a procedure identical with that described above. After 9 days the solution was filtered and the solvent was flash evaporated. Diphenylacetaldehyde and diphenylacetic acid were extracted from the resulting solid with diethyl ether and identified by NMR and IR.[32-34] The molybdenum-containing products, identified by NMR, were $(CpMoS)_2[S_2C(CH_3)]_2$ and $(CpMo)_2(S_2CH_2)[S_2C(CH_3)_2]$ in a 1:4.5 ratio.

Competition Reactions. Equimolar amounts of an ethylene adduct and $(CpMoS)_2S_2CH_2$ were dissolved in $CDCl_3$ in an NMR tube. The solution was degassed in two freeze–pump–thaw cycles, and the tube was sealed and warmed to room temperature. The NMR spectrum was recorded periodically over a period of 2 months, and the percent formation of $(CpMo)_2(SC_2H_4S)(S_2CH_2)$ was determined when no further spectral changes were observed. Results are given in Table I.

Determination of Equilibrium Constants. A $CDCl_3$ solution of known concentration in $(CpMoS)_2S_2CH_2$ was transferred to an NMR tube. One to four equivalents of *cis*- or *trans*-2-butene or *cis*-2-hexene were syringed or condensed into the tube. The NMR tubes were sealed at −195 °C. Concentrations were determined at 26 °C by integration of the ^1H NMR spectra, and equilibrium distributions were calculated when no further changes were observed (usually after 1 day, but concentrations were also checked after ~2 months). When the olefin was *cis*-stilbene or ethylene, only an upper or lower limit for the equilibrium constant could be determined. A solution of known concentration in alkyne adduct $(CpMo)_2(S_2CH_2)$(SCRCRS), where R = Ph or H, was transferred to an NMR tube. Hydrogen was added, and the NMR tube was sealed at −195 °C. After hydrogenation was complete no adduct formation was observed for *cis*-stilbene. For the ethylene system only the adduct was formed. Limiting values were calculated by determining that a 3% solution of the missing Mo species would be observable under identical conditions.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation and the National Institutes of Health and partial support by the Department of Energy and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Prof. Robert Sievers and Eric Williams for the high-resolution gas chromatographic identification of butene isomers.

Registry No. $(Cp'Mo)_2(S_2CH_2)(SCH_3)_2$, 86163-39-5; $(Cp'Mo)_2(S_2CH_2)(SC_2H_2S)$, 86163-40-8; $(CpMo)_2(S_2CH_2)(SC_2H_2S)$, 86163-46-4; $(CpMo)_2(S_2CH_2)$(SCPhCPhS), 86163-53-3; $(CpMo)_2(S_2CH_2)(SCCH_3CCH_3S)$, 86163-59-9; $(CpMo)_2(S_2CH_2)(SCCH_3C(CH_2CH_2CH_3)S)$, 86163-61-3; $(Cp'Mo)_2(S_2CH_2)$(SCPhCPhS), 86163-62-4; $(CpMo)(S_2CH_2)$(SCPhCPhS)(Cp'Mo), 86163-54-4; $(Cp'Mo)_2(S_2CH_2)(SCCH_3CCH_3S)$, 86163-60-2; $(CpMo)_2(S_2CH_2)(SC_2H_4S)$, 86163-55-5; $(Cp'Mo)_2(S_2CH_2)(SC_2H_4S)$, 86163-56-6; $(CpMo)_2(S_2CH_2)(SCH_2CH(CH_3)S)$, 86163-57-7; $(CpMo)_2(S_2CH_2)[SCH_2C(S)C(H)CH_3]$, 86163-48-6; $(CpMo)_2(S_2CH_2)[S_2C(CH_3)_2]$, 86163-51-1; $(CpMo)_2(S_2CH_2)_2$, 86163-52-2; $(CpMo)_2[S_2C(CH_3)_2](SC_2H_2S)$, 86163-58-8; $(CpMo)_2[S_2C(CH_3)_2](SC_2H_4S)$, 86163-63-5; $(CpMo)_2[S_2C(CH_3)_2][SCH_2C(S)CH_2]$, 86163-47-5; $(CpMo)_2[S_2C(CH_3)_2][SCH_2C(O)S]$, 86163-49-7; $(CpMo)_2[S_2C(CH_3)_2][S(Ph)_2CC(O)S]$, 86163-50-0; $(CpMo)_2(SC_2H_4S)$(SCHCPhS), 86163-44-2; $(Cp'Mo)_2(S_2CS)(SC_2H_2S)$, 86163-43-1; $(CpMoS)_2[S_2C(CH_3)_2]$, 86163-41-9; $(CpMoS)_2S_2CH_2$, 86163-42-0; $(CpMoS)_2(SH)_2$, 75675-64-8; $(Cp'MoS)_2S_2CH_2$, 86163-45-3; $[Cp'Mo(S)SH]_2$, 75675-65-9; $[CpMoSC_2H_4S]_2$, 78186-29-9; Cl_2CS, 463-71-8; CH_2Br_2, 74-95-3; CH_3Li, 917-54-4; acetylene, 74-86-2; phenylacetylene, 536-74-3; ethene, 74-85-1; propene, 115-07-1; butene, 25167-67-3; 2-butyne, 503-17-3; allene, 463-49-0; methylallene, 590-19-2; ketene, 463-51-4; diphenylketene, 525-06-4; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1; *cis*-2-hexene, 7688-21-3; *cis*-stilbene, 645-49-8.

Supplementary Material Available: Tables of observed and calculated structure amplitudes (17 pages). Ordering information is given on any current masthead page.

Synthesis of Some Polyimidazole Ligands Related to Zinc Enzymes

Ronald Breslow,* John T. Hunt, Richard Smiley, and Thomas Tarnowski

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Abstract: Methods have been developed for the synthesis of new ligands bearing imidazole groups. Tris(imidazolyl)ethane and tris(imidazolyl)butane derivatives have a more expanded geometry than the known tris(imidazolyl)carbinols, leading in at least one case to better binding to metals. Ligands carrying 2-phenylimidazole rings show altered properties because of the bulky phenyl substituent. Methods have been devised to prepare 4-substituted imidazole systems by a protecting group switch and to deoxygenate the carbinol groups of these ligands so as to remove ambiguity about their mode of binding.

In metalloenzymes, imidazole rings of histidine are frequently at least part of the metal-binding site. For example, in carbonic anhydrase[1] the zinc is bound to three imidazole ligands and in carboxypeptidase[2] and in thermolysin[3] the zinc is bound to two imidazole rings and a carboxylate anion, while in plastocyanine[4] copper is bound to two imidazole rings and two sulfur atoms. Because of the general occurrence of imidazole ligands in many metalloenzymes, we initiated a program a few years ago to develop good synthetic approaches to polyimidazole molecules that might mimic the binding and catalytic properties of some of these enzymes.

We reported[5] the first synthesis of ligand systems comprised of three imidazole units, in the compounds which we referred to as 2-TIC (tris(2-imidazolyl)carbinol; **1**) and 4-TIC (tris(4-imidazolyl)carbinol; **2**). Synthesis of the first type of system was achieved simply by metalation of N-protected imidazole at C-2, followed by reaction with diethyl carbonate and deprotection. In the synthesis of 4-TIC we protected imidazole both at nitrogen and at C-2 and then metalated at C-5. After reaction with diethyl

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(3) (a) Colman, P. M.; Jansonius, J. N.; Matthews, B. W. *J. Mol. Biol.* **1972**, *70*, 701. (b) Kester, W. R.; Matthews, B. W. *J. Biol. Chem.* **1977**, *252*, 7704.

(4) Cf. Scott, R. A.; Hahn, J. E.; Doniach, S.; Freeman, H. C.; Hodgson, K. O. *J. Am. Chem. Soc.* **1982**, *104*, 5364.

(5) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918. The values given of p*K*'s have been corrected in Table I of this paper for an ionic strength term.

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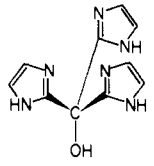
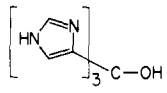


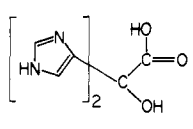
1 (2-TIC)



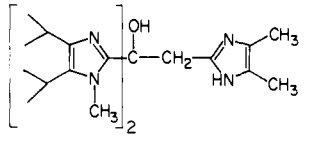
2 (4-TIC)

carbonate, removal of the protecting groups produced 4-TIC as a mixture in rapid equilibrium with various C-5 tautomers; only with the C-4 tautomers is metal coordination of the pyridine-type nitrogen possible for the three imidazole rings. By the use of similar approaches but reaction with carbonyl compounds other than diethyl carbonate we were also able to make a variety of related systems, including some (e.g., 3) which combine two imidazole rings and a carboxylate group as potential mimics for the binding site in carboxypeptidase and related compounds. As we pointed out, metal complexes of 4-TIC are generally more strongly bound than are those of 2-TIC, since there is greater charge dispersal in the complexes of 4-TIC. However, these compounds were not ideal models for the zinc-binding site in carbonic anhydrase and other enzymes.

One of the most obvious problems with these ligands is that human carbonic anhydrase B binds Zn^{2+} more than 1000 times as strongly as it binds Co^{2+}, but 2-TIC had a slightly greater affinity for Co^{2+} than for Zn^{2+} and the affinities of 4-TIC for the two metals were essentially the same.[5] A related situation pertains to apocarboxypeptidase A, which has more than 1000-fold preference for Zn^{2+} over Co^{2+}. In 4-BIG (bis(4-imidazolyl)glycolic acid; 3) the affinities for the two metals are again essentially



3 (4-BIG)



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identical.[5] It seemed likely that the increased preference for Zn^{2+} by these enzymes reflected a geometry closer to tetrahedral, while our 2-TIC, 4-TIC, and 4-BIG all hold their coordinating groups close together so as to produce a geometry which is more nearly octahedral. Thus one of our goals was to develop synthetic methods which would let us produce expanded ligand systems that could more closely approach the tetrahedral geometry suitable for binding Zn^{2+}.

In carbonic anhydrase a likely mechanism involves ionization of a zinc-bound water molecule to produce a bound hydroxide, which is the group that attacks carbon dioxide. Zinc complexes of our ligands 2-TIC and 4-TIC showed titration curves in which 0.5 equiv of hydroxide was consumed at a pH which varied with the concentration of the system. From this it was clear that we were producing hydroxide-bridged dimers, in which a single hydroxide ion was the link between two ligand–zinc systems. In order to solve this second general problem and retain appropriate chemical reactivity of the zinc-bound hydroxide, we wanted to synthesize ligand systems that carried extra groups to construct a cage around the bound hydroxide. Such a cage could prevent dimerization while permitting approach of a small substrate such as carbon dioxide.

A third general problem is that the three ligands we have discussed, 2-TIC, 4-TIC, and 4-BIG, carry a hydroxyl group which may itself act as a ligand for bound metals. This can be useful; Tagaki has described some systems[6] derived by modifications of our synthetic approach in which such a bound hydroxyl is used in a chemical process. However, for most purposes it seemed desirable to develop methods to remove such hydroxyls so that there would be no ambiguity about the groups bound to the metal,

(6) Tagaki, W., reported at Kyoto Conference on Biomimetic Chemistry, 1982.

Table I. A Comparison of the Binding Properties of 2-TIC (1) and of Homo 2-TIC (11)

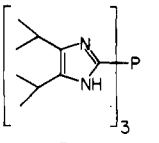
	1[a]	11[b]
pK_1	0.72	1.73
pK_2	3.25	4.78
pK_3	5.78	7.08
$pK(Co^{2+})$	6.47	7.38
$pK(Zn^{2+})$	5.93	7.16

[a] Data from ref 5 and Tang, C., Ph.D. thesis, Columbia University, 1978. [b] Determined as in ref 5.

and we would have true models for the ligand systems in the enzymes themselves.

The fourth general problem with the systems we constructed was that they were not, as their zinc complexes, effective catalysts for the hydration of carbon dioxide. The simple combination of zinc with an imidazole ligand system does not automatically lead to highly effective catalysts of this process, although there have been some reports to the contrary. Tabushi has claimed[7] that the hydration of carbon dioxide is strongly accelerated by a catalyst composed of the zinc complex of bis(imidazolyl)cyclodextrin (a compound we had first prepared[5] as a mimic for ribonuclease), by the zinc complex of a related cyclodextrinbis(histamine), by the zinc complex of histamine itself, and even by the simple ligand histamine. However, we find that the reported "catalysis" by histamine is simply a stoichiometric reaction of histamine with carbon dioxide to form a carbamate. The other zinc complexes give very low-level catalyses of carbon dioxide hydration, much less than was reported and in line with the modest catalyses which have been widely observed[9] for other simple metal complexes.

Brown has described[10-12] several polyimidazole ligand systems whose zinc complexes catalyze the hydration of carbon dioxide. In one such system (4) the initially reported[10] high catalytic activity seemed unreasonable on the basis of our experience with other ligand systems. Apparently there was some problem with the assay of activity for compound 4, and in subsequent publications[11,12] it has not been referred to. Brown has also described[11,12] two other systems with catalytic activity of good magnitude, and we have confirmed the reported activity of his zinc complex of ligand 5.



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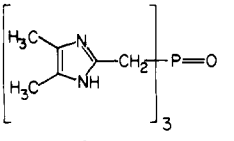

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However, this ligand and the related ligand 6 form zinc complexes that are insoluble in water, and for this reason these were assayed in solvents that are heavily organic mixtures of ethanol and water. It seems likely that the major feature of compounds 5 and 6 which made their zinc complexes good catalysts was their water insolubility, which made it necessary to move to a different solvent. In a less polar solvent the catalytic zinc hydroxide species will be formed at a lower pH. Thus another motivation for synthesizing further examples of trisimidazole ligand systems was to develop good models for the enzyme carbonic anhydrase with respect to its principal catalytic function, the hydration of carbon dioxide in *water* solution.

In this paper we describe solutions to the principal synthetic problems outlined above. We will describe elsewhere our work

(7) Tabushi, I.; Kuroda, Y.; Mochizuki, A. *J. Am. Chem. Soc.* **1980**, *102*, 1152.

(8) Breslow, R.; Doherty, J.; Guillot, G.; Lipsey, C. *J. Am. Chem. Soc.* **1978**, *100*, 3227.

(9) Woolley, P. "Biophysics and Physiology of Carbon Dioxide, Symposium"; Bauer, C., Gros, G., Bartels, H., Eds.; Springer-Verlag: West Berlin, 1979; p 216.

(10) Huguet, J.; Brown, R. S. *J. Am. Chem. Soc.* **1980**, *102*, 7571.

(11) Curtis, N. J.; Huguet, J.; Brown, R. S. *J. Am. Chem. Soc.* **1981**, *103*, 6953.

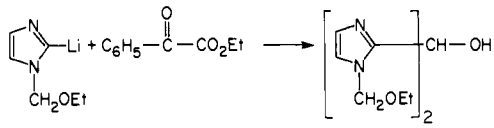
(12) Brown, R. S.; Salmon, D.; Curtis, N. J.; Kusuma, S. *J. Am. Chem. Soc.* **1982**, *104*, 3188.

on the catalytic properties of metal complexes of our ligands.

Results and Discussion

Geometrically Expanded Ligand Systems. Tris-imidazolylmethane ligands, 2-TIC and 4-TIC, hold the imidazole rings so close together that octahedral coordination is promoted. This was revealed in our studies of binding constants,[5] in which 2:1 complexes were formed with resulting sixfold coordination of the metals. Furthermore, the spectra of the Co^{2+} complexes with these ligands were characteristic of octahedral complexes.[5] Since in carbonic anhydrase the geometry is apparently closer to tetrahedral, which corresponds to a larger geometric separation of the imidazole rings, we decided to expand the central nucleus to which the imidazoles are attached. As one example, the methane nucleus was expanded to an ethane unit.

Several simple approaches were unsuccessful. Thus reaction of 2-lithio-*N*-(ethoxymethyl)imidazole with ethyl glyoxalate, with ethyl phenylglyoxalate, or with diethyl oxalate did not afford the hoped for tris- or tetrakisimidazole adducts. This was probably because of fragmentation of the intermediate pinacol dianions, as evidenced by the isolation of the N-protected bis(imidazolyl)carbinol **7** in the reaction with phenylglyoxalate ester. In a



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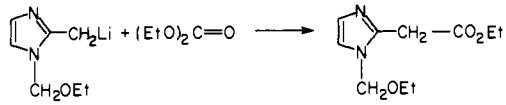
second approach to expanded ligands, N-protected 2-methylimidazole was metalated on the methyl group. Reaction of this species with diethyl carbonate did not afford the trisubstituted carbinol, apparently because of the first adduct is an imidazoleacetic ester **8** with acidic protons on the methylene carbon. We



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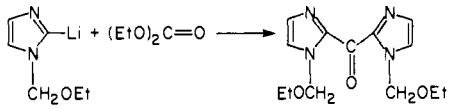
have found that this kind of ester reacts with organometallics at the methylene group to form an anion rather than by addition at the ester carbonyl, so an approach to an expanded ligand was adopted which avoided this difficulty. *N*-(Ethoxymethyl)imidazole was metalated at C-2 and allowed to react with the correct amount of diethyl carbonate under controlled conditions to afford the corresponding ketone **9**. This ketone reacted smoothly with metalated N-protected 2-methylimidazole to afford the corresponding carbinol **10**, and this could be deprotected with vigorous acid treatment to afford the tris(imidazolyl)ethanol derivative **11**.



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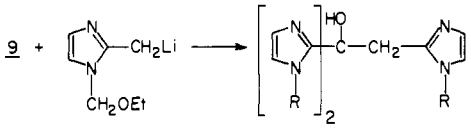
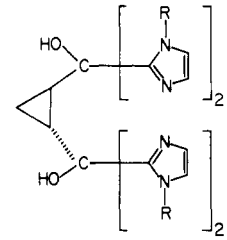


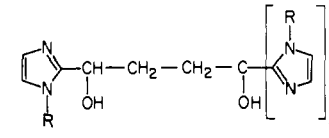
10 : R = CH_2OEt
11 : R = H

The fact that deprotection of **10** was more difficult than that involved in our previous synthesis of 2-TIC suggested that **11** was more basic than 2-TIC (and that as a result its protonated form was not as good a leaving group in the deprotection reaction). This conclusion was confirmed by our pK and metal-binding studies. As is indicated in Table I, the affinities of this ligand **11** for protons and also for cobalt and zinc are all increased over those for 2-TIC.

Other further expanded ligands are readily available. Thus reaction of the 2-lithioimidazole reagent with (E)-cyclopropanedicarboxylic ester afforded the tetrakisimidazole compound **12** which could be deprotected to **13**. Similarly, reaction of the lithioimidazole with the methyl ester of succinic semialdehyde afforded a tris(imidazolyl)butane derivative **14** which was deprotected to afford **15**. A related compound was also prepared from glutaric ester semialdehyde.

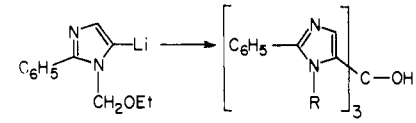


12 : R = CH_2OEt
13 : R = H



14 : R = CH_2OEt
15 : R = H

Ligands with Extra Steric Hindrance. As was discussed earlier, it was felt desirable to add extra groups to the imidazole rings so as to produce a cage structure that would not readily dimerize. We have approached this problem by the use of the readily available 2-phenylimidazole, while Brown has prepared some ligands (**4–6**) bearing bulky groups on carbons 4 and 5 of imidazole rings that are attached to a framework at C-2.[10–12] In a simple approach to our compounds, *N*-(ethoxymethyl)-2-phenylimidazole was treated with butyllithium. Metalation of such compounds occurs exclusively[13] on C-5, even when the nitrogen-protecting group is a simple methyl. The extra acidity of the C-5 proton is presumably due to electronic factors in the imidazole ring, such as partial charges induced when the pyrrole nitrogen acts as an electron donor and the pyridine nitrogen acts as an electron acceptor in one of the principal resonance forms of the ring. This would acidify the hydrogen at C-5, next to the nitrogen which carries a partial positive charge. Reaction of this lithioimidazole compound **16** with ethyl carbonate smoothly afforded the tris(imidazolyl)carbinol **17**, but attempted deprotection of **17** led to a problem. On treatment with strong acid the salt of the expected deprotected carbinol **18** was produced, but when this was neutralized, there was rapid dehydration[14] to produce a deep red material to which we assign structure **19**. Attempts to convert **19** back to a ligand with a tetrahedral central carbon by reduction or by organometallic reactions have not so far been successful.



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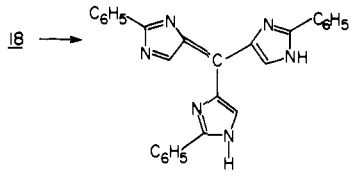
17 : R = CH_2OEt
18 : R = H



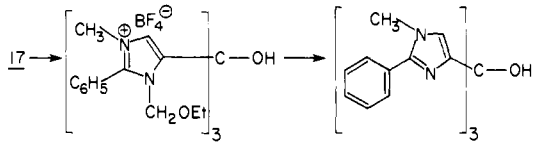
19

The dehydration involved in the formation of compound **19** was apparently not a problem with **17** in which the nitrogen-protecting groups were still in place. Accordingly it seemed desirable to synthesize such an N-protected caged ligand system but with the linkage at C-4 (required for metal binding) rather than at C-5

(13) In ref 5 we report similar metalation at C-5 for 2-blocked *N*-(ethoxymethyl)imidazole. We find such selectivity also for 2-blocked *N*-methylimidazole.

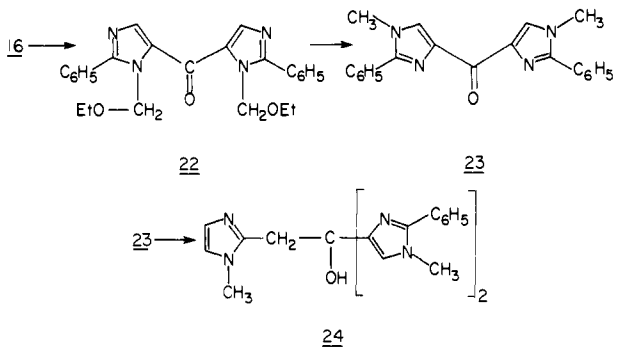
(14) For a related process: cf. Brown, R. S.; Huguet, J. *Can. J. Chem.* **1980**, *58*, 889.

of the imidazole systems. We have prepared organometallic derivatives substituted at C-4 from the corresponding 4-bromoimidazole compounds (cf. Experimental Section), but these were not as well behaved synthetically as the C-5 lithio compound **16**. For this reason we have adopted the strategy of a "protecting group switch" by which we reverse the substitution pattern. That is, compound **17** was methylated on the pyridine-type nitrogens (after protection of the hydroxyl group by silylation) and the resulting trication **20** then lost its ethoxymethyl groups on heating in aqueous acid. The resulting caged ligand **21**, liberated by neutralization of the resulting salt, was moderately stable although it did decompose on standing.



20 21

Another ligand carrying only two phenyl groups was prepared by a related strategy. The 5-lithio compound **16** was converted to the corresponding 5,5′-bis(imidazolyl) ketone **22** by oxidation of the corresponding carbinol, and this was subject to the protecting group switch to afford the related 4,4′ ketone **23**. When **23** was treated with the lithio derivative of 1,2-dimethylimidazole, it afforded structure **24**, a tris(imidazolyl)ethane derivative in which



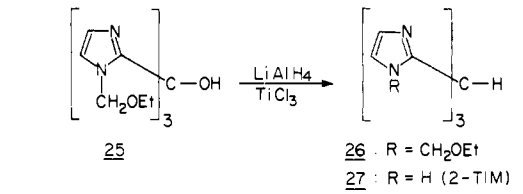
22 23

24

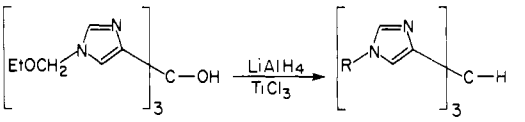
all three of the imidazole rings carry *N*-methyl groups and two of them carry bulky phenyl groups. As hoped for, **24** formed a 1:1 complex with Co^{2+} salts, and the spectrum of this complex did not change on addition of a second equivalent of the ligand. Furthermore, the addition of an equivalent of 2-TIC to this 1:1 complex did not lead to a spectroscopic change, suggesting that the cage of two phenyl groups hinders the approach of even this smaller second ligand. By contrast 2 equiv of 2-TIC form a clearly detectable 2:1 complex with Co^{2+}, as we have described previously.[5]

Removal of the Hydroxyl Groups. In order to remove the ambiguity about the nature of the coordinating groups in complexes of our ligands, we wanted to develop general methods to reduce the various alcohols to hydrocarbons. A variety of reducing agents were examined with 2-TIC and some of its precursors, the N-protected compounds. Hydrogenations were unsuccessful and reductions with lithium in ammonia gave poor yields and some reduction of the *N*-ethoxymethyl-protecting groups, while HI and red phosphorus did not reduce 2-TIC, nor was lithium aluminum hydride/aluminum chloride effective. However, lithium aluminum hydride/titanium trichloride (McMurry's reagent[15]) gave an excellent yield of **26** by reduction of the *N*-ethoxymethyl-protected 2-TIC (**25**), and a similar high yield of **29** with the corresponding 4-TIC derivative (**28**). Deprotection led to the new ligands tris(2-imidazolyl)methane (2-TIM) **27** and tris(4-imidazolyl)-methane (4-TIM) **30**, respectively.

This excellent reducing procedure was totally ineffective on any compounds in which the hydroxyl was attached to a carbon carrying lesss than three imidazole rings, however. Thus for the

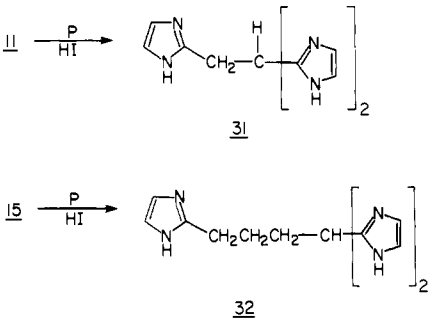


25 26 : R = CH_2OEt
27 : R = H (2-TIM)



28 29 : R = CH OEt
30 : R = H

reduction of the tris(imidazolyleethanol **11** and other such structures, a new procedure had to be devised. Remarkably, the same HI and red phosphorus procedure that had been unsuccessful with the tris(imidazolyl)carbinols was successful with these other cases, permitting us to prepare 1,1,2-tris(2-imidazolyl)ethane (**31**). Under similar conditions we also were able to prepare 1,1,4-tris(2-imidazolyl)butane (**32**), in which two hydroxyl groups were reduced from the precursor **15**.



31 32

Conclusions. Methods have been devised for the synthesis of trisimidazole and tetrakisimidazole ligand systems bound to frameworks larger than one central atom. In at least one case this leads to improved binding properties. Furthermore tris(imidazolyl)carbinols have been prepared with extra phenyl groups to help construct a cage, and the expected hindrance to the formation of 2:1 complexes with Co^{2+} has been observed. The problem of attaching such imidazole rings at C-4 has been solved by metalation and attachment at C-5, followed by a protecting-group switch. Methods have also been developed for the reductive removal of the hydroxyl groups of polyimidazolylcarbinols. These synthetic methods should prove generally useful in the preparation of novel ligand molecules, including mimics for metal-binding sites in enzymes.

Experimental Section

N-(Ethoxymethyl)imidazole, 2-TIC (**1**), and 4-TIC (**2**) were prepared as described earlier.[5] The metal-binding constants in Table I were determined by the method we have described.[5]

***N*-(Ethoxymethyl)-2-methylimidazole.** To a suspension of potassium *tert*-butoxide (56.1 g, 0.5 mol) in 20 mL of dry THF under nitrogen was added 2-methylimidazole (41.06 g, 0.5 mol). The mixture was cooled to −30 °C, an additional 100 mL of THF was added, and chloromethyl ethyl ether (47.3 g, 0.5 mol) was added dropwise over 2 h at −30 °C with stirring. The mixture was allowed to warm to room temperature overnight, the solid was filtered and washed with THF, and the combined filtrates were evaporated in vacuo. The residual oil was distilled and the fraction with a boiling point of 54–56 °C (1 mmHg) was redistilled as pure *N*-(ethoxymethyl)-2-methylimidazole: 50 g (71%); bp 45 °C (0.05 mmHg); ^1H NMR (60 MHz, $CDCl_3$) δ 1.17 (t, J = 7 Hz, 3 H), 2.43 (s, 3 H), 3.46 (q, J = 7 Hz, 2 H), 5.12 (s, 2 H), 6.92 (s, 2 H).

Bis(*N*-(ethoxymethyl)-2-imidazolyl) Ketone (9) and 1,1,2-Tris(*N*-(ethoxymethyl)-2-imidazolyl)-1-hydroxyethane (10). A flame-dried flask was charged, under nitrogen, with *N*-(ethoxymethyl)imidazole (13.7 g, 108 mmol) in 150 mL of dry THF. The solution was cooled to −78 °C in a dry ice/acetone bath, and 2.1 N butyllithium in hexane (47.6 mL, 100 mmol) was added over 5 min via syringe, and then the solution was

(15) Fieser, M.; Fieser, L. F. "Reagents for Organic Synthesis"; Wiley: New York, 1977; Vol. 6, p 588.

allowed to warm to −65 °C over 30 min.

The solution was again cooled to −78 °C and transferred by cannula into a flask containing diethyl carbonate (5.91 g, 50 mmol) in 50 mL of THF at −78 °C under nitrogen. The reaction mixture was allowed to warm to −40 °C, at which point a white precipitate had formed. Solid CO_2 was added to quench the reaction (higher temperatures favor the formation of the tris(imidazolyl)carbinol over the desired ketone). The reaction was then allowed to warm to room temperature.

The clear orange solution was evaporated in vacuo to a foam, which was partitioned between water and ethyl ether. A precipitate remained in the aqueous layer, which was washed with several additional portions of ether. The organic layers were pooled, dried over anhydrous sodium carbonate, filtered, and evaporated to give an oily mixture from which the starting imidazole was almost completely removed by distillation at high vacuum for 3 h. The remaining material was purified by dry column chromatography (2.5% triethylamine–2% methanol/ethyl ether; silica gel). Slow material was eluted with methanol and contained nearly pure ketone **9** by NMR: yield 3.09 g (23%). Material of this purity was taken on to further reaction: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.20 (t, J = 7 Hz, 6 H) 3.58 (q, J = 7 Hz, 4 H), 5.80 (s, 2 H), 7.39 (s, 2 H).

A solution of *N*-(ethoxymethyl)-2-methylimidazole (1.5 g, 10.7 mmol) in 80 mL of THF in a dry flask was cooled to −40 °C with stirring under nitrogen. Butyllithium (2.13 M in hexane) was added (4.7 mL, 10 mmol). The solution was stirred at −30 to −40 °C for 20 min, and then a solution of ketone **9** (2.78 g, 10 mmol) in 10 mL of THF was added. The reaction was allowed to warm slowly and stirred at room temperature for 24 h.

The solvent was removed and the product worked up with methylene chloride and water in the usual way. Residual imidazole was removed by distillation at 65 °C (0.1 mmHg), and the product was crystallized from diethyl ether at −20 °C to give 1.73 g (41.4%) of **10**, 1.40 g (33.5%) after recrystallization: mp 96–96.5 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.04 (t, J = 7 Hz, 6 H), 1.11 (t, J = 8 Hz, 3 H), 3.25–3.60 (2 q's, ratio 2:1, 6 H), 3.82 (s, 2 H), 5.32 (d, J = 10 Hz, 2 H), 5.39 (s, 2 H), 5.48 (d, J = 10 Hz, 2 H), 6.78 (1 H), 6.86 (3 H), 6.97 (2 H), 7.90 (1 H); MS (CI, methane), m/e 419, 401, 373, 293, 155, 127. Anal. Calcd for $C_{20}H_{30}N_6O_4$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.56; H, 7.19; N, 19.89.

1,1,2-Tris-(2-imidazolyl)-1-hydroxyethane (11). Deprotection of **10** required ca. 20 reflux in 4 N HCl. After neutralization the product **11** was obtained by crystallization from ethanol and then from water, as the monohydrate, in ca. 60% yield: ^{1}H NMR (60 MHz, CD_3OD) δ 3.62 (d, 2 H), 4.94 (s), 6.83 (s, 2 H), 6.96 (s, 4 H); MS (CI, isobutane), m/e 245, 227, 177, 163, 83, 69. Anal. Calcd for $C_{11}H_{12}N_6O{\cdot}H_2O$: C, 50.38; H, 5.38; N, 32.04. Found: C, 50.18; H, 5.48; N, 31.81. Anal. Calcd for $C_{11}H_{12}N_6O$ (the anhydrous compound): C, 54.09; H, 4.95; N, 34.41. Found: C, 54.17; H, 5.05; N, 34.34.

1,1,4-Tris(*N*-(ethoxymethyl)-2-imidazolyl)-1,4-dihydroxybutane (14). To a solution of *N*-(ethoxymethyl)imidazole (6.65 g, 52.77 mmol) in dry THF was added 1.9 *N* butyllithium in hexane (26 mL, 49.4 mmol) at −70 °C under nitrogen. The resulting yellow solution was stirred for 35 min, and then 3-carbomethoxypropionaldehyde (1.535 g, 1.323 mmol) was added via syringe. Normal workup afforded the product **14**, crystallized from ethyl acetate–hexane: yield 2.4 g (39.5%); mp 129–131 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.13 (t, J = 8 Hz, 3 H), 1.15 (t, J = 8 Hz, 3 H), 2.00–4.03 (m, 10 H), 4.88 (br t), 5.12 (s, 2 H), 5.42 (q(AB), 2 H), 5.45 (s, 2 H), 6.65–7.0 (m, 6 H), 7.5–8.0 (br s); ^{13}C NMR ($CDCl_3$) 14.570, 14.691, 28.100, 34.713, 64.138, 65.048, 72.753, 76.03, 119.770, 120.320, 120.860, 125.355, 125.659, 126.629, 149.138, 149.330, 150.170 ppm; MS (CI, methane), m/e 463, 445, 417, 337. Anal. Calcd for $C_{22}H_{34}N_6O_5$: C, 57.10; H, 7.41; N, 18.17. Found: C, 57.35; H, 7.49; N, 18.14.

1,1,4-Tris(2-imidazolyl)-1,4-dihydroxybutane (15). A solution of **14** (340 mg, 0.74 mmol) in 18 mL of 2.0 N HCl was refluxed for 72 h, and the solvent was removed in vacuo to leave an off-white, highly hydroscopic foam, the trihydrochloride of **15** (312 mg, 102%): ^{1}H NMR (90 MHz, D_2O) δ 2.0–2.25 (m, 2 H), 2.85–3.10 (t, 2 H), 5.38 (1 H), 7.55 (s, 2 H), 7.73 (s, 4 H). The free base of **15** was prepared by NH_3 neutralization and acetone extraction: ^{1}H NMR (80 MHz, D_2O) δ 1.7–2.0 (br m, 2 H), 2.2–2.6 (br m, 2 H), 4.82 (t, 1 H, J = 7 Hz), 7.06 (s, 4 H), 7.12 (s, 4 H); MS (CI, methane), m/e 289, 271, 255, 253, 221, 127, 69.

1,1,4-Tris(2-imidazolyl)butane (32). The trihydrochloride of **15** (208 mg, 0.53 mmol) and 2 mL of concentrated hydriodic acid (freshly distilled from red phosphorus) with red phosphorus (39 mg, 1.26 mmol) was sealed in a thick-walled glass tube at 70 K in vacuo. The tube was heated at 190–210 °C for 14 h and then opened, and an additional portion of red phosphorus was added (40 mg, 1.29 mmol). The tube was resealed and heated at 200 °C for an additional 4 h. The mixture was filtered and then neutralized with sodium hydroxide, and the yellowish white precipitate was collected and dried to give 108 mg (81%) of **32**. The compound was further purified by recrystallization from methanol–water: ^{1}H NMR (80 MHz, D_2O–D_2SO_4) δ 1.5–1.9 (m, 2 H), 2.2–2.55 (m, 2 H), 3.0 (t, J = 7.2 Hz, 2 H), 5.12 (t, J = 8 Hz, 1 H), 7.25 (s, 2 H), 7.43 (s, 4 H); MS (EI), m/e 256, 175, 161, 148.

***trans*-1,2-Bis(hydroxybis(*N*-(ethoxymethyl)-2-imidazolyl)methyl)-cyclopropane (12).** *trans*-Diethyl cyclopropane-1,2-dicarboxylate[16] was reacted with 6 equiv of 2-lithio-*N*-(ethoxymethyl)imidazole in the usual fashion and the product crystallized from ethyl ether to give 302 mg (32%) of **12** as a white powder: mp 113–114 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.0–1.3 (d of t, 12 H), 2.2–2.9 (m, 4 H), 3.0–3.6 (d of q, 8 H), 5.1 (s, 4 H), 5.2 (s, 4 H), 7.1 (m, 10 H). Anal. Calcd for $C_{29}H_{42}N_8O_6$: C, 58.18; H, 7.07; N, 18.72. Found: C, 57.97; H, 7.25; N, 18.52.

***trans*-Bis(hydroxybis(2-imidazolyl)methyl)cyclopropane (13).** Deprotection of **12** by 1.5 h reflux with 3 N HCl in 40% ethanol and then evaporation afforded the hydrochloride of **13**: ^{1}H NMR (60 MHz, D_2O) δ 1.95 (br, m, 2 H), 2.52 (br m, 2 H), 4.97 (s), 7.58 (s, 4 H), 7.75 (s, 4 H). The free base showed: MS (EI), m/e 366, 355, 348, 331, 330, 262, 203, 201, 185, 173, 163, 148.

1,1,2-Tris(2-imidazolyl)ethane (31). Treatment of **11** with phosphorus and HI, as described above, afforded **31** as a white solid in 50% yield: ^{1}H NMR (90 MHz, D_2O–D_2SO_4) δ 4.15 (d, J = 9 Hz), 5.35 (s, 7 H), 5.69 (t, J = 9 Hz, 1 H), 7.38 (s, 2 H), 7.50 (s, 4 H). Anal. Calcd for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.59; H, 5.35; N, 36.76.

Tris(*N*-(ethoxymethyl)-2-imidazolyl)methane (26). Tris(*N*-(ethoxymethyl)-2-imidazolyl)carbinol (**25**; 1.0 g, 2.47 mmol) in 5 mL of freshly distilled dimethoxyethane (DME) was added to a stirring suspension of $TiCl_3/LiAlH_4$ (1.25 g) in 33 mL of DME. The black reaction mixture was stirred and heated to reflux under nitrogen for 20 h and then filtered, and the filtrate was partitioned between water and methylene chloride in the usual fashion. The crystalline product was pure **26** by ^{1}H NMR. It had a melting point of 93.5–94.5 °C after recrystallization from cyclohexane: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.06 (t, J = 9.9 Hz, 9 H), 3.27 (q, J = 6.9 Hz, 6 H), 5.26 (s, 6 H), 6.30 (s, 1 H), 6.99 (s, 3 H), 7.04 (s, 3 H). Anal. Calcd for $C_{19}H_{28}N_6O_3$: C, 58.74; H, 7.27; N, 21.63. Found: C, 58.78; H, 7.25; N, 21.45.

Tris(2-imidazolyl)methane, 2-TIM (27). Compound **26** (860 mg, 2.1 mmol) was dissolved in a mixture of 16.9 mL of concentrated HCl, 25 mL of ethanol, and 25 mL of water, and the solution was refluxed for 12 h. The solvent was removed, and water was successively added and evaporated. The resulting trihydrochloride was neutralized by addition of sodium carbonate in 3–4 mL of water, and the water was evaporated to leave a light yellow solid. This was sublimed at 150–200 °C for 4 days to give 400 mg (84%) of **27** as a reddish pink solid, which could be recrystallized from ethyl acetate. The compound should be stored under an inert atmosphere, as it oxidized to reddish material rather easily in air: MS (CI, methane), m/e 215 (M + 1, 100), all other peaks less than 3% of parent.

***N*-(Ethoxymethyl)-2-phenylimidazole.** 2-Phenylimidazole was treated with NaH and then ethoxymethyl chloride in THF. The product was purified by chromatography (R_f 0.55, 50% $CHCl_3$–hexane, alumina) and distillation (110 °C (0.15 mmHg)): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.15 (t, J = 7.5 Hz, 3 H), 3.50 (q, J = 7.5 Hz, 2 H), 5.2 (s, 2 H), 7.1 (s, 2 H), 7.4 (m, 3 H), 7.8 (m, 2 H). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.09; H, 7.16; N, 13.88.

Tris(*N*-(ethoxymethyl)-2-phenyl-5-imidazolyl)carbinol (17). *N*-(Ethoxymethyl)-2-phenylimidazole (4.0 g, 19.8 mmol) was metalated in THF with butyllithium in the usual fashion, and diethyl carbonate (0.8 mL, 0.78 g, 6.6 mmol) was added dropwise to the −70 °C solution. The solution was allowed to warm to room temperature over 2 h, and water (50 mL) was added to quench the reaction. Evaporation of the THF afforded **17** as a solid, which was crystallized from benzene–hexane to give 3.6–3.9 g (85–92%): mp 200.5–202.5 °C (liquid turns pink); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.08 (t, J = 6.6 Hz, 9 H), 3.35 (q, J = 6.6 Hz, 6 H), 5.35 (s, 6 H), 5.87 (s, 1 H), 6.78 (s, 3 H), 7.35–7.55 (m, 9 H), 7.60–7.85 (m, 6 H). Anal. Calcd for $C_{37}H_{40}N_6O_4$: C, 70.23; H, 6.37; N, 13.28. Found: C, 70.44; H, 6.51; N, 13.44.

Bis(*N*-(ethoxymethyl)-2-phenyl-5-imidazolyl)carbinol. Reaction of the above lithio compound with methyl formate afforded this alcohol in 70% yield as a white solid, mp 160–161 °C, recrystallized from benzene–hexane: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.07 (t, J = 6.5 Hz, 6 H), 3.32 (q, J = 6.5 Hz, 4 H), 5.15 (d, J = 9.8 Hz, 2 H), 5.37 (d, J = 9.8 Hz, 2 H), 6.17 (s, 1 H), 7.05 (s, 2 H), 7.3–7.75 (m, 10–11 H). Anal. Calcd for $C_{25}H_{28}N_4O_3$: C, 69.42; H, 6.53; N, 12.95. Found: C, 69.42, H, 6.58; N, 12.80.

***N*-(Ethoxymethyl)-2-phenyl-5-(hydroxymethyl)imidazole.** Reaction

(16) (a) Wiberg, K. B.; Barnes, R. K.; Albin, J. *J. Am. Chem. Soc.* **1957**, *79*, 4994. (b) McCoy, L. Ll. *Ibid.* **1958**, *80*, 6568.

of the lithio compound with gaseous formaldehyde afforded this alcohol, mp 100.5–101 °C, crystallized from $CHCl_3$–hexane: ^1H NMR (60 MHz, $CDCl_3$) δ 1.12 (t, J = 7.5 Hz, 2 H), 3.39 (q, J = 7.5 Hz, 2 H), 4.20 (br, s, 1 H), 4.66 (s, 2 H), 5.30 (s, 2 H), 6.94 (s, 1 H), 7.3–7.8 (m, 5 H). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.96; H, 6.95; N, 11.89.

***N*-(Ethoxymethyl)-2-phenyl-5-carbethoxylmidazole.** Reaction of the lithio compound with ethyl chloroformate afforded this ester: bp 135–140 °C (0.5 mm); ^1H NMR (90 MHz, $CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 1.38 (t, J = 7 Hz, 3 H), 3.62 (q, J = 7 Hz, 2 H), 4.35 (q, J = 7 Hz, 2 H), 5.70 (s, 2 H), 7.4–7.57 (m), 7.75–7.95 (m). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.67; H, 6.79; N, 10.21.

(*N*-(Ethoxymethyl)-2-phenyl-5-imidazolyl)carboxylic Acid. Saponification of the above ester yielded this acid: m.p. 135–137 °C; ^1H NMR (90 MHz, CD_3OD) δ 1.14 (t, J = 7.5 Hz, 3 H), 3.32 (s), 3.58 (q, J = 7.5 Hz, 2 H), 4.74 (s, 1–2 H), 5.74 (s, 2 H), 7.45–7.65 (m, 2 H), 7.70–7.85 (m, 3 H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.20; H, 5.91; N, 11.38.

2-Phenyl-4(5)-bromoimidazole. A solution of 2-phenyl-4,5-dibromoimidazole[17] (8.01 g, 26 mmol) and sodium sulfite (6.56 g, 52 mmol) in 40 mL of 50% aqueous ethanol was refluxed for 46 h and then allowed to cool. Normal workup and chromatography afforded 2.93 g (51%) of product: mp 202–204 °C; ^1H NMR (90 MHz, acetone-d_6) δ 3.08 (br s, 1 H), 7.21 (s, 1 H), 7.3–7.5 (m, 3 H), 7.85–8.05 (m, 2 H). Anal. Calcd for $C_9H_7N_2Br$: C, 48.46; H, 3.16; N, 12.56; Br, 35.82. Found: C, 48.62; H, 3.12, N, 12.42; Br, 35.65.

***N*-Methyl-2-phenyl-4-bromoimidazole and *N*-Methyl-2-phenyl-5-bromoimidazole.** Sodium hydride 50% oil dispersion (260 mg, 5.4 mmol) was washed three times with hexane to remove the oil and then suspended in 20 mL of dry THF at 0 °C, and the above compound (1.10 g, 4.9 mmol) was added in one portion. The solution was allowed to come to room temperature over 30 min and then was cooled again to 0 °C. Methyl iodide (0.34 mL, 5.4 mmol) was added dropwise to the heterogeneous mixture. The solution was allowed to warm to room temperature gradually over 12 h and was then partitioned between chloroform and water in the normal way to yield 1.03 g of crude product.

Column chromatography on 95 g of silica gel ($CHCl_3$) gave 0.66 g (57%) of the 4-bromoisomer (R_f 0.06, chloroform) and 0.16 g (14%) of the 5-bromo isomer (R_f 0.03, chloroform). Each isomer could be recrystallized from 2:1 isopropyl ether–hexane. Direct crystallization of the crude product after workup (with a seed crystal) afforded a 42% yield of the 4-bromo compound. The 4-bromo isomer had a melting point of 68–69 °C: ^1H NMR (90 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 6.82 (s, 1 H), 7.2–7.7 (m, 5 H). Anal. Calcd for $C_{10}H_9N_2Br$: C, 50.66; H, 3.83; N, 11.82; Br, 33.70. Found: C, 50.78; H, 3.85; N, 11.71; Br, 34.14. The 5-bromo isomer had a melting point of 107–108 °C: ^1H NMR (90 MHz, $CDCl_3$) δ 3.62 (s, 3 H), 7.02 (s, 1 H), 7.2–7.77 (m, 5 H).

***N*-Methyl-2-phenyl-4-carbethoxyimidazole.** A solution of the above 4-bromo isomer (0.9 g, 3.8 mmol) in 20 mL of dry THF in a 100-mL round-bottom flask was cooled to −78 °C and treated with 2.38 N butyllithium in hexane (1.75 mL, 4.2 mmol, 1.1 equiv). The solution was stirred for 30 min at −78 °C and then transferred by cannula into a solution of diethyl carbonate (4.485 g, 3.8 mmol) in 20 mL of dry THF at −78 °C. The resulting solution was stirred for 30 min as it was allowed to warm to −40 °C. The reaction was quenched by addition of 1.0 N aqueous ammonium chloride, and ethyl ether was added to partition the reaction mixture. Normal workup and chromatography gave the desired ester, 0.33 g (38%). It could be further purified by Kugelrohr distillation at 165 °C (0.05 mmHg): ^1H NMR (90 MHz, $CDCl_3$) 1.40 (t, J = 7.1 Hz, 3 H), 3.71 (s, 3 H), 4.31 (q, J = 7.1 Hz, 2 H), 7.20 (s, 1 H), 7.38–7.65 (m, 2 H), 7.65–7.87 (m, 3 H). Anal. Calcd for $C_{13}H_{1N2}O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.66; H, 6.23; N, 11.91.

Bis(*N*-(ethoxymethyl)-2-phenyl-5-lmidazolyl) Ketone (22). A solution of bis(*N*-(ethoxymethyl)-2-phenyl-5-imidazolyl)carbinol (1.82 g, 4.2 mmol), pyridinium chlorochromate (1.33 g, 6.1 mmol), and sodium acetate (0.12 g, 1.4 mmol) in 50 mL of methylene chloride was stirred at room temperature for 19 h. Normal workup and flash chromatography (5% ethanol–chloroform, silica gel) gave 1.48 g (82%) of **22** (R_f 0.28) as a pale yellow oil which crystallized upon standing. Recrystallization from hexane–isopropyl ether afforded fine needles: mp 143–144 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.14 (t, J = 7 Hz, 6 H), 3.57 (q, J = 7 Hz, 4 H), 5.80 (s, 4 H), 7.3–7.6 (m, 6 H), 7.65–8.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) 14.812, 64.320, 73.906, 116.133, 128.631, 129.117, 129.481, 130.027, 131.483, 139.431, 154.902, 174.620 ppm; MS (CI, methane) m/e 431, 416, 402, 388, 343, 314, 203, 187, 159, 91.

Bis(*N*-methyl-2-phenyl-4-imidazolyl) Ketone (23). To a solution of **22** (0.97 g, 2.2 mmol) in 20 mL of reagent grade methylene chloride was added trimethyloxonium tetrafluoroborate (1.0 g, 6.8 mmol). The solution was stirred for 30 minutes, quenched with methanol, and then evaporated to afford bis(*N*(1)-ethoxymethyl-2-phenyl-*N*(3)-methylimidazolylium) ketone bis(tetrafluoroborate): ^1H NMR (90 MHz, acetone-d_6) δ 1.02 (t, J = 7 Hz, 6 H), 3.50 (q, J = 7 Hz, 4 H), 3.84 (s, 6 H), 5.72 (s, 4 H), 7.55–7.95 (m, 10 H), 8.58 (s, 2 H). Without further characterization, the salt was dissolved in 30 mL of 50% aqueous ethanol and 7 mL of concentrated HCl, and the solution was refluxed for 36 h. Normal workup and chromatography afforded 0.60 g of **23** (80% based on **22**). Crystallization from benzene–hexane yielded fine white needles: mp 204–206 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 3.71 (s, 6 H), 7.18–7.70 (m, 10 H), 8.16 (s, 2 H). Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.78; H, 5.48; N, 16.26.

1,1-Bis(*N*-methyl-2-phenyl-4-imidazolyl)-2-(*N*-methyl-2-imidazolyl)-1-hydroxyethane (24). A solution of *N*-methyl-2-methylimidazole (0.11 g, 1.2 mmol) in 10 mL of dry THF was stirred and cooled to −78 °C under nitrogen. At −78 °C, 2.38 M butyllithium in hexane was added (0.49 mL, 1.2 mmol) via syringe, and the solution was stirred for 20 min. The clear yellow solution was transferred by cannula into a suspension of **23** (0.33 g, 0.96 mmol) in 20 mL of THF at −78 °C. The cooling bath was removed, and the reaction mixture was stirred at room temperature overnight. Normal workup and careful chromatography afforded **24** in 19% yield, mp 187–190 °C after recrystallization from isopropyl ether–benzene: ^1H NMR (90 MHz, $CDCl_3$) δ 3.48 (s, 3 H), 3.56 (s, 6 H), 3.80 (s, 2 H), 6.62–6.88 (m, 4 H), 7.22–7.62 (m, 10 H); MS (CI, methane), m/e 439, 421, 371, 343, 203.

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Registry No. 9, 86119-36-0; **10**, 86119-37-1; **11**, 86119-38-2; **12**, 86119-39-3; **13**, 86128-94-1; **13**·*x*HCl, 86119-50-8; **14**, 86128-92-9; **15**, 86119-40-6; **15**·3HCl, 86119-51-9; **17**, 86119-41-7; **22**, 86119-42-8; **23**, 86119-43-9; **24**, 86119-44-0; **25**, 67319-13-5; **26**, 86119-45-1; **27**, 86119-46-2; **27**·3HCl, 86119-52-0; **31**, 86119-47-3; **32**, 86119-48-4; *N*-(ethoxymethyl)-2-methylimidazole, 86119-49-5; 3-carbomethoxypropionaldehyde, 13865-19-5; *trans*-diethyl cyclopropane-1,2-dicarboxylate, 3999-55-1; *N*-(ethoxymethyl)-2-phenylimidazole, 86119-53-1; bis(*N*-(ethoxymethyl)-2-phenyl-5-imidazolyl)carbinol, 86119-54-2; 2-phenylimidazole, 670-96-2; *N*-(ethoxymethyl)-2-phenyl-5-(hydroxymethyl)imidazole, 86119-55-3; *N*-(ethoxymethyl)-2-phenyl-5-carbethoxyimidazole, 86119-56-4; (*N*-(ethoxymethyl)-2-phenyl-5-imidazolyl)-carboxylic acid, 86119-57-5; 2-phenyl-4(5)-bromoimidazole, 86119-58-6; *N*-methyl-2-phenyl-5-bromoimidazole, 71045-44-8; *N*-mdthyl-2-phenyl-4-bromoimidazole, 86119-59-7; *N*-methyl-2-phenyl-4-carboethoxyimidazole, 86119-60-0; bis(*N*(1)-ethoxymethyl-2-phenyl-*N*(3)-methylimidazolylium) ketone bis(tetrafluoroborate), 86119-62-2; *N*-methyl-2-methylimidazole, 1739-84-0; *N*-(ethoxymethyl)imidazole, 67319-04-4; 2-methylimidazole, 693-98-1; chloromethyl ethyl ether, 3188-13-4; diethyl carbonate, 105-58-8; methyl formate, 107-31-3; formaldehyde, 50-00-0; ethyl chloroformate, 541-41-3; 4,5-dibromo-2-phenylimidazole, 56338-00-2; zinc, 7440-66-6.

(17) Obtained as an Aldrich Speciality Chemical.