

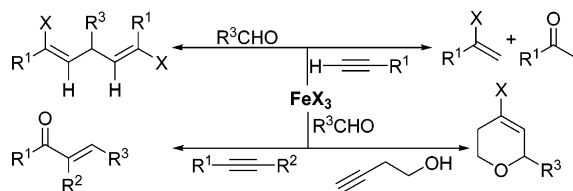
Fe(III) Halides as Effective Catalysts in Carbon–Carbon Bond Formation: Synthesis of 1,5-Dihalo-1,4-dienes, α,β -Unsaturated Ketones, and Cyclic Ethers

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Iron(III) halides have proven to be excellent catalysts in the coupling of acetylenes and aldehydes. When terminal acetylenes were used the main products obtained were 1,5-dihalo-1,4-dienes with (*E,Z*)-stereochemistry contaminated in some cases with (*E*)- α,β -unsaturated ketones. The former carbonyl derivatives were the sole products isolated when nonterminal aromatic alkynes were used. When homopropargylic alcohols were used, a Prins-type cyclization occurred yielding 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans. In addition, anhydrous ferric halides are also shown to be excellent catalysts for the standard Prins cyclization with homoallylic alcohols. Isolation of an intermediate acetal, calculations, and alkyne hydration studies provide substantiation of a proposed mechanism.

Introduction

The formation of carbon–carbon bonds constitutes the essence of synthetic organic chemistry.¹ Coupling reactions of alkynes and carbonyl compounds are important transformations since they efficiently generate new carbon–carbon bonds. From the existing methodology, the synthesis of propargylic alcohols by basic C–H activation in terminal acetylenes and further carbonyl addition is from the practical point of view one of the most popular reactions.² On the other hand, virtually all transition metals react with alkynes, in most cases evolving toward more elaborate complexes or organic products.³

As a result of our studies directed to the synthesis of marine natural products characterized by having cyclic

ethers as their main structural feature,⁴ we addressed our attention to the use of dicobalt hexacarbonyl-stabilized propargylic cations as an excellent synthetic tool to control the carbon–oxygen bond in the propargylic system.⁵ We were particularly interested in using such nonbasic conditions since in the synthesis of compounds isolated from the marine environment in the presence of compounds having halides is quite common,⁴ in most cases being noncompatible with the strong basic conditions needed, for instance, for the synthesis of the propargylic alcohols. Pondering the possibility of extending the use of acetylenes under nonbasic conditions to control the cyclic ether formation and to form carbon–carbon bonds, we decided to explore the direct coupling of such units and carbonyl derivatives using Lewis acids as catalysts.

Within the Lewis acid catalog, FeX_3 are inexpensive, environmentally friendly, and stable Lewis acids, described in the literature as effective agents for the

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(1) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, T., Eds.; Pergamon: Oxford, UK, 1991; Vol. 3.

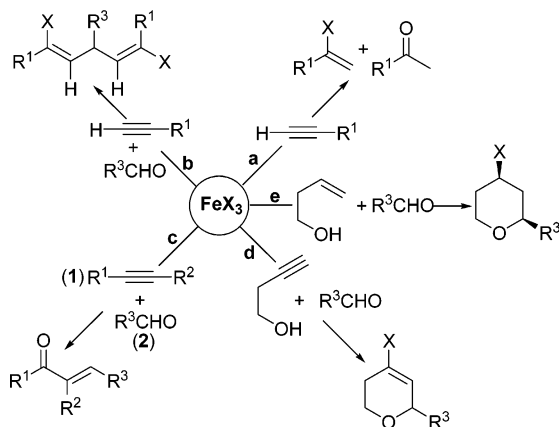
(2) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier Science Publishers: Amsterdam, The Netherlands, 1988.

(3) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834.

(b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119. (c) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1997.

(4) (a) Faulkner, D. *J. Nat. Prod. Rep.* **2002**, *19*, 1–48 and preceding issues. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909.

(5) (a) Betancort, J. M.; Martín, T.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **2003**, *68*, 3216–3224. (b) Díaz, D. D.; Martín, V. S. *Org. Lett.* **2000**, *2*, 335–337.

SCHEME 1. Reactions of FeX₃ with Different Unsaturated Substrates and Aldehydes

cleavage⁶ and formation⁷ of ethers, as oxidant agents,⁸ in cross coupling of alkenyl or aryl derivatives and Grignard reagents,⁹ for carbometalation of olefins,¹⁰ in the synthesis of 2-aryl-tetrahydrofurans,¹¹ for Nararov cyclizations,¹² in the allylation of aldehydes,¹³ among other applications.¹⁴ In this paper we would like to report on the scope and limitations of the use of iron(III) halides as effective catalysts in the coupling of acetylenes and aldehydes to achieve a wide variety of useful synthetic transformations in most cases depending on the structure of the alkyne (basically, terminal or nonterminal) used and/or the reaction conditions (Scheme 1). In addition, iron(III) halides were also found to be excellent catalysts for the Prins reaction with allylic alcohols.

Results and Discussion

Study of Reactivity between Alkynes and Iron-(III) Halides. Prior to carrying out the studies of coupling between alkynes and aldehydes we decided to explore the reactivity between acetylenes and iron(III) halides in the absence of carbonyl species (Scheme 1, route a). Table 1 summarizes the results obtained in this study. We found that aliphatic terminal alkynes (1-octyne) react with iron(III) halides (FeCl₃ and FeBr₃)¹⁵

TABLE 1. Synthesis of 2-Halovinyl and Methyl Ketone Derivatives from Terminal Acetylenes

entry	R ¹	R ²	X	acid	3:4	yield (%)
1	<i>n</i> -C ₆ H ₁₃	H	Cl	—	100:0	54
2	<i>n</i> -C ₆ H ₁₃	H	Br	—	100:0	51
3	<i>n</i> -C ₆ H ₁₃	H	Cl	HOAc	100:0	88
4	<i>n</i> -C ₆ H ₁₃	H	Cl	TFA	100:0	80
5	<i>n</i> -C ₆ H ₁₃	H	Br	BzOH	100:0	82
6	<i>n</i> -C ₆ H ₁₃	H	Cl	aspartic acid	100:0	75
7	<i>n</i> -C ₆ H ₁₃	H	Cl	CSA	38:62	80
8	<i>n</i> -C ₆ H ₁₃	H	Br	CSA	10:90	85
9	<i>n</i> -C ₆ H ₁₃	H	Cl	TsOH	100:0	70
10	<i>n</i> -C ₆ H ₁₃	H	Br	MsOH		
11	Ph	H	Cl	HOAc	0:100	82
12	Ph	H	Cl	CSA	0:100	80
13	Me	<i>n</i> -C ₅ H ₁₁	Cl	HOAc		
14	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	Cl	HOAc		

to give the corresponding 2-halovinyl **3**¹⁶ derivatives although with a moderate yield (entries 1 and 2). Nevertheless, when we used stoichiometric amounts of carboxylic acids, yields improved remarkably (entries 3–6). The use of sulfonic acid led to variable results. Thus, while using camphorsulfonic acid, the methyl ketone **4**¹⁷ was the major product (entries 7 and 8), tosyl acid provided only the vinyl halide **3** (entry 9), and methanesulfonic acid proved to be unsuitable for these transformations (entry 10). The extension of these reactions to aromatic alkynes such as phenylacetylene with both carboxylic and sulfonic acids (entries 11 and 12) produced only the ketone **4**. Interestingly, when acetic acid was used in addition to the methyl ketone **4**, a tiny amount (13%) of (*Z*)-4-chloro-4-phenylbut-3-en-2-one (**5**) was obtained. Internal acetylenes were found to be nonreactive under these conditions (entries 13 and 14). Of the different solvents screened (THF, CH₃CN, EtOAc, CHCl₃, CCl₄, CH₃NO₂, CH₂Cl₂, and 1,2-dichloroethane) we found the best conditions using CH₂Cl₂ and 1,2-dichloroethane.

Coupling Reactions of Nonoxygenated Alkynes and Aldehydes. After our initial studies between terminal acetylenes and iron(III) halides we explored the influence of such salts on coupling reactions of nonoxygenated alkynes and aldehydes (Scheme 1, routes b and c). In this session we will discuss a new stereoselective coupling of alkynes and aldehydes leading to (*E,Z*)-1,5-dihalo-1,4-dienes **6** and/or (*E*)- α,β -unsaturated ketones **7** catalyzed by iron(III) trihalides (Table 2).

Recently, Kabalka et al. reported that the use of BX₃ generates 1,5-dihalo-1,4-pentadienes by coupling between aryl aldehydes and aryl acetylenes, although the use of aliphatic alkynes and aldehydes in this process gave only traces of the desired products.^{18a} Similar results were obtained by the same authors with titanium(IV) halides, utilizing both aromatic and aliphatic alkynes and aldehydes.^{18b}

(6) (a) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477–5478. (b) Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1995**, *6*, 857–858. (c) Kartha, K. P. R.; Dasgupta, F.; Singh, P. P.; Srivastava, H. C. *J. Carbohydr. Chem.* **1986**, *5*, 437–444.

(7) Patney, H. K. *Synlett* **1992**, 567–568.

(8) (a) Takaki, K.; Yamamoto, J.; Matsushita, Y.; Morii, H.; Shishido, T.; Takehira, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 393–398. (b) Martín, S. E.; Garrone, A. *Tetrahedron Lett.* **2003**, *44*, 549–552.

(9) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863. (c) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599–606. (d) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 111–118.

(10) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978–979.

(11) Sharma, G. V. M.; Kumar, K. R.; Sreenivas, P.; Krishna, P. R.; Chorghade, M. S. *Tetrahedron: Asymmetry* **2002**, *13*, 687–690.

(12) Kuroda, C.; Koshio, H.; Koito, A.; Sumiya, H.; Murase, A.; Hirano, Y. *Tetrahedron* **2000**, *56*, 6441–6455.

(13) (a) Watahiki, T.; Akabane, Y.; Mori, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 3045–3048. (b) Watahiki, T.; Oriyama, T. *Tetrahedron Lett.* **2002**, *43*, 8959–8961.

(14) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995.

(15) Anhydrous FeCl₃ and FeBr₃ were purchased from the Aldrich Company.

(16) Cassagne, D.; Gillet, M.; Braun, J. *Bull. Soc. Chim. Fr.* **1979**, 140–144.

(17) Damiano, J. P.; Postel, M. *J. Organomet. Chem.* **1996**, *522*, 303–305.

TABLE 2. FeX₃-Promoted Stereoselective Coupling of Alkynes and Aldehydes

entry	R ¹	R ²	R ³	X	time	6:7	yield (%) ^a
1	<i>n</i> -C ₄ H ₉	H	<i>i</i> -C ₄ H ₉ ^b	Cl	10 m	73:27	96
2	<i>n</i> -C ₄ H ₉	H	<i>i</i> -C ₄ H ₉ ^b	Br	10 m	62:28	88
3	Ph	H	<i>i</i> -C ₄ H ₉ ^b	Cl	15 m	74:26	97
4	Ph	H	<i>i</i> -C ₄ H ₉ ^b	Br	20 m	75:25	96
5	Ph	H	cyclohexyl ^b	Cl	30 m	75:25	91
6	Ph	H	cyclohexyl ^b	Br	40 m	64:26	97
7	Bn	H	<i>n</i> -C ₆ H ₁₂ ^b	Cl	2 h	100:0	70
8	Bn	H	<i>n</i> -C ₆ H ₁₂ ^b	Br	5 h	100:0	44
9	<i>n</i> -C ₄ H ₉	H	Ph ^b	Cl	12 h		
10	Ph	CH ₃	cyclohexyl ^c	Cl	5 m	0:100	65
11	Ph	CH ₃	<i>i</i> -C ₄ H ₉ ^c	Cl	5 m	0:100	80
12	Ph	CH ₂ OH	<i>i</i> -C ₄ H ₉ ^c	Cl	5 m	0:100	33 ^d
13	Ph	CH ₂ OAc	<i>i</i> -C ₄ H ₉ ^c	Cl	5 m	0:100	52 ^d
14	Ph	CH ₂ CH=CH ₂	<i>i</i> -C ₄ H ₉ ^c	Cl	5 m		
15	Bn	<i>n</i> -C ₄ H ₉	<i>i</i> -C ₄ H ₉ ^c	Cl	5 m		
16	<i>n</i> -C ₅ H ₁₁	CH ₃	Ph ^c	Cl	5 m		
17	Ph	Ph	<i>i</i> -C ₄ H ₉ ^c	Cl	5 m	0:100	68

^a Yields are of products isolated by column chromatography based on starting aldehyde. ^b The reaction was run with a 1:2 equiv ratio of aldehyde and acetylene. ^c The reaction was run with a 1:1 equiv ratio of aldehyde and acetylene.

Our first task was to investigate the coupling between terminal alkynes and aldehydes (Table 2). We found that both aliphatic and aromatic terminal alkynes (entries 1–8) react with aliphatic aldehydes in the presence of stoichiometric amounts of iron(III) trihalide (FeCl₃ and FeBr₃) giving a mixture of (*E,Z*)-1,5-dihalo-1,4-dienes **6**¹⁸ and disubstituted (*E*)- α,β -unsaturated ketones **7**,¹⁹ the former being the major products in all cases. Trace amounts of the (*Z,Z*)-isomers were not detected.

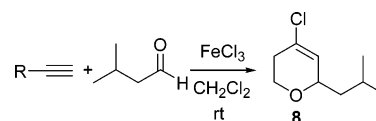
A variety of aldehydes and alkynes were examined for this coupling. The reaction works with both aliphatic and aromatic alkynes (entries 1–8), although the attempt to carry out the reaction with aromatic aldehydes was fruitless (entry 9). In addition, ketones were also unreactive.

As shown in Table 2, the yields of **6** were close to 70% (entries 1–7) except that of entry 8, which was only 44%, probably due to the greater bulkiness of the bromine. This steric hindrance may also be related to the reaction times. Thus, nonbulky aliphatic aldehydes (entries 1–4) reacted in similar periods of time but when the bulkiness increased, as occurred with cyclohexanal (entries 5 and 6), the reaction time became longer.

The coupling process is highly stereoselective as determined (in all cases *E,Z*) by ¹H and ¹³C NMR experiments (the *E,Z*-diene displays two sets of signals for the vinyl group).^{18a} The stereochemistry did not change despite varying the nature of the R¹ and R³ groups, thereby offering a new way to achieve the stereocontrolled C–C bond formation of such systems. In addition

(18) (a) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 1491–1493. (b) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 3415–3417.

(19) (a) Curini, M.; Epifano, F.; Maltese; Rosati, O. *Synlett* **2003**, 552–553. (b) Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 1613–1615. (c) Hayashi, A.; Yamaguchi, M.; Hirma, M. *Synlett* **1995**, 195–196.

TABLE 3. FeX₃-Promoted Coupling of Oxygenated Terminal Alkynes and Aldehydes

entry	R	time	yield (%)
1	CH ₂ OH	10 m	– ^a
2	CH ₂ OTBS	10 m	– ^a
3	(CH ₂) ₂ OH	15 m	97
4	(CH ₂) ₃ OH	12 h	– ^b
5	(CH ₂) ₄ OH	12 h	– ^b

^a Irresolvable mixture.

to 1,5-dihalo-1,4-pentadienes small amounts were obtained of (*E*)- α,β -unsaturated ketones (entries 1–6), as determined by constant coupling measurements by means of ¹H NMR spectra.^{17b} Such unsaturated carbonyl derivatives were absent when benzyl alkynes (entries 7 and 8) were used.

When nonterminal aromatic acetylenes were used we found the trisubstituted (*E*)- α,β -unsaturated ketones **7** to be the exclusive compounds obtained. The procedure is not valid for aliphatic (entries 15 and 16) and unsaturated skipped (entry 14) alkynes since irresolvable mixtures were produced. The catalytic system is, however, compatible with alcohols and their corresponding acetates although limited yields were obtained (entries 12 and 13). In such cases the system works well, even with 0.1 equiv of FeCl₃ as catalyst.

From the experimental point of view it must be emphasized that when terminal alkynes are used the acetylene:aldehyde ratio must be 2:1 equiv, leading to the corresponding 1,5-dihalo-1,4-pentadienes as the major products. However, when the trisubstituted-(*E*)- α,β -unsaturated ketones are the desired products, the nonterminal aromatic acetylenes must be used in a 1:1 ratio relative to the aldehyde.

Coupling Reactions of Oxygenated Alkynes and Aldehydes. To extend the synthetic use of the coupling between aldehydes and terminal acetylenes (Scheme 1, route d) we were interested in testing alkynes having oxygenated functions in the linear chain (Table 3). We found that only homopropargylic alcohols react properly yielding as sole detected product the 2-substituted dihydropyran **8** (entry 3). Propargylic alcohol and its TBS-ether yielded irresolvable mixtures (entries 1 and 2). Acetylenic alcohols having the hydroxyl group located at a different distal position remained unaffected (entries 4 and 5).

This Prins-type²⁰ cyclization provides a new method for accessing 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans²¹ that makes use of the direct coupling of homopropargylic alcohol and aldehydes induced by a stoichiometric amount of anhydrous ferric halides (FeCl₃ and FeBr₃) (Scheme 1, route d).²² In addition, we found also that FeX₃ is an excellent catalyst in the Prins cyclization (Scheme 1, route e), observing that the reaction between 3-buten-1-ol and several aldehydes proceeded satisfactorily, affording the corresponding *cis*-4-halo-2-alkyl tetrahydropyrans in good yields.²²

Consideration on the Reaction Mechanism. In accordance with our experimental results we can conclude that FeX_3 have two major roles when acetylenes and carbonyl compounds are used: as Lewis acids activating the carbonyl functionality and forming alkyne–iron complexes that may be an initial step in further chemical events. The relative importance of both behaviors strongly depends on the nature of the components used in terms of, for instance, the presence or absence of oxygen or other functional groups, internal or external acetylenes, steric hindrance, etc.

To rationalize the action modes of FeX_3 in acetylenic coupling we performed some calculations at the ab initio level. In the first instance, and following a path parallel to that of the experimental work, we focused our attention on the interaction between terminal acetylenic and iron(III) halides.

The theoretical study for the reaction between FeCl_3 and an alkyne compound is not trivial. One can reasonably assume that the FeCl_3 , as an electrophilic species, interacts with the nucleophilic triple bond to give a π -type complex. This kind of interaction involves weak bonds which require a relatively large basis set system with diffuse functions to be described, and taking into account the electron correlation also. Considering the above, we performed some ab initio calculations for three alkyne models (acetylene, propyne, and 2-butyne) using for geometry optimizations the mixed functional B3LYP,²³ for alkyl substructure the 6-311+G*²⁴ basis set, and for iron and chlorine atoms the pseudopotential basis set LANL2DZ.²⁵ We found, for the three alkynes considered, the three minima on the potential energy surface. However this outcome is not by itself proof of the existence of true structures: we need to evaluate the correlation energy.²⁶ A different and less expensive choice is supplied if one uses the Atoms in Molecules (AIM) method of Bader and co-workers.²⁷ Such a method is based on a careful analysis of electronic density topology and permits drawing molecular graphs, representing a network of bond paths linking together all pairs of atoms that are believed to be bonded to one another. Such graphs can be considered as the AIM definition of the bond.

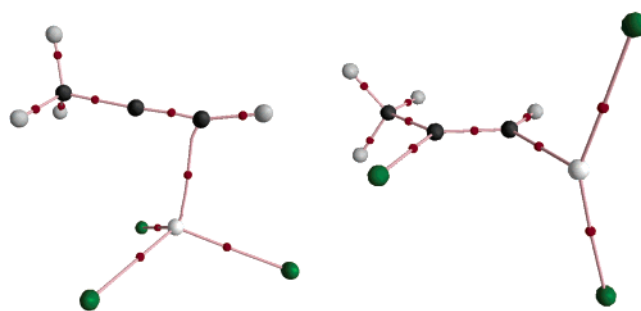


FIGURE 1. Molecular graphs corresponding to π -complex (a) and σ -complex (b) between propyne and FeCl_3 . Small dots into bond paths are the bonds critical points.

In accordance with Bader's methodology, and for an equilibrium structure, the existence of a bond path is both a necessary and a sufficient condition for the existence of a bond.²⁸ The bond path between two atoms is the line between two nuclei along which the electron density is the local maximum and includes a saddle point, the bond critical point, where the gradient of the electronic density vanishes.

To start the Bader analysis we need to compute a good electronic density but the pseudopotential basis sets cannot be used to obtain it. We performed a single-point energy calculation over previous optimized geometries, using B3LYP/6-311+G*, for all of the atoms involved. AIM analysis showed a propyne– FeCl_3 complex as the only stable structure (Figure 1a). The other two symmetric alkynes (acetylene and 2-butyne) gave conflicting structures that were too unstable. This fact could justify the absence of structures such as **3** or **4** when we use nonterminal alkynes.

Figure 1a shows the most relevant structural features of the π -complex. Metal is bonded *only* with the acetylenic terminal carbon with an almost perpendicular approach to the triple bond ($\text{C}\equiv\text{C}-\text{Fe}$ 87.3°). In addition, $\text{C}\equiv\text{C}$ and $\text{C}-\text{H}$ bond lengths become longer.

Analysis of charge distribution can show the electrophilic nature of FeCl_3 in this association. However, it is well-recognized that the concept of atomic charge in a molecule is difficult to define because it is not related to a true physical quantity and, therefore, is not rigorously defined in quantum mechanics. The essence of the AIM theory is the definition of an atom as it exists in the molecule. We can then find atomic charges, without the problems related to electronic distributions based on orbital methods, by simple integration of electronic density over the well-defined atomic basins. A charge transfer corresponding to 0.3 electrons between propyne and ferric chloride is in agreement with the electrophilic character and rationalizes the π -complex by use of species **I** and **II**.

Experimental evidence of methyl ketone **4** could be explained by **II**, even though it must be pointed out that

(20) For the synthesis of dihydropyrans using the Prins cyclization, see: (a) Sun, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430. (b) Dobbs, A. P.; Guesné, S. J. J.; Martinović, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880–7883. (c) Aubele, D. L.; Lee, C. A.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 4521–4523. (d) Dobbs, A. P.; Guesné, S. J. J.; Hursthouse, M. B.; Coles, S. J. *Synlett*, **2003**, 1740–1742. (e) Dobbs, A. P.; Martinović, S. *Tetrahedron Lett.* **2002**, *43*, 7055–7057. (f) Roush, W. R.; Dille, G. J. *Synlett* **2001**, 955–959. (g) Viswanathan, G. S.; Yang, J.; Li, C.-J. *Org. Lett.* **1999**, *1*, 993–995.

(21) For precedents in the synthesis of halovinyl tetrahydropyrans, see: (a) Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925–3927. (b) Chan, T. H.; Arya, P. *Tetrahedron Lett.* **1989**, *30*, 4065–4068. (c) Tsukayama, M.; Utsumi, H.; Kunugi, A.; Nozaki, H. *Heterocycles* **1997**, *45*, 1131–1142.

(22) For details about this process, see: Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *5*, 1979–1982.

(23) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

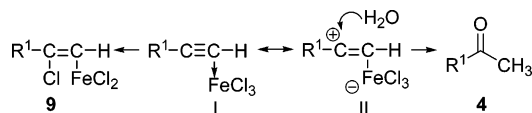
(24) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.

(25) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270–283. (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 284–298. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299–310.

(26) Muguet, F. F.; Robinson, G. W. *J. Chem. Phys.* **1995**, *102*, 3648–3654.

(27) (a) Bader, R. F. W. In *Atoms in Molecules: A Quantum Theory*; The International Series of Monographs of Chemistry; Halpen, J., Green, M. L. H., Eds.; Clarendon Press: Oxford, UK, 1990; pp 1–438. (b) Bader, R. F. W. *Chem. Rev.* **1991**, *91*, 893–928. (c) Popelier, P. In *Atoms in Molecules: An Introduction*; Prentice Hall: Harlow, New York, 2000; pp 1–164. (d) Gillespie, R. J.; Popelier, P. L. A. In *Chemical Bonding and Molecular Geometry: From Lewis to Electron Densities*; Oxford University Press: Oxford, UK, 2001; pp 134–268.

(28) Bader R. F. W. *Acc. Chem. Res.* **1985**, *18*, 9–15.



the dipolar structure does not contribute significantly to the ground-state structures as atomic charges over both alkyne carbons on the propyne and its π -complex are almost invariants. The lack of 0.3 electron when the propyne is complexed is mainly distributed between propargylic carbon and terminal hydrogen. In fact, only when the external electrophile conditions are different (Table 1, entries 7 and 8) and/or additional stabilization of the carbocation **II** is present (Table 1, entries 11 and 12) is a substantial amount of methyl ketone produced.

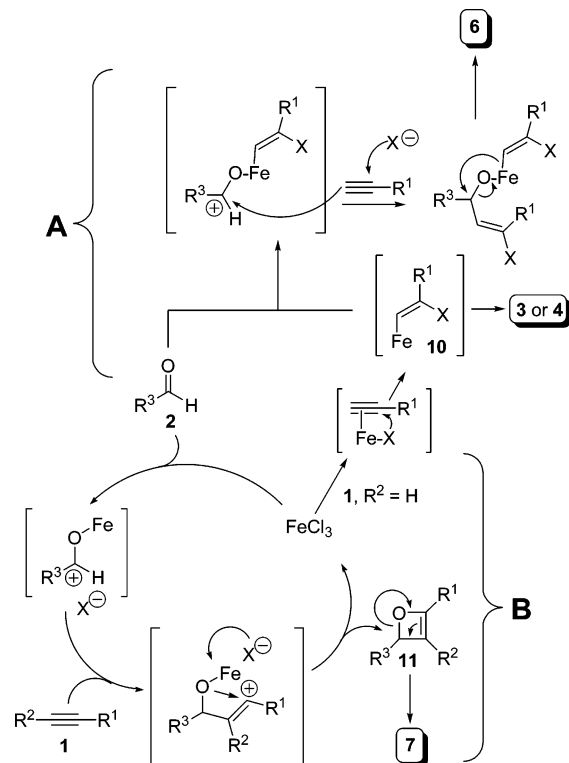
A π -complex can be transformed into a σ -complex after initial complexation. Found energy for calculated equilibrium geometry, using the previously cited basis-set, shows a greater stabilization to the σ -complex vs the π one at 3.11 kcal/mol. This geometry displays the metal atom coordinated to the terminal alkyne carbon as shown by the AIM molecular graph (Figure 1b). Such a complex could be the origin of vinyl halides **3**.

In light of these results, we postulate the overall mechanism outlined in Scheme 2 that considers two alternative pathways depending on the nature of the acetylene derivative. 1,5-Dihalo-1,4-pentadienes **6** formed only when a stoichiometric amount of FeX_3 was used. Region A outlines a proposal similar to that put forward by Kabalka et al.^{18b} in which the formation of **10** is supported by both the above-described calculation and the fact that the treatment of aliphatic terminal acetylenes with FeCl_3 led to 2-chloro-1-alkenes **3** or methyl ketones **4**. The formation of the (*E*)-trisubstituted α,β -unsaturated ketones **7** occurs even with use of a minuscule amount of the iron halide (≈ 0.1 equiv). The catalytic cycle outlined in region B invoked the formation of the oxetene **11**.²⁹ Any attempt to control the final balance of the obtained products under experimental conditions (temperature, addition order, solvent, etc.) proved fruitless. Thus the tendency to follow either the catalytic (B) or the stoichiometric pathway (A) depends basically on the substitution pattern of the used alkyne **1**.

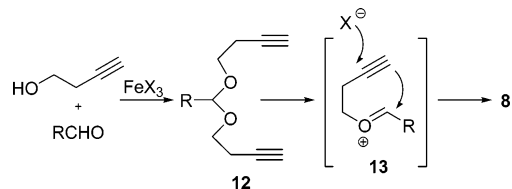
When a hydroxy group is located in the β -position relative to a carbon–carbon unsaturation, FeX_3 acts essentially as a Lewis acid (Scheme 3). Thus, when homopropargylic alcohol is used, the FeX_3 -mediated ionization of acetal **12** generates the oxonium ion **13** that is intramolecularly trapped by the carbon–carbon unsaturation with concomitant attack of the halide (Scheme 3). A similar mechanism may explain the Prins cyclization when homoallylic alcohols are used leading to halotetrahydropyran.

Conclusions. In summary, iron(III) halides proved to be excellent catalysts for the coupling of acetylenes and aldehydes. Thus, when terminal nonoxygenated acetylenes are used, the main process is the stereoselective reductive coupling leading to (*E,Z*)-1,5-dihalo-1,4-dienes as the major product. However, nonterminal aromatic alkynes led to trisubstituted (*E*)- α,β -unsaturated ketones

SCHEME 2. Plausible Mechanism for the Coupling of Nonoxygenated Alkynes and Aldehydes Catalyzed by Iron(III) Halides



SCHEME 3. Lewis Acid Role of FeX_3 in the Coupling of Homopropargylic Alcohol and Aldehydes



as the sole product even under catalytic conditions. The reaction with homopropargylic alcohol permits access to 2-alkyl-4-halo-5,6-dihydro-2H-pyrans in good yields. In addition, FeX_3 efficiently catalyzes the Prins coupling between homoallylic alcohol and aldehydes to lead to *cis*-4-halo-2-alkyl tetrahydropyrans. Experiments with terminal acetylenes and ab initio calculations are the base of a unified mechanism that rationalizes those reactions in which the complex formation between the alkyne and the iron(III) halides is the activating step. The Lewis acid role of such halides appears to be the key behavior in the coupling when homoallylic and homopropargylic alcohols are used. Further synthetic applications of the methodology described herein directed to the synthesis of some natural products are currently under way.

Experimental Section

Material and Methods. ^1H NMR spectra were recorded at 400 and 500 MHz, and ^{13}C NMR spectra were recorded at 100 MHz, VTU 300.0 K. Chemical shifts were reported in parts per million. The residual solvent peak was used as an internal reference.

For analytical and preparative thin-layer chromatography, silica gel ready-foils and glass-backed plates (1 mm) were used,

(29) (a) Martino, P. C.; Shevlin, P. B. *J. Am. Chem. Soc.* **1980**, *102*, 5429–5430. (b) Friedrich, L. E.; Lam, P. Y.-S. *J. Org. Chem.* **1981**, *46*, 306–311.

respectively, being developed with 254 nm UV light and/or sprayed with a solution of vanillin in EtOH:H₂SO₄:AcOH (15:1:1.3) and heated at 140 °C. Column chromatography was performed with silica gel (0.015–0.04 mm) and *n*-hexane/EtOAc solvent systems. All reagents were obtained from commercial sources and used without further purification. Solvents were dried and distilled before use. All reactions were performed under a dry nitrogen atmosphere.

General Procedure for the Transformation of Non-oxygenated Terminal Acetylenes into 2-Halo-1-alkenes.

Preparation of 2-Chloro-1-octene (3, R¹ = C₆H₁₃-*n*, X = Cl). To a stirred solution of 1-octyne (0.1 mL, 0.70 mmol) and acetic acid (0.05 mL, 0.70 mmol) in dry CH₂Cl₂ was added anhydrous FeCl₃ (110 mg, 0.70 mmol) in one portion at room temperature. The mixture was stirred until the solution became dark brown (ca. 2 min). Then water was added to the mixture and extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (*n*-hexane/EtOAc, 99/1) to provide **3** (R¹ = C₆H₁₃-*n*, X = Cl) (90 mg, 88%): ¹H NMR (CDCl₃) δ 0.90 (m, 3H), 1.30–1.55 (m, 10H), 2.34 (t, *J* = 7.4 Hz, 2H), 5.12 (d, *J* = 7.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.0 (q), 22.5 (t), 27.3 (t), 28.3 (t), 31.4 (t), 39.1 (t), 111.6 (t), 143.2 (s); IR (CHCl₃) (cm⁻¹) 2927.6, 1715.8; MS *m/z* (rel intensity) 303 (100), 147 (M)⁺ (8), 55 (57); Anal. Calcd for C₈H₁₅Cl: C, 65.52; H, 10.31. Found: C, 65.61; H, 9.90.

General Procedure for the Transformation of Non-oxygenated Terminal Acetylenes into Methyl Ketones.

Preparation of Octan-2-one (4, R¹ = C₆H₁₃-*n*). To a stirred solution of 1-octyne (0.1 mL, 0.70 mmol) and camphorsulfonic acid (158 mg, 0.7 mmol) in dry CH₂Cl₂ was added anhydrous FeBr₃ (200 mg, 0.70 mmol) in one portion at room temperature. The mixture was stirred until the solution became dark brown (ca. 2 min). Then water was added to the mixture and extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate and the solvent removed under reduced pressure. The crude was purified by flash column chromatography (*n*-hexane/EtOAc solvent systems) to provide **4** (R¹ = C₆H₁₃-*n*) (72 mg, 80%): ¹H NMR (CDCl₃) δ 0.81 (m, 3H), 1.23 (m, 6 H), 1.50 (m, 2H), 2.08 (s, 3H), 2.37 (t, *J* = 7.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.0 (q), 22.5 (t), 23.7 (t), 28.9 (t), 29.7 (q), 31.5 (t), 43.7 (t), 209.1 (s); IR (CHCl₃) (cm⁻¹) 2928.1, 1716.3; MS *m/z* (rel intensity) 128 (M)⁺ (15), 71 (25), 58 (100). Anal. Calcd for C₈H₁₆O: C, 74.94; H, 12.58. Found: C, 74.65; H, 12.20.

Typical Experimental Procedure for the Synthesis of (E,Z)-1,5-Dihalo-1,4-dienes. Preparation of (1Z,4E)-1,5-Dichloro-3-isobutyl-1,5-diphenylpenta-1,4-diene (6, R¹ = Ph, R² = H, R³ = C₄H₉-*i*, X = Cl).

To a stirred solution of phenylacetylene (0.2 mL, 1.90 mmol) and isovaleraldehyde (0.1 mL, 0.90 mmol) in dry CH₂Cl₂ was added anhydrous FeCl₃ (153 mg, 0.9 mmol) in one portion at room temperature. The mixture was stirred until TLC showed complete conversion of

the alkyne (ca. 5 min). Then water was added to the mixture and extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (*n*-hexane/EtOAc solvent systems) to provide **6** (R¹ = Ph, R² = H, R³ = C₄H₉-*i*, X = Cl) (217 mg, 70%): ¹H NMR (CDCl₃) δ 0.76 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 1.40 (t, *J* = 7.4 Hz, 2H), 1.59 (m, 1H), 3.72 (quint, *J* = 8.6 Hz, 1H), 5.88 (d, *J* = 10.4 Hz, 1H), 6.0 (d, *J* = 8.2 Hz, 1H), 7.40 (m, 8H), 7.59 (dd, *J* = 1.4, 7.7 Hz, 2H); ¹³C NMR (CDCl₃) δ 22.3 (q), 22.8 (q), 35.6 (d), 39.2 (d), 44.7 (t), 126.5 (d), 128.2 (d), 128.3 (d), 128.6 (d), 128.7 (d), 128.8 (d), 129.1 (d), 131.2 (d), 131.8 (s), 132.4 (s), 137.1 (s), 138.0 (s); IR (CHCl₃) (cm⁻¹) 3058.3, 2955.9, 1445.0, 759.1, 694.2; MS *m/z* (rel intensity) 344 (M - 1)⁺ (3), 287 (M - C₄H₉)⁺ (100), 215 (56). Anal. Calcd for C₂₁H₂₂Cl₂: C, 73.04; H, 6.42. Found: C, 73.07; H, 6.69.

Typical Experimental Procedure for the Synthesis of Aromatic α,β-Unsaturated Ketones. Preparation of (E)-2,5-Dimethyl-1-phenylhex-2-en-1-one (7, R¹ = Ph, R² = CH₃, R³ = C₄H₉-*i*).

To a stirred solution of 1-phenyl-1-propyne (0.1 mL, 0.80 mmol) and isovaleraldehyde (0.1 mL, 0.80 mmol) in dry CH₂Cl₂ was added anhydrous FeCl₃ (130 mg, 0.8 mmol) in one portion at room temperature. The mixture was stirred until TLC showed complete conversion of the alkyne (ca. 5 min). Then water was added to the mixture and extracted with CH₂Cl₂. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (*n*-hexane/EtOAc solvent systems) to provide **7** (R¹ = Ph, R² = H, R³ = C₄H₉-*i*) (129 mg, 80%): ¹H NMR (CDCl₃) δ 0.92 (d, *J* = 6.7 Hz, 6H), 1.74 (sep, *J* = 6.7 Hz, 1H), 1.96 (s, 3H), 2.17 (t, *J* = 7.0 Hz, 2H), 6.3 (t, *J* = 7.4 Hz, 1H), 7.44 (m, 3H), 7.61 (d, *J* = 8.1 Hz, 2H); ¹³C NMR (CDCl₃) δ 12.6 (q), 22.5 (q), 28.4 (d), 38.2 (t), 128.0 (d), 129.2 (d), 131.3 (d), 137.0 (s), 138.8 (s), 145.7 (d), 199.0 (s); IR (CHCl₃) (cm⁻¹) 2957.4, 1649.5, 1285.1, 706.4; MS *m/z* (rel intensity) 202 (M)⁺ (33), 105 (100), 77 (76). Anal. Calcd. for C₁₄H₁₈O: C, 83.20; H, 8.97. Found: C, 83.11; H, 9.02.

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Supporting Information Available: ¹H NMR and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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