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The Functionalization of Saturated Hydrocarbons. Part 24.+ The Use of *tert*-Butyl Hydroperoxide: GoAgg^{IV} and GoAgg^{V}.

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Key Words: Gif systems; Activation of alkanes; Selective functionalization; *tert*-Butyl hydroperoxide

Abstract: The use of *tert*-butyl hydroperoxide as an oxidant in Gif-type systems (GoAgg^{IV} and GoAgg^{V}) catalyzed by various Fe(III) species is examined. Regioselectivity studies of these systems have revealed several characteristics similar to those observed for other previously reported Gif-type reactions. A common reaction pathway for the GoAgg^{IV}and GoAgg^{V} oxidation systems and other Gif-type reactions (from alkane *via* alkyl hydroperoxide to ketone or alcohol) is seen.

INTRODUCTION

Due to its importance and challenging nature, the area of selective functionalization of saturated hydrocarbons has received much attention during the past two decades.[1] Most of the chemical models developed recently to functionalize alkanes have been inspired by the remarkable ability of biological systems that can selectively hydroxylate unactivated carbon-hydrogen bonds of alkanes under mild conditions.[2] Among those catalyzed by transition metals, iron has been recognized as an important metal for activation of various oxygen species. A number of models based on iron salts or complexes have therefore been developed.[3]

Gif-type reactions are another promising class of Fe- and Cu-based chemical models capable of oxidizing saturated hydrocarbons under mild conditions to mainly ketones.[4] The first significant member of the Gif family was the Gif^{III} system comprising Fe^0 suspended in a mixture of pyridine-acetic acid using dioxygen (O_2) as an oxidant and in the presence of H_2S.[5] Various Gif-type reactions have subsequently been developed employing either dioxygen as in the Gif^{IV} system or hydrogen peroxide (H_2O_2) as in the GoAgg^{II}, GoAgg^{III} and GoChAgg

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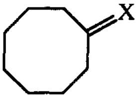
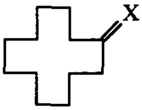


1 X = H_2
2 X = O
3 X = OH, H
4 X = Cl, H
43 X = *o*-pyridine
44 X = *p*-pyridine
45 X = $OOC(CH_3)_3$



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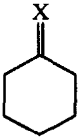
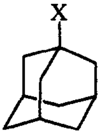
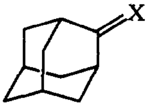
6 X = O
7 X = OH, H



8 X = H_2
9 X = O
10 X = OH, H

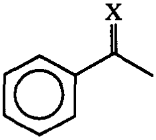


11 X = H
14 X = OH
15 X = *o*-pyridyl
16 X = *p*-pyridyl

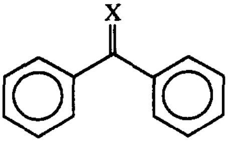


12 X = O
13 X = OH, H
17 X = *o*-pyridyl, H
18 X = *p*-pyridyl, H

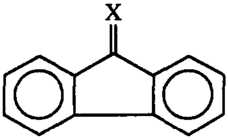
19



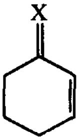
20 X = H_2
21 X = O
22 X = OH, H



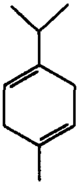
23 X = H_2
24 X = O
30 X = CH_2



25 X = H_2
26 X = O



27 X = H_2
28 X = O
29 X = OH, H



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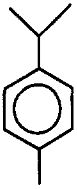

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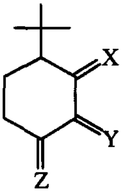
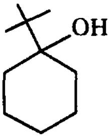


33 X=Y=Z=H_2
34 X=O; Y=Z= H_2
35 X=Z=H_2; Y=O
36 X=Y=H_2; Z=O



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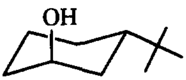

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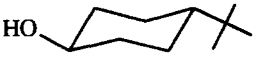

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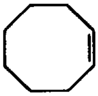

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systems.[6,7] The initial activation process of all Gif-type reactions is the generation of the high valent (formally) $Fe^V{=}O$ species from either Fe(II) and superoxide ion or the isoelectronic pair: Fe(III) and H_2O_2.[4]

The use of *tert*-butyl hydroperoxide (TBHP) in metal-catalyzed processes in the past has mostly dealt with the epoxidation of olefins.[8] Nevertheless, during the last decade TBHP has also turned out to be a useful oxidizing agent in metal-catalyzed oxidations of hydrocarbons. Different metal complexes (Fe, Cu, Ru, Mn, Co, Cr) have revealed this catalytic activity.[9]

To extend our studies in this area, the use of TBHP as a primary oxidant in a mixture of pyridine-acetic acid catalyzed by Fe(III) complexes to selectively oxidize various hydrocarbons was selected for further examination. This system has been designated as the $GoAgg^{IV}$ system, continuing the Geographical nomenclature of Gif-type reactions.[6]

RESULTS AND DISCUSSION

Mechanistic studies of the system utilizing TBHP for the Fe(III)-catalyzed functionalization of saturated hydrocarbons ($GoAgg^{IV}$ system) have previously demonstrated a common reaction pathway with those reported for various Gif-type reactions and related processes.[10] The reaction pathway involves transformation of alkanes *via* alkyl hydroperoxides to oxidized products. Dioxygen (O_2) was clearly shown to be the precursor of the oxygen atoms in the alkyl hydroperoxide, the alcohol and the ketone.[11]

Preliminary studies on the rate of oxidation of cyclooctane (**1**) employing $FeCl_3 \cdot 6H_2O$ (0.2 mmol) as a catalyst and TBHP (10 mmol) as an oxidant in a pyridine-acetic acid mixture at room temperature revealed that the oxidation rate was slow. The reaction took approximately 8 days to reach completion; nonetheless, the total amount of oxidized products was found to be impressive. The conversion of cyclooctane into the corresponding ketone and alcohol was approximately 30% with a quantitative yield for the overall reaction. Examination of the effects of temperature showed that increasing the temperature did effect a desirable rate enhancement. At 60°C, the rate of the reaction was around 10 times faster than that at room temperature (25°C), while the oxidations performed at 0°C gave almost no reaction during the 5 h time period studied. Moreover, the oxidation reaction of cyclooctane (50 mmol) at 60°C displayed superior results. The GLC analysis of the reaction mixture revealed the presence of 9.14 mmol of cyclooctanone (**2**) and 0.97 mmol of cyclooctanol (**3**). The efficiency of the reaction based on one mole of product derived from one mole of oxidant gave a quantitative efficiency of TBHP for this system. The utilization of other Fe^{III} species as catalysts such as $Fe(OAc)_3$ or $Fe(NO_3)_3 \cdot 9H_2O$ gave similar results with half-lives in the range of 20-25 h. The efficiency based on oxidant varied from 93.4 to 105.0 %.

Kinetic studies on the effects of the concentration of $FeCl_3 \cdot 6H_2O$ revealed that the rate of the oxidation relied strongly on the concentration of the Fe^{III} species. Interestingly, when the reaction was carried out using $FeCl_3 \cdot 6H_2O$ in a reagent quantity (5.0 mmol), less cyclooctanone (**2**) and cyclooctanol (**3**) were attained. The major product from the reaction was found to be cyclooctyl chloride (**4**). Further studies on the formation of alkyl chloride under these particular conditions will be reported in a forthcoming paper.[12]

An examination of the effects of ligands on the oxidation of cyclododecane (**5**) performed at ambient temperature is presented in Table 1.

Table 1. The GoAgg^{IV} oxidation of cyclododecane (**5**) in the presence of picolinic acid, imidazole and 2,2'-bipyridine.

Entry	Ligands*	Yield (%)**				$\frac{6}{7}$	Half-life (h)
		5	6	7	Σ		
1	none	66.1	26.7	2.7	95.9	9.9	126
2	PA	62.2	30.5	2.8	95.3	10.9	1
3	imid	63.8	29.8	2.7	96.3	11.0	<16
4	bpy	63.9	25.4	2.6	91.9	9.8	130

PA = picolinic acid; imid = imidazole; bpy = 2,2'-bipyridine.
*the ratio of Fe : ligand is 1:3, 1:50 and 1:3 for PA, imid and bpy, respectively.
**based on substrate.

It has previously been demonstrated that picolinic acid has a remarkable rate-enhancing effect in the GoAgg^{III} system[7a]. A similar rate-enhancing effect on the Fe-catalyzed oxidation process under GoAgg^{IV} conditions was also found (entry 2). The half-life of the reaction sharply decreased approximately 130 times compared with the ordinary GoAgg^{IV} system (entry 1). The result gained from the utilization of excess imidazole to catalyze the GoAgg^{IV} oxidation reaction (entry 3) was in good agreement with that reported by Fontecave *et al.* in CH_3CN solution.[9j] The rate of the oxidation in the presence of imidazole was approximately 9 times as fast as in the normal GoAgg^{IV} reaction. However, the ketone to alcohol ratio derived from the GoAgg^{IV} system (9.8-11.0:1) was found to be superior to that using imidazole (2:1).[9j] In contrast, the use of 2,2'-bipyridine did not result in any rate-enhancement or any increased yield of the desired products (entry 4).

Regioselectivity Studies

Unless stated to the contrary, GoAgg^{V} is GoAgg^{IV} + picolinic acid, an analogue of the GoAgg^{III} system. Various hydrocarbons were selected for evaluating the regioselectivity of this system. The results of the oxidation reaction of these selected substrates namely cyclohexane (**8**), cyclododecane (**5**), adamantane (**11**), benzene (**19**), ethyl benzene (**20**), diphenylmethane (**23**), fluorene (**25**), cyclohexene (**27**), 1,1-diphenylethylene (**30**) and γ-terpinene (**31**) employing the GoAgg^{V} system at room temperature are collected in Table 2.

The results in Table 2 show that the GoAgg^{V} oxidation system shares similar characteristics to the other Gif-type systems.[13] To illustrate this, the oxidation of cycloalkanes such as cyclohexane (**8**) and cyclododecane (**5**) (entries 1 and 2) provided the oxidized products, with the ketone being the major product. The yield of the desired products and the ketone to alcohol ratio observed using this particular system were found to be greater than those in analogous systems using H_2O_2 as an oxidant (GoAgg^{II} and GoAgg^{III}).[14] The attempted oxidation of benzene did not give any significant amounts of oxidized products, while the oxidation of alkyl benzenes such as ethyl benzene (**20**), diphenylmethane (**23**) and fluorene (**25**) clearly showed that the activation process

Table 2. The oxidation reaction of various hydrocarbons employing the GoAgg^{V} system.^{a}

Entry	Substrate (mmol)	Product (s) (mmol)	Σ (%)^{b}
1	**8** (50)	**9** (5.10), **10** (0.56)	
2	**5** (5)	**5**^{c}(3.11), **6** (1.53), **7** (0.13)	95.4
3	**11** (5)	**11**^{c}(2.89), **12** (0.73), **13** (0.07), **14** (0.65), **15** (0.39), **16** (0.13)	97.2 C^2/C^3 0.68
4	**19** (50)	-	
5	**20** (50)	**21** (4.38), **22** (0.58)	
6	**23** (5)	**23**^{c}(2.70), **24** (2.14)	96.8
7^{d}	**25** (5)	**25**^{c}(1.92), **26** (2.77)	93.8
8^{d}	**27** (50)	**28** (2.35), **29** (0.74)	
9^{e}	**30** (5)	**30**^{c}(3.01), **24** (1.82)	96.6
10^{d}	**31** (5)	**31**^{c}(0.23), **32** (4.69)	98.4

a) employing $Fe(NO_3)_3 \cdot 9H_2O$ (0.5 mmol), picolinic acid (1.5 mmol) and TBHP (10 mmol).
b) based on substrate. c) recovered substrate. d) using TBHP (5 mmol).
e) using TBHP (2.5 mmol).

was preferrentially taking place at the benzylic position yielding the corresponding carbonyl compounds in good yield (entries 4-7).[15] The same unique behavior as observed in typical Gif-type reactions in the oxidation of 1,2-disubstituted olefins such as cyclohexene (**27**) resulting in the production of cyclohex-2-en-1-one (**28**) and cyclohex-2-en-1-ol (**29**). No sign of cyclohexene epoxide formation was found (entry 8).[16] The oxidation of 1,1-diphenylethylene (**30**) as an example of a 1,1-disubstituted olefin gave benzophenone (**24**) in high yield (entry 9).[17] Moreover, the oxidation of γ-terpinene (**31**) yielded the aromatized product *p*-cymene (**32**) almost quantitatively (entry 10).

Unlike other Gif-type reactions, where a C^2/C^3 value of around 1.0 is seen[18], the oxidation of adamantane (**11**) by the GoAgg^{V} system revealed an overall C^2/C^3 value of approximately 0.68 (entry 3). However, no pyridine-coupled products (**17**, **18**) at the secondary position of adamantane were detected.

Comparative regioselectivity studies between the GoAgg^{III} and GoAgg^{V} systems toward the oxidation of *tert*-butylcyclohexane (**33**) presented in Table 3 clearly showed that the GoAgg^{V} system not only provided a greater amount of oxidized products, but also displayed more selectivity than that of the GoAgg^{III} system. For instance, the distribution of ketone formation revealed a ratio of 2-, 3- and 4-*tert*-butylcyclohexanone (**34**:**35**:**36**) of 1:70:26 for the GoAgg^{V} system, while in the GoAgg^{III} reaction a ratio of 1:9:3 was observed. The ratio of ketones (**34**+**35**+**36**) to secondary alcohols (**38**+**39**+**40**) was also different, varying from 5.5 for the

GoAgg^{III} system to 12.1 for GoAgg^{V} reaction. Furthermore, interestingly under GoAgg^{V} conditions there was no activation observed at the tertiary position of the molecule.

Table 3. The oxidation of *tert*-butylcyclohexane (**33**) by the GoAgg^{III} and GoAgg^{V} systems.[a]

Reaction conditions	Yield (%)[b]								Σ	**34:35:36**	ketones / 2° alcohols
	33[c]	**34**	**35**	**36**	**38**	**39**	**40**	**37**			
GoAgg^{III}	85.2	0.7	6.4	2.2	1.1	0.6	0	1.4	97.6	1:9:3	5.5
GoAgg^{V}	79.3	0.2	13.9	5.2	0.9	0.3	0.4	0	100.2	1:70:26	12.1

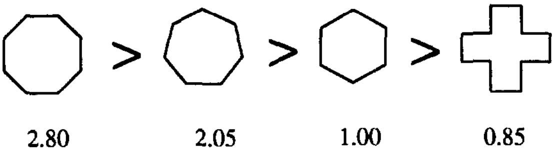
a) performed at RT. b) based on substrate. c) recovered substrate.

Competition studies on the reactivity of cycloalkanes toward oxidation under GoAgg^{V} conditions were carried out by mixing equimolar amounts of pairs of selected cycloalkanes prior to reaction. The results are presented in Table 4.

Table 4. Competition studies of cycloalkanes toward GoAgg^{V} oxidation.

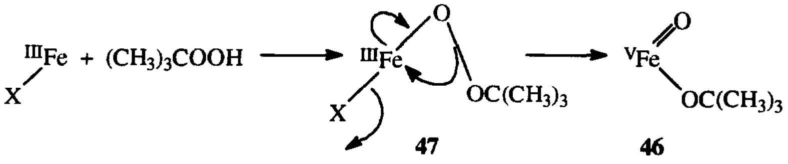
Cycloalkanes		Products (mmol)			
R^{1}	R^{2}	R^{1}-one	R^{1}-ol	R^{2}-one	R^{2}-ol
8	**41**	1.26	0.20	2.41	0.27
8	**1**	0.99	0.15	3.72	0.16
8	**5**	1.07	0.15	1.81	0.31

The relative reactivities of cycloalkanes calculated by normalization per number of C-H bonds in the molecule are shown below. Unlike the GoAgg^{III} system where cycloheptane (**41**) was reported to be the most reactive substrate among the cycloalkanes studied[19], the most reactive cycloalkane in the GoAgg^{V} oxidation reaction appeared to be cyclooctane (**1**).



Mechanistic studies

The mechanistic pathway of the GoAgg^{IV} oxidation system is considered to be similar to that postulated for other Gif-type reactions.[10] The first step of the activation process involves the formation of a high valent (formally) $^{V}Fe=O$ species (**43**) which could plausibly be derived from the rearrangement of the $^{III}Fe-OOC(CH_3)_3$ species (**44**) as shown below.



X = OAc, OH *etc.*

Indirect evidence for the existence of a high valent Fe species along the reaction pathway was supported from the competitive oxidation reaction between saturated hydrocarbons and alcohols.[20] The more alcohol applied to the oxidation system of a saturated hydrocarbon, the less oxidized product derived from the latter was seen. Nevertheless, according to the difference in the kinetic isotope effect (KIE) values and the regioselectivity observed from both the GoAgg^{II} and GoAgg^{IV} systems[11,21], a different high valent Fe species responsible for the initial activation process of saturated hydrocarbons in each of these two systems was perceived.

The formation of *tert*-butanol as a by-product from the reaction was monitored by ^{13}C NMR spectroscopy. It was found that more than 90% of *tert*-butanol was produced during the reaction. Under these particular conditions, $O_2^{\cdot}$ was formed in less than 10% based on the oxidant used.[11] The possible generation of a *tert*-butyl cation from the system was ruled out according to the observation obtained from the GoAgg^{IV} reaction in the presence of NaN_3. The results clearly showed that in the presence or absence of hydrocarbons, there was no *tert*-butyl azide $[(CH_3)_3C-N_3]$ formed. Also the solvent pyridine would immediately react with a cation.

The formation of intermediate A (**48**) postulated to be an $^{V}Fe-C$ sigma bonded species, rationalized as outlined in Figure 1, is believed to occur as a subsequent step *via* the insertion of the high valent Fe species into the C-H bond of the saturated hydrocarbon. In the presence of appropriate trapping reagents, this intermediate could be converted into monosubstituted alkyl derivatives.[12] On the other hand, Intermediate A could possibly be reduced *via* an electron transfer process to yield species (**49**) which would then undergo an O_2 insertion process to give the alkyl iron peroxy species (**50**).[10] The alkyl peroxy species could then undergo hydrolysis to furnish alkyl hydroperoxide (Intermediate B) before collapsing to ketone and alcohol as final products.

In the absence of O_2, however, it was conceivable that $^{V}Fe-C$ species (Intermediate A) could possibly undergo homolytic cleavage to give a carbon radical since some pyridine-coupled products were detected. The homolytic cleavage of the $^{V}Fe-C$ species was found to be highly dependent on the temperature. The results of

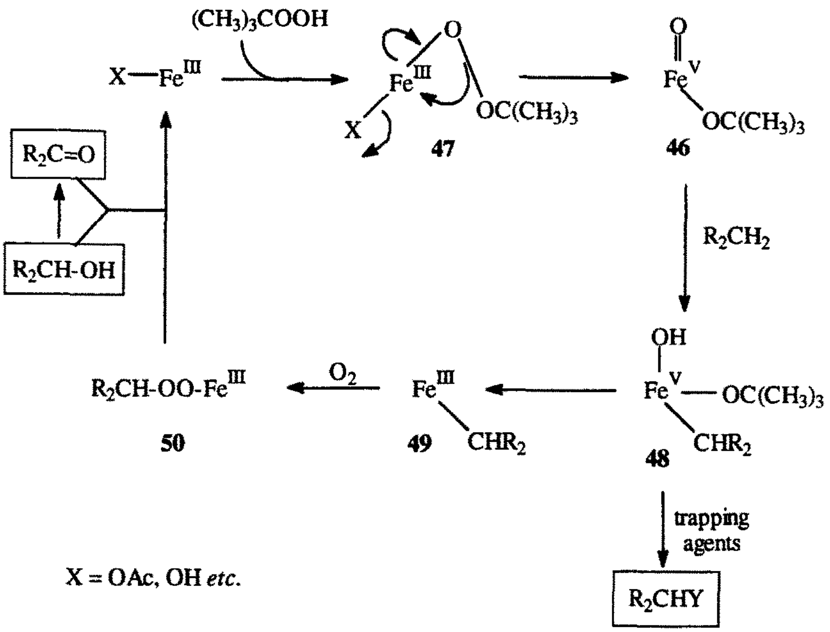


Figure 1. Proposed mechanism for the GoAgg^{IV} and GoAgg^{V} oxidation reactions.

a variable temperature study of the GoAgg^{IV} oxidation reaction of cyclooctane (1) under an argon atmosphere are presented in Table 5.

Table 5. The effects of temperature on the GoAgg^{IV} oxidation reaction of cyclooctane (1) under an argon atmosphere.[a]

Temp (°C)	Reaction time (d)	Product (mmol)			
		42	43	44	45
80	3	0.510	1.800	0.570	tr.
60	5	0.527	1.803	0.481	0.315
40	10	0.564	1.319	0.416	0.436
RT	14	0.453	0.482	0.196	0.692
0	20	0.410	0.210	0.092	0.801

a) employing $Fe(NO_3)_3 \cdot 9H_2O$ (1 mmol), cyclooctane (1) (50 mmol) and TBHP (10 mmol). tr. = traces.

The results given in Table 5 clearly demonstrate that the activation process in the absence of O_2 was only 20% efficient based on the oxidant. The amount of cyclooctyl pyridine-coupled products (**43**, **44**) was found to be significantly dependent on the temperature of the reaction. At room temperature and 0°C, these pyridine-coupled products (**43**, **44**) were detected as minor products, approximately 3-5% based on TBHP. Consequently, the possibility that the intermediate A is homolytically cleaved at room temperature or lower was found to be a minor pathway.

In addition, recent comparative studies dealing with the nature of Intermediate A in the $GoAgg^V$ system have clearly shown that the behavior of this intermediate toward trapping reagents is completely different from that exhibited by genuine carbon-centered radical.[22] Thus, an apparent paradox would again be posed if the participation of carbon-centered radical were imagined to be the first intermediate of this system.

Two additional products formed from the oxidation performed under an argon atmosphere were identified as cyclooctene (**42**) and cyclooctyl *tert*-butyl peroxide (**45**). Whereas the former is believed to arise *via* an elimination process from Intermediate A[23], the latter is proposed to be derived from ligand coupling in the same manner as other ionic trapping reagents.[12] Moreover, cyclooctyl *tert*-butyl peroxide (**45**) was found to be stable under the conditions and not to be a precursor for the formation of ketones or alcohols.[11]

CONCLUSION

The utilization of TBHP as an ultimate oxidant under Gif-type conditions has led to the development of new and powerful systems in Gif-type reactions, the $GoAgg^{IV}$ and $GoAgg^V$ systems. Under these conditions, the superior amounts of the desired products and the high selectivity for the formation of the ketone compared to other Gif-type and related reactions have been clearly shown. The mechanistic pathway of this oxidation system is believed to be similar to that proposed for other Gif-type reactions. Nevertheless, there are some unique features belonging to these systems which need to be further explored. For instance, differences in the regioselectivity and kinetic isotope effects observed for these systems were found. The adamantane selectivity (C^2/C^3) is about 0.7 instead of 1.0 and the KIE (kinetic isotope effect) is about 8.0±0.3[11] instead of 2.2±0.1.[21] Moreover, the capability of transforming alkanes efficiently into monosubstituted alkyl derivatives by various alkali metal salts is another distinct feature observed in the $GoAgg^{IV}$ system, but not in the $GoAgg^V$ variation.[12]

EXPERIMENTAL

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Authentic samples of cyclooctyl chloride[24], 1-*tert*-butylcyclohexanol[25], 3-*tert*-butylcyclohexanone[26], *cis*-3-*tert*-butylcyclohexanol[27], *trans*-3-*tert*-butylcyclohexanol[28], *cis*-4-*tert*-butylcyclohexanol[27], *trans*-4-*tert*-butylcyclohexanol[28], *tert*-butyl azide[29] were prepared according to previously reported methods and their identities were confirmed by IR, ^1H- and ^{13}C-NMR spectroscopy. The *ortho*- and *para*- pyridine-coupled products; cyclooctyl-, 1-adamantyl- and 2-adamantyl-pyridine were obtained from the photolysis of the corresponding Barton ester in a pyridine-trifluoroacetic acid mixture as reported previously.[6]

Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 spectrophotometer. ^1H and ^{13}C NMR spectra were performed in deuterochloroform with tetramethylsilane (TMS) as an internal reference on a Varian Gemini 200 or Varian XL

200E. Gas chromatography analysis was carried out on a Hewlett Packard 5890 series II instrument or on Chrompack Model 439 and 437S instruments equipped with a flame ionization detector with N_2 as a carrier gas. The columns used for chromatography were DB-WAX (30 m) or DB-5 (15 or 30 m) capillary columns from J&W Scientific (0.32 mm i. d., 25 µm film thickness). Gas chromatography-mass spectrometry (GC-MS) analysis was conducted on a Hewlett-Packard gas chromatograph Model 5790A coupled to a Hewlett-Packard 5970 mass selective detector (40 eV, electron impact).

Typical GoAgg^{III} system. A GoAgg^{III} reaction was carried out in a solution of pyridine (30 ml), acetic acid (3 ml), substrate (5.0 mmol), $FeCl_3 \cdot 6H_2O$ (54 mg, 0.2 mmol) and picolinic acid (78 mg, 0.6 mmol) in an Erlenmeyer flask under air. After adding 30% H_2O_2 in water (1.5 ml, 15.0 mmol) to start the oxidation reaction, the reaction mixture was stirred for 16 h at room temperature, followed by the usual work-up. Samples were analyzed by gas chromatography using napthalene or fluorene as internal standards.

Typical GoAgg^{IV} system. The reaction was conducted in the same way as that described in the GoAgg^{III} system except for employing $Fe(NO_3)_3 \cdot 9H_2O$ (202 mg, 0.5 mmol) or other iron complexes (0.5 mmol) and the use of 90% TBHP in a mixture of 5% *tert*-butanol and 5% water (1.1 ml, 10.0 mmol) as an oxidant *in lieu of* 30% H_2O_2.

Typical GoAgg^{V} system. The reaction was performed using the same procedure as employed in the GoAgg^{IV} system except for the addition of an extra ligand (generally picolinic acid 1:3 ratio of Fe^{III}:acid) to the system.

General work-up procedure. An aliquot (1.0 ml) was taken from the reaction mixture, acidified with 25% H_2SO_4 to a pH of approximately 2-3 and extracted twice with diethyl ether (5 ml each). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and water, dried ($MgSO_4$) and analyzed by gas chromatography after the addition of a known amount of an appropriate internal standard.

Studies on the effects of temperature and the concentration of Fe (III) species on the rate of the oxidation. The GoAgg^{IV} oxidation reaction of cyclooctane (50.0 mmol) was carried out in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ or $FeCl_3 \cdot 6H_2O$ or $Fe(OAc)_3$ (variable amount: 0.1, 0.2, 0.5 or 1.0 mmol) in pyridine (30 ml) and acetic acid (3 ml). The temperature of the reaction was raised up to 55-60°C or cooled down to 0-5°C and kept constant at that temperature prior to the addition of TBHP (1.1 ml, 10.0 mmol). Kinetic analysis or the quantification followed the procedure described earlier.

General procedure for the competition studies in the GoAgg^{V} system. GoAgg^{V} reactions were carried out employing a pair of hydrocarbons (25 mmol each) for the competition studies. Other procedures followed those described earlier for the typical GoAgg^{V} reaction.

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