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FULL PAPER

Eco-friendly methodology for the formation of aromatic carbon-heteroatom bond using green ionic liquids

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Abstract: A new sustainable method is reported for the aromatic carbon-heteroatom bond formation in solvent-free and mild conditions (no co-oxidant, no strong acid and no toxic reagents) using a new type of green ionic liquid. Bromination of methoxy arenes was chosen as a model reaction. The reaction methodology is based on only using natural sodium bromine, which is transformed into an electrophilic-brominating reagent within an ionic liquid, easily prepared from the melted salt $FeCl_3$ hexahydrate. Bromination reactions, using this *in situ* generated reagent, gave good yields and excellent regioselectivity in simple and environmentally friendly conditions. To understand the unusual bromine polarity reversal of sodium bromine without any strong oxidant, the molecular structure of the reaction medium was characterised by Raman and direct infusion electrospray ionisation mass spectroscopy (ESI-MS). An extensive computational investigation using density functional theory methods was performed to describe a mechanism that suggests indirect oxidation of Br^- through new iron adducts. The versatility of the methodology was successively applied to nitration and thiocyanation of methoxy arenes using KNO_3 and KSCN in melted hexahydrated $FeCl_3$.

Introduction

Electrophilic Aromatic Substitutions (SEAr) are very common synthetic reactions for the introduction of heteroatoms onto aromatic compounds. These transformations have been widely investigated for the preparation of aromatic derivatives functionalized by a halogen-, nitrogen- or sulphur-containing group. Among well-known examples, bromination of aryl compounds plays a pivotal role. Aryl bromides are some of the most common substrates for cross-coupling reactions and for the preparation of organometallic compounds. They are also key intermediates in the synthesis of various natural products and for the industrial production of drugs, pharmaceuticals, agrochemicals, fire-retardants, dyes and other various applications.[1,2]

Considering the significant importance of aryl bromides, numerous synthetic methods have been developed. However, these methodologies suffer from several drawbacks. They are based on two main strategies. The first one is the use of electrophilic-brominating agents such as Br_2, a hazardous, toxic, and corrosive reagent,[3–5] N-bromosuccinimide which requires delicate work-up,[6–9] bromodimethylsulfonium bromide,[10] pyridiniumbromide-perbromide,[11] 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one[12,13] or 1,3-dibromo-5,5-dimethylhydantoin;[14] necessitating a preparation far from eco-friendly.

The second strategy is based on biomimetic oxidative halogenation found in nature. This method consists in the *in situ* oxidation of bromide salts,[15] requiring strong oxidants such as oxone®,[16] ter-butyl hydroperoxide (TBHP),[17] nitric acid,[18] Selectfluor®[19] and ceric ammonium nitrate (CAN),[20] which are problematic due to their toxicity and the quantity of organic wastes generated during the treatment.

More recently, hydrogen peroxide or oxygen with vanadium and molybdene catalysts, NH_4VO_3, V_2O_5 or $H_2MoO_4{\bullet}2H_2O$, were used for mimicking the vanadium bromoperoxidase to oxidise bromide salts.[21–28] Even if these oxidants are non-toxic and that water is the only by-product, the associated catalysts are carcinogenic, mutagenic, or toxic for reproduction (CMR) compounds. When no catalyst is used for this reaction, strong acidic conditions, using HBr for example, and a large excess of H_2O_2 are necessary.[29–35]

In a sustainable perspective, many efforts are necessary to develop environmentally friendly reagents and procedures for the preparation of heteroatom substituted aromatic compounds.

In this work, we propose an unprecedented eco-friendly bromination methodology using only a green ionic liquid of melted $FeCl_3{\bullet}6H_2O$, without any strong co-oxidant or toxic reagent. We describe herein the synthetic potential of the methodology, characterise the nature of the reactive entities and investigate the peculiar bromination mechanism by density functional theory (DFT) calculations. Finally, this new green strategy was extended to the nitration and thiocyanation of methoxy aromatic substrates.

Results and Discussion

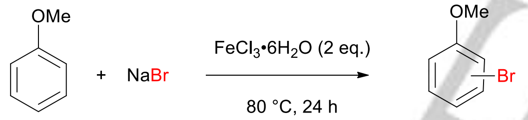
Bromination of aromatic derivatives using melted $FeCl_3{\bullet}6H_2O$ and NaBr

An alternative and green approach was considered to perform the bromination of aromatic compounds. Our strategy was based on the association of non-hazardous and eco-friendly brominating reagents, in mild conditions, preventing the use of any strong oxidant. Natural sodium bromine was chosen as the source of bromine. The challenge remained in oxidising the bromide ion with a mild oxidant in green conditions.

The use of natural sodium bromine to generate an electrophilic-brominating reagent was investigated using a mild, abundant and stable Lewis acid, $FeCl_3$, through the bromination of anisole as a model substrate (Table 1 and electronic supplementary information - ESI - for details).

First, the reaction was conducted solvent-free in supported conditions using anhydrous $FeCl_3$ (Table 1, entry 1). Silica and montmorillonite K10 supports were tested but conversions and yields remained poor. Molecular sieves, ensuring anhydrous conditions, were added to the reaction but conversion significantly decreased (Table 1, entry 2). The use of hydrated $FeCl_3•6H_2O$ was then tested in supported conditions and gave surprisingly similar conversion and yield as anhydrous $FeCl_3$ (Table 1, entry 3). However, the reactions using hydrated $FeCl_3•6H_2O$ in supported conditions were hardly reproducible because of a poor homogenization of the reaction medium, despite a strong mechanical stirring. Therefore, solvents were added or replaced the supports; but in both cases conversions collapsed (Table 1, entry 4 & 5). The simplest condition, using hydrated $FeCl_3•6H_2O$, no solvent and no support, was finally tested. After optimisation of the temperature, duration and NaBr/Fe ratios through a principal component analysis (PCA) (see ESI), excellent conversion and yield were obtained (Table 1, entry 6). As a control, anhydrous $FeCl_3$ in solvent-free and support-free conditions was tested and no conversion was observed (Table 1, entry 7).

Table 1. Bromination of anisole using anhydrous and hydrated $FeCl_3$ and NaBr.



Entry	Fe source	Conditions	Conv. (%)	Yield (%)
1	$FeCl_3$	support[a]	33 – 31	21 – 5
2	$FeCl_3$ + molecular sieve		9.5	2
3	$FeCl_3•6H_2O$		32 – 2.5	20 – 2.5
4	$FeCl_3•6H_2O$	support[a] & solvent[b]	traces	traces
5	$FeCl_3•6H_2O$	solvent[b]	0	0
6	**$FeCl_3•6H_2O$**	-	**93**	**85**
7	$FeCl_3$		0	0

Reaction conditions: $FeCl_3•6H_2O$, NaBr and anisole were put in a sealed tube under magnetic stirring at 80 °C for 24 h. [a] SiO_2 and MK10 were tested; [b] cyclohexane, methyl-tetrahydrofuran and diethylcarbonate were tested. Yields and conversions determined by gas chromatography-mass spectroscopy (GC-MS) using dodecane as internal standard.

The difference of reactivity between anhydrous and hydrated $FeCl_3$ in solvent-free and support-free conditions can be explained by their physical state (Table 2). Indeed, anhydrous $FeCl_3$ is solid at 80 °C and in the absence of any support or solvent the reaction cannot be correctly conducted. Hydrated $FeCl_3•6H_2O$ is liquid at 80 °C and seems to behave as the solvent of the reaction without deactivating solvation effects, as it was observed when other solvents were added to the reaction (Table 1, entry 4 & 5).

Table 2. Melting points of $FeCl_3$ salts.

Fe source	Melting Point
$FeCl_3$	306 °C[36]
$FeCl_3•6H_2O$	37 °C

Scope of the method

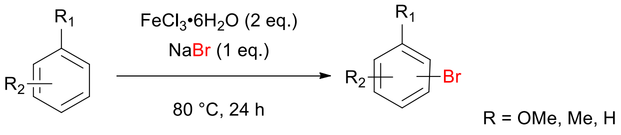
With the optimal reaction conditions in hand, a substrate scope was explored and the regioselectivity of bromination was investigated.

Methoxyarenes led to good conversions and yields with an excellent para regioselectivity (Table 3, entries 1-5). Interestingly no dibrominated product was observed; and no 4,4'-dimethoxybiphenyl was detected, indicating that no coupling occurred and suggesting that the reaction might not occur by a radical mechanism when using substrates with methoxy groups.

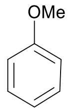
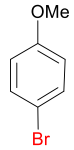
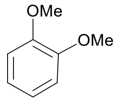
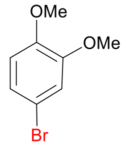
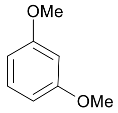
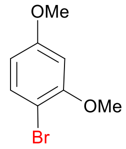
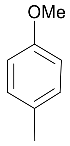
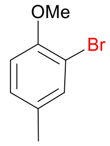
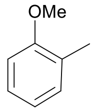
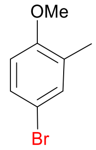
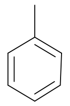
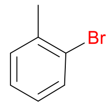
In details, anisole gave the expected *p*-bromoanisole with a good yield (Table 3, entry 1). This regioselective monobromination reaction is of particular relevance since bromoanisole finds numerous applications as an intermediate in synthetic chemistry, such as in the preparation of aryl 1,3-diketones and as substrate in Suzuki and Heck coupling reactions.[37–41] 1,2- and 1,3-dimethoxybenzene were brominated with satisfactory yields (Table 3, entries 2 & 3). Despite the proximity of the two methoxy groups, no demethylation was observed.[42–44] Methylanisole substrates gave good yields although the regioselectivity of the reaction is clearly oriented towards para (Table 3, entries 4 & 5). Interestingly, no bromination in benzylic position was observed, as long as there was a methoxy group. Indeed, bromination of toluene gave poor conversion and yield (Table 3, entry 6), and the absence of methoxy group allowed a partial radical bromination in benzylic position (yield of 17 %).

The presence of a methoxy group seemed to be a prerequisite for this reaction. As expected, bromination was limited to activated substrates since mild electrophilic-brominating reagents are used. However, the reaction showed a high selectivity for monobromination with an excellent para regioselectivity, while respecting the principles of green chemistry.

Table 3. Scope of the method. 1 mmol of $FeCl_3.6H_2O$.



Entry	Substrate	Product	Conv. (%)	Yield (%) (Regiosel. (%))

1[a]			93	85 (97)
2[b]			100	51 (100)
3[b]			97	51 (100)
4[b]			86	51 (100)
5[b]			100	75 (100)
6[b]			23	6 (100)

Reaction conditions: 0.5 mmol of NaBr and 0.5 mmol of the substrate were put in a sealed tube under magnetic stirring at 80 °C for 24 h. [a] Yields and conversions determined by GC-MS using dodecane as internal standard. [b] Yields and conversions determined by ^1H nuclear magnetic resonance (NMR) spectroscopy and based on starting compound.

According to these results, it seems that sodium bromide was successfully transformed into an electrophilic-brominating reagent without the use of any oxidant. Characterisation of the reaction medium, hydrated $FeCl_3•6H_2O$ with NaBr, was then investigated to enlighten this transformation.

Spectroscopic analyses of $FeCl_3•6H_2O$

The $FeCl_3•6H_2O$ hydrated salt was first characterised by Raman spectroscopy after heating at 80 °C. The Raman spectrum (see ESI) showed four characteristic bands, that could be identified by comparison with previous work of Sharma *et al.* on diversely hydrated $FeCl_3$ salts (Table 4).[45,46] The three low frequency bands could be assigned to the $FeCl_4^-$ anion, and the high frequency and broad band could be assigned to the $Fe(H_2O)_4Cl_2^+$ cation.

Table 4. Comparison of Raman frequencies in cm^{-1} of melted $FeCl_3•6H_2O$ between data from literature and the present study.

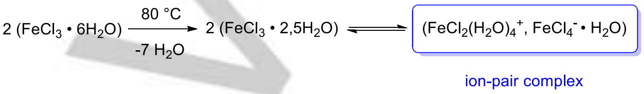
Raman frequencies (cm^{-1})	$FeCl_4^-$			$Fe(H_2O)_4Cl_2^+$
Sharma et al.	115 m	154 vw	337 vs	425 m bd
present work	121 m	163 vw	332 vs	409 m bd

m: medium, vw: very weak, vs: very strong, bd: broad.

Raman analysis suggested that the $FeCl_3•6H_2O$ hydrated salt could form a Fe(III) ion-pair complex ($(FeCl_2(H_2O)_4^+$, $FeCl_4^-)$), as described in the literature (Scheme 1).[36]

The ionic character of the hydrated salt at a temperature above its melting point was confirmed by measuring its conductivity. At 80 °C, the conductivity reached 15.5 $mS.cm^{-1}$, exceeding the limit of 10 mS.cm-1 corresponding to ionic liquids. Interestingly, the preparation of this type of ionic liquid is rapid and simple compared to general cases, that require multiple-steps synthesis and some treatments, especially for the organic cation.[47–50]

The melted $FeCl_3•6H_2O$ salt was also studied by direct infusion electrospray ionization in negative mode after heating at 80 °C (see ESI). The mass spectrum showed the molecular ion peak of the expected iron(III) chloride anion, $FeCl_4^-$ (m/z = 197.91), which is consistent with the Raman analyses (Scheme 1).



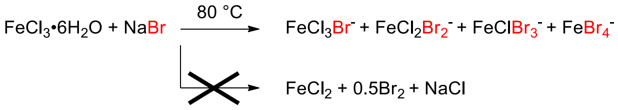
Scheme 1. Effect of temperature on $FeCl_3•6H_2O$ and the formation of iron(III) chloride species, observed by Raman and mass spectrometry.

Characterisation of $FeCl_3•6H_2O$ in the presence of NaBr

The salt mixture $FeCl_3•6H_2O$ and NaBr was also studied by direct infusion electrospray ionization in negative mode after heating at 80 °C (see ESI). The mass spectrum showed new molecular ion peaks corresponding to iron(III) mixed chloro-bromide anions $Fe(III)Cl_xBr_y^-$, as well as the remaining iron(III) chloride anions $FeCl_4^-$ (Scheme 2). The four iron(III) mixed chloro-bromide anions were detected. In each case, a bromine atom successively substituted a chlorine atom.

These new anionic species, $Fe(III)Cl_xBr_y^-$, were still completely soluble in the ionic liquid.

The redox potential of Br_2/Br^- and Fe(III)/Fe(II) are not compatible for the formation of Br_2, suggesting that these new $Fe(III)Cl_xBr_y^-$ anions might constitute the active iron species in the reaction and behave as the brominating reagents. They might replace $FeCl_4^-$ in the ion-pair complex ($FeCl_2(H_2O)_4^+$, $FeCl_4^-$) to form a new ion-pair complexes ($FeCl_2(H_2O)_4^+$, $FeCl_xBr_y^-$), as it has already been observed with several anion species found in association with $FeCl_2(H_2O)_4^+$.[51,52]



Scheme 2. Transformation of $FeCl_3•6H_2O$ in the presence of NaBr into new mixed chloro-bromide anionic species, detected by mass spectroscopy.

Computational studies were then performed to investigate the reactivity of $FeCl_3Br^-$, as a model of the $FeCl_xBr_y^-$ species, within the bromination reaction of anisole.

Computational studies

Molecular structure of the ($FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) ion-pair complex. The molecular structure of the ($FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) ion-pair complex was determined by density functional theory – Hartree-Fock (DFT-HF) calculations using Gaussian 16 package (See Section 3.1 of ESI). In the solid state, $FeCl_2(H_2O)_4^+$ has been found to crystallise in two forms, in which the chlorine atoms are either in *trans* or in *cis* position from the central iron atom, leading to *trans*-dichloride or *cis*-dichloride tetrahydrate cations.[52–54] The (*trans*-$FeCl_2(H_2O)_4^+$, $FeCl_4^-$) and (*cis*-$FeCl_2(H_2O)_4^+$, $FeCl_4^-$) complexes were constructed from these crystallographic data. A chlorine atom was replaced by a bromine atom in $FeCl_4^-$ generating the starting geometry structures of (*trans*-$FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) and (*cis*-$FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) (see ESI). The distance between the cation and the anion was increased by 2 Å allowing the system to orientate freely during the geometry optimisation. As expected, all optimised conformers showed a complex between the $FeCl_2(H_2O)_4^+$ cation and the $FeCl_3Br^-$ anion, since they carry opposite charges. However, this interaction was made through the halogen atoms, which normally bear negative charges. Interestingly, for the most stable conformers of the *cis*- and *trans*-complexes, the halogen atoms concerned are a chlorine atom of the $FeCl_2(H_2O)_4^+$ cation and the bromine atom of the $FeCl_3Br^-$ anion, with a distance of 2.84 - 2.99 Å (Figure 1 A. & B.). The partial atomic charges of these singular geometries were calculated using different models (Mulliken, Hirschfield, CM5 and APT, see ESI for details) and all showed a null to a positive charge, up to +0.30, of the bromine atom, while the charges of the chlorine atoms ranged between -0.34 and -0.71.

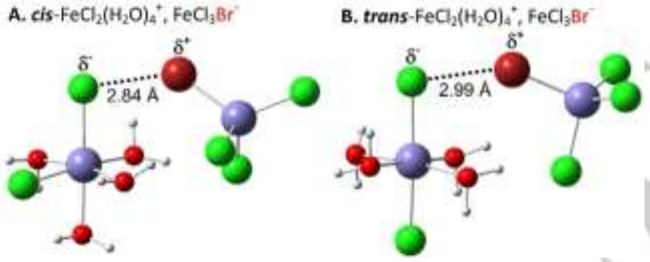


Figure 1. Optimised geometry of the most stable conformers of A. (*cis*-$FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) and B. (*trans*-$FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) complexes showing the partial charges and interatomic distances of Cl and Br.

These results highlight the fact that, after the central iron, the bromine atom is the most electron-deficient site in the ion pair complexes, making it an electrophilic site. The electrophilic behaviour of the bromine atom was then investigated in the reaction mixture, *i.e.* in the presence of anisole.

Exploration of the reactivity of $FeCl_3Br^-$ in the bromination reaction. Among the most stable conformers of (*cis*- and *trans*-$FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) complexes presenting similar Gibbs free energy, only the (*trans*-$FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) complex was considered for exploring the mechanism of the bromination reaction. Three constructions with different orientations of anisole were tested to explore different spatial approaches. The aromatic ring of anisole was initially presented parallel (0°), oblique (45°) and perpendicular (90°) to the iron dichloride axis of the *trans*-$FeCl_2(H_2O)_4^+$ cation (see ESI). After geometry optimisation, three conformations of similar level of free energy were obtained, in which the aromatic ring of anisole is systematically reoriented to become parallel to the interacting chlorine-bromine axis (see ESI). While the ion pair complex remained stable (Br-Cl distance at 2.86 Å), multiple interaction points between the bromine atom and several carbon atoms of the aromatic ring of anisole can be noticed (
Figure 2 A.). Indeed, Electrostatic Surface Potential of the most stable conformer shows the bromine-chlorine dipole and the superposition of the anisole ring with the bromine atom, generating a π-enyl interaction (
Figure **2** B.). Additionally, the partial atomic charge of the bromine atom was calculated and remained positive in every calculation model; up to +0.31 in APT charge model, which is even higher than the one without anisole.

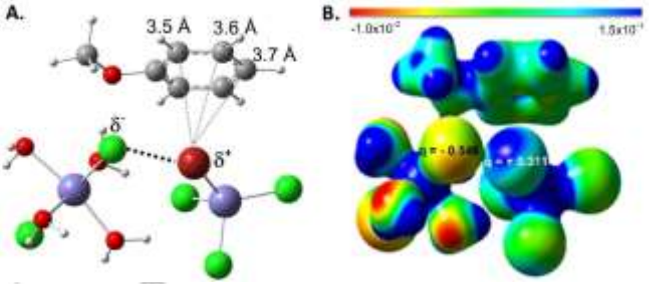
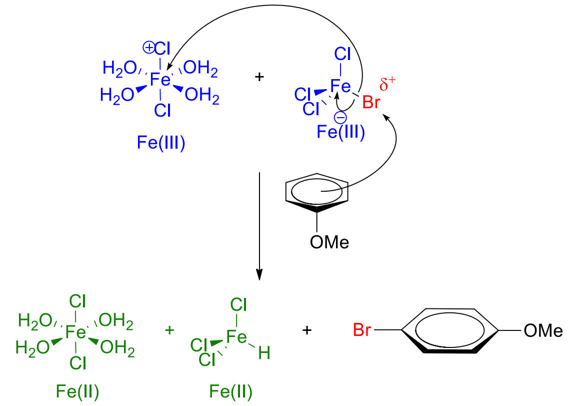


Figure 2. A. Optimised geometry and B. Electrostatic Surface Potential of the most stable conformer of (*trans*-$FeCl_2(H_2O)_4^+$, $FeCl_3Br^-$) in the presence of anisole.

These computational results clearly suggest a polarity inversion of the bromine atom, illustrated by the positive partial charge in the ion pair complexes. The presence of anisole does not alter the positive partial charge of the bromine atom, and even seems to increase it.

The Umpolung behaviour of the bromine atom in the reaction mixture of melted $FeCl_3 \cdot 6H_2O$ and anisole, makes it an electrophile donating bromine reagent and allows the nucleophilic attack of the anisole (Scheme 3). The nucleophilic attack leads to the reduction of the two iron atoms within the ion pair complex: $FeCl_2(H_2O)_4^+$ into $FeCl_2(H_2O)_4$ and $FeCl_3Br^-$ into $FeCl_3^-$. The re-aromatisation of the anisole ring occurs classically as in SEAr, and leads to the formation of $HFeCl_3$.



Scheme 3. Exploration of the bromination mechanism on anisole with the ion-pair complex ($FeCl_2(H_2O)_4^+$, $FeBr_3Cl^-$).

Electrophilic-brominating reagents are usually generated from bromide activated by a Lewis acid, from polybrominated organic compounds or from a bromine atom bound to a more electronegative atom. The methodology employed here shows that a simple and natural salt can become a source of “positive” bromine by the polarisation of an intermolecular halogen-halogen interaction.

Conclusion

A new methodology for the bromination of methoxy arenes was developed in unprecedented conditions of sustainability. The reaction was performed in a green ionic liquid, easily prepared from melted $FeCl_3 \cdot 6H_2O$ and a natural salt, NaBr, without the use of any additive. The absence of a strong oxidant, toxic solvent and hazardous brominating agent, and the use of inexpensive and abundant reagents made these conditions more appealing for the bromination of aromatic compounds compared to any reported systems. Even mild, these conditions afforded monobromo methoxy aryl products in satisfactory yields with an excellent regioselectivity. Mechanistic investigations revealed the formation of Fe-anionic species, involving the challenging transformation of sodium bromide into a brominating-electrophilic reagent. Finally, we applied this strategy in nitration and thiocyanation of methoxy aryl substrates, from biosourced and innocuous salts, KNO_3 and KSCN respectively. The nitro- and thiocyanato-arenes were obtained with efficiency and without polysubstitution, indicating the broad applicability of the methodology. The strategic design of the methodology could lead to significant improvements in aromatic electrophilic substitution and more broadly in green chemistry.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Aromatic Electrophilic Substitution • Liquid Ionic • mixed melted salts • DFT – HF calculation • sustainable chemistry

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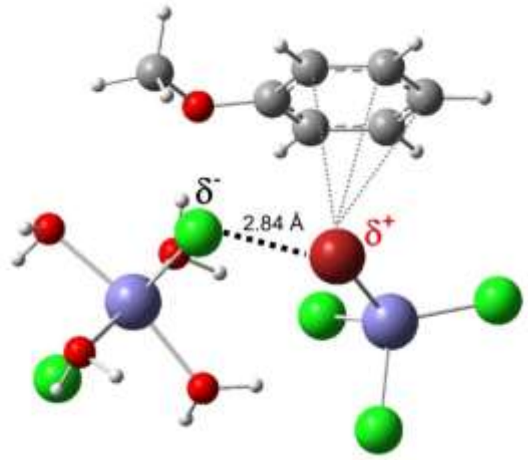

Polarity reversal: new methodology for C-heteroatom bond formation. The reaction is performed in a green ionic liquid easily prepared from melted $FeCl_3$•$6H_2O$ and natural salts NaBr, KSCN or KNO_3, under unprecedented conditions of sustainability. DFT calculations revealed a Fe-anionic species formation inducing the challenging transformation of the anionic substituent into an electrophilic reagent.