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Synthesis of Proline-Based N-Heterocyclic Carbene Ligands

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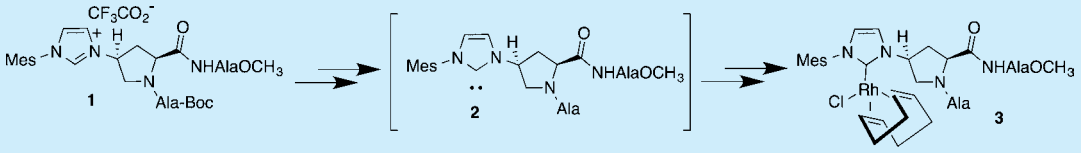
Supporting Information



ABSTRACT: The synthesis of proline-based N-heterocyclic carbene ligands is reported. An approach to a variety of proline-containing imidazolium NHC precursors is presented. The proline amino acids are shown to be compatible with peptide synthetic methods by incorporation into tripeptides. Following peptide synthesis, the carbene is generated and bound to rhodium.

Over the last 15 years small peptides have been used to catalyze nonbiological reactions ranging from acyl,[1] phosphoryl,[2] and sulfinyl[3] transfers to Baylis–Hillman reactions,[4] aldol reactions,[5] and epoxidations.[6] Metal binding peptides containing either natural or unnatural amino acids have been used to control or mimic enzyme activity and perform reactions that are not typically seen in biological systems.[7] In addition to the use of small peptides, there has been considerable success using single amino acids combined with other groups such as ureas.[8] Despite their success, one of the limiting factors in the use of peptides has been the number of amino acids that have the desired properties. For example, the number of natural amino acids that are strong electron donors is limited to imidazole and basic amines. Because of this, we have developed methods that provide amino acids that possess nucleophilic functionality in their side chains.[7d,9] These amino acids can then be incorporated into peptides or coupled to other metal ligands by simple amide formation.

Herein we report proline derivatives (**4**) that can be precursors to N-heterocyclic carbenes (NHCs; Figure 1). N-

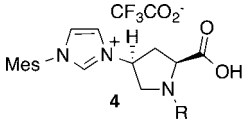
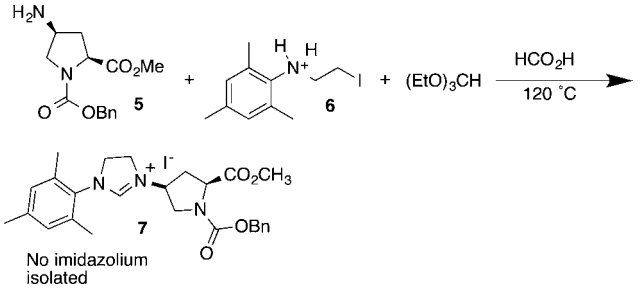


Figure 1. Proline imidazolium NHC precursor.

Heterocyclic carbenes have emerged as important molecules for both nucleophilic catalysis and as ligands for transition metals.[10] Proline was selected for this purpose since it is found in relatively small peptide sequences that have a stable secondary structure, and proline type scaffolds have been shown to have application in the synthesis of more traditional transition metal ligands.

The initial attempt to synthesize the desired molecule was to use chemistry developed in our group for the facile synthesis of NHC ligands from iodoamines.[11] However, the reaction between *cis*-aminoproline (**5**) and *N*-(2-iodoethyl)-mestylamine (**6**) did not proceed under a number of reaction conditions (Scheme 1).

Scheme 1. Attempted Direct Synthesis from 4-Aminoproline



After the failure of the initial attempt, a second route was initiated via the substitution of the triflate of *trans*-hydroxyproline. The triflate of the methyl and benzyl esters of *N*-carbobenzyloxy-protected *trans*-hydroxyproline (**10** and **11**) were formed by reaction with trifluoromethanesulfonic anhydride in the presence of pyridine. Treatment of the triflate with *N*-mesitylimidazole (**12**) provided the parent imidazole derivatives (**13** and **14**). With careful monitoring of the reaction time and temperature, the desired proline imidazolium can be obtained as a single enantiomer (at least 20:1 diastereomeric ratio). Following purification in the presence of trifluoroacetic acid, the trifluoroacetate salt was isolated. Attempts to remove the Cbz protecting group from carbamate **13** yielded the alkylation product **16** in high yield

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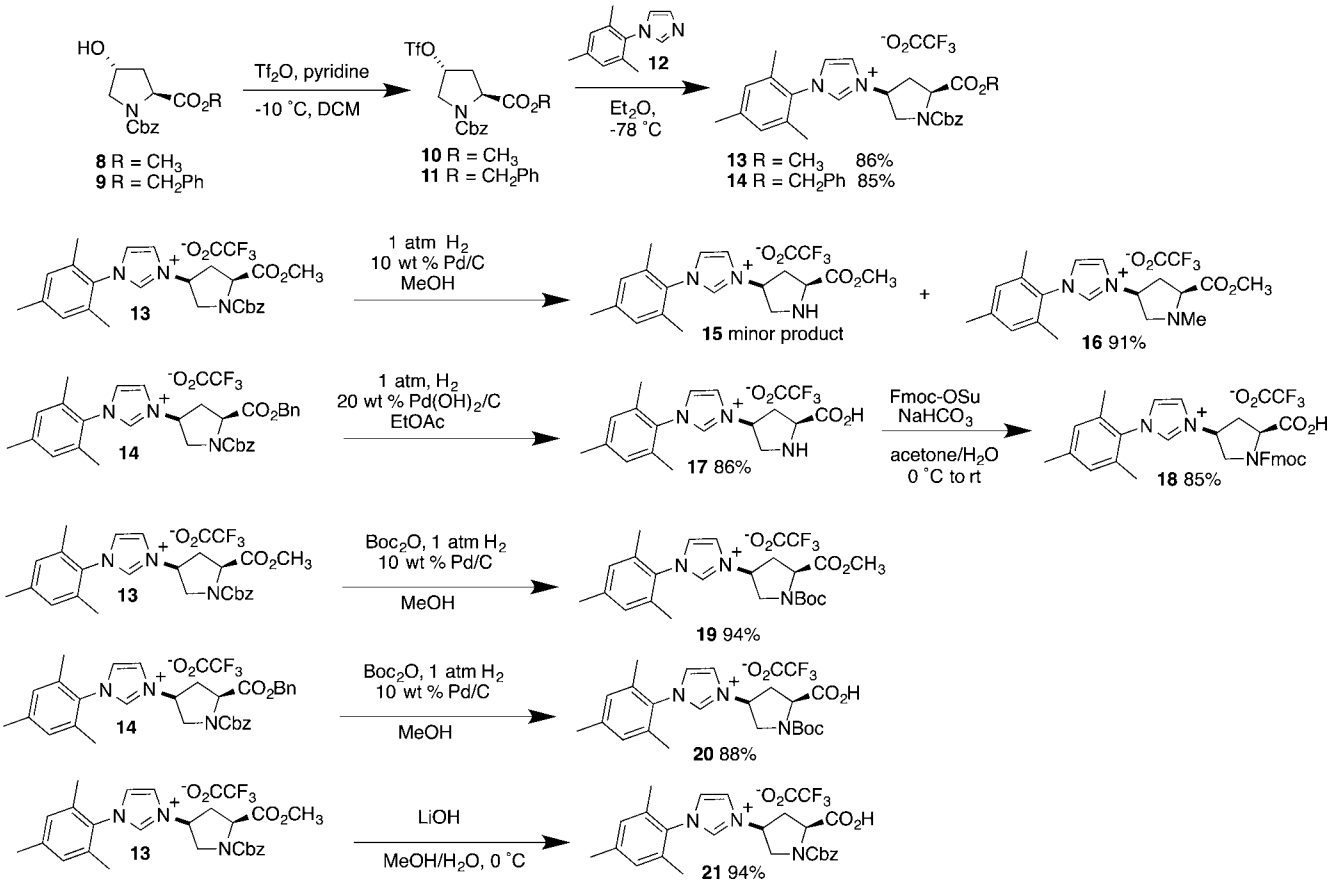
Scheme 2. Synthesis of Imidazolium Salts

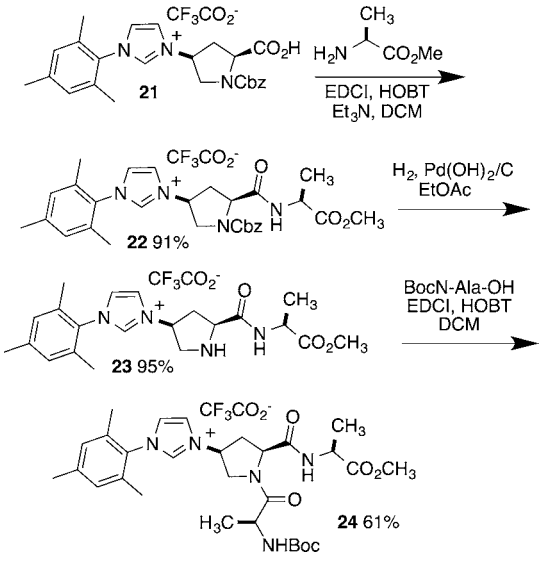


with only minor amounts of **15** being formed. However the deprotection of both the amine and acid could be performed on the benzyl ester, with palladium hydroxide, to provide the amino acid **17**. The free amine was then converted to the Fmoc carbamate (**18**). Additionally treatment of the Cbz methyl ester (**13**) with hydrogen and palladium on carbon in the presence of Boc anhydride provides the Boc-protected methyl ester (**19**). The same conditions with the benzyl ester (**14**) provide the Boc-protected acid (**20**). The Cbz-protected methyl ester could also be selectively hydrolyzed with lithium hydroxide at 0 °C to provide the Cbz acid (**21**) in high yield. These reactions were all performed without epimerization of the proline. NMR spectra run at room temperature generally exhibit two conformations that coalesce single peaks at elevated temperature (Scheme 2).

To demonstrate the ability to use these amino acids in standard peptide chemistry, the Cbz acid (**21**) was coupled with methyl alanine by standard EDC coupling in the presence of HOBT. Deprotection of the Cbz carbamate (**22**) followed by coupling with Boc alanine provided the tripeptide (**24**) (Scheme 3).

The ultimate goal of this chemistry is to provide a route to NHC ligands. To demonstrate the utility of this approach, a number of intermediates in this sequence have been converted to the corresponding NHC ligands and then complexed to rhodium. Reaction with silver oxide provided the silver NHC complex of the single amino acid **25** as well as the di- and tripeptides (**27** and **29**). It has been shown that such complexes are labile and readily undergo transmetalation with other metals.[12] Reaction with a rhodium COD chloride

Scheme 3. Synthesis of Imidazolium Tripeptide



dimer provided the rhodium complexes (**26**, **28**, and **3**) (Scheme 4).

We are currently using this chemistry in the synthesis of rhodium and palladium catalyst systems that would not be accessible without this methodology. Those metal complexes are being examined in a number of reactions. In addition to the incorporation of these NHCs into peptides, we are currently using the proline building block for the synthesis of

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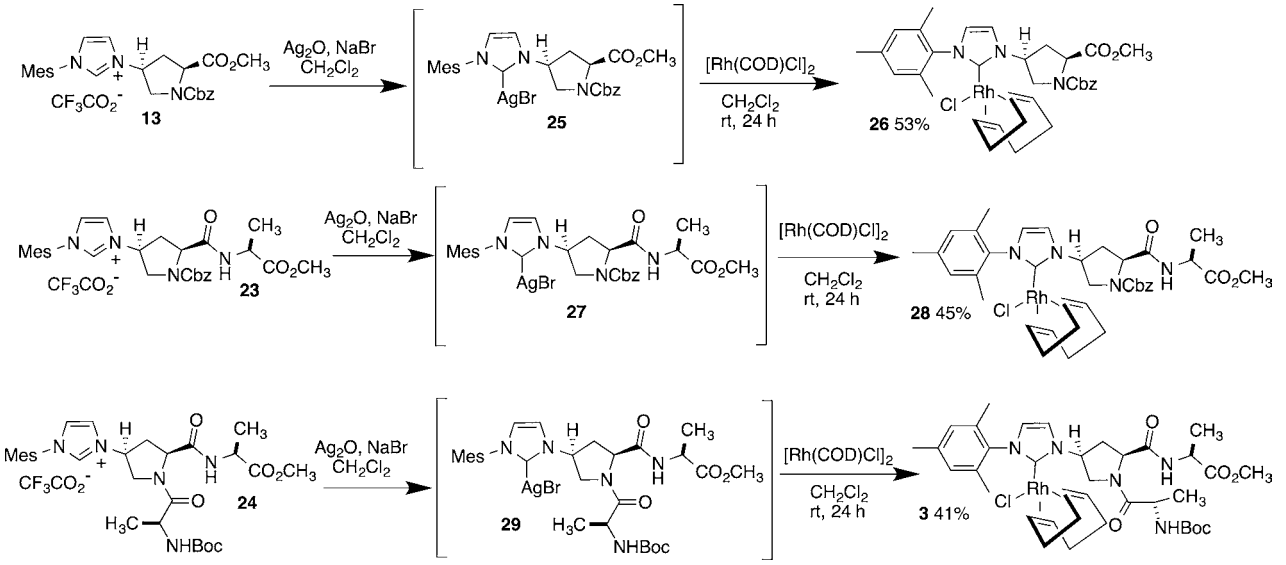
Scheme 4. Synthesis of Peptide and Amino Acid NHC Rhodium Complexes



simpler bidentate ligands where the other metal ligand is either phosphine or oxazoline.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all the compounds. 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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