Metal Free Amino-Oxidation of Electron Rich Alkenes Mediated by an Oxoammonium Salt

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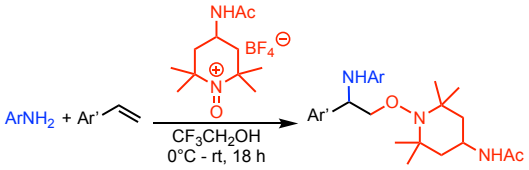


Abstract: 4-Acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (Bobbitt's salt) effectively activates electron rich alkenes and promotes the addition of anilines. This transformation provides a direct, transition metal free method for amino-oxidation of alkenes under mild conditions. The relative stereochemistry of the amino-oxidation is influenced by solvent effects, with both the syn and anti amino-oxidation products being accessible from identical starting materials.

Keywords: alkenes, amination, oxidation, oxoammonium, regioselective

The aminohydroxylation of alkenes is a powerful transformation to directly access amino-alcohols. Typically this reaction is performed using osmium based reagents (as in the Sharpless Aminohydroxylation[1]), but more recently copper catalysis,[2] palladium catalysis[3] and iridium photocatalysis[4] have also been applied to similar transformations. Less common is amino-oxygenation under metal free conditions, although some progress has been made in this area recently.[5] Interest in 1,2-aminoalcohols remains high, as these systems continue to be discovered in interesting molecules. Differentially substituted 1,2-aminoalcohols and related structural motifs are

common in complex natural products (Figure 1). Many of these examples possess significant biological activity (like bocconoline **1**[6] and oriciacridone A **2**[7]) or interesting structural features (like paniculidine F **3**[8]). A number of biologically active medicinal compounds like the norepinephrine uptake inhibitor **4**[9] and the antitumor agent AG-120 **5**[10] also possess a similar arrangement of functionality.

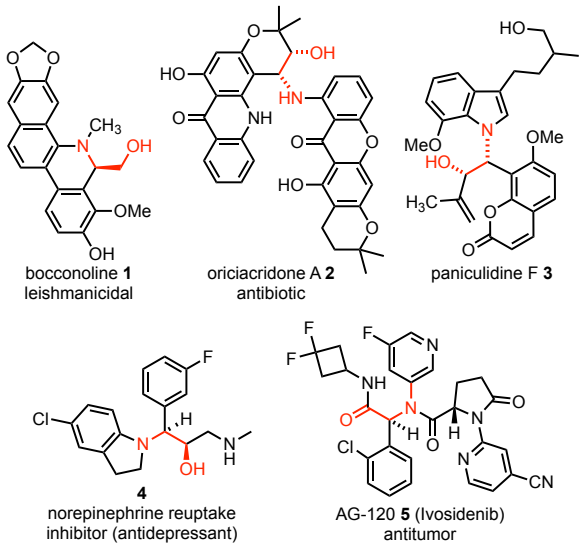


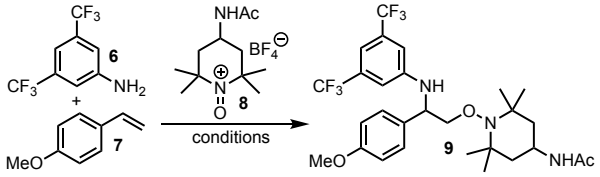
Figure 1. Amino-alcohols and Related Systems in Complex Molecules

Recently we began to evaluate the use of *N*-oxoammonium salts to promote a metal free amino-oxygenation of alkenes. *N*-Oxoammonium salts are most often used to oxidize alcohols to aldehydes and carboxylic acids,[11] but recent reports of allylic oxidation[12] and C-H activation[13] demonstrate that these salts are versatile organic oxidizing agents. An underutilized property of these reagents is their ability to activate alkenes for direct nucleophilic attack.[14] This was first described by Endo and co-workers, who noted that a chloro-oxoammonium salt gave chloro-oxidation products with electron rich alkenes.[15] More recently Liu and co-workers used an oxoammonium perchlorate salt and TMSCN in a carbotherification of enol ethers[16] and vinyl azides.[17] Donohoe and co-workers have also described the *in situ* formation of the *N*-oxoammonium salt, which then activates an alkene and provides a 1,2-dioxygenation product in a similar fashion.[18] To date the only amino-oxygenation reported with *N*-oxoammonium salts was made by Brower and co-workers who utilized an oxoammonium nitrate salt and silylated *N*-heterocycles to add to enol ethers,[19] and then applied these transformations to the synthesis of nucleoside analogs. These amino-oxidation reactions were limited to enamides

and enol ethers, with the authors noting that styrenes gave no addition products with nitrogen nucleophiles.

Inspired by the work of Donohoe[18] and Brower,[19] we began to explore the possibility of utilizing oxoammonium salts in a single step method for the amino-oxygenation of alkenes. Electron poor anilines were initially evaluated as the nitrogen source, as these systems have been shown to behave almost like alcohols when alkylated with trichlroroactimidates,[20] and therefore we felt that they would participate in alkene functionalizations like the previously utilized alcohols.[18] Additionally, some electron poor anilines (such as 2,4-dinitroanilines) can be removed by treatment with hydroxide to reveal the corresponding amine.[21] Bobbitt's salt **8** (4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate)[22] was chosen as the oxoammonium salt, as this reagent is stable and can be synthesized on large scale from inexpensive starting materials. Using 3,5-bis-trifluoromethylaniline **6**, 4-methoxystyrene **7** and Bobbitt's salt **8** as reactants, the potential for a direct metal free amino-oxidation was explored. Mixing the three reagents together in THF gave a promising 57% yield of the amino-oxidation product **9** (Table 1). The reaction seemed slow, however, and the oxoammonium salt had difficulty dissolving in the THF. Further optimization led to 2,2,2-trifluoroethanol emerging as the best solvent, which facilitated a rapid reaction in 98% isolated yield. MeCN, DMF and DCM also gave good yields of the addition product. Increasing the scale of the reaction to 2 mmols (entry 10) provided a very similar 92% yield (1.06 g of **9** was prepared in this reaction).

Table 1. Reaction of Aniline 6 with 4-Methoxystyrene 7 and Bobbitt's Salt 8[a]

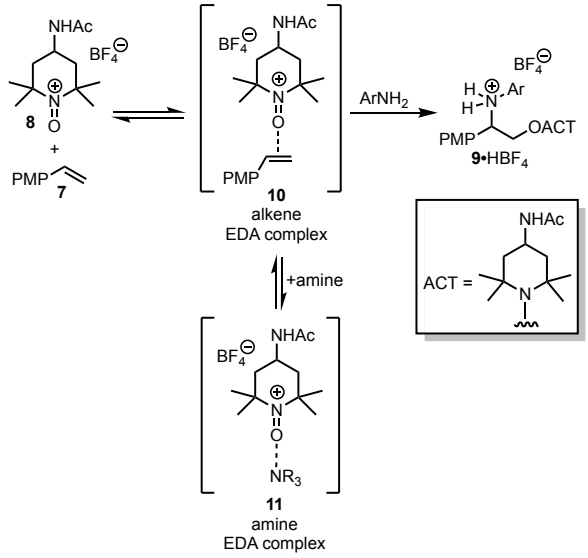


entry	solvent	time (h)	yield (%)
1	THF	20	57
2	THF	2	13
3	EtOH	20	38
4	EtOH	2	35
5	TFE[b]	20	94
6	TFE	2	98
7	DCM	2	94
8	DMF	2	92
9	MeCN	2	96
10[c]	TFE	2	92
11[d]	TFE	2	96
12[e]	TFE	2	0
13[f]	TFE	2	0

[a]Reaction conditions: 1 equiv of **6** and 1 equiv of **7** were dissolved in the solvent (0.2 M) and oxoammonium salt **8** (1.2 equiv) was added. [b]TFE = 2,2,2-trifluoroethanol; [c]Reaction was performed on 2 mmol (1.06 g of product) scale.; [d]One equiv of Na_2CO_3 was added; [e]One equiv of DBU was added; [f]One equiv of TMG was added.

Oxidation reactions with oxoammonium salts like **8** are often facilitated by the addition of an amine base.[11b,23] This is attributed to the HBF_4 side product generated from the reaction being problematic as it could polymerize the styrene **7** or protonate the aniline **6**, rendering the amine unable to participate in the addition. The addition of exogenous base was therefore evaluated. Addition of an inorganic base like sodium carbonate (Table 1, entry 11) had little effect, while the addition of strong amine bases like DBU and TMG (entries 12 and 13) proved to be detrimental and provided no product. The inhibition of the reaction with added DBU or TMG was attributed to the formation of an electron donor-acceptor (EDA) complex between the amine and the *N*-oxoammonium salt (complex **11**, Scheme 1). This amine EDA complex is hypothesized to compete with the alkene, slowing formation of an EDA complex with the alkene (**10**), which is required for the reaction to proceed as described in the proposed reaction mechanism below (Scheme 1). Addition of the aniline to the EDA complex **10** may occur through direct addition or through a stepwise mechanism to access the observed amino-oxidation product. EDA complexes similar to **10** have been proposed for other *N*-oxoammonium salt mediated alkene addition reactions where cyanide ion was utilized as the nucleophile.[16]

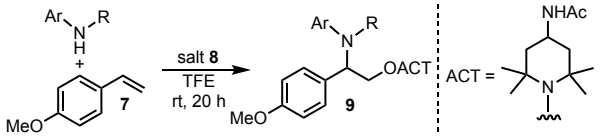
Scheme 1. Proposed Mechanism of the New Metal Free Amino-Oxidation of Alkenes



Studies on the amino-oxidation reaction next investigated the generality of the reaction with respect to the nitrogen nucleophile (Table 2). Counterintuitively, this process provides higher yields with more electron poor anilines. This trend can be explained by the complexation of the more basic anilines to the *N*-oxoammonium salt, which competes with binding of the alkene leading to reduced yields. Consistent with this hypothesis are the observations from Table 1, where the addition of DBU or TMG inhibited the amino-oxidation. This leads to some unusual selectivity differences with respect to the amine nucleophile. The aniline *N*-oxoammonium salt EDA complex appears to be very sensitive to substituents on the aromatic ring of the aniline, so that anilines with similar basicity react quite differently, with 2-iodoaniline (entry 7) providing a 63% yield while aniline (entry 13) provided no discernable addition product. The use of alkyl groups on the aniline were explored using *N*-methyl-2-nitroaniline (entry 11) and *N*-benzyl-2-nitroaniline (entry 12). While an addition product was formed from *N*-methyl-2-nitroaniline, the *N*-methyl group was lost during the transformation, and the addition product **9j** was instead isolated. This result may be rationalized by the oxidative demethylation of the *N*-methyl addition product. Oxidative demethylation of nitroanilines has been reported with *m*-CPBA,[24] $KMnO_4$[25] and CrO_3[26] previously, evidently the oxoammonium salt also can also effect this transformation. Use of the *N*-benzyl-2-nitroaniline provided only a complex mixture. This may be due to oxidation of the benzyl group by the oxoammonium salt, which is known to deprotect benzyl ethers.[27] The use of more basic aromatic amines (entry 13) and alkyl amines

gave only starting materials (entry 14), likely due to complexation with the oxoammonium salt which prevented the alkene addition reaction from occurring.

Table 2. Scope of the Amine in the Oxoammonium Salt Amino-Oxidation

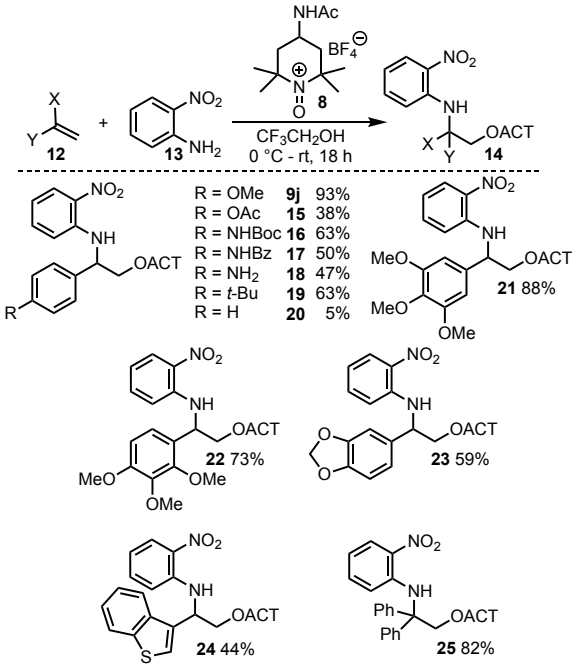


entry	amine	yield (%)
1	3,5-bis(trifluoromethyl)aniline	94 (**9a**)
2	2-chloro-5-trifluoromethylaniline	98 (**9b**)
3	2-trifluoromethylaniline	71 (**9c**)
4	2,5-dichloroaniline	72 (**9d**)
5	2,6-dichloroaniline	69 (**9e**)
6[a]	2-bromoaniline	61 (**9f**)
7[a]	2-iodoaniline	55 (**9g**)
8	methyl 2-aminobenzoate	51 (**9h**)
9	methyl 3-amino-4-chlorobenzoate	83 (**9i**)
10	2-nitroaniline	93 (**9j**)
11	*N*-methyl-2-nitroaniline	54 (**9j**[b])
12	*N*-benzyl-2-nitroaniline	0[c] (**9l**)
13	aniline	0 (**9m**)
14	piperidine	0 (**9n**)

[a]Reaction was performed for 2 h.[b]Yield is for the addition product without the *N*-methyl group.

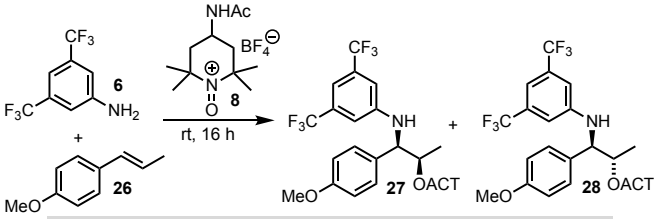
A number of styrenes were then evaluated in the amino-oxidation reaction using 2-nitroaniline as the amine (Table 3). Generally, an electron rich styrene was a requirement for good yields. Replacing the methoxy group with an acetoxy led to a reduced yield of 38% for adduct **15**. 4-Aminostyrene and some protected variants also participated in the addition in moderate to good yields (**16-18**, Table 3). While 4-*tert*-butyl styrene gave a 63% yield of the addition product **19**, only trace amounts of the addition product were obtained from styrene itself due to competing polymerization. The addition of multiple electron donating groups on the styrene was also explored, with adducts **21**, **22** and **23** providing good yields in the amino-oxidation. The use of vinyl heterocycles was also successful, with the benzothiophene substrate providing adduct **24** in 44% yield. 1,1-Disubstituted alkenes also participated in the transformation, with 1,1-diphenylethyene providing an 82% yield of the amino-oxidation product **25**. Simple alkyl substituted alkenes like 1-octene did not undergo the addition reaction and returned only unreacted starting material, so extended conjugation appeared to be necessary for the addition to proceed.

Table 3. Scope of the Alkene in the Oxoammonium Salt Amino-Oxidation



The use of 1,2-disubstituted alkenes was also explored with the reaction of *trans*-anethole **26** and 3,5-bis-trifluoromethyl aniline **6** (Table 4). Donohoe and co-workers had shown that a similar addition using a carboxylic acid nucleophile instead of an aniline provided high selectivity for the *syn* product, but the addition of aniline **6** to *trans*-anethole **26** provided virtually no selectivity when TFE was used as the solvent (the product ratios was determined by ^{1}H NMR). Donohoe and co-workers had employed HFIP as the solvent in their addition,[18] however, so changing the reaction solvent was investigated to improve the selectivity in the addition. A trend in dielectric constant (ε) of the solvent was found, with polar solvents (HFIP) favoring the formation of the *syn* diastereomer **27** while the less polar THF favored formation of the *anti* product **28**.

Table 4. Diastereoselectivity in the Oxoammonium Salt Mediated Amino-Oxidation

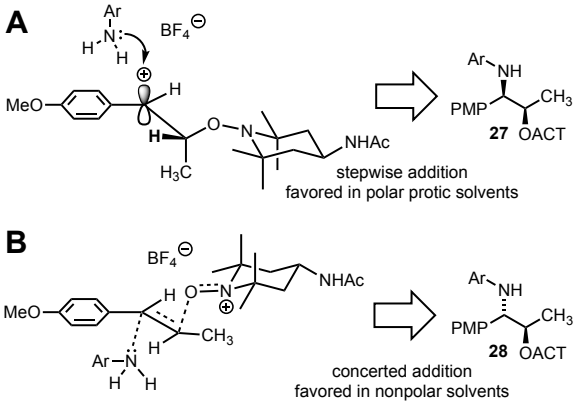


entry	solvent	ε	yield (%)	ratio (**27**:**28**)[a]
1	HFIP	17.8	76	74:26
2	DCM	8.9	60	60:40
3	TFE	8.5	80	48:52
4	THF	7.5	52	21:79

[a]Determined by ^{1}H NMR in CD_3CN.

The observed changes in selectivity of the reaction may be explained by a change in the reaction mechanism. In polar protic solvents like HFIP, the amino-oxidation may favor a stepwise pathway that involved a carbocation intermediate (Scheme 2A). The conformation of the carbon next to the cation is governed by the preference of the methyl group to stabilize the carbocation through hyperconjugation, with the hydrogen taking residence on the side of the aromatic ring to minimize steric interactions. Addition of the aniline opposite to the methyl group then provides the observed *syn* stereochemistry, as was noted by Donohoe.[18] Alternatively, in nonpolar solvents a more concerted transition state may be favored, with formation of the new C-N and C-O bonds taking place nearly simultaneously (Scheme 2B). With the large oxoammonium salt blocking one face of the alkene during the concerted addition, this transition state should favor the observed *anti* stereochemistry.

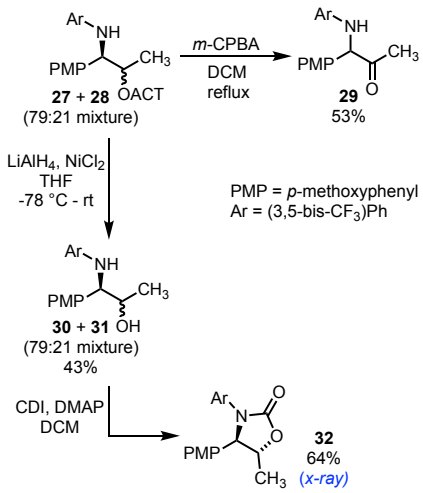
Scheme 2. Postulate for the Solvent Effect on Selectivity in the Amino-oxidation of Alkenes



The stereochemistry of the addition product **27** was verified by an x-ray diffraction structure on a cyclized derivative. The diastereomers **27** and **28** could not be separated, so modification of the system was explored (Scheme 3). While the OACT group could be removed under oxidative conditions to directly provide ketone **29**

with *m*-CPBA,[18] this made proof of the major diastereomer impossible. Cleavage of the OACT group was then attempted so a crystalline derivative could be found, but this cleavage proved to be difficult. While the similar N-O ethers have been removed with many reagents (such as Zn/AcOH,[28] Zn/TMSCl,[29] Na(Hg) amalgam,[30] Raney Ni/H_2,[31] $Mo(CO)_6$,[32] SmI_2,[33] and $LiAlH_4/NiCl_2$[34]), the OACT group could only be removed in a moderate 43% yield with the $LiAlH_4/NiCl_2$ conditions. The other reagents mentioned gave <15% of the desired alcohol products, usually resulting in a complex mixture. The alcohols **30** and **31** also could not be easily separated, so they were cyclized to the corresponding oxazolidine **32** using CDI. The major isomer cyclized more rapidly, and separation of the major oxazolidinone could be accomplished by preparative HPLC. Gratifyingly a crystal of oxazolidine **32** was amenable to analysis using x-ray diffraction, providing an unambiguous assignment of the stereochemistry of the major stereoisomer of the amino-oxidation.

Scheme 3. Functionalization of OACT Group and Proof of Stereochemistry



In summary, this investigation reports an alternative metal free method for the amino-oxidation of electron rich alkenes utilizing an inexpensive, readily synthesized *N*-oxoammonium salt as the key reagent. This transformation provides a direct, transition metal free method for amino-oxidation of alkenes with anilines under mild conditions. The transformation performs best with electron rich styrenes and electron poor anilines as reaction partners. The relative stereochemistry of addition is dependent on solvent effects, with both the syn and anti amino-oxidation products being accessible from identical starting materials. Future explorations using oxoammonium salts to activate alkenes for addition reactions are underway in our laboratory and will be reported

in due course.

Supporting Information: Full experimental procedures, indexed spectral data, copies of ^{1}H and ^{13}C NMR spectra and crystallographic data.

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Conflicts of Interest: The authors declare no competing financial interest.

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