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Co-catalyzed mild and chemoselective reduction of phenyl esters with $NaBH_4$: a practical synthesis of (*R*)-tolterodine

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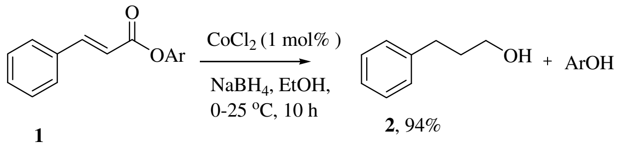
Abstract

$CoCl_2$ catalyzes effectively the chemoselective reduction of phenyl carboxylic esters to the corresponding saturated alcohols in high yields using $NaBH_4$ at ambient conditions. By employing this methodology, the synthesis of (*R*)-tolterodine, a muscarinic receptor antagonist, has been achieved in high yield and optical purity.

Sodium borohydride is a mild, inexpensive yet powerful reducing agent capable of reducing a wide range of functional groups such as aldehydes, ketones and imines.[1] Despite its low reactivity towards carboxylic esters,[2] recent studies have indicated that its reactivity towards carboxylic acids and esters can indeed be enhanced by the addition of certain additives such as $NaBH_4$–MX (MX = LiCl, $ZnCl_2$ $AlCl_3$, LiBr, $MgBr_2$, $MgCl_2$, $CaCl_2$),[3] KBH_4–MX (MX = $ZnCl_2$, $AlCl_3$, $MgCl_2$),[4] $NaBH_4$–CF $_3CO_2H$,[5] $NaBH_4$–H_2SO_4,[6] $NaBH_4$–I_2 [7] and $BH_3{\cdot}SMe_2$.[8] However, major disadvantages of the reported procedures in ester reductions include lack of generality,[9] use of harsh reaction conditions[10] and higher equivalents of $NaBH_4$ and additives.[11] Also the reductions of esters with OH, NH_2 and CN[12] substitutions at α-positions and C=C bonds in α,β-unsaturated esters have been reported with $NaBH_4$.[13] In this Letter, we report a simple procedure in which $CoCl_2{\cdot}6H_2O$ catalyzes the chemoselective reduction of phenyl esters, dihydrocoumarins and coumarins using $NaBH_4$ at ambient conditions to give the corresponding alcohols in high yields (Scheme 1).



Scheme 1. $CoCl_2$-catalyzed reduction of aryl esters with $NaBH_4$.

In continuation of our work[13a] on Co-catalyzed reductive cyclization of γ-cyano-α,β-unsaturated esters with $NaBH_4$, we surprisingly found that $CoCl_2$ catalyzed effectively the reduction of dihydrocoumarin **1a** to afford 2-(3-hydroxy-1-phenylpropyl)phenol (**2a**) in 93% yield in a single step (Table 1, entry **a**). In the absence of catalyst no reduction took place under the reaction conditions. When ethyl cinnamate (**1c**) was reacted, only the C=C bond was reduced to give ethyl 3-phenylpropanoate (**2c**) in 98% yield (entry **c**). When phenyl cinnamate (**1d**) was employed, both the C=C bond and the ester carbonyl functions were reduced to give 3-phenyl-1-propanol (**2d**) in 94% yield (entry **d**). Encouraged by this finding, we subjected various saturated and unsaturated phenyl esters to the reduction conditions, leading to saturated alcohols **2a**–**e** in good yields, the results are presented in Table 1. A noteworthy feature is that only phenyl esters were reduced selectively, while alkyl esters were not affected (entry **f**).

Phenols are readily protected as acetates, which are generally deprotected under strong basic or acidic conditions. In our study, we observed that the $CoCl_2{\cdot}6H_2O/NaBH_4$

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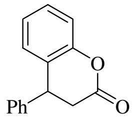
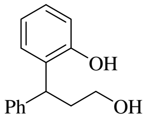
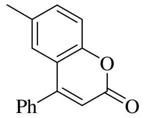
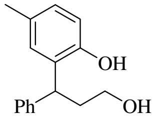
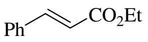
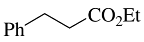
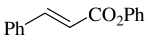
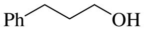
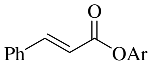
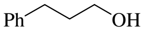
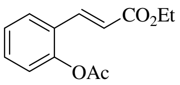
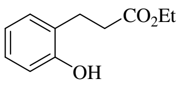
Table 1
$CoCl_2$-catalyzed chemoselective reduction of phenyl esters and coumarins with $NaBH_4$[a]

Entry	Ester **1a–q**	Product **2a–q**	Yield[b] (%)
a			93
b			89
c			98
d			94[c]
e[d]			93[c]
f			95
g	C_6H_5OAc	C_6H_5OH	99
h	$2\text{-}H_3CC_6H_4OAc$	$2\text{-}H_3CC_6H_4OH$	98
i	$2\text{-}H_3COC_6H_4OAc$	$2\text{-}H_3COC_6H_4OH$	97
j	$4\text{-}BrC_6H_4OAc$	$4\text{-}BrC_6H_4OH$	97
k	$4\text{-}ClC_6H_4OAc$	$4\text{-}ClC_6H_4OH$	97
l	$4\text{-}O_2NC_6H_4OAc$	$4\text{-}O_2NC_6H_4OH$	95
m	$4\text{-}NCC_6H_4OAc$	$4\text{-}NCC_6H_4OH$	83
n	$3\text{-}AcOC_6H_4OAc$	$3\text{-}AcOC_6H_4OH$	98
o	$4\text{-}EtO_2CC_6H_4OAc$	$4\text{-}EtO_2CC_6H_4OH$	94
p	1-Naphthyl–OAc	1-Naphthol	98
q	3-AcO–Pyridine	3-Hydroxypyridine	97

[a] Reaction conditions: ester (2 mmol), $NaBH_4$ (4 mmol), $CoCl_2 \cdot 6H_2O$ (1 mol %), EtOH (10 mL), 0–25 °C, 10 h.

[b] Isolated yields after chromatographic purification.

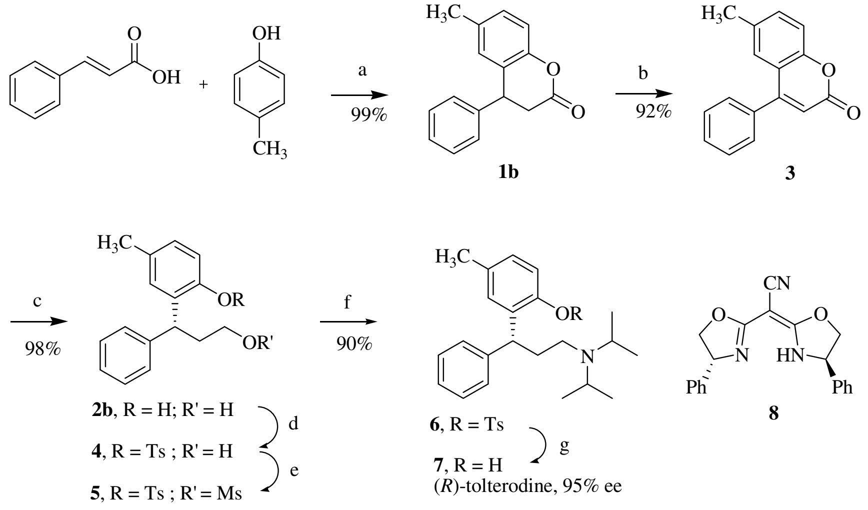
[c] Phenol was isolated in quantitative yields.

[d] Ar = $4\text{-}NO_2C_6H_4$.

combination was also quite successful for the deprotection of several phenolic acetates, with both electron-donating and -withdrawing groups, all occurring under neutral conditions to afford the respective phenols. This reductive deprotection proceeds chemoselectively, as it tolerates a number of other reducible groups such as halides, NO_2 and CN (entries **g–q**).

Next, the synthesis of (*R*)-tolterodine (**7**) was undertaken to demonstrate the potential application of the Co-catalyzed reduction of phenyl esters in synthesis (Scheme 2). (*R*)-Tolterodine is the first muscarinic receptor antagonist that has been specifically developed for the treatment of urinary incontinence. It acts on M2 and M3 subtype muscarinic receptors, but has a greater effect on the bladder than on the salivary glands in vivo, in both animal and humans.[14] (*R*)-Tolterodine is regarded as the drug of choice to treat overactive bladders in most patient groups.[14e] The literature reports several methods for the asymmetric synthesis of (*R*)-tolterodine.[15–18] However, most of the reported methods utilize difficult to handle reagents or expensive catalysts such as DIBAL-H and Rh, which make the synthesis less economical on large scale.

By following a simple methodology developed in our laboratory,[19] hydroarylation of cinnamic acid with *p*-cresol mediated by toluene-4-sulfonic acid was carried out to give dihydrocoumarin **1b** in 99% yield. Dehydrogenation of **1b** with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) afforded coumarin **3** in 92% yield.[20] The Co-catalyzed asymmetric reduction of coumarin **3** with 4 mol of $NaBH_4$ using (4*S*)-(+)-phenyl-α-[(4*S*)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile (**8**) as ligand [ethanol/DMF 5:2] gave the saturated alcohol **2b** in 98% yield.[21] It should be mentioned here that when the phenolic function was protected as its benzyl ether or methyl ether, (*R*)-tolterodine



Scheme 2. (a) Toluene-4-sulfonic acid, 130 °C, 3 h; (b) DDQ, dioxane, 110 °C, 12 h; (c) $CoCl_2 \cdot 6H_2O$ (1 mol %), ligand **8** (1.2 mol %), $NaBH_4$ (4 equiv), EtOH/DMF (5:2), 0 °C, 36 h, 95% ee; (d) TsCl in CH_2Cl_2 then aq NaOH, 45 °C, 3 h, 98%; (e) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C, 30 min; (f) diisopropylamine, NaI, Na_2CO_3, DMF, 80 °C, 6 h, 90% over two steps; (g) aq NaOH, MeOH reflux, 4 h, 82%.

was obtained in a lower yield due to the formation of mixtures of benzyl ethers or difficulties in the demethylation using BBr_3 in later stages. However, selective protection of the phenolic OH group as its tosylate **4** (*p*-toluenesulfonyl chloride in CH_2Cl_2 and aq NaOH), followed by protection of the free alcohol gave mesylate **5**. Displacement of the mesylate group of **5** with diisopropylamine (Na_2CO_3, NaI, in DMF) gave tosyl protected (*R*)-tolterodine **6,** which was then deprotected under basic conditions to afford (*R*)-tolterodine (**7**) in increased yield of 82%; 95% ee $\{[\alpha]_D^{25}$ +21.8 (*c* 1.5, CH_3OH)$\}$.[16] The enantiomeric excess of **4** was determined using Mosher's ester analysis and found to be 95%.

Mechanistically, it may be reasoned that the participation of the oxygen lone pair in resonance with aromatic rings results in a higher carbonyl bond order in phenyl esters than in the corresponding ethyl esters so that the addition of 'hydride' from the reagent is faster to the more reactive phenyl esters, which is rate determining; thus probably accounting for higher selectivity.

In conclusion, we have shown that $CoCl_2 \cdot 6H_2O$ in combination with $NaBH_4$ reduces specifically both C=C bond and ester carbonyls in the case of phenyl esters or coumarins in the presence of various other reducible groups such as CN and NO_2 under mild conditions to give the corresponding saturated alcohols. The methodology has been applied successfully to the synthesis of (*R*)-tolterodine (**7**) (61% overall yield and 95% ee). Ambient reaction conditions, easy handling and good chemoselectivity are advantages of this methodology; an alternative to expensive lithium aluminium hydride. The method has also proven useful in easy reductive removal of phenolic acetates as well.

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21. *Typical experimental procedure for the synthesis of (R)-2-(3-hydroxy-1-phenylpropyl)-4-methylphenol* (**2b**): To a mixture of coumarin **3** (944 mg, 4 mmol) in distilled ethanol (8 mL) and dry DMF (2 mL) were added $CoCl_2 \cdot 6H_2O$ (9.4 mg, 1 mol %) and ligand **8** (15.9 mg, 1.2 mol %). The reaction mixture was stirred for 30 min and then cooled to 0 °C, $NaBH_4$ (624 mg, 16 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 36 h. After the completion of the reaction (monitored by TLC), it was diluted with 50 mL of water and 50 mL of ethyl acetate. The organic layer was separated, washed with brine solution (2 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatographic purification using silica gel (230–400 mesh) and petroleum ether/ethyl acetate (70:30) as eluent afforded 948 mg of the saturated alcohol **2b** in pure form.

Spectral data for (R)-2-(3-hydroxy-1-phenylpropyl)-4-ethylphenol (**2b**): Yield: 98%; $[\alpha]_D^{25}$ +71.8 (*c* 1.0, CH_3OH); IR ($CHCl_3$, cm^{-1}) 702, 818, 1037 1255, 1446, 1504, 1610, 3170, 3419; ^1H NMR (200 MHz, $CDCl_3$): δ 1.97 (br s, 1H), 2.11–2.46 (m, 2H), 2.19 (s, 3H), 3.48–3.60 (m, 1H), 3.72–3.82 (m, 1H), 4.51–4.59 (dd, $J = 5.9$, 9.9 Hz, 1H), 5.96 (br s, 1H) 6.71–6.90 (m, 3H), 7.18–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.11, 36.95, 38.37, 59.70, 114.93, 125.13, 126.50, 127.50, 127.60, 127.96, 128.02, 130.24, 144.47, 151.67. Anal Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.27; H, 7.41.