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Deoxygenation of α,β-unsaturated acylphenols through ethyl *o*-acylphenylcarbonates with Luche reduction

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ABSTRACT

An efficient protocol for deoxygenation of α,β-unsaturated acylphenols through ethyl *o*-acylphenylcarbonates with Luche reduction is described. The reaction shows very good selectivity and tolerates a wide range of functionalities on α,β-unsaturated acylphenols, giving corresponding 2-allylphenols in good to excellent yields.

Flavanoids are considered to be particularly important secondary metabolites because of their antibacterial,[1] anticancer,[2] antioxidant,[3] and antiviral[4] properties. Flavans and flavan-3-ols such as (+)-catechin (**I**, Fig. 1), epicatechin (**II**, Fig. 1) or their dimers such as procyanidin B3 (**III**, Fig. 1) occur in citrus, tea, cocoa, and chocolate,[5] and have been shown to have potential salutary effects on health.[6] In 2005, a naturally occurring flavanoid myristinin A (**IV**, Fig. 1) was discovered, which is a DNA polymerase β inhibitor capable of blocking the repair of DNA damage induced by clinically used damaging agents and thereby potentiates their cytotoxicity.[7]

Most of the reported methods for enantioselective synthesis of flavan-3-ols and their derivatives employed 2-allylphenols as key intermediates.[7e,8] 2-Allylphenols can be prepared by Friedel–Craft alkylation of phenols with cinnamyl alcohols under acidic conditions,[8a,b] selective cross-metathesis of allylphenols with styrenes,[8c] Claisen rearrangement of alkenes,[8d] reductive isomerization of enones to alkenes,[8d,e] or deoxygenation of α,β-unsaturated acylphenols.[8f,g,9] The Friedel–Craft alkylation method needs harsh condition and gives unsatisfactory yields. The cross-metathesis and Claisen rearrangement of alkene methods give only moderate yields. Reductive isomerization of enones to alkenes employs long steps and affords less than 50% total yield. Although the fourth method performed by employing ethyl chloroformate and sodium borohydride in a two-step sequence gives more satisfied yields and has received much attention of late, this reduction frequently afforded the over-reduced products and cyclic byproducts. Some other protocols such as trialkoxylsilane/ZnX_2,[10] $NaBH_3CN$/TMSCl,[11a] $NaBH_3CN/ZnX_2$,[11b,c] $NaBH_3CN/BF_3{\cdot}Et_2O$,[11d] and lithium aluminum hydride/$AlCl_3$ system[12] for deoxygenation of α,β-unsaturated ketones have been reported. Though excellent conversions were obtained with trialkoxylsilane/ZnX_2 and $NaBH_3CN$/Lewis acid systems, two reduced isomers involving double-bond transfer were observed. Decarbonylation using lithium aluminum hydride and $AlCl_3$ proved overly harsh and resulted in other side reactions.[7e]

In 1978, Luche reported the selective conversion of α,β-unsaturated ketones to allylic alcohols using a mixture of lanthanide chlorides and $NaBH_4$.[13] Later the scope and limitation of the reaction was detected, and it was found that the 1,2-reduction of enones was best achieved by the use of $CeCl_3{\cdot}7H_2O/NaBH_4$ in ethanol or methanol.[14] Luche's discovery was a breakthrough in the reduction of unsaturated carbonyl compounds, since metal hydrides usually give a mixture of 1,2- and 1,4-reduction products, and it was rare to obtain the 1,2-reduction product exclusively and in good yield.

Inspired by Luche's work, deoxygenation of α,β-unsaturated acylphenols was performed by employing ethyl chloroformate

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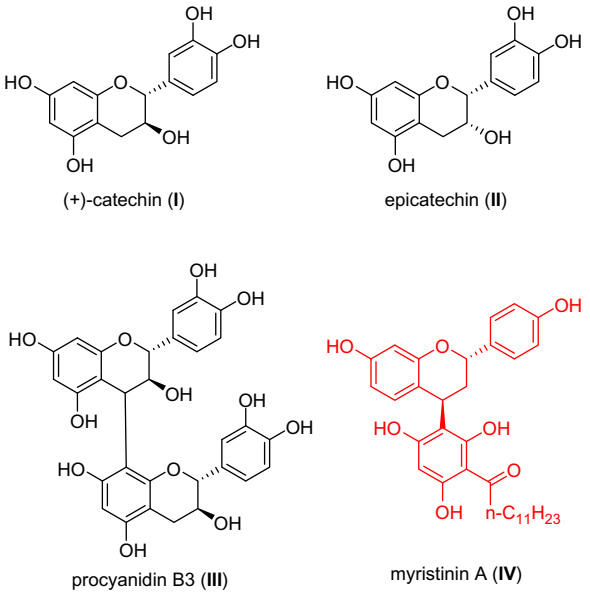


Figure 1. Structures of (+)-catechin (**I**), epicatechin (**II**), procyanidin B3 (**III**), and myristinin A (**IV**).

and lanthanide chlorides/$NaBH_4$ in a two-step sequence in this Letter.

In order to determine the optimized reaction conditions, (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1a**) was selected as the model substrate for this reaction and the borohydride reduction was performed below 0 °C to avoid the formation of cyclic byproduct.[8g] Several lanthanide chlorides were examined and the results are summarized in Table 1. Of the lanthanide chlorides tested, $CeCl_3{\cdot}7H_2O$ appeared to offer the best combination of yield and selectivity (Table 1, entry 2). $LnCl_3{\cdot}7H_2O$, $SmCl_3{\cdot}5H_2O$, $YCl_3{\cdot}6H_2O$, $YbCl_3{\cdot}6H_2O$, and $EuCl_3{\cdot}6H_2O$ were less effective, giving product **1b** in 93%, 91%, 90%, 89%, and 90% isolated yield, respectively, and a small amount of over-reduced product **1b′** (Table 1, entries 3–7). However, when the reduction was conducted without lanthanide chlorides, inferior selectivity was obtained (Table 1, entry 1).

The reaction was significantly affected by the solvent. The use of EtOH or MeOH, resulted in the product being formed in excellent yields and selectivities (Table 2, entries 1 and 2). However, dipolar aprotic solvents, such as acetonitrile and THF gave inferior results with the formation of the corresponding over-reduced product (Table 2, entries 3 and 4). The results obtained seem to be consistent with the mechanism of Luche reaction that lanthanoid ions were shown to preferentially coordinate to alcohols.[15] The undesired selectivity was obtained when *i*-PrOH was used as solvent, which may be accounted for by the low solubility of $CeCl_3{\cdot}7H_2O$ (Table 2, entry 5).[13]

Table 2
Deoxygenation of **1a** in the presence of different solvents[a]

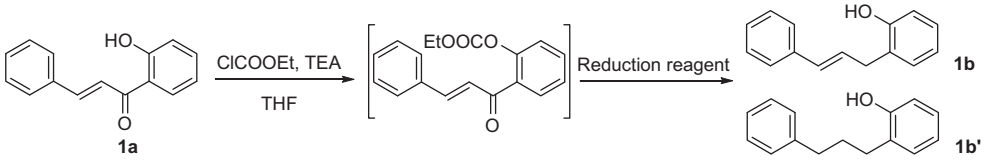
Entry	Solvent	Yield[b] (**1b**, %)	**1b**/**1b′**[c]
1	EtOH	96	100/0
2	MeOH	92	100/0
3	THF	66	75/25
4	MeCN	59	79/21
5	*i*-PrOH	77	85/15

[a] Reaction conditions: **1a** (1 mmol), ClCOOEt (1.1 mmol), TEA (1.1 mmol), −5 °C, 20 min; $NaBH_4$ (1.2 mmol), $CeCl_3{\cdot}7H_2O$ (1.2 mmol), 15 min.
[b] Isolated yields.
[c] The ratio was determined by NMR spectrum of crude reaction mixtures and the products were not isolated.

With the optimized reaction conditions in hand, we then explored the scope and generality of this reduction. Various α,β-unsaturated acylphenols bearing electron-withdrawing and donating substituents on the phenyl ring were investigated and both smoothly reacted and gave the desired 2-allylphenols in good to excellent yields (Table 3).[16] In particular, heterocycle (Table 3, entry 6), olefin group (Table 3, entry 7), and alkyl group (Table 3, entry 8) on α,β-unsaturated acylphenols were compatible, giving isolated purified products in 94%, 83%, and 76%, respectively. In addition, deoxygenation of o-hydroxyacetophenones (Scheme 1) with our method also efficiently afforded desired products **24b** and **25b** in 78% and 82% yield, respectively.

A plausible mechanism to rationalize this transformation is illustrated in Scheme 2. From the hard and soft acids and bases (HSAB) theory, it was deduced that the substitution of hydrides in BH_4^- by alkoxy groups increases the hardness of the reagent. The attack of the conjugate enone system is then enhanced at the hard site. The active species during the Luche reduction is believed to be an alkoxy borohydride,[15] which in combination with the hard cerium cation acts as a hard reducing agent. The involvement of cerium borohydrides has been discounted based on

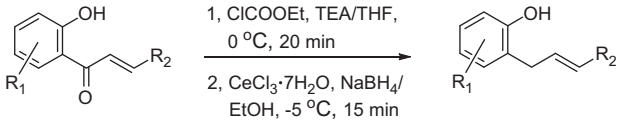
Table 1
Deoxygenation of **1a** in the presence of lanthanide chlorides[a]



Entry	Reduction reagent	Yield[b] (**1b**, %)	**1b**/**1b′**[c]
1	$NaBH_4$	81	90/10
2	$NaBH_4/CeCl_3{\cdot}7H_2O$	96	100/0
3	$NaBH_4/LnCl_3{\cdot}7H_2O$	93	99/1
4	$NaBH_4/SmCl_3{\cdot}6H_2O$	91	97/3
5	$NaBH_4/YCl_3{\cdot}6H_2O$	90	95/5
6	$NaBH_4/YbCl_3{\cdot}6H_2O$	89	93/7
7	$NaBH_4/EuCl_3{\cdot}6H_2O$	90	93/7

[a] Reaction conditions: **1a** (1 mmol), ClCOOEt (1.1 mmol), TEA (1.1 mmol), 0 °C, 20 min; reduction reagent (1.2 mmol), EtOH (10 mL), 15 min.
[b] Isolated yields.
[c] The ratio was determined by NMR spectrum of crude reaction mixtures and the products were not isolated.

Table 3
Deoxygenation of α,β-unsaturated acylphenols[a]



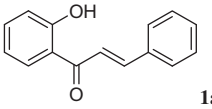
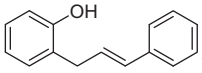
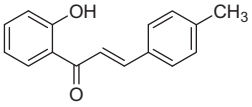
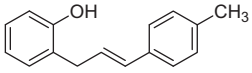
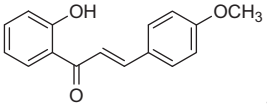
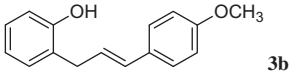
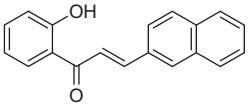
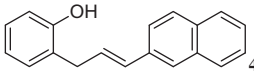
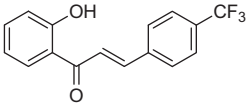
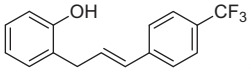
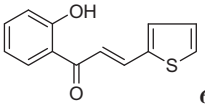
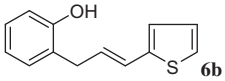
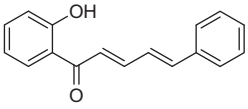
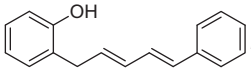
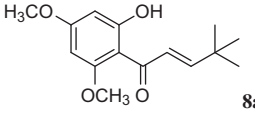
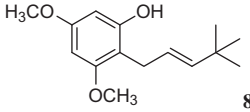
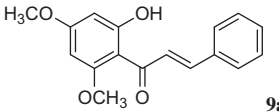
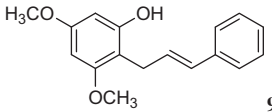
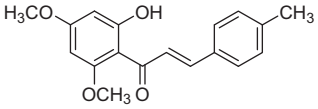
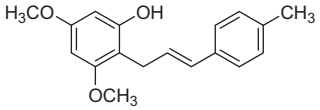
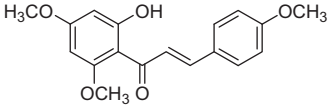
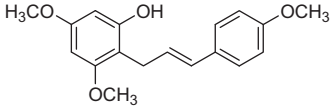
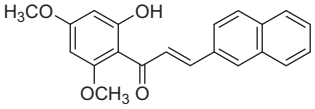
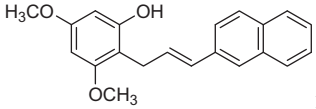
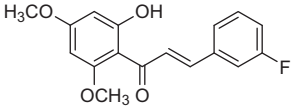
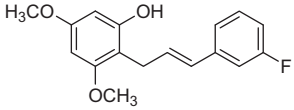
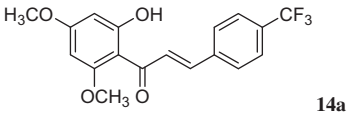
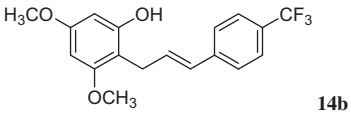
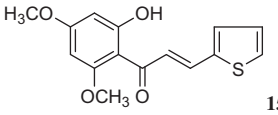
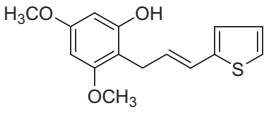
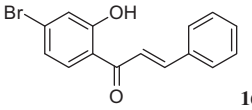
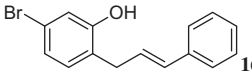
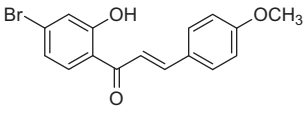
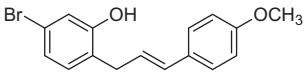
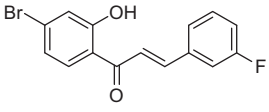
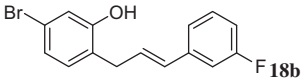
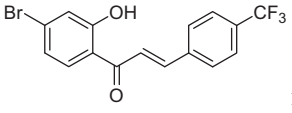
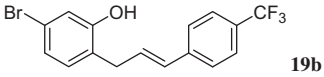
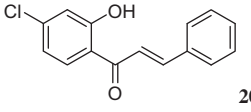
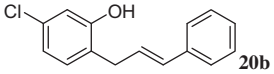
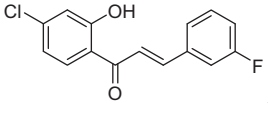
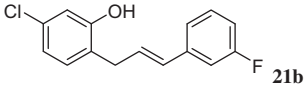
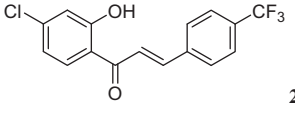
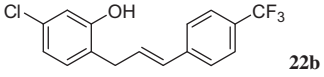
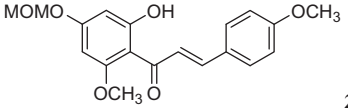
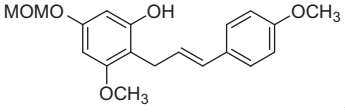
Entry	Starting materials	Products	Yield[b] (%)
1	 **1a**	 **1b**	93
2	 **2a**	 **2b**	91
3	 **3a**	 **3b**	90
4	 **4a**	 **4b**	89
5	 **5a**	 **5b**	90
6	 **6a**	 **6b**	94
7	 **7a**	 **7b**	83
8	 **8a**	 **8b**	76
9	 **9a**	 **9b**	96
10	 **10a**	 **10b**	93
11	 **11a**	 **11b**	87
12	 **12a**	 **12b**	91
13	 **13a**	 **13b**	87

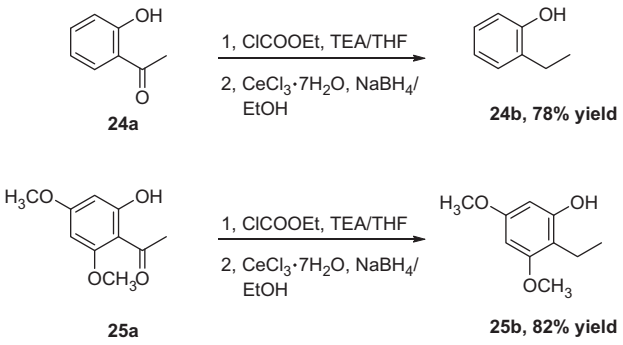
Table 3 (*continued*)

Entry	Starting materials	Products	Yield[b] (%)
14	 **14a**	 **14b**	88
15	 **15a**	 **15b**	90
16	 **16a**	 **16b**	85
17	 **17a**	 **17b**	89
18	 **18a**	 **18b**	88
19	 **19a**	 **19b**	95
20	 **20a**	 **20b**	90
21	 **22a**	 **21b**	87
22	 **23a**	 **22b**	91
23	 **23a**	 **23b**	93

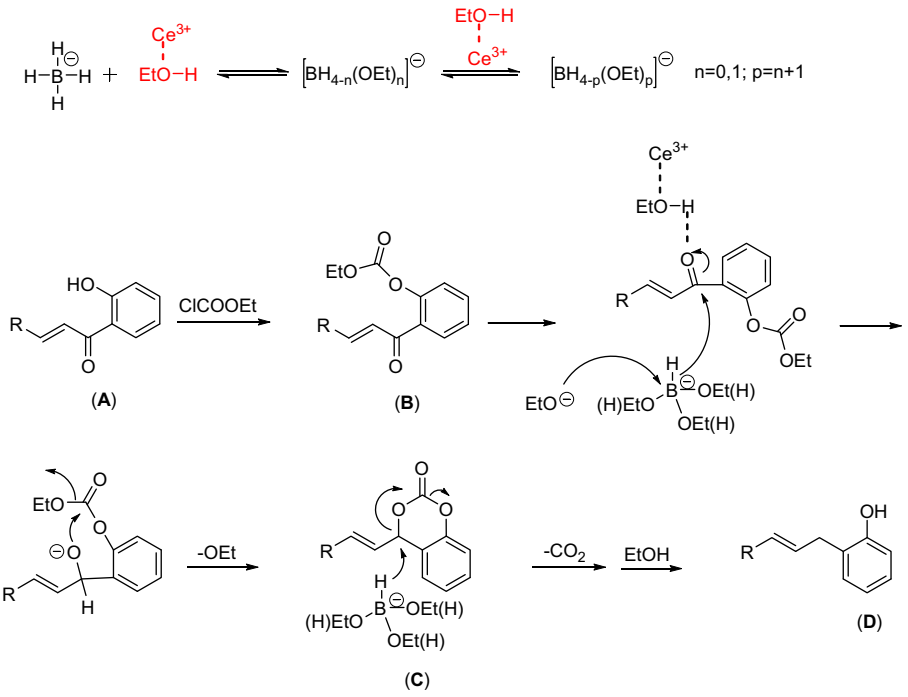
[a] Reaction conditions: **1a–23a** (1 mmol), ClCOOEt (1.1 mmol), TEA (1.1 mmol), 0 °C, 20 min; $NaBH_4$ (1.2 mmol), $CeCl_3{\cdot}7H_2O$ (1.2 mmol), EtOH (10 mL), 15 min.
[b] Isolated yields, and no over-reduced products were observed determined by NMR.

experimental evidence.[17] The mechanism is complicated by the fact that more than one type of borohydride is formed. The role of the cerium is twofold: (1) catalysis of the formation of alkoxyborohydrides; and (2) increasing the electrophilicity of the carbonyl carbon atom.[18] In the presence of TEA and ClCOOEt, α,β-unsaturated acylphenol [**A**] forms an intermediate [**B**] which on reaction with alkoxyborohydride (generated in situ by the reaction of EtOH and $NaBH_4$. By coordinating to the oxygen atom of the solvent, cerium increases the acidity of the medium and helps activating the carbonyl of the enone indirectly), forms a six member carbonate intermediate [**C**], followed by the elimination of carbon dioxide and protonation to form the final product [**D**].

In conclusion, we have reported the deoxygenation of α,β-unsaturated acylphenols by employing ethyl chloroformate and lanthanide chlorides/$NaBH_4$ in a two-step sequence. A broad spectrum of α,β-unsaturated acylphenols was reacted smoothly to provide 2-allylphenols in good to excellent yields. The simple procedure, short reaction times, high selectivity, and excellent



Scheme 1. Deoxygenation of *o*-hydroxyacetophenones.



Scheme 2. The plausible reaction mechanism.

isolated yields make this method well-suited for the generation of a combinatorial library of key intermediates for the synthesis of flavan-3-ols and their derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.109.

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