Recycling Titanocene Dichloride from the Petasis Methylenation Reaction

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Summary: A simple method for recycling the titanium species used in the Petasis methylenation reaction is described. Treatment of the titanocene oxide byproduct with chlorotrimethylsilane and pyridine allows regeneration, recovery, and successful reuse of titanocene dichloride in amounts corresponding to nearly 90% of the dimethyltitanocene reagent initially employed.

Introduction

Dimethyltitanocene, introduced by Petasis for the methylenation of heteroatom-substituted carbonyl compounds, has proven to be a valuable alternative to the Tebbe reagent. Unlike the latter, the Petasis reagent, which is easily prepared from methylmagnesium chloride and titanocene dichloride,[1] is relatively air- and water-stable. The two species afford somewhat complementary chemoselectivity: the Tebbe system, which requires a Lewis base to release the Ti carbene from its precursor, shows selective reactivity toward more basic substrates (e.g., amides), while the Petasis system selects for the more electrophilic carbonyl (e.g., esters).[2] When it is heated to 60−75 °C, dimethyltitanocene efficiently methylenates a wide variety of carbonyl compounds, nitriles, and even alkynes.[3] A useful feature of the Petasis system is that similar reactivity can be obtained from a number of other dialkyltitanocenes, including dibenzyl and bis(trimethylsilylmethyl) derivatives.[4] Petasis reagents are also tolerant of numerous functional groups, making them quite useful for natural products synthesis.[5] A significant drawback to the use of such systems is the formation of the strong oxygen−titanium bond,[6] which, while serving as the driving force of the reaction, has inhibited the development of versions that are catalytic in titanium.

We are interested in exploring the means to render organometallic catalysts and reagents reusable. Rising costs for both purchase and, more recently, disposal of such species are motivations for these efforts, as is a desire from an environmental perspective to maximize their utility before disposal. The ready availability of titanocene dichloride makes it a convenient reagent to examine for recyclability. Although Cp_2TiCl_2 is not particularly expensive (at least by today's standards), methods for its recycling would presumably be applicable to much more costly and comparably useful reagents such as Cp_2ZrCl_2. There have been scattered reports of the regeneration of Ti−Cl species (but not Cp complexes) from the corresponding oxo compounds. Hupperts and Fürstner demonstrated the use of chlorosilanes to convert titanium oxides into chlorides, effectively rendering the McMurry coupling catalytic.[7] We chose a similar approach to regenerate titanocene dichloride from the oxide formed during Petasis methylenation. Given the reduced oxophilicity of the bis(cyclopentadienyl)titanium moiety compared with that of simple inorganic Ti(IV), we reasoned that a moderately oxophilic chlorosilane should be effective in this case as well. Herein we describe conversion of the crude Ti-containing product of a Petasis transformation first into titanocene dichloride and then back into an active methylenating species: effectively a recycling of the Petasis reagent.

Results and Discussion

Typical Petasis-type methylenations use an excess of titanium reagent to achieve the desired outcome, even though the mechanism suggests that only 1 equiv should be necessary.[8] We began this study with an attempt to obtain reasonable conversion using a minimal excess of Ti-containing reagents prior to investigating the possibility of recycling the titanium. Part of this effort required defining conditions to keep the titanium in solution and amenable to later transformation. We prepared the Petasis reagent following the procedure of Payack et al.,[1] by addition of CH_3MgCl to Cp_2TiCl_2 in THF/toluene to give a 76% yield of a solution of $Cp_2Ti(CH_3)_2$.

Petasis methylenation generally proceeds best in the presence of a donor solvent[3a] that inhibits the formation of μ-oxo species of reduced solubility.[9] For simplicity of quantitation, we used cyclohexanone as the substrate to test feasibility. Methylenation of cyclohexanone using 1 equiv of dimethyltitanocene in THF/toluene was carried out at 80−85 °C. After 6 h the ^1H NMR showed complete disappearance of the signals at δ 6.05 and −0.16 ppm due to $Cp_2Ti(CH_3)_2$ and appearance of a new signal at δ 5.82 ppm, presumably due to Cp_2TiO, probably as a THF complex. The formation of methylenecyclohexane in 60−65% yield was confirmed by the appearance of the signal for its alkene hydrogens at δ 4.58 ppm.

In an initial attempt to regenerate Cp_2TiCl_2, the reaction mixture was treated directly with $(CH_3)_3SiCl$ at reflux overnight. NMR analysis revealed the presence of a mixture of Cp_2TiCl_2 (6.59 ppm), $CpTiCl_3$ (7.10 ppm), $[Cp_2TiCl]_2O$ (6.91 ppm), and $[(CH_3)_3Si]_2O$ (0.44 ppm); a black precipitate was also observed.

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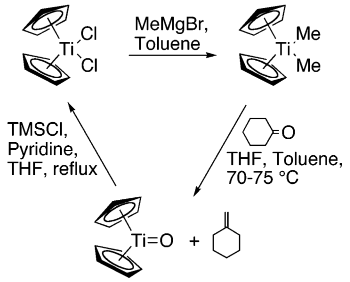
Scheme 1



In an attempt to maintain the solubility of Ti-containing material, pyridine was incorporated into the regeneration procedure. Pyridine is known to reverse the formation of titanium oxocyclobutanes starting from titanocene oxide by complexing the latter.[10] We assumed that pyridine would assist similarly in the recycling procedure by blocking the empty orbital on the oxide and diverting it toward O/Cl exchange in the presence of the chlorosilane. In this case, we repeated the cyclohexanone methylenation and then added a 10-fold excess of both pyridine and $(CH_3)_3SiCl$. After 8 h of reflux, the major Ti-containing materials were now the THF and pyridine complexes of Cp_2TiCl_2, appearing in the NMR at δ 6.59 and 6.49 ppm, respectively. This modification effectively suppressed the formation of other soluble titanium-containing species, as well as virtually eliminating the formation of insoluble material. Vacuum transfer removed all volatiles, including methylenecyclohexane, pyridine, $(CH_3)_3SiCl$, and $[(CH_3)_3Si]_2O$, leaving behind a semisolid residue of Cp_2TiCl_2 as a mixture of the pyridine and THF complexes.

Taking up this residue into THF and precipitating with hexane afforded essentially pure Cp_2TiCl_2 in 87% yield, based upon the amount of $Cp_2Ti(CH_3)_2$ initially used. We then reconverted the dichloride via the conventional procedure into $Cp_2Ti(CH_3)_2$. Despite physical losses associated with an extractive workup step, the dimethyl derivative could be isolated and used directly in subsequent methylenation. In this way, from an initial methylenation employing approximately 0.4 g of $Cp_2Ti(CH_3)_2$ reagent, four recyclings were achieved, on successively smaller scales. We reduced the amount of cyclohexanone in each run to maintain the same ketone-to-reagent ratio. Yields of methylenecyclohexane remained essentially constant from run to run at about 60%, and about 65% of usable dimethyltitanocene reagent was achieved after each recycling, relative to the previous run. The latter is consistent with an average 87% efficiency for recycling of titanocene oxide to dichloride, combined with a 75% yield for the conversion of the dichloride into dimethyltitanocene. Working on a larger scale (starting with 2.50 g of Petasis reagent), we found that the yields did not improve, but the recovered Petasis reagent was of higher purity after each recycling. Scheme 1 illustrates the process.

The consistent yields of methylenecyclohexane observed from run to run demonstrate that there is no significant loss in activity with respect to the titanium. Note that the volatile mixture obtained in the vacuum-transfer step containing excess chlorosilane and pyridine may itself be reused in subsequent regenerations of the titanocene reagent. Thus, proof of the concept of the strategy has been achieved. The only limit to the number of recyclings lies in the ability to mechanically handle the material and minimize loss in the preparation of the dimethyl derivative. Thus, improving the practicality of the procedure would depend on the development of improved conversions of the dichloride into the active methylenating reagent.

Conclusion

We have demonstrated a method for the recycling of the titanocene-based Petasis reagent based upon conversion of the oxide byproduct into the dichlorotitanocene starting material using a chlorosilane. Modifications of the process to improve its efficiency and to extend recycling to other early-transition-metal reagents are under study and will be reported in due course.

Experimental Section

General Considerations. Titanocene dichloride (Aldrich, 97%) and cyclohexanone were used as received. THF was freshly distilled from Na/benzophenone under N_2, and toluene and pyridine were dried over 3 Å molecular sieves under Ar for 2 days. Methylmagnesium chloride (Acros) was used as a 22% w/w solution in THF. Reactions were monitored by taking aliquots and assaying by ^1H NMR. All ^1H NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as an internal standard on an INOVA 400 MHz instrument, which was funded in part by a grant from the NSF (Grant No. CHE-9808183).

Synthesis of Dimethyltitanocene. The literature procedure[1] was used to prepare this reagent in 76% yield as a standard solution, 6.63% w/w in 2.1:1 THF/toluene. ^1H NMR: δ 6.058 (s, 10H), −0.152 (s, 6H) ppm.

Petasis Methylenation of Cyclohexanone and Reagent Regeneration (Representative Procedure). A round-bottom flask was flushed with Ar and charged with 6.7 mL (0.444 g, 2.13 mmol) of a standard 6.63% w/w solution of dimethyltitanocene and 0.209 g (2.13 mmol) of cyclohexanone. The mixture was then heated to 80−85 °C for 6 h under Ar. After the mixture was cooled to near room temperature, 1.688 g (21.3 mmol) of pyridine and 2.318 g (21.3 mmol) of trimethylsilyl chloride were added and the mixture was heated to 80−85 °C for 8 h. After this mixture was cooled, the volatiles were removed via vacuum transfer. The nonvolatile residue, after trituration from THF with hexane, afforded 0.462 g (87% yield) of titanocene dichloride as a deep purple solid. ^1H NMR: δ 6.59 (s) ppm. The dichloride was then reconverted to dimethyltitanocene using the literature procedure.

Methylenecyclohexane. The alkene was obtained as a pale yellow liquid admixed with THF, chlorotrimethylsilane, pyridine, toluene, and hexamethyldisiloxane (NMR yield 60−65%). ^1H NMR: δ 4.58 (t, 2H), 2.12 (m, 4H), 1.54 (m, 6H).

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