triflate-induced olefination also proceeded smoothly (68–77% yield) to afford the dissymmetric olefins **9b–d**[13] with essentially complete stereospecificity.[18,19]

Attempts to generalize this process to substituents other than phenyl (e.g., CH_3, Cl, $SnBu_3$) were not successful. However, we have now discovered that the phenylthio group in *cis*-**11**[13] is compatible with both stages of the olefination process (Scheme III). Moreover, this group can be readily replaced with high stereospecificity to allow general introduction of other organic groups. Considerable optimization of the first stage led to the use of PMDTA[20] in Et_2O at −90 °C to maximize the diastereoselectivity of addition. Trityl triflate-activated olefination of **12** cleanly afforded the (phenylthio)methylidene **13**. To establish the overall stereochemical course, the phenylthio group was displaced in a nickel-catalyzed coupling with PhMgBr.[21,22] This reaction proceeds readily at room temperature to afford **9a** in good yield. The coupling reaction is extremely sensitive to the purity of **13** and the Ni(dppp)Cl_2 catalyst. As shown in Table III, *the coupling proceeded with retention of configuration and 94% stereospecificity* using analytically pure catalyst. The use of Ph_2Zn[11b] increased the yield but afforded **9a** in lower ee.[23]

We can infer the stereostructure of **8a–d** by assuming a syn-cycloelimination to the olefins **9a–d**. Since the olefins are all of *S* configuration, this reduces to a structure for **8** that arises from exclusive equatorial attack by the *pro-R* face of the anions.[24] This pathway is consistent with other reactions of *cis*-**5**[4f] and with the extreme equatorial selectivity expected for bulky nucleophiles.[25] The electrophilic activation of the HWE process is believed to proceed via the *O*-trityl phosphonium ion[26] which captures the β-hydroxyl group prior to proton loss. Mechanistic studies are underway to establish the nature of these intermediates and the rate of their formation and breakdown.

In summary, we have documented a general procedure for the preparation of dissymmetric alkylidenes with high enantioselectivity. The mildness and high stereospecificity of the olefination reaction augur well for its application in synthesis.

Acknowledgment. We are grateful to the National Institutes of Health (GM 45532) for generous support of this research. C.-T.C. thanks the University of Illinois for a Graduate Fellowship.

Supplementary Material Available: Preparation and full spectroscopic characterization of *cis*-**5**, **8a–d**, **9a–d**, **10a–d**, *cis*-**11**, **12**, and **13** (16 pages). Ordering information is given on any current masthead page.

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(18) Stereospecificity is defined as 100[ee(**9**)]/[de(**8**)].

(19) The amino alcohol (*S*)-**6** can be recovered after HCl digestion and ion-exchange chromatography. The recoveries are low on a small scale due to water solubility and volatility.

(20) PMDTA: *P*enta*m*ethyl*d*iethylene*t*ri*a*mine. Standard conditions (*t*-BuLi/−78 °C) in THF, Et_2O, and DME gave **12** as a ∼3:1 mixture of isomers. However, with 2 equiv of PMDTA the selectivity increased in the order THF (3.9:1), toluene (8.7:1), Et_2O (11.1:1) at −78 °C.

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(22) This reaction is analogous to the catalyzed coupling of bromoalkylidenes to form dissymmetric olefins. (a) Walborsky, H. M.; Banks, R. B. *J. Org. Chem.* **1981**, *46*, 5074. (b) Walborsky, H. M.; Banks, R. B.; Banks, M. L. A.; Duraisamy, M. *Organometallics* **1982**, *1*, 667.

(23) We have demonstrated that (c-C_6H_{11})$_2$Zn coupled cleanly to afford the alkylidenes in 84% yield and 88% specificity. Further extensions are in progress.

(24) These anions are sp^2 hybridized with no C–Li contact. Dorow, R. L. Ph.D. Thesis, University of Illinois, Urbana, 1989.

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Amine Carbonyls of Zerovalent Titanium, Zirconium, and Hafnium. Structural Characterization of (1,4,7-Trimethyl-1,4,7-triazacyclononane)tetracarbonyltitanium(0)[1]

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Zerovalent metal carbonyl chemistry of the group 4 elements has remained very poorly explored in the past largely due to the unavailability of suitable precursors; e.g., binary carbonyls of titanium are exceedingly unstable, and those of zirconium and hafnium are unknown.[2] For this reason, (dmpe)Ti(CO)$_5$[3] was recently introduced as a useful synthetic equivalent of the unknown Ti(CO)$_7$ since the dmpe group was found to be easily displaced by Lewis bases under an atmosphere of CO to provide new zerovalent titanium carbonyls.[4] We now report that related zirconium and hafnium complexes of the formula (trmpe)M(CO)$_4$[3,5] also contain a labile phosphine group and thereby function as the first available synthetic equivalents of the unknown heptacarbonyls of these elements. In this communication the use of these labile phosphine carbonyls in the synthesis of the initial examples of amine carbonyls of the group 4 elements is described.[6] Amine carbonyls constitute an important class of coordination compounds and have been reported previously for virtually all later transition metals.[7] While acyclic amines such as $R_2NCH_2CH_2NR_2$ or $RN(CH_2CH_2NR_2)_2$, R = H, Me do not appear to form isolable group 4 carbonyl complexes under a variety of conditions,[8] the macrocyclic triamines tacn and Me$_3$tacn[3] react as shown in eqs 1 and 2 to provide the desired species, where L designates tacn or Me$_3$tacn and the bold numbers identify the products. Previously, Wieghardt and co-workers established that these amines form unusually robust carbonyl derivatives of the later transition metals.[9]

$$(\mathrm{trmpe})\mathrm{M(CO)_4} + \mathrm{L} \xrightarrow[\mathrm{DME}]{-25\ ^\circ\mathrm{C}} \mathrm{LM(CO)_4} + \mathrm{trmpe} \tag{1}$$

1, M = Zr, L = tacn; **2**, Me$_3$tacn; **3**, M = Hf, L = tacn

$$(\mathrm{dmpe})\mathrm{Ti(CO)_5} + \mathrm{L} \xrightarrow[\mathrm{THF}]{20\ ^\circ\mathrm{C}} \mathrm{LTi(CO)_4} + \mathrm{CO} + \mathrm{dmpe} \tag{2}$$

4, L = tacn, **5**, Me$_3$tacn

In a typical synthesis, a solution of (trmpe)Zr(CO)$_4$ (0.100 g, 0.22 mmol) and excess tacn (0.113 g, 0.88 mmol) in 45 mL of DME[3] was stirred under CO (1 atm) for 12 h at −25 °C. During this time a red precipitate formed, which was collected and crystallized from cold (−25 °C) CH_3CN/Et_2O to provide 0.060 g (82% yield) of **1**. By very similar procedures a 40% yield of **2** was obtained, while 70–80% yields of **3–5** were isolated. All products were air sensitive, thermally stable, red to dark red microcrystalline materials of satisfactory purity.[10] Interactions of (trmpe)Hf(CO)$_4$ and Me$_3$tacn failed to provide tractable products.

Infrared spectra of the tacn products **1**, **3**, and **4** showed carbonyl absorptions[11] at surprisingly low energies and were very similar to those of the corresponding anionic species $[(C_5Me_5)M(CO)_4]^-$.[12] Thus, the secondary amine, tacn, and $[C_5Me_5]^-$

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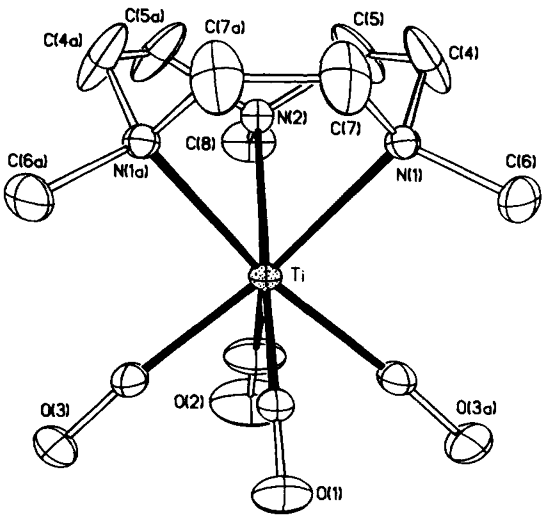

Figure 1. ORTEP drawing and labeling scheme for (1,4,7-trimethyl-1,4,7-triazacyclononane)tetracarbonyltitanium(0). Thermal ellipsoids are drawn with 35% probability boundaries, and hydrogen atoms are omitted for clarity. Selected interatomic distances (Å) and angles (deg): Ti–C(1) = 1.979 (6), Ti–C(2) = 2.009 (8), Ti–C(3) = 1.999 (5), Ti–N(1) = 2.378 (3), Ti–N(2) = 2.368 (4), C(1)–O(1) = 1.176 (7), C(2)–O(2) = 1.153 (10), C(3)–O(3) = 1.171 (6), C(1)–Ti–C(2) = 104.6 (3), C(1)–Ti–C(3) = 69.0 (2), C(2)–Ti–C(3) = 66.7 (2).

appear to have about the same donor ability to respective (tetracarbonyl)metal(0) units. By comparison, the tertiary amine products, **2** and **5**, have ν(CO) values closer to those of the corresponding $[(C_5H_5)M(CO)_4]^-$,[13] indicating that Me_3tacn is a somewhat weaker donor than tacn in these seven-coordinate complexes, perhaps for steric reasons. Interestingly, these vibrational data suggest that tacn is the strongest neutral donor ligand to zerovalent group 4 carbonyls presently known.

The molecular structure of **5** was determined by a single-crystal X-ray study and is shown in Figure 1, along with selected interatomic data. The metal–ligand coordination core is an unexceptional 4:3 piano stool, where the average Ti–C and C–O distances of 1.996 (6) and 1.167 (10) Å are in the range of corresponding values observed previously for the structurally related $[(C_5H_5)Ti(CO)_4]^-$: 1.994 (4) and 1.146 (6) Å, respectively.[13] A similar molecular structure has also been reported for $[t\text{-}BuSi(CH_2PMe_2)_3]Ti(CO)_4$.[15] As expected, the average Ti–N distance, 2.375 (4) Å, for this Ti(0) complex is longer than corresponding distances, 2.20–2.30 Å, recently reported for a series of Ti(III,IV) complexes containing Me_3tacn.[16] The coordinated Me_3tacn ligand in **5** has essentially the same interatomic distances and angles as those previously observed for other mononuclear complexes containing this ligand.[9,16,17]

In summary, labile phosphine carbonyls of zerovalent titanium, zirconium, and hafnium have been utilized as convenient synthetic equivalents of the corresponding unknown metal heptacarbonyls, $M(CO)_7$, in the synthesis of the first examples of amine complexes containing group 4 elements in their zero oxidation state. Extensions of this study are in progress.

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Supplementary Material Available: Crystallographic details for $[Me_3tacn]Ti(CO)_4$ including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (5 pages); listing of observed and calculated structure factors for $[Me_3tacn]Ti(CO)_4$ (4 pages). Ordering information is given on any current masthead page.

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(10) Satisfactory elemental analyses (C, H, N) have been obtained for compounds **1–5**.

(11) IR, ν(CO): (**1**) 1916 (m), 1769 (s) in DME; (**2**) 1923 (m), 1774 (s) in DME; (**3**) 1915 (m), 1774 (s) in DME; (**4**) 1916 (m), 1772 (s) in CH_3CN; (**5**) 1920 (m), 1776 (s) in CH_3CN, cm^{-1}.

(12) For example, for $[(C_5Me_5)Ti(CO)_4]^-$, ν(CO): 1914 (m), 1769 (s) cm^{-1} in DME. Kelsey, B. A.; Ellis, J. E. *J. Chem. Soc., Chem. Commun.* **1986**, 331.

(13) For example, for $[(C_5H_5)Ti(CO)_4]^-$, ν(CO): 1921 (m), 1777 (s) cm^{-1} in THF. Kelsey, B. A.; Ellis, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 1344.

(14) Dark red single crystals of **5** were obtained from CH_3CN/Et_2O at 0 °C. Crystal data: orthorhombic, *Pnma*, $a = 16.759$ (3) Å, $b = 11.769$ (3) Å, $c = 7.869$ (2) Å, $V = 1552.1$ (6) Å^3, $Z = 4$, $D(\text{calcd}) = 1.417$ g cm^{-3}, μ(Mo Kα) = 11.62 cm^{-1}, $T = 298$ K; crystal dimensions, 0.51 × 0.48 × 0.39 mm^3. The intensities of 1941 reflections were measured ($4° \leq 2\theta \leq 55°$) on a Nicolet R3m diffractometer using Mo Kα radiation. The structure was solved by direct methods, and all non-hydrogen atoms were refined anisotropically (full matrix least squares). Hydrogen atoms were included as idealized isotropic contributions. For 1748 independent reflections, 1271 were observed ($5\sigma F$). At convergence $R(F) = 0.0611$ and $R(wF) = 0.0669$. SHELXTL software, Nicolet. Madison, WI. Further data are available as supplementary material.

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Total Synthesis of Lactacystin

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Lactacystin (**1**) is a novel microbial product which was identified by Ōmura et al. after screening several thousand culture samples for the capacity to induce differentiation in a neuroblastoma cell line.[1,2] The great current interest in neurotrophic proteins, e.g., nerve growth factor, as therapeutic agents and neuroscience research tools[3-6] and the scarcity of **1** encouraged us to undertake the synthesis which is described herein. The availability of synthetic **1** should help to establish whether it is the first non-protein to possess useful neurotrophic activity.

N-Benzylserine methyl ester[7a] was transformed into the *cis*-oxazolidine derivative **2**,[7b] whose structure was confirmed by a ^{1}H NMR NOE study, together with the C(2) diastereomer (ratio 9:1); see Scheme I. The 9:1 mixture was converted via the lithium enolate–lithium bromide complex with isobutyraldehyde into one principal aldol product (**3**), which was obtained in 77% yield and >98% diastereomeric purity by trituration of the crude aldol

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