ACS Catalysis

Letter

pubs.acs.org/acscatalysis

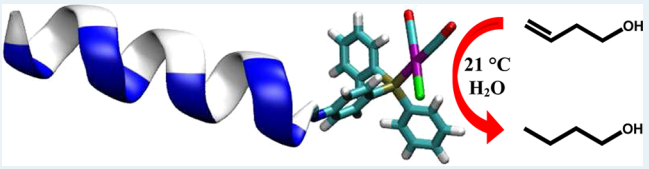
Active Hydrogenation Catalyst with a Structured, Peptide-Based Outer-Coordination Sphere

Avijita Jain,[†] Garry W. Buchko,* Matthew L. Reback, Molly O'Hagan, Bojana Ginovska-Pangovska, John C. Linehan,* and Wendy J. Shaw*

Pacific Northwest National Laboratory, Richland, Washington 99354, United States

Supporting Information

ABSTRACT: The synthesis, catalytic activity, and structural features of a rhodium-based hydrogenation catalyst containing a phosphine ligand coupled to a 14-residue peptide are reported. Both CD and NMR spectroscopy show that the peptide adopts a helical structure in 1:1:1 TFE/MeCN/H_2O that is maintained when the peptide is attached to the ligand and when the ligand is attached to the metal complex. The metal complex hydrogenates aqueous solutions of 3-butenol to 1-butanol at 360 ± 50 turnovers/Rh/h at 294 K. This peptide-based catalyst represents a starting point for developing and characterizing a peptide-based outer-coordination sphere that can be used to introduce enzyme-like features into molecular catalysts.



KEYWORDS: *outer-coordination sphere, peptide catalyst, bioinspired catalyst, hydrogenation catalysis, artificial enzyme*

An essential feature in the catalytic activity of metalloenzymes is a well-structured protein scaffold.[1−6] Although the majority of this scaffold does not interact directly with the metal (the outer-coordination sphere), its role in catalysis is well established with single-site mutagenesis that results in impeded or completely disabled enzymatic activity.[7] The outer-coordination sphere contributes channels that move substrates and products in a time-controlled manner between the buried active site and the exterior of the enzyme. Near the active site, weak interactions from precisely positioned amino acid residues in the scaffold control substrate specificity and product chirality as well as the hydrophobic and dielectric environment around the active site. Overall, the outer-coordination sphere creates a finely tuned cavity to control reactivity, resulting in faster rates than those observed for synthetic catalysts, with higher specificity and lower energy input. These observations suggest that attaching an outer-coordination sphere to organometallic catalysts has the potential to offer substantial improvements in catalysis.

Several groups have expanded our knowledge of the outer-coordination sphere using a top-down approach, generating synthetic enzymes by either modifying the active site of an enzyme or building a protein-like scaffold into which an active site is incorporated.[8−14] Because of the large size and complex nature of enzymes, a bottom-up approach of building a peptide-based outer-coordination sphere onto organometallic catalysts may allow the introduction of only the essential features of the outer-coordination sphere, resulting in enhanced catalytic activity while maintaining a relatively small catalyst. The bottom-up approach has largely focused on the synthesis and structural characterization of peptide-based metal complexes that have secondary or tertiary structure (or both) but have no demonstrated catalytic function.[15−21] Catalytic activity of complexes employing amino acid- and peptide-based catalysts in the absence of structural characterization have also been reported.[5,12,22−26]

Synthetic, peptide-based metal complexes that have been characterized structurally and catalytically are uncommon. Developing an elegant, if challenging, method for incorporating nonnatural amino acids with side chains modified to contain phosphines into peptides,[27] Gilbertson and co-workers synthesized a series of catalysts in which two phosphine-substituted amino acids were utilized to complex the metal. The resulting compounds were structurally characterized by NMR spectroscopy and shown to catalyze asymmetric hydrogenation.[28] Ball and co-workers utilized a simpler coordination approach by complexing dirhodium with tetracarboxylates composed of the side chains of acidic amino acids.[29,30] These catalysts were active for hydrosilylation; however, the synthetic method used to prepare the metal complex limits the presence of additional acidic amino acid residues in the sequence. In an important advancement in ligand design, amino acid and dipeptide phosphine derivatives were made by coupling the backbone amine, rather than the side chain, to the phosphine, allowing nearly any amino acid or peptide to be utilized.[31] Attaching two of these ligands to a metal complex resulted in catalysts with hydroformylation activity.

Together, these pioneering works demonstrate the ability to prepare and structurally characterize active peptide-based metal complexes. To advance the utilization of enzyme-like outer-coordination spheres in molecular catalysts, complexes containing longer peptides must be prepared and structurally

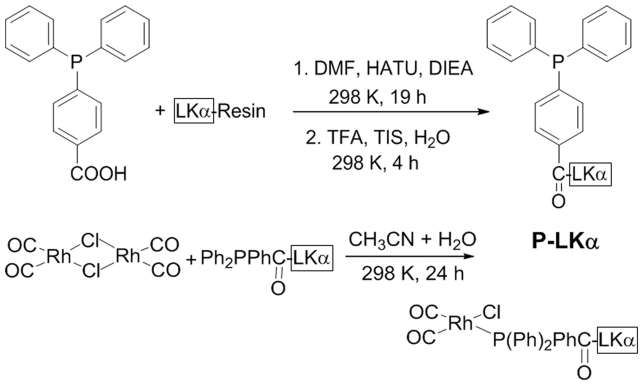
Received: June 28, 2012
Revised: August 11, 2012
Published: August 20, 2012

characterized, ideally using a simple strategy that attaches a single peptide at a single point to the metal complex.

Toward this goal, we report a high yield, single-step method of preparing a phosphine-substituted, 14-amino acid peptide by coupling the polypeptidyl N-terminus directly to 4-(diphenylphosphino)benzoic acid. The resulting ligand utilizes the single phosphine attachment point to complex only one peptidyl phosphine with a single rhodium metal. The peptide in both the ligand and ligand–metal complex were structurally characterized to assess the consequences of the chemistry on the peptide's structure and potential interactions of the peptide with the metal complex. The resulting active hydrogenation catalyst represents a starting point for the introduction of a variety of features in the outer-coordination sphere with which to test its function in molecular catalysts.

Peptide Selection and Complex Synthesis. By beginning with a structurally stable peptide, we anticipated that the attachment to the ligand would not alter the peptide's structure. Therefore, a model 14-residue amphipathic peptide, Ac-LKKLLKLLKKLLKL-NH_2 (LKα), which adopts a helical conformation in solution, was chosen.[32] The LKα-phosphine ligand (P–LKα) was synthesized by coupling 4-(diphenyl phosphino)benzoic acid to the peptide bound to a Rink-amide resin using standard solid phase peptide synthesis under an N_2 atmosphere, as shown in Scheme 1.[33] The ligand was cleaved from the resin and obtained in good yield (~80%). Complete coupling of the peptide to the phosphine was confirmed by a significant shift of the N-terminal amide, as observed in the $^1H-^{15}N$ HSQC spectrum before and after the reaction. Metalation of the designed ligand with *cis*-[Rh((CO)$_2$Cl)$_2$] yielded the rhodium phosphine complex, *cis*-[(CO)$_2$ClRh(P–LKα)], (Scheme 1). This complex was characterized by mass spectrometry, IR spectroscopy, and ^1H, ^{15}N and $^{31}P\{^1H\}$ NMR spectroscopy.

Scheme 1. Preparation of the Phosphine-Substituted Peptide, P–LKα (top) and the Metal Complex, *cis*-[(CO)$_2$ClRh(P–LKα)] (bottom)



The $^{31}P\{^1H\}$ NMR spectrum shows a resonance at 44.2 ppm (J_{Rh-P} = 166.3 Hz) with no unbound ligand, confirming complete incorporation of P–LKα into the metal complex. Infrared spectroscopy shows the presence of two metal-bound carbonyl groups, and mass spectrometry confirms the predicted molecular weight, all of which are consistent with the proposed metal complex structure shown in Scheme 1.

Structural Characterization. The $^1H^N$, $^{15}N^H$, and $^1H^\alpha$ chemical shifts for the free peptide (LKα), the phosphine-substituted peptide (P–LKα), and the phosphine-substituted peptide in the metal complex (*cis*-[(CO)$_2$ClRh(P–LKα)] were fully assigned using 2D ^1H NMR spectroscopy (NOESY, TOCSY, and $^1H-^{15}N$ HSQC) (Supporting Information Table S1). Data were collected in a solvent system in which all samples were soluble and the water resonance did not interfere with the assignment of the $^1H^\alpha$ chemical shifts: 33% MeCN, 33% TFE, 27% H_2O, and 7% D_2O at pH = 3.5. In addition to solubility, acetonitrile and trifluoroethanol are known to stabilize nascent structures.[34–36] As shown in Figure 1, the chemical shifts of the amide resonances for all three compounds are well dispersed in both the ^1H and ^{15}N dimension in the $^1H-^{15}N$ HSQC spectra. Such dispersion, especially for a highly repetitive peptide sequence, indicates the peptide has adopted an ordered structure in solution.[37] Aside from the L1 amide resonance of LKα, which shifts significantly upon the addition of the phosphine ligand to the N-terminus (Figure 1), there is little perturbation in the chemical shifts of the other peptide amide resonances in all three compounds, suggesting that the peptide adopts a similar structure in each compound.

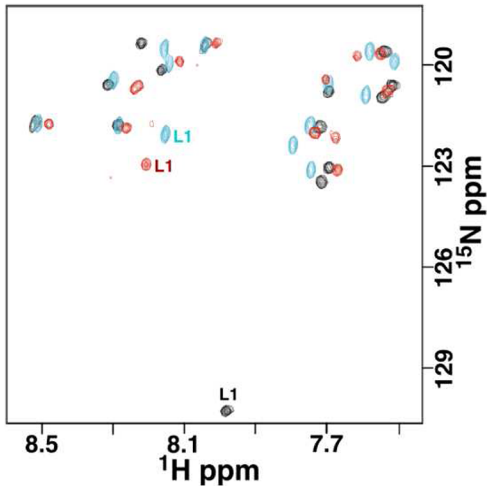


Figure 1. Overlay of the $^1H-^{15}N$ HSQC spectra of LKα (black), P–LKα (blue), and *cis*-[(CO)$_2$ClRh(P–LKα)] (red) collected in 1:1:1 TFE/MeCN/H_2O, 293 K. The large dispersion in chemical shifts is indicative of canonical structure, and the similarity in chemical shifts for each compound suggests the peptide adopts a similar structure in LKα, P–LKα, and *cis*-[(CO)$_2$ClRh(P–LKα)]. The large shift of L1 from LKα to P–LKα confirms attachment of the peptide to the ligand.

Analysis of the NOESY data indicates that the ordered structure is helical in nature, as illustrated in the expansion of the $^1H^N$ to $^1H^\alpha$ region in Supporting Information Figure S1. Throughout the sequence, long-range $^1H^N(i)$ to $^1H^\alpha(i-3)$ NOEs, characteristic of an α-helix, are observed. The helical nature is corroborated by circular dichroism data, as shown for *cis*-[(CO)$_2$ClRh(P–LKα)] in Figure 2. In the presence of 1:1:1 MeCN/TFE/H_2O and 1:3 MeCN/H_2O, negative bands with double minima at 222 and 208 nm are observed for *cis*-[(CO)$_2$ClRh(P–LKα)]. The double minimum is a distinct feature of an α-helical structure, although some dispersion in structure is suggested by the unequal intensity of the two negative bands. The likely source for the latter feature is a contribution of random coil conformations to the observed CD spectrum, as suggested by DeGrado and co-workers for the same feature observed in the CD spectrum of LKα in 0.15 mM

dx.doi.org/10.1021/cs3004177 | ACS Catal. 2012, 2, 2114–2118

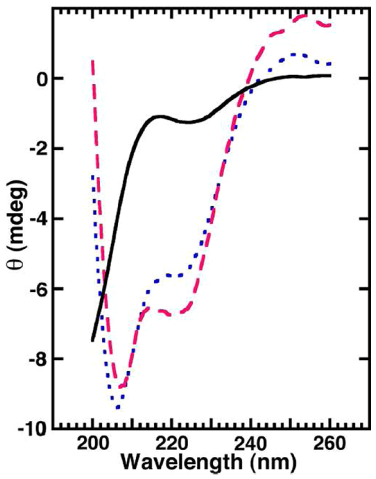


Figure 2. Circular dichroism spectrum of LKα in water (solid black) and *cis*-[$(CO)_2$ClRh(P−LKα)] in 1:3 MeCN/H_2O (dashed red) and 1:1:1 TFE/MeCN/H_2O (dotted blue). Helical structure is evident in the latter two solvents by the negative absorption bands at 222 and 208 nm^{-1}.

NaCl.[32] Therefore, this short peptide, while primarily helical in 1:1:1 MeCN/TFE/H_2O, may undergo some dynamic oscillations in solution that result in local opening of the helix. Although LKα was reported to form a four-helix bundle in 0.15 mM NaCl,[32] the narrow line widths of the resonances in the 1D ^{1}H NMR spectrum of LKα, P−LKα, and *cis*-[$(CO)_2$ClRh(P−LKα)] in 1:1:1 MeCN/TFE/H_2O are characteristic of monomeric compounds. No proton NOEs were observed between the peptide and the bulky phenyl groups, suggesting that the predominantly helical peptide is extended away from the active site, as depicted in Figure 3.

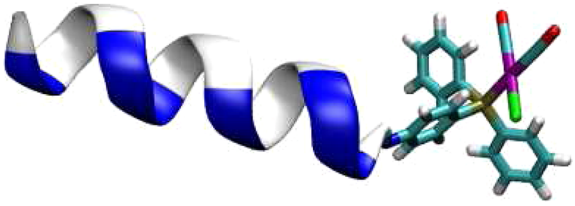


Figure 3. A simple cartoon of *cis*-[$(CO)_2$ClRh(P−LKα)]'s structure based on the NMR, CD, and IR data.

Catalytic Activity. The catalytic activity of *cis*-[$(CO)_2$ClRh-(P−LKα)] for hydrogenation of 3-buten-1-ol to 1-butanol in D_2O was tested in operando using high-pressure NMR spectroscopy. A specially designed PEEK tube[38,39] was used to introduce 500 psi H_2, employing a vortex mixer between scans to ensure adequate gas−liquid mixing. The turnover frequency for conversion of 3-buten-1-ol to 1-butanol was determined from the linear portion of the kinetic data and was found to be 360 ± 50 turnovers/Rh/h. This is a reasonable activity for a hydrogenation catalyst, although it is slower than the parent catalyst (*cis*-[$(CO)_2$ClRh(4-(diphenylphosphino)-benzoic acid)]) with no appended peptide, 1800 ± 300 turnovers/Rh/h. This suggests that although the active site is still accessible in the peptide-containing catalyst, the peptide does slow catalysis, possibly as a result of steric inhibition. The catalysis experiment was repeated by mixing uncoupled parent catalyst and free peptide (LKα) together. No significant difference was observed, as compared with the turnover rate of the parent catalyst alone, confirming that the mere presence of the peptide was not inhibiting catalysis.

The catalyst could be recovered and reused multiple times, achieving similar activities. Since the catalyst was unstructured in water, catalysis experiments were also performed in 1:3 MeCN/D_2O, a solvent system that induces a helical structure similar to that observed in 1:1:1 MeCN/TFE/H_2O (Figure 2). The turnover rate in 1:3 MeCN/D_2O was similar to the rate observed in D_2O. In a 1:1:1 mixture of MeCN/TFE/D_2O, no catalytic activity was observed, and although the physical explanation for catalyst inactivation by TFE is unknown, both CD and NMR spectroscopy show that the peptide is structured similarly in 1:3 MeCN/H_2O and 1:1:1 MeCN/TFE/H_2O (Figure 2), suggesting that the TFE interacts with the Rh. Direct investigation of the catalyst in operando by ^{31}P NMR revealed no observable differences in the ^{31}P NMR spectrum with the addition of 3-buten-1-ol and H_2. This suggests that *cis*-[$(CO)_2$ClRh(P−LKα)] is a catalyst precursor, requiring conversion into the catalytically active species during catalysis, which is consistent with the proposed mechanism for Wilkinson's-based catalysts.[40]

■ CONCLUSIONS

Using a bottom-up approach and implementing a simple synthetic strategy, we have developed an active peptide-based catalyst containing a peptide that has been structurally characterized and found to have a predominantly helical structure. Because the phosphine-substituted peptide may be prepared with any peptide sequence containing a free N-terminus, this method allows the incorporation of any peptide sequence into the peptide-based metal complex. The single point attachment of the ligand to the metal and the attachment of only one metal per peptide greatly simplifies characterization and purification by eliminating the possibility of unwanted dimeric to polymeric byproducts. The simplicity of this approach may allow more flexibility in the three-dimensional structure of the peptide around the metal complex, and ultimately, should be applicable to many types of organometallic catalysts.

The next step is to advance from peptides that contain only secondary structure, as demonstrated here, to peptides that adopt stable secondary *and* tertiary structures around the active site. The placement of functional groups with hydrogen bonding potential, such as $-NH_2$, $-OH$, and $-COOH$, on the phosphine phenyl rings may aid in stabilizing tertiary structures. Peptides with known tertiary structure and advanced computational design methods will assist the future development of catalysts with stabilized structures. These catalysts will allow the precise positioning of enzyme-like features to improve catalysis as well as allowing structure-based mechanisms to be established.

■ EXPERIMENTAL SECTION

General Procedures. Solution state ^{1}H and ^{31}P NMR spectra were recorded on Varian Inova or VNMRS spectrometers (500 to 800 MHz ^{1}H frequency). All ^{31}P{^{1}H} chemical shifts were externally referenced to phosphoric acid. Proton chemical shifts were internally calibrated to residual monoprotic solvent impurity.[41] Two-dimensional ^{1}H−^{1}H TOCSY and NOESY spectra and natural abundance ^{1}H−^{15}N HSQC spectra were collected for LKα, P−LKα, and *cis*-[$(CO)_2$ClRh(P−LKα)] at 293 K. Circular dichroism spectra

dx.doi.org/10.1021/cs3004177 | *ACS Catal.* 2012, 2, 2114−2118

were collected at 297 K on an Aviv model 410 spectropolarimeter (Lakewood, NJ).

Synthesis and Materials. All experiments were carried out using standard Schlenk or inert-atmosphere glovebox techniques. Acetonitrile was purchased from Alfa Aesar, and diethyl ether from Honeywell Burdick & Jackson. Solvents were dried using an Innovative Technology, Inc. PureSolv solvent purification system. Diisopropylethyl amine (DIEA), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (HOBT), 4-(diphenylphosphino)benzoic acid, and trifluoroacetic acid (TFA) were purchased from Sigma Aldrich. All chemicals were used as received. LKα was synthesized, with an N-terminal acetyl group or FMOC group, on the polystyrene-based Rink-Amide resin at the Protein Chemistry Technology Center, University of Texas, Dallas, TX.

Synthesis of 4-(Diphenylphosphino)Phenyl Amide−LKα (P−LKα). The coupling of 4-(diphenylphosphino)benzoic acid to LKα to make P−LKα was performed on the Rink Amide resin. The fluorenyl methoxy carbonyl (FMOC) group was removed by stirring the resin-bound peptide (0.3 g, 0.0675 mmol) (loading: 0.225 mmol/g) in 20 mL of 20% piperidine in *N*-methylpyrrolidone (NMP). The resin was then rinsed with 60 mL of NMP, followed by 60 mL of CH_2Cl_2, and filtered using a medium frit. 4-(Diphenylphosphino)benzoic acid (0.05 g, 0.135 mmol), HOBT (0.025 g, 0.067 mmol), and DIEA (0.12 uL, 0.067 mmol) were stirred for 25 min in 10 mL of DMF. The FMOC deprotected resin was then added to the above solution. The solution was stirred at room temperature for 19 h, followed by filtering using a medium frit and collection of the phosphine-modified peptidyl resin. The resin was rinsed with 100 mL DMF and 100 mL acetonitrile to remove unreacted 4-(diphenylphosphino)benzoic acid.

To cleave P−LKα from the resin, a mixture of TFA (4.75 mL), triisopropylsilane (0.125 mL), and water (0.125 mL) were added to the solid and stirred for 4 h. The resulting reaction mixture was filtered, and the volume of the filtrate was reduced to 1 mL under vacuum. The product was then flash-precipitated by addition of this solution to 60 mL of stirring diethyl ether (cold). Yield: 0.11 g, 0.05 mmol, 82.3%. $^{31}P\{^1H\}$ NMR (50% H_2O in CD_3CN): (−6.0 ppm). MALDI MS: *m*/*z* calcd for P−LKα: 1978; found: [P−LKα + $2H^+$], 1980.64.

Synthesis of *cis*-[$(CO)_2$ClRh(P−LKα)]. P−LKα (20 mg, 0.011 mmol) was dissolved in 10 mL of CH_2Cl_2. A 200 μL solution of *cis*-[$(Rh(CO)_2Cl)_2$] (17.6 mg, 0.005 mmol) in CH_2Cl_2 was added dropwise to the first solution over a course of 10 min. The reaction was stirred at room temperature for 24 h. The solvent was removed under vacuum. The resulting solid was washed with 50 mL of diethyl ether to remove unwanted impurities. $^{31}P\{^1H\}$ NMR (10% H_2O in CD_3CN: (44.2 ppm) (J_{Rh-P} = 166.3 Hz). Yield: 0.020 g, 0.009 mmol, 85.0%. MALDI MS *m*/*z* calcd for *cis*-[$(CO)_2$ClRh(P−LKα)]: 2173. Found: *cis*-[$(CO)_2$ClRh(P−LKα)] − $2H^+$], 2171. IR (KBr) ν_{CO}: 2002, 2077 cm^{-1}.

Catalysis. High pressure NMR experiments were performed at room temperature (~294 K) using a standard Varian two-channel probe. A high pressure PEEK cell[38,39] was used to allow in operando catalysis. Complete mixing was obtained by vortexing the PEEK tube between runs. Solutions were evacuated to 100 mT prior to the introduction of 500 psi H_2. The catalyst concentration used was 0.011 M, with a 3-buten-1-ol concentration of 3.8 M. Typically, the solvent used for catalysis was D_2O, but 1:3 MeCN/D_2O and 1:1:1 TFE/MeCN/D_2O were also used.

Pictorial representations of the molecule (Figure 3 and table of contents figure) were generated using the Visual Molecular Dynamics (VMD) program.[42]

■ ASSOCIATED CONTENT

Supporting Information

Table of $^1H^N$, $^1H^\alpha$, and $^{15}N^H$ chemical shifts; ^{31}P spectra of the ligand and the metal complex; MALDI spectrum of the metal complex. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mails: (W.J.S.) wendy.shaw@pnnl.gov, (J.C.L.) john.linehan@pnnl.gov, (G.W.B.) garry.buchko@pnnl.gov.

Present Address

[†]Department of Chemistry, Indiana University of Pennsylvania, Indiana, PA

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the U.S. Department of Energy Basic Energy Sciences, Chemical Sciences, Geoscience and Biosciences Division (A.J., J.C.L., and W.J.S.), the Office of Science Early Career Research Program through the Office of Basic Energy Sciences (G.W.B., M.L.R., B.G.-P. and W.J.S.), and the Center for Molecular Electrocatalysis, an Energy Frontier Research Center funded by the US Department of Energy, Office of Science, Office of Basic Energy Sciences (M.O.). Part of the research was conducted at the W.R. Wiley Environmental Molecular Sciences Laboratory, a national scientific user facility sponsored by U.S. Department of Energy's Office of Biological and Environmental Research (BER) program located at Pacific Northwest National Laboratory (PNNL). PNNL is operated by Battelle for the U.S. Department of Energy.

■ REFERENCES

(1) Nanda, V.; Koder, R. L. *Nat. Chem.* **2010**, *2*, 15.
(2) Karlin, S.; Zhu, Z.; Karlin, K. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14225.
(3) Karlin, S.; Zhu, Z. Y.; Karlin, K. D. *Biochemistry* **1998**, *37*, 17726.
(4) Thomas, C. M.; Ward, T. R. *Chem. Soc. Rev.* **2005**, *34*, 337.
(5) Shaw, W. J. *Catal. Rev.* **2012**, DOI: 10.1080/01614940.2012.679453.
(6) Lee, J.; Goodey, N. M. *Chem. Rev.* **2011**, *111*, 7595.
(7) Creighton, T. E. *Proteins*; W.H. Freeman and Company: New York, 1996.
(8) Kaplan, J.; DeGrado, W. F. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11566.
(9) Lu, Y.; Yeung, N.; Sieracki, N.; Marshall, N. M. *Nature* **2009**, *460*, 855.
(10) Marshall, N. M.; Garner, D. K.; Wilson, T. D.; Gao, Y.-G.; Robinson, H.; Nilges, M. J.; Lu, Y. *Nature* **2009**, *462*, 113.
(11) Rothlisberger, D.; Khersonsky, O.; Wollacott, A. M.; Jiang, L.; DeChancie, J.; Betker, J.; Gallaher, J. L.; Althoff, E. A.; Zanghellini, A.; Dym, O.; Albeck, S.; Houk, K. N.; Tawfik, D. S.; Baker, D. *Nature* **2008**, *453*, 190.
(12) Lombardi, A.; Nastri, F.; Pavone, V. *Chem. Rev.* **2001**, *101*, 3165.
(13) Ward, T. R. *Acc. Chem. Res.* **2011**, *44*, 47.
(14) Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1978**, *100*, 306.
(15) Laplaza, C. E.; Holm, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10255.

(16) Roy, S.; Shinde, S.; Hamilton, G. A.; Hartnett, H. E.; Jones, A. K. *Eur. J. Inorg. Chem.* **2011**, 1050.
(17) Salgado, E. N.; Radford, R. J.; Tezcan, F. A. *Acc. Chem. Res.* **2010**, *43*, 661.
(18) Moriuchi, T.; Hirao, T. *Acc. Chem. Res.* **2010**, *43*, 1040.
(19) Ogawa, M. Y.; Gretchikhine, A. B.; Soni, S.-D.; Davis, S. M. *Inorg. Chem.* **1995**, *34*, 6423.
(20) Barisic, L.; Cakic, M.; Mahmoud, H. A.; Liu, Y.-n.; Kraatz, H.-B.; Pritzkow, H.; Kirin, S. I.; Metzler-Nolte, N.; Rapic, V. *Chem.—Eur. J.* **2006**, *12*, 4965.
(21) Albada, H. B.; Wieberneit, F.; Dijkgraaf, I.; Harvey, J. H.; Whistler, J. L.; Stoll, R.; Metzler-Nolte, N.; Fish, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 10321.
(22) Christensen, C. A.; Meldal, M. *Chem.—Eur. J.* **2005**, *11*, 4121.
(23) Coquiere, D.; Bos, J.; Beld, J.; Roelfes, G. *Angew. Chem.* **2009**, *121*, 5261.
(24) Landis, C. R.; Clark, T. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5428.
(25) Breit, B.; Laungani, A. *Tetrahedron: Asymmetry* **2003**, *14*, 3823.
(26) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755.
(27) Gilbertson, S. R.; Wang, X. *J. Org. Chem.* **1996**, *61*, 434.
(28) Gilbertson, S. R.; Chen, G.; Kao, J.; Beatty, A.; Campana, C. F. *J. Org. Chem.* **1997**, *62*, 5557.
(29) Zaykov, A. N.; Popp, B. V.; Ball, Z. T. *Chem.—Eur. J.* **2010**, *16*, 6651.
(30) Zaykov, A. N.; MacKenzie, K. R.; Ball, Z. T. *Chem.—Eur. J.* **2009**, *15*, 8961.
(31) Laungani, A. C.; Slattery, J. M.; Krossing, I.; Breit, B. *Chem.—Eur. J.* **2008**, *14*, 1.
(32) DeGrado, W. F.; Lear, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 7684.
(33) Jain, A.; Lense, S.; Linehan, J. C.; Raugei, S.; Cho, H.; DuBois, D. L.; Shaw, W. J. *Inorg. Chem.* **2011**, *50*, 4073.
(34) Sonnichsen, F. D.; Van Eyk, J. E.; Hodges, R. S.; Sykes, B. D. *Biochemistry* **1992**, *31*, 8790.
(35) Arunkumar, A. I.; Kumar, T. K. S.; Sivaraman, T.; Yu, C. *Biol. Macromol.* **1997**, *21*, 299.
(36) Krittanai, C.; Panyim, S. *J. Biochem. Mol. Biol.* **2004**, *37*, 460.
(37) Buchko, G. W.; Niemann, G.; Baker, E. S.; Belov, M. E.; Smith, R. D.; Heffron, F.; Adkins, J. N.; McDermott, J. E. *Mol. BioSyst.* **2010**, *6*, 2448.
(38) Yonker, C. R.; Linehan, J. C. *Prog. Nucl. Magn. Reson. Spectrosc.* **2005**, *47*, 95.
(39) Yonker, C. R.; Linehan, J. C. *J. Organomet. Chem.* **2002**, *650*, 249.
(40) Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980.
(41) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.
(42) Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33−38.