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Iron-Catalyzed Cross-Coupling of Thioesters and Organomanganese Reagents**

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Dedicated to Prof. Dr. Matthias Beller on the occasion of his 60th birthday

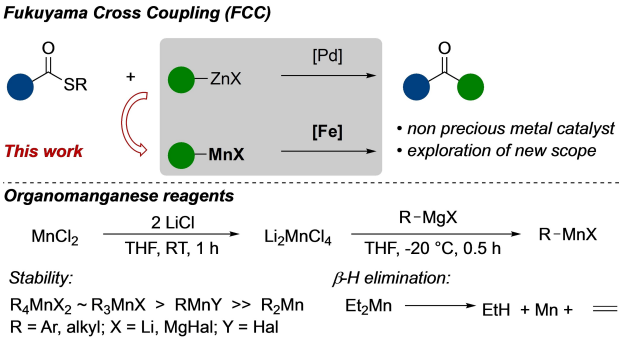
Abstract: We report a Fukuyama-type coupling of thioesters with aliphatic organomanganese reagents utilizing a cheap and easily available iron(III) precatalyst. The reactions exhibit a wide tolerance of solvents and functional groups, allowing for the conversion of thioesters derived from natural products and pharmaceutical compounds. A strong steric impact from each reaction component (carboxylic moiety, thiol substituent and manganese reagent) was displayed, which enabled regioselective transformation of dithioesters. Mechanistic investigations showed that the released thiolate does not act as a mere spectator ligand, but rather positively influences the stability of intermediate alkyl(II)ferrates.

Introduction

The palladium-catalyzed reaction between thioesters and organozinc reagents, generally known as Fukuyama cross-coupling (FCC),[1] constitutes a convenient method for the synthesis of ketones, as demonstrated by several synthetic applications.[2] Besides variations of the palladium catalyst,[3] other transition metals such as the non-precious nickel[4] or cobalt[5] were employed. For the transmetalation step, other less polar reagents such as arylboronic acids introduced by Liebeskind and Srogl[6] or siloxanes reported by Van der Eycken[7] require the presence of stoichiometric amounts of copper in addition to the palladium-based catalysts. To date, couplings using organoboronates,[8] -stannanes[9] and -indium reagents[10] were exclusively developed for palladium-based catalysts. The advantage of using thioesters instead of acid chlorides is their kinetic stability in the presence of water and the possibility to retain the functionality during other synthetic steps, including work-up, which makes them suitable for late-stage functionalizations.

Despite the broad success of organozinc reagents in FCC, the use of attractive non-precious metal catalysts is usually accompanied by limitations regarding the reactivity of organozinc reagents. This was also shown in our work on their Ni-catalyzed coupling with thioesters, wherein aliphatic zinc reagents were completely unreactive, thereby limiting the substrate scope.[4c] Other limitations also occur in Pd-catalyzed reactions, for example the need of stochiometric additives such as Zn(II) salts for the conversion of secondary alkyl reagents.[11] While more reactive Grignard reagents have been shown to resolve the reactivity issue under nonprecious metal catalysis with thioesters[12] or with acid chlorides,[13] the general applicability can be considerably limited. To bridge this gap in reactivity between Grignard and organozinc reagents, we embarked on the employment of organomanganese reagents, which possess a reportedly good functional group tolerance combined with a generally higher reactivity than their zinc analogues (Scheme 1).[14]

In early works, the reactivity of such "manganese Grignard reagents" was mainly studied in non-catalytic reactions or in Cu-



Scheme 1. Fukuyama cross-coupling and our iron-catalyzed coupling of organomanganese reagents.

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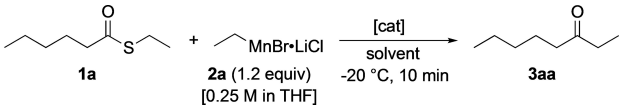
catalyzed couplings.[15] To the best of our knowledge, only limited examples of iron-catalyzed cross-couplings have been reported in this time frame (before 2000).[16] More recent publications contain further examples of inviolate potential of for example aryl manganese compounds or other stabilized manganese reagents in transition metal-catalyzed reactions utilizing Fe or Ni-catalysts.[17] For clarity, the employed reagents can be considered stabilized, since they were unable to undergo β-hydrogen elimination, which is a main decomposition pathway.[18] Another important feature of these reagents is their property to form higher substituted manganates ($LiMnR_3$ or Li_2MnR_4), which led to the recent discovery of a tandem Mn–I exchange/homocoupling, a reactivity thought to be reserved for RLi or RMgX reagents.[19] These literature examples inspire further studies of their so far less known potential, as shown in this work on iron-catalyzed cross-coupling reaction of β-hydrogen containing aliphatic organomanganese reagents with thioesters.

Results and Discussion

On the basis of previous literature, aliphatic manganese reagents were synthesized by treating Grignard reagent with $MnCl_2 \cdot 2$ LiCl.[17a] In the model reaction, thioester **1a** reacted with ethyl manganese bromide lithium chloride complex in the presence of potential catalysts (Table 1). Various transition metal salts provided the product **3aa** in low to moderate yields (Entries 2–6). To our delight, the use of broadly available iron catalysts resulted early on in quantitative conversions and very good yields (Entries 7–10), especially with iron(III) acetylacetonate (acac) (Entry 11). Slightly decreased yield was obtained using only 1 mol% of catalyst, which corresponds to turnover frequency of 516 h^{-1} (Entry 12). The reaction can be performed in almost any ethereal solvent with very good yields as well as in EtOAc (Entries 13–15). Highly polar co-solvents such as *N*-methyl pyrrolidone (NMP) showed a slightly decreased yield (Entry 16). This is in contrast to literature observations in iron-catalyzed Kumada cross-couplings of aryl halides with organomanganese and organomagnesium reagents, which usually perform better with NMP.[16a,c,20] Surprisingly, almost quantitative yields were obtained by using non-degassed THF (Entry 18).

Table 1. Optimization of reaction conditions for the synthesis of octan-3-one.[a]



1a — **2a** (1.2 equiv) [0.25 M in THF] — **3aa**

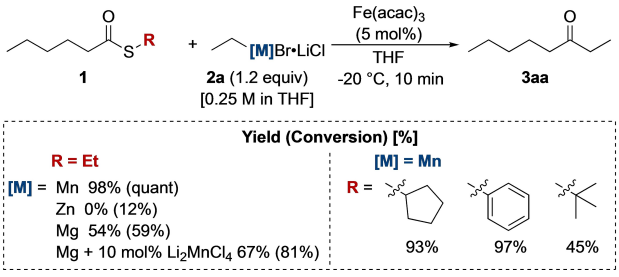
Entry	Catalyst	Solvent[b]	Conv. [%][c]	Yield [%][c]
1	none	THF	18	0
2	$Ni(acac)_2$	THF	95	52
3	$CoCl_2$[d]	THF	81	64
4	CuI[d]	THF	44	37
5	$Pd(PPh_3)Cl_2$	THF	26	18
6	$Mn(acac)_3$	THF	62	5
7	$FeCl_2$[d]	THF	92	82
8	$Fe(acac)_2$	THF	Quant	89
9	$FeCl_3$[d]	THF	Quant	84
10	$(FeCl_3)_2(tmeda)_3$	THF	Quant	89
11	$Fe(acac)_3$	THF	Quant.	91
12	$Fe(acac)_3$[e]	THF	Quant	86
13	$Fe(acac)_3$	THF/Et_2O	Quant	88
14	$Fe(acac)_3$	THF/1,4-dioxane[f]	98	90
15	$Fe(acac)_3$	THF/EtOAc	Quant.	92
16	$Fe(acac)_3$	THF/NMP	90	84
17	$Fe(acac)_3$	THF/DCM	83	71
18	$Fe(acac)_3$	THF[g]	Quant.	98 (78[h])

[a] Reaction conditions: thioester (53.4 mg, 333 μmol, 1 equiv.), EtMnBr·LiCl (400 μmol, 1.2 equiv. based on titre, usually ≤0.28 M in THF), [catalyst] (5 mol%), dry THF (1 mL), −20 °C, 10 min. [b] Mixture: THF/co-solvent = 8:5 (v/v). [c] Determined by quantitative GC-FID using pentadecane as internal standard. [d] 10 mol%. [e] 1 mol%. [f] Slurry due to melting point of the co-solvent. [g] Solvent has not been degassed. [h] Isolated yield.

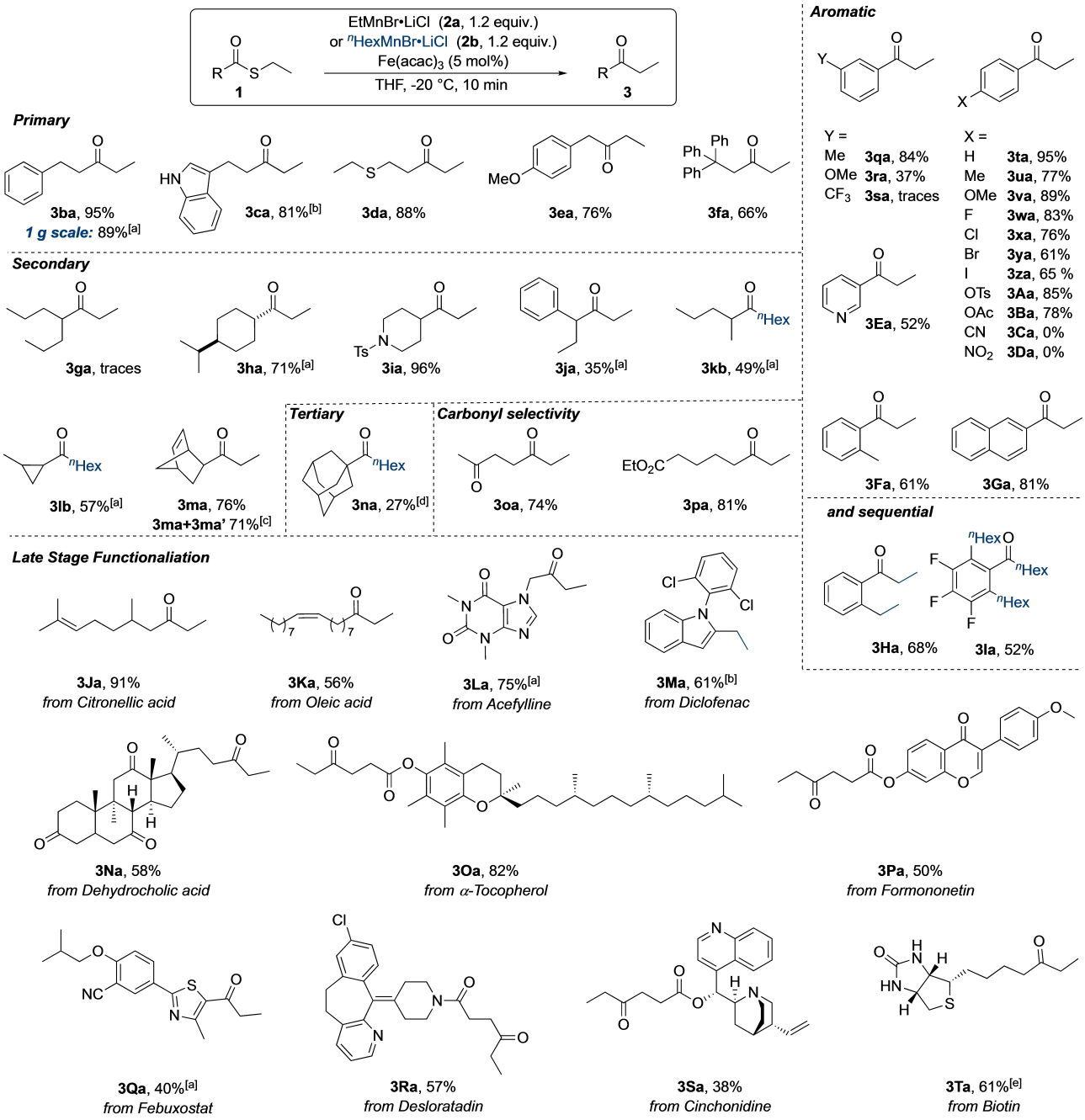
The performance of organomanganese reagents was more efficient compared to other organometallic compounds under identical reaction conditions (Scheme 2), for example to organozinc reagents, which furnished no product and also to Grignard reagents leading to moderate results and on prolonged reaction period to 1,2-addition. Addition of 10 mol% of $MnCl_2 \cdot 2$ LiCl to a reaction with Grignard reagent did not resolve this issue. Furthermore, a preliminary screening showed an influence of the thioester thiol moiety on the conversion (prim ~ Ar > sec ≫ tert). The 1,2-addition was never observed in the coupling of organomanganese reagents under the applied conditions for standard substrate, even if **3aa** was exposed to the reaction conditions.

Based on this initial screening, a series of *S*-ethyl thioesters was subjected to the coupling with ethyl manganese bromide (Scheme 3). Primary thioesters were converted in good to excellent yields to the products **3ba**–**fa**, including the sterically demanding 3,3,3-triphenyl substituted substrate **1f**. A strong steric influence on the reaction stems from the α-substitution of the thioester (*prim* > sec_{cyclic} > *tert* > *sec*). The complete breakdown of reactivity of the secondary substrate **1g** and similar aliphatic compounds contrasted with other secondary thioesters having an α-methyl group (**1k**), an α-phenyl group (**1j**) or being cyclic (**1h**, **1i**, **1l**, **1m**), which all underwent the transformation with moderate to excellent yields. The conducted experiments showed that the unreactive **1g** did not poison or slow down the conversion of primary thioester **1b**, yet, **1j** did.

The reaction performed well on a higher scale as exemplified for **3ba**. The diastereomeric ratio of **1h**, **1l** and **1m** (as pure *endo* diastereomer or 5:3 *endo:exo* mixture) remained unchanged.



Scheme 2. Iron-catalyzed Fukuyama cross-coupling with different transmetalating reagents and varying *S*-substituents.



Scheme 3. Coupling of various thioesters with ethyl manganese bromide. Isolated yields are given unless stated otherwise. Standard reaction conditions: thioester (1 mmol, 1 equiv.), EtMnBr·LiCl or ^{n}HexMnBr·LiCl (1.2 mmol, 1.2 equiv. based on titre, usually ≤ 0.3 M in not degassed THF), $Fe(acac)_3$ (17.7 mg, 50 µmol, 0.05 equiv.), dry THF (1 mL, not degassed), −20 °C, 10 min. [a] 15 min. [b] EtMnBr·LiCl (2.2 mmol, 2.2 equiv. based on titre, usually ≤ 0.3 M in THF). [c] Mixture of isomers: *endo*/*exo* = 5 : 3. [d] NMR yield. [e] EtMnBr·LiCl (3.2 mmol, 3.2 equiv. based on titre, usually ≤ 0.3 M in THF).

Worth mentioning is the successful synthesis of benzylic ketones **3ea** and **3ja** in good yields without decarbonylation products being detected via GC-MS. This indicates that formation of acyl radicals is unlikely, or their recombination with the metal centre is faster than a potential decarbonylation step. Selectivity towards catalytic conversion of the thioester moiety was observed with substrates containing a keto, ester or amide functionality leading to products **3oa**, **3pa** and **3La** in good yields. In our previous studies on the nickel-catalyzed FCC, we were unable to use benzoic acid derived thioesters.[4c] Gratifyingly, several aromatic thioesters with *o*-, *m*-, and *p*-substituents performed well in the coupling reaction. (Pseudo-)halides were tolerated under the reaction conditions furnishing **3wa**–**Ba** products in fair to good yields showing only traces of side products resulting from the oxidative addition into the C–X bond.

Especially, the tolerance of aryl iodides (**3za**) should be highlighted, since this is usually difficult for palladium-catalyzed cross-coupling reactions due to the competing occurrence of

Negishi coupling.[3b] Moreover, similar reactivity in iron-catalyzed sp^2-sp^3-cross-coupling is known for Grignard reagents, though in the presence of NMP.[20b] The reaction does not tolerate highly redox-active functionalities such as nitro-groups. Compounds containing a nitrile-group (e.g. **3Ca**) did not furnish product, which might be attributed to a coordination of the functional group to the active catalyst. This claim was substantiated with the addition of the thioester **1C** to the synthesis of **3aa**, which reduced the yield. A methyl group on the aromatic moiety did not affect the results much, only in the case of the sterically more demanding *ortho*-substituted thioester, a lower yield was obtained for the product **3Fa**. Interestingly, the employed *meta*-substituted benzoic acid thioesters **3ra** and **3sa** resulted in diminished yields, depending on the electronic properties of the substituent. Furthermore, a sequential reactivity was observed for the conversion of thioester derived from *ortho*-fluoro-functionalized benzoic acid yielding **3Ha** and **3Ia**, which formed through concurrent activation of the C–S and C–F bonds. This was found to be applicable to every *ortho*-halide substituted thioester. Similar reactivity was reported in instance of organomanganese reagents with *ortho*-chloro- or bromo-substituted phenones by Cahiez.[21] It should also be noted that heterocyclic cores, which might coordinate to metal and thus hinder the reaction, were tolerated in this case (products **3Ea** and **3ca**).

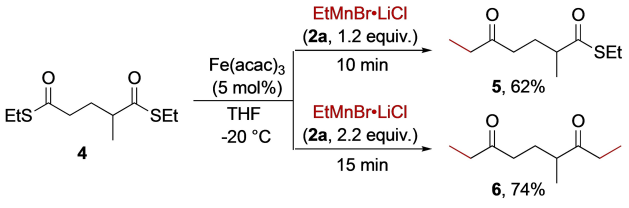
To explore the suitability of this method for late-stage functionalization, thioesters derived from citronellic acid **1J**, oleic acid **1K**, acefylline **1L**, dehydrocholic acid **1N**, α-tocopherol **1O**, formononetin **1P**, febuxostat **1Q**, desloratadin **1R**, cinochonidine **1S** and biotin **1T** could be converted in moderate to excellent yields. Some of the compounds were converted in a two-step strategy utilizing a linker, in order to extend the scope of suitable targets to amines and alcohols. Upon subjecting Diclofenac thioester **1M** to the reaction conditions, the sequential coupling/enamine formation was observed, leading to a functionalized indole derivative **3Ma**. Notably, no side reaction from the C–Cl bond activation occurred.

In addition, a useful regioselective coupling was demonstrated for sterically differentiated thioester **4** (Scheme 4). A selective mono-coupling of the primary thioester moiety was achieved by using 1.2 equivalents of the transmetalating reagent providing **5** in 62% yield. Whereas 2.2 equivalents of **2a** led to coupling of both thioesters to yield 79% of diketone **6** after slightly longer reaction time.

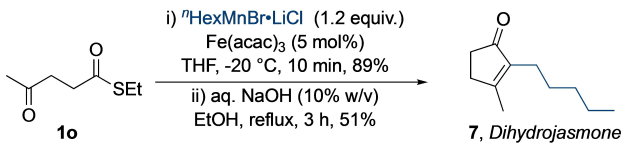
The reaction was also employed in the synthesis of dihydrojasmone, furnishing the precursor undecane-2,4-dione (**3ob**) in very good yield (Scheme 5). The diketone was then further converted to the natural product **7** by an aldol reaction known from previously described synthesis.[22]

Next, we explored the performance of different organomanganese reagents (Scheme 6). As expected, chain length of non-branched aliphatic organomanganese reagents had only a weak influence on reaction performance, as ketones **3bc** and **3bd** were obtained in very good yields. For the successful synthesis of **3bd** the reagent originated from the organolithium analogue. It can therefore be assumed that the reaction is independent on any Mg(II)-cations from the Grignard precursor. Also, secondary organomanganese reagents **2e** and **2f** were converted with high yields of 90% and 87%. *tert*-Butyl manganese bromide only led to traces of product, which was reasoned by its steric bulk leading to a low reactivity. The homobenzylic ketone **3bg** was obtained in fair yield.

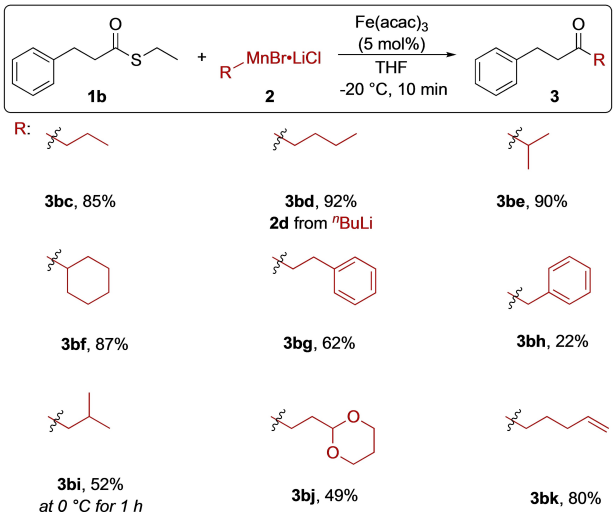
With this in mind, the role of the transmetalating reagent was assumed to be dependent on its ability to undergo β-hydrogen elimination.[18,23] Surprisingly, reactivity was observed with benzyl manganese halide as reagent, although in poor yield and with high amounts of bisbenzyl as homocoupling side product. This is in line with the results from iron-catalyzed cross-coupling of comparable Grignard reagents (Ph, Bn). These usually require a ligand or additive depending on the electronic properties of the coupling compounds.[24] To this end, experiments employing methyl- or phenyl-manganese reagent performed only poorly. The reaction of manganese reagent possessing sterically shielded β-hydrogen atoms yielded only traces of product **3bi** under standard conditions. However, the



Scheme 4. Selective mono- or double-coupling of dithioester **4**.



Scheme 5. Synthesis of the natural compound dihydrojasmone.



Scheme 6. Variation of the organomanganese reagent in the coupling with thioester **1b**.

reaction could be observed at 0 °C for 1 h. Functionalities such as double bond or acetal were tolerated, as demonstrated by the synthesis of **3 bj** and **3 bk**.

Then, we monitored the transformation of three thioesters with varying steric bulk (Figure 1). The conversion of substrate **1 a** was completed in less than 1 min which couldn't be further resolved by lowering the reaction temperature. The reintroduction of additional starting materials after complete reaction led to further conversion.

The strong influence of the substituent at the α-position was confirmed. The reason is possibly the steric interaction with the catalyst, enolization in the case of secondary thioesters and resulting inhibition. To underline the steric effect on tertiary substrates, the reacted solution containing **1 n** was treated with additional precatalyst after 30 minutes and increased conversion was observed (see Supporting Information). The low reactivity of secondary substrates could be resolved by employing more reactive *S*-aryl thioester (Scheme 7).[25] However, in direct comparison with primary thioesters no favoured conversion of *S*-aryl thioester was observed. Interestingly, Cahiez et al. used iron arylthiolate salts as precatalysts of a Kumada coupling of vinyl chlorides.[26] These results contrast the observed formation of disulfides and iron black, when iron salts were exposed to thiolate salts.

In order to gather mechanistic insights into the FCC procedure reported in this work, the behavior of $Fe(acac)_3$ under catalytically relevant conditions (that is, in the presence of an excess of thioester **1 a** and of a nucleophile) was analyzed by paramagnetic ^{1}H NMR. Due to the high paramagnetism of the Mn(II) ion in RMnBr species which prevented efficient NMR analysis of the reaction medium, an aliphatic Grignard reagent (*n*-octylMgBr) was used as a model species. $Fe(acac)_3$ is characterized in THF-d_8 by a well-defined ^{1}H NMR spectrum with two broad resonances at 21 ppm (6H) and −27 ppm (1H).[27] Those signals did not evolve upon addition of 6 equiv. of **1 a**, confirming the necessity of a reduced iron species to activate the thioester. Upon addition of 2 equiv. *n*-octylMgBr (vs. Fe) on a mixture of $Fe(acac)_3$ and 6 equiv. **1 a** after 2 minutes at 20 °C, a new downfielded broad peak appeared at +159 ppm (Figure 2).

In this context, such a highly downfielded broad resonance ($\Delta\nu = 660$ Hz) can be diagnostic of the β-protons of an aliphatic chain borne by a high-spin Fe(II) species ([Fe^{II}]-$CH_2C\underline{H}_2R$; the protons in the α-position being undetected). Similar examples of β-H in high-spin [Fe^{II}]-$CH_2C\underline{H}_2R$ complexes have been reported by Chirik ($\delta = 150$ ppm, $\Delta\nu = 555$ Hz for $LFe^{II}CH_2C\underline{H}_3$; L = bis(imino)pyridine ligand)[28] or more recently by Werncke ($\delta = 166$ ppm for $[(hmds)_2Fe^{II}CH_2C\underline{H}_2CH_2CH_3]^-$; hmds = N-$(SiMe_3)_2^-$).[29] In our case, the signal observed at 159 ppm quickly disappeared (full disappearance in 5 minutes), and was not observed in the absence of **1 a**. Concomitantly, GC-MS of the reaction medium after hydrolysis confirmed the formation of the coupling product *n*-octylC(O)Pent under these conditions (ca. 60 % vs. *n*-octylMgBr). These results show that alkyliron(II) intermediates can be detected when an iron source reacts with a Grignard reagent in the presence of a thioester. Albeit particularly elusive, the paramagnetic alkyliron(II) species detected in these conditions (Figure 2) displays an enhanced stability compared to what is obtained when $Fe(acac)_3$ is treated by *n*-octylMgBr in the absence of **1 a**. This indeed leads to formation of a dark-brown suspension and to a silent ^{1}H NMR spectrum in the +200/−200 ppm area, which is usually observed when iron salts are reduced in the absence of external stabilizing ligands.[30] Moreover, when **1 a** (10 equiv. vs. Fe) is

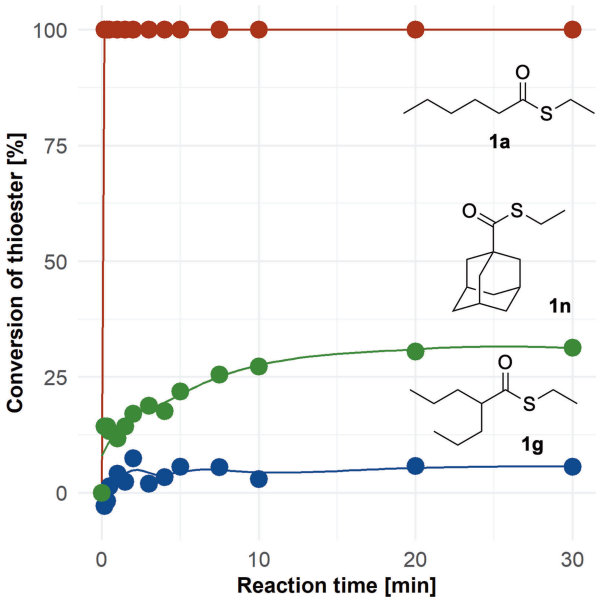
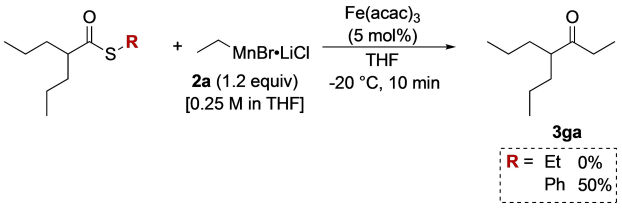


Figure 1. Conversion of different thioesters under catalytic conditions.



Scheme 7. Improving the reactivity of thioesters by modification of the S-substituent.

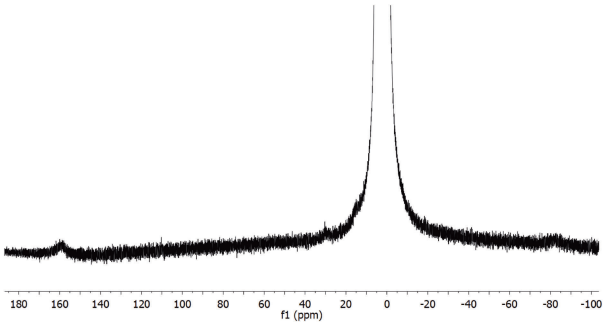


Figure 2. ^{1}H NMR spectrum (60 MHz) of $Fe(acac)_3$ in THF-d_8 in mixture with *n*-octylMgBr (2 equiv.) and **1 a** (6 equiv.) after 2 minutes at 20 °C.

added to this suspension, no trace of coupling product is observed, pointing towards the absence of reactivity of a too highly reduced iron species (that is, with an oxidation state lower than +II) in the coupling process.

Importantly, the observation of alkyliron(II) intermediates in conditions allowing the proficiency of the cross-coupling suggests that (i) **1a** or one of its byproducts formed upon the coupling process can play a role in the stabilization of the alkyl-Fe^{II} bond, and (ii) the latter is an on-cycle intermediate of the coupling. Due to the high instability of alkyliron(II) species in the absence of supporting co-ligand at room temperature, and aiming at investigating the reactivity of this oxidation state towards thioesters, we investigated more closely the reactivity of the more thermally stable organoferrous complex $[Fe^{II}(mes)_3]^-$ towards thioester **1a** (mes = 2,4,6-$Me_3C_6H_2$). The former complex is easily detected by its paramagnetic ^{1}H NMR signals at $\delta = 127$ (*meta*-H), 109 (*para*-CH_3) and 26 ppm (*ortho*-CH_3) in a 2/3/6 ratio (Figure 3a).

When $[Fe^{II}(mes)_3]^-$ was treated with 8 equiv. **1a**, the former progressively disappeared while a set of new paramagnetic signals was detected (Figure 3b). Two species **I** and **II** were formed ($\delta_I = 21$ and 16 ppm; $\delta_{II} = 32$, 13.1 and −2 ppm). After 2 h at 20 °C, no trace of $[Fe^{II}(mes)_3]^-$ was detected in the ^{1}H NMR spectrum, which solely showed **I** and **II** (Figure 3c). Detection of paramagnetic ^{1}H NMR signals in the +30/−10 ppm area may be indicative of the formation of various mes-Fe^{II} species, with either an intermediate spin ($S = 1$, triplet), as reported by Chirik,[31] or of oligonuclear structures with high-spin Fe^{II} ions ($S = 2$, quintet) which lead to more modest paramagnetic shifts due to antiferromagnetic Fe^{II}-Fe^{II} coupling.[32] Unfortunately, no sample suitable for X-ray diffraction, which could unambiguously assess a structure for **I** or **II**, could be obtained. However, intriguingly, formation of species **I** and **II** was also observed when $[Fe^{II}(mes)_3]^-$ was treated by 0.3 equiv. of EtSMgBr (Figure S4). Since the same distribution of species is obtained when $[Fe^{II}(mes)_3]^-$ is treated by EtSMgBr or by **1a**, along with some coupling product MesC(O)Pent in the latter case, this suggests that the thiolate anions EtS^-, generated at each coupling cycle involving thioester **1a**, are involved in the formation process of species **I** and **II**. These two complexes might thus involve ligation of Fe(II) ions by a combination of mesityl and thiolate anions in a mono- or polynuclear structure. In other words, in terms of reactivity in the FCC context, this means that the thiolate leaving group generated upon coupling of **1a** with the nucleophile (either RMgBr in those mechanistic studies or RMnBr in the FCC scope discussed herein) does not act as a mere spectator anion. Indeed, this shows that thiolate anions can also govern the nature of the distribution of on-cycle Fe(II) species. Ferrous thiolate intermediates can thus be generated progressively in the coupling process, stabilizing the Fe(II) oxidation state and preventing its reductive decomposition towards non-active species. Additionally, **I** and **II** reacted upon addition of 2 equiv. MesMgBr to afford back $[Fe^{II}(mes)_3]^-$, thus confirming their Fe(II) oxidation state (Figure 3d).

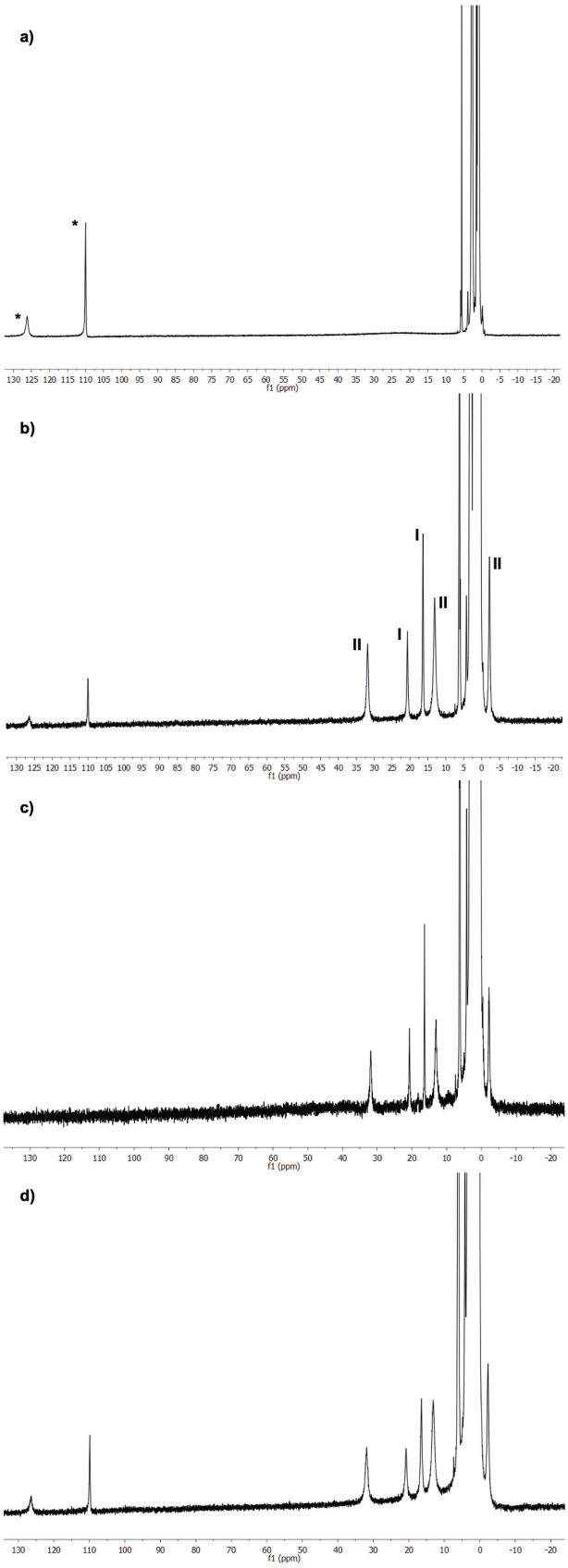


Figure 3. ^{1}H NMR studies of $[Fe(mes)_3]^-$ in THF-d_8: a) Mixture of MesMgBr (3.2 equiv.) and $FeCl_2$ at 20 °C. b) Treatment with **1a** (8 equiv.) after 20 min, c) after 2 h. d) Addition of further MesMgBr (2 equiv.); the starred peaks (*) belong to $[Fe(mes)_3]^-$.

Conclusion

In summary, we have developed an iron-catalyzed cross-coupling of thioesters with non-stabilized organomanganese reagents. A range of differently functionalized, natural and pharmaceutical compounds could be converted using the catalytic system. Influences on the reaction yield are determined by the steric demands of the carboxylic and the thiol moiety as well as the organomanganese reagent. Based on this steric dependence, we have demonstrated selective transformation for specific thioester motifs enabling regioselectivity. The low reactivity of some compounds could be lifted by modification of S-substituent. Paramagnetic NMR studies on model compounds gave insights into the possible participation of high spin alkyl iron(II) thiolates.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article. Additional data (e.g. fid files) can be obtained upon request from the authors.

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