Insights into the Cerium Chloride-Catalyzed Grignard Addition to Esters

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Abstract: Addition of methylmagnesium chloride to ester **1** in the presence of cerium chloride gave significantly better yields of the tertiary alcohol **2** than the reaction performed in the absence of cerium chloride. The beneficial effect of added cerium chloride is postulated to be due to suppression of the enolization of the ketone intermediate. The use of properly "activated" anhydrous cerium chloride which is proposed to generate a less basic, more nucleophilic species to overcome this undesired reaction was found to be critical. The activated cerium chloride was identified as the known seven-coordinate THF solvate, $[CeCl(\mu\text{-}Cl)_2(THF)_2]_n$. Inactive crystal forms were also identified and the key parameters for formation of the active form were delineated.

Keywords: C–C bond formation; cerium; crystal forms; Grignard reaction; solvent effects

Introduction

The preparation of tertiary alcohols from esters and Grignard reagents is well known, however in certain cases undesired reactions (enolization, reduction, and condensation) compete with formation of the alcohol. We investigated the impact of cerium chloride on the yield of diol **2** (Scheme 1) as this additive is known to afford improved yields of tertiary alcohols from ketones and esters, presumably owing to the less basic nature of the active organometallic species.[1] Despite extensive efforts, the solution structure of the reagent formed from cerium chloride and Grignard reagents is still unknown. Herein, we report our observations concerning the reaction of (*S*)-hydroxy ester **1** with methyl Grignard reagents (with and without cerium chloride) as well as the implications for the successful use of this reagent.

Results and Discussion

Diol **2** is a key intermediate in the synthesis of the potent, orally active, LTD_4-specific antagonist Singulair®. The yield and quality of the diol **2** (Scheme 1) obtained from the reaction of methyl Grignard reagents with (*S*)-hydroxy ester **1**[2] is dependent on the Grignard reagent employed (Table 1). Enolization of the intermediate methyl ketone by the basic Grignard reagent arises as a competitive reaction pathway and prevents complete conversion of this intermediate to the tertiary alcohol. For example, the use of MeMgCl produces 12–20% of the methyl ketone **3**,[2a] while MeMgBr produces 8–11% and MeMgI gives only 2–5% of this undesired side product (Table 1). The precise reason for this selectivity is not clear, however, the basicity of these reagents is clearly different. The concentration, solvent, temperature, organic ligand and halide are known to affect the Schlenk equilibrium and the selectivity observed may be due to the percent of dialkyl magnesium present in each of these reagents.[3]

Although MeMgI yields the best selectivity for production of the tertiary alcohol, the use of this reagent on a large scale is hindered by the fact that it is only available in diethyl ether and due to safety concerns we preferred to use THF as the solvent. MeMgCl reagent is commercially available as a 3 M solution in THF so we pursued the use of this reagent in conjunction with cerium chloride.

During the course of our investigation into the role of cerium chloride in this reaction we made several general observations consistent with previous studies in this area, including: (a) near anhydrous cerium chloride (*ca.* 1 weight % water) is essential, (b) the method of drying the cerium chloride is important,[4] (c) the reaction in the presence of cerium chloride performs better in THF than in other ethereal solvents,[5] (d) *activation*

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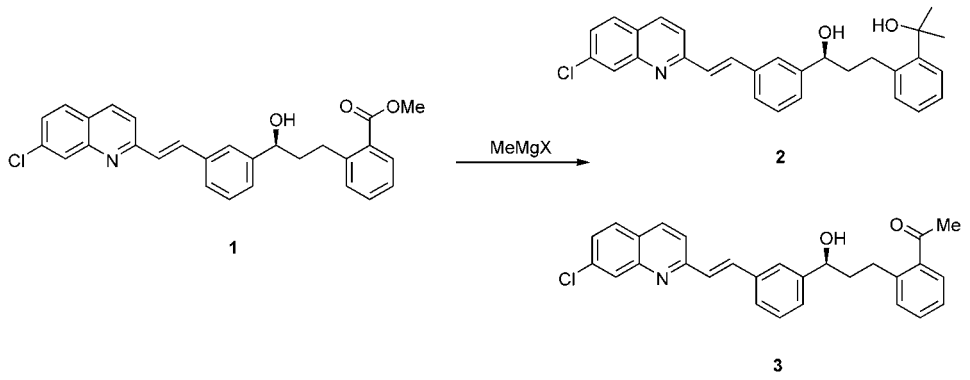

Scheme 1. Methyl Grignard addition to **1**.

Table 1. Reaction profile from various Grignard reagents.[a]

Grignard Reagent	% Conversion	% Diol **2**	% Methyl Ketone **3**
CH_3MgCl	99.5	79.3	20.2
CH_3MgBr	99.4	88.6	10.8
CH_3MgI	99.3	96.4	2.9

[a] Reaction conditions: **1** (6.6 mmol) in toluene was added to the Grignard reagent (32.8 mmol) in 1:1 diethyl ether:THF at $-10\,^{\circ}C$ and stirred at $0\,^{\circ}C$ for 2 h.

of the amorphous cerium chloride is required to achieve optimum results,[6] (e) catalytic amounts of cerium chloride give excellent results,[7] and (f) a reaction between the activated cerium chloride and the Grignard reagent generates the selective species.

Preparation of Nearly Anhydrous Cerium Chloride

Early in development, we realized that the use of nearly anhydrous cerium chloride was critical to obtaining a high yield of diol **2** in the Grignard reaction. The selectivity of the reaction with amorphous $CeCl_3$ with different water contents is shown in Table 2. Addition of cerium chloride to the reaction with MeMgCl resulted in an increase in the reaction rate and an improved yield of diol **2**. As shown in Table 2, the use of cerium chloride containing $<1\%$ water affected the desired reaction with the best selectivity.

Given these results, a procedure that reproducibly dries commercially available cerium chloride from 34% (w/w) to, $<1\%$ was required. We explored a number of options and determined that this can be accomplished using the two-step drying process that is discussed herein. Owing to the initial large amount of water, we found that it is best to begin the drying process at 90–100 °C under vacuum with a good nitrogen sweep.[8] In this manner the water content is reduced to 5–10 weight %. The temperature is then increased to 140 °C and the water content is decreased further to $<1\%$ (cerium chloride with this water level resulted in diol **2** with reduced methyl ketone impurity). The entire drying operation has been successfully demonstrated in various types of dryer systems at both laboratory and pilot plant scale.[9] Anhydrous cerium chloride is not particularly hygroscopic and can be stored for extended periods.

Table 2. Selectivity observed with amorphous $CeCl_3$ with different water contents.

H_2O wt %	% Conversion	% Diol **2**	% Methyl Ketone **3**
0.74	99.7	90.5	9.1
1.88	99.0	83.2	15.8
3.97	98.2	80.7	17.5

One potential concern was the stability of cerium chloride during the thermal dehydration. It is known that $CeCl_3$ degrades to HCl and its corresponding oxychloride product in the presence of water at elevated temperatures.[10] The elevated drying temperature can cause a reverse reaction between $CeCl_3$ and water that generates CeOCl and two equivalents of HCl. Therefore, the levels of Cl^- and Ce^{III} were monitored through a series of titration methods.[11,12] In most cases, excellent mass accountability was observed and the correct stoichiometry of metal to chloride (1:3) was calculated (see Table 3). However, there were several cases where incomplete mass balance was observed and a metal:chloride stoichiometry of less than 1:3 was observed. Solving two simultaneous equations that describe the 1:1 and 1:3 species behaviors in the titrations indicates

the presence of CeOCl. When including this species, approximately 100% of the sample mass can be accounted for (Table 3).

The possibility that Ce^{III} was being oxidized to Ce^{IV} was ruled out based on a thiosulfate titration method developed to determine the amount of I_2 present after the quantitative conversion of I^- (as KI) by Ce^{IV} as shown in Table 3. In every case, the amount of Ce^{IV} found was less than 0.5% (w/w) throughout the drying process.

Activation of Cerium Chloride

Activation of nearly anhydrous cerium chloride is crucial for the successful application of this reagent. When cerium chloride is activated under conditions of <20 mol % total water relative to $CeCl_3$ in a THF slurry, proper activation is physically observed by conversion of the grey amorphous solids to a white suspension of rod shaped crystals (Figure 1). Properly activated cerium chloride enhances the selectivity of the diol formation reaction to yield $>99\%$ diol **2** and $<1\%$ methyl ketone **3**.

Recently, the crystal structure of a THF solvate of anhydrous cerium chloride was reported to have a polymeric structure previously not identified for THF-solvated lanthanide halides.[13] In the structure, $[CeCl(\mu\text{-}Cl)_2(THF)_2]_n$, one chloride is in an axial position and the other two are in bridging positions. Single crystal X-ray crystallography of our rod-shaped cerium chloride crystals showed that their structure matches the reported structure (Figure 2). The same suspension of activated cerium chloride that produced the crystal for the X-ray study successfully provided the target selectivity ($<1\%$ **3**) in a Grignard reaction of MeMgCl with (*S*)-hydroxy ester **1**.

The incorporation of THF into the crystal structure may indicate why these reactions perform better in THF than other ethereal solvents. THF is more basic than diethyl ether and strongly coordinates to metals, especially oxophilic cerium.

Nearly anhydrous cerium chloride (<1.2 wt % water) has been successfully activated to rod-shaped crystals providing enhanced selectivity over a wide range of conditions. Proven activation conditions include isothermal age at temperatures between 30 to 67 °C for at least 2 h at concentrations between 20 to 80 g/L in sieve-dried THF with total water levels of <20 mol % relative to

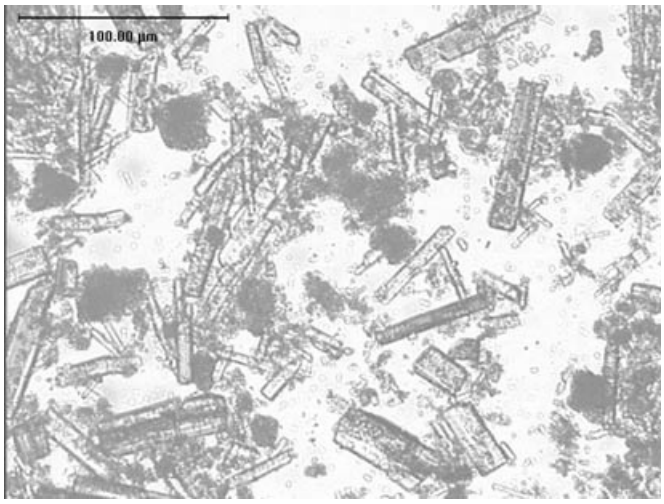

Figure 1. Microscopy of the rod form of $[CeCl(\mu\text{-}Cl)_2(THF)_2]_n$.

Figure 2. X-ray structure of the linear polymer $[CeCl(\mu\text{-}Cl)_2(THF)_2]_n$.

Table 3. Analysis of different cerium chloride samples.

	Sample No.				Theoretical Anhydrous
	1	2	3	4	
Ce(III)	57.7%	53.1%	54.7%	55.1%	56.85%
Ce(IV)	0.2%	0.3%	0.4%	0.1%	0.0%
O_2	0.0%	0.1%	0.1%	0.0%	0.0%
Cl	41.6%	39.0%	41.4%	41.9%	43.15%
KF	0.4%	7.3%	4.0%	2.5%	0.0%
TOTAL	99.9%	99.8%	100.6%	99.6%	100.0%
Ce(III)/Cl	**1.39**	**1.36**	**1.32**	**1.32**	**1.32**

cerium chloride (Table 4). *However, a portion of the total water content must come from the solvent*. Anhydrous THF has not been successfully used in the activation step. We found empirically that THF with a water content of 75–100 μg/mL reproducibly gave the desired crystal form after activation. Activation can also be accomplished *via* atmospheric or vacuum distillation, but these methods are more time consuming and solvent intensive. The activation concentration (over the 20–80 g/L range investigated) has no direct impact on the activation of cerium chloride.

During the course of this work, we have observed several inactive crystal habits of cerium chloride by microscopy, but have not been able to obtain crystals suitable for X-ray crystal analysis. With inactive (or in the absence of) cerium chloride, the reaction selectivity is reduced significantly (Table 5).

Improper activation is signified by the presence of either amorphous, tetrahedron, ovoid, rhomboid or irregular needle-shaped crystals of cerium chloride as identified by microscopy. Other solvated lanthanide trichlorides have been reported to exhibit many variations in crystal structures that may, as we have observed, have different reactivities.[12a]

Proper *versus* Improper Activation

A significant activation parameter is the total water content of the $CeCl_3$ slurry during activation. The impact of water during activation on reaction selectivity was investigated by varying the amount of water present in the cerium chloride slurry. Experiments were conducted using 0.5–1.0 molar equivalents of $CeCl_3$ and 5.0 molar equivalents of MeMgCl to substrate. Based on the experimental results presented in Table 6, the total water content should be maintained at <20 mol % water relative to $CeCl_3$ in the THF slurry in order to achieve proper activation resulting in target selectivity.

When calculated water concentrations are within the target range of <20 mol % water relative to $CeCl_3$ in the THF slurry, activation of cerium chloride can be accomplished *via* isothermal age at temperatures between 20 and 67 °C (Table 6, Entries 1–5). As the activation temperature is increased, the rate of conversion to rod-shaped crystals of cerium chloride increases. A temperature of 40 °C will provide rod-shaped crystals in *ca.* 2 h. Improperly activated crystals are formed when total water concentrations are >35 mol % water relative to $CeCl_3$ in the THF slurry and at activation temperatures between 20 and 67 °C (Table 6, Entries 6–8). We do not know the structure of the inactive crystal forms (Table 5); however, based on a study of the water concentration in the supernatant (Table 6, Entries 6 and 7) we propose that the inactive crystal form(s) are hydrates. Evidence for such hydrates has been shown by Evans et al. who reported a crystal structure for $[Ce(\mu\text{-}Cl)_2(H_2O)(THF)_2]_n$ that was formed from cerium chloride that contained water.[14] This structure contains an eight-coordinate cerium and all the chlorides are of the less reactive bridging type. Recall that the crystal structure that was shown to give the best selectivity is the seven-coordinate compound that contains the more reactive terminal chlorides (Figure 2).

Improper activation of cerium chloride can be physically observed by the transformation of amorphous cerium chloride into non-rod shaped crystals by microscopy. However, in a study to monitor the change in crystal habit during the preparation of inactive tetrahedron-shaped crystals, the rate of transformation from amorphous material into tetrahedrons was found to be slow (Table 7). These results show that improper activation

Table 4. Demonstration of cerium chloride activation.

Charge Basis of $CeCl_3$ (mol/mol Hydroxy Ester **1**)	Activation Method	Activation Concentration
1.0	Atmos. distillation (~ 67 °C)	Distill from 40 g/L to 80 g/L
1.0	Vac. Distillation (<30 °C)	Distill from 40 g/L to 80 g/L
1.0	Vac. Distillation (<30 °C)	Distill from 40 g/L to 80 g/L
0.5	Vac. Distillation (<30 °C)	Distill from 20 g/L to 40 g/L
0.5	Isothermal age at 40 °C for 2 h	80 g/L

Table 5. Selectivity of various cerium chloride habits.

Entry	Crystal Habit	% Conversion	% Diol **2**	% Methyl Ketone **3**
1	None	99.5	79.3	20.2
2	Amorphous	100.0	87.3	12.7
3	Tetrahedrons	99.9	84.9	10.8
4	Ovoids	99.9	89	10.4
5	Needles	100.0	93.9	6.1
6	Rods	100.0	99.2	0.8

Table 6. Impact of water on activation of $CeCl_3$ and methyl ketone level in reaction solution.

Entry	Mol equiv. $CeCl_3$ to Hydroxy Ester	Activation Temp. [°C]	Total Water Conc. of $CeCl_3$ in THF Slurry [μg/ml]			Calculated Water Relative to $CeCl_3$ [mol %]	% Methyl Ketone **3** Level in Reaction Solution
			Calculated conc.	Measured conc. in supernatant before activation	Measured conc. in supernatant after activation		
1	1	40	485	280	320	10.7	0.74
2	0.5	40	315	460	320	12.3	1.26
3	0.25	40	123	280	480	17.6	5.56
4	1	67	1159	959	270	19.9	0.82
5	1	40	1227	832	221	20.4	0.88
6	1	67	2037	1700	280	35.1	10.8
7	1	40	2287	1302	211	38.4	11.4
8	0.5	40	1990	–	–	74.4	18.0

Note: The effective charge of MeMgCl for all experiments was maintained at = 4.6 molar equivalents to substrate, assuming equimolar consumption of MeMgCl by water in the reaction mixture. This reduction in total Grignard does not have a significant impact on diol yield or purity.

(in cases of high water content) will not be indicated by tetrahedron formation in a typical time cycle (e.g., microscopy after a 2 h isothermal age at 40 °C).

Equivalents of Cerium Chloride

The effect of cerium chloride charges ranging from 0.25 to 3 molar equivalents to substrate was also investigated and the results are shown in Table 8. As the molar equivalents of cerium chloride decrease, so does its effectiveness in increasing selectivity in the diol formation reaction. Similar yield and selectivity was observed over the range of 0.5 to 3 molar equivalents of cerium chloride to substrate (Table 8) when either amorphous or activated cerium chloride is used. The reaction mixture remains heterogeneous throughout the reaction even with the lower levels of cerium chloride. Increasing the amount of amorphous cerium chloride did not change the selectivity. While not detrimental to the reaction, the use of 1.5 to 3 molar equivalents of cerium chloride leads to precipitation of solids during the work-up, due to high loads of cerium salts. Use of catalytic amounts of cerium chloride is ideal and simplifies the isolation process.

Dimitrov et al.[7] have reported that formation of a gel-like complex of as little as 0.05 equivalents of cerium chloride with a ketone prior to the addition of the organometallic reagent can still give excellent results. They suggested that the $Ce(OR)_3$ generated in the reaction was also acting as a catalyst for the addition. In fact, there have been reports of cerium triisopropoxide being used directly instead of the pre-catalyst, cerium chloride, in Grignard reactions.[15]

In order to gain a better understanding of why the different crystal habits gave such drastic differences in selectivity, we determined the cerium concentration at the following time points during the course of the reaction for several different crystal habits: (a) the solubility in THF, (b) the cerium concentration after the addition of the MeMgCl, and (c) at the end of the reaction (see Table 9).[16] The reaction mixture is heterogeneous throughout the reaction, even with only 0.5 equivalents of cerium chloride, so the solutions are saturated with the cerium species. One proposal that we considered

Table 7. Change in crystal habit during preparation of inactive tetrahedron-shaped cerium chloride.[a]

Age Time at 67 °C [h]	% Amorphous Material	% Rod-Shaped Crystals	% Tetrahedron-Shaped Crystals
0	100	0	0
1	50	50	0
17	40	50	10
20	20	20	60
24	20	5	75

[a] Isothermal age at 67 °C and 36.6 mol% water relative to cerium chloride, results based on microscopy.

Table 8. Effects of cerium chloride charge on level of methyl ketone in reaction solution.

Crystal Habit	Molar Equivalents of $CeCl_3$ to Substrate	Activation Conc. $CeCl_3$ in THF [g/L]	% Methyl Ketone Relative to Diol
Rods	0.25	20	5.56
Rods	0.5	40	0.5 to 1.70
Rods	0.5	80	0.7 to 1.0
Rods	1.0	80	$\leq$0.8
Rods	3.0	80	0.4
Amorphous	0.5	80	12.7
Amorphous	1.3	80	12.1

was that the different crystal habits of cerium chloride exhibited drastically different solubilities in THF and hence the amount of cerium available for the reaction varied.

We found that, regardless of the crystal form, the levels of cerium in solution are fairly consistent. However, the selectivity for these reactions is very different, generating between 0.8–12.7% of the methyl ketone **3**. *These observations indicate that a difference in the nature of the reacting species is controlling the selectivity, rather than the concentration of cerium in solution.*

Cerium–Grignard Complex

The addition of the Grignard reagent converts the crystalline cerium complex to an amorphous solid. After this addition the mixture has to be stirred for >0.5 h in order to observe the desired selectivity. The exact structure of the reactive species is unknown, however, two possible compositions are the "ate" complex $RMgX \cdot CeCl_3$ and the σ-alkyl species $RCeCl_2$ formed by transmetalation or some species generated by a Schlenk-like equilibrium from $RCeCl_2$.

Utimoto et al. described an $YbCl_3$-mediated reaction with Grignard reagents and found that the reaction time had a significant impact on the reactivity and selectivity of the reaction.[17] They proposed the rapid formation of a complex ($RMgBr \cdot YbCl_3$) that was highly reactive and gave good diastereoselectivity in their reaction. However, this complex could slowly undergo a transmetalation to give a dimer [$(RYbCl_2)_2$] that was not as reactive in their system.

In a separate study by Bartoli et al., the reaction between Grignard reagents and cerium chloride was conducted at $-78\,^{\circ}C$ where transmetalation was expected to be exceedingly slow, therefore the $RMgBr \cdot CeCl_3$ complex was proposed as the reactive species, not the organocerium species $RCeCl_2$.[18] Distinct reactive species were formed at different temperatures resulting in drastically different selectivity in two other studies with cerium chloride.[19]

In our case, the various crystal forms generate reactive species that exhibit unique selectivities in the reaction. We know that the properly activated cerium chloride is a seven-coordinate species and has terminal chlorides which are more reactive than bridging chlorides.[20] This could account for the ability of this crystal form to undergo the necessary transmetalation reaction.

Again, we do not know the structure of the inactive crystal forms and whether they contain bridging or terminal chlorides, however, based on a study of the water concentration in the supernatant (Tables 6 and 10) we propose that the inactive crystal forms most likely exist as hydrates.

When the active rod-shaped crystals are formed the water concentration in the THF supernatant increases, signifying release of bound water from cerium chloride. The converse is true for the inactive tetrahedron crystal form where the water level in THF decreases (Table 10).

Conclusion

In summary, our data have shown that properly activated cerium chloride modifies the selectivity of the meth-

Table 9. Cerium concentration over the course of the reaction.[a]

Crystal Form	Mol % Water in System	In THF Prior to Reaction	After Grignard Addition	End of Reaction	% Methyl Ketone **3**
Amorphous	54.65	19%	86%	63%	12.7
Tetrahedrons	46.94	12%	74%	53%	27.8
Rods	8.74	15%	85%	71%	0.8
Needles	14.70	19%	78%	79%	6.1

[a] Expressed in percent of the cerium charged to the reaction.

Table 10. Water content and resulting methyl ketone levels.

Crystal Form	Measured Conc. in Supernatant before Activation [ppm]	Measured Conc. in Supernatant after Activation [ppm]	% Methyl Ketone **3**
rods	89	201	1.8
tetrahedrons	1976	284	27.8

ylmagnesium chloride addition to (*S*)-hydroxy ester **1** by minimizing the formation of undesired ketone **3**. The attenuated basicity of the reagent formed in the cerium-catalyzed reaction allows it to add to substrates that are susceptible to enolization.

Despite extensive efforts, the solution structure of the reagent formed from cerium chloride and Grignard reagents is still unknown. The results of this study indicate that the nature of the reactive species is dependent on the manner in which the cerium chloride is activated and ultimately on the water content of the system. The different crystal forms observed in this study may cause either the formation of a complex with the Grignard reagent, the formation of an organocerium species *via* transmetalation or some species that results from a Schlenk-like equilibration. Our results do not indicate which of these possibilities is occurring.

We propose that a transmetalation occurs in the case of the properly activated cerium chloride and suggest that the seven-coordinate cerium with a reactive terminal chloride may be a requirement for successful transmetalation. The transmetalation may only be possible with the seven-coordinate structure that does not contain water. The reported structure for the cerium chloride crystal that contains a mole of water is eight coordinate with all less reactive bridging chlorides. In the case of the amorphous or improperly activated crystal forms the reactive species may simply be a complex between the Grignard reagent and cerium chloride [MeMgCl·$CeCl_3$] that does show some improvement in selectivity when compared to the reaction without cerium chloride (Table 5, Entries 1 and 2).[21]

In conclusion, our study has identified a cerium chloride crystal structure that leads to the enhanced selectivity reported in cerium chloride-catalyzed Grignard reactions and demonstrated that the total water content in the system during the cerium chloride activation was the critical factor controlling this useful reaction.

Experimental Section

General Methods

HPLC analyses were performed on a Hewlett Packard Series 1100 liquid chromatograph equipped with a UV detector (237 nm), and a Zorbax SB-Phenyl reverse phase analytical column (4.6 × 250 mm). The mobile phase was 0.1% TFA in acetonitrile/0.1% TFA in water and the flow rate was 2 mL/min. The HPLC yields refer to quantitative analysis of reaction mixtures using an analytically pure external standard. The area percent (LCAP) reported has been corrected for detector response. NMR spectra were recorded on Bruker AM-400 and AMX-400 spectrometers. Chemical shift references for ^{1}H spectra are residual $CHCl_3$ ($\delta = 7.27$). Chemical shift references for ^{13}C spectra are $CHCl_3$ ($\delta = 77.0$). All coupling constants are reported in hertz (Hz). Microanalysis was performed by Quantitative Technologies, Inc.

Drying of Cerium Chloride

Cerium chloride heptahydrate was dried until thermogravimeteric analysis (TGA) indicated that the total weight loss up to 275 °C was 0.5 wt % (ramp up rate of 20 °C under nitrogen). The drying operation was accomplished *via* a combination of vacuum tray drying and rotary vacuum drying, in a stepwise fashion utilizing a jacket temperature ramp up to 140 °C at a vacuum level of 50 mm Hg with a nitrogen sweep through the dryer.

In the pilot plant 299 kg of cerium chloride heptahydrate were charged into glass trays and placed in a vacuum tray dryer. Tray drying was accomplished through a stepwise heat up at a vacuum level of 50 mm Hg with a 0.5 SCFH nitrogen sweep through the dryer. The temperature ramp was 80 °C for 8 h followed by 140 °C for 35 hours. The stepwise heat up is necessary due to the significant initial water removal rate. Drying in the tray dryer was conducted until analysis of the cerium chloride showed 9.6 wt % loss up to 275 °C by TGA (2.4 wt % loss up to 160 °C and 7.2 wt % loss between 160 and 275 °C). At this point, 212 kg of partially dried cerium chloride were packaged. A total of 180 kg of the partially dried cerium chloride was then charged into a glass lined double cone type rotary dryer (32 ft^3 capacity). Rotary drying was conducted until analysis of the cerium chloride showed 0.5 wt % loss up to 275 °C by TGA. A total of 143 kg of the dried cerium chloride was packaged. Rotary drying conditions were steady at a vacuum level of 50 mm Hg, a jacket temperature of 140 °C and a rotational speed of 2 rpm. Total drying time under these conditions was 199 h. Periodic sampling and analysis during the rotary drying operation demonstrated that drying was linear at a rate of 1.1 wt % per 24 hours. Due to attrition during rotary drying, the bulk density of the cerium chloride increased from approximately 1.0 to 1.4 kg/liter.

Determination of Water in $CeCl_3$

Using a suitable volumetric titrator with Karl Fischer reagent as the titrant and pre-titrated methanol as a vessel solution,

we added *ca.* 1 g (accurately weighed) of sample and potentiometrically titrated to a single endpoint.

Determination of Rare Earth Metal in the 3+ Oxidation State in $CeCl_3$

About 250 mg of $CeCl_3$ sample were added to a clean, dry flask, 50 mL of water were added to form a thin slurry. About 20 mL of 0.2 M sodium acetate buffer (pH = 5.0) were added to dissolve the solids. Five drops of pyridine and 5 drops of xylenol orange indicator (1 mg/mL in water) were added and the light purple solution was titrated to a clear yellow endpoint with 0.05 M EDTA titrant.

Determination of Cl^- in $CeCl_3$

A standardized a solution of 0.1 N silver nitrate was prepared as described in USP or EP. About 80 mg of $CeCl_3$ were charged into a clean, dry beaker and dissolved in water. Two mL of concentrated nitric acid were added. The mixture was then titrated potentiometrically to a single endpoint using a suitable volumetric titrator with 0.1 N silver nitrate as a titrant.

Determination of Ce^{IV} in $CeCl_3$:

About 1 g $CeCl_3$ sample was charged into a clean, dry flask. Three g of KI and 5 drops of concentrated HCl were added. Then 1 g of $NaHCO_3$ was added and the mixture allowed to stand for at least 10 min protected from ambient light. One mL of starch indicator was added and the dark purple solution was titrated to a clear endpoint with 0.1 N sodium thiosulfate.

Determination of CeOCl in $CeCl_3$

Using the data from the EDTA and silver nitrate titrations, the following set of simultaneous equations was solved:

$$\frac{100 * V_{EDTA} * N_{EDTA}}{S_{EDTA}} = X + Y$$

and

$$\frac{100 * V_{AgNO_3} * N_{AgNO_3}}{S_{AgNO_3}} = 3X + Y$$

where V, N and S are the volume, normality and sample size of each titration. Calculating $246.5*X$ gives the weight percent of $CeCl_3$ in the sample and $191.58*Y$ gives the weight percent of CeOCl in the sample.

General Procedure for the Reaction with Methyl Grignard Compounds

A 125-mL jacketed flask equipped with an overhead stirrer, nitrogen inlet and thermocouple was charged with 10 mL of THF (diethyl ether for 3 M MeMgCl in THF) and 10.9 mL of 3 M Grignard reagent (32.7 mmol, MeMgBr and MeMgI are in diethyl ether). The reaction mixture was cooled to $-10\,^{\circ}C$ and an anhydrous solution of hydroxy ester 1 (3 g, 6.55 mmol) in toluene (28 mL) was added keeping the reaction temperature $<5\,^{\circ}C$. The reaction mixture was stirred for 2 h at $0\,^{\circ}C$ and an aliquot was assayed by HPLC.

[S-(*E*)-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-2-(1-hydroxy-1-methylethyl)benzenepropanol – Diol 2

A slurry of cerium chloride (2.61 g, 10.59 mmol) in dry THF (32.4 mL) was heated to $40\,^{\circ}C$ for 2 h. Microscopic examination of the slurry indicated that the amorphous solids were converted to rods/broken rods, the slurry was cooled to $-20\,^{\circ}C$, and a solution of methylmagnesium chloride (3 M in THF, 35.1 mL, 105 mmol) was added while maintaining the temperature below $5\,^{\circ}C$. After 1 h at $0\,^{\circ}C$, the reaction temperature was lowered to $-15\,^{\circ}C$ and an anhydrous solution of hydroxy ester (**1**, 9.62 g, 21 mmol) in toluene (100 mL) was added keeping the temperature $<5\,^{\circ}C$. The reaction mixture was agitated for 0.5 h after completion of the addition and then quenched by transfer into a cold ($5\,^{\circ}C$) acetic acid solution (2 M, 167 mL) keeping the temperature $<25\,^{\circ}C$. The separated organic layer was washed sequentially with 10 wt % Na_2CO_3 (167 mL) and 1 wt % Na_2CO_3 (167 mL). The separated organic layer was concentrated by vacuum distillation to a volume of 58 mL. The temperature of the solution was adjusted to $50\,^{\circ}C$ and heptane (6.1 mL) was added. The solution was seeded with crystalline diol 2 and allowed to develop a seed bed. Heptane (55 mL) was added over 4 h and then the batch was cooled to $20\,^{\circ}C$ over 3 h. Diol 2 was isolated by filtration, the filter cake was washed with 1:1 heptane:toluene (31 mL) and heptane (31 mL). The white solid was dried under vacuum at $40\,^{\circ}C$ to give the product: yield: 9.14 g (95%); ^1H NMR (250 MHz, $CDCl_3$): $\delta = 8.06–8.03$ (m, 2H), 7.69–7.56 (m, 4H), 7.50–7.10 (m, 9H), 4.68 (t, $J = 6.3$ Hz, 1H), 3.69 (bs, 1H), 3.32–3.06 (m, 2H), 2.81 (bs, 1H), 2.13 (m, 2H), 1.68 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$): $\delta = 156.88$, 148.46, 145.47, 145.15, 140.21, 136.16, 136.09, 135.46, 135.28, 131.42, 128.77, 128.67, 128.32, 128.00, 127.25, 127.01, 126.50, 126.24, 125.61, 125.56, 124.85, 119.45, 74.06, 72.82, 41.94, 32.09, 31.95, 29.64; anal. calcd. for $C_{29}H_{28}ClNO_2$: C 76.05, H 6.16; N, 3.06, Cl 7.74; found: C 76.09, H 6.22, N 3.04, Cl 7.48.

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