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Authors: Hosein Tafazolian and Joseph A Schmidt

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Cationic [(Iminophosphine)nickel(allyl)]$^+$ Complexes as the First Example of Nickel Catalysts for Direct Hydroamination of Allenes

Hosein Tafazolian and Joseph A. R. Schmidt*

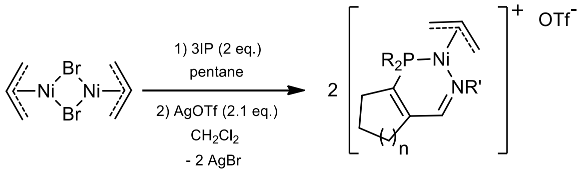
Abstract: The first example of nickel-catalyzed hydroamination of allenes is reported. The new cationic [(3-iminophosphine)nickel(allyl)]$^+$ catalysts have been fully characterized and act regioselectively in the catalytic hydroamination of allenes with secondary amines at room temperature.

Hydroamination, commonly noted as one of the most challenging and interesting addition reactions, is defined as N-H bond addition to a C-C multiple bond and is unobtainable without a catalyst, except in rare cases where the unsaturated substrate is highly activated. The distinctly negative entropy term coupled with only modest exothermicity explains the difficult nature of direct intermolecular hydroamination.[1] Despite its underlying complexity, the significance of this process relies on the broad potential utilization of the resulting products in pharmaceuticals and specialty chemicals.[1a, 1c] Although many early and late transition metals can promote hydroamination of C-C multiple bonds, due to issues involving substrate scope, cost, toxicity, and oxophilicity, many known reactive metal complexes are unsatisfactory for industrial utilization.[1a] These factors have led to the extensive investigation of late transition metals such as Ru, Rh, Pd, Ir, Pt and Au as some of the most promising candidates for broad application.[1a, 2] However, despite the demonstration of excellent reactivity profiles, one remaining unsolved problem is the cost of catalyst since these highly active late transition metal catalysts for hydroamination are very expensive. Thus, the development of a first row late transition metal hydroamination catalyst derived from Ni or Cu would be quite favorable. Recently, copper has shown promise in catalysis of C-N bond forming reactions, although direct hydroamination using copper has only recently emerged while the overall atom economy is low in other copper-based amination reactions due to the formation of byproducts.[3] Curiously, nickel-based catalysts have not been the subject of recent reports. With common accessible oxidation states of 0, +1, +2, and +3, it seems likely that the rich chemistry of nickel would include applications in hydroamination, since two unit oxidation state toggles are common in direct metal-catalyzed hydroamination.[1a, 4] However, surprisingly, virtually all reports of nickel-catalyzed hydroamination to date are limited to highly activated substrates or require very high temperatures. These nickel-catalyzed transformations, as studied by Togni,[5] Zargarian[6] and Garcia,[7] support a likely mechanism for nickel-catalyzed hydroamination of activated C-C multiple bonds (mainly acrylonitrile and related compounds) based on the electrophilicity of the Ni center. In research moving beyond these highly activated systems, Ackermann has described the intramolecular hydroamination of alkynes to form indoles.[8] Unfortunately, one drawback of Ackermann's system is the high temperature (120 ^oC) needed to obtain significant reactivity. The only well-defined report of nickel-catalyzed intermolecular hydroamination of unactivated C-C multiple bonds is a single paper by Hartwig in which the intermolecular hydroamination of 1,3-dienes to form allylamine products is reported.[9]

Although nickel-catalyzed C-N bond formation has attracted much interest, direct hydroamination catalyzed by nickel remains an unsolved challenge.[10] It is clear that metal-catalyzed hydroamination processes are dependent on both the metal utilized and the effects of the ancillary ligands employed. Both features impact the overall efficiency and operable mechanism in known systems. In our recent work involving the mechanistic study of palladium-catalyzed allene hydroamination, we showed that electronic effects in the supporting 3-iminophosphine (3IP) ligands often dictate the rate-limiting step in the mechanism for this process.[2f] With this understanding of ligand effects, we felt well poised to address the challenging reactivity of nickel analogues based on our previously reported palladium catalysts, especially as applied to allene hydroamination catalysis. Herein, we describe the first example of nickel-based allene hydroamination through the use of cationic [(3-iminophosphine)nickel(allyl)]$^+$ complexes.

Overall, the synthesis of allylnickel complexes proceeded similarly to our reported palladium analogues,[2q, 11] except for the fact that usage of a non-polar solvent is crucial in some steps to obtain the desired nickel complexes (Table 1).

Table 1. Cationic [(3IP)Ni(allyl)]$^+$ complexes.



1a-d

R'	R	N	Ni complex	Isolated yield (%)
^{t}Butyl	Phenyl	1	**1a**	87
2,6-Xylyl	Phenyl	1	**1b**	85
2,6-Xylyl	^{t}Butyl	1	**1c**	82
2,6-Xylyl	Phenyl	2	**1d**	91

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[*] Dr. H. Tafazolian, Prof. Dr. J. A. R. Schmidt
Department of Chemistry and Biochemistry, School of Green Chemistry and Engineering, College of Natural Sciences and Mathematics
The University of Toledo
2801 W. Bancroft St. MS 602, Toledo, Ohio, 43606-3390, USA
E-mail: joseph.schmidt@utoledo.edu

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Attempts to use other solvents in the complexation reaction of the allylnickelbromide dimer with the 3IP ligand, such as diethyl ether, tetrahydrofuran, dichloromethane or acetonitrile, led to intractable mixtures. As previously reported, allylnickelhalide dimers are only stable in nonpolar solvents, undergoing ligand redistribution/disproportionation reactions in more polar environments.[12] Once the nickel complexes were synthesized, they were characterized by NMR spectroscopy and elemental analysis. Suitable crystals of **1b** were grown from a saturated solution of the complex in tetrahydrofuran layered with pentane. Its structure was solved via direct methods (Figure 1).

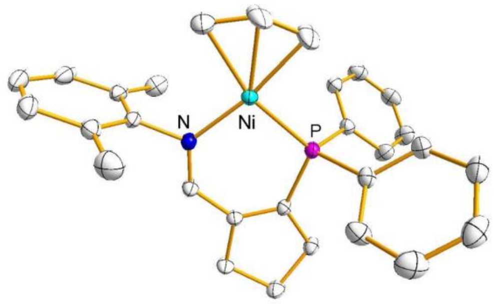


Figure 1. Crystal structure of **1b** (50% thermal ellipsoids); hydrogen atoms, triflate anion and cocrystallized solvent (THF) have been omitted for clarity; Selected bond distances (Å) and bond angle (deg): Ni-P, 2.174; Ni-N, 1.920; P-Ni-N, 99.3.

Once the desired allylnickel complexes were isolated, their reactivity in the catalytic hydroamination of allenes was explored. As a means to investigate catalyst activation, equimolar amounts of nickel complex **1b** and thiomorpholine were added to an NMR tube with C_6D_6 as solvent, and the reaction progress was observed every 10 minutes.

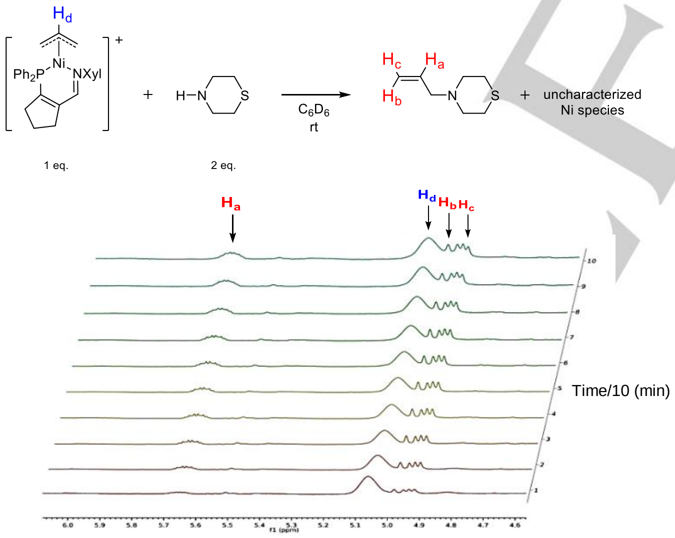
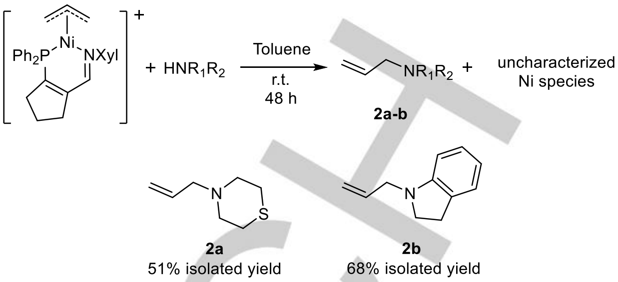


Figure 2. Time-resolved ^{1}H NMR spectra of equimolar reaction between **1b** and thiomorpholine (recorded every 10 minutes).

This time-resolved ^{1}H NMR data showed that after coordination of the secondary amine to the nickel precatalyst, N-allylthiomorpholine product peaks (the catalyst activation product) steadily grow in, while the allyl ligand peaks correspondingly diminished in tandem. At the final time point (100 minutes), the reaction had reached 22% N-allylthiomorpholine along with 78% unreacted catalyst (Figure 2).

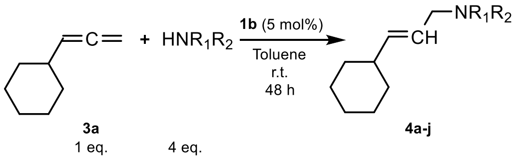
A similar stoichiometric reaction between **1b** and indoline led smoothly to the analogous N-allylindoline product (Scheme 1). The putative nickel hydride concurrently formed in this reaction is unstable, decomposing in the absence of allene substrate and eluding adequate characterization in our hands.

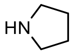
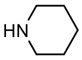
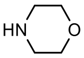
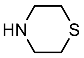
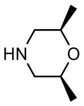
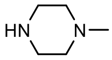
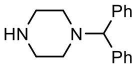


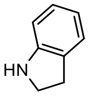
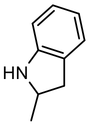
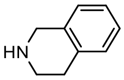
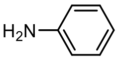
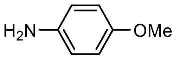
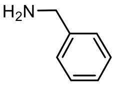
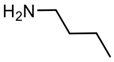
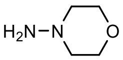
Scheme 1. Reaction of **1b** with secondary amines.

We previously observed a similar catalyst activation/first turnover product in palladium analogues of these nickel complexes, leading to their allene hydroamination activity.[2f] Thus, we set out to examine the catalytic activity of these newly synthesized nickel complexes in the hydroamination of mono-substituted allenes. A comparison of the catalytic activity of **1a**-**1d** using the reaction of cyclohexylallene with morpholine as a benchmark reaction showed that **1b** was the best catalyst, while **1c** had somewhat reduced reactivity (see SI for further details). Catalysts **1a** and **1d** showed low conversion values by NMR spectroscopy, with significant contamination by unidentified products. Thus, **1b** was chosen as the catalyst for utilization in a study of substrate scope in this reaction. Cyclohexylallene served as the allene precursor and was treated with a variety of amines (Table 2). Excess amine (4 equiv.) was utilized to increase the overall reaction rates, leading to moderate or better conversion after 48 hours. Secondary amines functioned well in this system, forming linear allylamine products in moderate to good yields. The production of linear products was not surprising as this is the thermodynamically favored product in these reactions.[2a] Primary amines of various types were invariably found to be unreactive, as observed in many cases with our less reactive Pd analogs.[11]

Table 2. Hydroamination of cyclohexylallene catalyzed by **1b**.[a]



Entry	HNR_1R_2	Product	Isolated yield (%)
1		**4a**	67
2		**4b**	52
3		**4c**	71
4		**4d**	91
5		**4e**	87
6		**4f**	50
7		**4g**	39

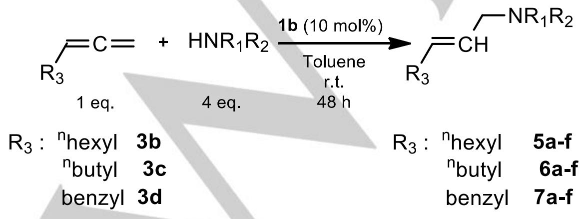
8		**4h**	92
9		**4i**	53[b]
10		**4j**	84
11		-	-
12		-	-
13		-	-
14		-	-
15	H_2N-NMe_2	-	-
16		-	-

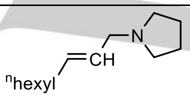
[a] Reactions were performed in small vials; toluene (2 ml) was added to **1b** (0.025 mmol, 5 mol%), followed by addition of amine (2 mmol, 4 eq.) and cyclohexylallene (0.5 mmol, 1 eq.). [b] Catalyst loading was increased to 0.05 mmol (10 mol%) and allowed to stir for 72 hours.

Although cyclooligomerization and polymerization of allenes is well-known,[13] very little of such byproducts was detected after 48 hours. During reaction optimization, it was found that using coordinating solvents (tetrahydrofuran, acetonitrile, or dioxane) resulted in lower conversions, possibly due to coordinative competition with the substrate amine. This was also examined through an NMR scale catalytic reaction in which cyclohexylallene, thiomorpholine and triethylamine (1 eq., 1 eq., and 2 eq., respectively) were allowed to react in the presence of 2.5 mol% of **1b**. As observed by frequent ^{1}H NMR spectra of the mixture, only 10% conversion after 30 h was detected, while 25% conversion was obtained in only 12 hours without triethylamine. Thus, it was concluded that coordination of the substrate amine plays a key role in this catalytic process, which is especially evident in comparison of entries 8 and 9 with methylindoline having less reactivity than indoline due to steric hinderance. Such effects were also observed in the related Pd catalysts.[2q]

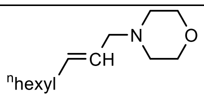
The substrate scope of this system was further investigated via hydroamination of additional mono-substituted allenes (**3b**, **3c** and **3d**) with secondary amines (Table 3). As with cyclohexylallene, all examples resulted in regioselective hydroamination of the allene to form the linear allylamine product as primarily the E isomer in moderate to good yields.

Table 3. Hydroamination of ^{n}hexyl-, ^{n}butyl- and benzylallene catalyzed by **1b**.[a]

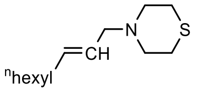




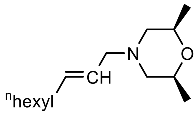
5a (63%)



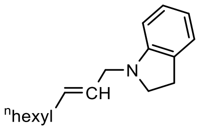
5b (82%)



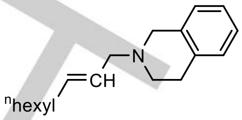
5c (93%)



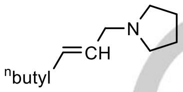
5d (90%)



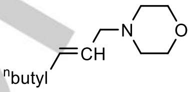
5e (80%)



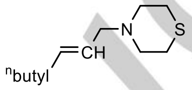
5f (91%)



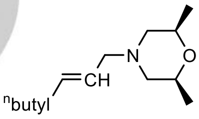
6a (75%)



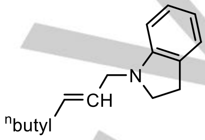
6b (60%)



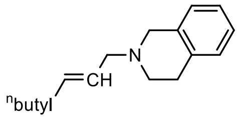
6c (82%)



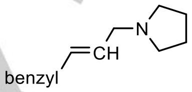
6d (79%)



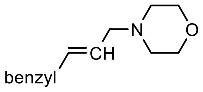
6e (76%)



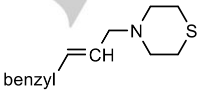
6f (79%)



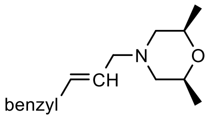
7a (91%)



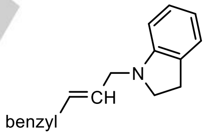
7b (83%)



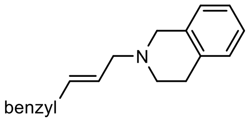
7c (81%)



7d (81%)



7e (79%)



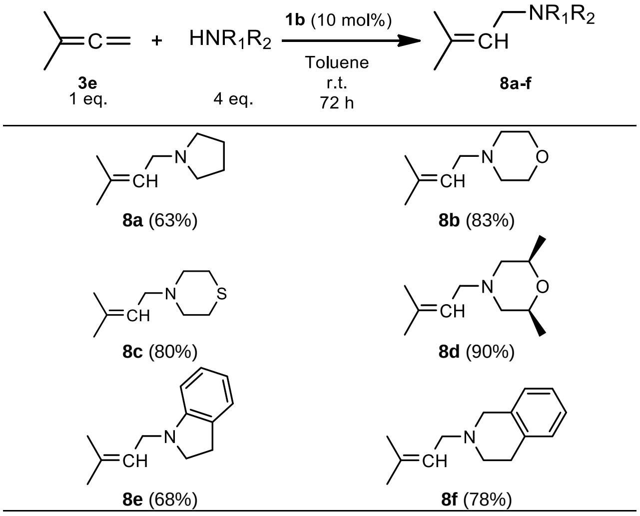
7f (77%)

[a] Reactions were performed in small vials; toluene (2 ml) was added to **1b** (0.05 mmol, 10 mol%), followed by addition of amine (2 mmol, 4 eq.) and allene (0.5 mmol, 1 eq.).

In one further effort to expand substrate scope, 1,1-dimethylallene was subjected to hydroamination. Reaction monitoring revealed that longer reaction times were required to obtain good yields in the hydroamination of 1,1-dimethylallene at room temperature (Table 4). Performing the reaction at higher temperatures unfortunately led to the formation of complex mixtures of products, rather than merely increasing reaction rate.

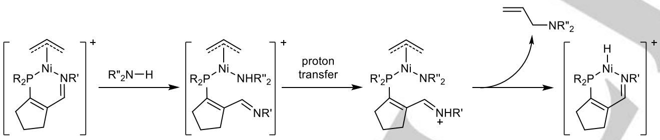
Despite a commonly believed misconception, mono-substituted allenes are readily available starting materials, easily generated from commercially available mono-substituted alkenes. One synthetic route to accomplish this is by treatment of alkenes with a dibromocarbene reagent to yield a dibromocyclopropane intermediate, followed by reaction with a Grignard reagent to open this three-membered ring, utilizing these three carbon atoms as the allene core.[14] The allylamines subsequently formed by hydroamination are then of great interest in pharmaceuticals, while alternate synthetic methods to obtain these products are often less efficient and lower yielding.[15]

Table 4. Hydroamination of 1,1-dimethylallene catalyzed by **1b**.[a]



[a] Reactions were performed in small vials; toluene (2 ml) was added to **1b** (0.05 mmol, 10 mol%), followed by addition of amine (2 mmol, 4 eq.) and allene (0.5 mmol, 1 eq.).

Mechanistically, the preliminary results reported herein show that cationic [(3IP)Ni(allyl)]$^+$ complexes behave similarly to their palladium analogues upon treatment with secondary amines. That is, coordination of a secondary amine leading to transient formation of a nickel-amido species constitutes a plausible activation pathway. Then, reductive elimination of an N-allylamine followed by oxidative ligation of the iminium proton to the nickel complex results in the active nickel hydride species, producing the corresponding first turnover products **2a** and **2b** (Scheme 2). Recently, Mashima proposed a similar intramolecular reductive elimination of amido and allyl units instead of nucleophilic attack on the allyl unit of a nickel complex as one of the key steps in the catalytic amination of allylic alcohols. Utilization of these inner sphere mechanisms, rather than ligand attack mechanisms, seems to fit well in several recent reports, as well as the chemistry presented herein.[2f, 16]



Scheme 2. Activation of the nickel precatalyst in the presence of amine.

In summary, we have described the synthesis of novel cationic [(3IP)Ni(allyl)]$^+$ complexes and their reactivity in the hydroamination of allenes with secondary amines, constituting the first example of nickel-catalyzed hydroamination of unactivated substrates. The resulting allylamines were isolated in good yields and characterized by NMR spectroscopy and mass spectrometry. These results revealed good efficiency and selectivity with these new nickel complexes, although we expect that higher reactivity can be achieved by further tuning the ligand system. Further study of the mechanism and continued expansion of the hydroamination substrate scope utilizing these novel nickel catalysts is ongoing.

Synthetic procedures and characterization data for nickel complexes and hydroamination products are available in the supporting information file. CCDC 1516985 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Acknowledgements

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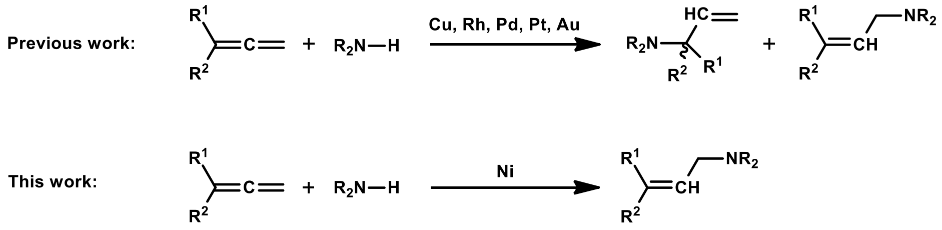

The first successful nickel-based catalysts for the hydroamination of allenes are reported. These new base-metal cationic [(3-iminophosphine)nickel(allyl)]$^+$ catalysts have been fully characterized and act regioselectively in the catalytic hydroamination of allenes with secondary amines to produce moderate to high yields of allylamines at room temperature.

Keywords:
Allyl ligands; Catalysis; Homogeneous catalysis; N,P ligands; Organometallic chemistry