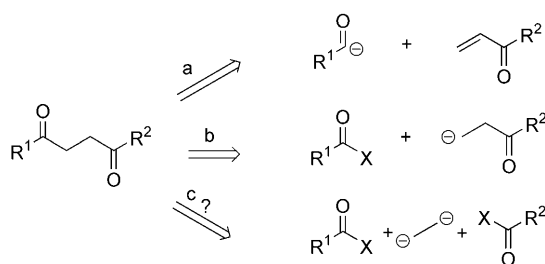


# Synthetic Methods

## Titanium-Mediated Synthesis of 1,4-Diketones from Grignard Reagents and Acyl Cyanohydrins\*\*

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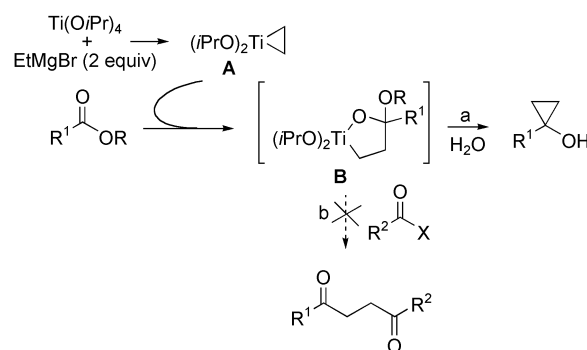
1,4-Diketones are important synthetic intermediates for the preparation of a wide range of five-membered cyclic compounds, including cyclopentenones,<sup>[1]</sup> furans, thiophenes, and pyrroles.<sup>[2]</sup> Various methods are used for the synthesis of 1,4-diketones,<sup>[3]</sup> including the conjugate addition of acyl anion equivalents to  $\alpha,\beta$ -enones (Scheme 1, path a),<sup>[4]</sup> and the less convenient reverse strategy involving the addition of homo-enolate equivalents to acid derivatives (Scheme 1, path b).<sup>[5]</sup>



**Scheme 1.** Strategies for the preparation of 1,4-diketones.

An alternative approach, which involves the addition of 1,2-dianion equivalents to two carboxylic acid derivatives (Scheme 1, path c) is unknown to date, principally because of the problems associated with the generation of 1,2-dianions and the subsequent selective addition to two distinct carboxylic acid derivatives.

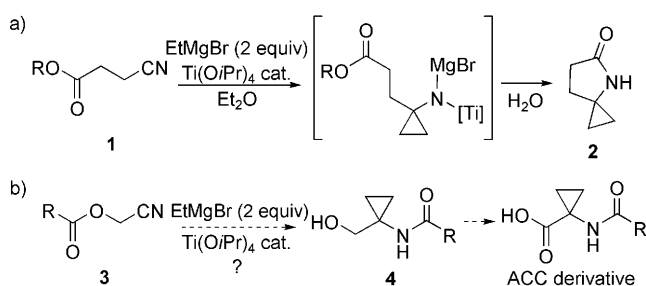
Group IV metal/ $(\eta^2$ -alkene) complexes are generally best represented as metallacyclopropanes,<sup>[6]</sup> suggesting the presence of two polar carbon–metal bonds.<sup>[7]</sup> The resulting 1,2-dianion reactivity pattern was observed with the  $(i\text{PrO})_2\text{Ti}/(\eta^2$ -ethylene) complex **A** and various acid derivatives,<sup>[8–11]</sup> as exemplified by the Kulinkovich reaction (Scheme 2). In this reaction, carboxylic esters are converted into cyclopropanols by the use of  $\text{EtMgBr}$  and  $\text{Ti}(\text{OiPr})_4$ , through a formal double nucleophilic addition of **A** to the same electrophilic carbon atom (Scheme 2, path a). The metallacycle intermediate **B** could be considered as a



**Scheme 2.** The Kulinkovich reaction.

homoenolate equivalent, and the addition of a second acid derivative would afford 1,4-dicarbonyl derivatives in one step (Scheme 2, path b).<sup>[12]</sup> To our knowledge, no sequential addition of two different carboxylic acid derivatives to titanacyclopropanes leading to 1,4-dicarbonyl compounds has been reported to date. We present herein our solution to this issue, which is the one-step formation of 1,4-diketones compounds from acyl-protected cyanohydrins.

As part of our investigations related to the titanium-mediated synthesis of cyclopropylamines from nitriles,<sup>[10]</sup> we have demonstrated that cyanoesters **1** were particularly good substrates, affording spirocyclopropane lactams **2** with a catalytic amount of  $\text{Ti}(\text{OiPr})_4$  (Scheme 3a).<sup>[13]</sup> Since amino-alcohols such as **4** are precursors of aminocyclopropanecar-



**Scheme 3.** Titanium-mediated cyclopropanation of cyanoesters.

boxylic acid (ACC) derivatives, we turned our attention to using carboxylate-protected cyanohydrins **3** with the aim to selectively provide acyl-protected cyclopropylamines **4** by cyclopropanation and subsequent acyl transfer (Scheme 3b).

In an initial experiment, cyanomethyl benzoate **3a**, prepared in one step from benzoic acid and chloroacetonitrile, was reacted under the conditions ( $\text{EtMgBr}$  (2 equiv),

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**Table 1:** Optimization of the reaction conditions.

| Entry <sup>[a]</sup> | Ti(OiPr) <sub>4</sub><br>[equiv] | EtMgBr<br>[equiv] | Solvent           | 4a<br>[%]        | 5a<br>[%] <sup>[b]</sup> |
|----------------------|----------------------------------|-------------------|-------------------|------------------|--------------------------|
| 1                    | 0.2                              | 2                 | Et <sub>2</sub> O | 12               | 45                       |
| 2                    | 1.1                              | 2.1               | Et <sub>2</sub> O | 10               | 67                       |
| 3                    | 1.1 <sup>[c]</sup>               | 2.1               | Et <sub>2</sub> O | 5                | 71 (69)                  |
| 4                    | 1.1                              | 3                 | Et <sub>2</sub> O | 6                | 70                       |
| 5                    | 1.1                              | 1.5               | Et <sub>2</sub> O | 3                | 17                       |
| 6                    | 1.1                              | 2.1               | THF               | 28               | 48                       |
| 7                    | 1.1 <sup>[d]</sup>               | 2.1               | THF               | 0 <sup>[e]</sup> | 44                       |
| 8                    | 0                                | 2.1               | Et <sub>2</sub> O | 0 <sup>[e]</sup> | 0                        |

[a] Unless otherwise mentioned, reactions were carried out with **3a** (1 mmol), Ti(OiPr)<sub>4</sub>, EtMgBr (solution in Et<sub>2</sub>O) in the indicated solvent (5 mL). [b] NMR yield. Yield of isolated product given in parentheses. [c] EtMgBr was added at 0°C. [d] [Cp<sub>2</sub>ZrCl<sub>2</sub>] was used instead of Ti(OiPr)<sub>4</sub>. [e] By-products resulting from the direct addition of EtMgBr to **3a** were obtained.

Ti(OiPr)<sub>4</sub> (0.2 equiv), Et<sub>2</sub>O) used for the synthesis of **2** (Table 1). The expected cyclopropylamine **4a** was obtained in only 12% yield. The main product was identified as the 1,4-diketone **5a**, that resulted from a formal addition of 1,2-ethylene dianion to both ester and nitrile moieties of the cyanoester. When the reaction was run with a stoichiometric amount of Ti(OiPr)<sub>4</sub>, a better yield of **5a** was obtained (Table 1, entry 2). The yield was again slightly increased by mixing the reagents at 0°C and subsequently warming the reaction mixture to room temperature (Table 1, entry 3). Interestingly, an excess of EtMgBr did not affect the reaction outcome (Table 1, entry 4). In contrast, lowering the amount of the Grignard reagent dramatically reduced the conversion, showing clearly the need of at least two equivalents of EtMgBr (Table 1, entry 5). When THF was used instead of Et<sub>2</sub>O as the solvent, the ratio of **4a**/**5a** was modified to favor the formation of the cyclopropane (Table 1, entry 6). The formation of **5a** was also performed using [Cp<sub>2</sub>ZrCl<sub>2</sub>], but the efficiency of the reaction was reduced (Table 1, entry 7). Only direct alkylation was observed when the reaction was run without the titanium catalyst (Table 1, entry 8).

The scope of the reaction was explored next (Table 2). Cyanoesters prepared from either donor- or acceptor-substituted aromatic acids are equally good substrates (Table 2, entries 1–4) and 1-furyl-substituted cyanoester **3f** was smoothly converted into **5f** (Table 2, entry 5). Use of aliphatic cyanoesters afforded the corresponding diketones in comparable yields (Table 2, entries 6–8), except for **3j** (Table 2, entry 9). In this latter case, the cyclopropane **4** was also obtained in a significant yield (12%). Diketones bearing a conjugated alkene moiety can also be obtained (Table 2, entries 10–11). Cyanoesters derived from substituted cyano-hydrins are well tolerated, thus allowing the construction of 1,5-disubstituted 5-hydroxy-1,4-diketones (Table 2, entry 12). Finally, the reaction is not limited to EtMgBr, as shown by the use of both *i*PrMgCl and H<sub>2</sub>C=CH-(CH<sub>2</sub>)<sub>2</sub>MgBr, thus giving access to diketones displaying other substitution patterns.

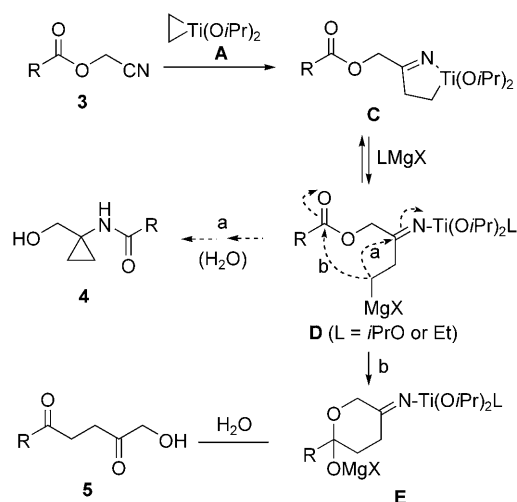
**Table 2:** Preparation of 1,4-dicarbonyl derivatives.

| Entry <sup>[a]</sup> | Substrate | Product | Yield<br>[%] <sup>[b]</sup> |
|----------------------|-----------|---------|-----------------------------|
| 1                    |           |         | 65                          |
| 2                    |           |         | 60                          |
| 3                    |           |         | 60                          |
| 4                    |           |         | 62                          |
| 5                    |           |         | 36                          |
| 6                    |           |         | 50                          |
| 7                    |           |         | 62                          |
| 8                    |           |         | 55                          |
| 9                    |           |         | 35                          |
| 10                   |           |         | 42                          |
| 11                   |           |         | 45                          |
| 12                   |           |         | 56                          |
| 13 <sup>[c]</sup>    |           |         | 40                          |
| 14 <sup>[d]</sup>    |           |         | 30                          |

[a] Unless otherwise mentioned, reactions were carried out with **3** (1 mmol), Ti(OiPr)<sub>4</sub> (1.1 equiv), EtMgBr (2 M in Et<sub>2</sub>O, 2.1 mmol) in Et<sub>2</sub>O (5 mL). [b] Yield of isolated product. [c] Used *i*PrMgBr instead of EtMgBr. [d] Used H<sub>2</sub>C=CH-(CH<sub>2</sub>)<sub>2</sub>MgBr instead of EtMgBr.

Although the yields are lower, the products were obtained as a single regioisomer (Table 2, entries 13–14).<sup>[14,15]</sup>

In light of the experimental results, a tentative rationale is proposed (Scheme 4). The first step would imply the insertion of the nitrile moiety of **3** into the titanacyclopentane intermediate **A** (obtained from Ti(OiPr)<sub>4</sub> and 2 equiv of EtMgBr) to provide the five-membered titanacycle **C**. The diketone **5** might be directly obtained from an intramolecular direct insertion of the ester C=O bond into the remaining titanium–carbon bond, however this possibility is unlikely because of obvious geometric constrictions. A more plausible



**Scheme 4.** Proposed mechanism for the formation of 1,4-dicarbonyl compounds.

pathway would involve a *C,N*-bis(metallated) intermediate such as **D**,<sup>[16]</sup> which results from the ring-opening of **C** by magnesium alkoxides or Grignard reagents. Several related metallacycle ring-openings have already been proposed in the literature.<sup>[17–19]</sup> For instance, the addition of Grignard reagents to five-membered oxatitanacyclopentanes has been proposed by Kulinkovich et al. to explain the need for excess Grignard in the synthesis of cyclopropanols.<sup>[17]</sup> Recently, the azatitanacyclopent-2-ene ring-opening has been postulated by Cha et al. to explain the nonselective cyclopropanation of nitriles.<sup>[18]</sup> The next step is the cyclization of the open bimetallic intermediate **D**. The amide **4** (Scheme 4, path a) could be obtained after acyl transfer of the metallated cyclopropylamine (not shown). The addition could alternatively occur on the ester moiety (Scheme 4, path b) to afford **E**. This last intermediate can be seen as a protected diketone, since it is not affected by an excess of Grignard reagent (see Table 1, entry 4). Finally, the diketone **5** can be obtained by hydrolysis of **E**. This indicates the divergent synthesis of **4** and **5** from the common intermediate **D**. Nevertheless, the astonishing difference in reactivity between cyanoesters **1** and **3** remains unexplained at the moment.

In conclusion, the 1,2-dianionic reactivity of titanacyclopentanes was applied for the first time to the synthesis of 1,4-dicarbonyl compounds by proceeding through a double nucleophilic addition. From a synthetic point of view, this method represents efficient access to  $\gamma$ -diketones from carboxylic acids, via the formation of acyl cyanohydrins. Additional work is underway to better understand the mechanism and expand the scope of this reaction.

## Experimental Section

EtMgBr (2.1 mmol, 3 M in Et<sub>2</sub>O) was added dropwise to a solution of the cyanoester **3** (1 mmol) and Ti(OiPr)<sub>4</sub> (0.33 mL, 1.1 mmol) in Et<sub>2</sub>O (5 mL) that was maintained at 0 °C under argon. After the addition of the Grignard reagent, the mixture was warmed to RT and stirred for 1 h. The turbid yellow mixture was quenched with water (1 mL), and

then EtOAc (10 mL) and 1 M HCl were added to obtain two clear phases. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with saturated aqueous NaHCO<sub>3</sub> and dried (MgSO<sub>4</sub>). After evaporation of the solvents, the residue was purified by flash chromatography on silica gel to afford the desired product (hexanes/EtOAc then EtOAc).

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