poly(phenylcarbonate)) often show useful combinations of high thermal stability and strength but may be difficult to form and process.[15] Polymers having all-carbon backbones usually have high hydrolytic stability. The structures of the carlons can be tailored to impart both stability and processability. They are easily formed from readily available precursors and their residual functionality provides the basis for post-synthetic modification and for cross-linking. At present, the reactions described here provide linear oligomers having molecular weights most suitable for use as prepolymers in thermosets and related materials, and a significant improvement in per-step yield will be required to achieve high mw linear polymers. Efforts to achieve this improvement are in progress.

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Insertion Reactions of Chromium–Carbene Complexes with Organic Nitriles and a Diastereoselective Alkylation of a Resulting Imino–Carbene Complex

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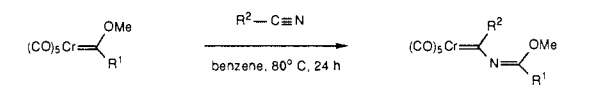
The reaction of Fischer carbene complexes of the group 6 metals with acetylenes has become a reaction of demonstrated importance in synthetic organic chemistry.[2] The reaction of the phenyl complex **1** with alkynes produces naphthol complexes where the newly formed benzene ring incorporates the acetylene in the C-2 and C-3 positions of the naphthalene ring. The study of the reactions of heteroatom-stabilized carbene complexes with other triply bonded functional groups has been limited to the carbon–nitrogen triple bond of cyanamides,[3] cyanates,[4] and thiocyanates[4] which react rapidly to give insertion products of the type **3** rather than heteroaromatic products as might be anticipated from their reaction with acetylenes. Nonetheless, the imino complexes **3** are potentially useful reagents for organic synthesis although at the present time the range of complexes that are available is rather limited. We wish to report that organonitriles undergo facile insertion into the metal–carbon bond of heteroatom-stabilized Fischer carbene complexes, the first observation of a reversible insertion of a nitrile, and the first stereoselective reaction of an imino complex in which the stereodifferentiation is a consequence

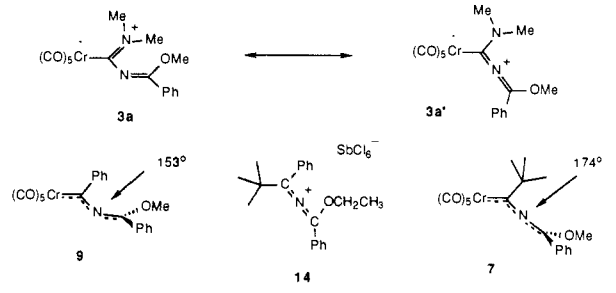
Table I. Insertions of Organonitriles into Complexes **1** and **12**[a]



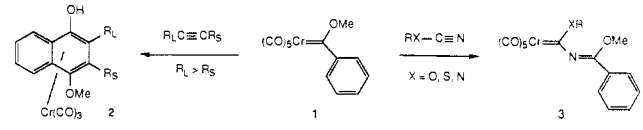
R¹	R²	insertion product	% yield	% recov of starting complex	tot mass balance
		Starting Complex **1**			
Ph	Me	**4**	36 (54[b])	38	74
	n-Pr	**5**	51	31	82
	i-Pr	**6**	73	9	82
	t-Bu	**7**	31 (53[c])	34	65
	CH_2Ph	**8**	72	7	79
	Ph	**9**	85	0	85
	p-$MeOC_6H_4$	**10**	93[d]	0	93
	2-furyl	**11**	92	0	92
		Starting Complex **12**			
Me	Ph	**13**	68[e]	–	–

[a] Unless otherwise specified all reactions were carried out at 0.13 M in **1** or **12** in benzene with 14 equiv of nitrile at 80 °C for 24 h under an argon atmosphere. [b] 10 equiv of nitrile, 5 days. [c] 5 equiv of nitrile, 5 days. [d] 2.4 equiv of nitrile, 4 days. [e] 3 equiv of nitrile, 38 h.

Scheme I



of a chiral center arising from the allenic nature of the C–N–C linkage in these complexes.



A variety of imino complexes can be made in moderate to excellent yields from both aliphatic and aryl nitriles. The typical procedure indicated in Table I involves heating the (pentacarbonyl)chromium–carbene complex with excess nitrile in benzene at 80 °C for 24 h. In the case of acetonitrile and 2,2-dimethylpropiononitrile slightly better yields can be obtained with longer reactions times. Successful insertion reactions include those with aryl- and alkyl-substituted carbene complexes. The mass balance of these reactions is quite good, and in none of these reactions could we isolate and identify any compound derived from an annulation reaction of the type observed with acetylenes. Imino complexes bearing a carbon substituent on the carbene carbon (R^2) have been reported as products in a few unrelated reactions,[7] but the insertion of organic nitriles into heteroatom-stabilized complexes has not been previously reported. A recent account[8] describes the insertion reactions of organonitriles into a nonstabilized complex (diphenyl), and it has been reported that the reaction of this same complex takes a different course with silyl nitriles.[9b]

The solid-state structures of a few complexes derived from the insertions of cyanamides,[3a,c] cyanates,[7a] and thiocyanates[4] have

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(1) (a) Eli Lilly Young Scholar, 1986–1987. (b) NIH predoctoral trainee, 1982–1986.

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(10) See supplementary material.

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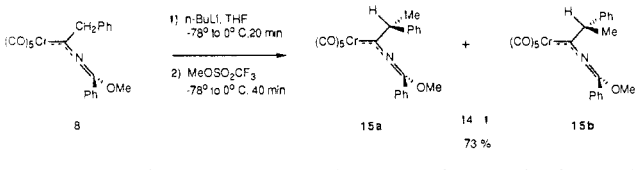
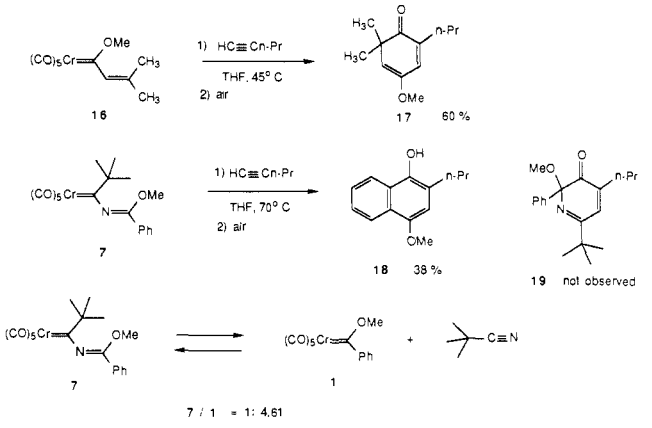
been determined. The first was that for the imino complex **3a** derived from the reaction of complex **1** with dimethylcyanamide.[3a,c] The C–N–C bond angle for the imino nitrogen is of interest because it should reflect on the relative importance of the two different nitrogen substituents in stabilizing the carbene carbon. The observed angle of 134° suggests that the resonance structure **3a** is more important than **3a'** and that the amino nitrogen carries the burden of stabilizing the carbene carbon. The imino nitrogen would be expected to be much more greatly involved in the stabilization of complexes where the amino nitrogen of **3a** is replaced by a group with a lesser propensity for electron donation via resonance. This expectation was realized in the structures of complexes of the type **3** for X = O,[7a] and X = S,[4] where the C–N–C angle of the imino ligand is widened with respect to that for **3a**. The structures of **7** and **9** reveal that this is also the case for imino complexes bearing a carbon substituent. In the benzonitrile insertion product **9** the angle has widened to 153°, and in the structure of the 2,2-dimethylpropiononitrile insertion product **7** the C–N–C linkage is nearly linear at 174°.[11] Examination of intramolecular contacts for the *tert*-butyl imino complex **7** suggests that the nearly linear C–N–C bond angle is not being determined by any intramolecular steric effects. A rehybridization of the nitrogen in complex **7** would be expected in order to accommodate the near linearity of the C–N–C angle, and further, as revealed by the X-ray structure of **7**, there is an axis of chirality about the C–N–C linkage. This is apparently the case for the 2-azaallenyl cation **14** in which carbon–nitrogen bond rotation is slow enough that the methylene protons of the ethoxy group are diastereotopic, but coalesce slightly above room temperature in the 1H NMR.[12]

The next question of concern in establishing the synthetic potential of imino–carbene complexes is whether there is sufficient hinderance to rotation about the C–N–C bonds such that the axis of chirality can serve to induce asymmetry in the reactions of these complexes. We were encouraged in this regard by the fact that the methylene protons of the phenylacetonitrile insertion product **8** are diastereotopic on the ^{1}H NMR time scale. More convincingly, when the methylene group of complex **8** is deprotonated with *n*-butyllithium and methylated, a mixture of separable diastereomers is obtained in 73% yield.[5,6] The kinetic ratio obtained from the crude ^{1}H NMR is 14:1 and the isolated ratio of the diastereomers from preparative TLC is 9:1. Each diastereomer will slowly epimerize at room temperature in a chloroform solution and a thermodynamic mixture of 1:1.65 in favor of **15b** can be obtained after 10 days starting from either diastereomer.[13]



The major kinetic isomer **15a** does not epimerize in the solid state and the structure of this diastereomer was determined by an X-ray diffraction analysis.[10] The C–N–C bond angle in this complex is 165.6° which is intermediate between the angles for the complexes **7** and **9**. The dihedral angle about the C–N–C azaallenyl linkage is nearly perpendicular at 94.1 (3)°, which is the angle between the two planes defined by CR(1)–C(12)–C(23) and by O(15)–C(14)–C(17). The reason for the kinetic diastereoselection in favor of the particular stereoisomer **15a** is not readily evident at this time. In this alkylation reaction the two key issues for consideration are the preferred conformation about the $C_{carbene}$–$C_{benzylic}$ bond of the anion generated from **8** and the direction of approach of the electrophile. Upon first consideration the stereoselectivity of the reaction can be accounted for by the

Scheme II



preferred approach of the electrophile *syn* to the methoxy group on the basis of the steric differences between methoxyl and phenyl, if it is assumed that the preferred conformation of the anion is that in which the H–C–Ph plane is parallel with the Cr–C–N plane and with the remaining hydrogen of the methylene *syn* to the metal. This consideration is weakened not only by the distances between the benzylic carbon and the methoxyl and phenyl groups but also by the expectation that the geometry of the azaallenyl substituent of the carbene carbon may be dramatically affected by the delocalization of the electrons of the benzylic carbanion generated from **8** onto the metal center. Further information concerning the source of the stereoselectivity in the alkylation of **8** may have to await structural data for the anion generated from **8**. Although the source of the steroselectivity of the alkylation reaction cannnot be determined with the present data, the fact that specific stereoisomers of imino–carbene complexes can be generated and isolated, by virtue of the axis of chirality about the azaallenyl linkage, may prove to be significant in the development of the applications of these complexes to synthetic organic chemistry.

One reaction of imino–carbene complexes that can be anticipated is the reaction with alkynes to produce 5-azacyclohexa-2,4-dienones. The imino complex **7** for example, can be considered to be a 2-aza analogue of an alkenyl–carbene complex. It has previously been shown that β,β-disubstituted alkenyl complexes of the type **16** will undergo a cyclohexadienone annulation with alkynes and, for the particular case shown with 1-pentyne, give rise to the cyclohexa-2,4-dienone **17**.[14] The reaction of the imino complex **7** with 1-pentyne gave, quite unexpectedly, the naphthol **18** as the sole product that was mobile on silica gel and none of the anticipated product **19** could be detected. This result suggests that the insertion of 2,2-dimethylpropiononitrile into the chromium–carbon bond of the phenyl–carbene complex **1** is reversible since the naphthol **18** is a known product from the reaction of complex **1** with 1-pentyne.[15] It was established that the imino complex **7** is in equilibrium with 2,2-dimethylpropiononitrile and the phenyl complex **1** and that the equilibrium favors the phenyl complex **1** by 4.61:1 at 80 °C. This equilibrium value can be reached from either side in 36 h in benzene and was determined in each case by the isolation of **1** and **7** where the total mass recovery of complex **1** and **7** after equilibrium is between 85 and 87% for each experiment. This is the first time that the insertion of a nitrile into the metal–carbon bond of a carbene complex has been shown to be reversible. Preliminary studies reveal that the insertion is reversible for other imino complexes as well.

These initial studies have prompted current investigations of several aspects of the chemistry of imino–carbene complexes. These include the effect of the nature of the organonitrile on the insertion/deinsertion equilibrium. With regard to their potential

(11) This effect has been observed in the structure of a cyanate insertion type product (ref 7a).
(12) Kupfer, R.; Wurthwein, E. U.; Nagel, M.; Allmann, R. *Chem. Ber.* **1985**, *118*, 643.
(13) The mass recovery of the 1:1.65 mixture of **15a** and **15b** after 10 days is 76% starting from **15b**.
(14) Tang, P. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1984**, *106*, 1132.
(15) (a) Chan, K. S.; Peterson, G. A.; Branvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9. (b) Dotz, K. H.; Muhlemeier, U.; Schubert, U.; Orama, O. *J. Organomet. Chem.* **1983**, *247*, 187.

for applications in organic synthesis, solutions are being sought to the unfavorable deinsertions of these complexes relative to their annulations with acetylenes, and also based on the successful stereoselective akylation of the benzyl complex **8**, the possibility of asymmetric induction in reactions at the carbon–nitrogen bond of the imino ligand are being examined.

Acknowledgment. This work was supported by the National Institutes of Health (PHS-GM 33589). The National Institutes of Health has provided a predoctoral training grant for D.C.Y. (GM 07151). The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA-14599).

Supplementary Material Available: Spectral and physical data for all new compounds and X-ray crystallographic data for compounds **7**, **9**, and **15a** (25 pages). Ordering information is given on any current masthead page.

^{11}B Nuclear Magnetic Resonance Studies of the Structure of the Transition-State Analogue Phenylboronic Acid Bound to Chymotrypsin[1]

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Several solution kinetic studies have suggested that the serine protease class of enzymes is subject to reversible inhibition by boric acid and boronic acid derivatives.[2] X-ray crystallographic studies of boronic acids attached to α-chymotrypsin (α-CHT)[3] and subtilisin[4] demonstrated that the boron atom is in a tetrahedral environment covalently bonded to the active center serine. Raman spectroscopic studies further supported this finding in the solid state.[5]

We report ^{11}B NMR studies on phenylboronic acid (PBA) in the absence and presence of α-CHT at pH 7.2, 22 °C, and our ability to deduce the solution structure around the boron atom when enzyme-bound. Under conditions of fast exchange of the boron nucleus between the bound and free states, both the chemical shift and the relaxation rates of the nucleus can be deduced from a "titration" of the boron resonance with limiting amounts of α-chymotrypsin. For ^{11}B (I, the nuclear spin is 3/2) in the limit of extreme narrowing ($\omega_I^2\tau_c^2 \ll 1$),[6] the quadrupole relaxation rate ($1/T_q$) is given by

$$R_q = 1/T_q = (2\pi^2/5)(1 + \eta^2/3)(e^2qQ/h)^2\tau_c \qquad (1)$$

where (e^2qQ/h) is the quadrupole coupling constant in Hz, τ_c is the correlation time, and η is the asymmetry parameter—a measure of the deviation of the electric field gradient from axial symmetry.

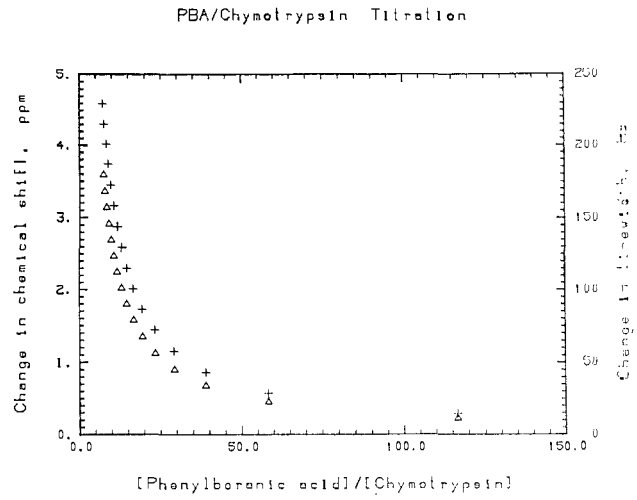

Figure 1. Dependence of the ^{11}B chemical shift (Δ) and line width (+) on the molar ratio of phenylboronic acid (fixed at 2.9 mM) to α-chymotrypsin (0.025–0.4 mM, 3× recrystallized from Worthington) at pH 7.2, 22 °C, in 0.05 M total phosphate buffer. Measurements were performed on an IBM WP-200 SY instrument operating at 64.2 MHz for ^{11}B. Chemical shifts are reported relative to external trimethylborate; there is an upfield chemical shift of the ^{11}B resonance on addition of α-chymotrypsin. The line width was corrected for viscosity induced effects by subtraction of the line width of ^{11}B in 2.9 mM phenylboronic acid but in the presence of the same concentration of diisopropylphosphoryl-α-chymotrypsin as used for native enzyme.

A comparison of the spin-lattice relaxation time (T_1) of 2.9 mM PBA (1.28 ms, measured by the inversion-recovery method) to the spin–spin relaxation time (T_2, 1.30 ms from the line width) demonstrates that the condition of extreme narrowing applies,[7] the principal relaxation mechanism is quadrupolar, and the contribution of field inhomogeneity to the line width is negligible. Addition of small, limiting amounts of α-CHT[8] broadened the boron resonance and shifted it upfield relative to free PBA. The chemical shift of the free PBA is 13.42 ppm relative to external $B(OMe)_3$. The "pK_a" of PBA is 8.85 for the midpoint of the trigonal-to-tetrahedral transition, hence at pH 7.2 there is a large preponderance of trigonal species. As a control, diisopropylphosphoryl-α-CHT[9] was added to PBA producing smaller broadening than did active enzyme and no change in chemical shift. This control served to subtract out the effect of viscosity induced broadening and the effects, if any, of nonspecific binding. The fast exchange condition was confirmed by a study indicating that the excess line width, after correction for the line width observed in the control, decreases with increasing temperature. From the dependence of the chemical shift and line width on α-CHT concentration, the chemical shift of the enzyme bound ^{11}B (−12.9 ± 0.2 ppm) and the $K_{dissociation}$ [(2.6 ± 0.3) × 10^{-5} M] could be calculated,[10] as well as the line width (1932 ± 14 Hz) of the resonance of the bound ^{11}B atom (Figure 1).

In the presence of 2.91 mM PBA and 0.2 mM α-CHT, a $1/T_1$ of 2160 s^{-1} and $1/T_2$ of 6068 s^{-1} were determined for the enzyme-bound ^{11}B atom, indicating nonextreme narrowing conditions.[11] The ratio R_2/R_1 is 2.81 and implies that $\omega_I\tau_c < 1.5$, thus

(1) Supported by the Rutgers University Busch Fund and the Rutgers Research Council. Presented in part at the 1987 meeting of the American Society of Biological Chemists, Philadelpha. Abbreviations: α-CHT, α-chymotrypsin; PBA, phenylboronic acid; T_1, spin–lattice relaxation time; T_2, spin–spin relaxation time; R_1, spin–lattice relaxation rate; R_2, spin–spin relaxation rate.

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(7) *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983; Vol. 1, pp 105–106.

(8) Incremental additions of 0.025–0.4 mM enzyme.

(9) Preparation described by Jordan et al. (Jordan, F.; Polgar, L.; Tous, G. *Biochemistry* **1985**, *24*, 7711–7717).

(10) Under fast exchange conditions and assuming a 1:1 complex between the PBA and α-CHT, $x_{obsd} = (1 - n)x_{free} + nx_{bound}$ where x is the observed line width or chemical shift or relaxation rate, n is the mole fraction of bound species, and x_{free} and x_{bound} are the quantities for uncomplexed and complexed material. A standard solution is $PBA_0 = (\Delta X_m/\Delta X)[\alpha\text{-CHT}]_0 - K_d$ (Dwek, R. A. *NMR in Biochemistry*; Clarendon Press: NY, 1983; pp 136–138), where PBA_0 and $[\alpha\text{-CHT}]_0$ are the initial total concentrations of PBA and enzyme, ΔX_m is the difference between fully bound and free inhibitor property, and ΔX is the difference between observed and totally free property.

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