Iron-catalyzed Michael reactions

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From experiment to theory and back

ABSTRACT

The catalysis of Michael reactions by FeCl$_3$ · 6 H$_2$O is an environmentally sound alternative to classical base catalysis. A number of β-diketones and β-oxo esters are cleanly converted with methyl vinyl ketone to the corresponding Michael reaction products within a few hours at ambient temperature with quantitative yields being achieved in most cases. The reaction can be performed solvent free and without any need for anhydrous or inert conditions. Due to quantitative chemo selectivity, work-up and purification are very simple. Iron compounds are readily available, and with respect to economical and environmental considerations, it is the transition metal catalyst of choice. Starting materials are converted stoichiometrically and atom-economically without any need of reagents or even solvents and without generation of any by-product. The mechanism of this process has been investigated by X-ray absorption and Raman spectroscopy, ESI-MS spectrometry as well as kinetic studies and DFT-calculations. Actually, a strong anion-dependence of the catalytic activity was predicted by our spectroscopic and theoretical studies which led to the development of a new catalyst system being about 10 times more active than FeCl$_3$ · 6 H$_2$O.

INTRODUCTION

One essential goal of present and future research in organic chemistry is the development of sustainable, efficient and selective synthetic processes. In this regard, catalysis is playing a key role, because it is involved in the production of about 80 percent of all chemical and pharmaceutical products. In particular, transition metal compounds are established catalysts in synthetic organic chemistry. Organic substrates are bound, activated, and converted within the coordination sphere of a metal centre. The role of iron in catalysis will become more important in the future. After aluminium, iron is the second frequent metal in the earth crust. Mankind has learned already more than 3000 years ago to routinely process iron in its elemental form. Most iron salts and complexes are commercially available in large amounts and at low costs or can be readily synthesized. In contrast to other established metal catalysts (e.g. Pd, Rh, Ru, Ir), Fe compounds are environmentally benign and show low toxicity.
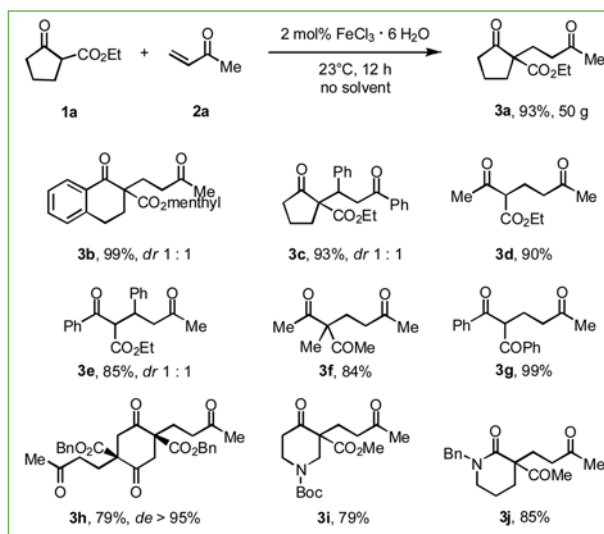
IRON-CATALYSIS OF THE MICHAEL REACTION

The Michael reaction is the conjugate addition of a soft enolate, commonly derived from a β-dicarbonyl compound **1**, to an acceptor activated olefin like enone **2a** resulting in a 1,5-dioxo constituted product **3** (1). Traditionally, these reactions are catalyzed by Brönsted bases such as tertiary amines, alkali metal alkoxides, or hydroxides. However, the strongly basic conditions are often a limiting factor since they can cause undesirable side- and subsequent reactions, such as aldol cyclizations and retro-Claisen type decompositions. To address this issue, acid (2) and metal catalyzed (3) Michael reactions have been developed in order to carry out the reactions under milder conditions.

A breakthrough in the field of iron-catalyzed Michael reactions was achieved in 1997 with the use of FeCl$_3$ · 6 H$_2$O (4). In Scheme 1 the reaction of β-oxoester **1a** with methyl vinyl ketone (**2a**) is given as an example, which was scaled up to 50 g of product **3a** (5). The efficiency of this iron catalyzed process is remarkable: No inert conditions are required, since oxygen and moisture are tolerated. As long as the starting materials and the product are liquid at ambient temperature no solvents are necessary. A few milligrams of FeCl$_3$ · 6 H$_2$O are simply added to a stoichiometric mixture of the starting materials.

With this method Brönsted basic conditions are avoided resulting in excellent chemoselectivities. Because of the quantitative conversions, workup and purification are extraordinary simple: Separation of the product from the catalyst is achieved by either distillation or filtration through some silica. Apart from these practical aspects, the catalyst FeCl$_3$ · 6 H$_2$O is in terms of ecological and economical considerations the transition metal compound of first choice. Scheme 1 gives an impression of the scope of this method (6). Best results are usually obtained with cyclic β-oxoesters; with 1 mol% FeCl$_3$ · 6 H$_2$O yields generally exceed 90 percent (**3a–3c**). Acyclic β-oxoesters and β-diketones require 5 mol% of the catalyst (products **3d–3g**). The conversion of substituted enones like chalcone requires elevated temperatures, e.g. 50°C in case of products **3c** and **3e**. Succinyl succinates can be converted in double Michael reactions to yield products like **3h** as cis-diastereomer (7). Furthermore, piperidine derivatives (8), lactones and lactams (9) can be applied as Michael donors. Malonates as donors do not react under the conditions of the iron catalysis, since they form no chelate complexes **9** (cf. Scheme 4) with Fe(III). Similarly, β-cyano esters and β-cyano ketones are not converted with iron, but ruthenium catalysts with optimal results (10). With regard to the acceptor, reaction of cyclic enones are only observed in rare cases and with low yields (11).


Scheme 1. Catalysis of the Michael reaction by FeCl$_3$ · 6 H$_2$O. Scope of Michael acceptors and donors.

INTRAMOLECULAR UND POLY-MICHAEL-REACTIONS

Medium size ring formation is often a challenging task in organic synthesis. With FeCl$_3$ · 6 H$_2$O as the catalyst the compound **4**, with both, a Michael donor and acceptor moiety, undergoes intermolecular reaction to furnish the annulated product **5** with two seven-membered rings as a single diastereomer (12). An attempt of macrocyclization (17-membered ring) by iron-catalyzed Michael reaction was not fruitful (13).

Quantitative conversion is one of the essential preconditions to achieve a significant molecular weight in a stepwise
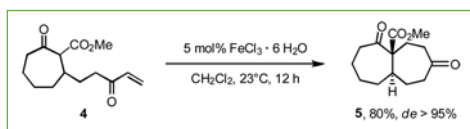
Scheme 2. An intermolecular Michael reaction catalyzed by FeCl₃ • 6 H₂O.
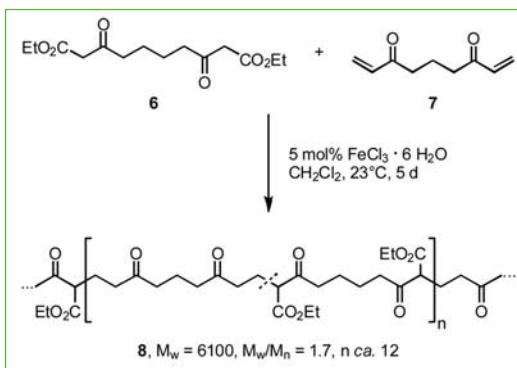
Scheme 3. A poly-Michael reaction catalyzed by FeCl₃ • 6 H₂O.

respectively. From these calculations it can therefore be concluded, that mono cationic bis-β-diketonates are supposingly the catalytically most active species.

polymerization process. Consequently, an iron catalyzed Michael reaction would be a suitable elementary step for a polyaddition. Bis-donor **6** and bis-acceptor **7** being readily accessible from common starting materials (14) were converted with FeCl₃ • 6 H₂O to yield a poly-addition product **8**. The material is an analogue to ethylene carbon monoxide copolymers (15) bearing an interesting constitution with carbonyl moieties all along the carbon backbone. According to molecular mass analysis performed by GPC the oligomeric product **8** contained an average of 24 monomeric units (n ≈ 12 in Scheme 3) (14). Although macromolecules like **8** will never be able to compete from an economic point of view with so far known polyaddition products, it maybe of academic interest to compare their properties with other structures.

MECHANISTIC INVESTIGATIONS

Proposed Catalytic Cycle

With respect to the mechanism of the iron-catalysis, the activity of FeCl₃ • 6 H₂O is closely related to its ability to give dionato chelate complexes **9** with β-dicarbonyl compounds. Without prior deprotonation – even in Brönsted acidic media – these deep coloured iron complexes are instantly formed. With this property Fe(III) is unique among all other transition metals, which require a stoichiometric amount of base for dionato-complex formation. Known for over 100 years, the significant colour of the complexes has been utilized for the detection of β-oxoesters and β-diketones. The chelate ligand in dionato complex **9** is planar and it is particularly stabilized by π-delocalization. Besides this thermodynamic stability the iron(III) centre (d^5) has 17 valence electrons when coordinated by six ligands in an octahedron, thus, its coordination sphere is kinetically labile. By ligand exchange the acceptor **2a** is coordinated at a vacant site to form species **10** (Scheme 4). The function of the centre metal is not only to hold the acceptor in proximity to the donor. Additionally, the acceptor is activated by Lewis acidity of the centre metal. Subsequently, the nucleophilic carbon atom of the dionato ligand is alkylated by the acceptor to form the bicyclic intermediate **11** with a coordinating enolate side chain. From this species **11** the product **3k** is liberated readily, and complex **9** regenerated by ligand exchange, since π-delocalization is obviously impossible in structure **11**.
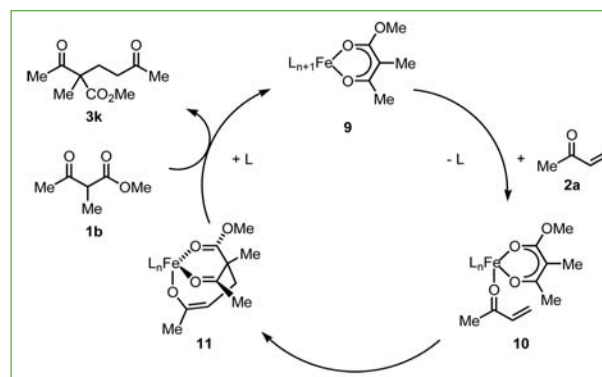
DFT-Calculations

While the mechanistic proposal depicted in Scheme 4 is in accordance with the experimental observation of first order kinetics in iron, direct experimental support for catalytic cycle and the intermediates was lacking. Therefore, quantum chemical density functional calculations were performed as an additional source of information (16). For these calculations, methyl 2-methyl-3-oxobutyrate (**1b**) was used as the Michael donor and methyl vinyl ketone (**2a**) as the acceptor. Since ligand exchange was supposed to be facile in the coordination sphere of iron (17), the relative stabilities of **9**, **10**, and **11** were computed. For the C–C coupling step **10→11**, however, transition states have been located to determine the reaction barrier. Several diketonates complexes with OH₂ and Cl⁻ as spectator ligands L have been investigated. In Figure 1 the energy profiles of two significant examples with L = OH₂ are shown: Series a with one diketonate and series b with two equatorial diketonates.
The intrinsic reaction barriers are 78 kJ/mol and 63 kJ/mol,

EXAFS-, Raman- and ESI-MS-Investigations

In order to get insight into the metal species of iron catalyzed Michael reactions X-ray absorption studies have been performed. Whereas EXAFS-spectroscopy is sensitive to the local environment of a central atom, including the number, distance and kind of surrounding atoms, XANES spectroscopy is an effective method to analyze the coordination geometry of a central atom (18). Iron salts exhibit a broad variety of pre-edge features (pre-peaks) in Fe–K edge spectra originating from 1s→3d transitions. The energy position and intensity are strongly dependent on the spin state, oxidation state and geometry (19).

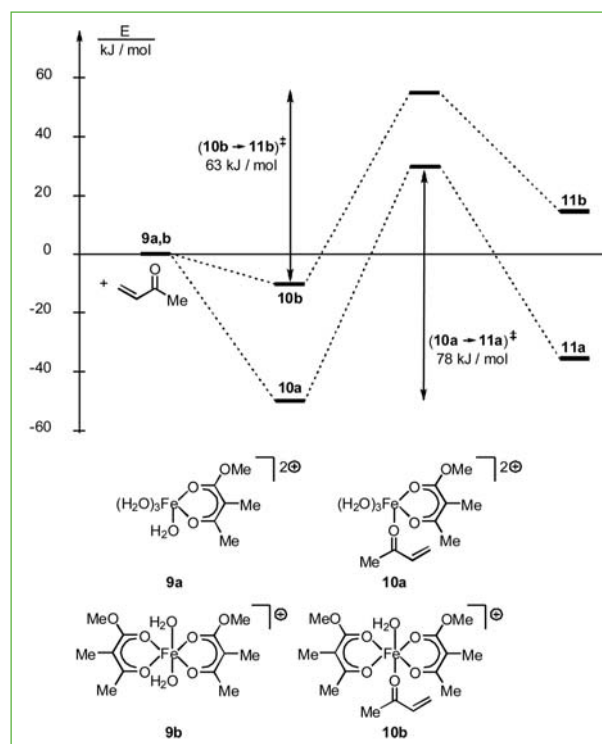Scheme 4. Mechanism of the iron-catalyzed Michael reaction.

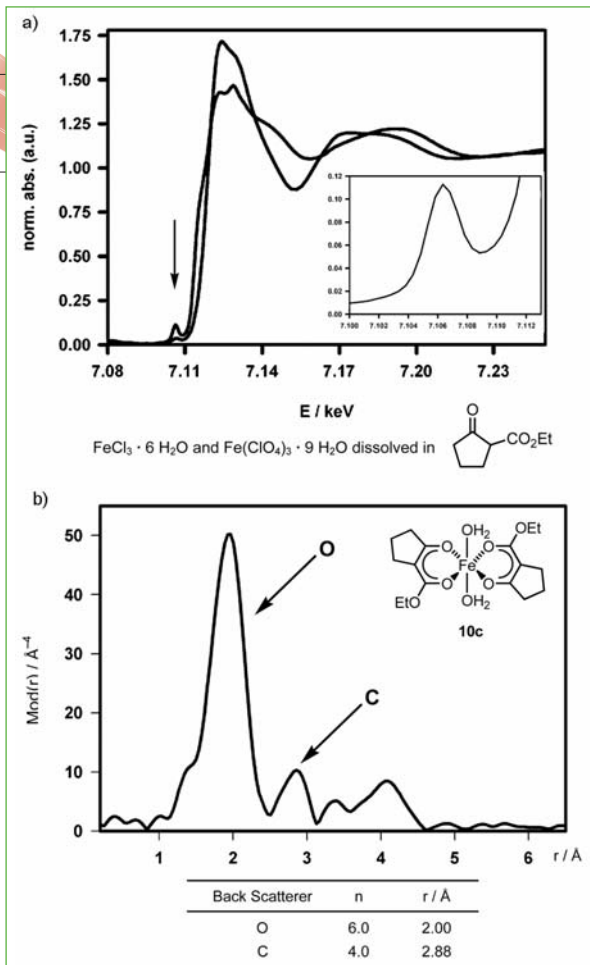Figure 1. DFT-Calculations on the two first steps of the catalytic cycle.

Figure 2. X-ray absorption spectroscopy (a) EXAFS-spectrum; (b) Fourier transformation and numerical analysis.

Back Scatterer	n	r / Å
O	6.0	2.00
C	4.0	2.88

The EXAFS spectra of $FeCl_3 \cdot 6 H_2O$ and $Fe(ClO_4)_3 \cdot 9 H_2O$ precatalysts *in operando* with β-oxoester **1a** as Michael donor are depicted in Figure 2a (20). A significant pre-edge peak is observed in case of $FeCl_3$ (see insert of Figure 2a). The Fourier transformation is shown in Figure 2b. It can be analyzed as following back scatterers: Six oxygen atoms with r = 2.00 Å and four carbon atoms with r = 2.88 Å being clearly compatible with a bis-β-diketonate complex **10c** (Scheme 5) as the dominating iron-species under reaction conditions. Moreover, pre-peak observable with $FeCl_3 \cdot 6 H_2O$ as the precatalyst is a clear indication of some tetrahedral species. When looking at the Raman spectrum of a reaction mixture, this species can be identified as $FeCl_4^-$ by its ν(A1) = 333 cm^{-1} band.

The initial rate of the reaction was determined in kinetic studies to be six times higher compared to $FeCl_3 \cdot 6 H_2O$ when applying $Fe(ClO_4)_3 \cdot 9 H_2O$ as the precatalyst. Actually, the rate of the reaction can be slowed down when adding aliquots of $BnNEt_3^+Cl^-$. Therefore, chloride ions behave like a catalyst poison. With view of the results from X-ray and Raman spectroscopy, the formation of $[FeCl_4]^-$ from Fe^{3+} and Cl^- can be regarded as a thermodynamic iron sink which removes iron from the pool of catalytically active iron species. Moreover, ESI-spectra of reaction mixtures confirm cationic bis-β-diketonato complexes like **10c**. In the negative mode of ESI-MS, $[FeCl_4]^-$ is detected as the predominant anionic species when $FeCl_3 \cdot 6 H_2O$ is used as the precatalyst.

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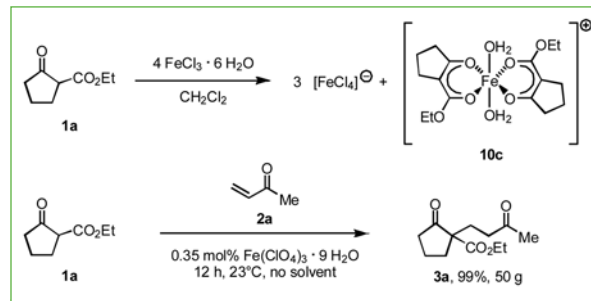
Scheme 5. Iron-species under reaction conditions and an improved protocol with chloride free catalyst.

CONCLUSION: REFINED RECIPE...

Summarizing up spectroscopic, kinetic and spectrometric investigations, four equivalents of $FeCl_3 \cdot 6 H_2O$ are needed to generate one equivalent of catalytically active bis-β-diketonato complex **10c**. Three equivalents of $[FeCl_4]^-$ are formed as the dominating iron-complex in solution (Scheme 5, first line). This species behaves like a thermodynamic iron-sink under reaction conditions. It removes $^3/_4$ of Fe(III), only $^1/_4$ remains catalytically active. Consequently, the absence of the coordinating counter ion, e.g. by using $Fe(ClO_4)_3 \cdot 9 H_2O$ as the precatalyst, results in significant rate enhancement of the catalysis. From this result, an optimized protocol for the iron catalysis was deduced, applying only 0.35 mol% of $Fe(ClO_4)_3 \cdot 9 H_2O$. With ca. 400 mg of the catalyst about 50 g of product **3a** can be prepared under solvent free conditions, at ambient temperature and within 12 h; the yield is quantitative (Scheme 5, second line).

REFERENCES AND NOTES

1. J. Christoffers, *Encyclopedia of Catalysis* (Ed. Horvath, I.), Wiley, New York, **5**, pp. 99-118 (2003).
2. H. Kotsuki, K. Arimura et al., *J. Org. Chem.* **64**, pp. 3770-3773 (1999).
3. a) J. Comelles, M. Moreno-Mañas et al., *Arkivoc*, pp. 207-238 (2005); b) J. Christoffers, *Eur. J. Org. Chem.*, pp. 1259-1266 (1998).
4. a) J. Christoffers, *Synlett*, pp. 723-732 (2001); b) J. Christoffers, *Chem. Commun.*, pp. 943-944 (1997); c) J. Christoffers, *J. Chem. Soc., Perkin Trans.* **1**, pp. 3141-3149 (1997).
5. J. Christoffers, *Org. Synth.* **78**, pp. 249-253 (2002); *Coll. Vol.* **10**, pp. 588-592 (2004).
6. a) A. Hinchcliffe, C. Hughes et al., *Org. Proc. Res. Dev.* **11**, pp. 477-481 (2007); b) M. E. Jung, S.-J. Min et al., *J. Org. Chem.* **69**, pp. 9085-9089 (2004); c) J. Christoffers, H. Oertling et al., *J. Prakt. Chem.* **342**, pp. 546-553 (2000).
7. a) J. Christoffers, Y. Zhang et al., *Synlett*, pp. 624-626 (2006); b) Y. Zhang, J. Christoffers, *Synthesis*, pp. 3061-3067 (2007).
8. J. Christoffers, H. Scharl, *Eur. J. Org. Chem.*, pp. 1505-1508 (2002).
9. a) J. Christoffers, H. Oertling et al., *Eur. J. Org. Chem.*, pp. 1665-1671 (2003); b) J. Christoffers, B. Kreidler et al., *Eur. J. Org. Chem.*, pp. 2845-2853 (2003).
10. a) S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **33**, pp. 225–233 (2000); b) T.-P. Loh, L.-L. Wei, *Tetrahedron* **54**, pp. 7615-7624 (1998); c) T. Naota, H. Taki et al., *J. Am. Chem. Soc.* **111**, pp. 5954-5955 (1989).
11. a) A. Mekonnen, R. Carlson, *Eur. J. Org. Chem.*, pp. 2005-2013 (2006); b) Y. Mori, K. Kakumoto et al., *Tetrahedron Lett.* **41**, pp. 3107-3111 (2000); c) G. Bartoli, M. Bosco et al., *Eur. J. Org. Chem.*, pp. 617-620 (1999).
12. J. Christoffers, *Tetrahedron Lett.* **39**, pp. 7083-7084 (1998).
13. J. Christoffers, H. Oertling, *Tetrahedron* **56**, pp. 1339-1344 (2000).
14. J. Christoffers, H. Oertling et al., *Synlett*, pp. 349-350 (2000).
15. E. Drent, P.H.M. Budzelaar, *Chem. Rev.* **96**, pp. 663-681 (1996).
16. S. Pelzer, T. Kauf et al., *J. Organomet. Chem.* **684**, pp. 308-314 (2003).
17. G. Gumbel, H. Elias, *Inorg. Chim. Acta* **342**, pp. 97-106 (2003).
18. H. Bertagnolli, T.S. Ertel, *Angew. Chem.* **106**, pp. 15-37 (1994); *Angew. Chem. Int. Ed.* **33**, pp. 45-66 (1994).
19. T.E. Westre, P. Kennepohl et al., *J. Am. Chem. Soc.* **119**, pp. 6297-6314 (1997).
20. M. Bauer, T. Kauf et al., *Phys. Chem. Chem. Phys.* **7**, pp. 2664-2670 (2005).