Ligand Effects on the Diastereoselectivities of Samarium Diiodide Promoted Pinacol Coupling

Henriette Lodberg Pedersen,[a] Torben Birk Christensen,[a] Rasmus Juel Enemærke,[a] Kim Daasbjerg,*[a] and Troels Skrydstrup*[a]

Keywords: Pinacol coupling / Aldehydes / Samarium diiodide / 1,2-Diols / Diastereoselectivity

The samarium diiodide pinacol coupling of benzaldehyde and cyclohexanecarboxaldehyde in the presence of a variety of polyethylene glycols, including derivatives containing carbohydrates has been studied. Whereas such complexing agents allow for the formation of 1,2-diols, in the case of benzaldehyde the *erythro*-isomer predominates with diastereoselectivities of up to 7:1, while with cyclohexanecarboxaldehyde a stereoselectivity of up to 10:1 was observed but in favor of the *threo*-isomer. This divergence in the stereoselectivity of these two aldehydes suggests the presence of two different mechanisms occurring in these pinacol coupling reactions.

Introduction

The intermolecular reductive coupling of ketones or aldehydes to 1,2-diol systems known as the pinacol coupling reaction may be effectively promoted by low-valent transition metals such as V, Nb, Ti, and Zr, with in general high diastereoselectivities for the *threo*-product.[1] Whereas the one-electron reducing agent, samarium diiodide, has also been extensively studied and affords high yields of the glycols, these intermolecular reactions both with aryl and alkyl aldehydes are characterized by their inability to provide for any synthetically useful stereoselectivity.[2] A few exceptions on modified substrates have been reported in the literature though. Uemura and coworkers found that SmI_2-induced pinacol coupling of tricarbonylchromium complexes of arylaldehydes afforded coupling products displaying a modest to high *threo*-selectivity depending on the substitution pattern of the aryl ring.[3] Interestingly, in the presence of HMPA, the reverse diastereomer (the *erythro*-isomer) was obtained. The same group recently reported that α-substituted ferrocenecarboxaldehydes possessing planar chirality also underwent pinacol coupling in the presence of SmI_2 with high *threo*-selectivity.[4]

With our desire to improve the diastereoselectivity of the SmI_2-induced pinacol coupling, we initiated a program to examine the effects metal ion binding ligands would have on these reactions. If a suitable ligand is successfully identified that gives a high *threo*-selectivity in these pinacol couplings, a long term goal would be to accomplish enantioselective versions of these reactions. The hard acid character of trivalent samarium, making it highly oxophilic, suggested that polyether complexes would be possible candidates for achieving this goal. Indeed, Imamoto and coworkers found that the addition of tetraethylene glycol dimethyl ether (tetraglyme) or dibenzyl ether to SmI_2 resulted in the formation of a complex which diminished unwanted pinacol couplings in Barbier-type reactions involving alkyl aldehydes.[5]

In this paper, we wish to report that the simple addition of polyether complexing agents to SmI_2 prior to the subjection of an arylaldehyde, represented by benzaldehyde, significantly increases the diastereoselectivities of this reaction, but in contrast to all other cases, the *erythro*-diol predominates. Quite remarkably, the same samarium(II) complexes also promote the pinacol coupling of an alkyl aldehyde such as cyclohexanecarboxaldehyde but in this case with high *threo*-selectivity.

Results and Discussion

Studies on the Pinacol Coupling of Benzaldehyde

In 1983, Kagan et al. reported that the addition of benzaldehyde to a THF solution of SmI_2 led to its rapid reductive coupling affording hydrobenzoin in high yield but with poor diastereoselectivity (*erythro*/*threo* = 1:1.3).[2a] We reasoned that polyetheral complexing agents could possibly influence the stereochemical outcome of this reaction by providing greater sterical bulk around the metal ion in the ketyl radical intermediate. Several crystal structures of such complexes with Sm^{III} ions have been reported.[6] The influence of other additives such as HMPA has been investigated, but in this case coupling products at the para position of the aromatic ring were mainly furnished with only 10% of the vicinal diol formed.[7] This was explained by the sterical encumbrance imposed by the coordinating HMPA molecules on the metal ion preventing the intermediate ketyl radical to undergo the normal pinacol coupling route. On the other hand, additives including TMEDA, DMF, *N*-methylpyrrolidinone, and *N*,*N*-dimethylacetamide led to product mixtures and low yields.[7]

[a] Department of Chemistry, Aarhus University,
Langelandsgade 140, 8000 Aarhus C, Denmark
Fax: (internat.) +4586196199
E-mail: ts@kemi.aau.dk

  1434−193X/99/0303−0565 $ 17.50+.50/0

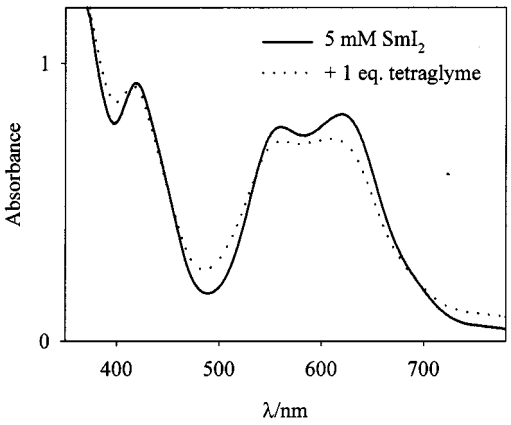
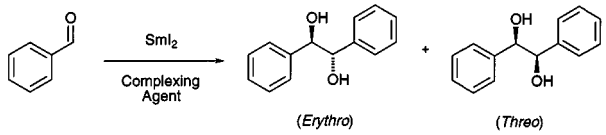


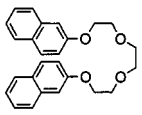
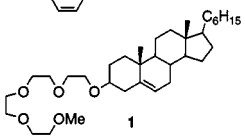
Figure 1. UV-vis spectra of SmI_2 in THF ($5 \cdot 10^{-3}$ M) alone and with 1 equiv. of tetraglyme added

In the first case, we studied the effect of tetraglyme on the pinacolization of benzaldehyde, an additive which was originally employed by Imamoto to diminish pinacol coupling byproducts in the benzyloxymethylation of alkyl aldehydes.[5] One equivalent of tetraglyme was added to the blue solution of samarium diiodide at room temperature prior to the addition of benzaldedyde. An immediate color change from blue to black with the partial precipation of a black solid occurred upon addition of the additive to the THF solution of SmI_2. Although a precipitate was not noticed by Imamato, we assume this is indeed the divalent samarium complex. The formation of the complex can be seen in the UV-vis spectrum under more diluted conditions where the complex is completely soluble (Figure 1). SmI_2 in THF shows absorbances at λ_{max} = 565 and 617 nm which correspond to the $4f^6 \rightarrow 4f^5d^1$ transition.[8] The latter is slightly shifted to a lower wavelength of λ_{max} = 609 nm upon addition of one equivalent of tetraglyme. Subjecting benzaldehyde to this mixture led to an instantaneous reaction with consumption of both the divalent samarium in solution and the precipitate. Although we were expecting some or all of the benzaldehyde to undergo dimerisation affording products similar to that observed with HMPA as an additive,[7] to our surprise only the normal pinacol coupling products were isolated in 83% yield (Table 1, entry 9). In addition, the diastereomeric ratio had risen from approx. 1:1.3 without tetraglyme *to an approx. 6:1 diastereomeric mixture*, but unlike that observed for other transition metals, the *erythro*-product was the favored isomer. Performing the reaction at −78°C had little observable effect on the reactivity of this complex, and the diastereoselectivities as those obtained at room temperature were comparable.

The addition of further equivalents of tetraglyme (Table 1, entries 10 and 11) likewise had little consequence on the yields and stereoselectivities suggesting that only one equivalent of tetraglyme complexes with the lanthanide metal ion and that under the reaction conditions no free samarium diiodide was reacting. On the other hand, addition of only a half of an equivalent of tetraglyme (entry 8) resulted in the formation of a diol with reduced diastereoselectivity.

Table 1. Ligand Effects on the SmI_2-promoted pinacol coupling of benzaldehyde



Entry	Complexing Agent	No. of equiv.	Yield	Diastereosel. (*Erythro*:*Threo*)
1	none	1	95%[a]	1:1.3
2	HMPA	2.8	10%[b]	n.d.[c]
3	Diglyme	1	85%	3.7:1
4	Diglyme	4	92%	4.8:1
5	Triglyme	1	85%	6.0:1
6	Triglyme	2	70%	6.4:1
7	Triglyme	4	n.d.	6.4:1
8	Tetraglyme	0.5	86%	3.9:1
9	Tetraglyme	1	83%	5.9:1
10	Tetraglyme	2	63%	6.4:1
11	Tetraglyme	4	n.d.	5.0:1
12	18-crown-6	1	n.d.	1:1
13		1	91%	1:1
14	 1	1	90%	6.3:1

[a] Taken from ref.[2a] – [b] Taken from ref.[7] – [c] n. d. = not determined.

To understand whether tetraglyme had any affect on the electron transferring properties of SmI_2, we examined this complex by cyclic voltammetry. The measurements were carried out with a glassy carbon electrode at 2 mM concen-

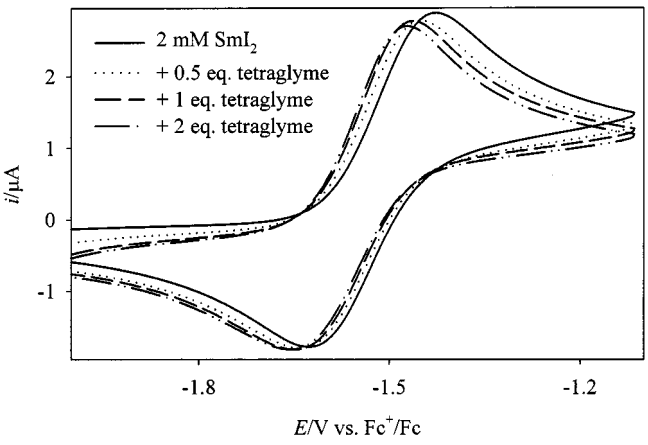


Figure 2. Cyclic voltammograms of SmI_2 recorded with 0, 0.5, 1 and 2 equivalents of tetraglyme added; $2 \cdot 10^{-3}$ M SmI_2 in THF/0.2 M nBu_4NPF_6 + 0.02 M nBu_4NI; electrode material: glassy carbon; sweep rate: 100 mV/s.

trations in THF solutions containing 0.2 M tetrabutylammonium hexafluorophosphate and 0.02 M tetrabutylammonium iodide and at a sweep rate of 100 mV/s. In Figure 2, the cyclic voltammograms of SmI_2 in THF alone and with varying equivalents of tetraglyme are shown. As can be seen from the oxidation peak, a small change occurs of −40 mV upon the addition of one equivalent of this complexing agent indicating that the reducing ability of SmI_2 is almost uneffected. That indeed this effect is small is also somewhat anticipated considering that the electron donating properties of the oxygen atoms in tetraglyme and other polyether ligands must be similar to that of the THF molecules bound to SmI_2 in the absense of tetraglyme. The change in the oxidation peak is noted 0.5 equivalents up until one equivalent of added tetraglyme, whereas further addition to two and ten equivalents (not shown in Figure 2) does not affect the voltammogram again implying that only a 1:1 complex is formed between tetraglyme and the divalent samarium species.[9]

Other simple etheral complexing agents were also investigated in the pinacol coupling of benzaldehyde as shown in Table 1. In general, the yields of the hydrobenzoin were relatively high. Triglyme (entries 5−7) proved equally effective as with tetraglyme whereas excess diglyme was necessary to afford comparable diastereosectivities (entries 3 and 4). This latter result also seems reasonable considering the fact that the known crystal structures of diglyme/Sm^{III} complexes contain two diglymes per metal ion.[6e] No increased effect could be seen from augmenting the steric bulkiness of the tetraglyme itself as with the cholesterol derivative **1** shown in entry 14 resulting in a 6.3:1 diastereoselectivity in favor of the *erythro*-isomer.

Of the six different ligands tested, two proved ineffective, namely 18-crown-6 (entry 12) and triethylene glycol di-2-naphthyl ether (entry 13). In the first case, the addition of the crown ether to the SmI_2 solution led to an instantaneous and complete precipitation of the divalent samarium as a violet solid leaving behind a clear and colorless supernatant. This complex was extremely inefficient in promoting the pinacol coupling as observed by the ^{1}H-NMR spectrum of the crude reaction mixture after 18 h, where only a trace of the hydrobenzoins were detected suggesting that the coordination sphere of the metal ion is completely saturated. This is in stark constrast to the almost instantaneous reactions observed for the other complexed SmI_2 species even at −78 °C. The almost 1:1 mixture of *erythro*- and *threo*-diols obtained suggests that it is uncomplexed samarium diiodide in equilibrium with the much more favored 18-crown-6 complex which is reacting. The crystal structure of a 18-crown-6 complex with a samarium(III) cation, namely $SmCl_3$, has been published, in which the oxygen atoms occupy equatorial positions whereas the halide atoms are apically oriented.[6d] We therefore assume that a similar disposition of the crown ether is taking place in the case of SmI_2. As the cyclic voltammetry studies also imply that polyetheral ligands do not effect greatly the redox properties of divalent samarium, we are led to the conclusion that the carbonyl substrate most likely complexes in the equatorial position of the Sm^{II} metal ion for efficient electron transfer to occur. Such a process may equally be taking place in electron transfer reactions with SmI_2 in THF alone, now assumed to possess five THF molecules encircling the metal ion in the same plane as observed in a recently published single crystal X-ray structure of this complex by Evans and collaborators.[10,11]

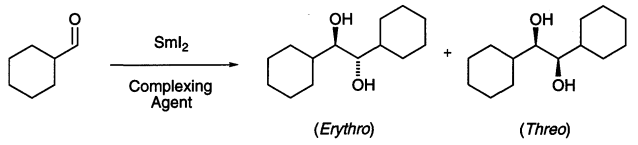
With the dinapthyl ether of triethylene glycol no diastereoselectivity was observed implying that the complex was not being formed between the ligand and SmI_2. This was confirmed by the lack of color change upon addition of the triethylene glycol derivative to the divalent samarium solution. The reduced basicity of the naphthyl ether oxygen atoms is the most probable explanation for the lack of effective coordination.

Studies on the Pinacol Coupling of Cyclohexanecarboxaldehyde

We then examined the reaction of cyclohexanecarboxaldehyde with the SmI_2/triglyme complex. Pinacol coupling reactions with this aldehyde in the presence of SmI_2 were previously reported to experience reaction times of approx. 2−4 h for completion with diastereoselectivities of 1.1:1 in favor of the *threo*-isomer which was confirmed in our laboratory.[2a,b] However, with the complexed reducing agent, the coupling reactions proceeded extremely slowly affording only a 25% yield of the vicinal diol after 72 h (Table 2, entry 2). This is direct evidence that pinacol coupling reactions with alkyl aldehydes are indeed retarded remarkably when only one equivalent of the complexing agent is added to SmI_2 prior to the addition of the carbonyl substrate. These results therefore give support to those earlier observed by Imamoto where tetraglyme was added to SmI_2-promoted Barbier reactions under the assumption that competing and unwanted pinacol coupling reactions would be retarded owing to the reduced ability of the carbonyl oxygen to coordinate to the metal ion.[5] The oxidation potential of SmI_2 appears to be only slightly affected by the addition of the polyethylene glycol derivatives suggesting that these complexing agents interfere with an inner sphere electron transfer mechanism occurring between SmI_2 and the carbonyl group. As benzaldehyde possesses a much lower LUMO energy level compared to cyclohexanecarboxyaldehyde, such rate differences with the aryl aldehyde are not so apparent.

The most remarkable feature of this coupling reaction is that although a low yield of the pinacol product was obtained, *the threo-isomer was now the preferred diastereoisomer in a ratio of 10:1*. This complete reversal of diastereoselectivity implies a possible mechanism shift between the pinacol coupling reactions of benzaldehyde and cyclohexanecarboxyaldehyde with SmI_2. Several attempts to improve the yields of the coupling product were made by changing the reduction properties of the metal ion. For example, Flowers has recently shown that the addition of excess LiCl or LiBr to SmI_2 in THF results in the formation of a much better reducing species, most likely due to halide

Table 2. Ligand Effects on the SmI_2-promoted pinacol coupling of cyclohexanecarboxaldehyde.



Entry	Complexing Agent	Yield	Diastereosel. (*Erythro*:*Threo*)
1	–	95%	1:1.1[a]
2	Triglyme (1 equiv.)	25%	1:10
3	Triglyme (1 equiv.) LiCl (10 equiv.)	60%	1:2.3
4	Triglyme (1 equiv.) LiBr (10 equiv.)	60%	1:2.3
5	Triglyme (4 equiv.) LiBr (2 equiv.)	53%	1:2.8

[a] Taken from ref.[2b]

exchange.[13,14] Whereas the addition of excess LiCl (entry 3) or LiBr (entry 4) to the SmI_2:triglyme complex prior to the addition of cyclohexanecarboxyaldehyde significantly decreased the reaction times of the coupling reaction, the diastereoselectivities were reduced to a disappointing 2.3:1 ratio, still in favor of the *threo*-isomer, compared to 10:1 without the halide exchange. It was assumed that the lithium cation may be in competition for complexation with triglyme, which was confirmed by performing an identical experiment without the presence of the triglyme giving both an identical yield of the diol and *erythro*/*threo* ratio. Reducing the number of equivalents of LiBr to two, in addition to using an access of triglyme did not change the ratio of the diastereomers significantly (entry 5). Even employing nBu$_4$NBr instead of LiBr had no significant effect as discussed below. As complexes of triglyme or tetraglyme with $SmCl_3$ are known it seems improbable that these polyethylene glycols do not coordinate to the corresponding divalent metal species. Instead it appears that the slow reaction times may be important for the high selectivity.

Studies with Polyethylene Glycol Ligands Containing Carbohydrates

With our previous fascination in the application of divalent samarium in carbohydrate chemistry,[16] we became interested in examining what effect carbohydrate-based ligands complexed with samarium diiodide would have on the diastereoselectivities of these coupling reactions. In particular, if the reaction could be biased to the *threo*-isomer, is there any chirality transfer from the sugar unit to the diol? Carbohydrates themselves are interesting candidates for the construction of polyether ligands as they exhibit an array of ethylene glycol motifs in varying restricted conformations.

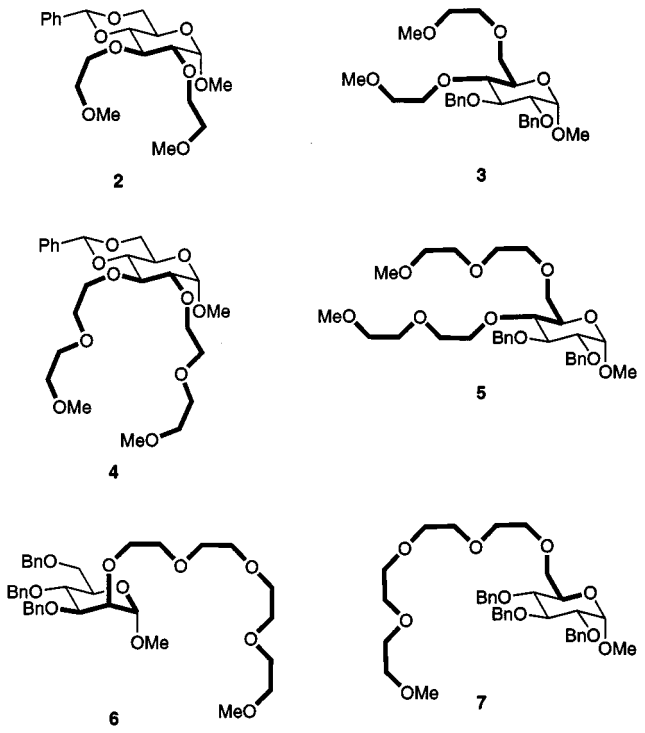


Figure 3. Various carbohydrate polyethylene glycol derivatives tested for in the SmI_2-promoted pinacol coupling

A series of glucose and mannose derivatives **2**–**7** containing polyether chains, as illustrated in Figure 3, was therefore prepared by simple alkylation of the free hydroxyl groups with the corresponding tosylates such that the sugar unit is located either in the middle or end of the polyether chain. Each carbohydrate unit was then premixed for 10 to 15 min with SmI_2 before the addition of benzaldehyde. In the case of the triglyme analogs **2** and **3** no color change was observed upon the addition of SmI_2 suggesting the possibility that a complex was not being formed at all. This was confirmed in part by the low diastereoselectivities obtained in the coupling reaction again in favor of the *erythro*-isomer, even though high yields of the hydrobenzoin were furnished (Table 3, entries 1 and 2). It is therefore apparent that the middle ethylene glycol unit of triglyme does not possess a conformational orientation around the O–C–C–O bond of approx. 60° (*gauche* conformation) for its complexation with SmI_2, nor can it be replaced by a three carbon spacer for efficient coordination to the Sm^{II} metal ion. This is somewhat surprising since the X-ray structure of the $SmCl_3$/tetraglyme complex shows exactly these *gauche* conformations for the central glycol units.[6b]

Extending the chain length to the pentaglyme analogues as in **4** and **5** improved the stereoselectivity to about equal with that observed for tetraglyme and triglyme (Table 3, entries 3 and 4). In this case too a darkening of the divalent samarium solution was seen suggesting that coordination

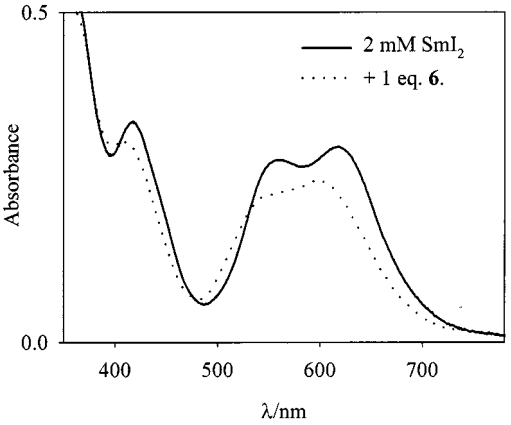


Figure 4. UV-vis spectra of SmI_2 in THF (2×10^{-3} M) alone and with 1 equivalent of **6** added

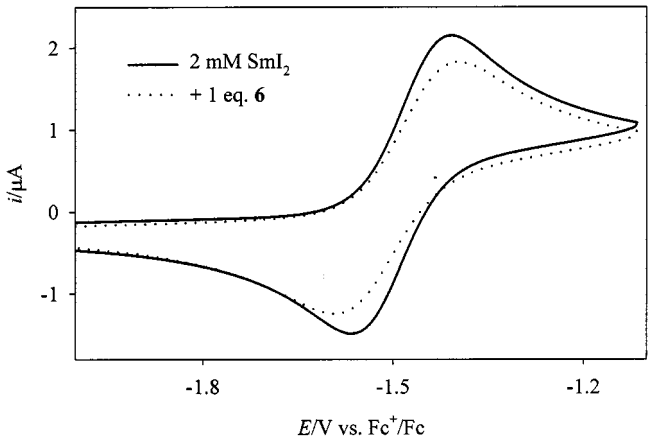
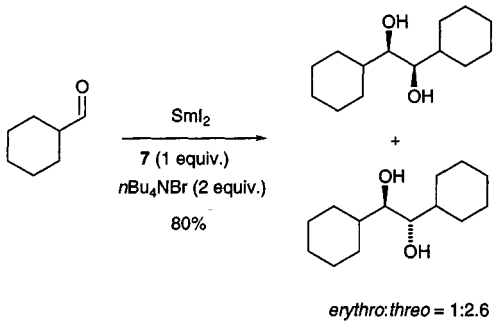


Figure 5. Cyclic voltammograms of SmI_2 recorded with 0 and 1 equivalents of **6** added; $2 \cdot 10^{-3}$ M SmI_2 in THF/0.2 M nBu_4NPF_6 + 0.02 M nBu_4NI; electrode material: glassy carbon; sweep rate: 100 mV/s.

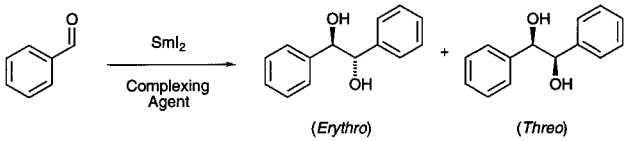
of the sugar derivative was taking place. Nevertheless, it does not appear that increasing the sterical bulkiness of the polyethylene glycol in the middle of the chain has a direct effect on the diastereoselectivity of the pinacol coupling.

Attaching a tetraglyme chain to the C2−OH position of mannose and the C6−OH position of glucose afforded other pentaglyme derivatives **6** and **7**, in which both possesses a locked *gauche* conformation at the end ethylenediol unit. Again both compounds showed signs of complexation with the darkening of the solution, although no precipitation was seen possibly owing to the much more lipophilic character of the carbohydrate protecting groups. The UV-vis spectrum of SmI_2 with one equivalent of the monosaccharide derivative **6** was similar to that of the tetraglyme complex (Figure 4), and as expected the oxidation peak in a CV scan was only slightly shifted compared to that of SmI_2 alone in THF (Figure 5). But in comparison with the above two examples only selectivites of up to 7:1 were obtained (Table 3, entries 5 and 6) which is not a substantial increase compared to the much simpler compounds, tetraglyme and triglyme. Finally, a single attempt was also made with **7** in the pinacol coupling of cyclohexanecarboxaldehyde in the presence of nBu_4NBr (2 equiv.), but again a low selectivity of 2.6:1 was obtained (Scheme 1).



Scheme 1. Pinacol coupling reaction of cyclohexanecarboxyaldehyde with the SmI_2/nBu_4NBr/**7** combination

Table 3. Effects on the SmI_2-promoted pinacol coupling of benzaldehyde with polyethylene glycol ligands containing carbohydrates

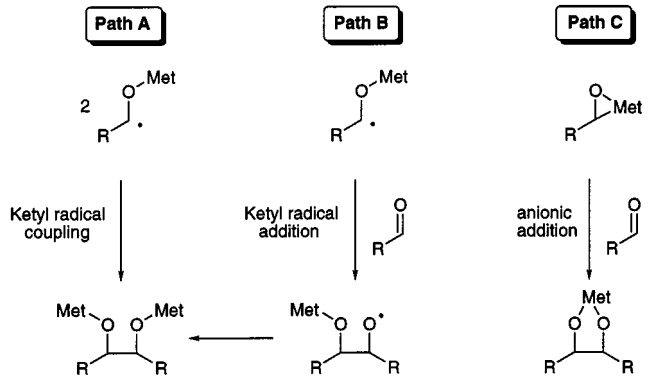


Entry	Complexing Agent	Yield	Diastereosel. (*Erythro*:*Threo*)
1	**2**	80%	2.8:1
2	**3**	80%	2.3:1
3	**4**	73%	6.5:1
4	**5**	67%	4.9:1
5	**6**	80%	7:1
6	**7**	80%	5.4:1

Mechanistic Considerations

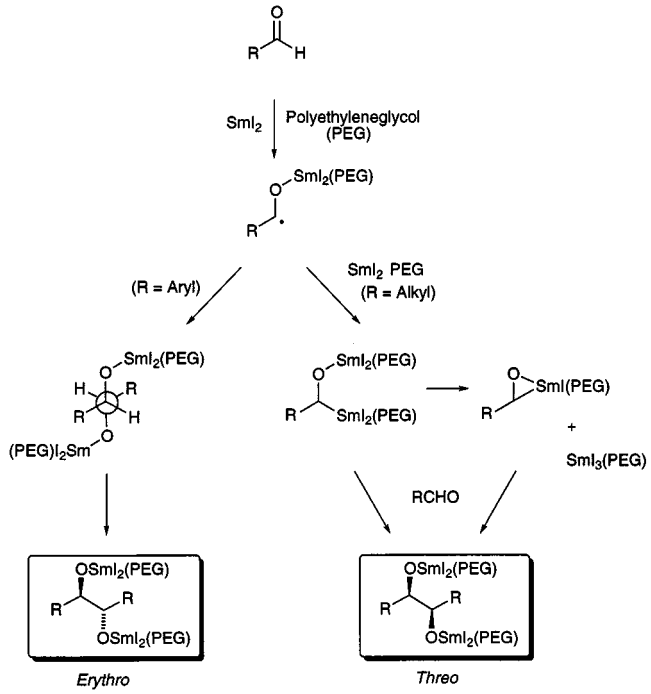
That the reaction of polyether complexes of SmI_2 between benzaldehyde and cyclohexanecarboxyaldehyde displays opposite diastereoselectivity indicates the possibility of different mechanisms taking place in these two reactions. Typical mechanisms which have previously been proposed for transition metal-promoted coupling reactions are illustrated in Scheme 2.[1] The first (path A) includes the initial one electron reduction of the carbonyl substrate and formation of a ketyl radical which then undergoes dimerisation to afford the diol. In path B, the ketyl radical adds directly to another carbonyl compound after which the oxyradical is reduced. Path C is somewhat similar but involves a two electron reduction of the carbonyl group with the formation of a metal oxirane which subsequently attacks a second carbonyl functionality.

The ketyl dimerisation mechanism is typical for intermolecular reactions involving low valent transition metals such as titanium, zirconium, and samarium.[17] However, the fast rate constants observed in 5-*exo* and 6-*exo* radical cycliza-



Scheme 2. Proposed mechanisms for the transition metal-promoted coupling pinacol reaction

tions onto aldehydes suggest that mechanism B may be more prominent in certain intramolecular pinacol coupling with these transition metals. On the other hand, metal oxirane species are observed with metals such as vanadium or niobium, which may allow for the preparation of mixed cross coupled products.[1]



Scheme 3. Mechanistic proposal for the pinacol coupling reaction induced by PEG-complexed SmI_2.

The fast reduction of benzaldehyde by SmI_2 with or without a polyethylene glycol complexing agent suggests the quick generation of a high concentration of the ketyl radical intermediate which subsequently leads to its homocoupling to afford hydrobenzoin (Scheme 3). The addition of complexing agents to the THF solution of divalent samarium increases the steric bulkiness of the metal ion and hindering the formation of any intermediates where a single metal ion is coordinated to both ketyl oxygen atoms. This is supported by the recent results of Uemura, where the addition of HMPA in the SmI_2-induced pinacol coupling of $(CO)_3Cr-ArCHO$ complexes shifts the selectivity from *threo* to *erythro*.[3] The lack of improved selectivities employing the cholesterol or carbohydrate derivatives is nevertheless puzzling as we assumed that increasing the steric bulk in the SmI_2-complex should potentially improve upon the diastereoselectivities.

In the case of the alkyl aldehyde, the slow reaction rates (from hours to days) in the one-electron transfer from SmI_2 to the carbonyl group implies that the concentration of the ketyl radical must be relatively low. It therefore seems improbable that ketyl radical coupling is a major pathway in the generation of the 1,2-diol. Instead ketyl radical addition to the carbonyl substrate or initial reduction of the ketyl radical to its dianion could dominant in these type of reaction (Scheme 3), although whether one or a combination of the two mechanisms is occurring is difficult to say from these preliminary studies.

We are now currently investigating the generality of these samarium diiodide-promoted pinacol coupling reactions as well as other ligands and their effect on the stereoselectivity. These results will be reported in due course

Experimental Section

General: Unless otherwise stated, all reactions were carried out under argon. THF was dried and freshly distilled over sodium/benzophenone. – NMR: Varian Gemini 200 (200 MHz and 50 MHz, for ^1H and ^{13}C, respectively). For ^1H NMR, $CDCl_3$ as solvent, TMS as internal standard, coupling constants are measured in Hz. Samarium diiodide was prepared according to the literature.[18]

Analytical electrochemical experiments were conducted in a standard electrochemical cell equipped with a working electrode made of glassy carbon and having a diameter of 1 mm, a reference electrode and a counter electrode made of platinum. The reference electrode consisted of a silver wire in 0.2 M nBu_4NPF_6 + 0.02 M nBu_4NI/THF. The signals from a home-built potentiostat were recorded using a Nicolet 4094c/4570 digital oscilloscope and the equipment was controlled by means of a PC. The relevant potentials were referred to the ferrocenium/ferrocene redox pair (Fc^+/Fc) with an estimated uncertainty of ± 5 mV. UV-vis spectra were recorded using a dip probe system from Ocean Optics. The system consisted of a fiber-optic spectrophotometer (S 1000) equipped with a transmission dip probe with a path length of 2.8 mm.

General Procedure for the Preparation of the Polyethylene Glycols 1–7: NaH (1.5 equiv./alcohol) was added to a solution of the alcohol in DMF (concentration of approx. 0.1 M) at 0°C. After stirring for 15 min at this temperature, the tosylate of the polyethylene glycol monomethyl ether (1.5 equiv./alcohol) was added, after which the mixture was heated to 95°C for 5 to 15 days depending on the rate of alkylation. The reaction mixture was then cooled to room temperature and a few drops of MeOH were added to neutralise the excess NaH. Ether and water were added, and the organic phase was washed three times with water, dried (Na_2SO_4) and evaporated to dryness in vacuo. Flash chromatography provided the modified polyethylene glycols.

***O*-(11-Methoxy)-3,6,9-trioxaundecylcholesterol (1):** Reaction time (18 h), flash chromatography (pentane/ethyl acetate, 2:1), yield (18%), $[\alpha]_D^{20}$ −21.4 (*c* 1.0, CH_2Cl_2). – IR (film): $\tilde{\nu}$ = 2935 cm^{-1}, 1467, 1380, 1253, 1199, 1110, 958. – ^1H NMR ($CDCl_3$): δ = 0.67 (s, 3 H, CH_3), 0.85 (s, 3 H, CH_3), 0.88 (s, 6 H, 2 × CH_3), 0.99 (s,

3 H, CH_3), 0.82−1.04 (m, 6 H), 1.74−2.43 (m, 20 H), 3.19 (m, 1 H, OCH), 3.38 (s, 3 H, OCH_3), 3.52−3.69 (m, 16 H, 8× CH_2), 5.34 (d, J = 5.2, 1 H, C=CH). − ^{13}C NMR ($CDCl_3$): δ = 11.9, 18.7, 19.4, 21.1, 22.6, 22.8, 23.8, 24.3, 28.0, 28.3, 28.4, 31.9, 35.8, 36.2, 36.9, 37.2, 39.1, 39.5, 39.8, 42.3, 50.2, 56.2, 56.8, 59.1, 67.3, 70.0, 70.9, 71.9, 79.5, 121.6, 141.0.

Methyl 4,6-*O*-Benzylidene-2,3-di-*O*-(2-methoxyethyl)-α-D-glucopyranoside (2): Reaction time (5 days), flash chromatography (CH_2Cl_2/acetone, 9:1), yield (54%), $[\alpha]_D^{20}$ +59.5 (*c* 1.1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2926 cm^{-1}, 1458, 1366, 1089, 1056. − ^{1}H NMR ($CDCl_3$): δ = 3.30 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 3.44−4.02 (m, 13 H, 4× CH_2O, H2, H3, H4, H6a, H6b), 4.26 (m, 1 H, H5), 4.83 (d, J = 3.5, 1 H, H1), 5.53 (s, 1 H, PhCH), 7.28−7.41 (m, 3 H, Ph), 7.42−7.54 (m, 2 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 55.8, 59.2, 59.4, 62.8, 69.6, 71.9, 72.6, 72.7, 72.8, 79.7, 81.1, 82.2, 99.6, 101.7, 126.5, 128.7, 128.7, 129.4, 137.9.

Methyl 2,3-Di-*O*-benzyl-4,6-di-*O*-(2-methoxyethyl)-α-D-glucopyranoside (3): Reaction time (7 days), flash chromatography (CH_2Cl_2/acetone, 50:3), yield (61%), $[\alpha]_D^{20}$ +52.0 (*c* 1.3, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2926 cm^{-1}, 1497, 1455, 1198, 1093, 1052. − ^{1}H NMR ($CDCl_3$): δ = 3.33 (s, 6 H, 2 × OCH_3), 3.34 (s, 3 H, OCH_3), 3.37−3.81 (m, 12 H, 4× CH_2O, H2, H4, H6a, H6b), 3.91 (dd, J = 9.5, 9.5, 1 H, H3), 3.95 (ddd, J = 11.0, 4.6, 4.6, 1 H, H5), 4.56 (d, J = 3.8, 1 H, H1), 4.62 (d, J = 12.2, 1 H, CHPh), 4.77 (d, J = 12.2, 1 H, CHPh), 4.83 (d, J = 10.6, 1 H, CHPh), 4.92 (d, J = 10.6, 1 H, CHPh), 7.21−7.41 (m, 10 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 54.9, 58.8, 69.4, 69.8, 70.5, 71.7, 71.9, 72.0, 73.2, 75.4, 78.0, 79.4, 81.6, 98.0, 127.3, 127.7, 127.8, 127.9, 128.1, 128.2, 138.0, 138.8.

Methyl 4,6-*O*-Benzylidene-2,3-di-*O*-(5-methoxy-3-oxapentyl)-α-D-glucopyranoside (4): Reaction time (7 days), flash chromatography (CH_2Cl_2/acetone, 15:2), yield (58%), $[\alpha]_D^{20}$ +39.3 (*c* 1.2, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2875 cm^{-1}, 1456, 1374, 1246, 1092, 992. − ^{1}H NMR ($CDCl_3$): δ = 3.27 (s, 3 H, OCH_3), 3.33 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.36−4.00 (m, 21 H, 8× CH_2O, H2, H3, H4, H6a, H6b), 4.22 (m, 1 H, H5), 4.80 (d, J = 3.5, 1 H, H1), 5.47 (s, 1 H, PhCH), 7.28−7.40 (m, 3 H, Ph), 7.42−7.56 (m, 2 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 55.0, 58.7, 58.8, 62.1, 68.9, 70.0, 70.3, 70.4, 70.7, 71.2, 71.6, 71.7, 72.0, 78.8, 80.5, 81.5, 98.9, 101.1, 125.9, 127.9, 128.7, 137.2.

Methyl 2,3-Di-*O*-benzyl-4,6-di-*O*-(5-methoxy-3-oxapentyl)-α-D-glucopyranoside (5): Reaction time (15 days), flash chromatography (CH_2Cl_2/acetone, 5:1), yield (56%), $[\alpha]_D^{20}$ +43.1 (*c* 1.2, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2877 cm^{-1}, 1497, 1455, 1354, 1246, 1198, 1097. − ^{1}H NMR ($CDCl_3$): δ = 3.29 (s, 3 H, OCH_3), 3.30 (s, 6 H, 2× OCH_3), 3.32−3.78 (m, 20 H, 8× CH_2O, H2, H4, H6a, H6b), 3.86 (dd, J = 9.4, 9.4, 1 H, H3), 3.89 (ddd, J = 10.8, 4.6, 4.6, 1 H, H5), 4.52 (d, J = 3.6, 1 H, H1), 4.58 (d, J = 12.0, 1 H, CHPh), 4.73 (d, J = 12.0, 1 H, CHPh), 4.79 (d, J = 11.0, 1 H, CHPh), 4.87 (d, J = 11.0, 1 H, CHPh), 7.18−7.39 (m, 10 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 54.9, 58.8, 69.4, 69.9, 70.3, 70.4, 70.6, 71.8, 72.0, 73.2, 75.4, 78.0, 79.4, 81.6, 98.0, 127.3, 127.7, 127.8, 127.9, 128.1, 128.2, 138.0, 138.7.

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-(11-methoxy-3,6,9-trioxaundecyl)-α-D-mannopyranoside (6): Reaction time (14 days), flash chromatography (pentane/EtOAc, 1:10), yield (83%), $[\alpha]_D^{20}$ +22.9 (*c* 1.2, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2872 cm^{-1}, 1497, 1454, 1363, 1199, 1108. − ^{1}H NMR ($CDCl_3$): δ = 3.38 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 3.52−3.98 (m, 21 H, 8× CH_2O, H2, H4, H5, H6a, H6b), 4.51 (d, J = 11.3, 1 H, CHPh), 4.62 (d, J = 11.3, 1 H, CHPh), 4.68 (d, J = 11.3, 1 H, CHPh), 4.68 (d, J = 12.2, 1 H, CHPh), 4.76 (d, J = 12.2, 1 H, CHPh), 4.83 (d, J = 1.8, 1 H, H1), 4.88 (d, J = 11.3, 1 H, CHPh), 7.14−7.44 (m, 15 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 54.5, 58.8, 69.1, 70.3, 70.4, 70.5, 70.7, 70.8, 71.3, 71.7, 71.8, 73.1, 74.6, 74.8, 76.3, 79.9, 99.0, 127.2, 127.3, 127.4, 127.5, 127.7, 128.1, 128.2, 138.3.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(11-methoxy-3,6,9-trioxaundecyl)-α-D-glucopyranoside (7): Reaction time (4 days), flash chromatography (pentane/EtOAc, 3:20), yield (81%), $[\alpha]_D^{20}$ +40.8 (*c* 1.2, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2875 cm^{-1}, 1497, 1455, 1359, 1195, 1109. − ^{1}H NMR ($CDCl_3$): δ = 3.31 (s, 6 H, 2× OCH_3), 3.43−3.73 (m, 21 H, 8× CH_2O, H2, H4, H5, H6a, H6b), 3.93 (dd, J = 9.6, 8.5, 1 H, H_3), 4.55 (d, J = 3.5, 1 H, H1), 4.59 (d, J = 11.1, 1 H, CHPh), 4.60 (d, J = 12.0, 1 H, CHPh), 4.74 (d, J = 12.0, 1 H, CHPh), 4.77 (d, J = 11.2, 1 H, CHPh), 4.81 (d, J = 11.1, 1 H, CHPh), 4.92 (d, J = 11.2, 1 H, CHPh), 7.15−7.35 (m, 15 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 55.2, 59.0, 69.7, 70.0, 70.4, 70.6, 70.9, 71.9, 73.4, 75.0, 75.8, 77.6, 79.8, 82.1, 98.2, 127.5, 127.7, 127.8, 127.9, 128.1, 128.4, 138.1, 138.4, 138.8.

General Procedure for Performing the Pinacol Coupling Reactions with Benzaldehyde: For reactions involving diglyme, triglyme or tetraglyme, these (0.4 mmol for 1 equivalent) were added to a stirred 0.1 M solution of SmI_2 in THF (4 mL, 0.4 mmol), and the mixture was allowed to stir for 10 min. With the other polyethylene glycols, the SmI_2 solution was added directly to an argon flushed flask containing these complexing agents (0.4 mmol) followed by stirring for 10 to 15 min. Thereafter benzaldehyde (33 μL, 0.3 mmol) was added and the mixture was stirred for 5 min and then quenched with aqueous NH_4Cl (sat.). CH_2Cl_2 was added and the organic phase was washed with water (2 times), dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (pentane/EtOAc, 3:1) afforded the benzohydroin (for yields, see Table 1 and 3). With **6** as the complexing agent, the flash chromatography was performed in CH_2Cl_2/diethyl ether (10:1) as this compound comigrated with the hydrobenzoin employing the standard eluent. Characteristic signals for the *erythro*-isomer in the ^{1}H-NMR spectrum: δ = 4.84 (s, 2 H, 2× CHPh); for the *threo*-isomer δ = 4.71 (s, 2 H, 2× CHPh).[17e]

The Pinacol Coupling Reaction with Cyclohexanecarboxaldehyde in the Presence of Triglyme: Triglyme (72 μL, 0.40 mmol) was added to a 0.1 M solution of SmI_2 in THF (4.0 mL, 0.40 mmol). After stirring for 15 min at 20°C, cyclohexanecarboxaldehyde (36 μL, 0.30 mmol) was added, and the reaction mixture was allowed to stir for 72 h. Aqueous NH_4Cl (sat.). was added followed by CH_2Cl_2, and the organic phase was washed with water (2 times), dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography (pentane/EtOAc, 5:1) afforded the diol (8 mg, 25%) as a 10:1 mixture of *threo*- and *erythro*-isomer, respectively. Characteristic signals for the *threo*-isomer in the ^{1}H NMR spectrum: δ = 3.33 (d, J = 6.0, 2 H, 2× OCH); for the *erythro*-isomer δ = 3.43 (dd, J = 2.4, 1.0, 2 H, 2× OCH).[2b]

The Pinacol Coupling Reaction with Cyclohexanecarboxaldehyde in the Presence of 7: To an argon flushed flask containing compound **7** (266 mg, 0.41 mmol) and nBu$_4$NBr (260 mg, 0.81 mmol) was added a 0.1 M solution of SmI_2 in THF (4 mL, 0.4 mmol). The dark violet solution was stirred for 15 min at 20°C, after which cyclohexanecarboxaldehyde (40 μL, 0.33 mmol) was added, and the solution was left stirring for 6 h. Aqueous NH_4Cl (sat.). was added followed by CH_2Cl_2, and the organic phase was washed with water (2 times), dried (Na_2SO_4) and evaporated in vacuo. Flash chromatography (pentane/EtOAc, 5:1) afforded the diol (29 mg, 77%) as a 2.6:1 mixture of *threo*- and *erythro*-isomer, respectively.

Acknowledgments

We thank the Danish National Science Foundation and Aarhus University for financial support and Lisbeth Andersen for technical assistance.

[1] For several reviews on the pinacol coupling: [1a] T. Wirth, *Angew. Chem.* **1996**, *108*, 65; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61. – [1b] R. G. Dushin, in *Comprehensive Organometallic Chemistry II* (Ed.: L. S. Hegedus), Pergamon, Oxford, **1995**, vol. 12, p. 1071. – [1c] A. Fürstner, *Angew. Chem.* **1993**, *105*, 171; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164. – [1d] G. M. Robertson, in *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon, New York, **1991**, vol. 3, p. 563. – [1e] J. E. McMurray, *Chem. Rev.* **1989**, *89*, 1513. – [1f] B. E. Kahn, R. D. Rieke, *Chem. Rev.* **1988**, *88*, 733.

[2] [2a] J. L. Namy, J. Souppe, H. B. Kagan, *Tetrahedron Lett.* **1983**, *24*, 765. – [2b] J. Souppe, L. Danon, J. L. Namy, H. B. Kagan, *J. Organomet. Chem.* **1983**, *250*, 227. – [2c] T. Honda, M. Katoh, *Chem. Commun.* **1997**, 369. – [2d] R. Nomura, T. Matsuno, T. Endo, *J. Am. Chem. Soc.* **1996**, *118*, 11666. – [2e] N. Miyoshi, S. Takeuchi, Y. Ohgo, *Chem. Lett.* **1993**, 2129.

[3] N. Taniguchi, N. Kaneta, M. Uemura, *J. Org. Chem.* **1996**, *61*, 6088.

[4] N. Taniguchi, M. Uemura, *Tetrahedron Lett.* **1998**, *39*, 5385.

[5] [5a] T. Imamoto, T. Takeyama, M. Yokoyama, *Tetrahedron Lett.* **1984**, 25, 3225. – [5b] T. Imamoto, T. Hatajima, N. Takiyama, T. Takeyama, Y. Kamiya, T. Yoshizawa, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3127.

[6] [6a] R. D. Rogers, R. D. Etzenhouser, J. S. Murdoch, *Inorganica Chimica Acta* **1992**, *196*, 73. – [6b] R. D. Rogers, R. D. Etzenhouser, J. S. Murdoch, E. Reyes, *Inorg. Chem.* **1991**, *30*, 1445. – [6c] R. D. Rogers, A. N. Rollins, M. M. Benning, *Inorg. Chem.* **1988**, *27*, 3826. – [6d] R. D. Rogers, L. K. Kurihara, *Inorg. Chem.* **1987**, *26*, 1498. – [6e] A. Sen, V. Chebolu, A. L. Rheingold, *Inorg. Chem.* **1987**, *26*, 1821.

[7] J.-S. Shiue, C.-C. Lin, J.-M. Fang, *Tetrahedron Lett.* **1993**, *34*, 335.

[8] [8a] D. F. Evans, G. V. Fazakerley, R. F. Phillips, *J. Chem. Soc. A* **1971**, 1931. – [8b] J. L. Namy, P. Girard, H. B. Kagan, P. Caro, *Nouv. J. Chim.* **1981**, *5*, 479. – [8c] Y. Okaue, T. Isobe, *Inorg. Chem. Acta* **1988**, *144*, 143.

[9] Rodgers *et al.* have reported the crystal structure of a $SmCl_3$:tetraglyme complex prepared by the addition of one equivalent of tetraglyme to the hydrate of $SmCl_3$ in water (ref.[6b]). In this structure, the oxygen atoms of tetraglyme are all nearly coplanar and lie in the equatorial plane of the complex.

[10] W. J. Evans, T. S. Gummersheimer, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *119*, 8999.

[11] Hou et al. have recently crystallized the ketyl radical complex obtained in the reaction of a samarium(II) aryloxide of 2,6-di-*tert*-butyl-4-methylphenol and fluorenone (ref.[12]) The sterically hindered aryloxide groups only allow the coordination of two THF molecules, hence making it difficult to make a comparison of our results with those of Hou et al.

[12] Z. Hou, T. Miyano, H. Yamazaki, Y. Wakatsuki, *J. Am. Chem. Soc.* **1995**, *117*, 4421.

[13] J. R. Fuchs, M. L. Mitchell, M. Shabangi, R. A. Flowers II, *Tetrahedron Lett.* **1997**, *38*, 8175.

[14] $SmBr_2$ has been shown to be a more potent reducing agent than SmI_2 (ref.[15]).

[15] A. Lebrun, J. L. Namy, H. B. Kagan, *Tetrahedron Lett.* **1993**, *34*, 2311.

[16] [16a] O. Jarreton, T. Skrydstrup, J.-M. Beau, *Chem. Commun.* **1996**, 1661. – [16b] T. Skrydstrup, O. Jarreton, D. Mazéas, D. Urban, J.-M. Beau, *Chem. Eur. J.* **1998**, *4*, 655. – [16c] D. Urban, T. Skrydstrup, J.-M. Beau, *J. Org. Chem.* **1998**, *63*, 2507. – [16d] T. Skrydstrup, D. Mazéas, M. Elmouchir, G. Doisneau, C. Riche, A. Chiaroni, J.-M. Beau, *Chem. Eur. J.* **1997**, *8*, 1342. – [16e] D. Urban, T. Skrydstrup, J.-M. Beau, *Chem. Commun.* **1998**, 955.

[17] See reference[1] and the following references: [17a] M. C. Barden, J. Schwartz, *J. Am. Chem. Soc.* **1996**, *118*, 5484. – [17b] A. Gansäuer, *Chem. Commun.* **1997**, 457. – [17c] T. A. Lipski, M. A. Hilfiker, S. G. Nelson, *J. Org. Chem.* **1997**, *62*, 4566. – [17d] T. Harao, B. Hatano, M. Asahara, Y. Muguruma, A. Ogawa, *Tetrahedron Lett.* **1998**, *39*, 5247. – [17e] M. C. Barden, J. Schwartz, *J. Org. Chem.* **1997**, *62*, 7520. – [17f] A. Gansäuer, M. Moschioni, D. Bauer, *Eur. J. Org. Chem.* **1998**, 1923.

[18] J. L. Namy, P. Girard, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693.

Received September 25, 1998
[O98436]