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Catalysis by Means of Fe-Based Lewis Acids

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Abstract The interest and use of iron salts as catalysts in organic chemistry has shown an exponential growth in the past years. There has been an increasing demand for environmentally friendly and sustainable chemical methods, distinguished by the low cost and environmentally benign character of the iron salts used. This chapter focuses on reactions in which iron salts produce activation on unsaturated functional groups provided by the Lewis-acid character of these salts.

Keywords Alkene · Alkyne · Catalysts · Fe · Lewis acids

Contents

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Alk	Alkyl
Ar	Aryl
bmim	Butylmethylimidazolium
Bn	Benzyl
cat	Catalytic
DCE	1,2-Dichloroethane
DMF	*N*,*N*-dimethylformamide
equiv	Equivalent(s)
Et	Ethyl
h	Hour(s)
HSAB	Hard and soft acids and bases
i-Bu	*iso*-Butyl
i-Pr	Isopropyl
Me	Methyl
min	Minute(s)
mol	Mole(s)
MS	Molecular sieves
NIS	*N*-iodosuccinimide
n-Pr	*n*-Propyl
Ph	Phenyl
rt	Room temperature
t-Bu	*tert*-Butyl
TfO	Trifloromethanesulfonate
TfOH	Trifluoromethane sulfonic acid
TMS	Trimethylsilyl
Ts	4-Toluensulfonyl

1 Introduction

Iron is the second most abundant metal on earth. It is a group 8 and period 4 element with [Ar] $3d^6 4s^2$ as electronic configuration. Iron as a metal is rarely found because it oxidizes readily in the presence of oxygen and moisture. Hence, it forms salts in its preferred oxidation state +2 and +3.

Iron halides are the most common of these salts [more specifically as a chloride: iron(II) chloride (ferrous chloride or $FeCl_2$) and iron(III) chloride (ferric chloride or $FeCl_3$)].

In 1963, Pearson introduced the hard and soft acids and bases (HSAB) principle, ordering Fe^{3+} as hard acid and Fe^{2+} as borderline acid [1]. Although the HSAB theory is qualitative, it has found widespread use in chemistry.[1] However, as a qualitative description it does not allow for the quantification of hardness or softness. Several attempts have been made to quantify hardness–softness on a normalized scale associated with physical properties, quantum mechanical principles using perturbation molecular orbital theory, and density functional theory [2–6]. According to this, Parr and Pearson obtained values of η (the absolute hardness) for molecules and ions relative to Al^{3+} as the metal with the highest value of 45.8 [2]. The expected increased hardness with increased oxidation state can be seen by comparing Fe^0 ($\eta = 3.9$), Fe^{2+} ($\eta = 7.2$), and Fe^{3+} ($\eta = 13.1$). Hence, Fe^0 is a soft Lewis acid. It should be noted that when transition-metal atoms act as Lewis acids it is usually in an excited valence state. Accordingly, iron atoms are $3d^8$ and not $3d^6\ 4s^2$ when acting as a Lewis acid. A correction of the η value for this effect will lower the corresponding numbers. Furthermore, the addition of three chloride ions to Fe^{3+} lowers the hardness considerably since the η value of Fe^{3+} must be considered as a hypothetical upper limit in discussing the Lewis-acid catalyzed chemistry of iron salts. As a matter of fact, any Lewis base lowers the η value of an ionic acid.

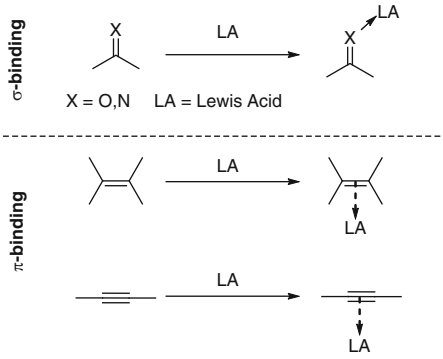
Despite these studies, the effect of Lewis acidity strongly depends on the type of the reaction that is promoted or catalyzed. In 1972, Olah et al. classified Lewis acids in Friedel–Crafts alkylation reactions [7]. Iron(III) and iron(II) chloride were classified as moderately active and weak, respectively. In 2000, Kobayashi et al. reported a further classification of Lewis acids based on the activity and selectivity in addition reactions of a silyl enolate to an aldehyde and an aldimine [8]. $FeCl_3$ was classified in the active group as aldimine selective, while $FeCl_2$ kept the same type of selectivity but in the weak group. According to Olah, $SnCl_4$ and $FeCl_3$ have strong affinities for Cl atoms (compared with $AlCl_3$) especially in carbonyl-containing solvents [9]. In addition, Sn^{4+} and Fe^{3+} are considered softer than Al^{3+}, although they are still classified as hard acids [10].

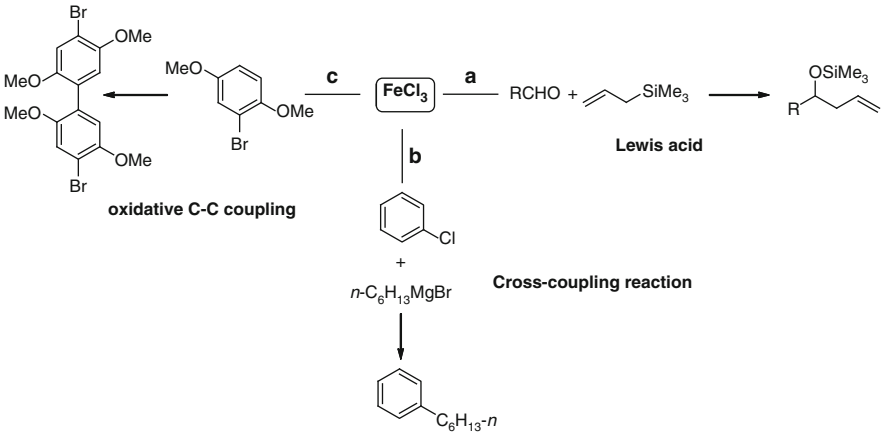
Apart from the hardness and softness, two reactivity-related features need to be pointed out. First, iron salts (like most transition metal salts) can operate as bifunctional Lewis acids activating either (or both) carbon–carbon multiple bonds via π-binding or (and) heteroatoms via σ-complexes. However, a lower oxidation state of the catalyst increases the relative strength of coordination to the carbon–carbon multiple bonds (Scheme 1).

Second, apart from a different mode of activation, different modes of reactivity are observed. Hence, for $FeCl_3$ reactions like oxidative C–C but also nonoxidative C–C couplings are as well observed as bond formation via Lewis-acid activation (Scheme 2) [11–16]. Depending on the reaction type, one or more mechanistic pathways are accessible at the same time, which makes it difficult to shed light into mechanistic details.

[1] Once acids and bases have been classified as hard or soft, a simple rule of the HSAB principle can be given: hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases.

Scheme 1 σ- and π-binding of bifunctional Lewis acid





Scheme 2 Iron can work as Lewis acid, organometallic and oxidation catalyst

Since aromatic substitutions, aliphatic substitutions, additions and conjugate additions to carbonyl compounds, cycloadditions, and ring expansion reactions catalyzed by Fe salts have recently been summarized [17], this section will focus on reactions in which iron salts produce a critical activation on unsaturated functional groups provided by the Lewis-acid character of these salts.

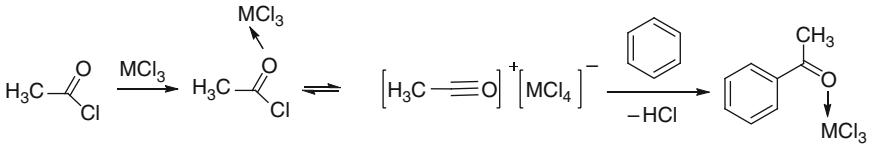
2 C–C Bond Formation

2.1 Aromatic C–C Bond Formations

In the early 1970s, Olah et al. investigated the Friedel–Crafts benzylation of benzene and toluene with benzyl chloride derivatives in the presence of various

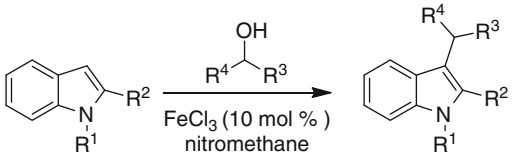
Lewis acids [7]. Friedel–Crafts catalysts were classified according to their activity in four categories: A, very active catalyst which also bring about intra- and intermolecular isomerizations; B_1 and B_2, moderately active and weak catalysts, respectively, which bring about no isomerization; and C, very weak or inactive catalysts. $FeCl_3$ was classified in the moderately active group B_1 providing high yields of benzylation with no extensive accompanying side reactions, whereas $FeCl_2$ was classified as a weak catalysts (group B_2) giving low yields of benzylation with no side reactions.

The toxic and/or hazardous properties of many solvents, notably chlorinated hydrocarbons, are making their use unadvisable, thus promoting the quest for novel reaction media. Since the pioneering work of Seddon [18], ionic liquids have emerged as a new class of stable, inert solvents with unique properties. Friedel–Crafts acetylations have been reported by Horváth using ionic liquids prepared from $FeCl_3$ and 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl) [19]. This group has shown that the mechanism of the Friedel–Crafts acetylation of benzene in the presence of MCl_3 (M = Al or Fe) is exactly the same in [bmim]Cl as in 1,2-dichloroethane (Scheme 3).



Scheme 3 Proposed mechanism of the Friedel–Crafts acetylation in the presence of MCl_3 (M = Al or Fe)

Furthermore, Jana et al. developed a $FeCl_3$-catalyzed C3-selective Friedel–Crafts alkylation of indoles, using allylic, benzylic, and propargylic alcohols in nitromethane as solvent at room temperature. This method can also be used for the alkylation of pyrrole (Scheme 4). The reactions were complete within 2–3 h without the need of an inert gas atmosphere leading to the C-3-substitution product exclusively in moderate to good yields [20].

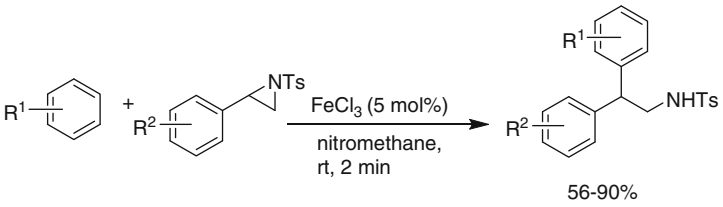


R^1 = H, Me, Ts
R^2 = Me
R^3 and R^4 = allylic, benzylic propargylic, and aromatic

Scheme 4 $FeCl_3$ catalyzed Friedel–Crafts alkylations of indoles with alcohols

The $FeCl_3$-catalyzed Friedel–Crafts reactions of electron-rich arenes with imines or aziridines provide a facile and convenient route for the synthesis of β-aryl

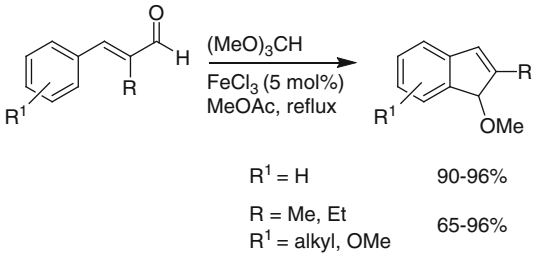
amines. Wu et al. found that the reactions of imines were highly substrate-dependent generating mono- or double-substitution products. The reaction of arenes with aziridines, however, led to a regioselective formation of the desired ring-opening products in moderate to good yields (Scheme 5) [21].



Scheme 5 $FeCl_3$ as efficient catalyst for reactions of electron-rich arenes with imines or aziridines

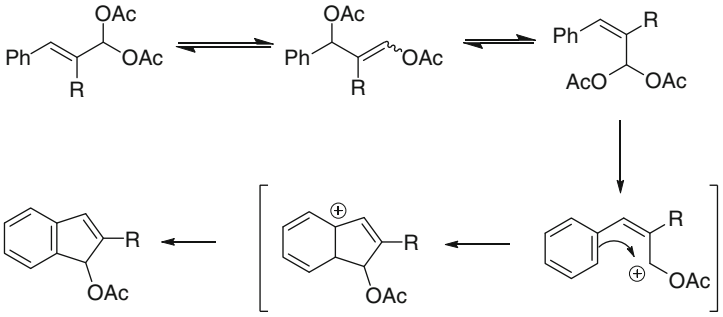
In 2007, Womack et al. published the conversion of 2-alkylcinnamyldehydes to 2-alkylindanones via a catalytic intramolecular Friedel–Crafts reaction. In the presence of 5–10 mol% $FeCl_3$ different in situ generated (*E*)-2-alkylcinnamaldehydes-derived dimethyl acetals cyclized to 1-methoxy-2-alkyl-*1H*-indenes in good to high yields (Scheme 6) [22]. The transformation corresponds to a formal intramolecular Friedel–Crafts acylation which is achieved with catalytic quantities of Lewis acid. This result is in strong contrast to traditional Friedel–Crafts acylations which require stoichiometric amounts of Lewis acid.

Scheme 6 Iron(III)-catalyzed conversion of 2-alkylcinnamaldehydes to 2-alkylindanones via a catalytic intramolecular Friedel–Craft reaction



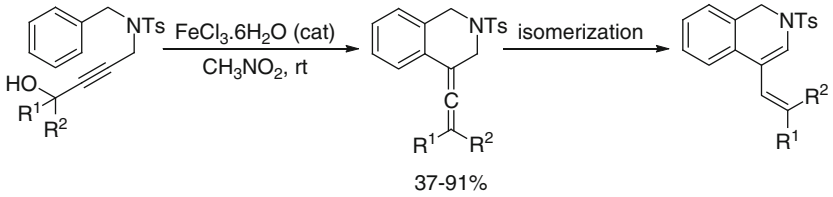
Womack's group improved the procedure using Ac_2O at room temperature in the presence of 4–6 mol% $FeCl_3$. The in situ generated acylals of 2-alkylcinnamaldehydes undergo an intramolecular Friedel–Crafts reaction to yield indenyl acetates at rt in the presence of catalytic amounts of Fe(III) (Scheme 7) [23]. Based on experimental results, the authors proposed an intramolecular Friedel–Crafts reaction in which an allylic oxocarbenium ion, derived from the in situ generated acylal, alkylates the phenyl group to form the indane skeleton (Scheme 7). A potential mechanism would be an allylic rearrangement of the acylal to a 1,3-diacetoxy-1-propene intermediate. This intermediate could regenerate either the *E*- or *Z*-acylal, resulting in isomerization of the double bond, or it could lead directly to the cationic species needed for the intramolecular Friedel–Crafts reaction.

As described above, propargylic alcohols can serve as electrophilic alkyl equivalents in intermolecular Friedel–Crafts reactions. However, the related intramolecular



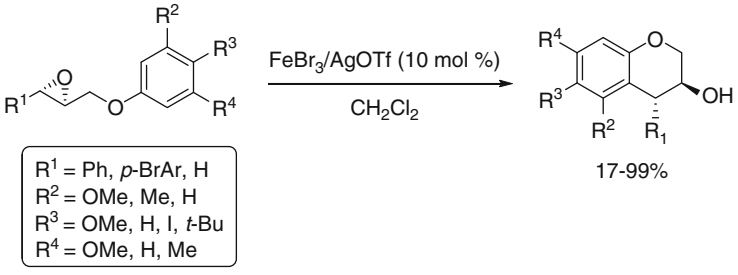
Scheme 7 Proposed mechanism to iron(III)-catalyzed indenyl acetate formation

Friedel–Crafts reaction remains unexplored, possibly due to the difficulty of the cycloalkyne formation. A mild, versatile, and efficient method for the one-step synthesis of substituted dihydro- and tetrahydroisoquinolines has been developed by the $FeCl_3 \cdot 6H_2O$-catalyzed intramolecular allenylation/cyclization reaction of benzylamino-substituted propargylic alcohols, representing the first example of the intramolecular Friedel–Crafts reaction of propargylic alcohols (Scheme 8) [24, 25]. $FeCl_3$, $InCl_3$, and $Yb(OTf)_3$ also exhibit good catalytic activity for the reaction.



Scheme 8 One-step synthesis of substituted dihydro- and tetrahydroisoquinolines by $FeCl_3 \cdot 6H_2O$-catalyzed intramolecular Friedel–Crafts

An interesting intramolecular Friedel–Crafts-type cyclization was developed by Pericàs et al. Thus, aryl glycidyl ethers reacted to 3-chromanols as the only reaction product when treated with a catalytic amount of $FeBr_3$ in the presence of AgOTf in CH_2Cl_2 at room temperature (Scheme 9) [26]. The addition of a silver salt proved to

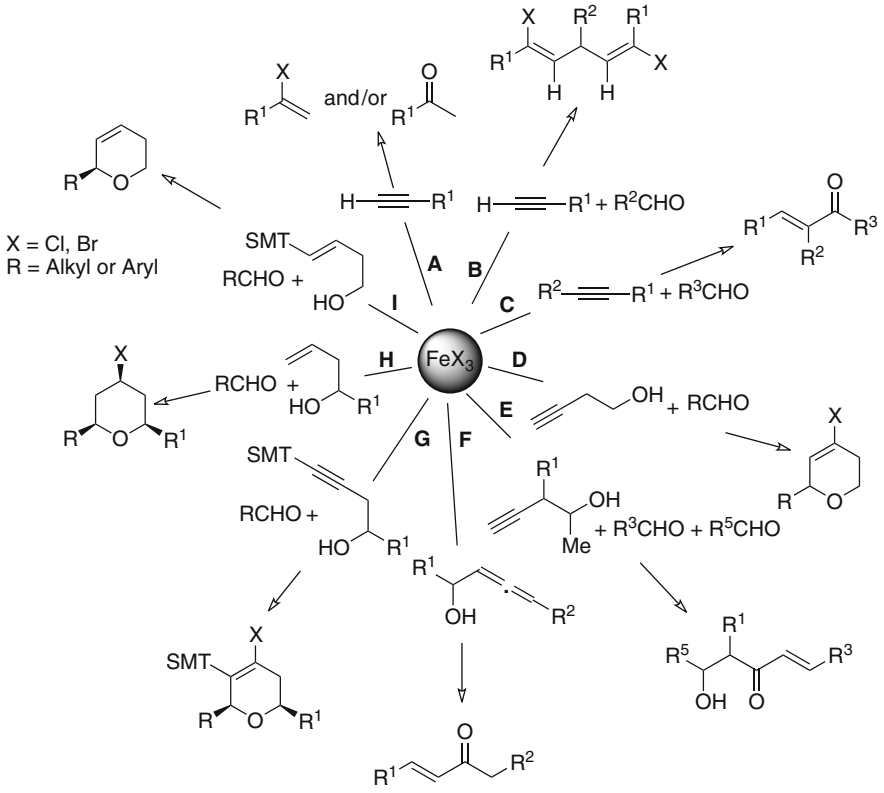


Scheme 9 Iron(III) bromide-mediated cyclization of aryl glycidyl ethers to 3-chromanols

be beneficial to both yield and reaction times most likely due to an activation of the $FeBr_3$ by abstracting a bromide from the iron center leading to a highly active Fe-based Lewis-acidic species.

2.2 Aliphatic C–C Bond Formation

Martín, Padrón, and coworkers have reported on the scope and limitations of the use of iron(III) halides as effective catalysts in the coupling of alkenes or acetylenes with aldehydes to achieve a wide variety of useful synthetic transformations. All these reactions are shown in Scheme 10, which serves as a guide through the aliphatic C–C bond formation section [27].



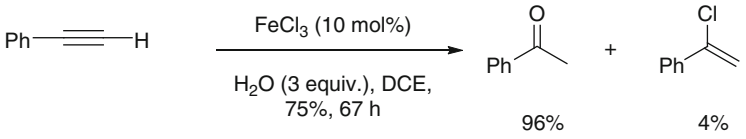
Scheme 10 Reactions of FeX_3 with different unsaturated substrates

2.2.1 Aliphatic C–C Bond Formation Using Acetylenes

Use of Nonfunctionalized Acetylenes

Terminal aliphatic alkynes (e.g., 1-octyne) react with iron(III) halides ($FeCl_3$ and $FeBr_3$) to give the corresponding 2-halovinyl derivatives (route A, Scheme 10). The moderate yields were remarkably improved upon addition of stoichiometric amounts of carboxylic acids.

On the basis of these results and Damiano's report [28], Darcel et al. described an iron-catalyzed hydration of terminal alkynes using catalytic amounts of iron(III) chloride (10 mol%). The reaction selectively leads to the corresponding methyl ketone derivatives (Scheme 11) [29]. Iron(II) species such as $FeCl_2$ or $Fe(OAc)_2$ were not able to promote the reaction, the starting phenylacetylene remained unchanged after several days at 75°C.



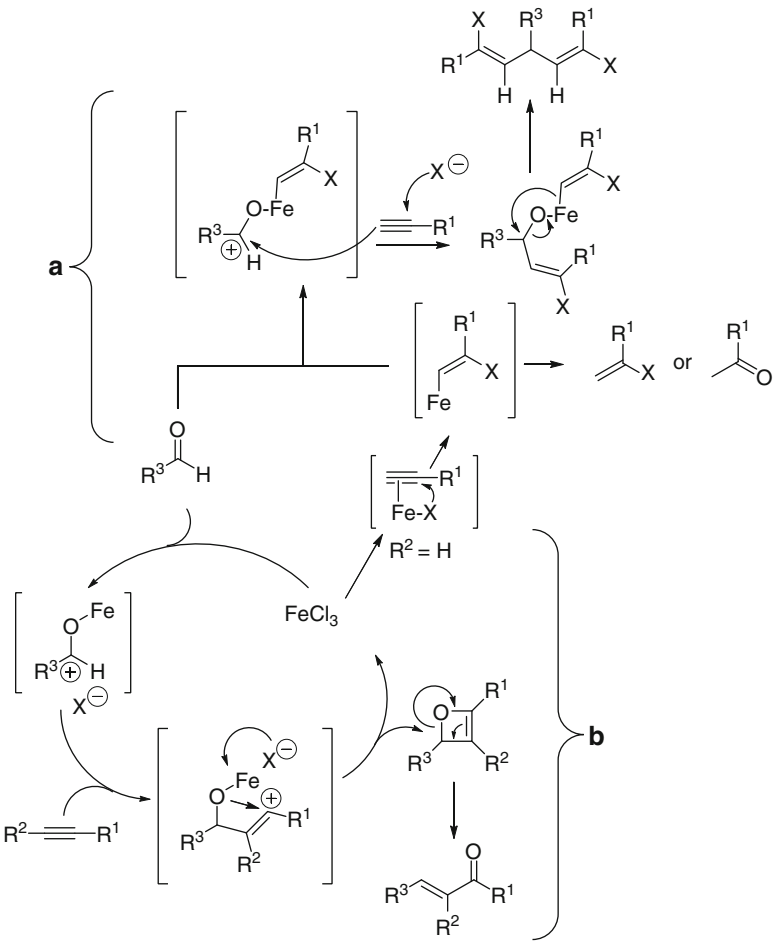
Scheme 11 Iron chloride-catalyzed hydration of terminal alkynes

The influence of iron(III) salts on coupling reactions of alkynes and aldehydes (Scheme 10, routes B and C) was also explored. In these routes, a new stereoselective coupling of alkynes and aldehydes was unmasked, which led to (*E,Z*)-1,5-dihalo-1,4-dienes (route B, Scheme 10) and/or (*E*)-α,β-unsaturated ketones (route C, Scheme 10) [27].

Both aliphatic and aromatic terminal alkynes reacted with aliphatic aldehydes giving exclusively a mixture of (*E,Z*)-1,5-dihalo-1,4-dienes and disubstituted (*E*)-α,β-unsaturated ketones, the former being the major products in all cases. When nonterminal aromatic acetylenes were used, the trisubstituted (*E*)-α,β-unsaturated ketones were the exclusive compounds obtained. The procedure was not valid for aliphatic and unsaturated alkynes. However, the catalytic system was found to be compatible with alcohols and their corresponding acetates although limited yields were obtained.

Experiments with terminal acetylenes, isolation of an intermediate acetal, alkyne hydratation studies, and ab initio calculations provide substantiation of a unified mechanism that rationalizes the reactions in which the complex formation between the alkyne and the iron(III) halides is the activating step (Scheme 12) [27].

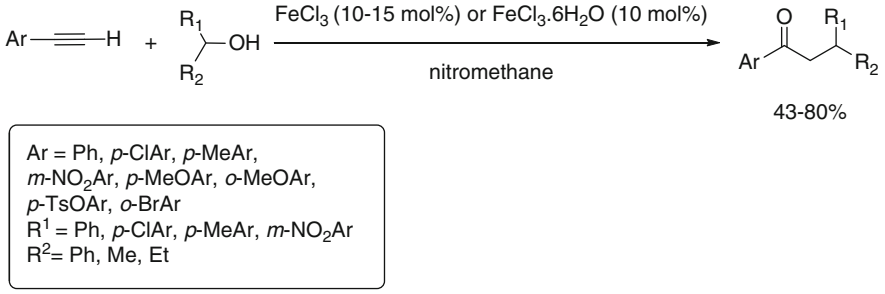
The above-postulated overall mechanism considers two alternative pathways depending on the nature of the acetylene derivative. Region **A** outlines a proposal in which the formation of the σ-complex intermediate is supported by the fact that the treatment of aliphatic terminal acetylenes with $FeCl_3$ led to 2-chloro-1-alkenes or methyl ketones (Scheme 12). The catalytic cycle outlined in region **B** invoked the formation of the oxetene. Any attempt to control the final balance of the obtained



Scheme 12 Lewis acid role of FeX_3 in the coupling of acetylenes and aldehydes

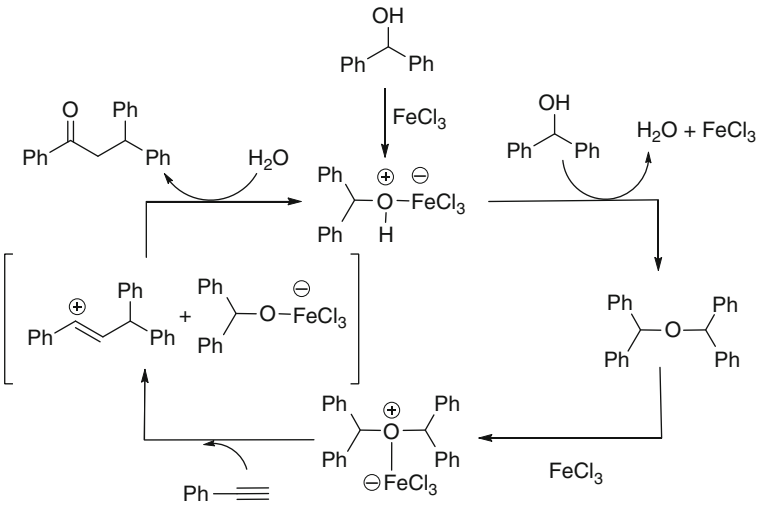
products under experimental conditions (temperature, addition order, solvent, etc.) proved fruitless (Scheme 12). Thus, the tendency to follow either the catalytic (**B**) or the stoichiometric pathway (**A**) depends basically on the substitution pattern of the alkyne used.

A direct C–C bond formation by utilization of benzyl alcohols as alkylating agent is very attractive as it would be environmentally benign, water being the only by-product. Recently, Jana and coworkers described $FeCl_3$-catalyzed, sequential C–C and C–O bond-forming reactions of benzylic alcohols with aryl acetylenes for the regioselective synthesis of aryl ketones (Scheme 13) [30]. The reaction provides a simple method for the synthesis of substituted arylketones under mild conditions. Electron-rich alkynes reacted more efficiently and gave higher yields than did the neutral or electron-deficient alkynes.



Scheme 13 Iron(III)-catalyzed addition of benzylic alcohols to aryl alkynes

$FeCl_3 \cdot 6H_2O$ turned out to be the catalyst of choice for this reaction, since the presence of water improved the yield. However, high yields of the desired ketones were obtained for electron-rich alkynes with anhydrous $FeCl_3$ at room temperature. Alcohols that are sensitive to acid-catalyzed dehydration were also tolerated under the present conditions (R^1 = Me or Et). Based upon experimental observations a mechanism for this reaction was proposed (Scheme 14).

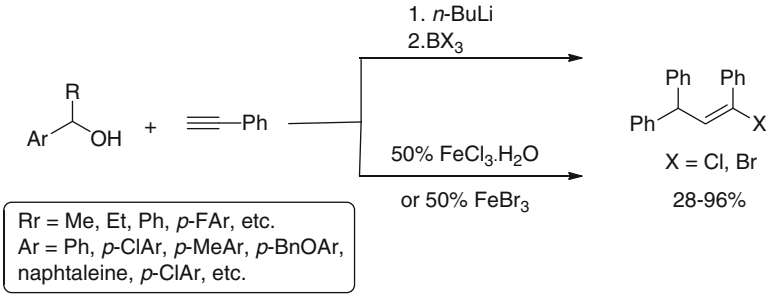


Scheme 14 Probable mechanism of iron(III)-catalyzed addition of benzylic alcohols to aryl alkynes

It was previously observed that with a catalytic amount of $FeCl_3$, benzylic alcohols were rapidly converted to dimeric ethers by eliminating water (Scheme 14). In the presence of an alkyne this ether is polarized by $FeCl_3$ and generates an incipient benzylic carbocation. The nucleophilic attack of the alkyne moiety onto the resulting benzyl carbocation generated a stable alkenyl cation, which suffer the nucleophilic attack of water (generated in the process and/or from the hydrated

$FeCl_3$ whenever used). To confirm the formation of the ether intermediate a separate experiment was performed between dimeric ether and phenylacetylene, observing that the dimeric ether reacted smoothly with phenylacetylene in the presence of $FeCl_3{\cdot}6H_2O$ to produce the desired ketone in a similar yield (≈42%) to that obtained when starting from the benzylic alcohol.

In 2009, Liu and coworkers accomplished an efficient method for preparing alkenyl halides via direct C–C bond formation of benzylic alcohols and aryl alkynes in CH_2Cl_2 by using 50 mol% of $FeCl_3{\cdot}6H_2O$ or 50 mol% $FeBr_3$ modifying the reaction conditions described by Jana. This method proved to be an excellent alternative to established procedures involving an excess boron trihalides and stoichiometric amounts of *n*-BuLi (Scheme 15) [31].



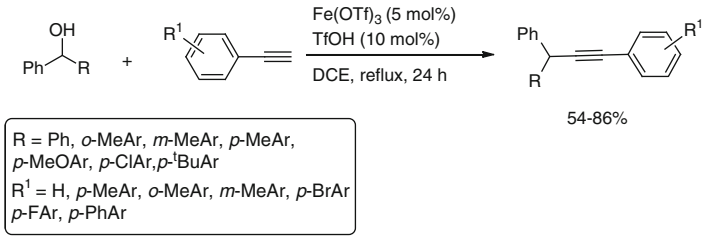
Scheme 15 Iron(III)-mediated synthesis of alkenyl halides via direct C–C bond formation of benzylic alcohols and aryl alkynes

Based on Jana's methodology, Liu increased the amount of $FeCl_3{\cdot}6H_2O$ (from 15 to 50 mol%) and changed the solvent (CH_2Cl_2 instead of CH_3NO_2). The desired alkenyl chloride was obtained in 82% yield using 40 mol% of $FeCl_3{\cdot}6H_2O$ at 50°C in CH_2Cl_2. Increase of the Lewis-acid dosage to 50 and 60 mol% gave 85 and 80% isolated yields of the products, respectively. The aryl alkynes with electron-donating groups gave higher yields of the desired products than those bearing electron-withdrawing groups, such as fluorine. Heteroaryl alkynes such as 3-ethynyl pyridine and alkyl alkynes were inactive in this reaction. Benzylic alcohols with carboxyl groups and alkyl alcohols remained inactive.

The plausible mechanism is based on the proposal by Jana and coworkers (Scheme 14). In this case, the *sp*-hybridized vinyl cation can be attacked by halide, instead of water, to give the *E*/*Z* isomer of the alkenyl halide. Compared with the systems using stoichiometric Lewis acid and strong base to prepare substituted alkenyl halides, the present method would provide an excellent alternative due to the environmentally benign system and atom efficiency.

Related to these strategies, $Fe(OTf)_3$/TfOH cocatalyzed the coupling reaction of terminal alkynes with benzylic alcohols in the absence of base by means of a sp–sp^3 C–C bond formation (Scheme 16) [32].

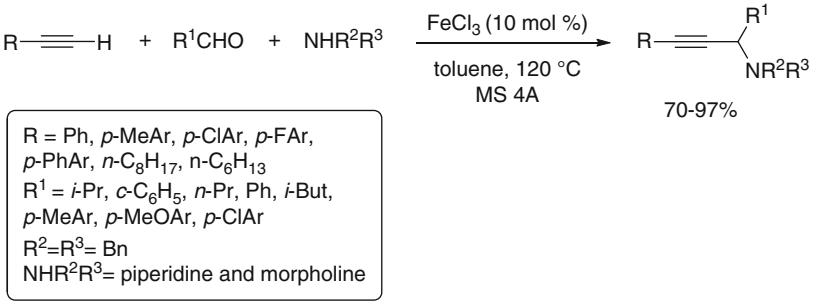
Although TfOH can also catalyze this reaction, the collaboration of $Fe(OTf)_3$ and TfOH was found to give higher yields and less side-reactions. The reaction was



Scheme 16 sp–sp^3 C–C bond formation via $Fe(OTf)_3$/TfOH-cocatalyzed coupling reaction of terminal aryl alkynes with benzylic alcohols

strongly influenced by the nature of the solvent. Polar solvents (DMF and $MeNO_2$) were not suitable for this transformation.

The coupling reactions of alkynes and aldehydes catalyzed by iron(III) salts have been discussed above (Scheme 10, routes B and C). The three-component coupling of aldehydes, alkynes, and amines is equivalent to the coupling reaction between alkynes and imines. Wang et al. reported such a three-component coupling catalyzed by $FeCl_3$ in the absence of any ligand (Scheme 17) [33].

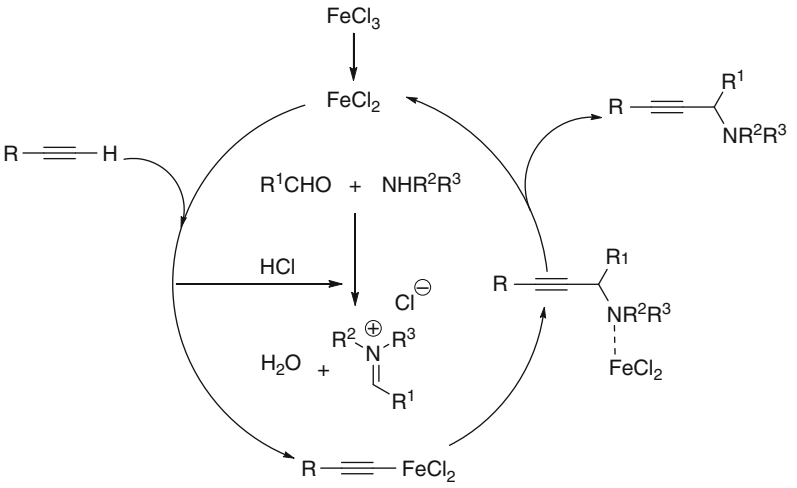


Scheme 17 Iron-catalyzed three-component coupling reactions of aldehydes, terminal alkynes, and amines

Several iron sources were screened in a model reaction of phenylacetylene, *iso*-butyraldehyde, and dibenzylamine. The three-component coupling reaction could be catalyzed by Fe(III) salts, Fe(III) oxide, or Fe(II) salts, such as $FeCl_3 \cdot 6H_2O$, $Fe(NO_3) \cdot 9H_2O$, $Fe_2(SO_4)_3$, Fe_2O_3, $Fe(acac)_3$, $FeCl_3$, and $FeCl_2$ in the absence of any ligand in toluene. The most effective catalyst for the reaction was anhydrous $FeCl_3$. In general, iron-catalyzed carbon–carbon and carbon–heteroatom bond formation reactions could be enhanced by a suitable ligand containing nitrogen or oxygen atoms. However, *N*-ligands and *O*-ligands did not assist in this three-component coupling reaction.

To check the scope of this coupling reaction, a study with different combinations of aldehydes, amines, and terminal alkynes was performed. Aromatic alkynes turned out to be more reactive than aliphatic ones. This study included aliphatic

and aromatic aldehydes and a variety of amines (cyclic, heterocyclic, and acyclic). However, aromatic secondary amines such as *N*-benzylaniline and *N*-methylaniline were less reactive and only trace amounts of the desired propargylamines were isolated. A possible mechanism is shown in Scheme 18.

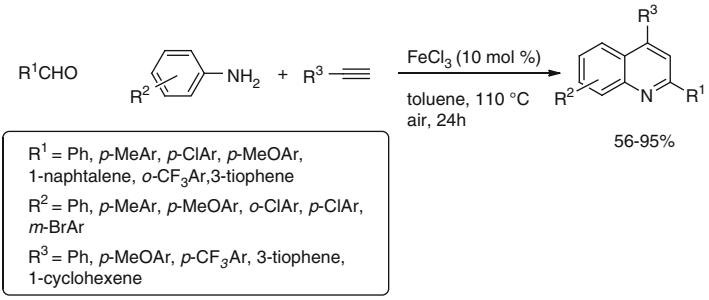


Scheme 18 Plausible mechanism of iron-catalyzed three-component coupling of aldehyde, alkyne, and amine

The precatalyst $FeCl_3$ is presumably reduced initially to a low-valent Fe(II) oxidation state. When $FeCl_2$ was used instead of $FeCl_3$ under the optimized reaction conditions, the corresponding propargylamine was isolated in 91% yield and a comparable catalytic activity for Fe(II) and Fe(III) was observed. The authors hypothesized that the generated HCl accelerates the formation of the immonium salt from the aldehyde and the secondary amines. $FeCl_3$ as a Lewis acid increases the electrophilic character of the starting aldehyde while stabilizing the immonium salt. The resulting Fe(III) alkynylate complex subsequently reacts with the immonium salt generated in situ to give the corresponding propargylamine and regenerates the Fe(II) catalyst for further reactions (Scheme 18).

Tu found that when aniline was used instead of the secondary amine under otherwise identical conditions 2,4-diphenyl-substituted quinoline was formed in 56% yield. Phenylacetylene and aniline were initially used as model substrates for exploring the aldehyde scope. With aromatic aldehydes the reactions proceeded smoothly to give the corresponding quinolines in moderate to good yields. A heteroaromatic aldehyde is also compatible with this transformation and the expected product was afforded in 83% yield. However, when aliphatic aldehydes were subjected to the reaction, the desired product was obtained in low yield (Scheme 19) [34].

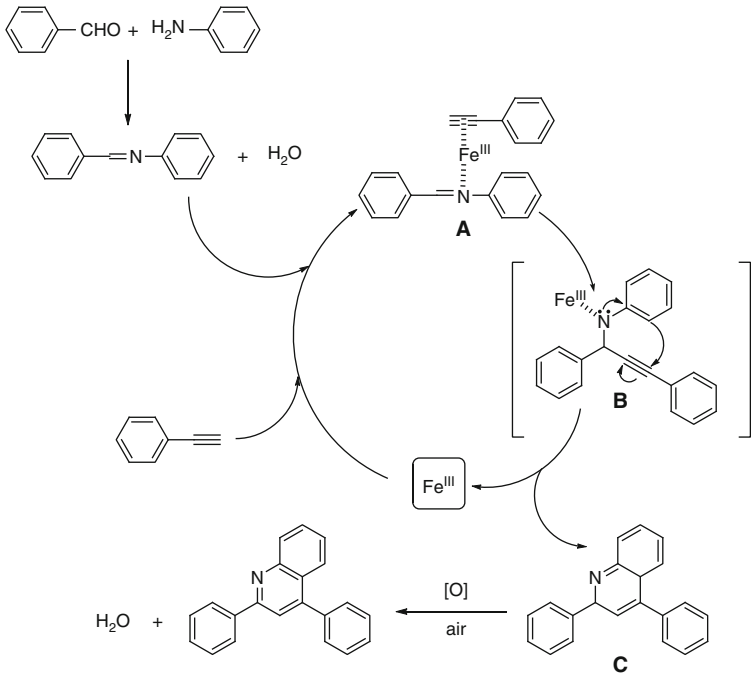
Subsequently, the scope of amines and alkynes in this reaction was investigated, and it was found that substituted anilines (R^2 = *p*-Me, *p*-MeO, *p*-Cl and *m*-Br) were



Scheme 19 Synthesis of quinolines by iron(III)-catalyzed three-component coupling/hydroarylation of aldehydes, alkynes, and amines

good substrates for this transformation. With regard to the alkyne scope phenylacetylenes, heteroaromatic alkynes, and aliphatic alkynes are suitable substrates.

Based on the experimental results above and together with Wang's previous work a tentative mechanism was proposed (Scheme 20) [33]. Thus, intermediate **A** is formed initially through coordination of imine and alkyne to the Lewis acid. This coordination sets the stage for an addition of the alkyne to the imine leading to the propargylamine intermediate **B**, which then undergoes an intramolecular

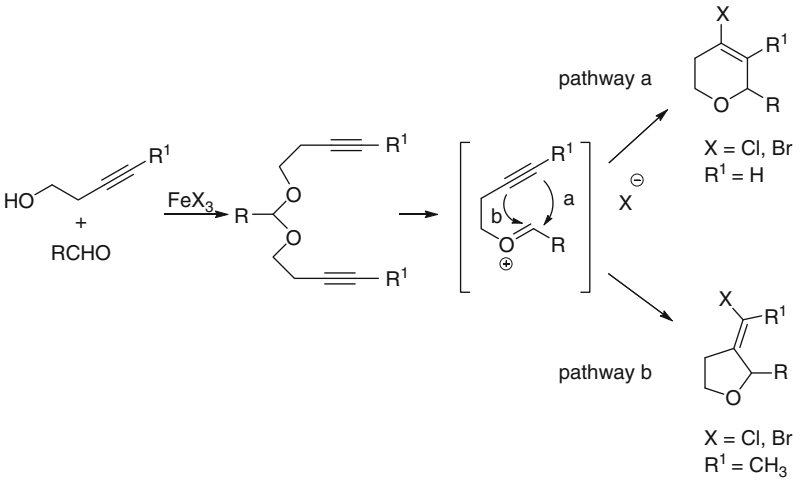


Scheme 20 Mechanism for iron-catalyzed tandem coupling/hydroarylation of aldehyde, aromatic alkyne, and anilines

hydroarylation of alkyne to the dihydroquinoline intermediate **C**. A final oxidation of **C** by O_2 in air affords the quinoline product. Compared to the similar $AuCl_3$-mediated process, the stronger Lewis acidity of $FeCl_3$ than $AuCl_3$ appears to be the main reason for the higher efficiency of the catalytic system.

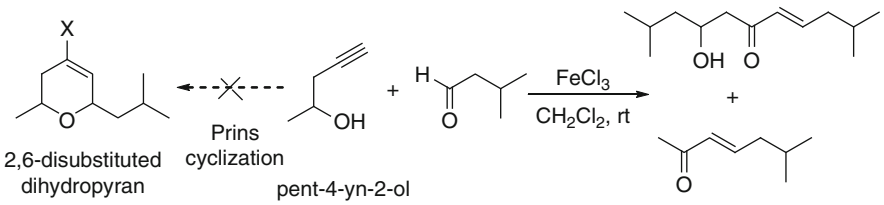
Use of Oxygenated Acetylenes

In the case of terminal alkynes having oxygenated functions in the linear chain (Scheme 10, route D), Martín, Padrón, and coworkers found that homopropargylic alcohols reacted properly, yielding 2-substituted dihydropyrans as sole products, probably via a Prins-type cyclization. This cyclization provides a new approach toward 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans through a concomitant C–C and C–O bond formation (Scheme 21) [35].



Scheme 21 Plausible mechanism for Prins-type cyclization promoted by iron(III) halides

The methodology proved to be broadly applicable, yielding the desired six-membered rings with a wide range of aldehydes, except for benzaldehyde. However, reactions with other aldehydes containing aromatic rings located in a distal position relative to the carbonyl group proceeded satisfactorily. When pent-3-yn-1-ol was used the tetrahydrofuran derivative was the major product. With other alkyne alcohols such as 4-pentyn-1-ol and 5-hexyn-1-ol no cyclization reaction was observed. Using a catalytic amount of $FeCl_3$ (0.1 equiv), the acetal was isolated as a single product in good yield (80%). When treated with more ferric chloride (1 equiv) this intermediate was transformed to the corresponding halovinyl tetrahydropyran. In light of this evidence, a plausible mechanism involves the acetal that, via FeX_3-mediated ionization, generates the oxonium ion that is intramolecularly trapped by the triple bond with further attack of the halide (Scheme 21).



Scheme 22 Coupling of secondary homopropargylic alcohols and aldehydes promoted by iron (III) halides

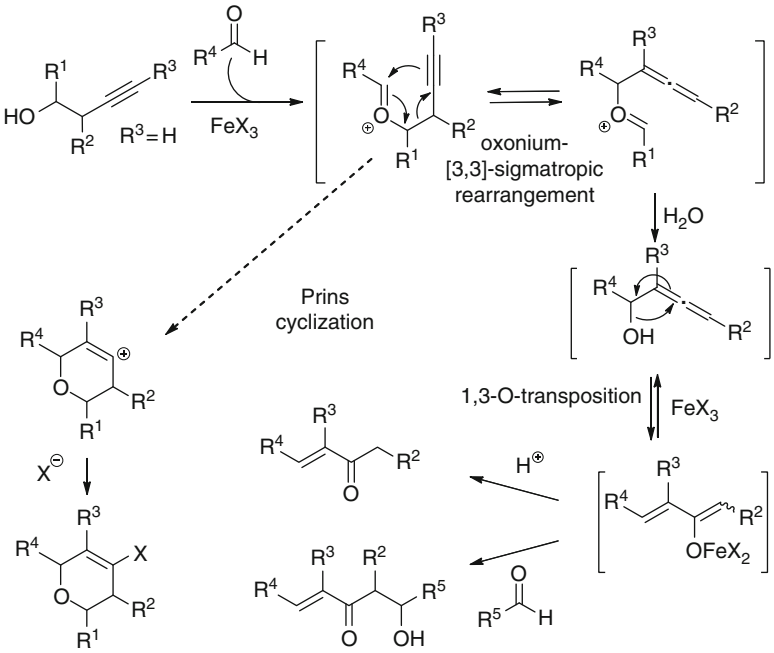
As an extension of this work, the same authors explored such methodology for the synthesis of 2,6-disubstituted dihydropyrans using secondary homopropargylic alcohols (Scheme 10, route E). Surprisingly, the treatment of pent-4-yn-2-ol and 3-methylbutanal in the presence of $FeCl_3$ led to unsaturated (*E*)-β-hydroxyketone and (*E*)-α,β-unsaturated ketone in 2.5:1 ratio and 65% yield, without any trace of the expected Prins-type cyclic product (Scheme 22) [36]. To test the anion influence in this coupling, $FeCl_3$ and $FeBr_3$ were used in a comparative study for the reaction of pent-4-yn-2-ol ($R^1 = R^4 = H$, $R^2 = Me$) and several aldehydes. A range of aldehydes except for benzaldehyde was transformed into unsaturated β-hydroxyketones in moderate to good yields.

A probable mechanistic scenario involves the addition of the secondary homopropargylic alcohols to the aldehydes promoted by ferric halide, thus generating an oxocarbenium ion that subsequently undergoes a 2-oxonium-[3,3]-sigmatropic rearrangement to an allenolate. Further intramolecular 1,3-oxygen transposition generates an unsaturated enolate. A subsequent coupling reaction with the suitable aldehyde or protonation leads to the unsaturated compounds (Scheme 23).

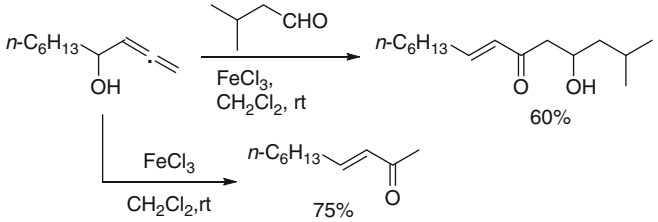
To support the 2,3-allenol as an intermediate in this reaction, 2,3-allenols were employed in test experiments as starting materials (Scheme 10, route F). The crossover aldol product was obtained as the sole product, when the reaction was run in the presence of the suitable aldehyde. In the absence of an aldehyde the corresponding (*E*)-α,β-unsaturated ketone was obtained (Scheme 24) [37].

Several ways to suppress the 2-oxonium-[3,3]-rearrangements might be envisioned. Apart from the introduction of a bulky substituent R^4 at the aldehyde (Scheme 23) a similar steric repulsion between R^4 and R^3 might also be observed upon introduction of a bulky auxiliary at R^4. A proof-of-principle for this concept was observed upon by using of a trimethylsilyl group as substituent R^3 in the alkyne moiety (Scheme 25, R^3 = TMS). This improvement provided an efficient access to polysubstituted dihydropyrans via a silyl alkyne-Prins cyclization. Ab initio theoretical calculations support the proposed mechanism. Moreover, the use of enantiomerically enriched secondary homopropargylic alcohols yielded the corresponding oxa-cycles with similar enantiomeric purity [38].

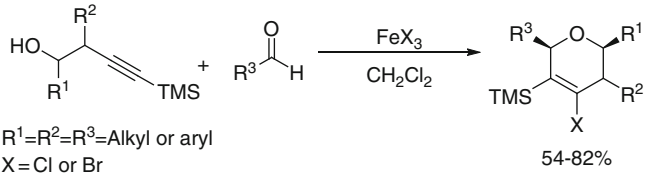
In furtherance of these studies, the reaction scope was broadened by employing homopropargylic amines to give the corresponding aza-cycles (Scheme 26) [39, 40]. Hence, the alkyne aza-Prins cyclization between homopropargyl tosyl amines



Scheme 23 Proposed mechanism for the addition of secondary homopropargylic alcohols to aldehydes promoted by iron(III) halides

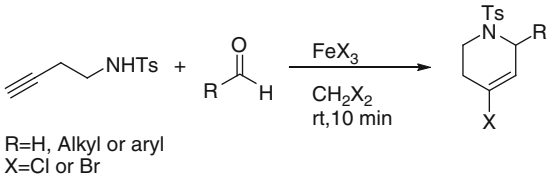


Scheme 24 Coupling of 2,3-allenols and aldehydes promoted by iron(III) halides



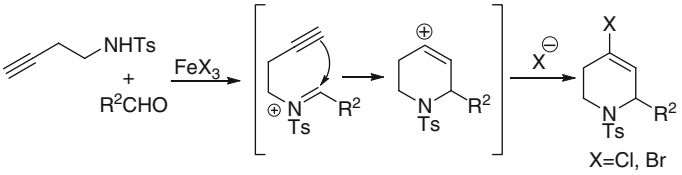
Scheme 25 Silyl alkyne-Prins cyclization of secondary homopropargylic alcohols and aldehydes using FeX_3 as a promoter

Scheme 26 Synthesis of 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines from *N*-tosyl homopropargyl amine and aldehydes using FeX_3 as promotor



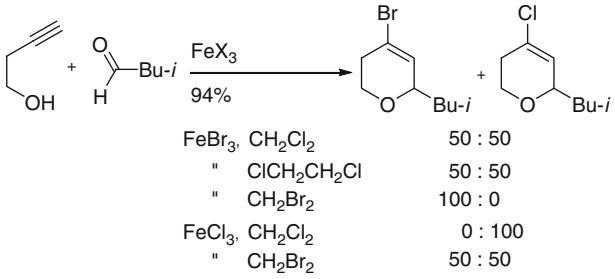
and aldehydes yielded 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines as sole products [41].

A plausible mechanism for this new alkyne aza-Prins cyclization is outlined in Scheme 27. Thus, reaction of the homopropargyl tosyl amine with an aldehyde promoted by ferric halide generates the *N*-sulfonyl iminium ion. This intermediate evolves to the corresponding piperidine, via the vinyl carbocation. Ab initio theoretical calculations support the proposed mechanism.



Scheme 27 Plausible mechanism of the alkyne aza-Prins cyclization promoted by iron(III)

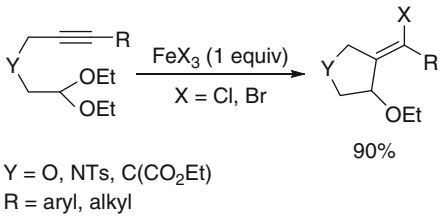
In both oxa- and aza-alkyne Prins cyclization an unexpected halide exchange with halogenated solvents presumably caused by the vinyl cation intermediates was observed [37]. From a synthetic point of view, it is important to use the correct combination of FeX_3 and X-containing solvent in order to avoid the undesired halide scrambling (Scheme 28).



Scheme 28 Halide exchange with halogenated solvents during the acetylenic Prins-type cyclization

Wang et al. reported that $FeCl_3$- and $FeBr_3$-promoted cyclization/halogenation of alkynyl diethyl acetals formed (*E*)-2-(l-halobenzylidene or alkylidene)-substituted five-membered carbo- and heterocycles. It was found that the 1:1 molar ratio

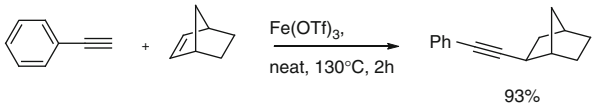
reaction of the acetal with $FeCl_3$ proceeded more efficiently at 0°C than at other temperatures and $FeCl_2$ did not initiate the reaction (Scheme 29) [42].



Scheme 29 Iron-promoted cyclization/halogenation of alkynyl diethyl acetals

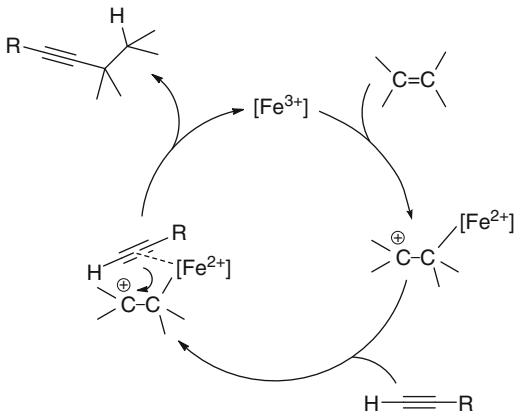
2.2.2 Aliphatic C–C Bond Formation Using Alkenes

Sakakura and coworkers reported the catalytic action of iron(III) triflate for the addition of acetylenes to olefins without the need for an inert gas atmosphere (Scheme 30) [43].



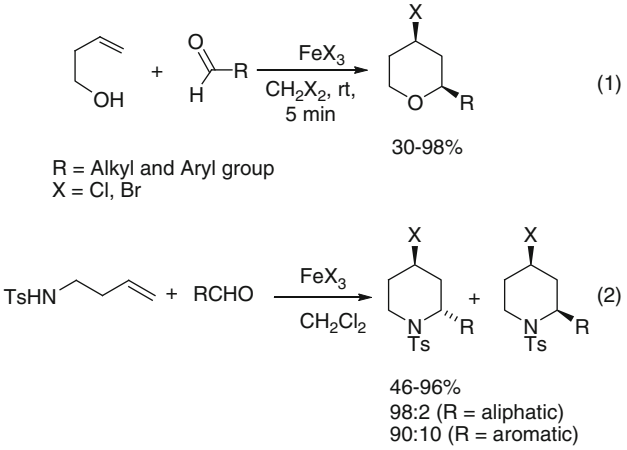
Scheme 30 $Fe(OTf)_3$-catalyzed addition of alkynes to alkenes

The reaction proceeds with isolated double bonds and electron-rich alkynes. Electron-withdrawing groups in the acetylene moiety decelerated the reaction. A plausible mechanism implies the activation of the olefin by coordination of the metal triflate followed by nucleophilic attack of the acetylene or acetylide (Scheme 31).



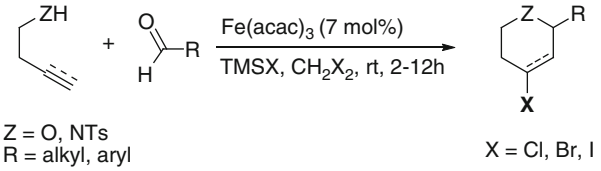
Scheme 31 Possible mechanism of iron(III)-catalyzed alkyne addition to alkenes

FeX_3 was also found to be an excellent promoter in the classical Prins cyclization (Scheme 10, route H), with the observation of a satisfactory reaction between 3-buten-1-ol and several aldehydes, affording the corresponding *cis*-4-halo-2-alkyl tetrahydropyrans in good yields [Eq. (1) in Scheme 32] [35]. In a similar manner, the methodology can be extended to the piperidine synthesis through an aza-Prins cyclization [Eq. (2), Scheme 32] [41].



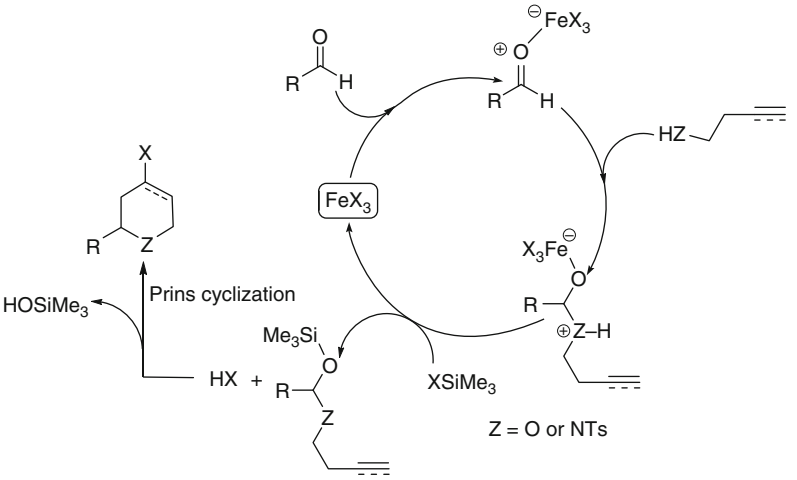
Scheme 32 Prins and aza-Prins cyclization using FeX_3 as a promoter

Whereas the Prins-type cyclizations reported in this and the preceeding chapter were performed using stoichiometric amounts of Fe salts as Lewis acids, a breakthrough in the field of catalysis was reported in 2009 when the first iron-catalyzed Prins- and aza-Prins cyclization was reported. The catalytic system, which is obtained by combining catalytic amounts of an iron salt with trimethylsilyl halides as a halide source, is widely applicable and promotes the construction of substituted six-membered oxa- and aza-cycles (Scheme 33) [44].



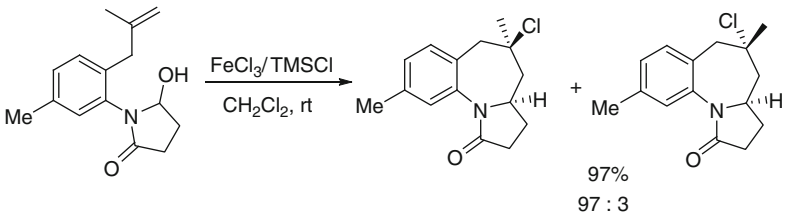
Scheme 33 The catalytic Prins cyclization leading to oxa- and aza-cycles

The catalytic cycle was devised relying on a ligand exchange between the iron complex and a chlorosilane, regenerating the iron(III) halide due to the more oxophilic character of the silicon (Scheme 34).



Scheme 34 Plausible mechanism for the iron-catalyzed Prins cyclization

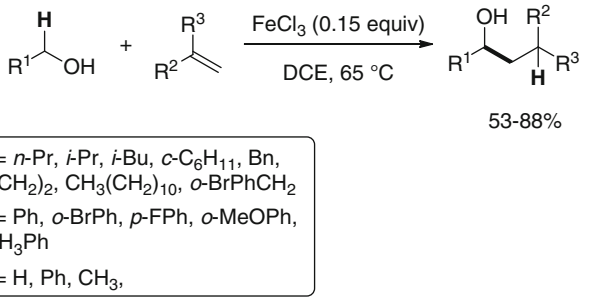
This catalytic system has been applied to the synthesis of the core of complex antibiotic tetrapetalones. Hong and coworkers have successfully established the *N*-acyliminium ion cyclization in the preparation of 1-benzazepine derivatives. A combination of $FeCl_3$ (0.5 equiv) and TMSCl (2 equiv) was selected as an optimized condition for such stereoselective cyclization (Scheme 35) [45].



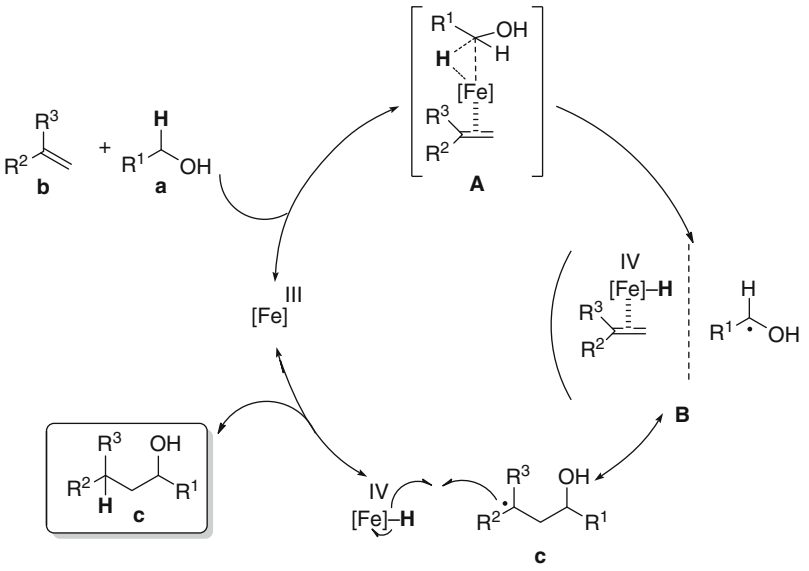
Scheme 35 Stereoselective Prins cyclization by iron(III)-catalyzed *N*-acyliminium ion cyclization

In 2009, Tu et al. developed a novel iron-catalyzed C(sp^3)–C(sp^3) bond-forming reaction between alcohols and olefins or tertiary alcohols through direct C(sp^3)–H functionalization. A series of primary alcohols were treated with alkenes or tertiary alcohols as their precursors, using the general catalysis system $FeCl_3$ (0.15 equiv)/1,2-dichloroethane (DCE) (Scheme 36) [46].

According to several deuterium-labeling experiments and previous results, a catalytic mechanism was proposed. Iron-initiated activation for cleavage of the C(sp^3)–H bond adjacent to oxygen of alcohol **a** is involved in the formation of **A**. The key step is the formation of a radical part **B** that evolves to free-radical species **C**. Subsequently, the metal hydride ($[Fe]^{IV}$–H) undergoes a hydrogen transfer to give the coupling product **c**, regenerating the iron catalyst $[Fe]^{III}$ (Scheme 37).



Scheme 36 Iron-catalyzed C(sp^3)–C(sp^3) bond formation through C(sp^3)–H functionalization



Scheme 37 Proposed mechanism of C(sp^3)–C(sp^3) coupling catalyzed by iron(III)

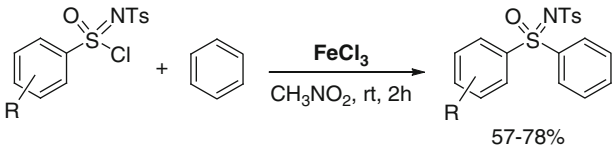
3 C–Heteroatom Bond Formation

3.1 Aromatic C–Heteroatom Bond Formation

Iron(III) chloride is a common catalyst used in electrophilic aromatic substitutions. In addition to those applications outlined above for the construction of aromatic C–C bonds, such salts have also been used for the introduction of heteroatom-based functional groups at the aromatic ring [47].

In 2000, Takata et al. reported the synthesis of diarylsulfoximines by the Friedel–Craft reaction of sulfonimidoyl chloride with aromatic compounds in the presence of

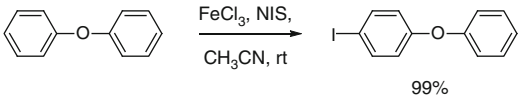
an equimolar amount of $FeCl_3$ (Scheme 38) [48]. The reaction was found to be very sensitive to both electronic and steric effects of the nucleophiles (aromatic hydrocarbons) employed. Additionally, the introduction of the electron-donating group on the benzene ring in the sulfonimidoyl chloride decreased the yield of the sulfoximines, presumably due to the stabilization of cationic intermediates.



Scheme 38 Synthesis of diarylsulfoximines by Friedel–Crafts reactions

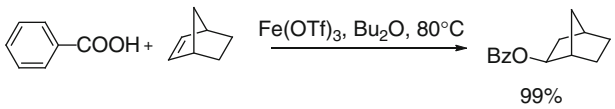
When used with *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimide, iron(III) chloride catalyzes the introduction of halogens into arenes. The reaction works well even with deactivated aromatic rings but in some cases the regioselective course is difficult to control (Scheme 39) [49].

Scheme 39 Halogenation of aromatic compounds catalyzed by $FeCl_3$



3.2 *Aliphatic C–Heteroatom Bond Formation*

Choi and Sakakura et al. reported that iron(III) triflate, in situ formed from $FeCl_3$ and triflic acid, efficiently catalyzes the intermolecular addition of carboxylic acids to various alkenes to yield carboxylic esters. The reaction is applicable to the synthesis of unstable esters, such as acrylates (Scheme 40) [50].

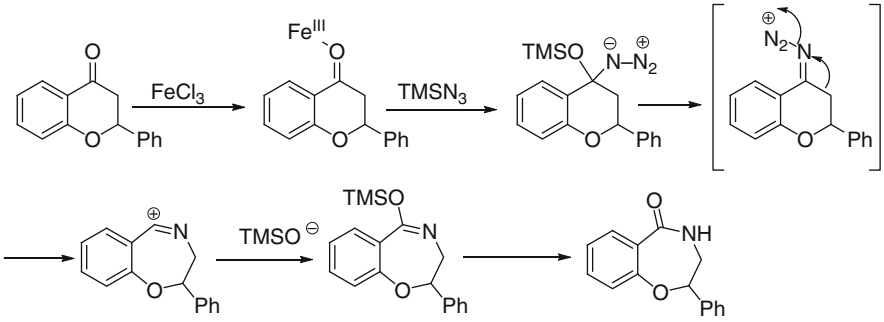


Scheme 40 Iron(III)-catalyzed intermolecular addition of carboxylic acids to alkenes

4 Rearrangements

Yadav's group reported that ketones undergo smooth rearrangement with $TMSN_3$ in the presence of catalytic amounts of $FeCl_3$ under mild conditions, to provide the corresponding amides, imides, and lactams in good yields with high selectivity. The

azido-Schmidt reaction involves the addition of azide to the ketone followed by rearrangement and ring expansion. Similar to the classical Schmidt reaction, the mechanism most likely involves a Lewis-acid activation of the carbonyl group followed by the addition of azide. The resulting iminodiazonium ions, which undergo ring expansion by loss of nitrogen and subsequent migration of the anti-substituent to the electron-deficient nitrogen, give the corresponding amide (Scheme 41) [51].



Scheme 41 Mechanism of the azido-Schmidt reaction catalyzed by $FeCl_3$

Acknowledgment We gratefully acknowledge financial support by the Spanish MICIIN (CTQ2008-06806-C02-01/BQU) and Canary Islands' ACIISI (PI 2007/022).

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