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Cerium(III) chloride-promoted chemoselective esterification of phenolic alcohols

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Dedicated to Professor Dr. Iwao Ojima on occasion of his 60th birthday

Abstract—A mild and operationally simple method for the chemoselective esterification of phenolic alcohols is described. The reaction overcomes the tyranny of protection, and capitalizes on the activation of acyl halides with cerium(III) chloride to selectively esterify alcohol hydroxyls in the presence of phenolic ones. The generality of the reaction was demonstrated with a series of phenolic alcohols of dietary relevance (vanillol, hydroxytyrosol, epicatechin), providing an expeditious entry into a series of compounds of relevance for biomedical research, some of which previously available only by enzymatic methods.

Despite the current excitement for the potential beneficial effects of polyphenols on human health,[1] there is still a great shortage of methods for the chemical modification and synthesis of these compounds, that generally occur as complex mixtures of analogues/homologues and are therefore difficult to obtain in pure form by isolation.[2] Of special relevance is the development of protocols to streamline the manipulation of hydroxy groups, releasing polyphenols chemistry from what has been cogently described as the 'protection racket'.[3] One of the most elementary synthetic problems in polyphenol chemistry is the chemoselective esterification of (poly)phenolic alcohols, since the ester moiety is widespread within dietary phenolics.[1] Under conditions of nucleophilic catalysis, phenols can be deprotonated, and therefore their reactivity in acylation reactions competes, and generally prevails, with that of alcohols.[3] The shift from acyl- to alkyl activation is an alternative and rational strategy to overcome this problem, and in previous work we have demonstrated the potential of the Mitsunobu reaction for the chemoselective esterification of phenolic alcohols.[3] Removal of the spent triphenylphosphine-azodicarboxylate redox pair, a major problem of the Mitsunobu reaction, could be solved in a simple way by gel-permeation on Sephadex LH-20.[3] However, relatively apolar compounds like the fatty esters of phenolic alcohols were not sufficiently retained by this stationary phase, and required a careful conventional chromatographic purification. Furthermore, when applied to secondary stereogenic centers, the Mitsunobu reaction leads to inversion of configuration, with breaching of the configurational integrity of a template, and unpredictable consequences on bioactivity. While undoubtedly an asset for diversity-oriented synthesis,[4] this stereochemical bias is a drawback for target-directed synthesis relying on a specific template.

To address these issues, we have investigated another mechanistic alternative to nucleophilic catalysis[5] for the acylation of phenolic alcohols, namely the Lewis acid catalysis by lanthanide salts.[6] Despite some nonencouraging literature precedents[7] and the sensitivity of polyphenolic alcohols to acids,[2] we found that, with

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the proper choice of promoter and acylating reagent, both issues could be solved.

The vanillyl ester **1c** is a simpler analogue of capsiate (**1b**), the nonpungent, NF-κB inhibitory[1] and fat-burning principle of bell peppers,[8] and shows the same biological profile of the natural product.[9] Its synthesis from vanillol (**1a**) was used to benchmark the effect of various Lewis acids and acylating reagents on the outcome of the esterification reaction, integrating proof of principle and target relevance. In a first set of experiments, cerium(III) chloride, indium(III) chloride and ytterbium(III) triflate were investigated (at 20% loading) as promoters, using THF as solvent and an equimolecular ratio of alcohol and acylating agent (chloride, anhydride). Indium(III) chloride was unable to promote the acylation of **1a** with nonanoyl chloride, while, as expected,[7] ytterbium(III) triflate gave a mixture of phenyl and alkyl esters. Conversely, cerium(III) chloride afforded nordihydrocapsiate (**1c**) as the only reaction product in a rewarding 53% yield. Though we had originally planned to screen a wider range of lanthanide salts, this promising result focused our attention on the use of cerium(III) chloride. Under the same conditions, nonanoic anhydride gave a disappointingly low conversion (15%), while a decrease of the lanthanide salt load to 0.5% had a remarkable upgrading effect on yield, that climbed to 70%. This somewhat unexpected result is presumably due to a decreased degradation of the reaction product, an unstable pro-quinoid compound,[10] in the reaction mixture. The optimized protocol[11] was next extended to the synthesis of other fatty esters of vanillol (compounds **1d**,**e**), obtaining yields comparable or even better to those achieved with the Mitsunobu esterification (see Table 1) (Fig. 1).

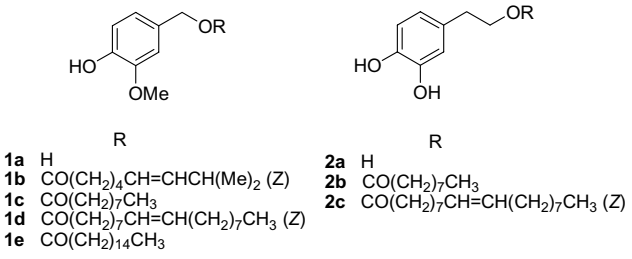


Figure 1.

Hydroxytyrosol (**2a**), the major antioxidant of olive oil,[12] was next investigated, since, in animal experiments, its fatty esters show potent protective activity against cardiovascular and neurodegenerative diseases.[13] The reaction of hydroxytyrosol, a catecholic alcohol, with nonanoyl and oleoyl chlorides afforded alkyl esters as the only reaction products (**2b**,**c**, 53% and 60% yield, respectively), validating the reaction also for nonbenzylic polyphenolic alcohols.[14] Due to the inorganic nature of the promoter and its use in catalytic amounts, the crude reaction mixtures were devoid of major impurities and could be purified in a quick way under normal aerobic laboratory conditions (Fig. 1).[15]

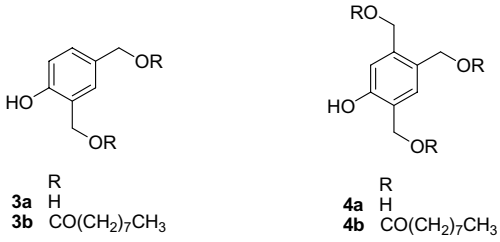


Figure 2.

Excellent chemoselectivity was also observed in the esterification of 2,4-bis(hydroxymethyl)phenol (**3a**) and 2,4,6-tris(hydroxymethyl)phenol (**4a**), two popular starting materials for the construction of dendrimers,[16] pointing to a broad utility of the reaction (Fig. 2).

Table 1. Acylation of (poly)phenolic alcohols with the couple $CeCl_3$–RCOCl[a]

Entry	Phenolic alcohol	Ester	Yield (%)
1	Vanillol (**1a**)	**1c**	70 (67)[b]
2	Vanillol (**1a**)	**1d**	60 (55)[b]
3	Vanillol (**1a**)	**1e**	58 (42)[b]
4	Hydroxytyrosol (**2a**)	**2b**	53 (41)[b]
5	Hydroxytyrosol (**2a**)	**2c**	52 (34)[b]
6	**3a**	**3b**	66
7	**4a**	**4b**	60
8	Epicatechin (**5a**)	**5b**	28[c]
9	Epicatechin (**5a**)	**5c**	26[c]
10	Epicatechin (**5a**)	**5d**	22[c]
11	Isoacetovanillol (**6b**)	**6c**	28
12	Isoacetovanillol (**6b**)	**6d**	27

[a] General conditions: THF (ca. 5 mL/mmol of substrate), RCOCl (1 mol equiv), $CeCl_3$ (0.05 mol equiv), rt.

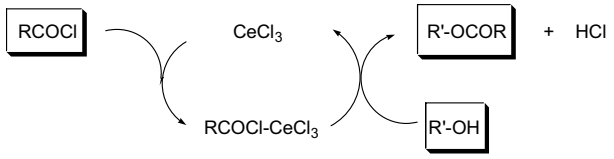
[b] Yields from the Mitsunobu esterification (see Ref. 3 for the experimental conditions).

[c] No reaction occurred under the conditions of Mitsunobu esterification.[3]

To further extend the scope of the reaction, we investigated the esterification of epicatechin (**5a**), a labile flavan-3-ol. The esterification of the secondary hydroxyl of epicatechin gives compounds of remarkable antioxidant properties and a wealth of potential application in the realm of nutrition and of cosmetics.[17] Compounds of this type have never been prepared before by direct esterification of epicatechin, but only by enzymatic hydrolysis of its peracylated derivatives,[18] and their chemical synthesis is therefore a daunting task. Epicatechin (**5a**) was totally unreactive under the conditions of the Mitsunobu esterification, presumably because of steric congestion,[19] but its reaction with nonanoyl, oleoyl and palmitoyl chlorides afforded the corresponding 3-esters (**5b**–**d**) with excellent chemoselectivity, and overall yield (28%, 26% and 22%, respectively) more than acceptable for compounds of this type (Fig. 3).[20]

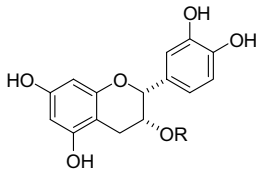
Esters of acetovanillol (**6a**) proved too elusive to be isolated because of their pro-quinoid nature, but the corresponding and more stable isoacetovanillol esters (compounds **6c**,**d**) could be synthesized and characterized (Fig. 3).[21]

The examples we have discussed show that cerium(III) chloride is a superior promoter for the chemoselective esterification of polyphenolic alcohols with acyl halides, making it possible to overcome the tyranny of protection and providing an expeditious entry into a series of (poly)phenolic esters of current interest for biomedical research and material sciences. From a mechanistic standpoint, the reaction presumably involves the formation of an electrophilic Lewis adduct between acyl chlorides and cerium(III) chloride. This is next quenched by the more nucleophilic alcohol hydroxyl of the substrate, with formation of the reaction products (an ester and hydrogen chloride), and regeneration of the lanthanide promoter (Scheme 1).

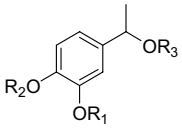


Scheme 1. Possible mechanism for the $CeCl_3$-promoted esterification of alcohols with acyl halides.

In blank experiments, stoichiometric or catalytic (0.3 M equiv) amounts of mineral acids (H_2SO_4) or sulfonic acids (triflic acid) were unable to promote the reaction of vanillol and nonanoyl chloride beyond a modest (but chemoselective) background conversion level (<10% yield). On the other hand, hydrochloric acid might play a role in the reaction, preventing phenol activation by deprotonation and therefore contributing to the chemoselectivity of the acylation.[22] While cerium(III) chloride could not promote the acylation of phenolic hydroxyls by acyl chlorides, its corresponding triflate could do it in combination with less potent acylating reagents like carboxylic anhydrides.[7] A possible explanation is that cerium(III) triflate forms Lewis adducts having a more pronounced acylium ion character than those of cerium(III) chloride, resulting in a higher, but unselective, reactivity with phenolic alcohols, at least at room temperature.[7] The poor conversion observed with the combination cerium(III) chloride/carboxylic anhydrides is not surprising, since formation of a mixed chelate with an additional adjacent oxygen function of the substrate is necessary for the acylation of alcohols under these conditions (Fig. 3).[23]



	R
5a	H
5b	$CO(CH_2)_7CH_3$
5c	$CO(CH_2)_7CH{=}CH(CH_2)_7CH_3$ (Z)
5d	$CO(CH_2)_{14}CH_3$



	R_1	R_2	R_3
6a	Me	H	H
6b	H	Me	H
6c	H	Me	$CO(CH_2)_7CH_3$
6d	H	Me	$CO(CH_2)_{14}CH_3$

Figure 3.

Taken together, these observation support the idea that lanthanides(III) catalysis in acylation reaction can be modulated by changes in the nature of the cation, its counterion, and the acylating species, extending the realm of chemical esterification to polyfunctional and labile compounds whose acylative manipulation has traditionally been limited to enzymatic reactions.[18,24]

Acknowledgements

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11. Under a nitrogen atmosphere, to a solution of vanillol (**1a**, 250 mg, 1.62 mmol) in dry THF (8 mL), nonanoyl chloride (292 μL, 1.62 mmol, 1 M equiv) and cerium(III) chloride (30 mg, 0.081 mmol, 0.5% M equiv) were added. After stirring at room temp. for 12 h, the reaction was worked up by removal of the solvent, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ (ca. 50 mL each). The organic phase was washed with brine, dried (Na_2SO_4) and evaporated, and the residue was purified by gravity column chromatography on silica-gel (hexanes–ethyl acetate, 7:3) to give 330 mg (70%) of **1c** as a colourless oil, having spectroscopic (^1H NMR, ^{13}C NMR, IR) data identical to those of an authentic sample, available from previous studies.[3,9]
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14. ^{1}H NMR data for **2b**: (300 MHz, $CDCl_3$): δ 0.91 (t, J = 6.5 Hz, 3H), ca. 1.45 (m, 10H), 1.62 (m, 2H), 2.28 (t, J = 6.5 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 4.20 (t, J = 7.2 Hz, 2H), 6.57 (br m, 1H), 6.68 (m, 2H). For **2c** (300 MHz, $CDCl_3$): δ 0.92 (t, J = 6.5 Hz, 3H), ca. 1.20 (m, 22H), 1.60 (m, 2H), 2.15 (m, 2H), 2.31 (t, J = 6.5 Hz, 2H), 2.79 (t, J = 7.0 Hz, 2H), 4.25 (t, J = 7.0 Hz, 2H), 5.38 (m, 2H), 6.57 (br m, 1H), 6.69 (m, 2H).
15. Because of their instability on silica gel, the hydroxytyrosol esters **2b**,**c**, as well as the catechin esters **5b–d**, were purified by gel permeation on Sephadex LH-20, using petroleum ether–EtOAc 1:1 to remove nonphenolic impurities, and next methanol to elute the reaction products.
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20. ^{1}H NMR data for **5b**: (300 MHz, CD_3OD): δ 0.85 (t, J = 6.5 Hz, 3H), ca. 1.25 (m, 10H), 1.63 (m, 2H), 2.31 (t, J = 6.5 Hz, 2H), 2.70 (dd, J = 17, 2.3 Hz, 1H), 2.86 (dd, J = 17, 4.5 Hz, 1H), 4.85 (br s, 1H), 5.35 (m, 1H), 5.93 (m, 2H), 6.80 (m, 2H), 6.98 (s 1H). Data for **5c**: (300 MHz, CD_3OD): δ 0.85 (t, J = 6.5 Hz, 3H), ca. 1.30 (m, 24H), 2.31 (t, J = 6.5 Hz, 2H) 2.80 (dd, J = 17, 2.3 Hz, 1H), 2.96 (dd, J = 17, 4.5 Hz, 1H), 4.85 (br s, 1H), 5.35 (m, 1H), 5.93 (m, 2H), 6.80 (m, 2H), 6.98 (s 1H). Data for **5d**: (300 MHz, CD_3OD): δ 0.88 (t, J = 6.5 Hz, 3H), ca. 1.25 (m, 24H), 1.63 (m, 2H), 2.31 (t, J = 6.5 Hz, 2H) 2.80 (dd, J = 17, 2.3 Hz, 1H), 2.96 (dd, J = 17, 4.5 Hz, 1H), 4.95 (br s, 1H), 5.35 (m, 1H), 6.00 (m, 2H), 6.83 (m, 2H), 6.98 (s 1H).
21. ^{1}H NMR data for **6c**: (300 MHz, $CDCl_3$): δ 0.85 (t, J = 6.5 Hz, 3H), 1.25–1.42 (m, 10H), 1.43 (d, J = 6.5 Hz, 3H), 1.59–1.65 (m, 2H), 2.31 (t, J = 6.5 Hz, 2H), 3.89 (s, 3H), 5.80 (q, J = 6.5 Hz, 1H), 6.83 (m, 2H), 6.96 (m, 1H). For **6d** (300 MHz, $CDCl_3$): δ 0.85 (t, J = 6.5 Hz, 3H), 1.19–1.37 (m, 24H), 1.40 (d J = 6.5 Hz, 3H), 1.61 (m, 2H), 3.25 (m, 2H), 3.84 (s, 3H), 5.80 (q, J = 6.5 Hz, 1H), 6.84 (m, 2H), 6.97 (m, 1H).
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