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Alkene Epoxidation Using Ni(II) Complexes of Chiral Cyclams

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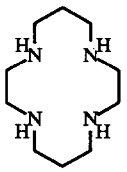
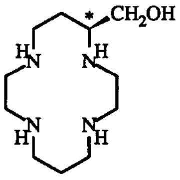
Abstract. *A series of optically active Ni(II)-cyclam complexes are active catalysts for the PhIO oxidation of alkenes; labeling and stereochemical studies suggest important mechanistic differences from heme catalysts.*

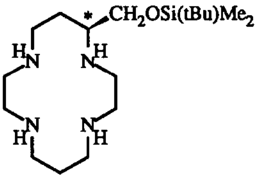
Curiosity about the mechanisms of biological oxidation and the search for new oxidation catalysts have spurred the study of nearly every transition metal as a potential olefin epoxidation catalyst. Iodosylarenes yield useful epoxidizing agents in the presence of Cr(III), Mn(III) and Fe(III) porphyrin complexes.[1] The porphyrin ligand is not a necessity; a number of metal complexes have recently been reported to mediate alkene oxidation,[2] and simple salts of Mn(II), Fe(III), Co(II) and Cu(II) also participate in PhIO oxidation of olefins.[3] Nickel has long been absent from this chemistry; however, concurrent work in our laboratory and Kochi's has established that certain multidentate ligands allow the use of Ni(II) as a catalyst.[4] Here, we report the results of alkene oxidation using Ni(II) complexes of substituted cyclams (1,4,8,11-tetraazacyclotetradecane).



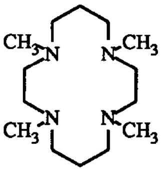
1a



1b



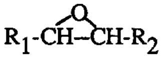
1c



1d

High oxidation states are a common feature of transition metal oxidation catalysts. Macrocyclic tetraamines are known to stabilize high oxidation states of ligated transition metals, and cyclam in particular facilitates formation of Ni(III) compounds.[5] Accordingly, we reasoned that the cyclam ligand might render common Ni^{2+} salts reactive toward oxygen atom transfer reagents. In particular, we hoped to take advantage of our recent synthesis of optically active cyclams bearing functionalized side chains.[6] Indeed, using iodosylbenzene as oxidant, we found that $Ni(NO_3)_2$ complexes of **1a-c** catalyzed the epoxidation of various aryl and alkyl-substituted alkenes. In a typical experiment, 0.1 mmol Ni-complex, 0.5 mmol alkene and excess (2 mmol) PhIO were stirred in 5 mL anhydrous CH_3CN at room temperature under N_2 atmosphere for 5 hours. Table I presents

Table I. Yields of olefin oxidation products using PhIO and Ni(1a-c)$(NO_3)_2$.[a]

Ligand	Substrate R_1-CH=CH-R_2		Products and Yields (%)			
	R_1	R_2	 R_1-$\overset{O}{CH-CH}$-R_2	PhCHO	other	
1a	Ph	H	26	2.7	phenylacetaldehyde	4.2
1b	Ph	H	26	8.3	phenylacetaldehyde	2.4
1c	Ph	H	28	2.5	phenylacetaldehyde	5.0
1a	Ph	Me (cis)	18 (cis)	8.0	phenylacetone	8.4
			15 (trans)		*t*-β-methylstyrene	3.2
1a	Ph	Me (trans)	60 (trans)	3.0	phenylacetone	4.0
1a	Ph	Ph (cis)	4.1 (cis)	9.0[b]	trans-stilbene	3.8
			3.8 (trans)		benzophenone	3.6
					benzil	1
1a	Ph	Ph (trans)	31 (trans)	8.8[b]	benzophenone	5.2
			1 (cis)		benzil	2.3
1a	-$(CH_2)_4$-		34		cyclohexenol	1.5
					cyclohexanone	1.9
					cyclohexenone	4.5

[a] See text for reaction conditions. After 5 hours, an aliquot was removed, filtered through a short plug of alumina and analyzed by GC. Yields are based on initial alkene concentration. [b] Actual yield was two-fold higher, stoichiometry of 2 was assumed.

examples of the yields of products obtained. The epoxide was the major product for each of the substrates studied. The reactions were slow, but nearly quantitative conversion was observed if additional PhIO was added after a few hours of reaction time. Thus, low yields at a given reaction time represent slow turnover, rather than low turnover.

The cyclam ligand is crucial to catalysis. We verified that $Ni(NO_3)_2$ alone does not mediate olefin oxidation under the reaction conditions.[3] Interestingly, the $Ni(NO_3)_2$ complex of N,N',N'',N'''-tetramethylcyclam, **1d**, was also ineffective as an oxidation catalyst, perhaps because its oxidation potential is significantly higher than that of the **1a** complex.[5] Comparative studies with ligands **1a-c** were carried out to ascertain the influence of additional ligating groups and steric encumbrance. Yields of epoxides from reactions of the **1b** complex were essentially the same as those of **1a** suggesting that the intramolecular hydroxyl group neither facilitates the reaction through ligation to nickel nor reduces the reactivity to a large extent. Use of the tert-butyldimethylsilyl derivative **1c** gave similar product distribution and yields. Epoxides of styrene and *trans*-β-methylstyrene formed in the presence of optically active **1b** and **1c** were analyzed with chiral NMR shift reagents. Unfortunately, no enantiomeric excess was observed, despite the ability of the hydroxyl group of **1b** to ligate to the nickel ion.[6]

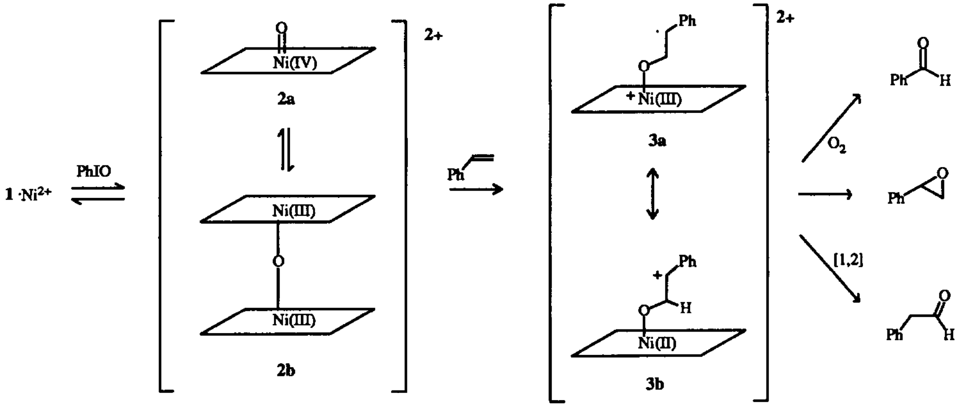
The results of substitution of the alkene present several similarities and differences to other oxidation systems which are interesting to compare. Like iron-porphyrins, the nickel-cyclam catalyzed reaction displayed E-Z stereoselectivity for stilbene substrates.[7] However, the preference in this case was reversed; *trans*-stilbene was considerably more reactive than *cis*-stilbene. In addition, *cis-trans* isomerization competed with oxidation in the reaction of *cis*-stilbene. Unlike heme systems, the stereospecificity is only moderate. Both *cis-β*-methylstyrene and *cis*-stilbene produced a mixture of *cis* and *trans* epoxides. These characteristics resemble the reactions of simple metal salts[3] and Mn(III) porphyrins.[8]

The reactions were also sensitive to the presence of O_2. Benzaldehyde was formed from stilbene and styrene oxidations when PhIO was used as the terminal oxidant, and its yield increased dramatically if O_2 was bubbled through the reaction mixture. Careful degassing reduced benzaldehyde formation to essentially zero. No reaction occurred with O_2 in the absence of PhIO. To trace the source of oxygen in oxidation products, experiments were carried out using 70% ^{18}O-labeled PhIO. Mass spectral analysis of products from the oxidation of *trans*-stilbene indicated that all of the epoxide oxygen (71% isotopic enrichment) and about half of the benzaldehyde oxygen (30% isotopic enrichment) are derived from PhIO.[9]

At this point, the structure of the oxidized nickel species formed upon addition of PhIO to **1**$\cdot Ni^{2+}$ in CH_3CN is unknown; however, two postulates are suggested in Scheme I by analogy to metal-porphyrin systems. A nickel-oxo species such as **2a** with a formal oxidation state of (IV) would result from complete oxygen atom transfer from PhIO. It is also possible that a μ-oxo Ni(III) dimer (**2b**) is formed. Either of these species could act as an electron acceptor in the presence of alkenes. Further studies are underway to characterize transient intermediates.

The observation that *trans*-stilbene is more reactive than *cis*-stilbene suggests that addition of **2** to olefins is radical-like; i.e. initial generation of a planar benzylic radical may be a driving force. The moderate stereospecificity in stilbene epoxidation is consistent with intermediate **3** as an open chain nickel alkoxide but not with concerted formation of an oxametallacycle as suggested in heme systems.[10] To be consistent with the ^{18}O labeling studies, the mechanism of benzaldehyde formation must involve O_2 trapping of a PhIO-oxidized olefin intermediate.[11] Resonance form **3a** indicates such a pathway in which a peroxy radical could be generated that would ultimately yield benzaldehyde on decomposition. When $PhI^{18}O$ is used, *trans*-stilbene generates partially labeled PhCHO while PhCHO from styrene oxidation is essentially unlabeled. It is interesting that this differs from the mechanism suggested for Fe-bleomycin-catalyzed oxidation of *cis*-stilbene in which O_2 trapping of a stilbene radical cation is proposed to generate benzaldehyde.[12] One can more easily visualize the appearance of rearrangement products ($PhCH_2CHO$, $PhCH_2COCH_3$, and PhCOPh) in which hydrogen or phenyl migration occurs by consideration of the cationic resonance form, **3b**. Finally, reductive elimination of either **3a** or **3b** is the major pathway yielding epoxide and regenerating **1**.

SCHEME I



In summary, complexation of a Ni(II) salt to a series of macrocyclic polyamine ligands has produced a new set of olefin epoxidation catalysts. Initial studies point to a mechanism that bears some similarities and several differences from heme-catalyzed oxidations. The reaction tolerates C-substitution on the ligand but not N-substitution on all four nitrogens. Ni(III) or higher oxidation states are implicated in the mechanism, and ligands stabilizing these species may also be of interest as mimics of nickel-containing redox enzymes.[13] Further structural modifications are anticipated to provide new insight on the scope of nickel-catalyzed redox chemistry.

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