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Molecular diversity approach to the synthesis of peptide-derived ruthenium complexes and their evaluation as oxidation catalysts

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Abstract

This paper reports the synthesis of a small library of peptide-derived ruthenium complexes as potential oxidation catalysts. Evaluation of the solid-supported complexes identified several potentially promising epoxidation catalysts. Liberation of the promising catalysts from the solid-support resulted in catalysts with improved activity.

Keywords: supported reagents/reactions.

The search for new oxidation catalysts with improved efficiency and selectivity is a continuing source of interest in the organic chemistry community. Among these catalysts, the metalloporphyrins have been the focus of much attention as alkene oxidants.[1] A number of contributions in this field have shown that the regioselectivity and stereoselectivity[2] of these reactions can be affected by the ligand architecture and donor properties around the metal.[3] However, the introduction of the structural diversity and varying donor properties necessary for catalyst optimization is not easily achieved in porphyrin systems.[4] Interestingly, the existence of non-heme-based biological metal-oxo catalysts[5] indicates that the synthesis of a peptide-derived ligand library could allow the generation of the necessary diversity for the discovery and optimization of novel oxidation catalysts.[6] This work describes the solid-phase synthesis of a small library of solid-supported peptide-derived ligands (dipeptides) and the evaluation of the corresponding ruthenium complexes using optimized conditions developed in our laboratories.

Diversity at the C-terminus was generated from elements Fmoc-Asn-OH, Fmoc-Lys(Boc)-OH, Fmoc-His(Trt)-OH, while diversity at the N-terminus was generated from **9a–c** (Scheme 1), phenanthroic acid and Fmoc-Asn-OH. Fig. 1 summarizes the structures generated. Fragments **1C–3C** were chosen because of the availability, simplicity and diverse donor properties of the

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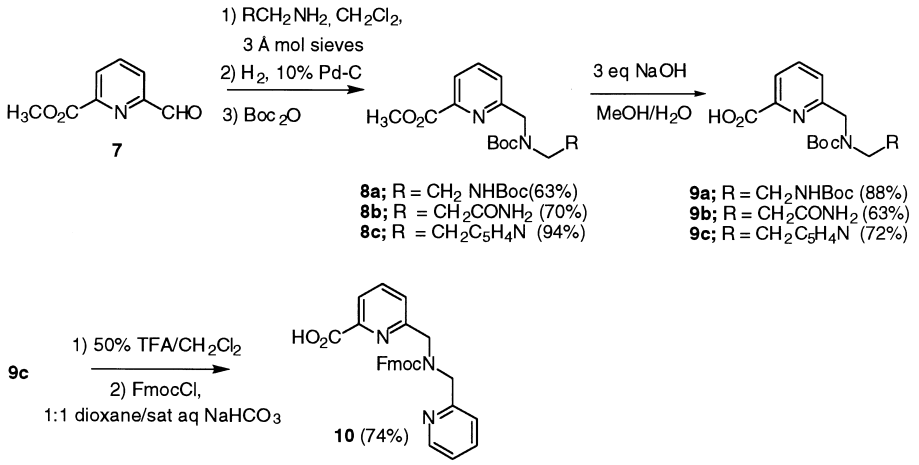
side-chain functionality (-NH_2, -$CONH_2$ and 4-imidazolyl). Fragments **1N**–**3N** were chosen as potential tridentate systems possessing a similar structure but significant variations in one of the donor groups. Fragments **4N** and **5N** are systems which are easily accessible and are structurally quite different from the other **N** fragments. Altogether, the small library generated thus possesses a number of significantly diverse structures. The synthesis of the diversity elements **9a**–**c** was accomplished from the known aldehyde **7** (Scheme 1).[5] First, the aldehyde was allowed to react with the appropriate amine and the resultant imine was reduced (H_2, Pd–C) affording the corresponding secondary amine. Boc protection (Boc_2O, CH_2Cl_2) of the secondary amine and hydrolysis of the ester group (NaOH, 1:1 MeOH:H_2O) gave the respective acids **9a**–**c**.



Scheme 1. Synthesis of diversity elements **9a**–**9c** and **10**

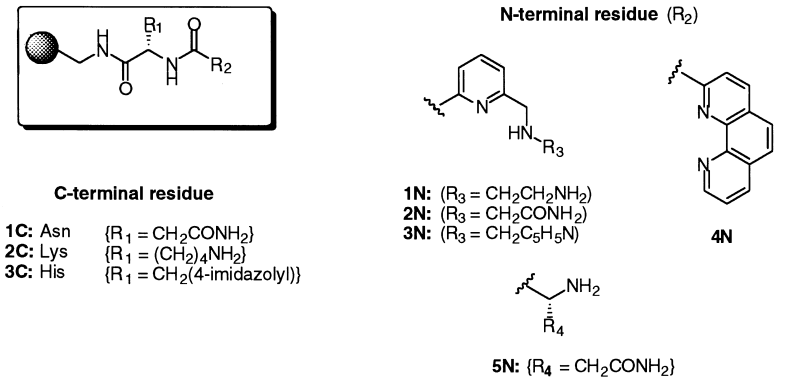


Figure 1. Ligand library composition

A library of 15 ligands was synthesized in a parallel fashion on aminomethylpolystyrene (AMP) resin using a combination of Fmoc/Boc chemistries and standard peptide coupling procedures. The library was then incubated with 1 equiv. of $RuCl_3 \cdot H_2O$[7] for 72 h at rt under nitrogen in degassed DMF to generate the ruthenium catalysts. The complexes were evaluated for their ability to catalyze the oxidation of *cis*-stilbene (10 equiv.) with PhIO (40 equiv.) in CH_2Cl_2. The

results from the these reactions are graphically shown in Fig. 2. All ruthenium complexes catalyzed the formation of benzaldehyde and *cis*-stilbeneoxide (in all cases *trans*-stilbene oxide was formed in quantities (~4%) comparable to the control (PhIO+*cis*-stilbene)). Some trends in the product distribution are apparent. More epoxide is formed by complexes possessing a histidine (**3C**) at the C-terminus. For example, Ru-**3C1N** generates more epoxide than Ru-**1C1N** and Ru-**2C1N**; Ru-**3C2N** generates more epoxide than Ru-**1C2N** and Ru-**2C2N**, etc. This trend is also apparent in the Ru-**xC4N** and Ru-**xC5N** series. Of the ligands possessing the fragments **1N**, **2N** and **3N**, epoxide formation increases as the variable donor changes from amine to amide to aromatic nitrogen with Ru-**3C3N** producing more epoxide than Ru-**3C1N** and Ru-**3C2N**; Ru-**2C3N** producing more epoxide than Ru-**2C1N** and Ru-**2C2N**, etc. The trend that begins to emerge is that aromatic nitrogen donors influence the character of the catalyst to favor epoxidation over oxidative cleavage. This trend is further supported by the activity of Ru-**3C4N** (possessing the phenanthroline group) and Ru-His-His which forms almost as much *cis*-stilbene oxide as the most active complex Ru-**3C3N** (39%). These data indicate that metal complexes can be fine-tuned to perform better by altering the donor groups and the ligand architecture around the metal center.

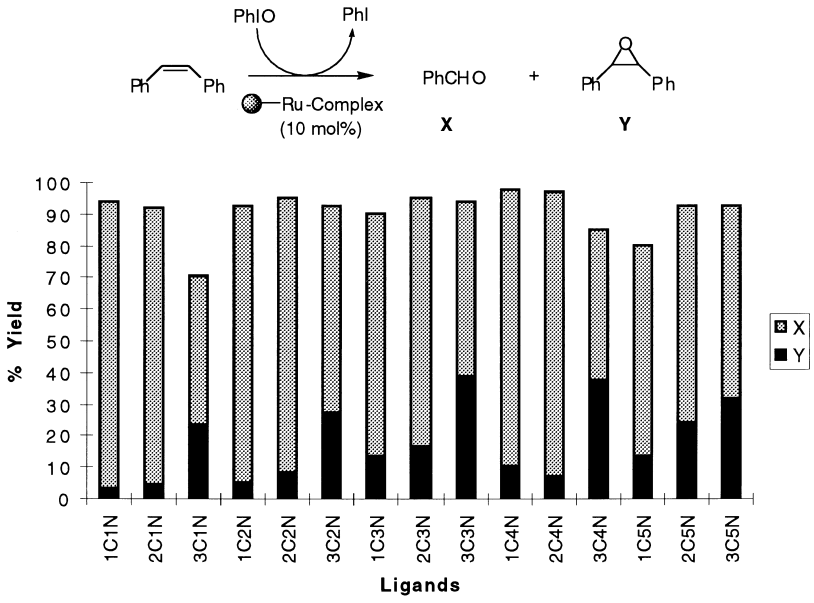


Figure 2. Product distribution in the oxidation reaction of *cis*-stilbene catalyzed by ruthenium complexes

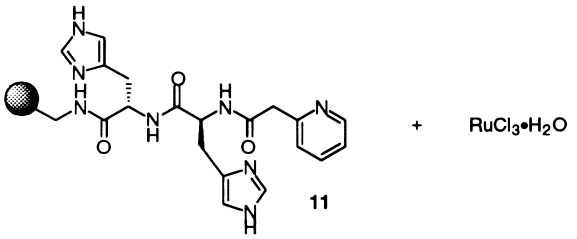
We also wished to address the performance of some of these catalysts in solution. To this end, ligands **1C4N**, **3C3N**, **1C4N** and His-His were synthesized on chlorotrityl resin and the respective Ru complexes were formed as described. Since we have shown that the catalytic activity of AMP-His-His-Ru is not affected by chlorotrityl resin cleavage conditions (1% TFA) we expected that liberation of the complexes from chlorotrityl resin with 1% TFA would not result in catalyst decomposition. Accordingly, the complexes Ru-**1C4N**, Ru-**3C3N**, Ru-**3C4N** and Ru-His-His were synthesized, liberated and evaluated as before [*cis*-stilbene oxide (10 equiv.) and PhIO (40 equiv.)]. Much to our surprise these performed much better as epoxidation catalysts in solution (Table 1) with Ru-His-His exhibiting no oxidative cleavage. The origin of these results is not clear

Table 1
Epoxidation activity of resin liberated ruthenium complexes

Entry	Ligand	% Yield (Supported catalyst) benzaldehyde	*cis*-stilbeneoxide
1	**3C3N**	6 (54)	88 (39)
2	**3C4N**	23 (48)	71 (38)
3	HisHis	n.d. (57)	94 (34)
4	**1C4N**	12 (88)	36 (10)

at this juncture. However, it is apparent that the catalysts Ru-**3C3N**, Ru-**3C4N** and Ru-His-His performed better than Ru-**1C4N** both in solution and in the solid-phase indicating that it is appropriate to screen the solid-supported complexes for lead structures.

In conclusion, we have synthesized a small library of peptide-derived ligands with diverse functionalities. 'On bead' evaluation of the corresponding complexes enabled the facile identification of active, novel and simple oxidation catalysts. Furthermore, liberation of the catalysts from the solid-support afforded superior epoxidation catalysts. Interestingly, a solid-supported catalyst which quite cleanly affords oxidative cleavage has also been identified (Ru-**1C1N**). This result is tantalizing in that it suggests the possibility of developing oxidative cleavage catalysts to carry out kinetic resolutions. These studies have also identified a trend that catalysts possessing aromatic nitrogen donors increase epoxidation over oxidative cleavage. As a quick test of this hypothesis we have synthesized a new complex (**11**+$RuCl_3 \cdot H_2O$) possessing an additional aromatic nitrogen donor which affords more epoxide (52%) than the original lead structures included in this study. Encouraged by these results, we have begun the synthesis of the next series of ligands based on a design strategy which uses different ligand architectures and incorporates aromatic nitrogen donors.



General Procedure for the generation of the library: The ligands were synthesized on AMP resin (100-200 mesh; 0.5 mmol/g loading, Advanced Chem Tech). All coupling reactions were carried out in a fritted 10 mL glass-stoppered vial with agitation from a rotary shaker. The resin was allowed to swell in CH_2Cl_2 (2×15 min), washed with 10% Et_3N in DMF (2×5 min) and the first residue (Fmoc-Asn-OH, Fmoc-Lys(Boc)-OH, Fmoc-His(Trt)-OH) (4 equiv.) was coupled with DIC/HOBt (4 equiv.) in DMF. The couplings were monitored by the Kaiser test. The resin was washed with DMF (4×1 min) and CH_2Cl_2 (4×1 min). Fmoc deprotection was accomplished with 20% piperidine in DMF (2×20 min). The resin was again washed with DMF (4×1 min) and CH_2Cl_2 (4×1 min). The resulting free amine was coupled with a second residue (**1N**–**5N**) as before except **4N** which required HOAt and longer coupling times (8 h). The acid labile protecting groups were removed using 50% TFA in CH_2Cl_2 (2×15 min). The ligands were washed with 10% Et_3N in DMF (2×5 min) before metal incubation.

General procedure for the synthesis of ClTrt-resin bound ligands: H_2N-Xxx-ClTrt (100–200 mesh; 1.0 mmol/g loading) was coupled with the corresponding amino acid (4 equiv. **10**, or

phenanthroic acid) using HOAt/DIPC (4 equiv.) in DMF over 90–120 min. Fmoc deprotection was accomplished with 20% piperidine in DMF (2×20 min).

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