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Iron-promoted C–C bond formation in the total synthesis of natural products and drugs

Julien Legros[*a] and Bruno Figadère[*b]

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Iron salts are inexpensive and almost innocuous; they are thus the promoters of choice, even in stoichiometric amounts, for the formation of carbon–carbon bonds in the backbone of complex molecules. This review encompasses the key role of iron complexes in the total synthesis of some natural products or pharmacologically important compounds.

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1.   Introduction

Iron (Fe) is the fourth most abundant element in the Earth's crust, and most of this iron is found as iron oxides, such as the minerals hematite (Fe_2O_3) or magnetite (Fe_3O_4).[1,2] For the biologist, iron is an essential element to most living beings, from single-celled microorganisms to humans, as illustrated for example by the Fe-containing protein hemoglobin.[3] However, for the synthetic chemist, iron salts are often intimately connected to the centenarian Friedel–Crafts reaction, an electrophilic aromatic substitution promoted by metal salts, often including FeX_3 (X = Br, Cl).[4] Recently, iron complexes have found increasing application in organic synthesis, especially as catalysts. Indeed, metal-catalysed reactions are essential utensils in the toolbox of the synthetic chemist, and only those combining criteria of efficiency, selectivity and reliability with

cost effectiveness and low toxicity shall hold a prominent position in the future.[5–8] In this demanding context, iron occupies a place that probably no other transition metal can dispute: it is truly inexpensive and most of its salts exhibit low toxicity and they are generally environmentally benign. A comparison between iron salts ($Fe(acac)_3$, $FeCl_{2,3}$), and some commonly used metal salts ($AlCl_3$, $CuCl_2$, $NiCl_2$, $CoCl_2$, $PdCl_2$) is given in Table 1.

Thus, iron complexes are by far the least expensive ones, with poor toxicity, environment poisoning or CMR classification (carcinogenic, mutagenic or toxic for reproduction). Only aluminium chloride is cheaper with higher LD_{50} and LC_{50} but it exhibits teratogenicity effects. Therefore, even when used in stoichiometric amounts, iron salts remain cheaper and safer that many other catalytic metal complexes, such as the palladium ones, broadly used in cross-coupling reactions. These decisive advantages make iron complexes the promoters of choice (under catalytic or even stoichiometric amounts) for elegant C–C bond formation, as required to build the carbon backbone of poly-functionalized molecules in the total synthesis of natural products and bioactive ingredients. This review thus aims at illustrating how iron salts play a key role in carbon skeleton buildings in the total synthesis of natural products or pharmacologically important compounds (Fig. 1).

2.   Cross-coupling reactions of organometallic reagents

Metal-catalysed cross-coupling reactions constitute one of the most straightforward and strongest methodologies to form C–C bonds.[9] In 1971 Tamura and Kochi reported for the first time successful and stereoselective examples of formal nucleophilic substitution between alkyl magnesium bromides and vinyl bromides in presence of very low catalytic loadings of $FeCl_3$ in THF (Scheme 1).[10,11] However, one year later Kumada and Corriu

[a]COBRA UMR 6014 Normandie Univ, Univ Rouen, INSA Rouen and CNRS 1 rue Lucien Tesnière, 76821 Mont-Saint-Aignan, France. E-mail: julien.legros@univ-rouen.fr

[b]CNRS, BioCIS UMR 8076 Labex LERMIT, Univ Paris Sud, and CNRS 5 rue J. B. Clément, 92296 Châtenay-Malabry, France. E-mail: bruno.figadere@u-psud.fr

Table 1 Comparison of various metal salts

Metal salts	Price[a] (€ per g)	Toxicity	LD$_{50}$[b] (mg kg^{-1})	LC$_{50}$[c] (mg L^{-1}, 96 h)
Fe(acac)$_3$	3–5	No significant toxicity reported	1872	Unknown
FeCl$_3$	18–28	No significant toxicity reported	1350	21.84
FeCl$_2$	14–19	No significant toxicity reported	450	4
AlCl$_3$	12–20	☣	3450	36.6
CuCl$_2$	15–22	☣	584	0.23
NiCl$_2$	37–46	☣ ☠ ☣	186	Unknown
CoCl$_2$	28–36	☠ ☣	418	0.33
PdCl$_2$	58–106	☣	200	Unknown

[a] Average range price for metal complexes with purity ≥ 99.9% taken from different providers. [b] Lethal dose. [c] Lethal concentration.

independently reported the cross-coupling reaction between Grignard reagents and organic halides by means of nickel catalysts, later extended to palladium complexes, and these transformations were then extensively studied leading eventually to the Nobel prize in 2010 to Negishi, Heck and Suzuki. The potential of Fe-catalysed cross-couplings remained in the shadow of palladium catalysis for many years and did not undergo much studies until Cahiez reported in 1998 a spectacular improvement allowing poorly reactive substrates, such as alkenyl chlorides, to be efficiently converted by using Fe(acac)$_3$ as catalyst and N-methylpyrrolidinone (NMP) as co-solvent; the yield jumped then from 5% in THF to 85% in this solvent mixture (Scheme 2).[12]

Therefore, methodology in Fe-catalysed cross-coupling reactions has met outstanding improvements, notably by Fürstner and Nakamura. Thus, the reaction scope has been extended to various Grignard reagents and numerous electrophilic partners such as vinyl-, aryl- and alkyl (pseudo)halides. Moreover, many efforts have also been devoted to the comprehension of the reaction mechanism. Whereas Kochi early suggested the formation of an active "reduced form of soluble iron" generated from organomagnesium reagents and iron chloride,[11] recent experimental and theoretical investigations suggest that the nature of the active iron species generated from either Fe(III) or Fe(II) and Grignard reagents depends on the nature of the latter (e.g. Ar- or alkyl-MgBr, presence of a hydrogen atom in the β-position).[13–18] To briefly summarize, two main pathways are generally considered: double-electron transfer or single-electron transfer mechanisms.[6,19]

Iron-catalysed coupling reactions with organometallics, such as Grignard reagents, have shown their great compatibility with various functional groups and it is then not surprising that they have then been frequently applied as a key step in total

Julien Legros was born in 1974 and educated at the Universities Paris East, and then Paris South-Faculty of Pharmacy where he received his PhD under the guidance of Dr D. Bonnet-Delpon and J.-P. Bégué (2002). After an Alexander von Humboldt post-doctoral position on iron catalysis with Prof. C. Bolm at the RWTH University (Aachen, Germany), he got a permanent position at the CNRS in 2004 (Univ Paris South-Faculty of Pharmacy) and then moved to the University of Rouen in 2011. Julien Legros is involved in synthetic methodology in non-conventional media (flow microreactors, hyperbaric conditions, fluorous solvents).

Bruno Figadère, born in 1960, was educated in Paris (University Pierre et Marie Curie) where he received his PhD under Dr G. Cahiez leadership. After a post-doctoral position at the University of California at Riverside with Prof W. H. Okamura (1988–1990) he got a permanent position at the CNRS and since then works at University of Paris Sud-Faculty of Pharmacy. He is currently director of the BioCIS laboratory. Bruno Figadère is involved in the chemistry of natural products, especially in total synthesis, pharmacomodulation and characterisation of new bioactive compounds from different origins.
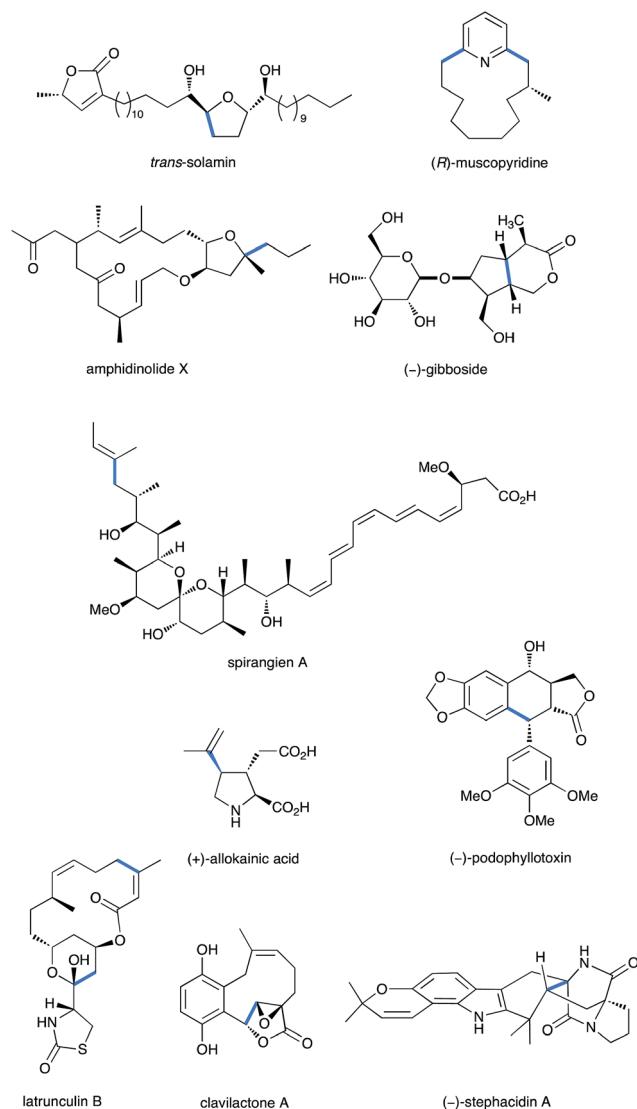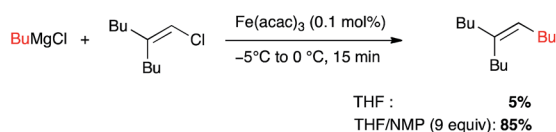
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Fig. 1 Some relevant examples of natural products synthesized through a Fe-promoted key step (highlighted in blue).

Scheme 1 First Fe-catalysed cross-coupling reaction with a Grignard reagent by Tamura and Kochi (1971).

Scheme 2 Improved conditions for Fe-catalysed cross-coupling with a Grignard reagent by Cahiez (1998).

syntheses of natural products and/or compounds of pharmacological interest, due to the ease, chemo- and stereoselectivity of the processes.[5,8,20,21]

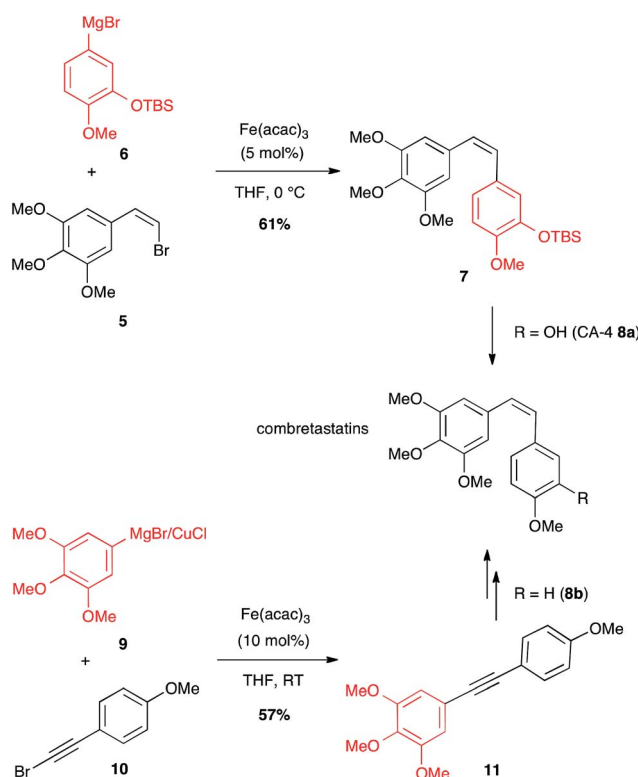## 2.1 With alkenyl and alkynyl (pseudo)halides

Aryl and alkyl Grignard reagents have been involved with various alkenyl and alkynyl electrophilic partners.

Alkenyl and alkynyl halides. Since the pioneering work of Kochi, vinyl halides have been widely used. For example, iron-catalysed coupling reaction of an homoallylic Grignard reagent **1** with a (*Z*)-bromoalkene **2** proceeded with complete maintaining of the geometry and led to a key diene **3** of defined *Z,E* configuration (70% yield), which after chemo- and enantioselective dihydroxylation will lead to *cis* and *trans* solamins, depending on the dihydroxylation procedures, two annonaceous acetogenins with cytotoxicity activity (Scheme 3).[22]

A (*Z*)-bromoalkene **5** has also been coupled under iron catalysis to an aryl Grignard reagent **6** to afford combretastatin-
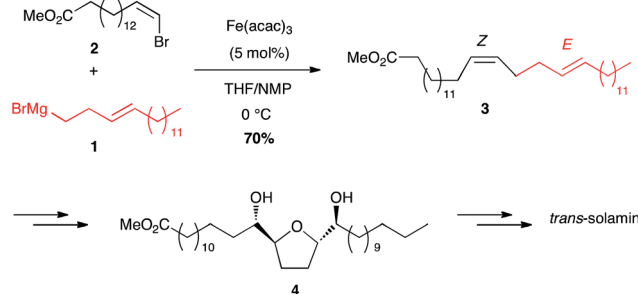
Scheme 3 Fe-catalysed cross-coupling of homoallylic magnesium bromide with a (*Z*)-bromoolefin for the synthesis of *trans*-solamin.
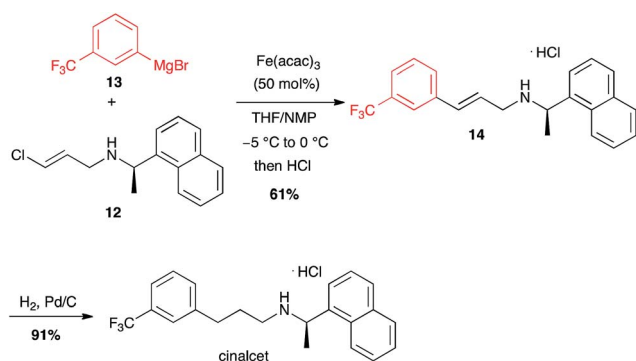

Scheme 4 Fe-catalysed cross-coupling for the synthesis of combretastatins.

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A4 (CA-4) protected as TBDMS ether **7** (61% yield), which after deprotection led to the desired anticancer compound **8a** (Scheme 4).[23] Later on, another Fe-catalysed path to access combretastatins has been described. This latter does not involve any olefin as coupling partner with the arene reagent, but a bromoalkyne: bimetallic aryl magnesium/copper halide **9** reacted with bromoarylacetylene **10** under iron catalysis to afford the corresponding bi(aryl)acetylene **11** (57% yield) that can be reduced to yield analogues of CA-4 **8b** (Scheme 4).[24] It is worth noting that this is the single known example of Fe-catalysed coupling between a Grignard reagent and a bromalkyne.

Interestingly, less reactive (E)-chloroolefins are also good substrates for iron-catalysed coupling with aryl Grignard reagents: cinacalcet, a drug used for the treatment of secondary hyperparathyroidism, was prepared on a kilogram scale using this reaction between **12** and **13** as a key step (Scheme 5).[25]

Another amine-containing molecule, naftifine, an antifungal drug, was prepared by an iron-catalysed coupling of a (E)-chloroolefin **15** and phenyl Grignard reagent in high yield (89%) and excellent stereoselectivity (Scheme 6).[26]

Vinyl (pseudo)halides. However greatest applications with vinyl electrophiles in total synthesis have been found with vinyl triflates, as established by Fürstner.[27] One of the major interest of these electrophiles is that enol triflates are readily accessible from the corresponding ketones (albeit with possible regioisomeric issues). Moreover, these triflates can in some cases be generated and used in cross-couplings without intermediate isolation.

This method has been mainly used to introduce a methyl group. Thus, the natural sesquiterpene (−)-α-cubebene has been prepared in 2006 by Fürstner involving, at a late stage, coupling of methylmagnesium bromide with the isolated alkenyl triflate **16** in the presence of Fe(acac)$_3$ (10 mol%) in a THF/NMP mixture, in high yield (90%). 4-epi-Cubebol has then been further obtained (Scheme 7).[28]

The same year, Isobe used this methodology to perform the synthesis of the right-hand segment of ciguatoxin.[29] A methyl group was then successfully introduced from an isolated triflate generated from PhNTf$_2$, using a stoichiometric amount of Fe(acac)$_3$ (89% from ketone **17**; Scheme 8).

Scheme 5 Fe-catalysed coupling of aryl magnesium bromide with a (E)-chloroolefin for the synthesis of cinacalcet.
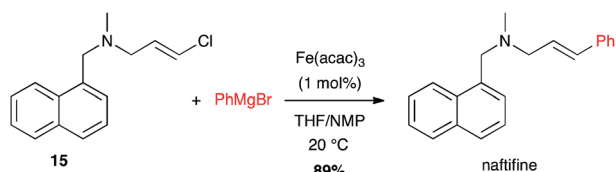
Scheme 6 Fe-catalysed coupling of phenyl magnesium bromide with a (E)-chloroolefin for the synthesis of naftifine.
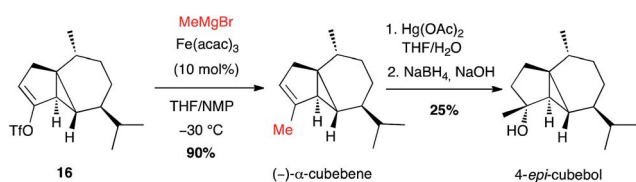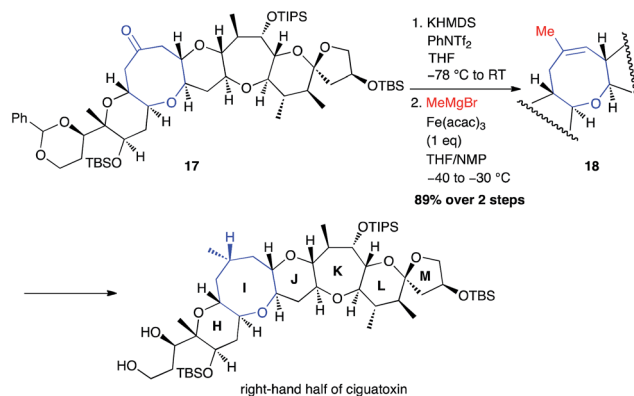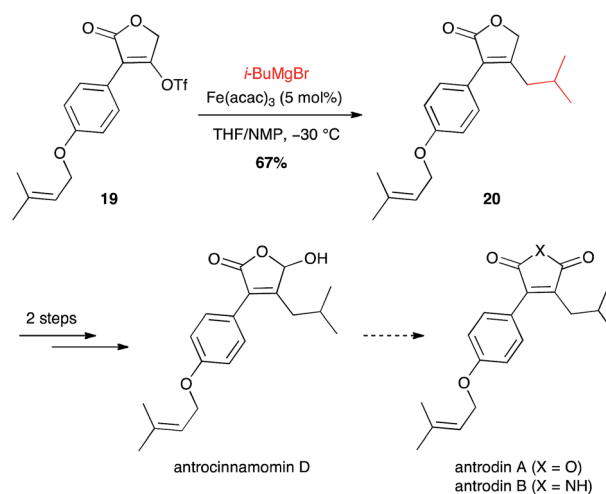

Scheme 7 Fe-catalysed coupling of methyl Grignard reagent with a vinyl triflate for the synthesis of (−)-α-cubebene and 4-epi-cubebol.

Scheme 8 Fe-catalysed coupling of methyl Grignard reagent with a vinyl triflate for the synthesis of the right-hand segment of ciguatoxin.
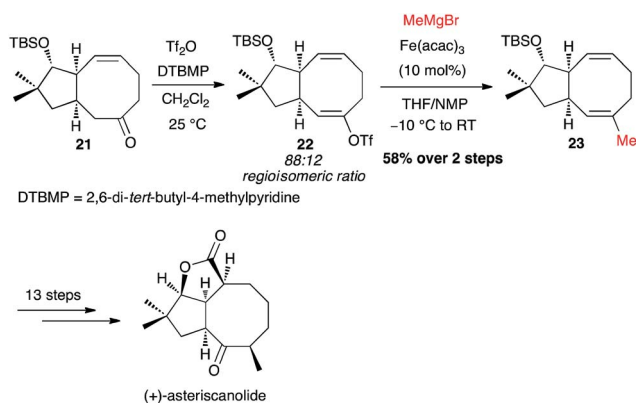

Scheme 9 Fe-catalysed coupling of methyl Grignard reagent with a vinyl triflate for the synthesis of antrocinnamomin D and antrodins.

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i-Butyl moiety has also been introduced for the synthesis of maleic anhydrides and derivatives, constituents of *Antrodia camphorata*: antrocinnamomin D and antrodins (Scheme 9).[30] Interestingly the coupling between i-BuMgBr and the vinyl triflate **19** with the inexpensive Fe(acac)$_3$ (5 mol%) was more efficient than the Suzuki–Miyaura coupling from i-BuB(OH)$_2$ and 10 mol% Pd(dppf)Cl$_2$ (67% *vs.* 55% yield for compound **20**).

Yu and Nicolaou independently investigated the Fe-catalysed cross-coupling with MeMgBr directly on a crude triflate. Thus, Yu's synthesis of (+)-asteriscanolide involved the coupling of triflate **22** at an intermediate stage, generated with a 88 : 12 regioisomeric ratio, affording the methylated adduct **23** in 58% yield from the ketone **21** (Scheme 10).[31]

In his synthesis of cylindrocyclophane by Nicolaou, two methyl groups were introduced simultaneously and the generation of the bis-triflate did not undergo any isomeric issues since it took place at a benzylic position, and the coupling occurred smoothly to afford the double methylated product **25** in 80% yield over two steps from **24** (Scheme 11).[32]

Scheme 10 Fe-catalysed coupling of methyl Grignard with a vinyl triflate for the synthesis of (+)-asteriscanolide.
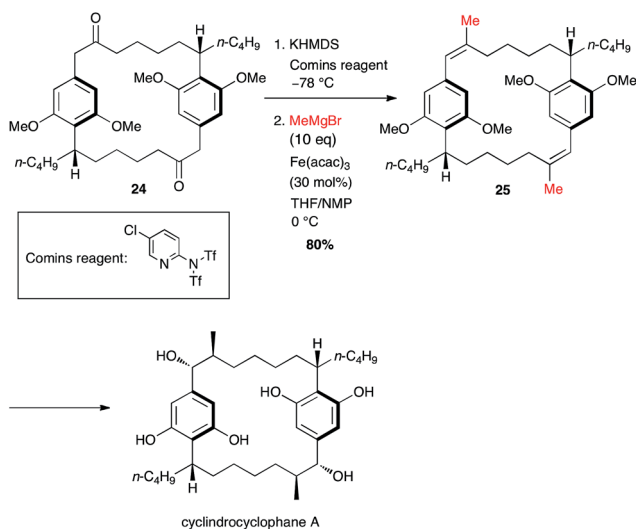
Scheme 11 Fe-catalysed coupling of methyl Grignard with a bis-vinyltriflate for the synthesis of cylindrocyclophane A.
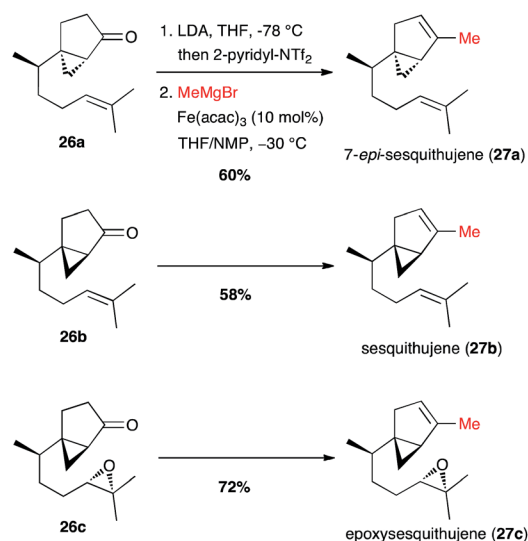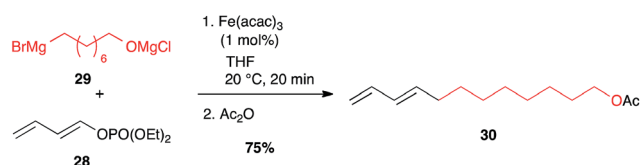

Scheme 12 Fe-catalysed coupling of methyl Grignard with a vinyl triflate for the synthesis of three members of the sesquithujene family.

Finally, Fürstner reported the full one-pot triflate formation/cross-coupling at the last step of the synthesis of sesquithujene natural products (Scheme 12).[33] Vinyl triflates were generated from **26a–c** under kinetic conditions with 2-pyridinyl-NTf$_2$, a Comins' reagent analogue, leaving unaffected the chiral cyclopropyl moieties. Then the reagents for the cross-coupling were added (MeMgBr, [Fe] cat. and NMP co-solvent), and the coupling products **27a–c** were obtained in 60–72% yield. Interestingly, under these conditions the coupling with the Grignard reagent reacted selectively with the vinyl triflate and the epoxide moiety remained unchanged in the synthesis of epoxysesquithujene **27c**.

Besides classical leaving groups met in cross-couplings (I, Br, OTf,…), phosphates can also be used on the electrophilic partner. Thus, dienol phosphate **28** reacted very well with alkyl Grignard reagent **29** at low iron catalyst loading (1 mol%) while maintaining the double bond geometry.[34,35] This strategy has been successfully used to access the Red Bollworm Moth (*Diaparopsis castanea*) pheromone **30** (75% over two steps, Scheme 13).[35]

Selective formation of (*Z*)-enol phosphate **31** from a keto-ester, followed by an iron-catalysed coupling with methyl-magnesium chloride, allowed Evans to prepare a key trisubstituted olefin **32**, en route to the total synthesis of salvinorin A, a potent κ opioid receptor agonist (Scheme 14).[36]

Scheme 13 Fe-catalysed coupling of an alkyl Grignard with a (*E*)-dienol phosphate for the synthesis of the *Diaparopsis castanea* pheromone.
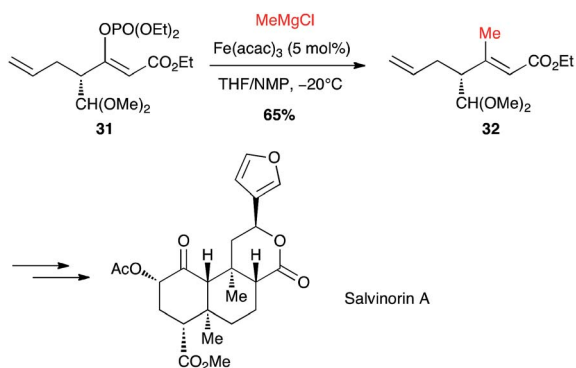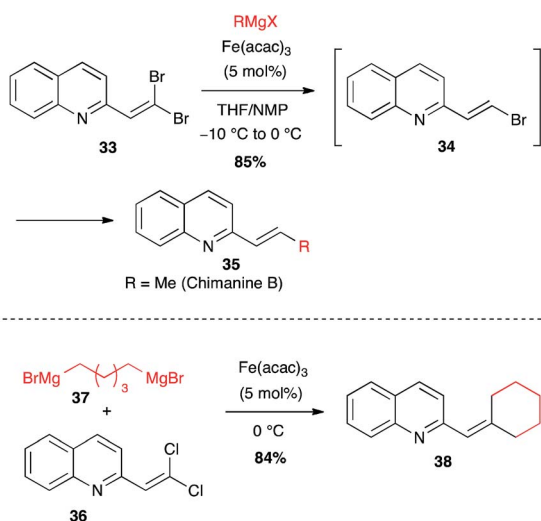
Scheme 14 Fe-catalysed coupling of methyl Grignard with a (Z)-enol phosphate for the synthesis of salvinorin A.

***gem*-Dihalogenoalkenes.** *gem*-Dihalogenoalkenes constitute an interesting and specific class of electrophiles with a particular behavior towards organo-magnesium and -lithium reagents in Fe-catalysed cross-couplings, which met application in the synthesis of natural products. Thus, bioactive compounds derived from the chimanines, natural 2-substituted quinolines isolated from a Rutaceae, were prepared from quinolyl-*gem*-dihalogenoalkenes and organomagnesium reagents in presence of Fe(acac)$_3$. While dibromo-compound **33** undergoes reduction to selectively afford the (E)-bromoalkene **34** (able to react by cross-coupling with a further equivalent of RMgX to afford **35**),[37] in contrast, 1,1-dichloroalkenes react rapidly to afford the disubstituted product, even if less than 2 equiv. of RMgX are used.[38] Thus, *gem*-dichlorovinyl quinoline **36** has been engaged in cross-coupling with bis-Grignard reagent **37** to perform an intermolecular followed by an intramolecular cross-coupling leading thus to an original cyclohexylidene moiety on this family of bioactive compounds (84% for **38**, Scheme 15).[38]

Very recently, Fürstner developed a brilliant methodology to access methyl-terminated alkynes from MeLi and *gem*-dichloro-
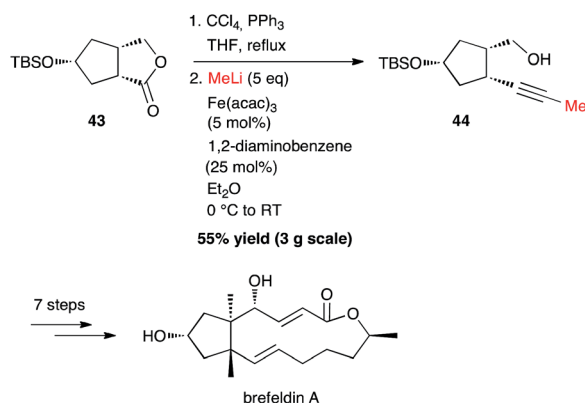
olefins obtained from lactones. These non-terminal alkyne moieties are then involved in ring closing alkyne metathesis (RCAM) and tulearin A and brefeldin A have been prepared through this pathway (Schemes 16 and 17).[39,40] The reaction between MeLi and *gem*-dichloroolefin **39**, affording the methyl-capped acetylenic compound **42**, is not *stricto sensu* a cross-coupling: a first Cl–Li exchange occurs and the MeCl formed is trapped by compound **40** and the rearrangement takes place to yield the target product **42** in 83% yield (Scheme 16). Even if this reaction is possible without catalyst, the presence of Fe(acac)$_3$ and 1,2-diaminobenzene (5 and 25 mol%, respectively) significantly enhanced the course of the reaction (2 h *vs.* 48 h reaction time without [Fe]). Thus, starting from **39**, tulearin A was obtained in 6 steps.[39]
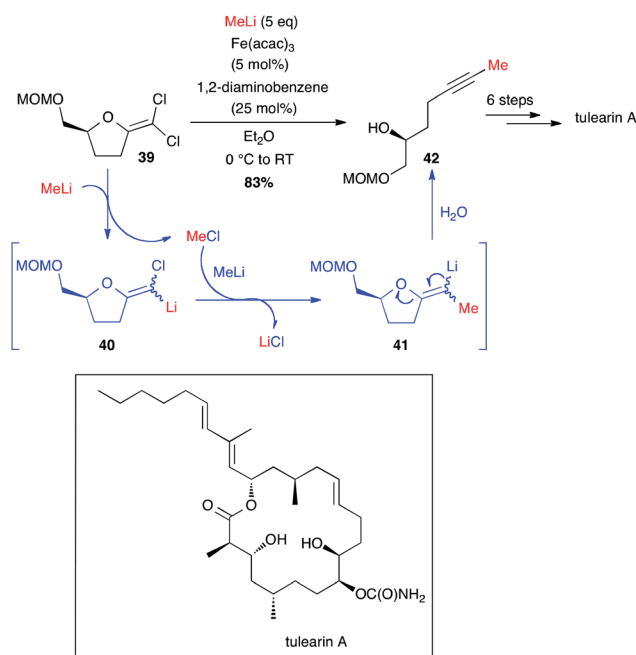
Scheme 16 Fe-catalysed coupling of methyl lithium with a *gem*-dichloroalkene for the synthesis of tulearin A.

Scheme 15 Fe-catalysed coupling of an alkyl Grignard with *gem*-dihaloalkenes for the synthesis of chimanine derivatives.

Scheme 17 Fe-catalysed coupling of methyl lithium with *gem*-dichloroalkene for the synthesis brefeldin A.

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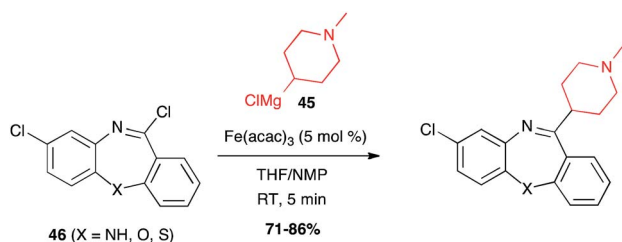This journal is © The Royal Society of Chemistry 2015

Interestingly, starting from 3 g of lactone **43**, it was possible to synthesize the methyl-capped alkyne **44** in 55% yield, as an intermediate for the preparation of brefeldin A, a most studied biologically active macrolide from *Penicillium decumbens* (Scheme 17).[40]

Imidoyl chloride. Olsson demonstrated the possibility to introduce various moieties on an imidoyl chloride with organomagnesium reagents to access benzodiazepine analogues (clozapines). Interestingly, the Grignard reagent **45** selectively reacted with the imidoyl chlorides **46** without affecting the chlorine atom connected to the arene (Scheme 18).[41]

2.2 With aryl (pseudo)halides

In contrast with palladium-catalysed cross-couplings, aryl-chlorides, -tosylates and -triflates have been shown to be the best partners for iron-catalysed reactions with Grignard reagents, bromo-/iodoarenes being poorer reagents.[42] Fürstner has developed many iron-catalysed coupling reactions between organomagnesium reagents and various Ar-X electrophilic partners, and showed that alkyl Grignard reagents react very well with aromatic and heteroaromatic triflates in high yields. FTY720, an immunosuppressive agent was thus prepared in a multigram scale by Fürstner through Fe-catalysed coupling of an alkyl Grignard reagent **47** and an aryl triflate **48** (64%, Scheme 19).[43]

In 2003, these coupling reactions have been applied to an elegant one-pot synthesis of an odoriferous alkaloid from animal origin, (*R*)-muscopyridine. Indeed, mixing 2-chloro-6-triflate-pyridine **50** with an enantiomerically pure alkyl

Grignard reagent **51** in the presence of an iron-salen salt (5 mol%) in a THF/NMP mixture resulted in a selective reaction with the–OTf group. Then, addition of 6-heptenylmagnesium bromide **52** (reacting on the C–Cl site), afforded the expected double adduct **53** (64%). This latter then underwent a ring-closing metathesis, and a hydrogenation to afford the expected natural product in 57% yield (Scheme 20).[44]

This group confirmed that halopyridines are indeed excellent substrates for iron-catalyzed Grignard couplings. Thus isooncinotine was prepared using as a key step the coupling of 2,6-dichloropyridine **54** with a functionalized alkyl Grignard reagent **55** in the presence of Fe(acac)$_3$ in the THF/NMP solvent mixture at 0 °C (83% yield of **56**; Scheme 21).[45]

In 2014, Schulz exemplified the coupling of 2-chloropyridine **57** with alkyl Grignard reagents under iron catalysis for the preparation of volatile pyridine alkaloids **58** produced by *Streptomyces* sp. (Scheme 22).[46]

Moreover, Risatti performed a high yielding Fe(acac)$_3$-catalysed coupling between a functionalized chloropyridine **59** and cyclopropylmagnesium bromide in their route to the synthesis of a dual NK-1/serotonin receptor antagonist (Scheme 23).[47]

It is worth noting that Sörensen has used a coupling with alkyl Grignard reagent **61** with the 2-chloropyridine **62** under

Scheme 18 Fe-catalysed coupling of a Grignard reagent with imidoyl chlorides to synthesize clozapines.
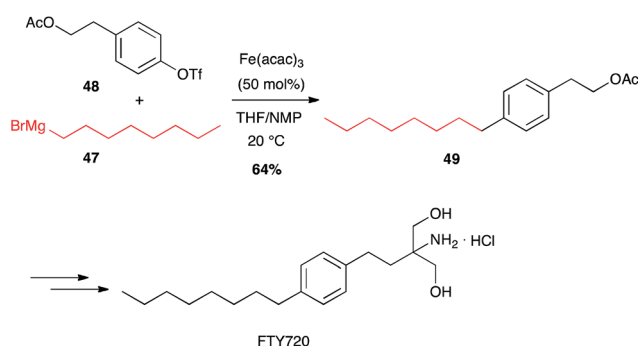
Scheme 19 Fe-catalysed coupling of octyl magnesium bromide with an aryl triflate for the synthesis of FTY720.
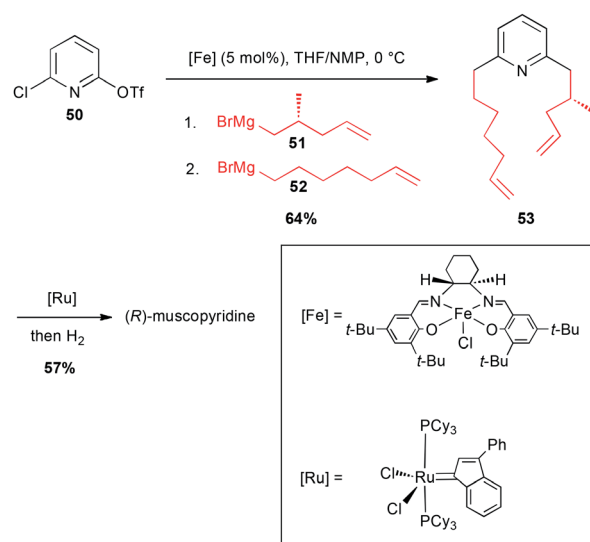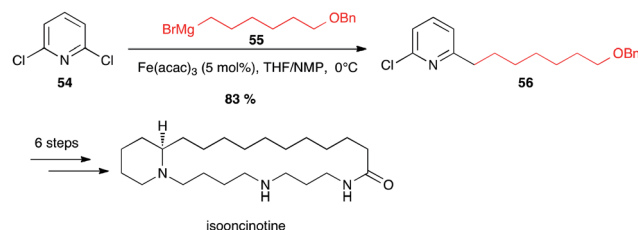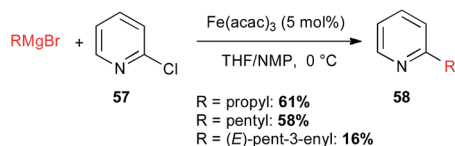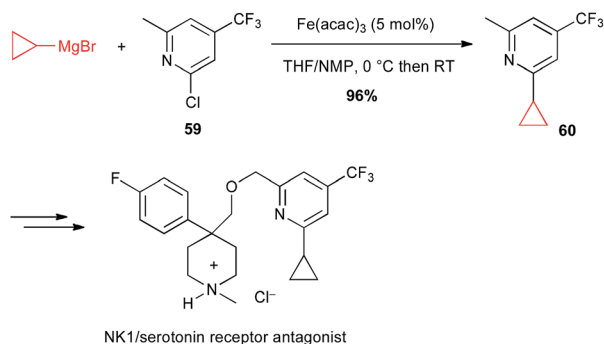
Scheme 20 Fe-catalysed coupling of alkyl Grignard reagents with a chloropyridinyl triflate for the synthesis of (*R*)-muscopyridine.
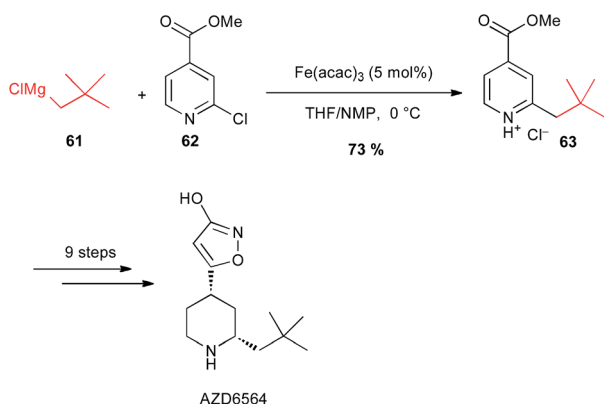
Scheme 21 Fe-catalysed coupling of alkyl Grignard with a dichloropyridine for the synthesis of isooncinotine.

Scheme 22 Fe-catalysed coupling of alkyl Grignard reagents with 2-chloropyridine for the synthesis of streptopyridines.

Scheme 23 Fe-catalysed coupling of cyclopropylmagnesium bromide with a chloropyridine derivative for the synthesis of a NK1/serotonin receptor antagonist.
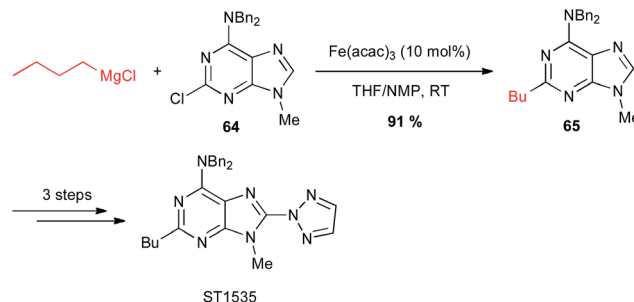

Scheme 24 Fe-catalysed coupling of alkyl Grignard with a 2-chloropyridine derivative for the synthesis of fibrinolysis inhibitor AZD6564.

iron catalysis for a large scale preparation (2 kg) of the 3-isoxazolol fibrinolysis inhibitor AZD6564 (Scheme 24).[48]

Iron-catalysed alkyl Grignard couplings can be applied to other heteroaryl halides. In particular, Cabri showed that a 2-chloropurine **64** can be coupled with *n*-butyl Grignard reagent in the presence of Fe(acac)$_3$ in the THF/NMP solvent mixture at 0 °C, to afford a key intermediate **65** in 91% yield in the total synthesis of the adenosine A$_{2A}$ receptor antagonist ST1535 (Scheme 25).[49]

2.3 With alkyl (pseudo)halides

Total synthesis of spirangien A has been in the focus of two different investigations with a Fe-catalysed step to introduce the terminal 2-butenyl fragment. Thus, Cossy has used an iron-

Scheme 25 Fe-catalysed coupling of alkyl Grignard with a 2-chloropurine derivative for the synthesis of adenosine A$_{2A}$ receptor antagonist ST1535.
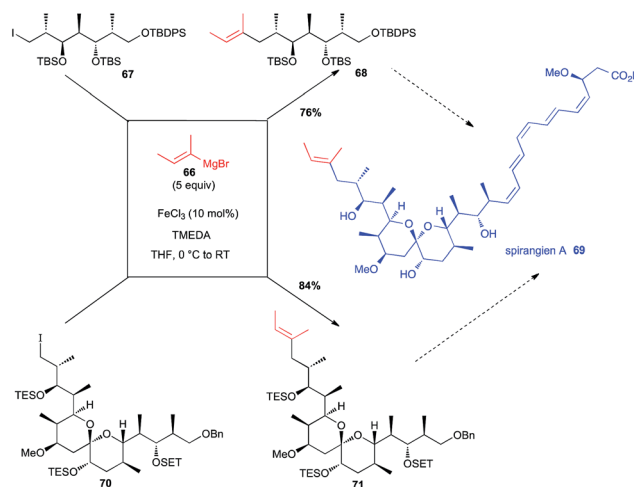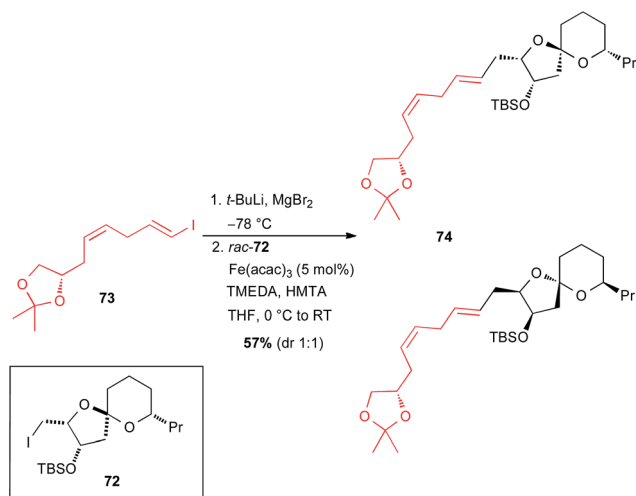

Scheme 26 Fe-catalysed coupling of a vinyl Grignard with a primary alkyl iodide for the synthesis of spirangien A.

catalysed coupling between an alkenyl Grignard reagent **66** and a primary alkyl iodide **67** in an early step of her synthesis of the spiroketal core of spirangien A (76% yield for **68**, Scheme 26).[50] It is worth noting that this reaction was much more efficient than the Negishi cross-coupling reaction. More recently, Rizzacasa used the same iron-catalysed coupling between **66** and a primary alkyl iodide **70**, but in a later step of their formal synthesis of spirangien A, still in good yield (84% yield for **71**, Scheme 26).[51]

In 2015, Totah and Lam reported the synthesis of a model fragment **74** of spirastrellolide A through an iron catalysed cross-coupling from *rac*-**72** (Scheme 27).[52] The vinyl Grignard reagent was generated *in situ* by I–Li exchange from enantiopure 1-iodo-1,4-diene **73**, followed by transmetallation with MgBr$_2$ without any issues, and the Fe-catalysed coupling with *rac*-**72** occurred to afford the target molecule **74** as a mixture of two diastereomers.

Secondary aliphatic bromides are also good substrates for iron-catalysed couplings with Grignard reagents. In this line, Cossy reported a coupling of a vinyl Grignard with a *C*-bromopyranoside **75** under Fe-catalysed conditions to prepare a key tetrahydropyrane **76** en route to the total synthesis of

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Scheme 27 Fe-catalysed coupling of a vinyl Grignard with a primary alkyl iodide for the synthesis of a model fragment of spirastrellolide A.
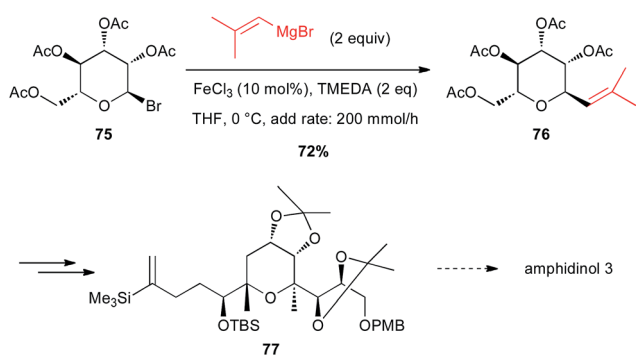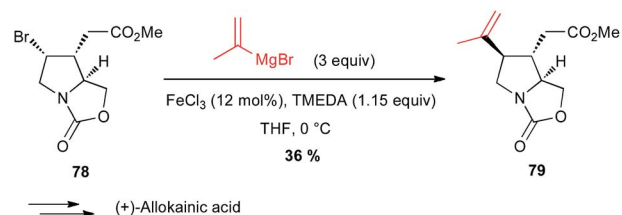
Scheme 28 Fe-catalysed coupling of a vinyl Grignard with a secondary alkyl bromide for the synthesis of a tetrahydropyrane core of amphidinol 3.

amphidinol 3. This cross-coupling exhibits excellent chemo- and diastereoselectivity since it tolerates the presence of acetoxy moieties and the product is obtained in 72% yield with dr = 9 : 1 (Scheme 28).[53]

Yamada also reported in their formal total synthesis of (+)-allokainic acid the use of an iron-catalysed coupling between a vinyl Grignard and a secondary bromoalkyl derivative **78**, although the yield of **79** remained low (36%) due to competitive opening of the pyrrolidine ring (Scheme 29).[54]

Iodocholestene was successfully reacted with an alkynyl Grignard reagent **80** under iron(ɪɪ)-catalysis to afford the natural

Scheme 29 Fe-catalysed coupling of a vinyl Grignard with a secondary alkyl bromide for the synthesis of (+)-allokainic acid.
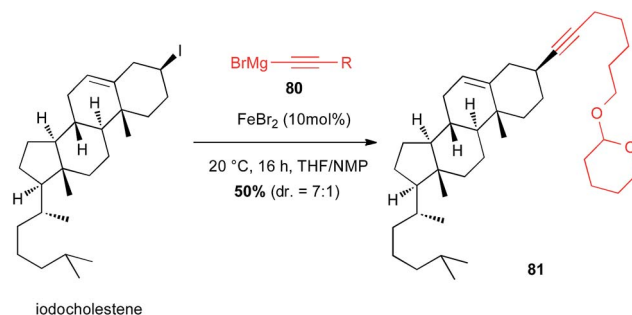
Scheme 30 Fe-catalysed coupling of an alkynyl Grignard with a secondary alkyl iodide for the synthesis of cholestene derivative.

product derived compound **81** in moderate yield (50%) and selectivity favouring retention of configuration (dr = 7 : 1) (Scheme 30).[55]

In 2015, an important breakthrough was reported by Nakamura who performed a Fe-catalysed enantioselective cross-coupling of racemic α-chloroesters with aryl Grignard reagents in presence of a C_2-symmetric bisphosphine ligand.[56] Moreover, this methodology allowed the preparation of the chiral non-racemic NSAID naproxen and dexibuprofen (Scheme 31). The coupling between chloropropionate **82** and the corresponding aryl magnesium bromides afforded the esters **83a** and **83b** with the same 74% ee for naproxen and dexibuprofen esters, respectively. However, saponification and crystallization with octyl amine allowed significant enantioenrichment to 86% and 98% ee, respectively. On a mechanistic standpoint, a catalytic
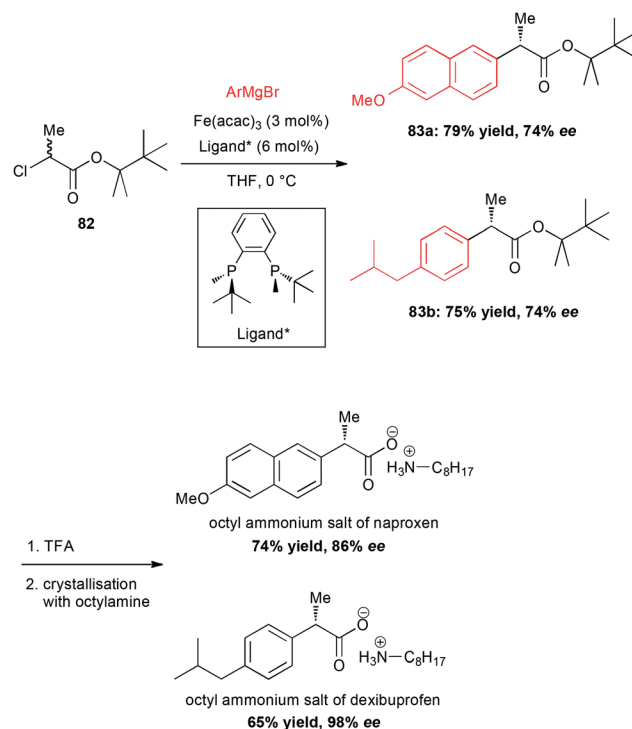
Scheme 31 Fe-catalysed enantioselective cross-coupling of racemic α-chloroesters with aryl Grignard reagents to prepare naproxen and dexibuprofen.

cycle involving a radical intermediate formed by halogen abstraction and Fe(ɪ) species with a chiral ligand has been proposed.
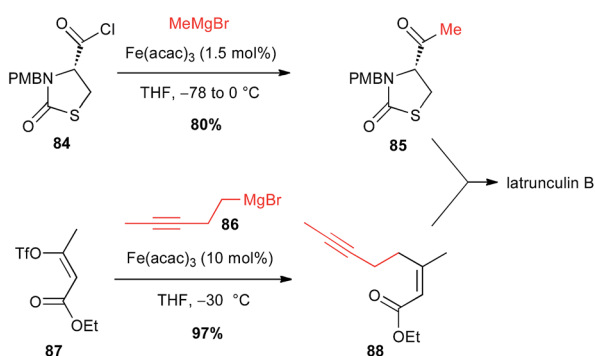
2.4 With acyl chlorides

Iron-catalysed processes are also powerful tools to access ketones: Grignard reagents in presence of Fe(acac)$_3$ catalyst were able to perform the formal nucleophilic substitution onto acyl chlorides and thioesters, without further addition to generate the tertiary alcohol, as demonstrated by Marchese.[57] In 2003, Fürstner extended this methodology to functionalized sophisticate molecules such as an enantiopure thiazolidinone **84** bearing an acyl chloride moiety, in his synthesis of latrunculin B. The reaction proceeds cleanly, affecting only the acyl group and affording thus the ketone **85** in good 80% yield. Moreover, a second Fe-catalysed step was also involved in this total synthesis between a homopropagylic Grignard reagent **86** and a vinyl triflate **87** (Scheme 32).[58]

More recently, the same group applied this reaction between a Grignard reagent **89** terminated with an acetylenic moiety and an acyl chloride **90** to prepare a precursor **91** of (*R*,*Z*)-muscenone (Scheme 33).[59]

2.5 Ring opening

Propargyl epoxides. The addition of Grignard reagents onto enantiopure propargyl epoxides has also been shown by

Scheme 32 Fe-catalysed acylation of an alkyl Grignard with an acyl chloride for the synthesis of latrunculin B.
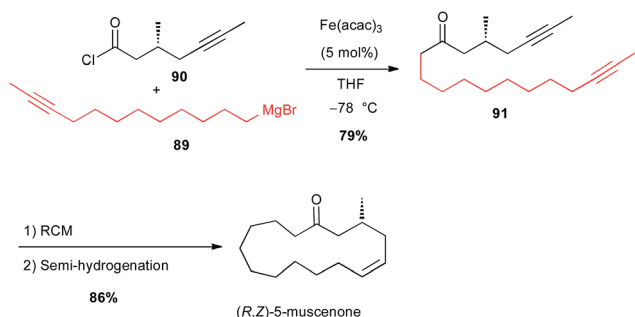
Scheme 33 Fe-catalysed acylation of an alkyl Grignard with an acyl chloride for the synthesis of (*R*,*Z*)-muscenone.

Fürstner to be a very elegant manner to obtain optically active allenols though S$_N$2′ process. Thus, this Fe(acac)$_3$-catalysed reaction proceeded with good C1 to axial chirality transfer (62% yield, dr > 8 : 1) for the preparation of a *syn* allenol **93**, which was a key intermediate in the total synthesis of amphidinolides X and Y, with regards to the oxygenated ring systems (Scheme 34 and Fig. 1).[60,61]

On the contrary, Lee found that iron-catalyzed S$_N$2′ opening of an intermediate epoxyalkyne **94** in their synthesis of
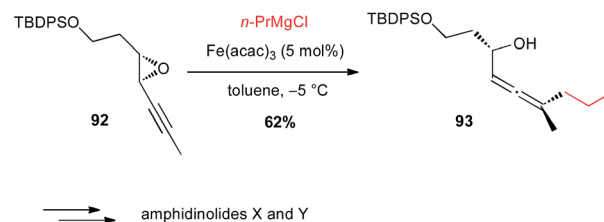
Scheme 34 Fe-catalysed coupling of propyl magnesium chloride with a propargyl epoxide for the synthesis of amphidinolides X and Y.
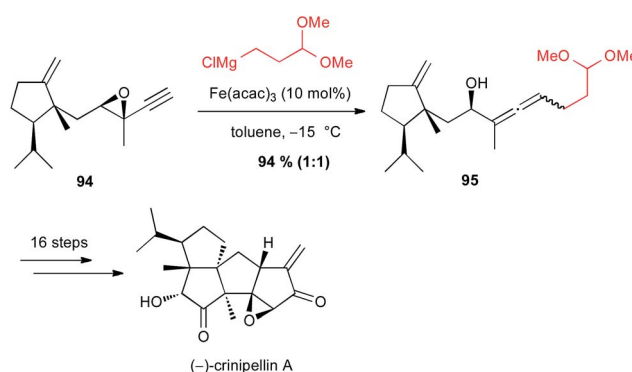
Scheme 35 Fe-catalysed coupling of a Grignard reagent with a propargyl epoxide for the synthesis of (−)-crinipellin A.
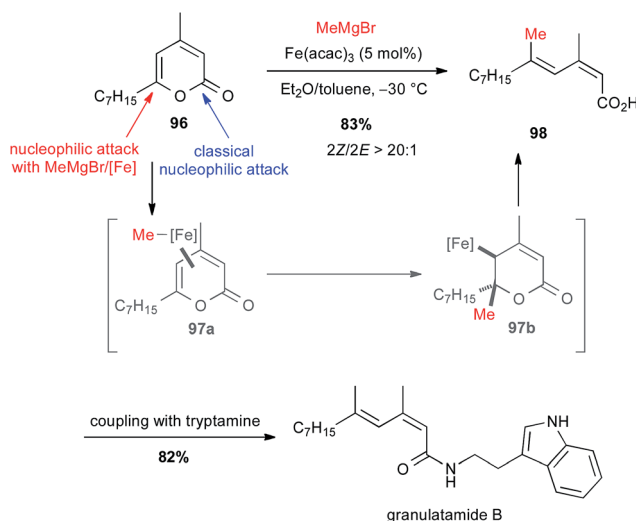
Scheme 36 Fe-catalysed ring-opening/cross-coupling with methyl Grignard and 2-pyrones for the synthesis of granulatamide B.

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(−)-crinipellin A was not diastereoselective, since **95** was obtained in 94% yield as a 1 : 1 mixture of two diastereomers (Scheme 35).[62]

2-Pyrones. The ring opening of 2-pyrones with nucleophiles classically occurs on the carbonyl group. In contrast, the reaction between 2-pyrones and Grignard reagents with $Fe(acac)_3$ in toluene or ether solvent (or a mixture of both) leads to the formation of 2,4-dienoic acids with selective 2*Z* configuration.[63] Thus, pyrone **96** reacted under these conditions to give dienoic acid **98** (2*Z*/2*E* > 20 : 1) in 83% yield. This latter, after peptidic coupling with tryptamine, leads to granulatamide B, a cytotoxic compound found in *Eunicella granulate* (Scheme 36).

The mechanism of this cross-coupling is supposed to go through a π-complex **97a** followed by conjugate addition of methyl iron on the γ,δ-olefin leading to intermediate **97b**, which affords by β-elimination the target compound **98** with desired geometry.

3. Lewis acid catalysis

Iron salts are much known as one of the first Lewis acids used in the Friedel–Crafts reaction. Bach used $FeCl_3$ in an intermolecular Friedel–Crafts reaction between a phenol derivative **99** and
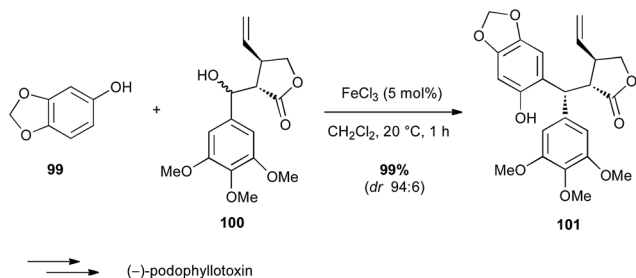
Scheme 37 Fe-catalysed Friedel–Crafts reaction with a benzyl alcohol for the synthesis of (−)-podophyllotoxin.
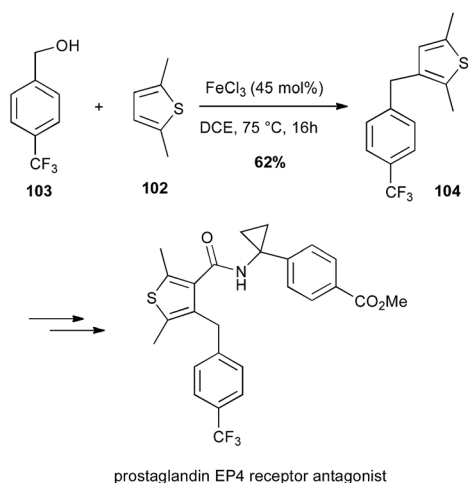
Scheme 38 Fe-catalysed coupling of 2,5-dimethylthiophene with benzyl alcohol for the synthesis of a prostaglandin EP4 receptor antagonist.
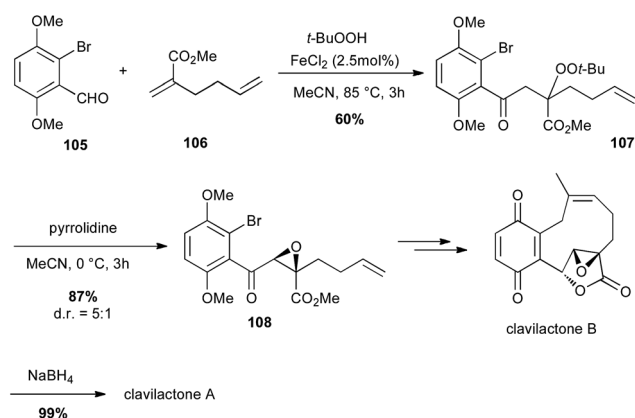
Scheme 39 Fe-catalysed carbonylation–peroxidation of an olefin for the synthesis of (+/−)-clavilactones A and B.

a functionalized benzyl alcohol **100** in the total synthesis of (−)-podophyllotoxin (Scheme 37).[64] Interestingly, $FeCl_3$ was by far the best catalyst for conversion and diastereoselectivity among several acids assessed (HBF$_4$, AuCl$_3$,…) leading to the target compound in almost quantitative yield and excellent dr.

The same iron catalyst was also successfully used in the coupling of 2,5-dimethylthiophene **102** with benzylic alcohol derivative **103** for the total synthesis of a prostaglandin EP4 receptor antagonist (Scheme 38).[65]

In 2010, Li described an interesting carbonylation–peroxidation of alkenes with aldehydes and hydroperoxides under 3-component conditions. The obtained β-peroxyketones can then offer an easy access to α-keto epoxides under basic conditions.[66] The same authors used this method to prepare a key intermediate in the total synthesis of racemic clavilactones A and B: the β-peroxyketone **107** was prepared (60%) and pyrrolidine treatment led to a *syn* epoxide **108** in very good yield (87%) and dr (5 : 1), which allowed them to obtain the key lactone fragment of clavilactones (Scheme 39).[67]

4. Carbocyclisation

During the 1980's, Takacs reported a powerful carbocyclisation proceeding through an intramolecular Fe(0)-catalysed ene reaction between allylic ethers and diene moieties.[68] In these reactions, Fe(0) is generated *in situ* from Fe(acac)$_3$, Et$_3$Al as a reductant and a ligand, such as bipyridine (bipy) or a bisoxazoline (box). In 2002, this methodology was successfully applied to the diastereoselective preparation of the key cyclopentane core of (−)-gibboside in the total synthesis of this natural iridoid glucoside isolated from *Patrinia gibbosa* (Scheme 40).[69] The reaction is very sensitive to impurities and the yield varied significantly (40–80%), but always affording **110** as a single isomer.

The Pauson–Khand reaction (PK) is also a powerful tool for synthesizing cyclopentenone systems.[70] While this [2 + 2 + 1] carbocyclisation is generally performed with Co$_2$(CO)$_8$ or Mo(CO)$_6$ in stoichiometric amounts or as catalysts under CO atmosphere, some limitations are observed with highly
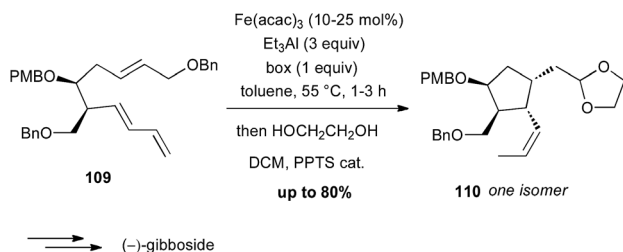
Scheme 40 Fe-catalysed enediene cyclisation for the synthesis of (−)-gibboside.

functionalised substrates. In contrast, Williams and Baik have shown that $Fe_2(CO)_9$ (2.6 equiv.) is an efficient promoter for PK reaction between allenes and alkynes, which tolerates various functional groups.[71] Shah and Williams have thus been able to perform the PK reaction on a substrate **111** bearing an oxazole moiety (61% yield), affording a precursor **112** of (+)-ileabethoxazole (Scheme 41).[72] Interestingly only the metal complex $Fe_2(CO)_9$ was able to promote the carbocyclisation with this substrate.
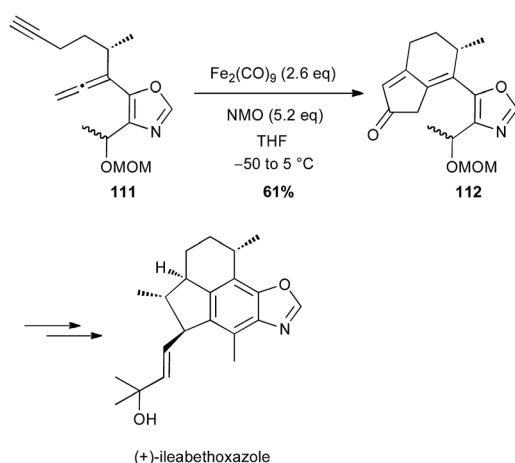
**Scheme 41** Fe-promoted Pauson–Khand reaction for the synthesis of (+)-ileabethoxazole.
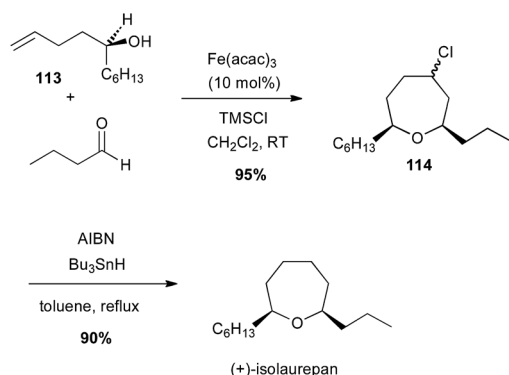
**Scheme 42** Fe-catalysed Prins cyclisation in the synthesis of (+)-isolaurepan.

Prins-type cyclisation generally occurs between homoallylic alcohols and an aldehyde under Brønsted or Lewis acidic conditions. In 2009, Padrón and Martín reported a catalytic Prins cyclisation from homoallyl amines or alcohols with catalytic iron(III) salt and stoichiometric TMSX leading to haloheterocycles.[73] Thus, an enantiopure tertiary bis-homoallylic alcohol **113** reacted with butyraldehyde in presence of $Fe(acac)_3$ (10 mol%) and TMSCl (likely generating $FeCl_3$ *in situ*) to afford the corresponding chlorooxepan **114** (95% yield), which after reduction led to (+)-isolaurepan (Scheme 42).[74]

Analogous iron(III)-catalysed Prins-type cyclisation was also used to access an indene molecule **116** (79% yield), which after demethylation and reduction afforded jungianol and its epimer (Scheme 43).[75]

Oxidative coupling promoted by iron(III) chloride is a powerful method for C–C bond formation between two arene moieties.[76] Thus, iron-mediated oxidative cyclisation of bi-aryl compounds **117** has been used for the preparation of the phenanthrene core of several alkaloids, which were prepared in a few more steps (Scheme 44).[77]
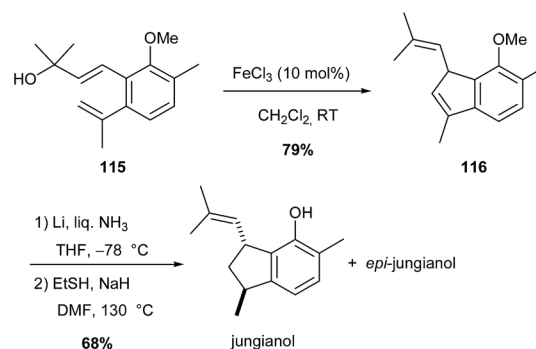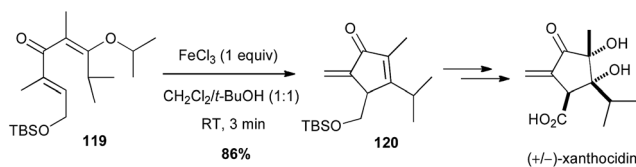
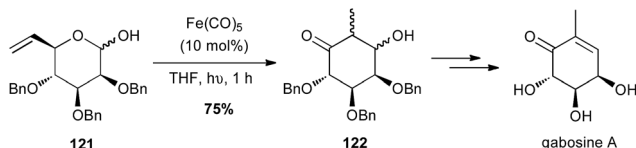**Scheme 43** Fe-catalysed Prins cyclisation in the synthesis of jungianol.
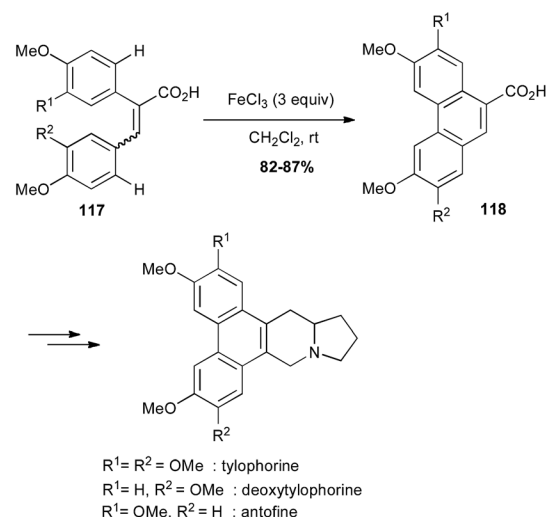
Scheme 44 Fe-catalysed oxidative cyclisation of a biaryl for the synthesis of tylophorine, deoxytylophorine and antofine.

Scheme 45 Fe-promoted Nazarov cyclisation of a divinyl ketone for the synthesis of (+/−)-xanthocidin.


Scheme 46 Fe-promoted isomerisation–aldolisation of a vinyl pyranose for the synthesis of gabosine A.

A modified Nazarov reaction on a divinyl ketone **119** promoted by iron trichloride (1 equiv.) allowed Shindo to obtain the key α-exo-methylene cyclopentadienone **120** in high yield (86%), en route to the total synthesis of (+/−)-xanthocidin, an antibiotic isolated from *Streptomyces xanthocidicus* (Scheme 45).[78]

Grée reported in 2011 that an intramolecular tandem Fe(CO)$_5$-catalysed isomerisation–aldolisation reaction starting from vinyl pyranose **121** allowed a short and elegant synthesis of natural products from the gabosine family (Scheme 46).[79]
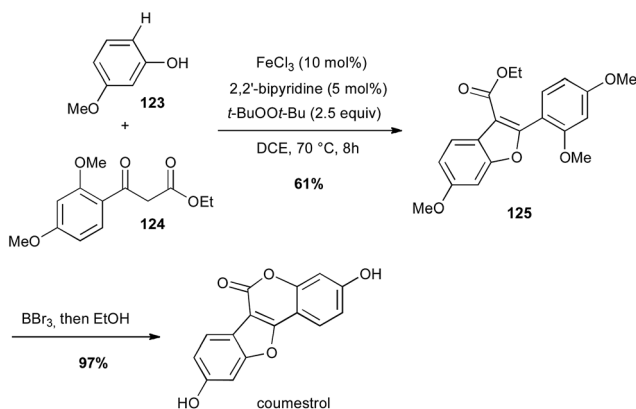
Scheme 47 Fe-catalysed coupling of a phenol with β-keto ester for the synthesis of coumestrol.
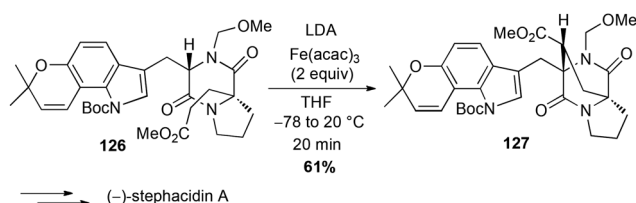
Scheme 48 Fe-catalysed oxidative coupling for the synthesis of (−)-stephacidin A.
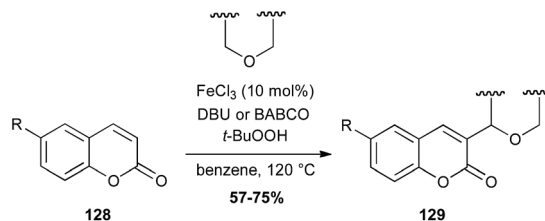
Scheme 49 Fe-catalysed coupling of coumarins with ethers.

5. C–H activation

Iron has also been used for direct C–H activation. For instance, cross-dehydrogenative coupling (CDC) between sp^2 C–H bond of a phenol **123** in the presence of a β-keto ester **124** and FeCl$_3$ allowed the preparation in a gram-scale of the benzofuran core of coumestrol, a natural estrogenic analogue, in good yield (Scheme 47).[80]

In 2006, Baran reported a formal intramolecular coupling between two sp^3 C–H bonds albeit the reaction goes through oxidative heterocoupling of two types of enolates. Enolates are generated in presence of LDA and the coupling takes place in presence of an oxidant, among which Fe(acac)$_3$ (2 equiv.) proved to be very efficient (61% yield of **127**). Thus, this method allowed the preparation in a gram-scale of the polycyclic core of (−)-stephacidin A, a natural estrogenic analogue (Scheme 48).[81]

Coumarin is a fragrant compound found in many plants. In 2015, an interesting radical coupling between coumarins **128** and ethers catalyzed by iron chloride in presence of TBHP has been described. This reaction allows the formation of a C–C bond between an sp^2 carbon of the coumarin and the carbon in α-position of the ether (Scheme 49).[82]

6. Conclusions

Iron-catalysed reactions are nowadays-key tools in the total synthesis of natural products and pharmacologically important chemical entities. While the cross-coupling reaction between Grignard reagents and numerous electrophiles is well documented and constitutes the most visible facet, iron catalysis is only at the dawn of its development. Innovative and powerful methodology, such as Fe-catalysed C–H activation, is still an under-explored field, which will become shortly a source of new applications, especially for the large-scale preparation of highly functionalised molecules. Moreover, the number of enantioselective transformations with iron is still low compared to other metals and such methodologies are definitely required in total synthesis. Attractiveness of iron salts relies for sure on their cost and their non-toxic property, but efficiency and selectivity observed in these chemical transformations are also the driving force of the efforts brought in these studies.

7. Acknowledgements

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