absence of dioxygen led to stoichiometric formation of (TSPP)Rh^I, diethylamine, and acetaldehyde in NaOH buffer solution (eqn (1)).



Kinetic experiments were conducted in D₂O at pH = 13 and 308 K in the absence of O₂ and ¹H NMR spectra were collected over at least three half-lives. The progress of reaction (1) was conveniently monitored by the disappearance of the pyrrole H signal of (TSPP)Rh^{III} at 9.0 ppm and the reaction rate was obtained from the ratio of intensity integration compared with an external standard (Fig. S1, ESI†). With the concentration of triethylamine remained approximately constant throughout the reaction, the first-order reaction rate of (TSPP)Rh^{III} was obtained together with the rate constant (Fig. 1A). And the first-order rate dependence on the concentration of NEt₃ was confirmed from the relationship between the values of *k*_{obs} and the corresponding concentration of NEt₃ (Fig. 1B). Activation parameters were evaluated from the temperature dependent rate constants ($\Delta H^\ddagger = 28.9 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = 20.3 \text{ eu}$, $\Delta G^\ddagger (298 \text{ K}) = 23.0 \text{ kcal mol}^{-1}$) (Fig. S2, ESI†).

Collman and co-workers discovered an unusual activation of the C–N bond of tertiary amines in the preparation of rhodium corroles.⁸ And the cleavage of the C–N bond involving the βC–H elimination mechanism was proposed. Chan and co-workers

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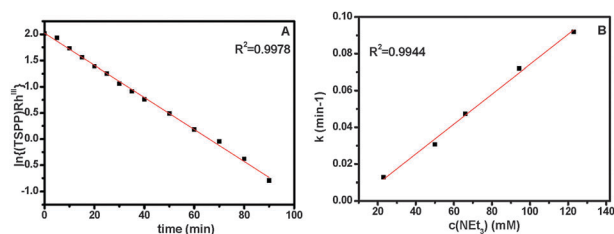


Fig. 1 (A) Concentration changes of (TSPP)Rh^{III} upon reaction with triethylamine, [NEt₃] = 50 mM at 308 K. (B) Dependence of the observed rate constant, k_{obs} , on the concentration of NEt₃ at 308 K.

also reported the cleavage of the C–N bond of tertiary amine by rhodium porphyrin chloride to form inert rhodium alkyls through a metalloradical process.⁹ However, for our aqueous system, the rapid oxidation of (TSPP)Rh^I to (TSPP)Rh^{III} by O₂ gave this system the capability to undergo catalytic oxidation processes.³ The catalytic oxidative *N*-dealkylation of tertiary amines was proposed to proceed through a four-step cycle involving: (a) amine coordination to (TSPP)Rh^{III} to give complex **1**; (b) βC–H elimination to form iminium ion **2** and (TSPP)Rh^I; (c) hydrolysis of **2** to produce the dealkylation product and corresponding carbonyl compound; and (d) regeneration of (TSPP)Rh^{III} by molecular oxygen (Scheme 2).

The catalytic oxidative *N*-dealkylation of tributylamine in water was examined as the model reaction for optimization of reaction conditions (Table 1). Dibutylamine and butyraldehyde were identified by GC-MS and ¹H NMR with a turnover number (TON) of 18 quantitatively determined by GC when heating the mixture of (TSPP)Rh^{III} and tributylamine under one atmosphere of dioxygen in water (Table 1, entry 1). Two reasons may account for the low TON: (1) the resulting product dibutylamine coordinated tenaciously to Rh(III) to form inert (TSPP)Rh^{III}–NHBu₂ (Scheme 2, step e); and (2) the solubility of tributylamine in water is quite low.¹⁰ The control experiment revealed that the reaction rate of the stoichiometric oxidation of triethylamine by (TSPP)Rh^{III} ($t_{1/2}$ = 4 min) was significantly slowed down ($t_{1/2}$ > 24 hours, Fig. S4, ESI†) in the presence of 20 equivalents of diethylamine. Taking advantage of the difference in basicity between tertiary amines and secondary amines (e.g. pK_a (tributylamine) = 10.89, pK_a (dibutylamine) = 11.25),¹¹ we intentionally introduced acids to capture the formed secondary amines so that the side reaction (Scheme 2, step e) was eliminated. As expected, the TON increased dramatically to 295 when 0.5 equivalents of HCl were added (Table 1, entry 2). Scanning commonly used acids, CF₃COOH was found to be the best choice. The TON increased gradually (Table 1, entries 3–9) and reached up to 887 when

Table 1 Acid effect in *N*-dealkylation reaction^a

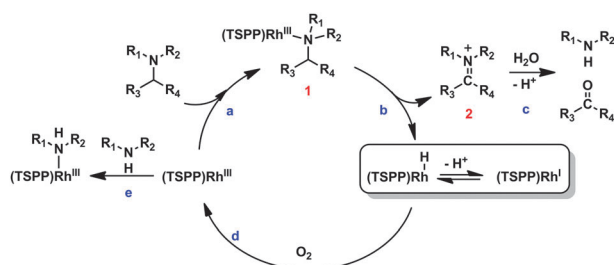
$\text{Bu-N-Bu} \xrightarrow[\text{O}_2]{(\text{TSPP})\text{Rh}^{\text{III}}} \text{Bu-N-Bu} + \text{CH}_3\text{CH}_2\text{CHO}$			
Entry	Acid	Acid/amine	TON ^b
1	None	—	18
2	HCl	0.5	295
3	CF ₃ SO ₃ H	0.5	499
4	C ₆ H ₅ SO ₃ H	0.5	494
5	CH ₃ COOH	0.5	347
6	CF ₃ COOH	0.5	631
7	CF ₃ COOH	0.3	416
8	CF ₃ COOH	0.8	887
9	CF ₃ COOH	1.0	588
10	CF ₃ COOH	1.2	0

^a Reaction conditions: 2.0 mmol of tributylamine, 1.0 μmol of (TSPP)Rh^{III} and acid in 1 mL of H₂O stirred for 2 h at 373 K under 1 atm O₂. ^b TON = $n(\text{dibutylamine})/n((\text{TSPP})\text{Rh}^{\text{III}})$, determined by GC.

0.8 equivalents of CF₃COOH were added (Table 1, entry 8). However, addition of 1.2 equivalents of acid completely shut down the reaction as tertiary amine substrates were largely protonated, which impeded the access of tertiary amines to (TSPP)Rh^{III} (Table 1, entry 10).

A series of aliphatic amines with linear, branched and cycloalkyl, and benzyl groups were investigated under optimum conditions (Table 2). Both triethylamine and tributylamine showed high reactivity (Table 2, entries 1 and 2). For asymmetric amines, the C–N cleavage showed a preference for the bulky groups. One such example is the 807 TON of *N*-ethyl-propan-2-amine and 342 TON of diisopropylamine products (Table 2, entry 3). The oxidation of *N,N*-dimethylhexanamine only produced the *N*-dehexylation product (Table 2, entry 4). However, when *N,N*-diethylcyclohexanamine and *N,N*-dicyclohexyl methanamine were used, no cyclohexanol was observed. Instead, *N*-ethylcyclohexanamine and dicyclohexanamine were detected, respectively (Table 2, entries 5 and 6). *N*-debenzylation was preferred for *N,N*-dimethylbenzylamine (Table 2, entry 7) and *N*-deethylation was favored for *N,N*-diethylbenzylamine (Table 2, entry 8). Thus, the activity of *N*-debenzylation is between *N*-demethylation and *N*-deethylation. Triethanolamine was also converted to the corresponding secondary amine with a TON of 392 (Table 2, entry 9), indicating good compatibility of the hydroxyl group.^{4b} The ester, aldehyde, phenol and C=C groups can also be tolerated in this catalytic transformation (Table 2, entries 10–12). The comparatively low TON of triallylamine may result from the competing reaction of the double bond with (TSPP)Rh^{III}.^{4a}

The initial attempt to expand the substrate scope to tertiary anilines failed due to the low solubility of anilines in water (e.g. *N,N*-diethylaniline: slightly soluble).¹⁰ To address this issue, we introduced a different solvent system and used *N,N*-diethylaniline as the model substrate (Table S6, ESI†). The highest TON = 219 was obtained in MeOH–H₂O (10/1) solution (Table 3, entry 1). Substituted *N,N*-diethylanilines were observed to produce corresponding secondary anilines where anilines with electron-donating groups on the phenyl ring gave better yields than those with electron-withdrawing groups (Table 3, entries 2–4). *N,N*-Dibutylaniline was also converted to *N*-butylaniline with a TON of 209 (Table 3, entry 5).



Scheme 2 (TSPP)Rh^{III} catalyzed aerobic oxidative *N*-dealkylation of tertiary amines in water.

Table 2 Scope of tertiary aliphatic amines^a

Entry	Substrates	Products	TON ^b
1 ^c			698
2			887
3 ^{c,d}			807
4 ^e			395
5			844
6			543
7 ^e			152
8 ^f			340
9 ^c	N(CH ₂ CH ₂ OH) ₃	NH(CH ₂ CH ₂ OH) ₂	392
10 ^{c,g}			126
11 ^{c,e}			80
12 ^h	N(CH ₂ CH=CH ₂) ₃	NH(CH ₂ CH=CH ₂) ₂	37

^a Reactions are performed under the optimum conditions (Table 1, entry 8). ^b GC results. ^c Determined by ¹H NMR. ^d 342 TON of *i*Pr₂NH was obtained. ^e Determined by the formed aldehyde. ^f The yield of Et₂NH was 50 TON. ^g EtOH was used as solvent. ^h 2.0 mmol of CF₃COOH was added.

Table 3 Scope of tertiary anilines^a

Entry	Substrates	Time/h	TON ^b
1	X = H, R = Me	4	219
2	X = OEt, R = Me	6	200 ^c
3	X = Br, R = Me	22	243 ^c
4	X = Ac, R = Me	22	120 ^c
5	X = H, R = Pr	6	209

^a Reaction conditions: 2.0 mmol of aniline and 1.0 μmol of (TSPP)Rh^{III} stirred at 363 K under 1 atm O₂ in MeOH–H₂O (10 : 1 (v/v)). ^b GC results. ^c Determined by ¹H NMR.

In summary, a green protocol for catalytic oxidative *N*-dealkylation of tertiary amines using dioxygen as the oxidant in aqueous solution is successfully mediated by rhodium(III) porphyrin complexes. Addition of acid inhibits the deleterious coordination of the resulting secondary amine to rhodium(III). Trapping the iminium ion intermediates for functionalization of the sp³ C–H bond adjacent to nitrogen is under further study.

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