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Short communication

Manganese-catalyzed aziridination of olefins with chloramine-T in water and buffered aqueous solutions

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ABSTRACT

A water-soluble, manganese-porphyrin complex was used to catalytically generate aziridines from olefins in moderate to good yields (up to 93%) upon optimization at room temperature and in aqueous media. Reactions using chloramine-T at slightly acidic to neutral pH values showed generally higher catalytic yields. Attempts to integrate this catalytic system into a DNA hybrid catalyst system to support asymmetric aziridination showed little promise, where steric bulk in the axial positions from activation of chloramine-T by this Mn-heme complex may influence its ability to associate with double-stranded DNA.

1. Introduction

Aziridination is an important C—N bond forming reaction [1–3], where these strained three-member rings are useful building blocks for organic synthesis and are often present in a wide range of bioactive molecules and natural products [4,5]. Although aziridine formation is not as well developed as cyclopropanation or epoxidation, there has been a wealth of aziridines accessible by metal-catalyzed *N*-atom transfer reactions from organoazides and hypervalent *N*-transfer agents [3,5–8]. One of the more popular nitrene sources is the hypervalent iodine complex, [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs). While PhI=NTs is a widely used, highly activated nitrene source for aziridination, it is expensive and has a relatively short half-life, which impacts its utility. Additionally, when PhI=NTs is employed for aziridinations, it yields equal molar amounts of iodobenzene that can lead to oxygenated by-products [9,10]. Other less activated *N*-transfer agents, like chloramine-T (sodium *N*-chloro-*p*-toluenesulfonamide) and tosyl azide [10–12], have been utilized for aziridination reactions catalyzed by Fe-, Cu-, Ru-, Mn-, and Co-complexes for the aziridination of olefins [9,11–14]. Aziridination in water and buffered aqueous solutions is also known [10,15–17], however there are many hurdles that must be overcome including solubility and stability issues associated with the reactants, reagents, and catalysts.

Specifically, we are interested in manganese-containing complexes based on salen and porphyrin ligand systems, which have been shown to be active catalysts for nitrene transfer to olefins in traditional organic solvents [13,18,19]. Alternatively there is a well-known, water-soluble porphyrin system (5,10,15,20-tetra-(*N*-methyl-4-pyridyl) porphyrin, TMPyP4), which has recently been employed to bind metal ions in DNA hybrid catalyst systems [20–22]. These and other DNA hybrid catalytic systems have been shown to be "greener" methods for C-atom transfer [23,24], Lewis acid catalysis [25], and various oxidative functionalization of organic starting materials [26,27]. Here, we report our efforts to study the catalytic capability of Mn-TMPyP4 (Fig. 1) to perform nitrene transfer to olefins in water and buffered aqueous solutions, and in a first generation of DNA hybrid catalyst systems for asymmetric aziridinations. This system captures the ligand environment associated with traditional porphyrin moieties, but it is highly water soluble due to its four pyridinium functional groups and has a strong propensity for binding to DNA due to its stabilized, planar structure.

2. Results & discussion

Aziridinations of olefins is a well-established process in organic solvents. Starting here, we chose to screen Ph = INTs, chloramine-T, and tosyl azide as potential *N*-transfer agents to generate *N*-tosyl-2-phenylaziridine from styrene. The average yields from three separate catalytic trials are shown in Table 1 and all reactions were carried out under an aerobic atmosphere in acetonitrile. In general, low yields were obtained, (0–11%, entries 1–3) but this likely stems from the poor solubility of

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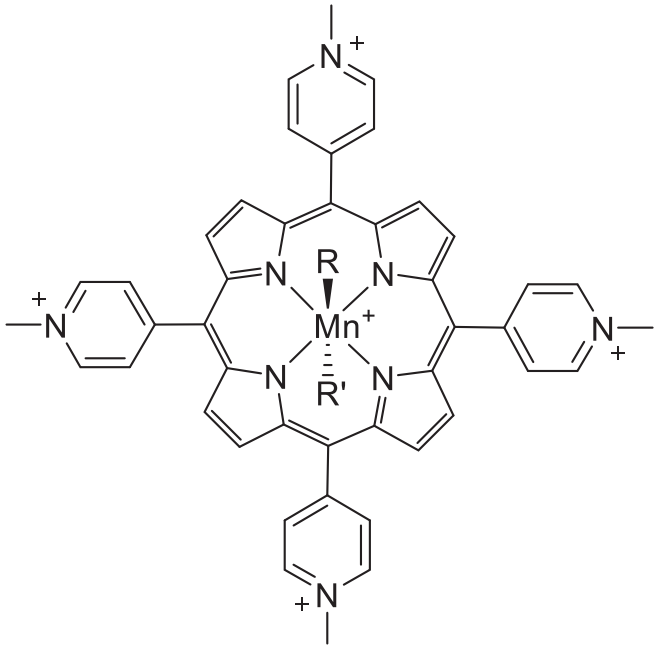


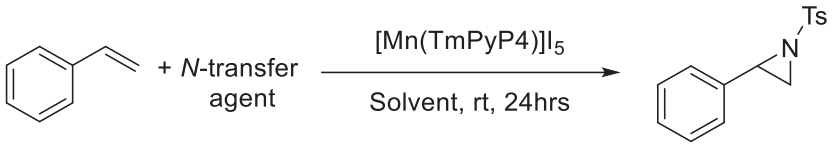
Fig. 1. Structure of 6-coordinate manganese(III)-TMPyP4, where R and R' groups are generally considered to be labile solvent-derived molecules.

[MnTMPyP4]I_5 in organic solutions. The desired aziridine was the major product observed in the PhI=NTs and chloramine-T trials, with the only discernable side-product being an amination by-product as observed by GC–MS (0–2% yield). It is unclear whether this byproduct is produced catalytically or if it is associated with aziridine ring-opening of the targeted product. Moving to water based reactions, chloramine-T was again the most reactive of the *N*-transfer reagent resulting in an average yield of 25% from 3 replicated trials (entry 4), while minimal change in yield was observed for PhI=NTs or TsN_3 (entries 5 & 6). The turnover numbers (TON) of this initial reactivity were low (<5) but it appears that the Ph = INTs and TsN_3 trials in water may only turn-over once before inactivating. In these trials, the amination by-product and a range of other side-products were observed, however, only the tosyl based amination product was observed in yields greater than 1% yield.

Optimization of this reaction with styrene after 24 h was investigated with our initial concern being a pH study to determine if this reaction or product stability was improved under acidic, neutral, or basic conditions. These were carried out in three different buffer systems to accommodate three different pH values. A 75 mM $NaC_2H_3O_2$ solution was adjusted with HCl to pH 4 for our slightly acidic trials, a 75 mM KH_2PO_4 solution was adjusted to pH 7 for our neutral pH trials, and a 75 mM $KHCO_3$ solution was adjusted to pH 10 for our basic conditions trial. The results for this pH study are reported in Table 1 entries 7–9. From this we can see there is not a significant difference in recorded reaction yields between the different pH values, but there is slightly more aziridination product is observed at pH 4 which we attribute to slightly higher stability of the *N*-tosyl-2-phenylaziridine at slightly acidic pH values over neutral or basic conditions (entries 8–9).

Typically, a large excess of olefin is needed to produce high yields in aziridination catalysis. However a related study using a Mn-corrole complex indicated that two nitrene transfer agents were required to generate a TsN = Mn(PhI=NTs) adduct, which was responsible for the aziridination of olefins where this process was independent of styrene concentration [28]. In our studies, various ratios of styrene:chloramine-T were examined (entries 7,10–14). Dropping the ratio from 10:1 styrene:chloramine-T to 3:1 styrene:chloramine-T saw a doubling of the yield from 24% to 49% (entry 7 vs entry 10.) Further changing of this

Table 1
Manganese catalyzed aziridination of styrene.



Entry	Nitrogen transfer	Substrate: N-trans agent ratio	Solvent	Aziridination %Yield[a]	Amination %Yield[a]	TON[b]
1	PhI=NTs	10:1	CH_3CN	8	trace	1.6
2	TsN_3	10:1	CH_3CN	trace	trace	0
3	chloramine-T	10:1	CH_3CN	11	2	2.2
4	PhI=NTs	10:1	water	4	12	0.8
5	TsN_3	10:1	water	5	9	1
6	chloramine-T	10:1	water	25	6	5
7	chloramine-T	10: 1	Buffer[c] (pH 4)	24	7	4.8
8	chloramine-T	10:1	Buffer[c] (pH 7)	20	5	4
9	chloramine-T	10:1	Buffer[c] (pH 10)	17	9	3.4
10	chloramine-T	3:1	Buffer[c] (pH 4)	49	–	10
11	chloramine-T	1:1	Buffer[c] (pH 4)	48	–	10
12	chloramine-T	1:2	Buffer[c] (pH 4)	56	–	11
13	chloramine-T	1:3	Buffer[c] (pH 4)	52	–	10
14	chloramine-T	1:5	Buffer[c] (pH 4)	53	–	11

[a] Concentrations based on toluene internal standard GC analysis. All reactions were done at 5 mol% catalyst loading based from nitrogen transfer agent, 3 mmol styrene, 0.3 mmol nitrogen transfer agent, 2 mL solvent, and reacted at room temperature for 24 h.
[b] Turnover Number for aziridination product.
[c] Buffer systems used here in were 75 mM acetate, phosphate, and bicarbonate buffers for pH 4.0, 7.0, and 10.0, respectively.

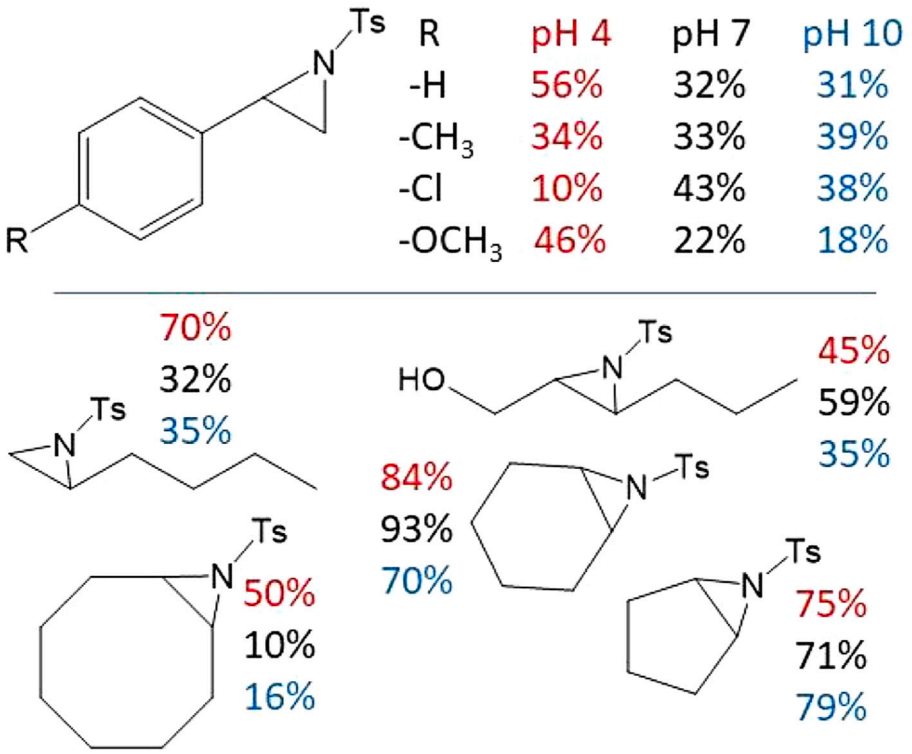


Fig. 2. Aziridination of olefins using 5 mol% [MnTMPyP4]I_5 with, 3 mmol olefin, 0.3 mmol chloramine-T and 2 mL of buffer. The yields shown in red are in 75 mM acetate buffer at pH 4, black are phosphate buffer at pH 7, and blue bicarbonate buffer are at pH 10. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ratio to a 1:1, stoichiometric ratio of styrene:chloramine-T resulted in no further improvement of the product yields (entry 11). We do note an increase in the product yield when this ratio is inverted to 1:2 styrene: chloramine-T, where this modification resulted in an improved the yield of *N*-tosyl-2-phenylaziridine to 56% (entry 12). Further increases in the chloramine-T concentration in these reactions where there is a 1:3 or 1:5 styrene:chloramine-T ratio produced no further increase in reaction yield (52% and 53%, respectively). Similar trend in the optimized *N*-transfer agent has been previously observed by Zhang with cobalt and iron catalytic systems, but the underlying reason for this optimized concentration is currently unknown [14,29]. Other side products are also observed in these reactions. Under conditions similar to those in Table 1, entry 12 a range of other styrene-derived products were generated at low yield, which may be due to product degradation or aberrant activation pathways (c.f. Fig. S1 in the supporting materials).

UV–visible absorption data (c.f. Fig. S2 in the supporting materials) shows a spectroscopic shift in the absorption intensity of two prominent transitions associated with Mn-TMPyP4, where the isolated catalyst shows nearly equal intensity in the 420 and 460 nm signals. Upon addition of chloramine-T to this sample, a systematic reduction in the intensity of the 430 nm transition and an increase in the 460 nm feature is recorded. This absorption shifts maximized at a 1:2 ratio of Mn-TMPyP4 to chloramine-T, where additional chloramine-T once again lowers the differences in intensity of these spectral features, which could indicate that a 1 to 2 stoichiometry of Mn-TMPyP4 to chloramine-T is required to activate this catalyst for aziridination in a similar fashion to Zdilla et al. [28]

Under these optimized conditions, alternative olefins where reacted with chloramine-T in a 1:2 olefin:chloramine-T ratio with 5 mol% manganese(III)-TMPyP4 in buffered aqueous media at pH 4, 7, and 10. All olefins studied here were converted to aziridination products with a wide-range of measured yields. Overall production of the aziridination product seems to be favored under slightly acidic (pH 4) to neutral pH (pH 7), where generally less aziridine products were recovered at pH 10 (Fig. 2). Anecdotally, there appears to be more side products generated from the aziridination of styrene than the aliphatic olefins, which may contribute to the disparate yields observed for the substituted styrene trials. Aziridines have traditionally shown instability at both low and high pH values, where this strained 3-member heterocycle is susceptible to ring opening under both conditions [30]. Specifically the low yields generally observed at pH 10, maybe due to instability of the aziridine unit at this pH. The aziridination products of the *para*-substituted styrenes show some weak correlation to the inductive and resonance effects associated with their substituents. However, it is unclear if this correlation is associated with a distinctive mechanistic step (or steps) within the reaction, or do these effects impact the relative stability of the aziridination products at different pH values. More detailed kinetic studies are required to directly connect the electronics of the substrate with the catalysis described herein. In general, the non-styrene olefins generated more product at pH 4, than other pH values. Once again, this is likely due to the stability of the product rather than some mechanistic dependence on the pH. The only outlier to this trend is the aziridination product of cyclopentene, which seems to have some additional stability over its counterparts. One possibility that this molecule has slightly more stability at high pH due to the inaccessibility to the aziridine moiety in this more congested 5-atom ring system.

Finally manganese(III)-TMPyP4 was added to 3 different DNA samples (salmon teste DNA, calf thymus DNA, and pUC19 plasmid DNA) to generate a DNA hybrid catalyst system for asymmetric aziridinations. Manganese(III)-TMPyP4 is a known “groove-binder” to B-DNA samples, [31] and several metal-TMPyP4 catalysts have been successfully adapted to perform chiral catalytic transformations using duplex DNA [21–23,24]. When approximately 2 mg of DNA is added as part of the optimized catalytic trial described in the data above (1:2 styrene: chloramine-T ratio with 5 mol% manganese(III)-TMPyP4 in buffered aqueous media at pH 7), the yield of these reactions was lowered significantly. With salmon teste DNA (stDNA), calf thymus DNA (ctDNA), and plasmid DNA (pUC19), the product yield was 8%, 19%,

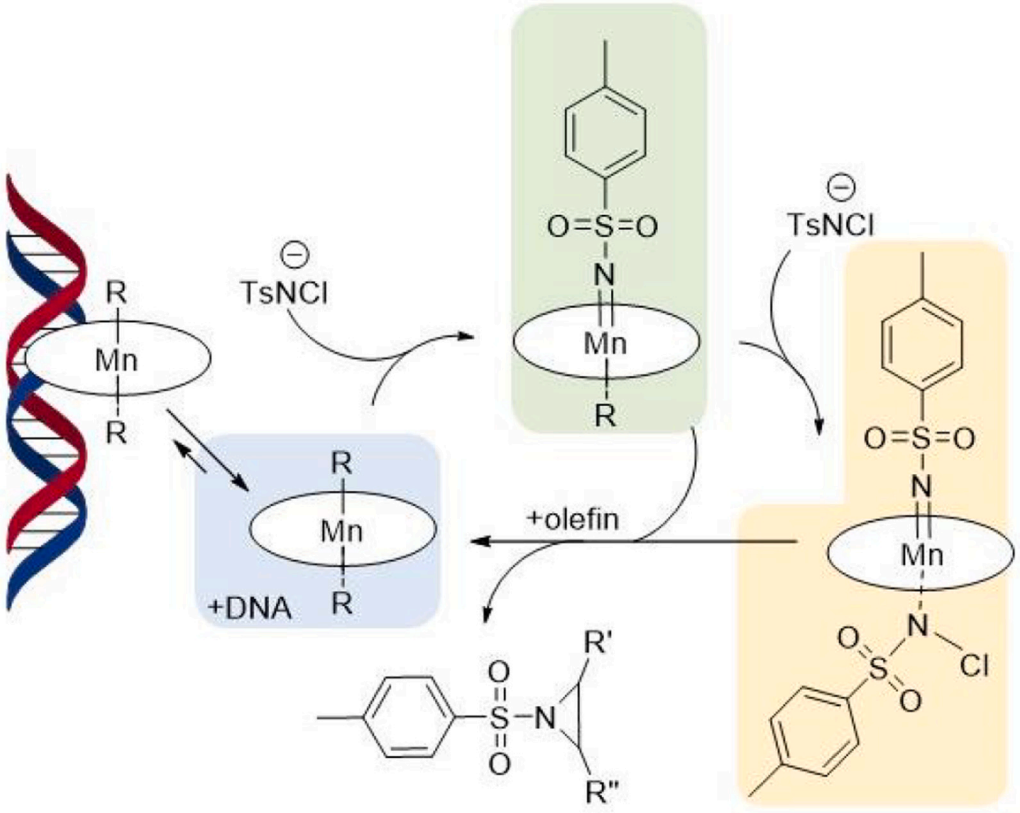


Fig. 3. DNA impact on proposed aziridination mechanism. Resting Mn-TMPyP4 is highlighted in blue which is in an equilibrium with the DNA bound Mn-TMPyP4 complex. The possible activated nitrene complexes are highlighted in green and yellow representing activated imido or an imido/amido complexes similar to the Mn-corrin like species reported by Zdilla et al. [28]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and 9%, respectively (Table S1) compared to 29% yield observed without DNA present. Upon isolating and analysis of the *N*-tosyl-2-phenylaziridine from these reactions, less than 3% *ee* is observed in these DNA hybrid catalytic trials. The poor catalytic turn-over suggest some of the catalyst is not available for reactivity and lack of enantioselectivity associated with these hybrid catalyst systems suggest that the catalytic moiety responsible for the aziridination products is not closely associated with the DNA samples. One possibility is that the Mn-TMPyP4/DNA adduct is not catalytically viable and a small concentration of unbound Mn-TMPyP4 is responsible for chloramine-T activation and catalysis (Fig. 3). We propose that a chloramine-T adduct of manganese-TMPyP4 reacts with the alkene to generate the aziridination product. However, it remains unclear if it is an imido-MnTMPyP4 complex (highlighted green in Fig. 3) or if it is an imido/amido complex (shown in yellow in Fig. 3). This is proposed imido/amido complex is similar to the manganese-corrin system described earlier, where either of these complexes could be capable of catalyzing the aziridination of an olefin. It is clear, however, from our data, that it is unlikely that Mn-TMPyP4 can be productively paired with double-stranded DNA to generate a DNA hybrid catalytic system capable of asymmetric aziridination. The chloramine-T adduct(s) add significant steric bulk to the Mn-TMPyP4 complex and limit the molecular shape needed for efficient DNA base-stacking or groove-binding modes.

3. Conclusions

Mn-TMPyP4 catalyzed aziridinations of olefins were performed using chloramine-T in aqueous solutions generating yields of up to 93% with only trace amounts of side products. The pH dependence of this aqueous process was studied, where more product was identified at slightly acidic pH values. This may be due to the relative stability of different aziridines or this may be due inductive or resonance effects on the catalytic system. In either case, these reactions show promise as aziridination catalysts in water, but they also warrant further study to fully identify their capabilities and role in organic methodology. Our initial efforts to generate asymmetric aziridination catalysts from Mn-TMPyP4 adducts of several double-strand DNAs did not result in a functional system, where the catalytic yields were significantly decreased in the presence of DNA and only a slight enantioselective excess was observed in the isolated *N*-tosyl-2-phenylaziridine. Considering the mechanistic requirements for chloramine-T activation, one possibility is that the bulky axial imido or amido species generated as a function of chloramine-T activation may limit the affinity of Mn-TMPyP4 complexes for DNA due to unfavorable steric interactions – which limits the likelihood that asymmetric aziridination can be accomplished using this particular combination of reactants, catalyst, and DNA.

CRediT author statement

DK Wolgemuth: Experimental data collection, writing original draft of manuscript. **SD Elmore**: Experimental data collection. **JD Cope**: Experimental data collection, writing, and editing. **PE Sheridan**: Experimental data collection. **SL Stokes**: Supervision, Writing, Reviewing, and Editing. **JP Emerson**: Supervision, Writing, Reviewing, and Editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.catcom.2020.106275.

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