Reductive Cleavage of 2,2,2-Trichloroethyl Esters by Titanocene Catalysis

Andreas Gansäuer* and Tobias Dahmen

Abstract: Esters are of widespread use for protecting carboxylic acids in organic synthesis. However, methods to cleave esters often employ harsh conditions. Herein, we report a new and mild method for the reductive cleavage of 2,2,2-trichloroethylesters (TCE esters). Our radical method employs Cp_2TiCl as an electron transfer catalyst and Zn dust as stoichiometric reducing agent. It avoids the use of strong Brønstedt-acids as well as aqueous conditions and can be carried out at room temperature.

Keywords: Catalysis · Protecting groups · Radicals · Synthesis · Titanocenes

In principle, the 2,2,2-trichloroethyl ester group (TCE ester) is a very attractive protecting group for carboxylic acids. There are many ways for the mild formation of esters compatible with various other functional groups.[1] Furthermore, the TCE moiety contains no stereocenters and yields sharp signals in ^{1}H-NMR spectroscopy (δ = about 5.0), which allows a straightforward assessment of the protection or deprotection process.

Mechanistically, the reductive cleavage of TCE esters with a base metal (*e.g.* Zn, Cd, In) consists of two steps:[2–4] In the first step, a metal-halogen-exchange reaction takes place and yields a β-metallated ester. This species inevitably undergoes fragmentation through 1,2-elimination of a metal carboxylate and formation of 1,1-dichloroethene (Scheme 1).

These methods for the cleavage of TCE esters require harsh conditions such as acidic media,[2a,3,4] buffered aqueous systems,[2b,2c] or elevated temperatures.[2d] To avoid these conditions, SmI_2, the currently most popular electron transfer (ET) reagent, can be used as an alternative reducing agent acting in single electron steps.[5]

However, while the use of SmI_2 results in mild conditions, its price of about 2.60 €/ mmol[6] makes it unattractive for use on large scale.

Therefore, the development of milder and cheaper conditions for TCE cleavage is still of interest. During the past two decades, it was demonstrated that Cp_2TiCl-based reagents are mild and selective ET reagents that can be employed in many synthethically useful reactions.[7] Hence, we investigated Cp_2TiCl as a catalyst for the deprotection of TCE esters.
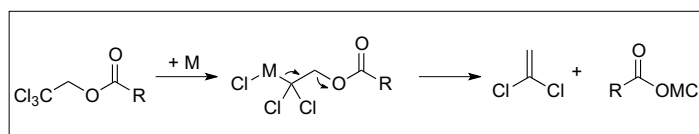
Aromatic carboxylic acid esters were used as substrates, because they are easily accessible and their reactions are straightforward to follow by TLC *via* UV detection. Benzoic acid TCE ester was investigated first. In the presence of 2 equiv. Zn dust and 10 mol-% Cp_2TiCl_2 in THF as solvent, only a disappointingly low yield of deprotected benzoic acid was obtained (Scheme 2).

We attributed this failure to formation of an inactive complex of Cp_2TiCl with benzoate. If the carboxylate forms a complex with Cp_2TiCl, it is most likely that this species is catalytically inactive. Furthermore, it is known that titanocene(III) complexes decompose in the presence of strong nucleophiles through loss of one $C_5H_5^-$ li-
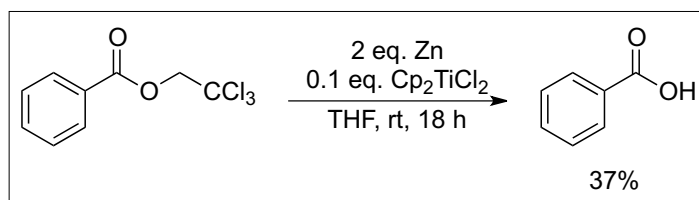
gand.[7] Both effects lead to a depletion of the catalytic efficiency and hence a low yield of the desired product.

We tried to shut down this decomposition pathway by three routes: First, through formation of a stable O–Si bond by the carboxylate *via* silylation with Me_3SiCl. The resulting RCO_2SiMe_3 esters are usually unstable towards hydrolysis during aqueous work-up. Second, through formation of carboxylate complexes with Lewis acidic metal cations. For this purpose, we added one equivalent of $ZnCl_2$ to the reaction mixture. The aim was to provide a Lewis acid for the removal of carboxylate from titanium. Third, through formation of a stable adduct with the titanocene to prevent formation of the titanocene carboxylate. To this end, we employed collidinium chloride (2,4,6-trimethylpyridinium chloride, Coll·HCl). We have recently shown that addition of Coll·HCl to solutions of Cp_2TiCl greatly stabilizes the titanocene through formation of the hydrogen-bonded complex $[Coll·H]^+[Cp_2TiCl_2]^-$ and therefore prevents decomposition.[8,9]

The results of the corresponding experiments are shown in Scheme 3. Only the third approach leads to satisfactory yields while reducing the reaction time significantly. These experimental condi-

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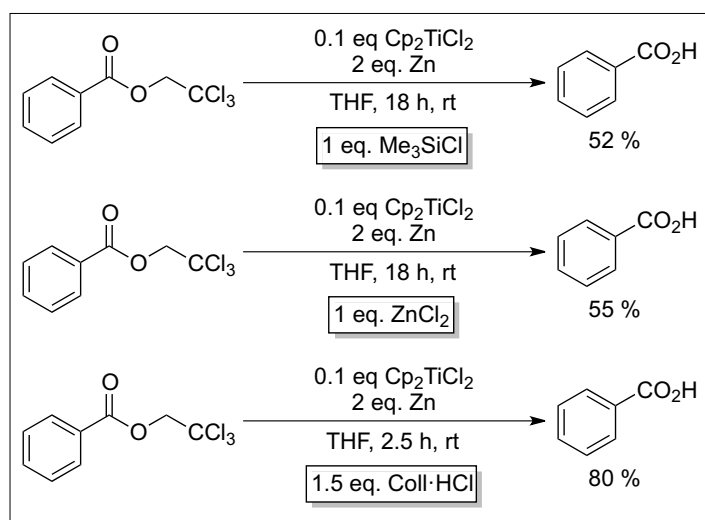E-mail: andreas.gansaeuer@uni-bonn.de

Scheme 1. TCE ester cleavage through metal-halogen-exchange followed by fragmentation.

Scheme 2. First attempted titanocene catalyzed deprotection of benzoic acid TCE ester.
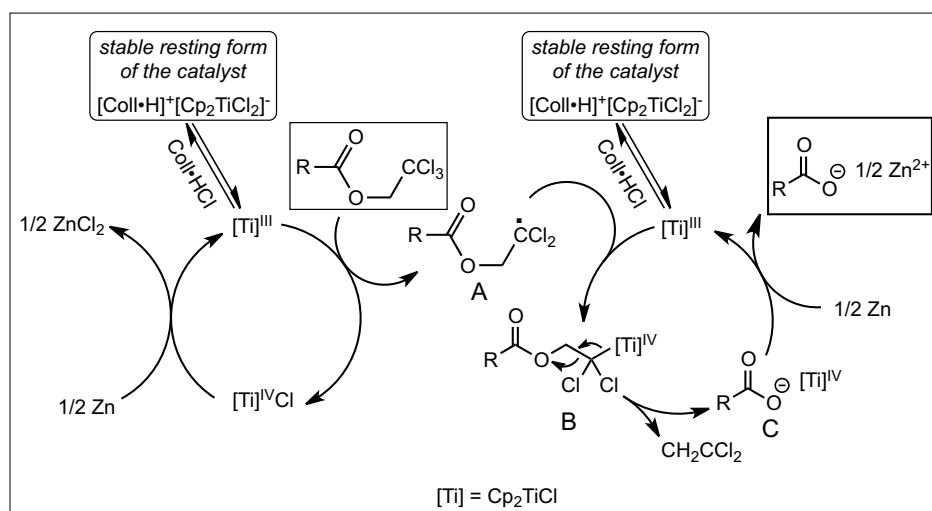
Scheme 3. Results of experiments with additives to the reaction mixture.

Table 1. Results of further deprotection experiments

Substrate	Product	Yield
		85%
		83%
		84%
		71%

tions were used for other substrates. In all cases, yields in the range of 80% could be achieved (see Table 1). Without Cp$_2$TiCl$_2$ the reaction is incomplete even after extended reactions times. Therefore, the stepwise removal of Cl⁻ *via* radicals is obviously faster and more efficient than metal–halogen-exchange in a two-electron step.

The proposed mechanism for the deprotection sequence is shown in Scheme 4. The first step is a halogen-atom-abstraction by Cp$_2$TiCl to yield carbon-centered radical A that is subsequently reduced by a second equivalent of Cp$_2$TiCl. The resulting β-metallated ester B undergoes fragmentation to yield 1,1-dichloroethene and titanocene carboxylate C. This carboxylate, as well as Cp$_2$TiCl$_2$ produced in the first reaction step, can be reduced by Zn to regenerate the catalytically active species. Coll·HCl does not affect the catalytic cycle directly but prevents decomposition of Cp$_2$TiCl.

In summary, we have devised a mild and efficient deprotection protocol for TCE esters. The use of radical intermediates is crucial for the success of the reaction.

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Scheme 4. Reaction mechanism for the catalytic radical deprotection of TCE esters with Cp$_2$TiCl as catalyst.