



Transesterification catalyzed by iron(III) β -diketonate species

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ABSTRACT

A practical and clean protocol for transesterification catalyzed by a 5 mol % *cheap*, non-toxic and moisture stable Fe(acac)₃ or other iron(III) β -diketonate species in *solvent*, such as heptane under azeotropic condition is developed. A remarkable rate enhancement was observed upon the addition of 5 mol % of an inorganic base, such as Na₂CO₃, which suggests that faster formation of a dimeric μ -alkoxy-bridged iron(III) species under alkaline conditions facilitates catalytic turnover. This system provides smooth transesterification over a wide range of structurally diverse esters and alcohols without disturbing functional groups. In addition, the use of iron β -diketonate complexes as catalysts is more environmentally friendly, safer, and economical than other transition-metal catalysts. Preliminary mechanistic studies indicate that the active catalyst is likely a dimeric μ -alkoxy-bridged iron(III) species, as determined by X-ray crystallography of [Fe(dbm)₂(O-*n*-Bu)]₂ derived from the alcoholysis of Fe(dbm)₃ under alkaline conditions.

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1. Introduction

Esterification is an important process in organic synthesis.¹ The transesterification of esters of volatile alcohols with heavier and more functionalized alcohols can be preferable to the direct condensation of an alcohol and a carboxylic acid because the dehydrating conditions used in direct condensations can be harsh and the solubility of carboxylic acids in some organic solvents can be poor. Because transesterification is an equilibrium driven process, both an acidic or basic catalyst and high temperatures, which constantly remove the evolved lower alcohol and shift the equilibrium to the product side, are required to promote this transformation. Over the years, numerous catalysts have been exploited to accelerate this equilibrium process, including protic and Lewis acids, organic, and inorganic bases, as well as various enzymatic systems.^{2–6} Notably, extremely mild room temperature catalytic transesterifications using reagents, such as dimeric fluororous distannoxanes⁷ and *N*-heterocyclic carbenes,⁸ have been described. While all of these methods are efficient and have some degree of general applicability, they all suffer from one or more drawbacks, including moisture sensitivity, toxicity, expense, harsh reaction conditions, or incompatibility with acid or base sensitive functional groups. Consequently, new atom efficient, cost-effective, environmentally benign, and broadly functional group compatible transesterification catalysts are desirable.

In recent years, there has been considerable interest in developing greener, more sustainable protocols for organic synthesis.⁹ Thus, iron, an environmentally benign and abundant element, has received much attention as a potential catalyst.¹⁰ Iron(III) chloride and other iron(III) salts are generally strong hard Lewis acids and behave as Brønsted acids in the presence of alcohols. These properties make Fe(III) ions extraordinary catalysts for the activation of carbonyl compounds. In addition, a variety of active iron(III) species can be formed when Fe(III) salts are complexed with hard Lewis bases or 1,3-dicarbonyl compounds.¹¹

Recent elegant work by Bolm and co-workers presented mild and practical inter- and/or intramolecular cross-couplings that established aryl-heteroatom bonds (e.g., C–N, C–S, and C–O bonds) utilizing cheap and environmentally friendly FeCl₃ in combination with an appropriate secondary or tertiary diamino ligand (i.e., *N,N'*-dimethyl ethylenediamine (DMEDA) or *N,N'*-dimethyl glycine). The use of a bulky β -diketone ligand (e.g., 2,2,6,6-tetramethyl-3,5-heptanedione (H-tmhd)), instead of an amino ligand, and an inorganic base is necessary to effect O-arylation. They also found that reaction efficiency is dramatically affected by the identity of the ligand.¹² While the precise nature of the catalytic species in the FeCl₃-tmhd-catalyzed system has not yet been identified, one can anticipate that the specific anionic β -diketonate ligand employed should influence the reaction kinetics and the reaction efficiency by modulating the structure of the iron catalyst.¹³ In another approach, Plietker's group revealed a nucleophilic nitrosyl iron(II) catalyst ([Bu₄N][Fe(CO)₃(NO)]) for the mild transesterification of vinyl acetate and activated electron-poor esters under neutral conditions.¹⁴ This procedure is much milder than the existing catalytic protocols and is highly tolerant of functional groups.

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Taking into account Plietker's successful demonstration of an iron-catalyzed transesterification, we wanted to explore more sustainable iron-derived catalytic systems.

Main group organometallic compounds usually act as Lewis acids and serve as templates to regulate organic reactions that occur in their coordination spheres.¹⁵ However, their structures are complicated, involving multinuclear interactions, ligand-metal binding, and substrate coordination.¹⁶ In addition, metal complexes with unique catalytic activities often undergo structural changes during reactions that make it difficult to identify the structure of the actual catalytic species and the active site on the metal center. Thus, to understand the active species of a catalytic system at the molecular level, one option is to design analogs with a coordination sphere similar to the atomic structure of the original template to gain better insights into the reactivity of the metal catalyst. Several precedents have shown that metal alkoxides or polynuclear μ -alkoxy metal complexes are reasonable intermediates for transesterification reactions and may be intimately involved in catalyst turnover.^{5,6} *In situ*-derived lithium alkoxy aggregates have been suggested as the primary reactants with carbonyl functionality during the course of transesterification.¹⁷ So far, only the μ -alkoxy distannoxane and titanium dialkoxide intermediates generated *in situ* from the alcoholysis of diorganotin dihalides (Bu_2SnX_2)^{5e} and oxotitanium acetylacetonate ($\text{TiO}(\text{acac})_2$)^{6a} under the transesterification conditions have been spectroscopically shown to be the active catalysts in mechanistic studies of Lewis acid-mediated transesterification reactions (Fig. 1).

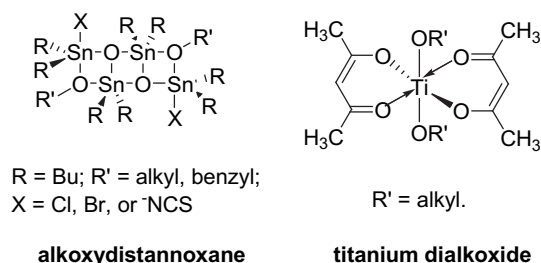
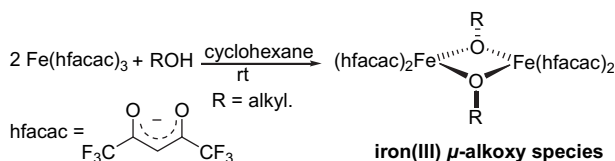


Fig. 1. Distannoxane and titanium catalysts for transesterification reactions.

On the other hand, one of the most striking properties of Fe(III) species is their tendency to hydrolyze in the presence of water or alcohols into oxophilic doubly μ -hydroxo or μ -alkoxy species in both neutral and alkaline solutions. The final stage of this hydrolysis is the formation of polymeric iron(III) aggregates.¹⁸ Nevertheless, it is easy to isolate iron(III) dimeric μ -alkoxy intermediates during the alcoholysis processes if they are stabilized by suitable ligands, such as 1,3-dicarbonyl compounds.¹⁹ For example, a series of dimeric μ -alkoxy iron(III) complexes that are even stable at room temperature have been synthesized by reacting iron(III) 1,1,1,5,5,5-hexafluoro-pentan-2,4-dionate ($\text{Fe}(\text{hfacac})_3$) with appropriate aliphatic alcohols in non-polar solvents (Scheme 1).²⁰ We expected that appropriately ligand-stabilized iron(III) μ -alkoxy species might serve as active catalysts for transesterification. Herein, we report our initial study regarding the development of a new transesterification process utilizing environmentally benign and inexpensive iron(III) β -diketonate species as catalysts under mild conditions. An initial



mechanistic study along with an X-ray structural analysis of the active catalyst has also been carried out.

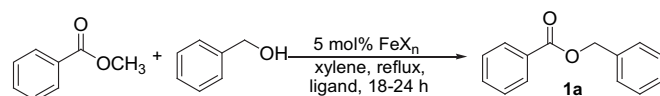
2. Results and discussion

2.1. Survey for an optimal catalytic system

Because of the precedent demonstrating that ligands have a strong effect on the iron-catalyzed carbon-heteroatom bond forming reactions, a study combining 5 mol % FeCl_3 with several ligands was conducted to evaluate the catalytic efficiency of transesterification between a 1:1 mixture of methyl benzoate and a less nucleophilic alcohol, benzyl alcohol, in xylene under azeotropic reflux conditions using a pressure-equalized Soxhlet extractor containing 4 Å molecular sieve pellets (Table 1). As expected, FeCl_3 did not effect this transformation in the absence of a ligand (Table 1, entry 1). In contrast, the desired transesterified product **1a** was obtained in the yields ranging from 8 to 20% when 10 mol % of a bidentate amine (e.g., *N,N'*-dimethylethylene-1,2-diamine (DMEDA), *N,N,N',N'*-tetramethylethylene-1,2-diamine TMEDA), or 2,2'-bipyridine (bipy) was employed as a chelating ligand (Table 1, entries 2–4). Apparently, hard nitrogen ligands cannot satisfy the valence requirement around FeCl_3 during the course of transesterification, and a background reaction catalyzed by the basic nitrogen ligands seems to predominate. Interestingly, the yield of the transesterification product increased to 48% when 10 mol % H-tmhd was employed as the ligand (Table 1, entry 5). This extraordinary ligand effect on the FeCl_3 catalyzed C–O bond exchange reaction is consistent with observations regarding the utility of this ligand in Bolm's O-arylation reaction. Another significant improvement in catalytic efficiency was achieved by increasing the amount of H-tmhd to 15 mol % (i.e., 3.0 equiv with respect to FeCl_3) and resulted in an 80% conversion of **1a** (Table 1, entry 6). Moreover, an 88% conversion was achieved when 15 mol % of the less hindered pentan-2,4-dione (H-acac) was employed instead of H-tmhd under the standard reaction conditions (Table 1, entry 7).

Table 1

Effects of iron salts and ligands on transesterification of methyl benzoate with benzyl alcohol^a



Entry	FeX_n	Ligand	Time (h)	Conv. ^h (%)	Yield ⁱ (%)
1	FeCl_3	None	24	0	0
2	FeCl_3	10 mol % DMEDA ^b	24	11	8
3	FeCl_3	10 mol % TMEDA ^c	24	23	20
4	FeCl_3	10 mol % bipy ^d	24	18	16
5	FeCl_3	10 mol % H-tmhd ^e	24	52	48
6	FeCl_3	15 mol % H-tmhd	24	80	77
7	FeCl_3	15 mol % H-acac ^f	24	88	85
8	FeCl_3	15 mol % Na-acac ^g	22	96	94
9	FeBr_3	15 mol % Na-acac	18	98	96
10	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	15 mol % Na-acac	24	92	89
11	$\text{Fe}(\text{acac})_3$	None	18	97	95
12	$\text{Fe}(\text{acac})_3$	5 mol % Cu_2O	18	97	94
13	No Fe	5 mol % Cu_2O	24	<7	— ^j

^a All reactions were performed in refluxed xylene in the presence of 5 mol % iron catalyst and indicated ligand under azeotropic reflux condition in the presence of 4 Å molecular sieves pellets.

^b DMEDA: *N,N'*-dimethyl ethylenediamine.

^c TMEDA: *N,N,N',N'*-tetramethylethylene-1,2-diamine.

^d bipy: 2,2'-bipyridine.

^e H-tmhd: 2,2,6,6-tetramethyl heptanes-3,5-dione.

^f H-acac: pentan-2,4-dione.

^g Na-acac: pentan-2,4-dione sodium salt.

^h Determined by GC and identified by GC–MS analysis.

ⁱ Yield of isolated product after chromatography.

^j Not determined.

Iron(III) β -diketonate complexes are cheap, non-toxic, moisture stable, commercially available, and environmentally friendly and often serve as metal organic chemical vapor deposition (MOCVD) precursors for iron oxide thin films.²¹ They are also used as reagents in carbon–carbon bond forming reactions and as Lewis acidic catalysts.^{10a,b} They are readily available by reacting FeX_3 salts with a β -diketone ligand in the presence (or absence) of an organic or inorganic base in an alcoholic solution.²² Under our standard transesterification conditions (i.e., FeCl_3 , H-tmhd or H-acac, refluxing xylene in the presence of the alcohol) a remarkable rate enhancement is observed upon the addition of β -diketone ligands. Thus, it is suspected that catalytically active $\text{Fe}(\text{tmhd})_3$ or $\text{Fe}(\text{acac})_3$ complexes are generated in situ.

To support this assumption, we treated 1.0 equiv FeCl_3 with 3.0 equiv H-acac in refluxing methanol. Indeed, $\text{Fe}(\text{acac})_3$ was formed and detected by ESIMS analysis. Furthermore, $\text{Fe}(\text{acac})_3$ could be isolated in 43% yield as a fine crystalline solid after the removal of unreacted FeCl_3 via an aqueous wash of the above reaction and recrystallization (see Supplementary data). This result suggests that $\text{Fe}(\text{acac})_3$ is the primary species formed in situ under the reaction conditions. However, the incomplete complexation of the acac-anion onto the iron(III) centers may have resulted in a low production of the catalyst, which in turn may be responsible for the low conversion in the transesterification reaction.

To facilitate the complete formation of $\text{Fe}(\text{acac})_3$, 15 mol % of the more nucleophilic sodium salt of acetylacetonate (Na-acac) was employed as the ligand instead of the acidic H-acac molecule in the model transesterification reaction involving a 1:1 ratio of methyl benzoate and benzyl alcohol. As expected, the reaction was finished after 22 h with 96% conversion, which indicates a significant rate enhancement is achieved upon a more efficient formation of $\text{Fe}(\text{acac})_3$ in situ (entry 8).²³ Furthermore, the process is compatible with other Fe(III) salts, such as FeBr_3 and hydrated FeCl_3 . The anticipated excellent yields were obtained, although with a slight decrease in conversion in the case of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (entries 9–10). To further demonstrate that the Fe(III) β -diketonate species might play a role in the transesterification process, 5 mol % commercial $\text{Fe}(\text{acac})_3$ was used in the model reaction. As expected, the desired benzyl benzoate **1a** was isolated in 95% yield within 18 h (entry 11).

Due to concerns that the use of impure iron salts would lead to variable results according to its commercial origin and its purity (predominantly copper contaminant),^{10j,12g} the test reaction was conducted in the presence of additional 5 mol % Cu_2O . No significant rate enhancement was found under performed condition (entry 12). In addition, when reaction was conducted in the presence of 5 mol % Cu_2O without iron catalyst, the reaction was proved inactive after 24 h (entry 13). On the other hand, Cahiez reported that the use of $\text{Fe}(\text{acac})_3$ gave the amenable results in the C–C bond coupling reaction regardless of the origin of the $\text{Fe}(\text{acac})_3$.^{10j} Thus the background reaction catalyzed by copper contaminant could be excluded.

Encouraged by this result, several commercially available iron (III) β -diketonate species with different electronic and steric properties were selected for further examination in the catalytic transesterification reaction. Table 2 shows the counterion effects for the iron catalysts on reaction time and conversion in the transesterification of methyl benzoate with benzyl alcohol. It was found that the catalytic activity of the iron(III) β -diketonate species is highly dependent on the ligand's electronic (i.e., withdrawing or donating) and steric attributes. In general, the catalytic efficiency follows the trend in the acidity of the neutral ligand ($\text{H-hfacac} > \text{H-dbm} \sim \text{H-acac} > \text{H-tmhd}$; compare entries 4 with 1–3) and decreases with increasing steric bulk on the ligand (compare entries 1 with 2). Among these catalysts examined, the least sterically hindered and most electronically deficient, $\text{Fe}(\text{hfacac})_3$, was the most efficient (entry 4), affording product **1a** in 96% yield after 14 h. Both $\text{Fe}(\text{acac})_3$

Table 2Ligand effects of Fe(III) β -diketonate species on the transesterification of methyl benzoate with benzyl alcohol^{a,b}

Entry	FeX_n	Time (h)	Conversion ^c (%)	Yield ^f (%)
1	$\text{Fe}(\text{acac})_3$	18 (8)	97 (99)	95 (97)
2	$\text{Fe}(\text{tmhd})_3$	28 (20)	89 (93 ^b)	86 (90)
3	$\text{Fe}(\text{dbm})_3$ ^c	18 (8)	96 (98)	94 (95)
4	$\text{Fe}(\text{hfacac})_3$ ^d	14 (6)	97 (99)	96 (96)
5	$\text{Fe}(\text{acac})_2$	40 (24)	25 (57)	22 (53)

^a All reactions were performed in xylene in the presence of 5 mol % Fe catalyst under azeotropic reflux condition.

^b Data in parenthesis correspond to 10 mol % catalyst used.

^c dbm: dibenzoylmethane.

^d hfacac: 1,1,1,5,5,5-hexafluoro-pentan-2,4-dione.

^e Determined by GC and identified by GC–MS analysis.

^f Yield of isolated product after chromatography.

and $\text{Fe}(\text{dbm})_3$ showed good catalytic activity and gave clean reactions that were completed in a short period of time (18 h) and afforded **1a** in 94–95% yield (entries 1 and 3). On the other hand, much weaker catalytic activity was observed with $\text{Fe}(\text{tmhd})_3$ due to the steric congestion of the bulky ligand, tmhd, only 89% conversion with 86% yield was obtained in a reasonable period of time (28 h, entry 2). Iron salts in the +2 oxidation state, such as $\text{Fe}(\text{acac})_2$, are not suitable for this transformation, as evidenced by the poor yield (24%) obtained after an extended reaction time (40 h, entry 5).

While $\text{Fe}(\text{hfacac})_3$ showed the best performance as a catalyst, the cost of the catalyst and the noxious nature of the H-hfacac ligand hamper its utility from both environmental and economic points of view. Thus, the cheap, moisture stable $\text{Fe}(\text{acac})_3$ was selected as the optimal catalyst for the rest of this study because it had an excellent catalytic activity when compared with the existing protocols.^{2–6} It is noteworthy that the reaction time is reduced by half when the catalyst loading is increased to 10 mol % (entries 1–5, data in parentheses).

2.2. Examination on solvent effects

The evaluation of other solvents in the model transesterification reaction catalyzed by $\text{Fe}(\text{acac})_3$ was also undertaken at 80 °C (Fig. 2). The non-polar solvent heptane was optimal among nine different aprotic solvents examined. Low conversions were observed with xylene and toluene (28%, and 23%, respectively). Polar solvents, such as 1,4-dioxane, methyl *tert*-butyl ether (MTBE), THF, and DMF inhibited the reaction to some degree, probably due to coordination of the solvent to the iron center, which diminished the Lewis acidity of the iron catalyst. It is noteworthy that very low

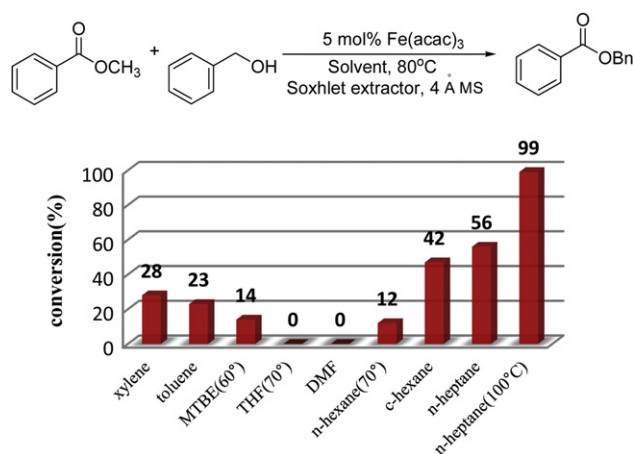


Fig. 2. Solvent effects in $\text{Fe}(\text{acac})_3$ catalyzed transesterification of methyl benzoate by benzyl alcohol.

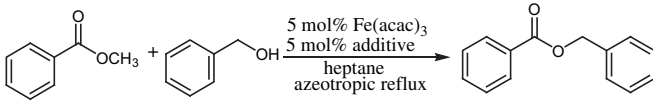
conversion was observed (12%) when *n*-hexane, a non-polar solvent (bp: 69 °C) was employed. Also, the conversion was higher when cyclohexane (bp: 81 °C) was utilized than that in toluene (bp: 111 °C).²⁴ These results strongly suggest that the optimal temperature for this iron-catalyzed transesterification is greater than 80 °C. Finally, the complete conversion of the reaction was found at reflux *n*-heptane (99% conversion, 100 °C).

2.3. Evaluating the effects of additives

We expected that the addition of organic nucleophiles, inorganic bases, or other activators might lead to higher catalytic efficiency in the ester–alcohol exchange process. Several activators that are widely used in standard esterification reaction for rate acceleration, including DMAP,²⁵ HOBT,²⁶ and HOAt²⁷ were chosen for evaluation in the model transesterification reaction. As shown in Table 3, the pyridine-derived compounds, DMAP and HOAt, were found to decrease catalytic efficiency (entries 2 and 3). This deactivation phenomenon may result from the coordination of the pyridyl moiety to the iron(III), thus occupying the coordination sites necessary for catalysis.²⁸ Interestingly, HOBT was found to accelerate the reaction by a factor of 1.5 in the early stages of the reaction (entry 4), but led to incomplete conversion even if the reaction time was extended to 24 h (entry 4, data in parentheses).

Inorganic bases were tested as additives to improve conversion in the Fe(acac)₃ catalyzed transesterification reactions. To our delight, significant rate enhancements were found with the inorganic bases investigated, with the exception of NaO-*t*-Bu (entries 5–8). Among them, Na₂CO₃ gave the fastest conversion and furnished the transesterified product in 99% conversion after 6 h (compare entry 8 with entries 6 and 7). A control experiment performed in the absence of any iron catalyst (i.e., only 5 mol % Na₂CO₃ was used) showed minimal conversion (entry 9, <5%), which indicated a background reaction catalyzed by Na₂CO₃ in the Fe(acac)₃–Na₂CO₃ catalytic system could be excluded. It is noteworthy that a slight reversed reaction of the transesterification product was observed in reactions involving K₂CO₃ and Na₂CO₃ (5–7%) upon standing at room temperature after completion of the reaction, presumably due to the reversed transesterification of benzyl benzoate catalyzed by Fe(acac)₂ in the presence of residual MeOH in the reaction mixture. Fortunately, this reversion of the equilibrium could be prevented by using an aqueous work-up to remove MeOH into the aqueous phase.

Table 3
The effects of additives



Entry ^a	Additives	Time	Conversion ^b (%)
1	None	18	97
2	DMAP ^c	18	48
3	HOAt ^d	18	87
4	HOBT ^e	6 (24)	87 (91)
5	NaO- <i>t</i> -Bu	8 (18)	67 (81)
6	CS ₂ CO ₃	8	97
7	K ₂ CO ₃	8	>99
8	Na ₂ CO ₃	6 (6 ^f)	>99 (99 ^f)
9	Na ₂ CO ₃ ^g	24 ^g	<5 ^g

^a Reaction condition: methyl benzoate (2.0 mmol), benzyl alcohol (2.0 mmol), Fe(acac)₃ (5 mol %), additive (5 mol %), heptanes (20 mL), azeotropic reflux.

^b Determined by GC analysis.

^c DMAP: 4-dimethylaminopyridine.

^d HOAt: 1-hydroxy-7-azabenzotriazole.

^e HOBT: 1-hydroxy benzotriazole.

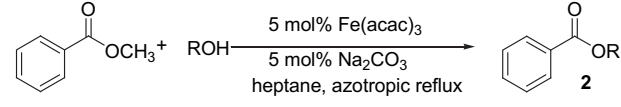
^f Fe(dbm)₃ (5 mol %) was used instead of Fe(acac)₃.

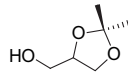
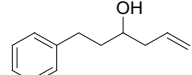
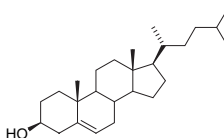
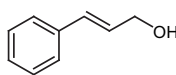
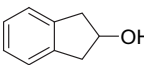
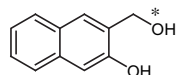

^g Blank experiment: in the absence of Fe(acac)₃.

2.4. The effect of protic nucleophiles

With the optimal protocol in hand (5 mol % Fe(acac)₃, 5 mol % Na₂CO₃, reflux in heptane), a diverse array of alcohols was explored using methyl benzoate as the test substrate. As shown in Table 4, the reactivity of a given alcohol toward transesterification depends strongly on the steric attributes of the alcohol. In general, the reaction rates follow the order of 1° (entries 1–3) > β-branched 1° (entry 4) > α,β-unsaturated 1° (entry 13) > 2° (entries 5–8) > phenolic (entries 9–11) >> 3° (entry 12). Benzylic, aliphatic, and acid sensitive acetonide protected primary alcohols underwent the exchange reaction smoothly, and we were able to achieve clean conversions in 6–8 h with 93–98% yields without dehydration or

Table 4
Effects of various alcohols on transesterification of methyl benzoate catalyzed by Fe(acac)₃^{a,b}



Entry	R-XH	Time (h)	Yield ^d (%)
1	PhCH ₂ OH	6 (18)	97 (97) (2a)
2	Ph(CH ₂) ₂ OH	7 (20)	96 (98) (2b)
3	CH ₃ (CH ₂) ₁₇ OH	7 (20)	98 (97) (2c)
4		8 (22)	93 (95) (2d)
5	PhCH(OH)CH ₃	10 (24)	96 (96) (2e)
6		14 (30)	97 (97) (2f)
7	L-(–)-Menthol	20 (42)	96 (93) (2g)
8		13 (30)	94 (97) (2h)
9	C ₆ H ₅ OH	24 (24)	12 (14) (2i)
10	4-Methoxyphenol	24 (24)	23 (26) (2j)
11	2-Naphthol	24 (24)	28 (32) (2k)
12	Ph ₃ COH	24 (24)	0 (0)
13		10 (20)	94 (96) (2l)
14		12 (32)	83 (92) (2m)
15 ^e		10 (22)	96 (95) (2n)
16		10 (20)	86 (83) (2o)
17 ^c	PhCH ₂ SH	24 (24)	46 (86 ^c) (2p)
18	PhCH ₂ NH ₂	24 (24)	88 (83) (2q)

^a All reactions were performed with 1 equiv of ester and protic nucleophile in *n*-heptane in the presence of 5 mol % Fe(acac)₃ and 5 mol % Na₂CO₃ under reflux condition.

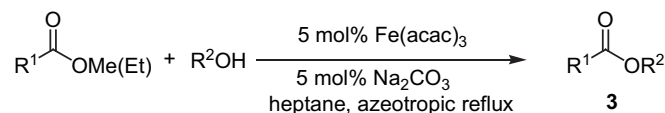
^b Data in parenthesis correspond to the 5 mol % Fe(acac)₃ catalysis in the absence of 5 mol % Na₂CO₃.

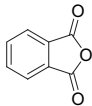

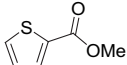
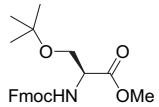
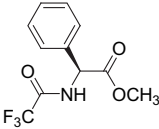

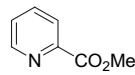
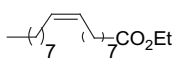
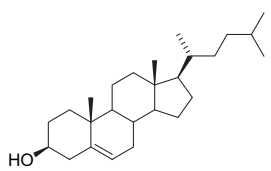
^c Benzylthiol (2.0 equiv) was used.

^d Isolated yields after column chromatography.

^e Asterisk signifies the reaction site.

Table 5
Effects of ester substrates on transesterification with various alcohols catalyzed by Fe(acac)₃^{a,b}



entry	Ester	Alcohols	Time (h)	Yield ^e (%)
1	CH ₃ (CH ₂) ₂ CO ₂ Et	Ph(CH ₂) ₂ OH	5 (10)	97 (95) (3a)
2	(CH ₃) ₂ CHCO ₂ Et	Ph(CH ₂) ₂ OH	6 (11)	96 (97) (3b)
3	(CH ₃) ₃ CCO ₂ Et	Ph(CH ₂) ₂ OH	24 (48)	82 (73) (3c)
4	MeO ₂ C(CH ₂) ₂ COOH	Ph(CH ₂) ₂ OH	8 (14)	97 (93) (3d)
5		Ph(CH ₂) ₂ OH	3 (5)	98 (96) (3e)
6 ^c		Ph(CH ₂) ₂ OH	4 (8)	95 (92) (3f)
7 ^{c,d}	4-Br-C ₆ H ₄ CO ₂ Et	CH ₃ (CH ₂) ₁₇ OH	7 (16)	98 (96) (3g)
8	4-NO ₂ -C ₆ H ₄ CO ₂ Et	CH ₃ (CH ₂) ₁₇ OH	5 (10)	98 (96) (3h)
9	4-Me ₂ N-C ₆ H ₄ CO ₂ Et	CH ₃ (CH ₂) ₁₇ OH	24 (24)	61 (43) (3i)
10	2-(HO)-C ₆ H ₄ CO ₂ Et	CH ₃ (CH ₂) ₁₇ OH	16 (35)	91 (94) (3j)
11		CH ₃ (CH ₂) ₁₇ OH	5 (10)	96 (96) (3k)
12	CH ₃ C(O)CH ₂ CO ₂ Me	CH ₃ (CH ₂) ₁₇ OH	6 (10)	98 (96) (3l)
13	<i>trans</i> -PhCH=CHCO ₂ Me	PhCH ₂ OH	5 (10)	95 (96) (3m)
14	(<i>R</i>)-Methyl lactate	PhCH ₂ OH	8 (18)	87 (91) (3n)
15	(<i>R</i>)-Methyl mandelate	PhCH ₂ OH	7 (15)	93 (90) (3o)
16		PhCH ₂ OH	6 (13)	82 (96) (3p)
17		PhCH ₂ OH	6 (12)	93 (92) (3q)
18		Ph ₂ CHOH	6 (12)	95 (92) (3r)
19		4-THPO(CH ₂) ₄ OH	28 (40)	86 (79) (3s)
20	Ph(CH ₂) ₂ CO ₂ Et	4-TBSO(CH ₂) ₄ OH	7 (15)	94 (92) (3t)
21			12 (22)	97 (99) (3u)

^a All reactions were performed with 1 equiv of ester and protic nucleophile in *n*-heptane in the presence of 5 mol % Fe(acac)₃ and 5 mol % Na₂CO₃ under reflux condition.

^b Data in parenthesis correspond to the 5 mol % Fe(acac)₃ catalysis in the absence of 5 mol % Na₂CO₃.

^c Performed in refluxed *n*-hexane.

^d Vinyl acetate (2.0 equiv) was used.

^e Isolated yields after column chromatography.

deprotection of the acetonide moiety (entries 1–4). The reaction of 2° alcohols is about two times slower than that of 1° alcohols (compare entries 1–4 with entries 5–8). To achieve a complete conversion of methyl benzoate with the sterically hindered L-(–)-menthol, a long reaction time is required (entry 7, 20 h). The current protocol did not proceed well with aromatic alcohols (12–28%, entries 9–11), presumably due to the reduced nucleophilicity of the phenolic substrates, or with 3° alcohols (entry 12) in the presence or absence of 5 mol % Na₂CO₃ even at prolonged reaction times, presumably due to the steric hindrance of 3° alcohols. Notably, an 11% elimination side-product was detected (1-indene) with basic sensitive 2,3-dihydro-1*H*-inden-2-ol in the presence of 5 mol % Na₂CO₃ (entry 14). However, no elimination was observed when the reaction was performed in the absence of Na₂CO₃ (entry 14, parenthesis).

By taking advantage of the significant rate differences between 1° and aromatic alcohols, one can carry out transesterification chemoselectively at the benzylic site of 3-hydroxymethyl-2-naphthol (entry 15). Another chemoselective esterification between primary and secondary alcohol was also carried out using racemic 1-phenylethane-1,2-diol. Its primary hydroxyl group was chemoselectively esterified in 86% yield, along with 5% di-benzoate product (entry 16). To further expand the catalytic utility, a more potent nucleophilic benzylthiol was investigated in the transesterification of methyl benzoate. However, an unsatisfactory yield (46%, entry 17) of the thioester product was obtained due to ease of oxidation of the thiol in the presence of high valent iron at elevated temperatures. Nevertheless, the chemical conversion can be improved to 86% by using 2 equiv of benzylthiol (entry 17, data in parentheses). Surprisingly, amidation with a strongly nucleophilic amine was sluggish; the resulting amide was obtained in a moderate yield at prolonged reaction times (entry 18). It is worth mentioning that the reaction rates are reduced by half in the absence of 5 mol % Na₂CO₃.

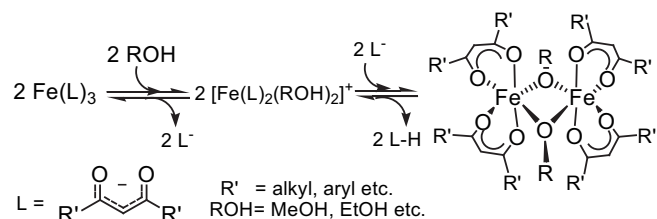
2.5. The scope of ester functional group compatibility

To gain insight into the scope of ester substrates and the functional group compatibility of the Fe(acac)₃-catalyzed transesterification reaction, a diverse array of functionalized esters was subjected to the standard reaction conditions with several primary, or secondary alcohols. As summarized in Table 5, the transesterification reactions were completed smoothly in quite short reaction times and afforded the desired products in 82–98% yield. In general, substrate reactivity follows the order of anhydride > vinyl acetate > heterocyclic ~ α, β-unsaturated ~ aliphatic ~ W-C₆H₄ (W=electron withdrawing group) > ketoester > α-branched aliphatic > hindered aliphatic > D-C₆H₄ (D=electron-donating group) esters. These ester scope results indicate that the current protocol is adaptable to various aliphatic esters, although long reaction times are required for tertiary esters (compare entries 1 and 2 with 3). Phthalic anhydride and vinyl acetate were esterified smoothly in short periods of time, even in low boiling hexane, although an excess of ester was employed in the case of vinyl acetate (entries 5 and 6). The esters bearing α, β-unsaturated π bonds (entry 13), α or β-ketoesters (entries 12 and 17), heteroaromatic thiophenes (entry 11), and electron-deficient arenes (entries 7 and 8) are transesterified efficiently and in good yield without any byproducts formed. In addition, mono-transesterified products from mono-methyl succinate were obtained in 98% yield, which indicates a chemoselective transesterification of the ester functionality in the presence of a carboxylic acid is attainable in our system (entry 4). Transesterification of an aromatic ester possessing a tertiary dimethylamino moiety (entry 9, 61% yield) was sluggish, probably due to the strong deactivation effect from the electron-donating amino group. By taking advantage of the significant rate difference between 1° and 2° alcohols, the transesterification can be conducted

chemoselectively on unmasked α-hydroxy esters such as lactate and mandelate without self-polymerization and racemization (entries 14 and 15).²⁹ It should be noted that deprotection occurred in the case of an Fmoc protected α-aminoester and only a moderate yield of the transesterified product was obtained (entry 16, 82%). In remarkable contrast, the yield could be improved to 96% without racemization and deprotection of the Fmoc moiety,³⁰ if the reaction was performed in the absence of Na₂CO₃, but this increase in yield was achieved at the cost of prolonged reaction times (entry 16, data in parentheses). Another base sensitive α-aminoester, such as (*S*)-*N*-trifluoroacetylphenylglycine methyl ester was also tolerant under optimal reaction, leading to the transesterified product in 92–93% yields without racemization in the presence (or absence) of 5 mol % Na₂CO₃ (entry 17). In addition, functional groups, such as acid- and base-sensitive TBS ethers, THP ethers, *tert*-butyl ethers, coordinating pyridines, and *cis* olefins, are also stable under the optimized conditions (entries 16 and 18–21).

3. Mechanistic studies

Iron(III) acetylacetonate (Fe(acac)₃) is known as a chelating host able to bind Lewis basic molecules, such as chlorinated solvents or olefins due to its electron-deficient vacant orbital.³¹ The catalyst is highly oxophilic and tends to hydrolyze to a dimeric oxo-μ-alkoxy species or to polynuclear iron-oxo aggregates.^{17,18} A precedent detailed kinetic and mechanistic studies of the ligand substitution process for Fe(III) β-diketonate complexes has revealed that they undergo fast solvolytic dissociation in alcoholic solvents, leading to cationic solvated species ([Fe(β-diketonate)₂(ROH)₂]⁺).²⁰ The solvated species further combine into binuclear μ-alkoxy species ([Fe(β-diketonate)₂(OR)₂) with the elimination of the β-diketone ligand even at room temperature. However, due to the associative substitution of the β-diketonate ligand, the binuclear μ-alkoxy species reversibly converts into the starting monomeric Fe(III) β-diketonate species under neutral conditions (Scheme 2).^{20,32}



Scheme 2. Solvolytic dissociation of the ligand and substitution of the oxygen-based ligands of iron(III) β-diketonate complexes under neutral conditions.

On the other hand, the dimeric dialkoxy-bridged iron(III) species are formed easily and irreversibly, and they can often be isolated in an alkaline environment.^{19g} Based on these literature precedents and the observation of a dramatic base-dependent rate enhancement in the Fe(acac)₃-catalyzed transesterifications (vide supra), it is likely that the highly oxophilic dimeric μ-alkoxy iron(III) species serves as the active catalyst rather than a monomeric Fe(acac)₃ in our catalytic system. To support our mechanistic hypothesis, a μ-alkoxy dimer **4**, derived from Fe(dbm)₃ and *n*-butanol, was prepared by reacting Fe(dbm)₃ with 1 equiv of Na₂CO₃ in refluxing heptane in the presence of an excess of *n*-butanol (20 equiv with respect to Fe(dbm)₃). The orange-red solid precipitated out upon cooling the reaction mixture to 0 °C. The moisture sensitive precipitate was isolated by filtration using a Schlenk apparatus under an inert atmosphere. An X-ray quality, centrosymmetric, deep red crystal with two [Fe(dbm)₂(O-*n*-Bu)] units bridged by the two oxygen atoms of the *n*-butoxide ligands was obtained in 47% yield by slow diffusion of a *n*-butanol layer into a CH₂Cl₂ solution of [Fe(dbm)₂(O-*n*-Bu)]₂ at room temperature (Fig. 3).

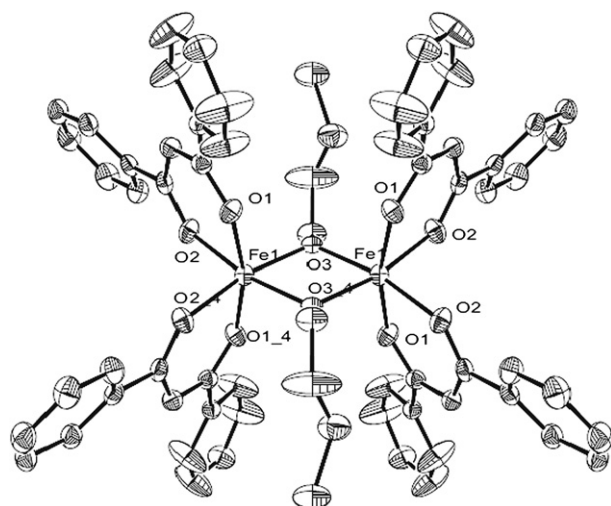
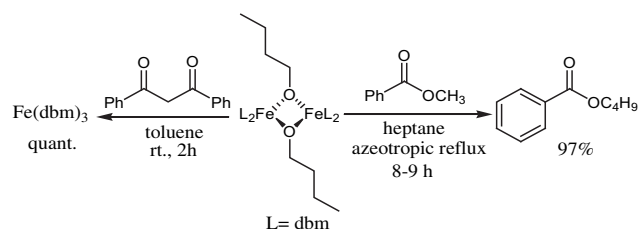


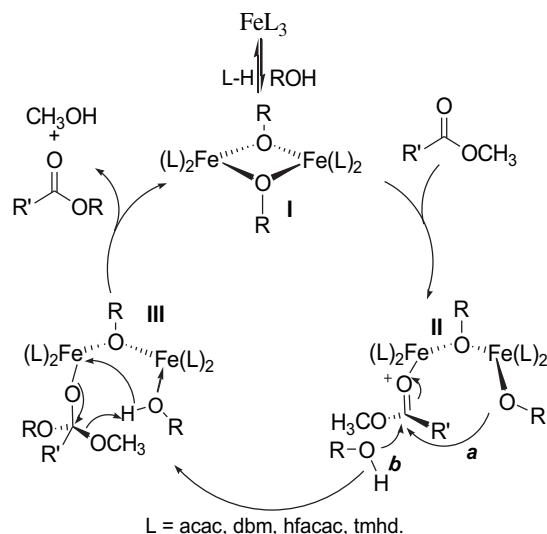
Fig. 3. ORTEP drawing of the complex $[\text{Fe}(\text{dbm})_2(\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3)]_2$ (**4**) with thermal ellipsoids (at the 50% probability level) and selected atom labels (H atoms are omitted for clarity).

To gain insight into the reaction mechanism and the role of dimeric $[\text{Fe}(\text{dbm})_2(\text{O}-n\text{-Bu})]_2$ (**4**) in the transesterification reaction, a stoichiometric amount of crystalline **4** was reacted with an equimolar amount of methyl benzoate in refluxing heptane. The desired transesterified product was isolated in 96% after 40 min (Scheme 3). Furthermore, complex **4** was converted to monomeric $\text{Fe}(\text{dbm})_3$ quantitatively upon treatment with a stoichiometric amount of H-dbm at room temperature. Moreover, the transesterification reaction between a 1:1 ratio of methyl benzoate and 1-butanol catalyzed by 5 mol % **4** exhibited a faster reaction rate (8–9 h, 99% conversion) than the reaction mediated by $\text{Fe}(\text{dbm})_3$ (18 h, 96% conversion, Table 2, entry 3). In light of all the results, it is suggested that complex **4** might be generated in situ during the course of the reaction and might be responsible for the subsequent transesterification reaction.



Scheme 3. Transesterification of methyl benzoate catalyzed by stoichiometric amount of $[\text{Fe}(\text{dbm})_2(\text{O}-n\text{-Bu})]_2$ (**4**) and associative transformation of **4** into the monomeric $\text{Fe}(\text{dbm})_3$.

Considering these results and other mechanistic studies of metal alkoxide catalyzed transesterifications in the literature,^{5g,6a} a preliminary hypothesis for the reaction mechanism is proposed in Scheme 4. Initial dissociation of the H-dbm or Na-dbm driven by nucleophilic substitution of the alcohol or sodium alkoxide leads to the formation of the μ -butoxy dimer **I**, which serves as the active catalyst and activates the ester to generate the cationic adduct **II**. Intramolecular exchange of the iron-alkoxide bond (path **a**) or intermolecular nucleophilic attack of the free alcohol (path **b**) on the electrophilic carbon center of the carbonyl moiety leads to an sp^3 hybridized tetrahedral intermediate **III**. The sterically congested **III** then collapses to regenerate the sp^2 hybridized carbonyl unit and the active catalyst **I** driven by the intramolecular nucleophilic substitution of the coordinated alcohol on the less hindered iron center, to the sterically congested tetrahedral alkoxide attached on



Scheme 4. Proposed catalytic cycle for iron(III) β -diketonate-catalyzed transesterification.

the left iron center of the intermediate **III**, along with the elimination of transesterified product and methyl alcohol.

4. Conclusion

In summary, we have developed a new and efficient transesterification protocol for various functionalized alcohols, as well as thiol and protic amine nucleophiles catalyzed by cheap, moisture stable, and commercially available $\text{Fe}(\text{acac})_3$ in non-toxic reflux hydrocarbon. This iron(III) catalyst system has several appealing features, including a high tolerance for diverse functional groups, an operationally simple procedure, cost efficiency, chemoselectivity, high chemical yields, and environmentally friendly compared to those achieved with conventional procedures. Applications involving diverse array substrates fully demonstrate the potential value of this method in the synthesis of complex esters. Mechanistic studies, X-ray crystallographic evidence, and the complex's high catalytic activity in transesterification reactions indicate that the active catalyst is likely a dimeric dialkoxy-bridged iron(III) species. Further applications of this new catalytic method for the synthesis of polyesters and the direct condensation of carboxylic acids using iron-based catalysts are being studied in our laboratory.

5. Experimental

5.1. General

^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Jeol JNMEX400 spectrometer (400 MHz, ^1H ; 100 MHz, ^{13}C); Bruker Advance 500 spectrometer (500 MHz, ^1H ; 125 MHz, ^{13}C) with CHCl_3 as an internal reference. Electron-impact (ESI) mass spectra were recorded on a Thermo Finnigan spectrometer equipped with LCQ Advantage ionization and Spectra System detector systems. Analytical GC was carried out with an Agilent 6890C GC equipped with an Agilent DB-WAX column (30 m \times 0.25 mm). Analytical GC–MS was carried out on a Varian CP-3800 GC/Saturn 2000 GC/MS spectrometer equipped with a CP-5860 column (30 m \times 0.25 mm \times 0.25 mm) using helium gas. Analytical TLC was visualized with UV light or with phosphomolybdic acid (PMA) and KMnO_4 staining agents. All reactions were run under nitrogen or argon atmosphere and the end products were isolated as pure materials. All products were purified by column chromatography or distillation under reduced pressure.

5.2. General procedure for catalyst screening (Table 2)

Catalyst (5 mol %) was stirred in xylene (10 mL) at room temperature under nitrogen atmosphere. A solution of methyl benzoate (272 mg, 256 μ L, 2 mmol) and benzyl alcohol (216 mg, 208 μ L, 2 mmol) in xylene (10 mL) was added via syringe. The resulting mixture was refluxed with the removal of the methanol by Dean–Stark apparatus or Soxhlet extractor in the presence of 4 Å MS and the reaction progress was monitored by TLC, ^1H NMR spectroscopy, and GC analysis. Evaporation of the organic solvent followed by column chromatography on silica gel (hexane/AcOEt=50/1) to provide the pure benzyl benzoate product.

5.3. Representative procedure for additive screening (Table 3)

To a 25 mL, one-necked, round-bottomed flask was placed Fe(acac)₃ (36 mg, 0.10 mmol, 5 mol %), benzyl alcohol (216 mg, 208 μ L, 2 mmol), and 5 mol % additive in 10 mL heptane at room temperature under nitrogen atmosphere. A solution of methyl benzoate (272 mg, 256 μ L, 2 mmol) in xylene (5 mL) was added via syringe. The resulting mixture was heated to reflux with the removal of the methanol by Dean–Stark apparatus and the reaction progress was monitored by TLC, ^1H NMR spectroscopy, and GC analysis. The reaction mixture then gradually cooled to room temperature and quenched with saturated aqueous NH₄Cl solution (5 mL), then extracted with 20 mL ethyl acetate. The combined organic layer was dried (anhydrous MgSO₄), filtered, and evaporated to give a crude product that was purified by column chromatography on silica gel (hexane/AcOEt=50/1) to provide the pure benzyl benzoate product.

5.4. Representative transesterification procedure catalyzed by Fe(acac)₃ and Na₂CO₃ as additive

To a 25 mL, one-necked, round-bottomed flask was placed Fe(acac)₃ (36 mg, 0.10 mmol, 5 mol %), benzyl alcohol (216 mg, 208 μ L, 2 mmol), and Na₂CO₃ (10.6 mg, 0.10 mmol, 5 mol %) in 10 mL heptane at room temperature under nitrogen atmosphere. A solution of methyl benzoate (272 mg, 256 μ L, 2 mmol) in heptane (10 mL) was added via syringe. The resulting mixture was heated to reflux with the removal of the methanol by Dean–Stark apparatus and the reaction progress was monitored by TLC, ^1H NMR spectroscopy, and GC analysis until completion of the reaction (6 h). The reaction mixture was then gradually cooled to room temperature and quenched with saturated aqueous NH₄Cl solution (5 mL), then extracted with 20 mL ethyl acetate. The combined organic layer was dried (anhydrous MgSO₄), filtered, and evaporated to give a crude product that was purified by column chromatography on silica gel (hexane/AcOEt=50/1) to provide the pure benzyl benzoate product 412 mg, 97% yield.

5.5. Synthesis of the dimeric [Fe(dbm)₂(O-*n*-Bu)]₂ (4)

To a 50 mL, two-necked, round-bottomed flask equipped with condenser was placed Fe(dbm)₃ (2178 mg, 3 mmol), Na₂CO₃ (318 mg, 3 mmol), and 1-butanol (4.45 g, 5.5 mL, 60 mmol, 20 equiv) in 20 mL heptanes under nitrogen atmosphere. The resulting mixture was heated to reflux for 2 h and then cooled to 0 °C on an ice bath. A large orange-red crystal was precipitated out from the solution. The orange-red crystal was separated by filtration using Schlenk apparatus under inert atmosphere and washed repeatedly with cold 1-butanol. The orange-red crystal was dissolved in 50 mL anhydrous CH₂Cl₂ and recrystallized by slow diffusion of the 1-butanol (30 mL) layer at room temperature, to afford the dimeric [Fe(dbm)₂(O-*n*-Bu)]₂ (4) as deep red fine crystal, 1623 mg, 47% yield. Anal. Calcd. For 4, C₆₈H₆₂Fe₂O₁₀: C, 70.96; H, 5.43. Found C, 70.64; H, 5.51.; M.W.

(C₆₈H₆₂Fe₂O₁₀, 1151); MS (ESI): 502 (1/2 (M-*n*-butanol); IR (CH₂Cl₂) 3063 (s), 1576 (s), 1528 (s), 1436 (s), 1384 (s), 1281 (w), 1251 (w), 1193 (w), 1023 (w), 783 (m), 765 (s), 713 (s), 677 (m).

5.6. Transesterification of [Fe(dbm)₂(O-*n*-Bu)]₂ (4) with methyl benzoate

In a dry 25 mL, two-necked, round-bottomed flask equipped with a Dean–Stark trap topped with a reflux condenser was added [Fe(dbm)₂(O-*n*-Bu)]₂ (4) (576 mg, 0.50 mmol), methyl benzoate (68 mg, 0.5 mmol) in anhydrous heptane (10 mL) under nitrogen atmosphere. The reaction mixture was heated to reflux until completion of the reaction as monitored by TLC analysis (40 min). Evaporation of the organic solvent followed by column chromatography on silica gel (hexane/AcOEt=100/1) to provide the pure butyl benzoate 171 mg, 96% yield.

5.7. Synthesis of Fe(dbm)₃ from [Fe(dbm)₂(O-*n*-Bu)]₂ (4)

In a dry 25 mL, two-necked, round-bottomed flask was placed [Fe(dbm)₂(O-*n*-Bu)]₂ (4) (127 mg, 0.118 mmol) in anhydrous heptane (10 mL) under nitrogen atmosphere. A solution of dibenzoylmethane (27 mg, 0.118 mmol) in toluene (10 mL) was added via addition funnel and the solution was turned to deep purple immediately. The reaction mixture was stirred at ambient temperature for an additional 2 h. The combined organic layers were evaporated under reduced pressure and then dried in vacuo to afford the Fe(dbm)₃ as a purple red solid, 86 mg, 99% yield. Anal. Calcd. For Fe(dbm)₃, C₄₅H₃₃FeO₆: C, 83.72; H, 5.15. Found C, 83.57; H, 5.36. M.W. (C₄₅H₃₃FeO₆, 726); MS (ESI): 749 (M+Na+H⁺, 43), 748 (M+Na, 100); IR (CH₂Cl₂): 3683 (br, w), 3055 (s), 1590 (m), 1527 (s), 1480 (s), 1451, 1377 (s), 1273 (s), 1247 (w), 1070 (w), 1023 (w), 942 (w), 772 (s), 739 (s), 669 (w), 621 (w).

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Supplementary data

Characterization data and ^1H , ^{13}C NMR spectra for products 2a–p, and 3a–t are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.009. These data include MOL files and InChIKeys of the most important compounds described in this article.

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