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Short Communication

Efficient oxidative coupling of amines to imines catalyzed by manganese(III) *meso*-tetraphenylporphyrin chloride under ambient conditions

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ABSTRACT

Highly efficient oxidative coupling of amines to imines by *tert*-butyl hydroperoxide (*t*-BuOOH) in the presence of metalloporphyrins has been reported. Manganese porphyrin showed excellent activity and selectivity for the oxidative coupling of amines to imines under ambient conditions. Moreover, a plausible mechanism involving high valence oxo intermediate has been proposed.

1. Introduction

Imines have been used as versatile substrates for nucleophilic addition, cycloaddition and reduction [1]. They can also be applied as lipoxygenase inhibitors, anti-inflammatory and anti-cancer agents [2]. Traditionally, imines are prepared by condensation of carbonyl compounds with amines in the presence of Lewis acid catalysts e.g. $TiCl_4$ [3], Al_2O_3 [4], $MgSO_4$ [5,6] or K-10 [7,8]. The methodologies reported have some disadvantages e.g. high reaction temperature, prolonged reaction period and requiring excessive costly dehydrating reagents. Therefore, direct synthesis of imines from amines by oxidative dehydrogenation attracted wide attention [9]. Among such procedures, metal-catalyzed oxidations by hydroperoxide or dioxygen were found to be efficient and widely applicable for converting amines to imines. Ruthenium complexes [10,11], dirhodium caprolactamate [12], $PdCl_2/PPh_3$ [13], $MnSO_4$ [14] and mercury (II) oxide-iodine [15] have been used as the catalysts.

As model catalysts of cytochrome P-450, metalloporphyrins could be used as an intermediate of oxygen carrier for biological systems. Metalloporphyrins have been widely applied as catalysts for various biomimetic oxidations [16]. However, only few investigations have been reported on metalloporphyrins-catalyzed oxidation of amines [17].

In our previous studies on biomimetic oxidations, metalloporphyins exhibited highly catalytic performance for oxidation of olefins, sulfides, alcohols and ketones with molecular oxygen as the sole oxidant [18]. Subsequently, an efficient oxidative coupling of amines to imines by *tert*-butyl hydroperoxide (*t*-BuOOH) in the presence of metalloporphyrins has been developed (Scheme 1) in this paper. Low amount of manganese porphyrin catalyst (0.03 mol%, based on substrate) was used for the oxidative coupling of amines to the corresponding imines under ambient conditions. Furthermore, high valence oxo intermediate was verified by *in situ* UV–vis spectroscopy in the oxidative coupling system, and a plausible mechanism has been proposed.

2. Experimental

Amines were obtained from Aldrich or Fluka without further purification unless indicated. Pyrrole was purified before using it. All the reagents were of analytical grade. Metalloporphyrins catalysts were prepared and characterized according to the procedures reported previously [18]. UV–vis spectra were recorded on a HITACHI U-3010 spectrophotometer. Elemental analysis data were obtained on Vario EL III. FT-IR spectra were recorded on a Bruker VERTEX70 spectroscopy.

2.1. General procedure for the catalytic oxidative coupling of amines to imines

Oxidant (*t*-BuOOH, 2 mmol) was added to 5 mL toluene containing benzylamine (1 mmol), catalyst (3.0×10^{-4} mmol) and 0.8 mmol naphthalene (as inert internal standard) at room temperature. The consumption of amines were monitored by GC (Shimadzu GC14C) and GC-MS (Shimadzu GCMS-QP2010 plus). The products were

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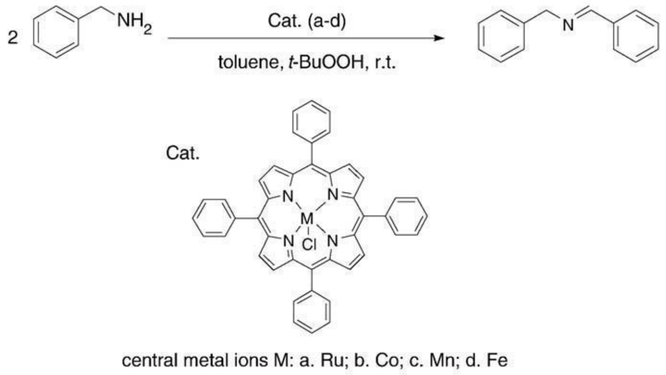


Scheme 1. Oxidative coupling of benzylamine catalyzed by metalloporphyrins catalysts.

purified according to the reported procedures and identified by GC retention times or the comparison of their mass spectra [7,19].

3. Results and discussion

3.1. Oxidative coupling of benzylamine catalyzed by various metalloporphyrins

The catalytic activity and selectivity of different metalloporphyrins for the oxidative coupling of amines to imines by *t*-BuOOH were investigated with benzylamine as a model substrate and the results are summarized in Table 1.

The oxidative coupling of benzylamine catalyzed by metalloporphyrins catalysts produces *N*-benzylbenzaldimine as the main product. As shown in Table 1, the catalytic activity of the metalloporphyrins appears to be dependent on the nature of their central ions. Manganese porphyrin was more effective compared with iron, cobalt and ruthenium porphyrins for the oxidative coupling of benzylamine under mild condition (entries 1–4). In addition, only 12% benzylamine could be converted when the catalyst was replaced by $MnCl_2$ with the same catalytic amount as metalloporphyrins (entry 5).

3.2. Effect of solvent on the oxidative coupling

With MnTPPCl as catalyst, the oxidative coupling of benzylamine in different solvents was investigated. The results are summarized in Table 2.

As shown in Table 2, solvent also plays an important role for the oxidation system. It seems that solvent with large dielectric constant is not suitable for the oxidative coupling of benzylamine except benzotrifluoride. Toluene and benzotrifluoride were more favorable for the oxidative coupling reaction compared with cyclohexane, dichloromethane, isopropanol and acetonitrile (entries 1 and 2). Toluene is often applied for radical reactions because of its reluctance to undergo radical addition, and benzotrifluoride is commonly used in metal-catalyzed oxidation [20]. Moderate yield of *N*-benzylbenzaldimine (76%) was obtained when cyclohexane was used as solvent (entry 3). Although cyclohexane is a commonly used model substrate for metalloporphyrin catalyzed oxidations, no oxidized products from cyclohexane were determined for this catalytic system. Other solvents with large dielectric constant e.g. dichloromethane, acetonitrile and isopropanol were used in the oxidative coupling of benzylamine, the product could be obtained with rather low yields (entries 4–6).

Table 1
Oxidative coupling of benzylamine catalyzed by various metalloporphyrins [a].

Entry	Catalyst	Conv. (%)	Yield[b](%)
1	MnTPPCl	>99	91
2	FeTPPCl	86	80
3	CoTPPCl	77	72
4	RuTPPCl	73	69
5	$MnCl_2$	12	10

[a] Benzylamine (1 mmol), catalyst (3.0×10^{-4} mmol), toluene (5 mL), *t*-BuOOH (2 mmol), 15 min, r.t.
[b] Based on benzylamine, determined by GC and GC-MS.

Table 2
Effect of solvent on the oxidative coupling of benzylamine catalyzed by MnTPPCl [a].

Entry	Solvent	Dielectric constant	Conv. (%)	Yield[b] (%)
1	Toluene	2.4	>99	91
2	Benzotrifluoride	9.2	>99	98
3	Cyclohexane	2.0	78	76
4	Dichloromethane	9.1	21	21
5	Isopropanol	18.3	18	18
6	Acetonitrile	37.5	13	13

[a] MnTPPCl (3.0×10^{-4} mmol), benzylamine (1 mmol), solvent (5 mL), *t*-BuOOH (2 mmol), 15 min, r.t.
[b] Based on benzylamine, determined by GC and GC-MS.

3.3. Oxidative coupling of various substrates catalyzed by MnTPPCl

To evaluate the scope of the catalytic system, various amines were subjected to the reaction system at room temperature (Table 3). As shown in Table 3, most substrates can be smoothly converted to corresponding imines with high conversion rate and excellent selectivity.

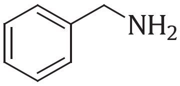
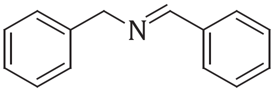
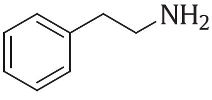
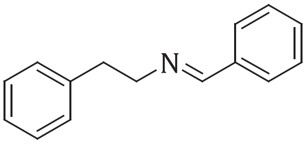
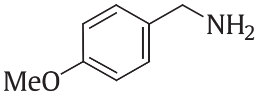
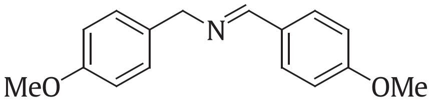
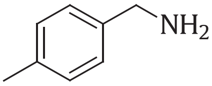
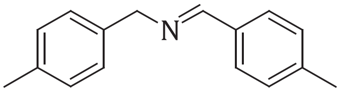
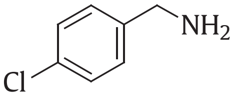
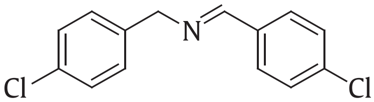
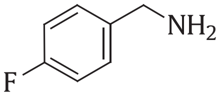
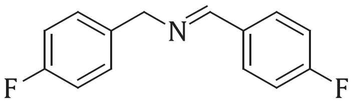
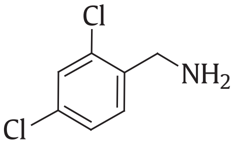
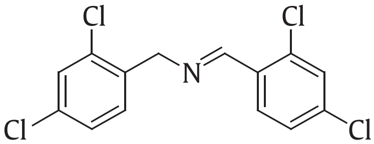
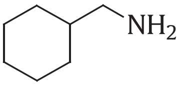
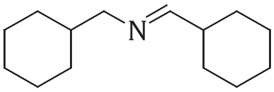
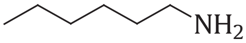
Most primary amines could be smoothly coupled to corresponding imines through oxidation by *t*-BuOOH in the presence of MnTPPCl under mild conditions. Small amount of aldehyde, direct oxidation product of amines, were detected for all the substrates in the oxidative coupling reactions. It is noteworthy that *N*-benzylidene-2-phenylethanamine was detected for the oxidation of phenylethylamine (entry 2). It could be attributed to the nucleophilic reaction between phenylethylamine and benzaldehyde [21], in which benzaldehyde was generated from the cleavage oxidative of C–C bond of 2-phenylacetaldehyde. Our previous works demonstrated that benzaldehyde could be produced in the cleavage oxidative of cinnamaldehyde catalyzed by metalloporphyrins [22].

Furthermore, the electronic and steric effects on the oxidative coupling of benzylamine were also well investigated with various substituents on the benzene ring (entries 3–6). The electronic property of substrates affects the selectivity of product, in which the electron-withdrawing group seems more favorable to the formation of imines products. The electron-donating groups (entries 3 and 4) and electron-withdrawing groups (entries 5 and 6) retard the oxidative coupling so that slightly longer reaction times are required. The influence of steric effects can be illustrated from the oxidative coupling of (2,4-dichlorophenyl) methanamine, in which its conversion only reaches 70% after reacted for 3 h (entry 7). In addition, oxidative coupling of non-aromatic primary amines e.g. cyclohexylmethanamine and 1-hexanamine also proceed smoothly with high conversion and yield (entries 8 and 9).

3.4. Plausible mechanism for oxidative coupling of benzylamine catalyzed by MnTPPCl

The results from the controlled experiment have demonstrated that manganese porphyrin is crucial for the oxidative coupling of benzylamine. Meanwhile, it was found that the reaction was completely inhibited when the radical trap was used, which suggested that the oxidative coupling of benzylamine with manganese porphyrin should involve radical species. Generally for the metalloporphyrins-catalyzed oxidations, high valence intermediate is accepted as the active species, which could transfer oxygen to substrate directly.

Table 3
Oxidative coupling of various amines catalyzed by MnTPPCl [a].

Entry	Amines	Products	Time (h)	Conv. (%)	Yield[b] (%)
1			0.25	>99	91
2			0.5	>99	89[c]
3			1.0	>99	73
4			1.0	>99	88
5			0.5	97	95
6			0.5	>99	96
7			3.0	70	57
8			2.0	>99	91
9			1.0	>99	96

[a] MnTPPCl (3.0×10^{-4} mmol), substrate (1 mmol), toluene (5 mL), *t*-BuOOH (2 mmol), rt.

[b] Based on amines, determined by GC and GC-MS, residual product was aldehyde.

[c] Residual product was benzaldehyde.

While for the present system, it seems that no oxygen transformation to substrate is involved.

High valence manganese porphyrin in the catalytic system was verified from the *in situ* UV–vis spectroscopy as shown in Fig. 1. The characteristic absorption peak of MnTPPCl was at 476 nm. By adding *t*-BuOOH and benzylamine into the reaction system, *in situ* measurement revealed a new absorption peak at 520 nm, while the characteristic absorption peak of MnTPPCl was weakened gradually. These evidence indicated that a new metalloporphyrins species with absorption peak at 520 nm is an active catalytic intermediate expected as high valence manganese porphyrin [23–26].

Benzylamine could be oxidized in two stages to the corresponding *N*-benzylbenzaldimine *via* benzaldehyde intermediate with metal oxides such as copper compound [27], HgO–I_2 [28]. Benzaldehyde was also detected in the present manganese porphyrin catalyzed oxidative coupling reaction. Attempts to explore whether aldehyde was the intermediate for the oxidative coupling reaction by the reaction of benzaldehyde with benzylamine in the presence of *t*-BuOOH was

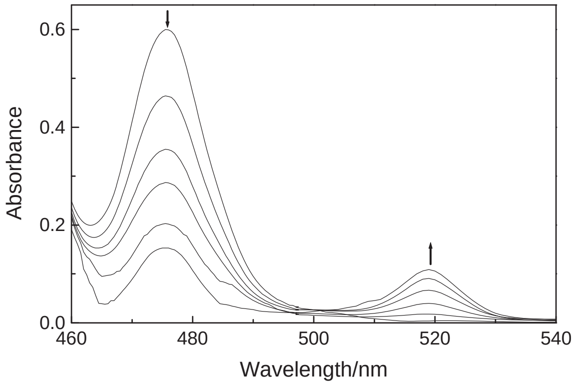


Fig. 1. *In situ* UV–vis spectra of manganese porphyrin for the oxidative coupling reaction system (time scan with 3 min intervals), MnTPPCl (3.0×10^{-4} mmol), benzylamine (1 mmol), toluene (5 mL), *t*-BuOOH (2 mmol), rt.

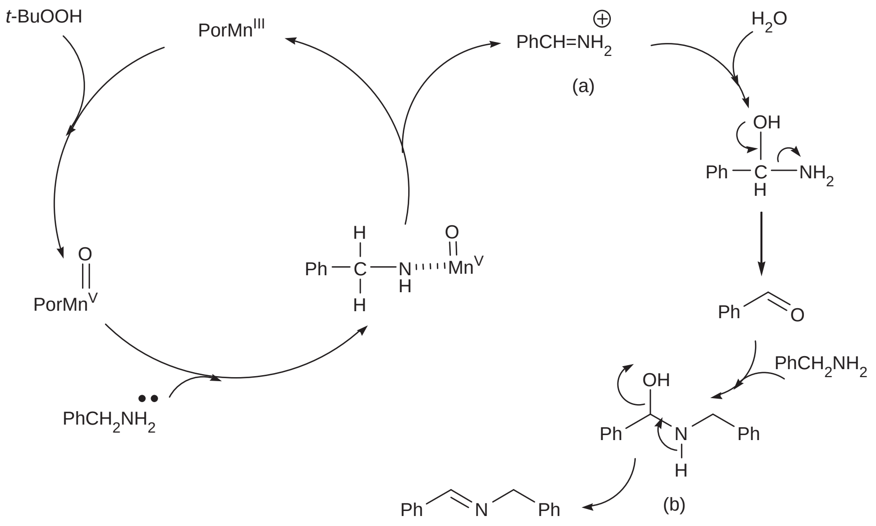


Fig. 2. A plausible reaction mechanism for oxidative coupling of benzylamine catalyzed by MnTPPCl in presence of *t*-BuOOH.

successful. The formation of *N*-benzylbenzaldimine was the result of the nucleophilic attack of benzaldehyde by a second molecule of benzylamine followed with the removal of a water molecule. This reaction course in the present system could be further confirmed from the result using phenylethylamine as substrate (entry 2 in Table 3). The product with loss of one methylene group could be attributed to the reaction between phenylethylamine and benzaldehyde, in which benzaldehyde was generated from the cleavage oxidative of C–C bond of 2-phenylacetaldehyde. In addition, no benzaldehyde was determined in the stirring solution with catalyst, oxidant and *N*-benzylbenzaldimine, which indicated that benzaldehyde could not be generated from the imines hydrolysis in this catalytic system.

On the basis of previous observations, a plausible reaction mechanism for the oxidative coupling of benzylamine with MnTPPCl as catalyst has been proposed as shown in Fig. 2. Through the reaction with benzylamine, the role of high valence manganese intermediate in the present system is to produce Schiff-base imine intermediate (a). Then, benzaldehyde was generated from the hydrolysis of Schiff-base imine intermediate with the elimination of molecule ammonia [29]. The nucleophilic attack of benzaldehyde by a second molecule of benzylamine gives the intermediate (b). The coupled imine product was generated by the removal of a water molecule from the intermediate (b) [30,31].

As the results listed in Table 3, solvent has a great influence on the oxidative coupling reaction. Generally in those reactions involves ions, large dielectric constant of solvent has negative effect on the reaction rate, which consists with the presence of Schiff-base imine intermediate (a) in the present system. In addition, the formation of *N*-benzylbenzaldimine is related with the nucleophilic attack of benzaldehyde by a second molecule of benzylamine, which may be influenced by the frontier orbital energy of the benzaldehyde and benzylamine according to the frontier molecular orbital theory.

Based on the fact that the electronic property of substrates affects the selectivity of product as shown in Table 3, calculations were performed with the Gaussian03W package using the density functional theory (DFT) [32]. Full geometry optimizations of substrates with different electronic property (e.g. 4-chloro-benzylamine and 4-methyl-benzylamine, 4-chloro-benzaldehyde and 4-methyl-benzaldehyde) were performed employing Beck's three parameter Lee–Yang–Parr correlation functions (B3LYP) combined with 6–31 + G (d, p) basis set. The optimized structures and frontier orbital energy for the substrates are presented in Fig. 3. As shown in Fig. 3, the frontier orbital energy gap of 4-methyl-benzaldehyde and 4-methyl-benzylamine was 0.252 a.u. (5.33 eV), while the gap for the 4-chloro-benzaldehyde and 4-methyl-benzaldehyde was 0.196 a.u. (6.86 eV). According to the frontier molecular orbital theory, the stronger

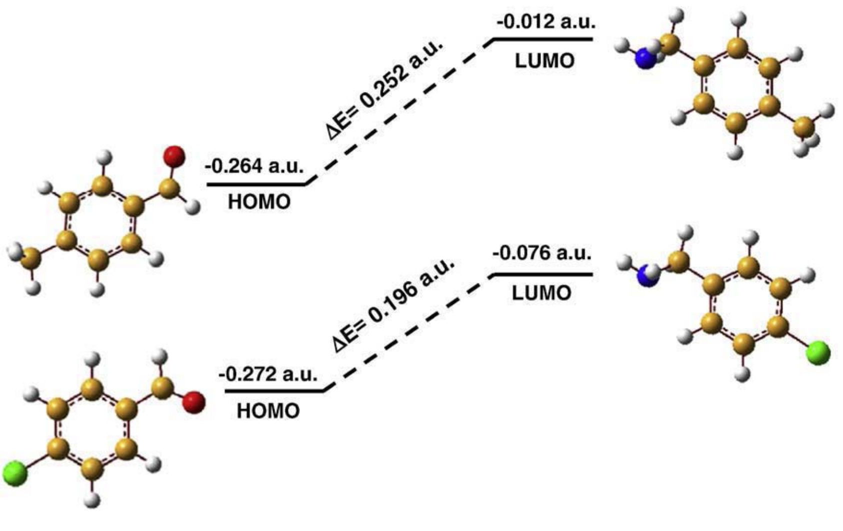


Fig. 3. The calculated frontier molecular orbital energy and energy gap of amines with different electronic property.

interaction of two reactant molecules could take place when the two molecules has lower frontier energy gap [33–35]. Therefore, the efficiency differences between the substrates with different electronic properties in the current oxidative coupling system could be well explained from the calculation results. Meanwhile, the mechanism of the nucleophilic attack of benzylamine to benzaldehyde could also be confirmed indirectly from the calculation results.

4. Conclusion

In conclusion, manganese(III) *meso*-tetraphenylporphyrin chloride has been proven to be an excellent catalyst for oxidative coupling of amines to imines in the presence of *tert*-butyl hydroperoxide. The oxidative coupling was through a radical process with formation of high valence manganese intermediate, which was confirmed by *in situ* UV–vis spectroscopy.

Acknowledgments

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