Scandium Triflate Catalyzed Transesterification of Carboxylic Esters

Nicole Remme, Katharina Koschek, Christoph Schneider*

Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax +49(341)9736599; E-mail: schneider@chemie.uni-leipzig.de
Received 30 November 2006

Abstract: The direct transesterification of carboxylic esters is efficiently catalyzed with Sc(OTf)$_3$ (10 mol%) in boiling alcoholic solvent. Methyl, ethyl, isopropyl, and allyl esters were prepared from a broad range of different substrates in high yields. The application of microwave irradiation led to significantly reduced reaction times.

Key words: carboxylic esters, catalysis, scandium, transesterification

Carboxylic esters are among the most versatile organic compounds. Accordingly, a broad number of synthetic procedures have been developed for their preparation.[1] Besides the traditional acid-catalyzed reaction of a carboxylic acid with an alcohol, the most often utilized method includes the treatment of an activated carboxylic acid derivative, which is either prepared in a separate reaction or formed in situ with an alcohol in the presence of a base. Alternatively, transesterification reactions have been employed for the conversion of one ester into another ester.[2] Such processes are subject to acid and base catalysis and are based upon a thermodynamic equilibrium. Among the most frequently used catalysts are titanium alkoxides developed by Seebach et al.[3] and tetraalkyl distannoxanes introduced by Otera et al.[4] Whereas titanium alkoxides need to be employed at catalyst loadings of typically 20 mol% or more the distannoxanes are extremely efficient catalysts even down to 0.05 mol%. Simple Bu$_2$SnO (10 mol%) has been shown by Giannis et al. to be a good transesterification catalyst as well.[5]

In 1995 Yamamoto et al. demonstrated the potential of Sc(OTf)$_3$ to function as an esterification catalyst. They showed that the reaction of carboxylic acid anhydrides with alcohols was efficiently catalyzed through Sc(OTf)$_3$ to furnish carboxylic esters in high yields.[6] The anhydrides employed may be formed in situ from the corresponding acids and *para*-nitro benzoic acid anhydride and the esters were obtained with comparable yields. Subsequently, Otera discovered that Sc(OTf)$_3$ successfully catalyzed the conversion of *N*-acyl oxazolidinones into esters in high yields and short reaction times.[7] Since both anhydrides and imides constitute reactive carboxylic acid derivatives it was unclear whether regular esters with attenuated carbonyl activity were suitable substrates for a Sc(OTf)$_3$-catalyzed transesterification process as well.

We started our investigations with the model reaction depicted in Scheme 1. Ethyl phenyl acetate (**1a**) was treated with Sc(OTf)$_3$ in refluxing methanol and the progress of the reaction was followed by GC analysis. With 10 mol% catalyst full conversion was reached within 10 hours and the product **2a** was isolated in 91% yield. When the catalyst amount was lowered to just 1 mol% the reaction time rose to 96 hours but the product was still isolated in 95% yield.[8] Thus, although 1 mol% Sc(OTf)$_3$ appeared to be sufficient for full conversion at elevated temperatures all further experiments were conducted with 10 mol% Sc(OTf)$_3$ in refluxing alcoholic solvent in order to reduce the reaction times to an acceptable level.

10 mol% Sc(OTf)$_3$, 10 h: 91%
1 mol% Sc(OTf)$_3$, 96 h: 95%

Scheme 1

Using these conditions, various aliphatic carboxylic esters **1** were then converted into the corresponding methyl esters **2** within 6–12 hours in high yields (Table 1).[9]

Functional groups such as halogen atoms, cyano, hydroxyl, and phosphonyl groups were readily tolerated and suffered no decomposition during the reaction. In fact, some functionalized esters such as (*S*)-ethyl mandelate (entry 3) and ethyl phosphono acetate (entry 8) were among the most reactive substrates included in this study. Most importantly, chiral centers even adjacent to the ester group were not affected and completely retained their absolute configuration. Thus, (*S*)-methyl mandelate and (*R*)-methyl β-hydroxy butyrate were obtained in the same ee as the starting esters (entries 3 and 4). A diester was successfully converted into the corresponding dimethyl ester in slightly prolonged reaction times presumably due to the presence of two ester groups (entry 9). Surprisingly, even esters carrying tertiary amino and Boc-protected amino groups underwent the Sc(OTf)$_3$-catalyzed transesterification reaction albeit in only moderate yields (entries 10–12). Aromatic and conjugated esters proved to be less reactive requiring extended reaction times. The product esters were, however, obtained in good to excellent yields (entries 13–16).

Subsequently, this protocol was extended to the formation of ethyl, isopropyl and allyl esters, all of which were formed in good to excellent yields when refluxed with 10

Table 1 Sc(OTf)$_3$-Catalyzed Transesterification with Methanol
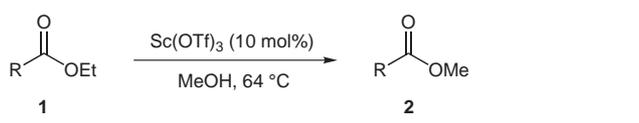
Entry	R	Time (h)	Yield (%)[a]
1	PhCH$_2$-	10	91
2	Me(CH$_2$)$_6$-	8	98
3	(S)-PhCH(OH)-	6	97 (>99% ee)[b]
4	(R)-MeCH(OH)CH$_2$-	10	98 (>97% ee)[c]
5	NCCH$_2$-	8	89
6	Br(CH$_2$)$_4$-	12	80
7	(+/–)-PhCH(Cl)-	12	89
8	(EtO)$_2$P(O)CH$_2$-	0.5	98
9	EtO$_2$CCH$_2$CH(OH)CH$_2$-	24	89[d]
10	BocNH(CH$_2$)$_2$-	8	62
11	BocNH(CH$_2$)$_3$-	29	77
12	(S)-N-Benzylpyrrolidine-	72	72 (>99% ee)[b]
13	PhCH=CH-	65	97
14	p-OHC$_6$H$_4$	168	81
15	o-OHC$_6$H$_4$	144	72
16	p-NO$_2$C$_6$H$_4$	168	98

[a] Isolated yield of chromatographed material.
[b] Determined by chiral HPLC on a OD-phase.
[c] Determined by ^{19}F NMR on the derived Mosher ester.
[d] Dimethyl 3-hydroxyglutarate is obtained as product.

mol% Sc(OTf)$_3$ in the respective alcohols (Table 2). Allyl esters were obtained in particularly high yields and short reaction times which is worth mentioning in light of their facile palladium-catalyzed deprotection giving rise to the corresponding acids (entries 1–5). On the other hand, formation of isopropyl esters required prolonged heating reflecting the steric bulk in the alcohol component (entries 9 and 10).

There are some limitations to this method. Not surprisingly, esters containing acid-labile acetal moieties did not survive the Lewis acidic reaction conditions. Thus, 2,3-*O*-isopropylidene dimethyl tartrate upon reaction with ethanol and Sc(OTf)$_3$ was converted into diethyl tartrate in 90% yield. The attempted conversion of ethyl acetoacetate into methyl acetoacetate did not yield any product for a yet unclear reason although the starting ester was slowly consumed. Finally, *tert*-butyl esters were not accessible via this method presumably due to the steric bulk of the alcohol component.

In an attempt to shorten the reaction times required for the transesterification event we tested microwave conditions

in some of the reactions.[10] (S)-Ethyl mandelate was irradiated with allyl alcohol in a microwave oven at 140 °C and otherwise identical reaction conditions to furnish (S)-allyl mandelate within only 20 minutes in excellent yield and ee (Scheme 2). Methyl *para*-nitro benzoate was converted into ethyl *para*-nitro benzoate likewise within 6 hours at 140 °C. Thus, although we have not conducted an extensive study, these experiments clearly show the beneficial effect and compatibility of microwave irradiation on the Sc(OTf)$_3$-catalyzed transesterification.
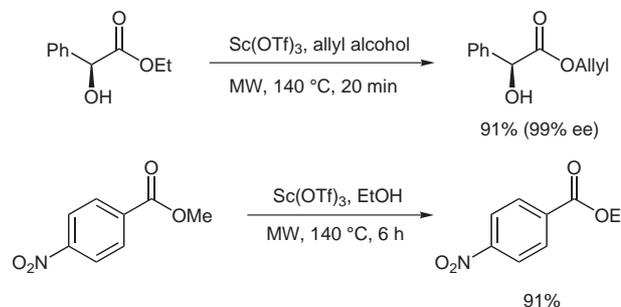
Scheme 2

In conclusion, we have shown that Sc(OTf)$_3$ is a powerful catalyst for the direct transesterification in typically very high yields. A broad range of different functional groups was readily tolerated and chiral centers even adjacent to the carboxyl group were not affected. The application of microwave irradiation substantially reduced the reaction times.

References and Notes

(1) Excellent review: Otera, J. *Esterification*; Wiley-VCH: Weinheim, **2003**.
(2) Specialized reviews about transesterification: (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449. (b) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971.
(3) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.
(4) (a) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383. (b) Otera, J.; Danoh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
(5) Baumhof, P.; Mazitschek, R.; Giannis, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4077.
(6) (a) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413. (b) Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265.
(7) Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* **2001**, 637.
(8) At room temperature no full conversion could be achieved even with 10 mol% catalyst and prolonged reaction times.
(9) **Typical Experimental Procedure.**
A solution of the ester (1.00 mmol) in the respective alcohol (10 mL) was treated with 49.0 mg (0.10 mmol, 10 mol%) Sc(OTf)$_3$ and refluxed for the indicated reaction time. The reaction mixture was cooled to r.t. and filtered over a short

Table 2 Sc(OTf)$_3$-Catalyzed Transesterification with Allyl Alcohol, Ethanol, and Isopropanol
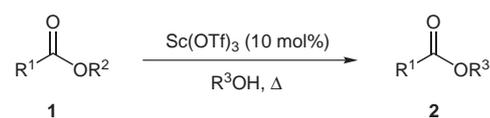
Entry	R^1	R^2	R^3	Time (h)	Yield (%)[a]
1	PhCH$_2$-	Et	Allyl	11	95
2	Me(CH$_2$)$_6$-	Et	Allyl	8	86
3	(S)-PhCH(OH)-	Et	Allyl	6	94 (>99% ee)[b]
4	(+/–)-PhCH(OH)-	Me	Allyl	6	96
5	(+/–)-PhCH(Cl)-	Et	Allyl	10	92
6	Me(CH$_2$)$_6$-	Me	Et	8	97
7	(+/–)-PhCH(OH)-	Me	Et	6	98
8	(S)-MeOCH(NHBoc)-	Me	Et	12	66[c]
9	(S)-PhCH(OH)-	Et	i-Pr	72	84 (>99% ee)[b]
10	Me(CH$_2$)$_6$-	Et	i-Pr	132	90

[a] Isolated yield of chromatographed material.
[b] Determined by chiral HPLC on a OD-phase.
[c] $[\alpha]_D^{20}$ –18.8 (c 0.5, EtOH) {lit.[5] $[\alpha]_D^{20}$ –17.0 (c 2, EtOH)}.

plug of silica gel. All volatiles were evaporated in vacuo and the residue was purified by chromatography with mixtures of Et$_2$O and pentane. All esters prepared were characterized by NMR, IR, and MS and gave spectroscopic data matching the reported data. The ee values of the (S)-mandelate esters were determined by HPLC on a chiral OD-phase with hexane–i-PrOH = 90:10, flow rate 1.0 mL/min. The ee of (R)-methyl β-hydroxy butyrate was determined by ^{19}F NMR analysis of the corresponding Mosher ester. For the microwave experiments a microwave reactor 'microPREP A'

(MLS GmbH, Germany) with a single magnetron (max. 1200 W, pulsed irradiation, 2.45 GHz), terminal 320 controller, and easy CONTROL 06 software was used. An internal ATC-FO 300 fiberoptic sensor inserted into the reaction vessel was employed to measure the temperature inside the reaction mixture accurately and adjust the temperature to the set temperature automatically.

(10) Excellent review about microwave-accelerated reactions: Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; *Angew. Chem.* **2004**, *116*, 6408.