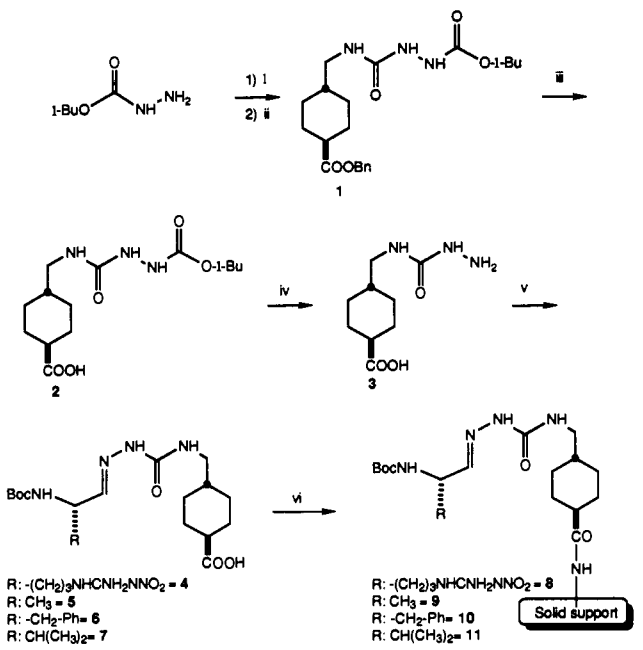
Scheme I[a]



[a] (i) Carbonyldiimidazole/DMF; (ii) *trans*-4-(aminomethyl)cyclohexanecarboxylic acid benzyl ester/triethylamine; (iii) H_2/Pd; (iv) trifluoroacetic acid/0 °C; (v) Boc amino acid aldehyde/NaOAc reflux in ethanol; (vi) MBHA resin/(benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate.

Table I[a,b]

Boc-(D)Leu-Pro-argininal	Boc-(D)Phe-Glu-argininal
Boc-(D)Leu-Ser-argininal	Boc-Ala-Ala-Pro-alaninal
Boc-Asn-Leu-Thr-argininal	Boc-Ala-Ala-Pro-valinal
Boc-Leu-Thr-argininal	Boc-Ala-Ala-Pro-phenylalaninal

[a] The hydroxyl group in the side chains of Boc-Ser-OH, Boc-Thr-OH, and Boc-Tyr-OH was protected as the benzyl ether. The carboxylate in the side chain of Boc-Glu-OH was protected as the benzyl ester. [b] Reference 14.

98% yield from the corresponding acid).[9] The product of this reaction, **1** was hydrogenated, to give crystalline **2** in 75% overall yield. This product was then treated with trifluoroacetic acid (TFA), to give crystalline **3**, in 95% yield. This material was allowed to react with α-Boc-N^g-L-argininal[10] and base, to give pure **4** in 75% yield. Coupling of **4** to the commercially available MBHA resin[11] gave the insoluble support **8**, with a coupling efficiency of 99.9%.[12] This material had all of the physical and chemical properties required for the automated synthesis of PAs. In a similar manner derivatives **5**–**7** gave supports **9** through **10**, which are useful for the preparation of the corresponding peptide aldehydes. Table I shows a few examples of peptide aldehydes prepared via this technique. We found that amino acids containing other functionalities can readily be incorporated into peptide aldehydes. The use of benzyl ether protection for the hydroxyl group and benzyl ester for the carboxyl group allows for the incorporation of Thr, Ser, Tyr, Asp, and Glu into peptide aldehydes, via this technique. A final deprotection by catalytic hydrogenation gives the fully deprotected peptide aldehyde.

Standard automated Boc protocols[13] and resin **5** can be used to prepare protected PA semicarbazones on supports (with coupling yields that are greater than 98%) and then cleaved with dilute aqueous acid/formaldehyde, to give the protected free PAs in good yield. We have found that PA arginals containing various hydrogen/Pd labile protecting groups (e.g., N^g-nitro, benzyl ether, and benzyl esters) can be deprotected, in a single step, to give the unprotected PAs after purification by reverse-phase HPLC.[14]

In conclusion, we have developed a highly efficient method for the automated synthesis of peptide aldehydes. This method relies on the crystalline heterobifunctional linkers **4**–**7**, which are prepared in greater than 50% overall yield without chromatographic purification. This preformed linker may be attached to resins, such as the 1% cross-linked MBHA polystyrene resin, to give insoluble supports (**8**–**11**) which are suitable for use in conventional peptide synthesizers. We have used this method to prepare over 100 different peptide aldehydes. The investigation of the scope and limitations of this method, and the biological properties of the new synthetic PAs will be the subject of future reports.

Supplementary Material Available: Experimental details for the preparation of **1**–**11** and a general procedure for the synthesis of peptide aldehydes using the novel supports **8**–**11** (10 pages). Ordering information is given on any current masthead page.

(8) To the best of our knowledge, this method for preparing semicarbazides has not previously been reported. It has been observed that amino carbonyl imidazolides decompose at room temperature to give isocyanates; see: Staab, H. A.; Benz, W. *Justus Liebigs Ann. Chem.* **1961**, *648*, 72.

(9) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Robert E. Krieger Publishing Company: Malabar, FL, 1986; Vol. 2, p 942.

(10) We found that this material was best prepared by the method of Fehrentz and Castro; see: Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676. Goel, O. P.; Krolls, U.; Stier, M.; Kesten, S. *Org. Synth.* **1988**, *67*, 69–75.

(11) Pietta, P. G.; Marshall, G. R. *J. Chem. Soc. D* **1970**, 650–651.

(12) Coupling yields and loading of the resin were determined via the method of Kaiser et al.: Kaiser et al. *Anal. Biochem.* **1970**, *34*, 595.

(13) Barany, G.; Merrifield, R. B. Solid-Phase Peptide Synthesis. In *The Peptides*; Academic Press, Inc.: New York, **1980**; Vol. 2, pp 1–284.

(14) All new compounds were characterized by NMR, elemental analysis or mass spectra.

Cross Relaxation without TOCSY: Transverse Rotating-Frame Overhauser Effect Spectroscopy

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Rotating-frame Overhauser effect spectroscopy (ROESY or CAMELSPIN)[1,2] NMR techniques measure transverse nuclear Overhauser enhancements. Transverse magnetization is "locked" by a constant-phase radiofrequency (rf) field about the *y*-axis of the rotating frame, and cross relaxation can occur.[3] Studies of peptides,[4] proteins,[5] nuleic acids,[6-8] and oligosaccharides[9] have used ROESY. The ROE is indispensable when the NOE is weak ($\omega_0\tau_c \approx 1.12$).

An annoying problem in ROESY is *coherent* magnetization transfer by TOCSY[10] that occurs by *J*-coupling pathways[11-14] and is unrelated to cross relaxation. It seemed like an inescapable

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(1) Bothner-By, A. A.; Stephens, R. L.; Lee, J.-M.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811.

(2) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207.

(3) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect In Structural And Conformational Analysis*; VCH Publishers, Inc.: New York, 1989.

(4) Davis, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 3471.

(5) Matsoukas, J. M.; Bigam, G.; Zhou, N.; Moore, G. J. *Peptides* **1990**, *11*, 359.

(6) Loschner, T.; Engls, J. W. *Nucleic Acids Res.* **1990**, *18*, 5083.

(7) Andre, F.; Demassier, V.; Bloch, G.; Neumann, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 6784.

(8) Bauer, C. J.; Frenkiel, T. A.; Lane, A. N. *J. Magn. Reson.* **1990**, *87*, 144.

(9) Leeflang, B. R.; Bouwstra, J. B.; Kerekgyarto, J.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1990**, *208*, 117.

(10) Braunschweiler, L.; Ernst, R. R. *J. Magn. Reson.* **1983**, *53*, 521.

(11) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 2820.

(12) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 7197.

(13) Neuhaus, D.; Keeler, J. *J. Magn. Reson.* **1986**, *68*, 568.

(14) Bax, A. *J. Magn. Reson.* **1988**, *77*, 134.

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feature of the experiment, making sugars, alkaloids, and natural products with narrow-bandwidth networks of J-coupled spins unsuitable for ROESY. Off-resonance spin locking to reduce TOCSY gives a mixture of transverse, σ_{tr}, and longitudinal, σ_{ln}, cross-relaxation rates depending on resonance offset; for a nonequivalent proton pair and isotropic reorientation with correlation time τ_c,[1-4,14-16]

$$(\sigma_{rf})_{ij} = (\sin\theta_i \sin\theta_j)(\sigma_{ln})_{ij} + (\cos\theta_i \cos\theta_j)(\sigma_{tr})_{ij} \quad (1)$$

where $\theta_i = \tan^{-1}\{\Delta\omega_i/\gamma B_1\}$ etc. show the tilt of the effective spin-locking field away from the xy-plane, σ_{rf} is the measured rotating-frame cross-relaxation rate, and[4]

$$(\sigma_{ln})_{ij} = \frac{\gamma^4\hbar^2}{10r_{ij}^6}\left(\frac{6}{1 + 4\omega_0^2\tau_c^2} - 1\right)\tau_c \quad (2)$$

$$(\sigma_{tr})_{ij} = \frac{\gamma^4\hbar^2}{10r_{ij}^6}\left(\frac{3}{1 + \omega_0^2\tau_c^2} + 2\right)\tau_c \quad (3)$$

As $\theta_{ij} \to 0$, $\sigma_{rf} \to \sigma_{tr}$. Note that $\sigma_{tr} > 0$ even for $\omega_0\tau_c \gg 1$. We retain this advantage with our sequence, but eliminate TOCSY. A simple DANTE sequence[17] for spin locking[18] suppresses TOCSY no better than a continuous weak spin-locking field.[14]

In our multiple-pulse (MP) version we suppress TOCSY, use strong pulses, and position the carrier anywhere in the spectral bandwidth. To preclude TOCSY, the *scaling factor* λ, defined by[19]

$$\lambda = \frac{1}{t_s}\frac{\partial\beta}{\partial\omega} \quad (4)$$

where β is the net rotation angle of the sequence, t_s its duration, and ω the resonance offset, *should be nonzero over the frequency range of interest*.[20-23] During a delay, for example, $\lambda \to 1$ and there is no TOCSY; during a strong continuous pulse, however, $\lambda \to 0$ and TOCSY can occur. The MP sequence should also boil down to a net rotation along the y-axis of the rotating frame, periodically mimicking the long constant y-phase pulse it replaces. Transverse magnetization is thus held in a fixed phase relationship over long times, to observe cross relaxation.[3] Finally, the z-component, n_z, of the net rotation axis should remain small off resonance, minimizing distortions arising from tilted spin-locking fields.

The simplest useful sequence is $180°(x)\ 180°(-x)$. On resonance this sequences takes a spin vector initially along the y-axis through a trajectory past the south pole, to the $-y$ axis, and then back again. Near resonance, the net rotation can be shown to be $R_y(4\theta)$, where θ is the tilt of the effective field. Spin magnetization is rotated around the y-axis by a strongly offset-dependent angle; magnetization initially along the y-axis is spin locked on average. Near resonance, $\lambda = 2/\pi \approx 0.637$ *independent* of B_1, allowing high-power application with the transmitter in the center of the spectrum and negligible TOCSY. Neglecting relaxation during the actual trajectory, the observed cross-relaxation rate for strong irradiation near resonance is

$$(\sigma_{mp})_{ij} = \frac{(1 + \sin\theta_i \sin\theta_j)(\sigma_{tr})_{ij} + (\cos\theta_i \cos\theta_j)(\sigma_{ln})_{ij}}{2} \quad (5)$$

which reduces to $\sigma_{mp} = (1/2)(\sigma_{tr} + \sigma_{ln})$ as $\theta_{ij} \to 0$ and is strictly positive for all values of τ_c. That σ_{mp} is the mean cross-relaxation rate is not surprising when the spins spend equal time along the

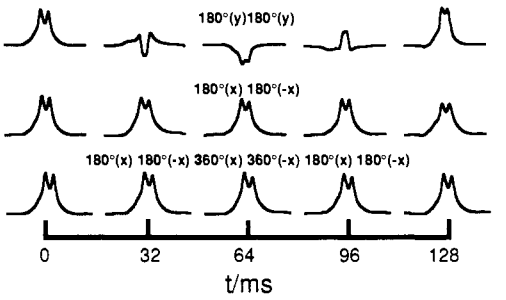

Figure 1. Comparison of spin-lock pulse sequences that can be used in the ROESY experiment. The two-spin system of 2,3-dibromothiophene has been prepared in the state $(I_{1y} - I_{2y})$ and then allowed to evolve under the spin-locking sequence for the times indicated; the high-field doublet is displayed. The chemical shift difference is 170 Hz, $\gamma B_1/2\pi = 4$ kHz, and $J_{HH} = 5.9$ Hz. The top trace shows the effect of TOCSY when a windowless series of $180°(y)$ pulses is centered on the low-field multiplet (equivalent to continuous irradiation). The unwanted transfer is suppressed in the next two traces, using the new sequences $180°(x)\ 180°(-x)$ or $180°(x)\ 180°(-x)\ 360°(x)\ 360°(-x)\ 180°(x)\ 180°(-x)$. Both sequences are effective at spin locking, as evidenced by the lack of any phase change in the spectrum.

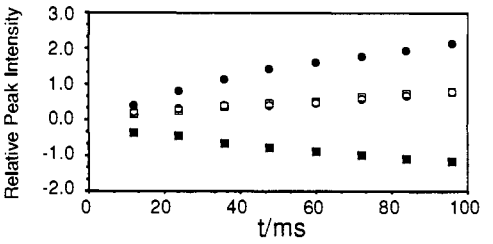

Figure 2. Plots of the Leu $C_\alpha H$ peak intensity in the difference spectrum of 8 mM gramicidin S in DMSO-d_6 at 20 °C and 295 MHz after selective inversion of the Phe NH resonance. The conventional transient NOE buildup is shown for comparison. Of the three ROE curves, the conventional method yields the fastest rate. The curves under T-ROESY show qualitatively the same behavior. ■ = longitudinal NOE, ● = conventional ROESY, ○ = $180°(x)\ 180°(-x)$ spin lock, □ = $180°(x)\ 180°(-x)\ 360°(x)\ 360°(-x)\ 180°(x)\ 180°(-x)$ spin lock. The two sequences give essentially identical results.

y- and z-axes.[24,25] Our experiment is thus the cross-relaxation analogue of the classic rotary echo experiment,[26] in which the longitudinal and transverse relaxation rates for a single spin are known to average.[27] Further off resonance, the trajectories change, changing σ_{mp}. A field of B_1 kHz will cover nearly $\pm 0.5B_1$ kHz bandwidth with $180°(x)\ 180°(-x)$. With TOCSY eliminated, larger bandwidths proportionately increase B_1. As spin magnetization is nearly perpendicular to the B_1 field, this multiple-pulse experiment measures *transverse* cross-relaxation in the rotating frame, analogous to the measurement of $T_{2\rho}$. We propose the name T-ROESY for these kinds of measurements.

The net spin lock axis for the $180°(x)\ 180°(-x)$ sequence is improved by $180°(x)\ 180°(-x)\ 360°(x)\ 360°(-x)\ 180°(x)\ 180°(-x)$, with $\lambda = 1/\pi \approx 0.318$, but a cubic dependence of n_z with respect to small changes in the pulse lengths. The two sequences are compared with continuous y-irradiation in Figure 1 for a pair of J-coupled spins in which little ROE is expected. The lack of TOCSY between spins with a chemical shift difference of 170 Hz with 4-kHz irradiation shows that TOCSY is not a problem in T-ROESY.

Corroborating experiments were carried out on the cyclic decapeptide gramicidin S in DMSO-d_6 at 20 °C and 295 MHz, in which σ_{ln} and σ_{tr} are of opposite sign and a genuine ROE is expected.[4] Using difference spectroscopy, the measured ROE buildup of the Leu $C_\alpha H$ resonance after selective inversion of the

(15) Griesinger, C.; Ernst, R. R. *J. Magn. Reson.* **1987**, *75*, 261.
(16) Farmer, B. T.; Brown, L. R. *J. Magn. Reson.* **1989**, *72*, 197.
(17) Morris, G. A.; Freeman, R. *J. Magn. Reson.* **1978**, *29*, 433.
(18) Kessler, H.; Griesinger, C.; Kerssebaum, R.; Wagner, K.; Ernst, R. R. *J. Am. Chem. Soc.* **1987**, *109*, 607.
(19) Waugh, J. S. *J. Magn. Reson.* **1982**, *50*, 30.
(20) Aue, W. P.; Ernst, R. R. *J. Magn. Reson.* **1978**, *31*, 533.
(21) Morris, G. A.; Nayler, G. L.; Shaka, A. J.; Keeler, J.; Freeman, R. *J. Magn. Reson.* **1984**, *58*, 155.
(22) Shaka, A. J.; Keeler, J.; Freeman, R.; Morris, G. A.; Nayler, G. L. *J. Magn. Reson.* **1984**, *58*, 161.
(23) Shaka, A. J.; Keeler, J. *Prog. NMR Spectrosc.* **1987**, *19*, 47.
(24) Griesinger, C.; Otting, G.; Wüthrich, K.; Ernst, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 7870.
(25) Briand, J.; Ernst, R. R. *Chem. Phys. Lett.* **1991**, *185*, 276.
(26) Solomon, I. *Phys. Rev. Lett.* **1951**, *2*, 301.
(27) Torrey, H. C. *Phys. Rev.* **1949**, *76*, 1059.

Phe NH resonance is plotted in Figure 2, with the transient NOE for comparison. A 5-kHz field centered on the NH resonance has been used. The MP sequences give a somewhat slower buildup than continuous irradiation, in agreement with eqs 1 and 5.

The suppression of TOCSY in T-ROESY experiments is an important advance. In the two-dimensional version of the experiment, absorption-mode line shapes can be achieved along the lines of ref 15.

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Synthesis of Lanthanide(II) Complexes of Aryl Chalcogenolate Ligands: Potential Precursors to Magnetic Semiconductors

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The synthesis of molecular precursors to semiconducting II–VI materials has attracted considerable attention since these materials are technologically important as optical materials and often difficult to synthesize by conventional methods.[2,3] Among these are a class known as the diluted magnetic semiconductors, which are ternary alloys of conventional II–VI materials, such as HgTe, substituted with paramagnetic centers such as Mn^{2+} or Fe^{2+}. These materials have a wide range of potential magnetooptic applications.[3] The rare earth monochalcogenides LnQ (Ln = Yb, Eu, Sm; Q = S, Se, Te) are of interest in this area due to the great variety of dilute magnetic semiconductors they could be used to form, such as $Hg_{1-x}Sm_xTe$, as well as for their range of magnetic properties.[4] Conventional high-temperature syntheses of these materials, particularly those containing the heavier chalcogenides, are difficult and often hindered by impurities incorporated due to the high oxophilicity of the rare earth centers.[5] The synthesis of precursor complexes to rare earth monochalcogenides, with the elements combined on a molecular level in the correct stoichiometry, allows for purification before pyrolytic cleavage and might afford the ability to process these materials at much lower temperatures. Reported complexes of the lanthanide metals with heavier chalcogenide ligands (Se, Te) are very few, but some examples exist of stable compounds of trivalent lanthanide ions coordinated by selenium and tellurium-containing ligands,[6] though

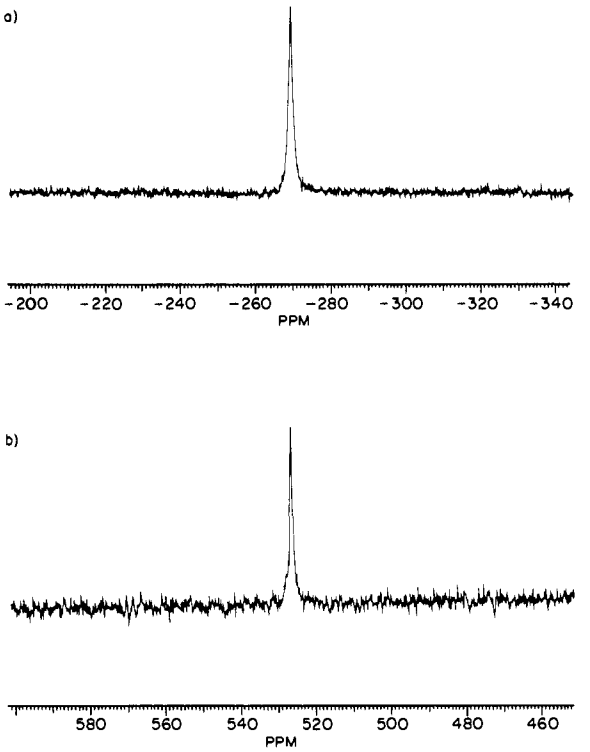

Figure 1. (a) ^{125}Te NMR spectrum of $Yb(TeMes)_2THF_{2-3}$ (**1**) in d_8-THF, referenced to external Me_2Te (δ = 0 ppm).[17] Resonance observed after 10 200 scans with sweep width = 100 000 MHz, pulse width = 3.0 μs, and relaxation delay = 0.1 s. (b) ^{171}Yb NMR spectrum of **1** referenced to external $YbCp_2^*THF_2$ (δ = 0 ppm).[18] Resonance observed after 2030 scans with the same parameters as above but a relaxation delay of 1.6 s.

divalent analogues have not been reported previously. We report here the synthesis of several members of a new class of compounds, lower chalcogenide complexes of the divalent lanthanide metals, which we find to be promising precursors to rare earth monochalcogenides.

Our most successful synthesis involves metathesis of halide ligands on divalent lanthanide metals[7] with alkali-metal salts of aryl selenolates or tellurolates (eq 1). Ytterbium was the metal

$$LnX_2THF_{2-3} + 2KQMes \xrightarrow[DME]{THF} Ln(QMes)_2THF_{2-3} + 2KX \quad (1)$$

Ln = Yb, Sm, Eu; X = I, Br; Q = Se, Te; Mes = 2,4,6-trimethylphenyl

selected for initial study because of its diamagnetism in the +2 oxidation state, allowing characterization by multinuclear NMR spectroscopy, and oxidation state confirmation by magnetic measurements. The lanthanide elements exhibit similar chemistry, allowing complexes analogous to the characterized ytterbium models to be synthesized with samarium and europium.

To produce stable complexes, the organic group on the chalcogenide must be bulky in order to sterically saturate the divalent lanthanide ion and maintain a monomeric or low nuclearity structure, allowing solubility in organic solvents and blocking possible decomposition pathways.[9] Syntheses of analogous

(1) Shell Doctoral Fellow.

(2) (a) Steigerwald, M. L.; Sprinkle, C. R. *J. Am. Chem. Soc.* **1987**, *109*, 7200. (b) Bochmann, M.; Webb, K.; Harman, M.; Hursthouse, M. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29* (6), 638. (c) Brennan, J. G.; Siegrist, T.; Carroll, P. J.; Stuczynski, S. M.; Reynders, P.; Brus, L. E.; Steigerwald, M. L. *Chem. Mater.* **1990**, *2*, 403. (d) Steigerwald, M. L.; Rice, C. E. *J. Am. Chem. Soc.* **1988**, *110*, 4228. (e) Bochmann, M.; Coleman, A. P.; Webb, K. J.; Hursthouse, M. B.; Mazid, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30* (8), 973.

(3) Glass, A. M. *Science* **1987**, *235*, 1003.

(4) *Handbook of the Physics and Chemistry of Rare Earths*; Gschneidner, K. A., Eyring, L. R., Eds.; North-Holland: Amsterdam, 1979; Vol. 2, Chapter 19; Vol. 4, Chapter 31.

(5) (a) Petzel, T. *Inorg. Nucl. Chem. Lett.* **1974**, *10*, 119. (b) Hickey, C. F.; Gibson, U. J. *J. Appl. Phys.* **1987**, *62* (9), 3912. (c) Nakahara, J. F.; Takeshita, T.; Tschetta, M. J.; Beardry, B. J.; Gschneidner, K. A. *J. Appl. Phys.* **1988**, *63* (7), 2331.

(6) (a) Schumann, H.; Albrecht, I.; Gallagher, M.; Hahn, E.; Janiak, C.; Kolax, C.; Loebel, J.; Nickel, S.; Palamidis, E. *Polyhedron* **1988**, *7* (22/23), 2307. (b) Berg, D. J.; Burns, C. J.; Andersen, R. A.; Zalkin, A. *Organometallics* **1989**, *8*, 1865. (c) Berg, D. J.; Burns, C. J.; Andersen, R. A.; Zalkin, A. *Organometallics* **1989**, *8*, 1865.

(7) (a) Watson, P. L.; Tulip, T. H.; Williams, I. *Organometallics* **1990**, *9*, 1999. (b) Namy, J. L.; Girard, P.; Kagan, H. B.; Caro, P. E. *Nouv. J. Chim.* **1981**, *5* (10), 479.

(8) Spectral data for $Yb(TeMes)_2THF_{2-3}$ (**1**): ^1H NMR (d_8-THF, 300 MHz) δ 6.62 (s, 4 H), 3.58 (THF), 2.42 (s, 12 H), 2.04 (s, 6 H), 1.73 ppm (THF); $^{13}C\{^1H\}$ NMR δ 145.4, 132.1, 125.5, 117.9 (aromatics), 68.2 (THF), 33.4 (o-CH_3), 26.3 (THF), 20.8 (p-CH_3). Anal. Calcd for $YbTe_2C_{28}H_{42}O_{2.5}$ (2.5 coordinated THF): Yb, 20.4; Te, 30.1; C, 39.7; H, 5.0. Found: Yb, 20.5; Te, 29.8; C, 39.2; H, 5.1.

(9) *Advances In Organometallic Chemistry*; Evans, W. J., Ed.; Academic Press, Inc.: New York, 1985; Vol. 24, p 131.

0002-7863/92/1514-3159$03.00/0