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Regioselective Hydration of Alkynes by Iron(III) Lewis/Brønsted Catalysis

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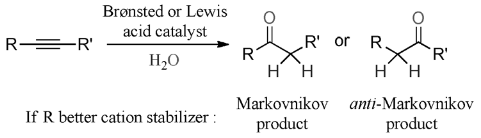
Abstract: The triflimide iron(III) salt $[Fe(NTf_2)_3]$ promotes the direct hydration of terminal and internal alkynes with very good Markovnikov regioselectivities and high yields. The enhanced carbophilic Lewis acidity of the Fe^{III} cation mediated by the weakly-coordinating triflimide anion is crucial for the catalytic activity. The iron(III) metal salt can be recycled in the form of the $OPPh_3/[Fe(NTf_2)_3]$ system with similar activity and selectivity. However, spectroscopic and kinetic studies show that $[Fe(NTf_2)_3]$ hydrolyzes under the reaction conditions and that catalytically less active Brønsted species are formed, which points to a Lewis/Brønsted co-catalysis. This triflimide-based catalytic system is regioselective for the hydration of internal aryl-alkynes and opens the door to a new synthetic route to alkyl ketophenones. As a proof of concept, the synthesis of two antipsychotics Haloperidol and Melperone, with general butyrophenone-like structure, is shown.

Keywords: alkynes · anions · ketones · regioselectivity · iron · hydration

Introduction

The hydration of alkynes is a 100% atom-economical process that allows easy access to carbonyl compounds (Scheme 1).[1,2] As agreed by many authors,[1] two main issues remain to be addressed for this transformation: 1) the use of nontoxic and inexpensive first-row transition metals as catalysts, and 2) the regioselective hydration of asymmetrical internal alkynes without anchimeric assistance. Here, advances regarding these two chemical challenges will be presented.



Scheme 1. Hydration of alkynes catalyzed by Brønsted or Lewis acid catalysts.

A plethora of Brønsted and Lewis acids have been used as catalysts for the otherwise kinetically inhibited hydration.[3–6] Among them, Hg^{II} salts[3] present the best catalytic activity, which has allowed in the past century the manufacture of acetaldehyde from acetylene on an industrial scale.[7] However, this and other acetylene-based hydration transformations had to be restricted due to the high toxicity of the Hg compounds. As possible alternative catalysts, many other Brønsted acids and metal salts and complexes have been investigated, and two of them, Au and Ru, deserve further consideration. On one hand, Au^I, which is isoelectronic to Hg^{II}, shows excellent alcohol-mediated hydration rates[5] and, on the other hand, Ru complexes catalyze *anti*-Markovnikov hydration of terminal alkynes ($R'=H$ in Scheme 1) to produce aldehydes.[6] As a result, the more active and selective catalysts for the hydration of the alkynes are still based on toxic and/or expensive late-transition metals.

Looking at the first-row transition metals, only the more electron-rich, that is, copper and zinc, have shown some success as catalysts for the hydration of alkynes, whereas the catalytic behavior of the rest, to the best of our knowledge, have not been reported.[1] An explanation for this may be due to the fact that a “soft” Lewis acidity is needed to properly interact with the soft π-nucleophile alkyne, and only those late-first-row transition-metal cations, having a full n*d* level, present suitable Lewis acidity to activate the alkyne towards hydration. It is well-known that metals become more oxophilic and less carbophilic when going from right to left in the periodic table or, in other words, harder Lewis acids hamper alkyne activation. However, an exception can be found in high-spin d^5 Fe^{III} compounds having a semi-full 3d level. This electronic configuration imparts to the cation, to some extent, similar bond properties to those in full 3d levels and, indeed, we have recently found that Fe^{III} triflimide, $[Fe(NTf_2)_3]$, catalyzes the regioselective Markovnikov hydrothiolation of styrenes without poisoning of the metal catalyst by the sulfur nucleophile.[8] The low-coordinating anion $^{-}NTf_2$ is essential to provide a strong but soft Lewis acidity to the Fe^{III} cation, increasing the carbophilicity of Fe^{III}.[9] Thus, it was envisaged that $[Fe(NTf_2)_3]$ might be able to activate alkynes in the presence of water and trigger

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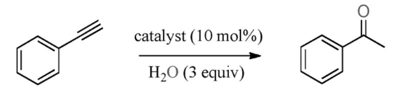
a general hydration of alkynes. In addition, the ability of Fe^{III} to activate benzylic positions is also well-known,[10] which might also control the regioselectivity of the process in asymmetrical aryl alkynes. We can confirm that a general and regioselective hydration indeed occurs, although the formation of catalytically active protons in situ also takes place, so a Lewis/Brønsted co-catalysis must be considered. The addition of catalytic amounts of triphenylphosphane oxide to the triflimide-based acids allows recycling of the catalyst without loss of catalytic activity.

Results and Discussion

Pearson's (hardness-softness) rules dictate that hard cations bound to soft anions become softer. This effect is predicted by molecular orbital theory, which shows that orbital overlap between the occupied n*d* levels of the metal and unoccupied orbitals of the ligands generates a more stabilized LUMO in the final compound. To maintain a strong Lewis acidity, the ligands must be weakly coordinating. Thus, if Fe^{3+} is combined with soft, low-coordinating ligands, an increase in the π-carbophilicity of the final compound should be expected. Looking into possible candidates, on one hand, inorganic low-coordinated ligands such as $^{-}PF_6$, $^{-}BF_4$ or $^{-}SbF_6$ are unsuitable because they are in equilibrium with the corresponding Lewis acids: $XF_n^{-} \rightarrow XF + F^{-}$, thus generating iron fluoride salts in situ. However, organic low-coordinating anions such as triflate (^{-}OTf) or triflimide ($^{-}NTf_2$) might successfully induce the particular π-Lewis acidity required to activate alkynes.[11] To study the catalytic activity of different Fe^{III} salts and other metals in the hydration of alkynes, the addition of water to phenylacetylene (**1**) was chosen as a test reaction (Table 1). We first compared $FeCl_3$ and $[Fe(NTf_2)_3]$ because a chlorine-assisted $FeCl_3$-catalyzed hydration of alkynes has recently been reported (Table 1, entries 1–4).[12] In that procedure, hydrochlorination of the alkyne occurs in the presence of $FeCl_3$ but only when 1,2-dichloroethane (DCE) is used as solvent and when the reaction is run under a low pressure of oxygen, which apparently maintains the activity of the catalyst through the hydrochlorination-hydrolysis process.[13] Our results indicate that the triflimide salt performs better than $FeCl_3$ (compare Table 1, entries 1–3) and, moreover, oxygen was not required with the former catalyst (Table 1, entry 4). It appears then that $[Fe(NTf_2)_3]$ catalyzes the direct addition of water to alkyne **1** without the need to form an intermediate vinyl chloride species and, thus, the use of toxic chlorinated solvents can be avoided. To check this, different solvents were tested (Table 1, entries 5–13) and, interestingly, those solvents containing low-coordinating oxo-groups gave better results (Table 1, entries 5–7). The rest of solvents tested, including stronger oxo-coordinating (Table 1, entries 8 and 9), cyano (entry 10), arene (entry 11), aqueous (entry 12), and amide (entry 13) compounds gave yields of **2** below 50%. The relatively nontoxic 1,4-dioxane was therefore chosen as reaction solvent for the study.

Table 1. Comparison between $FeCl_3$ and $[Fe(NTf_2)_3]$ in the hydration of phenylacetylene (**1**) either under oxidative chlorine-assisted conditions or not, and screening of solvents.



1 **2**

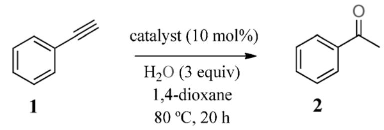
Entry[a]	Catalyst	*t* [h]	Solvent	**2** [%][b]
1	$FeCl_3$	67	DCE	19
2[c]				46
3[c,d]	$FeCl_3$+3 $AgNTf_2$	20		39
4[d]				51
5[d]			1,4-dioxane	96
6[d]			EtOAc	92
7[d]			$EtNO_2$	72
8[d]			DME	12
9[d]			*i*PrOH	17
10[d]			MeCN	40
11[d,e]			Toluene	20
12[d]			H_2O	5
13[d]			DMF	0

[a] Standard reaction conditions: Phenylacetylene (**1**; 0.25 mmol, 28 μL), water (0.75 mmol, 14 μL), catalyst (0.025 mmol), solvent (0.5 mL), 80 °C, 20 h. [b] GC yield using dodecane as internal standard. [c] In the presence of 5 bar O_2. [d] Catalyst was preformed as [$FeCl_3$ (10 mol%)+3 $AgNTf_2$ (30 mol%)] in the corresponding solvent (0.5 mL) for 30 min at room temperature. [e] The major product observed was generated from the hydroarylation reaction between toluene and phenylacetylene.

The catalyst screening included a variety of metal iron(III) salts, using as anions ^{-}Cl, ^{-}Br, $^{-}acac$, $^{-}PF_6$, $^{-}SbF_6$, ^{-}OTf and $^{-}NTf_2$, fifteen different metal triflimides $[M(NTf_2)_n$, n = 1-3], and finally the Brønsted acids HOTf and $HNTf_2$.[14] The results for the Markovnikov hydration of phenylacetylene (**1**) with water (3 equiv.) using 1,4-dioxane as solvent, at 80 °C for 20 h, are shown in Table 2. No catalytic activity was found for ^{-}Cl, ^{-}Br, $^{-}acac$, and $^{-}PF_6$, and a moderate increase occurred when $^{-}SbF_6$ or ^{-}OTf were used as anions for Fe^{III} (entries 1–8). However, an excellent conversion was found for $[Fe(NTf_2)_3]$ (96% yield to **2**; entry 9). The catalyst can also be prepared from the hexahydrate salt $FeCl_3{\cdot}6H_2O$ (entry 10) and the possible catalytic activity from metal impurities in the iron salt was considered negligible because the use of ultrapure (>99.99%) iron(III) gave similar results (entry 11).

To investigate whether the high activity was correlated with an increase in the softness of the Lewis acidity of Fe^{III}, Electronic Paramagnetic Resonance (EPR) and UV/Vis spectroscopy measurements were carried out for $FeCl_3$, $[Fe(OTf)_3]$, and $[Fe(NTf_2)_3]$. Results in Figure 1 show a gradual unpairing of the $3d^5$ electrons when going from $FeCl_3$ to $[Fe(OTf)_3]$ and finally to $[Fe(NTf_2)_3]$, the latter having a pure high-spin configuration (Figure 1). The promotion of electrons from the t_{2g} to the e_g orbitals is triggered by the low-coordinating nature of the corresponding anions, which, in turn, is translated into an expansion of the 3d orbitals and, ultimately, into a softer Lewis acidity for $[Fe(NTf_2)_3]$. In addition, UV/Vis spectroscopy (Figure 2) confirmed the electronic rearrangement in the Fe^{III} frontier orbitals, because the typical transition band t_{2g}–e_g present in the low-spin

Table 2. Catalyst screening for the Markovnikov hydration of phenylacetylene (**1**) with water (3 equiv) to give acetophenone (**2**).



Entry[a]	Catalyst	**2** [%][b]
1	$FeCl_3$	<5
2[c]		<5
3	$FeBr_3$	<5
4	$Fe(acac)_3$	0
5[d]	$FeCl_3$+3 $AgPF_6$	<5
6[d]	$FeCl_3$+3 $AgSbF_6$	53
7[d]	$FeCl_3$+3 AgOTf	17
8	$Fe(OTf)_3$	16
9[d]	$FeCl_3$+3 $AgNTf_2$	96
10[d]	$FeCl_3{\cdot}6H_2O$+3 $AgNTf_2$	86
11[c,d]	$FeCl_3$+3 $AgNTf_2$	68
12[d]	$FeCl_2$+2 $AgNTf_2$	19
13	$Fe(NTf_2)_2$	20
14	HOTf	21
15	$HNTf_2$	23
16	$LiNTf_2$	<5
17	$AgNTf_2$	<5
18[d]	CuCl+$AgNTf_2$	<5
19[d]	$CuCl_2$+2 $AgNTf_2$	<5
20[d]	$ZnCl_2$+2 $AgNTf_2$	<5
21[d]	$MnCl_2{\cdot}4H_2O$+2 $AgNTf_2$	<5
22[d]	$CoCl_2$+2 $AgNTf_2$	<5
23[d]	$NiCl_2{\cdot}6H_2O$+2 $AgNTf_2$	0
24[d]	$RhCl_3$+3 $AgNTf_2$	56
25[d]	$RuCl_3$+3 $AgNTf_2$	90
26[d,e]	Hg_2Cl_2+2 $AgNTf_2$	100
27[d]	$AuCl_3$+3 $AgNTf_2$	99
28[d]	AuCl+$AgNTf_2$	29

[a] Standard reaction conditions: Phenylacetylene (**1**; 0.25 mmol, 28 μL), water (0.75 mmol, 14 μL), catalyst (0.025 mmol), 1,4-dioxane (0.5 mL), 80 °C, 20 h. [b] GC yield using dodecane as internal standard. [c] $FeCl_3$ (99.99 %) was used. [d] Catalyst was preformed as [MCl_n (10 mol %)+*n* Ag salt] in 1,4-dioxane (0.5 mL) for 30 min at room temperature. [e] Reaction was carried with 5 mol % Hg_2Cl_2.

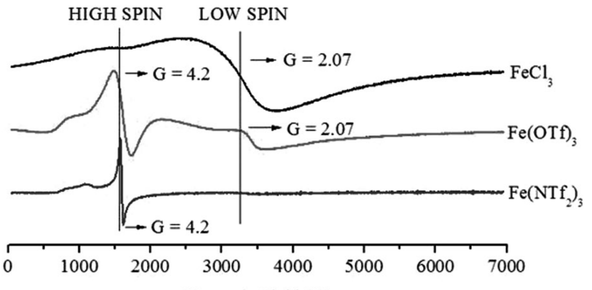


Figure 1. EPR experiments for three iron(III) salts.

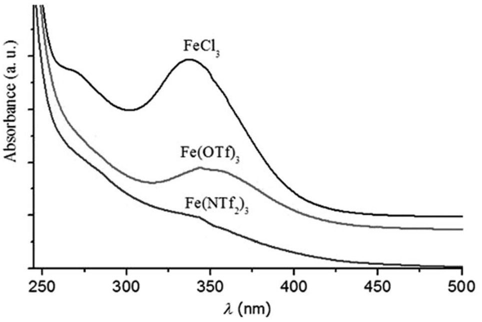


Figure 2. UV/Vis spectra for three iron(III) salts.

$FeCl_3$ disappears gradually when going to [$Fe(OTf)_3$] and finally to [$Fe(NTf_2)_3$], as expected for a high-spin d^5 metal species.

Fe^{II} triflimide, generated either in situ or not, is mainly inactive (Table 2, entries 12 and 13) and so are the Brønsted acids HOTf and $HNTf_2$ at 10 mol % (Table 2, entries 14 and 15). The triflimide metal salts of Li^+, Ag^+, Cu^+, Cu^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, and Ni^{2+} were also inactive for the hydration of phenylacetylene (**1**), obtaining yields of acetophenone (**2**) of below 5 % in all cases (Table 2, entries 16–23, respectively). These results reflect the importance of having a strong but soft Lewis acid to activate the alkyne. Other metal(III) species such as Rh^{3+} and Ru^{3+} (isoelectronic to Fe^{3+}) triflimides showed good catalytic activities (Table 2, entries 24 and 25) and, as expected, Hg^+ and Au^{3+} showed complete conversion of **1** (Table 2, entries 26 and 27). Not surprisingly, Au^+ performed poorly (Table 2, entry 28) because no alcohol-assisted mechanism can operate under these reaction conditions.

It is remarkable that iron was found to have a comparable catalytic activity to that of gold—the recognized most active metal catalyst for the hydration of alkynes after mercury salts—under our standard reaction conditions. Kinetic experiments indicate a similar initial catalytic activity for both metals (Figure 3 A), even after adding substoichiometric

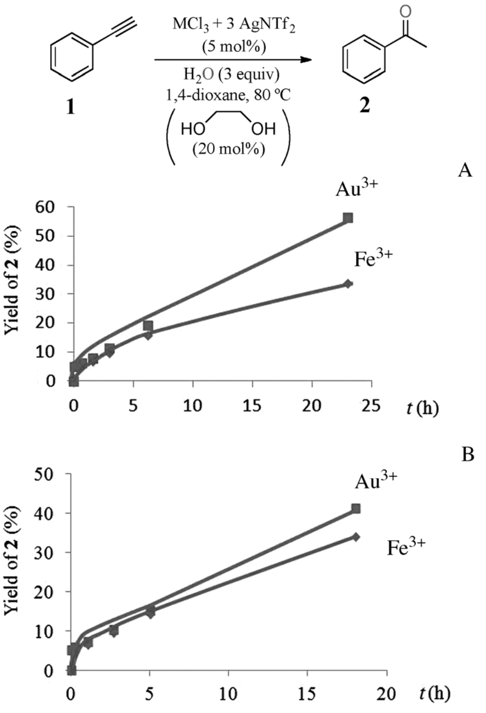


Figure 3. Hydration of **1** in the presence of catalytic amounts of preformed ferric and gold triflimide salts A) without or B) with ethylene glycol as sub-stoichiometric additive.

amounts of a chelating hydroxyl-containing molecule such as ethylene glycol to the reaction medium (Figure 3 B).

In view of the good catalytic results obtained with [Fe(NTf$_2$)$_3$], the reactivity of various terminal (Table 3, entries 1–11) and internal alkynes (entries 12 and 13) was studied under the optimized conditions, giving good to excellent yields of ketone after isolation. Aromatic electron-rich **3**, **7**, **8**, and **9** (entries 2, 6, 7, and 8, respectively) and aromatic electron-poor alkynes **4**, **5**, and **6** (entries 3, 4, and 5, respectively) performed well, and alkyl alkynes **10**, **11**, and **12** (entries 9, 10, and 11, respectively) also formed the corresponding aliphatic ketones in very good yields. Furthermore, the hydration of symmetrical internal alkynes **13** and **14** (entries 12 and 13) was also accomplished to give the corresponding ketones in good yields. The Markovnikov product was obtained exclusively in all cases.

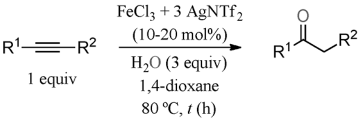
Given the good reactivity found for internal alkynes, and keeping in mind the regioselectivity of Fe^{III} with respect to the benzylic positions, we explored the [Fe(NTf$_2$)$_3$]-catalyzed hydration of asymmetrically substituted aryl-alkyl alkynes. Results in Table 4 (entries 1–3) show total regioselectivity of the reaction to give the corresponding phenylketones **16**, **18**, and **20**. In the case of phenylenynones (Table 4, entry 4) the hydration also occurs regioselectively in the benzylic position, but the 1,3-dicarbonyl compound thus obtained undergoes an iron(III)-catalyzed retro-Claisen[15] reaction to form acetophenone (**2**) as the only product. For aryl-aryl asymmetrical internal alkynes (Table 4, entry 5) the corresponding product was also obtained with full regioselectivity albeit with lower yield.

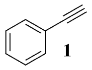
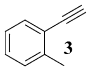
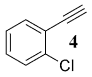
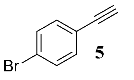
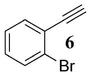
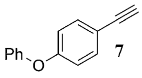
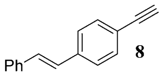
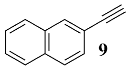
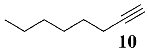
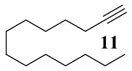
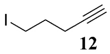
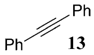
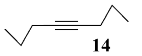
Because the hydration of aryl-alkyl asymmetrical internal alkynes progresses with very good regioselectivity and high yields, resulting in the formation of butyrophenones, we applied the Fe^{III}-catalyzed procedure to the synthesis of two commonly-used antipsychotics with butyrophenone structure, Haloperidol (**24**) and Melperone (**25**; Scheme 2). Thus, precursor **26** was prepared by Sonogashira reaction (see the Supporting Information, Scheme S2) and submitted to [Fe(NTf$_2$)$_3$]-catalyzed hydration conditions to smoothly achieve the common intermediate **27** in high yield and selectivity. Nucleophilic addition[16] of the corresponding amines gave Haloperidol (**24**) and Melperone (**25**) in high yields.

Looking into the possibility of recycling the catalyst, successive reaction cycles were performed with: 1) free [Fe(NTf$_2$)$_3$], 2) the diphosphane complex [(PPh$_3$)$_2$Fe(NTf$_2$)$_3$], and 3) the OPPh$_3$/[Fe(NTf$_2$)$_3$] system, and also the Brønsted acid HNTf$_2$ for comparative purposes (Figure 4).

A study of reusability for the three Fe^{III} catalytic species showed that triphenylphosphane oxide with

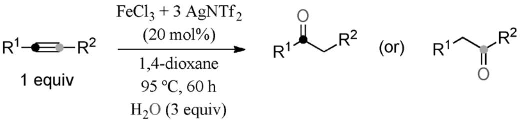
Table 3. Fe(NTf$_2$)$_3$-catalyzed hydration of different alkynes with water (3 equiv) to give the corresponding ketones (X = conversion).



Entry[a]	Alkyne	Product	t [h]	X [%][b]	Yield [%][c]
1	 **1**	**2**	20	96	93
2	 **3**	**3b**	40	100	94
3	 **4**	**4b**	40	98	94
4	 **5**	**5b**	40	100	80
5	 **6**	**6b**	60	100	84
6	 **7**	**7b**	20	100	93
7	 **8**	**8b**	20	100	99
8	 **9**	**9b**	20	100	79
9[d,e]	 **10**	**10b**	60	100	90
10[d,e]	 **11**	**11b**	60	92	79
11[d,e]	 **12**	**12b**	60	100	68
12[f,e]	 **13**	**13b**	60	94	86
13[f,e]	 **14**	**14b**	60	96	71

[a] Standard reaction conditions: Alkyne (0.5 mmol), water (1.5 mmol, 27 μL), FeCl$_3$ (0.05 mmol, 8 mg), AgNTf$_2$ (0.15 mmol, 60 mg), 1,4-dioxane (1 mL), 80 °C, 20 h. [b] GC conversion refers to the disappearance of the alkyne using dodecane as internal standard. [c] Isolated product yield. [d] Catalyst 15 mol %. [e] Reaction was carried at 95 °C. [f] Catalyst 20 mol %.

Table 4. Fe(NTf$_2$)$_3$-catalyzed hydration of different asymmetrical internal alkynes with water (3 equiv) to give the corresponding ketones (X = conversion).



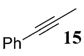
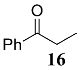
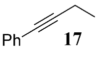
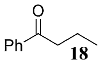
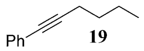
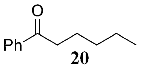
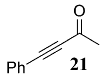
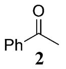
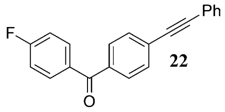
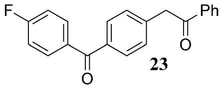
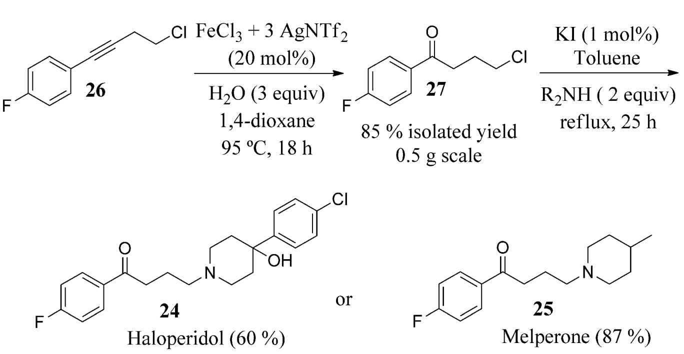
Entry[a]	Alkyne	Main product	X [%][b]	Rs[c]	Yield [%][d]
1	 **15**	 **16**	100	>99:<1	80
2	 **17**	 **18**	100	100:0	92

Table 4. (Continued)

Entry[a]	Alkyne	Main product	X [%][b]	Rs[c]	Yield [%][d]
3	 **19**	 **20**	99	100:0	99
4	 **21**	 **2**	100	100:0	84
5	 **22**	 **23**	40	$>99{:}<1$	32[e]

[a] Standard reaction conditions: Alkyne (0.5 mmol), water (1.5 mmol, 27 μL), $FeCl_3$ (0.1 mmol, 16 mg), $AgNTf_2$ (0.3 mmol, 120 mg), 1,4-dioxane (1 mL), 95 °C, 60 h. [b] GC conversion refers to the disappearance of the alkyne using dodecane as internal standard. [c] Regioselectivity determined by GC-MS and ^1H NMR analysis. [d] Isolated product yield. [e] GC yield.



Scheme 2. Synthesis of Haloperidol and Melperone with the iron(III) regioselective hydration of the internal alkyne **26** as a key step.

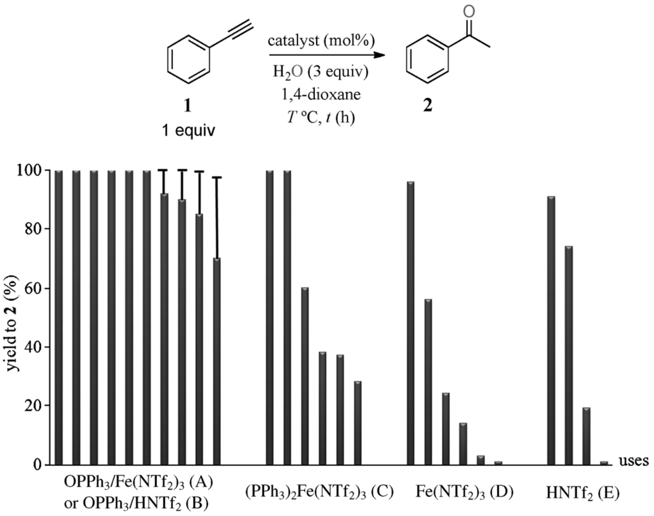


Figure 4. Study of reusability for various catalytic systems for the hydration of phenylacetylene (**1**) to give acetophenone (**2**) with water (3 equiv.) under different conditions: A) $[Fe(NTf_2)_3]$ (20 mol %), $OPPh_3$ (40 mol %), 100 °C, 20 h; B) $HNTf_2$ (60 mol %), $OPPh_3$ (40 mol %), 100 °C, 20 h; C) $[(PPh_3)_2Fe(NTf_2)_3]$ (20 mol %), 100 °C, 20 h; D) $[Fe(NTf_2)_3]$ (10 mol %), 80 °C, 20 h; E) $HNTf_2$ (10 mol %), 100 °C, 48 h.

either $[Fe(NTf_2)_3]$ or $HNTf_2$ turns out to be the most stable system, being highly active after six cycles of reaction (additional lines represent system B). In contrast, when working with $[(PPh_3)_2Fe(NTf_2)_3]$, generated in situ by reaction of $[(PPh_3)_2FeCl_3]+3[AgNTf_2]$, the catalytic activity decreased after the third use. The use of free $[Fe(NTf_2)_3]$ is not suitable for recycling. Thus, we must infer that the presence of $OPPh_3$ in the reaction medium has a stabilizing effect because the weak phosphane oxide interaction ($M\cdots O=PPh_3$, $M=Fe^{3+}$ or H^+) avoids catalyst decomposition. In the case of the Brønsted acid $HNTf_2$ used alone, although it was certainly active under conditions of increased temperature and time, it was not recyclable. With these results in hand, we considered again the possibility that H^+ species generated in situ were responsible for either part or all of the catalytic activity—a question of particular importance in metal triflate-triflimide catalyzed-reactions—although the results in Table 2 (entries 14–15) seemed to indicate the opposite.[17] To address this question, the apparent activation energy (E_a) values (Figure S3 and S6) were calculated for $[Fe(NTf_2)_3]$ and $HNTf_2$ from kinetics parameters (Figure S1, S2, S4, and S5) and the E_a for Fe^{3+} was found to be about 20 kJ mol^{-1} lower than for H^+ (Table 5).

Table 5. Values of apparent activation energies for the Markovnikov hydration of phenylacetylene (**1**) with water (3 equiv) catalyzed by (10 mol %) of catalyst.

Catalyst	E_a [kJ mol^{-1}]
$Fe(NTf_2)_3$	110 ± 0.1
$HNTf_2$	130 ± 0.2

To further assess this question, we calculated and plotted (Figure S7, S8, S9, and S10) the initial Turnover Frequencies (TOF_0's, calculated from initial rates) versus different concentrations of Fe^{3+} and H^+ (up to 60 mol %), and significant differences were found (compare Figure 5 and Figure 6). Whereas an expected linear trend was determined for

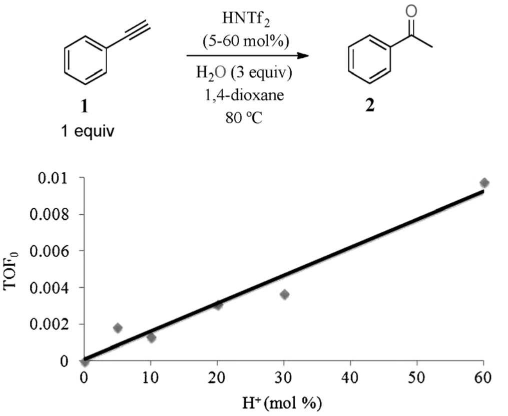


Figure 5. TOF_0 values versus various mol % of $HNTf_2$ for the hydration of phenylacetylene (**1**) to give acetophenone (**2**) with water (3 equiv) at 80 °C.

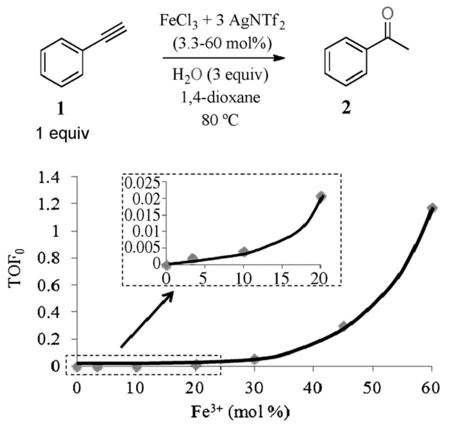


Figure 6. TOF_0 values versus different mol % of $FeCl_3$+3[$AgNTf_2$] for the hydration of phenylacetylene (**1**) to give acetophenone (**2**) with water (3 equiv) at 80 °C.

$HNTf_2$ (Figure 5), a rather unusual variation of the TOF_0 was found for [$Fe(NTf_2)_3$] (Figure 6), showing no saturation values at high amounts of catalyst but, instead, an exponential increase. This could be explained by the increasing Brønsted acidity of the partially hydrated [$Fe(H_2O)_n(NTf_2)_3$] species.

To check whether the presence of the triflimide anion is responsible for an increase in the catalytic activity of [$Fe(NTf_2)_3$], additional experiments (Figure S11 and S12) were carried out in which the catalytic activity for the hydration of **1** was measured after adding nonactive triflimide salts (Figure 7). It was found that the reaction rate was 2–3 times higher when an equimolar amount of another triflimide salt was added, regardless the nature of the cation (Brønsted H^+ , Lewis Zn^{2+}, organic imidazolium). Thus, it seems that the increase in the catalytic activity of the Lewis catalyst could be related to an acidity enhancement caused by the triflimide network and water molecules. Further studies in this regard are in progress.

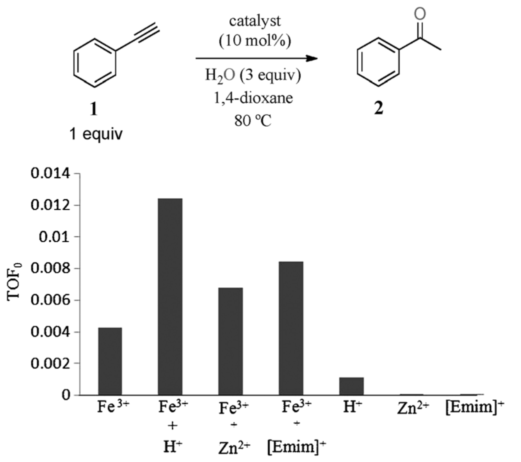


Figure 7. TOF_0 values of different catalytic species for the hydration of phenylacetylene (**1**) to give acetophenone (**2**) with water (3 equiv) at 80 °C. In all cases, the anion was $^-NTf_2$ and the reaction was catalyzed by 10 mol % of each species.

Spectroscopic evidence for the possible formation of $HNTf_2$ from [$Fe(NTf_2)_3$] species under the reaction conditions were obtained from in situ ^{19}F NMR measurements (Figure 8). As can be seen, the peak corresponding to [$Fe(NTf_2)_3$] disappears in the presence of water and a new peak ($\delta \approx -78.5$ ppm), very proximal to that corresponding to $HNTf_2$ ($\delta \approx -78.0$ ppm) appears during the reaction, disappearing at the end of the reaction. Concomitantly, new signals ($\delta \approx -70.0$ ppm and -72.0 ppm), perhaps corresponding to iron triflimide-type compounds, appear at the end of the reaction. These observations would be in accordance with the possible reaction mechanism depicted in Scheme 3.

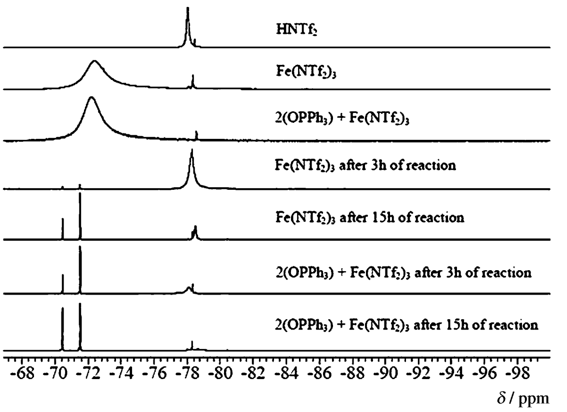
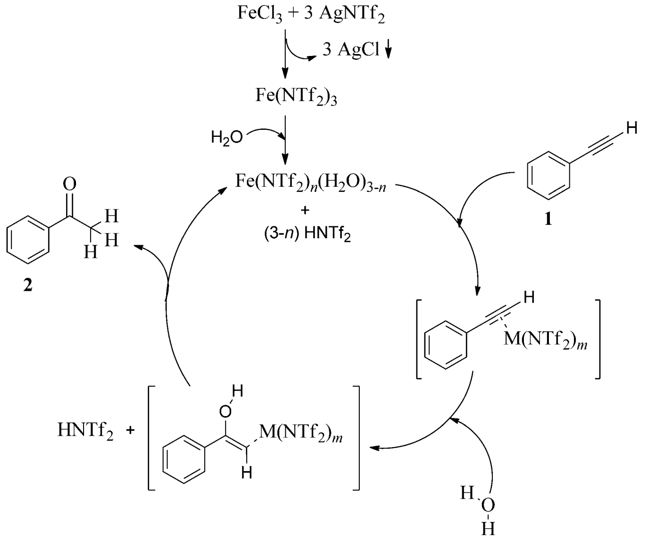


Figure 8. ^{19}F NMR spectra of different triflimides recorded during the hydration of phenylacetylene (**1**) with water (3 equiv) to give acetophenone (**2**).

Addition of 2,6-di-*tert*-butylpyridine completely inhibits the reaction, which confirms the need for H^+ for the reaction to proceed. Therefore, we must conclude that a Brønst-



Scheme 3. Tentative mechanism for the Markovnikov hydration of phenylacetylene (**1**) with water (3 equiv.) to give acetophenone (**2**), catalyzed by [$Fe(NTf_2)_3$]. M = Fe^{3+} and/or H^+.

ed/Lewis co-catalysis seems to operate under these reaction conditions. Nevertheless, a neat Brønsted catalysis after hydrolysis of the iron(III) triflimide salt cannot be discarded.

Conclusion

The regioselective Markovnikov hydration of terminal and internal aryl-alkyl alkynes is achieved by using iron(III) triflimide compounds in catalytic amounts. Hydrolysis of the salt readily occurs to give catalytically active protons. Kinetic experiments point to a possible Lewis/Brønsted co-catalysis or even just a neat Brønsted catalysis. The use of triphenylphosphane oxide allows the catalyst to be recycled. The regioselective hydration in the benzylic position gives access to a formal acylation of aromatic rings, and the synthesis of Haloperidol and Melperone illustrates the potential use of this synthetic protocol in organic synthesis.

Experimental Section

General methods: Reagents and solvents were obtained from commercial sources (Aldrich) and were used without further purification otherwise indicated. All the products obtained were characterised by GC-MS, ^{1}H- and ^{13}C-NMR, and DEPT. When available, the characterisation given in the literature was used for comparison. Gas chromatographic analyses were performed in an instrument equipped with a 25 m capillary column of 5% phenylmethylsilicone. GC/MS analyses were performed on a spectrometer equipped with the same column as the GC and operated under the same conditions. ^{1}H, ^{13}C, DEPT and ^{19}F were recorded in a 300 MHz instrument using $CDCl_3$ as solvent containing TMS as internal standard. IR spectra of the compounds were recorded on a spectrophotometer by impregnating the windows with a dichloromethane solution of the compound and leaving to evaporate before analysis. Absorption spectra were recorded on an UV/Vis spectrophotometer (UV0811M209, Varian) and EPR experiments were carried out with a Bruker EMX/X equipment.

Typical reaction procedure for acetophenone (2) (Table 3, entry 1): $FeCl_3$ (97%, Aldrich, 8.0 mg, 10 mol%) and $AgNTf_2$ (97%, Aldrich, 60.0 mg, 30 mol%) were placed in a 2 mL vial, and 1,4-dioxane (1 mL) was added. The mixture was magnetically stirred at RT for 30 min, then phenylacetylene (56 μL, 0.5 mmol) and water (28 μL, 1.5 mmol) were added and the mixture was placed in a pre-heated oil bath at 80°C and magnetically stirred for 20 h. After cooling, *n*-hexane (20 mL) was added (precipitation of the catalyst was observed). The liquid was filtered under gravity and the filtrate was concentrated under reduced pressure to give **2** (56 mg, 93%) as a yellow oil. GC-MS: *m*/*z* (%): 120 (40) $[M]^{+\cdot}$, 105 (100), 77 (40), 51 (40); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.88 (m, 2H), 7.55–7.47 (m, 1H), 7.45–7.37 (m, 2H), 2.56 ppm (s, 3H).

Typical reaction procedure for reusing the $OPPh_3/[Fe(NTf_2)_3]$ system (Figure 4, A): $FeCl_3$ (97%, Aldrich, 16.0 mg, 20 mol%), $AgNTf_2$ (97%, Aldrich, 120.0 mg, 60 mol%) and $OPPh_3$ (55.6 mg, 40 mol%) were placed in a 10 mL round-bottomed flask, then 1,4-dioxane (1.5 mL) was added. The mixture was magnetically stirred at RT for 30 min, then phenylacetylene (56 μL, 0.5 mmol) and water (28 μL, 1.5 mmol) were added and the mixture was placed in a pre-heated oil bath at 100°C and magnetically stirred for 20 h. After cooling, *n*-hexane (20 mL) was added (precipitation of the catalyst was observed). The liquid was decanted, the remaining catalyst was washed with hexane, and the liquid was decanted again. The combined organic phases were analyzed by GC. The catalyst was dried for 4 h and used in a subsequent run.

Synthesis of haloperidol (24) and melperone (25) from compound 26 (Scheme 2)

Compound 27: $FeCl_3$ (97%, Aldrich, 85.0 mg, 10 mol%) and $AgNTf_2$ (97%, Aldrich, 624.0 mg, 30 mol%) were placed in a 25 mL round-bottomed flask, 1,4-dioxane (5 mL) was added and the mixture was magnetically stirred at RT for 30 min. Compound **26** (430 μL, 2.6 mmol) and water (140 μL, 7.8 mmol) were added and the mixture was placed in a pre-heated oil bath at 80°C and magnetically stirred for 18 h. After cooling, *n*-hexane (60 mL) was added (precipitation of the catalyst was observed) and the liquid was filtered under gravity. The filtrate was concentrated under reduced pressure and the resulting yellow oil residue was purified by flash column chromatography on silica (hexane/EtOAc, 80:20). Fractions were concentrated under reduced pressure and, after drying under vacuum, the resulting residue compound **27** (406 mg, 85%) was obtained as a yellow oil. R_f = 0.66 (20% EtOAc/hexane). GC-MS: *m*/*z* (%): 200 (1) $[M]^{+\cdot}$, 164 (1), 138 (43), 123 (100), 107 (10); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.97 (m, 2H), 7.17–7.09 (m, 2H), 3.68 (t, *J* = 6.2 Hz, 2H), 3.15 (t, *J* = 7.0 Hz, 2H), 2.22 ppm (tt, *J* = 7.0, 6.2 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 197.3 (C=O), 166.1 (d, ^1J(C,F) = 254.7 Hz; C-F), 133.2 (d, ^4J(C,F) = 4.3 Hz; C), 130.6 (d, ^3J(C,F) = 9.3 Hz; 2×CH), 115.9 (d, ^2J(C,F) = 22.2 Hz; 2×CH), 44.6 (CH_2), 35.2 (CH_2), 26.7 ppm (CH_2).

Haloperidol (**24**): Compound **27** (150 mg, 0.75 mmol), 4-(4-chlorophenyl)-4-hydroxypiperidine (321 mg, 1.5 mmol), and KI (2 mg, 1 mol%) were placed in a 10 mL cylindrical sealed vial. Anhydrous toluene (2.5 mL) was added and the mixture was placed in a pre-heated oil bath at 125°C and magnetically stirred for 25 h. After cooling, the reaction mixture was washed with EtOAc (3×10 mL) and the liquid was filtered under gravity. The filtrate was concentrated under reduced pressure and the resulting brown oil residue was purified by flash column chromatography on silica ($EtOAc/MeOH/NH_4OH$, 95:5:1). Fractions were concentrated under reduced pressure and, after drying under vacuum, Haloperidol **24** (168 mg, 60%) was obtained as a brown solid. R_f = 0.6 ($EtOAc/MeOH/NH_4OH$, 95:5:1). GC-MS: *m*/*z* (%): 375 (1) $[M]^{+\cdot}$, 237 (98), 224 (100), 206 (26), 165 (8), 123 (16), 95 (7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.95 (m, 2H), 7.41–7.35 (m, 2H), 7.32–7.26 (m, 2H), 7.17–7.08 (m, 2H), 3.53 (br s, OH), 3.01 (t, *J* = 6.8 Hz, 2H), 2.97–2.88 (m, 2H), 2.67–2.55 (m, 4H), 2.20–2.07 (m, 2H), 2.06–1.98 (m, 2H), 1.77–1.67 ppm (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 198.0 (C=O), 164.0 (d, ^1J(C,F) = 254.7 Hz; C-F), 146.4 (C), 133.4 (d, ^4J(C,F) = 2.7 Hz; C), 132.9 (C), 130.7 (d, ^3J(C,F) = 9.3 Hz; 2×CH), 128.4 (2×CH), 126.1 (2×CH), 115.6 (d, ^2J(C,F) = 21.9 Hz; 2×CH), 70.6 (CH_2), 57.4 (CH_2-N), 49.1 (2×CH_2-N), 37.6 (2×CH_2), 36.0 (CH_2), 21.0 ppm (CH_2).

Melperone (**25**): Compound **27** (150 mg, 0.75 mmol), 4-methylpiperidine (280 μL, 1.5 mmol) and KI (2 mg, 1 mol%) were placed in a 10 mL cylindrical sealed vial. Anhydrous toluene (2.5 mL) was added and the mixture was placed in a pre-heated oil bath at 125°C and magnetically stirred for 25 h. After cooling, the reaction mixture was washed with EtOAc (3×10 mL) and the liquid was filtered under gravity. The filtrate was concentrated under reduced pressure and the resulting brown oil residue was purified by flash column chromatography on silica ($EtOAc/MeOH/NH_4OH$, 95:5:1). The fractions were concentrated under reduced pressure and, after drying under vacuum, Melperone **25** (171 mg, 87%) was obtained as a brown solid. R_f = 0.5 ($EtOAc/MeOH/NH_4OH$, 95:5:1). GC-MS: *m*/*z* (%): 263 (1) $[M]^{+\cdot}$, 165 (4), 125 (54), 112 (100), 95 (9), 70 (6); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.94 (m, 2H), 7.13–7.05 (m, 2H), 2.99–2.85 (m, 4H), 2.42 (t, *J* = 7.3 Hz, 2H; CH_2-CO), 2.02–1.88 (m, 4H), 1.64–1.53 (m, 2H), 1.42–1.27 (m, 1H), 1.26–1.13 (m, 2H), 0.88 ppm (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 198.3 (C=O), 165.5 (d, ^1J(C,F) = 254.1 Hz; C-F), 133.5 (d, ^4J(C,F) = 3.3 Hz; C), 130.6 (d, ^3J(C,F) = 9.3 Hz; 2×CH), 115.5 (d, ^2J(C,F) = 21.9 Hz; 2×CH), 57.8 (CH_2-N), 53.6 (2×CH_2-N), 36.2 (CH_2), 33.8 (2×CH_2), 30.6 (CH), 21.7 (CH_3), 21.4 ppm (CH_2).

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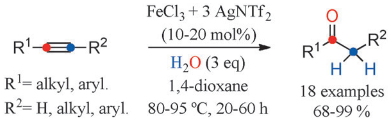
Just add water! The triflimide iron(III) salt [Fe(NTf_2)$_3$] promotes the direct hydration of terminal and internal alkynes with very good Markovnikov regioselectivities and high yields (see scheme).



Regioselective Hydration

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Regioselective Hydration of Alkynes by Iron(III) Lewis/Brønsted Catalysis