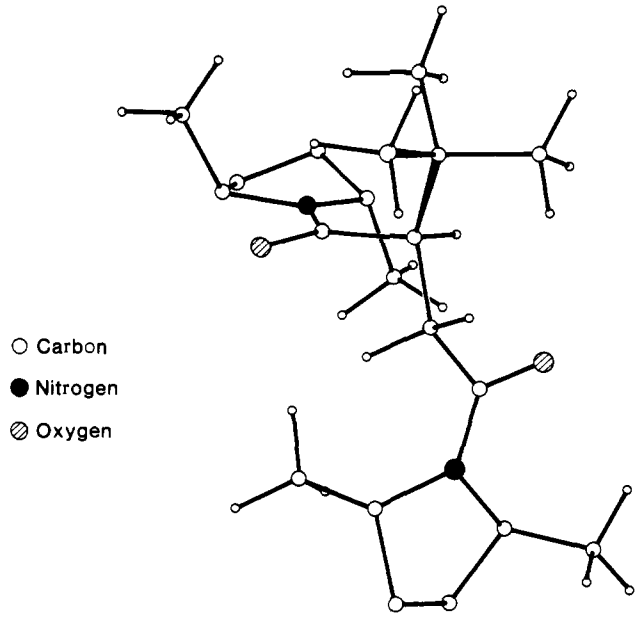

Figure 1. Solid-state conformation of **6a** from single-crystal X-ray analysis.

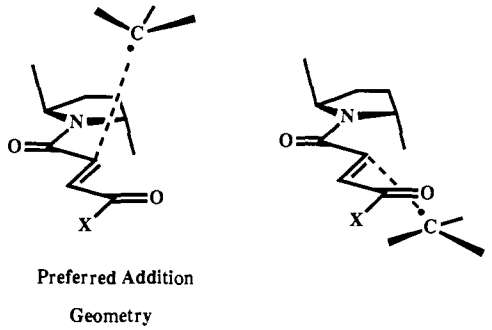

Figure 2. Model for radical addition to chiral alkenes.

The main isomer **6a** gave crystals (from hexane, mp = 91-92 °C), on which a single-crystal X-ray analysis was carried out.[16] The structure for isomer **6a** is presented in Figure 1, and examination of the structure indicates that the new stereogenic center has been formed with the *R* configuration. Because of the different priorities of the *n*-butyl and *tert*-butyl groups in structures **4** and **6**, the major adduct formed in the radical addition to both **1** and **2** is the result of addition from the analogous face of both alkenes (see structures **5a** and **6a**) even though the configuration of the newly formed centers is different. The ratio of products **6a**:**6b** is 16:1 at 110 °C, and at 20 °C, the ratio is **6a**:**6b** = 40:1.

The diastereoselectivity observed for radical addition to **1** and **2** can be understood by the model shown in Figure 2. The dimethylpyrrolidine auxiliary fixes the dimethyl groups of the auxiliary relative to the alkene faces by virtue of the favored conformation as shown about the carbonyl C-C_α bond and the C_2 axis of the pyrrolidine group. In fact, molecular mechanics calculations suggest that the conformation about the carbonyl C-C_α bond shown in Figure 2 is favored by over 3 kcal/mol over the other planar conformation possible in which the carbonyl oxygen and amide nitrogen have exchanged positions. The nucleophilic radical has a required approach to the olefin on a vector over the pyrrolidine, and this sterically protects one face of the olefin from addition. In support of the model, we note that addition of hexyl radical to the end of **1** remote from the amide occurs without significant diastereoselectivity. That steric effects are important in the selectivity observed is also suggested by the fact that the bulky *tert*-butyl radical gives higher selectivities than the smaller *n*-hexyl radical.

The observation of significant selectivities in radical additions to unsaturated amides with C_2 symmetry auxiliaries opens the possibility for the use of free radicals in the construction of stereogenic centers with defined configuration. The success achieved by the use of sterically hindered radicals in these additions is noteworthy since construction of structures of this type by carbanionic alkylation procedures would be particularly difficult.

Acknowledgment. N.A.P. thanks the NIH (HL17921) and NSF for generous financial support.

Supplementary Material Available: Tables of bond lengths and angles (19 pages); tables of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

(16) Space group $P2_1$; a = 3.678 (10) Å; b = 17.575 (10) Å; c = 6.253 (5) Å; β = 106.78 (5)°; V = 1018.1 Å^3; Z = 2; ρ_{calcd} = 1.098 g cm^{-3}; μ(Cu Kα) = 4.77 cm^{-1}. Tables of parameters, bond lengths and angles, and observed and calculated structure factors are available from the Cambridge Crystallographic Data File and as supplementary material.

Oxidation of Methylhydrazine at a Metal Center. Stereoselective Synthesis of *cis*-Methyldiazene, NH=N(CH$_3$)

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We have recently reported the preparation and some aspects of the fundamental reaction chemistry of monosubstituted *cis*-aryldiazenes, *cis*-NH=NR (R = aryl group).[1,2] These are simple but significant molecules because they are often invoked as reactive intermediates in a wide range of organic transformations (that usually involve loss of dinitrogen)[3,4] and are thought to be ubiquitous reactive metabolites responsible (as alkylating agents) for the carcinogenic activity often found in molecules containing the diazo functionality.[5]

Thus far our synthetic approach, entailing the displacement of *cis*-NH=NR from [*trans*,*trans*-W(NH=NR)(CO)$_2$(NO)(PPh$_3$)$_2$$^+$][PF$_6^-$] by bromide ions, has been limited to the preparation of *aryl*diazenes because the key tungsten complex is prepared by a 1,1-insertion reaction of an aryldiazonium cation into the W-H bond of *trans*,*trans*-W(H)(CO)$_2$(NO)(PPh$_3$)$_2$ (**1**),[6] and simple non-aryl diazonium salts (RN$_2$$^+$, R = H, alkyl) are unstable. Herein we report that a route to *cis*-methyldiazene has been developed, involving selective oxidation of methylhydrazine coordinated to a tungsten complex, that provides the first synthetic entry to cis-monosubstituted diazenes that contain an alkyl group.

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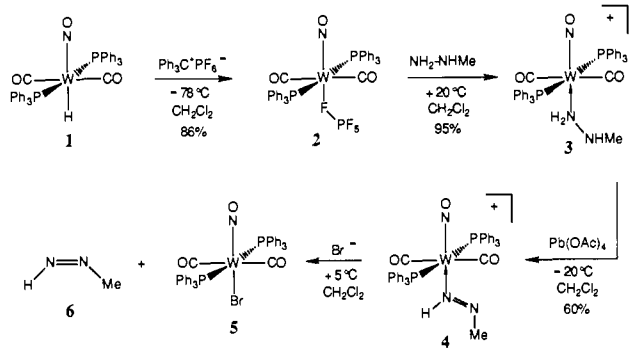
Scheme I



Reaction of **1** with $[Ph_3C^+][PF_6^-]$ (−78 °C, CH_2Cl_2) gives triphenylmethane and yellow crystals of *trans,trans*-$W(\eta^1\text{-}FPF_5)(CO)_2(NO)(PPh_3)_2$ (**2**) in high yield (the synthetic route is shown in Scheme I).[7] **2** is spectroscopically similar to the known neutral complexes $W(X)(CO)_2(NO)(PPh_3)_2$ (X = unidentate anion),[6] and the weakly coordinated hexafluorophosphato ligand[8] of **2** is cleanly displaced by methylhydrazine (20 °C, CH_2Cl_2) to give a yellow salt, $[trans,trans\text{-}W(NH_2NHMe)(CO)_2(NO)(PPh_3)_2^+][PF_6^-]$ (**3**), almost quantitatively. Oxidations of coordinated hydrazines to give corresponding diazene ligands (NR=NR; R = H, alkyl, aryl) have been reported, with steric factors apparently determining whether the oxidation proceeds to afford *cis*- or *trans*-diazene geometries.[9] We find that treatment of CH_2Cl_2 solutions of **3** with $Pb(OAc)_4$ at −20 °C results in selective oxidation of the methylhydrazine ligand to give yellow-orange $[trans,trans\text{-}W(NH{=}NMe)(CO)_2(NO)(PPh_3)_2^+][PF_6^-]$ (**4**) in good yield. Other reagents commonly used to oxidize hydrazines, such as HgO, H_2O_2, and MnO_2, were ineffectual in carrying out the **3** → **4** transformation. ^1H and ^{31}P NMR data clearly indicate that the methyldiazene ligand of **4** is formed as a single geometrical isomer, assigned as *cis*-NH=NMe on the basis of a 5% enhancement of the N*H* resonance (δ 12.71, br s, CD_2Cl_2) on irradiation of the NCH_3 signal (δ 2.62, d, $^4J_{HH}$ = 1.5 Hz) in a ^1H NMR NOE difference spectrum, and by a single-crystal X-ray diffraction study of **4**.[10,11]

The solid-state molecular structure of **4** is an interesting one; a perspective view of the complex cation and salient metrical parameters for the methyldiazene ligand are shown in Figure 1. The ligands of **4** are arranged in a pseudooctahedral fashion about the W atom. Steric constraints imposed by the bulky octahedral metal center are probably responsible for the observed *cis*-NH=NMe geometry as this allows for an *E* disposition of W with respect to the diazenyl methyl group. **4** is the first structurally characterized monosubstituted alkyldiazene complex, and it differs in two key ways from structurally well established NH=NR (R = H or aryl)[12] complexes: (i) the N(2)—N(3) distance of 1.330 (16) Å is significantly longer than N—N distances found in coordinated NH=NH and NH=N—aryl ligands (usually ranging from ~1.22 to ~1.26 Å)[13] and (ii) the N(3)—C(1) distance of 1.336 (22) Å is shorter (by >0.1 Å) than that expected for a typical N—C single bond. The relatively large errors associated with these parameters and the lack of other monosubstituted alkyldiazene structures for comparison make a detailed analysis of these differences unwarranted at present. Nonetheless, it is noteworthy that, in the presence of a base catalyst such as DBU, **4** can be induced to undergo tautomerization to give the hydrazone complex $[W(NH_2N{=}CH_2)(CO)_2(NO)(PPh_3)_2^+]$;[14] thus **4**, with its long N—N and short N—C bonds, appears to manifest a structural basis for this facile isomerization.

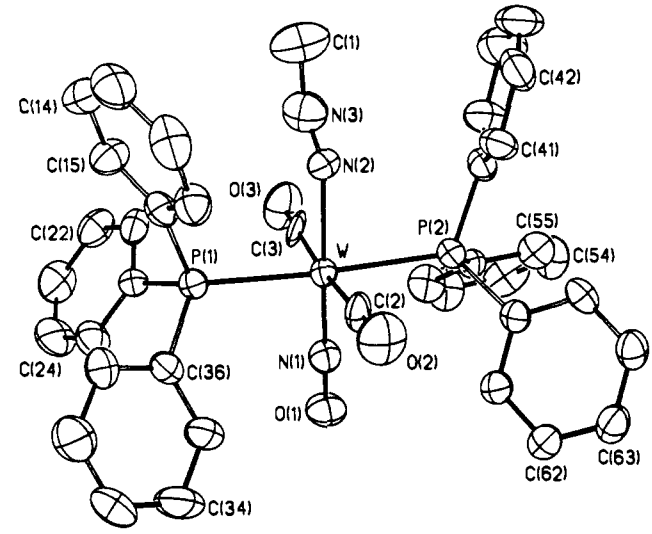


Figure 1. Molecular structure and atom numbering scheme for the cation of $4{\cdot}Me_2C{=}O{\cdot}Et_2O$. The hydrogen atoms have been omitted for clarity. Selected metrical parameters: W–N(2) = 2.215 (9) Å, N(2)–N(3) = 1.330 (16) Å, N(3)–C(1) = 1.336 (22) Å, W–N(2)–N(3) = 117.5 (9)°, N(2)–N(3)–C(1) = 118.5 (17)°.

Solutions of **4** (CD_2Cl_2, 5 °C, anaerobic conditions) react with $[n\text{-}Bu_4N^+][Br^-]$ to release the methyldiazene ligand, affording *trans,trans*-$W(Br)(CO)_2(NO)(PPh_3)_2$ (**5**)[6] (identified by IR and ^{31}P NMR) and free *cis*-NH=NMe (**6**) as shown in Scheme I.[7] The ^1H NMR spectrum of **6** exhibits resonances at δ 3.87 (d, $^4J_{HH}$ = 1.6 Hz, NH=NC*H*$_3$) and δ 15.2 (br, N*H*=NCH$_3$); the UV-vis spectrum of **6** shows a weak n → π^* absorption at λ_{max} = 3520 Å.[15] The stereochemistry of **6** was inferred from (i) the X-ray structure of **4** and (ii) the established stereoselectivity of analogous displacements of *cis*-NH=NR (R = aryl), but this route to **6** unfortunately does not allow for facile, definitive ^{15}N labeling. At 5 °C, **6** undergoes a slow reaction to give N_2 and CH_4, and we are presently probing the details of this decomposition.

In summary, *cis*-NH=NMe can be prepared stereoselectively at a tungsten center by oxidation of coordinated methylhydrazine and then displaced under mild conditions under which the free *cis*-NH=NMe molecule exhibits moderate stability. This provides the first synthetic route to the key cis isomers of monosubstituted alkyldiazenes and complements the existing synthetic methodology for preparing *cis*-NH=NR (R = aryl). We are currently exploring the general utility of this reaction sequence in preparing other *cis*-NH=NR from hydrazines.

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(13) The N–N distance in $[\mu\text{-}N_2H_2\{Ru(PPh_3)(dttd)\}_2]$ is 1.301 (14) Å. Sellmann, D.; Böhlen, E.; Waeber, M.; Huttner, G.; Zsolnai, L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 981.

(14) Hillhouse, G. L.; Smith, M. R., unpublished results.

(15) For *trans*-NH=NMe (CH_3CN solution): ^1H NMR δ 3.87 (d, J ~ 2 Hz), 15.6 (v br). UV-vis λ_{max} = 3620 Å. Tsuji, T.; Kosower, E. M. *J. Am. Chem. Soc.* **1971**, *93*, 1992.

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Supplementary Material Available: Experimental, spectroscopic, and analytical details and tables of atomic coordinates, bond angles and distances, anisotropic thermal parameters, and hydrogen-atom coordinates (10 pages); listing of observed and calculated structure factors (28 pages). Ordering information is given on any current masthead page.

Enantioselective Complexation of Simple Amides by a C_2 Host Molecule

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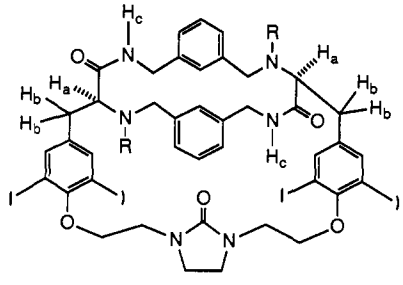
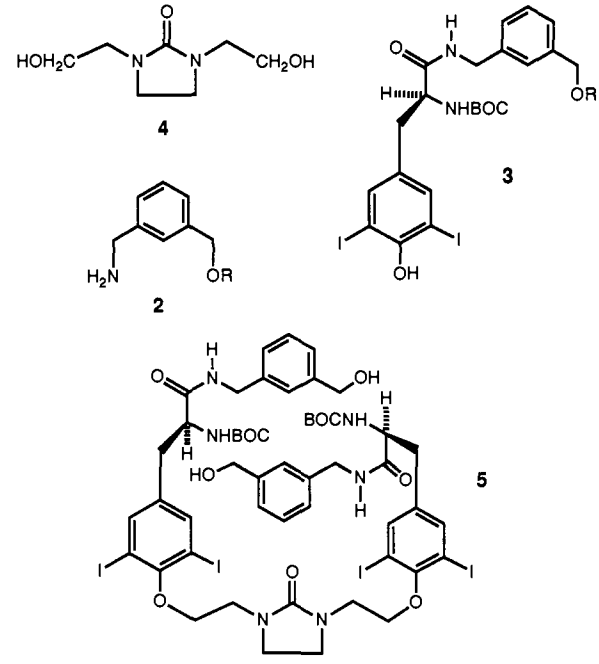
The creation of hydrogen bonds provides an effective driving force for forming molecular complexes in organic solvents.[1] When several hydrogen bonds can be made during complexation, substrates are often oriented within the binding site in geometries that maximize hydrogen bonding. When oriented binding in one geometry (or at most a few) can be achieved, there is potential for highly selective substrate binding. In this communication, we describe an enantiomerically pure, C_2 host molecule (**1**) that binds donor/acceptor guests by multiple hydrogen bonds. As we will show, **1** binds simple amides in benzene and distinguishes both energetically and spectrally between certain enantiomeric amides. This study describes one of the few synthetic hosts that show a measurable difference in its binding energies with enantiomeric neutral guests.[2]



1a R = H
1b R = CH_2Ph

Synthesis of **1** begins with L-BOC-diiodotyrosine. After condensation (DCC, HOBt, THF, 76%) with benzylic amine **2** (R = $SiPh_2tBu$) to give **3**, we used a double Mitsunobu reaction to join the phenolic peptide side chain to the diethanolurea **4**[3] and deprotected with Bu_4NF to provide **5** (39% yield). We then converted the benzylic alcohols to bromides (Ph_3P, CBr_4), removed the BOC protecting groups (TFA, CH_2Cl_2), and carried out an alkylative double macrocyclization (iPr_2NEt, CH_3CN, 2.5 mM, reflux) to give **1a** (23-47% yield from **5**). Treatment with excess BnBr gave **1b**.



X-ray structures of **1a** and **1b** were determined (see supplementary data).[4] As with a related meso host,[1h] **1** was found in two distinct conformations. These conformations differ most significantly by the orientation of their bridgehead hydrogens (H_a), which may point either away from (**1a**) or in toward (**1b**) the center of the host. Each conformation has an internal cavity which is occupied by CH_2Cl_2 in the crystal.

In addition to binding donor/acceptor heterocycles such as imidazole in organic solvents, **1b** (~2.0 mM) forms complexes with unhindered carboxylic amides in C_6D_6 (see Table I). Upon complexation, the NMR spectra of host and guest undergo major changes. For example, with *N*-methylacetamide the amide N-H's of both host and guest shift downfield by >1.0 ppm. The acetyl methyl undergoes a 0.5-ppm unfield shift, which is compatible with its location near a shielding face of an aromatic ring. We observed similar shifts in the other amide complexes examined. In the case of the *N*-methylacetamide complex, difference NOE studies further established proximity of the acetyl methyl with both the bridgehead hydrogens (H_a) and the amide N-H's (H_c) of the host. We also observed a strong intramolecular NOE between H_a and H_c. These NMR results are compatible with a structure for the complex that is related to the X-ray conformation of **1b** and found by molecular modeling to be as follows.

To locate low-energy structures of the **1b**/amide complex, we carried out local conformational searches using molecular dy-

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