Preparation and Reactions of (Alkaneimidoyl)lanthanides

Hajime Ito

1996

Preface

The studies presented in this thesis have been carried out under the direction of Professor Yoshihiko Ito at Kyoto University during 1991-1996. The studies are concerned with the preparation and reactions of (alkaneimidoyl)lanthanides.

The author wishes to express his sincerest gratitude to Professor Yoshihiko Ito for his kind guidance and valuable suggestions throughout this work. The author is deeply grateful to Professor Masahiro Murakami for his constant advice and valuable discussions during the course of this work. The author is also indebted to Professor Kohei Tamao and Dr. Masaya Sawamura for their helpful suggestions and discussions. Thanks are due to Dr. Eiji Ihara, Dr. Michinori Suginome, Messrs. Teiji Kawano, Miunoru Hayashi, Hideki Amii, Hideaki Oike, Ichiro Komoto, Hideyuki Oyama, Kenichiro Itami, Hiroshi Miyazoe, Miss Sanae Mine, and other members of Prof. Ito's research group for their active collaborations. The author wishes to thank to Mr. Haruo Fujita for the mesurement of 400MHz NMR spectra, Mr. Tadao Kobatake for the measurement of Mass spectra.

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Contents

General Introduction

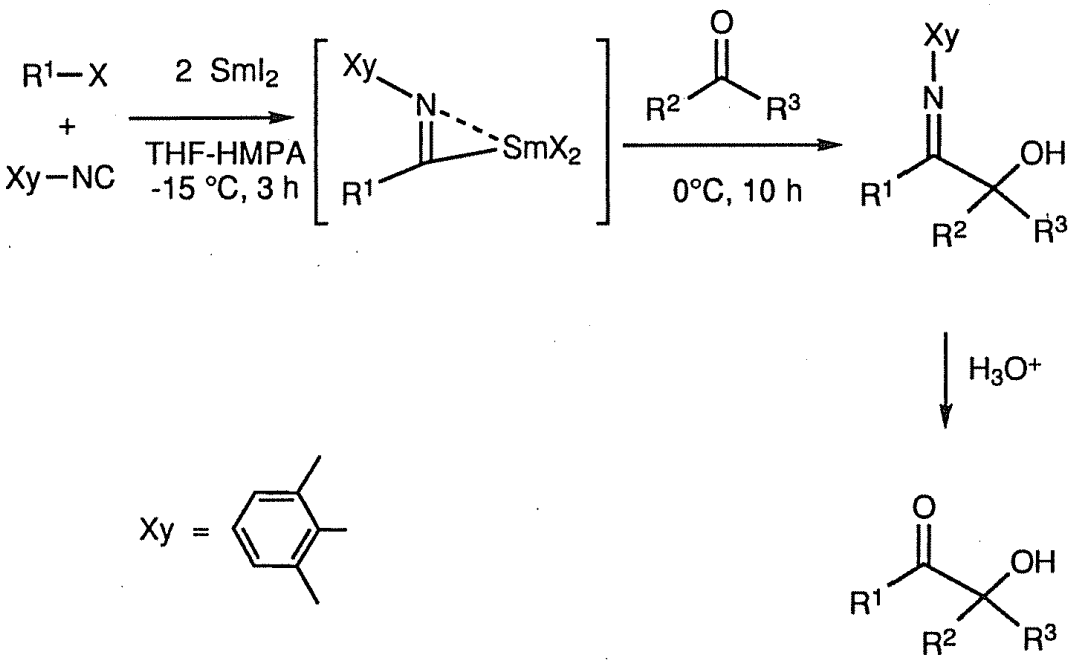
Organic synthesis has developed dramatically for the several decades. The new synthetic methodologies contributed significantly to satisfying the basic needs for materials.[1] Recent progress of organic synthesis make numerous useful reactions available for complex natural compounds which had hardly been synthesized in the past. Total synthesis of biologically active compounds has been a major part of application of synthetic chemistry to life science. As a result creative chemical approaches based on the use of synthetic organic chemistry to produce new molecule for study can increasingly contribute to a sophisticated understanding of how molecules function. In this trend, there are great demands for more effective reactions for synthesis of molecules that are powerful tools to understand complexity of life.[2]

Application of lanthanide reagents to organic synthesis is currently one of the most rapidly developing areas of synthetic chemistry.[3] A great number of synthetic reactions have been explored by the use of lanthanides reagents, and some of them have become indispensable protocols in modern organic synthesis. The lanthanide are the 15 elements that belong to the third group and sixth period in the periodic table. These elements are generally called f-block elements or inner transition elements, since (with the exception of lanthanum) they possess 4f electrons. Lanthanide elements exhibit unique physical and chemical properties which differ from those of main group elements and d-block transition elements. Numerous synthetic reactions and new methodologies have been explored by utilizing the characteristic properties of lanthanides. Extensive use of lanthanide elements were initiated only after the pioneering work by Kagan and Luche[3a-c)].

Some of them are superior to existing methods, and are the method of choice in synthesis. One of the most significant developments in this field over last decade has been the emergence of Sm(II) iodide as a powerful, yet selective, reducing agent. Another important applications of lanthanide reagents to synthetic organic chemistry is the use of organocerium reagent in carbonyl addition reaction to highly enolizable substrate.

The purpose of this thesis is to describe the studies that are concerned with the new investigation of preparations and reactions of (alkaneimidoyl)lanthanide(III) and to show that this reagent is a powerful tools for synthesis of molecules that are useful to the investigation of material science as well as life science. (Alkaneimidoyl)lanthanide(III) employed in this study is a novel three component coupling intermediate which is in situ generated with high selectivities and good yields by a novel three component coupling reaction. This thesis also describes its applications to the total synthesis of natural and ^{13}C labeled unnatural compounds which may be useful probes for understanding biochemical events.

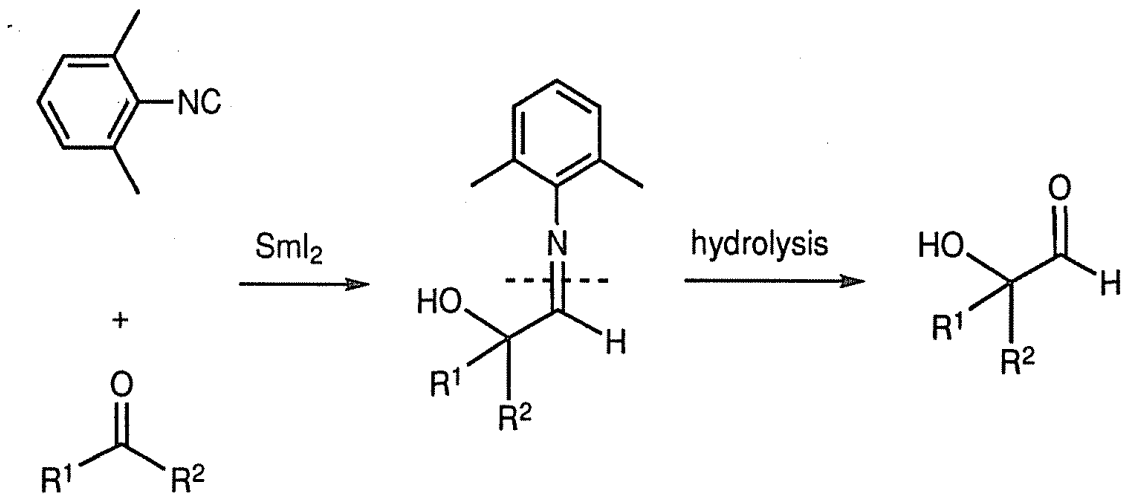
Scheme 1.



The first report of synthetic utility of (alkaneimidoyl)samarium(III) was published in 1990 by Ito's group.[4] A new synthetic access to α-hydroxy ketones by samarium(II) iodide-mediated three-component coupling of organic halides, an isocyanide, and carbonyl compounds was disclosed in the report. It is noted that the mild reaction conditions for the three component coupling may tolerate various functional groups including terminal acetylenes and trimethylsilyl ethers (Scheme 1.) .

Chapter 1 describes a new generation of (α-hydroxyalkaneimidoyl) samarium(III) species by samarium(II) iodide-mediated coupling reaction of carbonyl compounds and isocyanide and a synthetic application for preparation of α-hydroxy aldehyde. An (α-hydroxy alkaneimidoyl)samarium(III) species is generated *in situ* by treatment of a carbonyl compound with two equivalents of samarium(II) iodide in the presence of 2,6-xylyl isocyanide. Subsequent treatment of water affords α-hydroxy imines, which are converted by acid-catalyzed hydrolysis to the corresponding α-hydroxy aldehydes (Scheme 2.) .

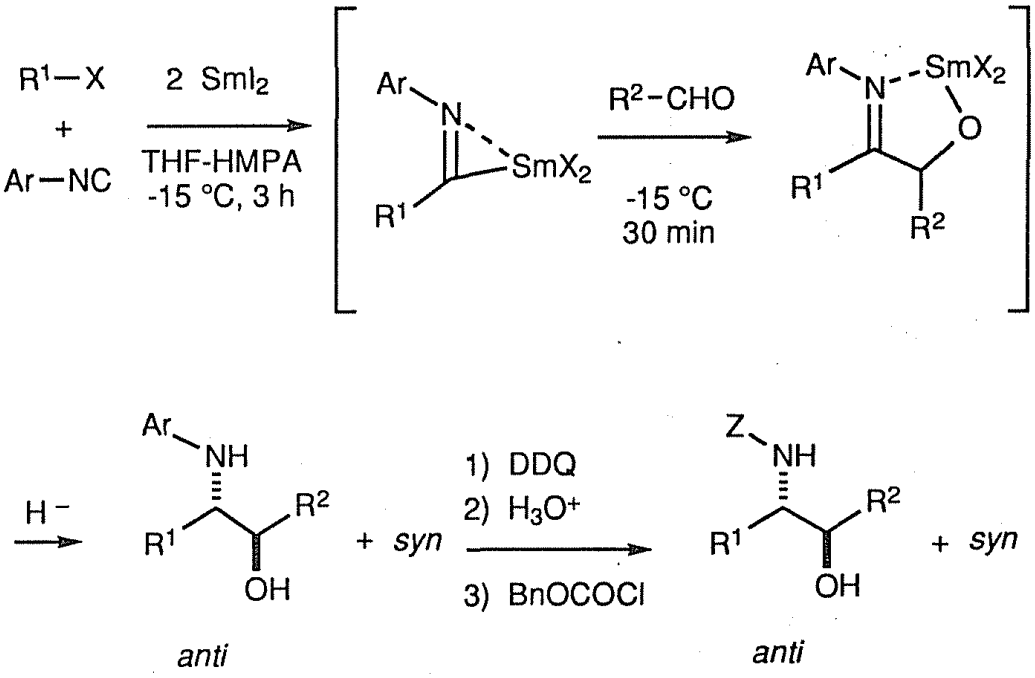
Scheme 2.



Chapter 2 describes a new stereoselective synthetic method for 2-amino alcohols on the basis of (alkaneimidoyl)samarium(III) reagent. Preparation of an isocyanide having a removable *N*-aromatic substituent was attempted. 4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl isocyanide, which was prepared from commercially available 3,5-xylenol, underwent the samarium iodide-mediated coupling reaction with organic halides and carbonyl compounds. Reduction of the reaction mixture with $NaBH_4$ selectively afforded *anti* 2-(arylamino) alcohols, which were then subjected to oxidative dearylation to the corresponding 2-(pri-

mary amino) alcohols via desilylation with TBAF followed by oxidation with DDQ (Scheme 3.). The synthesis of 2-amino alcohols presented a synthetic usefulness of the aromatic isocyanide as an aminomethylene equivalent. Finally, the synthetic utility was demonstrated by total synthesis of a ceramide

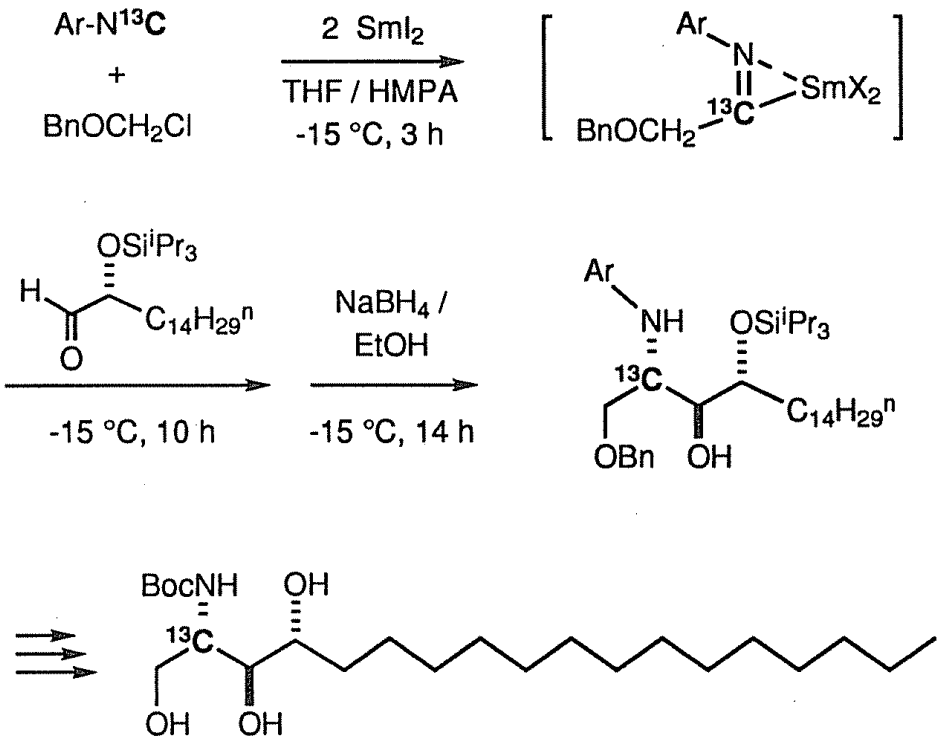
Scheme 3.



Chapter 3 deals with preparation of a ^{13}C-labeled isocyanide and its application to the total synthesis of [2-^{13}C]D-*ribo*-C18-phytosphingosine. The understanding of structural features of biologically active compounds in solution is required to gain insight into the binding interaction between these molecules and their cellular receptors. There has been great advancement of NMR spectroscopy, particularly in isotope-assisted techniques to elucidate the conformation of such molecules in solution.[5] This situation has created an increased need for synthetic methods of the incorporation of a ^{13}C nuclide at desired positions of target molecules with defined configurations.[6,7] This chapter describes a total synthesis

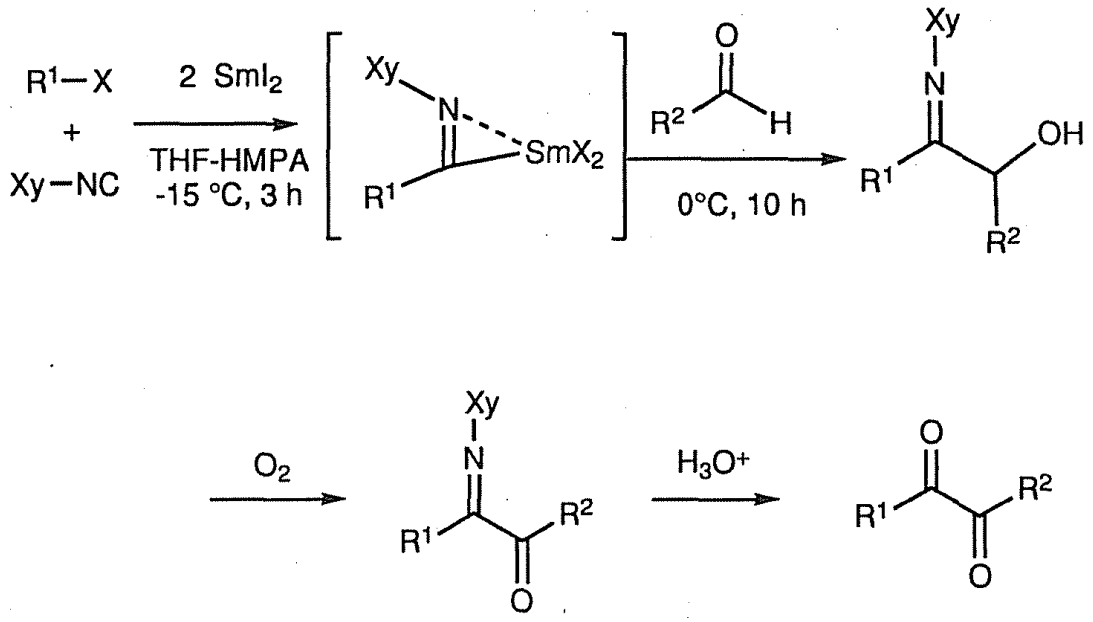
of the labeled phytosphingosine on the basis of the use of the isocyanide as a $^{13}CH–NH_2$ precursor in the SmI_2-mediated three-component coupling reaction, wherein regio- and stereoselective incorporation of a ^{13}C nuclide in the carbon skeleton is achieved (Scheme 4.) .

Scheme 4.



Chapter 4 is concerned with a new method for the synthesis of unsymmetrical α-diketones. Autoxidation of α-hydroxy imines, prepared by samarium(II) iodide-mediated three-component coupling of an organic halide, 2,6-xylyl isocyanide, and a carbonyl compound, afforded the corresponding α-keto imines, which were hydrolyzed to α-diketones in high yield (Scheme 5.) .

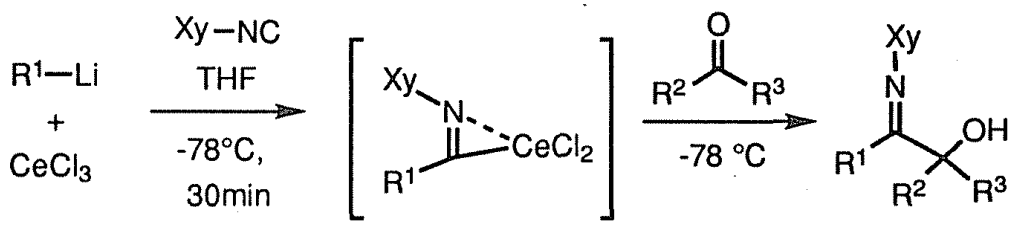
Scheme 5.



In chapter 5, (alkaneimidoyl)lanthanide(III) reagents and their reactions with carbonyl compounds are described. It was found that organolanthanide reagents prepared in situ by transmetallation reactions from alkyllithiums or alkylmagnesiums undergo insertion reaction with isocyanide to give (alkaneimidoyl)lanthanide(III) intermediates. The generation of the (alkaneimidoyl)lanthanide(III) intermediates was performed by adding alkyllithium to a mixture of an anhydrous lanthanide salt and 2,6-xylyl isocyanide in tetrahydrofuran at -78 °C. Among a series of lanthanide salts, $CeCl_3$ effected the quantitative conversion of the isocyanide to afford an orange solution of (alkaneimidoyl)cerium(III). Although $LaCl_3$, SmI_3, and $Sm(OTf)_3$ were found to be highly reactive, multiple insertion of the isocyanide ensued. (Alkaneimidoyl)cerium(III) could also be prepared by the reaction of dialkylmagnesium with $CeCl_3$ and 2,6-xylyl isocyanide at -45 °C. The

(alkaneimidoyl)cerium(III) thus prepared reacted with a carbonyl compound to afford an addition product, *i.e.*, an α-hydroxy imine (Scheme 6.) . The present reactions for the preparation of (alkaneimidoyl)cerium(III) provide a convenient synthetic equivalent to a nucleophilic acyllanthanide species with a wide variation for the acyl group. In the absence of lanthanide salt, the reaction of alkyllithium with 2,6-xylyl isocyanide led to the trimerization of the isocyanide to afford an indole derivative.

Scheme 6.



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Chapter 1

Synthesis of α-Hydroxy Aldehyde by Samarium(II) Iodide-Mediated Coupling Reaction of Carbonyl Compounds and Isocyanide

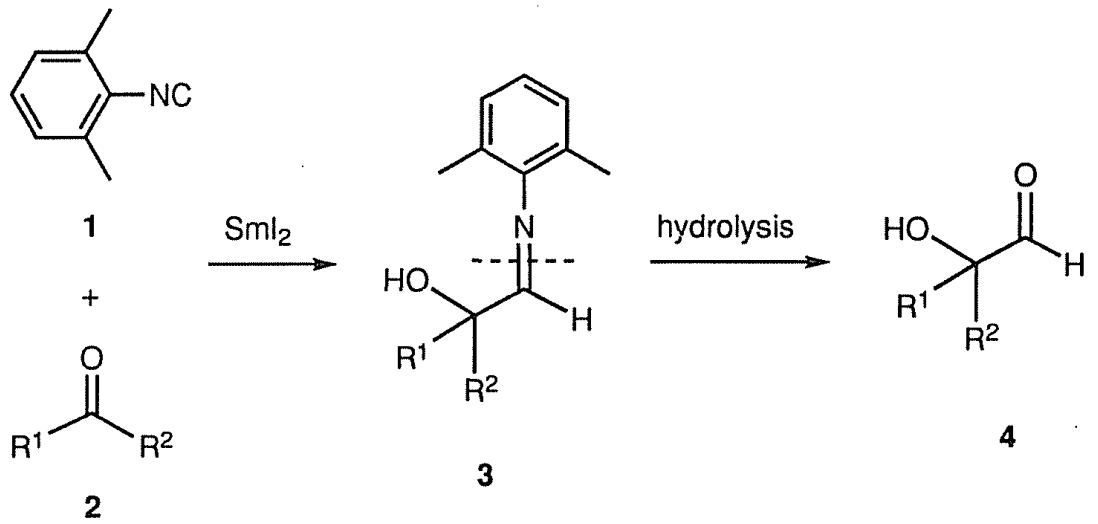
Abstract

A new strategy for the synthesis of α-hydroxy aldehyde by samarium(II) iodide-mediated coupling reaction of carbonyl compounds and isocyanide is disclosed. An (α-iminoalkyl)samarium(III) species is generated *in situ* by treatment of an carbonyl compounds with two equivalents of samarium(II) iodide in the presence of 2,6-xylyl isocyanide. Subsequent treatment of water affords α-hydroxy imines, which are converted by acid-catalyzed hydrolysis to the corresponding α-hydroxy aldehydes.

The synthesis of polyoxygenated natural products, such as macrolides and ionophore antibiotics, has attracted considerable attention in recent years. Hydroxy aldehyde are particularly attractive intermediates because further elaboration provides an expedient route to highly functionalized and stereochemically complex polyoxygenated backbones. The aldol reaction, which produces a β-hydroxy ketone, is a useful and straightforward process for constructing a carbon framework with oxygen functionality in a 1,3-relationship and has found numerous synthetic applications.[1] Synthetic access to α-hydroxy ketones has been provided most commonly by oxidation at the α-position of ketones (or their enol derivatives)[2] and by addition of masked[3] or unmasked[4] acyl anion equivalents to carbonyl compounds.

Previous reports from our laboratory[5] and that of Walborsky[6] have documented metalation of an isocyano carbon by α-addition of organometallic compounds to isocyanides. The resulting [α-(*N*-substituted imino)alkyl]metal compounds can be utilized as synthetic equivalents of acyl anions. (α-

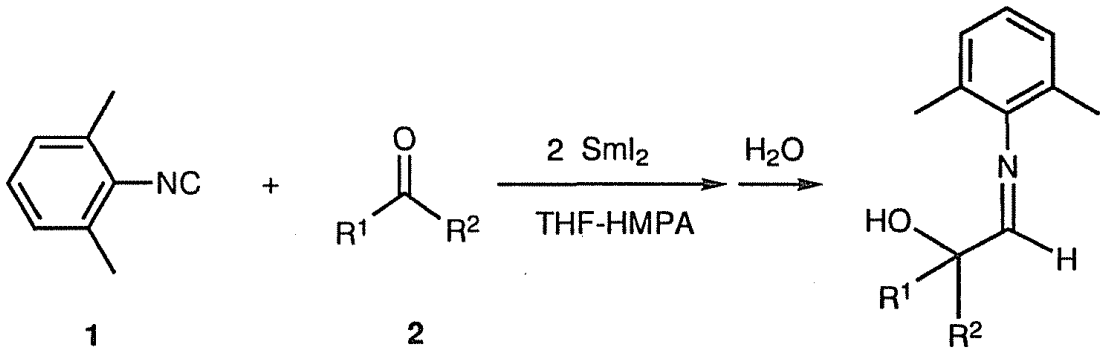
Scheme I



Iminoalkyl)samarium(III) compounds especially have found useful and novel synthetic applications.[5c] Herein, we report a new method of the synthesis of α-hydroxy ketones by samarium(II) iodide-mediated coupling reaction of carbonyl compounds and isocyanide as shown in Scheme I.

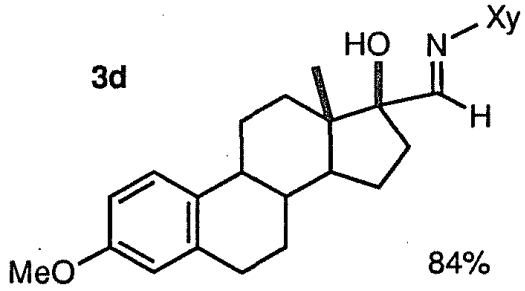
Synthesis of α-Hydroxy Aldehydes[7] by SmI_2-Mediated Coupling of Ketones and Isocyanide. Reduction of ketones by samarium(II) iodide in the presence of the isocyanide **1** afforded α-hydroxy aldimines **3** (Scheme II). The use of an aldehyde in place of a ketone was unsuccessful, because of the rapid formation of pinacol.[8] It has been reported that reduction of a carbonyl compound with samarium(II) iodide in the presence of CH_3OD led mainly to the α-deuterated alcohol.[9] Taking into account this result and the mechanistic observations dis-

Scheme II



3a $R^1 = R^2 = Et$ 76%
3b $R^1, R^2 = -(CH_2)_5-$ 66%
3c $R^1 = Me, R^2 = PhCH_2CH_2$ 70%

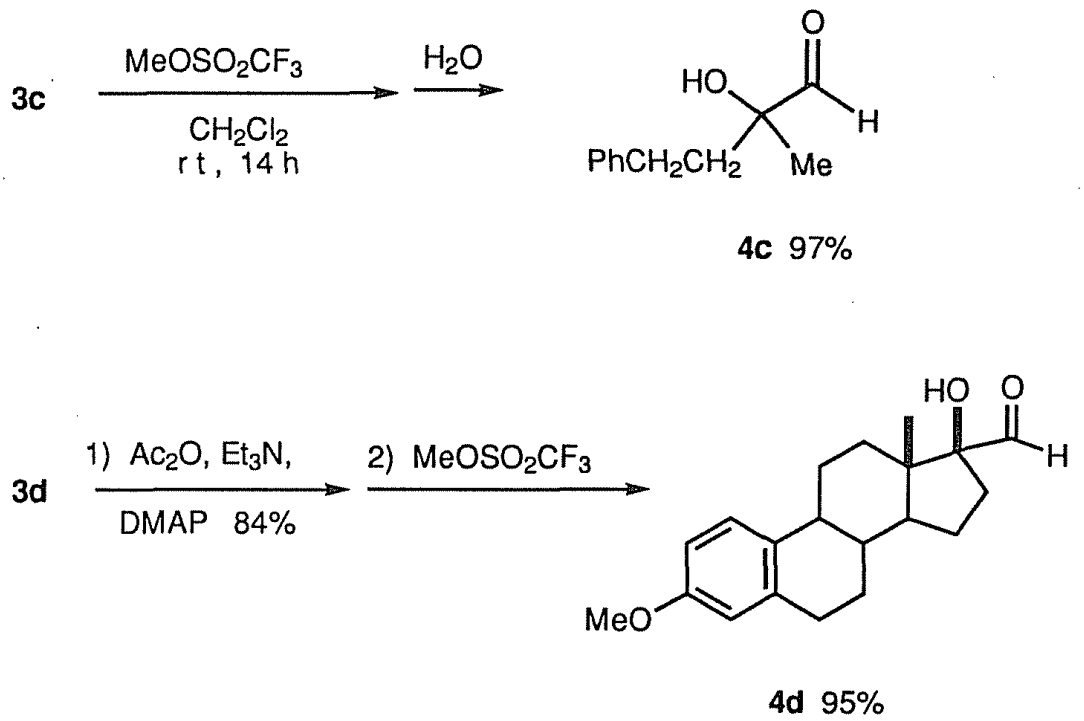
3d



84%

cussed later, we assume that the reaction proceeds via an oxymethylsamarium(III) intermediate, which adds to isocyanide. However, all attempts to trap the resulting (α-iminoalkyl)samarium(III) intermediate with carbonyl compounds failed, probably because of steric effects. α-Hydroxy aldimines were converted to the corresponding α-hydroxy aldehydes by alkylation of the imino nitrogen with methyl triflate followed by hydrolysis (Scheme III).

Scheme III



Conclusions

The samarium(II) iodide-mediated coupling reaction described here provides a new and convenient method for the synthesis of a variety of α-hydroxy aldehyde. The reaction was found to have wide generality. The compatibility of various functionalities with the reaction conditions fulfills the requirements for the construction of multi-functional carbon frameworks.

Experimental Section

General. Column chromatography was performed with silica gel 60 (E. Merck, Darmstadt), 230–400 mesh. Preparative TLC was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra were acquired in chloroform-*d*. Carbon chemical shifts were recorded relative to chloroform-*d* (δ 77.0). Na_2SO_4 was used to dry organic layers after extraction. All reactions except for the hydrolyses of imines were performed under a dry nitrogen atmosphere.

Unless otherwise noted, materials were obtained from commercial sources. THF was distilled from $LiAlH_4$, and HMPA from CaH_2. 2,6-Xylyl isocyanide (**2**) was prepared according to literature.[10] A THF solution of samarium(II) iodide was prepared according to the procedure of Kagan *et al.*[11]

3-[(2,6-Xylylimino)methyl]-3-pentanol (3a). To a mixture of samarium metal (180 mg, 1.2 mmol) and 1,2-diiodoethane (282 mg, 1.0 mmol) at 0 °C was added THF (12 mL), and the mixture was then stirred at 0 °C for 15 min and at rt for 3 h. HMPA (0.6 mL, 3.4 mmol), **1**(44 mg, 0.33 mmol), and 3-pentanone (43 mg, 0.50 mmol) were added to the mixture. After the mixture stirred at rt for 8 h, H_2O (a drop), ether (10 mL), and hexane (20 mL) were added. Filtration through a short column of Florisil® followed by column chromatography on silica gel pretreated with Et_3N (ether : hexane = 1 : 10) gave **3a** as a pale yellow oil (76%): IR (neat) 3464, 1666 cm^{-1}; ^1H NMR δ 1.00 (t, J = 7.4 Hz, 6 H), 1.61–1.90 (m, 4 H), 2.13 (s, 6 H), 4.30–4.45 (br, 1 H), 6.90–7.27 (m, 3 H), 7.65 (s, 1 H); ^{13}C NMR δ 7.8, 18.5, 31.1, 76.0, 124.0, 127.0, 128.1, 148.9, 170.6. Anal. Calcd for

$C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.38. Found: C, 76.61; H, 9.79; N, 6.41.

1-[(2,6-Xylylimino)methyl]-1-cyclohexanol (3b). To a mixture of samarium metal (180 mg, 1.2 mmol) and 1,2-diiodoethane (282 mg, 1.0 mmol) at 0 °C was added THF (12 mL), and the mixture was then stirred at 0 °C for 15 min and at rt for 3 h. HMPA (0.6 mL, 3.4 mmol), **1** (44 mg, 0.33 mmol), and cyclohexanone (49 mg, 0.50 mmol) were added to the mixture at -15 °C, and stirring was continued for 22 h at -15 °C. A drop of H_2O, ether (10 mL), and hexane (20 mL) were added. Filtration through a short column of Florisil® followed by column chromatography on silica gel pretreated with Et_3N (ether : hexane = 1 : 3) gave **3b** as a pale yellow oil (66%): IR (neat) 3464, 1668 cm^{-1}; ^1H NMR δ 1.25–2.05 (m, 10 H), 2.09 (s, 6 H), 4.31 (br s, 1 H), 6.90–7.08 (m, 3 H), 7.71 (s, 1 H); ^{13}C NMR δ 18.0, 21.3, 25.2, 35.3, 72.3, 123.9, 126.8, 128.0, 148.8, 171.2. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.93; H, 9.23; N, 6.08.

2-Methyl-4-phenyl-1-(2,6-xylylimino)-2-butanol (3c). By a procedure similar to that for **3b**, the title compound was obtained from Sm (180 mg, 1.2 mmol), 1,2-diiodoethane (282 mg, 1.0 mmol), HMPA (0.6 mL, 3.4 mmol), **1** (44 mg, 0.33 mmol), and 4-phenyl-2-butanone (74 mg, 0.50 mmol). IR (neat) 3452, 1670 cm^{-1}; ^1H NMR δ 1.50 (s, 3 H), 1.90–2.22 (m, 2 H), 2.16 (s, 6 H), 2.56–2.75 (m, 1 H), 2.84–3.04 (m, 1 H), 4.57 (br s, 1 H), 6.95–7.15 (m, 3 H), 7.16–7.38 (m, 5 H), 7.75 (s, 1 H); ^{13}C NMR δ 18.3, 26.0, 30.2, 41.7, 73.4, 124.1, 125.9, 126.9, 128.1, 128.3, 128.4, 142.0, 148.6, 170.5. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.90; H, 8.38; N, 4.88.

3-Methoxy-17β-[(2,6-xylylimino)methyl]estra-1,3,5(10)-trien-17α-ol

(3d). By a procedure similar to that for **3a**, the title compound was obtained from Sm (180 mg, 1.2 mmol), 1,2-diiodoethane (282 mg, 1.0 mmol), HMPA (0.6 mL, 3.4 mmol), **1** (44 mg, 0.33 mmol), and 3-methoxyestra-1,3,5(10)-trien-17-one (126 mg, 0.44 mmol). The stereochemical assignment was based on the assumption that the usual α-attack at C-17 of steroids occurred. $[\alpha]^{24}_{D}$ +29.4° (*c* 1.05, acetone); IR (neat) 3424, 1660 cm^{-1}; ^{1}H NMR δ 1.10 (s, 3 H), 1.20–2.40 (m, 13 H), 2.15 (s, 6 H), 2.80–3.00 (m, 2 H), 3.79 (s, 3 H), 4.79 (br s, 1 H), 6.66–6.77 (m, 2 H), 6.93–7.23 (m, 4 H), 7.98 (s, 1 H); ^{13}C NMR δ 14.2, 18.4, 23.7, 26.2, 27.5, 29.7, 33.3, 35.0, 39.3, 43.9, 47.5, 50.4, 55.1, 84.3, 111.5, 113.8, 124.0, 126.2, 127.1, 128.1, 132.2, 137.8, 148.9, 157.5, 170.2. Anal. Calcd for $C_{28}H_{35}NO_2$: C, 80.54; H, 8.45; N, 3.35. Found: C, 80.30; H, 8.55; N, 3.33.

2-Hydroxy-2-methyl-4-phenylbutanal (4c). A mixture of **3c** (44 mg, 0.16 mmol) and methyl triflate (60 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 14 h, diluted with sat. *aq* $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with 0.1 N HCl and with sat. *aq* NaCl. Drying and evaporation of solvent followed by gel permeation chromatography ($CHCl_3$) yielded the title compound (97%). IR (neat) 3464, 1736 cm^{-1}; ^{1}H NMR δ 1.35 (s, 3 H), 2.00 (t, *J* = 8.3 Hz, 2 H), 2.40–2.60 (m, 1 H), 2.68–2.88 (m, 1 H), 3.27 (br s, 1 H), 7.10–7.40 (m, 5 H), 9.49 (s, 1 H); ^{13}C NMR δ 22.8, 29.5, 39.0, 77.8, 126.1, 128.3, 128.5, 141.2, 203.3.

17α-Acetoxy-3-methoxyestra-1,3,5(10)-triene-17β-carbaldehyde (4d). To **3d** (131 mg, 0.314 mmol) in THF (0.5 mL) were added Et_3N (0.5 mL), a catalytic amount of DMAP, and Ac_2O (150 mg, 1.47 mmol). The mixture was

stirred at rt for 18 h, diluted with water, and extracted with Et_2O. Drying and evaporation of solvent followed by column chromatography on silica gel (ether : hexane = 1 : 5) yielded the corresponding acetate (84%): ^{1}H NMR δ 1.08 (s, 3 H), 1.20–1.70 (m, 6 H), 1.80–2.40 (m, 6 H), 1.98 (s, 3 H), 2.18 (s, 6 H), 2.85–2.95 (m, 2 H), 3.00–3.20 (m, 1 H), 3.78 (s, 3 H), 6.64–7.26 (m, 6 H), 7.70 (s, 1 H); ^{13}C NMR δ 15.1, 19.2, 21.2, 24.2, 26.0, 27.6, 29.8, 32.1, 32.6, 38.9, 43.4, 46.3, 48.6, 55.2, 92.4, 111.6, 113.9, 123.7, 126.2, 127.1, 128.1, 132.2, 138.0, 150.2, 157.6, 168.9, 170.3. A mixture of the acetate (30 mg, 65 μmol) and methyl triflate (50 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 1 d, diluted with sat. *aq* $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with 0.1 N HCl and with sat. *aq* NaCl. Drying and evaporation of solvent followed by column chromatography (ether : hexane = 1 : 5) yielded the title compound (95%). mp 125 °C (Et_2O–hexane); $[\alpha]^{24}_D$ +30.7° (*c* 0.90, acetone); IR (neat) 1734, 1726 cm^{-1}; ^{1}H NMR δ 1.04 (s, 3 H), 1.30–2.45 (m, 12 H), 2.16 (s, 3 H), 2.61–2.81 (m, 3 H), 3.77 (s, 3 H), 6.63 (d, J = 2.6 Hz, 1 H), 6.70 (dd, J = 2.6, 8.4 Hz, 1 H), 7.15 (d, J = 8.4 Hz, 1 H), 9.54 (s, 1 H); ^{13}C NMR δ 14.7, 20.7, 24.2, 25.8, 27.3, 29.7, 30.7, 32.0, 38.6, 43.1, 47.1, 48.1, 55.2, 93.6, 111.5, 113.8, 126.2, 132.0, 137.9, 157.5, 171.1, 201.0. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.02; H, 7.82.

References and notes

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Chapter 2

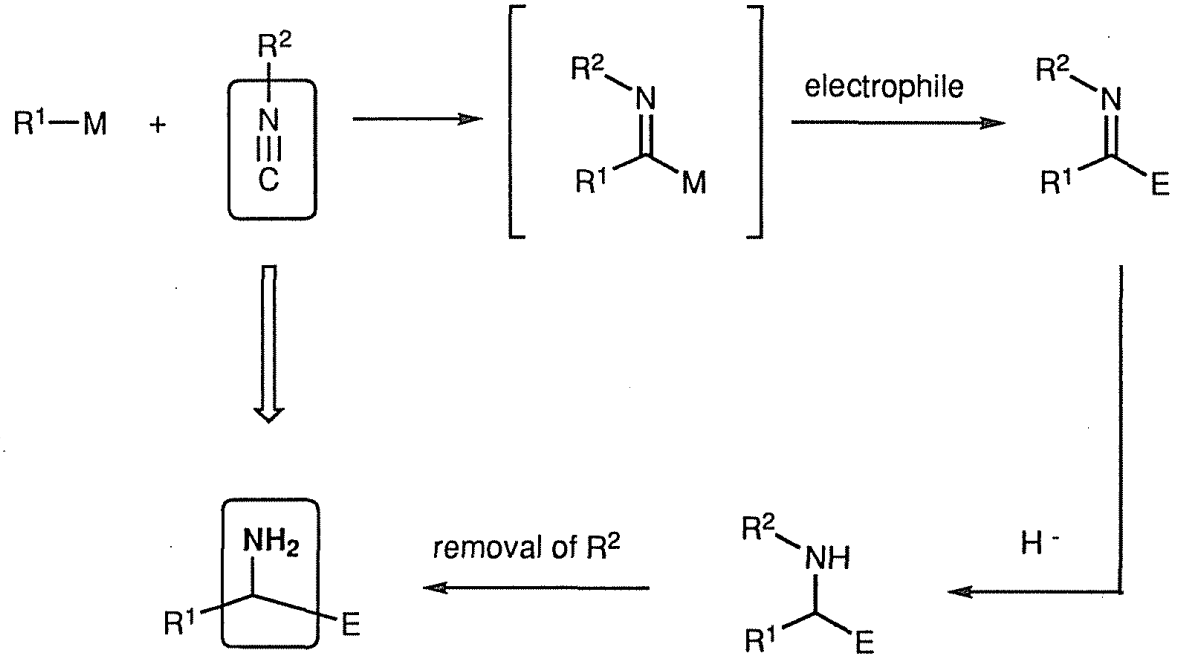
Stereoselective Synthesis of 2-Amino Alcohols by Use of an Isocyanide as an Aminomethylene Equivalent

Abstract

Preparation of an isocyanide having a removable *N*-substituent and its application to the stereoselective synthesis of 2-amino alcohols are described. 4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl isocyanide was prepared from commercially available 3,5-xylenol. The isocyanide underwent the samarium iodide-mediated coupling reaction with organic halides and carbonyl compounds. Reduction of the reaction mixture with $NaBH_4$ selectively afforded *anti* 2-(arylamino) alcohols, which were then deprotected to the corresponding 2-(primary amino) alcohols via desilylation with TBAF followed by oxidation with DDQ. A ceramide was successfully synthesized by use of the present stereoselective synthetic method for 2-amino alcohols, demonstrating a new synthetic utility of the isocyanide as an aminomethylene equivalent.

Carbon monoxide inserts into carbon–metal bonds and can therefore be utilized as a useful carbonyl synthon in a variety of carbonylation reactions.[1] Isocyanides, nitrogen analog of carbon monoxide in terms of electronic structure, are also known to undergo insertion into carbon–metal bonds. For synthetic purposes, the resulting (α-iminoalkyl)metal compound is reacted with electrophiles to produce imines, which are then converted to the corresponding carbonyl compounds via acid-catalyzed hydrolysis of the imino group.[2] Consequently, the nitrogen atom is lost, the isocyanide being used as a *masked* carbonyl synthon. It would give the isocyanide additional synthetic value, one inaccessible from carbon monoxide, if the imino group of the product could be *unmasked* without the loss of the nitrogen atom. A feasible approach along this line would involve synthetic elaborations of the imine with reduction to a secondary amine and subsequent removal of the *N*-substituent, affording the corresponding primary amine

Scheme I

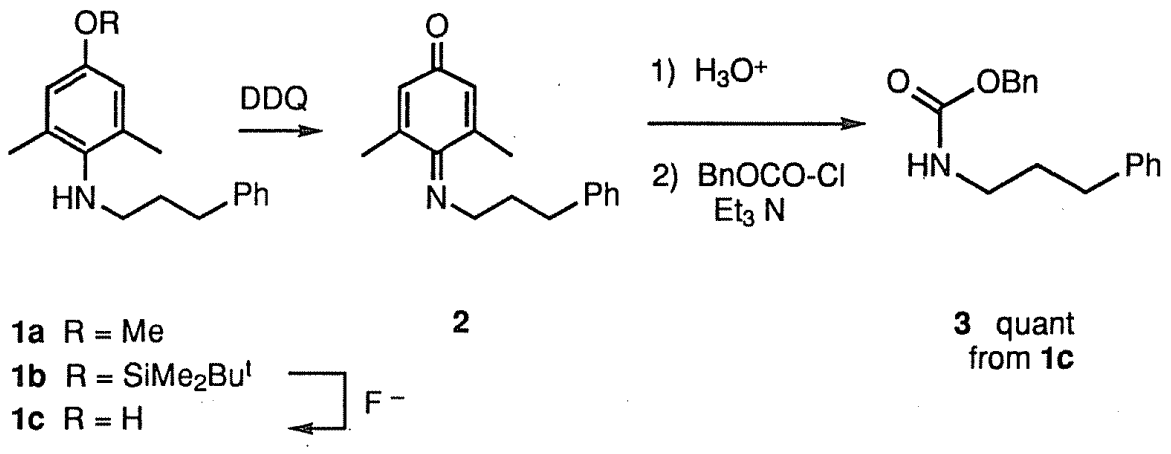


(Scheme I). Although intrinsic, the synthetic utilization of the isocyanide as an aminomethylene equivalent has not yet been well exploited.

Recently, we reported[2f,h] the samarium(II) iodide-mediated[3] three-component coupling of an organic halide, 2,6-xylyl isocyanide and a carbonyl compound, which gives rise to an α-hydroxy imine. Herein, we report preparation of an isocyanide having a removable *N*-substituent,[4] which is applicable to the stereoselective synthesis of 2-amino alcohols.[5] The synthesis of ceramide (**11**), of current interest in terms of its biological activities,[6,7] is also described.

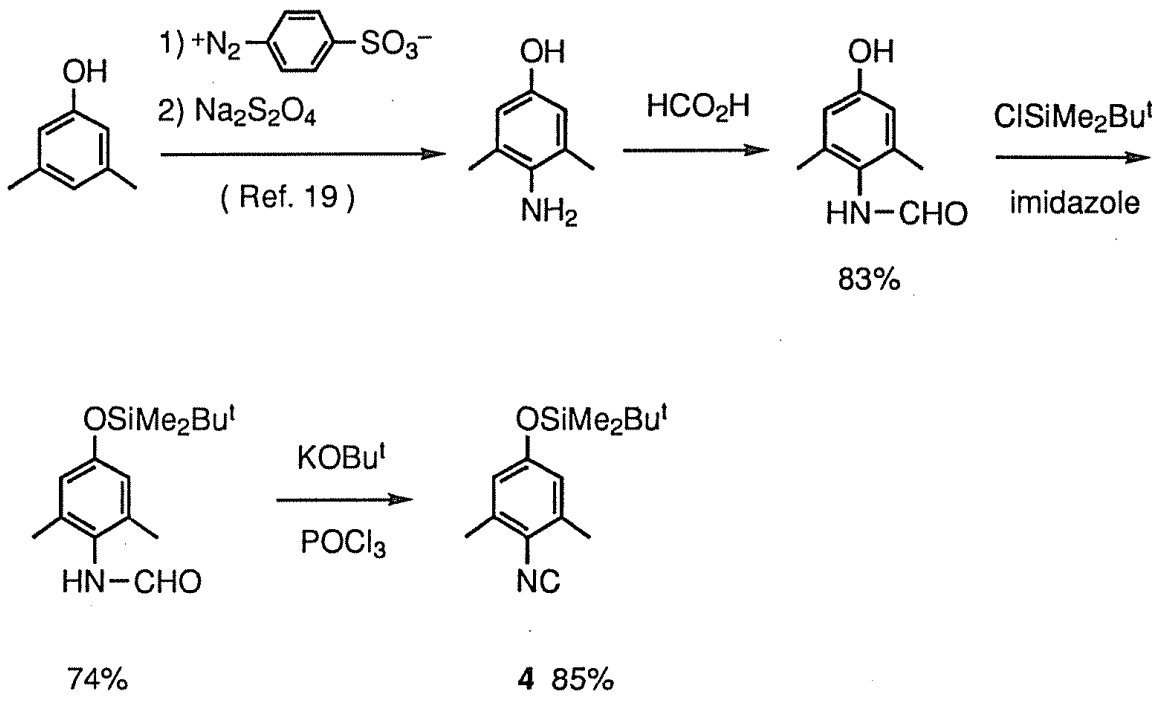
Oxidative Removal of a 4-Oxy-2,6-xylyl Substituent of an Amine. The 4-(methoxy)phenyl group has been used for protection of amide nitrogens in β-lactam synthesis, where it is oxidatively removed.[8] Taking into account that the 2,6-disubstituted phenyl group is suitable for the *N*-substituent of the isocyanide utilized in the samarium(II) iodide-mediated three-component coupling reaction,[2h] the possibilities of the oxidative cleavage of 4-oxy-2,6-xylidine derivatives **1a–c** were examined (Scheme II). By use of ammonium cerium(IV)

Scheme II



nitrate (CAN) as an oxidant, **1a** and **1c** were deprotected to afford amine **3** in moderate yield (66% and 56%, respectively)[9] whereas the reaction of **1b** was very slow. When 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as an oxidant, **1a** and **1b** gave a complex mixture.[10] Facile deprotection was achieved with the 4-hydroxyxylidine derivative **1c**; upon treatment with an equimolar amount of DDQ at 0 °C for 15 min, **1c** was converted to quinone monoimine **2** and, after removal of the resulting DDHQ by filtration, an acid-catalyzed hydrolysis of the filtrate afforded the deprotected amine quantitatively. Furthermore, the 4-hydroxy derivative **1c** was readily obtained by desilylation of the 4-siloxy derivative **1b** with tetrabutylammonium fluoride (TBAF). These experiments disclosed that the 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl substituent of an amine can be easily removed by desilylation and subsequent oxidation with DDQ.

Scheme III



Synthesis of 2-Amino Alcohols. On the basis of the preliminary studies mentioned above, 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl isocyanide (**4**) was prepared from commercially available 3,5-xylenol as shown in Scheme III.

Next, the samarium(II) iodide-mediated three-component coupling reaction with isocyanide **4** and subsequent oxidative *N*-dearylation to the corresponding 2-amino alcohol were examined. Following the protocol reported previously,[2h] **4** successfully coupled with an organic halide and a carbonyl compound. The resulting reaction mixture was reduced *in situ* with various hydride reducing agents. Whereas reduction with stereodemanding L-Selectride® was sluggish, only poor selectivities were obtained by use of LAH, $NaBH_3CN$, and $NaBH(OAc)_3$. In

Table I. Stereoselective Syntheses of 2-Amino Alcohols from Organic Halides, **4**, and Aldehydes

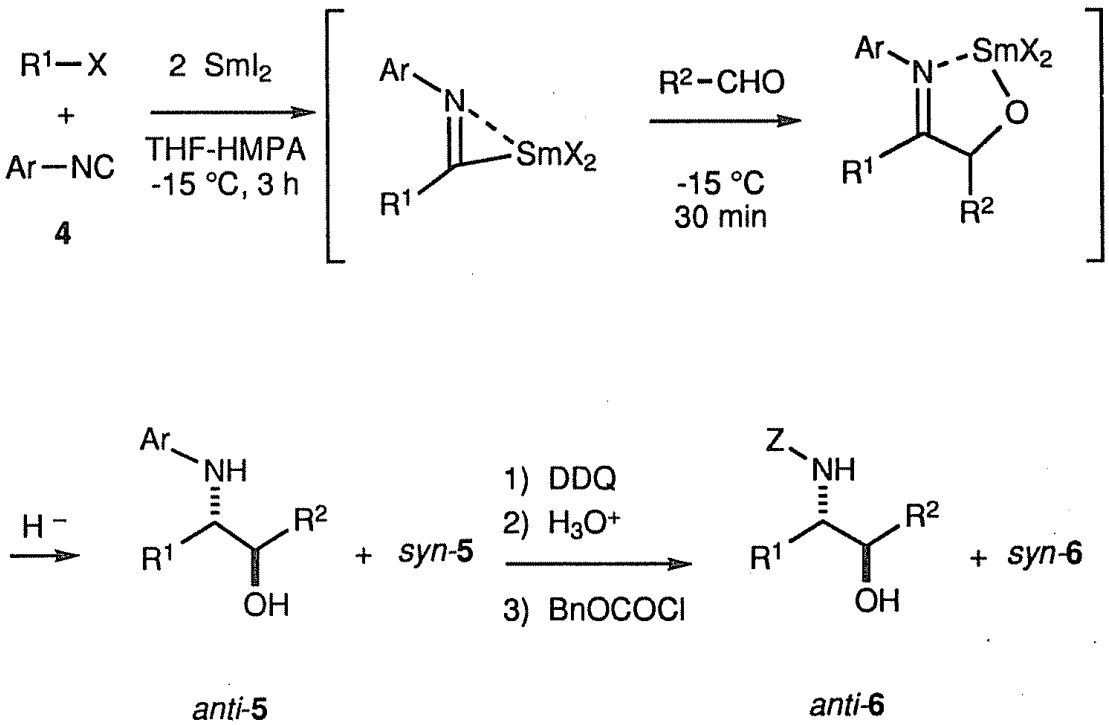
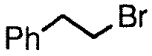
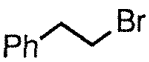
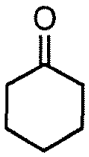


Table I. (continued)

run	R^1–X	R^2CHO	H^-	**5**, yield [a] (%)	*anti* : *syn*	**6**, yield [b] (%)
1		Et–CHO	$NaBH_4$	**5a**, 99	86 : 14	—
2			$NaBH_4$ /EtOH	86	90 : 10	—
3			$NaBH_4$ / ^iPrOH	93	94 : 6	**6a**, 99
4			$NaBH_4$ / ^tBuOH	88	91 : 9	—
5	Et–Br		$NaBH_4$	**5b**, 86	87 : 13	—
6			$NaBH_4$ / ^iPrOH	83	95 : 5	**6b**, 89
7	^iPr–I	Et–CHO	$NaBH_4$	**5c**, 99	98 : 2	**6c**, 90
8			$NaBH_4$ / ^iPrOH	98	98 : 2	—
9	Et–Br	^iPr–CHO	$NaBH_4$	**5d**, 91	97 : 3	**6d**, 99
10			$NaBH_4$ / ^iPrOH	99	94 : 6	—
11			$NaBH_4$	**5e**, 97	—	**6e**, 89

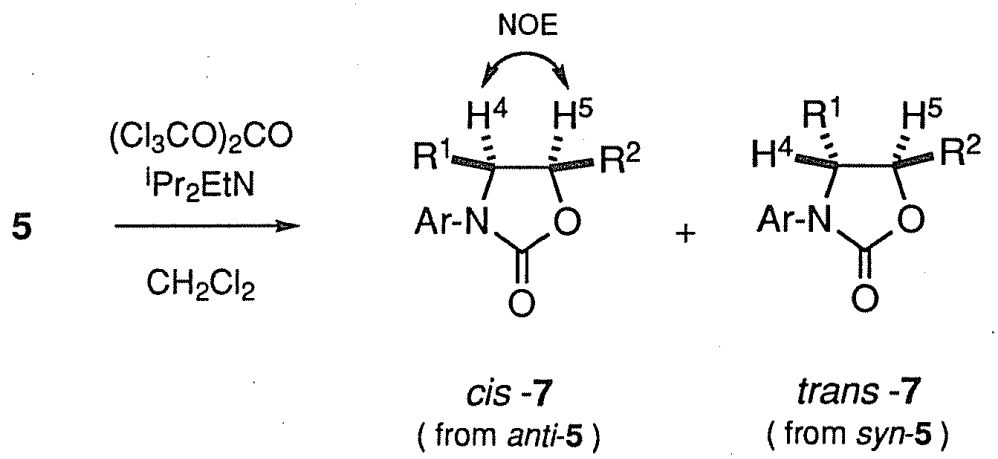
[a] Isolated yields based on aldehydes. [b] Isolated yields based on **5**.

contrast, $NaBH_4$, one of the simplest of hydride agents, exhibited good selectivity favoring *anti*-**5**. Notably, the stereochemical outcome was influenced by the addition of alcohols to the mixture as a co-solvent and, in particular, 2-propanol improved the selectivity significantly in some cases. The syntheses of a variety of 2-(arylamino) alcohols **5** by use of $NaBH_4$ are summarized in Table I.

Next, the 2-(arylamino) alcohols **5** thus obtained with good stereoselection were deprotected via desilylation with TBAF followed by oxidation with DDQ to afford the corresponding 2-(primary amino) alcohols **6** in high yield (Table I).

For assignment of the stereochemistry, the 2-amino alcohols **5** were converted to the 1,3-oxazolidin-2-ones **7** by treatment with triphosgene. The *cis*-relationship of the vicinal 4- and 5-protons of **7** was elucidated based on their ^1H NMR coupling constants ($J_{4\text{-}5}$).[5b,d,11] The major isomer shows a coupling constant of 6.9–7.8 Hz which suggests a *cis*-arrangement, while that of the minor isomer is 5.8–5.9 Hz (Table II). Both 4- and 5-protons of *cis*-isomers resonate at lower field than those of *trans*-isomers. The stereochemical assignment of **7a** and **7d** was confirmed by NOE experiments.

Table II. ^{1}H NMR Data of 7 in $CDCl_3$



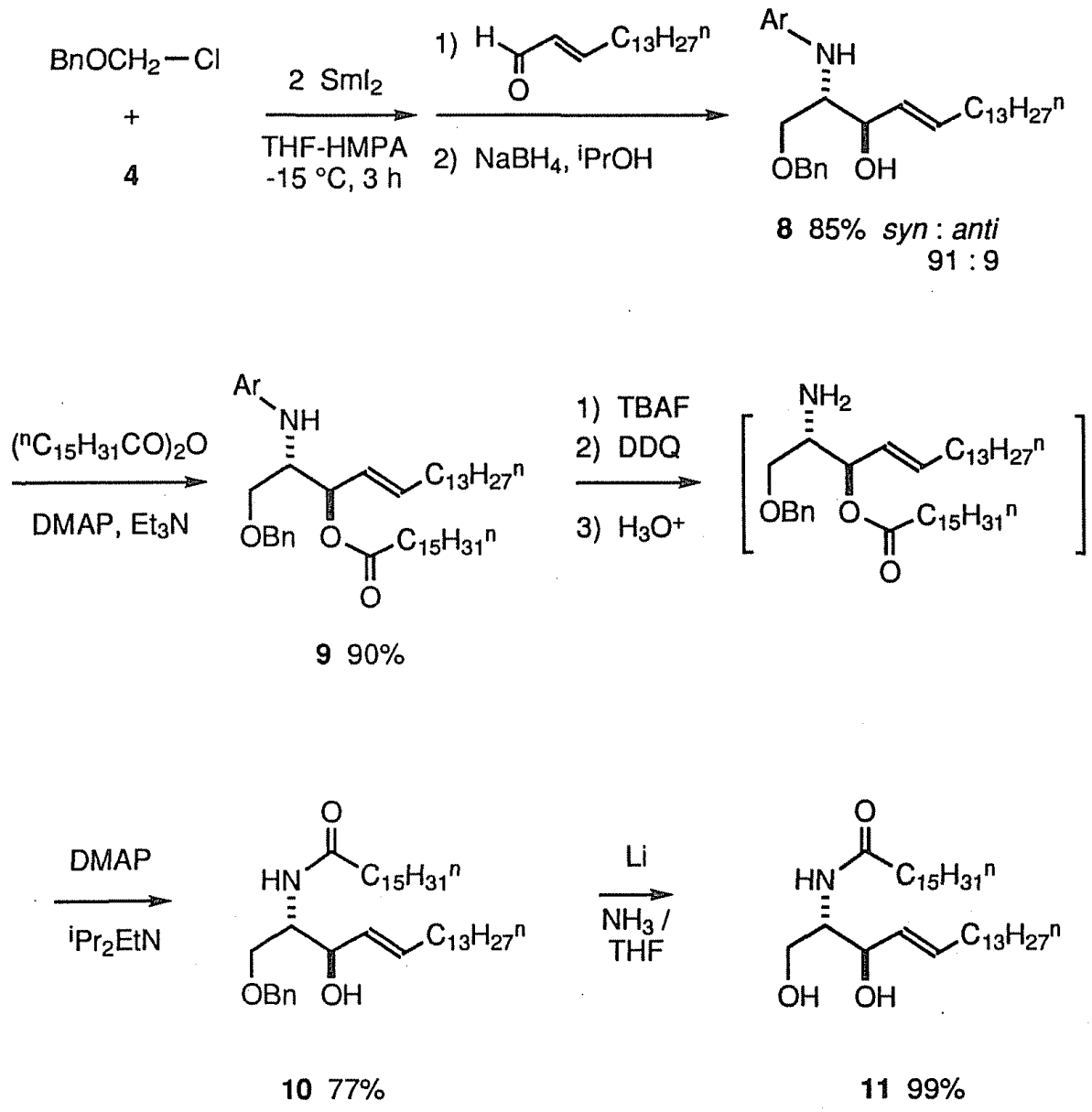
7	*cis* -isomer (major)			*trans* -isomer (minor)		
	H^4 (δ)	H^5 (δ)	$J_{4\text{-}5}$ (Hz)	H^4 (δ)	H^5 (δ)	$J_{4\text{-}5}$ (Hz)
7a	4.12	4.56	7.4	3.66	4.25	5.8
7b	4.05	4.64	7.8	3.53	4.26	5.9
7c	3.91	4.48	6.9		— [a]	
7d	3.89	4.37	7.3	3.65	4.04	5.8

[a] Not specified.

Synthesis of a Ceramide. Glycosphingolipids are constituents of cell membranes and play biologically important roles,[6] which have stimulated interests in their synthesis.[7] The present stereoselective synthetic method for 2-amino alcohols was next applied to the synthesis of a ceramide, the hydrophobic skeleton

of glycosphingolipids. The α-oxy imine, prepared by coupling of benzyl chloromethyl ether, the isocyanide **4** and 2-hexadecenal, was reduced *in situ* by $NaBH_4$ to give the corresponding *anti*-2-amino alcohol **8** stereoselectively (91 : 9). Then, a palmitoyl group was temporarily introduced onto the allylic hydroxyl group for protection against oxidation in the following step. Desilylation of **9** with TBAF followed by oxidative removal of the aryl group gave a primary amine.

Scheme IV



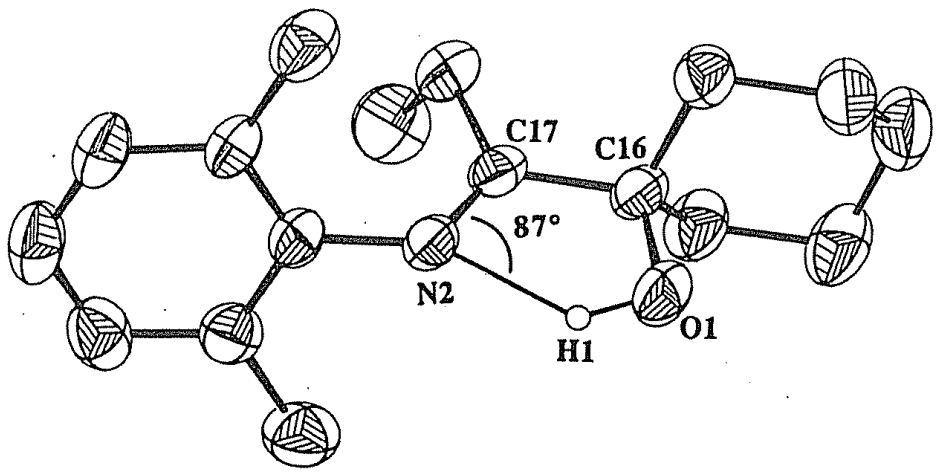
Notably, successive treatment of the crude amine with a catalytic amount of 4-(dimethylamino)pyridine promoted migration of the palmitoyl group from the allylic oxygen to the primary amino group affording the amide **10**. Finally, the benzyl group was removed by Birch reduction to give the (±)-ceramide **11**.[7a] Thus, a convenient and general synthetic route to ceramides was established.

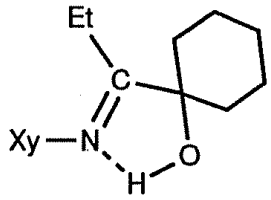
Interpretation of Stereochemical Outcome. The α-hydroxy imine **12** crystallized in orthorhombic form from hexane. X-ray diffraction study[12] revealed a conformation involving intramolecular hydrogen bonding[13] (Figure 1). The 2,6-xylyl group is oriented away from the hydroxyl group and is almost perpendicular to the imino plane. As mentioned in the previous report,[2h] the ^{13}C NMR spectra of α-hydroxy imines show only one set of signals for the carbons in the 2,6-xylyl group; with α-hydroxy imines derived from symmetrical ketones, five signals are observed for the eight carbons in the 2,6-xylyl group due to experiencing magnetic equivalence. On the other hand, α-hydroxy imines which are derived from aldehydes and consequently have an asymmetric center in the molecule exhibit magnetic non-equivalence of the eight carbons in the 2,6-xylyl group. This magnetic behavior is consistent with the presence of intramolecular hydrogen bonding in solution as well as in the crystalline state.

Considering the Lewis acidity of samarium(III), one might expect that the intermediary samarium(III) alkoxide takes an analogous conformation involving 5-membered chelation instead of the hydrogen bonding.[14] On the basis of this conformation, the stereoselection observed in the hydride reduction is reasonably attributed to the attack of hydride from the less-hindered side of the 5-membered ring.

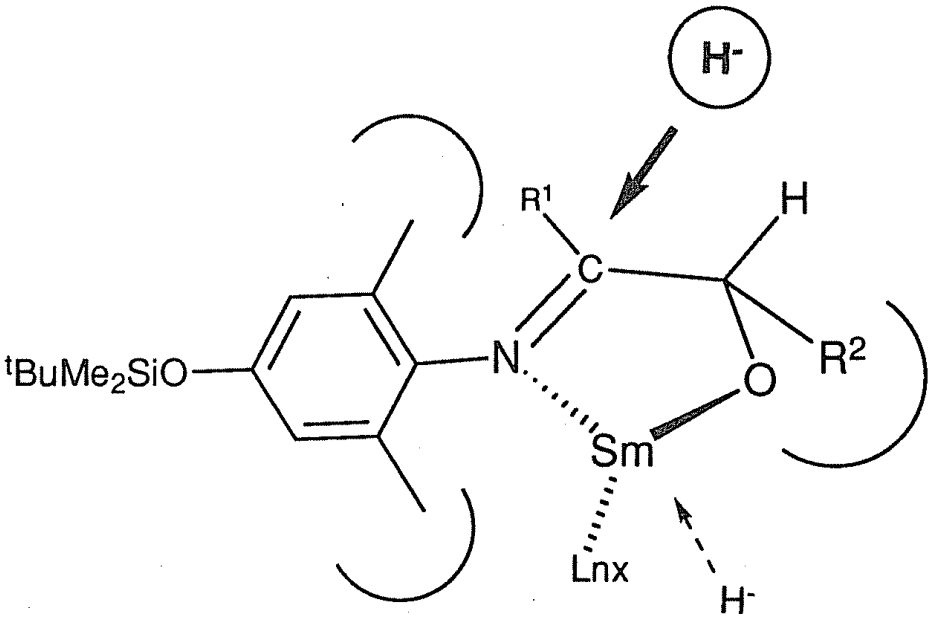
Lanthanide(III) ions, being frequently used as shift reagents, are well known

Figure 1. Top: Single crystal structure of α-hydroxy imine **12** (35% probability ellipsoids). Selected bond lengths (Å): O1–H1, 0.97(3); N2–H1, 1.83(3); N2–C17,1.276(2).
Bottom: Proposed course of hydride attack.





12



to bind to alcohols.[15] In addition, lanthanide ions catalyze the reaction of $NaBH_4$ with alcohols to give sodium alkoxyborohydrides,[16] which are more reactive than $NaBH_4$.[17] Although the precise species involved in the present reduction is unclear, alcohol complexation with samarium(III) ion and/or formation of sodium alkoxyborohydrides are probably responsible for the effect of the alcohol co-solvents on the stereoselectivity.

Conclusions

The present stereoselective synthesis of 2-amino alcohols from alkyl halides, the isocyanide **4** and aldehydes demonstrates an *intrinsic* synthetic utility of the isocyanide as an aminomethylene equivalent. In addition, two step removal of the 4-(siloxy)aryl group of an amine will provide new procedures of reductive and alkylative amination of carbonyl compounds, which are now under investigation in our laboratory.

Experimental Section

General. Column chromatography was performed with silica gel (Wakogel C-200). Preparative TLC was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra were acquired in chloroform-*d*. Where appropriate, NMR data only for the major stereoisomer are described. Na_2SO_4 was used to dry organic layers after extraction. All reactions were performed under a dry nitrogen atmosphere.

Unless otherwise noted, materials were obtained from commercial sources and purified appropriately. THF was distilled from sodium diphenyl ketyl, DMF, CH_2Cl_2 and HMPA from CaH_2, and toluene from $LiAlH_4$. 2-Hexadecenal was prepared by the literature procedure.[18]

4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl Isocyanide (4). A mixture of 4-amino-3,5-xylenol (5.7 g, 41.5 mmol), prepared from 3,5-xylenol by the literature procedure,[19] and formic acid (11 mL) in toluene (80 mL) was heated at reflux for 3 h in Dean-Stark apparatus. On cooling, white solids precipitated. After filteration, the solids were washed with water and toluene, and dried to give crude 4-(formamido)-3,5-xylenol (5.7 g, 83%).

To a mixture of 4-(formamido)-3,5-xylenol (5.7 g, 34.5 mmol) and *tert*-butylchlorodimethylsilane (7.8 g, 52 mmol) in DMF (40 mL) was added Et_3N (10.5 g, 104 mmol). The mixture was stirred at rt for 20 h, diluted with water, and extracted with ether. Filtration of the organic layer through a short column of silica gel followed by recrystallization from ether–hexane gave *N*-formyl-4-(*tert*-butyldimethylsiloxy)-2,6-xylidine (7.1 g, 74%).

A solution of trichloromethyl chloroformate (1.6 mL, 13.3 mmol) in CH_2Cl_2 (10 mL) was added to *N*-formyl-4-(*tert*-butyldimethylsiloxy)-2,6-xylidine (2.58 g, 9.23 mmol) in CH_2Cl_2 (8 mL) and Et_3N (9 mL) at -78 °C over 1 h.[20] The mixture was stirred at -78 °C for an additional 1 h, allowed to warm to rt, diluted with *aq*. NH_3, stirred for 2 h, extracted with ether, and washed with sat *aq*. NaCl. The title compound was obtained by vacuum distillation (2.08 g, 86%): bp 107 °C (0.35 mmHg). ^{1}H NMR δ 0.20 (s, 6 H), 0.97 (s, 9 H), 2.36 (s, 6 H), 6.55 (s, 2 H); ^{13}C NMR δ -4.4, 18.2, 19.0, 25.6, 119.1, 120.3 (t, $J_{C\text{-}N}$ = 12.5 Hz), 136.4, 155.5, 166.3. Anal. Calcd for $C_{15}H_{23}NOSi$: C, 68.91; H, 8.87; N, 5.36. Found: C, 68.67; H, 8.97; N, 5.20.

4-[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino-6-phenyl-3-hexanol (5a). A mixture of samarium powder (180 mg, 1.2 mmol) and 1,2-diiodoethane (282 mg, 1.0 mmol) in THF (12 mL) was stirred at rt for 2 h. HMPA (0.6 mL, 3.4 mmol)[21] was added and, after the reaction mixture was cooled to -15 °C, 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl isocyanide (**4**, 105 mg, 0.40 mmol) and (2-bromoethyl)benzene (93 mg, 0.50 mmol) were successively added. The reaction mixture was stirred for 2 h and propionaldehyde (18 mg, 0.31 mmol) was added. Stirring was continued for an additional 30 min and then 2-propanol (1 mL) and $NaBH_4$ (100 mg, 2.6 mmol) were added. The mixture was stirred for 16 h at -15 °C, diluted with water (3 drops) and hexane (30 mL), and filtered through a short column of Florisil. The filtrate was subjected to preparative TLC (ether : hexane = 1 : 3) to afford the title compound **5a** as an oil (123 mg, 93%): ^{1}H NMR δ 0.18 (s, 6 H), 0.93 (t, J = 7.5 Hz, 3 H), 0.98 (s, 9 H), 1.35–1.55 (m, 2 H), 1.65–1.95 (m, 2 H), 2.22 (s, 6 H), 2.45–2.70 (m, 1 H), 2.75–2.95 (m, 1 H), 3.16 (ddd, J = 2.9, 4.9,

7.8 Hz, 1 H), 3.44–3.60 (m, 1 H), 6.50 (s, 2 H), 7.06–7.32 (m, 5 H); ^{13}C NMR δ -4.4, 10.7, 18.1, 19.2, 25.7, 26.1, 32.2, 32.9, 59.5, 74.0, 120.3, 125.7, 128.3, 130.4, 138.1, 142.1, 149.8. Anal. Calcd for $C_{26}H_{41}NO_2Si$: C, 73.02; H, 9.66; N, 3.27. Found: C, 72.76; H, 9.86; N, 3.21.

4-[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino-1-phenyl-3-hexanol (5b). By a procedure similar to that for **5a**, the title compound was obtained from bromoethane, **4**, and 3-phenylpropanal (83%): ^{1}H NMR δ 0.19 (s, 6 H), 0.89 (t, J = 7.4 Hz, 3 H), 0.99 (s, 9 H), 1.38–1.56 (m, 2 H), 1.65–1.80 (m, 2 H), 2.24 (s, 6 H), 2.40–3.00 (m, 4 H), 3.08 (dt, J = 3.4, 6.8 Hz, 1 H), 3.60–3.72 (m, 1 H), 6.50 (s, 2 H), 7.15–7.35 (m, 5 H); ^{13}C NMR δ -4.4, 11.1, 18.1, 19.2, 23.7, 25.7, 32.7, 34.3, 62.6, 71.3, 120.2, 125.9, 128.4, 130.8, 137.9, 142.0, 150.0. Anal. Calcd for $C_{26}H_{41}NO_2Si$: C, 73.02; H, 9.66; N, 3.27. Found: C, 72.76; H, 9.38; N, 3.24.

4-[4-(*tert*-Butyldimethylsiloxy-2,6-xylyl]amino-5-methyl-3-hexanol (5c). By a procedure similar to that for **5a**, the title compound was obtained from 2-iodopropane, **4**, and propionaldehyde (98%): ^{1}H NMR δ 0.16 (s, 6 H), 0.92–1.03 (m, 18 H), 1.26–1.64 (m, 2 H), 1.85–2.10 (m, 2 H), 2.25 (s, 6 H), 2.87–3.18 (br, 1 H), 3.14 (t, J = 5.0 Hz, 1 H), 3.41–3.61 (m, 1 H), 6.47 (s, 2 H); ^{13}C NMR δ -4.5, 10.7, 18.1, 19.0, 19.4, 21.2, 25.7, 26.1, 30.1, 64.1, 74.4, 120.5, 128.7, 139.1, 149.1. Anal. Calcd for $C_{21}H_{39}NO_2Si$: C, 68.99; H, 10.75; N, 3.83. Found: C, 68.72; H, 10.54; N, 3.89.

4-[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino-2-methyl-3-hexanol (5d). By a procedure similar to that for **5a** except for the absence of 2-propanol, the title compound was obtained from bromoethane, **4**, and 2-methylpropanal

(91%): ^{1}H NMR δ 0.17 (s, 6 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.98 (s, 9 H), 1.08 (d, J = 7.3 Hz, 3 H), 1.39–1.75 (m, 3 H), 2.25 (s, 6 H), 3.06–3.21 (m, 2 H), 6.49 (s, 2 H); ^{13}C NMR δ -4.5, 11.6, 18.1, 19.1, 19.6, 22.2, 25.7, 31.1, 59.5, 76.3, 120.2, 130.2, 138.6, 149.5. Anal. Calcd for $C_{21}H_{39}NO_2Si$: C, 68.99; H, 10.75; N, 3.83. Found: C, 68.94; H, 10.76; N, 3.72.

1-[1-[4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl]amino-3-phenylpropyl]cyclohexanol (5e). By a procedure similar to that for **5a** except for the absence of 2-propanol, the title compound was obtained from (2-bromoethyl)benzene, **4**, and cyclohexanone (97%): ^{1}H NMR δ 0.22 (s, 6 H), 1.02 (s, 9 H), 1.40–2.15 (m, 12 H), 2.15–2.38 (m, 1 H), 2.26 (s, 6 H), 2.44–2.61 (m, 1 H), 3.07 (dd, J = 2.6, 8.1 Hz, 1 H), 3.20–3.60 (br, 1 H), 6.55 (s, 2 H), 6.85–6.93 (m, 2 H), 7.10–7.25 (m, 3 H); ^{13}C NMR δ -4.4, 18.2, 19.5, 21.5, 22.1, 25.7, 26.1, 32.0, 33.9, 34.9, 35.4, 63.6, 72.9, 120.6, 125.7, 128.18, 128.22, 129.3, 138.9, 141.8, 149.7. Anal. Calcd for $C_{29}H_{45}NO_2Si$: C, 74.46; H, 9.70; N, 2.99. Found: C, 74.39; H, 9.71; N, 2.90.

4-*N*-(Benzyloxycarbonyl)amino-6-phenyl-3-hexanol (6a). To **5a** (62 mg, 0.145 mmol) in THF (0.5 mL) was added TBAF (1 M in THF, 0.2 mmol). The reaction mixture was stirred for 1 h at rt, and then filtered through a short column of silica gel. After evaporation of volatiles, the residue was dissolved in CH_2Cl_2 (1 mL), to which DDQ (33 mg, 0.145 mmol) was added at 0 °C. The mixture was stirred for 30 min, filtered through Celite, evaporated, dissolved in MeOH (1 mL) and *aq*. HCl (0.1 M, 0.5 mL), and stirred at rt for 10 h. Saturated *aq*. Na_2CO_3 (0.5 mL) and benzyl chloroformate (120 mg, 0.70 mmol) were added to the mixture at

0 °C. The mixture was allowed to warm up to rt over 10 h. Extraction with ether followed by column chromatography (ether : hexane = 1 : 1) gave **6a** (47 mg, 99%): ^{1}H NMR δ 0.94 (t, J = 7.3 Hz, 3 H), 1.35–1.52 (m, 2 H), 1.65–1.95 (m, 2 H), 2.08 (br d, J = 4.9 Hz, 1 H), 2.50–2.85 (m, 2 H), 3.45–3.80 (m, 2 H), 4.95–5.05 (m, 1 H), 5.12 (s, 2 H), 7.05–7.45 (m, 10 H); ^{13}C NMR δ 10.3, 26.2, 30.8, 32.5, 55.1, 66.9, 76.0, 125.9, 128.1, 128.2, 128.3, 128.4, 128.5, 136.4, 141.6, 156.7. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.38; H, 7.88; N, 4.13.

The syntheses of **6b–e** were carried out according to the above procedure.

4-*N*-(Benzyloxycarbonyl)amino-1-phenyl-3-hexanol (6b). ^{1}H NMR δ 0.94 (t, J = 7.3 Hz, 3 H), 1.25–1.80 (m, 4 H), 2.36 (br d, J = 5.2 Hz, 1 H), 2.65 (dt, J = 13.8, 8.2 Hz, 1 H), 2.89 (dt, J = 13.8, 6.9 Hz, 1 H), 3.47–3.79 (m, 2 H), 4.70–4.93 (m, 1 H), 5.11 (s, 2 H), 7.14–7.40 (m, 10 H); ^{13}C NMR δ -4.4, 11.1, 18.1, 19.2, 23.7, 25.7, 32.7, 34.3, 62.6, 71.3, 120.2, 125.9, 128.4, 130.8, 137.9, 142.0, 150.0. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.12; H, 7.66; N, 4.25.

4-*N*-(Benzyloxycarbonyl)amino-5-methyl-3-hexanol (6c). ^{1}H NMR δ 0.89–1.04 (m, 9 H), 1.25–1.65 (m, 3 H), 1.85–2.03 (m, 1 H), 3.45–3.65 (m, 2 H), 4.60–4.75 (br, 1 H), 5.11 (s, 2 H), 7.30–7.40 (m, 5 H); ^{13}C NMR δ 10.3, 17.7, 20.3, 25.7, 28.3, 60.5, 67.0, 74.2, 128.1, 128.2, 128.5, 136.4, 157.2. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.75; H, 8.51; N, 5.27.

4-*N*-(Benzyloxycarbonyl)amino-2-methyl-3-hexanol (6d). ^{1}H NMR δ 0.85–1.04 (m, 9 H), 1.25–1.50 (m, 1 H), 1.52–1.90 (m, 3 H), 3.29 (dd, J = 3.3, 8.0

Hz, 1 H), 3.61–3.77 (m, 1 H), 4.95–5.10 (br, 1 H), 5.11 (s, 2 H), 7.30–7.40 (m, 5 H); ^{13}C NMR δ 10.6, 18.9, 19.0, 21.0, 30.8, 54.6, 66.6, 79.8, 128.0, 128.1, 128.5, 136.6, 156.4. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.67; H, 8.72; N, 5.23.

1-[1-*N*-(Benzyloxycarbonyl)amino-3-phenylpropyl]cyclohexanol (6e). ^1H NMR δ 1.1–1.8 (m, 12 H), 1.88–2.10 (m, 1 H), 2.53–2.85 (m, 2 H), 3.63 (dt, *J* = 2.6, 10.6 Hz, 1 H), 4.90–5.25 (m, 1 H), 7.10–7.45 (m, 10 H); ^{13}C NMR δ 21.7, 21.8, 25.5, 31.0, 32.7, 34.5, 34.8, 58.2, 66.8, 73.5, 125.8, 127.99, 128.05, 128.3, 128.5, 136.6, 142.0, 157.0. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.09; H, 7.89; N, 3.85.

Preparation of 1,3-Oxazolidin-2-ones 7. To a mixture of 2-(arylamino) alcohol **5** (0.5 mmol) and *i*-Pr_2EtN (0.2 mL) in CH_2Cl_2 (0.5 mL) at 0 °C was added triphosgene (0.3 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at rt overnight. After the addition of aqueous NH_4OH (30%, 0.5 mL), the mixture was extracted with ether, dried, and subjected to column chromatography to give **7** (80–90 %). **7a**: ^1H NMR δ 0.20 (s, 6 H), 0.98 (s, 9 H), 1.14 (t, *J* = 7.3 Hz, 3 H), 1.60–2.00 (m, 4 H), 2.07 (s, 3 H), 2.24 (s, 3 H), 2.41 (t, *J* = 8.1 Hz, 2 H), 4.12 (q, *J* = 7.4 Hz, 1 H), 4.56 (ddd, *J* = 7.4, 4.6, 3.3 Hz, 1 H), 6.54–6.60 (m, 2 H), 6.90–6.97 (m, 2 H), 7.16–7.30 (m, 3 H). **7b**: ^1H NMR δ 0.19 (s, 6 H), 0.73 (t, *J* = 7.4 Hz, 3 H), 0.97 (s, 9 H), 1.20–1.70 (m, 2 H), 1.80–2.20 (m, 2 H), 2.17 (s, 3 H), 2.21 (s, 3 H), 2.70–3.15 (m, 2 H), 4.05 (ddd, *J* = 9.2, 7.8, 5.0 Hz, 1 H), 4.64 (ddd, *J* = 11.2, 7.8, 2.3 Hz, 1 H), 6.50–6.59 (m, 2 H), 7.15–7.40 (m, 5 H). **7c**: ^1H NMR δ 0.18 (s, 6 H), 0.54 (d, *J* = 6.5 Hz, 3 H), 0.87 (d, *J* = 6.5 Hz, 3 H), 0.97 (s, 9 H), 1.15 (t, *J* =

7.2 Hz, 3 H), 1.70–2.00 (m, 3 H), 2.18 (s, 3 H), 2.26 (s, 3 H), 3.91 (dd, J = 9.1, 6.9 Hz, 1 H), 4.48 (ddd, J = 10.1, 6.9, 3.3 Hz, 1 H), 6.50–6.59 (m, 2 H). **7d**: ^{1}H NMR δ 0.18 (s, 6 H), 0.75 (t, J = 7.4 Hz, 3 H), 0.96 (s, 9 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.17 (d, J = 6.5 Hz, 3 H), 1.51–1.95 (m, 2 H), 2.00–2.18 (m, 1 H), 2.20 (s, 3 H), 2.24 (s, 3 H), 3.89 (q, J = 7.3 Hz, 1 H), 4.37 (q, J = 7.3 Hz, 1 H), 6.50–6.57 (m, 2 H).

(*E*)-1-Benzyloxy-2-[4-(*tert*-butyldimethylsiloxy)-2,6-xylyl]amino-octadec-4-en-3-ol (8). By a procedure similar to that for **5a**, the title compound was obtained from benzyl chloromethyl ether, **4**, and 2-hexadecenal (85%): ^{1}H NMR δ 0.19 (s, 6 H), 0.90 (t, J = 6.8 Hz, 3 H), 0.99 (s, 9 H), 1.20–1.44 (br, 22 H), 2.03 (q, J = 6.6 Hz, 2 H), 2.24 (s, 6 H), 3.13 (q, J = 3.4 Hz, 1 H), 3.22 (d, J = 9.1 Hz, 1 H), 3.50 (dd, J = 3.4, 9.3 Hz, 1 H), 3.71 (dd, J = 2.9, 9.3 Hz, 1 H), 4.23–4.35 (m, 1 H), 4.38 (d, J = 11.8 Hz, 1 H), 4.49 (d, J = 11.8 Hz, 1 H), 5.50 (dd, J = 5.4, 15.4 Hz, 1 H), 5.65–5.85 (m, 1 H), 6.50 (s, 2 H), 7.25–7.42 (m, 5 H); ^{13}C NMR δ -4.4, 14.1, 18.1, 18.8, 22.7, 25.7, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 60.0, 70.4, 73.8, 73.9, 120.0, 127.7, 127.9, 128.4, 130.2, 131.1, 132.1, 137.5, 137.7, 150.1. Anal. Calcd for $C_{39}H_{65}NO_3Si$: C, 75.06; H, 10.50; N, 2.24. Found: C, 74.92; H, 10.30; N, 2.35.

(*E*)-1-Benzyloxy-2-[4-(*tert*-butyldimethylsiloxy)-2,6-xylyl]amino-3-(palmitoyloxy)octadec-4-ene (9). To a mixture of **8** (72 mg, 0.12 mmol), Et_3N (0.5 mL, 3.6 mmol), and 4-(dimethylamino)pyridine (5 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added palmitic anhydride (200 mg, 0.4 mmol). The reaction mixture was stirred at rt overnight and then subjected to column chromatography (ether : hexane = 1 : 10) to give **9** (89 mg, 90%): ^{1}H NMR δ 0.16 (s, 6 H), 0.89

(t, J = 6.8 Hz, 6 H), 0.97 (s, 9 H), 1.26 (br s, 46 H), 1.45–1.65 (m, 2 H), 2.02 (q, J = 6.2 Hz, 2 H), 2.19 (s, 6 H), 2.10–2.25 (m, 2 H), 3.10–3.20 (br, 1 H), 3.25–3.50 (m, 3 H), 4.41 (d, J = 12.0 Hz, 1 H), 4.48 (d, J = 12.0 Hz, 1 H), 5.44–5.62 (m, 2 H), 5.77 (dt, J = 14.6, 6.2 Hz, 1 H), 6.47 (s, 2 H), 7.25–7.40 (m, 5 H); ^{13}C NMR δ -4.4, 14.1, 18.1, 18.8, 22.7, 24.9, 25.7, 28.9, 29.17, 29.22, 29.3, 29.5, 29.7, 31.9, 32.4, 34.5, 59.2, 68.8, 73.2, 74.4, 120.1, 125.1, 127.5, 127.6, 128.3, 130.6, 135.6, 137.8, 138.1, 149.9, 172.6. Anal. Calcd for $C_{55}H_{95}NO_4Si$: C, 76.60; H, 11.10; N, 1.62. Found: C, 76.85; H, 11.29; N, 1.53.

(*E*)-1-Benzyloxy-2-palmitamidooctadec-4-en-3-ol (10). To **9** (43 mg, 0.05 mmol) in THF (0.5 mL) was added TBAF (1 M in THF, 0.08 mmol). The reaction mixture was stirred for 30 min at rt, and then filtered through a short column of silica gel. After evaporation of volatiles, the residue was dissolved in CH_2Cl_2 (0.5 mL), to which at 0 °C was added DDQ (12 mg, 0.05 mmol). The mixture was stirred for 30 min, filtered through Celite, evaporated, dissolved in MeOH (1 mL) and *aq*. HCl (0.1 M, 0.2 mL), and stirred at rt for 6 h. Saturated aqueous Na_2CO_3 (0.5 mL) was added and the mixture was extracted with AcOEt, dried and evaporated. To the residue were added CH_2Cl_2 (0.5 mL), Et_3N (0.5 mL, 3.6 mmol), and 4-(dimethylamino)pyridine (5 mg, 0.04 mmol). The mixture was stired at reflux for 2 d, evaporated, and subjected to column chromatography ($CHCl_3$) to afford **10** (20 mg, 77%): ^{1}H NMR δ 0.88 (t, J = 6.2 Hz, 6 H), 1.25 (br s, 46 H), 1.50–1.70 (m, 2 H), 2.01 (q, J = 6.3 Hz, 2 H), 2.19 (t, J = 7.3 Hz, 2 H), 3.32 (d, J = 8.4 Hz, 1 H), 3.61 (dd, J = 9.6, 2.9 Hz, 1 H), 3.80 (dd, J = 9.6, 3.1 Hz, 1 H), 3.98–4.24 (m, 2 H), 4.44 (d, J = 12.0 Hz, 1 H), 4.68 (d, J = 12.0 Hz, 1 H), 5.44 (dd, J = 15.7, 5.9 Hz, 1 H), 5.73 (dt, J = 15.7, 6.3 Hz, 1 H), 6.16 (d, J = 7.8 Hz,

1 H), 7.25–7.40 (m, 5 H); ^{13}C NMR δ 14.1, 22.7, 25.8, 29.19, 29.25, 29.30, 29.4, 29.5, 29.67, 29.72, 31.9, 32.3, 36.9, 52.7, 70.0, 73.7, 74.3, 127.9, 128.1, 128.6, 129.1, 133.4, 137.3, 173.3. Anal. Calcd for $C_{41}H_{73}NO_3$: C, 78.41; H, 11.72; N, 2.23. Found: C, 78.12; H, 11.71; N, 2.22.

(*E*)-2-Palmitamidooctadec-4-ene-1,3-diol (11). To lithium (4.5 mg, 0.65 mmol) in liquid NH_3 at -78 °C was added **10** (12 mg, 19 μmol) in THF (0.5 mL). After the reaction mixture was stirred at -78 °C for 2 h and at -40 °C for 4 h, NH_4Cl and MeOH were added. The mixture was allowed to warm up to rt, filtered, evaporated, and subjected to column chromatography (MeOH : $CHCl_3$ = 1 : 10) to afford **11** (10 mg, 99%), ^{13}C NMR spectrum of which was identical to that of a natural sample: ^{13}C NMR δ 14.1, 22.7, 25.7, 29.1, 29.2, 29.3, 29.5, 29.7, 31.9, 32.3, 36.8, 54.4, 62.5, 74.7, 128.8, 134.3, 173.9.

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(9) The produced (3-phenylpropyl)amine was isolated as a benzyl carbamate **3**.

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(12) Crystal data: $C_{17}H_{25}NO$, M = 259.4, orthorhombic, space group *Pbca*, a = 14.182 (3), b = 16.776 (3), c = 13.264 (3) Å, U = 3156 (1) Å^3, Z = 8, D_c = 1.09 g/cm^3, Cu K_α radiation (λ = 1.54178 Å), μ = 4.45 cm^{-1}. Intensity data were measured on a Mac Science MXC3 diffractometer using ω-2θ scan technique. 2636 unique reflections within $3 \leq 2\theta \leq 130°$ were collected. The structure was solved by a direct method and refined anisotropically by the full-matrix least-squares to R = 0.066, R_w = 0.058, and S = 1.43 for 2332 reflections. All hydrogen atoms were located on a difference electron density map. The thermal parameter of each hydrogen atom was assumed to be isotropic and equal to that of the bonded atom.

(13) The OH group lies in the imino plane formed by N2, C16 and C17, making a planer 5-membered arrangement. The hydrogen bond N2•••H1 is oriented considerably inside of the direction of conventionally viewed nitrogen sp^2 lone pairs (∠C17–N2–H1 = 86.8(8)°) and the O1–H1•••N2 geometry is nonlinear (127(2)°), both presumably due to the constraints imposed by the 5-membered arrangement.

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Chapter 3

Regio- and Stereoselective Incorporation of a ^{13}C Nuclide into D-*ribo*-Phytosphingosine *via* SmI_2-Mediated C–C Formation with ^{13}C-Labeled Isocyanide

Abstract

Preparation of a ^{13}C-labeled isocyanide and its application to the total synthesis of [2-^{13}C]D-*ribo*-C_{18}-phytosphingosine are described. The synthesis of the labeled phytosphingosine is based on the use of the isocyanide as a ^{13}CH–NH_2 precursor in the SmI_2-mediated three-component coupling reaction, wherein regio- and stereoselective incorporation of a ^{13}C nuclide in the carbon skeleton is achieved.

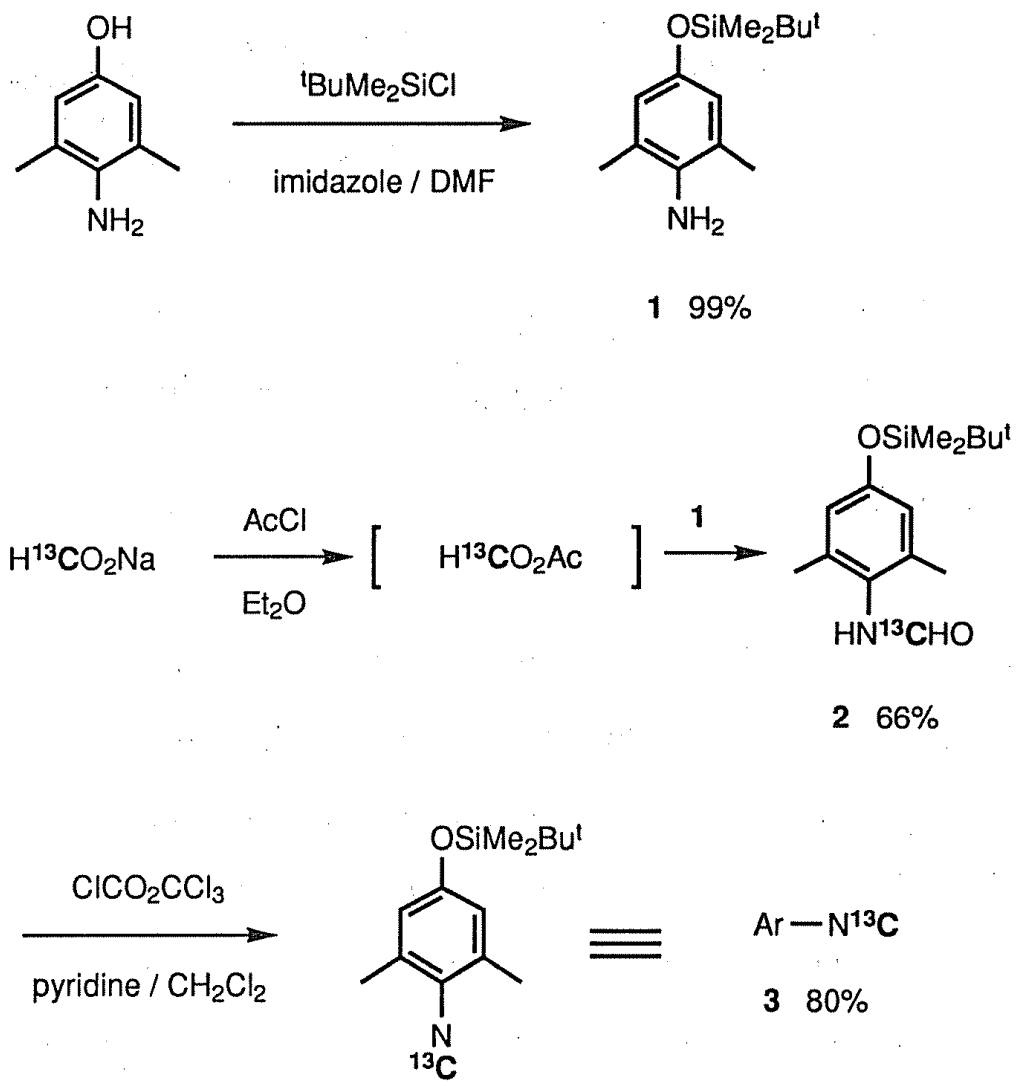
The understanding of structural features of biologically active compounds in solution is required to gain insight into the binding interaction between these molecules and their cellular receptors. There has been great advancement of NMR spectroscopy, particularly in isotope-assisted techniques to elucidate the conformation of such molecules in solution.[1] Hence, the use of compounds labeled with a ^{13}C nuclide becomes a powerful tool for structural studies.[2] This situation has created an increased need for synthetic methods of the incorporation of a ^{13}C nuclide at desired positions of target molecules with defined configurations. On the other hand, recent investigations concerning the role of sphingolipids in cellular surface have prompted intensified interest in their structural aspects.[3] We report here preparation of a ^{13}C-labeled isocyanide and its application to the stereoselective total synthesis of [2-^{13}C]D-*ribo*-C_{18}-phytosphingosine, a lipophilic component broadly distributed in animal as well as plant sphingolipids. The synthesis of the labeled phytosphingosine is based on the use of the isocyanide as a $^{13}CH–NH_2$ precursor in the SmI_2-mediated three-component coupling reaction,[4] wherein regio- and stereoselective incorporation of a ^{13}C nuclide is achieved.

First, a ^{13}C nuclide was installed in the starting aromatic isocyanide. Sodium formate with 99% ^{13}C enrichment, a commercially available compound, was treated with acetyl chloride. The resultant mixed anhydride was subsequently reacted with an aromatic amine **1** to give a labeled formamide **2**. Dehydration of **2** with trichloromethyl chloroformate furnished isocyanide (**3**) with the isocyano carbon labeled by a ^{13}C nuclide.

Next, [2-^{13}C]D-*ribo*-C_{18}-phytosphingosine (**13**) was synthesized on the basis of the synthetic route shown in Scheme 2-4. An optically active aliphatic

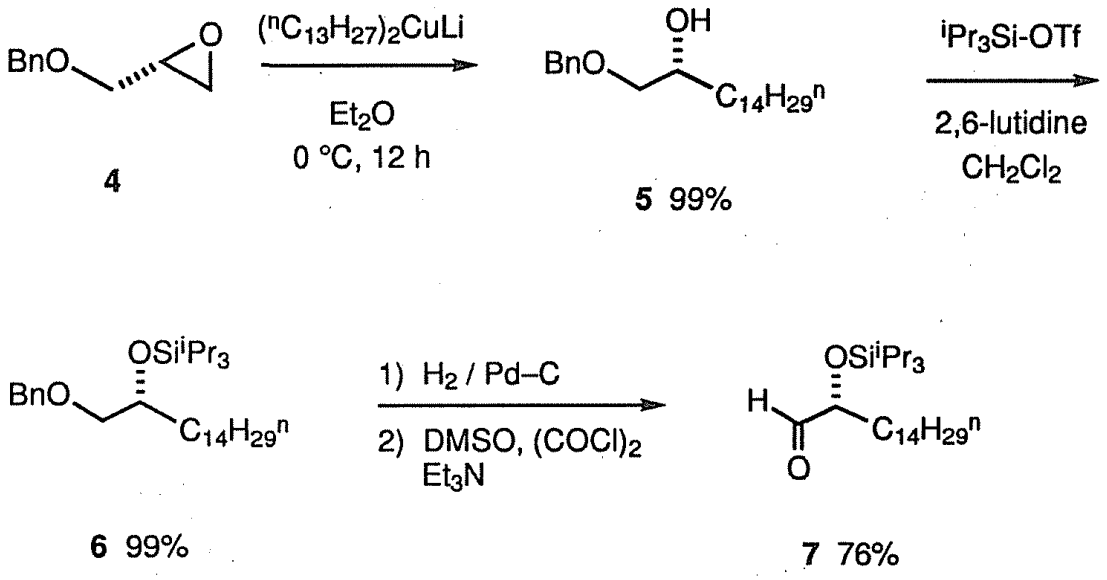
aldehyde **7**, (*R*)-2-(triisopropylsiloxy)pentadecanal, was prepared from a chiral

Scheme 1.



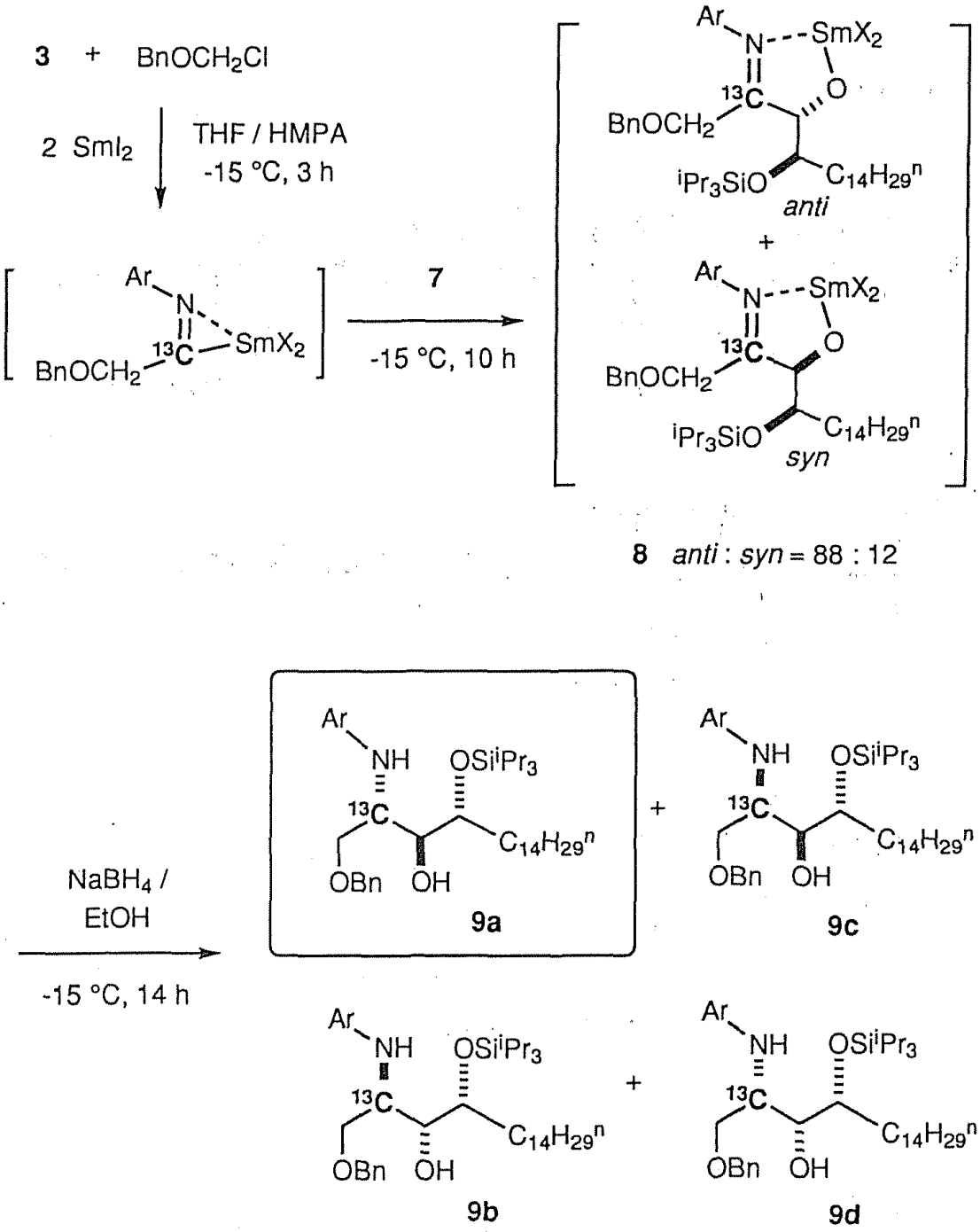
glycidol derivative **4**. A long aliphatic chain was introduced by alkylation of lithium dialkylcuprate with **4**. The secondary hydroxyl group of the ring-opened product **5** was protected as a triisopropylsilyl ether, giving **6**. Debenzylation by hydrogenolysis on Pd–C and the subsequent Swern oxidation of the resultant primary alcohol furnished the a-siloxy aldehyde **7**. ^{13}C-Labeled (imidoyl)–Sm(III), generated by the SmI_2-mediated coupling of the isocyanide **3** with benzyl

Scheme 2.



chloromethyl ether,[4] underwent the addition to the a-siloxy aldehyde **7** with fair 1,2-asymmetric induction (88:12). The stereoisomer expected based on Felkin's model,[5] designated as *anti*-**8** in Scheme 1, was produced preferentially. Addition of NaBH4 to the resultant reaction mixture in the presence of ethanol[6] led to stereoselective reduction of the imino functionality to afford a mixture of stereoisomers of amino alcohol (**9**). The isomers ratio was estimated as **9a**:**9b**:**9c**:**9d** = 86:11:2:<1[7] on the basis of the HPLC analysis of the sample obtained from an analogous pilot experiment using an unlabeled correspondent to **3** (*vide infra*). The fine stereoselection during the hydride reduction (*ca.* 98:2) is formulated as arising from the attack of hydride from the less-hindered side of the 5-membered chelate ring of *anti*-**8**. After the major isomer **9a** was isolated in 85% by MPLC, the aromatic substituent of the nitrogen atom was removed through desilylation by KF, oxidation to quinone imine by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Scheme 3.

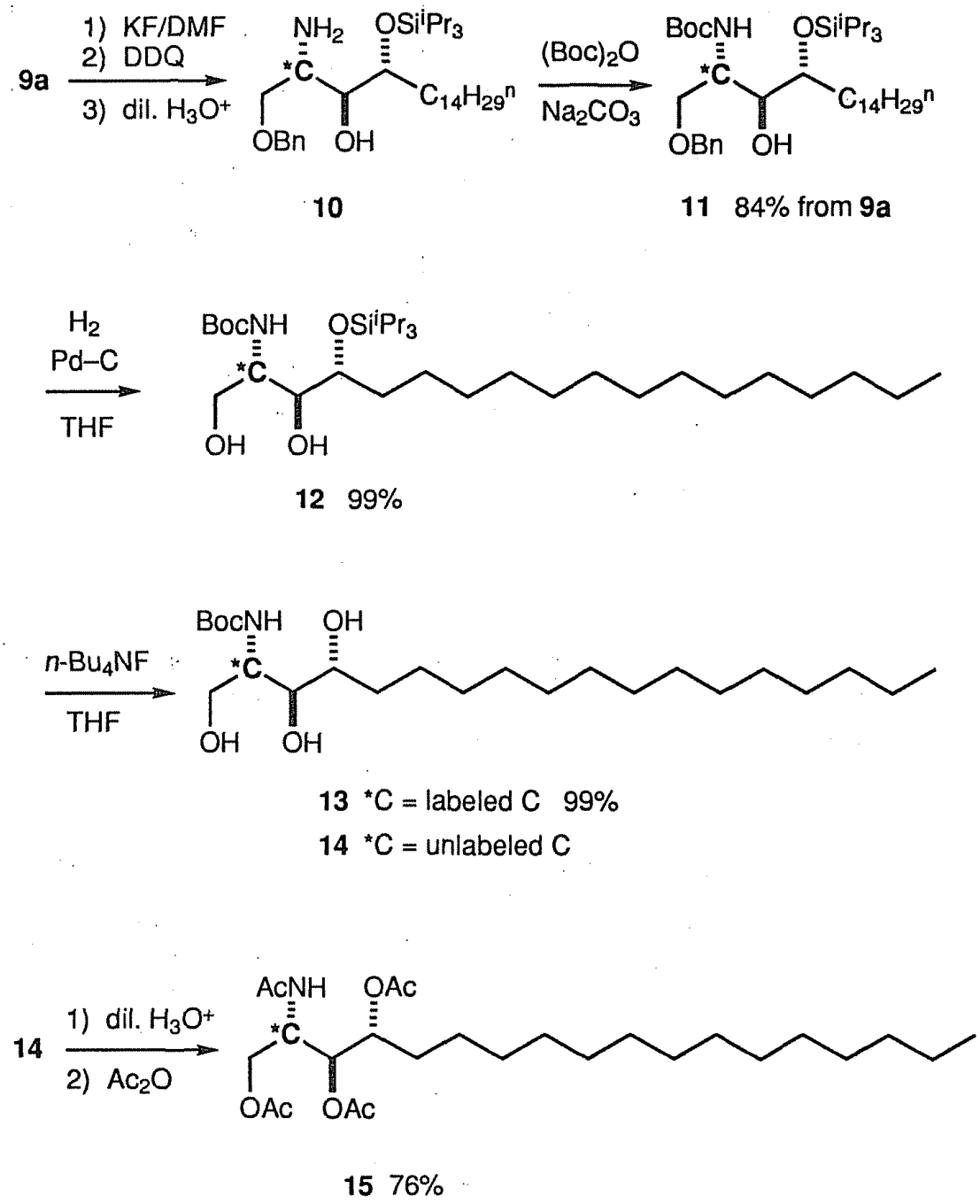


(DDQ), and acidic hydrolysis.[4c] Then, the primary amino group of **10** was protected with *t*-butoxycarbonyl (Boc) group.[8] Debenzylation of **11** by hydrogenolysis and the subsequent cleavage of triisopropylsilyl ether by *n*-

Bu4NF completed the synthesis of [2-^{13}C]D-*ribo*-C18-phytosphingosine having the Boc-protected amino group (**13**).[9]

A reaction sequence identical with that for the labeled **13**, starting from an

Scheme 4.



unlabeled isocyanide corresponding to **3**, led to the synthesis of the unlabeled counterpart **14**. Removal of the Boc-group under acidic conditions followed by acetylation with Ac_2O gave rise to the tetraacetate of D-*ribo*-C_{18}-phytosphingosine (**15**). Comparison of the physical data (^1H NMR, ^{13}C NMR, and optical rotation) of **15** with literature values[9] confirmed the identity of **15**, and hence, of [2-^{13}C]D-*ribo*-C_{18}-phytosphingosine (**13**).

In summary, an optically active labeled phytosphingosine was stereoselectively synthesized by the use of the ^{13}C-labeled isocyanide **3** as a $^{13}CH–NH_2$ precursor. Although ^{13}C-labeled carbon monoxide is an important source of a ^{13}C nuclide, it is not easy to control the stoichiometry of the precious gaseous material. Moreover, many carbonylation reactions require a high CO pressure. The availability of ^{13}C-labeled isocyanide and its efficient use in the stereocontrolled construction of a carbon skeleton, as demonstrated here, promise to open a new synthetic pathway to a wide range of biologically interesting compounds with specific labeling, which will provide the means of detailed structural investigation.

Experimental Section

General. Column chromatography was performed with silica gel 60 (E. Merck, Darmstadt), 230–400 mesh. Preparative TLC was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra were acquired in chloroform-*d*. Carbon chemical shifts were recorded relative to chloroform-*d* (d 77.0). Na_2SO_4 was used to dry organic layers after extraction. All reactions except for the hydrolyses of imines were performed under a dry nitrogen atmosphere. *(R)*-(Benzyloxymethyl)oxirane was purchased from DAISO co., ltd. Tridecanyllithium was prepared by a standard procedure.

4-(*tert*-Butyldimethylsiloxy)-2,6-xylidine (1). To a mixture of 4-amino-3,5-xylenol (2.74 g, 20.0 mmol) and imidazole (2.72 g, 40.0 mmol) in DMF (10 mL) at room temperature was added *tert*-butylchlorodimethylsilane (4.50 g, 30.0 mmol). The reaction mixture was stirred for 12 h, diluted with water, and extracted with ether. The organic extracts were washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, and distilled under vacuum to furnish the title compound (5.01 g, 99%): bp 115 °C (2 mmHg).

[*formyl*-^{13}C]-*N*-Formyl-4-(*tert*-butyldimethylsiloxy)-2,6-xylidine (2). To a stirred suspension of $H^{13}CO_2Na$ (345 mg, 5.0 mmol) in ether (1 mL) at room temperature was added acetyl chloride (393 mg, 5.0 mmol). After the reaction mixture was stirred for 12 h, *i*-Pr_2EtN (1.0 mL, 5.7 mmol) and **1** (1.26 g, 5.0 mmol) were added. The reaction mixture was stirred for 24 h, diluted with water, extracted with AcOEt, dried over $MgSO_4$, and concentrated. The residue was subjected to silica-gel column chromatography (ether:hexane = 1:1) to afford the title compound as a mixture of two isomers (55:45) (830 mg, 66%): ^1H NMR

($CDCl_3$) major δ 0.18 (s, 6H), 0.97 (s, 9H), 2.23 (s, 6H), 6,58 (s, 2H) 7.03 (d, J = 3.0 Hz, 1H), 8.01 (dd, J_{CH} = 193 Hz, J = 3.0 Hz, 1H); minor δ 0.20 (s, 6H), 0.98 (s, 9H), 2.18 (s, 6H), 6,56 (s, 2H), 6.80 (br, 1H), 8.37 (dd, J_{CH} = 194 Hz, J = 0.38 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -4.4, 18.1, 18.6, 18.8, 25.6, 119.4, 119.8, 125.7, 126.5, 136.5, 137.0, 154.7, 154.8, 159.7 (^{13}C), 165.3 (^{13}C).

[*isocyano*-^{13}C]-4-(*tert*-Butyldimethylsiloxy)-2,6-xylyl Isocyanide (3). To a solution of **2** (800 mg, 2.87 mmol) in pyridine (5 mL) and CH_2Cl_2 (10 mL) at -78 °C was added trichloromethyl chloroformate (0.36 mL, 3.0 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 1 h at -78 °C, and for additional 1 h at 0 °C, diluted with an aqueous solution of ammonium hydroxide (30%, 1 mL) and $NaHCO_3$ (1 mL), and then extracted with hexane. The organic extracts were subjected to silica-gel column chromatography (ether:hexane = 1:1), and then to vacuum distillation, affording the title compound (601 mg, 80%): bp 107 °C (0.35 mmHg); ^1H NMR ($CDCl_3$) δ 0.19 (s, 6H), 0.97 (s, 9H), 2.35 (s, 6H), 6.54 (s, 2H); ^{13}C NMR ($CDCl_3$) δ -4.4, 18.2, 19.0, 25.6, 119.1, 136.4, 155.5, 166.2 (^{13}C); HRMS *m/z* calcd for $^{13}C^{12}C_{14}H_{23}NOSi$: 262.1583, found 262.1582.

(*R*)-1-Benzyloxy-2-hexadecanol (5). To a suspension of CuI (3.05 g, 16.0 mmol) in Et_2O (30 mL) at -30 °C was added a solution of tridecanyllithium (32 mmol) in ether (36 mL). After the reaction mixture was stirred for 30 min, **4** (1.70 g, 10.4 mmol) was added dropwise. The reaction mixture was stirred at -30 °C for 2 h, and at 0 °C for 12 h, diluted with a saturated aqueous solution of NH_4Cl, and extracted with ether. The organic extracts were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. The residue was subjected to silica-gel column chromatography (ether:hexane = 1:10) to afford the title compound (3.58 g, 99%): $[\alpha]S(_{23,D})$ -3.2 ° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$)

δ 0.89 (t, J = 6.0 Hz, 3H), 1.26 (br, 24H), 1.35–1.50 (m, 2H), 2.34 (br, 1H), 3.33 (dd, J = 9.4, 8.0 Hz, 1H), 3.52 (dd, J = 9.4, 3.2 Hz, 1H), 3.74–3.90 (m, 1H), 4.56 (s, 2H) 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.5, 29.3, 29.5, 29.7, 31.9, 33.1, 70.4, 73.3, 74.7, 127.7, 128.4, 138.0. Anal. Calcd for $C_{23}H_{40}O_2$: C, 79.25; H, 11.57. Found: C, 79.24; H, 11.87.

(*R*)-1-Benzyloxy-2-(triisopropylsiloxy)hexadecane (6). To a mixture of **5** (3.58 g, 10.3 mmol) and 2,6-lutidine (2.3 mL, 20 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triisopropylsilyl trifluoromethanesulfonate (4.0 mL, 15 mmol). The mixture was stirred at room temperature for 10 h, diluted with a saturated aqueous solution of $NaHCO_3$, and extracted with ether. The organic extracts were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. The residue was subjected to silica-gel column chromatography (ether:hexane = 1:20) to afford the title compound **6** (5.14 g, 99%) as an oil: ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 6.7 Hz, 3H), 1.06 (br s, 18H), 1.27 (br s, 24H), 1.45–1.69 (m, 2H), 3.36–3.50 (m, 2H), 3.98 (quintet, J = 5.5 Hz, 1H), 4.54 (s, 2H), 7.27–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.1, 18.1, 22.7, 24.5, 29.4, 29.6, 29.7, 30.0, 31.9, 34.9, 71.5, 73.3, 74.3, 127.4, 127.6, 128.3, 138.6. Anal. Calcd for $C_{32}H_{60}O_2Si$: C, 76.12; H, 11.98. Found: C, 76.40; H, 12.23.

(*R*)-2-(Triisopropylsiloxy)hexadecanal (7). A mixture of **6** (2.0 g, 4.0 mmol) and 5% Pd/C (250 mg) in THF (30 mL)–EtOH (1 mL) under dihydrogen (150 atm) was stirred at 50 °C for 2 d. The reaction mixture was filtered, concentrated, and subjected to silica-gel column chromatography (ether:hexane = 1:10) to afford (*R*)-2-(triisopropylsiloxy)-1-hexadecanol (1.6 g, 97%).

To a stirred solution of this alcohol (409 mg, 0.99 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added oxalyl chloride (190 mg, 1.5 mmol). After 5 min,

dimethylsulfoxide (117 mg, 1.5 mmol) was added and the reaction mixture was stirred for 30 min at that temperature. Et_3N (1 mL) and a saturated aqueous solution of $NaHCO_3$ were added and the mixture was extracted with ether. The organic extracts were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. The residue was subjected to silica-gel column chromatography (ethyl acetate:hexane = 1:100) to afford the title compound (320 mg, 79%) as an oil: $[\alpha]S(24,_D)$ +9.4 ° (*c* 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 6.2 Hz, 3H), 1.01–1.15 (m, 21H), 1.21–1,50 (br, 24H), 1.54–1.69 (m, 2H), 4.07 (dt, *J* = 5.9, 2.2 Hz, 1H), 9.63 (d, *J* = 2.2 Hz 1H); ^{13}C NMR ($CDCl_3$) δ 12.2, 14.1, 17.9, 22.7, 23.9, 29.36, 29.40, 29.5, 29.7, 31.9, 33.5, 77.6, 204.9. Anal. Calcd for $C_{25}H_{52}O_2Si$: C, 72.75; H, 12.70. Found: C, 72.62; H, 12.95.

[2-^{13}*C*]-(2*S*,3*S*,4*R*)-1-Benzyloxy-2-[4-(*tert*-butyldimethylsiloxy)-2,6-xylyl]amino-4-(triisopropylsiloxy)octadecan-3-ol (9a). A mixture of samarium powder (180 mg, 1.2 mmol) and 1,2-diiodoethane (282 mg, 1.0 mmol) in THF (10 mL) was stirred at room temperature for 2 h. HMPA (0.5 mL, 2.8 mmol) was added and, after the reaction mixture was cooled to -15 °C, [*isocyano*-^{13}*C*]-4-(*tert*-butyldimethylsiloxy)-2,6-xylyl isocyanide (**3**, 105 mg, 0.40 mmol) and benzyl chloromethyl ether (78 mg, 0.50 mmol) were successively added. The reaction mixture was stirred for 2 h and **7** (123 mg, 0.30 mmol) was added. Stirring was continued for an additional 10 h, and then ethanol (1 mL) and $NaBH_4$ (100 mg, 2.6 mmol) were added. The mixture was stirred for 14 h at -15 °C, diluted with water (3 drops) and hexane (30 mL), and filtered through a short column of Florisil. The filtrate was subjected to MPLC (ethyl acetate:hexane = 1:30) to afford the title compound **9a** as an oil (204 mg, 85%): ^1H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.90 (t, *J* = 6.0 Hz, 3H), 0.99 (s, 9H), 1.05 (s, 2H), 1.18–1.32 (br, 26H), 2.24

(s, 6H), 3.00–3.20 (m, 2H), 3.45–3.60 (m, 1H), 3.63–4.10 (m, 4H), 4.40 (d, J = 11.9 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 6.50 (s, 2H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -4.4, 12.9, 14.1, 18.21, 18.24, 18.8, 22.7, 24.7, 25.7, 29.4, 29.6, 29.7, 30.1, 31.9, 34.0, 55.8 (^{13}C), 70.4 (d, J_{CC} = 39.6 Hz), 73.7, 74.4, 75.3 (d, J_{CC} = 39.1 Hz), 120.0, 127.6, 127.7, 128.4, 130.8, 137.77, 137.81, 149.8.

[2-^{13}*C*]-(2*S*,3*S*,4*R*)-1-Benzyloxy-2-[(*tert*-butoxycarbonyl)amino]-4-(triisopropylsiloxy)octadecan-3-ol (11). A mixture of **9a** (105 mg, 0.131 mmol), water (0.1 mL) and potassium fluoride (58 mg 1.0 mmol) in DMF (1 mL) was stirred at room temperature for 3 h. Volatiles were removed under vacuum, and the residue was extracted with ether. The organic extracts were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, concentrated, and dissolved in CH_2Cl_2 (1 mL), to which DDQ (50 mg, 0.22 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 3 h, filtered through Celite, and concentrated. The residue was dissolved in THF (1 mL) and dilute HCl (1 M, 0.1 mL). After the mixture was stirred for 10 h, a saturated aqueous solution of Na_2CO_3 (0.5 mL) and di-*tert*-butyl dicarbonate (100 mg, 0.46 mmol) were added. The mixture was stirred at room temperature for 10 h, and extracted with ethyl acetate. The organic extracts were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated. The residue was subjected to silica-gel column chromatography (ether:hexane = 1:20) to afford the title compound **11** (73 mg, 84%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.1 Hz, 3H), 1.07 (s, 21H), 1.26 (br, 24H), 1.43 (s, 9H), 1.55–1.70 (m, 2H), 2.73 (t, J = 4.9 Hz, 1H), 3.51–3.53 (m, 1H), 3.40–3.73 (m, 1H), 3.82 (br, J_{CH} = 138 Hz, 1H), 3.71–4.00 (m, 2H), 4.53 (s, 2H), 5.11 (br d, J = 9.1 Hz, 1H) 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 18.2, 22.7, 25.3, 28.4, 29.3, 29.6, 29.7, 30.0, 31.9,

32.0, 50.7 (^{13}C), 70.0 (d, J_{CC} = 40.0 Hz), 73.4, 73.8, 74.6 (d, J_{CC} = 41.1 Hz), 79.2, 127.5, 127.7, 128.4, 138.0, 155.3.

[2-^{13}*C*]-(2*S*,3*S*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]4-(triisopropylsiloxy)octadecane-1,3-diol (12). A mixture of **11** (47 mg, 0.071 mmol) and 5% Pd/C (50 mg) in THF (0.5 mL)) under a dihydrogen atmosphere was stirred room temperature for 15 h. The reaction mixture was filtered, and the filtrate was concentrated to afford the title compound **12** (40 mg, 99%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.2 Hz, 3H), 1.09 (s, 21H), 1.25 (br, 24H), 1.43 (s, 9H), 1.55–1.74 (m, 2H), 2.66 (t, J = 4.3 Hz, 1H), 2.75–2.96 (m, 1H), 3.30–4.10 (m, 4H), 3.74 (br, J_{CH} = 134 Hz, 1H), 5.09 (br d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 14.1, 18.1, 22.7, 25.4, 28.3, 29.4, 29.5, 29.7, 31.9, 32.3, 51.9 (^{13}*C*), 62.8 (d, J_{CC} = 38.5 Hz), 74.3, 75.2 (d, J_{CC} = 41.1 Hz), 79.5, 155.5.

[2-^{13}*C*]-(2*S*,3*S*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]octadecane-1,3,4-triol (13). A mixture of **12** (40 mg, 0.070 mmol) and tetrabuthylammonium fluoride (0.2 mmol) in THF (0.7 mL) was stirred for 3 h. The mixture was concentrated and the residue was purified by silica-gel column chromatography (ethyl acetate:hexane = 2:1) to afford the title compound **13** (29 mg, 99%) as white solids: $[\alpha]S(_{23,D})$ +7.7 ° (*c* 1.2, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.24 (br s, 24H), 1.40–1.60 (m, 2H), 1.44 (s, 9H), 3.40–4.20 (m, 7H), 3.81 (br, J_{CH} = 137 Hz, 1H), 5.43 (br d, J = 7.2 Hz, 1H); ^{13}C NMR (CD_3OD:$CDCl_3$ = 5:1) δ 12.7, 21.7, 25.0, 28.5, 28.8, 31.1, 31.4, 52.2 (^{13}*C*), 60.5 (d, J_{CC} = 39.4 Hz), 71.4, 74.6 (d, J_{CC} = 40.4 Hz), 78.4, 155.8; HRMS *m/z* calcd for $^{13}C^{12}C_{22}H_{48}NO_5$ (M+H): 419.3568, found 419.3558.

(2*S*,3*S*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]octadecane-1,3,4-triol (14). By a procedure similar to that for **13**, the title compound was obtained from

unlabeled 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl isocyanide.

(2*S*,3*S*,4*R*)-1-*O*,2-*N*,3-*O*,4-*O*-Tetraacetyl-2-aminooctadecane-1,3,4-triol (16). A solution of **14** (19 mg, 0.045 mmol) and water (0.05 mL) in trifluoroacetic acid (0.5 mL) was stirred at room temperature for 10 h. After volatiles were removed under vacuum, Ac_2O (150 mg, 1.47 mmol), Et_3N (0.5 mL), THF (0.5 mL), and a catalytic amount of DMAP were added. The mixture was stirred at room temperature for 18 h, diluted with water, and extracted with ether. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was subjected to silica-gel column chromatography (ethyl acetate:hexane = 2:1) to yield the title compound **16** (17 mg, 76%) as white solids: $[\alpha]S(_{24,D})$ +27.8 ° (*c* 0.73, $CHCl_3$) [lit. $[\alpha]_D$ +28.0 ° (*c* 1.30, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 6.1 Hz, 3H), 1.24 (br, 24H), 1.71 (m, 2H), 2.01 (s, 3H), 2.03 (s, 6H), 2.07 (s, 3H), 3.98 (dt, *J* = 11.6, 3.1 Hz, 1H), 4.32 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.39–4.53 (m, 1H), 4.92 (dt, *J* = 8.8, 3.9 Hz, 1H), 5.09 (dd, *J* = 8.3, 3.0 Hz, 1H), 5.97 (d, *J* = 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.8, 21.1, 22.7, 23.3, 25., 28.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 47.6, 62.9, 71.9, 73.0, 169.7, 170.1, 170.9, 171.2. Anal. Calcd for $C_{26}H_{47}O_7N$: C, 64.30; H, 9.75; N, 2.88. Found: C, 64.07; H, 9.61; N, 2.80.

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(6) The same stereoselectivity of the reduction was observed when 2-propanol was used instead of ethanol.

(7) The assignment of the stereochemistries for the minor isomers is tentative.

(8) Introduction of a long-chain fatty acid on the primary amino group in-

stead of Boc-protection at this stage would lead to the synthesis of a ceramid.

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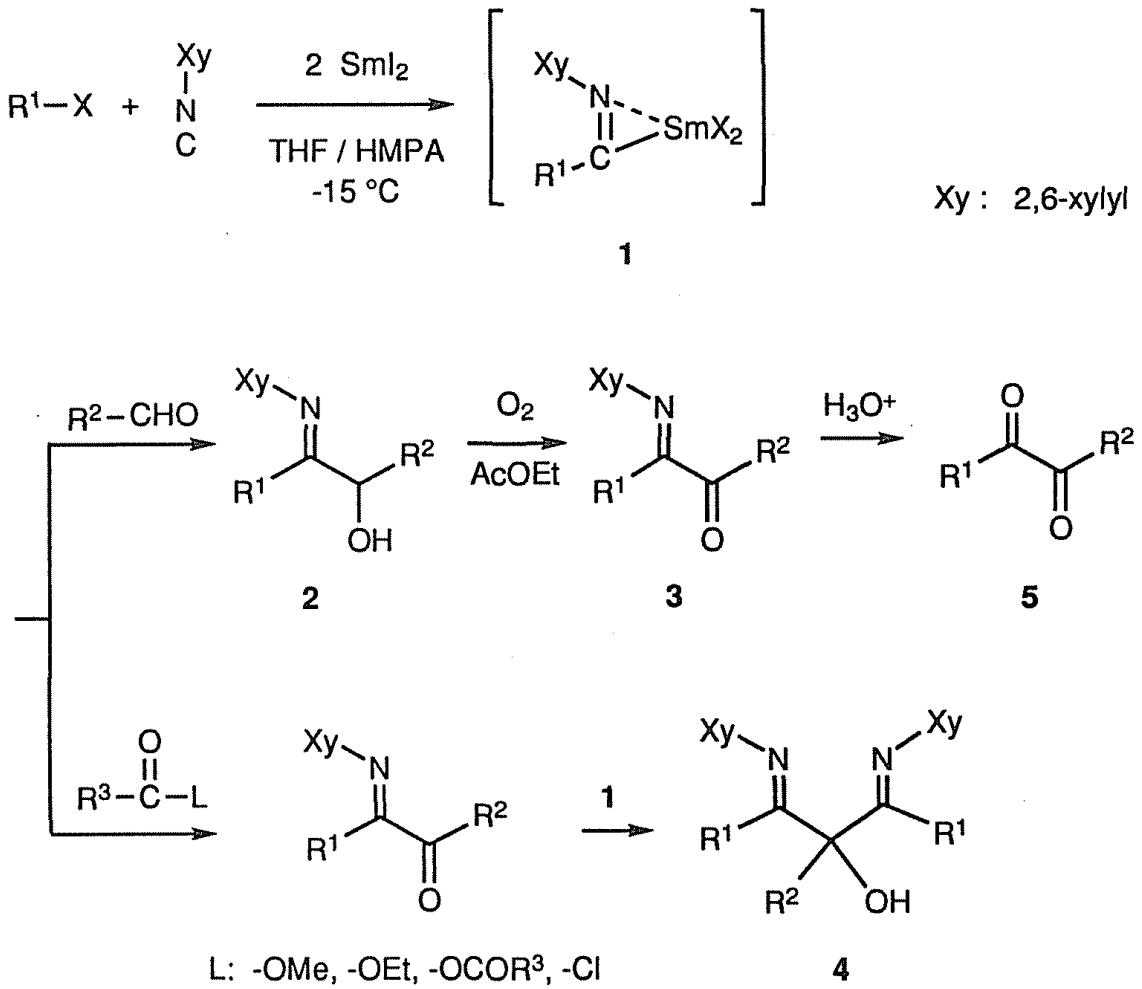
Chapter 4

Synthesis of Unsymmetrical α-Diketones via Autoxidation of α-Hydroxy Imines

Abstract

A new method for the synthesis of unsymmetrical α-diketones is developed. Autoxidation of α-hydroxy imines, prepared by samarium(II) iodide-mediated three-component coupling of an organic halide, 2,6-xylyl isocyanide, and a carbonyl compound, afforded the corresponding α-keto imines, which were hydrolyzed to α-diketones in high yield.

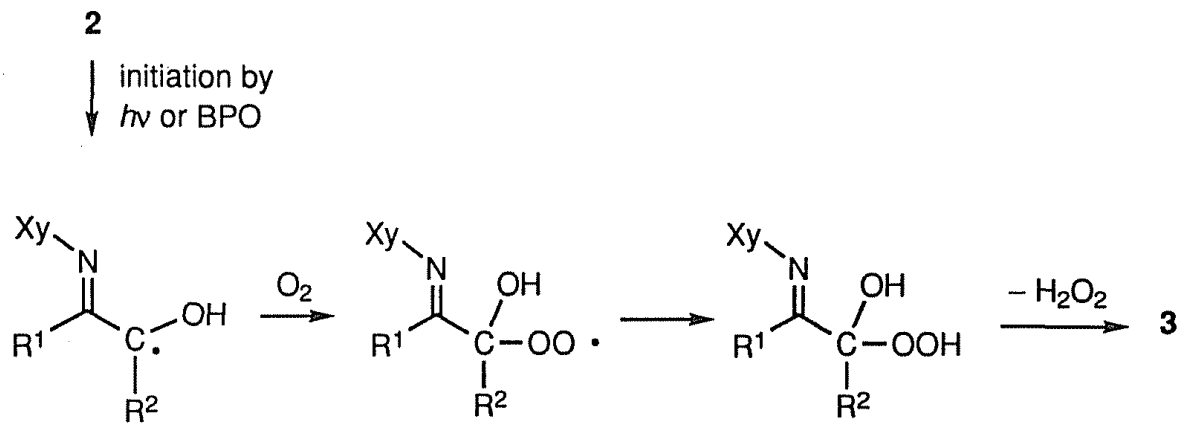
Due to their utility in organic synthesis and their biological activities, α-diketones have attracted considerable attention, and several important preparative methods for α-diketones have been developed.[1] Recently, we reported the synthesis of α-hydroxy imines **2** by the samarium(II) iodide-mediated three-component coupling of an organic halide, 2,6-xylyl isocyanide, and a carbonyl compound.[2]



3, 5	R^1	R^2	3, 5	R^1	R^2
a	$PhCH_2CH_2$	Et	**d**	Et	Ph
b	$PhCH_2CH_2$	*i*-Pr	**e**	$BnO(CH_2)_4$	2-Furyl
c	*i*-Pr	$PhCH_2CH_2$	**f**	*c*-Hexyl	2-Pyridyl

Further potential utilities of the (α-iminoalkyl)samarium(III) intermediate **1** involved in the reaction have been explored. However, attempts to prepare α-keto imines by the direct acylation were unsuccessful, because the α-keto imine once formed is so electrophilic and attacked by **1** again to afford a tertiary alcohol **4** as the major product. Herein, we describe a new synthetic method for unsymmetrical α-diketones via autoxidation of α-hydroxy imines **2** and subsequent hydrolysis of the imino group.

α-Hydroxy imines **2**, prepared according to the protocol reported previously,[2] were found to be very susceptible to autoxidation, *i.e.*, just on standing in air at room temperature, the formation of the corresponding α-keto imines **3** was observed. Efficient autoxidation of **2** to **3** was carried out by a simple procedure of bubbling oxygen into a refluxing solution of **2** in AcOEt.[3] Addition of a catalytic amount of benzoyl peroxide (BPO) accelerated the autoxidation. Although the precise mechanism is not clear, the reaction may proceed via a hydroxymethyl radical **6** formed initially by light or by benzoyl peroxide. Capture of the radical **6** by oxygen followed by hydrogen atom transfer from an α-hydroxy imine **2** gives a hydroperoxide together with the regeneration of the radical **6**. Elimination of hydrogen peroxide from the hydroperoxide gives rise to an α-keto imine **3**.[4]



The imino group of the α-keto imine **3** thus obtained was hydrolyzed by treatment with aqueous acid affording the corresponding α-diketone **5**. According to the present method, the same unsymmetrical α-diketone can be synthesized via two synthetic routes, *i.e.*, one incorporating R^1 from an organic halide and R^2 from an aldehyde, and the other vice versa (either **3b** or **3c** Æ **5b**).

In conclusion, a new and convenient synthetic route to a variety of α-diketones from organic halides, 2,6-xylyl isocyanide and aldehydes through samarium(II) iodide-mediated three-component coupling, autoxidation, and hydrolysis was established.

Experimental

General. Column chromatography was performed with silica gel (Wakogel C-200). Preparative TLC was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra were acquired in chloroform-*d*. Where appropriate, NMR data only for the major stereoisomer are described. Na_2SO_4 was used to dry organic layers after extraction. All reactions were performed under a dry nitrogen atmosphere.

Unless otherwise noted, materials were obtained from commercial sources and purified appropriately. THF was distilled from sodium diphenyl ketyl, DMF, CH_2Cl_2 and HMPA from CaH_2, and toluene from $LiAlH_4$.

6-Phenyl-4-(2,6-xylylimino)-3-hexanone (3a): The following describes the typical procedure for the synthesis of α-keto imines **3** through α-hydroxy imines **2**. The preparative procedure of α-hydroxy imines **2** was slightly modified from the previous report.[2] To a mixture of 2,6-xylyl isocyanide (**2**, 52 mg, 0.40 mmol),[5] HMPA (0.7 mL, 4.0 mmol), and SmI_2 (1.1 mmol) in THF (13 mL)[6] at -15 °C was added 2-phenylethyl bromide (92 mg, 0.50 mmol). After the mixture was stirred for 2 h, propionaldehyde (20 mg, 0.34 mmol) was added and the mixture was stirred at that temperature for an additional 3 h. Then, H_2O (a few drops), Et_2O (10 mL), and hexane (10 mL) were added to the reaction mixture, which was filtered through a short column of Florisil pretreated with Et_3N. The filtrate was evaporated and the residue was dissolved in AcOEt (35 mL), to which O_2 was bubbled with stirring at 80 °C for 11 h. Column chromatography on silica gel (ether : hexane = 1 : 5) gave **3a** as an yellow oil (88 mg, 87%): IR(neat) 1706, 1646cm^{-1}; ^1H NMR δ1.19 (t, J = 7.3, 3 H), 1.93 (s, 6 H), 2.50–2.69 (m, 4 H), 3.05 (q, J = 7.3, 2 H), 6.90–7.26 (m, 8 H); ^{13}C NMR δ7.9, 17.9, 30.8, 32.0, 123.9,

124.4, 126.3, 128.0, 128.2, 128.5, 140.5, 146.9, 168.9, 202.8.

2-Methyl-6-phenyl-4-(2,6-xylylimino)-3-hexanone (3b): From SmI_2 (1.1 mmol), HMPA (0.7 mL, 4 mmol), 2-phenylethyl bromide (92 mg, 0.50 mmol), **2** (52 mg, 0.40 mmol), pivalaldehyde (25 mg, 0.35 mmol) as described for **3a**. Autoxidation was carried out in the presence of BPO (3 mg, 12 mmol): IR (neat) 1702, 1644 cm^{-1}; ^1H NMR δ1.22 (d, J = 6.9, 6 H), 1.95 (s, 6 H), 2.47–2.67 (m, 4 H), 3.93 (sep, J = 6.9, 1 H), 6.90–7.27 (m, 8 H); ^{13}C NMR δ18.1, 18.4, 30.8, 31.9, 33.8, 123.8, 124.4, 126.2, 128.05, 128.15, 128.4, 140.4, 147.0, 168.5, 205.5.

5-Methyl-1-phenyl-4-(2,6-xylylimino)-3-hexanone (3c): From SmI_2 (1.1 mmol), HMPA (0.7 mL, 4 mmol), 2-iodopropane (86 mg, 0.51 mmol), **2** (52 mg, 0.40 mmol), 3-phenylpropanal (46 mg, 0.34 mmol) as described for **3a** [isolated by preparative TLC (ether : hexane = 1 : 10). Autoxidation was carried out in the presence of BPO (6 mg, 25 mmol): IR (neat) 1706, 1642 cm^{-1}; ^1H NMR δ1.08–1.30 (m, 6 H), 2.01 (s, 6 H), 2.25–2.58 (m, 1 H), 3.02 (t, J = 7.7, 2 H), 3.34 (t, J = 7.7, 2 H), 6.82–7.38 (m, 8 H); ^{13}C NMR δ18.1, 18.9, 29.9, 31.4, 40.5, 123.4, 124.1, 126.0, 127.9, 128.1, 128.4, 141.0, 146.8, 172.7, 201.7.

1-Phenyl-2-(2,6-xylylimino)-1-butanone (3d): From SmI_2 (1.1 mmol), HMPA (1.0 mL, 5.7 mmol), bromoethane (56 mg, 0.51 mmol), **2** (52 mg, 0.40 mmol), benzaldehyde (36 mg, 0.34 mmol) as described for **3a**: IR (neat) 1676, 1598 cm^{-1}; ^1H NMR δ1.01 (t, J = 7.7, 3 H), 2.13 (s, 6 H), 2.45 (q, J = 7.7, 2 H), 6.90–7.10 (m, 3 H), 7.47–7.69 (m, 3 H), 8.17–8.23 (m, 2 H) ^{13}C NMR δ9.8, 18.5, 23.8, 123.7, 124.9, 128.1, 128.4, 130.3, 133.6, 135.3, 147.1, 172.4, 193.7.

6-Benzyloxy-1-furyl-2-(2,6-xylylimino)-1-hexanone (3e): From SmI_2 (1.1 mmol), HMPA (0.7 mL, 4 mmol), 1-benzyloxy-4-bromobutane (118 mg, 0.49 mmol), **2** (51 mg, 0.39 mmol), furfural (39 mg, 0.41 mmol) as described for

3a [isolated by preparative TLC (ether : hexane = 1 : 5)]. Autoxidation was carried out in the presence of BPO (3 mg, 12 mmol): IR (neat) 1656 cm^{-1}; ^1H NMR δ1.44–1.56 (m, 4 H), 2.08 (s, 6 H), 2.42 (t, J = 7.6, 2 H), 3.33 (t, J = 5.9, 2 H), 4.39 (s, 2 H), 6.59 (q, J = 1.8, 1 H), 6.91–7.10 (m, 3 H), 7.20–7.38 (m, 5 H), 7.72–7.79 (m, 2 H); ^{13}C NMR δ18.3, 22.5, 29.5, 29.7, 69.5, 72.8, 112.5, 123.3, 123.8, 124.7, 127.4, 127.5, 128.1, 128.3, 138.4, 146.9, 148.0, 150.7, 170.1, 179.4.

2-Cyclohexyl-1-(pyrid-2-yl)-2-(2,6-xylylimino)-1-ethanone (3f): From SmI_2 (1.0 mmol), HMPA (0.7 mL, 4 mmol), bromocyclohexane (82 mg, 0.50 mmol), **2** (51 mg, 0.39 mmol), 2-pyridinecarbaldehyde (43 mg, 0.40 mmol) as described for **3a** [isolated by gel permeation chromatography]: IR (neat) 1692, 1658 cm^{-1}; ^1H NMR δ1.04–2.50 (m, 16 H), 2.84 (tt, J = 11.3, 3.4, 1 H), 6.59–7.09 (m, 3 H), 7.31–8.21 (m, 3 H), 8.56–8.75 (m, 1 H); ^{13}C NMR δ18.1, 26.1, 30.0, 44.7, 121.5, 123.1, 126.7, 127.18, 127.24, 136.7, 147.2, 148.6, 152.0, 175.9, 198.5.

1-Phenyl-3,4-hexandione (5a): A solution of **3a** (125 mg, 0.43 mmol) in THF (15 mL)–*aq*. HCl (0.5 N, 10 mL) was stirred at room temperature for 50 min. $NaHCO_3$ (0.44 g, 5.2 mmol) was added and the mixture was extracted with AcOEt, dried, and evaporated. Column chromatography on silica gel (ether : hexane = 1 : 10) gave **5a** as an yellow oil (80 mg, 99%): IR (neat) 1716 cm^{-1}; ^1H NMR δ1.07 (t, J = 7.2, 3 H), 2.75 (q, J = 7.2, 2 H), 2.87–2.99 (m, 2 H), 3.06–3.16 (m, 2 H), 7.13–7.35 (m, 5 H); ^{13}C NMR δ6.8, 29.0, 29.5, 37.7, 126.3, 128.3, 128.5, 140.4, 198.8, 200.0.

2-Methyl-6-phenyl-3,4-hexandione (5b): From **3b** (38 mg, 0.12 mmol) as described for **5a** [THF (5 mL)–*aq*. HCl (0.5 N, 5 mL), room temperature, 1.5 h, isolated by preparative TLC (ether : hexane = 1 : 5)]. From **3c** (16 mg, 0.052

mmol) as described for **5a** [THF (2.5 mL)–*aq*. HCl (0.5 N, 2.5 mL), room temperature, 1.5 h]: IR (neat) 1716 cm^{-1}; ^1H NMR δ1.06 (d, J = 7.0, 6 H), 2.87–2.98 (m, 2 H), 3.04–3.15 (m,.2 H), 3.35 (sep, J = 7.0, 1 H), 7.15–7.35 (m, 5 H); ^{13}C NMR δ17.3, 29.0, 33.7, 38.3, 126.3, 128.3, 128.5, 140.3, 199.5, 202.9.

1-Phenyl-1,2-butandione (5d): From **3d** (26 mg, 0.10 mmol) as described for **5a** [THF (10 mL)–*aq*. HCl (1 N, 5 mL), 80 °C, 1 h, isolated by preparative TLC (ether : hexane = 1 : 8)]: IR (neat) 1738, 1678 cm^{-1}; ^1H NMR δ1.21 (t, J = 7.3, 3 H), 2.92 (q, J = 7.3, 2 H), 7.45–7.57 (m, 2 H), 7.61–7.71 (m, 1 H), 7.94–8.05 (m, 2 H); ^{13}C NMR δ6.8, 32.1, 128.9, 130.1, 132.0, 134.6, 192.6, 203.9.

6-Benzyloxy-1-furyl-1,2-hexandione (5e): From **3e** (57 mg, 0.15 mmol) as described for **5a** [THF (10 mL)–*aq*. HCl (0.3 N, 5 mL), room temperature, 30 min, isolated by preparative TLC (ether : hexane = 1 : 5)]: IR (neat) 1718, 1664, 1106 cm^{-1}; ^1H NMR δ1.56–1.87 (m, 4 H), 2.95 (t, J = 6.8, 2 H), 3.50 (t, J = 5.8, 2 H), 4.50 (s, 2 H), 6.58–6.63 (m, 1 H), 7.19–7.41 (m, 5 H), 7.65 (d, J = 3.7, 1 H), 7.75 (d, J = 0.75, 1 H); ^{13}C NMR δ19.8, 29.0, 37.1, 69.8, 72.9, 112.9, 124.7, 127.5, 127.6, 128.3, 138.4, 148.8, 149.1, 176.5, 200.1.

2-Cyclohexyl-1-(pyrid-2-yl)-1,2-ethandione (5f): From **3f** (72 mg, 0.23 mmol) as described for **5a** [THF (10 mL)–*aq*. HCl (0.5 N, 5 mL), room temperature, 45 min, isolated by gel permeation chromatography]: IR (neat) 1712, 1696 cm^{-1}; ^1H NMR δ1.11–2.07 (m, 10 H), 2.90 (tt, J = 11.0, 3.6, 1 H), 7.46–7.56 (m, 1 H), 7.83–7.94 (m, 1 H), 8.05 (d, J = 7.8, 1 H), 8.70 (d, J = 4.4, 1 H); ^{13}C NMR δ25.3, 25.7, 27.0, 47.1, 123.1, 127.9, 137.1, 149.6, 151.2, 195.7, 208.7.

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(2) Murakami, M.; Kawano, T.; Ito, H.; Ito, Y. *J. Org. Chem.* **1993**, *58*, 1458.

(3) Autoxidation of an a-hydroxy ketone having the same substituents as the α-hydroxy imine **2a** ($R^1 = PhCH_2CH_2$, $R^2 = Et$) under more forcing conditions (in the presence of BPO, 80 °C, 28 h) afforded a 1 : 4 mixture of the a-diketone **5a** and the starting compound. This result indicates the higher susceptibility of a-hydroxy imines toward autoxidation.

(4) When the autoxidation of **2** was carried out in the presence of triphenylphosphine, triphenylphosphine oxide was obtained quantitatively together with an a-keto imine. Autoxidation of triphenylphosphine itself in the absence of **2** failed to proceed under the similar conditions, whereas treatment of triphenylphosphine with hydrogen peroxide promptly afforded triphenylphosphine oxide. These results may be ac-

counted for by assuming the generation of hydrogen peroxide during the course of the autoxidation of **2**.

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(6) Girard, P.; Namy, L.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

Chapter 5

Preparation of (Alkaneimidoyl)lanthanides and Their Reactions with Carbonyl Compounds

Abstract

The preparation of (alkaneimidoyl)lanthanide(III) reagents and their reactions with carbonyl compounds were studied. Alkyllithium was added to a mixture of an anhydrous lanthanide salt and 2,6-xylyl isocyanide in tetrahydrofuran at -78 °C. Among a series of lanthanide salts, $CeCl_3$ effected the quantitative conversion of the isocyanide to afford an orange solution of (alkaneimidoyl)cerium(III). Although $LaCl_3$, SmI_3, and $Sm(OTf)_3$ were found to be highly reactive, multiple insertion of the isocyanide ensued. (Alkaneimidoyl)cerium(III) could also be prepared by the reaction of dialkylmagnesium with $CeCl_3$ and 2,6-xylyl isocyanide at -45 °C. The thus-prepared (alkaneimidoyl)cerium(III) reacted with a carbonyl compound to afford an addition product, *i.e.*, an α-hydroxy imine. The present reactions for the preparation of (alkaneimidoyl)cerium(III) provide a convenient synthetic equivalent to a nucleophilic acyllanthanide species with a wide variation for the acyl group. In the cace of absence of lanthanide salt, the reaction of alkyllithium with 2,6-xylyl isocyanide led to the trimerization of the isocyanide to afford an indole derivative.

The migratory insertion of carbon monoxide into a metal–alkyl bond to furnish an acylmetal is one of the most fundamental elementary processes in organometallic chemistry. The isocyano carbon of an isocyanide also undergoes insertion into a metal–alkyl bond to afford an (alkaneimidoyl)metal compound (hereafter *alkaneimidoyl* is abbreviated to *imidoyl*), which has found successful synthetic applications.[1] On the other hand, since the appearance of seminal papers by Luche[2] and Kagan,[3] ever-increasing research activities have been directed toward the use of lanthanide reagents for synthetic purposes.[4] In many cases, however, the intermediate organolanthanide has not been established as being definitive. Hence, the preparative methods of new organolanthanide reagents, which are thermodynamically stable, are yet to be developed. Recently, we have found that the SmI_2-mediated coupling of aryl isocyanide with an alkyl halide furnishes an (imidoyl)samarium(III) species, which is reasonably stable up to 0 °C in the presence of hexamethylphosphoric triamide.[5] The (imidoyl)samarium(III) disclosed unique chemical properties in terms of nucleophilicity and basicity, that set itself apart from the existing analogous imidoyl complexes of the main group and transition elements. Of much interest is the behavior of imidoyl complexes of other lanthanide series. This paper describes the results of our study on the preparation of (imidoyl)lanthanide(III) reagents and their reactions with carbonyl compounds.

Results and Discussion

Preparation of (Imidoyl)lanthanide by the Reaction of Isocyanide with a Lanthanide Salt and Organolithium.

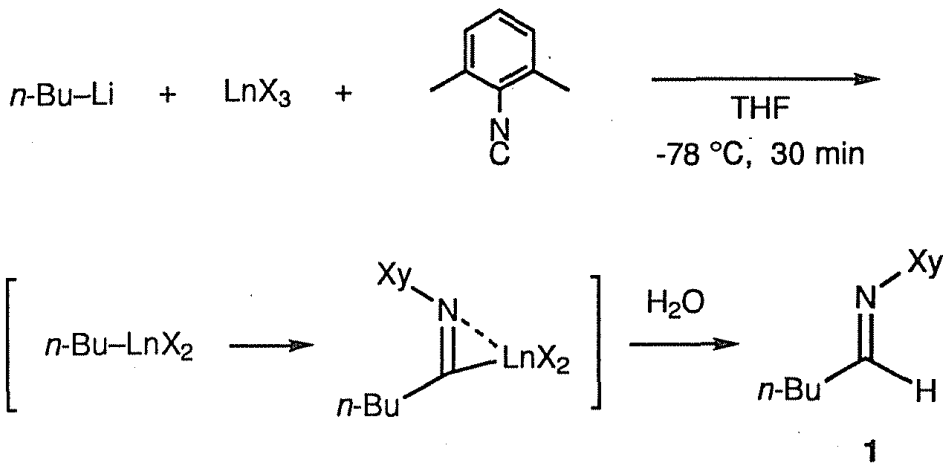
The reaction of a lanthanide(III) salt with organolithium has been assumed to generate the corresponding organolanthanide through transmetallation, although the precise structure of the intermediate is equivocal.[6] Thus, butyllithium (1.0 equiv) was added to a white milky suspension of an anhydrous lanthanide(III) salt (1.1 equiv) and 2,6-xylyl isocyanide (1.0 equiv) in tetrahydrofuran (THF) at -78 °C. The reaction mixture was stirred for 30 min and then quenched with water. The results with a series of lanthanide salts are shown in Table 1. The use of $CeCl_3$ effected the complete conversion of the isocyanide to afford an orange solution with dissolution of the lanthanide salt and, after hydrolysis, an aldimine (**1**) was produced quantitatively (Run 2). As fuller discussion will be presented later, the reaction of butyllithium alone with 2,6-xylyl isocyanide at -78 °C results in the quantitative formation of an anomalous product through trimerization of the isocyanide.[7] The fact that no such trimer was produced with $CeCl_3$ suggested that, prior to a direct reaction of free butyllithium with the isocyanide, a putative butylcerium(III) was formed by transmetallation between butyllithium and $CeCl_3$. Subsequently, an exclusive single insertion of 2,6-xylyl isocyanide into the C–Ce bond occurred to afford (imidoyl)cerium(III), for which we assumed a η^2-bound structure (*vide infra*).

Although $LaCl_3$, SmI_3, and $Sm(OTf)_3$ were found to also be highly reactive, multiple insertion of the isocyanide ensued (Runs 1, 4, and 5). In the cases of $EuCl_3$ and $GdCl_3$, the isocyanide remained unreacted after 30 min at -78 °C with

the appearance of the white milky suspension being unchanged. After hydrolysis, no **1** was obtained (Runs 6 and 7). Since neither was produced the aforementioned trimer, it is unlikely that butyllithium remained unchanged. A "complexing salt" or "butyllanthanide", which encumbered the reaction with the isocyanide, might have been formed.

When 1,1,3,3-tetramethylbutyl isocyanide was used instead of 2,6-xylyl isocyanide under conditions analogous to those used in Run 2, no **1** was obtained after hydrolysis. This result disclosed that a tertiary alkyl isocyanide is less reactive toward organocerium(III) than an aromatic isocyanide.

Table 1. Reaction of Isocyanide with Lanthanide Salts and Butyllithiu
(Xy=2,6-xylyl

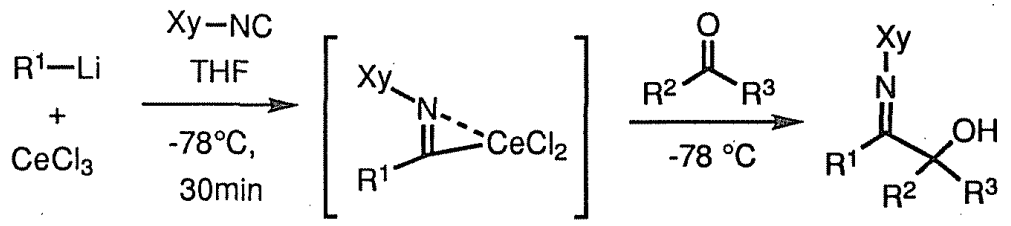


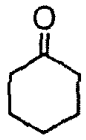
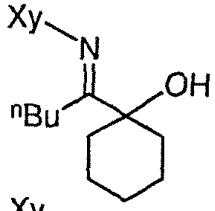
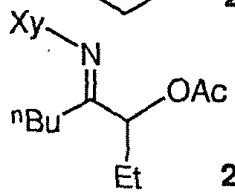
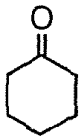
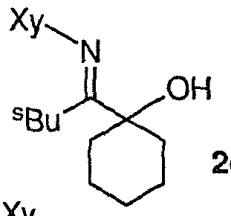
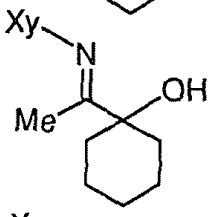
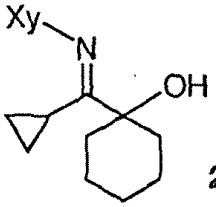
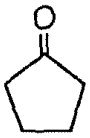
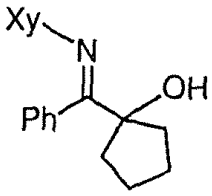
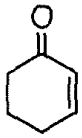
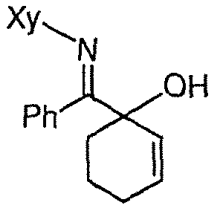
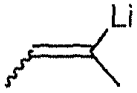
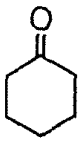
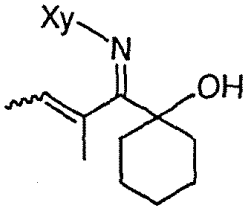
Run	LnX_3	Yield of **1** (%)	Yield of Oligomers (%)
1	$LaCl_3$	63	21
2	$CeCl_3$	99	0
3	$SmCl_3$	14	0
4	SmI_3	43	30
5	$Sm(OTf)_3$	13	74
6	$EuCl_3$	0	0
7	$GdCl_3$	0	0
8	$YbCl_3$	21	4
9	$Yb(OTf)_3$	10	0

Reactions of (Imidoyl)lanthanides with Carbonyl Compounds.

The addition of other organolithium reagents to a mixture of 2,6-xylyl isocyanide and $CeCl_3$ also produced an orange solution of the corresponding (imidoyl)cerium(III). When a carbonyl compound was reacted with the (imidoyl)cerium(III) at -78 °C, an addition product, *i.e.*, an α-hydroxy imine (**2**) was obtained in moderate to high yields.The (imidoyl)cerium(III) was stable at temperatures of up to -40 °C, and the reaction at higher temperature led to a gradual collapse of the intermediate to decrease the yield of **2**. Selected examples of the synthesis of a-hydroxy imines from a variety of organolithiums and carbonyl compounds are shown in Table 2. The methyl, phenyl, and vinyl groups were easily coupled with the isocyanide (Runs 1,6–8), whereas the incorporation of these groups in the skeleton of an α-hydroxy imine using organic halides as the source in SmI_2-mediated three-component coupling was unsuccessful.[5] An alkynylcerium failed to react with the isocyanide, in contrast to the reaction with carbonyl compounds.[6d] a-Hydroxy imines were obtained as well by the reaction with an aldehyde (Run 2), and even with cyclopentanone (Run 6), which is extremely susceptible to enolization when treated with nucleophilic organometal-

Table 2. Reactions of (Alkaneimidoyl)cerium(III) with Carbonyl Compounds (Xy = 2,6-xylyl)



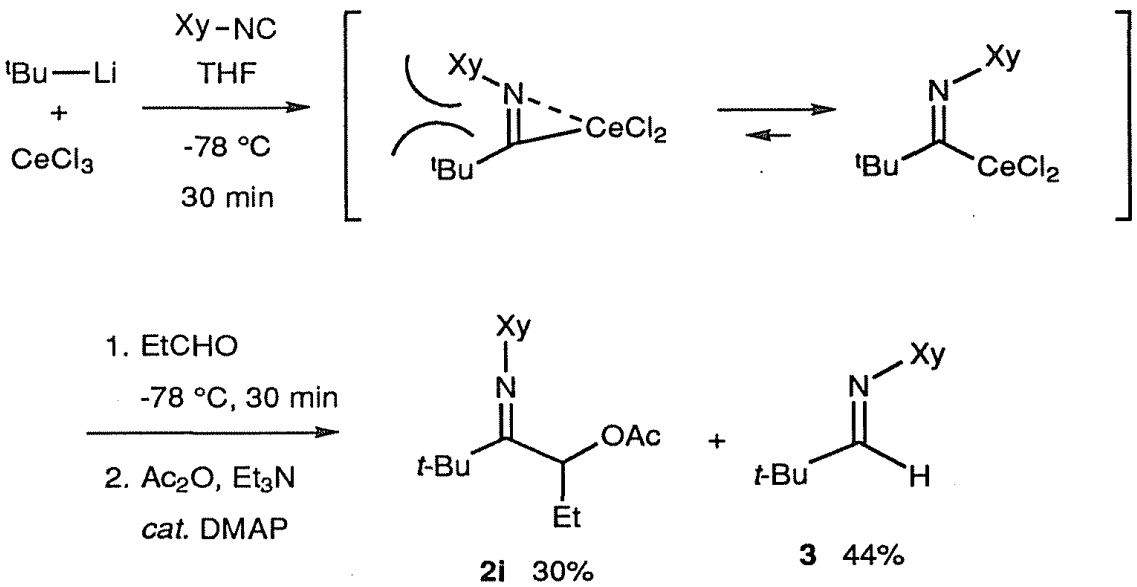
Run	R^1–Li	$R^2R^3C{=}O$	Product (2)	Yield (%)
1	^{n}Bu–Li		 **2a**	99
2	^{n}Bu–Li	EtCHO	 **2b**	95 a)
3	^{s}Bu–Li		 **2c**	90
4	Me–Li		 **2d**	68
5			 **2e**	54
6	Ph–Li		 **2f**	83
7	Ph–Li		 **2g**	80
8			 **2h**	87

a) The reaction was quenched by adding Ac_2O, Et_3N, and 4-(dimethylamino)pyridine.

lics. On the contrary, (imidoyl)lithium prepared from 1,1,3,3-tetramethylbutyl isocyanide with butyllithium according to Walborsky's procedure,[1a-1c] failed to add to cyclopentanone. Thus, the low basicity of the (imidoyl)cerium(III) reagent is noteworthy. Like other organolanthanides, (imidoyl)cerium(III) underwent a selective 1,2-addition to an α,β-unsaturated ketone (Run 7).

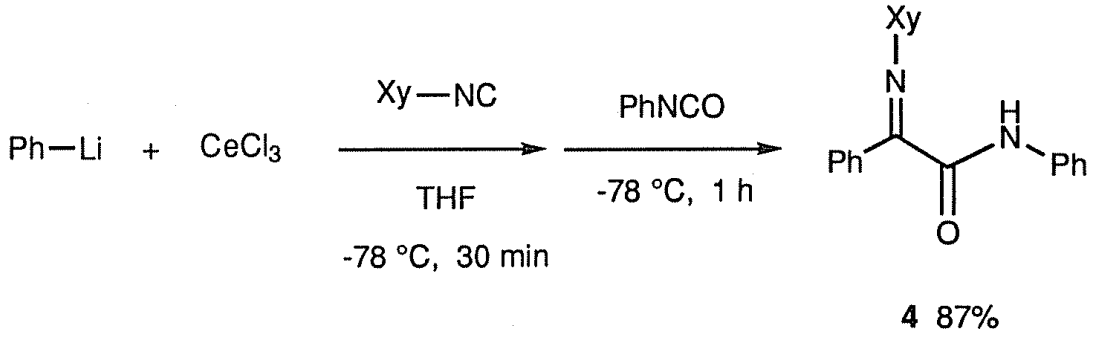
Whereas secondary as well as primary alkyllithium reagents furnished **2** in good yield, the reaction of (imidoyl)cerium(III) derived from *tert*-butyllithium with propionaldehyde afforded **2i** in only 30% yield together with an aldimine **3** in 44% yield (Scheme 1). The low-yield coupling with the aldehyde might have been due to the collapse of the intermediate (imidoyl)cerium(III) species. We suspect that the steric repulsion between the bulky *tert*-butyl group and the 2,6-xylyl group disfavors the η^2-bound structure. The *tert*-butyl group is pushed away to the other side of the imino group, thereby rendering η^2-binding difficult. The enforced η^1-complex is less stable to decompose gradually, even at -78 °C.

Scheme 1.



When phenyl isocyanate was reacted with the PhLi-derived (imidoyl)cerium(III), an amide **4** was produced in 87% yield (Scheme 2).

Scheme 2.



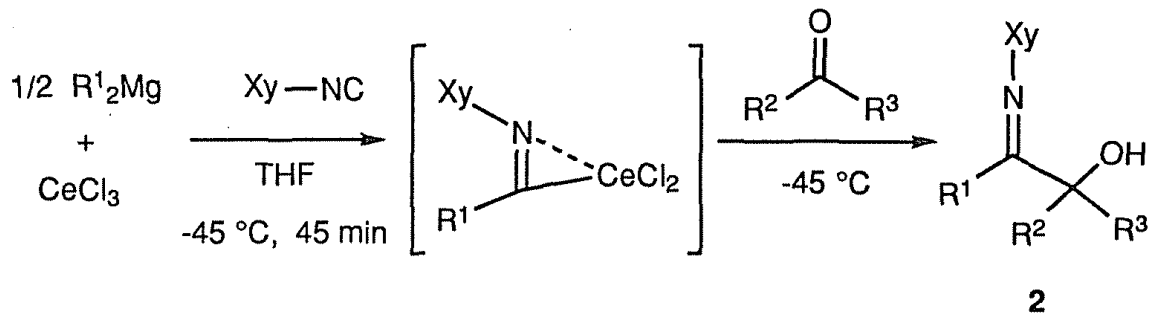
Preparation of (Imidoyl)cerium by the Reaction of Isocyanide with $CeCl_3$ and Dialkylmagnesium.

The relative ease of formation of Grignard reagents (RMgX) from organic halides together with a wide variation of the group R led us to examine their use instead of alkyllithium. It has been reported that the use of the Grignard reagent–$CeCl_3$ system in reactions with carbonyl substrates affords the addition products in high yield.[8] However, an attempted reaction of the Grignard reagent with 2,6-xylyl isocyanide in the presence of $CeCl_3$ failed to proceed at temperatures ranging from -78 °C to 0 °C, possibly due to the sluggish process of transmetallation.[9]

The use of dialkylmagnesium for transmetallation with a lanthanide salt has been documented,[6c,10] and was thus applied to a reaction with 2,6-xylyl isocyanide. An ether solution of dibutylmagnesium (0.25 mmol) was added to a

mixture of 2,6-xylyl isocyanide (0.50 mmol) and $CeCl_3$ (0.55 mmol) in THF at -78 °C. Being stirred at that temperature for 90 min, the reaction mixture also became orange, suggesting the formation of an (imidoyl)cerium(III) species. Subsequent quenching with water gave the aldimine (1) in 70% yield. Moreover, the addition of dibutylmagnesium at -45 °C led to a quantitative conversion of the isocyanide. Since no reaction occurred upon treatment of dibutylmagnesium alone with 2,6-xylyl isocyanide at temperatures up to 0 °C, it is likely that transmetallation between dibutylmagnesium and $CeCl_3$ proceeds quite efficiently at -45 °C, yielding butylcerium(III), which is then coupled with the isocyanide. Notably, both butyl groups of dibutylmagnesium were utilized in the coupling. These results may be accounted for by assuming the concurrent occurrence of transmetallation at both Mg–C linkages at -45 °C. Table 3 presents the results of the addition reactions of the diorganylmagnesium-derived (imidoyl)cerium(III) reagents to carbonyl compounds. Primary and secondary alkyl, phenyl, and vinyl groups were successfully coupled with the isocyano carbon in the initial C–C bond-forming step. The second coupling of the (imidoyl)lanthanides with carbonyl compounds proceeded efficiently to produce a-hydroxy imines in good yield. Di-*t*-butylmagnesium failed to undergo a-addition to the isocyanide.

Table 3. Reactions of $R^1{}_2Mg$-Derived (Imidoyl)cerium(III) with Carbonyl Compounds (Xy = 2,6-xylyl)



Run	$R^1{}_2Mg$	$R^2R^3C{=}O$	2	Yield (%)
1	$^nBu_2Mg$	cyclohexanone	**2a**	87
2	$^sBu_2Mg$	cyclohexanone	**2c**	89
3	Ph_2Mg	Et-CHO	**2j**	95 a)
4	$(PhCH_2)_2Mg$	cyclohexanone	**2k**	79
5	$(Me_2C{=}CH)_2Mg$	cyclohexanone	**2l**	78

a) The reaction was quenched by addition of Ac_2O, Et_3N, and 4-(dimethylamino) pyridine. The product was isolated as the acetylated derivative.

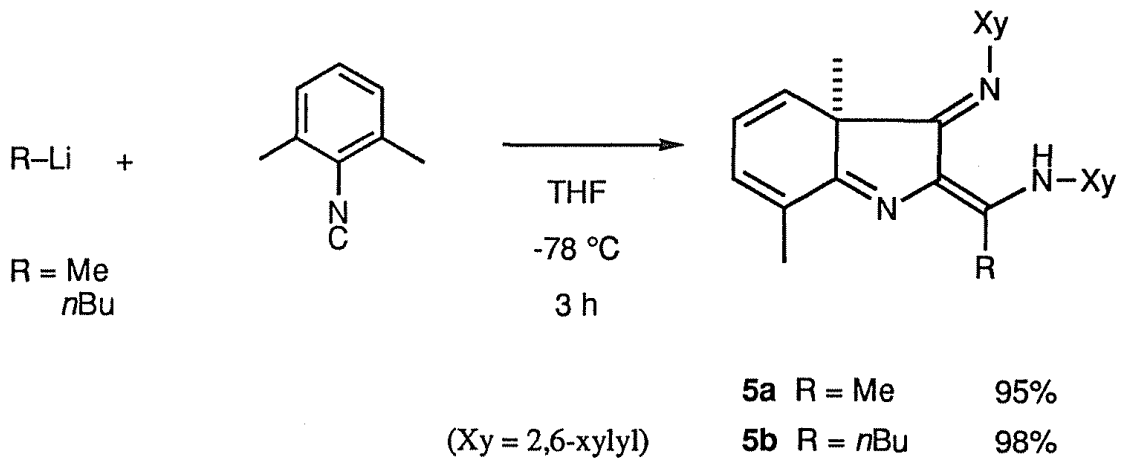
Alkyllithium-Mediated Anomalous Trimerization of 2,6-Xylyl Isocyanide

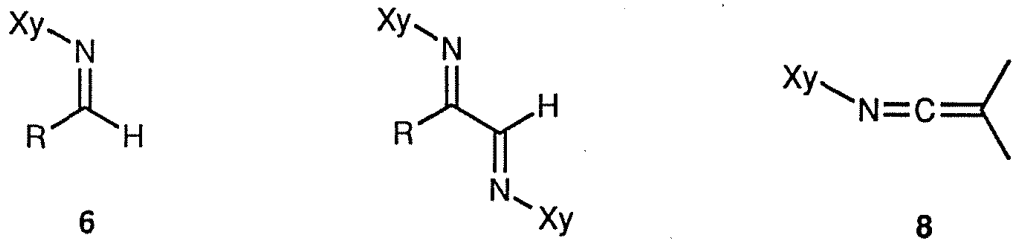
Isocyanides undergo insertion into metal–alkyl bonds to furnish (alkaneimidoyl)metal compounds; e.g., the reaction of *tert*-alkyl isocyanide with alkyllithium furnishes an (alkaneimidoyl)lithium intermediate, which has found successful synthetic applications.[1] Unlike with carbon monoxide, the successive multiple occurrence of this elementary process is possible with isocyanides, leading to the formation of oligomers[11] and polymers.[12] Alkaneimidoyl complexes of the transition, lanthanide, and actinide series have been the subject of intense research.[13,14] Most of them adopt a η^2-bonding mode. In contrast, the structural features of alkaneimidoyl complexes of main group elements have received little attention.[15] η^1-Bonding through a C–Li linkage has been conventionally assumed for (alkaneimidoyl)lithium intermediates. We now report the alkyllithium-mediated anomalous trimerization of aryl isocyanide, which infers the bonding properties of the intermediate organolithium species.

2,6-Xylyl isocyanide (0.50 mmol) was treated with methyllithium (0.50 mmol) in THF at -78 °C. The color of the solution changed from yellow to red, and after 3 h became dark blue with quantitative conversion of the isocyanide. The dark blue color disappeared the instant a drop of water was added to the mixture, and after chromatography, 0.16 mmol of an indole derivative **5a** was obtained (95% based on 2,6-xylyl isocyanide). When 0.25 mmol of methyllithium was used under otherwise identical conditions, 0.078 mmol of **5a** was produced and half of 2,6-xylyl isocyanide remained unreacted. Therefore, it is likely that the lithio derivative of **5a** traps two more equivalents of methyllithium, which are inert toward the free isocyanide probably due to the

steric reason. The skeletal arrangement of the anomalous product **5a** was deduced as depicted below on spectroscopic grounds.[16] Three molecules of 2,6-xylyl isocyanide and one methyl group coming from methyllithium constitute **5a**. Recrystallization from CH_2Cl_2–MeCN provided single crystals suitable for an X-ray crystallographic analysis, which finally established the exact structure of **5a** (Figure 1).[17] The location of the double bonds was assigned on the basis of the bond distances. The hydrogen atom H1 found on a difference electron density map, together with N1, C5, C6, C7, and N3 forms a 6-membered cyclic geometry, indicating the presence of an N3•••H1 hydrogen bond [N3–H1 = 2.00(2) Å, N1–

Scheme 4.





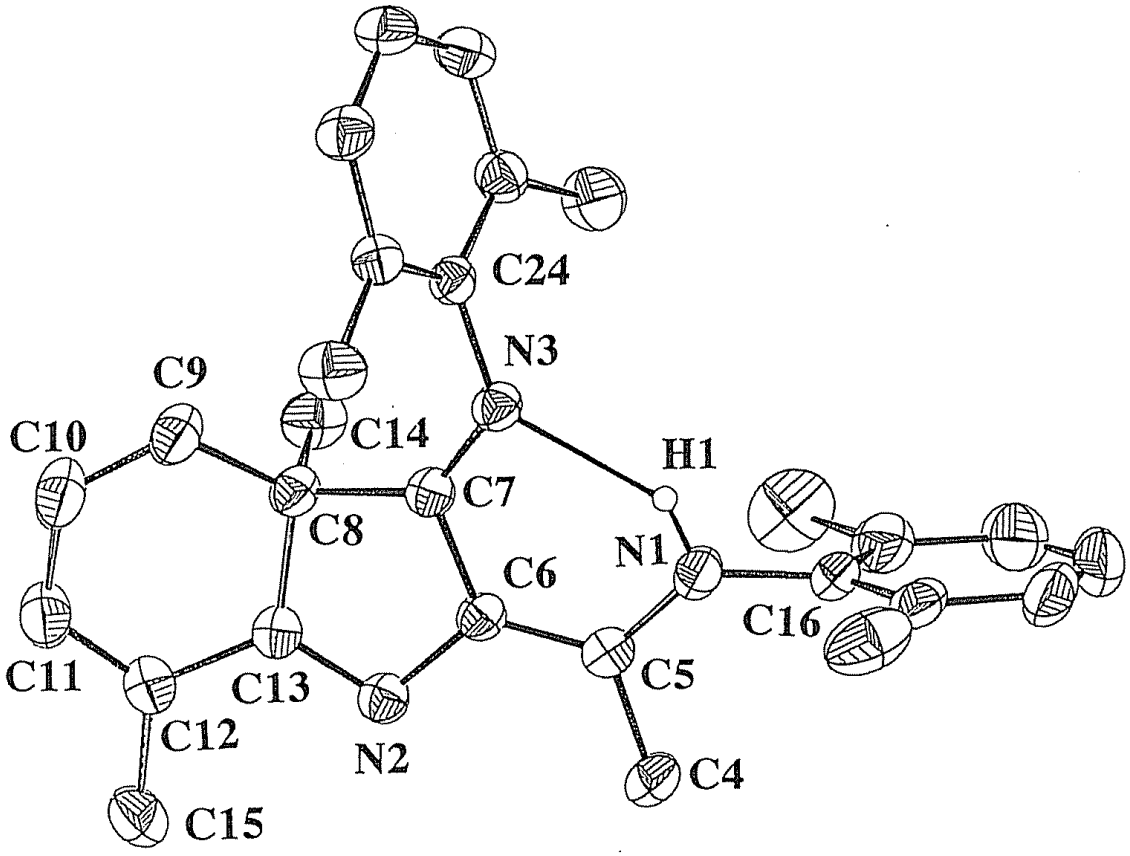
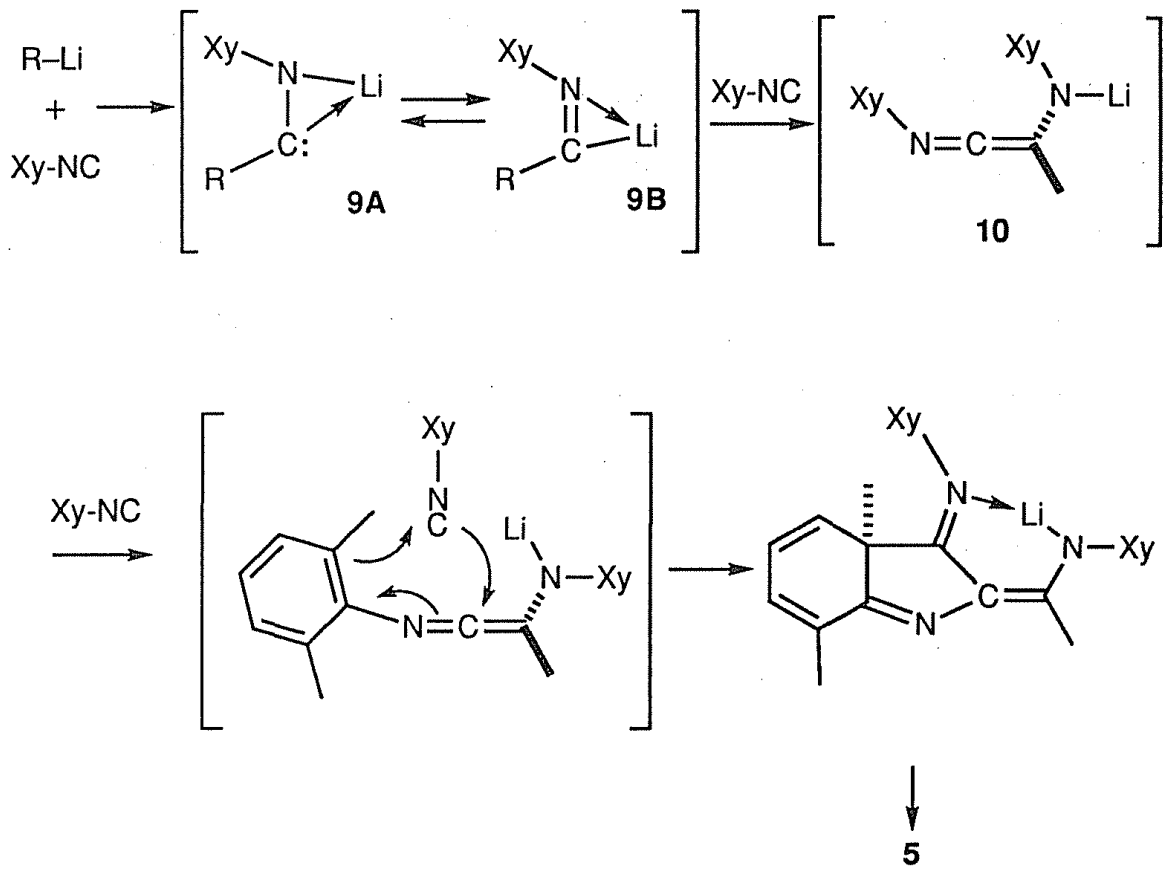


Figure 1. Molecular structure of **5a** with the hydrogen atoms except H1 omitted for clarity (35% probability thermal ellipsoids). The selected bond distances (Å): N1–H1, 0.93(2); N1–C5, 1.357(2); C5–C6, 1.369(2); C6–C7, 1.456(2); N3–C7, 1.288(2); N2–C6, 1.404(2); N2–C13, 1.299(2); C7–C8, 1.534(2); C8–C9, 1.497(3); C8–C13, 1.514(2); C9–C10, 1.340(3); C10–C11, 1.446(3); C11–C12, 1.349(3); C12–C13, 1.447(3).

H1–N3 = 138(2)°]. The use of butyllithium instead of methyllithium furnished an analogous indole **5b** as well. However, a complex mixture was obtained when other aryl isocyanide having no substituents at the *o*-positions was reacted with alkyllithium.

In marked contrast to the cases of RLi–*tert*-alkyl isocyanide,[1] R_2Zn–2,6-xylyl isocyanide[18] and $RSmX_2$–2,6-xylyl isocyanide,[11c,19] neither the mono insertion product **6** nor the double insertion product **7** was obtained at all even when the reaction was quenched with water at an earlier stage. The lithio derivative of **5a** was prepared by treatment of **5a** with butyllithium. However, regeneration of the isocyanide was not observed, being suggestive of the irreversibility of this trimerization.

Scheme 5

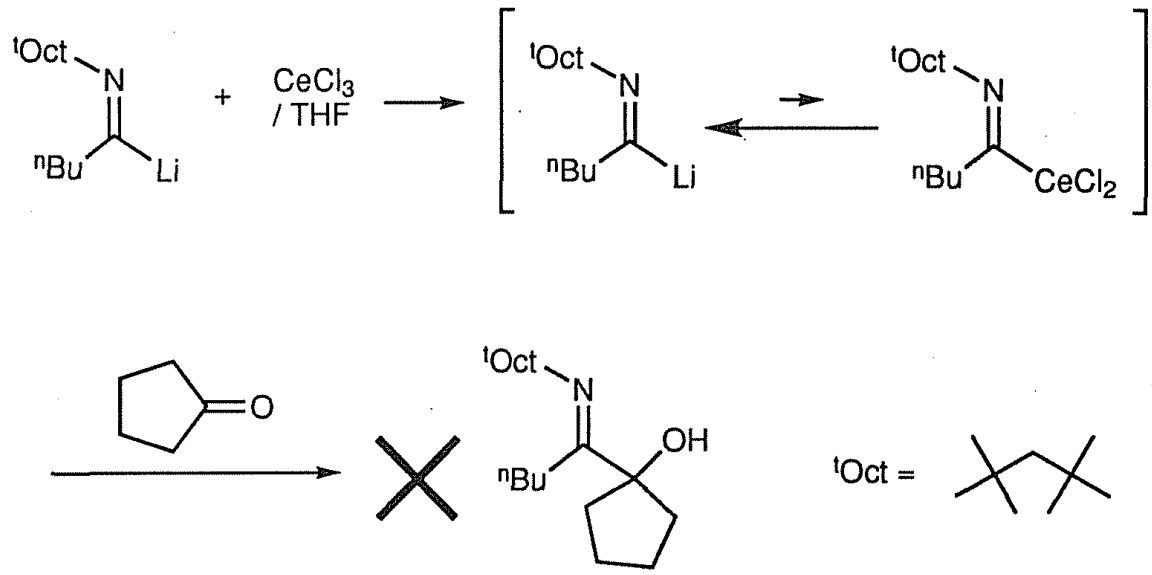


The coupling of carbenes with isocyanides to yield ketenimines has been documented well.[20] It has been also reported that N-(2,6-xylyl)ketenimine **8** reacts with 2,6-xylyl isocyanide to afford an indole via formal [4+1] cycloaddition.[21,22] Furthermore, the direct formation of an analogous indole derivative by the reaction of a metal carbene complex with aryl isocyanide is known.[23] On the basis of these precedents, it would be reasonable to presume the following mechanism for the formation of **2**; initial coupling of alkyllithium with 2,6-xylyl isocyanide yields a transitory η^2-(alkaneimidoyl)lithium **9**.[24] Besides **9B**, a carbene-like resonance form (**9A**) is viewed as an important contributor to the description of the (alkaneimidoyl)lithium. The subsequent coupling with the second equivalent of 2,6-xylyl isocyanide, presumably carbene-like one, affords the ketenimine intermediate **10**. The third incorporation of 2,6-xylyl isocyanide via formal [4+1] cycloaddition furnishes the indole skeleton. A related discussion of the carbenoid character of (η^2-acyl)thorium complexes has been given, based upon the formation of indole analogs in the reactions with aryl isocyanides.[25]

In conclusion, the facile formation of the anomalous product **5** by alkyllithium-mediated trimerization of 2,6-xylyl isocyanide infers the structural features of the transient organolithium species. Assumption of an aminocarbene character for the initial coupling product, and a ketenimine structure for the second coupling product accounts for the present reaction pattern on analogy with the organic and organometallic precedents.

Mechanistic Features of Preparation of (Imidoyl)lanthanide.

A Et_2O solution of iminolithium reagent (1.0 equiv) prepared by a Walborsky procedure[1)] was added to a white milky suspension of an anhydrous $CeCl_3$ (III) salt (1.1 equiv) in tetrahydrofuran (THF) at -78 °C. The resultunt orange suspension stired for 30 min and added cyclopentanone (1.0 equiv) ,which is susceptible to enolization toward iminolithium reagent. However, none of adduct was obtained. This result showed that transmetalation between iminolithium and $CeCl_3$ did not occured in this reaction condition and also suggested that transmetalation took place prior to insertion of isocyanide into C-metal bond in the presence of $CeCl_3$ salt.

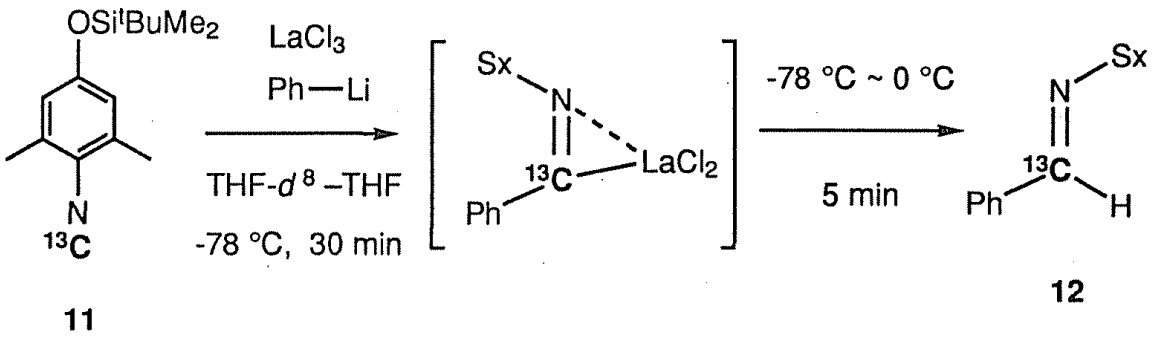


In the reported procedure of the organolithium–$CeCl_3$ system for a carbonyl addition reaction, after organolithium was treated with $CeCl_3$ at -78 °C for 30 min, a carbonyl compound was added.[6a)] When phenyllithium was treated with $CeCl_3$ at -78 °C for 30 min, and then with the isocyanide at that temperature for an additional 30 min, the insertion reaction stopped halfway. However, the

subsequent addition of cyclopentanone to the mixture furnished 1-phenylcyclopentanol in 20% yield together with the a-hydroxy imine (**2f**) in 29% yield (Scheme 3). Although evidence for a discussion of the nature of actual species involved in the reaction with the isocyanide is rather sparse, at least two different organocerium species can be assumed to explain this anomalous result. The transitory one initially formed is sufficiently reactive to undergo a-addition to the isocyanide, and is gradually converted to another species which is less reactive toward the isocyanide, but is still so reactive as to add to cyclopentanone.

On the basis of the structures of the related (formimidoyl)lanthanide complexes,[26] a η^2-bound structure may be presumed for the (imidoyl)lanthanide(III) species. Whether it adopts a monomeric or aggregated form is unclear. In order to obtain structural information, a NMR study was carried out using a ^{13}C-labeled 4-(*tert*-butyldimethylsiloxy)-2,6-xylyl (Sx) isocyanide (**11**).[27] Thus, the isocyanide **11** was treated with phenyllithium and a diamagnetic salt, $LaCl_3$, at -78 °C for 30 min. The ^{13}C NMR spectra (-78 °C) of the supernatant of the reaction mixture showed a distinct resonance at 271.6 ppm, which conformed to the expectation for the imidoyl carbon bound to La of the proposed (imidoyl)lanthanum structure. Notably, the signal at 271.6 ppm disappeared in the spectrum measured shortly after the temperature was raised to 0 °C over 5 min. Instead, there appeared a new peak at 163.5 ppm, which was ascribed to the formimidoyl carbon of an aldimine (**12**). It seemed that the thermal decomposition of an (imidoyl)lanthanum occurs via the abstraction of a hydrogen atom from THF or the 2,6-xylyl group.

Scheme 6.



Conclusion

The straightforward preparation of acyllanthanides has met difficulties from a synthetic point of view: A stable acylcerium(III) species is inaccessible by way of the carbonylation of alkylcerium(III).[28] The generation of stable acylsamarium(III) reagents by the reduction of an acid chloride[29] or by reductive carbonylation of an alkyl halide[30] is limited to acyl groups having tertiary a-carbon atoms. Since the imino functionality of an imine can be easily converted to a carbonyl group by acidic hydrolysis, the present reactions for the preparation of (imidoyl)cerium(III) provide a convenient synthetic equivalent to a nucleophilic acyllanthanide species. As compared with the SmI_2-mediated three-component coupling,[5] a wider variation for the acyl group becomes available by this procedure without the use of carcinogenic hexamethylphosphoric triamide.

Experimental Section

General.

Column chromatography was performed with silica gel 60 (E. Merck, Darmstadt), 230–400 mesh. Preparative thin-layer chromatography (TLC) was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra were acquired in chloroform-*d* at 200 MHz and 50 MHz, respectively. The carbon chemical shifts were recorded relative to chloroform-*d* (d 77.0). Na_2SO_4 was used to dry the organic layers after extraction. All of the reactions were performed under a dry nitrogen atmosphere. Unless otherwise noted, all materials were obtained from commercial sources. THF was distilled from sodium diphenylketyl. 2,6-Xylyl isocyanide was prepared according to the literature.[31] An ether solution of diorganylmagnesium was obtained by the addition of dioxane to an ether solution of a Grignard reagent.[32] A reaction vessel was immersed in a dry ice–MeCN bath to carry out the reaction at -45 °C.

Synthesis of 1-[1-(2,6-Xylylimino)pentyl]cyclohexanol (2a) by the Reaction of the BuLi-Derived (Imidoyl)cerium(III) with Cyclohexanone.

Cerium trichloride heptahydrate (205 mg, 0.55 mmol) was dried under vacuum at 50 °C for 1 h and at 140 °C for 2 h. After being cooled to room temperature, THF (2 ml) was added and the mixture was vigorously stirred for 12 h. 2,6-Xylyl isocyanide (65 mg, 0.50 mmol) was added to the resulting milky white suspension, which was then cooled to -78 °C. To this was added a hexane solution of butyllithium (300 ml, 0.50 mmol). After the mixture was stirred at that temperature for 30 min, cyclohexanone (39 mg, 0.40 mmol) was added. The reaction mixture was stirred for additional 1 h. Then, the temperature was al-

lowed to rise to room temperature. A drop of water was added, and the mixture was passed through a Florisil pad to remove insoluble materials. The filtrate was subjected to silica-gel column chromatography (ether:hexane = 1:10) to afford **2a** as oil (114 mg, 99%).

3-Acetoxy-4-(2,6-xylylimino)octane (2b). Pale-yellow oil. ^{1}H NMR δ = 0.76 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H), 0.91–1.52 (m, 4H), 1.82–2.15 (m, 4H), 1.95 (s, 3H), 1.98 (s, 3H), 2.16 (s, 3H), 5.27 (dd, J = 8.0, 4.8 Hz, 3H), 6.81–7.00 (m, 3H) ^{13}C NMR δ = 10.5, 13.5, 18.0, 18.1, 21.0, 23.0, 25.9, 27.7, 31.7, 77.0, 122.8, 125.1, 125.9, 127.7, 127.9, 147.4, 170.9, 172.6. Anal. Found: C 74.44; H 9.65; N 4.62%. Calcd for $C_{18}H_{27}NO_2$: C 74.70; H 9.40; N 4.84%.

1-[2-Methyl-1-(2,6-xylylimino)butyl]cyclohexanol (2c). Pale-yellow oil. ^{1}H NMR δ = 0.83 (t, J = 7.2 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 1.10–1.95 (m, 12H), 2.04 (s, 6H), 2.45–2.67 (m, 1H), 5.30–5.65 (br, 1H), 6.85–7.05 (m, 3H); ^{13}C NMR δ = 12.8, 15.5, 18.3, 21.8, 25.4, 25.9, 35.0, 35.1, 38.7, 75.9, 122.6, 125.2, 127.58, 127.63, 146.6, 180.2. Anal. Found: C 79.40; H 10.18; N 4.79%. Calcd for $C_{19}H_{29}NO$: C 79.39; H 10.17; N 4.87%.

1-[1-(2,6-Xylylimino)ethyl]cyclohexanol (2d). Colorless solid. ^{1}H NMR δ = 1.18–1.45 (m, 1H), 1.54–2.05 (m, 9H), 1.71 (s, 3H), 1.97 (s, 6H), 5.36 (s, 1H), 6.87–7.09 (m, 3H); ^{13}C NMR δ = 14.7, 17.5, 21.6, 25.4, 35.2, 74.5, 123.2, 125.9, 127.9, 146.7, 176.0. Anal. Found: C 78.10; H 9.54; N 5.66%. Calcd for $C_{16}H_{23}NO$: C 78.32; H 9.45; N 5.71%.

1-[Cyclopropyl(2,6-xylylimino)methyl]cyclohexanol (2e). Pale-yellow oil. ^{1}H NMR δ = 0.45–0.72 (m, 4H), 1.17–1.97 (m, 11H), 2.01 (s, 6H), 5.54–5.68 (br, 1H), 6.83–7.01 (m, 3H); ^{13}C NMR δ = 6.9, 13.0, 18.0, 22.0, 25.6, 36.1, 75.7, 122.8, 125.6, 127.6, 145.9, 176.2. Anal. Found: C 79.93; H 9.48; N 4.93%.

Calcd for $C_{18}H_{25}NO$: C 79.66; H 9.28; N 5.16%.

1-[Phenyl(2,6-xylylimino)methyl]cyclopentanol (2f). Colorless solid. ^{1}H NMR δ = 1.60–2.10 (m, 8H), 2.08 (s, 6H), 5.51 (s, 1H), 6.50–6.89 (m, 3H), 7.02–7.25 (m, 5H); ^{13}C NMR δ = 18.4, 24.0, 38.9, 84.5, 123.1, 125.7, 126.3, 127.5, 127.7, 128.5, 135.1, 146.7, 175.7. Anal. Found: C 82.16; H 7.92; N 4.77%. Calcd for $C_{20}H_{23}NO$: C 81.87; H 7.90; N 4.77%.

1-[Phenyl(2,6-xylylimino)methyl]cyclohex-2-en-1-ol (2g). Colorless oil. ^{1}H NMR δ = 1.52–2.24 (m, 6H), 1.87 (s, 3H), 2.23 (s, 3H), 5.89 (d, J = 10.1 Hz, 1H), 6.07–6.20 (m, 1H), 6.11 (s, 1H), 6.76–6.87 (m, 2H), 6.90–7.02 (m, 1H), 7.12–7.28 (m, 5H); ^{13}C NMR δ = 18.1, 18.4, 18.5, 24.6, 34.9, 73.5, 123.4, 124.6, 126.8, 127.4, 127.7, 128.0, 128.9, 132.3, 135.1, 145.9, 174.6. Anal. Found: C 82.32; H 7.60; N 4.59%. Calcd for $C_{21}H_{23}NO$: C 82.59; H 7.59; N 4.59%.

1-[2-Methyl-1-(2,6-xylylimino)but-2-enyl]cyclohexanol (2h). Colorless oil. ^{1}H NMR δ = 1.12–1.95 (m, 10H), 1.61 (s, 6H), 2.06 (s, 6H), 5.21 (s, 1H), 5.28–5.49 (m, 1H), 6.82–7.00 (m, 3H); ^{13}C NMR δ = 18.2, 21.8, 22.0, 22.6, 25.4, 35.5, 76.7, 123.2, 126.3, 127.7, 130.9, 146.5, 179.1. Anal. Found: C 79.87; H 9.75; N 4.81%. Calcd for $C_{19}H_{27}NO$: C 79.95; H 9.53; N 4.91%.

4-Acetoxy-2,2-dimethyl-3-(2,6-xylylimino)hexane (2i). Pale-yellow oil. ^{1}H NMR δ = 0.75 (t, J = 7.4 Hz, 3H), 1.31 (s, 9H), 1.50–1.61 (m, 2H), 1.98 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 5.54 (dd, J = 9.4, 3.6 Hz, 1H), 6.76–7.00 (m, 3H); ^{13}C NMR δ = 10.7, 18.1, 18.2, 20.9, 26.3, 28.8, 41.2, 74.1, 121.9, 122.8, 124.7, 127.5, 127.9, 147.7, 170.2, 174.2. Anal. Found: C 74.45; H 9.39; N 4.79%. Calcd for $C_{18}H_{27}NO_2$: C 74.70; H 9.40; N 4.84%.

***N*,2-Diphenyl-2-(2,6-xylylimino)acetamide (4).** Yellow solid. ^{1}H NMR δ = 2.01 (s, 6H), 6.51–7.00 (m, 3H), 7.12–7.45 (m, 8H), 7.71–7.80 (m, 2H), 9.82

(br s, 1H); ^{13}C NMR δ = 18.9, 120.0, 124.8, 125.0, 126.0, 128.2, 128.6, 129.5, 129.7, 130.6, 132.2, 138.1, 146.4, 161.3, 161.4. Anal. Found: C 80.21; H 6.04; N 8.34%. Calcd for $C_{22}H_{20}N_2O$: C 80.46; H 6.14; N 8.53%.

Synthesis of 2c by the Reaction of the *s*-Bu$_2$Mg-Derived (Imidoyl)cerium(III) with Cyclohexanone. Cerium trichloride heptahydrate (205 mg, 0.55 mmol) was dried under vacuum at 50 °C for 1 h and at 140 °C for 2 h. After being cooled to room temperature, THF (2 ml) was added and the mixture was vigorously stirred for 12 h. 2,6-Xylyl isocyanide (65 mg, 0.50 mmol) was added to the resulting milky white suspension, which was then cooled to -45 °C. To this was added an ether solution of di-*s*-butylmagnesium (640 ml, 0.25 mmol). The mixture was stirred at that temperature for 45 min, and then cyclohexanone (39 mg, 0.40 mmol) was added. After the reaction mixture was stirred at -45 °C for 1 h, the temperature was allowed to rise to room temperature. A drop of water and ether (2 ml) were added, and the mixture was passed through a Florisil pad to remove insoluble materials. The filtrate was subjected to silica-gel column chromatography (ether:hexane = 1:10) to afford **2c** as oil (102 mg, 89%).

2-Acetoxy-1-phenyl-1-(2,6-xylylimino)butane (2j). Pale-yellow oil. ^{1}H NMR δ = 1.07 (t, J = 7.4 Hz, 3H), 1.76 (s, 3H), 1.86–2.05 (m, 2H), 2.17 (s, 3H), 2.20 (s, 3H), 5.60 (t, J = 6.2, 1H), 6.74–6.85 (m, 2H), 6.87–7.00 (m, 1H), 7.15–7.32 (m, 5H); ^{13}C NMR δ = 10.3, 18.1, 18.4, 21.0, 25.9, 78.2, 122.7, 124.5, 126.8, 127.1, 127.3, 128.0, 128.1, 129.3, 136.0, 147.5, 168.3, 171.1. Anal. Found: C 77.87; H 7.66; N 4.49%. Calcd for $C_{20}H_{23}NO_2$: C 77.64; H 7.49; N 4.53%.

1-[2-Phenyl-1-(2,6-xylylimino)ethyl]cyclohexanol (2k). Pale-yellow oil.

^{1}H NMR δ = 1.15–1.40 (m, 1H), 1.58–1.92 (m, 9H), 1.87 (s, 6H), 3.56 (s, 2H), 5.15 (s, 1H), 6.74–6.81 (m, 2H), 6.87–6.94 (m, 3H), 7.02–7.11 (m, 3H); ^{13}C NMR δ = 18.3, 22.3, 26.0, 36.4, 36.5, 76.1, 123.9, 126.6, 126.9, 128.4, 128.6, 129.9, 135.7, 146.7, 176.7. Anal. Found: C 81.91; H 8.44; N 4.28%. Calcd for $C_{22}H_{27}NO$: C 82.20; H 8.47; N 4.36%.

1-[3-Methyl-1-(2,6-xylylimino)but-2-enyl]cyclohexanol (2l). Pale-yellow oil. ^{1}H NMR δ = 1.18 (s, 3H), 1.15–1.90 (m, 10H), 1.61 (d, J = 1.2 Hz, 3H), 2.06 (s, 6H), 5.43–5.61 (br, 1H), 5.62–5.68 (m, 1H), 6.82–7.03 (m, 3H); ^{13}C NMR δ = 18.3, 20.4, 21.8, 25.4, 25.6, 35.8, 75.1, 117.7, 123.4, 126.8, 128.1, 140.4, 146.3, 175.0. Anal. Found: C 79.95; H 9.68; N 4.72%. Calcd for $C_{19}H_{27}NO$: C 79.95; H 9.53; N 4.91%.

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(17) Crystal data for **5a**: $C_{28}H_{31}N_3$, M = 409.6, orthorhombic, space group *Pbca* (no. 61), a = 13.814(5), b = 36.808(8), c = 9.151(2) Å, Z = 8, V = 4653(2) Å^3, r_{calcd} = 1.17 g/cm^3, Cu$K\alpha$, l = 1.54178 Å, m = 4.55 cm^{-1}, T = 293 K, 4497 reflections measured, 3891 independent, 3563 [F > 1.0s(F)] included in the refinement, anisotropical refinement for non-hydrogen atoms by full-matrix least-squares with a program package CrystanG (Mac Science), 384 parameters, R = 0.054, R_W = 0.062, isotropic refinement for the hydrogen atom H1, refinement with isotropic thermal parameters calculated from those of the bonded atoms for other hydrogen atoms.

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