Amine Oxidation

Factors Influencing the Regioselectivity of the Oxidation of Asymmetric Secondary Amines with Singlet Oxygen

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Abstract: Aerobic amine oxidation is an attractive and elegant process for the α functionalization of amines. However, there are still several mechanistic uncertainties, particularly the factors governing the regioselectivity of the oxidation of asymmetric secondary amines and the oxidation rates of mixed primary amines. Herein, it is reported that singletoxygen-mediated oxidation of 1° and 2° amines is sensitive to the strength of the α -C–H bond and steric factors. Estima-

Introduction

Imines are valuable synthetic intermediates with a myriad of applications, including the synthesis of pharmaceuticals, dyes, as well as fine and agricultural chemicals.^[1] Traditional methods of imine preparation^[2] (Scheme 1a) suffer from drawbacks related to the need to remove water and the high reactivity of aldehydes, which often result in the formation of unwanted byproducts. For these reasons, the development of an alternative strategy for the direct oxidation of amines to imines has attracted much interest.^[3] A range of methods for the preparation of secondary imines by catalytic condensation of primary amines with alcohols (Scheme 1 b)^[4] or by homocondensation of the corresponding primary amines (Scheme 1 c) are known.^[5-9] The reported procedures for the cross-coupling of amines are generally limited to the use of anilines, sterically hindered amines, or alkyl amines in superstoichiometric amounts (Scheme 1 d).^[10] The majority of procedures for the oxidation of primary amines do not form aldimines, because oxidative coupling with the starting material yields imines bearing identical R groups (Scheme 1 c).

The use of singlet oxygen $({}^{1}O_{2})$ is an elegant, metal-free method for the oxidation of organic compounds.^[11-13] Recently,

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tion of the relative bond dissociation energy by natural bond order analysis or by means of one-bond C–H coupling constants allowed the regioselectivity of secondary amine oxidations to be explained and predicted. In addition, the findings were utilized to synthesize highly regioselective substrates and perform selective amine cross-couplings to produce imines.



Scheme 1. Methods for the synthesis of imines from amines.

we developed a fast and clean method for the oxidation of primary and secondary amines in a flow photoreactor.^[14,15] Precise control over reaction conditions allowed for divergence in product formation in the oxidation of primary amines. The expected oxidative coupling (Scheme 1 c) occurred in CH₂Cl₂ (0.5 M) at room temperature; however, conditions were found (THF, 0.1 M, -50 °C) under which nucleophilic attack of the unoxidized amine on the in situ-generated primary aldimine did not occur, providing the first example of unstable primary aldimines being efficiently generated from their corresponding amines.^[14] Subsequent treatment of the solution exiting the photoflow reactor with Me₃SiCN/*n*Bu₄NF or methyl cyanoacetate resulted in the formation of α -aminonitriles^[14] or α -cyano- α -ester epoxides,^[16] respectively.

Although the oxidation of amines by ${}^{1}O_{2}$ has been shown to be a powerful tool for their rapid functionalization, ${}^{[13, 14, 16]}$ factors that influence the regioselectivity of ${}^{1}O_{2}$ oxidation of mixed primary or unsymmetrical secondary amines have not

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Scheme 2. Selected examples of aerobic oxidation of asymmetric secondary amines and competing oxidation between electron-rich and electron-deficient benzylamines.

been studied.^[17] Reports of aerobic oxidations of asymmetric *para*-substituted secondary benzylamines^[18] did not describe any selectivity (Scheme 2).^[13,19]

Herein, we present our findings suggesting that the rate of ${}^{1}O_{2}$ -mediated oxidation of primary and secondary amines is directly proportional to the bond dissociation energy (BDE) of the C–H bonds adjacent to the nitrogen atom. The relative BDEs can be estimated theoretically by natural bond order (NBO) analysis or experimentally by means of ${}^{1}J_{CH}$ coupling constants obtained by NMR spectroscopy.^[20] These methods provided an estimation of C–H bond hybridization, and with these data we could predict the selectivity prior to oxidation. In addition, we show that the inherent selectivity can be overridden by significant steric hindrance (Scheme 1 e).

Results and Discussion

The commonly accepted mechanism for the oxidation of amines by ${}^{1}O_{2}$, generated by energy transfer from an excited dye, begins with the formation of an exciplex between ${}^{1}O_{2}$ and the lone pair of the amine (Scheme 3). Subsequent single electron transfer (SET) followed by deprotonation of the methylene proton leads to the benzylic radical shown in Scheme 3, path I. Alternatively, hydrogen-atom abstraction also results in the



Scheme 3. Proposed mechanisms for singlet-oxygen-mediated oxidation of secondary amines.

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same benzylic radical (path II). This radical can then undergo SET with a hydroperoxy radical to form an iminium ion, which is quickly deprotonated to yield the desired imine.^[21] According to both these mechanisms, hydrogen peroxide is formed as a side product, the presence of which has been observed and utilized previously.^[16]

We first examined electronic control of secondary amine oxidation in an attempt to determine the relevant effects and to clarify the nature of the process (path I or II), which is beset by inconsistencies in the prior literature. For example, Zhao et al.^[5k] reported that the stability of the radical formed on hydrogen-atom abstraction by ${}^{1}O_{2}$ determines the selectivity (path II), whereas König et al.^[21] found that the presence of electron-donating and electron-withdrawing groups on the benzyl ring increased and decreased the rate of oxidation, respectively, which indicates path I.

Evaluation of mechanistic path I

First, we explored the oxidation of *N*-benzyl-4-methoxybenzylamine (**1**, Figure 1): a 5 mgmL^{-1} solution of amine **1** and



Figure 1. Photooxidation of *N*-benzyl-4-methoxybenzylamine (1) and relevant (CH=N) ¹H NMR peaks.

tetraphenylporphyrin (TPP) (0.02 mg mL⁻¹, 1.5 mol%)^[22] in THF (2 mLmin⁻¹) was mixed with oxygen gas (2 mLmin⁻¹) via a Tmixer prior to entering the 7.5 mL flow photooxidation module at 25 $^{\circ}$ C.^[23] A back-pressure regulator (7 bar) was mounted at the end of the system to increase the solubility of oxygen gas. The reaction mixtures were analyzed by ¹H NMR spectroscopy immediately following solvent evaporation, as imines are known to be readily hydrolyzed and yields of the isolated products are strongly dependent on the purification process.^[24] The selectivity was determined by integration of the imine protons (CH=N) to give the relative ratio of the four oxidation products (2:3:4:5 1.00:1.14:0.94:1.04, Figure 1).^[25] Four products were observed as opposed to two as a result of hydrolysis and cross-condensation of the initial pair of imines (3/4) upon rotary evaporation of the crude reaction mixture in the presence of trace amounts of water.^[26]

lmines 2 and 3, formed by oxidation of the benzylamine side, do not isomerize to imines 4 and 5,^[24,27] and thus the ini-

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of 4%

tial ratio of photooxidation products, and hence the selectivity, can be quantified by the sum of the integrals for the respective peaks of the product pairs (2+3 and 4+5; 1.08:1.00).^[28] Other solvents such as ethyl acetate, toluene, and CH_2CI_2 afforded the same oxidation ratio. To determine whether the oxidation proceeds via a charged benzylic intermediate (path I), several *para*-substituted secondary amines were investigated (Table 1, entries 1–4).

Table 1. Correlation of A-side oxidation with the difference in $\% s$ $character.^{[a]}$							
Ph	$\frac{A}{H} \frac{B}{H} R \frac{O_2, \text{ TPP, LEE}}{\text{THF, R}}$	A-side oxidation $Ph \nearrow N \frown Ph$ $Ph \frown N \frown R$	B-side oxidation $R \sim N \sim Ph$ $R \sim N \sim R$				
Entry	R	∆%s cł NBO	naracter (B—A) ¹ J _{CH} /5	% of A side [O]			
1	4-OMePh	0.01	0.01	52			
2	4-NO₂Ph	-0.11	0.08	55			
3	4-MePh	0.01	0.00	52			
4	3,4,5-OMePh	0.03	0.02	57			
5	1-naphthyl	-0.19	0.00	52			
6	2-naphthyl	0.34	-0.01	55			
7	2-OMePh	0.26	0.36	71 ^[c]			
8	2-CIPh	0.36	0.44	62			
9	2-FPh	0.41	0.42	62			
10	2,6-CIPh	0.70	0.76	> 95			
11	2,6-FPh	0.66	0.88	90			
12	2,3,4,5,6-FPh	0.75	1.14	> 95			
13	Mes	0.36	0.01	81			
14	<i>t</i> Bu	-0.07	-0.41	43			
15	leelamine	_ ^[b]	-0.34	36			
16	1-adamantyl	-0.34	-0.51	38			
[a] Full conversion was observed for all substrates. For full experimental details, see the Supporting Information. [b] NBO analysis of this substrate was not performed. [c] Average yield over four experiments with a range							

The ratio of imine products obtained on photooxidation of the *p*-nitro-monosubstituted dibenzylamine derivative (1.2:1, Table 1, entry 1) was similar to the results obtained for the oxidation of the mono *p*-methoxy derivative. In fact, the introduction of substituents in either the *para* or the *meta* position did not lead to any significant differences in the oxidation selectivity, and oxidation of the unsubstituted benzyl side was slightly favored. Based on the relative acidities of *p*-NO₂- and *p*-OMesubstituted compounds ($pK_a = 10.8$ and 19.1 for phenols; 20.9 and 27 for anilines),^[29] we expected there to be a significant difference, as well as a switch in selectivity, if the reaction proceeded via path I. However, this was not observed, which suggests that the acidity of this proton does not significantly influence the outcome of the oxidation.

From what is known computationally of benzyl radicals,^[30] extension of the conjugated systems to naphthyl groups makes radical delocalization less efficient, and the calculated BDEs of 1-naphthyl and 2-naphthyl C–H bonds are higher than those of benzylic C–H bonds by about 1 kcal mol⁻¹. This is reflected in the poor selectivity observed (Table 1, entries 5 and

6) and led us to investigate the influence of BDE on oxidation selectivity.

Ortho-functionalized asymmetric dibenzylamines: a combination of electronic and steric effects

Further investigation of substitution of the aromatic ring revealed a good degree of selectivity for *ortho*-substituted asymmetric dibenzylamines (62–69%; Table 1, entries 7–9).^[31] Moreover, the photooxidation of *ortho*-disubstituted aromatics resulted in almost complete selectivity for oxidation of the unsubstituted benzyl side (90–95%; Table 1, entries 10–12).

Since inductive effects are only observed over short distances and electronegative substituents increase neighboring BDEs,^[32] we hypothesized that the BDE of the C–H bond is the main determinant of selectivity. An NBO analysis of the substrate scope was undertaken in an attempt to quantify this selectivity trend.^[33] A general trend was observed in which the C–H bonds adjacent to the nitrogen atom in the most selective substrates had higher differences in hybridization (%s character) than less selective substrates (Table 1). Hybrid orbital theory explains that an increase in hybridization of the carbon-centered orbital leads to a higher BDE (sp > sp² > sp³).^[34] The calculated differences in the %s character of the two C–H bonds α to the nitrogen atom are summarized in Table 1.

The %s character can also be determined experimentally from one-bond C–H coupling constants $({}^{1}J_{CH} = 5 \times \% s)$.^[35, 36] Coupled ¹³C NMR spectra were used to determine the ${}^{1}J_{CH}$ values of the two sets of C–H bonds α to the nitrogen atom in each substrate (Table 1). The differences in hybridization of the C-H bonds in the substrates indicate a strong inductive effect on hybridization. Incorporation of electronegative groups at the ortho position increases the electronegativity of the ipso carbon atom, and thereby p character is withdrawn from the adjacent benzylic carbon atom.^[37] As a result, less p character is available for the benzylic C-H bonds, hence the observed increase in s character. As the substrates examined only include aromatic rings substituted with groups more electronegative than hydrogen,^[38] we did not observe any preferential oxidation of the substituted side. Oxidation of the unsubstituted benzyl side was always preferred, that is, the difference in %s character is directly related to the rate of oxidation. Although this difference was higher for the difluoro- than for the respective dichloro-substituted compound (Table 1, entries 11 and 10, respectively), the observed ratio of imine products revealed a lower selectivity. Che et al.^[13] previously noted the importance of steric hindrance. In our case, the greater steric bulk of chlorine in comparison with fluorine (A values: 0.43 versus 0.15)^[39] can explain the observed selectivities.

For a more detailed investigation of steric effects, a mesityl derivative (Table 1, entry 13) was prepared. For this substrate, each of the benzyl C–H bonds has nearly the same %s character and should therefore result in a poorly selective oxidation. However, analysis of the photooxidation products revealed that oxidation occurred predominantly (81%) at the less hindered side (A value of CH₃ is 1.7),^[39] demonstrating that steric effects play an important role in selectivity as well.

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Changing the regioselectivity

On the basis of the above results, we hypothesized that by exchanging one of the aromatic rings with a group that is less inductively withdrawing, such as an sp³-hybridized alkyl group, the regioselectivity of oxidation could be tuned away from the benzylic position. However, efforts to study aliphatic amines were challenging due to the instability of the alkyl-substituted imines formed after oxidation,^[24] which prevented quantification of the reaction selectivity.^[40]

These issues are avoided when a quaternary carbon atom is in the β position of the alkyl chain.^[41] Oxidation of secondary amines bearing benzyl and neopentyl residues (Table 1, entries 14–16) did not result in high selectivity towards the benzyl side, as has been reported in other oxidation systems.^[42] Conversely, we observed an inversion in selectivity, with a slight preference for oxidation of the alkyl side (57–64%). These results were supported by the estimated differences in %s character, obtained by NBO analysis or ¹³C NMR spectroscopy (Table 1). The negative differences for these substrates reflects the stronger (higher %s character) C–H bonds of the benzylic side than the alkyl side, which leads to the predicted preference for oxidation away from the benzyl group.

Design of highly selective substrates

The differences in %s character could be used to design even more selective substrates. For example, an increase in the percentage of oxidation at the neopentyl side could be obtained by exchanging the benzyl group (Δ %s character: -0.07; Table 1, entry 14) with a more inductively withdrawing group such as 2-fluorobenzyl or 2,6-diflurobenzyl (Δ %s character: -0.44 and -0.72, respectively, Table 2, entries 1 and 2). The latter (Table 2, entry 2) resulted in almost complete selectivity (92%) for oxidation on the alkyl side. Moreover, photooxidation of the dichloro derivative (Table 2, entry 3) resulted in selective oxidation of the alkyl side, with only trace amounts of benzyl-side oxidation. These results are in complete agreement with the described stereoelectronic effects (Table 1).

To further illustrate the influence of steric hindrance on selectivity, we replaced the benzyl group of *N*-benzylneopen-

Table 2. Electronic and steric effects enhance oxidation selectivity awayfrom an aromatic ring.							
R N H	$\bigvee \frac{O_2, \text{ TPP, I}}{\tau_{\text{res}}}$	LED 420 nm	A-side oxidation $R \frown N \frown tBu$ $R \frown N \frown R$	B-side oxidation tBu N tBu tBu N R			
Entry F	R	Δ %s char NBO	acter (B—A) ¹ J _{CH} /5	% of A side [O]			
1 2	2-FPh	-0.44	-0.81	29			
2 2	2,6-FPh	-0.72	-1.35	8			
3 2	2,6-ClPh	-0.76	-1.17	< 5			
4 N	Mes	-0.42	-0.43	12			
[a] Full conversion was observed for all substrates. For full experimental details, see the Supporting Information.							

tylamine with a mesityl group (Table 2, entry 4). Photooxidation now occurred predominantly on the alkyl side with 88% selectivity. To the best of our knowledge, these results are the first examples of selective imine formation as the result of amine oxidation away from the benzylic position of a disubstituted amine.

A plot of the oxidation selectivity versus the difference in %s character is shown in Figure 2.^[43] Substrates with little influence over the selectivity occupy the middle of the graph, whereas those with groups that exhibit a slow rate of oxida-



Figure 2. Percentage A-side oxidation (see Tables 1 and 2) plotted versus the difference in %s character between the C–H bonds on the A and B sides, as determined experimentally. Labels for the data points *x.y* represent Table *x*, entry *y*. The plot (only diamonds) was fitted by means of a linear fit with the equation y = 34.3x + 53.6. The uncertainty due to NMR integration is represented by the error bars (see Supporting Information for equation). Entries for which steric hindrance has a significant impact are shown in circles (see Figure 3).

tion relative to benzyl lie in the upper right corner. Those with increased rates^[44] resulting in selectivity towards the alkyl side lie in the bottom left. We propose that the plot in Figure 2 can be used as a predictive model for asymmetric secondary amines bearing substituents that lack significant steric bulk. In addition, we believe that relative steric effects can be accounted for in structurally similar groups (2,6-F/Cl/Me versus H) according to their respective *A* values.^[39]

The data points shown in circles (Figure 2) were not used for the linear fit due to the influence of steric bulk on the reaction selectivity. Figure 3 depicts the percentage of deviation of *ortho*-disubstituted examples from the predictive model versus their respective A values.^[39,45] For dibenzyl amines, positive A values are used, placing the data point in the upper right quadrant of the plot, whereas for benzyl alkyl amines, the opposite of the respective A value is used, placing the data point in the lower left quadrant. The observed linear dependence nicely shows that steric effects complement the inherent elec-

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Figure 3. Percentage deviation from the predictive model plotted versus the *A* values. Positive *A* values correspond to R^2 groups containing sterically bulky substituents and negative *A* values to R^1 groups with sterically bulky substituents. Positive deviation means the points lie above the fitted line and negative values correspond to points that lie below the line. Labels for the data points *x*,*y* represent Table *x*, entry *y*.

tronic influence (Figure 2), which allows for the prediction of the regioselective outcome for secondary amine oxidations.

Selective cross-condensation of amines

We expected the selectivities observed above to translate into the rates of oxidation for primary amines as well. For example, due to the difference in their %s character (0.88), the photooxidation of an equimolar mixture of 2,6-difluorobenzylamine (**9**, 27.78 %s) and benzylamine (**8**, 26.90 %s) was expected to exhibit a similar degree of selectivity to that observed for the respective secondary amine (90%, Scheme 4a).^[46] To avoid formation of *N*-benzylidenebenzylamine (**4**), which results from the condensation between benzylamine and benzaldimine, the photooxidation was performed at -50 °C in THF (conditions for generating primary imine).^[14] Imine **7** was indeed obtained

a) Selective Oxidation of Asymmetrical 2° Amine



b) Utilization of Selective Amine Oxidation for an Oxidative Coupling of 1° Amines



c) Oxidative Coupling of 1° Amines with Similar %s Characters of C Attached to N Atoms



Scheme 4. Strategies for selective oxidative imine synthesis.[46]

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in 85% yield,^[46] corresponding to oxidation of the unsubstituted benzyl amine (Scheme 4b).

For two amines bearing C-H bonds with similar %s character adjacent to the nitrogen atom, such as benzylamine (8) and *p*-methoxybenzylamine (12), similar rates of oxidation would be expected, as is evidenced by the lack of selectivity in the corresponding secondary amine (Table 1, entry 1). Accordingly, when a 1:1 mixture of 8 and 12 (each with 26.90 %s) underwent photooxidation under oxidative coupling conditions (CH₂Cl₂, RT) four imine products were obtained in a ratio of 1.2:1 favoring the unsubstituted side. These results were similar to those reported in Table 1 (entry 1) and were consistent with the literature reports on oxidations of amine mixtures.^[19c] The desired secondary imine 13 could, however, be efficiently generated from amines with similar benzylic C-H bonds by first oxidizing one of them ($\mathbf{8}$, -50 °C, THF) and treating the resulting primary aldimine 10 with amine 12, as shown in Scheme 4c, which gave 92% of 13 as a pure compound following evaporation. Simply exchanging the substrates results in the formation of the opposite imine 15 in 94% yield.

Conclusion

We found that the selectivity observed in singlet-oxygen-mediated oxidations of primary and secondary amines is determined by the BDE of the competing C-H bonds adjacent to the nitrogen atom. This suggests that oxygen-mediated oxidations likely proceed via a hydrogen-atom abstraction pathway (Scheme 3, path II). NBO analysis and NMR spectroscopy can be used as predictive tools to estimate the differences in %s character. Good and excellent selectivity could be observed with differences greater than 0.3 and 0.7%, respectively. In addition, it was shown that steric hindrance plays an important role in the regioselective outcome and can overpower the intrinsic preferences. The predictive power of these differences can be utilized not only for photooxidation of asymmetrical secondary amines, but also for primary amines. Finally, to the best of our knowledge, we have given the first accounts both of selective imine formation away from a benzylic position as well as the selective equimolar cross-coupling of two different amines, without the limitation of using aromatic or sterically hindered amines.

Experimental Section

General procedure for the photooxidation of secondary amines^[47]

A solution of amine (50 mg) and TPP (1 mg) in THF (10 mL) was pumped by a Vapourtec R2 + pump with a flow rate of 2 mL min⁻¹. In an ETFE T-mixer (IDEX Health and Science) the substrate solution was mixed with oxygen (99.995%, < 3.0 ppm mol⁻¹ H₂O; ALPHA-GAZ 1 O₂, Werk DEF 2 Krefeld-Gellep), which was delivered from an oxygen gas tank. Gas pressure was regulated to 20 bar and the flow adjusted to 5 mL min⁻¹ with a gas-flow controller (Influx, SV1B5-AlO5). This solution was then pumped through the 7.5 mL photoreactor consisting of fluorinated ethylene–propylene copolymer (FEP) tubing (IDEX Health and Science, natural color, 1.57 mm

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outer diameter, 0.76 mm inner diameter) wrapped around a glass plate ($7 \times 9 \text{ cm}^2$) in two layers. A 30 cm piece of tubing was used for connection of the T-mixer with a photoreactor. A 0.5 mL precooling loop covered with aluminum foil was placed additionally in the bath before the photoreactor. An LED module (OSA Opto Light, OLM-018 B, 420 nm emission wavelength, 72 W; Manson HCS-3202 power supply) was mounted in front of this plate at a distance of 3 cm. The photoreactor was suspended in a water bath. A piece of FEP tubing (30 cm) was used for connection of the outlet of photoreactor to a 7 bar back-pressure regulator (average pressure in the system was around 9 bar). The residence time in the photoreactor was performed at 30 °C. Analysis of the product mixture was performed by relative integration of characteristic and non-overlapping signals of imines in ¹H NMR spectra.^[48]

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- [43] Experimentally derived values for the differences in %s character were used. NBO-derived values can also be used (see Figure S1 in the Supporting Information).
- [44] Relative to benzyl.
- [45] For the optimized three-dimensional structures of secondary amines bearing sterically bulky groups, see the figures in Table S4 in the Supporting Information.
- [46] Yields were determined by ¹H NMR spectroscopy with 1,2,4,5-tetramethylbenzene as an internal standard.
- [47] For the graphical scheme, see the Supporting Information.
- [48] For the list of the peaks used for determining the product ratio by ¹H NMR spectroscopy, see the Supporting Information.

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FULL PAPER

Amine Oxidation

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Factors Influencing the Regioselectivity of the Oxidation of Asymmetric Secondary Amines with Singlet Oxygen



Selective imine synthesis: The influence of electronic and steric factors on the singlet-oxygen-mediated oxidation of 1° and 2° amines was investigated. Estimation of the relative bond dissociation energy (BDE) by natural bond order (NBO) analysis or from one-bond C–H coupling constants allowed the regioselectivity of secondary amine oxidations to be explained and predicted, and the findings were utilized to design a selective approach towards 2° imines by oxidative cross-couplings of 1° imines (see scheme).

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