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COMMUNICATIONS

Published on Web 07/30/2005

A Modular and Efficient Synthesis of Functional Titanocenes

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Group 4 metallocenes and titanocenes, in particular, continue to be of substantial importance in their own right[1] as efficient reagents and catalysts[2] and as a promising class of antitumor agents.[3] Currently, synthetic interest in these compounds concentrates on the incorporation of polar functional groups into the cyclopentadienyl ligands, especially for cytotoxicity studies.[4]

However, access to these functional complexes that are also important as catalysts is noticeably limited by the linear synthetic sequences employed for their preparation.[5] Because the $TiCl_2$ fragment is rather electrophilic, polar nucleophilic groups have to be introduced at the ligand preparation stage before metalation.[6] This can be disadvantageous as the presence of protic functional groups is excluded, for example.

Modular routes offer more general synthetic perspectives. This is especially so for approaches featuring building blocks containing a [$TiCl_2$] moiety for the rapid preparation of large numbers of complexes. However, such sequences have remained elusive, as yet.[5]

Here, we address exactly these issues by reporting such a titanocene synthesis. To employ the planned building blocks, it is mandatory that they contain functional groups more reactive toward nucleophiles than the $TiCl_2$ fragment. To this end, we decided to attach highly electrophilic carboxylic acid chlorides to the titanocene framework for the first time. Our concept for the synthesis of the novel titanocene building blocks is outlined in Figure 1.

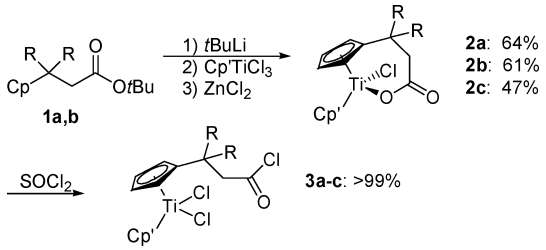


Figure 1. Synthesis of the titanocene building blocks **3a**−**3c**: **a**, R═CH_3, Cp′ = Cp; **b**, R=$(CH_2)_5$, Cp′ = Cp; **c**, R═CH_3, Cp′ = Me_5Cp). For the preparation of **1a**,**b**, see Supporting Information.

We exploited the high stability of titanocenes toward acidic reaction conditions by treating **2a** with $SOCl_2$. Acid chloride **3a** was formed quantitatively and used without further purification. Similar yields were obtained for the other building blocks, **3b** and **3c**, investigated in this study. Complex **2a** was obtained from **1a** in 64% yield over two steps by metalation and ester cleavage in 20 g batches. Thus, our strategy allows the straightforward preparation of structurally diverse and highly reactive titanocene building blocks on a large scale.

We then turned our attention to the introduction of the pivotal functional groups. The optimized conditions for the acylation of **3a** with benzylamine to yield **4a** are shown in Figure 2.

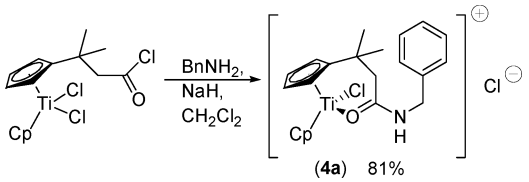
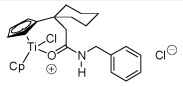
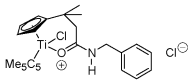
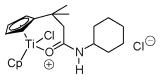
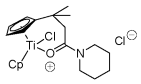
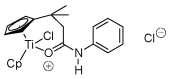
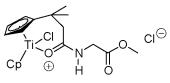
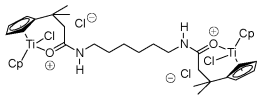
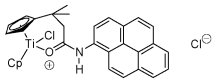


Figure 2. Optimized conditions for the synthesis of **4a**.

Table 1. Acylation Reactions of Titanocene Building Blocks **3a**−**c** with Amines (see Supporting Information for experimental and structural details)

[Ti]	product	yield
3b		**4b**/59
3c		**4c**/75
3a		**5**/84
3a		**6**/79
3a		**7**/61
3a		**8**/84
3a		**9**/85
3a		**10**/72

NaH constituted the best base as the byproducts are either volatile (H_2) or removed by filtration (NaCl). Amines were inadequate. The hydrochlorides could not be removed from **4**.

As summarized in Table 1, our optimized conditions proved to be general in the preparation of amides from primary, secondary, benzylic, and aromatic amines in high yields, amply demonstrating the power of our modular approach.[6] These compounds are cationic through complexation of titanium by the carbonyl group in solution. At present, the mechanistic details of the cation formation remain unresolved. Compounds **4a**, **4b**, **5**, and **8** have been characterized by X-ray crystallography and display this behavior in the solid state also, as shown for **8** in Figure 3.

10.1021/ja054185r CCC: $30.25

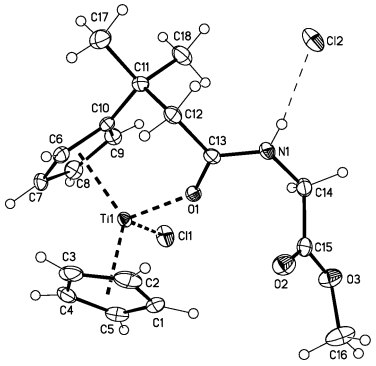
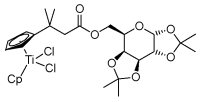
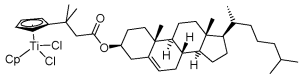
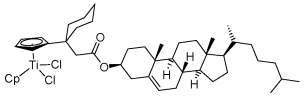
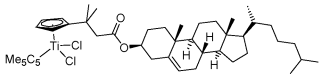
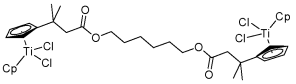
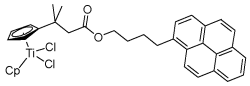


Figure 3. Molecular structure of **8** in the solid state.

Table 2. Acylation Reactions of Titanocene Building Blocks **3a**−**c** with Alcohols (for experimental details and compound characterization, see Supporting Information)

[Ti]	product	yield
3a		**11**/92
3a		**12a**/74
3b		**12b**/81
3c		**12c**/86
3a		**13**/98
3a		**14**/79

These results are in sharp contrast to the only other cationic titanocene complex that contains an amide, albeit without an N−H bond. This complex had to be prepared by the action of a Lewis acid or a Meerwein salt to replace chloride by noncoordinating anions, such as tetrafluoroborate.[7] In our case, the presence of the strong hydrogen bond between the amide proton and chloride (Cl2) provides extra stabilization of chloride lacking in the case above.[8] Such stabilization of cationic intermediates has been postulated to be essential for biological activity.[4]

Our approach proved powerful in the preparation of functional titanocenes with groups that have not been attached covalently to the metallocene before. Complex **8** constitutes the first example of a titanocene containing a covalently attached natural amino acid and opens the field for peptide-modified titanocenes. Metallocenes of this type have recently attracted considerable interest in bio-organometallic and medicinal chemistry.[9] Compound **10** with the fluorescence label 1-aminopyrene is valuable for identifying the binding sites of titanocenes to biomolecules in cytotoxicity and DNA intercalation studies. The high yielding preparation of dinuclear **9** also highlights the potential of our strategy. This otherwise difficult to prepare compound is pertinent for linking biomolecules and as a catalyst in reductive epoxide openings.[10] Gratifyingly, **3b** and **3c** gave similar yields in the preparation of **4b** and **4c** from benzylamine as **3a**. This amply demonstrates the value of our approach for a modular synthesis as steric effects do not markedly affect the performance of the acylation reaction.

As shown in Table 2, alcohols also proved to be excellent nucleophiles in acylation reactions. The examples demonstrate that a galactose derivative and cholesterol can be attached to the metallocene fragments in high to excellent yields to deliver the desired **11** and **12a**−**12c**. As before, varying the titanocene building block **3a**, **3b**, and **3c** did not result in a substantial variation of the yields in the acylation reaction. In CH_2Cl_2, **3a** constitutes one of the rare examples of an organometallic gelator.[11] Complex **14** containing a fluorescence label and a DNA intercalating group was obtained in good yield and the dimeric **13** in almost quantitative yield. In contrast to the amides, all ester-substituted titanocenes were not cationic, as judged by their NMR spectra, and distinctly more soluble in organic solvents.

In summary, we have demonstrated that functional titanocene complexes, relevant to applications in catalysis, bioinorganic, and medicinal chemistry, can be accessed quickly and in large numbers by a modular approach featuring novel titanocene building blocks. It has become clear that titanocenes are quite tolerant to polar functional groups that can additionally promote the formation of cationic intermediates and even stabilize them.

Acknowledgment. We are indebted to the SFB 624 Template-Vom Design chemischer Schablonen zur Reaktionssteuerung for generous financial support.

Supporting Information Available: Experimental procedures, spectral, and crystal structure details. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA054185R