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A Nucleophilic Fe Catalyst for Transesterifications under Neutral Conditions

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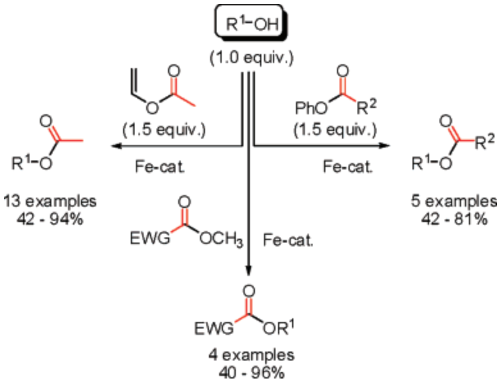
ABSTRACT



Carboxylic esters belong to the most important functional groups in organic chemistry. Strong efforts have been made in developing mild catalytic procedures for their preparation. Among the various methods developed to date, transesterifications have occupied an important space. In the present paper, a new catalytic method for this process based on the use of nucleophilic Fe(–II) complexes is presented. Evidence for the formation of an intermediate acyl Fe complex will be presented as well as investigations on scope and limitations.

Within the past years, the use of less toxic and expensive transition metals as environmentally benign catalysts has gained increasing importance in organic chemistry. In particular Fe-derived catalysts moved into the research focus due to their ubiquitous availability and low toxicity.[1] Recently, we initiated a research program aimed toward the use of nucleophilic Fe complexes as novel catalysts for organic syntheses. As a part of these investigations, we were able to develop a protocol for allylic substitutions based on the use of catalytic amounts of $[Bu_4N][Fe(CO)_3(NO)]$[2] as a nucleophilic Fe(−II) complex that allowed for a regioselective allylic substitution or amination.[3] On the basis of recent progress on the use of isoelectronic $[Co(CO)_4]^-$ as catalyst for transesterifications[4] and with regard to the seminal contribution of Coleman on the use of stoichiometric amounts of acyl Fe complexes in various organic reactions,[5] we speculated that our nitrosyl Fe(−II) complex could act as a potential acyl carrier in transesterification reactions. These transformations are particularly challenging since they are in equilibrium.[6]

Due to the importance of this reaction for organic synthesis, a plethora of stoichiometric or catalytic methods has been developed.[7] The majority of methods, in which

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[1] (a) Review on Fe catalysis: Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Review on Fe-catalyzed cross-couplings: Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624.

[2] (a) Hieber, W.; Kahlen, N.; *Chem. Ber.* **1958**, *91*, 2223. (b) Hieber, W.; Kahlen, N. *Chem. Ber.* **1958**, *91*, 2234.

[3] (a) Plietker, B. *Angew. Chem.* **2006**, *118*, 1497; *Angew. Chem., Int. Ed.* **2006**, *45*, 1469. (b) Plietker, B. *Angew. Chem.* **2006**, *118*, 6200; *Angew. Chem., Int. Ed.* **2006**, *45*, 6053. (c) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A. *Angew. Chem.* **2007**, DOI: 10.1002/ange.200703874; *Angew. Chem., Int. Ed.* **2007**, DOI: 101002/anie.200703874.

[4] (a) Wack, H.; Drury, W. J., III; Taggi, A. E.; Ferraris, D.; Lectka, Th.; *Org. Lett.* **1999**, *1*, 1985. (b) Sun, H.; Zhang, J.; Liu, Q.; Yu, L.; Zhao, J.; *Angew. Chem.* **2007**, *119*, 6180; *Angew. Chem., Int. Ed.* **2007**, *46*, 6068.

[5] Coleman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342 and references cited therein.

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transition metal catalysts are used, employ either Lewis acidic[8] or alkoxide-based complexes,[7,8] which limits their scope due to their incompatibility with certain functional groups. Among the metal-catalyzed protocols developed to date, Otera's tin-based catalysts proved to possess the broadest applicability.[6] Organocatalytic protocols are somewhat complementary. In general, a nucleophilic species, such as a nitrogen base[9] or carbene, is employed.[10] These procedures are much milder and allow for a selective transesterification paired with a higher tolerance for functional groups.

We started our investigation on the acylation of sterically hindered L-menthol in the presence of vinyl acetate. We were delighted to find that the reaction proceeds under the reaction conditions known from the allylic substitution (Figure 1).

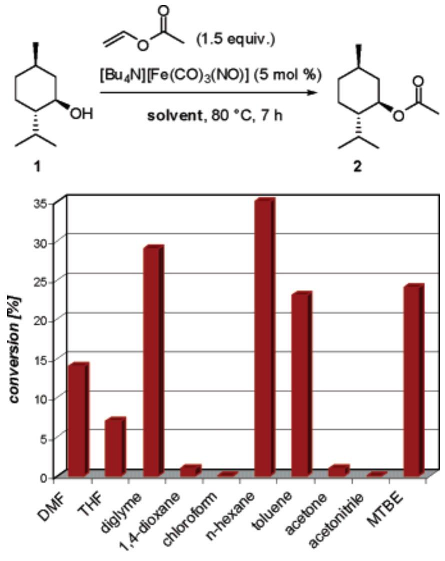
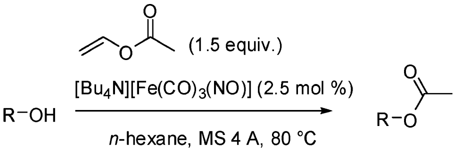
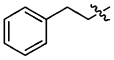
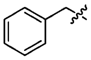
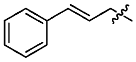
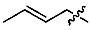
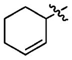
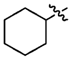
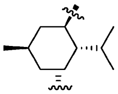
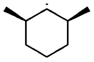
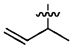
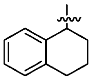
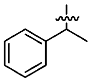
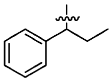
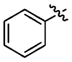
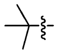
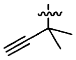


Figure 1. Solvent effects in Fe-catalyzed transesterification of L-menthol.

Moreover, further solvent screening indicated that methyl *tert*-butyl ether and *n*-hexane increase the reactivity significantly.

Table 1. Fe-Catalyzed Acylation of Alcohols



entry [a]	R	product	time (h)	yield (%) [b]
1		**3**	5	86
2		**4**	9	84
3		**5**	9	88
4		**6**	5	91[c]
5		**7**	12	83
6		**8**	24	58
7		**2**	24	63
8		**9**	24	-
9		**10**	16	71[c]
10		**11**	24	42
11		**12**	24	63
12		**13**	24	62
13		**14**	24	76
14		**15**	24	90[c]
15		**16**	24	-
16		**17**	24	-

[a] All reactions were performed on a 1 mmol scale in the presence of vinyl acetate (1.5 mmol), 4 Å MS (100 mg), and Fe catalyst (0.025 mmol) under a N_2 atmosphere in *n*-hexane (1 mL). [b] Isolated yield. [c] Yield according to GC integration (internal standard: *n*-dodecane).

Whereas the addition of ligands had no significant influence on the course of the reaction, the addition of 4 Å molecular sieves (MS) proved beneficial. Under optimized conditions, a decrease in the catalyst loading down to only 2.5 mol % and a reduction of the acyl donor down to only 1.5 equiv was possible. Having in hand the optimized conditions, we were keen to explore the reaction scope (Table 1). As expected, the rate of this transformation is dependent on steric congestions. Whereas primary and secondary alcohols are esterified in good to excellent yields, tertiary and sterically hindered secondary alcohols are almost unreactive. The low reactivity, however, might be compensated if the OH group is located in an allylic position.

With regard to the applicability of this process to the synthesis of more complex substrates, we subsequently turned our attention to the identification of alternative carboxyl donors. Although enol esters are available, the use of simple and readily accessible carboxyl donors possesses synthetic and practical advantages, among which the recy-

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(6) (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449. (b) Otera, J. *Acc. Chem. Res.* **2004**, *37*, 288.

(7) For an excellent monography on this topic, see: Otera, J. *Esterfication: Methods, Reactions and Applications*; Wiley-VCH: Weinheim, Germany, 2003.

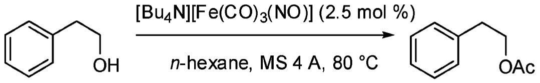
(8) Stanton, M. G.; Gagné, M. R. *J. Org. Chem.* **1997**, *62*, 8240.

(9) Taber, D. F.; Amedoi, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

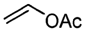
(10) For a recent review on transesterifications, see: Grassa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971.

cling of the activating group is the most prominent one. Hence some common acyl donor reagents were subjected to the standard reaction conditions. Gratifyingly, we found phenyl acetate to work equally well in the transesterification process although at the cost of prolonged reaction times (entry 2, Table 2). Alternative acyl donors, however, reacted in low conversions or even noncatalyzed in a sluggish way (entries 3 and 4, Table 2).

Table 2. Variation of the Acyl Donor



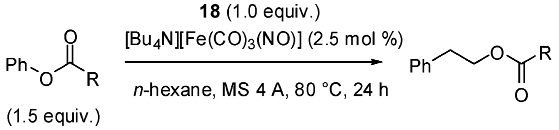
18 **3**

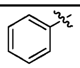
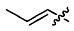
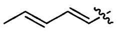
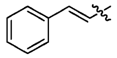
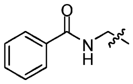
entry [a]	R	time (h)	conversion (%) [b]
1		5	95 (31)
2	Ph–OAc	24	94 (11)
3	H_3C–OAc	24	21 (-)
4	Ac–OAc	24	68 (64)
5	Cl–Ac	24	65 (61)

[a] All reactions were performed on a 1 mmol scale in the presence of the acyl donor (1.5 mmol), 4 Å MS (100 mg), and Fe catalyst (0.025 mmol) under a N_2 atmosphere in *n*-hexane (1 mL). [b] Conversion according to GC integration. Conversion of the reaction in the absence of Fe catalyst is given in parentheses.

In the process of these investigations, different phenyl esters were prepared following standard procedures and were subjected to the transesterification conditions (Table 3). Under the standard reaction conditions, functionalized carboxylic acid esters possessing one or more π-bonds or heterofunctionalities such as amide groups are esterified efficiently (Table 3). Whereas primary hydroxyl groups are esterified in good yields, sterically more hindered secondary and tertiary alcohols were unreactive.

Table 3. Fe-Catalyzed Acylation of Alcohols

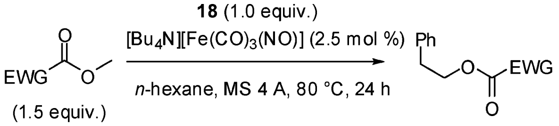


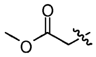
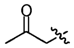
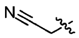
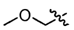
entry [a]	R	product	yield (%) [b]
1		**19**	67
2		**20**	80
3		**21**	68
4		**22**	81
5		**23**	42

[a] All reactions were performed on a 1.5 mmol scale in the presence of alcohol **18** (1.0 mmol), 4 Å MS (100 mg), and Fe catalyst (0.025 mmol) under a N_2 atmosphere in *n*-hexane (1 mL). [b] Isolated yield.

The activating groups used so far increase the electrophilicity of the carbonyl carbon in order to facilitate the initial addition of the Fe-based transesterification catalyst. The strategy of using an electron-withdrawing activator in order to increase the electrophilicity of otherwise less electrophilic carbonyl groups is necessary for transesterifications using electron-rich carboxylic moieties. The situation for the reaction between an alcohol and a carboxylic acid that is activated by an electron-withdrawing neighboring group is somewhat different. The inherent higher electrophilicity of the carbonyl group should allow for a transesterification without the use of any activating group. In order to test this hypothesis for our reaction, some activated methyl esters were subjected to the reaction conditions (Table 4).

Table 4. Fe-Catalyzed Transesterification of Electron-Poor Methyl Esters

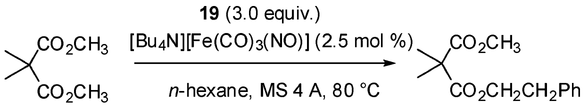


entry [a]	EWG	product	yield (%) [b]
1		**24**	87[c]
2		**25**	40
3		**26**	92
4		**27**	96

[a] All reactions were performed on a 1.5 mmol scale in the presence of alcohol **18** (1.0 mmol), 4 Å MS (100 mg), and Fe catalyst (0.025 mmol) under a N_2 atmosphere in *n*-hexane (1 mL). [b] Isolated yield. [c] 3 mmol of alcohol **18** was used. The yield refers to the bis(2-phenyl ethyl) ester.

Fortunately, the activation by an electron-withdrawing functional group allows for the mild transesterification of different carboxylic acid methyl esters. Moreover, the transesterification is applicable to sterically hindered carboxylic esters, as well. Hence, subjecting malonate **28** to the standard reaction conditions led to the isolation of product **29** in moderate yield (Scheme 1). In sharp contrast to the transesterification using dimethylmalonate **24**, even in the

Scheme 1. Fe-Catalyzed Transesterification of Sterically Hindered Malonate **28**



28 56% **29**

excess of alcohol **18**, no double transesterification was observed. This might be the result of the increase in steric hindrance after the first transesterification event.

Although this result is of limited practical interest, it sheds some light into the mechanism of this reaction. The successful transesterification excludes the intermediate formation of a ketene as it is observed under thermal conditions. In analogy to the transesterifications catalyzed by tertiary N bases, such as DMAP, we propose the reaction to proceed via an intermediate carboxyl Fe complex **iv**, which is formed upon nucleophilic displacement of the activating group in the original acyl donor **ii**. The second nucleophilic attack of alcohol **iii** leads to the formation of the desired product while regenerating the catalytically active Fe catalyst. A mechanistic rationale for this unprecedented reaction is shown in Figure 2.

In the present communication, we summarized our initial results on the use of nucleophilic Fe(−II) complexes as catalyst for the mild transesterification of vinyl acetates, phenyl carboxylates, and activated electron-poor esters using primary, secondary, and tertiary (activated) alcohols. The catalyst used in these studies allows for the reaction to be performed under neutral conditions, which is in sharp contrast to the alkoxide-based or Lewis acidic metal catalysts employed in the majority of transesterification protocols.

Future work will concentrate on an extension of the reaction scope and on mechanistic investigations aimed toward the identification of catalytic intermediates. If our mechanistic hypothesis holds true, the present reaction would be the first example of a catalytically active acyl Fe complex and might open the door for an entire new field of Fe catalysis in organic chemistry.

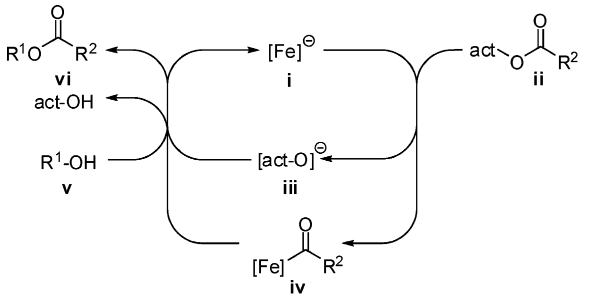


Figure 2. Mechanistic proposal.

Acknowledgment. Financial support by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and the Deutsche Krebshilfe is gratefully acknowledged.

Supporting Information Available: Characterization data for all new compounds and experimental procedures are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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