

## The Functionalization of Saturated Hydrocarbons. Part 25.<sup>+</sup> Ionic Substitution Reactions in GoAgg<sup>IV</sup> Chemistry: The Formation of Carbon-Halogen Bonds

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**Abstract:** GoAgg<sup>IV</sup> chemistry (Fe (III) species, *tert*-butyl hydroperoxide in a mixture of pyridine and acetic acid) in the presence of LiCl can transform saturated hydrocarbons efficiently into the corresponding alkyl chlorides. The transformation into monosubstituted alkyl derivatives by "ionic trapping" reagents arising from the interception of the first intermediate of the system supports the presence of a high valent <sup>V</sup>Fe-C species. Mechanistic studies suggest a possible pathway operating *via* an Fe-centered ligand coupling. In addition, the production of alkyl chlorides and alkyl bromides could also be achieved employing this system in the presence of halogenating reagents such as CCl<sub>4</sub> and BrCCl<sub>3</sub>.

### INTRODUCTION

Although the selective functionalization of saturated hydrocarbons under mild conditions is not an easy task owing to the high energy of the carbon-hydrogen bond in the alkane molecule, the development of methods capable of transforming this ample class of organic substances into more valuable compounds has not ceased.<sup>1</sup> The drive to achieve this goal has been greatly stimulated by the remarkable ability of several biological systems, particularly Cytochrome P-450 and Methane monooxygenase enzymes.<sup>2</sup> Accordingly, a number of heme- and non-heme containing chemical models have been developed.<sup>3</sup>

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The conversion of unactivated carbon-hydrogen bonds into carbon-halogen bonds generally could be accomplished by the use of free radical processes; however, the selectivity of these systems is difficult to control. The chlorination reaction of saturated hydrocarbons employing molecular chlorine ( $\text{Cl}_2$ ), for instance, invariably gives mixtures of compounds.<sup>4</sup> Moreover, drastic conditions are normally required. Due to the importance of alkyl halides as intermediates for functional group interconversion in organic synthesis, alternative procedures for the construction of carbon-halogen bonds under mild conditions have been developed. The formation of carbon-chlorine and carbon-bromine bonds, for example, has been reported by several groups.<sup>5</sup> Nevertheless, these reactions call for further development.

Since 1983, various Gif-type reactions have been established.<sup>6,7</sup> The iron or copper catalysts employed are generally commercially available and inexpensive. Various active forms of oxygen species have been studied and utilized as oxidants such as superoxide ion ( $\text{O}_2^{\cdot-}$ ) in the Gif<sup>III</sup> and Gif<sup>IV</sup> systems; hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) in the GoAgg<sup>II</sup>, GoAgg<sup>III</sup> and GoChAgg systems and *tert*-butyl hydroperoxide (TBHP) in the GoAgg<sup>IV</sup> and GoAgg<sup>V</sup> systems.<sup>6,8</sup> All of these reactions are performed in a mixture of pyridine-acetic acid. Alkane oxidation by Gif-type reactions provides the oxidized products, with the ketone being the major component.<sup>7</sup> However, in the presence of appropriate trapping reagents, the formation of ketone is diverted to monosubstituted alkyl derivatives.<sup>7</sup>

Previous studies on the selective substitution of C-H bonds by C-Cl and C-Br bonds by Gif-type reactions showed that alkyl chlorides and alkyl bromides could be obtained by employing the Gif<sup>III</sup> system in the presence of  $\text{CCl}_4$ ,  $\text{CHBr}_3$  or  $\text{CBr}_4$ , respectively.<sup>9</sup> More recent studies detailed the use of  $\text{BrCCl}_3$  for the construction of C-Br bonds in the GoAgg<sup>II</sup> and GoAgg<sup>III</sup> systems.<sup>10</sup> Mechanistic studies clearly showed that the formation of C-Cl and C-Br bonds occurred *via* non-radical type reactions.<sup>9,10</sup>

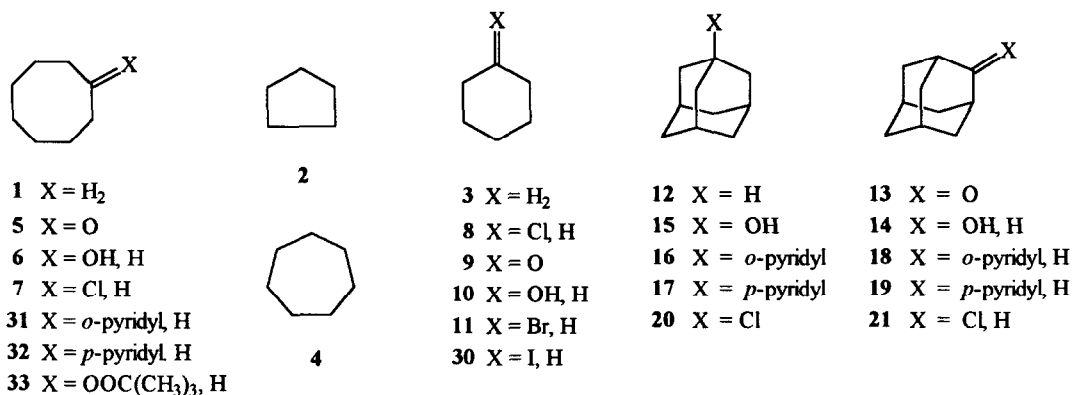
Even though an attempt to use inorganic salts such as LiBr to functionalize alkanes has been made before in the GoAgg<sup>III</sup> system<sup>10</sup>, no alkyl bromide was formed. The process of ketonization was found to prevail. We report herein for the first time under Gif-type conditions the efficient construction of C-Cl bonds directly from unactivated C-H bonds of saturated hydrocarbons employing the GoAgg<sup>IV</sup> system in the presence of alkali metal salts. The formation of alkyl chlorides and alkyl bromides could also be attained by this system using halogenating agents employed in other Gif-type reactions.<sup>9,10</sup>

## RESULTS AND DISCUSSION

Further examination of the functionalization of saturated hydrocarbons was inspired by the observation that alkyl chloride was produced in high yield under GoAgg<sup>IV</sup> conditions employing  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  in reagent quantity.<sup>8f</sup>

### *The Construction of C-Cl Bonds*

In order to confirm the previous results obtained from the chlorination of cyclooctane (**1**), various cycloalkanes such as cyclopentane (**2**), cyclohexane (**3**) and cycloheptane (**4**) were employed in the chlorination reaction. The results revealed the generality of this reaction. The formation of alkyl chlorides was found to be in the range of 5.21-5.96 mmol giving an efficiency for TBHP of around 52-60%.<sup>11</sup>



A series of control experiments was performed. It was shown that in the absence of FeCl<sub>3</sub>·6H<sub>2</sub>O or an oxidant (TBHP) there was no alkyl chloride formation. The replacement of FeCl<sub>3</sub>·6H<sub>2</sub>O with lithium chloride (LiCl) emphasized the necessity of the Fe<sup>III</sup> species for successful reaction since in the absence of the Fe<sup>III</sup> species no reaction took place. However, it is particularly noteworthy that the chlorination reaction could be fruitfully carried out employing a combination of a catalytic amount of FeCl<sub>3</sub>·6H<sub>2</sub>O and an excess of LiCl. The results of the effects of varying the quantity of LiCl on the chlorination reaction are shown in Table 1.

**Table 1.** The effects of LiCl on the GoAgg<sup>IV</sup> chlorination reaction of cyclooctane (**1**).<sup>a</sup>

LiCl (mmol)	Product (mmol)				Efficiency of TBHP (%)
	5	6	7	Σ	
0	0.54	0.30	1.26	2.20	44.0
1	0.63	0.30	1.40	2.33	46.6
5	0.49	0.11	2.13	2.73	54.6
10	0.40	0.13	3.08	3.61	72.2
15	0.17	0.09	3.92	4.18	83.6

a) the reactions were carried out employing FeCl<sub>3</sub>·6H<sub>2</sub>O (0.5 mmol) and TBHP (5 mmol) at 60 °C.

The results clearly revealed that the more LiCl was added to the system, the more cyclooctyl chloride was attained. The formation of alkyl chloride from the GoAgg<sup>IV</sup> system was different from that reported by Que and coworkers.<sup>5h,5i</sup> In the former system the alkyl derivative could be produced from the system employing a catalytic amount of FeCl<sub>3</sub>·6H<sub>2</sub>O and free chloride ion in the solution; however, in the latter system

the alkyl chloride was reported to require stoichiometric amounts of iron complex and not involve the participation of free halide.<sup>5h,5i</sup>

The catalytic turnover number of the GoAgg<sup>IV</sup> chlorination reaction employing Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O and free chloride ion (LiCl) was evaluated. The results as presented in Table 2 show that a high efficiency based on the oxidant and high catalytic turnover number could be achieved from this system. For instance, the use of 0.1 mmol of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O gave a 90% efficiency based upon TBHP and a turnover of 75 per catalyst molecule for the formation of cyclooctyl chloride (7).

**Table 2.** The catalytic turnover of the GoAgg<sup>IV</sup> chlorination reaction of cyclooctane (1).<sup>a</sup>

Fe <sup>III</sup> (mmol)	Product (mmol)				Efficiency of TBHP (%)	Turnover No.	
	5	6	7	Σ		Chlorination	Overall
1.0	–	–	10.02	10.02	100.2	10	10
0.5	0.39	–	9.11	9.50	95.0	18	19
0.2	0.87	–	8.16	9.03	90.3	41	43
0.1	1.49	–	7.49	8.98	89.8	75	90

a) the reactions were carried out using LiCl (15 mmol) and TBHP (10 mmol) at 60°C.

The possibility that *tert*-butyl hypochlorite was being formed *in situ* from the reaction of TBHP and LiCl and that this was the actual chlorinating agent was considered. However, this possibility was ruled out since a reaction employing *tert*-butyl hypochlorite in place of TBHP and LiCl resulted in the formation of only 0.550 mmol of cyclohexyl chloride (8) with an efficiency based on the oxidant of only 5.5%.

Furthermore, the possibility that molecular chlorine (Cl<sub>2</sub>) could be the actual chlorinating agent, presumably generated from the oxidation of chloride ion by TBHP was taken into consideration. The attempted chlorination of benzene by the GoAgg<sup>IV</sup> reaction gave evidence for discarding this possibility. Unlike the chlorination of benzene employing Cl<sub>2</sub> and a Lewis acid such as FeCl<sub>3</sub><sup>12</sup>, no chlorination of benzene was observed.

The results of comparative studies on the effects of the Fe<sup>III</sup> species employing 1 mmol of various Fe<sup>III</sup> salts and 15 mmol of LiCl are presented in Table 3. A range of Fe<sup>III</sup> species could be used to carry out the GoAgg<sup>IV</sup> chlorination reaction (entries 1-5). The highest ratio of cyclohexyl chloride (8) to cyclohexanone (9) was obtained when Fe(acac)<sub>3</sub> was employed (entry 3). Interestingly, in the reaction using Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O and 3 equivalents of picolinic acid (entry 7), the oxidation reaction prevailed over the chlorination reaction. The same phenomenon could be seen when 2,6-dipicolinic acid (2,6-DPA) was added to the system (entry 8). Nevertheless, with a ratio of 1:1 of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O and picolinic acid chlorination was found to be the predominant reaction pathway (entry 6). These results strongly suggested that the reaction pathway for the chlorination reaction could take place *via* an Fe-centered ligand coupling process where chloride was a necessary ligand. This hypothesis was logical since when 3 equivalents of picolinic acid was applied to the

system, the Fe species was coordinatively saturated with 3 picolinic acid ligands. Moreover, this idea was substantiated by a series of experiments examining the effects of water in the GoAgg<sup>IV</sup> chlorination reaction. While the total activation in the reaction remained constant, the more water was added to the system, the less

**Table 3.** The effects of Fe<sup>III</sup> species on the GoAgg<sup>IV</sup> chlorination reaction of cyclohexane (**3**).

Entry	Fe <sup>III</sup> species	Product (mmol)				$\frac{8}{9}$
		9	10	8	$\Sigma$	
1	FeCl <sub>3</sub> ·6H <sub>2</sub> O	0.95	0.15	5.38	6.48	5.66
2	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	0.72	0.17	4.98	5.87	6.92
3	Fe(acac) <sub>3</sub>	0.34	0.12	4.95	5.41	14.56
4 <sup>a</sup>	FeBr <sub>3</sub>	0.57	0.22	1.55	3.25	4.32
5	FeF <sub>3</sub>	0.75	0.17	5.79	6.71	7.72
6	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O + PA (1:1)	1.14	0.19	5.03	6.36	4.41
7	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O + PA (1:3)	3.37	0.44	0.41	4.22	0.12
8	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O + 2,6-DPA(1:3)	2.21	0.27	1.21	3.69	0.55
9	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O + bipy (1:3)	1.25	0.19	4.26	5.70	3.41

\*the reaction was carried out using LiCl (15 mmol) and TBHP (10 mmol) at 60°C.

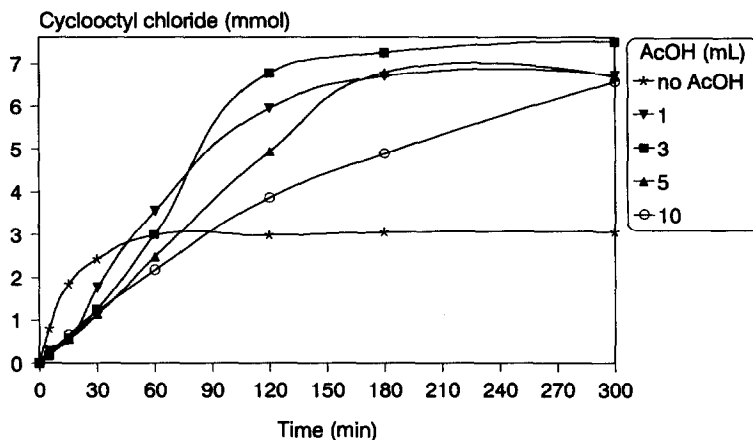
a) accompanied with cyclohexyl bromide (**11**) 0.91 mmol.

PA = picolinic acid; 2,6-DPA = 2,6-dipicolinic acid; bipy = 2,2'-bipyridine.

chlorinated product was attained. The principal reason for these observations could be that the chloride ligands on the iron were replaced by the stronger hydroxy or picolinic acid ligands.

The effect of pH on the GoAgg<sup>IV</sup> chlorination was examined and it was found that the optimal pH for the reaction was approximately 5.7. Variation of pH of the system by adding a variable amount of AcOH was found to influence the rate of the reaction. In the absence of AcOH (pH 6.1), the reaction took place very fast (half-life 30 min), but gave a lesser amount of the desired product. Comparative results are given in Fig 1.

Having gained insight from the previous results that the oxidation products (ketones and alcohols) were derived from the interaction of an intermediate and O<sub>2</sub>,<sup>13</sup> it was manifest that the removal of O<sub>2</sub> from the reaction system would increase the yield of alkyl chlorides. Thus, the cyclooctane (**1**) chlorination reaction was carried out using of 1 mmol of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O in the presence of 20 mmol of LiCl and 10 mmol of TBHP at 60°C under an argon atmosphere resulting in the exclusive production of cyclooctyl chloride (**7**). The half-life of the reaction was approximately 110 mins.



**Figure 1.** The effects of acetic acid in the GoAgg<sup>IV</sup> chlorination of cyclooctane (**1**).

Even though the chlorination could be readily effected at 60°C, attempts were made to carry out the reaction at ambient temperature. Table 4 shows the amount of products, the efficiency of the reaction based on TBHP and the half-life of the GoAgg<sup>IV</sup> chlorination of cyclooctane (**1**) at room temperature.

**Table 4.** The GoAgg<sup>IV</sup> chlorination of cyclooctane (**1**) at room temperature.<sup>a</sup>

Entry	System, conditions	Product (mmol)				$\frac{7}{5}$	Half-life for chlorination (h)
		5	6	7	$\Sigma$		
1	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	1.48	0.16	5.05	6.69	3.41	44
2	FeCl <sub>3</sub> ·6H <sub>2</sub> O	2.54	0.25	5.44	8.23	2.14	50
3	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O + NaSCN (1:1)	1.73	0.15	5.88	7.76	3.40	20
4	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O + NaSCN (1:3)	1.30	0.21	3.55	5.06	2.73	16

a) the reactions were carried out employing Fe<sup>III</sup> species (1 mmol), LiCl (20 mmol) and TBHP (10 mmol).

The results presented in Table 4 show that the chlorination reaction under GoAgg<sup>IV</sup> conditions could be successfully performed with Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O or FeCl<sub>3</sub>·6H<sub>2</sub>O (entries 1 and 2). The half-lives of the reaction were found to be 44 and 50 h. Remarkably, the addition of 1 equivalent of NaSCN to the system provided a two-fold rate enhancement of the reaction and a higher yield of the cyclooctyl chloride (entry 3). However, when more NaSCN was added to the reaction, less desired product was obtained (entry 4).

Besides the utilization of LiCl, the construction of C-Cl bonds was also accomplished in the same manner as that utilized in other Gif-type reactions employing halogenated compounds such as CCl<sub>4</sub>, CHCl<sub>3</sub> and

$\text{CH}_2\text{Cl}_2$ .<sup>9,10</sup> The chlorination reaction could be performed at ambient temperature by the GoAgg<sup>V</sup> system comprising of an Fe<sup>III</sup> species and picolinic acid. The results are collected in Table 5.

**Table 5.** The chlorination of cyclohexane (**3**) using chlorinating reagents.

Reagents*	Product (mmol)				$\frac{8}{9}$
	9	10	8	$\Sigma$	
–	3.46	0.47	–	3.93	
$\text{CCl}_4$	1.91	0.19	2.04	4.14	1.07
$\text{CHCl}_3$	2.80	0.33	0.85	3.98	0.30
$\text{CH}_2\text{Cl}_2$	3.57	0.41	0.39	4.37	0.11

\*employing 30 mmol of each reagent.

Even though the ratio of alkyl chloride to ketone obtained was not as high as that observed from the methodology employing LiCl described earlier, the use of  $\text{CHCl}_3$  as a chlorinating agent provided informative guidance for a mechanistic pathway. The total activation of the system was found to be constant in the absence or the presence of excess  $\text{CHCl}_3$  which is known to be a hydrogen atom source for carbon-centered radicals.<sup>14</sup> This result strongly implied that the formation of alkyl chloride from the GoAgg<sup>IV</sup> reaction did not involve a carbon-centered radical pathway. Capture of intermediate A by trapping reagents to produce alkyl chloride as proposed in the Gif-type systems was therefore reasonable.<sup>9,10</sup>

The regioselectivity of the system using adamantane (**12**) as a substrate was examined and the results are shown in Table 6. From the outcome of the reactions as indicated by the product distributions, the activation process was found to take place at the tertiary position preferentially over the secondary position, giving a  $\text{C}^2/\text{C}^3$  value of 0.55 for the chlorination with LiCl and 0.53 for that using  $\text{CCl}_4$  as a chlorinating agent. Nevertheless, it is noteworthy that there were no secondary adamantyl pyridine-coupled products (**18**, **19**) obtained in either case. Although the  $\text{C}^2/\text{C}^3$  value derived from the GoAgg<sup>IV</sup> chlorination (0.53–0.55) was found to be less than that derived from typical Gif-type oxidation reactions (around 1)<sup>15</sup>, the  $\text{C}^2/\text{C}^3$  value obtained from the chlorination of adamantane *via* carbon-centered radicals employing  $\text{CCl}_4$  and radical initiators was reported to be far lower than that observed from the GoAgg<sup>IV</sup> system. For instance, the use of  $\text{R}_2\text{NH}^{\cdot+}$  or  $\text{CCl}_3^{\cdot}$  as a radical chain initiator in the chlorination of adamantane (**12**) using  $\text{CCl}_4$  reported by Billups *et al.* gave a  $\text{C}^2/\text{C}^3$  value of 0.003.<sup>16</sup> Tabushi and coworkers have also demonstrated that the utilization of di-*tert*-butyl peroxide (DTBP) and benzoyl peroxide (BPO) as radical initiators for adamantane chlorination provided a  $\text{C}^2/\text{C}^3$  ratio of 0.02 and 0.05, respectively.<sup>17</sup>

**Table 6.** The chlorination of adamantane (**12**) by the GoAgg<sup>IV</sup> system.

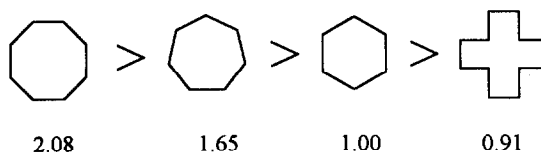
Reagent	Yield (%) <sup>a</sup>								Σ	C <sup>2</sup> /C <sup>3</sup>
	<b>12</b> <sup>b</sup>	<b>13</b>	<b>14</b>	<b>15</b>	<b>16</b>	<b>17</b>	<b>20</b>	<b>21</b>		
LiCl <sup>c</sup>	54.7	8.9	0.6	6.1	6.8	2.3	11.1	4.9	95.4	0.55
CCl <sub>4</sub> <sup>d</sup>	72.4	3.2	0.3	2.9	–	–	12.7	4.8	96.3	0.53

a) based on substrate. b) recovered substrate. c) employing Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (1 mmol), LiCl (15 mmol) and TBHP (10 mmol) at 60°C. d) employing Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (1 mmol), picolinic acid (3 mmol) and CCl<sub>4</sub> (30 mmol) at RT.

A study of the relative reactivities of cycloalkanes towards the chlorination reaction employing LiCl under GoAgg<sup>IV</sup> conditions revealed the same trend in relative reactivity as that observed for the oxidation reaction.<sup>8f</sup> By normalization per C-H bond, cyclooctane (**1**) was found to be the most reactive substrate among cycloalkanes studied. The results are shown in Table 7.

**Table 7.** Competition studies between cycloalkanes toward the GoAgg<sup>IV</sup> chlorination reaction.

Cycloalkanes		Product (mmol)	
R <sup>1</sup>	R <sup>2</sup>	R <sup>1</sup> -Cl	R <sup>2</sup> -Cl
<b>3</b>	<b>2</b>	2.27	4.36
<b>3</b>	<b>1</b>	2.36	6.54
<b>3</b>	<b>4</b>	1.93	3.61



### The Construction of C-Br Bonds

Employing the same methodology applied in the GoAgg<sup>IV</sup> chlorination, the effect of lithium bromide (LiBr) towards the corresponding bromination reaction under GoAgg<sup>IV</sup> conditions was studied. The results are shown in Table 8.



**Table 8.** The effects of LiBr on the GoAgg<sup>IV</sup> bromination of cyclohexane (3).<sup>a</sup>

LiBr (mmol)	Product (mmol)				Efficiency of TBHP
	9	10	11	Σ	
1	2.10	0.43	0.60	3.13	31.3
3	1.48	0.44	0.67	2.59	25.9
5	0.34	0.26	0.65	1.25	12.5
10	0.10	0.06	0.51	0.67	6.8
15	—	—	0.58	0.58	5.8

a) the reaction was carried out employing Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (1.0 mmol) and TBHP (10 mmol) at 60 °C.

Although cyclohexyl bromide (11) was detected as one of the products derived from the reaction, when more LiBr was added to the reaction, the total amount of functionalization attained was less. Unlike the efficiency obtained from the GoAgg<sup>IV</sup> oxidation or chlorination system, the efficiency of this reaction was found to be only around 5.8-6.7%. The reason for this was believed to be that the reaction of bromide ion with the oxidant occurred parallel to the bromination of saturated hydrocarbons.

The construction of C-Br bonds under GoAgg<sup>IV</sup> conditions, however, could also be achieved as shown in Table 9, by using brominating agents such as those applied to other Gif-type reactions: BrCCl<sub>3</sub>, CBr<sub>4</sub> and CHBr<sub>3</sub>.<sup>9,10</sup>

**Table 9.** The GoAgg<sup>IV</sup> bromination reactions of cyclohexane (3) using brominating agents.

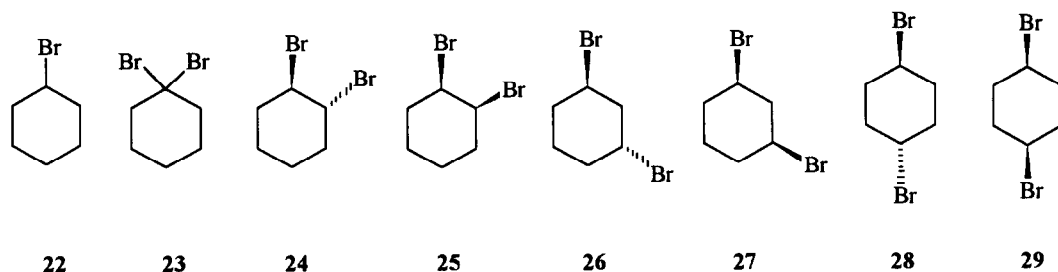
Reagents*	Product (mmol)				$\frac{11}{9}$
	9	10	11	Σ	
—	3.46	0.47	—	3.93	
BrCCl <sub>3</sub>	—	—	3.34	3.34	
CBr <sub>4</sub>	0.12	0.10	0.86	1.08	7.17
CHBr <sub>3</sub>	0.18	0.11	1.20	1.49	6.67

\*employing 10 mmol.

Among the brominating agents studied, BrCCl<sub>3</sub> turned out to be the most efficient brominating agent to construct the C-Br bond under GoAgg<sup>IV</sup> conditions. The utilization of BrCCl<sub>3</sub> provided cyclohexyl bromide (11) as the sole reaction product. The efficiency based on TBHP was found to be 33.4%. Moreover, it was

found plausible to carry out these reactions at room temperature employing the system comprising of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  and picolinic acid (GoAgg<sup>V</sup>).

Comparative studies on the utilization of two brominating agents: LiBr and  $\text{BrCCl}_3$  towards the bromination of bromocyclohexane (**22**) under GoAgg<sup>IV</sup> conditions provided informative results. In the case of LiBr, it was clearly observed that the major product from the bromination reaction was *trans*-1,2-dibromocyclohexane (**24**) which was the same as that observed from the free radical bromination (Skell-Walling effect).<sup>18</sup> Therefore, the possibility that bromide ion was oxidized to bromine ( $\text{Br}_2$ ) which subsequently was captured by carbon-centered radical and propagated the radical chain is probable. The carbon radical was believed to arise from the homolytic cleavage of Intermediate A of the reaction.<sup>8f</sup> In contrast, in the bromination employing  $\text{BrCCl}_3$  (Table 10), the major product was found to be the diequatorial substituted *cis*-1,3-dibromocyclohexane (**27**). Moreover, the distribution of other products was observed to be completely different from that seen from the free radical bromination (entry 1). The product distribution pattern derived from the GoAgg<sup>IV</sup> bromination, however, was found to be somewhat different from that previously observed in the GoAgg<sup>III</sup> system.<sup>10b,c</sup>



**Table 10.** Comparison of the regio- and stereoselectivity for radical chain bromination, the GoAgg<sup>III</sup> and GoAgg<sup>IV</sup> bromination reactions.

Entry	Percent						
	<b>23</b>	<b>24</b>	<b>25</b>	<b>26</b>	<b>27</b>	<b>28</b>	<b>29</b>
1 <sup>a</sup>	0.0	41.0	14.0	0.8	16.0	21.1	7.2
2 <sup>b</sup>	0.0	7.7	0.0	1.9	27.9	45.2	17.3
3 <sup>c</sup>	20.4	2.9	0.0	17.0	29.0	16.1	14.4

a) Value for radical chain bromination (from ref 10 b,c). b) Values from GoAgg<sup>III</sup> system (from ref. 10b,c). c) Values from GoAgg<sup>IV</sup> system.

Utilizing similar methodology to that applied for the formation of C-Cl bonds employing LiCl, the formation of C-I bonds could also be accomplished. Thus, the oxidation of cyclohexane (**1**) by the GoAgg<sup>IV</sup> system in the presence of 10 mmol of sodium iodide (NaI) resulted in the formation of 0.264 mmol of cyclohexyl iodide (**30**) as the sole product (5.2% efficiency based on TBHP).

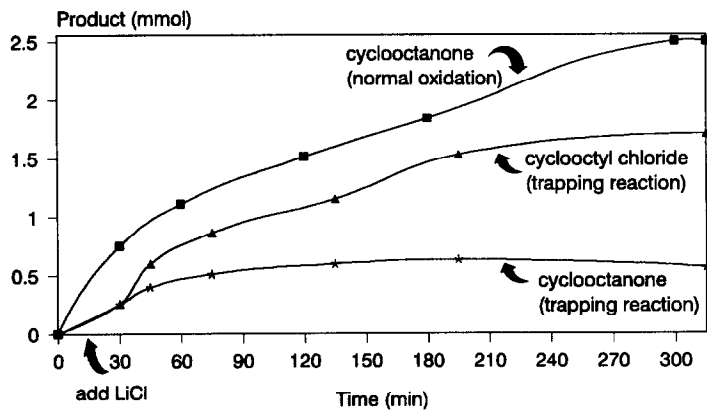
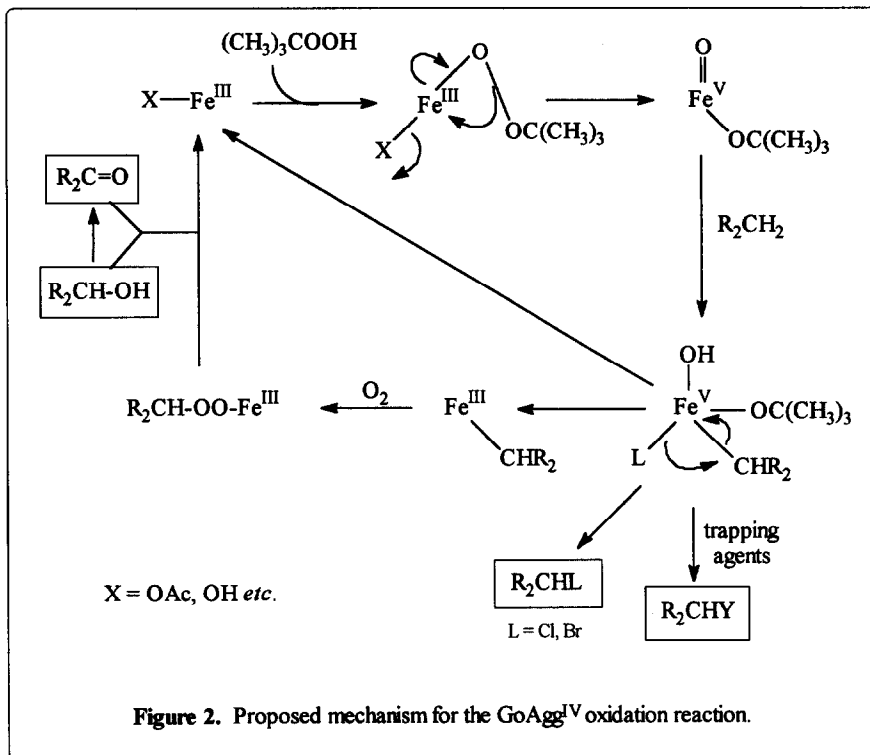
Attempts to create C-F bonds by this methodology employing lithium fluoride (LiF) were not successful. Normal oxidation of cyclohexane (**3**) or cyclooctane (**1**) under the GoAgg<sup>IV</sup> system using FeF<sub>3</sub> or Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O in the presence of LiF prevailed giving ketonic and alcoholic products with no sign of alkyl fluoride formation.

### *Mechanistic Studies*

The proposed mechanistic pathway for the activation process of the GoAgg<sup>IV</sup> system is outlined as shown in Fig. 2. The formation of the high valent (formally) <sup>V</sup>Fe=O species takes place initially, followed by the insertion of the high valent Fe species into the C-H bond of the saturated hydrocarbon to generate an <sup>V</sup>Fe-C sigma bonded species (Intermediate A). Since the GoAgg<sup>IV</sup> system does not contain a reducing agent such as Zn in the Gif<sup>IV</sup> system or H<sub>2</sub>O<sub>2</sub> in the previous GoAgg systems, the chemistry of the <sup>V</sup>Fe-C bonded species therefore predominates. The transformation into monosubstituted alkyl derivatives arising from the interception of Intermediate A by an ionic trapping reagent such as LiCl was thereby in accordance with the persistence of such a high valent Fe species. A study of the addition of LiCl at a certain time along the reaction pathway, as depicted in Fig. 3, clearly revealed that LiCl intercepted the same intermediate which, in the absence of LiCl, would eventually produce ketones and alcohols.

As previously demonstrated, in the absence of suitable trapping reagents Intermediate A could possibly undergo homolytic cleavage to form carbon-centered radicals depending on the reaction temperature.<sup>8f</sup> This postulation was verified by a study of the effects of variable amounts of LiCl on the GoAgg<sup>IV</sup> oxidation of cyclooctane (**1**) under an argon atmosphere. As presented in Table 11, the results clearly reveal that in the presence of sufficient trapping reagent, no pyridine-coupled products were formed. The sole product observed was cyclooctyl chloride (**7**) with quantitative efficiency based on TBHP. When the amount of trapping reagent was reduced, the formation of pyridine-coupled products (**31**, **32**) and mixed peroxide (**33**) was detected. Consequently, it was conceived that Intermediate A was captured efficiently by LiCl and that it could possibly collapse into carbon radicals *via* a homolytic process when low concentrations of trapping agents were employed.

The mechanistic pathway for the functionalization of saturated hydrocarbons is therefore rationalized that in the presence of suitable covalent trapping reagents (BrCCl<sub>3</sub>, CCl<sub>4</sub>), Intermediate A could be converted into monosubstituted alkyl derivatives. In the absence of appropriate covalent trapping reagents, it was conceivable that ligand coupling could be operating giving rise to the formation of other types of monosubstituted derivative and regenerating the Fe(III) species to continue the catalytic cycle.



**Figure 3.** Comparative kinetic analysis of the effect of the addition of LiCl after 15 min. of incubation time and the normal GoAgg<sup>IV</sup> oxidation of cyclooctane (**1**) at 60°C.

**Table 11.** The effects of varying amounts of LiCl on the GoAgg<sup>IV</sup>oxidation reaction under an argon atmosphere at 60°C.<sup>a</sup>

LiCl (mmol)	Product (mmol)			
	8	31	32	33
20	9.94	—	—	—
15	10.02	—	—	—
10	6.87	0.22	0.09	tr.
5	4.11	0.26	0.10	0.10
3	2.67	0.34	0.13	0.42

a) employing Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (1 mmol), cyclooctane (1) (50 mmol) and TBHP (10 mmol). tr. = traces.

In addition, recent comparative studies concerned with the nature of Intermediate A in the GoAgg<sup>IV</sup> system have shown that the behavior and relative reactivity of carbon-centered radical towards trapping reagents under conditions employed for functionalizing saturated hydrocarbons is completely different from that observed in the GoAgg system. This informative finding strengthened the postulation of such a high valent Fe-C bond as the first intermediate of Gif-type systems.<sup>19</sup>

### CONCLUSIONS

A simple chemical model: the GoAgg<sup>IV</sup> system, provides an efficient alternative for the construction of C-Cl bonds under mild conditions. In addition, in the presence of suitable halogenating agents (CCl<sub>4</sub>, BrCCl<sub>3</sub>), the transformation of C-H bonds into C-Cl and C-Br bonds can also be achieved. This use of anions is found for the first time under Gif-type conditions. It could possibly be explained by the intermediacy of a relatively long lived high valent Fe species. Further examination of the variation of alkali metal salts for selective transformation of saturated hydrocarbons to other functional groups by this system is in progress.<sup>20</sup>

### EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer 881 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were performed in deuteriochloroform 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, on Chrompack Model 439 or 437S instruments equipped with a flame ionization detector with N<sub>2</sub> 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). Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck, Kieselgel 60 F-254). Column chromatography

was performed on silica gel (Merck, Kieselgel 60, 230-400 mesh). Solvents were used either as purchased or dried and purified by standard methods under pure, dry argon.

All chemicals, unless otherwise stated, were purchased as the highest purity commercially available and were used without further purification. Authentic samples of cycloheptyl chloride<sup>21</sup>, cyclooctyl chloride<sup>21</sup>, 1,3-*cis*-dibromocyclohexane<sup>22</sup>, 1,3-*trans*-dibromocyclohexane<sup>22</sup>, 1,4-*cis*-dibromocyclohexane<sup>22</sup>, 1,4-*trans*-dibromocyclohexane<sup>22</sup> and 1,1-dibromocyclohexane<sup>10c,23</sup> were prepared according to previously reported methods and their identities were confirmed by IR, <sup>1</sup>H- and <sup>13</sup>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.<sup>24</sup>

*Typical GoAgg<sup>IV</sup> halogenation using LiCl or LiBr.* A GoAgg<sup>IV</sup> oxidation reaction of hydrocarbon (50 mmol) was carried out in the presence of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (404 mg, 1.0 mmol) or other iron complexes (1.0 mmol), LiCl or LiBr (15 mmol) in a solution of pyridine (30 ml), acetic acid (3 ml). The temperature of the reaction was raised up to 55-60°C and kept constant at that temperature prior to the addition of 90% TBHP (1.1 ml, 10 mmol). The reaction mixture was stirred for 4-5 h, followed by the usual work-up (see below). Samples were analyzed by gas chromatography using naphthalene or fluorene as internal standards.

*Typical GoAgg<sup>V</sup> halogenation using halogenating agents.* The reaction was conducted in the same way as that described in the GoAgg<sup>III</sup> halogenation reaction<sup>10c</sup> except employing Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (202 mg, 0.5 mmol) or other iron complex (0.5 mmol) in the presence of 3 equivalents of picolinic acid and the use of TBHP (1.1 ml, 10.0 mmol) as an oxidant *in lieu* of 30% H<sub>2</sub>O<sub>2</sub>.

*General work-up procedure.* An aliquot (1.0 ml) was taken from the reaction mixture, acidified with 25% H<sub>2</sub>SO<sub>4</sub> to a pH of approximately 2-3 and extracted twice with diethyl ether (5 ml each). The combined organic extracts were washed with saturated solution of NaHCO<sub>3</sub> and water, dried (MgSO<sub>4</sub>) and analyzed by gas chromatography after the addition of a known amount of an appropriate internal standard.

*Studies on the GoAgg<sup>IV</sup> bromination reaction of cyclohexyl bromide using LiBr or BrCCl<sub>3</sub>.* The normal GoAgg<sup>IV</sup> bromination reaction of cyclohexyl bromide (3.24 g, 20 mmol) was carried out in the presence of either LiBr (20 mmol) or BrCCl<sub>3</sub> (20 mmol) at 60°C. The reaction mixture was stirred for 10 h, followed by the usual work-up and analyzed by gas chromatography using naphthalene as an internal standard.

*General procedure for the competition studies in the GoAgg<sup>IV</sup> system.* GoAgg<sup>IV</sup> chlorination reactions were carried out employing a pair of hydrocarbons (25 mmol each) in the presence of LiCl (20 mmol) for the competition studies. Other procedures followed those described earlier for the typical GoAgg<sup>IV</sup> reaction.

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