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Perfluoroalkylation

Paradigm Shift from Alkaline (Earth) Metals to Early Transition Metals in Fluoroorganometal Chemistry: Perfluoroalkyl Titanocene(III) Reagents Prepared via Not Titanocene(II) but Titanocene(III) Species

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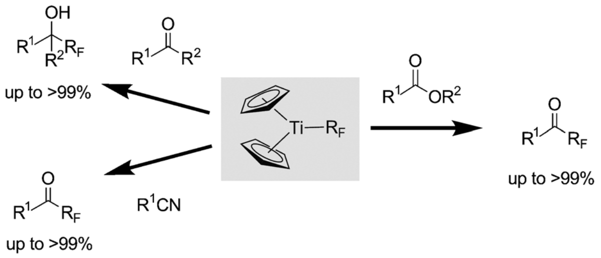
Abstract: Perfluoroalkyl (R_F) titanocene reagents [$Cp_2Ti^{III}R_F$] synthesized via [$Cp_2Ti^{III}Cl$] rather than [Cp_2Ti^{II}] show new types of perfluoroalkylation reactions. The [$Cp_2Ti^{III}R_F$] reagents exhibit a wide variety of reactivity with carbonyl compounds including esters and nitriles, and selectivities far higher than those reported for conventional R_FLi and R_FMgX reagents.

Introduction

Organofluorine compounds have attracted great interest in recent years because of their important applications in materials[1] and biological[2] sciences. Generally, synthetic methods for fluorine-containing compounds are classified into 1) carbon–fluorine bond-forming reactions with fluorinating reagents,[3] 2) carbon–carbon bond-forming reactions with fluoroalkylating reagents,[4] and 3) carbon–carbon bond-forming reactions employing fluorine-containing building blocks, for example, fluorinated carbonyl compounds.[5] The carbon–carbon bond-formation (CCF) method is among the most efficient in construction of the target carbon skeleton and fluorofunctionalization thereof. However, the CCF method based on anionic fluoroalkyl metal reagents such as alkyl lithium compounds, which have been widely employed for nonfluorinated systems, is often not applicable to fluorinated counterparts. Perfluoroalkyl (R_F) metal reagents are generally recognized as unstable and difficult to prepare because of facile α- or β-metal fluoride (MF) elimination.[6] Therefore, a coexisting carbonyl electrophile is employed for in situ halogen–metal exchange reactions of perfluoroalkyl halides and subsequent carbonyl addition of perfluoroalkyl lithium reagents at low temperature.[7] Herein, we report the in situ preparation of perfluoroalkyl titanocene reagents not via titanocene(II) species but via titanocene(III) monochloride, and their new types of perfluoroalkylation reactions: perfluoroalkylation of nitriles and carbonyl compounds including esters. The present work can thus be regarded as a paradigm shift from alkaline (earth) metals to early transition metals in fluoroorganometal chemistry. The perfluoroalkyl titanium(III) reagents show a wide range of reactivity and far higher selectivity than conventional reactions reported for perfluoroalkyl lithium and Grignard reagents (Scheme 1).



Scheme 1. Reactions of perfluoroalkyl titanium(III) reagents.

Results and Discussion

We first thought that perfluoroalkyl titanocene reagents with electron-donating and sterically demanding Cp ligands could stabilize the unstable perfluoroalkyl metal reagents by preventing α- or β-fluoride elimination through electronic and steric shielding effects (Scheme 2).[8] The perfluoroalkyl titanocene halide reagents would be synthesized by oxidative addition of perfluoroalkyl halides to the widely employed titanocene(II) species generated with two equivalents of alkyl metal species such as alkyl lithium and Grignard reagents according to the general preparative procedures.[9]

First, we attempted to synthesize perfluoroalkyl titanocene reagents by treating titanocene(IV) dichloride with two equiva-

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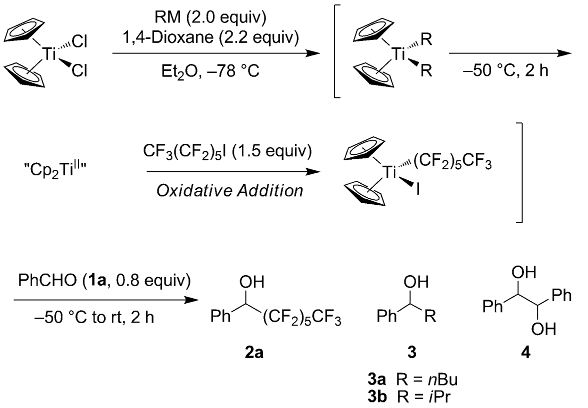


Scheme 2. Attempted synthesis and reactions of perfluoroalkyl titanocene reagents.

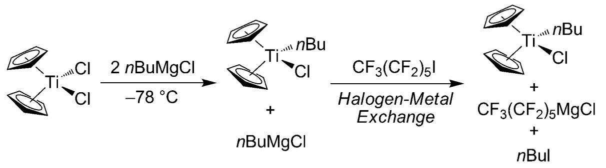
Table 1. Synthesis and reactions of perfluoroalkyl titanium(III) reagents with benzaldehyde (**1a**).

Entry	RM	Yield of **2a** [%]	Yield of **3** [%]	Yield of **4** [%]
1	*n*BuLi	0	0	48[a]
2	*n*BuMgCl	40[a]	48[a]	0
3	*i*PrMgCl	quant.	0	0

[a] Determined by ^{1}H NMR analysis.

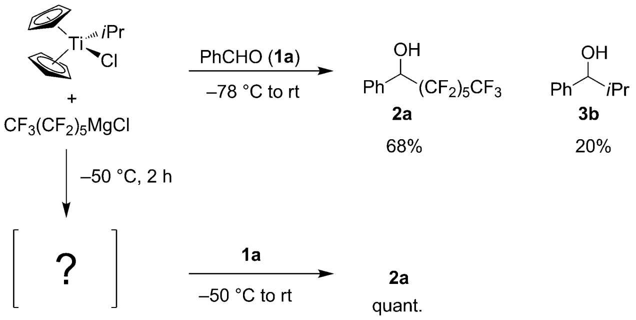
lents of *n*BuLi, *n*BuMgCl, or *i*PrMgCl at −78 °C and subsequent oxidative addition of perfluoroalkyl halides to the titanocene(II) species formed on increasing the temperature to −50 °C (Table 1).[10–13] With *n*BuLi, however, no perfluoroalkylation was observed in the reaction with benzaldehyde (**1a**), and pinacol coupling product **4** was obtained instead (Table 1, entry 1). The corresponding Grignard reagent *n*BuMgCl led to perfluoroalkylation product **2a** along with alkylation product **3a** in a ratio of 1:1 (Table 1, entry 2). In contrast, *i*PrMgCl gave a quantitative yield of isolated perfluoroalkylation product **2a** (Table 1, entry 3).

The following findings are significant: The fact that *n*BuLi solely provided the pinacol coupling product implies that $CF_3(CF_2)_5I$ did not oxidatively add to the titanocene(II) species generated with two equivalents of *n*BuLi. The titanocene(II) species gave pinacol coupling product **4** by single-electron transfer (SET) to benzaldehyde (Table 1, entry 1). Attempted reduction of the titanocene(IV) dihalide with two equivalents of *n*BuMgBr at −78 °C gave no pinacol coupling product but a 1:1 mixture of perfluoroalkylation product **2a** and alkylation product **3a** (Table 1, entry 2). This result indicates no reduction to the titanocene(II) species but halogen–metal exchange reaction of $CF_3(CF_2)_5I$ with the Grignard reagent. Butyllithium is more nucleophilic than the corresponding Grignard reagent and hence bis-transmetalates the titanocene(IV) species to eventually give the low-valent titanocene(II) species (Scheme 2). In contrast, at low temperature (−78 °C), only one equivalent of the less nucleophilic Grignard reagent transmetalates [Cp_2TiCl_2], the remaining equivalent of the Grignard reagent gives the perfluoroalkyl Grignard reagent by halogen–metal exchange with the perfluoroalkyl iodide at −50 °C (Scheme 3), and thus a 1:1 mixture of the perfluoroalkylation and alkylation products results. Indeed, ^{1}H NMR analysis of a mixture of two equivalents of the alkyl Grignard reagent, perfluoroalkyl iodide, and titanocene(IV) dichloride prior to the addition of benzaldehyde showed the formation of one equivalent of 1-iodobutane (*n*BuI) by halogen–metal exchange reaction.



Scheme 3. Halogen–metal exchange with the remaining Grignard reagent.

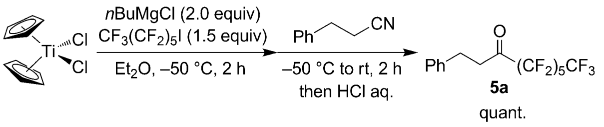
The question arises why *i*PrMgCl gave a quantitative yield of perfluoroalkylation product, in contrast to the 1:1 mixture of perfluoroalkylation and alkylation products obtained with *n*BuMgCl. To gain an insight into the reaction mechanism, perfluoroalkylation reactions of an aldehyde and a nitrile were carried out with two equivalents of *i*PrMgCl or *n*BuMgCl with or without raising the reaction temperature to ambient temperature (Schemes 4–6).



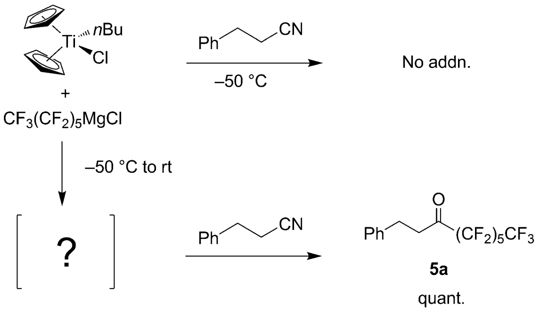
Scheme 4. Temperature effect on the perfluoroalkylation of benzaldehyde.

Even with two equivalents of *i*PrMgCl, a mixture of perfluoroalkylation product **2a** and alkylation product **3b** was obtained at −78 °C to room temperature (Scheme 4). At low reaction temperature, the *i*Pr group could be retained on the titanium center to give isopropyl carbinol **3b**, as opposed to exclusive formation of perfluoroalkylation product **2a** on raising the reaction temperature to −50 °C.

The reaction of the nitrile with two equivalents of *n*BuMgBr, which gave a 1:1 mixture of perfluoroalkylation and alkylation products of benzaldehyde at low temperature, resulted in contrast in quantitative formation of perfluoroalkylation product **5a** on warming to ambient temperature (Scheme 5). However, perfluoroalkyl Grignard and monoalkyl titanocene(IV) reagents[14] did not give the (perfluoro)alkylation products of nitriles.



Scheme 5. Quantitative perfluoroalkylation of a nitrile.

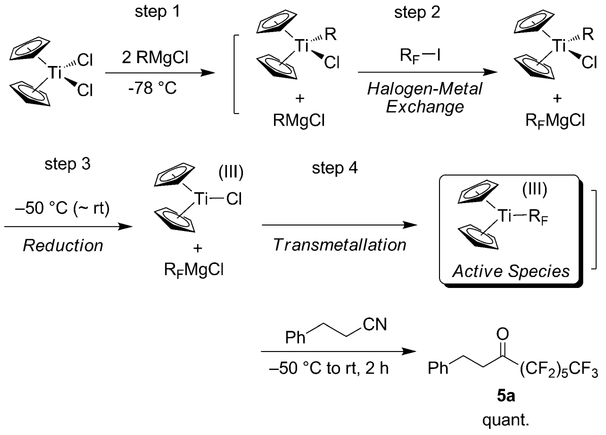


Scheme 6. Temperature effect on the perfluoroalkylation of a nitrile.

On increasing the reaction temperature to ambient temperature, the active perfluoroalkyl titanocene species could be generated even with two equivalents of *n*BuMgCl (Scheme 6). This transformation is quite similar to that in the mixture of two equivalents of isopropyl Grignard reagent, perfluoroalkyl iodide, and $[Cp_2TiCl_2]$.

The question remains whether β-hydride elimination or reduction of Cp_2Ti^{IV} to Cp_2Ti^{III} provides the active perfluoroalkyl titanocene species on raising the reaction temperature. The ^1H NMR spectrum of a mixture of two equivalents of *i*PrMgCl, perfluoroalkyl iodide, and titanocene(IV) dichloride did not show any formation of propene ($\delta \approx 4.8$–5.8 ppm) by β-hydride elimination. Moreover, the use of two equivalents of cyclohexyl Grignard reagent instead of *i*PrMgCl did not result in a signal for the higher-boiling cyclohexene at $\delta \approx 5.7$ ppm.

To clarify the intermediacy of perfluoroalkyl titanium(III) reagents, $[Cp_2Ti^{III}Cl]$ was prepared as a green solution according to the literature procedure[15] from $[Cp_2TiCl_2]$ and one equivalent of *i*PrMgCl at room temperature. The separately prepared perfluoroalkyl Grignard reagent was added to the solution of $[Cp_2Ti^{III}Cl]$ at −78 °C. After stirring the mixture at −50 °C for 2 h, β-phenylpropionitrile was added to give perfluoroalkylation product **5a** in 57% yield (Scheme S1 in the Supporting Information). Alternatively, a mixture of $[Cp_2TiCl_2]$, *i*PrMgCl (2 equiv), and perfluorohexyl iodide prepared at −50 °C generated a paramagnetic species that was observable by EPR spectroscopy at ambient temperature and indicated the presence of Ti^{III} species. These findings could be explained as follows: As shown in Scheme 7, only one of the two equivalents of the Grignard reagent transmetalates $[Cp_2Ti^{IV}Cl_2]$ at low temperature (step 1). Addition of R_FI to the mixture containing the remaining Grignard reagent leads to the formation of the perfluoroalkyl Grignard reagent via halogen–metal exchange reaction (step 2). On increasing the reaction temperature, $[Cp_2Ti^{IV}RCl]$ is reduced to $[Cp_2Ti^{III}Cl]$[15] (step 3). Transmetalation of the perfluoroalkyl Grignard reagent provides the active $[Cp_2Ti^{III}R_F]$ species, which is now reactive even with nitriles (step 4). These results indicate the formation of perfluoroalkyl titanocene(III) species.



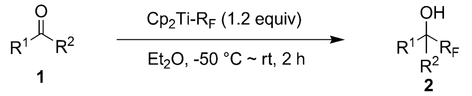
Scheme 7. Reaction of a perfluoroalkyl titanocene(III) species with a nitrile.

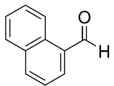
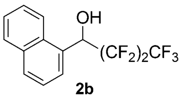
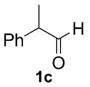
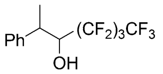
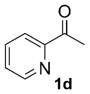
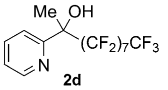
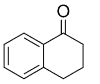
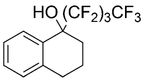
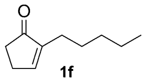
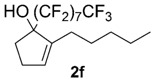
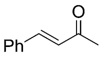
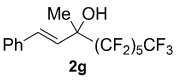
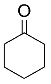
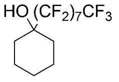
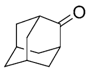
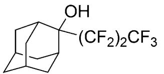
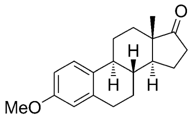
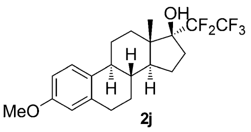
The Lewis acidity of perfluoroalkyl titanocene reagents was found to be increased by the electron-withdrawing perfluoroalkyl group, and they smoothly underwent addition reactions to carbonyl compounds and nitriles (Scheme 1). The high reactivity of perfluoroalkyl titanocene reagents is in sharp contrast to alkyl zirconocene and titanocene reagents, which did not react with these electrophiles in the absence of methylaluminoxane or silver perchlorate.[9,16] We have thus developed reactive perfluoroalkyl titanocene(III) reagents, starting from two equivalents of isopropyl Grignard reagent, titanocene dichloride, and perfluoroalkyl halides, not by oxidative addition of perfluoroalkyl halides to the widely employed titanocene(II) species but via titanocene(III) monochloride.

Several carbonyl substrates **1** including aldehydes and ketones were then investigated (Table 2). The addition to aromatic and aliphatic aldehydes of other perfluoroalkyl groups such as C_3F_7 and C_4F_9 also gave perfluoroalkylated products in 81 and 79% yield, respectively (Table 2, entries 1 and 2). Even ketone substrates such as α-tetralone and 17-keto steroid, which are problematic owing to their easily enolizable nature,[17] afforded virtually quantitative yields, much higher than those obtained with the corresponding lithium and Grignard reagents (Table 2, entries 4 and 9). α-Face-selective perfluoroalkylation leading to 17β-hydroxy steroid **2j** was confirmed by NOE correlation of 18-Me and 17-OH. Enone substrates, which show the problem of 1,2- versus 1,4-addition, chemoselectively gave 1,2-addition products in 80 and 94% yield, respectively (Table 2, entries 5 and 6).

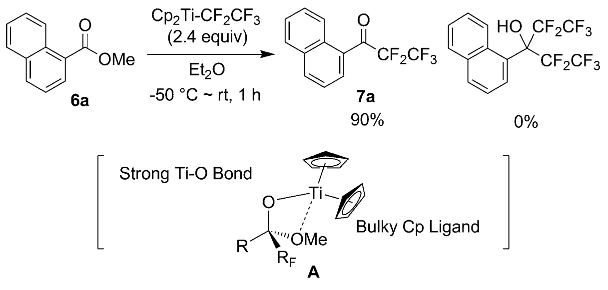
The reaction of ester **6a** with more than two equivalents of perfluoroalkyl titanocene(III) species selectively provided perfluoroalkyl ketone **7a** in high yield rather than the tertiary alcohol (Scheme 8). There has been no report, however, on the reaction of esters with alkyl or even allyl titanocene(III or IV) reagents. The specific formation of perfluoroalkyl ketones is in sharp contrast to reports by Gassman and O'Reilly on perfluoroalkyl lithium species providing ketones or tertiary alcohols, depending on the aliphatic and aromatic ester substrates em-

Table 2. Perfluoroalkylation of a variety of carbonyl compounds.



Entry	Substrate	Product	Yield [%]
1	 **1b**	 **2b**	81
2	 **1c**	 **2c**	79 (68:32)[a]
3	 **1d**	 **2d**	52
4	 **1e**	 **2e**	quant.
5	 **1f**	 **2f**	80
6	 **1g**	 **2g**	94
7	 **1h**	 **2h**	76
8	 **1i**	 **2i**	92
9	 **1j**	 **2j**	quant. (>99:1)[a]

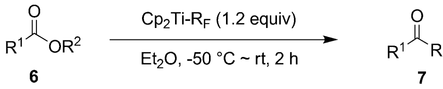
[a] Ratio of diastereomers.

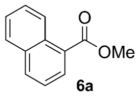
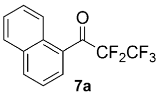
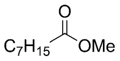
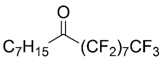
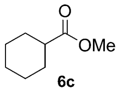
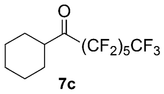
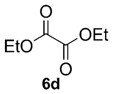
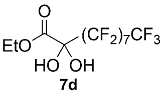
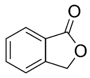
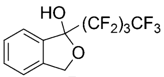
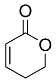
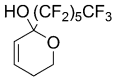


Scheme 8. Specific perfluoroalkylation of esters leading to ketones.

ployed, respectively.[7] In addition to the strong affinity of titanium for oxygen, the highly electron-withdrawing nature of the perfluoroalkyl group and steric shielding effect of the Cp ligand on titanium are the key to stabilizing the tetrahedral intermediate **A** leading eventually to perfluoroalkyl ketones such as **7a** in high yield (Scheme 8). Reactions with esters **6** smoothly proceeded to provide the corresponding perfluoroalkylated ketones **7**, irrespective of the type of ester substrate (Table 3). Aromatic and aliphatic esters led to the desired products in good to excellent yields (Table 3, entries 1–3). In addition, diethyl oxalate and lactones afforded the hydrate (Table 3, entry 4) and hemiacetals (Table 3, entries 5 and 6), respectively.

Table 3. Perfluoroalkylation of a variety of esters.



Entry	Substrate	Product	Yield [%]
1	 **6a**	 **7a**	71
2	 **6b**	 **7b**	quant.
3	 **6c**	 **7c**	80
4	 **6d**	 **7d**	69
5	 **6e**	 **7e**	90
6	 **6f**	 **7f**	69

Conclusion

We have uncovered the synthesis of perfluoroalkyltitanocene reagents, not via titanocene(II) species but via titanocene(III) monochloride. The unique reactivity and high selectivity of the perfluoroalkyltitanocene(III) reagents is highlighted by new types of perfluoroalkylation reactions of carbonyl compounds including esters and nitriles. This new and unique method can be applied for (asymmetric) trifluoromethylation, which will be reported in due course. The perfluoroalkyltitanocene(III) reagents are thus instrumental in initiating a paradigm shift in fluoroorganometal chemistry.

Experimental Section

General procedure for perfluoroalkylation of aldehydes, ketones, and esters

*i*PrMgCl (2.0 M in Et_2O, 0.24 mL, 0.48 mmol), 1,4-dioxane (46 μL, 0.54 mmol), and perfluorohexyl iodide (78 μL, 0.36 mmol) were added to a solution of $[Cp_2TiCl_2]$ (59.8 mg, 0.24 mmol) in Et_2O (2.4 mL) at −78 °C. After stirring at −50 °C for 2 h, benzaldehyde (**1a**; 20 μL, 0.20 mmol) was added and the mixture stirred at room temperature for 2 h. The mixture was quenched with 1 N HCl and extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by silica-gel column chromatography (hexane/AcOEt 20/1) to give 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-1-phenylheptan-1-ol (**2 a**) in quantitative yield (85.2 mg).

General procedure for perfluoroalkylation of nitriles

*i*PrMgCl (2.0 M in Et_2O, 0.24 mL, 0.48 mmol) and then perfluorohexyl iodide (78 μL, 0.36 mmol) were added to a solution of [Cp_2TiCl_2] (59.8 mg, 0.24 mmol) in Et_2O (2.4 mL) at −78 °C. After stirring at −50 °C for 2 h, β-phenylpropionitrile (26 μL, 0.20 mmol) was added and the mixture stirred at room temperature for 2 h. The mixture was quenched with 1 N HCl and extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by silica-gel column chromatography (hexanes) to give 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-1-phenylnonan-3-one (**5 a**) in quantitative yield (90.4 mg).

Keywords: alkylation · fluorine · metallocenes · synthetic methods · titanium

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