Regioselective Rhodium-Catalyzed Allylic Amination

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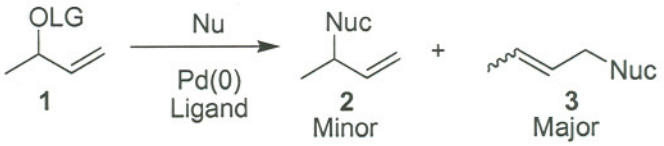
Introduction

Amines are ubiquitous in nature and represent fundamental building blocks in organic synthesis. Enantiomerically enriched allylamines are particularly useful intermediates for target direct synthesis, and have commonly been prepared from amino acids and related chiral pool derivatives. The metal-catalyzed allylic amination reaction provides a method for preparing chiral non-racemic allylamines; however, there is currently no direct method for the synthesis of primary allylamines. The specific goal of the following research is the development of a regio- and enantiospecific rhodium-catalyzed allylic amination for a direct construction of primary allylamines.

Background Information

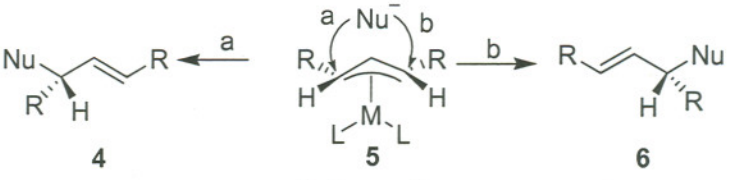
(*i*) Allylic Alkylation

Historically, the metal-catalyzed allylic alkylation reactions have been catalyzed by palladium complexes.[1] However, the problem with this approach is that the nucleophile generally attacks at the least sterically hindered site of the π-allyl intermediate in an unsymmetrical allyl fragment.[2] This leads to regioselectivity problems making it difficult to form chiral non-racemic products (Scheme1).



Scheme 1

In order to circumvent regioselectivity problems, allylic alcohols that lead to symmetrical π-allyl intermediates have been utilized (Scheme 2).[3] Though this is a nice solution to the problems of controlling regioselectivity, the synthetic utility of this method is greatly diminished due to the necessity to incorporate symmetry in target-directed synthetic applications.



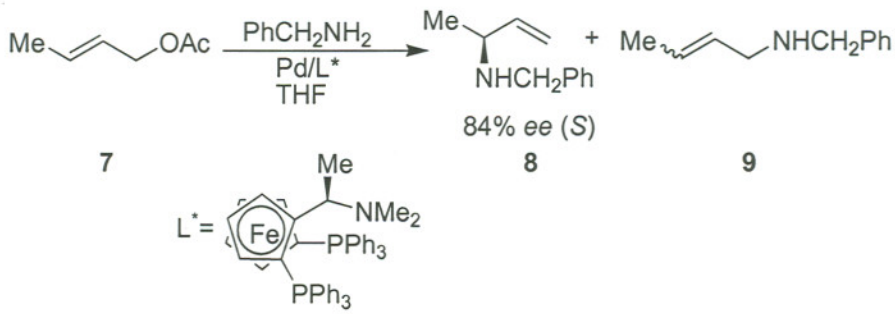
Scheme 2

Many other metals, including rhodium, were examined as catalysts in allylic substitution.[4] Interestingly, rhodium gave greatly improved regioselectivity in a wide array of substrates. In 1984, Tsuji reported that secondary allylic alcohol derivatives lead to the branched alkylation products using a rhodium complex. This demonstrated that rhodium can avoid the regioselectivity issues of the allylic alkylation. Evans and Nelson then demonstrated that rhodium catalyzed allylic alkylations are also stereospecific.

(*ii*) Allylic Amination

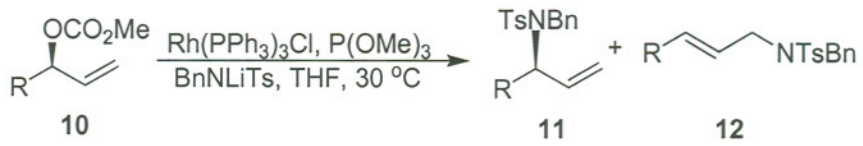
One of the most common methods for synthesizing amines, specifically primary amines, is alkylation.[5] In order to obtain a primary amine, ammonia is utilized along with a reducing agent; however, a major drawback to using ammonia is multi-alkylation.

It has also been shown that palladium catalysts can be used to produce allylic amines stereoselectively. In 1990, Hayashi published a regio- and stereoselective reaction using a chiral palladium catalyst with butenyl acetates that resulted in an allylic amine (Scheme 3).[6]



Scheme 3

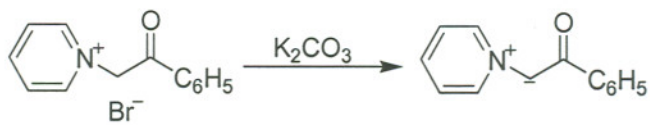
In 1999, Evans' group developed a rhodium catalyzed reaction that results in the synthesis of a secondary *N*-tosyl benzylamine in an enantiospecific and regioselective manner.[7] In order to achieve optimum regioselectivity in the amination, they found that Wilkinson's catalyst *modified* with triorganophosphites and lithium counter ion of the nucleophile was utilized in order to soften the nucleophile. Hence, enantiomerically enriched allylic carbonates undergo amination with retention in absolute configuration (Scheme 4). One of the disadvantages of this approach is with the deprotection of the amine.[8] Depending on the nature of the compound, the established deprotection conditions are often too harsh.



10 **11** **12**

Scheme 4

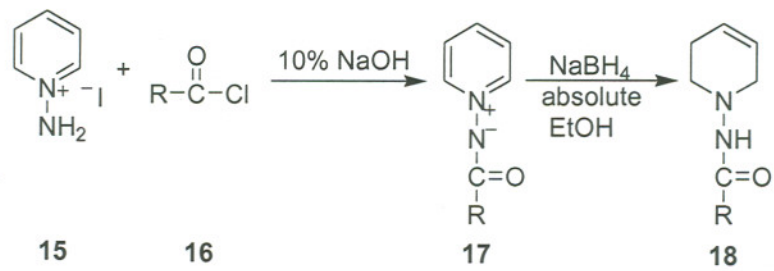
In 1935, Krohnke discovered that stable crystalline pyridinium ylides could be formed and that they undergo a range of nucleophilic reactions.[9] His group produced many nitrogen ylides over approximately thirty years and observed the pyridine ylides to be the most stable, and therefore of synthetic interest. The first pyridinium ylide synthesized involved the treatment of *N*-phenacyl pyridinium bromide, **13**, with potassium carbonate in order to afford **14** (Scheme 5).



13 **14**

Scheme 5

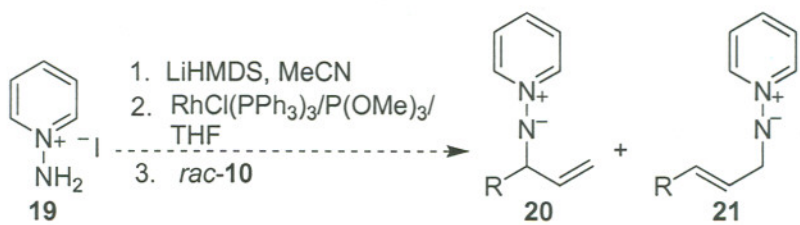
In 1982, Knaus published the synthesis of a group of *N*-[Phenylcarbonyl)imino] pyridinium ylides, **17**, (Scheme 6).[10] It was believed that these aminopyridinium ylides should react in a similar manner to the carbon version reported by Krohnke (Scheme 6). We envisioned that, **17**, would serve as an effective nucleophile in the allylic alkylation developed by the Evans' Group.



Scheme 6

Results and Discussion

Preliminary studies involving **17** under the rhodium reaction conditions demonstrated that the ylide was completely unreactive. We envisioned the ylide of the aminopyridinium iodide, **15**, would be more nucleophilic and less sterically hindered. When aminopyridinium iodide, **15**, was subjected to the allylic amination the resulting the secondary amination product, azanide **20**, was obtained as a crystalline intermediate with excellent regioselectivity (by ^{1}H-NMR) (Scheme 7).



Scheme 7

Optimization of the reaction conditions demonstrated the key to the reaction is having two equivalents of base and a polar solvent (Table 1).

Table 1: Survey of solvent and base in the rhodium catalyzed allylic amination.

Entry[a]	*Solvent*	*Equiv. Base*[b]	*Yield (%)*[c]
1	THF	1	0
2	THF	2	0
3	THF/MeCN	1	70-90
4	THF/MeCN	2	0

[a]Reactions were carried out on a 0.25 mmol reaction scale using 10 mol% Wilkinson's Catalyst [$Rh(PPh_3)_3Cl$] modified with 40 mol% $P(OMe)_3$ in THF/MeCN with 2 eq. of aminopyridinium iodide and 4 eq. LHMDS, at 0 °C to RT for 12 hours. [b]LHMDS. [c]Isolated Yields. [d]No product was formed when reaction was submitted to reaction conditions containing no catalyst.

Several different allylic carbonates were examined in the reaction to determine the substrate scope (Table 2). Complete conversion of the allylic carbonate was observed in all cases, *via* crude NMR, and isolated yields were approximately 70-90%.

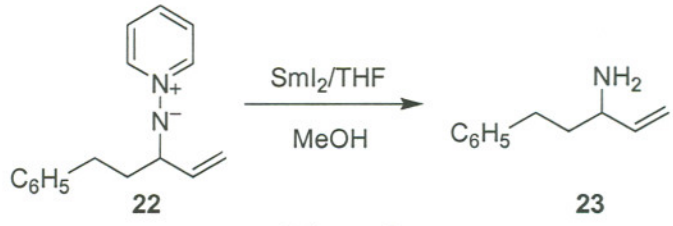
Table 2: Results of the rhodium catalyzed allylic amination

Entry	Allylic carbonate R=[a]	2^o:1^o[b]	Yield (%)[c]
a	Me	>19:1	68
b	^{n}Pr	>19:1	72
c	^{i}Pr	>19:1	90
d	Ph	>19:1	89
e	Cy	>19:1	71
f	$Ph(CH_2)_2$	>19:1	92

[a]All reactions were carried out on a 0.75 mmol reaction scale using 10 mol% Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] and 40 mol% $P(OMe)_3$ in THF/MeCN with 2 eq. of aminopyridinium iodide and 4eq LHMDS, at 0°C to RT for 12 hours. [b]Regioselectivity was determined by crude ^{1}H NMR. [c]Isolated Yields.

Having established the utility of this nucleophile conditions were sought to reveal the amine. Preliminary results demonstrated that the treatment of **20f** with SmI_2 furnished the amine, **23**, in 35% yield (Scheme 8). Extended reaction time also did not improve the yield. A possible problem is that the SmI_2 is quenched in the presence of any air. Therefore, the reaction could not be monitored *via* thin layer chromatography without adding more SmI_2. The SmI_2 procedure followed used a

very dilute concentration (0.04M); however, using a higher concentration, as many procedures do, may help facilitate the bond cleavage.[11,12,13]



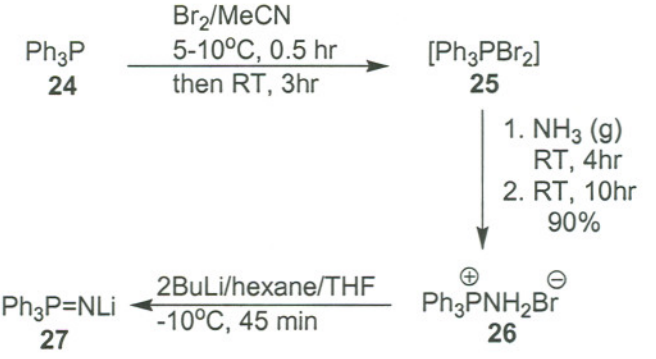
Scheme 8

Future Work

Additional efforts will now concentrate on the optimization of the deprotection to afford the free amine. The first approach will be to increase the concentration of the SmI_2 solution. Another viable option is to acylate the nitrogen with trifluoroacetic acid anhydride (TFAA), then cleave with SmI_2 in a one pot synthesis.[13] Friestad demonstrated that a TFA group should facilitate the cleavage of the N-N bond of hydrazines. This hypothesis came from a chelation model that was proposed by Flowers that ß-substituents could facilitate SmI_2 reduction reactions.[14]

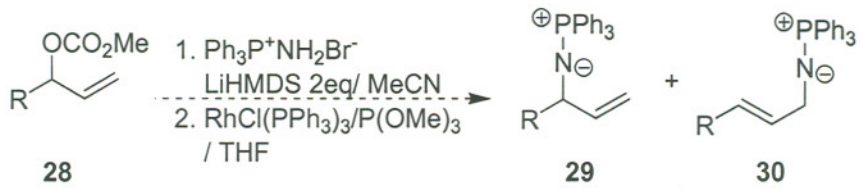
The allylic amination reaction will also be conducted on a chiral non-racemic carbonate to show enantiospecificity. Another possibility is to demonstrate the enantioselective variant using a chiral iridium catalyst.[15]

This reaction will also be expanded to encompass a variety of other ylides, which will likely include phosphorus, sulfur and carbon ylides. One such ylide was reported in 1991 by H.J. Cristau, the synthesis of *N*-(triphenylphosphoranylidene)carbamate was prepared by direct acylation using *N*-lithiated triphenylphosphine imide.[16] The precursor to the lithiated triphenylphosphine imide is aminotriphenylphosphonium bromide, **26**, which was reported stable to hydrolysis and easily prepared in large quantities (Scheme 9).



Scheme 9

We anticipate that with deprotonation the triphenylphosphonium bromide, **26**, will react with an allylic carbonate in a similar fashion as the pyridinium iodide resulting in an allylic amine as shown in Scheme 10. The N-P bond should be easier to cleave than the N-N bond of the pyridinium ylide, with the possibility that acid could cleave the triphenyl phosphine resulting in the free amine. If the N-P bond could be cleaved using acid, this reaction would provide a direct ammonia equivalent.



28 29 30

Scheme 10

Conclusion

We have developed a regioselective rhodium catalyzed allylic amination using aminopyridinium iodide as an amine equivalent. This is the first example of using an ylide in allylic alkylation chemistry and opens the door to research into the use of other ylides. Obtaining ylide intermediates may also provide useful in constructing bicycles and other scaffolds of natural products.

Experimental Data

The allylic carbonates were prepared according to literature procedures. [17,18] Aminopyridinium iodide was obtained from Aldrich with no further purification. ^{1}H was recorded at 400MHz and ^{13}C NMR was recorded at 100MHz both on a Varian Inova spectrometer. NMR solvent for ^{1}H NMR was D_2O and the ^{13}C solvent was deuterated DMSO. Chemical shifts were reported in parts per million, and coupling constants were reported in Hertz. Flash chromatography purification was performed with 60Å silica gel from Sorbent Technology. Reverse phase flash chromatography was performed on 60Å, C18 silica gel from Sorbent Technology. All reactions were carried out under argon atmosphere using flame-dried glassware.

Further purification of compounds is in progress. This will include IR data, High Pressure Reverse Phase Liquid Chromatography, and also x-ray crystallography of one of the azanides, in addition to NMR data for the remaining azanides containing no spectral data below.

(1-phenylprop-2-en-1-yl)(pyridinium-1-yl)azanide (20d) (representative example for allylic amination). Trimethyl phosphite (12 μL, 0.10 mmol) was added directly to a red suspension of Wilkinson's catalyst (23 mg, 0.025 mmol) in anhydrous THF (1.0 mL), and the mixture was stirred under an atmosphere of argon at room temperature for *ca.* 15 minutes resulting in a light yellow homogeneous solution. In a separate flask, lithium bis(trimethylsilyl)amide (237 μL, 0.1 mmol, 1.0 M solution in THF) was added to a suspension of aminopyridinium iodide (111 mg, 0.05 mmol) in anhydrous acetonitrile (1.5 mL) at 0°C and the ylide was allowed to form over *ca.* 15 minutes resulting in a heterogeneous purple solution with a white precipitate. The catalyst solution was added to the ylide solution *via* Teflon® cannula. The allylic carbonate (0.22 mmol) was then added *via* a tared 500 μL gas-tight syringe to the catalyst/ylide mixture, and the reaction was allowed to slowly warm up to room temperature over *ca.* 12 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase flash chromatography (eluting with 30% methanol/water) affording the azanide as a colorless solid (89%): ^{1}H NMR (400 MHz, D_2O) δ 8.62 (d, *J*=5.7 Hz, 2H), 8.31 (t, *J*=7.7 Hz, 1H), 7.83 (t, *J*=7.1 Hz, 2H), 7.28 (s, 5H), 6.12-6.03 (m, 1H), 5.18 (d, *J*=5.9 Hz, 1H), 4.95 (d, *J*=7.4 Hz, 1H); ^{13}C NMR

(100 MHz, DMSO) δ 145.18 (o), 136.52 (o), 129.74 (o), 129.38 (o), 128.66 (o), 120.79 (e), 69.87 (o).

(1-methylprop-2-en-1-yl)(pyridinium-1-yl)azanide (20a): ^{13}C NMR (100 MHz, DMSO) δ 144.57 (o), 138.23 (o), 129.32 (o), 129.06 (o), 119.96 (e), 62.30 (o), 19.04 (o).

(1-propylprop-2-en-1-yl)(pyridinium-1-yl)azanide (20b): ^{1}H NMR (400 MHz, D_2O)δ 8.68 (d, *J*=6.1 Hz, 2H), 8.36 (t, *J*=7.7 Hz, 1H), 7.93 (t, *J*=7.0 Hz, 2H), 5.61 (dt, *J*=17.0, 9.65 Hz, 1H), 5.02 (d, *J*=10.2 Hz, 1H), 4.84 (d, *J*=17.2 Hz, 1H), 3.81-3.76 (m, 1H), 1.64-1.45 (m, 2H), 1.38-1.23 (m, 2H), 0.81 (t, *J*=7.3, 3H); ^{13}C NMR (100 MHz, DMSO) δ 144.43 (o), 143.72 (o), 137.01 (o), 129.31 (o), 121.31 (e), 105.68 (o), 66.98 (o), 34.76 (e), 19.43 (e), 14.60(o).

(1-isopropylprop-2-en-1-yl)(pyridinium-1-yl)azanide (20c): ^{1}H NMR (400 MHz, D_2O)δ 8.69 (d, *J*=6.4 Hz, 2H), 8.36 (t, *J*=7.8 Hz, 1H), 7.93 (t, *J*=7.2 Hz, 2H), 5.68 (dt, *J*=17.0, 9.87 Hz, 1H), 5.05 (d, *J*=10.4 Hz, 1H), 4.80 (d, *J*=17.2 Hz, 1H) 3.54 (dd, *J*= 9.4, 6.8 Hz, 1H), 1.85 (sextet, *J*= 6.8 Hz, 1H), 0.96 (d, *J*=6.8 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H).

(1-cyclohexylprop-2-en-1-yl)(pyridinium-1-yl)azanide)(20e): 1H NMR (400 MHz, D_2O) δ 8.62 (d, *J*=5.9 Hz, 2H), 8.31 (t, *J*= 15.6, 7.8 Hz, 1H), 7.88 (t, *J*=14.1, 7.0 Hz, 2H), 5.62 (dt, *J*= 18.5, 9.2 Hz, 1H), 5.00 (d, *J*=10.2 Hz, 1H), 4.73

(d J=17.4 Hz, 1H), 3.51 (t, J=16.4, 8.2 Hz, 1H), 1.79 (d, J= 12.5 Hz, 1H), 1.65-1.51 (m, 5H), 1.17-0.91 (m, 5H).

[1-(2-phenylethyl)prop-2-en-1-yl)(pyridinium-1-yl)azanide (20f): ^{1}H NMR (400 MHz, D_2O)δ 8.53 (d, J=6.5 Hz, 2H), 8.26 (t, J=7.8 Hz, 1H), 7.82 (t, J=6.5 Hz, 2H), 7.21-7.10 (m, 5H), 5.58 (dt, J=16.8, 9.6 Hz, 1H), 5.06 (d, J=10.2 Hz, 1H), 4.76 (d, J=17.2 Hz, 1H), 3.63-3.61 (m, 1H), 2.64-2.5 (m, 2H), 1.88-1.77 (m, 2H).

Sumarium(II) Iodide: 1,2-diiodoethane (2.8 g, 10 mmol) in a solution of THF (250 mL) was added dropwise over *ca.* 1 hour to samarium metal (3.0 g, 20 mmol) under an atmosphere of argon at 0°C. Solution went from cloudy orange to a dark blue-green. Samarium iodide solution (0.04 M) was warmed to RT and stored under argon in the presence of excess metal.

5-phenylpent-1-en-3-amine (23): Samarium iodide in THF (0.04 M) was added under an atmosphere of argon to a solution of **20f** (45 mg, .20 mmol) *via* a 50 mL gas-tight syringe at room temperature until solution remained blue-green in color (15 eq). Reaction opened to air after *ca.* 15 hours to quench samarium iodide. Reaction mixture was concentrated *in vacuo* and purified *via* flash chromatography (eluting with 5% MeOH/$CHCl_3$) to afford a white solid.

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