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Highly Chemoselective Esterification Reactions and Boc/THP/TBDMS Discriminating Deprotections under Samarium(III) Catalysis†

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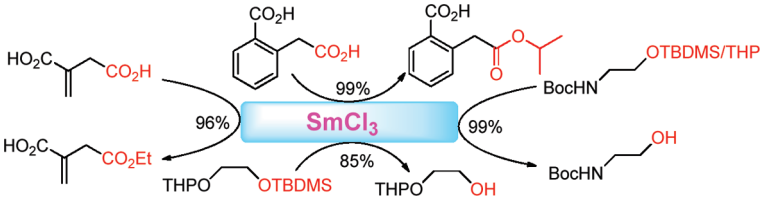
ABSTRACT



The usefulness of $SmCl_3$ as an excellent catalyst for chemoselective esterifications and selective removal of acid sensitive protecting groups such as Boc, THP, and TBDMS in the presence of one another is demonstrated through suitable examples.

Esterification, one of the most simple but most sought-after reactions in organic chemistry, can be carried out under acid catalysis or in the presence of bases.[1] The former, which proceeds via a tetrahedral intermediate, often does not work well with sterically hindered acids and is unsuitable if acid-labile functional groups exist on the substrates. Direct methyl ester formation using diazomethane or base-mediated esterification employing dimethyl sulfate or alkyl halides are other options; these reagents, however, pose toxicity, safety, and handling problems. Use of activated acids such as acid chlorides or mixed anhydrides is another alternative but requires additional reaction steps and reagents.

Selective deprotection of one acid-labile protecting group in the presence of a second one is another challenge in many synthetic sequences. The lack of a milder protocol for esterification, or selective deprotection, can appear as a bottleneck during the planning or execution stages of synthetic strategies and could narrow down the flexibility of a reaction scheme. In this communication, we address both of these issues and demonstrate the catalytic potential of $SmCl_3$ in chemoselective esterification reactions and selective deprotection of one acid-labile protecting group in the presence of another one.

Recently, we have reported a $SmCl_3$ mediated one-pot protocol for the preparation of highly functionalized benzothiophenes from 2,2′-dithiodibenzoyl chloride and cyclic 1,3-diones.[2] During this investigation, we serendipitously discovered the high potential of $SmCl_3$ to esterify benzothiophene-carboxylic acids of the type **1a** and **2a** in the presence of alcoholic solvents (Table 1). A comparative assessment of the esterification potential of $SmCl_3$ and other Lewis acids was then made using diphenyl acetic acid and isopropanol as the reactants. Reactions involving 50 mol % of these Lewis acids were carried out, and the outcome after 36 h at 80 °C was monitored. $SmCl_3$ gave a 54% yield and clearly had an upper hand in esterifying these sterically hindered substrates. The corresponding yields for other Lewis acids tested were as follows: $Sc(OTf)_3$ (45%), $ZnCl_2$ (36%), $InCl_3$ (30%), $MnBr_2$ (24%), and $MgCl_2$ (10%).

Table 1 lists the substrates chosen to demonstrate the chemoselectivity and functional group tolerance of $SmCl_3$

† Respectfully dedicated to Professor C. V. Asokan (deceased) for being a great source of inspiration.

(1) (a) Otera, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2044. (b) Nahmany, M.; Melman, A. *Org. Biomol. Chem.* **2004**, *2*, 1563.

(2) Gopinath, P.; Nilaya, S.; Debi, T. R.; Ramkumar, V.; Muraleedharan, K. M. *Chem. Commun.* **2009**, 7131.

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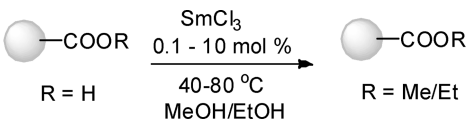
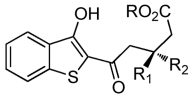
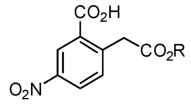
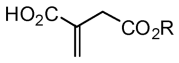
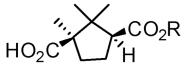
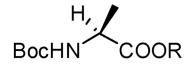
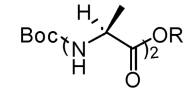
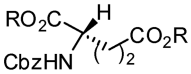
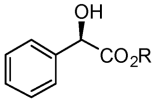
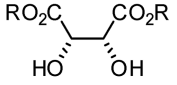
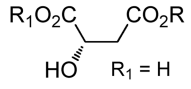
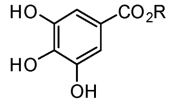
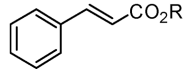
Table 1. Esterifications under $SmCl_3$ Catalysis



	acids (R = H)	*t* (h) / temp (°C)	$SmCl_3$ mol %	esters	% yield [a]
					
1a	$R_1 = R_2 = CH_3$	72/80	3	**1b** R = Et	94
2a	$R_1 = H$, $R_2 = Ph$	72/80	3	**2b** R = Et	97
3a		48/80	1	**3b** R = Et	93
4a		17/80	1	**4b** R = Et	96[b]
5a		96/80	5	**5b** R = Et	83
6a		144/40	10	**6b** R = Et	52 (69)[c]
		144/40	10	**6c** R = Me	64 (80)[c]
7a		144/50	10	**7b** R = Me	54 (70)[c]
8a		48/80	1	**8b** R = Et	91
9a		16/80	1	**9b** R = Et	96
10a		46/80	0.1	**10b** R = Et	96
11a		48/80	0.5	**11b** R, R_1 = Et	94
		3/80	1	**11c** R = Et, R_1 = H	46[d]
12a		130/80	10	**12b** R = Me	74
13a		96/80	10	**13b** R = Et	96

[a] Isolated yield. [b] 4% of the diester (**4c**) was also isolated. [c] Yield based on recovered starting material. [d] 30% of the diester **11b** was also isolated.

during esterification. The highly efficient and preferential reactivity of an aliphatic carboxyl group in the presence of aromatic or α,β-unsaturated carboxyl groups was observed in the cases of 5-nitrohomophthalic acid (**3a**) and itaconic acid (**4a**). They respectively gave 93% and 96% yields of the monoethyl esters **3b** and **4b** with just 1 mol % of the catalyst!

Similarly, the secondary carboxyl group in camphoric acid (**5a**) underwent selective esterification to give 83% of the mono ethyl ester **5b** with 5 mol % of $SmCl_3$. The stability of the *tert*-butyloxycarbonyl group to Sm(III) was then tested using BocAlaOH (**6a**) and BocAlaAlaOH (**7a**), as this could be of use in the area of peptide synthesis. The C-terminal free acid BocAlaOH, when esterified with 10 mol % of the catalyst in ethanol at 40 °C, gave 52% of the ester **6b** (69% based on the starting material recovered). Esterification with methanol was more efficient and afforded 64% of the corresponding ester **6c** (80% based on the starting material recovered). The dipeptide **7a** was esterified using 10 mol % of the catalyst, and a yield of 54% (70% based on the recovered starting material) was obtained on heating the mixture at 50 °C for 6 days. Although there was clean conversion to the corresponding esters, attempts to improve the yield by increasing the temperature resulted in the removal of the Boc− group in these substrates. Boc-containing carboxylic acids are generally esterified through a mixed anhydride approach or using carbodiimide, alkyl halides, or diazomethane.[3] Ceric ammonium nitrate or 2-ethoxy-l-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ) has also been shown to esterify Boc-amino acids at room temperature, but these require molar equivalents of the reagents.[4] Esterification of Boc-Ala-OH with the present approach using 10 mol % of $SmCl_3$ afforded Boc-Ala-OMe with 64% yield, which is comparable to reported yields with CAN-mediated esterification. Esterification using imidazole carbamates, reported by Heller and Sarpong, is a recent addition to this field and uses ~2 molar equiv of the reagent in acetonitrile at 80 °C to esterify aromatic, arylalkyl, and amino acid derivatives.[5] Entries 9 to 13 list efficient esterifications of mandelic, tartaric, malic, gallic, and cinnamic acids. Interestingly, some degree of selectivity between two carboxyl groups in malic acid could be attained, and the mono ester **11c** was isolated in 46% yield by fine-tuning the reaction conditions.

To explore the generality of esterification, homophthalic acid was chosen as the substrate, and esterifications using MeOH, EtOH, ^{n}BuOH, ^{t}BuOH, isoamyl alcohol, allyl alcohol, BnOH, cyclohexanol, and IPA were carried out in the presence of 1−5 mol % of the catalyst. All except ^{t}BuOH underwent efficient esterifications, and the results summarized in Table 2 clearly show the high catalytic potential of Sm(III) in chemoselective catalytic esterifications.

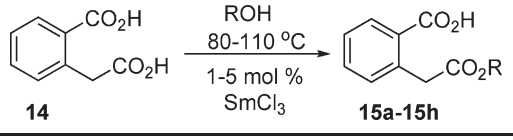
Since the Boc− group was largely unaffected during esterification (entries 6 and 7, Table 1), it was natural to study the relative stabilities of other acid-sensitive protecting groups under similar conditions, as the selective

(3) (a) Gunic, E.; Chow, S.; Rong, F.; Ramasamy, K.; Raney, A.; Yunzhi, Li, D.; Huang, J.; Hamatake, R. K.; Hong, Z.; Girardet, J.-L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2456. (b) Fu, X.; Jiang, S.; Li, C.; Xin, J.; Yang, Y.; Ji, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 465. (c) Guetzoyan, L.; Ramiandrasoa, F.; Dorizon, H.; Christine, D.; Bridoux, A.; Rogier, C.; Pradines, B.; Perreé-Fauvet, M. *Bioorg. Med. Chem.* **2007**, *15*, 3278.

(4) (a) Kuttan, A.; Nowshudin, S.; Rao, M. N. A. *Tetrahedron Lett.* **2004**, *45*, 2663. (b) Zacharie, B.; Connolly, T. P.; Penney, C. L. *J. Org. Chem.* **1995**, *60*, 7072.

(5) Heller, S. T.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4572.

Table 2. Preparation of Homophthalic Acid Mono Esters **15a−15h**



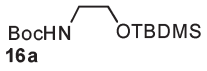
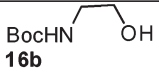
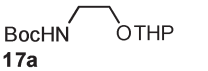
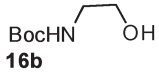
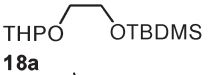
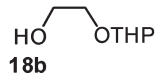
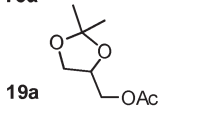
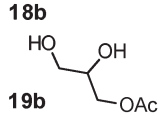
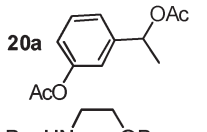
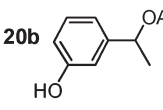
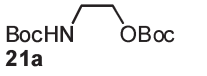
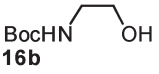
14 **15a-15h**

entry	R	*t* (h)	temp (°C)	% yield
a	MeOH	8	80	97[a]
b	EtOH	10	80	99[a]
c	^{n}BuOH	40	90	90[b]
d	isoamyl alcohol	48	90	90[b]
e	allyl alcohol	48	90	82[b]
f	benzyl alcohol	48	110	67[b]
g	cyclohexanol	48	110	83[b,c]
h	isopropanol	34	90	99[b]

[a] 1 mol % of $SmCl_3$ was used. [b] 5 mol % of $SmCl_3$ was used. [c] 5 equiv of cyclohexanol in 2 mL of toluene were used.

deprotection of one group in the presence of the other could have significant synthetic value. Our explorations along these lines started by evaluating the deprotection propensities of the Boc vs TBDMS group in N- and O-protected ethanolamine **16a** (Table 3). Excitingly, use of 1 mol % of $SmCl_3$ in ethanol at 80 °C led to efficient deprotection of the TBDMS group after 16 h, giving 99% of Boc-ethanolamine (**16b**). A similar result was obtained upon using the THP group in combination with the Boc group as in entry 2 (**17a**). When a combination of TBDMS and THP as in **18a** was exposed to 1 mol % of $SmCl_3$ in ethanol at 40 °C, preferential deprotection of the TBDMS group to give 85% of 2-((tetrahydro-2*H*-pyran-2-yl)oxy)-ethanol (**18b**) was observed. Increasing the temperature, however, led to the deprotection of both TBDMS and THP groups in this case.

Table 3. Boc/TBDMS/THP Discriminating Deprotections under $SmCl_3$ Catalysis[a]

no.	starting materials	product	*t* (h)	% yield
1	 **16a**	 **16b**	16	99
2	 **17a**	 **16b**	18	99
3	 **18a**	 **18b**	40	85[b]
4	 **19a**	 **19b**	7	88
5	 **20a**	 **20b**	24	76
6	 **21a**	 **16b**	72	73[c] (94)[d]

[a] Reactions were carried out with 1 mol % $SmCl_3$ in ethanol at 80 °C. [b] Reaction temp in this case was 40 °C. [c] 10 mol % $SmCl_3$ was used in this case. [d] Yield based on the starting material recovered.

As expected, the isopropylidene group was more labile when compound **19a** was exposed to similar deprotection conditions, leading to a 88% yield of **19b**. Based on this observation, the selectivity between phenolic and benzylic acetate groups was studied using **20a**. Interestingly, the phenolic acetate group underwent smooth deprotection in this case to give a 76% yield of the benzylic acetate **20b**. It is important to note that prolonged heating can result in the removal of both of the −OAc groups in **20a**. Since the −NHBoc group was stable during deprotection, we were interested to know the fate of −OBoc under similar conditions. Toward this end, a solution of the N- and O-Boc protected ethanolamine (**21a**) was heated at 80 °C in the presence of 10 mol % of $SmCl_3$ in ethanol for 72 h. Selective −OBoc deprotection took place, affording 73% of the Boc-ethanolamine (94% based on the recovered starting material) which showed the differential reactivity of Boc-carbamate and Boc-carbonate linkages.

The most noteworthy examples for chemoselective deprotection include the following: selective removal of the TBDMS group by PPTs, $Fe(OTs)_3 \cdot 6H_2O$/MeOH, Ce(IV) triflate, LiOAc, $CeCl_3 \cdot 7H_2O$, LiOH/DMF, Phosphomolybdic acid/SiO_2, $LiCl \cdot H_2O$/DMF, or 1-chloroethyl chloroformate/MeOH;[6] removal of alkyl silyl ether groups in the presence of aryl silyl ethers using TMSBr/MeOH;[7] discrimination of benzylic OTBDMS from phenolic OTBDMS using NIS;[8] selective deprotection of the primary −OTBDMS group in the presence of the secondary −OTBDMS using catalytic CBr_4 in methanol under photochemical conditions,[9] removal of MOM groups using the TMSOTf (or TESOTf)/2,2′-bipyridyl system;[10] deprotection of 1,3-oxothio- and dithioacetals using the $CeCl_3 \cdot 7H_2O$−NaI system;[11] acetal deprotection using BiI_3,[12] Ce(OTf)$_3$−wet CH_3NO_2, or Bi(OTf)$_3$/THF−H_2O, $Bi(NO_3) \cdot 5H_2O/CH_2Cl_2$ or I_2/acetone;[13] deprotection of acetals in the presence of ketals using the triethylsilyl triflate (TESOTf)−2,6-lutidine system;[14] acetonide deprotection using $BiCl_3$;[15] deprotection of N,O-acetonide using

(6) (a) Zaidi, J. H.; Fauq, A. H.; Ahmed, N. *Tetrahedron Lett*. **1998**, *39*, 4137. (b) Bothwell, J. M.; Angeles, V. V.; Carolan, J. P.; Olson, M. E.; Mohan, R. S. *Tetrahedron Lett*. **2010**, *51*, 1056 and references cited therein. (c) Ankala, S. V.; Fenteany, G. *Tetrahedron Lett*. **2002**, *43*, 4729. (d) Kumar, G. D. K.; Baskaran, S. *J. Org. Chem*. **2005**, *70*, 4520. (e) Farras, J.; Serra, C.; Vilarrasa, J. *Tetrahedron Lett*. **1998**, *39*, 327. (f) Yeom, C.-E.; Kim, Y. J.; Lee, S. Y.; Shin, Y. J.; Kim, B. M. *Tetrahedron* **2005**, *61*, 12227.

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TMSOTf/CH_2Cl_2,[16] or $BiBr_3$/CH_3CN;[17] removal of aromatic acetate using ammonium acetate;[18] deprotection of PMB ether using $CeCl_3 \cdot 7H_2O$−NaI/CH_3CN;[19] removal of aryl aldehyde 1,1-diacetate in the presence of phenolic acetate using $InBr_3$/PEG;[20] and selective deprotection of *tert*-butyl esters in the presence of −N-(PhF) groups using $ZnBr_2$ in CH_2Cl_2.[21] Since the substrates chosen in each of the above studies are different, a comparative assessment of the efficiency of the catalysts involved is difficult. The details presented in Table 3, however, confirm that $SmCl_3$ can offer promise in the selective deprotection of acid labile protecting groups. *Comparison of esterification and deprotection conditions (*Tables 1 and 3*) shows that the reaction time and temp are the main factors that make the selectivity possible between Boc/TBDMS/THP groups.*

The most notable among the chemoselective esterifications include the following: esterification of α-hydroxy carboxylic acids using boric acid[22] or *N*-methyl-4-boronopyridinium halide;[23] esterification of hydroxy acids using a NaY faujasite−dimethyl carbonate system;[24] Mitsunobu conditions for chemoselective esterification between phenolic acids and alcohols;[25] and competitive esterification of sp^3-C tethered carboxyl groups in the presence of sp^2- or *sp*-C tethered ones using CBr_4/MeOH.[26] Ogawa et al. have reported a monoesterification protocol for dicarboxylic acids using CH_2N_2 in the presence of alumina as the solid support; adsorption of one of the acid groups in these cases leaves the other one free for esterification.[27] Selective esterification of aliphatic carboxyl groups in the presence of aromatic carboxyl groups in homophthalic acid and similar systems has been reported by Rodriguez et al.[28] as well as Ram and Charles.[29] The former method makes use of a 2,2-dimethoxypropane (excess)/MeOH/TMSCl system, and an ∼98% yield of homophthalic acid monomethyl ester was obtained on using 10 mol % of TMSCl along with > 10 mol equiv of 2,2-dimethoxypropane. As per the latter procedure, 10 mol % of $NiCl_2 \cdot 6H_2O$ catalyzed the selective monoesterification of homophthalic acid and itaconic acid to give **15b** and **4b** in 95% and 86% yields, respectively. Catalytic esterification using MsOH supported on active carbon is another method that can give good selectivity toward aliphatic carboxyl groups in the presence of aromatic or conjugated ones, and an 82% yield of homophthalic acid monoethyl ester (**15b**) and a 92% yield of itaconic acid monoethyl ester (**4b**) were obtained upon using 1.2 g of the solid-supported catalyst per 0.1 mol of the acids.[30] *In comparison, the $SmCl_3$-based method reported here requires only 1 mol % of the catalyst for near-quantitative formation of mono esters in these cases!*

In summary, we have unraveled the usefulness of $SmCl_3$ as an efficient catalyst in esterification and deprotection reactions, which proceeded with excellent chemoselectivity in the presence of competing functional groups. Retention of Boc and peptidic amide groups during esterification, selective esterification of an aliphatic carboxylic acid group in the presence of aromatic or α,β-unsaturated carboxyl groups, and selective deprotection of a TBDMS or THP group in the presence of Boc and a TBDMS group in the presence of THP are the key highlights.

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Supporting Information Available. Experimental and spectral details of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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