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Discovery of Novel Catalysts for Alkene Epoxidation from Metal-Binding Combinatorial Libraries**

Matthew B. Francis and Eric N. Jacobsen*

The quest for practical routes to chiral intermediates has inspired extensive research activity in the field of asymmetric catalysis, which has resulted in the development of numerous useful, highly enantioselective reactions. The vast majority of effective catalysts discovered thus far are metal complexes bearing specific ligands that direct the outcome of the catalytic reaction through control of the steric and electronic properties of the metal center. While progress has been made in elucidating the nature of these interactions, the identification of this finely tuned match between the metal ion and its coordination environment remains difficult and continues to limit the pace of reaction discovery.

Research directed toward the development of new systems for asymmetric catalysis can be divided into two phases. In the initial lead discovery phase effort is directed toward screening a wide variety of metal complexes with the goal of identifying a novel catalyst system for the reaction of interest. This is typically followed by a lead optimization stage wherein a highly enantioselective and reactive system is sought through systematic variation of the ligand components and reaction conditions. In the latter context, combinatorial chemistry has already emerged as a powerful tool: useful chiral catalysts have been obtained through the synthesis and analysis of parallel libraries of structural analogues based on a previously identified design motif.[1] However, despite the utility of combinatorial chemistry for the efficient investigation of systems that involve numerous interrelated variables, the application of such strategies to catalyst lead discovery remains underexplored. We reported recently the application of metal-binding combinatorial libraries to the identification of coordination complexes.[2] Herein we describe the successful elaboration of this strategy to the discovery of novel catalyst leads for a reaction of synthetic interest, namely the asymmetric epoxidation of olefins with hydrogen peroxide.

Because of the extreme sensitivity of oxidation systems to the exact coordination environment around the metal center[3] an ideal library design for the discovery of epoxidation catalysts—and selective catalysts in general—should consist of the widest possible variety of metal ions bound by an assortment of ligands, providing diverse coordination environments. Our initial approach to such a library design is depicted in Scheme 1. The general structural motif involves

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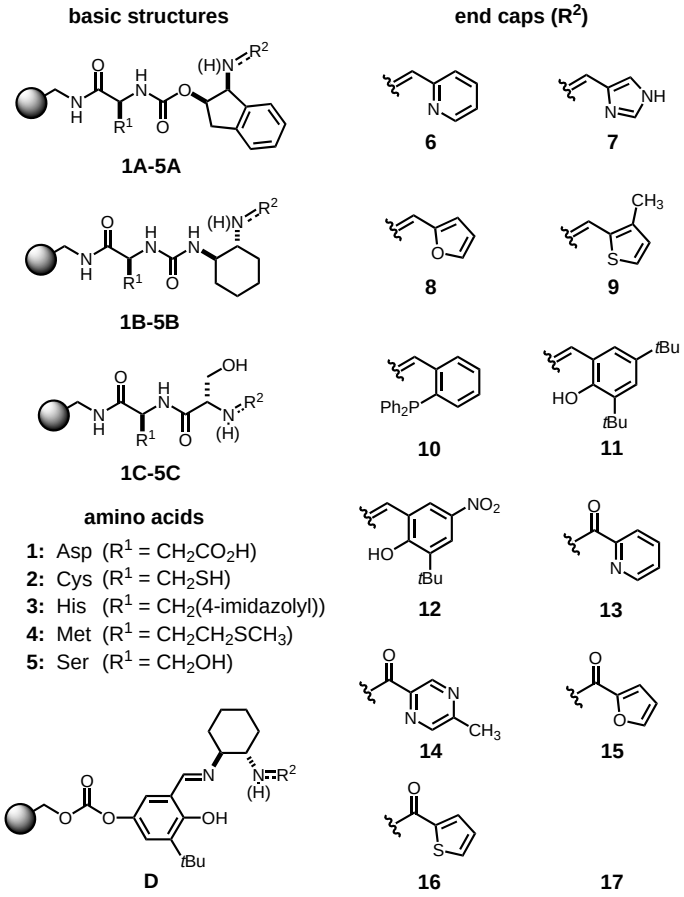

Scheme 1. Composition of a ligand library for transition metals. Sixteen basic core structures were synthesized on a polystyrene support (0.6 mmol g^{-1} loading, 100–200 mesh particle size), represented by the shaded sphere. A series of 12 end caps were attached, and resulted in the formation of 192 potential ligand structures.

the joining of potential metal-binding moieties by chiral linking groups, and is envisioned to provide a binding pocket for metal-ion guests. Thus, five amino acids that displayed a variety of donor side chains were coupled to aminomethyl polystyrene (100–200 mesh particle size, 0.6 mmol g^{-1} loading) by standard peptide coupling techniques.[4] Three linking elements were attached to these building blocks. Derivatives of 1-amino-2-indanol (**1A**–**5A**) and *trans*-1,2-diaminocyclohexane (**1B**–**5B**) were chosen to represent conformationally restricted backbones, and the amino acid serine was incorporated to furnish less rigid binding environments (**1C**–**5C**). In order to include structures similar to known epoxidation catalysts, salicylimine **D** was prepared by coupling 6-*tert*-butyl-4-hydroxysalicylaldehyde to polystyrene substituted with 4-benzyloxybenzyl alcohol (Wang resin), followed by condensation with one equivalent of 1,2-diaminocyclohexane. A series of 12 capping agents **6**–**17**, chosen to incorporate a range of heterocycles, phosphanes, and salicylimines through imine and amide bond formation, were attached to the resulting 16 basic structures. The resulting library of 192 potential ligands was then pooled in preparation for metal ion insertion.

A set of 30 metal ion sources, which differed in metal ion identity, oxidation state, and counterion, was chosen for incorporation. A pool of the ligand library was exposed to a 0.02 M solution[5] of each metal ion in THF or THF/MeOH for 1 hour. Facile isolation of the desired complexes was achieved by filtration and thorough rinsing of the beads. After the entire catalyst library was pooled, visual detection of the metal-complex colors combined with the application of qualitative inorganic staining reagents[2] indicated that approximately 80% of the 5760 possible metal–ligand complexes had been prepared (Figure 1). In all cases, the binding of metal ions to the unfunctionalized polymer support was not observed.

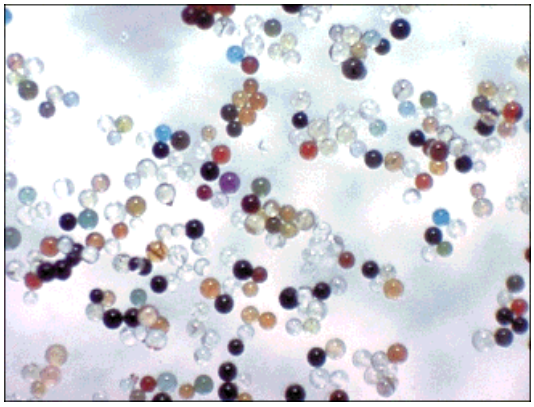

Figure 1. Portions of the ligand library depicted in Scheme 1 were exposed in separate reaction vessels to each of the 30 metal ion sources listed in Figure 2. This microscope photo shows the colors of the potential 5760 metal–ligand complexes after recombination. Each polymer bead is 90 μm in diameter.

The identification of catalysts from large libraries is a challenging endeavor. In addition to issues of rate and turnover number,[6] the ability to distinguish desired reactivity from nonproductive or unselective pathways is of crucial importance. In the present context, we have chosen to directly assay the products of catalytic reactions by using high-throughput chromatographic techniques. In the case of parallel libraries this allows the full and unambiguous evaluation of each catalyst synthesized, and this approach can be used to accurately screen for virtually any reaction. In addition, while the screening of catalyst mixtures by this technique may not yield reliable information about enantioselectivity, it can be used to rapidly differentiate pools of catalysts that produce the desired product from pools of catalysts that do not. In this way catalyst libraries too large for parallel screening can be reduced to manageable numbers of catalyst candidates in an efficient manner.

Our strategy for the identification of epoxidation catalysts therefore involved a three step process. First, the entire pooled catalyst library was screened for compatible reaction conditions for the epoxidation of the model substrate *trans*-β-methylstyrene (TBMS). This screening led to the identification of aqueous H_2O_2 as a viable oxidant.[7] Its low cost, lack of deleterious by-products, and ease of handling make hydrogen peroxide a particularly practical oxidant; however, the associated disproportion and homolytic bond cleavage pathways have limited its use with most epoxidation systems.[8] The optimal solvent system was found to be a 1/1 mixture of CH_2Cl_2 and *tert*-butanol, which was selected for its inertness

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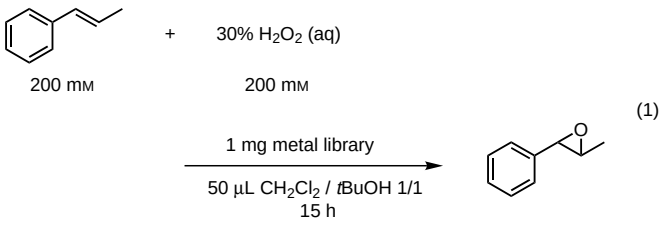
toward redox reactions and its ability to dissolve appreciable amounts of aqueous H_2O_2 while still swelling the polystyrene beads.

The second stage in the screening process involved the determination of active metal libraries for the epoxidation of TBMS with aqueous H_2O_2. For this purpose catalyst sub-libraries were prepared that contained a mixture of all 192 ligands and each individual metal source. Samples of the catalyst pools[9] were exposed to 50 μL of a TBMS/H_2O_2 solution (each 0.2 M) in CH_2Cl_2/*t*BuOH (1/1) for 15 h [Eq. (1)].



(1)

Subsequent GC analysis of the reaction solutions revealed that several of the metal libraries demonstrated epoxidation activity, with those prepared with $VOSO_4$ and $FeCl_2$ proving the most effective (Figure 2).[10] A screen of the unbound metal ion sources indicated that $VOSO_4$ displayed epoxidation activity in the absence of the ligand library; however, the activity in iron libraries was strongly dependent on the presence of the ligands. It was also observed that the source of iron was important, with complexes prepared with $FeCl_2$ being roughly twofold more active for epoxidation than $FeCl_3$ libraries, and much more active than those prepared with $Fe(acac)_3$ or $Fe(OAc)_2$ (not shown).

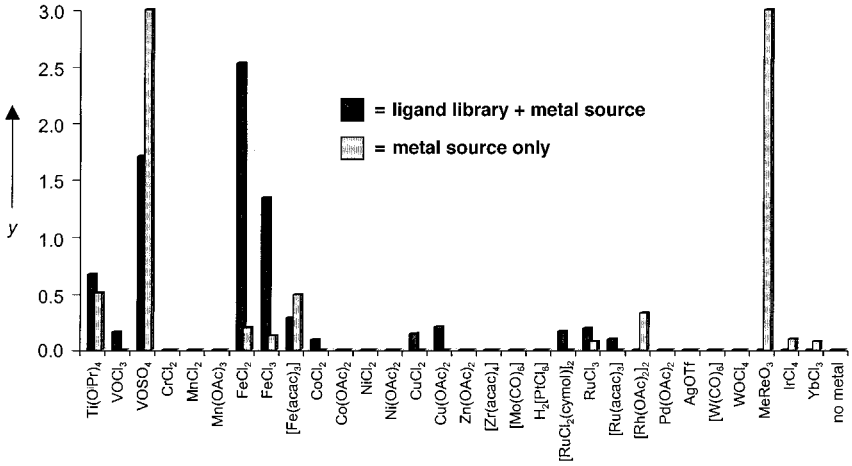


Figure 2. Epoxidation activity as a function of metal ion source under the conditions described in Equation (1). The *y* axis represents the ratio of detected epoxide product relative to an internal standard (relative yield). The dark bars represent the activity of each metal ion in the presence of the pooled ligand library, and the light gray bars indicate the activity of the metal ion sources in the absence of the ligands.

Upon determining that $FeCl_2$-derived libraries displayed ligand-promoted epoxidation catalysis, the third step in the screening process was to identify the ligand components necessary for catalytic activity. The ligand library was prepared in 12 batches, each containing a mixture of the 16 basic structures and a different end cap, and the corresponding $FeCl_2$ complexes were screened under the conditions described above for the epoxidation of TBMS. From the resulting data (Figure 3) it is evident that the end caps have a dramatic effect on epoxidation activity, with pyridine-containing end caps **6** and **13** producing the most active catalyst libraries. Piperazine cap **14** promoted epoxidation to a lesser extent, while all of the other end cap libraries led to very low levels of epoxide formation.

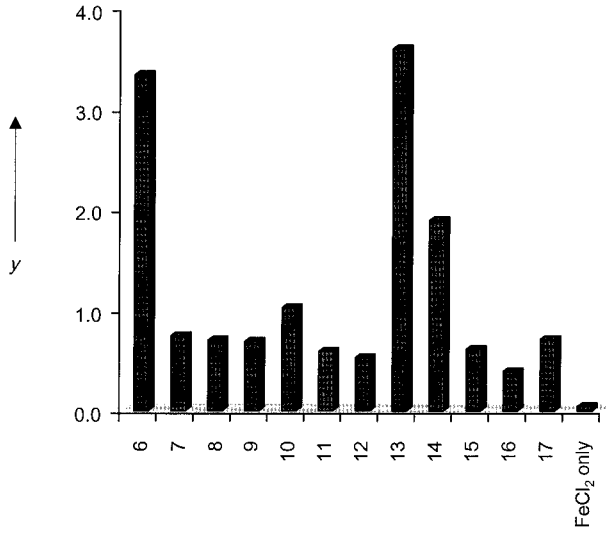


Figure 3. Epoxidation activity for end cap sub-libraries prepared with $FeCl_2$ as the metal ion source. The *y* axis represents the yield of epoxide product relative to an internal standard, and corresponds to a mixture of the sixteen basic ligand structures with the indicated end cap.

The next logical step in the deconvolution of the catalyst library would be to identify active catalyst structures by evaluating only the sixteen compounds corresponding to the most active end cap pools. However, by overlooking the least active end cap libraries singularly active catalysts present among pools of inactive structures might be missed. We therefore chose to evaluate all of the 192 ligand structures individually[11] to check the validity of this strategy. Following metal complex formation with $FeCl_2$, each library member was screened in a parallel fashion for the epoxidation of TBMS with 30% H_2O_2, and a representation of the epoxide yield data appears in Figure 4. A quick inspection of the data reveals the presence of three ligand structures (**5C-6**, **5C-13**, and **2C-13**) that produce catalysts that are substantially more active than other structures in the library.

A comparison of the corresponding structures (**18**–**20**) reveals several similarities. First, all of the structures exhibit the expected pyridine-containing end caps **6** and **13**, which indicates that at least in this case a simple ligand deconvolution strategy would not have missed the most active catalysts. Second, the incorporation of serine as a linking

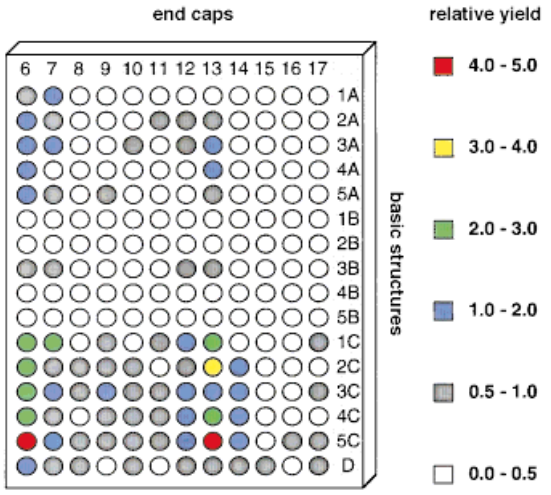
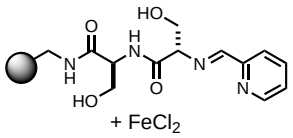
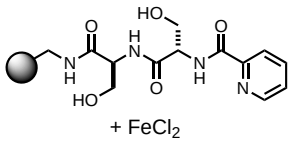


Figure 4. Epoxidation activity in a parallel library of iron complexes. Relative product yields are represented in a color-coded format (right), with the most active (red) combinations reaching 59% conversion. In all cases, the *cis*-epoxide product was not observed. The labeling of the ligands corresponds to Scheme 1.

group (**C**) gives rise to high levels of catalytic activity, while analogous structures with linking groups **A** and **B** are much less active. Finally, the amino acid attached to the solid support has a significant influence on catalytic activity, with serine-containing structures **18** and **19**, and cystine-containing



18



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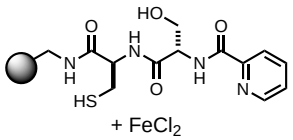

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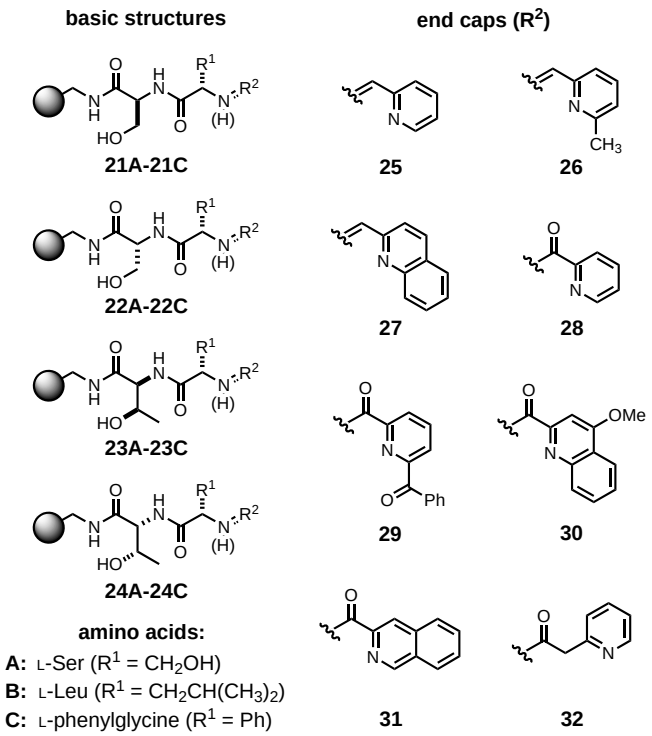
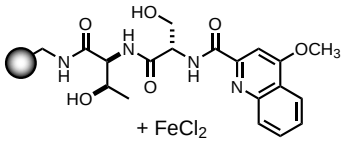
20 showing product yields twice as high as analogues prepared with other amino acids. The structures of all three ligands were confirmed by resynthesis and electrospray-MS analysis.[12]

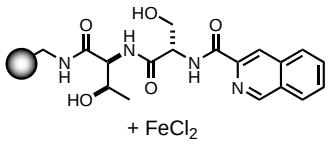
While these complexes represent structurally novel epoxidation catalysts, their value as lead structures would be greatly enhanced if they produced the epoxide products with measurable enantioselectivity. In fact, catalysts **18** and **19** did effect the epoxidation of TBMS in 4 and 7% ee, respectively; however, a better chiral ligand with higher enantioselectivities would clearly be desirable. To this end we have screened the parallel library[10] depicted in Scheme 2 for the epoxidation of TBMS, which led to the identification of structures **33**–**35** as moderately enantioselective catalysts.[13] Up to 78% conversion of TBMS can be obtained (with the epoxide as the sole reaction product) by using the optimized reaction conditions of 1.5 equiv of 30% H_2O_2 and 5 mol% of **34**.[12, 14]



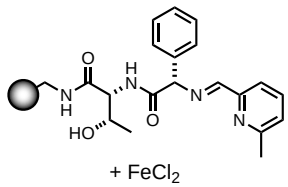
Scheme 2. Composition of an optimization library based on identified epoxidation catalysts. Twelve basic core structures were synthesized, followed by attachment of eight end caps and incorporation of $FeCl_2$. The library of 96 compounds was prepared on a polystyrene support (0.6 mmol g^{-1} loading, 100–200 mesh particle size), represented by the shaded sphere.



33: 20% *ee* (*R*,*R*)



34: 20% *ee* (*R*,*R*)



35: 15% *ee* (*S*,*S*)

These experiments serve to illustrate the ability of combinatorial chemistry to discover catalysts that bear no structural resemblance to previously known systems. Through the efficient screening of a library of 5760 ligand–metal complexes three novel, highly efficient catalysts have been discovered for the epoxidation of TBMS with aqueous H_2O_2. An initial parallel optimization library has produced moderately enantioselective variants, which indicates that the evolution of additional libraries to obtain catalysts that produce synthetically useful enantioselectivities is worthy of pursuit. The identified structures show a synergistic depend-

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ence on metal ion, counterion, and all ligand components, and therefore would have been difficult to identify using traditional approaches. Furthermore, the screening method used in these studies should be immediately applicable to the discovery of catalysts for almost any desired reaction, and we are currently evaluating the scope of this strategy in our laboratories.

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Keywords: asymmetric catalysis · combinatorial chemistry · epoxidations · solid-phase synthesis

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[4] Experimental details for the library synthesis have been furnished as supporting information.

[5] For each metal library prepared the solution volume was chosen such that at least two equivalents of the metal source were available for complex formation.

[6] A recent advance in the screening of catalyst libraries has been the ingenious use of thermographic imaging to detect the heat generated by exothermic reactions that occur at reactive centers, thus distinguishing polymer-bound catalysts from pools of inactive structures. S. J. Taylor, J. P. Morken, *Science* **1998**, *280*, 267 – 270. See also M. T. Reetz, M. H. Becker, K. M. Kühling, A. Holzwarth, *Angew. Chem.* **1998**, *110*, 2792 – 2795; *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 2647 – 2650.

[7] Since the activity of a metal library could be a reflection of either the reaction efficiency or the number of catalysts present, all oxidants that showed detectable epoxidation activity were subjected to the deconvolution procedure outlined herein. In addition to H_2O_2(aq), anhydrous TBHP was also found to be effective, although a completely different set of active metals was obtained (which will be discussed elsewhere). No epoxidation activity was detected for oxidants such as O_2, $NaIO_4$, 4-phenylpyridine-*N*-oxide (4-PPNO), and *N*-methylmorpholine-*N*-oxide (NMO).

[8] Nevertheless, some examples have appeared, see a) C. Bolm, D. Kadereit, M. Valacchi, *Synlett* **1997**, *6*, 697 – 688; b) D. E. De Vos, B. F. Sels, M. Reynaers, Y. V. Subba Rao, P. A. Jacobs, *Tetrahedron Lett.* **1998**, *39*, 3221 – 3224; c) W. A. Herrmann, R. W. Fischer, D. W. Marz, *Angew. Chem.* **1991**, *103*, 1706 – 1708; Angew. *Chem. Int. Ed. Engl.* **1991**, *30*, 1638 – 1641; d) A. M. Al-Ajlouni, J. H. Espenson, *J. Am. Chem. Soc.* **1995**, *117*, 9243 – 9250; e) J. Rudolph, K. Reddy, J. P. Chiang, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 6189 – 6190; f) K. Sato, M. Aoki, M. Ogawa, T. Hashimoto, R. Noyori, *J. Org. Chem.* **1996**, *61*, 8310 – 8311; g) T. G. Traylor, S. Tsuchiya, Y. S. Byun, C. Kim, *J. Am. Chem. Soc.* **1993**, *115*, 2775 – 2781; h) P. Pietikainen, *Tetrahedron* **1998**, *54*, 4319 – 4326; i) T. Schwenkreis, A. Berkessel, *Tetrahedron Lett.* **1993**, *30*, 4785 – 4788.

[9] 1 mg library samples (equivalent to 10 copies of the full ligand set) were screened.

[10] Many other metal – ligand libraries produced a variety of non-epoxide reaction products or catalyzed the nonproductive disproportionation of H_2O_2 to O_2 and water.

[11] The facile synthesis of parallel ligand libraries was accomplished with an IRORI directed synthesis system.

[12] See supporting information.

[13] As would be expected, nearly all of the 96 $FeCl_2$ complexes provided good levels of epoxidation activity, which confirmed the validity of **18** and **19** as catalyst lead structures. However, ligands prepared with end cap **32** showed uniformly poor reactivity, which indicates that proper attachment of the pyridine ring to the peptide chain is of crucial importance.

[14] As immobilization of these catalysts to polymeric supports might influence their activity, the evaluation of soluble analogues is underway and will be reported in due course.

Long-Range Electron Transfer through DNA Films**

Shana O. Kelley, Nicole M. Jackson, Michael G. Hill,* and Jacqueline K. Barton*

The possibility of efficient DNA-mediated charge transport has been debated since the discovery of the double helix.[1, 2] Photoinduced electron transfer between reactants bound to DNA, or between bases contained within the π stack, has led to varied conclusions regarding the nature of DNA as a medium for long-range charge transport.[3–5] Consistently, however, species well stacked within the helix have exhibited remarkably fast electron transfer over long distances.[3] Indeed, the integrity of the base stack itself appears necessary for efficient long-range electron transfer, as perturbations caused by intervening mismatches or bulges greatly diminish the yields of DNA-mediated charge transport.[3, 6]

Electrochemistry has been used extensively to investigate the kinetics of electron transfer through self-assembled monolayers on solid surfaces.[7] Systems that feature redox-active head groups held at variable distances by aliphatic alkanethiols or conjugated linkers have yielded important information regarding the ability of different media to promote long-range electronic coupling. In an effort to investigate DNA-mediated electron transfer involving *ground-state* reactants, we have applied these methods to study redox-active intercalators bound at discrete sites within the individual helices of a DNA monolayer on gold.

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