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Development of Building Blocks for the Synthesis of N-Heterocyclic Carbene Ligands

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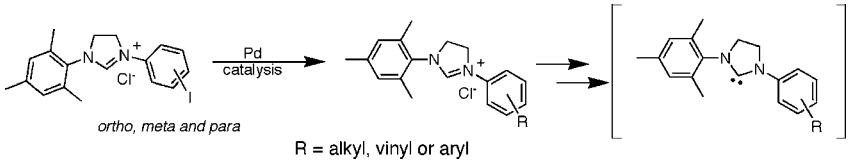
ABSTRACT



The synthesis of a series of NHC building blocks that can then be incorporated into more complicated structures by palladium catalysis is reported. This approach is used for the synthesis of three amino acids containing NHC side chains. The ability to use the amino acids in solid-phase peptide synthesis to make NHC-containing peptides is also demonstrated. Additionally, the NHC side chain can be deprotected and coordinated to a catalytically active transition metal. Finally, it is illustrated that the building blocks participate in Suzuki coupling to provide access to substituted NHC ligands.

N-Heterocyclic carbenes (NHCs) have emerged as an important class of ligands for transition metals and are beginning to play a role in transition-metal catalysis.[1,2] Since their original disclosure by Öfele in 1968,[3] a number of chemists have investigated first their properties as ligands and later the characteristics of these complexes in a variety of catalytic reactions. Transition-metal complexes with these ligands have proven to be effective in the Heck reaction,[4] Suzuki and Sonogashira couplings,[5,6] aryl amination,[7,8] amide α-arylation,[9] hydrosilylation,[10] Kumada coupling,[11] hydrogenation,[12,13] hydroformylation,[14] alkyne coupling,[15] olefin cyclopropanation,[16] arylation of aldehydes,[17] and of course, olefin metathesis.[18] Thus far, there have been a select number of examples of their use in asymmetric catalysis.[12,13,19−22] In addition to emerging as useful ligands in transition-metal chemistry, there are numerous examples of NHCs being used in nucleophilic catalysis.[23−32]

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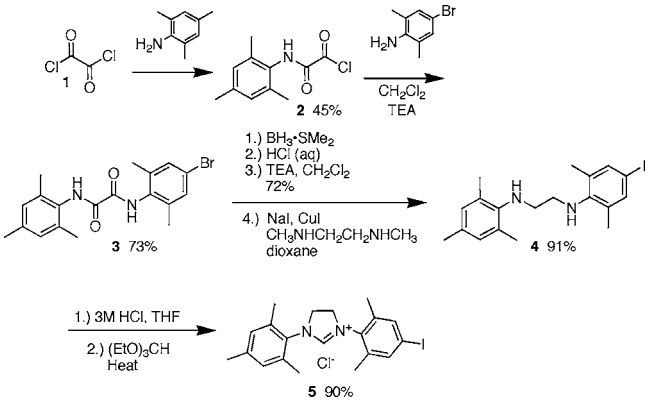
There are a number of synthetic routes to N-heterocyclic carbenes available. However, most of these routes are not compatible with the synthesis of complex molecules containing diverse and sensitive functionality. These routes involve the use of strong base, strong acid, or strongly reducing conditions.[2,13] We report here the synthesis of a series of NHC building blocks that can then be incorporated into more complicated structures by palladium catalysis. This approach is used in this paper for the synthesis of three amino acids containing NHC side chains. We also illustrate that the amino acids can be used in solid-phase peptide synthesis to make NHC-containing peptides. Additionally, the NHC side chain can be deprotected and coordinated to a catalytically active transition metal. Finally, we show that the building blocks participate in Suzuki coupling to provide access to substituted NHC ligands.

The approach taken toward the synthesis of more complex NHC ligands was to develop a building block containing a latent carbene moiety **5** (Scheme 1). If compatible with the necessary chemistry, chloride salt **5** could then be incorporated into larger structures by a variety of different reactions. Proceeding through salts such as **5** is a common route to NHC ligands; however, to our knowledge there are limited examples of chemistry that has been worked out to use these salts as latent carbenes in other reactions prior to carbene generation.

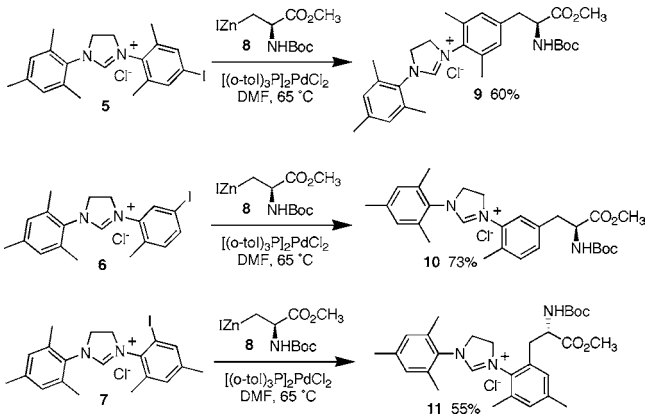
Scheme 1



The desired approach required an unsymmetrical diamine. Reaction of oxalyl chloride with 1 equiv of 2,4,6-trimethylaniline provided **2**, which could then be reacted with a *p*-bromoaniline derivative to give the diamide **3** (Scheme 1). Reaction of **3** with borane dimethyl sulfide complex gave the desired diamine. Exchange of bromide for iodide and reaction with triethylorthoformate provided the salt **5**.

Chloride salt **5** was then tested to determine if it could be used in palladium-catalyzed coupling reactions. Para, meta, and ortho isomers (**5**, **6**, and **7**) were examined to determine if they would undergo palladium-catalyzed coupling with metalated amino acid **8** (Scheme 2). In all three cases, these iodides coupled to provided amino acids **9**−**11** in good yield.

Scheme 2



Having found that salts such as **5**−**7** can be used in palladium-catalyzed coupling, the next goal was to adjust the functionality of protected amino acids and determine if solid-phase peptide chemistry can be used to synthesize more complex ligands. It is also necessary to be able to convert molecules such as **9** to the desired carbene in the presence of the amino acid functionality.

Reaction of **9** with the anion of chloroform generated from KOH and chloroform or by decarboxylation of the sodium salt of trichloroacetic acid gives the chloroform adduct (**12**) (Scheme 3). Grubbs and others have shown that heating adducts of this type generates the free carbene which can be trapped with a metal.[33] This approach provided a route to the amino acid NHC ruthenium complexes but was not compatible with additional chemistry such as conversion of the ester to the free acid or removal of the Boc group. It seems rather unlikely that the chloroform adducts would be sufficiently stable to allow multiple reaction steps while attached to a solid support.

Another method for the conversion of salts such as **9** to a NHC is by reaction with silver(I) oxide. Stirring the salt **9** with Ag_2O provided the silver carbene complex (**14**) (Scheme

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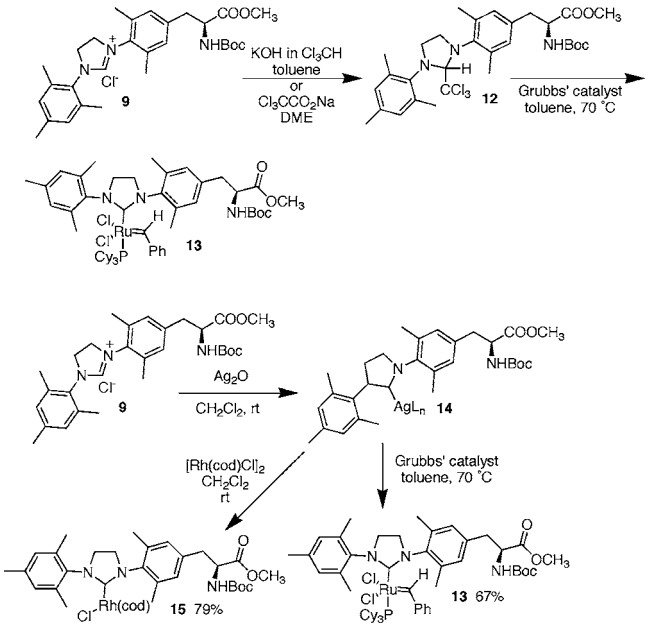
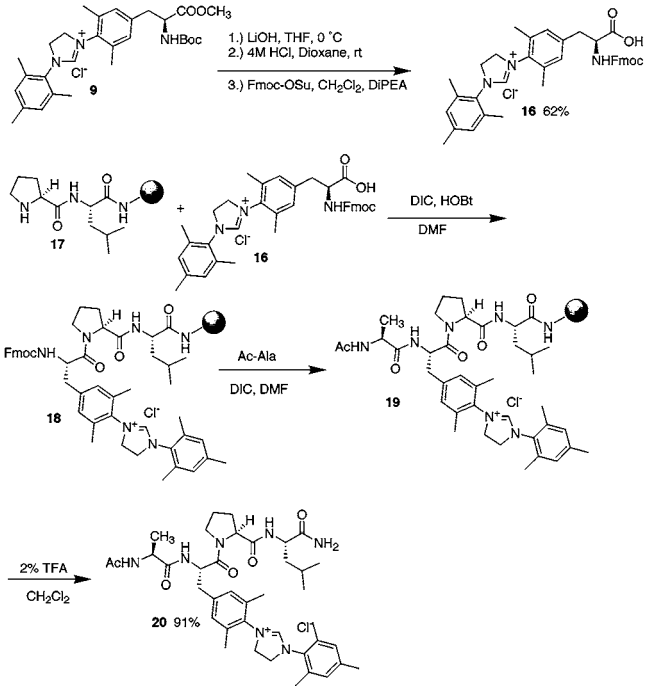
Scheme 3



3). Silver NHC complexes are very labile and readily undergo exchange with metals such as rhodium or ruthenium.[34] Reaction with Grubbs bisphosphine catalyst provided the ruthenium NHC phosphine complex (**13**). Reaction with rhodium cyclooctadiene chloride dimer afforded the rhodium complex **15**.

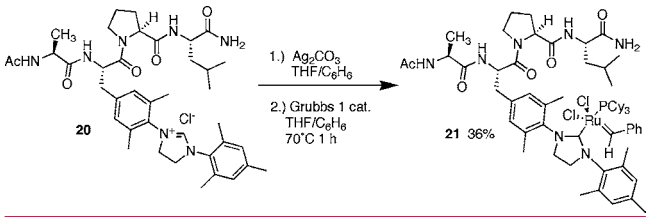
Scheme 4



Before they can be used in solid-phase peptide synthesis, the NHC-containing amino esters must be converted to amino acids by hydrolysis of the methyl ester. Additionally, it was desirable to protect the amino acid as the FMOC carbamate. Hydrolysis with lithium hydroxide followed by treatment with hydrochloric acid in dioxane gave the free amino acid, which was treated without isolation with FMOC-OSu to provide the FMOC-protected amino acid (**16**) (Scheme 4). To determine the ability to use such amino acids in standard peptide couplings, this amino acid was coupled into a four-residue peptide. Reaction of FMOC acid **16** on the supported dipeptide proceeded smoothly using DIC as the coupling agent. Removal of the FMOC protecting group followed by coupling of FMOC-alanine gave a tetrapeptide (**19**) that was removed from the support with TFA. Chloride salt (**20**) was fully characterized.

Reaction of the tetrapeptide with silver carbonate provided the silver NHC complex, which was then exchanged with Grubbs (I) catalyst to provide the ruthenium complex (**21**) (Scheme 5). This complex was identified by the characteristic

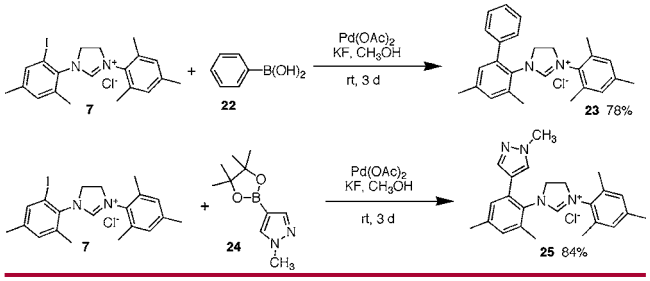
Scheme 5



proton resonance for the proton on the benzylidene carbon (19.07 vs 20.01 in CD_2Cl_2 for the Grubbs (I) precursor). This complex was also found to be a competent metathesis catalyst catalyzing the polymerization of norbornadiene at room temperature.

In addition to providing a route to amino acid containing NHC ligands, salts such as **7** can be used to synthesize a variety of different NHC ligands. Compound **7** was substituted using the Suzuki reaction. Reaction of the iodide with both boronic acids and boronic esters provides the substituted salt. Thus far, we have used this reaction in the synthesis of salts substituted with benzene (**23**) and pyrazole (**25**) groups (Scheme 6).

Scheme 6



We are currently using this reaction in the synthesis of catalyst systems that have not been accessible prior to this methodology. Specifically compounds **5**−**7** will be of value

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for the synthesis of a variety of different NHC ligands systems. The general approach reported here should prove useful in the synthesis of novel chiral and achiral NHC ligands.

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Supporting Information Available: Experimental procedures, spectra, and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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