Synthesis of α-Hydroxy Ketones by Samarium(II) Iodide-Mediated Coupling of Organic Halides, an Isocyanide, and Carbonyl Compounds

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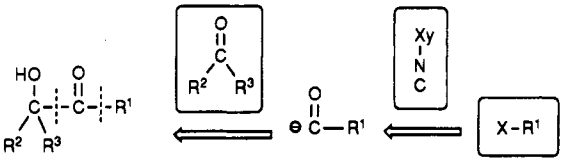
A new strategy for the synthesis of α-hydroxy ketones by samarium(II) iodide-mediated three-component coupling of organic halides, an isocyanide, and carbonyl compounds is disclosed. An (α-iminoalkyl)samarium(III) species is generated in situ by treatment of an organic halide with 2 equiv of samarium(II) iodide in the presence of 2,6-xylyl isocyanide. Subsequent treatment of the mixture with a carbonyl compound affords α-hydroxy imines, which are converted by acid-catalyzed hydrolysis to the corresponding α-hydroxy ketones. The mild reaction conditions employed are compatible with a variety of functionalities including terminal acetylenes and trimethylsilyl ethers. Application of the method to the synthesis of α-hydroxy aldehydes is also presented.

The synthesis of polyoxygenated natural products, such as macrolides and ionophore antibiotics, has attracted considerable attention in recent years. Hydroxy ketones 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-Iminoalkyl)samarium(III) compounds especially have found useful and novel synthetic applications.[5c] Herein, we report a full account of the synthesis of α-hydroxy ketones by samarium(II) iodide-mediated[7] coupling of organic halides, 2,6-xylyl isocyanide, and carbonyl compounds as shown in Scheme I. Syntheses of α-hydroxy aldehydes by samarium(II) iodide-mediated coupling of ketones with 2,6-xylyl isocyanide are also described.

Scheme I



Synthesis of α-Hydroxy Ketones by SmI_2-Mediated Three-Component Coupling of Organic Halides, an Isocyanide, and Carbonyl Compounds. The samarium(II) iodide-mediated three-component coupling reaction involves generation of an (α-iminoalkyl)samarium(III) intermediate by the initial coupling of an organic halide with an isocyanide and subsequent addition of the intermediate to a carbonyl compound. The (α-iminoalkyl)-samarium(III) intermediate was readily generated by treatment of an organic halide (1) with 2 equiv of samarium(II) iodide in the presence of 2,6-xylyl isocyanide (2)[8] in THF containing HMPA at −15 °C. After the mixture was stirred for 3 h, the disappearance of the deep purple color of samarium(II) iodide indicated complete reduction of the organic halide. Subsequent treatment of the reaction mixture with a carbonyl compound afforded the corresponding α-hydroxy imine (3). The syntheses of a variety of α-hydroxy imines are summarized in Table I.

Both alkyl bromides and iodides could be employed; alkyl chlorides failed to react because the reduction of alkyl chlorides by samarium(II) iodide requires reaction temperatures of around 60 °C.[9] Not only primary and secondary alkyl groups but also tertiary alkyl groups were efficiently introduced onto the isocyano carbon. The successful coupling of tertiary alkyl groups with the isocyano carbon is in contrast to the unsatisfactory result reported for the samarium(II) iodide-mediated *Barbier*-

(1) Review: (a) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1. (b) Mukaiyama, T. In *Organic Reactions*, Vol. 28; Dauben, W. G., Ed.; John Wiley and Sons, Inc.; 1982; p 203. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, Chapter 2.

(2) Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* **1991**, 281 and references cited therein.

(3) Ager, D. J. In *Umpoled Synthons*; Hase, T. A., Ed.; Wiley: New York, 1987; p 19.

(4) (a) Seyferth, D.; Weinstein, R. M.; Wang, W. L. *J. Org. Chem.* **1983**, *48*, 1144. (b) Hiiro, T.; Morita, Y.; Inoue, T.; Kambe, N.; Ogawa, A.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 455. (c) Collin, J.; Namy, L.-L.; Dallemer, F.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118.

(5) (a) Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1988**, *53*, 4158. (b) Murakami, M.; Ito, H.; Bakar, W. A. W. A.; Baba, A. B.; Ito, Y. *Chem. Lett.* **1989**, 1603. (c) Murakami, M.; Kawano, T.; Ito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2437.

(6) (a) Niznik, G. E.; Morrison, W. H.; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 600. (b) Marks, M. J.; Walborsky, H. M. *J. Org. Chem.* **1981**, *46*, 5405. (c) Marks, M. J.; Walborsky, H. M. *J. Org. Chem.* **1982**, *47*, 52.

(7) Reviews on synthetic application of organolanthanides: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *24*, 6573. (b) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15. (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(8) Replacement of 2,6-xylyl isocyanide with other isocyanides such as hexyl isocyanide or 4-tolyl isocyanide afforded not (α-iminoalkyl)-samarium(III) but a complex mixture including a reductive de-isocyanation product. It has been reported that cyclohexyl and *tert*-butyl isocyanides were reductively cleaved by $(C_5Me_5)_2Sm(THF)_2$: Evans, W. J.; Drummond, D. K. *Organometallics* **1988**, *7*, 797.

(9) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.

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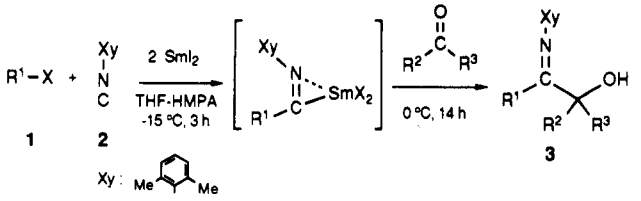
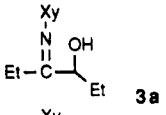
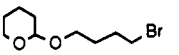
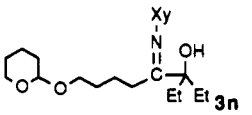
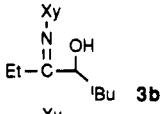
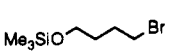
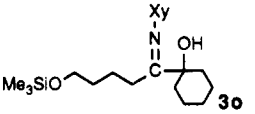
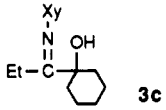
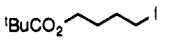
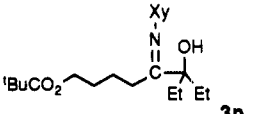
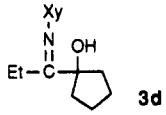
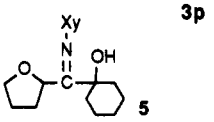
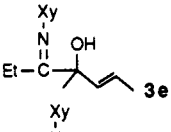
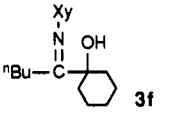
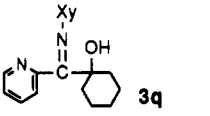
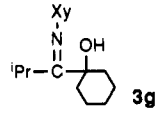
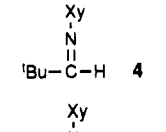
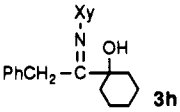
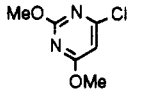
Table I. SmI_2-Mediated Reactions of Organic Halides, Isocyanide, and Carbonyl Compounds



entry	R^1–X	R^2R^3C=O	product	yield, %	entry	R^1–X	R^2R^3C=O	product	yield, %
1	Et–Br	EtCHO	 **3a**	75	15			 **3n**	97
2	Et–Br	^{t}BuCHO	 **3b**	94	16			 **3o**	99
3	Et–Br		 **3c**	80	17			 **3p**	73
4	Et–Br		 **3d**	99	18			 **5**	90
5	Et–Br		 **3e**	94	19			**5**	90
6	^{n}Bu–Br		 **3f**	87	20			 **3q**	99
7	^{i}Pr–I		 **3g**	99	21			**5**	99
8	^{t}Bu–Br		 **4**	90	22			complex mixture	—
9	$PhCH_2$–Br		 **3h**	37	23			**3r**	34
10		^{i}PrCHO	**3l**	91	24	$BnOCH_2$–Cl	EtCHO	**3s**	86
11			**3j**	93	25	$BnOCH_2$–Cl		**3t**	99
12			**3k**	74	26	$BnOCH_2$–Cl		**3u**	99
13			**3l**	81	27	$BnOCH_2$–Cl		**6v**	70
14			**3m**	99					

like reaction of *tert*-butyl bromide with 2-octanone in the absence of HMPA.[10] The (α-iminoalkyl)samarium(III) species generated from *tert*-butyl bromide was susceptible to protonolysis and afforded aldimine **4** in 90% yield (entry 8). However, steric requirements precluded C–C bond formation with the carbonyl compound. The reaction

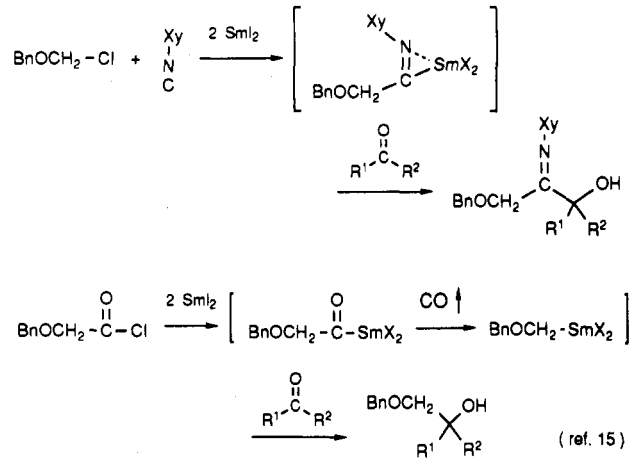
employing benzyl bromide was complicated by competing dimerization;[10] 1,2-diphenylethane was formed along with the desired product (37%, entry 9). It has been reported that phenyl[9] and vinyl[11] radicals, intermediates in samarium(II) iodide-mediated reactions, abstract hydrogen from the THF solvent more rapidly than they are reduced by samarium(II) iodide. Hydrogen abstraction generates α-tetrahydrofuryl radical, and indeed, the use of iodobenzene or vinyl bromide in the present reaction resulted in the formation of THF-containing adduct **5** (entries 18 and 19). Comparison of three isomeric bromopyridines revealed a notable difference in reaction products (entries 20–22). 2-Bromopyridine coupled with the isocyanide and cyclohexanone to afford desired product **3q**, whereas the reaction employing 3-bromopyridine gave **5** as the sole product. Utilization of 4-bromopyridine resulted in a complex mixture which included **5**. The reaction of the 4-chloropyrimidine derivative gave the corresponding α-hydroxy imine **3r** in 34% yield along with adduct **5** (~20%).

The (α-iminoalkyl)samarium(III) species, generated from an organic halide and the isocyanide, is highly nucleophilic and undergoes addition not only to aldehydes but also to ketones without enolization or reduction. Notably, cyclopentanone and β-tetralone, which are exceptionally prone to enolization and, hence, difficult to alkylate, readily coupled with the (α-iminoalkyl)samarium(III) intermediate (entries 4 and 27).[12] The success of the reaction with these enolizable ketones implies that the basicities of the (α-iminoalkyl)samarium(III) intermediates are low, as are organocerium compounds.[13] In coupling reactions with α,β-unsaturated ketones, 1,2-adducts were selectively produced (entries 5 and 26).[14]

The compatibility of a variety of functional groups with the present mild reaction conditions renders this three-component coupling reaction particularly attractive. Neither carbon–carbon double nor triple bonds are affected (entries 12 and 13). Notably, terminal acetylenic compounds bearing acidic hydrogen are also tolerated, which also suggests the less basic character of the intermediate (α-iminoalkyl)samarium(III) species. Alkyl halides bearing a hydroxyl or a cyano group cannot be utilized. However, protection of the hydroxyl group as a benzyl or tetrahydropyranyl ether allows the reaction to proceed (entries 14 and 15). Furthermore, trimethylsilyl and pivaloyl groups, which are often cleaved by organolithium and Grignard reagents, can also be employed (entries 16 and 17). The sterically less demanding acetyl functionality is not suitable.

The sammarium(II) iodide-mediated three-component coupling provides a useful and practical approach to the synthesis of α,α′-dihydroxy ketones, a common structural feature of a broad range of natural products such as keto sugars, corticosteroids, and anthracycline antibiotics. The stability of the benzyl ether linkage to the present reaction conditions renders it possible to use benzyl chloromethyl ether as a starting halide, as demonstrated by entries 24–27.[5c] When an aldehyde was employed, α-acetoxy imine **3s** was isolated after the reaction mixture was quenched with acetic anhydride. It has been reported that the samarium(II) iodide-mediated reaction of an α-alkoxy acid chloride results in the extrusion of carbon monoxide from what is presumed to be an (α-alkoxyacyl)samarium(III) intermediate and gives an (alkoxymethyl)samarium(III) species.[15] In contrast, the present reaction proceeds in the reverse direction, i.e., the isocyanide, which is isoelectronic with carbon monoxide, is inserted into the (alkoxymethyl)samarium(III) intermediate (Scheme II).

Scheme II



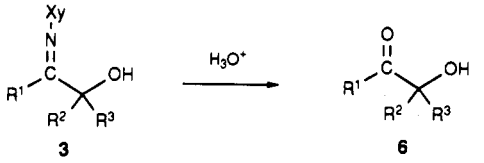
Of interest is the fact that only one set of five resonances is observed for 2,6-xylyl group in the ^{13}C NMR spectra of **3** derived from symmetrical ketones. The presence of only one set of resonances suggests that the xylyl group is perpendicular to the C=N plane (the perpendicularity of these two groups gives the molecule a mirror symmetry) and that either the syn isomer or the anti isomer is exclusively favored in solution. Distortion of a xylyl group out of a C=N plane has been observed in an X-ray diffraction study of an *N*-2,6-xylyl bis(organosilyl)imine derivative.[16] The ^{13}C NMR spectra of **3** derived from aldehydes exhibit magnetic nonequivalence of the carbon atoms within the xylyl group, and this nonequivalence suggests that hindered rotation about the (2,6-xylyl)–N bond is occurring. Assignments of peaks in selected ^{13}C NMR spectra are provided in the supplementary material.

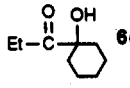
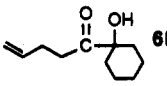
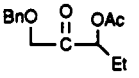
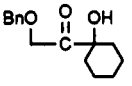
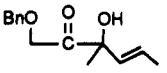
α-Hydroxy imines **3** were transformed to the corresponding α-hydroxy ketones **6** in good yield by acid-catalyzed hydrolysis of the imino group (Table II). α-Hydroxy ketones **6c** and **6k** were obtained by treatment of **3c** and **3k**, respectively, with 1% H_2SO_4 in MeOH–H_2O at 70 °C. Hydrolysis of α,α′-dioxy-substituted imines **3s–u** could be performed under much milder conditions. Treatment with the slightly acidic media of benzene–MeOH–H_2O containing 0.1% HCl at room temperature for 20 min completed the hydrolysis of α,α′-dioxy-substituted imines **3s–u**. This three-component coupling reaction has been applied to the synthesis of a 2-keto sugar.[5c]

Synthesis of α-Hydroxy Aldehydes[17] by SmI_2-Mediated Coupling of Ketones and Isocyanide. Reduction of ketones by samarium(II) iodide in the presence of the isocyanide **2** afforded α-hydroxy aldimines **7**

(10) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
(11) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064.
(12) In entry 27, the product was isolated after being hydrolyzed to α-hydroxy ketone **6v**.
(13) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(14) Fukuzawa, S.; Sato, K.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1990**, 939.
(15) Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 4847.
(16) Ito, Y.; Suginome, M.; Matsuura, T.; Murakami, M. *J. Am. Chem. Soc.* **1991**, *113*, 8899.

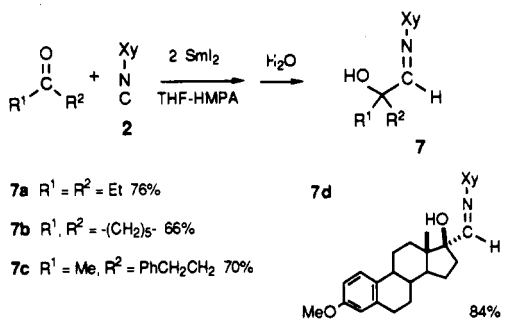
Table II. Hydrolysis of α-Hydroxy Imines 3



entry	3	method[a]	product	yield, %
1	3c	A	 6c	70
2	3k	A	 6k	81
3	3s	B	 6s	81
4	3t	B	 6t	92
5	3u	B	 6u	71

[a] A: 1% H_2SO_4 in MeOH–H_2O, 70 °C. B: 0.1% HCl in C_6H_6–MeOH–H_2O, rt.

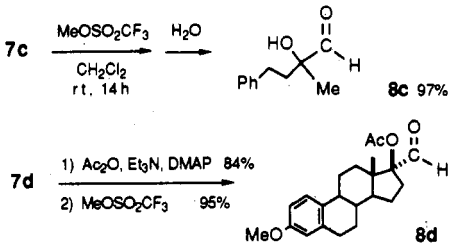
Scheme III



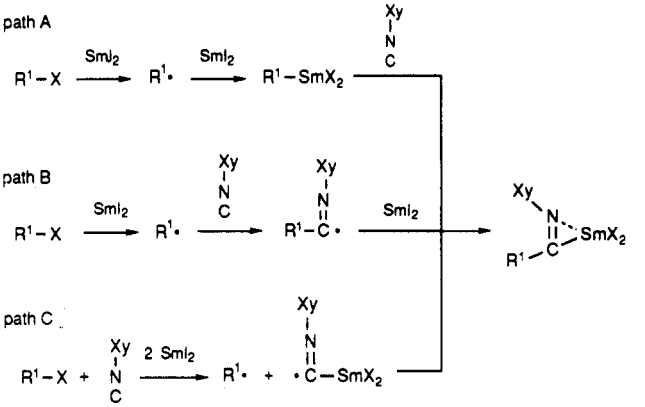
(Scheme III). The use of an aldehyde in place of a ketone was unsuccessful because of the rapid formation of pinacol.[18] It has been reported that reduction of a carbonyl compound with samarium(II) iodide in the presence of CH_3OD led mainly to the α-deuterated alcohol.[19] Taking into account this result and the mechanistic observations discussed 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 IV).

Discussion of the Possible Mechanisms for the Generation of (α-Iminoalkyl)samarium(III). Three routes are conceivable for the generation of the (α-iminoalkyl)samarium(III) species (Scheme V). The first pathway involves an alkylsamarium(III) species, which is formed by means of successive one-electron transfers from 2 equiv of samarium(II) iodide to an organic halide. The

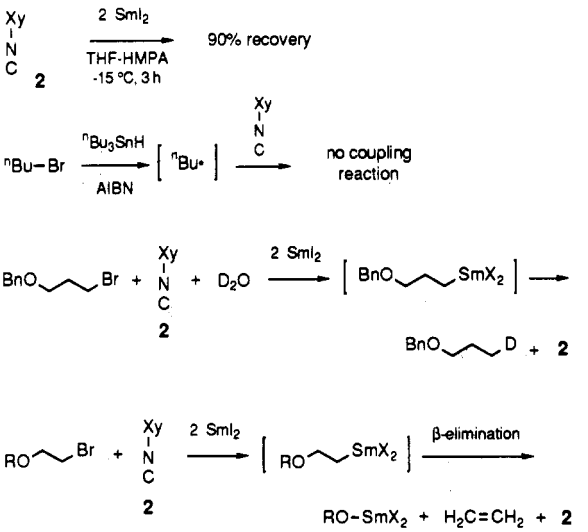
Scheme IV



Scheme V



Scheme VI



alkylsamarium(III) species undergoes α-addition to the isocyanide (path A). The second pathway involves direct addition of an organic radical, generated by one-electron transfer to an organic halide from samarium(II) iodide, to the isocyanide. The resulting α-iminoalkyl radical is subsequently reduced by samarium(II) iodide to give an (α-iminoalkyl)samarium(III) species (path B). The third pathway is the concurrent transfer of a single electron to both the organic halide and to the isocyanide. The two resulting radical species undergo radical coupling (path C).

The experiments illustrated in Scheme VI were carried out to clarify the mechanism. The failure of 2,6-xylyl isocyanide to react with samarium(II) iodide in the absence of an organic halide eliminates path C. (2,6-Xylyl isocyanide was recovered unchanged in 90% yield.) An alkyl radical formed by the reaction of alkyl bromide with tributyltin hydride did not undergo addition to 2,6-xylyl isocyanide.[20] When the samarium(II) iodide-mediated

(17) For syntheses of α-hydroxy aldehydes, see: Adamczyk, M.; Dolence, E. K.; Watt, D. S.; Christy, M. R.; Reibenspies, J. H.; Anderson, O. P. *J. Org. Chem.* **1984**, *49*, 1378 and references cited therein.

(18) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765.

(19) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37* (*Suppl*), 175.

reaction of an alkyl halide with the isocyanide was carried out in the presence of D_2O, deuterated alkane with a high percent of deuterium incorporation (R-D:R-H = >95:5) was obtained along with unchanged isocyanide. These findings exclude the addition of an organic radical to the isocyanide (path B) and support the intermediacy of an alkylsamarium(III) species. Whereas reactions with alkyl halides bearing oxy substituents at the α-, γ-, or δ-positions worked well, β-oxy-substituted halides such as 2-(trimethylsiloxy)ethyl bromide and 2-(benzyloxy)ethyl bromide failed to react with the isocyanide; 2-(benzyloxy)ethyl bromide gave benzyl alcohol. The formation of benzyl alcohol may be accounted for by assuming the intermediacy of a β-oxy-substituted alkylsamarium(III) which undergoes β-elimination. On the basis of these observations, we believe that the α-addition of the organosamarium(III) species to the isocyanide (path A) is the most likely mechanism for the generation of the (α-iminoalkyl)-samarium(III) intermediate.[21]

On the basis of the previous studies of η^2-(α-iminoalkyl) complexes of erbium and yttrium,[22] which have been isolated and fully characterized, a η^2-complex can be rationalized for the structure of (α-iminoalkyl)samarium-(III) species. However, the isolation and structural elucidation of (α-iminoalkyl)samarium(III) species have been unsuccessful so far.

Conclusions

The samarium(II) iodide-mediated three-component coupling described here provides a new and convenient method for the synthesis of a variety of α-hydroxy ketones. The reaction was found to have wide generality. The compatibility of various functionalities with the reaction conditions fulfills the requirements for the construction of multifunctional 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 the literature.[23] A THF solution of samarium(II) iodide was prepared according to the procedure of Kagan et al.[10] 1-(Benzyloxy)-3-bromopropane was prepared by bromination of 3-(benzyloxy)-1-propanol with CBr_4–PPh_3. 1-Bromo-4-(trimethylsiloxy)-butane was prepared by the literature procedure.[24] 4-Iodobutyl pivalate was prepared by treatment of pivaloyl chloride with NaI in THF. 1-Bromo-4[(tetrahydropyran-2-yl)oxy]butane was prepared by treatment of 4-bromo-1-butanol with 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of *p*-TsOH.

4-(2,6-Xylylimino)-3-hexanol (3a). The following is a typical procedure for the synthesis of α-hydroxy imines **3** by SmI_2-mediated three-component coupling. To a mixture of 2,6-xylyl isocyanide (**2**, 66 mg, 0.50 mmol), HMPA (0.8 mL, 4.3 mmol), and SmI_2 (1.6 mmol) in THF (16 mL) at −15 °C was added bromoethane (82 mg, 0.75 mmol). After the reaction mixture was stirred for 3 h, propionaldehyde (23 mg, 0.40 mmol) was added, and the resulting mixture was stirred at 0 °C for an additional 14 h. Then, H_2O (a few drops) and hexane (30 mL) were added to the reaction mixture. Filtration through a short column of Florisil followed by preparative TLC (ether:hexane = 1:3) gave **3a** as a pale yellow oil (75%): IR (neat), 3392, 1660, cm^{-1}; ^1H NMR δ 0.96 (t, J = 7.3 Hz, 3 H), 1.10 (t, J = 7.3 Hz, 3 H), 1.50–1.75 (m, 1 H), 1.85–2.25 (m, 3 H), 1.98 (s, 3 H), 2.02 (s, 3 H), 4.43 (dd, J = 3.5, 6.9 Hz, 1 H), 4.90 (s, 1 H), 6.90–7.10 (m, 3 H); ^{13}C NMR δ 9.3, 10.2, 18.1, 18.2, 23.7, 27.7, 72.0, 123.2, 125.7, 126.2, 127.9, 128.0, 146.6, 176.3; HRMS calcd for $C_{14}H_{21}NO$ m/z 219.1623, found 219.1604.

The syntheses of **3b–r** and **3t** were carried out according to the above procedure; only the amounts of reactants are given.

2,2-Dimethyl-4-(2,6-xylylimino)-3-hexanol (3b): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), bromoethane (82 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), pivalaldehyde (22 mg, 0.25 mmol); IR (neat) 3448, 1660 cm^{-1}; ^1H NMR δ 0.93 (t, J = 7.8 Hz, 3 H), 1.10 (s, 9 H), 2.03 (s, 6 H), 2.05–2.35 (m, 2 H), 4.11 (s, 1 H), 4.2–4.7 (br, 1 H), 6.87–7.07 (m, 3 H); ^{13}C NMR δ 10.3, 18.2, 19.0, 26.7, 27.2, 36.6, 78.5, 123.3, 125.0, 126.6, 128.0, 128.1, 146.6, 177.6. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.43; H, 10.37; N, 5.54.

1-[1-(2,6-Xylylimino)propyl]cyclohexanol (3c): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), bromoethane (82 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (39 mg, 0.40 mmol); IR (neat) 3360, 1660 cm^{-1}; ^1H NMR δ 0.82 (t, J = 7.7 Hz, 3 H), 1.15–1.95 (m, 10 H), 2.00 (s, 6 H), 2.17 (q, J = 7.7 Hz, 2 H), 5.43 (br s, 1 H), 6.85–7.07 (m, 3 H); ^{13}C NMR δ 10.6, 17.9, 21.7, 22.6, 25.5, 35.2, 75.1, 123.1, 125.7, 128.0, 146.5, 179.6; HRMS calcd for $C_{17}H_{25}NO$ m/z 259.1936, found 259.1922.

1-[1-(2,6-Xylylimino)propyl]cyclopentanol (3d): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), bromoethane (82 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclopentanone (21 mg, 0.25 mmol); IR (neat) 3368, 1660 cm^{-1}; ^1H NMR δ 0.83 (t, J = 7.6 Hz, 3 H), 1.75–2.06 (m, 8 H), 2.01 (s, 6 H), 2.11 (q, J = 7.6 Hz, 2 H), 5.5–5.7 (br, 1 H), 6.88–7.10 (m, 3 H); ^{13}C NMR δ 10.8, 18.0, 22.6, 24.9, 38.9, 84.1, 123.1, 125.7, 128.0, 146.8, 178.1. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32, H. 9.45; N, 5.71. Found: C, 78.37; H, 9.56; N, 5.76.

(*E*)-4-Methyl-5-(2,6-xylylimino)-2-hepten-4-ol (3e): SmI_2 (1.6 mmol), HMPA (0.8 mL, 4.3 mmol), **2** (66 mg, 0.50 mmol), bromoethane (82 mg, 0.75 mmol), (*E*)-3-penten-2-one (34 mg, 0.40 mmol); IR (neat) 3352, 1662 cm^{-1}; ^1H NMR δ 0.81 (t, J = 7.7 Hz, 3 H), 1.56 (s, 3 H), 1.78 (dd, J = 1.5, 6.4 Hz, 3 H), 2.00 (s, 3 H), 2.03 (s, 3 H), 2.12 (q, J = 7.7 Hz, 1 H), 2.14 (q, J = 7.7 Hz, 1 H), 5.63 (dd, J = 1.5, 15.4 Hz, 1 H), 5.75–6.00 (br, 1 H), 5.94 (dq, J = 6.4, 15.4 Hz, 1 H), 6.85–7.10 (m, 3 H); ^{13}C NMR δ 10.7, 17.8, 23.0, 25.0, 75.3, 123.2, 125.7, 125.8, 126.4, 128.0, 134.1, 146.1, 177.7. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.50; H, 9.46; N, 5.90.

1-[1-(2,6-Xylylimino)pentyl]cyclohexanol (3f): SmI_2 (1.5 mmol), HMPA (0.75 mL, 4.3 mmol), 1-bromobutane (103 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (24.5 mg, 0.25 mmol); IR (neat) 3360, 1660 cm^{-1}; ^1H NMR δ 0.69 (t, J = 7.2 Hz, 3 H), 0.95–2.20 (m, 16 H), 1.99 (s, 6 H), 5.3–5.7 (br, 1 H), 6.85–7.05 (m, 3 H); ^{13}C NMR δ 13.3, 18.0, 21.7, 23.2, 25.5, 27.8, 29.4, 35.2, 75.1, 123.1, 125.7, 128.0, 146.5, 178.9. Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.66; H, 10.22; N, 4.87.

1-[2-Methyl-1-(2,6-xylylimino)propyl]cyclohexanol (3g): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), 2-iodopropane (127.5 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (24.5 mg, 0.25 mmol); IR (neat) 3324, 1642 cm^{-1}; ^1H NMR δ 1.03 (d, J = 7.2 Hz, 6 H), 1.12–1.97 (m, 10 H), 2.02 (s, 6 H), 2.86 (sep, J = 7.2 Hz, 1 H), 5.30–5.60 (br, 1 H), 6.84–7.10 (m, 3 H); ^{13}C NMR δ 18.3, 19.3, 21.9, 25.5, 31.5, 35.2, 76.0, 122.7, 125.2, 127.7, 146.6, 180.3; HRMS calcd for $C_{18}H_{27}NO$ m/z 273.2093, found 273.2101.

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(22) Evans, W. J.; Hanusa, T. P.; Meadows, J. H. *Organometallics* **1987**, *6*, 295.

(23) Ugi, I.; Meyer, R. In *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 1060.

(24) Krüerke, U. *Chem. Ber.* **1962**, *95*, 174.

1-[2-Phenyl-1-(2,6-xylylimino)ethyl]cyclohexanol (3h): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), benzyl bromide (128 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (25 mg, 0.25 mmol); IR (neat) 3340, 1654 cm^{-1}; ^1H NMR δ 1.15–2.00 (m, 10 H), 1.86 (s, 6 H), 3.55 (s, 2 H), 4.95–5.25 (br, 1 H), 6.70–7.15 (m, 8 H); ^{13}C NMR δ 17.8, 21.8, 25.4, 35.8, 36.0, 75.6, 123.4, 126.1, 126.3, 127.9, 128.1, 129.3, 135.2, 146.1, 176.2; HRMS calcd for $C_{22}H_{27}NO$ *m/z* 321.2093, found 321.2100.

2-Methyl-6-phenyl-4-(2,6-xylylimino)-3-hexanol (3i): SmI_2 (1.6 mmol), HMPA (0.8 mL, 4.3 mmol), 2-phenylethyl bromide (139 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), 2-methylpropionaldehyde (29 mg, 0.40 mmol); IR (neat) 3384, 1660 cm^{-1}; ^1H NMR δ 0.96 (d, *J* = 6.6 Hz, 3 H), 1.28 (d, *J* = 7.0 Hz, 3 H), 1.99 (s, 3 H), 2.04 (s, 3 H), 2.15–2.45 (m, 5 H), 4.40 (d, *J* = 1.6 Hz, 1 H), 4.55–5.10 (br, 1 H), 6.90–7.35 (m, 8 H); ^{13}C NMR δ 14.8, 18.0, 18.7, 20.8, 31.1, 31.8, 32.8, 76.1, 123.5, 125.7, 126.36, 126.41, 127.96, 128.04, 128.1, 128.6, 140.1, 146.4, 174.3; HRMS calcd for $C_{21}H_{27}NO$ *m/z* 309.2093, found 309.2110.

1-[3-Phenyl-1-(2,6-xylylimino)propyl]cyclohexanol (3j): SmI_2 (1.6 mmol), HMPA (0.9 mL, 5.2 mmol), 2-phenylethyl bromide (139 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (39 mg, 0.40 mmol); IR (neat) 3368, 1654 cm^{-1}; ^1H NMR δ 1.25–2.00 (m, 10 H), 2.07 (s, 6 H), 2.35–2.60 (m, 4 H), 5.2–5.6 (br, 1 H), 6.75–7.30 (m, 8 H); ^{13}C NMR δ 18.0, 21.6, 25.5, 31.9, 32.2, 35.1, 75.2, 123.5, 125.6, 126.2, 127.9, 128.2, 128.5, 140.7, 146.5, 178.1. Anal. Calcd for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.17. Found: C, 82.09; H, 8.83; N, 4.09.

1-[1-(2,6-Xylylimino)-4-pentenyl]cyclohexanol (3k): SmI_2 (1.5 mmol), HMPA (1.0 mL, 5.7 mmol), 4-bromo-1-butene (101 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (29 mg, 0.30 mmol); IR (neat) 3364, 1660 cm^{-1}; ^1H NMR δ 1.15–2.35 (m, 14 H), 2.01 (s, 6 H), 4.75–4.92 (m, 2 H), 5.0–5.4 (br, 1 H), 5.45–5.65 (m, 1 H), 6.85–7.07 (m, 3 H); ^{13}C NMR δ 17.9, 21.6, 25.4, 29.0, 29.6, 35.1, 75.1, 115.1, 123.3, 125.5, 128.1, 136.8, 146.4, 178.0. Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 80.03; H, 9.61; N, 4.92.

1-[1-(2,6-Xylylimino)-11-dodecynyl]cyclohexanol (3l): SmI_2 (1.5 mmol), HMPA (1.0 mL, 5.7 mmol), 11-bromo-1-undecyne (173 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (39 mg, 0.40 mmol); IR (neat) 3320, 1660 cm^{-1}; ^1H NMR δ 0.8–2.8 (m, 29 H), 2.00 (s, 6 H), 4.6–5.4 (br, 1 H), 6.85–7.10 (m, 3 H); ^{13}C NMR δ 18.0, 18.3, 21.7, 25.4, 28.36, 28.44, 28.6, 28.8, 29.6, 29.9, 35.2, 68.0, 75.0, 84.6, 123.1, 125.6, 128.0, 146.5, 178.9; HRMS calcd for $C_{26}H_{39}NO$ *m/z* 381.3032, found 381.3042.

1-[4-(Benzyloxy)-1-(2,6-xylimino)butyl]cyclohexanol (3m): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4.0 mmol), 1-(benzyloxy)-3-bromopropane (172 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (24.5 mg, 0.25 mmol); IR (neat) 3360, 1660 cm^{-1}; ^1H NMR δ 1.15–2.30 (m, 12 H), 1.99 (s, 6 H), 2.05–2.30 (m, 2 H), 3.24 (t, *J* = 6.0 Hz, 2 H), 4.29 (s, 2 H), 5.25–5.60 (br, 1 H), 6.86–7.10 (m, 3 H), 7.15–7.40 (m, 5 H); ^{13}C NMR δ 18.2, 21.9, 25.6, 25.9, 26.5, 35.3, 69.7, 72.5, 75.4, 123.4, 125.8, 127.6, 127.7, 128.3, 128.5, 138.3, 146.7, 178.8; HRMS calcd for $C_{25}H_{33}NO_2$ *m/z* 379.2511, found 379.2520.

3-Ethyl-8-[(tetrahydropyran-2-yl)oxy]-4-(2,6-xylylimino)-3-octanol (3n): SmI_2 (1.6 mmol), HMPA (0.8 mL, 4.3 mmol), 1-bromo-4-[(tetrahydropyran-2-yl)oxy]butane (178 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), 3-pentanone (34.5 mg, 0.40 mmol); IR (neat) 3364, 1660 cm^{-1}; ^1H NMR δ 0.96 (t, *J* = 7.3 Hz, 6 H), 1.15–2.20 (m, 16 H), 2.04 (s, 6 H), 3.05–3.20 (m, 1 H), 3.35–3.60 (m, 2 H), 3.65–3.80 (m, 1 H), 4.41 (br s, 1 H), 5.37 (br s, 1 H), 6.85–7.05 (m, 3 H); ^{13}C NMR δ 8.2, 18.8, 19.3, 21.8, 25.4, 30.0, 30.1, 30.5, 31.7, 61.9, 66.2, 78.6, 98.4, 123.2, 125.46, 125.54, 128.1, 147.0, 177.3; HRMS calcd for $C_{23}H_{37}NO_3$ *m/z* 375.2723, found 375.2792.

1-[5-(Trimethylsiloxy)-1-(2,6-xylylimino)pentyl]cyclohexanol (3o): SmI_2 (1.6 mmol), HMPA (1.0 mL, 5.7 mmol), 1-bromo-4-(trimethylsiloxy)butane (134 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (39 mg, 0.40 mmol); IR (neat) 3375, 1662 cm^{-1}; ^1H NMR δ 0.04 (s, 9 H), 1.15–2.20 (m, 16 H), 2.00 (s, 6 H), 3.36 (t, *J* = 5.7 Hz, 2 H), 5.3–5.6 (br, 1 H), 6.85–7.10 (m, 3 H); ^{13}C NMR δ –0.7, 18.0, 21.7, 22.2, 25.5, 29.4, 32.8, 35.2, 61.4, 75.0, 123.2, 125.6, 128.0, 146.4, 178.9. Anal. Calcd for $C_{22}H_{37}NO_2Si$: C, 70.35; H, 9.93; N, 3.73. Found: C, 70.35; H, 9.98; N, 3.81.

3-Ethyl-8-(pivaloyloxy)-4-(2,6-xylylimino)-3-octanol (3p): SmI_2 (1.6 mmol), HMPA (0.8 mL, 4.3 mmol), 4-iodobutyl pivalate (213 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), 3-pentanone (34.5 mg, 0.40 mmol); IR (neat) 3368, 1732, 1662 cm^{-1}; ^1H NMR δ 0.96 (t, *J* = 7.3 Hz, 6 H), 1.14 (s, 9 H), 1.15–1.45 (m, 4 H), 1.60–2.15 (m, 6 H), 2.04 (s, 6 H), 3.84 (t, *J* = 6.0 Hz, 2 H), 5.36 (br s, 1 H), 6.85–7.05 (m, 3 H); ^{13}C NMR δ 8.3, 18.9, 21.5, 27.1, 29.2, 29.8, 31.7, 38.6, 63.2, 78.7, 123.4, 125.5, 128.2, 146.8, 176.9, 178.3; HRMS calcd for $C_{23}H_{37}NO_3$ *m/z* 375.2773, found 375.2788.

1-[(2-Pyridyl)(2,6-xylylimino)methyl]cyclohexanol (3q): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), 2-bromopyridine (119 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (25 mg, 0.25 mmol); IR (neat) 3384, 1654 cm^{-1}; ^1H NMR δ 1.15–1.95 (m, 10 H), 2.02 (s, 6 H), 5.51 (br s, 1 H), 6.70–6.90 (m, 4 H), 7.10–7.20 (m, 1 H), 7.35–7.45 (m, 1 H), 8.52 (d, *J* = 5.0 Hz, 1 H); ^{13}C NMR δ 18.2, 21.9, 25.4, 36.0, 76.1, 122.7, 123.1, 123.5, 125.8, 127.7, 135.8, 146.8, 148.5, 154.1, 173.2; HRMS calcd for $C_{20}H_{24}N_2O$ *m/z* 308.1889, found 308.1886.

2,4-Dimethoxy-6-[(1-hydroxycyclohexyl)(2,6-xylylimino)-methyl]pyrimidine (3r): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), 6-chloro-2,4-dimethoxypyrimidine (131 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (25 mg, 0.25 mmol); IR (neat) 3416, 1582 cm^{-1}; ^1H NMR δ 1.10–2.40 (m, 10 H), 2.05 (s, 6 H), 3.85 (s, 3 H), 3.92 (s, 3 H), 4.94 (s, 1 H), 5.93 (s, 1 H), 6.75–6.95 (m, 3 H); ^{13}C NMR δ 18.3, 21.7, 25.3, 35.8, 54.0, 55.0, 75.4, 100.3, 123.5, 125.6, 127.7, 146.2, 162.9, 164.6, 171.3, 172.8; HRMS calcd for $C_{21}H_{27}N_3O_3$ 369.2052, found *m/z* 369.2072.

1-[2-(Benzyloxy)-1-(2,6-xylylimino)ethyl]cyclohexanol (3t): SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), benzyl chloromethyl ether (117.5 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), cyclohexanone (25 mg, 0.25 mmol); IR (neat) 3400, 1668 cm^{-1}; ^1H NMR δ 1.2–2.1 (m, 10 H), 1.98 (s, 6 H), 3.92 (s, 2 H), 4.31 (s, 2 H), 4.7–4.8 (br, 1 H), 6.85–7.05 (m, 3 H), 7.05–7.35 (m, 5 H); ^{13}C NMR δ 17.9, 21.6, 25.4, 35.3, 65.8, 73.6, 75.3, 123.2, 125.4, 127.4, 127.8, 128.3, 136.9, 146.4, 174.4. Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.98. Found: C, 78.53; H, 8.53; N, 3.91.

3-Acetoxy-1-(benzyloxy)-2-(2,6-xylylimino)pentane (3s). To a mixture of 2,6-xylyl isocyanide (**2**, 66 mg, 0.50 mmol), HMPA (0.7 mL, 4 mmol) and SmI_2 (1.5 mmol) in THF (15 mL) at –15 °C was added benzyl chloromethyl ether (117.5 mg, 0.75 mmol). After the mixture was stirred for 3 h, propionaldehyde (14.5 mg, 0.25 mmol) was added, and the resulting mixture was stirred at 0 °C for an additional 14 h. Then, pyridine (158 mg, 2.0 mmol), a catalytic amount of 4-(dimethylamino)pyridine, and Ac_2O (153 mg, 1.5 mmol) were added successively. The temperature was allowed to warm to rt over 3 h, and hexane (30 mL) was added. Filtration through a short column of Florisil followed by preparative TLC (ether:hexane = 3:8) gave **3s** as a pale yellow oil (86%): IR (neat) 1740, 1678 cm^{-1}; ^1H NMR δ 1.10 (t, *J* = 7.3 Hz, 3 H), 1.85–2.14 (m, 2 H), 1.93 (s, 3 H), 1.97 (s, 3 H), 2.15 (s, 3 H), 3.83 (d, *J* = 13.8 Hz, 1 H), 3.88 (d, *J* = 13.8 Hz, 1 H), 4.34 (d, *J* = 11.8 Hz, 1 H), 4.51 (d, *J* = 11.8 Hz, 1 H), 5.52 (dd, *J* = 4.2, 8.6 Hz, 1 H), 6.81–7.42 (m, 8 H); ^{13}C NMR δ 10.4, 17.8, 17.9, 21.0, 25.7, 67.9, 73.5, 75.4, 123.1, 124.7, 125.6, 127.4, 127.8, 127.9, 128.0, 128.4, 137.3, 146.8, 170.1, 171.1; HRMS calcd for $C_{22}H_{27}NO_3$ *m/z* 353.1990, found 353.1970.

(*E*)-1-(Benzyloxy)-3-methyl-2-(2,6-xylylimino)hex-4-en-3-ol (3u). To a mixture of 2,6-xylyl isocyanide (**2**, 66 mg, 0.50 mmol), HMPA (0.8 mL, 4.3 mmol), and SmI_2 (1.5 mmol) in THF (15 mL) at –15 °C was added benzyl chloromethyl ether (117.5 mg, 0.75 mmol). After the mixture was stirred for 3 h, (*E*)-3-penten-2-one (21 mg, 0.25 mmol) was added, and the resulting mixture was stirred at –10 °C for an additional 14 h. Then, H_2O (a few drops) and hexane (30 mL) were added to the reaction mixture. Filtration through a short column of Florisil followed by preparative TLC (ether:hexane = 1:10) gave **3u** (99%): IR (neat) 3384, 1676 cm^{-1}; ^1H NMR δ 1.61 (s, 3 H), 1.73 (dd, *J* = 1.2, 6.3 Hz, 3 H), 1.94 (s, 3 H), 2.00 (s, 3 H), 3.84 (d, *J* = 12.2 Hz, 1 H), 3.89 (d, *J* = 12.2 Hz, 1 H), 4.26 (s, 2 H), 5.45 (s, 1 H), 5.72 (dd, *J* = 1.2, 15.4 Hz, 1 H), 5.93 (dq, *J* = 15.4, 6.3 Hz, 1 H), 6.88–7.10 (m, 5 H), 7.21–7.40 (m, 3 H); ^{13}C NMR δ 17.79, 17.83, 25.9, 65.9, 73.6, 75.3, 123.4, 125.5, 125.8, 126.0, 127.4, 127.7, 127.8, 127.9, 128.3, 134.2, 137.0, 146.0, 172.9; HRMS calcd for $C_{22}H_{27}NO_2$ *m/z* 337.2042, found 337.2050.

2,2-Dimethyl-1-(2,6-xylylimino)propane (4). To a mixture of 2,6-xylyl isocyanide (**2**, 66 mg, 0.50 mmol), HMPA (0.7 mL,

4 mmol), and SmI_2 (1.5 mmol) in THF (15 mL) at −15 °C was added *tert*-butyl bromide (103 mg, 0.75 mmol). After the mixture was stirred at −15 °C for 3 h, H_2O (a few drops) and hexane (30 mL) were added to the reaction mixture. Filtration through a short column of Florisil followed by preparative TLC (ether:hexane = 1:3) gave **4** as a pale yellow oil (90%): IR (neat) 1690, 1668 cm^{-1}; ^1H NMR δ 1.22 (s, 9 H), 2.06 (s, 6 H), 6.85–7.05 (m, 3 H), 7.52 (s, 1 H); ^{13}C NMR δ 18.0, 26.6, 37.1, 123.1, 126.7, 127.8, 150.8, 174.5. Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.78, H, 10.24; N, 7.53.

1-[(Tetrahydrofuran-2-yl)(2,6-xylylimino)methyl]cyclohexanol (5). By a procedure similar to that for **3a**, the title compound was obtained from SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), iodobenzene (153 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), and cyclohexanone (24.5 mg, 0.25 mmol): IR (neat) 3524, 3368, 1656 cm^{-1}; ^1H NMR δ 1.15–2.35 (m, 14 H), 1.99 (s, 3 H), 2.01 (s, 3 H), 3.55–3.70 (m, 1 H), 3.80–3.95 (m, 1 H), 4.20–4.30 (m, 1 H), 4.6–4.8 (br, 1 H), 6.80–7.05 (m, 3 H); ^{13}C NMR δ 17.97, 18.01, 21.5, 21.7, 25.3, 25.5, 29.6, 35.8, 36.1, 68.3, 76.8, 78.7, 122.8, 123.2, 126.0, 127.9, 146.9, 177.3; HRMS calcd for $C_{19}H_{27}NO_2$ m/z 301.2042, found 301.2012.

2-(Benzyloxy)-1-(1,2,3,4-tetrahydro-2-hydroxynapth-2-yl)ethan-1-one (6v). By a procedure similar to that for **3u**, the crude α-hydroxy imine was obtained from SmI_2 (1.5 mmol), HMPA (0.7 mL, 4 mmol), benzyl chloromethyl ether (117.5 mg, 0.75 mmol), **2** (66 mg, 0.50 mmol), and β-tetralone (36.5 mg, 0.25 mmol). The crude α-hydroxy imine was dissolved in benzene (10 mL) and treated with a methanol solution of HCl (concd HCl/MeOH = 1/100, 2 mL) at rt for 30 min, and then $NaHCO_3$ (336 mg, 4 mmol) was added. Filtration through a short column of silica gel followed by preparative TLC (ether:hexane = 7:5) gave **6v** (70%): IR (neat) 3468, 1724 cm^{-1}; ^1H NMR δ 1.80–2.12 (m, 2 H), 2.73 (dd, J = 2.0, 17.0 Hz, 1 H), 2.76–2.92 (m, 1 H), 2.92–3.17 (m, 2 H), 3.24 (d, J = 17.0 Hz, 1 H), 4.50 (s, 2 H), 4.63 (s, 2 H), 7.00–7.22 (m, 4 H), 7.28–7.42 (m, 5 H); ^{13}C NMR δ 24.5, 30.7, 38.1, 71.5, 73.3, 77.4, 126.1, 126.2, 128.0, 128.1, 128.5, 128.6, 129.5, 132.2, 134.8, 136.8, 210.2. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.99; H, 6.86.

Hydrolysis of 3. Method A. To α-hydroxy imine (0.20 mmol) in MeOH (5 mL) was added aqueous H_2SO_4 (10%, 0.5 mL), and the mixture was stirred under the conditions specified below. MeOH was removed by evaporation, and H_2O was added to the residue. The mixture was extracted with AcOEt, and the organic layer was washed with 1 N HCl (3 times) and with saturated aqueous NaCl. Drying and evaporation of solvent yielded the corresponding α-hydroxy ketone. **6c** (70 °C, 14 h): ^1H NMR δ 1.09 (t, J = 7.3 Hz, 3 H), 1.13–1.83 (m, 10 H), 2.59 (q, J = 7.3 Hz, 2 H), 3.1–3.8 (br, 1 H). **6k** (70 °C, 1 h): IR (neat) 3504, 1706, 1646 cm^{-1}; ^1H NMR δ 1.15–1.88 (m, 10 H), 2.35 (q, J = 7.0 Hz, 2 H), 2.66 (t, J = 7.3 Hz, 2 H), 3.2–3.5 (br, 1 H), 4.98 (d, J = 8.8 Hz, 1 H), 5.04 (d, J = 15.2 Hz, 1 H), 5.66–5.93 (m, 1 H). **Method B.** To α,α'-dioxy-substituted imine (0.20 mmol) in benzene (10 mL) at rt was added a methanol solution of HCl (concd HCl/MeOH = 1/100, 3 mL). The mixture was stirred for 20 min, and then $NaHCO_3$ (336 mg, 4 mmol) was added. Filtration through a short column of silica gel followed by preparative TLC gave the corresponding α,α'-dioxy-substituted ketone. **6s**: IR (neat) 1740 cm^{-1}; ^1H NMR δ 0.97 (t, J = 7.4 Hz, 3 H), 1.65–1.95 (m, 2 H), 2.12 (s, 3 H), 4.17 (d, J = 17.5 Hz, 1 H), 4.24 (d, J = 17.5 Hz, 1 H), 4.58 (d, J = 11.9 Hz, 1 H), 4.63 (d, J = 11.9 Hz, 1 H), 5.13 (dd, J = 4.6, 7.8 Hz, 1 H), 7.28–7.43 (m, 5 H). **6t**: IR (neat) 3488, 1724 cm^{-1}; ^1H NMR δ 1.14–1.75 (m, 10 H), 3.03 (br s, 1 H), 4.42 (s, 2 H), 4.60 (s, 2 H), 7.28–7.42 (m, 5 H); ^{13}C NMR δ 20.7, 25.0, 33.9, 71.1, 73.3, 77.9, 127.95, 128.02, 128.5, 137.0, 211.0. **6u**: IR (neat) 3488, 1732 cm^{-1}; ^1H NMR δ 1.41 (s, 3 H), 1.70 (dd, J = 1.5, 6.6 Hz, 3 H), 3.57 (s, 1 H), 4.38 (s, 2 H), 4.58 (s, 2 H), 5.51 (dd, J = 1.5, 15.5 Hz, 1 H), 5.83 (dq, J = 15.5, 6.6 Hz, 1 H), 7.34 (s, 5 H).

3-[(2,6-Xylylimino)methyl]-3-pentanol (7a). 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), **2** (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 **7a** 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 (7b). 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), **2** (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 **7b** 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 (7c). By a procedure similar to that for **7b**, 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), **2** (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 (7d). By a procedure similar to that for **7a**, 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), **2** (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}; ^1H 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 (8c). A mixture of **7c** (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 saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with 0.1 N HCl and with saturated aqueous NaCl. Drying and evaporation of solvent followed by gel permeation chromatography ($CHCl_3$) yielded the title compound (97%): IR (neat) 3464, 1736 cm^{-1}; ^1H 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 (8d). To **7d** (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%): ^1H 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 saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with

0.1 N HCl and with saturated aqueous 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}; ^1H 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.

Supplementary Material Available: ^{13}C NMR spectra with peak assignments for **3a,c,g–i,l–n,p–s,u**, **5**, and **8c** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.