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Iron(III)-Catalyzed Halogenations by Substitution of Sulfonate Esters

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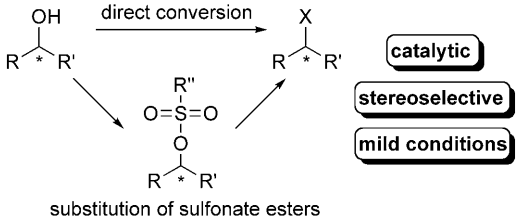
Abstract: A novel halogenation reaction from sulfonates catalyzed by iron(III) is described. The reaction can be performed as a stoichiometric or a catalytic version. This reaction provides a convenient strategy for the efficient access to structurally diverse secondary chlorides, bromides and iodides. The stereochemical course of the reaction is governed by the substrate and the experimental conditions. Secondary alcohols modified as quisylates or pysylates are substantially more reactive. Aliphatic quisylates proceed with overall inversion of configuration under catalytic conditions. Chemoselectivity in bismesylates was observed in favour of the secondary mesylate. Additionally, based on the experimental results, a possible catalytic cycle for the halogenation has been proposed.

Keywords: catalysis; halogenation; iron; leaving groups; substitution

Introduction

Alkyl halides are very useful as feedstocks for further chemical transformations and as synthetic targets in their own right because of their presence in many natural products with important biological activities such as lauroxanes and chlorosulfolipids.[1] The synthesis of halogenated compounds from alcohols represents a fundamental transformation in organic chemistry.[2] Numerous methods have been published,[2] which can be summarized mainly in two major strategies: (i) a direct conversion from the alcohol *via* an intermediate such as an alkoxyphosphonium halide and (ii) through its transformation into a suitable leaving group such as a sulfonate ester (Scheme 1). However, in terms of functional group tolerance, side reactions, and reaction conditions, most of these methods might have several drawbacks. Indeed, most of the direct conversion processes are stoichiometric, and the complete removal of the phosphine oxide by-product is not always straightforward. In addition, nucleophilic substitutions of sulfonate esters require large amounts of metal halides and harsh reaction conditions.

Within our program directed to the asymmetric total synthesis of lauroxanes,[3] we found several problems in the conversion of the cyclic secondary alcohols to the corresponding halides. Elimination, poor yields, low stereoselectivity and environmentally unfriendly conditions are the main disadvantages of the existing methods. Indeed, these problems have been described by many authors during the synthesis of these types of natural products.[4] Therefore, the

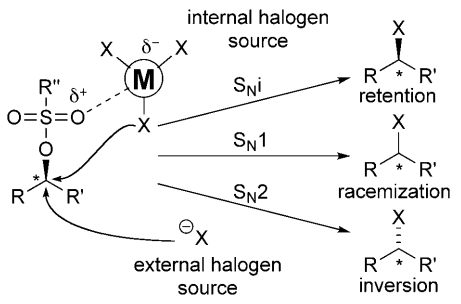


Scheme 1. Main strategies and areas for improvement.

search for new methodologies to carry out this type of transformation is highly important. In this sense, the use of transition metals could be a good alternative, because they can act as Lewis acids by diminishing the partial negative charge in the leaving group through chelating interactions, resulting in an increase of the rate of the reaction and/or, may act through a different type of mechanism, such as the S_Ni (substitution nucleophilic internal), in which both halogen and alkyl group bound to the metal, provide the final halide by a reductive elimination (Scheme 2). However, the use of transition metals to promote this transformation can scarcely be found in the literature.[5]

Recently, Lepore et al. have reported that 2-(2-methoxyethoxy)ethyl 2-(alkoxysulfonyl)benzoates (PEG sulfonates) and quisylates undergo nucleophilic displacement at carbon with excess of halide anion or with 200 mol% of a titanium(IV) salt.[6] These PEG sulfonates and quisylates show an acceleration of the reaction rates compared to the tosylates. The authors proposed that the polyether chain or the quinolin-8-yl group coordinates the metal cation, simultaneously stabilizing the negative charge on the living sulfonate and attracting the nucleophile to effect the overall substitution. Additionally, the authors claim that the stereochemical outcome for the substitution is retention of configuration by an S_Ni mechanism.[6b,c,7] This method has since been utilized by Kim et al. in the total synthesis of (+)-microcladallene B.[4e] However, in a very detailed study by Braddock, Burton and coworkers, it was shown that the stereochemical outcome undergoes inversion or partial inversion of the configuration at the reacting center and any observed retention of configuration is likely due to neighbouring group participation or diastereoselective attack on a carbocation rather than an S_Ni mechanism.[8] Therefore, the search for new methodologies that allow the metal-catalyzed[9] stereoselective synthesis of alkyl halides under mild conditions is extremely important (Scheme 1).

In this regard, we have considered the use of iron salts in this transformation, because iron is one of the most abundant metals on earth and its salts are considered to be environmentally benign. In addition, we have been able to develop in our group, an iron catalytic system formed from FeX_3 or $Fe(acac)_3$ and trimethylsilyl halide to perform Prins cyclization processes.[10] Herein, we describe the scope and limitations of the first iron-catalyzed halogenations by direct substitution of sulfonates.



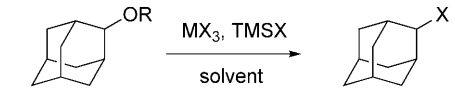
Scheme 2. Transition metals as Lewis acid in the halogenation reaction. Possible stereochemical courses.

Results and Discussion

As a model study we chose 2-adamantyl methanesulfonate (**1**). As shown in Table 1, we first examined the reaction using stoichiometric amounts of $FeCl_3$ with different solvents (Table 1, entries 1–4). Solvents having a strong coordination ability such as THF gave no product. A non-polar solvent such as benzene afforded the product in moderate yield. The use of halogenated solvents such as $CHCl_3$ gave the reaction with very good yields albeit with long reaction times. Gratifyingly, it was found that the reaction took place, with 98% yield, in a few minutes in CH_2Cl_2. However, under identical conditions $AlCl_3$ or $InCl_3$ showed poor conversion and low yields (Table 1, entries 5 and 6). 2-Bromoadamantane was also obtained when $FeBr_3$ was used instead of $FeCl_3$ (Table 1, entry 7). These results prompted us to investigate the catalytic version of this reaction. Considering our previous results in the Prins cyclization we decided to use as the external halide source the corresponding trimethylsilyl halide (TMSX).

A control experiment confirmed that in the absence of $FeCl_3$ no product was obtained. Subsequently, our evaluation turned to the catalyst loading. We observed that 7.5 to 10 mol% of $FeCl_3$ was the optimal amount and decreasing the catalyst load led to longer reaction times and lower yields (Table 1, entries 8–11). However, reaction times were increased compared to the stoichiometric version. Noteworthy, the reaction proceeded with similar yields and slightly longer reaction times, when $Fe(acac)_3$ was used instead of $FeCl_3$ (Table 1 entry 12). Even more interesting is that this last result opens the possibility to obtain brominated and iodinated derivatives by the use of the suitable and commercially available trimethylsilyl halides as halogen source (Table 1, entries 13 and 14). After these good results, $Fe(acac)_3$ was used in the catalytic version for further investigations since it is less hygroscopic and easier to handle than $FeCl_3$. All reactions were carried out at room temperature because longer reaction times and poorer reactivity were observed at 10 °C or 0 °C. It is necessary to emphasize the simplicity of the process and work-up: most of these reactions do not require further purification by column chromatography, simply washing with water, drying the organic phase with $MgSO_4$, filtering and concentrating are sufficient. Additionally,

Table 1. Optimization of the reaction conditions.



R = Ms, **1**
R = H, 2-adamantanol

Entry[a]	R	MX_3 (mol%)	TMSX (equiv.)	Solvent	Time	Yield [%][b]
1	Ms	$FeCl_3$ (100)	–	THF	12 h	0
2	Ms	$FeCl_3$ (100)	–	benzene	12 h	40
3	Ms	$FeCl_3$ (100)	–	$CHCl_3$	24 h	92
4	Ms	$FeCl_3$ (100)	–	CH_2Cl_2	5 min	98
5	Ms	$AlCl_3$ (100)	–	CH_2Cl_2	2 h	30
6	Ms	$InCl_3$ (100)	–	CH_2Cl_2	2 h	55
7	Ms	$FeBr_3$ (100)	–	CH_2Cl_2	10 min	99
8	Ms	$FeCl_3$ (20)	TMSCl (1.2)	CH_2Cl_2	45 min	97
9	Ms	$FeCl_3$ (10)	TMSCl (1.2)	CH_2Cl_2	1.5 h	96
10	Ms	$FeCl_3$ (7.5)	TMSCl (1.2)	CH_2Cl_2	3.5 h	96
11	Ms	$FeCl_3$ (5)	TMSCl (1.2)	CH_2Cl_2	5 h	92
12	Ms	$Fe(acac)_3$ (7.5)	TMSCl (1.2)	CH_2Cl_2	4 h	97
13	Ms	$Fe(acac)_3$ (7.5)	TMSBr (1.2)	CH_2Cl_2	2 h	96
14	Ms	$Fe(acac)_3$ (7.5)	TMSI (1.2)	CH_2Cl_2	2 h	87
15	H	$FeCl_3$ (100)	–	CH_2Cl_2	1 d	0
16	H	$FeCl_3$ (10)	TMSCl (2)	CH_2Cl_2	1 d	0

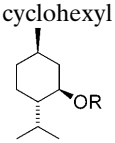
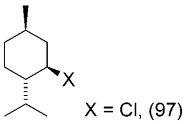
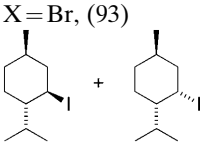
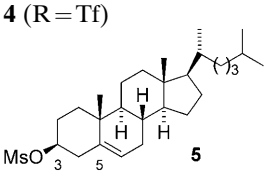
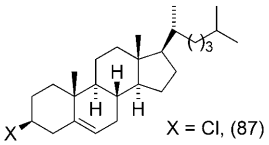
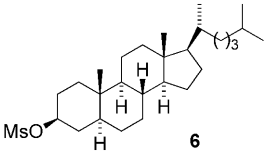
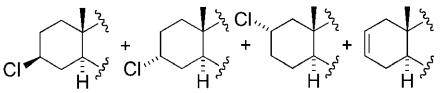
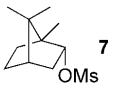
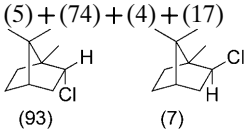
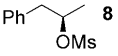
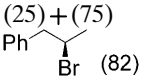
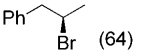
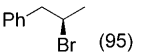
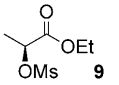
[a] All reactions were carried out at room temperature.
[b] Yield of isolated product. THF = tetrahydrofuran, acac = acetylacetonate.

when the reaction was carried out with 2-adamantanol either under stoichiometric or catalytic conditions, the substrate remained unchanged (Table 1, entries 15 and 16).[11]

Once having ensured the optimal conditions (stoichiometric and catalytic versions), the generality and the scope of the halogenation reaction was investigated by using a variety of substrates possessing secondary sulfonates (Table 2). Thus, cyclohexyl methanesulfonate was transformed into chlorocyclohexane with quantitative conversion, using the stoichiometric version (Table 2, entry 1). Additionally, the chloro-, bromo-, and iodocyclohexanes were obtained with excellent conversions using catalytic conditions (Table 2, entries 2–4). Furthermore, (1*R*,2*S*,5*R*)-menthyl methanesulfonate (**2**) was converted into the corresponding chloride and bromide in excellent yields (Table 2, entries 5 and 6). We also prepared a multigram quantity of pure menthyl chloride (10 g) with no significant variation of the reaction results (89% yields). Moreover, the catalytic version using $Fe(acac)_3$ and trimethylsilyl halides (TMSX) as halide source works quite well (Table 2, entries 7–9). A small amount of neomenthyl iodide was detected during the preparation of menthyl iodide. A control experiment confirmed that in absence of $Fe(acac)_3$ no products were obtained, when TMSCl and TMSBr were used. However, TMSI promoted the reaction without $Fe(acac)_2$, albeit with lower yields. This catalytic version also works with menthol tosylate (**3**) to provide the menthyl chloride, although with lower yield and longer reaction time (Table 2, entry 10).[12] However, no reaction was observed when the triflate of menthol (**4**) was used under these conditions (Table 2, entry 11). Noteworthy, all these reactions proceed with retention of configuration. The stereochemical outcome observed in this substrate has been previously described.[13,14] It is attributed to the formation of a carbocation or ion pair and is the conformation of the menthyl framework and not the leaving group that determines the resultant stereochemistry of the product.[15]

The methanesulfonate of cholesterol (**5**) was converted into the corresponding chloride, bromide and iodide products in good yields with overall retention of the configuration (Table 2, entries 12–15). This stereochemical outcome is the result of a non-classical carbocation that is obtained by neighbouring participation of the homoallylic alkene, and therefore a partial bond is only formed between C-5 and C-3 on the α face of the steroid.[16] On the other hand, when the stoichiometric version was applied to 5α-cholestan-3β-ol mesylate (**6**), we obtained the chloride with retention of configuration (3β-configuration) as the major product along with some of the 2α-chloride isomer and a small amount of the chloride with inversion of configuration (3α-configuration). Meanwhile, the elimination product was not detected (Table 2, entry 16). This result is surprising, considering that in this substrate there is no possibility of neighbouring

Table 2. Exploring the scope and limitations of halogenations reaction with sulfonates.

Entry	Substrate	FeX_3 (mol%)	TMSX (equiv.)	Product and Yield[a] or Product Distribution[b] [%]	Time
1[b,c]	cyclohexyl methanesulfonate	$FeCl_3$ (100)	–	chlorocyclohexane (100)	10 min
2[b,c]	cyclohexyl methanesulfonate	$FeCl_3$ (10)	TMSCl (1.2)	chlorocyclohexane (100)	16 h
3[b,c]	cyclohexyl methanesulfonate	$Fe(acac)_3$ (10)	TMSBr (1.2)	bromocyclohexane (100)	16 h
4[b,c]	cyclohexyl methanesulfonate	$Fe(acac)_3$ (10)	TMSI (1.2)	iodocyclohexane (100)	16 h
5	 **2** (R = Ms)	$FeCl_3$ (100)	–	 X = Cl, (97)	5 min
6	**2** (R = Ms)	$FeBr_3$ (100)	–	X = Br, (95)	20 min
7	**2** (R = Ms)	$Fe(acac)_3$ (10)	TMSCl (1.2)	X = Cl, (99)	3 h
8	**2** (R = Ms)	$Fe(acac)_3$ (10)	TMSBr (1.2)	X = Br, (93)	1 h
9	**2** (R = Ms)	$Fe(acac)_3$ (10)	TMSI (1.2)	 (76) (8)	2 h
10	**3** (R = Ts)	$Fe(acac)_3$ (10)	TMSCl (1.2)	X = Cl, (75)	20 h
11	**4** (R = Tf)	$Fe(acac)_3$ (10)	TMSCl (1.2)	NR[d]	5 h
12	 **5**	$FeCl_3$ (100)	–	 X = Cl, (87)	5 min
13	**5**	$Fe(acac)_3$ (10)	TMSCl (1.2)	X = Cl, (75)	16 h
14	**5**	$Fe(acac)_3$ (10)	TMSBr (1.2)	X = Br, (56)	16 h
15	**5**	$Fe(acac)_3$ (10)	TMSI (1.2)	X = I, (63)	10 min
16[b]	 **6**	$FeCl_3$ (100)		 (79) (5) (16) (0)	5 min
17[b]	**6**	$Fe(acac)_3$ (10)	TMSCl (1.2)	(5) + (74) + (4) + (17)	12 h
18[b]	 **7**	$FeCl_3$ (100)	–	 (93) (7)	20 min
19[e]	**7**	$FeCl_3$ (10)	TMSCl (1.2)	(25) + (75)	2 d
20	 **8**	$Fe(acac)_3$ (10)	TMSBr (1.2)	 (82)	16 h
21[f]	**8**	$Fe(acac)_3$ (10)	TMSBr (1.2)	 (64)	16 h
22[g]	**8**	$Fe(acac)_3$ (10)	TMSBr (1.2)	 (95)	16 h
23	 **9**	$FeBr_3$ (100) or $Fe(acac)_3$ (10)	– TMSBr (1.2)	NR[d]	7 d

[a] Yield of isolated product.
[b] A quantitative conversion was observed in most reactions but for practical reasons it is more appropriate to show a distribution of products based on ^1H NMR.
[c] Due to the volatility of the final product, the reaction was carried out in deuterated chloroform.
[d] NR = the substrate does not react.
[e] Conversion 23%.
[f] This reaction was carried out at 0 °C.
[g] This reaction was carried out at 5 °C.

group participation (*cf.* cholesterol **5**), and the conformation of a six-membered ring is more flexible than in the case of menthol, and if a free secondary carbocation is formed, an equimolecular mixture of nucleophilic substitution products would be expected.[8] Conversely, mesylate **6** gave the chloride under catalytic conditions with the 3α-configuration as the major product along with the elimination product, chlorinated isomer (2α-configuration) and only traces of the chloride with the 3β-configuration (Table 2, entry 17).

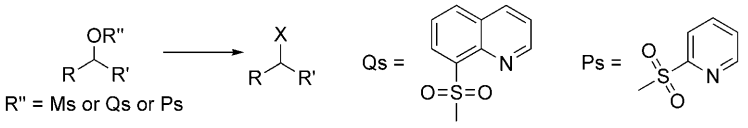
In a similar way, the bornyl methanesulfonate (**7**) gave the chloride with retention of configuration when the stoichiometric conditions were applied (Table 2, entry 18). By contrast, under catalytic conditions isobornyl chloride was obtained as the major product, that is, the stereochemical course of the reaction was inversion of configuration. In this case, the reaction took place using $FeCl_3$ as catalyst instead of $Fe(acac)_3$, however a low conversion was observed after 2 days (Table 2, entry 19).

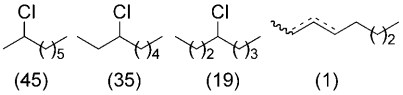
Taking into account the previous results with the methanesulfonate of cholesterol (**5**), we examined the halogenation reaction with a mesylate derivative of the enantiopure homobenzylic alcohol **8**. Under standard catalytic conditions, the homobenzylic bromide was obtained in good yields. However, the specific rotation indicates a partial inversion of configuration {$[\alpha]_D^{25}$: −4.7 (*c* 1.0 in CH_2Cl_2)} (Table 2, entry 20).[17] Nonetheless, when the reaction was performed at 0 °C or 5 °C, the stereochemical course of the reaction was retention of configuration {$[\alpha]_D^{25}$: −26.6 (*c* 2.0 in CH_2Cl_2) and $[\alpha]_D^{25}$: −26.1 (*c* 2.0 in CH_2Cl_2), respectively} (Table 2, entries 21 and 22).[17] Apparently, the mesylate derived from (*R*)-1-phenyl-2-propanol (**8**) could possibly react by neighbouring group participation under these conditions, *via* a phenonium ion,[18] leading to the observed retention of configuration in this substrate by double inversion.

In order to establish the influence due to electronic aspects of the substrate, the mesylate of *S*-ethyl lactate (**9**) was also used. Surprisingly, no reaction was observed when mesylate **9** was submitted to stoichiometric and catalytic conditions (Table 2, entry 23). We believe that the ester group competes with the methanesulfonate group by chelation of the Fe(III) and this prevents the reaction from proceeding. Also, the poor ability of the ester group to stabilize a positive charge on the α-carbon should contribute to the failure of the reaction.

We also examined the halogenation reactions on aliphatic enantiopure secondary alcohols under both types of reaction conditions. When aliphatic mesylate **10** was used under stoichiometric conditions, we obtained a mixture of several products including nucleophilic substitution products such as 2-chlorooctane, 3-chlorooctane and 4-chlorooctane with small amounts of elimination products (Table 3, entry 1). Based on this result an intramolecular single-step mechanism might be ruled out. All the products can be postulated to derive from a common secondary carbocation (or corresponding ion pair) at the 2-position. Direct trapping of the carbocation yields 2-chlorooctane. Alternatively, 1,2-hydride shifts and subsequent trapping allow the formation of the 3-chloro- and 4-chlorooctanes. Elimination under Saytzev orientation explains the presence of internal alkenes. However, mesylate **10** under catalytic conditions provided mostly substitution products, 2-chlorooctane being the major product, although the reaction takes several days (Table 3, entry 2).

Table 3. Halogenation reactions of aliphatic enantiopure mesylate, 8-quinolinesulfonate (quisylates) and 2-pyridinesulfonates (pysylates).



Entry	Substrate	FeX_3 (mol%)	TMSX (equiv)	Product Distribution[a] (%)	$[\alpha]_D^{25}$[b]	Time
1	 R = Ms (**10**)	$FeCl_3$ (100)	–	 (45) (35) (19) (1)	0.0[c] (*c* 1.2)	5 min
2	R = Ms (**10**)	$Fe(acac)_3$ (10)	TMSCl (1.2)	(68) + (24) + (5) + (3)	+22.8[c] (*c* 1.1)	5 d
3	R = Qs (**11**)	$FeCl_3$ (100)	–	(52) + (26) + (12) + (10)	+4.9[c] (*c* 0.42)	2 h
4	R = Qs (**11**)	$Fe(acac)_3$ (10)	TMSCl (1.2)	(92) + (0) + (0) + (8)	+36.7[c] (*c* 1.25)	16 h
5	R = Ps (**12**)	$FeCl_3$ (100)	–	(34) + (30) + (22) + (14)	+1.9[c] (*c* 0.51)	5 min
6	R = Ps (**12**)	$Fe(acac)_3$ (10)	TMSCl (1.2)	(88) + (10) + (0) + (2)	+5.8[c] (*c* 0.95)	16 h

[a] A quantitative conversion was observed in most reactions but for practical reasons it is more appropriate to show a distribution of products based on ^{1}H NMR.

[b] $[\alpha]_D^{25}$ values are in CH_2Cl_2.

[c] $[\alpha]_D^{25}$ values are corrected according to the proportion of 2-chlorooctane observed in ^{1}H NMR and the concentration is in range of 0.004 to 0.02 g mL^{-1} respect to the 2-chlorooctane (see text).

In order to establish the stereochemical course of the reaction, we compared the specific rotation of the mixture of products from the reaction[19] with a sample of (2*S*)-chlorooctane prepared by Appel chlorination (CCl_4, PPh_3)[20] of (2*R*)-octan-2-ol. To accomplish this, we first checked the values of the specific rotation of (2*S*)-chlorooctane in a wide range of concentrations in CH_2Cl_2. We observed that the specific rotation was unaffected within the range of concentration between 0.004 and 0.02 $g\,mL^{-1}$ ($[\alpha]_D^{25}$: $+34.3 \pm 1.1$).[21] Hence the specific rotations of the reaction products were analyzed in this range of concentrations. We also verified that the specific rotation values arise from the 2-chlorooctane enantiomers and not from products resulting by hydride shifts, such as 3-chlorooctane and 4-chlorooctane.[22] Additionally, a control experiment showed that (2*S*)-chlorooctane was configurationally stable to the experimental conditions of the catalytic version [TMSCl, $Fe(acac)_3$, CH_2Cl_2, room temperature] at least for 5 days. However, loss of specific rotation was observed when (2*S*)-chlorooctane was subjected to the experimental conditions of the stoichiometric version ($FeCl_3$, CH_2Cl_2, room temperature) for 10 min.[23] The reaction products of the latter control experiment were analyzed by ^1H NMR and a mixture of 2-chloro-, 3-chloro- and 4-chlorooctane was observed in a ratio of 1.0:0.9:0.6, respectively. In an attempt to rationalize the racemization of the final product, (2*S*)-chlorooctane, racemic mixtures of 3-chlorooctane and 4-chlorooctane were prepared, from the corresponding alcohols using the Appel chlorination protocol; and subjected to the experimental conditions of the stoichiometric version for 10 min. A mixture of 2-chloro-, 3-chloro- and 4-chlorooctanes was obtained in both cases with ratios of 1.0:0.9:0.6 and 1.0:0.9:0.7, respectively. Therefore, the racemization could be caused in a two ways: the *in situ* product epimerization by S_N2 chloride exchange and/or by the formation of 2-chlorooctanes from products arising from hydride shifts, i.e., the 3-chloro- and 4-chlorooctanes. It should be mentioned that the reactions with mesylate derivatives, in the stoichiometric version, are very fast (*ca.* 5 min) and that species of iron(III) generated in the course of the reaction are much less reactive than $FeCl_3$, although a 100 mol% of $FeCl_3$ is necessary for the reaction to be complete.[24]

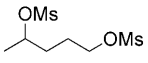
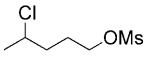
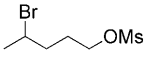
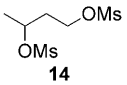
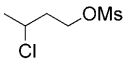
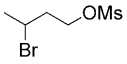
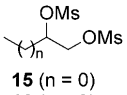
The specific rotation measurements show that the reaction proceeds with racemization under stoichiometric conditions (Table 3, entry 1). Nonetheless, under catalytic conditions the stereochemical outcome is partial inversion of configuration (Table 3, entry 2), indicating that part of the racemization occurs also in the substitution, since the final product is stable under these conditions.[25] Similar results were reported by Dubac and co-workers using TMSCl and $BiCl_3$ as catalyst.[26]

Taking into account these results we decided to explore the use of different kinds of sulfonate derivatives as leaving groups, with the purpose of shortening the reaction times of the catalytic version in aliphatic substrates and providing a better chelation of Fe(III) with the leaving group. Thus, we turned our attention to 8-quinolinesulfonate (quisylate, Qs)[27] and 2-pyridinesulfonate (pysylate, Ps),[28,29] considering that a better chelating agent in the leaving group might be necessary to achieve further enhancement of the halogenation reactions. Thus for aliphatic secondary alcohols, under catalytic conditions, mesylate **10** and pysylate **12** all led to the same stereochemical outcome: partial inversion of configuration (Table 3, entries 2 and 6). However, quisylate **11** proceeds with overall inversion of configuration (Table 3, entry 4).[30] By analysis of the reaction times and yields, the pysylate and quisylate groups are clearly superior leaving groups under these conditions than mesylate. It seems obvious that the pysylate and quisylate nitrogen lone pairs can coordinate the iron atom and activate the leaving group. This type of leaving group has been called nucleophile assisting leaving groups (NALGs).[31] The rate enhancement afforded by a NALG is not necessarily due to an increase in the nucleofugacity of the leaving group. NALG should also interact with nucleophiles in the course of the reaction to decrease the transition state energy of the rate-limiting step.

In addition to the stereochemical course of the reaction we examined the chemoselectivity in substrates where two methanesulfonate groups are present, one in a primary alcohol and the other in a secondary one. In order to compare the reactivity of primary versus secondary sulfonates, a series of racemic bismesylates were reacted with $FeCl_3$ and $FeBr_3$ under the stoichiometry conditions (Table 4). The halogenation reaction works quite well for 1,4-pentanediol bismesylate (**13**) and 1,3-butanediol bismesylate (**14**), with excellent yields and most importantly, with exclusive formation of the halogenated compound in the position of the secondary methanesulfonate group (Table 4, entries 1–4). Satisfyingly, no migration and elimination products were observed in these reactions. This clearly demonstrates the poor reactivity of primary methanesulfonates under these reaction conditions, which is completely opposite to an S_N2-type reaction. However, when the reaction was carried out with 1,2-propanediol bismesylate (**15**) or 1,2-undecanediol bismesylate (**16**), the substrate remained unchanged (Table 4, entries 5 and 6). Apparently, a better chelation of the iron core with the 1,2-bissulfonates reduces the power as a Lewis acid of the iron halides, preventing the reaction from taking place.

With the aim of providing a possible mechanism for this halogenation reaction, seven reactivity trends were considered to be revealing. First, the lack of re-

Table 4. Chemoselectivity of $FeCl_3$ and $FeBr_3$ reactions with substrates containing two methanesulfonate groups.

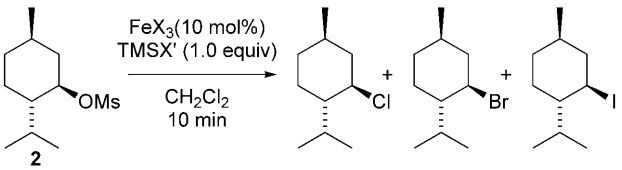
Entry	Substrate[a]	FeX_3 (mol%)	Product and Yield[b]	Time
1	 **13**	$FeCl_3$ (100)	 92 %	2 h
2	**13**	$FeBr_3$ (100)	 91 %	30 h
3	 **14**	$FeCl_3$ (100)	 95 %	2 h
4	**14**	$FeBr_3$ (100)	 93 %	2 h
5	 **15** (n = 0) **16** (n = 8)	$FeCl_3$ (100)	NR[c]	2 d
6	**15** (n = 0) **16** (n = 8)	$FeBr_3$ (100)	NR[c]	2 d

[a] All starting materials and products are racemic.
[b] Yields of isolated product.
[c] NR = the substrate does not react.

activity of free alcohols in the catalytic version, under our experimental conditions (Table 1, entry 16), rules out any mechanism involving activation of the silicon-halogen bond by iron(III) halides.[26] Second, substrates such as 2-adamantyl methanesulfonate (**1**), where an S_N2 mechanism is improbable, work well under both types of conditions. Third, obtaining halogenated isomers and elimination products preclude an intramolecular single-step mechanism and can be rationalized in terms of positive charge formation at the carbinol carbon. Fourth, the poor reactivity observed in the methanesulfonates of primary alcohols and α-hydroxy esters may be associated with reduced ability to stabilize a positive charge. Fifth, the rate enhancement is afforded by the use of NALG such as, quisylate and pysylate. Sixth, the stereochemical outcome of the reaction is partial inversion of the configuration when aliphatic mesylates were used, however overall inversion was observed with aliphatic quisylates under catalytic conditions. Seventh, when substrates with less propensity to give elimination or migration reactions and where the stereochemical course is not controlled by the substrate, such as methanesulfonate **6**, we found that the reaction afforded as major products those with retention of configuration, under stoichiometric conditions. By contrast, under catalytic conditions the major product was that with inversion of configuration. These results allow us to postulate a plausible mechanism based on a non-solvent separated S_N1 mechanism where ion pair species are involved.[32]

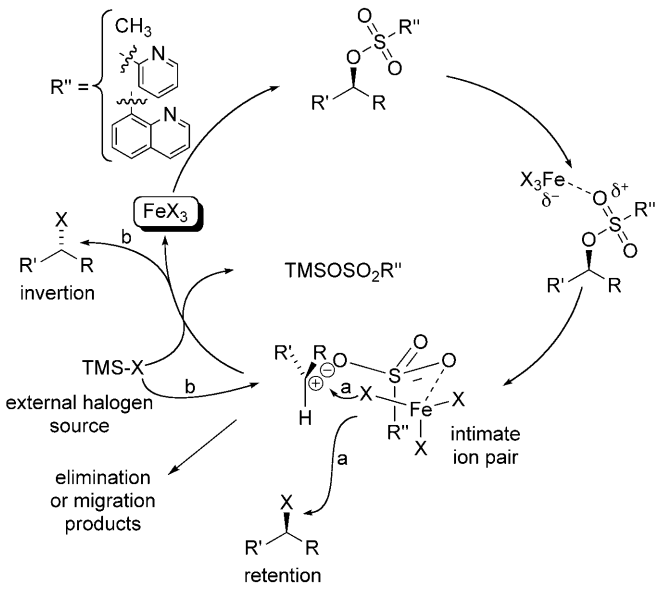
In the catalytic version, the halogen atom in the final product may have its origin directly from the catalyst, Fe(III),[33] or from the external halogen source, TMSX. In an attempt to clarify this point, we tested the reaction with the mesylate **2** using 10 mol% of the catalyst FeX_3 and 1.0 equiv. of the external halogen source with a different halogen TMSX′ (Scheme 3). Surprisingly, when the catalyst was $FeCl_3$ and the halogen source was TMSBr, only menthyl bromide was obtained. However, when $FeBr_3$ and TMSCl were used a mixture of menthyl chloride and bromide was obtained in an 80:20 ratio. Also, when the reaction was carried out with $FeBr_3$ and TMSI only menthyl iodide was obtained. In general, the halogen atom comes from TMSX, except when the halogen attached to the FeX_3 is a better nucleophile than the one in the TMS.

According to all these observations we reasoned that a plausible catalytic cycle could be readily initiat-



FeX_3	TMSX'	product distribution		
$FeCl_3$	TMSBr	trace	100	–
$FeBr_3$	TMSCl	80	20	–
$FeBr_3$	TMSI	–	0	100

Scheme 3. Experiments with the menthyl mesylate **2** to determine the halogen source.



Scheme 4. Plausible mechanism for the iron-catalyzed halogenation reaction.

ed *via* activation of the sulfonate with the iron salt that acts as a Lewis acid. The FeX_3 induces the formation of an intimate ion pair *via* coordination with one of the oxygen atoms of the corresponding sulfonate group and the "external or internal" halide nucleophile reacts with the cation from the rear or the front, resulting in the formation of the product with inversion or retention of the configuration, respectively (Scheme 4). In the stoichiometric version, the high stability of the Fe–O bond and the fact that the iron salt is the only source of halide, constitute the thermodynamic sink which drives the conversion but demands the use of a full equivalent amount of the iron-(III) salts. Therefore, a way to complete a catalytic cycle was devised by addition of an external halogen source, such as TMSX, with a more oxyphilic character, capable of releasing the iron and producing the subsequently iron-catalyst regeneration (FeX_3) for the next catalytic cycle.

Conclusions

We have developed a novel halogenation reaction of sulfonates using stoichiometric amounts of FeX_3 (X = Cl, Br), and the catalytic version using 10 mol% of FeX_3 (X = Cl, Br, acac) and trimethylsilyl halides (TMSX) as the halide source. This catalytic method also permits the construction of chloro, bromo and iodo compounds by the suitable combination of an iron(III) source and the corresponding trimethylsilyl halide. The stereochemical course of the reaction is governed by the substrate and by the experimental conditions. Additionally, the reaction also affords chemoselectivity in favour of the secondary mesylate, when 1,3- and 1,4-bismesylate substrates are submitted to the stoichiometric conditions. This protocol provides a convenient strategy for efficient access to structurally diverse secondary halides. The extensions of this reaction to more structurally complex products are under development and the results will be reported in due course.

Experimental Section

^{1}H NMR spectra were recorded at 500, 400 or 300 MHz, ^{13}C NMR spectra were recorded at 75 or 100 MHz, and chemical shifts are reported relative to internal Me_4Si. Coupling constants are given in Hz. Specific rotations were determined for solutions in chloroform or dichloromethane at 25 °C. Column chromatographies were performed on silica gel, 60 Å and 0.2–0.5 mm. Compounds were visualized by use of UV light, 2.5% phosphomolybdic acid in ethanol or vanillin with acetic and sulfuric acid in ethanol with heating. Commercial reagents were used without further purification. $FeCl_3$ (97%), $FeBr_3$ (98%) and $Fe(acac)_3$ (99.9%) were purchased from Sigma–Aldrich and used directly. All solvents were purified by standard techniques. Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous magnesium sulfate was used for drying solutions.

General Procedure for the Halogenation Reactions (Stoichiometric Version)

To a solution of the methanesulfonate derivative (0.2 mmol) in CH_2Cl_2 (2 mL) and under nitrogen, was added MX_3 and the mixture was stirred at room temperature until TLC showed the end of the reaction. Then, it was poured into H_2O and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under vacuum. When it is necessary, the crude obtained was purified by flash chromatography, yielding the halogenated compound.

General Procedure for the Halogenation Reactions (Catalytic Version)

To a solution of the methanesulfonate derivative (0.2 mmol) in CH_2Cl_2 (2 mL) and under nitrogen, were added the TMSX (1.2 equiv.) and the MX_3 (10 mol%) and the mixture was stirred at room temperature until TLC showed the end of the reaction. Then, it was poured into H_2O and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under vacuum. When it is necessary, the crude obtained was purified by flash chromatography, yielding the halogenated compound.

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[19] Due to the volatility of some of the products, the reaction was poured into H_2O and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated at atmospheric pressure and the crude mixture was purified by flash chromatography using pentane as eluent. Thus, an inseparable mixture of 2-chlorooctane, 3-chlorooc-

tane, 4-chlorooctane and small amounts of alkene was obtained.
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[21] (2*S*)-Chlorooctane has a positive specific rotation as prepared by Appel chlorination: $[\alpha]_D^{25}$: +33.0 (CH_2Cl_2, *c* 0.40), $[\alpha]_D^{25}$: +35.3 (CH_2Cl_2, *c* 0.60), $[\alpha]_D^{25}$:+32.0 (CH_2Cl_2, *c* 0.80), $[\alpha]_D^{25}$: +34.6 (CH_2Cl_2, *c* 1.00), $[\alpha]_D^{25}$: +34.25 (CH_2Cl_2, *c* 1.20), $[\alpha]_D^{25}$:+35.4 (CH_2Cl_2, *c* 1.40), $[\alpha]_D^{25}$: +35.1 (CH_2Cl_2, *c* 1.60), $[\alpha]_D^{25}$: +34.9 (CH_2Cl_2, *c* 1.80), $[\alpha]_D^{25}$ +34.1 (CH_2Cl_2, *c* 2.00).
[22] Using a silica gel chromatography column, with pentane as eluent, we were able to increase the amount of 2-chlorooctane within a mixture of 2-, 3- and 4-chlorooctanes, from a 70:25:5 ratio to 78:20:2. We observed that the specific rotation was unchanged {$[\alpha]_D^{25}$ +22.8 (CH_2Cl_2, *c* 1.1) and $[\alpha]_D^{25}$: +22.6 (CH_2Cl_2, *c* 1.1), respectively}, which clearly suggests that the contribution of the 3- and 4-chlorooctanes to the specific rotation is negligible, therefore indicating that the reaction conditions yield the racemic mixture of 3- and 4-chlorooctanes.
[23] *In situ* product epimerization by S_N2 halide exchange can sometimes be a problem with the more nucleophilic halides, iodide and bromide, but is rarely seen with chloride, see ref.[2b]
[24] The theoretical amount of $FeCl_3$ necessary for the stoichiometric version should be 33 mol%. However, even with 60 mol% of $FeCl_3$ the reaction is not completed (86% of conversion). This clearly indicates that the species of iron(III) generated in the course of the reaction are less reactive than the $FeCl_3$.
[25] A control experiment confirmed that in absence of $Fe(acac)_3$ no products were obtained when TMSCl was used for at least five days.
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[27] Few works have been reported for the use of quisylate as a leaving group: a) E. J. Corey, G. H. Posner, R. F. Atkinson, A. K. Wingard, D. J. Halloran, D. M. Radzik, J. J. Nash, *J. Org. Chem.* **1989**, *54*, 389–393; b) see refs.[6c,8]
[28] According to the names for sulfonate derivatives as leaving groups (mesyl, tosyl, nosyl, etc.), we propose for the 2-pyridinesulfonyl and 2-pyridinesulfonate systems the abbreviated names of pysyl and pysylate, respectively.
[29] To the best of our knowledge the pysylate group had only been used once as a leaving group to give inversion of configuration in nucleophilic bromination reactions using stoichiometric amounts of magnesium dibromide: S. Hanessian, M. Kagotani, K. Komaglou, *Heterocycles* **1989**, *28*, 1115–1120.
[30] Quisylate (**10**) and pysylate (**11**) did not react when treated with TMSCl (1.2 equiv.) for at least two days in the absence of catalytic amounts of the $Fe(acac)_3$.
[31] S. D. Lepore, D. Mondal, *Tetrahedron* **2007**, *63*, 5103–5122.
[32] M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 5th edn., Wiley, New York, **2007**, Chapter 10, pp 389–674.
[33] It should be emphasized that the storage of R_3SiX generates traces of free acid HX by hydrolysis: A. D. Dilman, S. L. Ioffe, *Chem. Rev.* **2003**, *103*, 733–772. On the other hand, in the presence of free acid HX, $Fe(acac)_3$ is hydrolyzed to the corresponding iron(III) halide: D. D. Miller, D. Van Campen, *Am. J. Clin. Nutr.* **1979**, *32*, 2354–2361.

