Iron-Mediated Aminations

Intramolecular Aromatic Amination through Iron-Mediated Nitrene Transfer**

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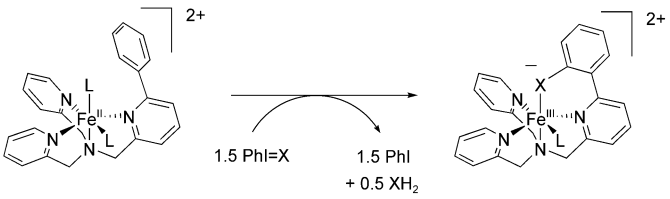
Much attention has been concentrated on metal-catalyzed atom and group transfers to organic molecules as a strategy for carbon–heteroatom bond formation in synthetic organic chemistry. Similar to isolobal epoxidation reactions,[1] nitrene (that is, RN=) transfer to olefins (that is, aziridination) can be catalyzed by metalloporphyrins,[2] iron corroles,[3] as well as low-coordinate copper complexes and salts.[4] Nitrene insertions to give aliphatic C–H bond aminations have also been effected by metalloporphyrins or cytochrome P450.[5,6] In contrast, metal-catalyzed arene amination is practically unknown,[6] even though free organonitrenes will readily add to aromatics.[7] Substoichiometric and unselective naphthalene amination by an uncharacterized adduct of iron(II) chloride and chloramine-T has been reported,[8] along with a handful of possibly analogous organometallic ligand transformations.[9] By analogy to oxoiron species that mediate heme monooxygenase chemistry,[10] high-valent imido complexes are typically invoked as reactive intermediates in these amination reactions,[2,11] although imido complexes of iron are generally very rare.[12] Recently, we reported the efficient intramolecular *ortho*-hydroxylation of an α-phenyl substituent on a non-heme iron(II) complex of modified tris(2-pyridylmethyl)amine (TPA), $[(6\text{-PhTPA})Fe^{II}(NCCH_3)_2](ClO_4)_2$, driven by added *tert*-butyl hydroperoxide (^{t}BuOOH).[13] Indirect evidence suggested the formation of an oxoiron(IV) reactive hydroxylating species. Given the precedence for the use of iodonium ylides as oxene and nitrene precursors,[14] specifically including the conversion of $[(TMC)Fe^{II}(OTf)_2]$ to $[(TMC)Fe^{IV}{=}O](OTf)_2$ (TMC = tetra-*N*-methylcyclam),[15] we investigated the reactivity of $[(6\text{-PhTPA})Fe^{II}(NCCH_3)_2](ClO_4)_2$ with iodosobenzene (PhIO) and phenyl-*N*-tosylimidoiodinane (PhINTs). We report herein efficient and selective *ortho*-hydroxylation and amination reactions of the α-aromatic substituent afforded by these respective reagents (Scheme 1).[16,17]

Aliquots of a stock solution of $[(6\text{-PhTPA})Fe^{II}(NCCH_3)_2]^{2+}$ (1.0 mM in acetonitrile) were added to solid samples of the PhI = X (X = O, NTs) reagents, and the resulting suspensions were stirred vigorously at room temperature, either anaerobically or in air. The initially pale-yellow solutions turned dark blue as the solids dissolved; this required about 1–2 min for PhINTs, and 20–30 min for PhIO. UV/Vis spectra of the stable endpoint chromophores were recorded, revealing distinct Fe^{III} ligand-to-metal charge-transfer (LMCT) bands suggestive of differential *ortho* substitutions of the phenyl substituent (Figure 1). The intensities of these bands were found to depend on the stoichiometric ratio, with maxima obtained at approximately 1.6:1.0 PhI=X/Fe^{II} for both reagents, irrespective of the presence of oxygen, thus supporting the stoichiometry of Scheme 1. Further addition of iodonium reagents resulted in irreversible bleaching of these chromophores.



Scheme 1. Overview of the hydroxylation (X = O) and amination (X = NTs) reactions; L is presumably CH_3CN.

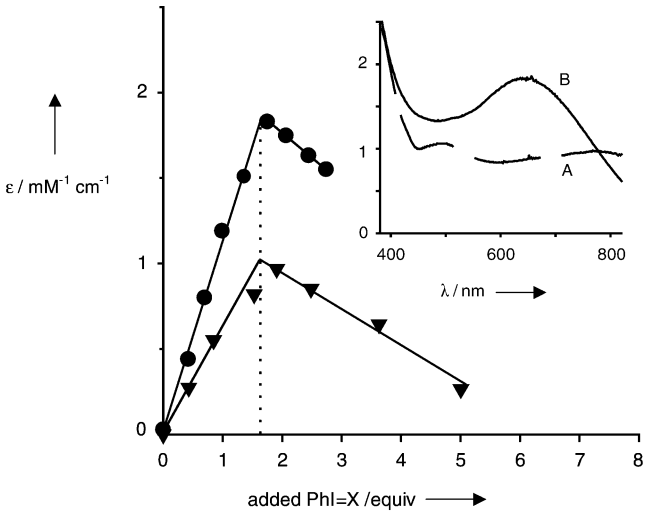


Figure 1. Plot of product LMCT extinction versus PhI = X stoichiometry (X = O, ▼, 780 nm, anaerobic reaction; TsN, ●, 650 nm, aerobic reaction); inset shows PhIO (A) and PhNTs (B) product spectra. All data recorded in CH_3CN solution at 228 K from reactions carried out at room temperature.

The PhIO product chromophore was entirely consistent with the formation of $[(6\text{-}(o\text{-O-}C_6H_4)\text{-TPA})Fe^{III}(NCCH_3)]^{2+}$, as observed in the tBuOOH reaction, and the maximum extinction was consistent with a 65% yield.[13] The PhINTs-derived chromophore was assigned to formation of $[(6\text{-}(o\text{-TsN-}C_6H_4)\text{-TPA})Fe^{III}(NCCH_3)]^{2+}$, the tosylanilide analogue of the previously characterized *ortho*-phenolate complex. Precipitation of the TsNIPh product solution with cold toluene afforded an amorphous blue powder, the sulfur content of which was consistent with ≥63% incorporation of

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one TsN equivalent into the isolated crude product.[18] Unequivocal evidence for nitrene addition was obtained by electrospray ionization mass spectrometry, which yielded cations at m/z 590.3 and 621.4, consistent with the respective formulations $[(6\text{-}(o\text{-TsN-}C_6H_4)\text{-TPA})Fe^{II}]^+$ and $[(6\text{-}(o\text{-TsN-}C_6H_4)\text{-TPA})Fe^{III}(OMe)]^+$. The product obtained from $[(d_5\text{-PhTPA})Fe^{II}(NCCH_3)_2]^{2+}$ gave product cations at m/z 594.3 and 625.4, showing the loss of one deuterium atom, while the use of isotopically enriched $PhI^{15}NTs$ showed the expected one-mass-unit upshift. Taken together, these results are uniquely consistent with the substitution of a tosyl nitrene group for hydrogen on the 6-phenyl ring.

Investigation of the product chromophores by resonance Raman spectroscopy provided clear evidence for participation of donor atoms bearing the anticipated *ortho*-aryl substituents in the putative LMCT bands (Figure 2). The

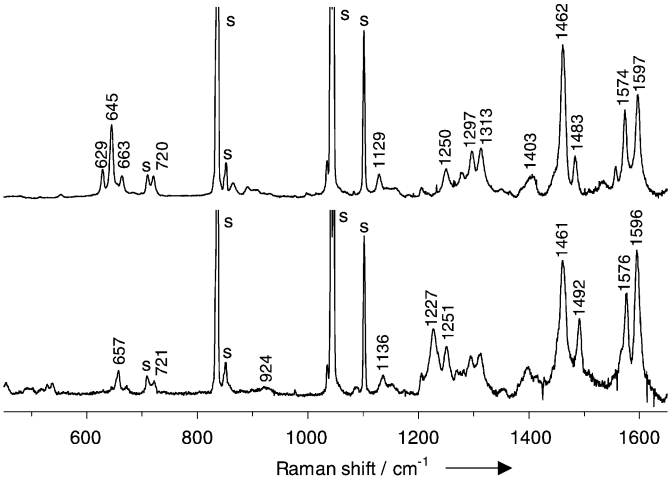

Figure 2. Resonance Raman spectra (647.1 nm excitation) of LMCT chromophores for the PhIO (top) and PhINTs (bottom) reactions, recorded from frozen CD_3CN solutions.

PhIO product gave a response characteristic of the monomeric phenolate complex $[(6\text{-}(o\text{-O-}C_6H_4)\text{-TPA})Fe^{III}(NCCH_3)]^{2+}$,[13] while the PhINTs reaction product exhibited a surprisingly similar, yet distinct, spectrum. Despite the lack of resonance Raman data on metal anilide complexes in the literature, modes at 657 and 1227 cm^{-1} in the latter spectrum were assigned to vibrations with predominant $\tilde{\nu}$(Fe-N) and $\tilde{\nu}$(C-N) character, respectively, by analogy to modes at 645 and 1250 cm^{-1} in the phenolate spectrum.[19]

High-resolution electrospray mass spectral and NMR spectroscopic data were obtained from product ligands stripped from the metal ion by the addition of aqueous NH_4OH and recovered by extraction into diethyl ether. The aniline ligand was characterized by a parent cation corresponding to $[6\text{-}(o\text{-TsNH-}C_6H_4)\text{-TPA-H}]^+$ with $m/z =$ 536.21108 amu (versus $m/z = 536.21147$ calcd for $C_{31}H_{30}N_5O_2S$); an ion shift to m/z 540.23652 amu was recorded for the 6-d_5-PhTPA product (versus m/z 540.23658 amu calcd for $C_{31}H_{26}D_4N_5O_2S$). ^{1}H NMR analysis revealed the PhINTs product extracts to be a mixture of the expected *ortho*-*N*-tosyl aniline product, unmodified 6-PhTPA, and 6-$(o\text{-HO-}C_6H_4)$-TPA in a 1.0:0.3:0.1 ratio in C_6D_6 solution (Figure 3). Also observed in the extracts was 0.3 equiv $TsNH_2$

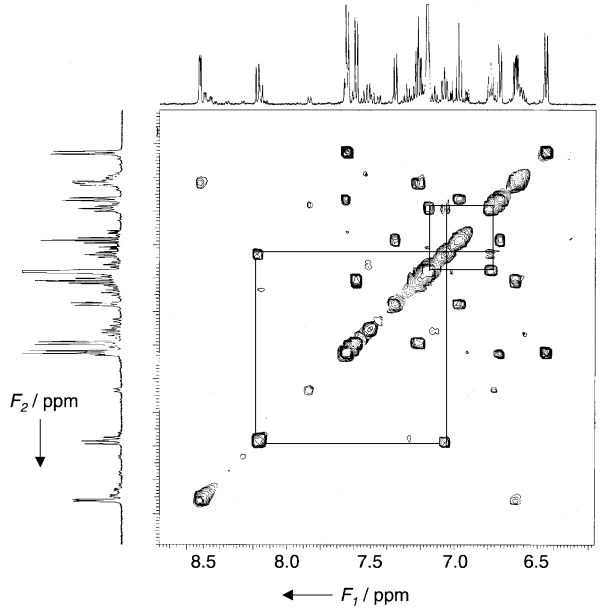

Figure 3. ^{1}H NMR COSY plot (500 MHz) of ligand extracts from PhINTs reaction in C_6D_6 solution at 293 K. Cross-peaks arising from the arene ring of the aniline product are denoted.

per aniline molecule, but no PhI. Total ligand recovery of 70% against charged 6-PhTPA was determined by integration against an internal standard (BHT). Attribution of the missing mass to handling losses would imply 70% overall anilide formation resulting from $\approx$80% oxidative conversion of 6-PhTPA with $\approx$90% selectivity for anilide. This assessment was consistent with the UV/Vis spectrum, which clearly lacked significant contribution from the phenolate LMCT chromophore near 780 nm, and with the sulfur analysis. The 0.3 equiv $TsNH_2$ formed per mole of aminated 6-PhTPA is in accordance with the stoichiometry shown in Scheme 1. Regardless, 6-$(o\text{-TsNH-}C_6H_4)$-TPA was recovered in 50% absolute yield, so the least-favorable limits accommodated by the product distribution are $\geq$60% selectivity for anilide and $\geq$55% oxidative ligand conversion, and these lower limits are inversely correlated. ^{1}H NMR signals of 6-$(o\text{-TsNH-}C_6H_4)$-TPA were distinct from those of authentic 6-$(o\text{-HO-}C_6H_4)$-TPA and consistent with the formulation (Figure 3). Doublets at 7.64 and 6.45 ppm ($^3J_{HH} = 7.5$ Hz) and a singlet at 1.67 ppm, in a 2:2:3 intensity ratio, were assigned to the tosyl substituent. The aryl ring gave rise to four signals at 8.18 (H'_m, adjacent to the *ortho* amino group, dd: $^3J_{HH} = 8.0$ Hz; $^4J_{HH} =$ 1.0 Hz.), 7.06 (H_p, ddd: $^3J_{HH} = 8.0$, 7.2 Hz; $^4J_{HH} = 1.0$ Hz), 6.78 (H_m, ddd: $^3J_{HH} = 8.0$, 7.2 Hz; $^4J_{HH} = 1.0$ Hz), and $\approx$7.16 ppm (H_o, overlap with solvent); these signals were absent in the 6-d_5-PhTPA product spectrum. A singlet at 12.98 ppm ($^1J_{^{15}N\text{-}^1H} =$ 81 Hz) was assigned to the aniline proton, *H*N(Ts)Ar, and the

striking downfield shift was suggestive of hydrogen bonding to other nitrogen atoms.

Extracted product ligands from the PhIO reaction were determined to be a mixture of the 6-*o*-HO-C_6H_4-TPA product phenol and unmodified 6-PhTPA, in a 1.8:1.0 ratio in $CDCl_3$ solution; a total ligand recovery of 68% was obtained. Again assuming mass loss resulted solely from handling, the estimated total yield of phenol was 64%, in accord with the UV/Vis spectrophotometric yield.

The use of an *ortho*-deuterium isotope label (that is, 6-*o*-d_1-PhTPA) gave evidence of fractional 1,2 hydrogen shifts ("NIH shifts")[20] in both PhI=X oxidations. ^{1}H NMR analysis indicated the formation of three product ligand isotopomers, *o*-d_1, *m*-d_1, and d_0, respectively resulting from *ortho* substitution at the unlabeled carbon atom, or substitution at the labeled carbon atom with either deuterium migration to the *meta* carbon position, or loss of deuterium. Thus, the fraction of the first isotopomer corresponded to an intramolecular isotope effect ("k_H/k_D"), and the ratio of the latter two gave the NIH shift. For three PhIO reactions, an average respective phenol isotopomer distribution of 48.1(4):24.5(9):27.4(9) was observed. A single determination of 77(1)% total deuterium retention was obtained by mass spectrometry. Correction of these data for residual ^{1}H atoms in the labeled site (3(1)%) yielded $k_H/k_D = 0.98(4)$, and a 50(3)% NIH shift. These results were identical to those obtained for the ^{t}BuOOH reaction, consistent with formation of a common hydroxylating intermediate, namely an oxoiron(IV) species.[13]

The average of three PhINTs reactions yielded a 55(2):24(2):21(4) isotopomer ratio for the product aniline, and 68(1)% deuterium retention was measured in one trial by mass spectrometry. These data yield $k_H/k_D = 1.3(1)$, and a 57(7)% NIH shift. The data indicate a shift from inverse to normal for the isotope effect of the reaction of a presumed tosylimidoiron(IV) species compared to an oxoiron(IV) species. This change reflects an increased contribution to the transition state for hydrogen-atom transfer (Scheme 2; step b, $k_H/k_D > 1$) relative to attack of the more electrophilic nitrene (Scheme 2; step a, $k_H/k_D < 1$).[21] This result represents the first observation of an NIH shift for an aromatic substitution other than a hydroxylation.

In conclusion, we have demonstrated efficient non-heme iron-mediated oxene and nitrene transfer reactions from iodonium ylides to give selective aromatic hydroxylation and amination, the latter representing an entirely novel class of reactivity. The present results strongly suggest a common reaction mechanism involving the formation of oxo- and imido-iron(IV) species as reactive intermediates (Scheme 2). Proportional consumption of iron(II) ions and the accumulation of a chromophore with increasing PhI=X addition (Figure 1) is consistent with operation of an Fe^{II}/Fe^{IV} couple in the reaction; rapid oxidation to the final iron(III) product complex apparently occurs after arene modification. Given the utility of the Fe(TPA) family of catalysts for olefin epoxidation and *cis*-dihydroxylation,[22] the possibilities of analogous olefin aziridination and hydroxyamination, and even aromatic amination, are clearly implied. Moreover, the apparent generation of an imidoiron(IV) species suggests the possibility of complementing the recent characterization of high-valent non-heme oxoiron(IV) complexes.[15] Finally, we also note that iron–anilide coordination chemistry is curiously sparse, and that the reactivity discovered here should afford a general route towards a range of such complexes.[13]

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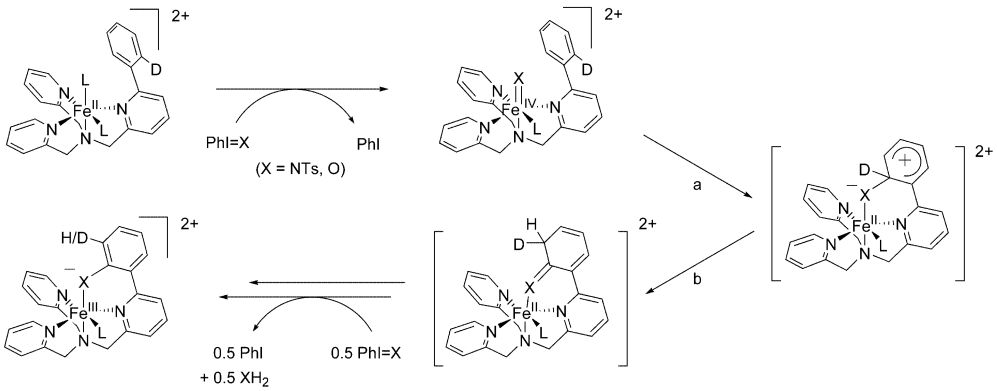

Scheme 2. Common mechanism for observed NIH shifts in the hydroxylation and amination reactions; L is presumably CH_3CN.

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