The first site-specific mechanism involves the dissociation of HbO_2 prior to Fe^{III}·NTA binding:

$$HbO_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Hb + O_2$$

$$Hb + Fe^{III}\cdot NTA \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Hb\cdot Fe^{III}\cdot NTA$$

$$Hb\cdot Fe^{III}\cdot NTA \xrightarrow{k_3} MetHb\cdot Fe^{II}\cdot NTA$$

Assuming the deoxy forms of Hb (Hb and $Hb\cdot Fe^{III}$·NTA) are at steady-state conditions, the reaction rate is

$$d[MetHb]/dt = \frac{k_1k_2k_3[HbO_2][Fe^{III}\cdot NTA]}{(k_{-2} + k_3)(k_{-1}[O_2]) + k_2k_3[Fe^{III}\cdot NTA]}$$

with

$$k_{obsd} = \frac{k_1k_2k_3}{(k_{-2} + k_3)(k_{-1}[O_2]) + k_2k_3[Fe^{III}\cdot NTA]}$$

The second site-specific mechanism involves the binding of Fe^{III}·NTA to HbO_2 prior to the dissociation of O_2:

$$HbO_2 + Fe^{III}\cdot NTA \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} HbO_2\cdot Fe^{III}\cdot NTA$$

$$HbO_2\cdot Fe^{III}\cdot NTA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Hb\cdot Fe^{III}\cdot NTA + O_2$$

$$Hb\cdot Fe^{III}\cdot NTA \xrightarrow{k_3} MetHb\cdot Fe^{II}\cdot NTA$$

Assuming equilibrium conditions for the ternary complex ($HbO_2\cdot Fe^{III}$·NTA) formation and steady-state conditions for the deoxyHb species ($Hb\cdot Fe^{III}$·NTA), the mechanism gives the reaction rate

$$d[MetHb]/dt = \frac{k_1k_2k_3[HbO_2]_t[Fe^{III}\cdot NTA]}{(k_{-1}[O_2] + k_3)(k_{-2} + k_2[Fe^{III}\cdot NTA])}$$

where

$$[HbO_2]_t = [HbO_2] + [HbO_2\cdot Fe^{III}\cdot NTA]$$

$$k_{obsd} = \frac{k_1k_2k_3}{(k_{-1}[O_2] + k_3)(k_{-2} + k_2[Fe^{III}\cdot NTA])}$$

A third possible mechanism of electron transfer involves a simple outer-sphere process with no metal binding to the protein:

$$HbO_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Hb + O_2$$

$$Hb + Fe^{III}\cdot NTA \xrightarrow{k_3} MetHb + Fe^{II}\cdot NTA$$

Again, assuming steady-state conditions for deoxyHb, the rate of MetHb formation is

$$d[MetHb]/dt = \frac{k_1k_3[HbO_2][Fe^{III}\cdot NTA]}{k_{-1}[O_2] + k_3[Fe^{III}\cdot NTA]}$$

with

$$k_{obsd} = \frac{k_1k_3}{k_{-1}[O_2] + k_3[Fe^{III}\cdot NTA]}$$

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Kinetics and Mechanisms of Metal Reduction by Hemoglobin. 2. Reduction of Copper(II) Complexes

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The kinetics of the reduction of Cu(II) complexes by hemoglobin (Hb) are consistent with two mechanisms: (1) a simple outer-sphere mechanism in which electron transfer occurs over the heme edge and (2) a site-specific mechanism requiring the formation of a metal–chelate–protein ternary complex prior to electron transfer. Both mechanisms are operative in Cu(II) reduction by the β subunits. The site-specific mechanism involves metal binding to Cys β-93. The α subunits reduce Cu(II) strictly through the simple outer-sphere mechanism. The extent of Cu(II) reduction by the α subunits is a function of the π overlap of the metal–chelate with the porphyrin ring. Copper(II)–bis(bathocuproine), with a favorable redox potential and orbital overlap, is reduced by both the α and β subunits. In contrast, aquocopper(II) and copper(II)–nitrilotriacetate (NTA) reduction is limited to the β subunits. The initial rate of Fe^{III}·NTA reduction by hemoglobin is enhanced by 50% upon addition of aquocopper(II). The K_m value for Fe^{III}·NTA decreases from 1.5 to 0.5 mM. The mechanism for this enhancement involves Cu(I) serving as an electron mediator for Fe(III) reduction.

The kinetics and mechanisms of Fe(III) and Cu(II) reduction by myoglobin (Mb),[1] hemoglobin (Hb),[18] and cytochrome b_5[2] have been recently reported by our laboratory to involve two outer-sphere mechanisms: (1) a site-specific mechanism that requires binding of the metal to the protein prior to electron transfer and (2) a simple outer-sphere mechanism in which electron transfer occurs over the exposed heme edge. The rate and mechanism of reduction are determined by the reduction potential and stability constant of the protein–metal–chelate ternary complex. The reduction of Fe(III) chelates by Mb and cytochrome b_5 occurs strictly through the simple outer-sphere mechanism. We have demonstrated that Hb reduces Fe(III) complexes through both mechanisms depending upon the stability constant and the nature of the electron-transfer orbitals of the metal–chelate. The reduction of Cu(II) complexes by Mb and cytochrome b_5 involves the site-specific mechanism. For Mb, histidines are involved at the binding site.

The outer-sphere oxidation of Hb by Cu(II) has been described by Rifkind et al.[3,4] to involve Cys β-93 through a site-specific mechanism. This residue is not directly involved in the Fe(III) binding site. In contrast to our findings with Fe(III), Rifkind found that only the β subunits are redox-active with Cu(II); oxidation of only half of the total hemes was observed. Also,

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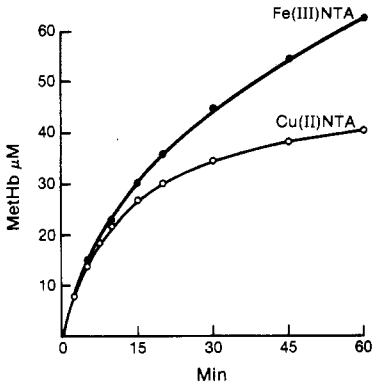

Figure 1. Time course of Cu^{II}·NTA and Fe^{III}·NTA reduction. Concentrations were 100 μM heme and 500 μM Cu^{II}·NTA or Fe^{III}·NTA in HEPES buffer, pH 7.0, at 25 °C.

Cu(II) precipitated Hb at neutral pH when Cu(II):heme molar ratios exceed 1:2. The instability of Hb at higher Cu(II) concentrations was attributed to the metal binding to the α chain, which denatured the protein. In Rifkind's studies, aquocopper(II) was used exclusively.

Copper deficiency causes anemia. However, the role of copper in iron metabolism remains unclear. Copper is not essential for the mucosal uptake of dietary iron; however, copper facilitates the incorporation of iron into protoporphyrin IX.[5] This interaction has been attributed to the activity of ceruloplasmin, a copper metalloenzyme that facilitates the oxidation of Fe(II).[6] This theory has been questioned due to the rapid aerobic oxidation of Fe(II) in vitro and the lack of anemia associated with Wilson's disease, where ceruloplasmin levels are low.[7] We propose that the interaction between the metals may be a function of the ability of copper to enhance Fe(III) reduction by heme proteins. This investigation describes the reduction of Cu(II) by Hb and the factors that influence the rate and mechanism of reaction.

Materials and Methods

Reagents. Hb was isolated from fresh human red cells as previously described.[18] All other reagents were purchased from Sigma. HEPES (*N*-(2-hydroxyethyl)piperazine-*N'*-ethanesulfonic acid) buffer contained 20 mM NaHEPES and 140 mM NaCl, and the pH was adjusted to 7.0 with solid $NaHCO_3$.

Metal–chelate solutions [Fe^{III}·NTA and Cu(II) complexes with NTA, EDTA, cit (citrate), ATP, His, phen (1,10-phenanthroline), and bath (bathocuproine)] were prepared as previously described.[18] Cu^{II}·ATP was prepared immediately prior to the experiment and kept on ice to minimize hydrolysis.

Measurements. A typical test solution contained 100 μM heme, 100 or 500 μM metal–chelate, and 2 mM bpy (2,2'-bipyridine) in HEPES buffer, pH 7.0. The reaction was carried out in a temperature-controlled shaking water bath or spectrophotometer at 25 ± 0.5 or 37 ± 0.5 °C. The reaction was monitored by the formation of Fe^{II}·3bpy or MetHb as previously described.[18] All spectrophotometric measurements were performed on a Hitachi 110A dual-beam UV–vis spectrophotometer.

The initial rates of Fe^{II}·3bpy formation were determined at Fe^{III}·NTA concentrations ranging from 100 μM to 1 mM in the presence and absence of 100 μM aquocopper(II) at 37 °C. Fe^{II}·3bpy concentration was determined at 30, 60, 90, 120, 180, 240, and 300 s. The plot of A_{520} vs time was linear over the initial 120 s. The initial rate (velocity) of Fe^{III}·NTA reduction is reported in μM/min.

Results

Cu^{II}·NTA Reduction by Hb. Hb was denatured after 30-min incubation with 500 μM Cu^{II}·NTA at 37 °C. Precipitation was avoided by decreasing the temperature to 25 °C or lowering the Cu(II):heme ratio to 1:1, i.e., 100 μM heme and 100 μM Cu^{II}·NTA. At 25 °C, the initial rates of Cu^{II}·NTA and Fe^{III}·NTA reduction are similar, although Hb oxidation by Cu^{II}·NTA is limited to only 50% of the hemes (Figure 1). We have reported[8]

Table I. Redox Potentials and Stability Constants of Cu(II) Complexes

chelator (Cu:chelator)	redox potential $E°$, V	ref	stability constant log K	ref
neocuproine[a] (1:2)	+0.59	9	11.0	12
H_2O	+0.17	9		
phen (1:2)	+0.17	10	15.8	12
His (1:2)			18.1	12
EDTA (1:1)	+0.13	11	18.7	12
NTA (1:1)			12.9	12
ATP (1:2)			6.1	12
cit (1:2)			5.9	12

[a] Bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) is structurally similar to neocuproine (2,9-dimethyl-1,10-phenanthroline). The redox potential and stability constant of Cu^{II}·2bath are assumed to be similar to those of Cu^{II}·2neocuproine.

Table II. Extent of Heme Oxidation of Cu(II) Chelates[a]

chelator (Cu:chelator)	Cu(II) concn, μM	% MetHb	chelator (Cu:chelator)	Cu(II) concn, μM	% MetHb
bath (1:2)	250	100	phen (1:2)	400	79
H_2O	200	54	His (1:2)	500	64
cit (1:2)	500	59	NTA (1:1)	500	46
ATP (1:10)	200	61			

[a] The maximum oxidation of Hb (% MetHb) by various Cu(II) chelates was determined at the specified Cu(II) concentrations, which were the maximum possible without precipitation of the protein. Other test conditions were identical with those described in Figure 2.

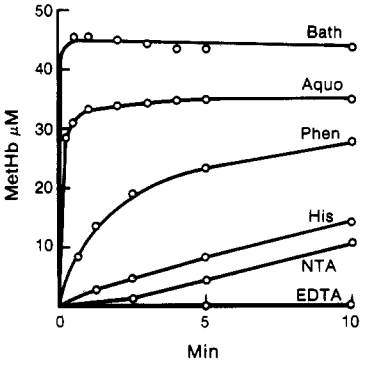

Figure 2. Effect of chelation on Cu(II) reduction. Concentrations were 100 μM heme and 100 μM Cu(II)–chelate in HEPES buffer, pH 7.0, at 25 °C.

that Cu^{II}·NTA reduction is completely inhibited when Cys β-93 is blocked with NEM. These results are consistent with Rifkind's observations that only the β hemes are oxidized by Cu(II).[4]

Effect of Chelation on Cu(II) Reduction. Cu(II) complexes (metal:chelator) with EDTA (1:1), NTA (1:1), cit (1:2), ATP (1:10), His (1:2), phen (1:2), and bath (1:2) were tested along with aquocopper(II) for their effect on the rate and extent (percentage of hemes oxidized) of reaction with Hb. The stability constants and redox potentials of these complexes are listed in Table I. The initial reduction rates for several Cu(II) complexes could not be measured accurately by conventional spectrophotometric methods at 25 °C due to the rapid reduction rates. However, their relative rates, shown in Figure 2, are

bath > aquo = cit = ATP > phen > His = NTA ≫ EDTA

Cu^{II}·2bath, with the highest redox potential, had the fastest rate

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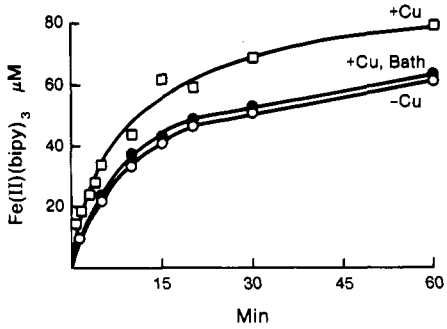

Figure 3. Effect of Cu(II) on Fe^{III}·NTA reduction. Concentrations were 100 μM heme, 100 μM Fe^{III}·NTA, and 2 mM bpy in HEPES buffer, pH 7.0, at 37 °C, with 50 μM aquocopper(II) and 2 mM bath added where indicated.

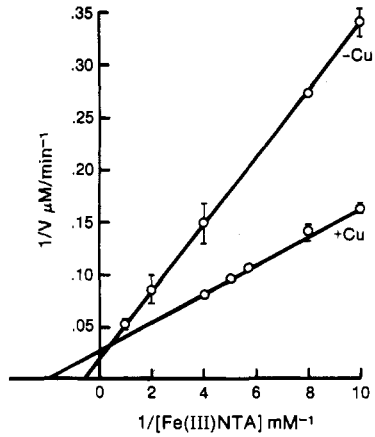

Figure 4. Effect of Cu(II) on the kinetic parameters of Fe^{III}·NTA reduction. The initial velocities of Fe^{II}·3bpy formation were determined at Fe^{III}·NTA concentrations ranging from 100 μM to 1 mM in the presence and absence of 100 μM aquocopper(II). K_m and V_{max} were determined by Lineweaver–Burk analysis of the initial velocities.

of reduction. Cu^{II}·cit and Cu^{II}·ATP are weak complexes and displayed rates that were similar to those of aquocopper(II). The other Cu(II) chelates form stronger complexes and exhibited slower rates of reduction. A site-specific mechanism is consistent with the correlation between the rates of Cu(II) reduction and the redox potentials and stability constants of the metal–chelates.

Oxidation of the α Hemes. The extent of heme oxidation appears to depend upon the destabilization of Hb by Cu(II) and the redox potential of the Cu(II)–chelate. Cu(II) complexes denature Hb to varying degrees. The maximum concentration of the Cu(II)–chelate added without immediate precipitation of the protein is indicated in Table II. Cu^{II}·2bath was able to oxidize all hemes while the other chelates oxidized between 50 and 75% of the hemes in the order

$$\text{bath} > \text{phen} > \text{His} = \text{ATP} = \text{cit} > \text{aquo} = \text{NTA}$$

Only bath and phen oxidize >75% of the hemes, which may relate to the π-orbital overlap of these chelators with the porphyrin ring to effect a simple outer-sphere electron transfer.

Role of Cu(II) in Fe^{III}·NTA Reduction by Hb. The reduction of Fe^{III}·NTA was determined in the presence and absence of aquocopper(II) (Figure 3). Cu(II) enhances the initial rate of Fe^{III}·NTA reduction by 50%. Lineweaver–Burk analysis of the initial rates, based on two experiments, indicates that Cu(II) enhances the rate by decreasing the K_m value for Fe^{III}·NTA from 1.5 to 0.5 mM (r = 0.985, Figure 4). V_{max} is not altered significantly.

Cu(II) could influence Fe^{III}·NTA reduction by Hb through two mechanisms: (1) the binding of Cu(II) to Hb may induce conformational changes in the protein that favor Fe(III) binding as evidenced in the lower K_m, and (2) Cu(II) may mediate Fe^{III}·NTA reduction by initially being reduced by Hb and subsequently donating its electron to Fe^{III}·NTA by the scheme

$$\text{Hb} + \text{Cu(II)} \rightarrow \text{MetHb} + \text{Cu(I)}$$

$$\text{Cu(I)} + \text{Fe}^{III}\text{·NTA} \rightarrow \text{Cu(II)} + \text{Fe}^{II}\text{·NTA}$$

The second mechanism, in which Cu(I) acts as an electron mediator, is most likely due to the rapid redox reaction between aquocopper(II) and Hb. The inability of Cu(II) to enhance Fe^{III}·NTA reduction in the presence of bath, a strong Cu(I) chelator (log K = 19.1 for neocuproine),[11] supports this mechanism (Figure 3).

Discussion

The reduction of Cu(II) complexes by Hb involves both site-specific and outer-sphere mechanisms. The β subunits reduce Cu(II) primarily through the site-specific mechanism. We have confirmed Rifkind's finding that Cys β-93 is involved in Cu(II) binding. The site-specific reduction rate is dependent upon (1) the formation of the metal–chelate–protein complex, which is inversely proportional to the stability constant of the metal–chelate, and (2) the reduction potential of the ternary complex. The β subunits can also reduce Cu(II) complexes through the simple outer-sphere mechanism over the heme edge. The α subunits reduce Cu(II) strictly through this mechanism. The simple outer-sphere reduction rate is a function of (1) the redox potential and (2) the nature of the electron-transfer orbitals of the Cu(II)–chelate.

Cu^{II}·2bath, with the highest redox potential, has the fastest reduction rate of the chelates tested. It is the only complex to completely oxidize both the α and β subunits. Other Cu(II) complexes (aquo, NTA, cit, ATP, and phen) oxidize between 50 and 79% of the subunits with only partial oxidation of the α subunits. The reduction of aquocopper(II) and Cu^{II}·NTA is limited to only the β subunits. Cu^{II}·2bath and Cu^{II}·2phen are reduced by Hb to the greatest extent, 100% and 79%, respectively. Both chelators have extended π orbitals that are able to overlap with the porphyrin π system to form an extended pathway for electron transfer through the simple outer-sphere mechanism. Of the biological chelators tested, ATP and citrate are the most effective in Cu(II) reduction.

The oxidation of Mb by Cu(II) complexes has been reported to involve both site-specific and outer-sphere mechanisms. The reduction of Cu(II) complexes with Gly, His, NTA, and EDTA involves binding of the metal–chelate to histidines on Mb.[1] Augustin and Yandell[13] proposed an electron transfer over the heme edge of Mb on the basis of the parallel of the rate constants with the redox potentials of several Cu(II) complexes, including phen, neocuproine, and bpy. These findings are consistent with our observations that Cu(II) is reduced by Hb through both mechanisms depending upon the properties of the metal–chelate. Cu(II) complexes with extended π orbitals, such as those studied by Augustin and Yandell, readily overlap with the porphyrin ring of Mb, which favors the simple outer-sphere mechanism. In contrast, our laboratory used Cu(II) complexes that do not form an extended π pathway for electron transfer. The reduction of these complexes is primarily through the site-specific mechanism.

The reduction of metal complexes by cytochrome c is also reported to involve both outer-sphere[13,14] and site-specific[15-17] mechanisms. As with Hb and Mb, the mechanism of reduction is dependent upon the metal–chelate.

The initial rate of Fe^{III}·NTA reduction by Hb is enhanced by 50% in the presence of aquocopper(II). Kinetic analysis of the

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data reveals that copper decreases the K_m value for Fe^{III}·NTA from 1.5 to 0.5 mM by serving as an electron mediator. Cu(II) is initially reduced by Hb to Cu(I), which subsequently reduces Fe^{III}·NTA. This interaction may be the mechanism by which copper prevents anemia by enhancing the reduction of Fe(III) required for heme synthesis.

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Dicopper(I) Carbonyl Tropocoronands. Preparation, Structural Characteristics, and Reactivity of Neutral Binuclear Cu–CO Macrocyclic Compounds

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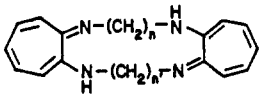
The synthesis, structure, and chemical properties of stable tropocoronand (TC) copper(I) carbonyl compounds are described. These molecules form in the reaction of copper(I) salts with Li_2(TC-*n*,*n*′) (*n*,*n*′ = 5,5 and 6,6) under a CO atmosphere in tetrahydrofuran solution. An X-ray diffraction study of [$Cu_2(CO)_2$(TC-5,5)] (**1**) revealed a binuclear structure with both trigonal-planar metal atoms coordinated to a terminal carbon monoxide ligand (ν_{CO} = 2071 cm^{-1}). The two copper atoms are located at opposite faces of the macrocycle, separated by a distance of 4.132 (1) Å. Infrared, UV–vis, and ^1H and ^{13}C NMR spectroscopic data are also reported. The compounds are sensitive to air and temperatures above 35 °C, decomposing to form mononuclear cupric species. Compound **1** is photochemically inert. Both compounds undergo CO substitution reactions in the presence of alkynes and strong nucleophiles. Addition of *n*-butyllithium leads to an intermediate, postulated to be a copper alkyl species, which can serve as an in situ catalyst for the conjugate addition of Grignard reagents to cyclohexenone. Crystal data for $C_{26}H_{30}N_4O_2Cu_2$ (**1**): triclinic, $P\bar{1}$, a = 10.977 (2) Å, b = 11.725 (2) Å, c = 10.216 (1) Å, α = 78.86 (1)°, β = 94.22 (1)°, γ = 106.29 (1)°, V = 1237.9 Å^3, Z = 2. The structure was refined to R_1 = 0.048 on the basis of 2375 data having $F_o > 4\sigma(F_o)$.

Introduction

Tropocoronand macrocycles[1] have proved to be a versatile class of ligands for the complexation of divalent first-row transition metals. For mononuclear copper(II)[2] and nickel(II)[3] complexes, the geometry about the metal center is governed largely by the length of the polymethylene linker chains in H_2(TC-*n*,*n*′). With



(TC-n,n′)H_2

n,n′= 3,3; 4,4; 4,5; 5,5; 6,6

the tropocoronand ligand H_2(TC-6,6), a binuclear copper(II) complex was obtained in which the metal ions are bridged asymmetrically by acetate and methoxide groups.[4] The present study was initiated to determine whether other binuclear systems could be accessed by using these new macrocyclic ligands, especially for metals in the +1 oxidation state such as copper(I) and rhodium(I). Homobinuclear complexes of these low-valent metals are potentially useful for the binding of small (C_1 or C_2) molecules, for bimetallic activation, or for studies of the conformational preferences of two metals in a macrocyclic host.

The preparation and characterization of neutral tropocoronand complexes containing the (μ-alkyne)dicopper(I) core have been previously reported.[5] We now describe the molecules [$Cu_2(CO)_2$(TC-5,5)] (**1**) and [$Cu_2(CO)_2$(TC-6,6)] (**2**). These compounds, briefly mentioned in a review of metal tropocoronand chemistry,[6] are stable under mild conditions to the loss of carbon monoxide. Following the first X-ray structural characterization[7] of the neutral copper(I) carbonyl complex [Cu(CO){HB(pz)$_3$}], where HB(pz)$_3$ = hydrotris(1-pyrazolyl)borate, several copper carbonyl compounds, mostly ionic species, have been prepared and isolated.[8] A variety of species, including three-coordinate,[9] pseudo-four-coordinate,[10] binuclear,[11] and bridged binuclear (μ-carbonyl)dicopper(I)[12] units, has been structurally characterized. Additional complexes, such as CpCuCO and Cp*CuCO, where Cp and Cp* = cyclopentadienyl and pentamethylcyclopentadienyl anions, respectively, are known but have not yet been fully characterized structurally.[13] Compounds **1** and **2** expand this class of molecules to include neutral, three-coordinate, binuclear copper(I) carbonyl species. The solubility of **1** in most organic solvents has also facilitated exploration of its reaction chemistry.

Experimental Section

General Methods. Grignard and lithium reagents were purchased from Aldrich Chemical Co. and used as received, except for *n*-butyllithium (BuLi), which was titrated[14] periodically to determine the active alkyllithium content. Reagent bottles were flushed with argon, sealed with electrical tape, and stored at 4 °C. Aliquots of reagents were

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