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Nucleophilic Iron Catalysis in Transesterifications: Scope and Limitations

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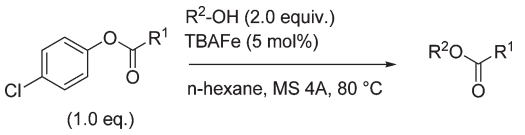

The ester bond is one of the most common structural motifs found in nature. Apart from the condensation between an acid and an alcohol, transesterifications represent another mechanistic alternative for the preparation of this compound class. The present paper summarizes our most recent investigations in this field, using nucleophilic iron complexes as catalysts for transesterifications under neutral conditions. This new type of metal catalyst complements the existing methodologies, which rely on Lewis acidic metal complexes. Investigations on scope and limitations, stereochemical course, and chemoselectivities will be presented.

Introduction

Transition metal-catalyzed reactions are among the most powerful tools in modern organic synthesis. The use of only catalytic amounts of a metal complex often allows for a significant reduction of the activation energy barrier, which in turn allows reactions to be done at lower temperature. The cost savings by use of catalytic reactions can be increased if metal complexes based upon readily available, nontoxic metals are used. With regard to these both economical and ecological arguments iron catalysis has faced a tremendous resurrection within the past years.

Most of the catalytic reactions known today employ iron salts which function as either Lewis acids or alkyl transfer agents after in situ transformation to tetraalkyl ferrates.[1] However, whereas the metal center in this type of ferrate still possesses the oxidation state of +II or +III, catalysis in which the metal itself is reduced to the oxidation state −II is still somewhat uncommon.[2] Our group got involved in the latter type of catalysis three years ago. Upon the basis of seminal contributions from Hieber,[3] Roustan,[4] and Zhou[5] we were able to develop a regioselective allylic substitution by employing a combination of $[Bu_4N][Fe(CO)_3(NO)]$ (TBAFe)[6] and triaryl phosphines[7] or N-heterocyclic carbenes[8] as monodentate basic ligands. Upon the basis of the assumption that a nucleophilic attack of the electron-rich catalyst at a positively charged olefinic carbon atom is involved in the first step of this transformation we recently were able to extend the reaction scope by using esters as reactive substrates in transesterifications (Scheme 1).[9]

Apart from the importance of transesterifications in organic chemistry the Fe-catalyzed version of this reaction represents the first example for the use of an acyl−iron complex in catalysis.[10] A deeper understanding on factors influencing the reactivity and stability of these complexes might pave the way toward the development of further catalytic transformations in which similar complexes are reactive intermediates (e.g., carbonylation, cross-coupling, etc.).

Hence we initiated an in-depth investigation on the scope and limitations of this new catalytic transformation with the

(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. (c) Plietker, B.; *Iron Catalysis in Organic Synthesis*; Wiley-VCH, Weinheim, Germany, 2008.

(2) Plietker, B.; Dieskau, A. *Eur. J. Org. Chem.* **2009**, 775.

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

(4) (a) Roustan, J. L. A.; Houlihan, F. *J. Organomet. Chem.* **1988**, *353*, 215. (b) Cygler, M.; Ahmed, F. R.; Forgues, A.; Roustan, J. L. *Inorg. Chem.* **1983**, *22*, 1026. (c) Roustan, J. L. A.; Forgues, A. *J. Organomet. Chem.* **1980**, *C13*−*C16*, 184.

(5) (a) Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974. (b) Zhou, B.; Xu, Y. *J. Org. Chem.* **1988**, *53*, 4421.

(6) For the preparation of TBAFe see ref 8b.

(7) (a) Allylic alkylation: Plietker, B. *Angew. Chem.* **2006**, *118*, 1497. *Angew. Chem., Int. Ed.* **2006**, *45*,1469. (b) Allylic amination: Plietker, B. *Angew. Chem.* **2006**, *118*, 6200. *Angew. Chem., Int. Ed.* **2006**, *45*, 6053; (c) Allylic sulfonation: Jegelka, M.; Plietker, B. *Org. Lett.* **2009**, *11*, 3462.

(8) (a) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A. *Angew. Chem.* **2008**, *120*, 204. *Angew. Chem., Int. Ed.* **2008**, *47*, 198. (b) Holzwarth, M.; Dieskau, A.; Tabassam, M.; Plietker, B. *Angew. Chem.* **2009**, *121*, 7387. *Angew. Chem., Int. Ed.* **2009**, *48*, 7251.

(9) Magens, S.; Ertelt, M.; Jatsch, A.; Plietker, B. *Org. Lett.* **2008**, *10*, 53.

(10) Collman, J. P. *Acc. Chem. Res.* **1975**, 342 and references cited therein.

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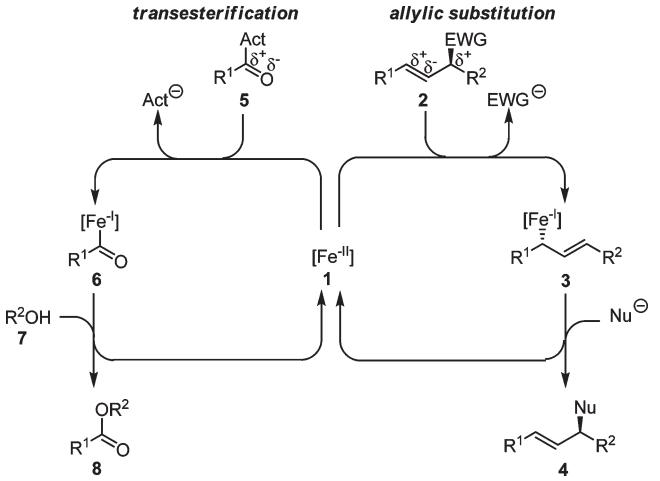
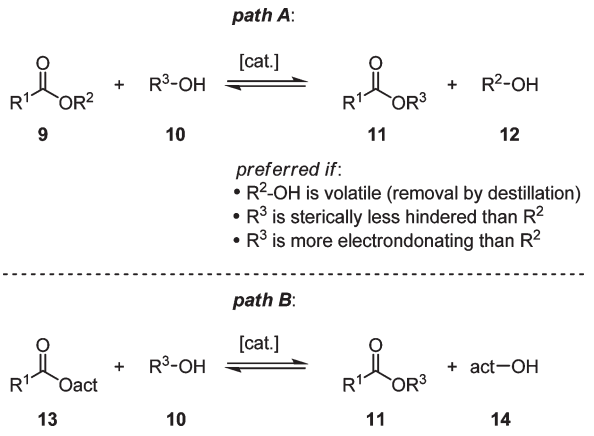
SCHEME 1. Catalysis Involving Nucleophilic Iron Complexes



SCHEME 2. Transesterification Strategies



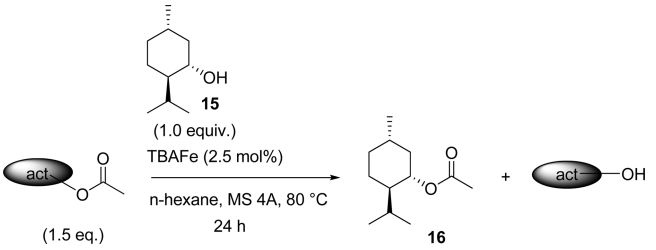
aim to get more information on the interplay of structural parameters like substitution pattern of acyl donor, carboxylic acid, and alcohol.

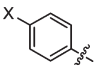
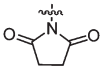
Results and Discussion

The use of nucleophilic metal catalysts for transesterifications might be regarded as being complementary to the existing methods, in which Lewis acidic catalysts or metal alkoxides are employed.[11,12] However, independent of the catalytic mechanism transesterifications oppose a synthetic challenge to methodology development since substrate and product are in equilibrium of an almost identical energetic level. To shift the equilibrium to the desired direction an excess of one of the two substrates is usually employed. However, an excess of one of the substrates can be avoided if R^3OH is sterically less hindered or more nucleophilic than the resulting alcohol R^2OH and the backreaction is significantly slowed down (path A, Scheme 2). If these synthetic strategies are not applicable activated esters are employed in which the activating group is either volatile or undergoes a subsequent irreversible reaction (path B, Scheme 2).

(11) Stanton, M. G.; Gagné, M. R. *J. Org. Chem.* **1997**, *62*, 8240.
(12) Otera, J. *Esterfication—Methods, Reactions and Applications*; Wiley-VCH, Weinheim, Germany, 2003.

TABLE 1. Optimization of the Acyl Donor

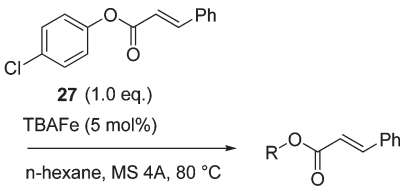


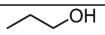
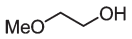
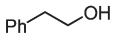
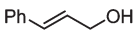
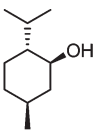
entry[a]	act	yield [%][b]
1	 **17**	63
2	 **18**	92
3	 **19**	20
4	 **20** (X = H)	28
5	**21** (X = CH_3)	32
6	**22** (X = C(=O)CH_3)	28
7	**23** (X = OMe)	30
8	**24** (X = Cl)	41
9	 **25**	< 5
10	 **26**	< 5

[a]All reactions were performed on a 1 mmol scale, using 2.5 mol % TBAFe, (−)-menthol **15** (1.0 mmol), and the corresponding acyl donor (1.5 equiv) in dry *n*-hexane (1 mL) in the presence of molsieves 4 Å at 80 °C and stopped after 24 h. [b]Isolated yields.

Variation of the Acyl Donor. Initial efforts concentrated on the use of vinyl acetate as acyl donor.[9] This compound is commercially available and inexpensive. The formation of acetaldehyde as a volatile side product pushes the equilibrium to the product side. However, the preparation of structurally diverse vinyl carboxylates is not always easy to perform. Preparative readily accessible aryl esters were found to be suitable vinyl ester surrogates; however, transesterifications with these acyl donors were successful only in the presence of primary alcohols.[9] To broaden the scope of potential acyl donors we prepared and screened different enol and aryl acetates under standard reaction conditions in the presence of menthol (−)-**15** as a sterically hindered secondary alcohol (Table 1).

TABLE 2. Scope and Limitations Part I: The Alcohol Scope

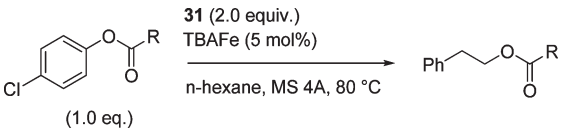


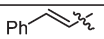
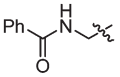
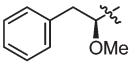
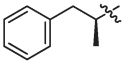
entry[a]	Substrate	product	time [h]	Yield [%][b]	ref.
1	 **28**	**38**	24	82	[13]
2	 **29**	**39**	48	86	[14]
3	 **30**	**40**	72	72	[15]
4	 **31**	**41**	24	91	[9]
5	 **32**	**42**	24	96	[16]
6	 **33**	**43**	24	88	[17]
7	 **34**	**44**	24	79	[18]
8	 **35**	**45**	48	86	[19]
9	 **36**	**46**	48	76	[20]
10	 **37**	**47**	70	73	[21]
11	 **15**	**48**	70	67	[22]

[a]All reactions were performed on a 0.5 mmol scale, using 5 mol % TBAFe, (−)-alcohol (2 equiv), and *p*-chloro aryl cinnamate **28** (1 equiv) in dry *n*-hexane (0.5 mL) in the presence of molsieves 4 Å at 80 °C. [b]Isolated yields.

Among the tested acyl donors cyclopentenone-derived vinyl acetate **18** proved to be the most active one. This compound is accessible upon reaction of cyclopentanone with triethyl orthoacetate under basic conditions. However, the reaction conditions required for the preparation of ortho-esters are somewhat incompatible with, e.g., stereocenters at the α-carbon atom. Hence, with regard to the applicability of this process the more stable aryl esters appeared to be an appropriate alternative. We were delighted to find that *p*-chloro-substituted aryl acetate **24** led to a significant increase in the isolated yield (entry 8, Table 1). Alternative common activating groups, however, gave poor results (entries 9 and 10, Table 1).

TABLE 3. Scope and Limitations Part II: The Acid Scope



entry[a]	R	product	time [h]	Yield [%][b]	ref.
1	 **27**	**41**	24	91	[9]
2	 **49**	**58**	24	89	[23]
3	 **50**	**59**	2	82	[9]
4	Ph **51**	**60**	14	84	[9]
5	 **52**	**61**	14	84	[24]
6	 **53**	**62**	14	82	[25]
7	 **54**	**63**	14	83	
8	 **55**	**64**	14	86	
9	 **56**	**65**	3	66 (*ee:* 98 %)	
10	 **57**	**66**	24	69 (*ee*: 98 %)	

[a]All reactions were performed on a 0.5 mmol scale, using 5 mol % TBAFe, (−)-2-phenylethanol **31** (2 equiv), and *p*-chloro aryl esters **27** and **49**−**57** (1 equiv) in dry *n*-hexane (0.5 mL) in the presence of molsieves 4 Å at 80 °C. [b]Isolated yields.

Scope and Limitations. We subsequently investigated scope and limitations of the TBAFe-catalyzed transesterification using *p*-chloro aryl esters as acyl donors. To circumvent a loss of material due to volatility of the resulting products we employed *p*-chloro aryl cinnamate **27** as activating ester in this investigation (Table 2).

(13) Castle, K.; Hau, C. S.; Sweeney, J. B.; Tindall, C. *Org. Lett.* **2003**, *5*, 757.
(14) Crosignani, S.; White, P. D.; Steinauer, R.; Linclau, B. *Org. Lett.* **2003**, *5*, 853.
(15) Sinha, A. K.; Sharma, A.; Swaroop, A.; Kumar, V. *Tetrahedron* **2007**, *63*, 1000.
(16) Parrish, J. P.; Dueno, E. E.; Kirn, S.-I.; Jung, K. W. *Synth. Commun.* **2000**, *30*, 2687.
(17) Mali, R. S.; Papalkar, A. S. *J. Chem. Res., Synop.* **2001**, *10*, 433.
(18) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944.
(19) Akermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729.
(20) Funasaka, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 148.
(21) Hanessian, S.; Gomtsyan, A.; Maiek, N. *J. Org. Chem.* **2000**, *65*, 5623.
(22) Ye, S.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2001**, *66*, 5717.

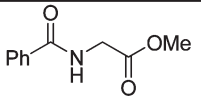
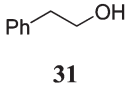
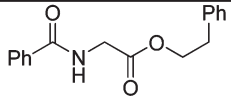
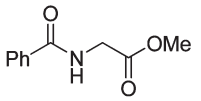
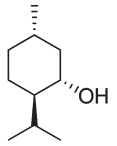
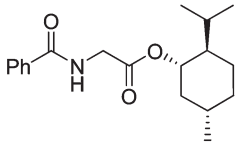
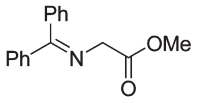
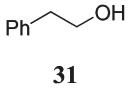
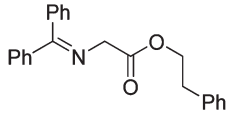
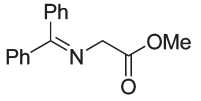
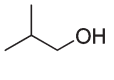
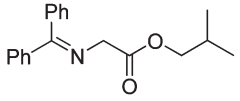
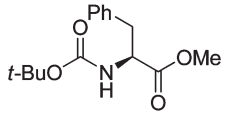
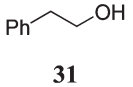
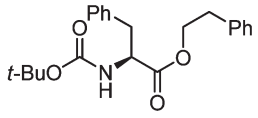
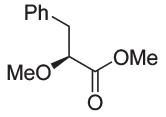
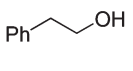
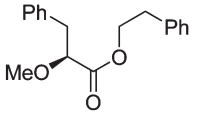
A variety of alcohols were transformed into the corresponding cinnamates **38**−**48** in good to excellent yields. In general the sterically less hindered primary alcohols are more reactive; however, prolonging the reaction times led to good isolated yields even on sterically hindered secondary alcohols (entries 7−11, Table 2). Transferring the reaction conditions to the transesterification of different *p*-chloro aryl esters with 2-phenyl ethanol **31** proved the reaction to be applicable to various carboxylic acid residues (Table 3).

A variety of functionalized activated aryl esters **27** and **49**−**57** are reactive in the revised transesterification protocol. In particular stereocenters at α-carbon atoms were shown to undergo transesterifications without loss of stereochemical integrity (entries 9 and 10, Table 3). These results underline the strength of this protocol. Although temperatures of 80 °C appear to favor a thermal epimerization the neutral reaction conditions allow for an excellent conservation of chirality. To obtain further proof for this result enantiomerically pure arylester **56** was subjected to the transesterification, using (−)- or (+)-menthol **15**. We were pleased to find the reaction to proceed with high conversion rates and a high degree of stereochemical integrity independent of the configuration of **15** (Scheme 3).

Apart from aryl groups as activators in transesterifications even simple methyl esters possessing an electron-withdrawing group at the α-carbon atom are suitable substrates for Fe-catalyzed transesterification with different alcohols (Table 4).

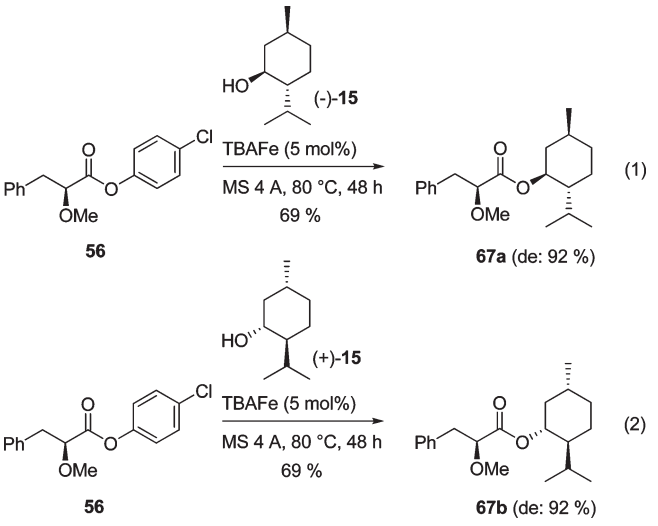
Fortunately, no epimerization of the sensitive stereocenter at the α-carbon atom was observed. Acid-labile and base-sensitive protecting groups are stable under the reaction conditions. The functional group tolerance and stereoconservation are the two most important aspects in this reaction, which makes the protocol amenable to complex molecule synthesis. Hence, future developments are directed to an extension of this methodology toward an application, e.g., in peptide bond formation. Finally we were delighted to find this catalytic transformation to be applicable in intramolecular transesterfications

TABLE 4. Transesterification of α-Activated Methyl Esters

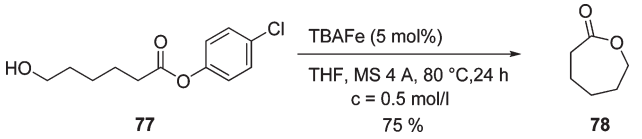
entry[a]	substrate	alcohol	product	time [h][b]	Yield [%][b]	Ref.
1	 **68**	 **31**	 **59**	15	84	[9]
2	 **68**	 **(-)-15**	 **73**	24	42	[26]
3	 **69**	 **31**	 **74**	24	96	
4	 **69**	 **72**	 **75**	17	84	
5[c]	 **70**	 **31**	 **76**	40	96 (*ee*: 98 %)	
6	 **71**	 **31**	 **65**	24	72 (*ee*: 98 %)	

[a]All reactions were performed on a 0.5 mmol scale, using 5 mol % TBAFe, alcohol (2 equiv), and the corresponding methylesters (1 equiv) in dry *n*-hexane (0.5 mL) in the presence of molsieves 4 Å at 80 °C. [b]Isolated yields. [c]10 mol % TBAFe.

SCHEME 3



SCHEME 4. Fe-Catalyzed Macrolactonization

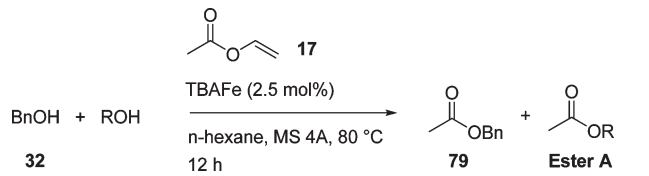


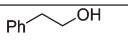
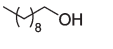
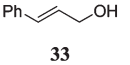
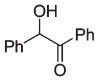
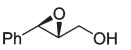
to give seven-membered macrolactone **78** in good yields without oligo- or polymerization as side reactions even in concentrations up to 0.5 mol/L (Scheme 4).

Chemoselectivity. The examples listed above indicate the Fe-catalyzed transesterification to possess a good functional group tolerance. The chemoselective transformation of an alcohol into an ester in the presence of further reactive hydroxyl groups, however, would be one of the ultimate goals, since the chemoselectivity is directly transferred into the chemical efficiency of a multistep synthesis by making protecting group operations redundant.[27] To gain an insight into this issue the Fe-catalyzed transesterification of two different alcohols in the presence of vinylacetate as acyl donor was investigated (Table 5).

To exclude factors like volatility of one alcohol compared to another benzyl alcohol was chosen as a reference. In general electron-rich alcohols are more reactive in transesterifications. The presence of an allylic or benzylic double bond significantly increases the reactivity, while electron-withdrawing functional groups decrease the reactivity. Furthermore, steric bulk plays a central role when it comes to reactivity. In general secondary alcohols are less reactive.

TABLE 5. Relative Reactivities of Different Alcohols



entry[a]	ROH	Ester A	k_{rel}[b]	Yield [%][c]	ref.
1	 **31**	**84**	1	81	[9]
2	 **80**	**85**	0.79	80	[28]
3	 **33**	**86**	1.18	86	[9]
4	 **36**	**87**	0.53	83	[9]
5	 **37**	**88**	0.31	67	[29]
6	 **81**	**89**	0.02	33	[30]
7	 **82**	**90**	0.42	77	[31]
8	 **83**	**91**	0.72	86	[32]
9	 **34**	**92**	0.45	83	[9]
10	 **35**	**93**	0.45	79	[9]

[a]All reactions were performed on a 1 mmol scale, using 2.5 mol % TBAFe, benzylalcohol **32** (1 mmol), alcohol (1 mmol), and vinylacetate **17** (1.5 mmol) in dry *n*-hexane (1 mL) in the presence of molsieves 4 Å at 80 °C and stopped after 12 h. [b]$k_{rel} = c(\mathbf{79})/c(\text{ester A})$, calculated via GC integration. [c]Combined isolated yields.

Furthermore, oxiranes in proximity to the reactive hydroxyl group are tolerated. The corresponding acetates were formed in good yields without formation of byproducts.

Summary

Herein we summarize the results of a comprehensive study on transesterifications catalyzed by the neutral and nucleophilic metal complex $[Bu_4N][Fe(CO)_3(NO)]$. Within the course of these studies *p*-chloro aryl esters were found to be suitable and reactive acyl donors allowing for the successful acylation

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(30) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 4817.
(31) Takeshita, M.; Yaguchi, R.; Akutsu, N. *Tetrahedron: Asymmetry* **1992**, *3*, 1369.
(32) Man, K. T.; Klawonn, M.; Bhor, S.; Doebler, C.; Anilkumar, G.; Hugl, H.; Maegerlein, W.; Beller, M. *Org. Lett.* **2005**, *7*, 987.

of a variety of primary and secondary alcohols. Moreover, epimerization labile acyl donors possessing a stereocenter in proximity to the carbonyl group are transformed into the corresponding esters with full stereointegrity. Furthermore, methyl esters possessing an electron-withdrawing functional group at the α-carbon are reactive substrates in transesterifications. Since the enantiopurity of the starting materials is fully transferred into the product an application of this method toward complex molecule synthesis is possible, a fact that is emphasized by the broad functional group tolerance of this mild transesterification method. Future research in this field includes the extension of the nucleophile spectra toward N-, S-, and C-nucleophiles.

Experimental Section

General Remarks. All solvents were purified by distillation over CaH_2 prior to use. Flash chromatography was done on silica gel 60 (230−400 mesh), using head pressure by means of compressed air. Infrared spectra (IR) were recorded as a thin film between KBr plates. Proton and carbon nuclear magnetic resonance spectra were recorded in chloroform (d-1) and referenced to the solvent signal or to the internal standard TMS. The multiplicities of the signals are given as d (doublet), t (triplet), q (quartet), and m (multiplet). GC yields were obtained with *n*-dodecane as internal standard that was added in an amount equal to the quantitative yield of the reaction.

General Procedure for Transesterifications. A 10 mL Schlenk tube was charged at room temperature with $[Bu_4N][Fe(CO)_3NO]$ (2.5−10 mol %) and molsieves 4 Å (50−100 mg) under an N_2 atmosphere. Dry *n*-hexane (1 mL/mmol) was added. After 15 min of stirring at room temperature the alcohol and the aryl/vinyl ester were added. The tube was immediately closed and heated to 80 °C. After cooling to room temperature the reaction mixture underwent direct purification by means of flash chromatography.

Acknowledgment. The authors are grateful to the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for financial support.

Supporting Information Available: Copies of ^1H NMR spectra and spectral data for all esters. This material is available free of charge via the Internet at http://pubs.acs.org.