Heteroatom Chemistry
Volume 11, Number 1, 2000

Nucleophilic Addition of Organocerium Reagents to α-Alkoxy Hydrazones: A New Type of Elimination Reaction to α-Hydroxynitriles

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Received 5 April 1999; revised 30 August 1999

ABSTRACT: *We studied the nucleophilic addition of organocerium reagents to α-alkoxy hydrazones. The results depend upon the organocerium reagents, the nature of protection for the hydroxy group, and the solvents used. Contrary to Grignard reagents, organocerium reagents derived from Grignard reagents effectively add to α-alkoxy hydrazones. In addition, a new type of elimination reaction of α-alkoxy hydrazones to the corresponding nitriles by methyl chloroformate was found. This methodology is an efficient and potentially practical synthetic route to β-hydroxy amines.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:65–72, 2000

INTRODUCTION

Organolanthanide reagents have played an important role in organic synthesis during the past twenty years. One of the most useful reagents among them is the organocerium reagent derived from anhydrous cerium chloride and an organolithium (written as $CeCl_3$/RLi) or Grignard reagent [1]. Organocerium reagents were initially used to promote nucleophilic additions of alkyllithium and Grignard reagents to carbonyls by Imamoto et al. [2]. Since then, they have been extended to facilitate addition reactions of various alkyllithium or Grignard reagents to a wide range of electrophilic compounds [3]. Denmark and coworkers have detailed studies of the effect of reagent stoichiometry on the efficiency of organocerium additions to hydrazones, and concluded that 1:1 $CH_3Li/CeCl_3$ afforded optimal yields of addition products, in spite of the fact that $CeCl_3$ was not completely dissolved in the solution [4]. Recently, Evans' group critically examined the structure and composition of anhydrous $CeCl_3$ and found that an indefinite amount of water and/or hydroxyl groups existed in the anhydrous $CeCl_3$, suggesting that the organocerium reagents were better described as $CeCl_3(H_2O)_n$/RLi [5].

The nucleophilic addition of organometallic reagents to aldehydes, ketones, imines, and imine derivatives has been extensively investigated [6]. A few studies showed that the addition of organoceriums to chiral α, α-dialkoxy hydrazones proceeded with high diastereoselectivity, and the resulting hydrazines were converted to enantiomerically enriched α-amino acetals [7]. Denmark reported that organocerium addition to (S)-(−)-1-amino-2-(methoxymethyl)pyrrolidine-hydrazones gave rise to high yields of hydrazines with excellent diastereoselectivity [8]. This can be attributed to the formation of the chelation-controlled intermediate of cerium with the oxygen on the methoxyethoxy side chain and nitrogen. Recently, the diastereoselective addition reaction of organocerium reagents to 4- and 5-oxazolidonecarbaldehydes was reported by Andrew *et al.* [9]. They proposed a seven-membered Ce^{+3} chelated transition state and that stereoelectronic effects resulted in high diastereoselectivity. In absence of studies on the nucleophilic addition of organocerium reagents to α-alkoxy hydrazones, we initiated a

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 CCC 1042-7163/00/010065-08

project to exploit this reaction with hopes that the results would provide some insight to a better understanding of the structure and reaction mechanism of organocerium reagents [10].

RESULTS AND DISCUSSION

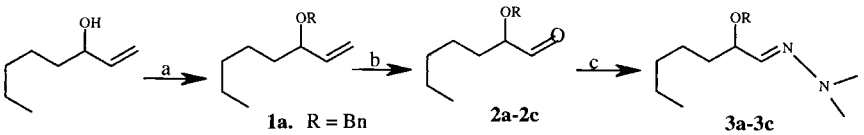
We chose commercially available 1-octen-3-ol as starting material. Treatment of the alcohol with BnBr/NaH [11], MEMCl/NaH [12], or Ph_3CCl/DMAP [13] gave the corresponding 2-alkoxy-1-octene **1**. This was followed by ozonolysis and provided α-alkoxy aldehyde **2** [14]. Subsequent treatment of the aldehydes with *N, N*-dimethylhydrazine furnished the desired α-alkoxy hydrazones **3** (Scheme 1). The addition of organocerium reagents to the hydrazones was investigated using the following general procedure: $CeCl_3 \cdot 7H_2O$ was dried at 140°C and 0.001 Torr over 12 hours and tetrahydrofuran (THF) added. After stirring for 2 hours at room temperature, the resulting mixture was cooled to the desired temperature. The organolithium or Grignard reagent was added, and the reaction mixture was stirred for 1 hour followed by addition of the hydrazones. The reaction mixture was stirred for 30 minutes at the same temperature and warmed to room temperature with stirring for an additional 2 hours. After adding trapping reagents, the reaction mixture was stirred for 5 hours and the reaction was quenched by water. The results of these addition reactions are outlined in Table 1.

The reaction of the hydrazones with organocerium reagents gave the expected addition products **4**. However, in some cases, we obtained nitriles **5** unexpectedly (Scheme 2). It is well known that the elimination reaction of hydrazones to nitriles can be implemented by the action of hydrazonium salts and bases (Scheme 3). First, the reaction of aldehydes and *N,N*-dimethylhydrazine with methyl iodide provides hydrazonium salts, and then elimination of trimethylamine with bases (e.g., CH_3O^-/CH_3OH) yields the desired nitriles. Kinetic studies have shown that C-H bond cleavage is more advanced in the transi-

TABLE 1 The Reaction of Organoceriums with α-Alkoxy Hydrazones

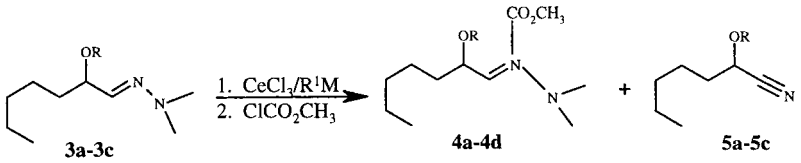
En	*R¹M*	*Rᶠ*	*Sol*	*T*(°*C*)	*Product*	*Y%*[g]	*Ds*[h]
1	MeLi	Bn	THF	−78	**4a**	85	50:50
2	PhLi	Bn	THF	−78	**5a**	66	
3	t-BuLi	Bn	THF	−78	**4b**	78	54:46
4	BuLi	Bn	THF	−78	**5a**	55	
5	MeMgBr	Bn	THF	0	**4a**	78	50:50
6	*i*-PrMgCl	Bn	THF	0	**4c** + **5a**	75 (1:9)	56:44
7	MeLi	Ph_3C	THF	−78	**5b**	82	
8	*t*-BuLi	Ph_3C	THF	−78	**5b**	83	
9	PhLi	Ph_3C	THF	−78	**5b**	66	
10	MeMgBr	Ph_3C	THF	0	**5b**	87	
11	*i*-PrMgCl	Ph_3C	THF	0	**5b**	88	
12	MeLi	MEM	THF	−78	**4d**	75	53:47
13	MeLi[a]	MEM	THF	−78	**5c**	76	
14	*t*-BuLi	MEM	THF	−78	**5c**	72	
15	MeMgBr	MEM	THF	0	**4d** + **5c**	75 (1:1.5)	51:49
16	MeLi	MEM	Et_2O	−78	**5c**	78	
17	t-BuLi	MEM	Et_2O	−78	**5c**	7	
18	MeMgBr	MEM	Et_2O	0	**4d** + **5c**	15 (1:2)	52:48
19	MeLi	Bn	Et_2O	−78	**4a** + **5a**	82 (3:1)	50:50
20	*t*-BuLi	Bn	Et_2O	−78	**4b** + **5a**	78 (1:3.3)	55:45
21	MeMgBr	Bn	Et_2O	0	**4a** + **5a**	75 (1.5:1)	50:50
22	*i*-PrMgCl	Bn	Et_2O	0	**4c**	70	54:46
23	MeLi	Ph_3C	Et_2O	−78	**5b**	83	
24	MeMgBr	Ph_3C	Et_2O	0	**5b**	82	
25	MeLi	Bn	DME	−42	**4a**	79	50:50
26	*t*-BuLi	Bn	DME	−42	**5a**	80	
27	MeMgBr	Bn	DME	−42	**4a** + **5a**	78 (3.3:1)	50:50
28	MeLi	Ph_3C	DME	−42	**5b**	60	
29	*t*-BuLi[a]	Bn	THF	−78	**5a**	76	
30	MeMgBr[a]	Bn	THF	0	**5a**	82	
31	MeLi[b]	Ph_3C	THF	−78	**5b**	75	
32	*i*-PrMgCl[c]	Bn	THF	0	na		
33	MeLi[d]	Ph_3C	THF	−78	na		
34	*t*-BuLi[d]	Ph_3C	THF	−78	na		
35	*t*-BuLi[e]	Ph_3C	THF	−78	na		

[a]The freshly opened bottles of organolithium or Grignard reagents.
[b]Trapping by ethyl chloroformate.
[c]Trapping by dimethyl carbonate.
[d]Quenched by water without adding trapping reagents.
[e]Trapping by deuterium oxide.
[f]Bn, Benzyl; MEM, (2-Methoxyethoxy)methyl; Ph_3C, Triphenylmethyl.
[g]The ratios correspond to **4:5**.
[h]The diasteromeric ratios of hydrazines **4** were determined by ^1H NMR and/or HPLC.



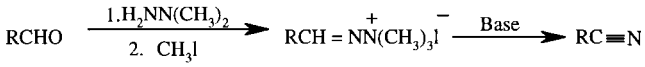
a. (1a) Bn/NaH/THF, 78%; (1b) Ph_3CCl/DMAP/CH_2Cl_2, 85%; (1c) MEMCl/NaH/THF, 45%
b. $O_3/(CH_3)_2S/CH_2Cl_2$. c. $H_2NN(CH_3)_2/CH_2Cl_2/Na_2SO_4$.

SCHEME 1



4a. R = BN, $R^1 = CH_3$; **4b.** R = Bn, R^1 = *tert*-Bu; **4c.** R = Bn, R^1 = iso-Pr;
4d. R = MEM, $R^1 = CH_3$; **5a.** R = Bn; **5b.** $R = Ph_3C$; **5c.** R = MEM

SCHEME 2



SCHEME 3

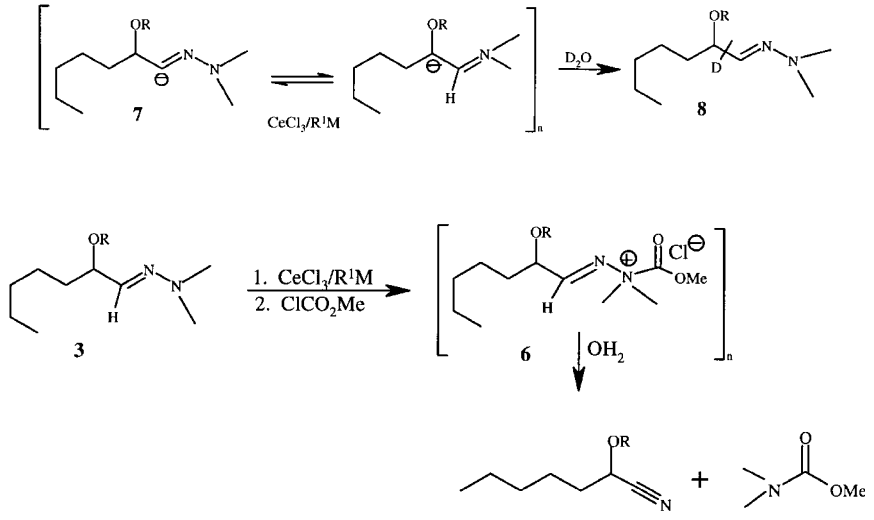
tion state than N-N bond breaking, and that the eliminative process occurs through an E2 transition state [15]. It has also been reported that strong alkali bases (e.g., lithium dialkylamides) promoted elimination from α-hindered hydrazones to nitriles in the absence of auxiliary reagents [16]. In an attempt to determine whether the nitriles had already been formed before addition of methyl chloroformate to the reaction mixture, we quenched the reaction with water (entries 33, 34 in Table 1), and the original hydrazones were obtained after work-up. Furthermore, when D_2O was used as the trapping agent (entry 35 in Table 1), no incorporation of deuterium was found in the hydrazones. We assume that anion **7** is not formed, otherwise deuterated hydrazone **8** would result, but in the presence of methyl chloroformate, intermediate **6** is formed, which leads to the nitriles by elimination of *N,N*-dimethylcarbamate, a better leaving group than dimethylamine anion (Scheme 4).

It should be noted that steric effects play an important role in the elimination process. Hydrazone **3b** with the bulky triphenylmethyl protecting group gives only elimination product with various organocerium reagents and solvents, while the addition of methyllithium to **3b** in ether affords the corresponding hydrazine [17]. We presume that the nucleophilic attack of organocerium reagents on α-alkoxy hydrazones is sterically sensitive and demands a surrounding with less steric hindrance, owing to the large radius of cerium^{+3}. We were also surprised to find organocerium reagents derived from freshly opened bottles of alkyllithium and magnesium reagents had the tendency to yield elimination products. For example, entries 13, 29, and 30 (Table 1) gave rise to a 100% yield of nitriles. Nevertheless, using older bottles of the corresponding organometallic reagents, entries 3, 5, 12, afforded complete addition products. Denmark et al. previously reported different chemical behavior from organolanthanide reagents derived from newly opened vs. older bottles of organolithium reagents [4,18]. Thus it seems that not only do concentrations of hydroxide ion in organolithium and Grignard reagents have a definite influence on the properties of organocerium reagents, but that the organoceriums derived from the newly opened organometallic reagents are less nucleophilic. It is also noteworthy that the solvents have some effect on the reaction path to the nitriles and hydrazines, and overall, THF facilitates the nucleophilic addition over ether and 1,2-dimethoxyethane (DME).

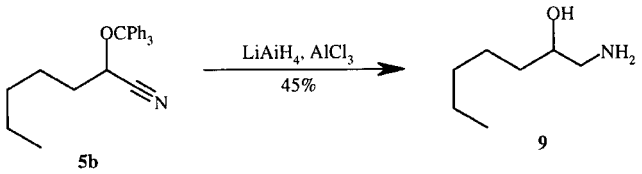
Treatment of the nitrile **5b** with $LiAlH_4/AlCl_3$ in ether directly provides β-hydroxy amine **9** in 45% yield (Scheme 5) [19].

In contrast to Grignard reagents, which do not undergo nucleophilic addition to α-alkoxy hydrazones in various solvents [17], organocerium reagents from Grignard reagents react with hydrazones to give high yields of addition products (e.g., entries 5, 22 in Table 1). Most of the nucleophilic additions of organocerium reagents to α-alkoxy hydrazones lack diastereoselectivity, which can be explained by the fact that the cerium ion can not form a tight five-membered ring chelation model, due to its large ion radius. Neither the erythro diastereomer (Cram open-chain model) nor the threo (a chelation-controlled model) is predominant, which suggests that partial chelation controlled intermediates still exist in the transition state. Presumably, the five-membered ring intermediate is much less tightly bound than that of lithium ion, and thus high diastereoselectivity is not observed.

In summary, we have demonstrated that the nucleophilic addition of organocerium reagents to α-alkoxy hydrazones affords high yields of β-alkoxy hydrazines. In combination with diverse reduction methods of hydrazines to amines [20], this sequence could become an efficient approach to β-amino alcohols, which are common subunits in a variety of



SCHEME 4



SCHEME 5

biologically important compounds [21]. Also, by choosing bulky protecting groups for the hydroxy group, this reaction scheme provides a facile and efficient synthetic route to α-hydroxy nitriles.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Varian 300 MHz spectrometer with either chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) or TMS as a reference peak. Coupling constants (J) are reported in Hz. IR spectra were recorded on a Magna-IR spectrometer 550. High-resolution mass spectra (HRMS) were obtained on a Kratos MS50TC Magnetic Sector Mass Spectrometer. Elemental analyses were performed by Atlantic Microlab Inc. Norcross, GA.

All commercially available chemicals were purchased from Aldrich Chemical Company, Milwaukee, WI. Butyllithium was titrated before use [22]. THF and ether were freshly distilled from sodium/benzophenone. All reactions were performed under an argon atmosphere in oven-dried (140 °C) glassware.

3-Benzyloxy-1-octene (**1a**)

THF (40 mL) and NaH (57% oil dispersion, 2.19 g, 52.0 mmol, 1.3 equiv) were placed in a 100 mL three neck round-bottom flask fitted with gas inlet, septum, and a drying tube. 1-Octen-3-ol (5.13 g, 40 mmol, 1 equiv) was added dropwise through a syringe at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Benzyl bromide (8.89 g, 52.0 mmol, 1.3 equiv) was added dropwise, and the resulting mixture was stirred at room temperature for 48 hours. The reaction was quenched by 5% HCl (30 mL). The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel (elution with hexane, hexane/ethyl acetate 4:1) gave pure product **1a** (6.39 g, 78%). ^{1}H NMR: 0.90 (t, 3H, J = 6.8), 1.10–1.75 (m, 8H), 3.74 (q, 1H, J = 6.9), 4.37 (d, 1H, J = 12.0), 4.62 (d, 1H, J = 12.0), 5.15–5.25 (m, 2H), 5.70–5.85 (m, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR: 13.9, 22.5, 24.9, 31.7, 35.4, 70.0, 80.6, 116.9, 127.4, 127.8, 128.4, 139.1, 139.4.

3-Triphenylmethyloxy-1-octene (**1b**)

To a 100 mL three neck round-bottom flask equipped with a septum, gas inlet, magnetic stirring bar, and reflux condenser was added CH_2Cl_2 (40 mL), 1-octen-3-ol (2.1 g, 16 mmol, 1 equiv), Ph_3CCl (5.0 g, 18 mmol, 1.1 equiv), DMAP (0.080 g, 1.4 mmol, 0.04 equiv), and TEA (30 mL). The reaction mixture was

refluxed for 24 hours. After cooling to room temperature, the reaction mixture was poured into ice water (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were washed with saturated NH_4Cl solution (30 mL), water (30 mL), dried ($MgSO_4$), and concentrated to give crude product. Chromatography (elution with hexane/ethyl acetate 5:1) afforded **1b** (4.5 g, 75%). ^{1}H NMR: 0.94 (t, 3H, J = 6.8), 0.90–1.30 (m, 8H), 3.85–3.95 (m, 1H), 4.74–4.82 (m, 2H), 5.58–5.73 (m, 1H), 7.18–7.27 (m, 9H), 7.47–7.58 (m, 6H); ^{13}C NMR: 13.9, 22.4, 23.8, 31.7, 35.5, 75.4, 87.1, 113.5, 126.9, 127.6, 129.2, 140.2, 145.5.

2-Benzyloxyheptanal (**2a**)

A solution of **1a** (9.0 mmol, 1.8 g) and methanol (0.37 mL) in CH_2Cl_2 (50 mL) was cooled to −78°C. A steady stream of ozone was bubbled through the solution until a pale blue color appeared. Dimethyl sulfide (6.5 mL) was added at −78°C, and the reaction mixture was allowed to warm to room temperature and stirred for 24 hours. Excess dimethyl sulfide and solvents were evaporated under reduced pressure. Chromatography was performed on the resulting residue with hexane/ethyl acetate 10:1 to afford the desired product **2a** (1.7 g, 89%). ^{1}H NMR: 0.86 (t, 3H, J = 6.9), 1.15–1.70 (m, 8H), 3.74 (td, 1H, J_1 = 6.6, J_2 = 2.1), 4.52 (d, 1H, J = 11.7), 4.66 (d, 1H, J = 11.7), 7.28–7.41 (m, 5H), 9.64 (d, 1H, J = 2.4); ^{13}C NMR: 13.82, 22.31, 24.44, 29.92, 31.48, 72.50, 83.5, 128.1, 128.1, 128.6, 137.7, 204.1.

2-Triphenylmethyloxyheptanal (**2b**)

Ozonolysis of a solution of **1b** (3.7 g, 10 mmol) and methanol (0.40 mL) in CH_2Cl_2 (50 mL) at −78°C as described above provided **2b** (3.27 g, 88%). ^{1}H NMR: 0.94 (t, 3H, J = 7.6), 1.30–1.89 (m, 8H), 3.93–3.99 (m, 1H), 7.25–7.40 (m, 9H), 7.50–7.60 (m, 6H), 8.78 (d, 1H, J = 3.6); ^{13}C NMR: 14.0, 22.4, 23.6, 32.0, 32.2, 75.6, 78.6, 127.6, 128.1, 128.8, 144.0, 203.0.

(*E*)-*2-Benzyloxyheptanal N,N-Dimethylhydrazone* (**3a**)

To a solution of **2a** (2.0 g, 9.8 mmol, 1 equiv) in CH_2Cl_2 (50 mL) were added Na_2SO_4 (10 g) and *N, N*-dimethylhydrazine (1.11 mL, 14.6 mmol, 1.5 equiv). The reaction mixture was heated at reflux for 10 hours. The reaction mixture was allowed to cool to room temperature, filtered, and the Na_2SO_4 was washed with ethyl acetate. The combined organic solvents were concentrated, and the residue was purified by chromatography (hexane/ethyl acetate 10:1) to provide hydrazone **3a** (2.3 g, 92%). ^{1}H NMR: 0.86 (t, 3H, J = 6.3), 1.20–1.80 (m, 8H), 2.77 (s, 6H), 3.90 (q, 1H, J = 6.8), 4.44 (d, 1H, J = 11.6), 4.57 (d, 1H, J = 11.6), 6.41 (d, 1H, J = 6.8), 7.20–7.38 (m, 5H); ^{13}C NMR: 14.0, 22.5, 24.9, 31.7, 34.4, 42.9, 70.3, 79.7, 127.3, 127.8, 128.2, 137.5, 138.9.

(*E*)-*2-triphenylmethyloxyheptanal N,N-Dimethylhydrazone* (**3b**)

The same procedure as described above afforded 85% of **3b**. ^{1}H NMR: 0.89 (t, 3H, J = 7.2), 1.21–1.75 (m, 8H), 4.15–4.22 (m, 1H), 6.02 (d, 1H, J = 6.4), 7.20–7.38 (m, 9H), 7.48–7.60 (m, 6H); ^{13}C NMR: 14.08, 22.57, 24.1, 32.0, 36.1, 42.4, 74.6, 87.0, 126.8, 127.6, 129.2, 139.7, 145.1.

3-(2-Methoxyethoxy)methyloxy-1-octene (**1c**)

To a stirred solution of 1-octene-3-ol in 10 mL of dry THF was added sodium hydride (57% oil dispersion, 252 mg, 6.00 mmol, 1.2 equiv) at 0°C. After the resulting suspension was stirred for 1 hour at 0°C, MEMCl (747 mg, 6.00 mmol, 1.2 equiv) was added dropwise to the suspension. The reaction mixture was stirred for 1 hour at 0°C and for 4 hours at room temperature. The reaction was quenched by 10 mL of water. The aqueous layer was extracted with ether (3 × 30 mL). The combined organic extracts were dried by sodium sulfate and concentrated under reduced pressure to give a yellow oil. Column chromatography afforded **1c** as a colorless liquid (45%); R_f = 0.75 (hexane/ethyl acetate 2:1); IR (CCl_4): 1040, 1108, 1466, 2932; ^{1}H NMR: 0.88 (t, 3H, J = 6.9), 1.24–1.66 (m, 8H), 3.40 (s, 3H), 3.56 (t, 2H, J = 5.1), 3.60–3.67 (m, 2H), 3.75–3.86 (m, 2H), 4.02 (q, 1H, J = 6.6), 4.65 (d, 1H, J = 6.6), 4.78 (d, 1H, J = 6.6), 5.14–5.24 (m, 2H), 5.60–5.73 (m, 1H); ^{13}C NMR: 13.9, 22.5, 24.9, 31.6, 35.2, 58.9, 66.8, 71.8, 77.4, 92.7, 117.1, 138.5. MS/CI: 234.2 ($M + NH_4^+$), 217.2 ($M + H^+$), 205.3, 204.2.

(*E*)-*2-(2-Methoxyethoxy)methyloxyheptanal N,N-Dimethylhydrazone* (**3c**)

A solution of **1c** (9.00 mmol, 1.96 g) and methanol (0.37 mL) in CH_2Cl_2 (50 mL) was cooled to −78°C. A steady stream of ozone in oxygen was bubbled through the solution until a pale blue color appeared. Dimethyl sulfide (6.5 mL) was added at −78°C, and the reaction mixture was stirred at room temperature over 24 hours. Excess dimethyl sulfide and solvents were evaporated under reduced pres-

sure. The resulting residue was used without further purification. To a solution of this residue in CH_2Cl_2 (50 mL) was added Na_2SO_4 (10 g) and *N,N*-dimethylhydrazine (1.11 mL, 14.6 mmol). The reaction mixture was heated to reflux for 10 hours. The reaction mixture was allowed to cool to room temperature, filtered, and the Na_2SO_4 was washed with ethyl acetate. The combined organic solvents were concentrated, and chromatography was performed with hexane/ethyl acetate 6:1 to provide hydrazone **3c** as a yellow liquid (two steps, 1.8 g, 77%). R_f = 0.28 (hexane/ethyl acetate 4:1); IR (CCl_4): 1036, 1108, 1468, 1597, 2931; ^{1}H NMR: 0.87 (t, 3H, *J* = 7.2), 1.25–1.75 (m, 8H), 2.76 (s, 6H), 3.38 (s, 3H), 3.54 (t, 2H, *J* = 4.8), 3.62–3.80 (m, 4H), 3.75–3.86 (m, 2H), 4.15 (q, 1H, *J* = 6.8), 4.67 (d, 1H, *J* = 7.2), 4.80 (d, 1H, *J* = 7.2), 6.36 (d, 1H, *J* = 6.8); ^{13}C NMR: 13.9, 22.5, 24.8, 31.6, 34.2, 42.7, 58.9, 66.9, 71.7, 76.7, 93.1, 136.4. MS/EI: 260.2, 189.1, 171.1, 155.2, 111.1, 128.1, 89.1, 73.1, 59.1, 45.0; HRMS calcd for $C_{13}H_{28}N_2O_3$: 260.2099; found: 260.2099.

General Experimental Procedure for the Reaction of α-Alkoxy Hydrazones with Organocerium Reagents

A 50 mL two-neck round-bottom flask equipped with stopper, magnetic stirring bar, and gas inlet was charged with $CeCl_3 \cdot 7H_2O$ (373 mg, 1.00 mmol, 2 equiv), which was slowly heated to 140°C at 0.001 Torr and dried over 12 hours. After cooling under vacuum, the flask was vented to argon through the gas inlet. THF, ether, or DME (6 mL) was added to the flask. The resulting suspension was stirred for 2 hours at room temperature and cooled to −78°C. An organometallic reagent (1.00 mmol, 2 equiv) was added through a syringe, and the reaction mixture was stirred for 1 hour at −78°C. An α-alkoxy hydrazone (0.500 mmol, 1 equiv) in 2 mL of the corresponding solvent was added via syringe and the resultant mixture was stirred at −78°C for 30 minutes and at room temperature for 1.5 hours. Methyl chloroformate (0.42 mL, 5.0 mmol, 10 equiv) was added through a septum, and the reaction mixture was stirred for 5 hours at room temperature. The reaction was quenched with 30 mL of water and the mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with 30 mL water, dried ($MgSO_4$), and concentrated to afford a crude product, which was purified by chromatography.

Methyl (*N,N-Dimethylamino*) (*2-benzyloxy-1-methylheptyl*) *carbamate* (**4a**)

colorless oil; R_f = 0.32 (hexane/ethyl acetate 10:1); IR (CCl_4): 1100, 1310, 1447, 1699, 2830, 2950; ^{1}H NMR: 0.90 (t, 3H, *J* = 6.8), 1.18 (d, 3H, *J* = 6.8), 1.25–1.75 (m, 8H), 2.70 (br, 6H), 3.61 (br, 1H), 3.75 (br, 3H), 4.22 (br, 1H), 4.43 (d, 1H, *J* = 11.2), 4.56 (d, 1H, *J* = 11.2), 7.20–7.40 (m, 5H); ^{13}C NMR: 13.9, 22.5, 23.9, 29.3, 29.5, 32.0, 44.4 (br), 44.9 (br), 51.8, 69.5, 71.9, 79.4, 127.0, 127.6, 128.0, 138.0, 138.9; MS/CI: 359 (M + Na^+), 337 (M + H^+), 243, 229, 165, 119, 91, 69. Anal. Calcd for $C_{19}H_{32}N_2O_3$: C, 67.82; H, 9.59; N, 8.33. Found: C, 68.35; H, 9.69; N, 8.08.

Methyl (*N,N-Dimethylamino*) (*2-benzyloxy-1-tert-butylheptyl*) *Carbamate* (**4b**) *[23]*

colorless oil; R_f = 0.18 (hexane/ethyl acetate 10:1); IR (CCl_4): 1087, 1299, 1437, 1696, 2870, 2954; ^{1}H NMR: 0.90 (t, 3H, *J* = 6.8), 1.18 (d, 9H, *J* = 4.0), 1.25–1.45 (m, 6H), 1.60–1.75 (m, 2H), 2.60–2.90 (m, 6H), 3.67 (s, 1.5H), 3.78 (m, 2.5H), 4.08 (br, 0.5H), 4.47 (d, 1H, *J* = 11.6), 4.53 (br, 0.5H), 4.59 (d, 1H, *J* = 11.6), 7.2–7.4 (m, 5H); ^{13}C NMR: 14.1, 22.6, 26.7, 29.2, 31.3, 32.0, 35.3, 43.8, 52.0, 65.5, 70.05, 80.1, 119.1, 127.1, 128.1, 139.1. Anal. Calcd for $C_{22}H_{38}N_2O_3$: C, 69.80; H, 10.12; N, 7.40. Found: C, 69.78; H, 10.20; N, 7.27.

Methyl (*N,N-Dimethylamino*) (*2-benzyloxy-1-isopropylheptyl*) *Carbamate* (**4c**)

colorless oil; R_f = 0.51 (hexane/ethyl acetate 7:1); IR (CCl_4): 1095, 1298, 1438, 1706, 2871, 2955; ^{1}H NMR: 0.90 (t, 3H, *J* = 6.4), 0.96–1.04 (m, 6H), 1.20–1.80 (m, 8H), 2.15 (br, 1H), 2.66 (d, 3H, *J* = 16), 2.78 (d, 3H, *J* = 16), 3.60–3.80 (m, 4H), 4.04 (br, 0.5H), 4.42–4.58 (m, 2.5H), 7.2–7.4 (m, 5H); ^{13}C NMR: 13.88, 20.27 (d), 22.5, 25.4, 27.4, 30.1, 32.1, 44.5 (d), 51.9, 65.4, 70.1, 79.8, 127.2, 128.6, 129.8, 139.4. Anal. Calcd for $C_{21}H_{36}N_2O_3$: C, 69.19; H, 9.95; N, 7.68. Found: C, 69.64; H, 10.24; N, 7.57.

Methyl (*N,N-Dimethylamino*) (*2-methoxyethoxymethyloxy-1-methylheptyl*) *Carbamate* (**4d**)

pale yellow oil; R_f = 0.16 (hexane/ethyl acetate 4:1); IR (CCl_4): 1043, 1100, 1311, 1440, 1702, 2252, 2889, 2940; ^{1}H NMR: 0.90 (t, 3H, *J* = 6.8), 1.17 (d, 3H, *J* = 6.8), 1.25–1.50 (m, 6H), 1.67–1.75 (m, 2H), 2.70 (br, 6H), 3.39 (s, 3H), 3.55 (t, 2H, *J* = 5.2), 3.65–3.80 (m, 6H), 4.10 (br, 1H), 4.76 (q, 2H, *J* = 6.0); ^{13}C NMR: 13.9, 22.5, 24.1, 30.8, 32.0, 44.8, 51.9, 56.4, 58.9, 67.3, 71.6, 79.7, 95.1, 119.0, 121.5, 131.4. Anal. Calcd for $C_{16}H_{34}N_2O_5$: C, 57.46; H, 10.25; N, 8.38. Found: C, 57.37; H, 10.49; N, 8.07.

N,N-Dimethylcarbamate

^{1}H NMR: 2.90 (br, 6H), 3.68 (3H); ^{13}C NMR: 27.7, 82.0, 154.1.

2-Benzyloxyheptanenitrile (**5a**) *[24]*

colorless oil; R_f = 0.46 (hexane/ethyl acetate 10:1); IR (CCl_4): 1020, 1090, 1245, 1440, 1565, 2870, 2950, 3025; ^{1}H NMR: 0.90 (t, 3H, J = 6.8), 1.15–1.60 (m, 6H), 1.82–1.91 (m, 2H), 4.16 (t, 1H, J = 6.6), 4.53 (d, 1H, J = 11.6), 4.87 (d, 1H, J = 11.6), 7.28–7.41 (m, 5H); ^{13}C NMR: 13.9, 22.4, 24.4, 31.1, 33.4, 67.7, 72.2, 118.4, 128.2, 128.4, 128.7, 136.1. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.32; H, 8.72; N, 6.32.

2-Triphenylmethyloxyheptanenitrile (**5b**)

white solid; m.p. 63.5–64.0% C; R_f = 0.40 (hexane/ethyl acetate 10:1); IR (KBr): 1060, 1200, 1299, 1350, 1480, 2700, 2780, 2920; ^{1}H NMR: 0.89 (t, 3H, J = 6.8), 1.08–1.81 (m, 8H), 4.13 (dd, 1H, J_1 = 7.6, J_2 = 4.4), 7.23–7.38 (m, 9H), 7.43–7.50 (m, 6H); ^{13}C NMR: 13.8, 22.5, 24.0, 31.1, 34.4, 63.2, 88.8, 118.6, 127.7, 128.0, 128.6, 142.8; Anal. Calcd for $C_{26}H_{27}NO$: C, 84.51; H, 7.37; N, 3.79. Found: C, 84.49; H, 7.46; N, 3.74.

2-Methoxyethoxymethyloxyheptanenitrile (**5c**)

pale yellow oil; R_f = 0.42 (hexane/ethyl acetate 4:1); IR (CCl_4): 1028, 1112, 1173, 1367, 1467, 1746, 2857, 2944; ^{1}H NMR: 0.92 (t, 3H, J = 6.8), 1.30–1.40 (m, 4H), 1.50–1.60 (m, 2H), 1.86 (m, 2H), 3.41 (s, 3H), 3.55–3.65 (m, 2H), 3.75–3.79 (m, 2H), 4.43 (t, 1H, J = 6.6), 4.78 (d, 1H, J = 7.0), 4.83 (d, 1H, J = 7.0); ^{13}C NMR: 13.8, 22.2, 24.3, 31.0, 33.2, 58.9, 64.8, 67.6, 71.4, 94.4, 118.4. MS/CI: 233.1 (M + NH_4^+), 216.1 (M + H^+), 214.1 (M − H), 185.9, 181.0, 169.0, 126.8, 94.0, 89.0. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; 6.51. Found: C, 61.98; H, 9.58; N, 6.30.

2-Hydroxyheptamine (**9**)

A solution consisting of anhydrous $AlCl_3$ (143 mg, 1.07 mmol, 4 equiv) and 1 mL of ether was transferred to a suspension of $LiAlH_4$ (39.3 mg, 1.04 mmol, 4 equiv) at room temperature. Nitrile **5b** (100 mg, 0.27 mmol, 1 equiv) in ether (1 mL) was added. The resulting mixture was stirred for 4 hours and the reaction was quenched by cautious addition of 5% hydrochloric acid solution (15 mL). The aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were dried by sodium sulfate and concentrated under reduced pressure to give product **9** (16 mg, 45%). Yellow semisolid; IR (CCl_4): 3354, 2956, 2928, 2858, 1550, 1450; ^{1}H NMR ($CDCl_3$, 300 MHZ): 0.88 (t, 6H, J = 6.6, CH_3), 1.25–1.50 (m, 8H), 2.17 (3H, NH_2, OH), 2.52 (dd, 1H, J = 12, 8.4), 2.85 (dd, 1H, J = 12, 8.4), 3.48–3.58 (m, 1H, CH); ^{13}C NMR: 14.0, 22.6, 25.3, 31.8, 34.8, 46.5, 70.6. MS: 113.1, 89.0, 83.1, 60.0, 55.1, 44.2; HRMS. Calcd for $C_7H_{17}NO$, 131.13101; Found, 131.13080.

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