Oxidative Coupling of Benzylamines into *N*-Benzylbenzaldimines with MnTPPCl/*t*-BuOOH

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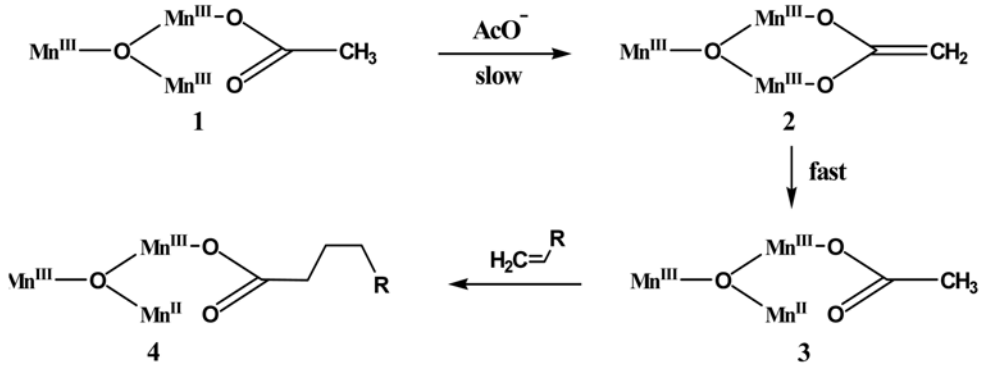
Mn(III)-based oxidative free radical cyclizations and annulations have been extensively investigated.[1] The rate determining step in the oxidation of acetic acid by $Mn(OAc)_3$ involves an oxo-centered triangle of Mn(III) with bridging acetates,[2] 1. The loss of a proton from 1 gives 2[3] that undergoes rapid electron transfer to the oxo-centered metal system forming 3.3 adds to the alkene to produce 4 (Scheme 1).

Benzylamine has been catalytically transformed into *N*-benzylbenzaldimine **8** *via* various pathways.[4-7] 3-Methyl-umiflavin[4] promotes conversion of $C_6H_5CH_2NH_2$ to **8** under acid catalyzed thermal conditions. Aerobic oxidative dehydrogenation of benzylamine[5] is catalyzed by molybdenium-vanadium salt to yield **8**. Clay-catalyzed reaction of benzylamine[6] is suggested to involve $C_6H_5CH_2$=NH that react another benzylamine for the formation of **8**. Polypyrrole catalyst[7] is effective in the dehydrogenation of benzylamine with O_2 to make **8**. The same reaction[8] is also catalyzed by a aniline trimer. Monoamine oxidases[9,10] catalyze the oxidation of primary amines to give iminium cation that is hydrolyzed to form the aldehydes. Benzylamines[11] undergo oxidative coupling to give **8** by Mn(II)/tert-BuOOH. Here Mn(II) is oxidized to Mn(IV)=O by action of *tert*-BuOOH, which is the actual oxidizing agent for the multi-oxidation steps.

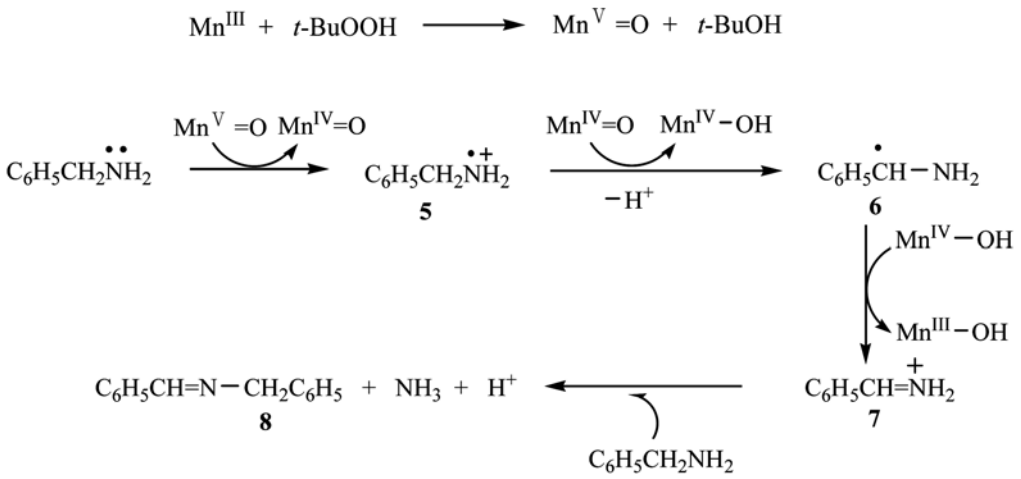
Variously substituted benzylamines undergo oxidative reactions to give **8** by the catalysis of Mn(V)=O that is formed from MnTPPCl/*t*-BuOOH. The series of reactions follow similar steps of reaction to those of reference 11. Mn(III) ion of MnTPPCl may make a complex with TBHP to give Mn(V)=O that may provoke electron transfer from benzylamine forming aminium cation, $C_6H_5CH_2\overset{+}{\cdot}NH_2$ **5**. **5** becomes acidic enough to expel benzylic proton to produce $C_6H_5\dot{C}H\text{-}\dot{N}H_2$ **6** that is oxidized by Mn(IV) with formation of $C_6H_5CH{=}\overset{+}{N}H_2$ **7**. Benzaldehyde might result from hydrolysis of **7**. However our control experiment at sub-zero temperature shows no trace of benzaldehyde (aldehydic proton : δ= 10 ppm) but indicates instead gradual increase of benzylic hydrogen of **8** (benzylic proton : δ = 4.84 ppm) with reaction time of 5, 10, 15, 30 min and 1 hr, respectively. This clearly tells hydrolysis of **7** do not occur at all. Instead **7** reacts with benzylamine to yield a complex that fragments to give **8** and NH_3 (Scheme 2 and Table 1).

The yield of *N*-benzylbenzaldimines stays within 90-95%. Electronic effects of substituents show no appreciable influence on yield. Comparable yields are observed between electron-withdrawing and electron-donating groups. Only *o*-, *m*-, dichlorobenzylamine (entry 8) takes reaction time of 4h for the oxidation. This may be due to steric hindrance of *o*-chloro-group. Neucleophilic addition of benzylamine to benzylidenemalonitriles in CH_3CN[12] is known to occur. α-Methylbenzylamine shows extremely slow reactivity towards the oxidation due to the steric effect of α-methyl group. Cyclohexylamine and *n*-heptylamine indicate no occurrence of the oxidative process. This could be ascribed to stronger bond dissociation energy of α-C-H that prevents cleavage of



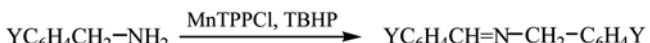
Scheme 1

[a]Dr. Thakur was a visiting scholar from Shree Shankaracharya College of Engineering & Technology on a grant from BK21 (2001).

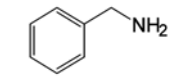
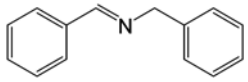
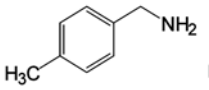
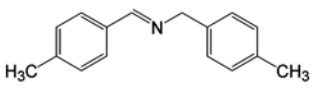
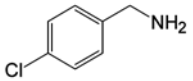
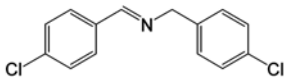
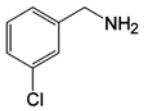
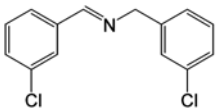
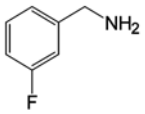
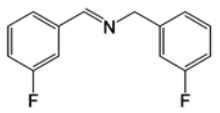
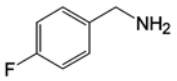
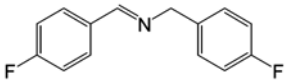
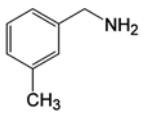
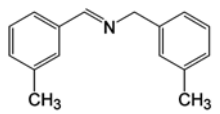
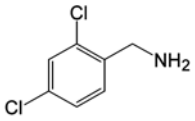
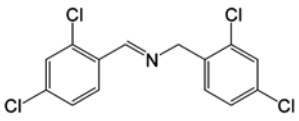


Scheme 2

Table 1. Oxidative Coupling of Benzylamines by MnTPPCl/TBHP



Substrate	TBHP	MnTPPCl	CH_3CN
1 mmol	1 mmol	0.01 mmol	1 mL

Entry	Substrate	Product	Yield[a,b]
1			94%
2			91%
3			93%
4			94%
5			93%
6			90%
7			91%
8			95%

[a]All the reactions were run for 1h except for entry 8. Entry 8 takes 4 h for the complete reaction to take place. [b]Isolated yield.

proton from **5**. $C_6H_5CH_2OH$ can hardly undergo oxidation because stronger oxidation potential may prohibit formation of **5**.

The reaction mechanism may involve oxo-manganese complex (Mn^V=O) which engenders electron transfer that is followed by deprotonation, oxidation, and coupling with extrusion of NH_3. The oxidation potential of $C_6H_5CH_2NH_2$ is quite important in determining the reactivity because $C_6H_5CH_2OH$ is not oxidized under the same condition. The oxidation is influenced by steric hindrance and α-C-H bond strength. Steric effect can be profound enough to delay the reaction in case of *o,p*-dichlorobenzylamine.

Experimental Section

Materials. All the reagents are commercially available from major supplier. MnTPPCl is the Manganese(III) 5,10,15,20–tetra(4-pyridyl)-21*H*,23*H*-porphine chloride tetrakis (methochloride) which is supplied from Aldrich.

Oxidative Coupling Reactions of Benzylamine by *tert*-Butyl Peroxide Catalyzed by MnTPPCl. $C_6H_5CH_2NH_2$ (1 mmol) was added at r.t. to solution of CH_3CN (1 mL) containing MnTPPCl (0.01 mmol). That was stirred for 15 min. *t*–BuOOH (1 mmol) was then mixed with the foregoing solution and the reaction went on for 1 h. The reaction mixture underwent evaporation with rotatory evaporator. The residue was put to Silicagel chromatography with 1 : 9 ratio of ethyl acetate/*n*-hexane. The product was identified utilizing ^1H and ^{13}C NMR, and mass spectrum.

Control Experiment for the Reaction Mechanism in Oxidative Couplings of Benzyl Aldehyde. Benzylamine (5 mmol), *t*–BuOOH (5 mmol), MnTPPCl (0.25 mmol) and CH_3CN (5 mL) were reacted in the same manner of the coupling reactions. An aliquot of reaction mixture was withdrawn periodically for the NMR analysis to detect the formation of C_6H_5CHO (δ= 10 ppm) and **4** (δ= 4.84 ppm). The analysis of NMR shows gradual formation of 4 and indicates asbsence of benzaldehyde.

***N*–Benzylbenzaldimine:** ^1H NMR ($CDCl_3$, 200 MHz): δ 4.88 (s, 2H), 7.40–7.49 (m, 8H), 7.83–7.85 (d, 2H), 8.45 (s, 1H).

^{13}C NMR ($CDCl_3$, 200 MHz): δ 64.9 (CH_2 aliphatic 1C), 126.8-136.6 (CH benzene 10C), 136.1 C=N-C benzene 1C), 139.2 (C benzene 1C) 164.8 (C from N-imine 1C). MS (EI, 70 eV) *m/z* 194 ($M^{\bullet+}$), 117, 104, 91.

***N*–(4–Methylbenzyl) 4–methylbenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ2.32 (s, 3H), 2.36 (s, 3H), 4.75 (s, 2H), 7.15–7.21 (m, 6H), 7.63–7.67 (d, 2H), 8.32 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 20.9 (CH_3 aliphatic 1C), 21.3 (N=C-CH_3 aliphatic 1C), 64.6 (CH_2 aliphatic 1C), 127.8–129.2 (CH benzene 8C), 133.6 (C=N-C benzene 1C), 136.3 (C benzene 2C), 140.8 (C benzene 1C), 161.5 (C from N-imine 1C). MS (EI, 70 eV): *m/z* 223 ($M^{\bullet+}$), 208, 131, 105.

***N*–(4–Chlorobenzyl) 4–chlorobenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ4.74 (s, 2H), 7.26–7.67 (m, 6H), 7.68–7.71 (d, 2H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 64.0 (CH_2 aliphatic 1C), 128.5-129.3 (CH benzene 8C), 132.7 (C benzene 1C), 134.3 (C=N-C benzene 1C), 136.7 (C benzene 1C), 137.5 (C benzene 1C), 160.7 (C from N-imine 1C). MS (EI, 70 eV): *m/z* 263 ($M^{\bullet+}$), 225, 151, 125, 89.

***N*–(3–Chlorobenzyl) 3–chlorobenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ4.75 (s, 2H), 7.23–7.62 (m, 6H), 7.78–7.79 (d, 1H), 8.29-8.30 (d, 1H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ64.1 (CH_2 aliphatic 1C), 125.9-130.8 (CH benzene 8C), 134.3 (C benzene 1C), 134.8 (C benzene 1C), 137.6 (C=N-C benzene 1C), 141.0 (C benzene 1C), 160.7 (C from N-imine 1C). MS (EI, 70 eV): *m/z* 263 ($M^{\bullet+}$), 228, 151, 25, 89.

***N*–(3–Fluorobenzyl) 3–fluorobenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ4.79 (s, 2H), 6.94–7.57 (m, 8H), 8.38 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ64.1 (CH_2 aliphatic 1C), 113.7-130.1 (CH benzene 8C), 138.1 (C=N-C benzene 1C), 160.9 (C benzene 1C), 161.7 (C benzene 1C), 161.7 (C benzene 1C), 164.2 (C from N-imine 1C). MS (EI, 70 eV): *m/z* 231 ($M^{\bullet+}$), 201, 135, 122, 109.

***N*–(4–Fluorobenzyl) 4–fluorobenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ4.49 (s, 2H), 6.94–7.76 (m, 6H), 7.78–7.79 (d, 2H), 8.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 64.0 (CH_2 aliphatic 1C), 115.1 (CH benzene 8C), 132.2 (C=N-C benzene 1C), 134.9 (C benzene 1C), 161.7 (C benzene 1C), 163.1 (C from N-imine 1C), 165.5 (C benzene 1C). MS (EI, 70 eV): *m/z* 231 ($M^{\bullet+}$), 212, 137, 122, 109.

***N*–(3–Methylbenzyl) 3–methylbenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ2.33 (s, 3H), 2.36 (s, 3H), 4.76 (s, 2H), 7.13–7.63 (m, 8H), 8.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ21.5 (N=C-CH_3 aliphatic 1C), 21.6 (CH_3 aliphatic 1C), 65.3 (CH_2 aliphatic 1C), 125.3-131.8 (CH benzene 8C), 136.3 (C=N-C benzene 1C), 138.3 (C benzene 2C), 139.4 (C benzene 1C), 162.4 (C from N-imine 1C). MS (EI, 70 eV): *m/z* 223 ($M^{\bullet+}$), 208, 131, 118, 105, 91, 77.

***N*–(3–Iodobenzyl) 3–iodobenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ4.72 (s, 2H), 7.02-7.71 (m, 6H), 7.72-7.75 (d, 1H), 8.13–8.14 (d, 1H), 8.24 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 64.4 (CH_2 aliphatic 1C), 94.9 (C benzene1C), 94.9 (C benzene 1C), 126.5-138.6, 143.3 (CH benzene 8C), 139.9 (C=N-C benzene 1C), 141.5 (C benzene 1C), 161.0 (C from N-imine 1C). MS (EI, 70 eV): *m/z* 447 ($M^{\bullet+}$), 320, 244, 217, 165, 90.

***N*–(2,4–Dichlorobenzyl) 2,4–dichlorobenzaldimine:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ4.85 (s, 2H), 7.19–7.34 (m, 5H), 8.01–8.06 (d, 1H), 8.77 (s, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ61.4 (CH_2 aliphatic 1C), 127.1-133.4 (CH benzene 8 C), 133.9 (C=N-C benzene 1C), 135.3 (C benzene 1C), 135.8 (C benzene 1C), 137.3 (C benzene 1C), 158.7 (C from N-imine 1C). MS (EI, 70 eV): *m/z* 333 ($M^{\bullet+}$), 185, 159, 123, 89.

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References

1. Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.
2. Hessel, L. W.; Romers, C. *Rec. Tran. Chem.* **1969**, *88*, 545.
3. (a) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10. (b) Fristad, W. E.; Hershberger, S. S. *J. Org. Chem.* **1985**, *50*, 1026. (c) Fristad, W. E.; Peterson, J. R.; Ernst, A. B. *J. Org. Chem.* **1985**, *50*, 3143. (d) Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429. (e) Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, *28*, 1493.
4. Kim, J. M.; Bogadan, M. A.; Mariano, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 10591.
5. Neumann, R.; Levin, M. *J. Org. Chem.* **1991**, *56*, 5707.
6. Bank, S.; Jewett, R. *Tetrahedron Lett.* **1991**, *32*, 303.
7. Higuchi, M.; Ikeda, I.; Hirao, T. *J. Org. Chem.* **1997**, *62*, 1072.
8. Hirao, T.; Fukuhara, S. *J. Org. Chem.* **1998**, *63*, 7534.
9. (a) Silverman, R. B. *Acc. Chem. Res.* **1995**, *28*, 355. (b) Silverman, R. B.; Wang, X. *J. Org. Chem.* **1998**, *63*, 7357.
10. Miller, J. R.; Edmondson, D. E. *Biochemistry* **1999**, *38*, 13670.
11. Kim, S. S.; Thakur, S.; Song, J. Y.; Lee, K. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 499.
12. Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 2188.