POINT LOMA NAZARENE UNIVERSITY

Pyrazolylformamidines as Building Blocks for N-Metallocyclic Carbenes

A senior research honors project discussion and examination

in

Organic Chemistry

by

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Committee Review By:

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I. BACKGROUND

Carbenes are a class of organic molecule that are becoming increasingly prevalent in the field of organometallic catalysis. Discovered in a stable form first in 1988, a carbene was thought simply to be a laboratory anomaly. Further research has since shown an application towards aiding synthetic mechanisms of many other organic reactions.[01] A carbene is a neutral carbon atom, within a molecule, that is bound to a lone pair of electrons. Nitrogen-heterocyclic carbenes are a class of carbenes that have shown significant stability. A carbene carbon that is flanked by two nitrogen atoms provide the capability for orbital hybridization and overlap. The lone-pair electron extending from nitrogen fill the empty p-orbital of the carbene carbon. Typically, these electrons exist in their ground state to σ-electron orbitals. However, for aromatic, vinylic, or any other molecule with a displacement of electron density (ie: nitrogen lone pair electrons) due to π-orbital overlap, a carbene is able to supply its electrons into this hybridized system.[02] Furthermore, carbenes express molecule-specific stereo-electronic properties that are dictated by intramolecular orbital overlap of coordinated metals and/or ligands. Therefore, as each carbene molecule is able to be constructed differently, it is able to react as a catalyst species in a unique manner due to its molecular composition and consequential orbital overlaps.

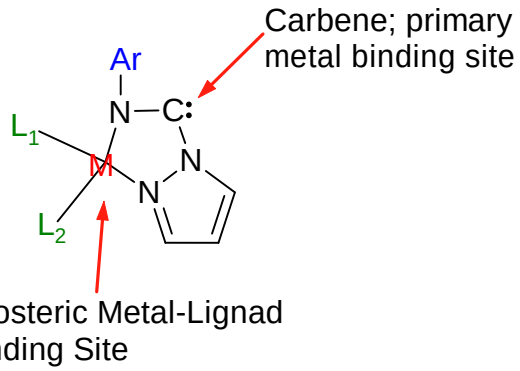
As a class of catalyst, carbenes are useful for a wide array of reactions. As a specific molecule, however, each carbene is useful only for an incredibly specific reaction process. Is it possible, then, to construct one carbene molecule that contains the functional range to catalyze a multitude of different reactions? Such a carbene would be a multi-tool! It would allow chemists, researchers, manufacturers, and more with the opportunity to purchase one tool that could accomplish a feat of their reactions. This would save money and promote productivity. This topic has been the driving force of my laboratory experimentation and exploration.

II. RATIONALE of PROJECT EXPLORATION

If the electronic properties of a molecule are able to be altered, then the carbene reactivity will consequently be altered. This is accomplished by the depth of electron orbital overlap through hybridization of an unsaturated organic molecule.[03] Before diving in to the possibilities of structure design, let us first take a look at the traditional use of a carbene.

A carbene commonly coordinates with a metal during the step-wise synthesis of new material during a catalytic cycle. The carbene acts as both a strong σ-donor and π-acceptor. The metal coordinates with the carbene, harvesting its electrons, binds to the reactant species, catalyzes the product species, and then dumps its electrons back onto the carbene. In short, the metal acts as a site of catalytic activity for the formation of new product species. If a carbene-metal catalyst is able to influence other molecular species vie electronic coordination, then why can't the same principle be applied to the construction of our multitool? If a metal species is to bind at an allosteric site on our nitrogen-heterocyclic carbene molecule, then it will carry the capacity to influence the reactant formation caused by the carbene-metal catalytic properties. The allosteric metal coordinates and communicates over an "electron highway" to our carbene metal, providing it with one specific reactivity state to bind to reactant species. If the allosteric metal changes its electronic or oxidative state, then the orbital overlap shifts, thus altering the pathway of the "electron highway." With this change, the electronic communication to the carbene metal changes, resulting in the preference for the carbene metal to interact differently with reactant species and form different product. Such electronic/oxidative tuning is accomplished by binding ligand groups to the metal prior to, or following, the metal's attachment at the allosteric site. Different ligand groups communicate by orbital overlap to their coordinated metal, thus influencing the orbital overlap and communication to the molecule's respective carbene metal.

FIGURE I



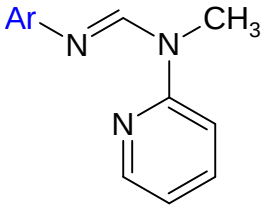
Beyond the customization of our allosteric metal and the allosteric metal's ligand groups exist the backbone of the carbene molecule itself. Although this particular component is not necessarily tunable during the run of one reaction, it is able to provide a different array or reactivity ranges that are themselves tunable. A carbene backbone that is capable of coordinating other metal atoms typically contain nitrogen atoms in a cyclic fashion – this molecule is called a "Nitrogen-Metallocyclic Carbene" (NMC). Nitrogen's unbonded σ-orbital allows the metal atom to dentate the molecule at these positions.

Consider the option of choosing between one of two carbene precursor backbone molecules. Their only difference is the amount of carbon atoms, the amount of nitrogen atoms, the position of the nitrogen atoms, the arrangement of molecular bonds, and how many double bonds (and therefore π-orbitals) exist. In a typical laboratory setting, this would allow a chemist to perform two independently unique reactions. Now consider the possibility of binding one of four metals to this NMC. A chemist that owns a single carbene is now able to perform four reactions instead of one! To broaden the possibilities further, consider the option of binding up to two ligand groups onto this metal that will attach to the NMC. There are ten possible configurations that may exist between ligand groups and the metal. Combined with four metal

options, there are forty different synthetic mechanisms possible for this one carbene catalyst. For a chemist with two NMC precursor structures, there are eighty possible mechanisms achievable.

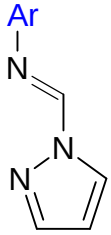
The priority of my research entailed the synthesis of a new carbene backbone structure – an NMC precursor. In the past, we have accomplished the synthesis of a stable NMC beginning with a six-membered nitrogen ring – see [FIGURE II]. New exploration has since been put into the synthesis of a comparable NMC using a five-membered nitrogen – see [FIGURE III].

FIGURE II



"Pyridyl Formamidine"

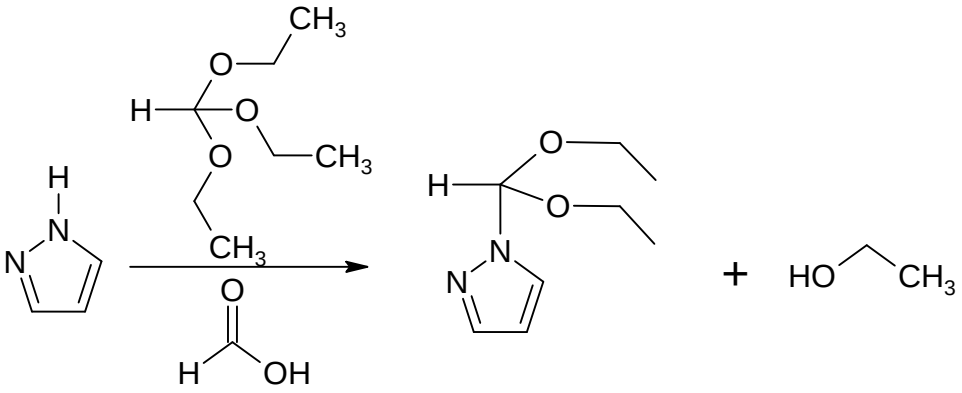
FIGURE III



"Pyrazolyl Formamidine"

III.a. METHODS; SYNTHESIS of PYRAZOLYL FORMAMIDINE

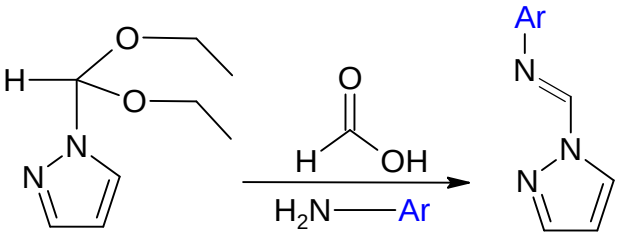
FIGURE IV



Step one, of two, in the synthetic pathway of pyrazolyl formamidine. Pyrazole (CAS:288-13-1) reacts with triethyl orthoformate (CAS:122-51-0) and formic acid (CAS:64-18-6) to form our intermediate species 1-(1',1'-diethoxy)pyrazole and ethyl alcohol.

Into a 25 mL round bottom flask, combine 1:4 parts pyrazole to triethyl orthoformate, and add 4 drops of formic acid for each 100 mmol of combined solution present [ie: 20. mmol pyrazole, 80. mmol TEOF, 4 drops formic acid]. Attach to short-path distillation head. Heat in a sand bath 135 ºC, pulling slow vacuum once distillate first appears; let reaction hold for ~4 hours. Neutralize remaining formic acid catalyst and ethyl alcohol product with sodium carbonate. This step was preformed and recorded by DDN-I-68.[04]

FIGURE V

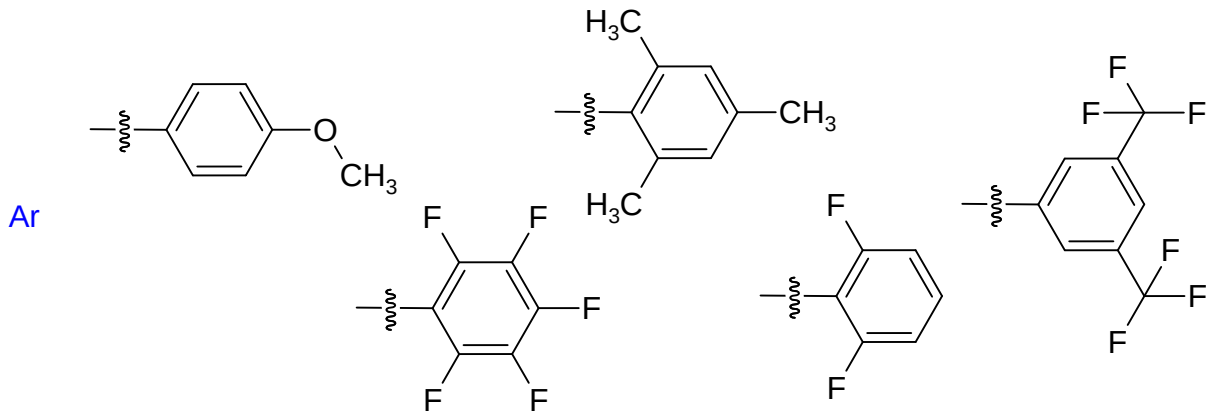


Step two, of two, in the synthetic pathway of pyrazolyl formamidine. The methyldiethoxy is replaced by an aromatic amine via a substitution reaction. The result product is the desired pyrazolyl formamidine – the backbone of our multitool NMC.

Into a microwave tube with a stirbar, combine equal parts 1-(1',1'-diethoxy)pyrazole and phenylamine, and add one drop of formic acid for each 2mmol of combined solution present [ie: 1.0mmol 1-(1',1'-diethoxy)pyrazole, 1.0 mmol phenylamine, 1 drop formic acid]. Place in microwave reactor, open vessel, and run for 2.0 hours at 150 ºC.

To purify product, pour hexanes over product solution into the microwave tube. Stir and observe either the formation of crystalline solid or non-crystalline oil. Pour off supernatant hexanes (keeping supernatant solution) and repeat. Remove volatile hexane solvent en vacuo and record H^1-NMR of both hexane-soluble and hexane-insoluble material. Note that the recovery of the organic product may exist in either phase, depending on the specific phenylamine added in each separate reaction. H^1-NMR structure elucidation displays which phase contains the organic product.

FIGRURE VI

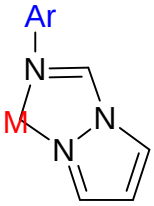


For which Ar represents any of, but is not limited to, the above aromatic structures. The five aromatic structures shown above are: 4-methoxyphenyl, 2,3,4,5,6-pentaflourophenyl, 2,4,6-trimethylphenyl, 2,6-diflourophenyl, and 3,5-bis(trifluoromethyl)phenyl (from left to right). These structures appear as shorthand "Ar" in [FIGURE II], [FIGURE III], and [FIGURE V]. Note that the synthesis of an NMC precursor was not successful with either 2,3,4,5,6-pentaflourophenyl or 3,5-bis(trifluoromethyl)phenyl in reaction with pyrazolyl formamidine. Stable and pure product, however, was observed with Ar groups 4-methoxyphenyl, 2,4,6-trimethylphenyl, and 2,6-diflourophenyl in reaction with pyrazolyl formamidine.

III.b. DISCUSSION; SYNTHESIS of PYRAZOLYL FORMAMIDINE

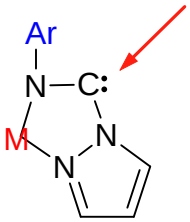
We have now synthesized the carbene backbone of focus: pyrazolyl formamidine. Recall [FIGURE III], a cyclic molecule of five members with a branching formamidine-aryl group. As mentioned before, the coordination of a metal into the carbene backbone is possible prior to the molecule becoming a carbene. The metal would dentate the electron groups of two nitrogen atoms withing the molecule, as shown below in [FIGURE VII].

FIGURE VII



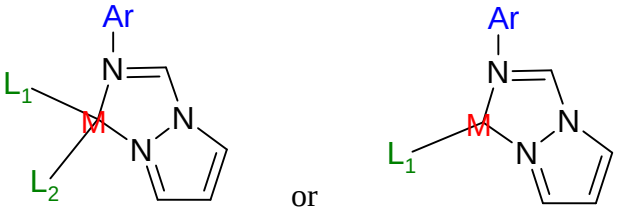
Deprotonation to yield the nitrogen-metallocyclic carbene would therefore look like:

FIGURE VIII



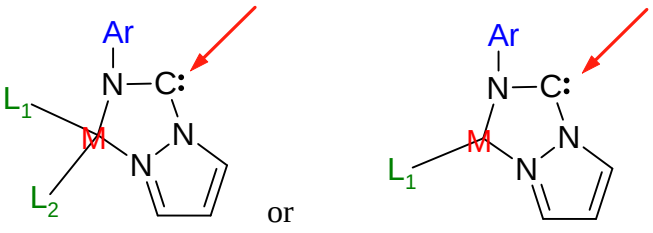
Notice the red arrow. The carbon at this position is the *carbene.* Likewise, the addition of ligand groups to the metal prior to coordination with the molecule would yield:

FIGURE IX



Subsequent deprotonation of the ligand-NMC precurser molecule would yield the following ligand-NMC.

FIGURE X

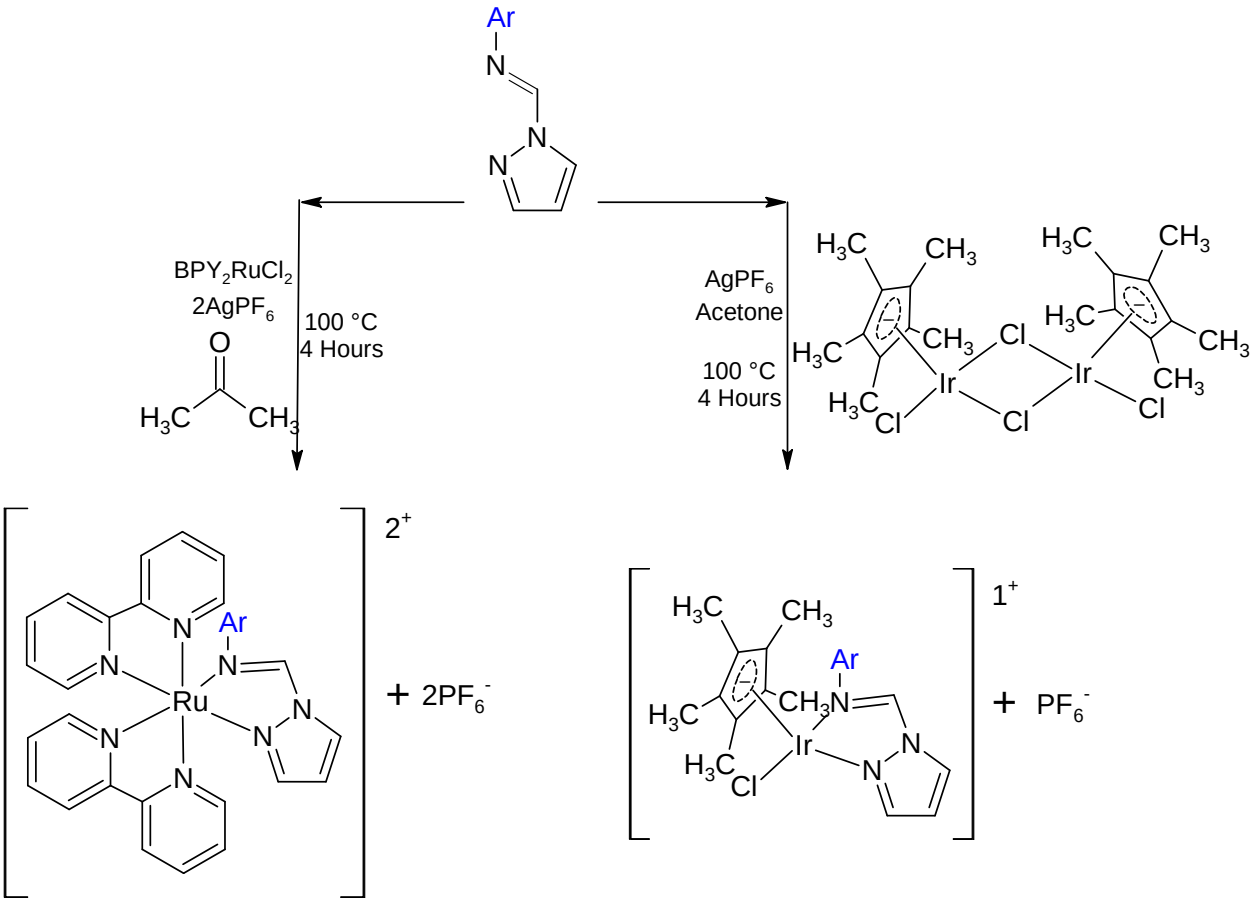


The generation of a pure and stable form of [FIGURE X] could coordinate with a metal at the carbene site (red arrow) and allow the synthetic catalysis of new species in a reactant mixture. The attainment of a molecule, such as [FIGURE X] has been the driving force behind these experiments. Prior research has shown that the synthesis of a ligand-NMC has proven successful

when beginning with a pyridyl base, see [FIGURE II], instead of a pyrazyl base, see [FIGURE III].

IV.a. METHODS; SYNTHESIS of an NMC

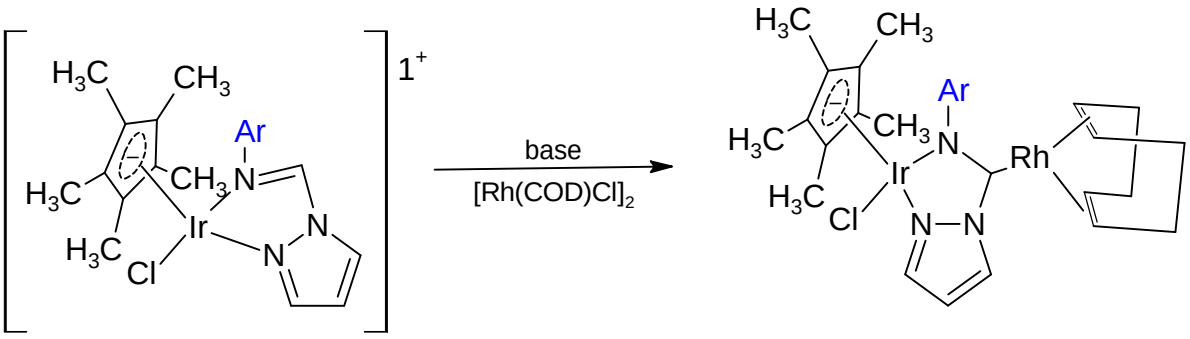
FIGURE XI



Two proposed synthetic pathways are displayed above. The left pathway complexes our [(1E)-N-phenolpyrazol-1-imine] backbone onto ruthenium bisbipyridine. A 1:1:2:1 mixture of [(1E)-N-phenolpyrazol-1-imine], Bis-(2,2'-bipyridine)dichlororuthenium(II)hydrate (CAS:98014-14-3), silver hexafluorophosphate (CAS:26042-63-7), and acetone produces our desired ligand-nitrogen-metallocyclic-precarbene. The likewise reaction of a 1:1:1:1 mixture of [(1E)-N-phenolpyrazol-1-imine], Dichloro(pentamethylcyclopentadienyl)iridium(III)dimer (CAS:12354-

84-6), silver hexafluorophosphate (CAS:26042-63-7), and acetone yield our complexed iridium-pentamethylcyclopentadienyl-nitrogen-metallocyclic-precarbene.

FIGURE XII



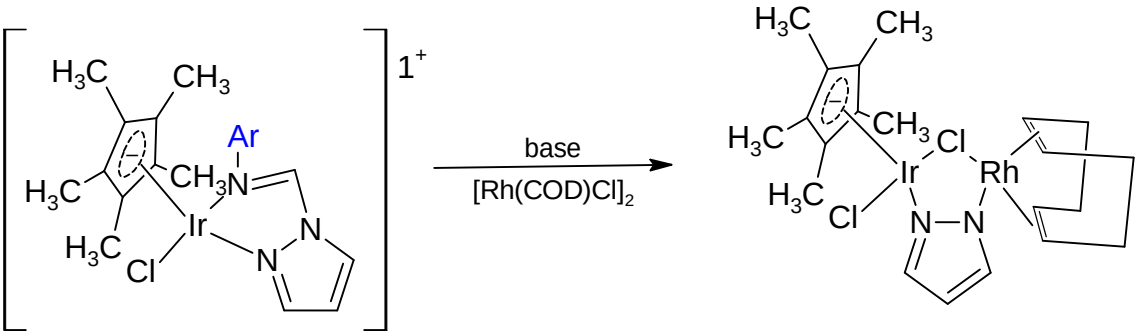
The formation of a stable NMC – a Rh(COD)-NMC – is proposed by the mechanism above, in which complexed NMC precursor is treated with a base and Chloro(1,5-cyclooctadiene)rhodium(I) dimer (CAS:12092-47-6).

IV.b. DISCUSSION; SYNTHESIS of an NMC

The synthesis of the iridium precarbene from [FIGURE XI] matches the predicted base model structure demonstrated in [FIGURE IX]. In order to activate this species, the proton at the amidine carbon must be abstracted. Then, a new metal species will be able to coordinate with our carbene upon subsequent introduction. The desired product from the synthetic pathway listed in [FIGURE XII] did not fare out. Crystal structure shows, however, the alternate formation of a different species, shown as the product of [FIGURE XIII], below.

[next page]

FIGURE XIII



The amide carbon was itself cleaved from the precarbene structure. The Rh(COD) complex did not associate with the carbene in a stable manner. In fact, the carbene cannot be claimed to have formed.

V. FURTHER RESEARCH

The synthesis of a nitrogen-metallocyclic carbene molecule using a pyrazolyl formamidine backbone did not result in the formation of a proper carbene. Problems may have arisen with the base of choice during the synthetic step highlighted in [FIGURE XIII]. Beyond this step occurring late in the synthetic pathway, further attention may be placed on the beginning synthetic steps. More specifically, the synthesis, extraction, and purification of the pyrazolyl formamidine from [FIGURE V] needs extra attention. The use of formic acid and its relative ratio may have led to detrimental results that were not observed in other experiments used in building pyridyl-based NMCs. Conversely, the exploration of a different nitrogenous base besides pyrazole may prove more useful in the synthesis of stable, tunable, nitrogen-metallocyclic carbenes.

Sources

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