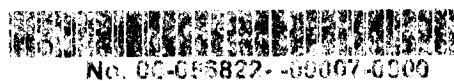


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Solicitud de Patente de Modelo de utilidad para: **"DERIVADOS DE
ESPIROPIPERIDINA PARA EL CONTROL DE PLAGAS"**

Solicitante: **SYNGENTA PARTICIPATIONS AG.**

**RESPUESTA AL EXAMEN DE BUSQUEDA DE
ANTERIORIDADES**

MARGARITA CASTELLANOS ABONDANO, mayor de edad,
identificada y domiciliada como aparece al pie de mi firma, en atención a su
oficio No. 6467 notificado el 14 de mayo de 2010, atentamente me permito dar
repuesta al mismo de la siguiente manera:

Presento copia completa de los artículos requeridos por ese Despacho como
resultado de la búsqueda de anterioridades:

• CIGANEK: "Tertiary Carbinamines by Addition of Organocerium Reagents to
Nitriles" J. ORG. CHEM., Vol. 57, 1992, pages 4521-4527, XP002325113

Cpd. 23



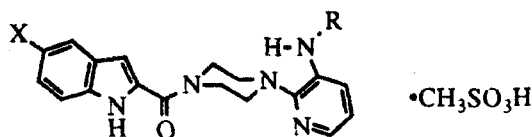
DESIGN AND SYNTHESIS OF A CONFORMATIONALLY CONSTRAINED ANALOG OF THE BIS(HETEROARYL)PIPERAZINE (BHAP) HIV-1 REVERSE TRANSCRIPTASE INHIBITOR ATEVIRDINE

Michael J. Genin^a, Constance G. Chidester^b, Douglas C. Rohrer^c, and Donna L. Romero^{a*}

^aMedicinal Chemistry Research, ^bPhysical and Analytical Chemistry, and ^cComputer-Aided Drug Design
Upjohn Laboratories, 301 Henrietta St., Kalamazoo, MI 49001

Abstract: The design and synthesis of a novel conformationally constrained spiro analog of the BHAP class of HIV-1 reverse transcriptase inhibitors, based on the molecular modeling and the X-ray crystal structure of the clinical candidate atevirdine, is described.

The discovery of the bis(heteroaryl)piperazine (BHAP) class of HIV-1 reverse transcriptase (HIV-1 RT) inhibitors has led to the development of the clinical candidates atevirdine mesylate and delavirdine mesylate.¹⁻⁴ Both of these compounds are potent inhibitors of HIV-1 RT and show promise for the treatment of HIV infection. Recently, we have been interested in probing the biologically active conformation of these molecules so that we might be able to design analogs with enhanced activity and/or metabolic stability.



	X	R	RT inhibition in vitro		Inhibition of viral replication (PBMC), ED ₅₀ (μM)
			% (100 μM)	IC ₅₀ (μM)	
Atevirdine	-OCH ₃	-Et	92	5.2	0.001
Delavirdine	-NHSO ₂ Me	-i-Pr	98	1.1	0.0001

Accurate conformational analyses of BHAP structures required the availability of suitable molecular mechanics parameters. Substructure searches of the Cambridge Crystallographic Database⁵ were conducted in order to determine the structural characteristics of the various portions of the BHAP molecule, especially the piperazine ring and substituent conformational preferences, for use in parameter development. These data revealed that the piperazine ring preferred a chair conformation with the amide-piperazine nitrogen planar and the pyridine-piperazine nitrogen tetrahedral. Once the molecular mechanics potentials were adjusted to accurately predict these results, systematic conformational searches of the four rotatable bonds were performed on a BHAP prototype^{6,7} with the pyridine ring bonded to the piperazine in either the axial or equatorial position. The preferred energy minimized conformation of the BHAP (Figure 1) had the pyridine-ring bond equatorial to the piperazine with its ring plane nearly perpendicular to the piperazine ring and the 3-alkylamino side-chain on the side opposite the nearest axial protons. These orientations apparently minimize steric interactions.

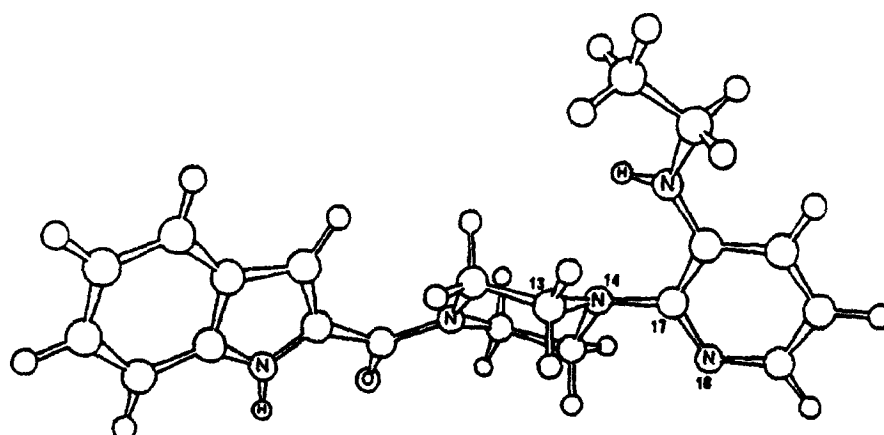


Figure 1. Minimum energy conformation of a BHAP prototype.

The X-ray crystal structures of atevirdine (**Figure 2**) and atevirdine hydrochloride have been solved⁸ and the results confirm the molecular modeling analysis discussed above. In the solid state, these BHAP molecules adopt an extended conformation with the piperazine linker existing in a chair conformation and the pyridine equatorial with respect to the piperazine. However, one unique feature observed in both crystal structures was an intramolecular hydrogen bond between the 3-(ethylamino)pyridinyl hydrogen and the lone pair of the piperazine nitrogen attached to the 2-position of the pyridine ring. The N-N distances were 2.71(1)Å for atevirdine and 2.80(1)Å for atevirdine hydrochloride. We hypothesized that this hydrogen bonded ground state conformation may also be the biologically active conformation of the BHAPs. To test this hypothesis, we designed the constrained analog 1, wherein the five-membered spiro ring system acts as a permanent conformational lock in place of the intramolecular hydrogen bond.

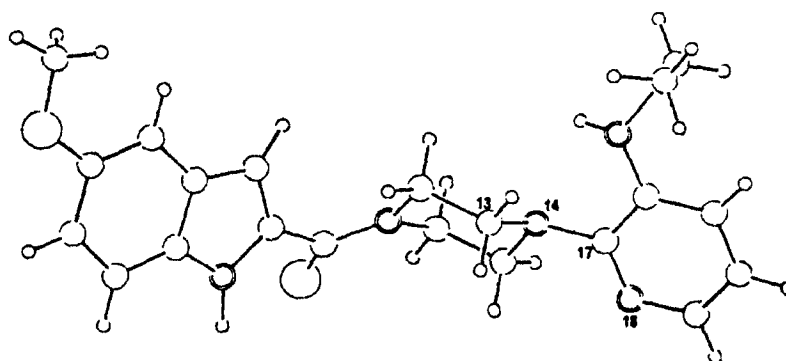
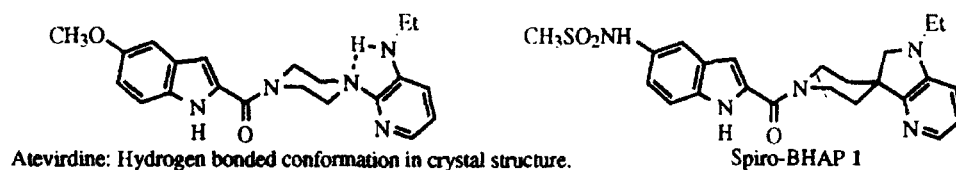


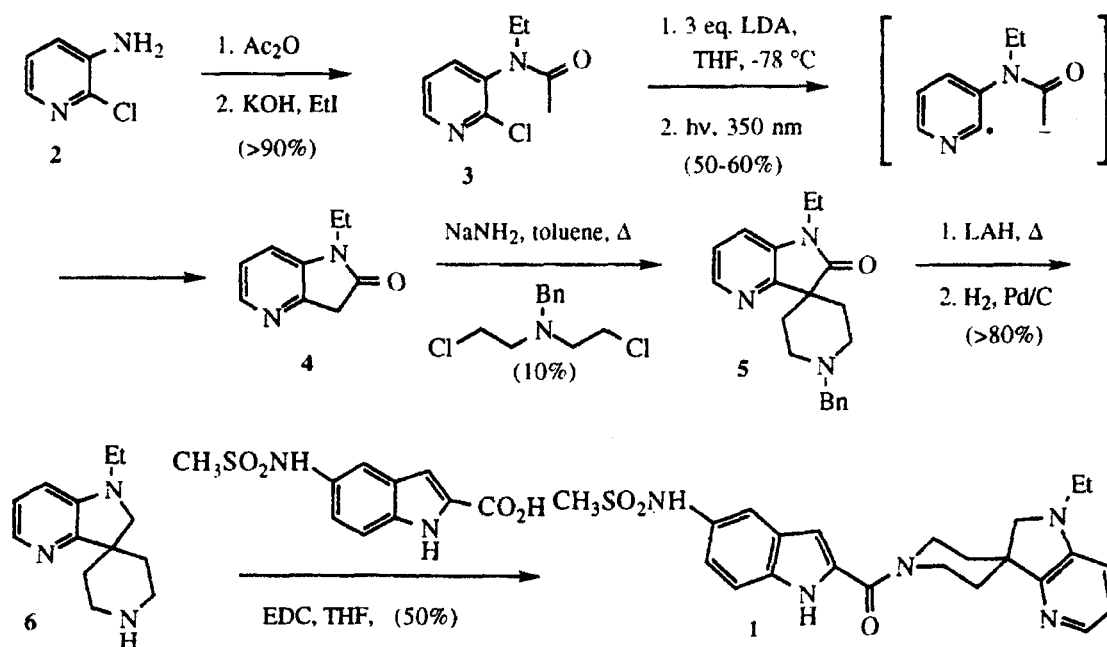
Figure 2. X-ray crystal structure of atevirdine.



SYNTHESIS

The key intermediate in the synthesis of the targeted spiro-BHAP is the novel spiro system **6** (Scheme 1). While the synthesis of spiroindolines is preceded, ^{9,10} the synthesis of analogous spiroazaindolines is not. Thus, the route we embarked upon began with the acylation of 2-chloro-3-aminopyridine, **2**, followed by alkylation of the resulting amide to provide **3** in high yields. This material was then converted to the azaoxindole **4** via a photocatalyzed radical-anion cyclization. ¹¹ This reaction proceeded very cleanly to give **4** in yields ranging from 50–60%. Following literature precedent ⁹ for conversion of an oxindole into a similar spirocyclic system (~51% yield), azaoxindole **4** was treated with NaNH₂ and N-benzyl-bis-2-chloroethylamine in refluxing toluene to afford the desired 5-membered spiro system **5** in low yields (10%). Unfortunately, various combinations of bases (BuLi, NaH, KH), solvent systems (toluene, THF, DMF), and temperatures (-78 to +100 °C) led to similar or worse yields of **5**. Nevertheless, reduction of **5** followed by deprotection gave the desired spiropiperidine intermediate, **6**, which was coupled to the indole-2-carboxylic acid derivative to afford the spiro-BHAP analog **1**. ¹²

Scheme 1



477
498

BIOLOGICAL EVALUATION

The spiro-BHAP analog **1** was tested for its ability to inhibit HIV-1 RT¹³ *in vitro* and was found to inhibit the enzyme by 38% at 100 μ M. This compound is much less active than atevirdine (92-98% RT inhibition at 100 μ M).^{1,2,14} In the X-ray structures of atevirdine and atevirdine hydrochloride the torsion angles defined by N18-C17-N14-C13 were found to be 114.7(7)° and 129.5(4)°, respectively. This same angle was estimated to be 112° in the earlier molecular modeling study of atevirdine. Molecular modeling of spirocyclic **1**^{15,16} shows that the pyridine ring is nearly orthogonal to the plane of the piperidine ring (Figure 3) and that the 5-membered spiro system is highly rigid. The torsion angle defined by N18-C17-C14-C13 was estimated to be 79°. This, however, does not exactly mimic the analogous torsion angles found in atevirdine and atevirdine hydrochloride. If the relative conformation of the pyridine and piperazine moieties observed in the X-ray structure of atevirdine correspond to the biologically active conformation, then the differences in this region of spirocyclic **1** could account for the loss in RT inhibitory activity. For example, since the pyridine nitrogen was found to be protonated in the X-ray structure of atevirdine hydrochloride, this nitrogen may form a critical hydrogen bond with the RT enzyme. Thus optimum positioning of this nitrogen would be critical for good bioactivity. In fact, analogs of atevirdine in which the pyridine ring is replaced with a benzene ring exhibit a loss of RT inhibitory activity demonstrating the importance of the pyridine nitrogen.⁴ Extensive variation of the right-hand heterocyclic portion of the BHAP template has also demonstrated the importance of the 3-(alkylamino)pyridine moiety in obtaining good RT inhibitory activity. In other words, the mere presence of the indolyl(piperazine) portion of the template is not sufficient to produce inhibition.⁴ Therefore, the reduced activity of spiro analog **1** could also be partially accounted for by the presence of a tertiary amine at the 3-pyridine position rather than a secondary amine such as that found in atevirdine. For example, an analog containing a 3-(diethylamino)pyridyl piperazine and an unsubstituted indole moiety possessed reduced RT inhibitory activity relative to its 3-(ethylamino)pyridyl parent (60% vs 96% inhibition of RT at 100 μ M).⁴ Thus, it is probable that the rigid nature of the spirocyclic BHAP analog **1** which prevent it from exactly mimicking the enzyme bound conformation of atevirdine, and/or the presence of the less preferred tertiary amine instead of a secondary amine contribute to the lessened activity of spirocycle **1**. We look upon this preliminary result as promising, since **1** is a highly constrained system and its RT inhibitory activity indicates that we are beginning to approach the bioactive conformation of the BHAPs.

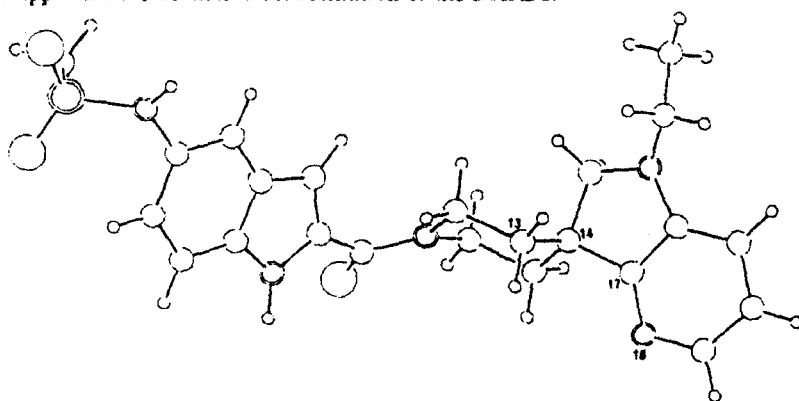


Figure 3. Energy minimized conformation of the spiro-BHAP analog **1**.^{13,14}

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CONCLUSION

In this study we have prepared the conformationally constrained spiro-BHAP analog **1** based on molecular modeling and X-ray crystallography of atevirdine. This BHAP analog contains a novel spiro heterocyclic system, **6**, which has not been previously synthesized. Although **1** was less active than either atevirdine or delavirdine, the fact that it retained some RT inhibitory activity is encouraging. Therefore, it is likely that the biologically active conformation of the BHAP template is similar to the conformation induced by this spiro system. We feel this result warrants the pursuit of other related spiro-BHAP analogs.

Acknowledgment. The authors gratefully acknowledge Dr. Fritz Reusser and Ms. Irene W. Althaus for performing the biological testing of **1**.

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8. The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre. Experimental for the X-ray Structure Determination of atevirdine and atevirdine hydrochloride. Crystal data for atevirdine: $C_{21}H_{24}N_5O_2$; formula wt. = 379.5; orthorhombic; space group $Pca2_1$; $Z=4$; $a=10.843(2)$, $b=15.55(1)$, $c=11.427(3)$ Å $V=1927(1)$ Å³; calculated density = 1.31 g cm⁻³; absorption coefficient $\mu = 0.6$ mm⁻¹; clear narrow plate 0.05 x 0.07 x 0.5 mm mounted on a glass fiber. Of 1380 unique reflections measured, 1153 had intensities $> 3\sigma$. Crystal data for atevirdine hydrochloride: $C_{21}H_{25}N_5O_2 \cdot HCl$; Formula wt = 415.9; monoclinic; space group $P2_1/c$; $Z=4$; $a=9.704(1)$, $b=27.375(3)$, $c=8.186(2)$ Å, $\beta=108.79(2)^\circ$ $V=2058.7(1)$ Å³; calculated density = 1.34 g cm⁻³; absorption coefficient $\mu = 1.77$ mm⁻¹; clear prism 0.10 x 0.15 x 0.45 mm mounted on a glass fiber. Of 3117 unique reflections measured, 2506 had intensities $> 3\sigma$.
Final agreement parameters for atevirdine were: $R=0.058$ for all 1380 reflections, and 0.048 for the 1153 reflections having $F_o^2 \geq 3\sigma$; standard deviation of fit = 3.4. Final population factors for alternate ethyl carbon positions were 58% and 42%. There is an intramolecular hydrogen bond between the NH of the ortho pyridine substituent and the piperazine nitrogen, (N-N distance: 2.732(8) Å), and an intermolecular hydrogen bond between the NH of the indole and the carbonyl oxygen in the symmetry related molecule at $1-x, 2-y, z-0.5$; (N-O distance: 2.889(5) Å).
Final agreement parameters for atevirdine hydrochloride were: $R=0.083$ for all 3117 reflections, and 0.073 for the 2506 reflections having $F_o^2 \geq 3\sigma$; standard deviation of fit=3.1. There are intramolecular hydrogen bonds between the NH of the ortho pyridine substituent and the piperazine nitrogen, (N-N distance: 2.801(5) Å), and between the NH of the indole and the carbonyl oxygen (N-O distance 2.584(4) Å). In addition the chlorine accepts hydrogens from the protonated pyridine

nitrogen in the same symmetry, from the pyridine substituent NH in the molecule related by a translation in *z*, and from the indole NH in the molecule related by the *c* glide (N-Cl distances 3.105(4), 3.329(3), and 3.276(3), respectively).

Intensity data for both structures were measured at low temperature, -120°C, on a Siemens P2₁ diffractometer, using $\theta/2\theta$ scans with scan widths $\geq 3.4^\circ$ and a scan rate of 2°/min. (atevirdine), and 4°/min. (atevirdine hydrochloride). Graphite monochromatized CuK α radiation was used, ($\lambda(\text{CuK}\alpha) = 1.5418\text{\AA}$), with maximum $2\theta = 135^\circ$. The total time spent counting background, half at each end of the scan, was equal to the time spent scanning. Ten reflections periodically monitored showed no trend towards deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $(0.01I)^2$ (atevirdine), or $(0.05I)^2$ (atevirdine hydrochloride), where the coefficient of *I* was calculated from the variations in intensities of the monitored reflections. Cell parameters were determined by least squares fit of $K\alpha_1$ 2θ values ($\lambda K\alpha_1 = 1.5402$) for 25 high 2θ reflections.¹⁷ An Lp correction appropriate for a monochromator with 50% perfect character was applied.

Both structures were solved by direct methods; atevirdine was solved using MULTAN80;¹⁸ DIREC¹⁹ was used to solve atevirdine hydrochloride. Least squares refinements included coordinates for all atoms and anisotropic thermal parameters for nonhydrogen atoms, with the exception that the disordered ethyl carbons in atevirdine were kept isotropic and hydrogens on those atoms were not included. Temperature factors for hydrogens were assigned as one-half unit higher than the equivalent isotropic temperature factors for the attached carbon. The function minimized in the refinement was $\sum w(F_o - F_c)^2$, where weights *w* were $1/\sigma^2(F_o)$. In the final cycles all shifts were $\leq 0.3\sigma$. Atomic form factors were from Doyle and Turner,²⁰ and, for hydrogen, from Stewart, Davidson and Simpson.²¹ The CRYM system of computer programs was used.¹⁹

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12. Representative physical data for **1** crystallized from MeOH/Et₂O, mp 240-241 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.14 (t, *J* = 7.12 Hz, 3 H), 1.70-1.85 (m, 2 H), 2.05-2.20 (m, 2 H), 2.90 (s, 3 H), 3.13 (q, *J* = 7.22 Hz, 2 H), 3.30 (s, 2 H), 3.55 (br, 2 H), 4.45-4.55 (m, 2 H), 6.59-6.67 (m, 3 H), 6.90 (dd, *J* = 5.0, 8.0 Hz, 1 H), 7.08 (dd, *J* = 2.1, 8.7 Hz, 1 H), 7.34 (d, *J* = 8.7 Hz, 1 H), 7.50 (s, 1 H), 7.75 (dd, *J* = 1.2, 5.0 Hz, 1 H), 9.40 (s, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 11.28, 19.52, 34.55, 38.77, 42.26, 43.15, 64.18, 104.84, 112.24, 112.58, 116.46, 120.61, 122.56, 127.89, 129.64, 130.97, 133.97, 137.35, 145.00, 161.91. HRMS Calcd. for C₂₃H₂₇N₅O₃S: 453.1834. Found: 453.1830.
13. This assay has been described by us previously in references 1-4.
14. In an analogous HIV-1 RT assay system, **1** inhibited the enzyme 45% at 50 μM , compared to delavirdine which inhibited 99% at 50 μM .
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reaction mixture was stirred for 20 min at -78°C and at 0°C for 20 min. The resulting suspension was dissolved in a mixture of dry THF (8 mL) and dry TMEDA (16 mL) and after 5 min a solution of **35** (2.04 g, 4 mmol) in dry THF (8 mL) was added at 0°C . The reaction mixture was stirred at this temperature for 3 h, quenched with water, and extracted with ether. The combined extracts were washed with water, dried, concentrated, and purified by silica gel chromatography (elution with 0.5% methanol and 25% ether in petroleum ether up to 2% methanol in ether) to give **36a** (1.15 g, 62%) as a light yellow gum: IR (neat, cm^{-1}) 3417 (br), 1660; ^1H NMR (300 MHz, C_6D_6) δ 7.67–7.60 (m, 2 H), 7.03–6.95 (m, 3 H), 6.73–6.65 (m, 2 H), 6.60–6.55 (m, 2 H), 6.30 (d, $J = 6.9$ Hz, 1 H), 5.58 (br s, 1 H), 5.51 (d, $J = 6.9$ Hz, 1 H), 5.47 (t, $J = 2.5$ Hz, 1 H), 4.65 (br d, $J = 11.0$ Hz, 1 H), 4.60 (d, $J = 6.2$ Hz, 1 H), 4.35 (br s, 1 H), 4.20 (t, $J = 9.3$ Hz, 2 H), 3.24 (s, 3 H), 2.55–2.33 (m, 2 H), 2.08 (ddd, $J = 13.5$, 10.9, 6.2 Hz, 1 H), 1.67 (dd, $J = 13.5$, 3.9 Hz, 1 H), 1.46 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.5, 151.0, 143.3, 138.1 (2 C), 135.0, 128.9, 128.8 (2 C), 128.7, 118.4 (2 C), 115.0 (2 C), 109.6, 99.3, 88.6, 85.7, 84.8, 80.5, 69.6, 64.3, 55.1, 35.0, 30.2, 21.7; MS m/z (M^+) calcd 468.1607, obsd 468.1607.

(1*Z*,2-*endo*,3-*exo*,6-*endo*)-6-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-(4,5-dihydro-2-furanyl)-1-[2-(4-methoxyphenoxy)ethenyl]-3-methyl-3-(phenylthio)-7-oxabicyclo[2.2.1]heptan-2-ol (**36b**). *tert*-Butylchlorodiphenylsilane (1.10 g, 4 mmol) was added in one portion to a stirred solution of **36a** (0.94 g, 2 mmol) and imidazole (340 mg, 5 mmol) in dry DMF (1.0 mL) at rt. The mixture was stirred under N_2 for 16 h, poured into water, and extracted with ether. The combined extracts were washed with brine, dried, concentrated, and purified by silica gel chromatography (elution with 0.25% methanol and 12% ether in petroleum ether up to 1% methanol and 50% ether in petroleum ether) to give **36b** (0.42 g, 30%) as a colorless oil: IR (neat, cm^{-1}) 3390 (br), 1670; ^1H NMR (300 MHz, C_6D_6) δ 7.77–7.67 (m, 2 H), 7.65–7.60 (m, 4 H), 7.20–7.05 (m, 6 H), 7.03–6.95 (m, 3 H), 6.65–6.55 (m, 4 H), 6.34 (s, 1 H), 6.20 (d, $J = 6.9$ Hz, 1 H), 5.60 (t, $J = 2.4$ Hz, 1 H), 5.34 (d, $J = 6.9$ Hz, 1 H), 5.04 (dd, $J = 10.2$, 3.5 Hz, 1 H), 4.50 (d, $J = 5.9$ Hz, 1 H), 4.45–4.27 (m, 2 H), 3.25 (s, 3 H), 2.53–2.45 (m, 2 H), 1.67–1.57 (m, 1 H), 1.57 (s, 3 H), 1.39 (dd, $J = 13.0$, 3.9 Hz, 1 H), 1.09 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 159.5, 156.0, 151.9, 144.5, 138.1 (2 C), 136.6 (2 C), 136.4 (2

C), 135.4, 132.7, 132.6, 130.39, 130.37, 129.8 (2 C), 128.5, 128.1 (4 C), 118.4 (2 C), 114.8 (2 C), 107.5, 99.3, 88.5, 85.2, 84.8, 81.6, 69.6, 63.9, 55.1, 36.0, 30.0, 27.0 (3 C), 22.2, 19.1; MS m/z (M^+) calcd 706.2784, obsd 706.2775.

(3*aa*,4*a*,7*b*,9*a*,10*a*,11*a*)-7-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2,3,3*a*,4,7,8,9,10,11,11*a*-decahydro-4-(4-methoxyphenoxy)-10-methyl-10-(phenylthio)-6,9-epoxycyclodeca[*b*]furan-11-one (**37**). A stirred mixture of **36b** (184 mg, 0.26 mmol) and anhydrous K_2CO_3 (180 mg, 1.3 mmol) in degassed anhydrous decalin (5.2 mL) was heated at gentle reflux under N_2 for 1 h. The total reaction mixture was purified by alumina chromatography (activity III, elution with 5–80% ether in petroleum ether) to give **37** (113 mg, 61%) as a colorless gum: IR (CHCl_3 , cm^{-1}) 1716; ^1H NMR (300 MHz, C_6D_6) δ 7.62–7.58 (m, 4 H), 7.55–7.53 (m, 2 H), 7.23–7.10 (m, 6 H), 7.00–6.95 (m, 3 H), 6.90–6.85 (m, 2 H), 6.80–6.73 (m, 2 H), 5.42 (dd, $J = 6.6$, 1.6 Hz, 1 H), 4.93 (quintet, $J = 8.6$ Hz, 1 H), 4.47 (d, $J = 7.9$ Hz, 1 H), 4.33 (ddd, $J = 9.3$, 7.6, 1.7 Hz, 1 H), 4.30–4.21 (m, 2 H), 4.20 (dd, $J = 7.8$, 5.9 Hz, 1 H), 3.87 (td, $J = 8.0$, 2.7 Hz, 1 H), 3.37 (s, 3 H), 2.44 (dddd, $J = 12.0$, 7.6, 6.0, 2.6 Hz, 1 H), 1.70 (ddd, $J = 13.1$, 7.3, 5.9 Hz, 1 H), 1.69–1.59 (m, 1 H), 1.55 (ddd, $J = 12.9$, 9.3, 8.0 Hz, 1 H), 1.25 (s, 3 H), 1.09 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) ppm 205.9, 160.0, 154.8, 152.7, 137.3 (2 C), 136.0 (2 C), 135.8 (2 C), 133.6, 133.3, 131.3, 130.3 (2 C), 129.1 (2 C), 129.0, 128.2 (2 C), 128.1 (2 C), 118.4 (2 C), 114.9 (2 C), 99.7, 86.2, 83.2, 78.8, 71.0, 69.4, 64.1, 55.2, 47.3, 33.8, 33.0, 27.0 (3 C), 21.2, 19.3; MS m/z (M^+) calcd 706.2784, obsd 706.2771.

Acknowledgment. We express our thanks to the National Institutes of Health (Grant GM-30827) and Eli Lilly and Co. for financial support, to Dirk Friedrich for the extensive NMR studies, and to Eugene Hickey for the computer calculations.

Supplementary Material Available: 300-MHz ^1H NMR spectra of **23**, **24**, **27**, and **30–37**, as well as the final calculated (MM3) atomic coordinates for A–D as they appear in Figure 2 (16 pages). This material is contained in many 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.

Tertiary Carbinamines by Addition of Organocerium Reagents to Nitriles and Ketimines

Engelbert Ciganek

The Du Pont Merck Pharmaceutical Co., Inc., Wilmington, Delaware 19880-0353

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Organocerium reagents, prepared by reaction of aromatic and primary and secondary alkylolithium reagents with anhydrous cerium chloride, add to nitriles twice to give tertiary carbinamines in often excellent yields. Addition of $n\text{-BuCeCl}_2$ to acetophenone is about 4 times faster than addition to benzonitrile. Only 1,2-diaddition is observed in the reaction of MeCeCl_2 with cinnamonnitrile. The species formed in the double addition of organocerium reagents to nitriles are sufficiently basic to generate a benzyne intermediate by abstraction of an aromatic proton and nucleophilic enough to undergo an intramolecular Chichibabin reaction. Reaction of N -unsubstituted ketimines or their lithium salts with organocerium reagents permits the synthesis of tertiary carbinamines with three different groups on the tertiary carbon center.

Introduction

Tertiary carbinamines (amines in which one bond from nitrogen is to a tertiary carbon atom) are usually prepared by addition of carbocations to nitriles (the Ritter reaction¹). This reaction requires strongly acidic conditions which may cause skeletal rearrangements and which may not be compatible with other groups present in the substrate.

Hydrolysis of the initially formed acyl derivatives of tertiary carbinamines is often difficult, necessitating strongly acidic or basic conditions. Another route to these amines is the reduction of tertiary nitro compounds.² Treatment

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(2) For some examples, see: (a) Asaro, M. F.; Nakayama, I.; Wilson, R. B., Jr. *J. Org. Chem.* 1992, 57, 778. (b) Lalonde, J. J.; Berghreiter, D. E.; Wong, C.-H. *J. Org. Chem.* 1988, 53, 2333. (c) Cariou, M.; Hazard, R.; Jubault, M.; Tallec, A. *J. Chem. Res. (S)* 1986, 184. (d) Cowan, J. A. *Tetrahedron Lett.* 1986, 27, 1205. (e) Osby, J. O.; Gansam, B. *Tetrahedron Lett.* 1985, 26, 6413. (f) Bonnett, R.; Clark, V. M.; Giddey, A.; Todd, A. J. *Chem. Soc.* 1959, 2087.

of diaryl ketoximes with sodium in liquid ammonia followed by alkylation gives tertiary carbinamines, but the reaction is limited in scope.³ Reaction of organometallic species, such as organolithium compounds and Grignard reagents, with nitriles usually gives imines.⁴ Double addition of these reagents to nitriles to give tertiary carbinamines has been reported in only a few isolated or special cases. Thus some Grignard reagents add twice to nitriles in refluxing toluene, but imines are usually the major products and the reaction fails with benzonitrile and phenylacetonitrile.⁵ Allylmagnesium halides add twice to nitriles⁶ as do Grignard reagents to α -alkoxy nitriles,^{6c,7} 2-hydroxybenzonitrile,⁸ and cyanogen.⁹ α,α -Dibutylbenzylamine is formed in low yield in the reaction of *n*-butyllithium with benzonitrile at room temperature.¹⁰

Organometallic reagents such as organolithium compounds and Grignard reagents do not normally add to *N*-unsubstituted ketimines. Tertiary carbinamines have been obtained in such reactions by replacing the hydrogen atom in the imines by groups such as arylsulfenyl,¹¹ acyl,¹² or trimethylsilyl.¹³ The imine salts obtained on addition of Grignard reagents to α -alkoxy nitriles react with alkyl- and aryllithium compounds to give tertiary carbinamines in addition to other products, but the reaction fails with other nitriles.¹⁴ The products obtained on addition of methyl- or ethylmagnesium iodide to benzoylacetonitrile react with allylmagnesium bromide to give the corresponding tertiary carbinamines.¹⁵

The reaction of nitriles with organolanthanide reagents¹⁶ has received little attention, possibly because of the report¹⁷ that the reagent prepared from anhydrous cerium chloride and *n*-butyllithium reacts with 4-cyanobenzophenone to give, after 3 h at -65°C , only the adduct to the carbonyl group [2-(4-cyanophenyl)-2-hexanol] in 48% yield. The reagent prepared from *n*-butylmagnesium chloride and anhydrous cerium chloride adds to phenylacetonitrile to give the imine in low yield.^{18,19} Derivatives

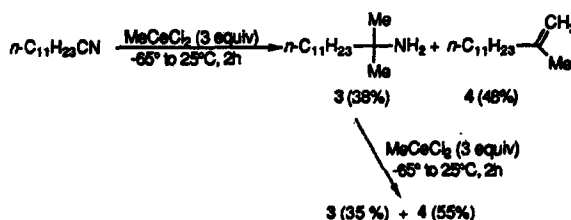
Table I. Double Addition of Organocerium Reagents to Nitriles



entry	R ¹	R ²	conditions	product	yield (%)
1	<i>n</i> -C ₁₁ H ₂₃	Me	-65°C , 5 h	3	64 ^a
2	<i>i</i> -Pr	<i>i</i> -Pr	25°C , 20 h	5	32
3	<i>t</i> -Bu	<i>n</i> -Bu	25°C , 2.5 h	6	82
4	cycloheptyl	Me	25°C , 20 h	7	42
5	1-adamantyl	Me	25°C , 20 h	8	75
6	Ph	<i>i</i> -Pr	25°C , 20 h	9	50
7	Ph	<i>s</i> -Bu	25°C , 5 h	10	64
8	MeC ₆ H ₄ CH ₂	<i>n</i> -Bu	25°C , 20 h	11	16
9	Ph	Ph	25°C , 20 h	12	98
10	4-PhC ₆ H ₄	<i>i</i> -Pr	25°C , 2 h	13	47
11	2-furyl	2-furyl	25°C , 2 h	14	89
12	<i>i</i> -Pr	2-thienyl	25°C , 2 h	15	14
13	1-naphthyl	Me	25°C , 2 h	16	41 ^b

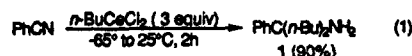
^a The conversion was 94%; unreacted *n*-C₁₁H₂₃CN was recovered in 31% yield. ^b In addition, naphthalene was isolated in 32% yield.

Scheme I



of secondary carbinamines have been prepared by addition of organocerium reagents to *N*-benzylaldimines,^{19,20} *N,N*-disubstituted hydrazones,²¹ and oxime ethers.²²

Double Additions of Organocerium Reagents to Nitriles. Organocerium reagents prepared¹⁷ from anhydrous cerium chloride and primary and secondary alkylolithium and aromatic lithium reagents were found to add to nitriles twice to give tertiary carbinamines in often excellent yields. Thus reaction of 3 equiv of *n*-BuCeCl₂²³ with benzonitrile at -65°C and stirring the mixture at 25°C for 2 h gave α,α -dibutylbenzenemethanamine (1) in 90% yield (eq 1). The same yield was obtained when the



reaction was carried out at -65°C for 5 h. Reagents prepared from other anhydrous lanthanide chlorides gave the following yields in the reaction of eq 1: PrCl₃, 74%; NdCl₃, 86%; YbCl₃, 74%; LaCl₃, 20%.²⁴ Yttrium chloride

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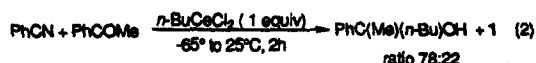
(21) (a) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* 1987, 109, 2224. (b) Weber, T.; Edwards, J. P.; Denmark, S. E. *Synlett.* 1989, 20.

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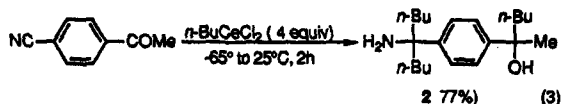
(23) The notation R₂CeCl₂ is used throughout this paper; the exact nature of these reagents has not yet been determined.¹⁶

(24) The yield was identical whether LaCl₃·7H₂O, dried at 140 – 150°C under vacuum, or commercially available anhydrous LaCl₃ was employed. However, the possibility exists that some of the other lanthanide chlorides that failed to react cannot be dehydrated cleanly by simple vacuum drying.

produced the amine 1 in 3% yield. The chlorides of the following lanthanides failed to react under the conditions of eq 1: Sm, Eu, Gd, Tb, Dy, Ho, Er.²⁴ Because CeCl_3 is the cheapest of the rare earth chlorides, it was used exclusively in all subsequent reactions. When the ratio of $\text{C}_6\text{H}_5\text{CN}:\text{CeCl}_3:n\text{-BuLi}$ was 1.3:2:4 (1.5 equiv of " $n\text{-Bu}_2\text{CeCl}$ ") the yield of 1 was 60%, and when the ratio was 1:1:3 (1 equiv of " $n\text{-Bu}_2\text{Ce}$ ") the yield was 44%. Therefore, an $\text{RLi}:\text{CeCl}_3$ ratio of 1:1 was adopted for further investigations of this reaction. Employing an equimolar ratio of benzonitrile and $n\text{-BuCeCl}_2$ gave amine 1 in 33% yield in addition to unreacted benzonitrile; the monoadduct, valerophenone imine was formed in only 0.4% yield. The second addition of $n\text{-BuCeCl}_2$ to benzonitrile is thus considerably faster than the first. As shown below, such a rate difference is not always observed. Competition of benzonitrile and acetophenone for a limited amount of $n\text{-BuCeCl}_2$ (eq 2) showed that addition to the cyano group in



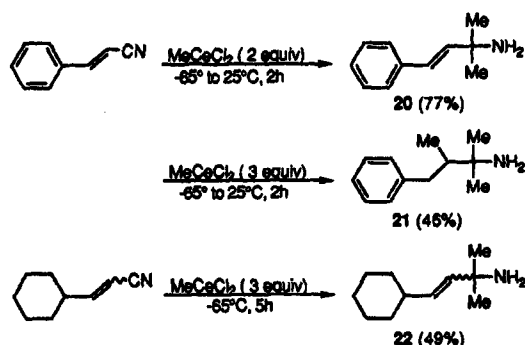
this system is about 4 times slower than addition to the carbonyl group. Reaction of 4-cyanoacetophenone with 4 equiv of $n\text{-BuCeCl}_2$ at room temperature gave the triadduct 2 in 77% yield (eq 3). When this reaction was



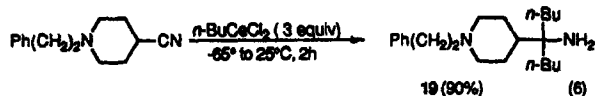
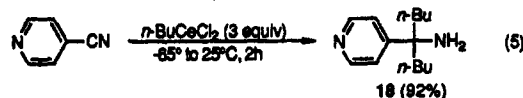
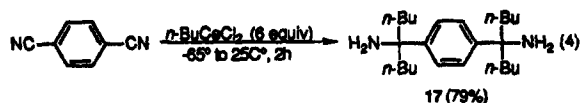
carried out under the conditions described by Imamoto et al. (1.3 equiv of $n\text{-BuCeCl}_2$, -70°C , 5 h),¹⁷ the triadduct 2 was isolated in 10% yield.

Additional examples of the double addition of organocerium reagents to nitriles are listed in Table I. Many of these reactions have not been optimized. The yields can probably be increased in some cases by carrying out the reactions at -65°C to suppress olefin formation, a common side reaction with aliphatic nitriles. Thus when the reaction mixture of entry 1 was warmed to room temperature before workup, 2-methyl-1-tridecene (4) was formed in 48% yield (Scheme I). The internal olefin was absent within detectability by ^1H NMR spectroscopy. Olefin 4 was also formed when amine 3 was treated with 3 equiv of MeCeCl_2 (but not with anhydrous CeCl_3 alone) at 25°C (Scheme I). The mechanism of this conversion of a primary amine into an olefin is unknown.²⁵ It appears to be limited in scope since neither 1-decylamine nor 4-phenylpiperidine gave olefins with MeCeCl_2 . The low yield in the reaction of $n\text{-BuCeCl}_2$ with 4-tolylacetonitrile (entry 8) was not unexpected because of the presence of acidic α -protons in the substrate. α,α -Bis(2-furanyl)-2-furanmethanamine (14), the product in entry 11, proved to be rather unstable, decomposing slowly at room temperature and quickly on attempted molecular distillation; it was characterized as the 4-tolylurea. When the reaction of MeCeCl_2 with 1-naphthalenecarbonitrile (entry 13) was carried out at -65°C for 6 h, the diadduct 16 and the imine of 1-acetylnaphthalene were formed in a ratio of 1:3; the starting material was completely absent. Thus in this reaction the first addition is somewhat faster than the second. The naphthalene formed in the room temperature reaction appears to be the result of a base-catalyzed elim-

Scheme II



ination of acetone imine from the diadduct 16. The reactions of $n\text{-BuCeCl}_2$ with 1,4-dicyanobenzene (eq 4), 4-pyridinecarbonitrile (eq 5), and 1-phenethylpiperidine-4-carbonitrile (eq 6) further demonstrate the versatility of this transformation.



Reaction of 2 equiv of MeCeCl_2 with cinnamitrile gave the 1,2-diadduct 20 exclusively.²⁶ When 3 equiv was employed, the triadduct 21 was obtained (Scheme II). A similar reaction has been observed in the addition of PhYbCl_2 to benzalacetophenone to give 2,2,3,4-tetraphenylpropanol, and a mechanism involving a metallocycle intermediate has been proposed.²⁷ Addition of the third methyl group requires the presence of a phenyl group in the β position: when it was replaced by a cyclohexyl group, the diadduct 22 was formed exclusively even with 3 equiv of the reagent (Scheme II). To avoid olefin formation, the reaction was carried out at low temperatures, but no triadduct was detected in a second experiment in which the temperature was raised to 25°C for 2 h.

The reagents formed by reaction of lithium phenylacetylide and $t\text{-BuLi}$ with CeCl_3 did not add to nitriles at room temperature. The lack of reactivity of $t\text{-BuCeCl}_2$ was surprising since reaction of this species with N,N -disubstituted hydrazones has been reported to proceed at or below room temperature.^{21a} On the other hand, the uncatalyzed addition of bulky Grignard reagents to nitriles requires elevated reaction temperatures.²⁸ The species obtained from Grignard reagents and anhydrous cerium chloride¹⁸ also did not furnish tertiary carbinamines on reaction with nitriles.

(25) The formation of olefins in the reaction of lithium tetraalkyl ate complexes with epoxides has been postulated to proceed by elimination of "cerium oxide" as the final step: (a) Ukaji, I.; Fujisawa, T. *Tetrahedron Lett.* 1988, 29, 5165. (b) Ukaji, Y.; Yoshida, A.; Fujisawa, T. *Chem. Lett.* 1990, 157.

(26) Exclusive 1,2-addition has been reported in the reaction of organocerium reagents with 1,3-oxazolidines (masked N -substituted imines): Pridgen, L. N.; Mokhallati, M. K.; Wu, M.-J. *J. Org. Chem.* 1992, 57, 1237 and references cited therein.

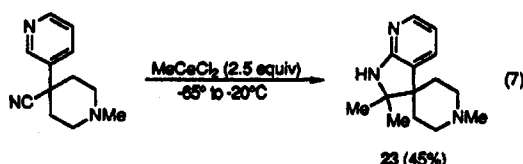
(27) Hou, Z.; Fujiwara, T.; Jintoku, N.; Mine, K.; Yokoo, K.; Taniguchi, H. *J. Org. Chem.* 1987, 52, 3524.

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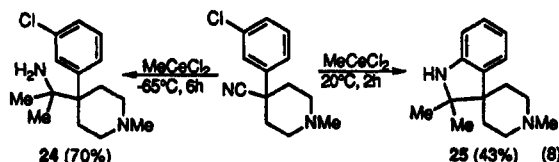
Table II. Addition of Organocerium Reagents to Imines

$\begin{array}{c} R^1 \\ \\ R^2 - NH \end{array} \xrightarrow{R^3CeCl_2 (3 \text{ equiv})} \begin{array}{c} R^1 \\ \\ R^2 - C - NH_2 \\ \\ R^3 \end{array}$					
R ¹	R ²	R ³	conditions	product	yield (%)
n-Bu	t-Bu	Me	25 °C, 2 h	27	62
Ph	n-Bu	Me	-65 °C, 5 h	28	71
Ph	Ph	n-Bu	25 °C, 2 h	29	79

The species generated in the diaddition of organocerium reagents to nitriles are strongly nucleophilic as evidenced by the intramolecular Chichibabin reaction²⁹ depicted in eq 7. They are also sufficiently basic to abstract an aromatic

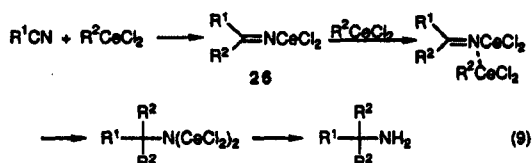


proton to generate a benzyne intermediate³⁰ with the ultimate formation of the spiroindoline 25 (eq 8).



When this reaction was carried out at -65 °C for 6 h, only the diadduct 24 was observed; oddly, when the mixture was then stirred at room temperature for 16 h, no further reaction occurred and no spiroindoline 25 was isolated under these conditions.

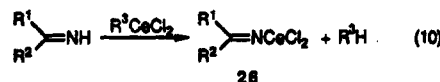
The mechanism of the double addition of organocerium reagents to nitriles is open to speculation. The first step is presumably formation of an adduct resembling 26 (eq 9). Coordination of another molecule of R²CeCl₂ with the



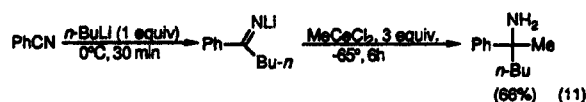
imine nitrogen and intramolecular transfer of the second R² group is not unreasonable in view of the high electrophilicity of cerium. The involvement of ate complexes such as Li⁺(CeCl₄)⁻ and the role of the solvent, THF, must be also considered. Transmetalation to give R¹R²C=N-CeR²Cl may occur as well.

Addition of Organocerium Reagents to Ketimines. N-Unsubstituted ketimines react with organocerium reagents to give tertiary carbinamines (Table II). This transformation permits the synthesis of tertiary carbinamines with three different groups on the tertiary carbon center. The first step is presumably formation of the imine

salt 26 (eq 10) which is a likely intermediate in the addition to nitriles as well (eq 9). As in the latter reaction, t-Bu-CeCl₂ failed to add to ketimines. The ketimines were



prepared by addition of organolithium reagents to nitriles followed by hydrolysis. Alternatively, the lithium salt of the ketimine may be allowed to react with the organocerium reagent directly (eq 11); under these conditions, 12% of valerophenone imine was also isolated, and the conversion was thus 78%.



Experimental Section

General. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were determined in CDCl₃ unless otherwise specified. Melting points were measured in an unsealed capillary tube and are uncorrected. HRMS were determined by chemical ionization (NH₃) or by electron ionization.

Materials. Starting materials and reagents were obtained from Aldrich Chemical Co., Milwaukee, WI, unless stated otherwise. The THF used was EM Science anhydrous grade (stored over 4A sieves).

α,α-Dibutylbenzenemethanamine (1). General Procedure for the Generation and Addition of Organocerium Reagents to Nitriles and Ketimines. CeCl₃·7H₂O (15.0 g, 40.2 mmol) was dried with magnetic stirring at 140–150 °C (0.1 mm) for 2 h. A glass wool plug was inserted into the adapter connecting the flask to the vacuum source, and entrained solids were returned into the flask by frequent tapping. Nitrogen was added slowly, and the flask was cooled in an ice bath. THF (80 mL) was added, and the suspension was stirred at 25 °C for 2 h. n-BuLi (16 mL of a 2.5 M solution in hexanes, 40 mmol) was added, keeping the temperature below -50 °C. The mixture was stirred in a dry ice/acetone bath for 30 min, and benzonitrile (1.34 g, 13 mmol) in 2 mL of THF was added. Stirring at -65 °C was continued for 5 h. Concentrated NH₄OH (25 mL) was added at less than -40 °C, and the mixture was brought to 25 °C and filtered with the aid of Celite. The solids were washed several times with CH₂Cl₂, and the aqueous layer of the filtrates was extracted twice with CH₂Cl₂. The combined organic phases were dried and concentrated. The residue was taken up in 30 mL of toluene and stirred with 30 mL of 3% H₃PO₄ for 15 min. The toluene layer was extracted with two 10-mL portions of water, and the combined aqueous phases were washed once with toluene and made basic with concd NH₄OH. The mixture was extracted several times with CH₂Cl₂, and the residue obtained on removal of the solvent from the dried (MgSO₄) extracts was short-path distilled to give 2.53 g (90%) of 1, boiling at a bath temperature of 80–130 °C (0.003 mm) [lit.¹⁰ bp 152 °C (15 mm)]: ¹H NMR δ 7.2–7.4 (m, 5 H), 1.8 (m, 2 H), 1.6 (m, 2 H), 1.4 (br, 2 H), 1.2 (m, 6 H), 1.0 (m, 2 H), 0.8 (t, J = 6 Hz, 6 H); ¹³C NMR δ 13.892, 23.102, 25.776, 43.858, 57.518, 125.580, 125.599, 127.823, 147.535. Anal. Calcd for C₁₅H₂₃N: C, 82.13; H, 11.49; N, 6.39. Found: C, 81.80; H, 11.52; N, 6.14. The hydrochloride of 1 had mp 209–216 °C after crystallization from water. Anal. Calcd for C₁₅H₂₃ClN: C, 70.42; H, 10.24; N, 5.48. Found: C, 70.27; H, 10.34; N, 5.45.

Competition Experiment. A suspension of 20 mmol of n-BuCeCl₂ in 40 mL of THF was prepared as described above, and a solution of 2.40 g (20 mmol) of acetophenone and 2.06 g (20 mmol) of benzonitrile in 4 mL of THF was added below -50 °C. The cooling bath was removed, and the reaction was quenched after 2 h. The ¹H NMR of the crude product showed the presence of PhC(Me)(n-Bu)OH¹⁷ and 1 in a ratio of 78:22.

4-(1-Amino-1-butylpentyl)-α-butyl-α-methylbenzenemethanol (2). The reaction shown in eq 3 was carried out with 1.45 g (10 mmol) of 4-cyanobenzophenone to give 2.45 g (77%) of 2, bp 180–200 °C bath temperature (0.003 mm): ¹H NMR δ 7.3–7.4 (AB q, J = 8 Hz, 4 H), 0.9–1.8 (m, 21 H), 1.6 (s, 3 H), 0.8

(29) For a review of the Chichibabin reaction, see: Pozharzki, A. F.; Simonov, A. M.; Doron'kin, V. N. *Usp. Khim.* 1978, 47, 1933; *Russ. Chem. Rev. (Engl. Transl.)* 1978, 47, 1042. For examples of intramolecular Chichibabin reactions, see: (a) Hawes, E. M.; Wibberley, D. G. *J. Chem. Soc. C* 1966, 315. (b) Hawes, E. M.; Davies, H. L. *J. Heterocycl. Chem.* 1973, 10, 39.

(30) The formation of indolines by intramolecular cyclization of (3-chlorophenyl)alkylamines under the influence of strong bases has been shown to proceed by a benzyne mechanism: (a) Huisgen, R.; Koenig, H. *Chem. Ber.* 1959, 92, 203. (b) Huisgen, R.; Koenig, H.; Blecker, N. *Ibid.* 1959, 92, 424. (c) Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* 1979, 827.

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(t, $J = 6$ Hz, 9 H); HRMS calcd for $C_{21}H_{39}NO$ [(M + H)⁺] 320.29534, measured 320.29612. Anal. Calcd for $C_{21}H_{39}NO$: C, 78.94; H, 11.67; N, 4.38. Found: C, 78.77; H, 11.81; N, 4.36.

2-Methyl-2-tridecanamine (3). The crude product was dissolved in hexanes and stirred with excess 10% HCl. The precipitate was collected, washed with hexanes, and reconverted into the free base, 1.58 g (64%), bp 100–120 °C bath temperature (0.1 mm): ¹H NMR δ 1.2–1.4 (narrow m, 22 H), 1.1 (s, 6 H), 0.9 (t, $J = 6$ Hz, 3 H); ¹³C NMR δ 13.873, 22.489, 24.368, 29.163, 29.493, 30.198, 30.234, 31.745, 45.066, 49.177 (some signals were not completely resolved); HRMS calcd for $C_{14}H_{29}N$ [(M + H)⁺] 214.2535, measured 214.2542. The hydrochloride had mp 118–119 °C after crystallization from *i*-PrOH. Anal. Calcd for $C_{14}H_{29}N$: C, 67.30; H, 12.91; N, 5.61. Found: C, 67.54; H, 13.03; N, 5.54. Unreacted dodecyl cyanide (0.75 g, 31%) was isolated from the hexane layer.

2-Methyl-1-tridecene (4). The hexane phases from the experiment carried out at 25 °C (Scheme I) were dried, the solvent was removed, and the residue was short-path distilled (110 °C bath temperature, 5 mm) to give 4: ¹H NMR δ 4.7 (2 s, 2 H), 2.0 (t, $J = 7$ Hz, 2 H), 1.7 (s, 3 H), 1.2–1.4 (m, 18 H), 0.9 (t, $J = 6$ Hz, 3 H); ¹³C NMR δ 13.892, 22.177, 22.525, 27.552, 29.200, 29.410, 29.493, 31.872, 109.347, 146.089 (some of the signals were not completely resolved); HRMS calcd for $C_{14}H_{26}$ 196.21910, measured 196.21967. An authentic sample of 4 was prepared as follows: to a suspension of 7.1 g (20 mmol) of methyltriphenylphosphonium bromide in 20 mL of dry THF was added at 0 °C 8.3 mL (21 mmol) of 2.5 M *n*-BuLi in hexanes, the mixture was stirred in an ice bath for 2 h, and 2-tridecanone (3.0 g, 15.1 mmol) in 2 mL of THF was added. After stirring at 25 °C for 18 h, water was added and the mixture was extracted several times with hexanes. Removal of the solvents and short-path distillation of the residue gave 2.41 g (81%) of 4, bp 100–130 °C bath temperature (1 mm), identical by ¹H and ¹³C NMR with the sample described above. Treatment of 0.5 g of 4 with 0.2 g of *p*-toluenesulfonic acid in 5 mL of acetic acid at 25 °C overnight resulted in a ca. 1:4 mixture of 4 and the internal olefin 2-methyl-2-tridecene. The ¹H NMR of the latter had δ 5.1 (t, 1 H), 1.6 (s, 3 H), 1.7 (s, 3 H) among others.

2,4-Dimethyl-3-(1-methylethyl)-3-pentanamine (5): bp 90–110 °C bath temperature (5 mm); ¹H NMR δ 2.0 (septet, $J = 7$ Hz, 3 H), 0.9 (d, $J = 7$ Hz, 2 H); ¹³C NMR δ 18.877, 33.078, 58.096. The hydrochloride had mp >320 °C after crystallization from 2-propanol. Anal. Calcd for $C_{10}H_{21}N$: C, 61.99; H, 12.49; N, 7.23. Found: C, 62.19; H, 12.76; N, 7.08.

5-(1,1-Dimethylethyl)-5-nonanamine (6): bp 90–110 °C bath temperature (5 mm); ¹H NMR δ 1.2–1.6 (m, 12 H), 1.0 (t + s + br, 17 H); ¹³C NMR δ 14.098, 23.922, 28.122, 27.533, 35.978, 38.115, 56.913; HRMS calcd for $C_{13}H_{29}N$ [(M + H)⁺] 200.2378, measured 200.2383.

α,α -Dimethylcycloheptanemethanamine (7): bp 100 °C bath temperature (10 mm); ¹H NMR δ 1.2–1.8 (m, 15 H), 1.0 (s, 6 H); ¹³C NMR δ 27.707, 27.845, 28.074, 28.797, 50.578, 52.327; HRMS calcd for $C_{10}H_{22}N$ [(M + H)⁺] 156.17452, measured 156.1743.

α,α -Dimethyltricyclo[3.3.1.1^{2,7}]decane-1-methanamine (8): ¹H NMR δ 2.0 (m, 3 H), 1.5–1.9 (m, 12 H), 1.2 (br, 2 H), 1.0 (s, 6 H); ¹³C NMR δ 25.081, 28.689, 36.011, 37.028, 37.897, 53.306. The hydrochloride had mp >320 °C (lit.³¹ no mp or analysis given). Anal. Calcd for $C_{19}H_{34}N$: C, 67.95; H, 10.53; N, 6.10. Found: C, 67.79; H, 10.76; N, 6.03.

α,α -Bis(1-methylethyl)benzenemethanamine (9): bp 100 °C bath temperature (0.003 mm); ¹H NMR δ 7.1–7.5 (m, 5 H), 2.2 (septet, $J = 7$ Hz, 2 H), 1.1 (br, 2 H), 0.8 (d, $J = 7$ Hz, 6 H), 0.7 (d, $J = 7$ Hz, 6 H); ¹³C NMR δ 16.730, 17.462, 33.658, 62.379, 125.663, 127.128, 127.329, 143.626. The hydrochloride had mp >320 °C after crystallization from DMF. Anal. Calcd for $C_{15}H_{22}N$: C, 68.55; H, 9.74; N, 6.15. Found: C, 68.55; H, 9.77; N, 6.03.

α,α -Bis(1-methylpropyl)benzenemethanamine (10): mixture of two diastereomers; bp 120 °C bath temperature (0.003 mm); ¹H NMR δ 7.2–7.5 (m, 5 H), 1.6–2.0 (m, 3 H), 1.0–1.4 (m, 3 H), 0.6–1.0 (m, 14 H); HRMS calcd for $C_{18}H_{28}N$ [(M + H)⁺]

220.2065, measured 220.2081. Anal. Calcd for $C_{18}H_{28}N$: C, 82.13; H, 11.49; N, 6.39. Found: C, 81.93; H, 11.67; N, 6.23. The hydrochloride had mp >320 °C after crystallization from 90% 1-butanol. Anal. Calcd for $C_{18}H_{28}N$: C, 70.42; H, 10.24; N, 5.48. Found: C, 70.47; H, 10.38; N, 5.34.

α,α -Dibutyl-4-methylbenzenemethanamine (11): bp 90 °C bath temperature (0.001 mm); ¹H NMR δ 7.1 (AB q, $J = 8$ Hz, split further, 4 H), 2.6 (s, 2 H), 2.3 (s, 3 H), 1.3 (m, 12 H), 0.9 (t, $J = 7$ Hz, split further, 6 H); ¹³C NMR δ 14.029, 20.859, 23.239, 25.867, 39.234, 46.101, 53.727, 128.547, 130.369, 134.891, 135.477; HRMS calcd for $C_{17}H_{29}N$ [(M + H)⁺] 248.2378, measured 248.2376.

α,α -Diphenylbenzenemethanamine (12). The product was identical by IR and ¹H and ¹³C NMR spectroscopy with an authentic sample (Lancaster Synthesis).

α,α -Bis(1-methylethyl)-1,1'-biphenyl-4-methanamine (13): bp 180–195 °C bath temperature (0.002 mm); ¹H NMR δ 7.3–7.6 (m, 9 H), 2.3 (septet, $J = 7$ Hz, 2 H), 1.4 (br, 2 H), 0.9 (d, $J = 7$ Hz, 6 H), 0.8 (d, $J = 7$ Hz, 6 H); ¹³C NMR δ 16.844, 17.618, 33.814, 62.485, 125.777, 126.862, 126.923, 127.871, 128.622, 138.354, 140.881, 142.929. Anal. Calcd for $C_{19}H_{23}N$: C, 85.38; H, 9.42; N, 5.24. Found: C, 85.48; H, 9.60; N, 5.15. The hydrochloride had mp >320 °C after crystallization from 85% aqueous 1-BuOH. Anal. Calcd for $C_{19}H_{23}N$: C, 75.10; H, 8.62; N, 4.61. Found: 74.94; H, 8.74; N, 4.44.

α,α -Bis(2-furanyl)-2-furanmethanamine (14). To 3.40 g (50 mmol) of furan in 20 mL of THF was added below –10 °C 16 mL (40 mmol) of 2.5 M *n*-BuLi in hexanes. After 4 h at 25 °C the mixture was cannulated below –40 °C into a stirred suspension of $CoCl_2$ prepared from 15.0 g (40 mmol) of $CoCl_2 \cdot 7H_2O$ as described for the synthesis of 1. After 30 min at –65 °C, 2-furancarbonitrile (1.23 g, 1.3 mmol) in 3 mL of THF was added, and the mixture was stirred without cooling for 4 h and worked up to give 3.05 g of 14 of about 89% purity as determined by ¹H NMR: yield 2.71 g (89%); ¹H NMR δ 7.4 (s, 3 H), 6.3 (narrow m, 3 H), 6.1 (narrow m, 3 H), 2.5 (br, 2 H); ¹³C NMR δ 56.080, 107.141, 110.181, 142.133, 155.180; HRMS calcd for $C_{13}H_{12}NO_4$ [(M + H)⁺] 230.08172, measured 230.08062. The 4-tolylurea of 14 was crystallized from DMF; it turned dark at ca. 160 °C but had no definite mp: ¹H NMR (in $DMSO-d_6$) δ 8.6 (s, 1 H), 7.6 (s, 3 H), 7.2 (s + d, $J = 8$ Hz, 3 H), 7.0 (d, $J = 8$ Hz, 2 H), 6.4 (narrow m, 3 H), 6.2 (narrow m, 3 H), 2.2 (s, 3 H). Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.71; H, 5.00; N, 7.68.

α -(1-Methylethyl)- α -(2-thienyl)-2-thiophenemethanamine (15). To a solution of 6.72 g (41 mmol) of 2-bromothiophene in 30 mL of THF was added below –50 °C 16 mL (40 mmol) of 2.5 M *n*-BuLi in hexanes. After 10 min at –60 °C the mixture was cannulated into a stirred suspension of 40 mmol of anhydrous $CoCl_2$ in 40 mL of THF prepared as described for the synthesis of 1. After 30 min at –65 °C 2-methylpropanenitrile (0.92 g, 1.3 mmol) in 2 mL of THF was added, and the mixture was stirred for 2 h without cooling and worked up. The basic fraction (0.90 g) was short-path distilled (130–145 °C bath temperature, 0.002 mm) to give 0.55 g of 15 of ca. 80% purity (0.44 g, 14%): ¹H NMR δ 7.2 (d, 2 H), 7.0 (d, 2 H), 6.9 (t, 2 H), 2.6 (septet, $J = 7$ Hz, 1 H), 2.0 (br, 2 H), 0.9 (d, $J = 7$ Hz, 6 H); ¹³C NMR δ 17.571, 39.700, 62.534, 123.144, 123.501, 126.532, 153.705; HRMS calcd for $C_{17}H_{16}NS_2$ [(M + H)⁺] 238.07241, measured 238.07365. The phenylurea of 15 had mp 228 °C after crystallization from DMF: ¹H NMR (in $DMSO-d_6$) δ 8.6 (s, 1 H), 6.9–7.4 (m, 15 H), 2.8 (septet, $J = 7$ Hz, 1 H), 0.8 (d, $J = 7$ Hz, 6 H). Anal. Calcd for $C_{19}H_{20}N_2OS_2$: C, 64.01; H, 5.65; N, 7.86. Found: C, 63.70; H, 5.37; N, 7.91.

α,α -Dimethyl-1-naphthalenemethanamine (16): ¹H NMR δ 8.9 (d, $J = 8$ Hz, 1 H), 7.9 (d, $J = 8$ Hz, 1 H), 7.8 (d, $J = 8$ Hz, 1 H), 7.6 (d, $J = 8$ Hz, 1 H), 7.3–7.5 (m, 3 H), 1.8 (2 s, 8 H); ¹³C NMR δ 33.285, 53.865, 122.760, 124.811, 124.894, 125.132, 127.565, 128.107, 129.224, 131.220, 135.010, 144.956; HRMS calcd for $C_{15}H_{16}N$ [(M + H)⁺] 186.1283, measured 186.1292.

$\alpha,\alpha,\alpha',\alpha'$ -Tetrabutyl-1,4-benzenedimethanamine (17): bp 175–190 °C bath temperature (0.001 mm); ¹H NMR δ 7.2 (s, 4 H), 0.9–1.8 (m, 28 H), 0.8 (t, $J = 6$ Hz, 12 H); ¹³C NMR δ 13.962, 23.156, 25.909, 43.660, 57.337, 125.208, 144.939. Anal. Calcd for $C_{24}H_{40}N_2$: C, 79.73; H, 12.30; N, 7.77. Found: C, 79.91; H, 12.42; N, 7.68. The hydrochloride had mp 297–302 °C after crystallization from EtOH. Anal. Calcd for $C_{24}H_{40}Cl_2N_2$: C, 66.49; H,

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10.69; N, 6.46. Found: C, 66.04; H, 10.90; N, 6.29.

α,α -Dibutyl-4-pyridinemethanamine (18): bp 130–150 °C bath temperature (0.003 mm); ^1H NMR δ 8.6 (d, J = 6 Hz, split further, 2 H), 7.3 (d, J = 6 Hz, 2 H), 1.4–1.8 (m + br, 8 H), 1.2 (m, 6 H), 0.8–1.0 (m, t, J = 7 Hz, 8 H); ^{13}C NMR δ 13.727, 22.892, 25.537, 43.299, 57.408, 121.030, 149.421, 156.727; HRMS calcd for $\text{C}_{14}\text{H}_{25}\text{N}_2$ [(M + H) $^+$] 221.2015, measured 221.2018. The dihydrochloride had mp 218–222 °C dec after crystallization from 2-propanol. Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{Cl}_2\text{N}_2$: C, 57.34; H, 8.94; N, 9.55. Found: C, 57.27; H, 9.02; N, 9.55.

α,α -Dibutyl-1-(2-phenylethyl)-4-piperidinemethanamine (19): bp 180–205 °C bath temperature (0.001 mm); ^1H NMR δ 7.2–7.3 (m, 5 H), 3.1 (d, J = 11 Hz, 2 H), 2.8 (m, 2 H), 2.6 (m, 2 H), 2.0 (t, J = 11 Hz, 2 H), 0.9–2.7 (m, 19 H), 0.9 (t, J = 7 Hz, 6 H); ^{13}C NMR δ 13.992, 23.413, 25.364, 25.858, 33.695, 36.982, 43.665, 54.213, 54.432, 60.614, 125.827, 128.226, 128.556, 140.485. Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{N}_2$: C, 79.94; H, 11.59; N, 8.47. Found: C, 79.69; H, 11.62; N, 8.06. The dihydrochloride crystallized from 95% aqueous 2-propanol as the monohydrate, mp 270–272 °C dec. Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{Cl}_2\text{N}_2\cdot\text{H}_2\text{O}$: C, 62.69; H, 10.04; N, 6.65. Found: C, 62.75; H, 10.19; N, 6.50.

trans-2-Methyl-4-phenyl-3-buten-2-amine (20): bp 110–140 °C bath temperature (5 mm); ^1H NMR δ 7.2–7.4 (m, 5 H), 6.4 (d, J = 16 Hz, 1 H), 6.3 (d, J = 16 Hz, 1 H), 1.4 (br, 2 H), 1.3 (s, 6 H). ^{13}C NMR δ 30.601, 50.697, 124.958, 126.166, 127.036, 128.437, 137.281, 140.128. The hydrochloride had mp 218–219 °C after crystallization from 2-propanol. Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{ClN}$: C, 66.83; H, 8.16; N, 7.08. Found: C, 66.77; H, 8.20; N, 7.03.

α,α,β -Trimethylbenzenepropanamine (21): bp 110–130 °C bath temperature (3 mm); ^1H NMR δ 7.1–7.3 (m, 5 H), 3.0 (d/d, J = 13/3 Hz, 1 H), 2.1 (d/d, J = 13/11 Hz, 1 H), 1.6 (m, 1 H), 1.3 (br, 2 H), 1.1 (s, 6 H), 0.8 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 27.688, 28.457, 38.025, 46.576, 51.685, 125.506, 128.070, 128.985, 142.041. The hydrochloride had mp 192–193 °C after crystallization from EtOH. Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{ClN}$: C, 67.47; H, 9.43; N, 6.55. Found: C, 67.40; H, 9.51; N, 6.51.

4-Cyclohexyl-2-methyl-3-buten-2-amine (22). The starting material, 3-cyclohexane-2-propenenitrile, was prepared as follows: a mixture of 3.36 g (30 mmol) of cyclohexanecarboxaldehyde, 10.0 g (33 mmol) of (cyanomethylene)triphenylphosphorane (K and K), and 20 mL of THF was heated under reflux for 18 h, the solvent was removed, the residue was stirred with 20 mL of ether, and the mixture was filtered. Removal of the solvent from the filtrate and short-path distillation of the residue at 120–140 °C bath temperature (5 mm) gave 2.95 g (72%) of 3-cyclohexane-2-propenenitrile as a 77:23 mixture of *trans* and *cis* isomers. Treatment with MeCeCl_2 afforded 22 as a ca. 80:20 mixture of *trans* and *cis* isomers, bp 90–115 °C bath temperature (10 mm). *trans*-22: ^1H NMR δ 5.5 (d, J = 16 Hz, 1 H), 5.4 (d/d, J = 16/6 Hz, 1 H), 1.9 (m, 1 H), 1.6–1.8 (m, 4 H), 1.2 (s, 6 H), 1.0–1.2 (m, 8 H); ^{13}C NMR olefinic C at δ 135.624, 136.796, *cis*-22: ^1H NMR δ 5.4 (d, J = 12 Hz, 1 H), 5.0 (d/d, J = 12/11 Hz, 1 H), 2.6 (m, 1 H), 2.6 (s, 3 H) among others. ^{13}C NMR olefinic C at δ 131.156, 137.675. The hydrochloride of *cis* + *trans*-22 had mp 133–134 °C after crystallization from MeCN. Anal. Calcd for $\text{C}_{11}\text{H}_{22}\text{ClN}$: C, 64.84; H, 10.88; N, 6.87. Found: C, 64.65; H, 11.04; N, 6.80.

1',2'-Dihydro-1,2',2'-trimethylspiro[piperidine-4,3'(3H)-pyrrolo[2,3-b]pyridine] (23). A suspension of 10 mmol of MeCeCl_2 was prepared as described for the synthesis of 1, and 0.81 g (4 mmol) of 1-methyl-4-(3-pyridyl)-4-piperidinecarbonitrile³² in 4 mL of THF was added. The mixture was stirred at –20 °C for 30 min and then worked up. The crude product was crystallized from ethyl acetate to give 0.42 g (45%) of 23: mp 153.5–155 °C; ^1H NMR δ 7.8 (d, J = 7 Hz, 1 H); 7.6 (d, J = 7 Hz, 1 H), 6.5 (d/d, J = 7/8 Hz, 1 H), 4.5 (br s, 1 H), 2.8 (m, 2 H), 2.4 (m + s, 5 H), 1.7–2.0 (m, 4 H), 1.2 (s, 6 H); ^{13}C NMR δ 23.960, 30.666, 46.133, 46.323, 52.240, 64.931, 112.965, 128.963, 133.059, 145.796, 162.068. Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{N}_3$: C, 72.68; H, 9.15; N, 18.16. Found: C, 72.59; H, 9.05; N, 18.15.

4-(3-Chlorophenyl)- α,α ,1-trimethyl-4-piperidinemethanamine (24). A suspension of 40 mmol of MeCeCl_2 prepared as described for the synthesis of 1 was treated at –60 °C with a solution of 3.12 g (13.3 mmol) of 1-methyl-4-(3-chlorophenyl)-4-

piperidinecarbonitrile³³ in 5 mL of THF, and the mixture was stirred at –65 °C for 6 h. Isolation as described above and crystallization of the crude product from 1-propanol gave 2.56 g (70%) of 24 in two crops: mp 92–93 °C; ^1H NMR δ 7.2–7.3 (m, 4 H), 2.7 (m, 2 H), 2.3 (m, 2 H), 2.1 (s, 3 H), 2.0 (m, 2 H), 1.8 (m, 2 H), 1.2 (very broad, 2 H), 1.0 (s, 6 H); ^{13}C NMR δ 25.657, 29.328, 45.854, 48.069, 52.107, 73.925, 126.130, 127.842, 128.931, 129.838, 133.958, 142.884. Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{ClN}_2$: C, 67.52; H, 8.69; N, 10.50. Found: C, 67.46; H, 8.67; N, 10.47.

1',2,2-Trimethyl-1,2-dihydrospiro[3H-indole-3,4'-piperidine] (25). The reaction was carried out as described for 24 above except that 2.80 g (11.9 mmol) of 1-methyl-4-(3-chlorophenyl)-4-piperidinecarbonitrile was used, and the reaction mixture was stirred at 25 °C for 2 h. Chromatography of the crude product (silica, EtOAc/Et₃N, 97:3) gave 0.69 g (27%) of 4-(3-chlorophenyl)-1-methylpiperidine followed by 1.19 g (43%) of 25: ^1H NMR δ 7.6 (d, J = 7 Hz, 1 H), 7.1 (t/d, J = 7/1 Hz, 1 H), 6.8 (t/d, J = 8/1 Hz, 1 H), 6.7 (d, J = 8 Hz, 1 H), 3.6 (br, 1 H), 2.8 (d/t, J = 12/3.5 Hz, 2 H), 2.6 (t/d, J = 12/3.5 Hz, 2 H), 2.5 (s, 3 H), 1.9 (t/d, J = 12/4.5 Hz, 2 H), 1.8 (d, J = 13 Hz, split further, 2 H), 1.3 (s, 6 H); ^{13}C NMR δ 24.043, 30.931, 46.338, 46.550, 52.331, 66.956, 109.498, 117.607, 126.065, 127.021, 135.124, 149.081. The fumarate had mp 193–194 °C after crystallization from 9:1 1-propanol/H₂O. Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_4$: C, 65.88; H, 7.57; N, 8.09. Found: C, 65.97; H, 7.57; N, 7.98.

2-(1,1-Dimethylethyl)-2-hexanamine (27). The starting material, 2,2-dimethyl-3-heptanamine, was prepared as follows: to 32 mL (80 mmol) of 2.5 M *n*-BuLi in hexanes and 30 mL of THF was added at –10 °C 5.0 g (60 mmol) of 2,2-dimethylpropanenitrile. The mixture was stirred at 0 °C for 30 min and treated with H₂O, and the product was extracted into ether. Short-path distillation (100 °C bath temperature, 15 mm) gave 7.27 g (90%) of the imine: ^1H NMR δ 9.0 (br s, 1 H), 2.2 (t, J = 6 Hz, 2 H), 1.5 (br m, 2 H), 1.4 (m, 2 H), 1.1 (s, 9 H), 0.9 (t, J = 7 Hz, 3 H); ca. 5% of the geometrical isomer was present (δ 2.5, t). 27 had bp 80–100 °C bath temperature (10 mm): ^1H NMR δ 1.2–1.5 (m, 6 H), 0.9–1.0 (2 s + t + br, 17 H); ^{13}C NMR δ 14.056, 21.747, 23.569, 25.190, 26.407, 36.442, 37.330, 55.266. Anal. Calcd for $\text{C}_{10}\text{H}_{23}\text{N}$: C, 76.36; H, 14.74; N, 8.90. Found: C, 75.95; H, 14.64; N, 8.95.

α -Butyl- α -methylbenzenemethanamine (28). (a) From Valerophenone Imine. Valerophenone imine (α -butylbenzenemethanimine) was prepared from benzonitrile and *n*-BuLi as described under 27. Reaction under the conditions given in Table II gave 28: bp 80 °C bath temperature (0.002 mm); ^1H NMR δ 7.2–7.5 (m, 5 H), 1.6–1.8 (m, 2 H), 1.5 (br s, 2 H), 1.4 (s, 3 H), 1.0–1.3 (m, 4 H), 0.8 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 13.892, 23.038, 26.435, 31.056, 44.966, 54.808, 125.049, 125.846, 127.961, 149.055. The hydrochloride had mp 153–156 °C after crystallization from acetonitrile. Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{ClN}$: C, 67.43; H, 9.43; N, 6.55. Found: C, 67.40; H, 9.55; N, 6.49.

(b) Via *N*-Lithiovalerophenone Imine. Benzonitrile (0.69 g, 6.7 mmol) in 2 mL of THF was added at 0 °C to 2.7 mL (6.7 mmol) of 2.5 M *n*-BuLi in hexanes and 3 mL of THF. The mixture was stirred at 0 °C for 30 min and cannulated into a stirred suspension of 20 mmol of MeCeCl_2 (prepared as described for the synthesis of 1), keeping the temperature below –60 °C. Isolation after 6 h at –65 °C gave 0.78 g (66%) of 28, identical with the product obtained above. The neutral product was valerophenone imine (12%).

α -Butyl- α -phenylbenzenemethanamine (29). Benzophenone imine (2.37 g, 1.31 mmol) was treated with *n*-BuCeCl₂ under the conditions give in Table II. The crude product was dissolved in ether and treated with a solution of HCl in ether to give 2.86 g (79%) of the hydrochloride of 29, mp 237–239 °C. Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{ClN}$: C, 74.03; H, 8.04; N, 5.08. Found: C, 73.88; H, 8.10; N, 5.02. The free base had ^1H NMR δ 7.2–7.4 (m, 10 H), 2.2 (m, 2 H), 1.8 (br s, 2 H), 1.1–1.4 (m, 4 H), 0.8 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 13.983, 23.166, 26.288, 42.375, 60.905, 126.093, 126.514, 127.952, 148.945.

Acknowledgments. I thank Mr. J. T. Rescinito for technical assistance, Dr. P. L. Watson for expert advice

(32) This compound was prepared from 3-pyridineacetonitrile by the method of ref 33a.

(33) (a) Cammack, T.; Reeves, P. C. *J. Heterocycl. Chem.* 1986, 23, 73. (b) Ciganek, E.; Cook, L. U.S. Patent 5,019,650, 1991.

on lanthanide chemistry, and Professors R. H. Grubbs and B. M. Trost for helpful discussions.

Registry No. 1, 41718-44-9; 2, 141983-52-0; 3, 32836-50-3; 3-HCl, 141983-74-6; 4, 18094-01-4; 5, 141983-53-1; 5-HCl, 141983-77-9; 6, 141983-54-2; 7, 141983-55-3; 8, 3433-03-2; 8-HCl, 1660-17-9; 9, 42044-72-4; 9-HCl, 141983-78-0; 10, 141983-56-4; 10-HCl, 141983-79-1; 11, 141983-57-5; 12, 5824-40-8; 13, 141983-58-6; 13-HCl, 141983-80-4; 14, 141983-59-7; 14 *p*-tolylurea derivative, 141983-81-5; 15, 141983-60-0; 15 phenylurea derivative, 141983-82-6; 16, 141983-61-1; 17, 141983-62-2; 17-2HCl, 141983-91-7; 18, 141983-63-3; 18-2HCl, 141983-83-7; 19, 141983-64-4; 19-2HCl, 141983-84-8; 20, 141983-65-5; 20-HCl, 141983-85-9; 21, 141983-66-6; 21-HCl, 141983-86-0; *cis*-22, 141983-71-3; *cis*-22-HCl, 141983-72-4; *trans*-22, 141983-67-7; *trans*-22-HCl, 141983-73-5; 23, 141983-68-8; 24, 141983-69-9; 25, 141983-70-2; 25-fumarate, 141983-87-1; 27, 99868-56-1; 28, 33083-81-7; 28-HCl, 141983-88-2; 29, 22308-24-3; 29-HCl, 19274-92-1; CeCl_3 , 7790-86-5; BuCeCl_2 , 94616-73-6; MeCeCl_2 , 94616-84-9; *i*- PrCeCl_2 , 119021-56-6; *s*- BuCeCl_2 , 141983-75-7; PhCeCl_2 , 99354-16-2; benzonitrile, 100-47-0; acetophenone, 98-86-2; α -butyl- α -methylbenzenemethanol, 4396-98-9; 4-cyanobenzophenone, 1503-49-7; dodecanenitrile, 2437-25-4; 2-methylpropionitrile, 78-82-0; 2,2-dimethylpropio-

nitrile, 630-18-2; cycloheptanecarbonitrile, 32730-85-1; 1-adamantanecarbonitrile, 23074-42-2; *p*-tolylacetonitrile, 2947-61-7; 4-phenylbenzonitrile, 2920-38-9; 2-furancarbonitrile, 617-90-3; 1-naphthalenecarbonitrile, 88-53-3; 2-furanylcium dichloride, 141983-76-8; 2-thienylcerium dichloride, 138769-83-2; 2-tridecanone, 593-08-8; 2-methyl-2-tridecene, 62060-10-0; naphthalene, 91-20-3; furan, 110-00-9; 2-bromothiophene, 1003-09-4; *p*-phenylenedicarbonitrile, 623-26-7; 4-pyridinecarbonitrile, 100-48-1; 1-phenethyl-4-piperidinecarbonitrile, 23793-56-8; (*E*)-cinnamonitrile, 1885-38-7; (*Z*)-3-cyclohexylacrylonitrile, 78978-70-8; (*E*)-3-cyclohexylacrylonitrile, 22031-57-8; 1-methyl-4-(3-pyridyl)-4-piperidinecarbonitrile, 104742-20-3; 1-methyl-4-(3-chlorophenyl)-4-piperidinecarbonitrile, 126555-97-3; (*E*)-2,2-dimethyl-3-heptanimine, 141983-89-3; valerophenone imine, 16659-09-9; benzophenone imine, 1013-88-3; (*Z*)-2,2-dimethyl-3-heptanimine, 141983-90-6.

Supplementary Material Available: ^{13}C NMR spectra of 4, 6, 7, 11, and 16 for which elemental analyses were not obtained (5 pages). This material is contained in many 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.

Calixarenes. 27. Synthesis, Characterization, and Complexation Studies of Double-Cavity Calix[4]arenes

C. David Gutsche* and Keat Aun See

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

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The ease with which calix[4]arenes can be selectively substituted at the distal phenolic oxygens is employed to advantage to build a second cavity and create two classes of "double-cavity calixarenes". Through the use of 3,5-dinitrobenzoyl chloride, 3-nitro-5-carbomethoxybenzoyl chloride, 3,5-dinitrobenzyl chloride, or 3-nitro-5-carbomethoxybenzyl chloride the diesters 2 and 16, diethers 3 and 17, and ether-ester 10 have been prepared. The second cavity is built by reduction of the nitro groups to amino groups to give compounds 4, 5, 13, 18, and 19 followed by treatment with a diacyl chloride. The products obtained from 4, 5, and 13 are double-spanned double-cavity calix[4]arenes; those from 18 and 19 are single-spanned double-cavity calix[4]arenes. A study of the complexation characteristics of the double-spanned double-cavity calixarenes (6, 7, and 14) shows the diester double-cavity calix[4]arene 6 to be the most effective of the three in forming complexes with acidic compounds (i.e., phenols and carboxylic acids) as well as basic compounds (i.e., pyridines, imidazoles, aliphatic amines). The K_{assoc} values range from < 5 to 55 M^{-1} and are dependent both on the shape and the acidity or basicity of the guest. Several lines of evidence, including molecular modeling studies, indicate that complexation occurs at the side rather than the bottom of the host molecule, providing an explanation for the differences in K_{assoc} for various pairs of guests and also establishing the rationale for the synthesis of the single-spanned double-cavity calix[4]arenes (20, 21) which form quite strong complexes ($K_{\text{assoc}} > 10^3$) with certain guests such as resorcinol.

The calix[4]arenes¹ are easily synthesized cavity-containing molecules possessing hydroxyl groups on the "lower rim" and potentially free para positions on the "upper rim". Several of the methods for achieving upper rim functionalization have been developed in this laboratory,² our major attention in the past having been devoted to the cavity on which these introduced functions reside. The hydroxyl groups, however, also provide convenient points for attachment of various moieties, as numerous other workers have actively demonstrated.³ The present paper deals

with this latter aspect of calixarene functionalization and describes methods whereby a second cavity is introduced into the calix[4]arenes. The program had its inception in the discovery that calix[4]arenes can be converted in good yield to compounds containing a pair of 3,5-dinitrobenzoyl moieties attached in a 1,3-fashion to oxygens on the lower rim (i.e., positions 25 and 27).⁴

Synthesis of Double-Spanned Double-Cavity Calix[4]arenes

The three double-spanned double-cavity calix[4]arenes that have been synthesized for a comparison of their complexing abilities are designated as the diester double-spanned double-cavity calix[4]arene 6, the ester-ether double-spanned double-cavity calix[4]arene 14, and the diether double-spanned double-cavity calix[4]arene 7. They are prepared as described below.

(4) See: K. A.; Fronczek, F. R.; Watson, W. H.; Gutsche, C. D. *J. Org. Chem.* 1991, 56, 7256.

(1) (a) Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; Royal Society of Chemistry: London, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicuna, J.; Böhrer, V., Eds.; Kluwer Academic: Dordrecht, 1991.

(2) Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* 1985, 50, 5795. Gutsche, C. D.; Levine, J. A.; Sulejeth, P. K. *J. Org. Chem.* 1985, 50, 5802. Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* 1988, 110, 6153.

(3) For example, see: Collins, E. M.; McKervey, M. A.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* 1965, 372. Arnaud-Nau, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaltner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* 1989, 111, 8681.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 2010-09-06

Abogada

MARGARITA CASTELLANOS ABONDANO

Solicitante: SYNGENTA PARTICIPATIONS AG

ASUNTO

Radicación 06-66822

Trámite 011

Evento 378

Actuación 430

Oficio

Folios 002 11686

Patente de Invención ☒

Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒

Cap. I ☐

Cap. II ☒

No. de solicitud internacional

PCT/IB2004/004083

Fecha de presentación internacional 2004-12-09

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: folios 192 a 414 (como se radicó inicialmente)

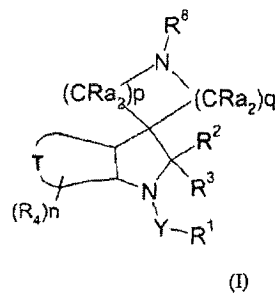
Reivindicaciones (1 a 9): folios 464 a 471 (como se modificó mediante oficio de 2010-08-12)

Prioridad: Gran Bretaña, 0328905.5 de 2003-12-12

2. Objeto de la invención

Título de la solicitud: Derivados de espiropiperidina para el control de plagas

El objeto de la presente solicitud de patente de invención consiste en: un compuesto de la fórmula



Los significados de los sustituyentes se encuentran en los folios 464 a 469.

La invención se catalogó como A01N43/40, según la Clasificación Internacional de Patentes (IPC).

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Las fórmulas (I') y (II) del capítulo reivindicatorio estudiado son idénticas y no es claro por qué se usan diferentes números para designarlas.

El compuesto de fórmula (I') no está plenamente definido porque los significados de los sustituyentes involucran posibles sustituciones que no se han especificado, lo cual es totalmente especulativo. Por ejemplo, R1 puede significar heteroarilalquilo de C1 a C6. No

se indica nada sobre cuál puede ser la parte heteroarilo y este término abarca cientos de posibilidades (o tal vez miles). Así mismo, a lo largo de todo el capítulo reivindicatorio, se usa la palabra arilo o heteroarilo para designar los posibles significados de los diversos sustituyentes R, pero nunca se especifica a cuál arilo se refiere la solicitante. Este tipo de denominación es completamente genérica. De las miles de posibilidades abarcadas por tales denominaciones genéricas se encuentran muy pocos ejemplos que proporcionen un soporte completo en la descripción. A la solicitante ya se había notificado una vez sobre este tema y en el nuevo capítulo reivindicatorio allegado siguen apareciendo estas denominaciones genéricas.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que si a pesar de la respuesta al presente oficio subsistieren los impedimentos para la concesión, se denegará la patente.

4. Unidad de invención (artículo 25 D 486)

La solicitud no tiene unidad de invención porque la estructura que sirve de base para los miles de compuestos reivindicados ya era conocida del documento Ciganek, Tertiary carbinamines by addition of organocerium reagents to nitriles and ketimines, J. Org. Chem. 1992, 57, 4521-4527 (folios 480 a 486 del expediente), véase ecuación 7. Por lo tanto, el elemento común ya era conocido y, por lo tanto, falta unidad de invención.

5. Determinación del Estado de la Técnica

La fecha tomada en cuenta para determinar el estado de la técnica es 2003-12-12, la cual corresponde a la fecha de la prioridad reivindicada.

Debido a la falta de definición del objeto de la solicitud y a que esta oficina no está facultada para seleccionar uno de los muchos compuestos reivindicados que no conforman un concepto común inventivo entre sí, no es procedente efectuar el examen de patentabilidad solicitado, mientras no se especifique cuál es el objeto de la solicitud que tenga unidad de invención. A la solicitante ya se había notificado una vez sobre este tema y al nuevo capítulo reivindicatorio allegado aún falta unidad de invención. En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que si a pesar de la respuesta al presente oficio subsistieren los impedimentos para la concesión, se denegará la patente.

6. Notificación

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

10 SET. 2011

CONCEPTO TÉCNICO No. 3172	EXAMINADOR TÉCNICO Código No. 202043
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