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Synthesis and Catalytic Activity of Amino Acids and Metallopeptides with Catalytically Active Metallocyclic Side Chains

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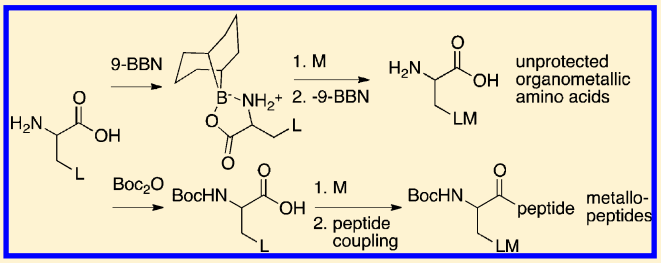
Supporting Information

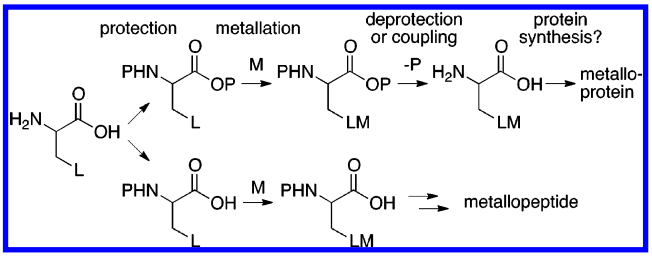
ABSTRACT: Two approaches to prepare amino acids with catalytically active organometallic side chains are presented. These methods are notable in that they provide access either free or N-protected compounds that are structurally analogous to naturally occurring amino acids. The N-protected organometallic amino acids are compatible with standard peptide coupling conditions and can be used to prepare catalytically active metallopeptides.



The design and synthesis of catalytically active metallopeptides[1] and metalloproteins[2] has received considerable attention, due to the potential for peptides and proteins to impart selectivity to metal catalysts using molecular recognition.[3] Most methods developed thus far involve metal binding to a peptide backbone or side chains,[4] covalent or noncovalent bioconjugation of a peptide with a metal-binding ligand or metal complex,[5] or incorporation of amino acids with metal binding ligands[6] into a peptide. Using these methods, researchers have developed a range of catalytically active metallopeptides and artificial metalloenzymes for synthetic applications.[1,2]

Herein, we describe two approaches for the synthesis of organometallic amino acids that enable direct incorporation of catalytically active metal complexes into peptides (Scheme 1).

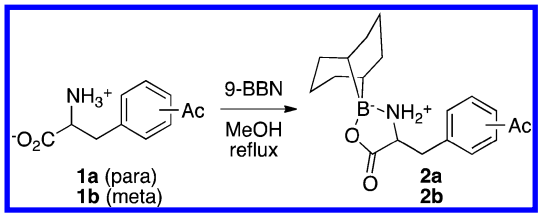
Scheme 1. Approaches To Synthesize Organometallic Amino Acids for Preparation of Metalloproteins and Peptides



Importantly, the organometallic amino acids were designed to mimic, as closely as possible, natural amino acids in order to maximize their compatibility with potential in vivo incorporation efforts.[6] Preserving the native amino acid structure was also expected to minimize structural perturbations to peptides, including these amino acids, and to ensure close proximity of the metal center and the chiral peptide scaffold. Prior to this work, no general method existed for the preparation of unprotected amino acids with side chains containing catalytically active transition-metal centers,[7] and most protected compounds include extended tethers[8] between the amino acid moiety and the organometallic fragment. Because both of these limitations arise primarily from the well-established metal-binding ability of the amino acid moiety,[9] protecting group strategies that would enable installation of a range of metal centers while still allowing amino acid deprotection without compromising the activity of the metal center were required.

Particularly attractive in this regard was the 9-borabicyclononanyl (9-BBN) group, which enables simultaneous protection of both the amine and carboxylic acid functionalities and can be readily removed using ethylenediamine.[10] The 9-BBN aducts of *p*- and *m*-acetylphenylalanine (**1a**,**b**, respectively) were therefore prepared and purified by washing with hexanes (Scheme 2).

Scheme 2. Amino Acid Protection using 9-BBN



The resulting compounds, **2a**,**b**, were then reacted with a range of amines and hydrazines to generate imines and hydrazines **3** (Scheme 3). Reaction of these compounds with either $NaPdCl_4$ or $[Cp^*IrCl_2]_2$ according to standard literature procedures led to the formation of the 9-BBN protected organometallic amino acids **4**.[11] These were typically isolated as crude solids, and the free amino acids **5** could then be readily prepared by simply stirring these complexes in THF solutions

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Scheme 3

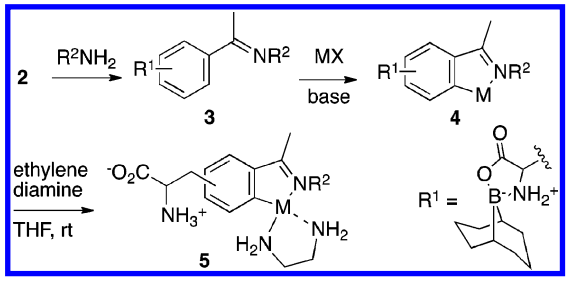
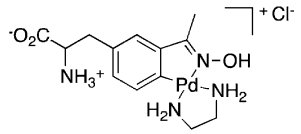
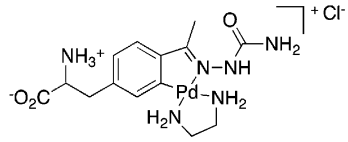
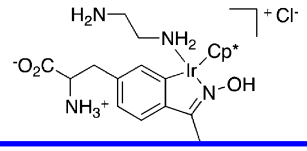


Table 1. Representative Organometallic Amino Acids

Entry	Structure (**5**)	Yield (%) **3**	Yield (%) **5**[1]
1		**3a** (90)	**5a** (58)
2		**3b** (89)	**5b** (20)
3		**3c** (93)	**5c** (30)

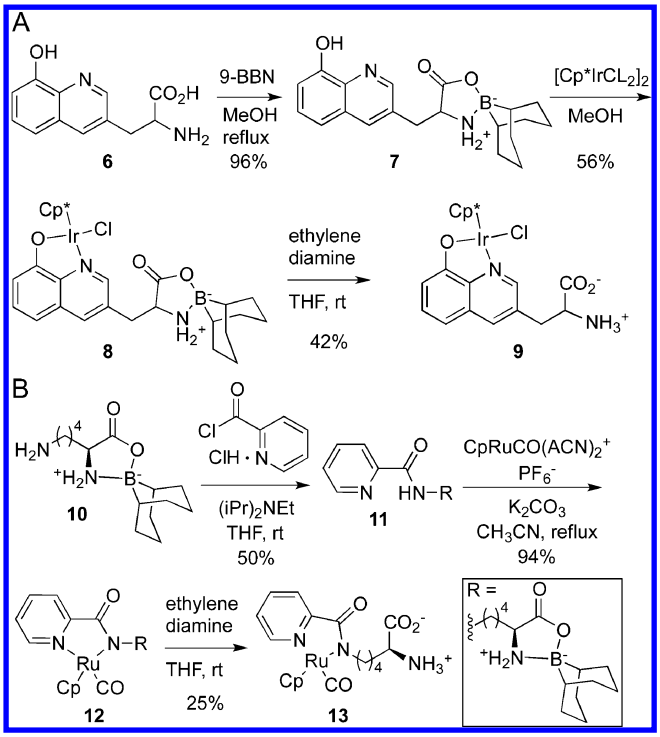
[1]Cumulative yield over metalation and deprotection steps.

of ethylenediamine (Table 1).[10] The amino acids precipitated from solution and could be further purified by precipitation from methanol/ether solution if necessary. The ethylenediamine was typically observed to displace chloride from the metal center, binding in either a mono- or bidentate fashion, depending on the number of coordination sites available.

To demonstrate the generality of the BBN protecting group for the synthesis of unprotected organometallic amino acids, two additional compounds were prepared by analogous routes. Specifically, a 9-BBN-protected hydroxyquinoline-based amino acid was reacted with $[Cp^*IrCl_2]_2$ to provide the corresponding Cp*Ir–hydroxyquinoline chloride complex, which was deprotected to yield amino acid **9** (Scheme 4). In addition, the known 9-BBN-protected lysine **10** was acylated with 2-pyridinecarboxylic acid chloride and reacted with $[CpRuCO(ACN)_2]PF_6$ to provide complex **12**, which was deprotected to yield amino acid **13**.[12]

Thus, a structurally diverse set of Pd-, Ir-, and Ru-based amino acids were prepared. The Pd and Ir compounds were designed to mimic the planar aromatic side chains of phenylalanine and tyrosine, while the last compound is a pyrolysine[13] mimic. These compounds are water-soluble and are readily taken up by *E. coli*, as judged by their inhibition of cell growth (see the Supporting Information). While these compounds are therefore highly promising candidates for aqueous organometallic catalysis or in vivo incorporation in *E. coli*,[6] their potential for use in standard peptide synthesis procedures[14] required installation of either the Boc or Fmoc protecting group.

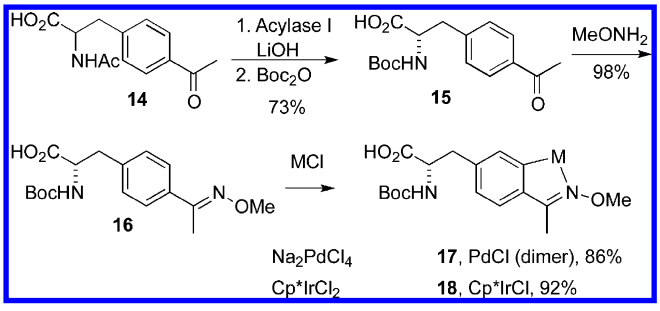
Scheme 4. Synthesis of Hydroxyquinoline- and Lysine-Based Amino Acids 9 and 13



To avoid introducing additional protection steps to the syntheses outlined above and potential for decomposition of the metal centers in these compounds, we instead pursued a monoprotecting group strategy that would mask the amine functionality with either a Boc or Fmoc group based on recent work by several groups using tethered amino acid–metal complexes.[8] For in vitro peptide synthesis, enantiopure amino acids were also required (*E. coli* only incorporates *S* amino acids into proteins; thus, racemic samples can be used for in vivo studies[6]); therefore, an enzymatic resolution was used to prepare enantiopure acetylphenylalanine **15**.[15] This material was then Boc-protected, converted to the corresponding methoxyimine, and reacted with either $NaPdCl_4$ or $[Cp^*IrCl_2]_2$ to yield the Boc-protected metallacyclic amino acids **17** and **18** (Scheme 5).

To demonstrate the utility of these compounds for the site-specific introduction of metal centers into peptide scaffolds, standard peptide coupling conditions[14] were used to prepare tetrapeptides **20** and **21** (Scheme 6). The 2-aminoisobutyric acid (Aib)–proline motif in peptide **19** is known to enforce a *β*-

Scheme 5. Synthesis of Resolved, Protected Pd and Ir Amino Acids 17 and 18



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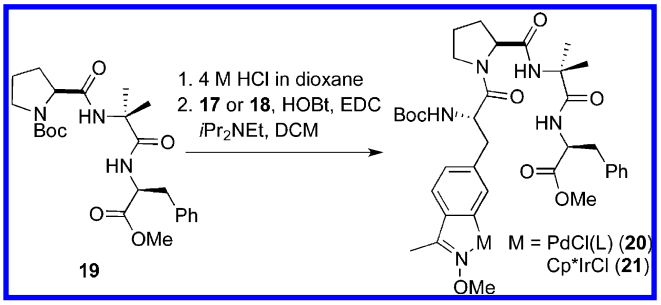
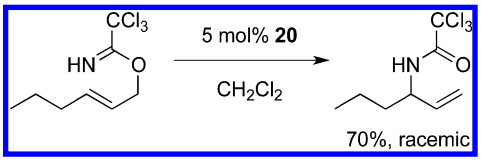
Scheme 6. Peptide Coupling using Amino Acids 17 and 18



turn structure and has been used by many groups, notably Miller and co-workers,[16] to generate highly selective catalysts for a range of chemical transformations using organic amino acids. Peptide-based coordination complexes based on β-turn peptides have also been generated.[17] We hypothesized that incorporating organometallic catalysts into this platform would greatly expand the range of catalytic transformations possible using unique selectivity afforded by peptide catalysts. By using preformed organometallic complexes as side chains, catalysts not available via simple coordination of metal ions, such as the metallacycles described herein, can be selectively introduced into peptides. NMR and mass spectroscopic analysis of **20** and **21** indicated that the metal centers remained unperturbed by the peptide coupling conditions. Several analogues of **20** and **21**, involving substitution of L-proline with D-proline, variation of the terminal phenylalanine residue, and addition of an additional amino acid to form pentapeptides, were also prepared (data not shown). Attempted removal of the Boc group from **20** and **21** using TFA led to decomposition of the metallopeptides, and while these compounds were stable to the piperidine conditions typically used to remove the Fmoc group, synthesis of Fmoc-protected amino acids as shown in Scheme 6 was complicated by Fmoc removal during the methoxyamine condensation.

All peptides remained catalytically active toward known reactions for analogous non-peptide metallacycle complexes, including Ir-catalyzed transfer hydrogenation[11b] and Pd-catalyzed imidate rearrangements[18] (Scheme 7). Unfortunately,

Scheme 7. Representative Imidate Rearrangement Catalyzed by Palladacycle Peptide 20



the small set of compounds investigated thus far provided no enantioinduction in either of these reactions. Control experiments using either $[Cp^*IrCl_2]_2$ or $PdCl_2$ or as catalysts for these reactions provided no conversion, indicating that release of metal complexes from the peptides was probably not responsible for the observed nonselective reactions. Presumably, the metal fragment in each case adopted a conformation that placed it outside the influence of the peptide. Further studies are underway to confirm the secondary structure (conformation) of these peptides and to identify alternate peptide architectures to provide selectivity in a range of chemical transformations.

In summary, we have described synthetic approaches for the preparation of a range of unprotected and N-protected organometallic amino acids. These compounds are structural analogues of natural amino acids, making them ideal vehicles for incorporation of organometallic complexes into peptides and potentially proteins. The compatibility of these amino acids with standard peptide coupling conditions allowed the facile preparation of a small set of catalytically active metallopeptides. The ability of peptide-based catalysts to provide enantioselectivity and site selectivity in a range of organo-catalyzed reactions[16] suggests that metallopeptides analogous to those prepared hold great promise in similar selectivities in metal-catalyzed reactions.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and full characterization of all synthetic compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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