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Novel methods towards synthesis of pyrroles and applications of Titanium mediated hydroamination reactions.

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NOVEL METHODS TOWARDS SYNTHESIS OF PYRROLES AND APPLICATIONS OF TITANIUM MEDIATED HYDROAMINATION REACTIONS.

BY

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ABSTRACT

NOVEL METHODS TOWARDS SYNTHESIS OF PYRROLES AND APPLICATIONS OF TITANIUM MEDIATED HYDROAMINATION REACTIONS.

BY

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Several new pyrroles have been synthesized by hydroamination of diynes, which were catalyzed by titanium-based catalysts. The diynes include terminal and internal diynes, which was not very stable at room temperature. The catalyst used for this pyrrole synthesis were chelating dipyrrolyl ligands based on *N*, *N*-di(pyrrolyl-α-methyl)-*N*-methylamine (dpma) and 5,5-dimethylpyrrolylmethane (dmpm) catalysts.

Attempt has been made to synthesize vinylpyrroles as an extension of the work on hydroamination chemistry. The Diels-Alder chemistry of these vinylpyrroles is also investigated.

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Abbreviations

1 NMP.....*N*-methyl pyrrolidine

2 dpma.....Di(pyrrolyl-α-methyl)methylamine

3 dmpm.....5,5-Dimethylpyrrolylmethane

4 dppm.....5,5-Di-*n*-propyldipyrrolylmethane

5 dap.....α-(Dimethylaminomethyl)pyrrole

6 PMB.....*p*-Methoxybenzylamine

7 DMSO.....Dimethylsulfoxide

8 DMAD.....Dimethylacetylenedicarboxylate

Chapter 1

Introduction

Hydroamination is the formal direct addition of an N—H bond to a C—C multiple bond. Hydroamination of alkynes is a desirable transformation in organic chemistry from a synthetic point of view as the products are important bulk chemicals, fine chemicals and building blocks in organic chemistry. This reaction is of potential industrial importance because every year several million tons of various amines are produced worldwide, and 80% of pharmaceutical products have C—N bonds (Figure 1-1).[1] The hydroamination reaction is atom economical with 100% efficiency; therefore, efficient hydroamination processes offer significant economical and environmental benefits compared to classical methods[2] for the synthesis of the mentioned target compounds. From a thermodynamic point of view, addition of amines or ammonia across alkynes and olefins is possible since the corresponding reactions are exothermic to thermoneutral in nature. Some olefin additions to ammonia and amines are close to thermoneutral.

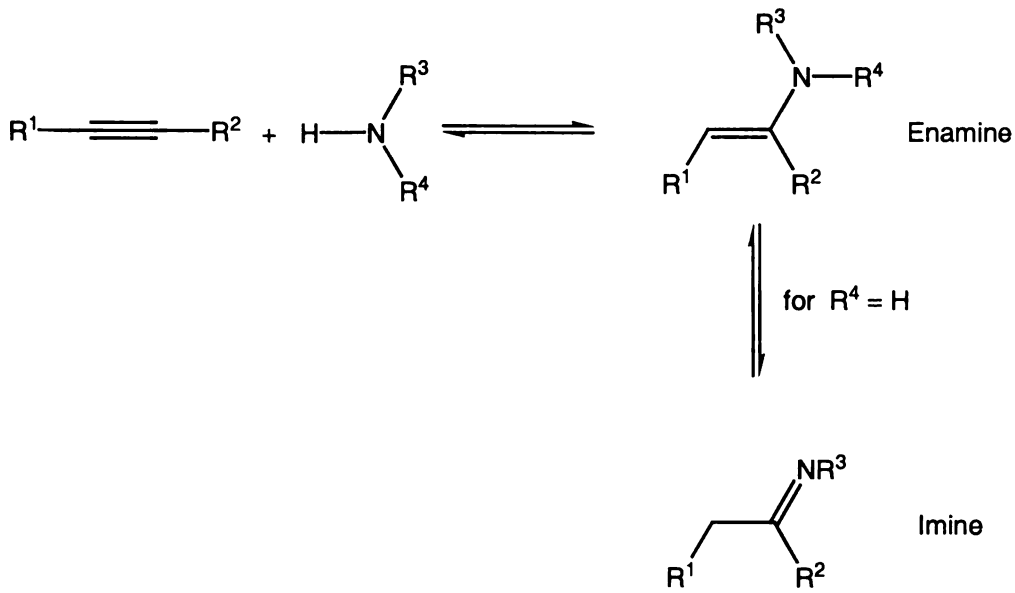


Figure 1-1. Alkyne hydroamination

To illustrate this fact, two representative sets of thermodynamic data for the reactions of ammonia and ethylamine with ethylene are represented in Figure 1-2.[3] Not much information is available on $\Delta H°$ data for addition of ammonia or amines to alkynes. Therefore, comparison between thermodynamics of amine addition to alkynes versus that to alkenes is not possible. However, addition of ammonia to acetylene is estimated (AM1-semiemperical calculations) to be ~63 kJ mol^{-1} more exothermic than that to ethylene.[1] Regarding this estimation, the hydroamination of alkynes is supposed to be more favorable than the corresponding hydroamination of alkenes.

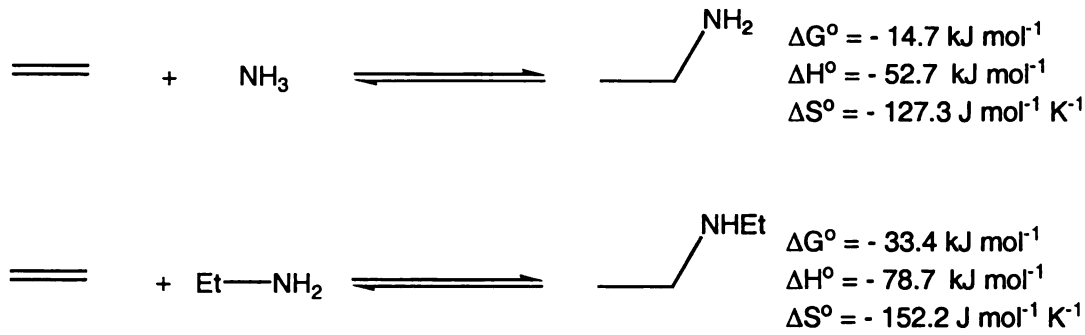


Figure 1-2. Thermodynamic data comparing hydroamination of amines and ammonia

A high activation barrier exists for the direct addition of amines across C—C multiple bonds, which arise from electrostatic repulsion between the electron lone pair at the nitrogen atom, and the electron rich π-bond of the alkyne or alkene. However, one cannot achieve hydroamination by increasing the temperature because of the negative reaction entropy $\Delta S°$ of the amine addition (Figure 1-2), the equilibrium of the reaction is shifted back to the starting reactants with increasing temperature.[4]

In contrast to the hydroamination of alkenes, which yields amines, the hydroamination of alkynes gives enamines and imines (Figure 1-1). These imines and enamines can be reduced by standard organic procedures to give amines, if those are the desired products. Alkenes are inexpensive compared to alkynes but the hydroamination of unactivated alkenes is a challenging problem, and the hydroamination of alkenes remains an unsolved synthetic problem. However, great progress has been achieved in developing hydroamination procedures for unactivated alkynes in the last couple of years. Since the above mentioned thermodynamical data suggest that the hydroamination of alkynes is possible more easily than that of alkenes, it is a reasonable approach to develop efficient catalytic hydroamination protocols for alkynes first and subsequently apply the obtained

knowledge to the related procedures for alkenes. In this context, one could say that hydroamination of alkynes can be seen as a basis for future hydroamination of alkenes. Howk[5] discovered one of the earliest examples of hydroamination reactions in 1954 wherein ammonia and primary amines add to alkenes in the presence of alkali metals or their hydrides, but the reaction typically requires harsh conditions (175 °C-200 °C, 800-1000 atm). The yields were poor and often yielded mono and multiple hydroamination products. Pez[6] reported an efficient metal-amide catalyzed addition of diethylamine and ammonia to ethylene and propylene. Kruse[7] reported one of the earliest hydroamination reactions of alkynes, wherein ammonia added across the carbon-carbon triple bond at 300-350 °C in the presence of silica or alumina catalyst, while amines required zinc or cadmium acetate catalyst.

Hydroamination of alkynes can either be an intramolecular or intermolecular reaction, the latter one being the more difficult of the two. This is can be argued in terms of the entropy decrease going from intramolecular to intermolecular hydroamination. Even though both the processes involve a decrease in the entropy, the decrease is going to be more for the intermolecular one compared to the intramolecular hydroamination.

There have been a number of different transition metals used for the hydroamination procedure, like mercury and thalium salts, alkali metals, lanthanides, actinides, zirconium, ruthenium, rhodium, palladium, gold complexes and titanium. By way of introduction and to place titanium-catalyzed reactions in a context, a brief discussion of a few different hydroamination catalysts is provided.

1.1.1 Hydroamination using Hg and Tl salts

Mercury and thallium complexes catalyze reactions involving terminal alkynes. Hudrlik,[8] reported a low yield of the hydroamination product, which was an aziridine enamine, from the reaction of 1-octyne and aziridine in presence of mercuric acetate as the catalyst (Figure 1-3).

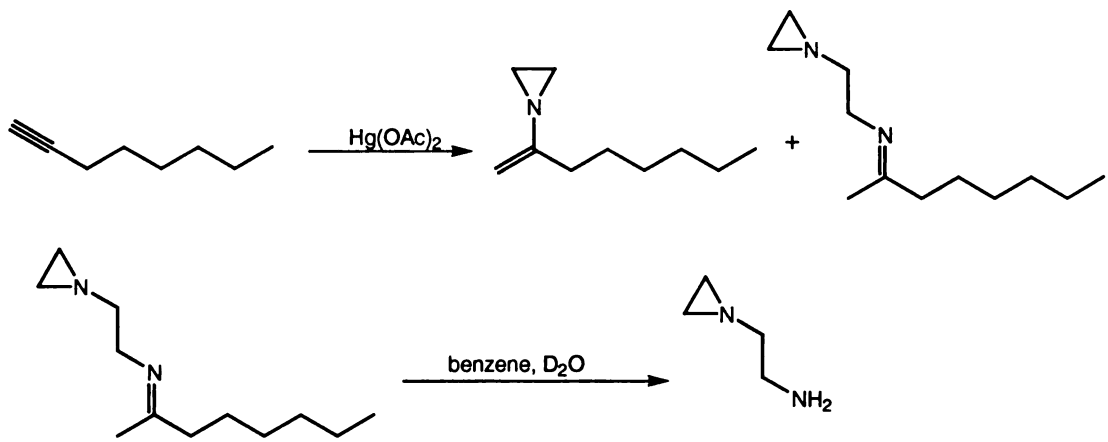


Figure 1-3. Hydroamination of terminal alkyne with Hg salt

Another reaction with pyrrolidine and 1-octyne was also reported in good yield, to give a saturated amine but then one had to deal with the problem of formation of an iminium salt intermediate,[9] (for example, addition of mercury or proton to the initial aminomercuration adduct), which is easily reduced to a saturated amine. The use of aziridine effectively prevents the formation of the iminium salt because of the strain involved in generating an sp^2 center in a three-membered ring, and hence facilitates formation of the enamine. Though this is one of the earliest examples of alkyne hydroamination to give enamines and saturated amines, this procedure is not of significance, because one would have to deal with using mercury as stoichometric reactant. However, this example did pave the way for further catalyst development. Even

though one could achieve product formation in this reaction using the procedure by Barleunga,[10] wherein catalytic amount of mercury (II) chloride and acetate were used, the method is still not desirable due to the precipitation of metallic mercury.

Barleunga,[11] further modified this method and used thallium (III) acetate instead of mercury (II) complexes for the hydroamination of phenylacetylene with primary aromatic amine in a stoichometric ratio.

1.1.2 Hydroamination using alkali metals

In 1999, Knochel,[12] reported the first base-catalyzed hydroamination of alkynes with substituted anilines and heterocyclic amines. They reported the hydroamination of phenylacetylene with diphenylaniline and *N*-methyl aniline in the presence of catalytic amounts of CsOH in NMP(*N*-methylpyrrolidine) at 90-120 °C leading to corresponding enamines in 82% and 46% yield, respectively (Figure 1-4).

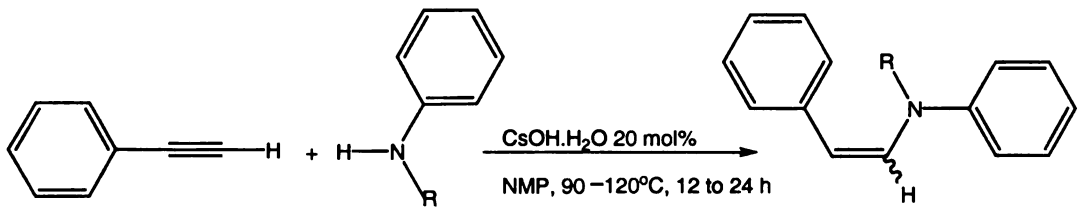


Figure 1-4. Base catalyzed hydroamination of alkynes

Recently,[13] the same group reported a base-catalyzed intramolecular hydroamination of 2-(2-alkynyl)anilines to form substituted indoles in 61-90% yield. The cyclization reaction is fast at room temperature and tolerates several functional groups enabling the preparation of a variety of polyfunctional indoles. This interesting cyclization was also extended to various heterocyclic amines such as amino pyridines.

1.1.3 Hydroamination using lanthanides and actinides

Marks,[14] provided the first example, an intramolecular hydroamination of amino alkynes catalyzed by organolanthanides, $Cp'_2LnCH(SiMe_3)_2$ (Ln= La, Nd, Sm, Lu; $Cp'=\eta^5-Me_5C_5$) and $Me_2SiCp''_2LnCH(SiMe_3)_2$ (Ln= Nd, Sm; $Cp''=\eta^5-Me_4C_5$), which offers a new route to a diverse variety of heterocycles and natural product skeletons. The same catalysts also perform intermolecular hydroamination of internal alkynes with primary amines yielding imines with good percentage yields.[15] (Figure 1-5).

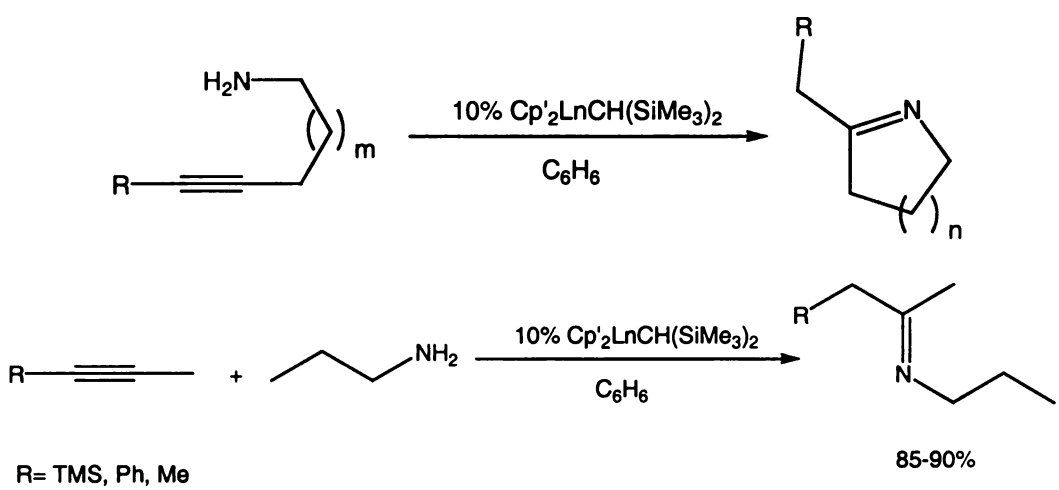


Figure 1.5. Hydroamination of alkynes catalyzed by lanthanides

Eisen,[16] provided the first example of catalytic intermolecular hydroamination of terminal alkynes with aliphatic amines using actinides, such as thorium and uranium yielding imines and enamines. An interesting aspect to note is that the regioselectivity of the products can be tuned by the alkyne and the metal used. The uranium-based catalysts predominantly yield aldimines in 80-90 % yields, whereas the thorium-based catalyst

gives only the ketimines in somewhat poor yields if the alkyne is internal, but for terminal alkyne the yield is around 80% (Figure 1-6).

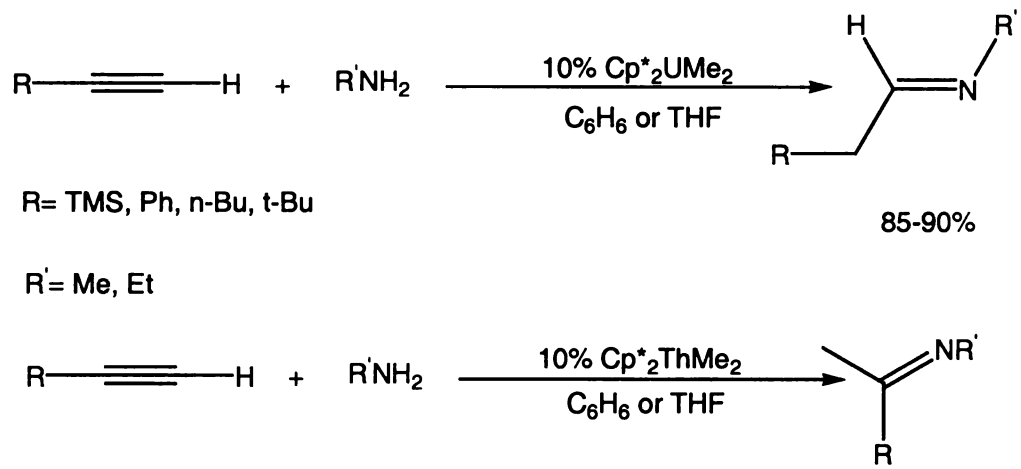


Figure 1.6. Hydroamination of alkynes catalyzed by actinides

Roesky,[17] reported the synthesis of mono- and bis(N-*iso*-propyl-2-(*iso*-propylamino)troponiminato)yttrium amides, $[(i\text{Pr})_2\text{ATI}]\text{Y}[\text{N}(\text{SiMe}_3)_2]$ and $[(i\text{Pr})_2\text{ATI}]_2\text{Y}[\text{N}(\text{SiMe}_3)_2]$ and used it as a catalyst for the intramolecular hydroamination of cyclic amines. These complexes were the first cyclopentadienyl-free catalysts for the intramolecular hydroamination reaction. The reaction requires around 2.0 mol% of the catalyst and goes to completion in less than an hour (Figure 1-7).

Recently Hultzch,[18] also reported a yttrium-based catalyst for the intramolecular hydroamination of alkenes and alkynes. Schafer,[19] has also reported a scandium-based cationic catalyst for the intramolecular hydroamination of alkynes.

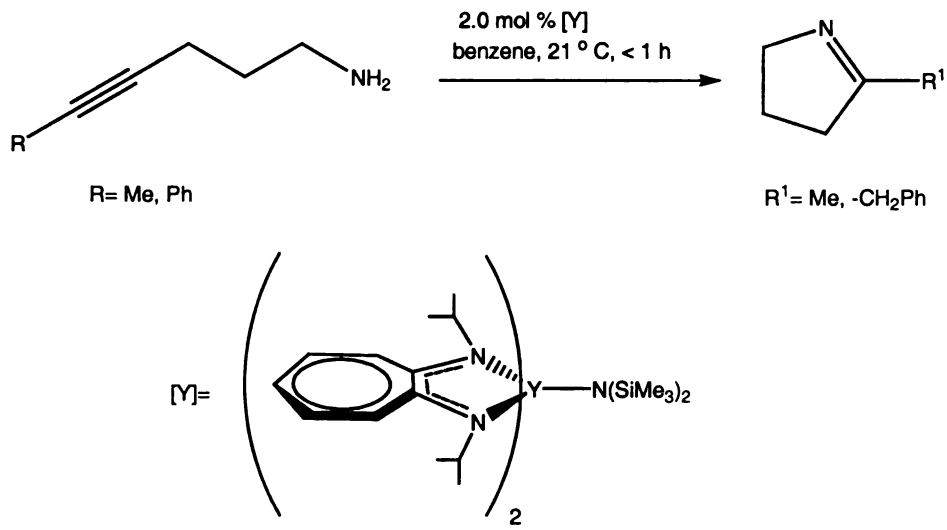


Figure 1.7. Hydroamination of alkynes with yttrium amides

1.1.4 Hydroamination using ruthenium complexes

Ruthenium-catalyzed intermolecular hydroamination was first reported by Uchimaru,[20] wherein phenylacetylene reacted with *N*-methylaniline in the presence of $Ru_3(CO)_{12}$ to afford *N*-methyl-*N*-(α-styryl) anilines in high yields (Figure 1-8).

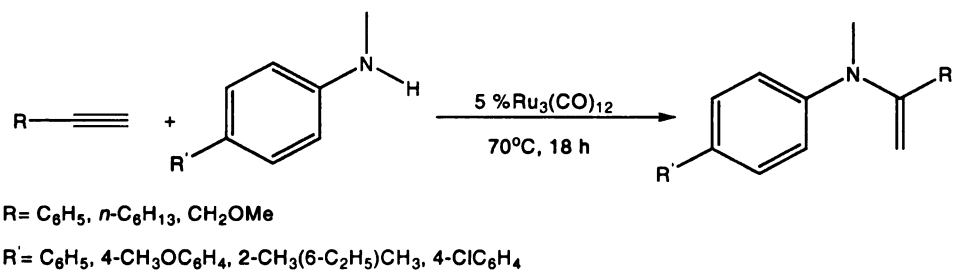
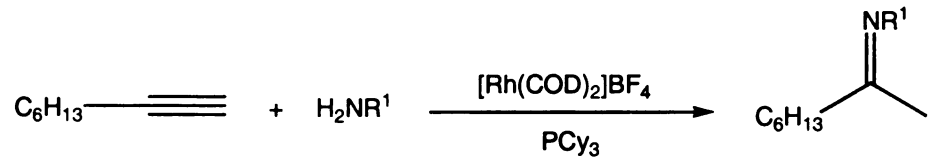


Figure 1-8. Hydroamination of alkynes catalyzed by ruthenium complex

Another example of a $Ru_3(CO)_{12}$ catalyzed hydroamination reaction of phenylacetylene and aromatic amines was provided by Wakatsuki,[21] where in the presence of an additive like NH_4PF_6(0.3 mol %), gave imines in high yields. In absence of the additive, a poor yield of 3 % was obtained under the same conditions.

1.1.5 Hydroamination using rhodium complexes

Beller,[22] reported a hydroamination reaction of terminal alkynes with substituted anilines in the presence of cationic rhodium (I) catalyst, $Rh[(COD)_2]BF_4$, under very mild reaction conditions to yield up to 99% of the corresponding imines (Figure 1-9). Other rhodium complexes like, $[Rh(COD)Cl]_2$, [Rh(COD)(acac)], $[Rh(PPh_3)_3Cl]$ and $RhCl_3.xH_2O$ in combination with different phosphine ligands show no hydroamination activity.



R^1=C_6H_5, 2-Me-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4,3-F-C_6H_4

Figure 1-9. Hydroamination of alkynes catalyzed by rhodium complex

This method was further extended for a one-pot protocol for the synthesis of branched amines directly from alkynes by in situ addition of organometallic compounds. Messerle and Turner,[23] recently reported an intramolecular hydroamination of alkynes catalyzed by cationic rhodium and iridium complexes.

1.1.6 Hydroamination using palladium complex

Müller,[24] reported an intramolecular hydroamination of 6-amino-1-hexyne catalyzed by 1 mol% of $Pd(CH_3CN)_4(BF)_2$ to generate the intermediate 2-methylene piperidine. Subsequent 1,3-hydrogen-shift leads to isomerisation of the initially formed enamine to the more stable imine to afford 2-methyl-1,2-dehydropiperidine in 67% yield (Figure 1-10).

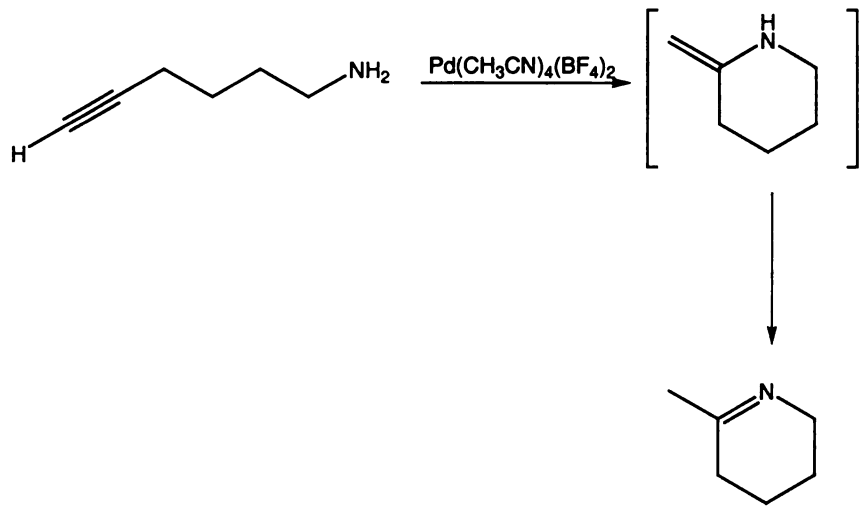


Figure 1-10. Hydroamination of alkynes catalyzed by palladium complex

1.1.7 Hydroamination using gold complex

Tanaka and Hayashi,[25] recently published a Au (I) catalyzed, $[(Ph_3P)AuCH_3]$ with acidic promoters, heteropoly acids in particular to give ketimines, with around 80-90% yield (Figure 1-11). Some of the heteropoly acids used were $H_3PW_{12}O_{40}$, $H_3MoW_{12}O_{40}$, and $H_4SiW_{12}O_{40}$, which were particularly effective giving high yields of the ketimines. In the absence of the acidic promoter the hydroamination did not work nor did the reaction

work in absence of the Au catalyst. Some other acidic promoters like ammonium hexafluorophosphate and tetrafluoroborate were able to activate the alkyne, but gave only modest yields. A typical example of the reaction between aniline and phenylacetylene, using 0.2 mol% $(Ph_3P)AuCH_3$ and 1 mol% $H_3PW_{12}O_{40}$, proceeded to give *N*-(α-methylbenzylidene)aniline in 98% yield.

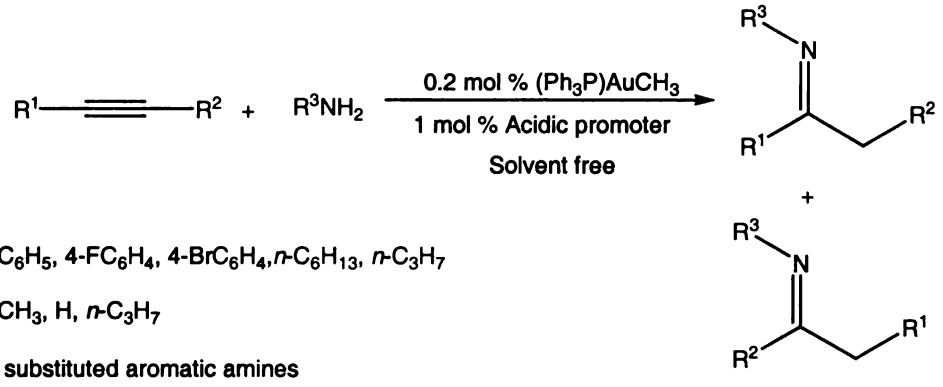


Figure 1-11. Hydroamination of alkynes catalyzed by gold complex

In these reactions, the products obtained were a mixture of the corresponding imine and enamine, the former being the major component. In addition, internal alkynes took longer reaction times compared to the terminal alkynes and gave moderate yields of 50-60%.

1.1.8 Hydroamination using Group IV complexes

a) Zirconium

In 1992, Bergman[26] reported that zirconium bisamides, $Cp_2Zr(NHR)_2$, catalyze the intermolecular hydroamination of alkynes with sterically hindered primary amines to give enamines or their tautomeric imines (Figure 1-12).

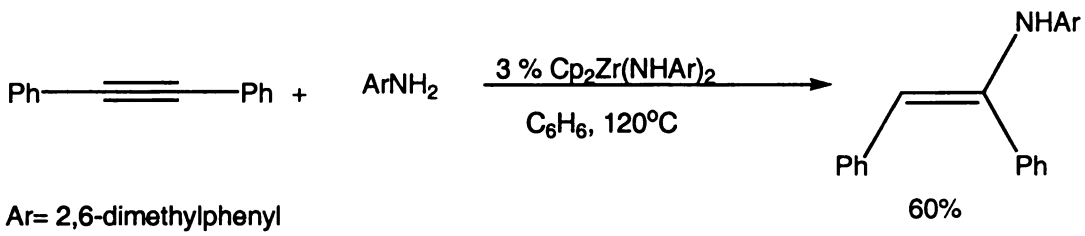


Figure 1-12. Hydroamination of alkynes catalyzed by zirconium complex

A transient imido complex, $Cp_2Zr{=}NAr$ is obtained by thermolysis of the biamides, which undergoes a reversible [2 + 2] cycloaddition with the internal alkyne to provide azametallacyclobutene (Figure 1-13). The rate-determining step is the α-elimination of the amine to give the imido complex. Further, the metallacyclobutene reacts with the amine to form the enamine and $Cp_2Zr{=}NAr$, beginning the catalytic cycle again. The addition of alkynes to $Cp_2Zr{=}NAr$ occurs regioselectively to metallacycles, with the larger alkyne substituent located α to the metal center. The hydrolysis of metallacycles gives enamines and imines, which are the net result of anti-Markovnikov addition to the alkyne.

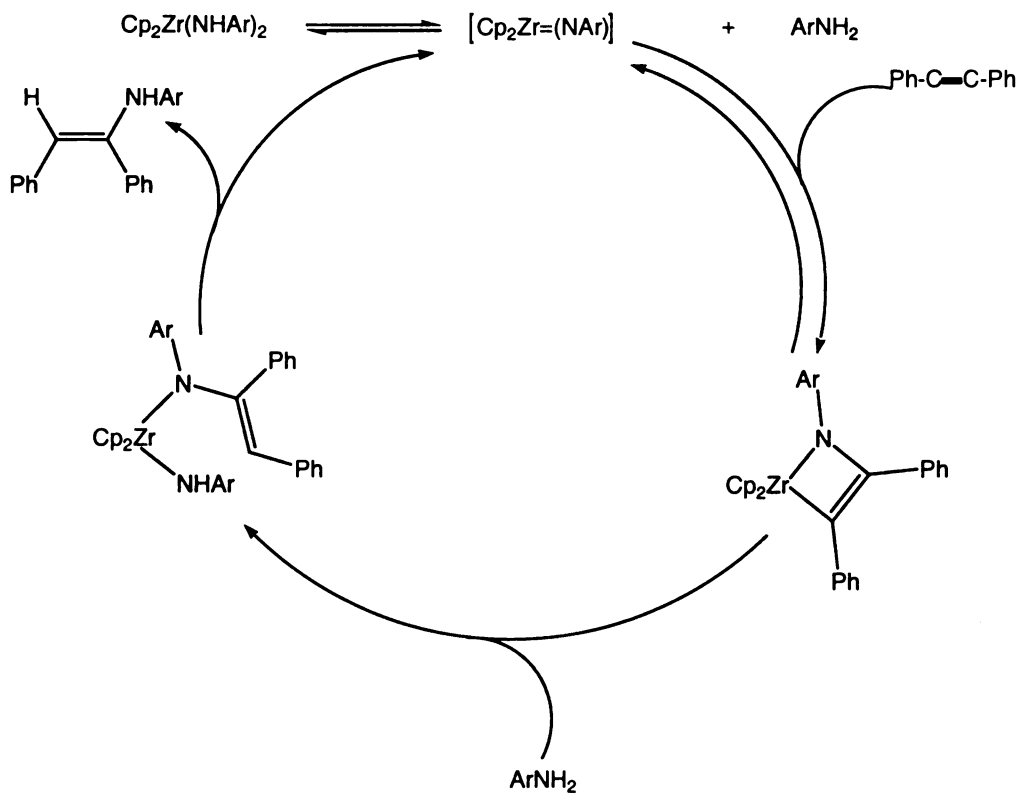


Figure 1-13. Bergman's mechanism for hydroamination for alkynes

A drawback for this reaction is the slow rate and its limitation of using disubstituted alkynes. Also, attempts to hydroaminate olefins such as ethylene, allylbenzene and norbornene with bisamide $Cp_2Zr(NHR)_2$, and corresponding amines with temperatures up to 160 °C were unsuccessful.

In 1993, Bergman[27] reported hydroamination of terminal alkynes with zirconium bisamides, $Cp_2Zr(NHR)_2$, followed by hydrolysis to give predominantly the anti-Markovnikov product.

b) Titanium

The earliest example of titanium-catalyzed hydroamination was provided by Rothwell,[28] wherein titanium bis(phenylamido) complex (**I**) catalyzes the reaction of aniline and 3-hexyne to give *N*-phenylimine of 3-hexanone (Figure 1-14). The titanium phenylamido complex (**II**) does not show any evidence of hydroamination with 3-hexyne even after heating at 110 °C for days, probably due to pyridine inhibition.

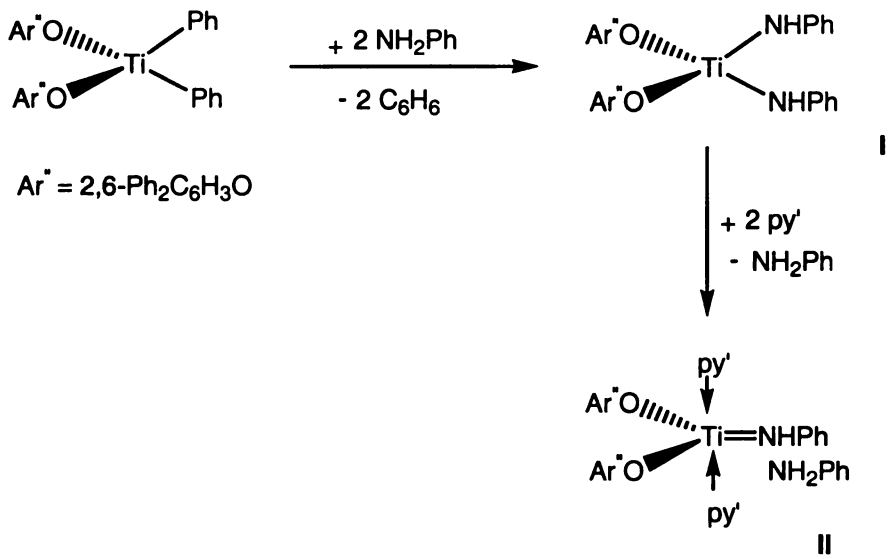


Figure 1-14. First example of titanium catalyzed hydroamination of alkynes

Livinghouse[29] provided further evidence of titanium-catalyzed hydroamination, wherein $CpTiCl_3$ catalyzed the intramolecular hydroamination of γ-aminoalkyne (Figure 1-15). This intramolecular hydroamination results in an imidotitanium-alkyne [2+2] cycloaddition, which is used in the synthesis of the indolizidine alkaloid (±)-monomorine.

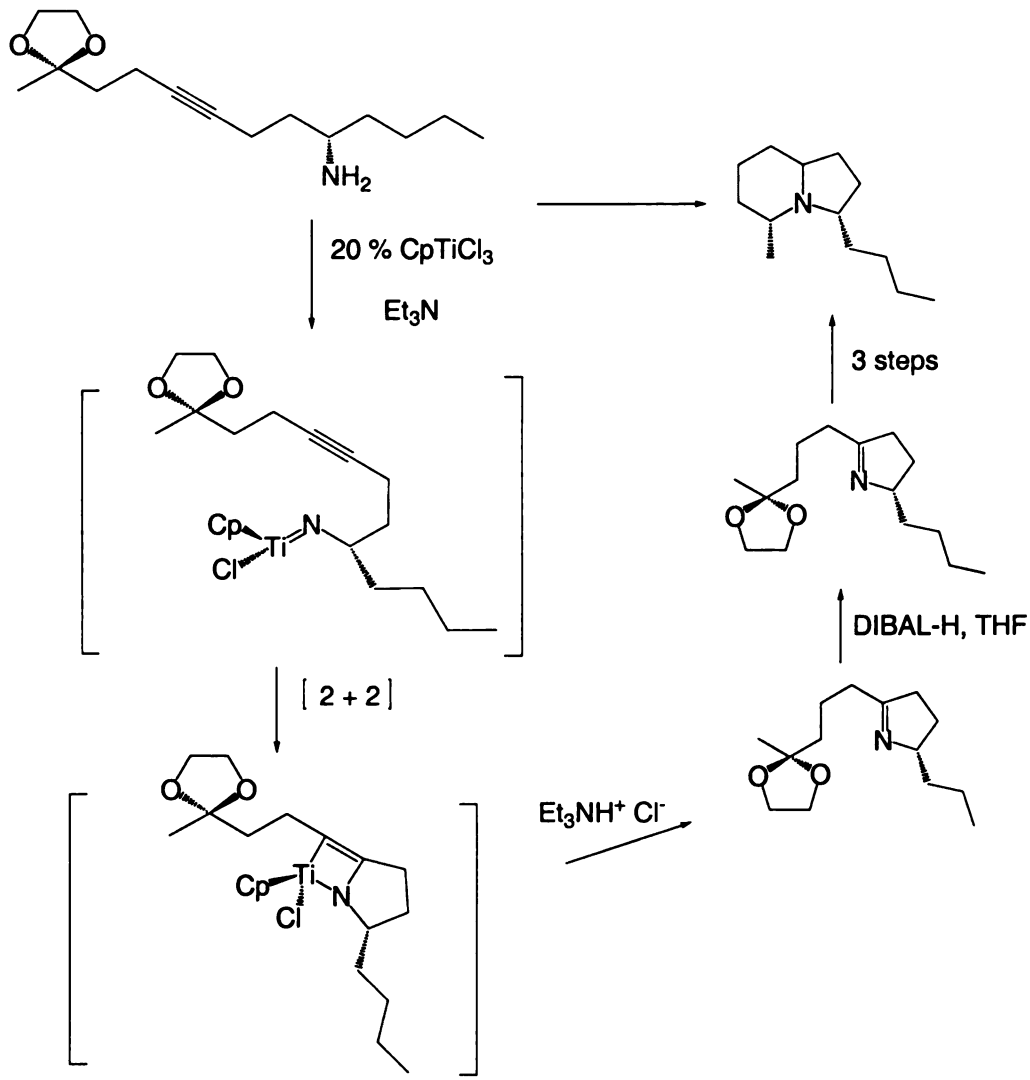


Figure 1-15. Synthesis of (±)-monomorine via intramolecular hydroamination.

Another alkaloid, (+)-Preussin was also synthesized, with a crucial intramolecular imidotitanium-alkyne [2+2] cycloaddition step, followed by an acyl condensation to give, (+)-Preussin[30] (Figure 1-16). The overall yield for the synthesis was around 35-44%. Another example of intramolecular hydroamination, published by Livinghouse,[31] was the synthesis of dihydropyrrole and tetrahydropyridine derivatives by 20 mol% $Cp_2Ti(CH_3)_2Cl$ and $CpZr(CH_3)_2Cl$ catalysts, with a reasonably good yield of 80-90%.

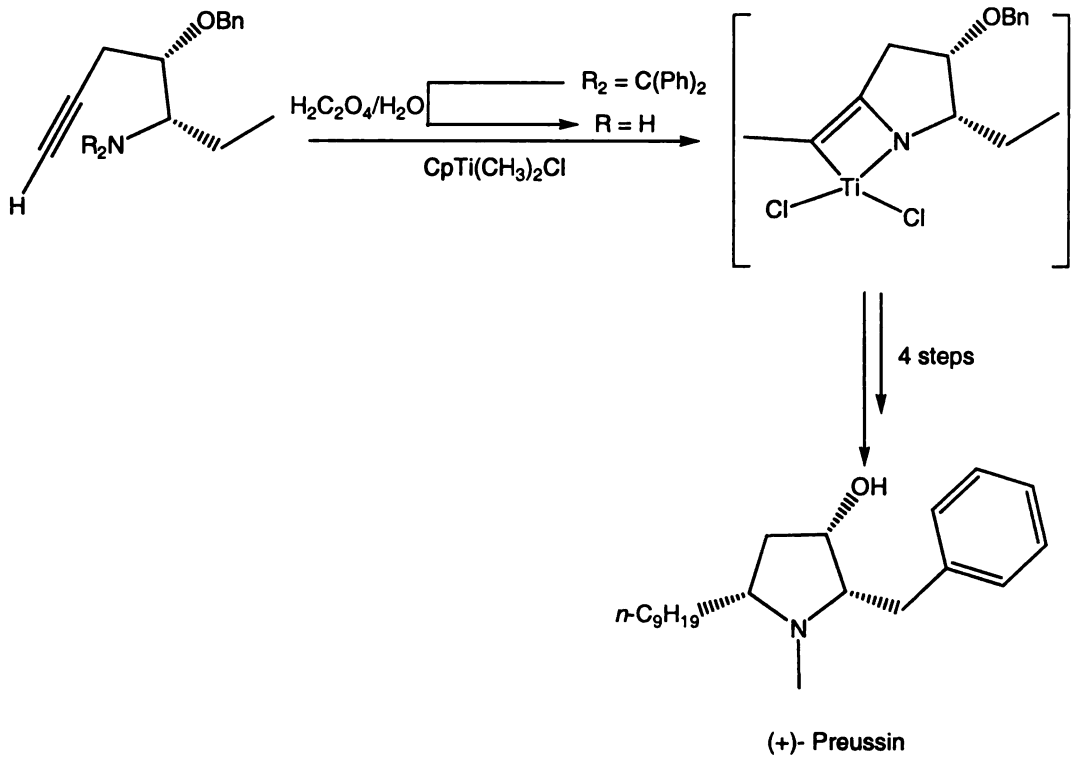


Figure 1-16. Synthesis of (+)-preussin via intramolecular hydroamination catalyzed by titanium

In 1999 Doye,[32] reported an intermolecular hydroamination of alkynes and aromatic amines with commercially available Cp_2TiMe_2 to give amines, obtained by reduction of enamines and imines, in relatively good yield of 65-80% yield. This hydroamination did not work well with benzylamine or with terminal alkynes. Replacing the aromatic substituent on the alkyne with an alkyl group, also leads to a drastic decrease in the yield. In many cases, the enamines and the imines obtained by hydroamination were hydrolyzed by silica to give ketones in 70-85% yield (Figure 1-17). For unsymmetrical substituted alkynes, the hydroamination reactions occur with high regioselectivity

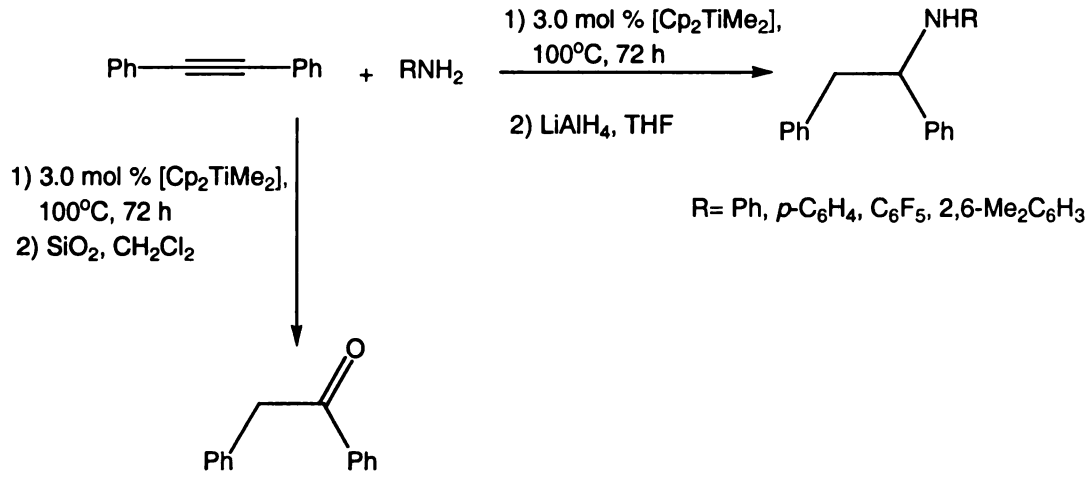


Figure 1-17. Hydroamination of alkynes with Cp_2TiMe_2 as catalyst

The mechanism for this hydroamination is similar to Bergman's mechanism.[33]

In 2000 Doye,[34] reported an ammonia equivalent in the dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes by using benzhydrylamine. This procedure combined with reduction of the initially formed imines, gives primary amines with 70% yield (Figure 1-18).

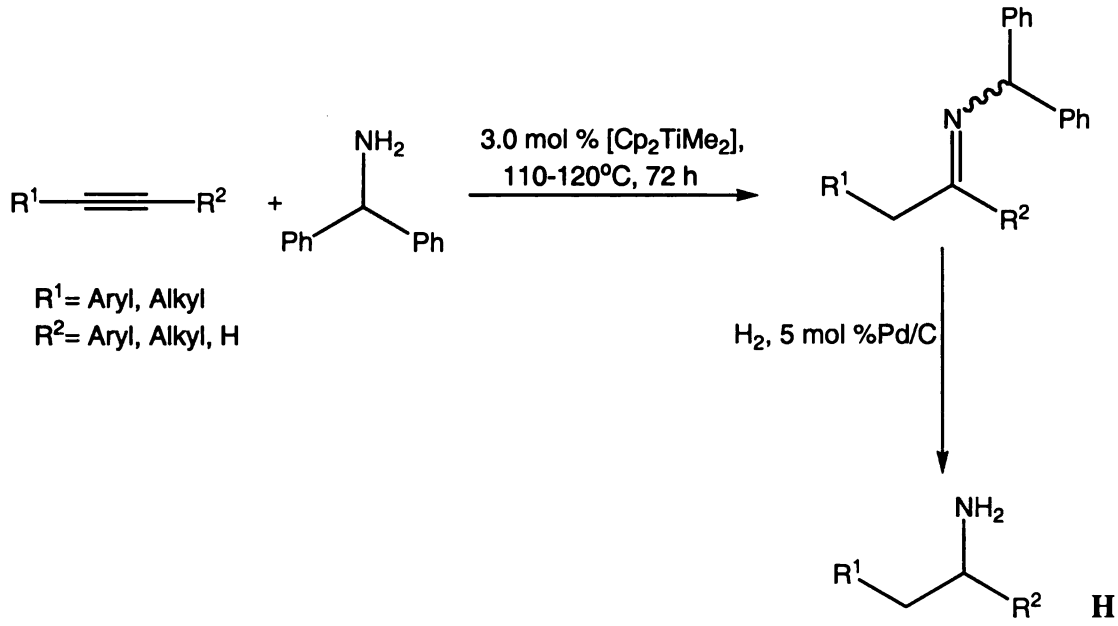


Figure 1-18. Hydroamination of alkynes with Cp_2TiMe_2 as catalyst and benzhydrylamine

This is an improvement over the previously reported work, where only secondary amines where obtained, by reduction of the imines formed during hydroamination. Also, initial experiments of alkyne hydroamination using benzylamine as the ammonia equivalent had limited success, because benzylamine shows a very low reactivity with the dimethyltitanocene-catalyzed hydroamination reactions. The hydroamination shows good results with bisaryl alkynes and alkyl aryl alkynes, but the reaction is relatively slow and requires 72h to proceed to completion. In contrast, the reactions employing bisalkyl alkynes do not proceed to completion even after 72h. The hydroamination reactions occur with high regioselectivity for terminal alkynes and alkyl aryl alkynes.

Cp_2TiMe_2-based reactions have also been reported by Doye[35] that catalyze the intramolecular hydroamination and cyclization of aminoalkynes to give five- and six-membered cyclic imines within 4-6 h. The imines can be subsequently reduced with

sodium borohydride and zinc chloride at room temperature to give cyclic amines in 70-85% yields.

In 2002, Doye[36] modified his titanocene-based catalyst by replacing the Cp group with Cp^*, i.e. the pentamethylcyclopentadienyl ligand. In his previous paper,[33] a mechanistic study showed that unfavorable equilibria between titanium imido complexes, imido complex dimers, and bisamides are responsible for the decreased reactivity of sterically less demanding amines. So, the use of bigger, space-demanding ligands at the titanium center should result in faster reactions with smaller amines. The hydroamination carried out by this modified ligand gives excellent results for intermolecular addition of various sterically less hindered *n*-alkyl- and benzylamines to internal alkynes with yields in the typical range of 70-90%. The hydroamination reactions occur with high regioselectivity giving the anti-Markovnikov products.

Recently, Doye reported a highly active catalyst for the intermolecular hydroamination of terminal and internal alkynes using catalytic amounts of Ind_2TiMe_2 as the catalyst (Ind=Indenyl).[37] This catalyst performs hydroamination of internal and terminal alkynes with primary aryl, *tert*-alkyl, *sec*-alkyl and *n*-alkylamines (Figure 1-19).

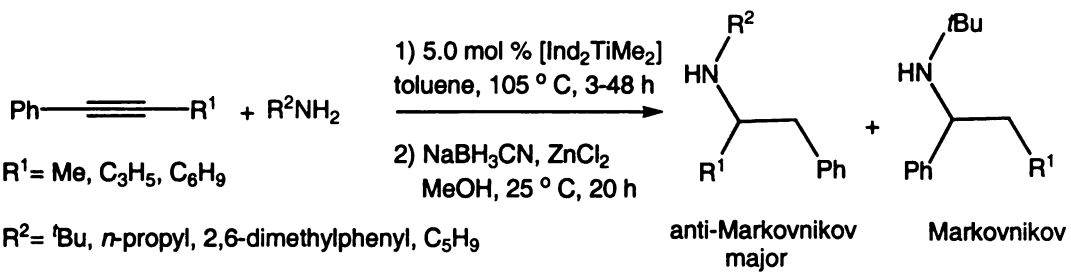


Figure 1-19. Hydroamination of alkynes with Indenyl-based titanium catalyst

The major product of hydroamination of terminal arylalkynes is always the anti-Markovnikov product, whereas alkylalkynes react with arylamines to give the Markovnikov product.

In 2002 Richeson,[38] reported the formation of Ti(IV) terminal imido complex possessing a guanidinate ancillary ligands, which catalyzes the intermolecular hydroamination of alkynes (Figure 1-20). Terminal alkynes react more rapidly, with higher yields of the imine than internal alkynes and also less bulky arylamines and aliphatic amines are effective for the hydroamination of alkynes with the guanidinate-based titanium catalyst.

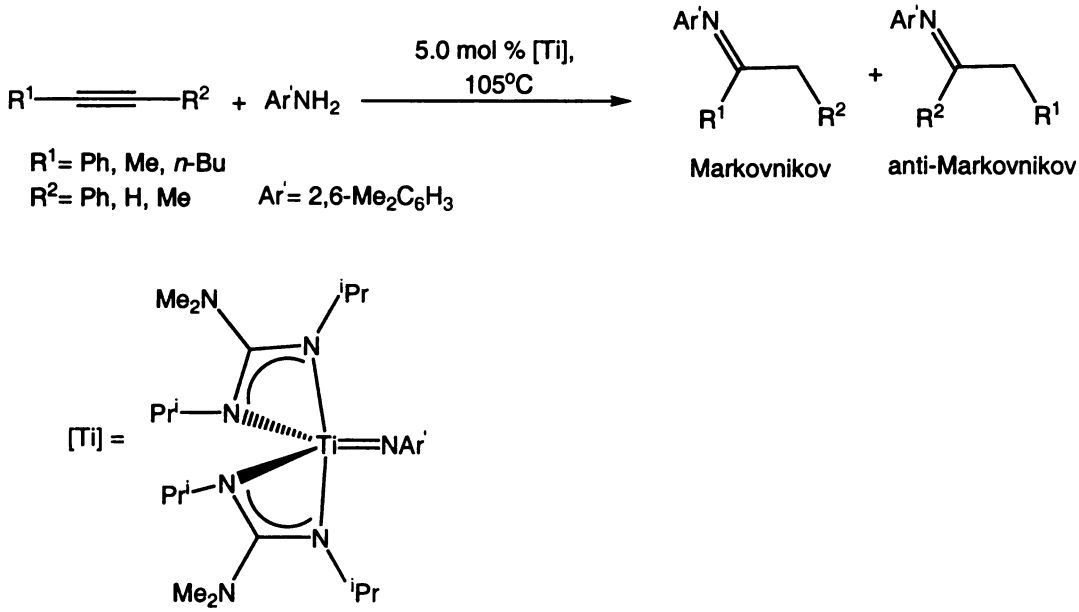


Figure 1-20. Hydroamination using guanidinate ancillary ligands on titanium

The catalyst exhibits reactivity comparable with the Cp_2TiMe_2 and $Cp_2Zr(NHAr)_2$ catalyst precursors of Doye and Bergman, respectively. It is interesting to note, that phenylacetylene preferentially undergoes anti-Markovnikov addition, while hydroamination of 1-hexyne generates predominantly Markovnikov products. The

authors attribute this complex regioselectivity to the sterics of the bis(guanidinate) framework.

Beller[39] reported the intermolecular hydroamination of terminal alkynes using a titanocyclopropene-based catalyst to yield the anti-Markovnikov product selectively (Figure 1-21). Before this communication, the only group that reported intermolecular hydroamination of terminal alkynes using titanium-based catalysts was the Odom group.

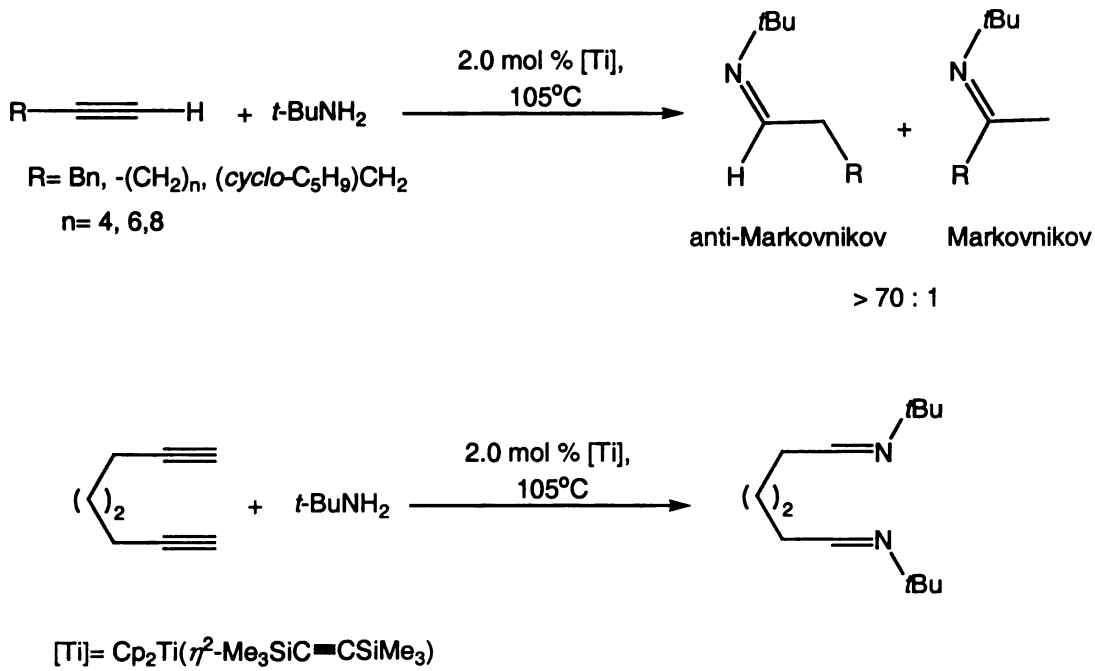


Figure 1-21. Hydroamination of terminal alkynes using titanocyclopropene-based catalyst

The titanium complexes ([$Cp_2Ti(\eta^2$–$Me_3SiC{\equiv}CSiMe_3$)] and ([$Cp_2Ti(\eta^2$–$Me_3SiC{\equiv}CPh$)] are synthesized by reaction of titanocene dichloride with the corresponding silylated alkyne. The hydroamination of terminal alkynes with *tert*-butylamine in the presence of the catalyst yielded imines with more than 90% yield with

a typical reaction time of a day. The reaction gave predominantly anti-Markovnikov products, except when using aniline, where Markovnikov products are preferentially observed. For terminal alkynes with shorter alkyl substituents the hydroamination was complete in two hours. This is the also the first communication wherein dihydroamination of diynes is reported to give diimines in 90% yield. A further modification of this reaction to give α-branched amines was reported by Beller[40] a year later, wherein the corresponding hydroaminated products obtained in the above reaction were treated with a nucleophile, e.g. *n*-BuLi and PhLi to provide α-branched amines.

Recently Bergman[41] reported the use of group-4 bis(sulfonamido) complexes in the intramolecular hydroamination of alkynes and allenes. Odom[42] reported better efficiency of titanium tetrakis(amido) complexes compared to Cp-based species. By replacing the ligands with electron-withdrawing groups the metal center can be made more electron deficient and catalytic activity of the titanium metal center can be increased. Bergman employed electron-withdrawing and sterically demanding bis(sulfonamido) ligands (Figure 1-22). Replacing the aryl group on the sulfur by trifluoromethyl and methyl groups yields a new titanium catalyst, which converts aminoallenes selectively to the corresponding cyclic imines with corresponding yield of more than 80%.

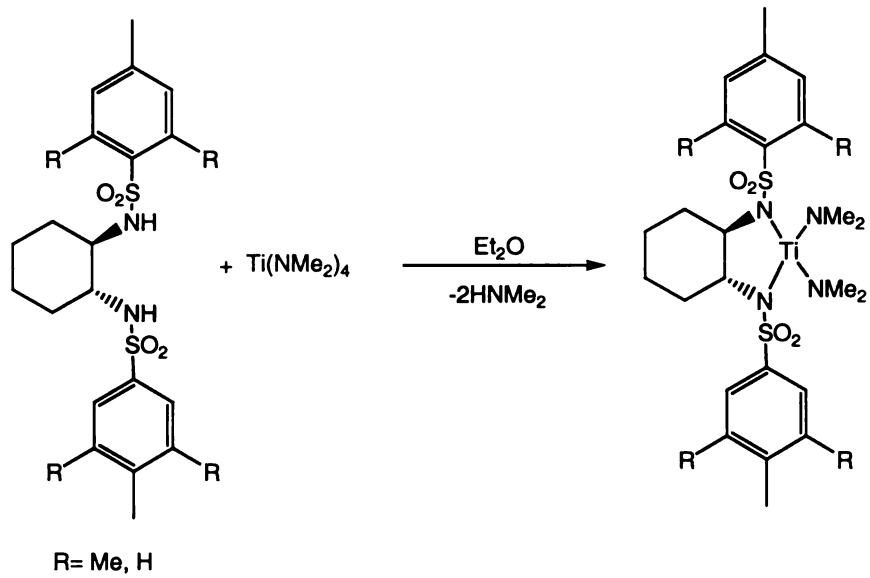
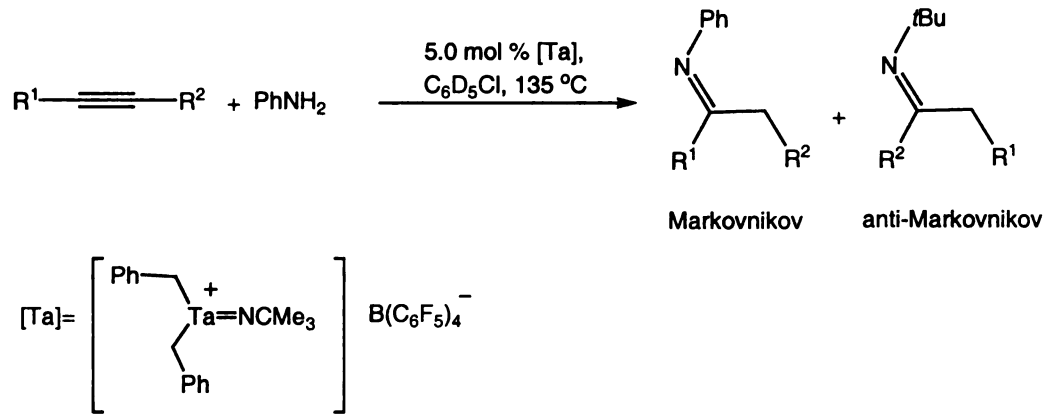


Figure 1-22. Hydroamination of alkynes and allenes with group-4 bis(sulfonamido) complexes

Bergman's group also reported,[43] the synthesis of the new neutral and cationic imidotantalum complexes, which catalytically hydroaminate alkynes. This is the only group, which has reported hydroamination by group-5 transition metals other than Lorber's group.[44] Cationic group-5 imido complexes are promising as potential hydroamination catalysts, since these compounds are isoelectronic to the group-4 catalysts. Hydroamination of diphenylacetylene by aniline in the presence of 5 mol% $[(PhCH_2)Ta{=}NCMe_3]^+$ at 135 °C gave the imine and enamine products in 3:1 ratio in 26% yield (Figure 1-23). An increased yield of 95% was obtained by in situ generation of $[(PhCH_2)Ta{=}NCMe_3]^+$.



R¹and R² = Et and Et, *n*-Pr and Me, Ph and H, *n*-Pr and H, Ph and Me

Figure 1-23. Hydroamination of alkynes with cationic imido complex of tantalum

Hydroamination of internal alkynes was slower than terminal ones and dialkylacetylenes react more slowly than diphenylacetylene. 1-phenylpropyne failed to react or to give hydroamination products. The tantalum imido species also catalyzes an unusual hydroamination/hydroarylation reaction between norbornene and aniline.

Ackermann,[45] reported the catalytic intermolecular hydroamination of internal alkynes by $TiCl_4$. He also prepared a titanium imido catalyst, obtained by the reaction between $TiCl_4$ and excess of $^tBuNH_2$ in a halogenated solvent, to give $[Cl_2(py)_3Ti{=}N^tBu]$ (Figure 1-24).

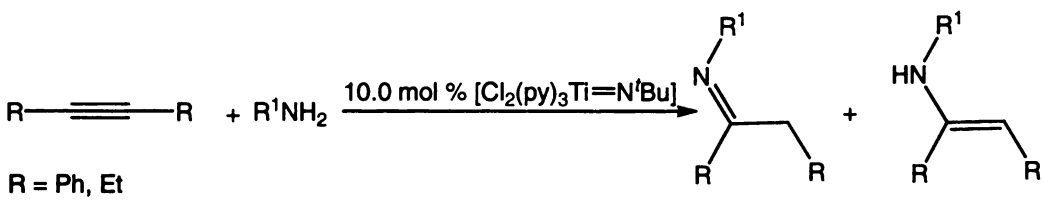
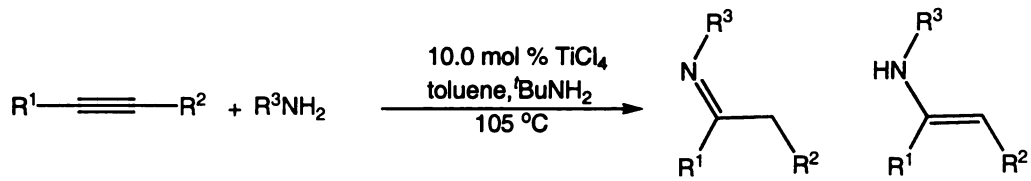


Figure 1-24. Hydroamination of internal alkynes with titanium imido complex

This catalyst performs the hydroamination reaction of internal alkynes such as diphenylacetylene and phenyl substituted internal alkynes with $^tBuNH_2$ to give good to

moderate yields of the hydroaminated product. On the other hand, a catalytic amount of $TiCl_4$ performs hydroamination with diphenylacetylene and phenyl-substituted internal alkynes with different halogen-substituted amines to give over 80% yield of the hydroaminated product (Figure 1-25).



$R^1$and R^2 = Ph and Ph, Ph and Me, ^{n}Pr and ^{n}Pr

R^3 = Ph, 4-$MeC_6H_4NH_2$, 4-$FC_6H_4NH_2$, 2-$ClC_6H_4NH_2$, 3,5-$Me_2C_6H_3NH_2$
4-Br-2-$MeC_6H_3NH_2$, 2-$IC_6H_4NH_2$, 4-$EtO_2CC_6H_4NH_2$

Figure 1-25. Hydroamination of internal alkynes with titanium tetrachloride

Furthermore, this methodology proves tolerant to halide substituents on the aromatic ring of the amine, allowing expansion of this methodology in the one-pot synthesis of substituted indoles.

Schafer[46] reported the preparation and characterization of amidate complexes of both titanium and zirconium and their application as catalysts for the intramolecular hydroamination of alkynes. The catalyst was prepared from reacting amide proligands with $Ti(NMe_2)_4$ and $Zr(NMe_2)_4$ (Figure 1-26).

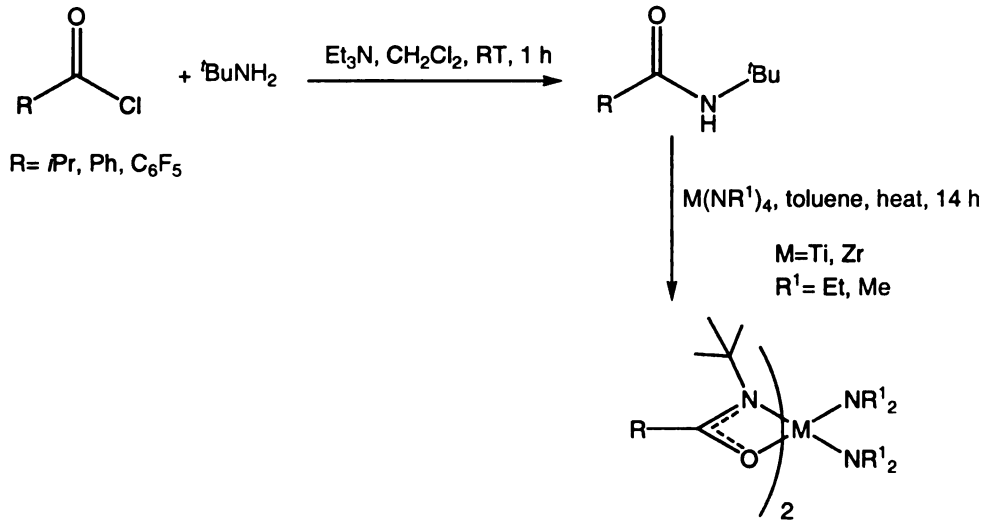


Figure 1-26. Use of amidate complexes of group-4 metals for intramolecular hydroamination

As expected, the titanium analogues prepared from phenyl and *iso*-propyl proligands are more active catalysts than their zirconium derivatives. Also, incorporation of electron-withdrawing substituents on the carbonyl moiety of the amidate ligand dramatically enhances catalytic activity. Hence, it is observed that pentafluorophenyl substituent on the titanium amidate ligand does hydroamination in 15 minutes compared to the alkyl substituted amidate ligand. Hydroamination results show that a catalytic amount of the titanium amidate complex yields over 90% of the hydroaminated imine product when the reaction is carried out with 1-hexyne and substituted amines.

The reaction predominantly yields the anti-Markovnikov product (>90%) with *tert*-butylamine and *iso*-propyl amine, while with 2,6-dimethylaniline, the Markovnikov product is favored (>90%). These catalysts also perform intramolecular hydroaminations of alkynes and can be tuned for intermolecular hydroaminations by modifying the amidate ligands.

1.1.9 Research in the Odom group

Early research, in our lab was aimed towards the use of non-cyclopentadiene based systems for hydroamination of alkynes, as previously all known titanium based catalysts were metallocene based. Odom[47] published the use of $Ti(NMe_2)_4$ as a catalyst for the hydroamination of alkynes with primary amines such as aniline. The hydroamination reaction predominantly gave the Markovnikov addition product, which is in contrast to the catalyst Me_2TiCp_2 that yields the *anti*-Markovnikov product (Figure 1-27).

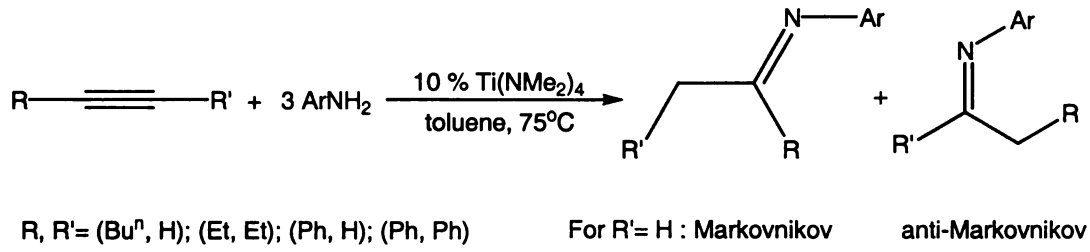


Figure 1-27. Hydroamination of alkynes with catalytic amounts of $Ti(NMe_2)_4$

The ratio of Markovnikov:*anti*-Markovnikov products varied from 3:1 to >50:1 with the different substrates examined. The hydroamination is fast and takes around two hours for 1-hexyne but for internal alkynes such as 3-hexyne, it is slow and the yields are around 80-90%. The reaction works with aromatic amines such as aniline but was low yielding with benzylamines and alkyl amines such as *t*-butylamine.

Further modifications to this catalyst was reported,[48] where instead of $Ti(NMe_2)_4$ as the catalyst, $Ti(dpma)(NMe_2)_2$, where dpma is di(pyrrolyl-α-methyl)methylamine. The catalyst is prepared from $Ti(NMe_2)_4$ and H_2dpma in near quantitative yield (Figure 1-28).

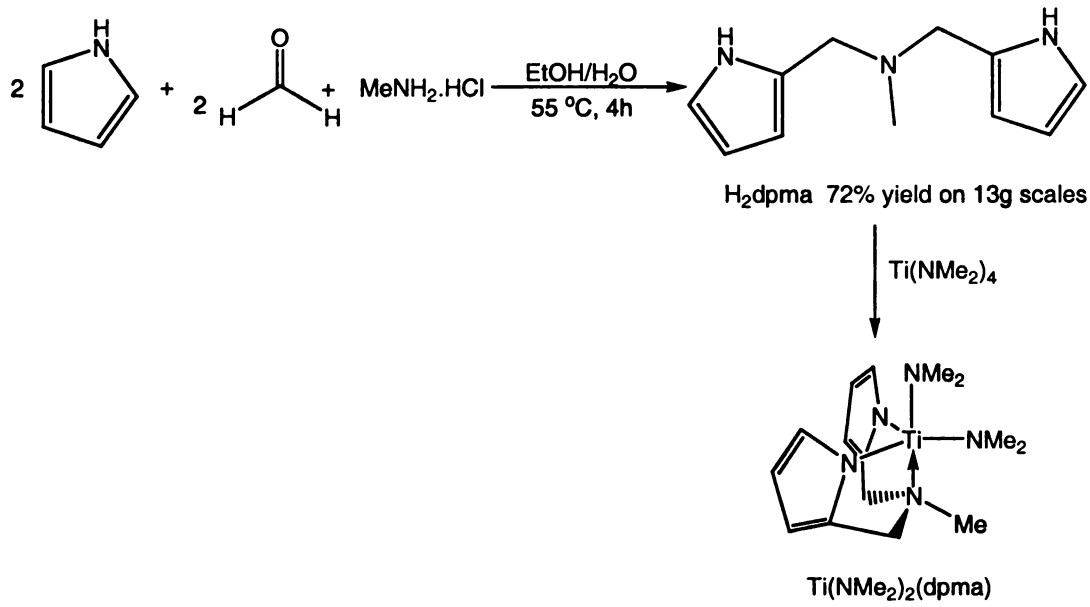


Figure 1-28. Synthesis of $Ti(dpma)(NMe_2)_2$

H_2dpma is readily prepared in a single step from a Mannich reaction between two equivalents of pyrrole, two equivalents of formaldehyde and one equivalent of methylamine hydrochloride.[49] The hydroamination of alkynes using $Ti(dpma)(NMe_2)_2$ gave imines in yields up to 90% for some substrates. Some of the catalyses were slow at 75 °C, giving low conversions after days of reaction time. In general, hydroaminations involving internal alkynes were slow with alkyl amines, such as cyclohexylamine. By increasing the temperature to 130 °C, the yields of the products increased after reasonable reaction times. The hydroamination of 1-phenylpropyne has the nitrogen attachment β to the phenyl group and this is one of the examples where hydroamination using $Ti(dpma)(NMe_2)_2$ and Me_2TiCp_2 gave the same product. The same product is obtained for both the catalysts if diphenylacetylene is used as a substrate for hydroamination. The selectivity for the formation of the Markovnikov product is greater if $Ti(dpma)(NMe_2)_2$ is used as the catalyst in hydroamination. Also, hydroamination using amines such as benzylamine and

benzhydrylamine is possible with $Ti(dpma)(NMe_2)_2$. The reaction times are slow but give reasonable yields of the products, around 70-90%. Benzhydrylamine shows poor regioselectivity with the Markovnikov product being favored only 3:1, Benzylamine gives very high Markovnikov selectivity. These results are in marked contrast to catalysis with $Ti(NMe_2)_4$, where both benzylamine and benzhydrylamine reactions with 1-hexyne displayed poor yields and selectivities under the same conditions.

A new catalyst[50] was reported in 2003, which was obtained by reacting $Ti(NMe_2)_4$ with 5,5-dimethylpyrrolylmethane (H_2dmpm). $Ti(dmpm)(NMe_2)_2$ was prepared in an attempt to decrease steric constraints and to increase Lewis acidity of the metal center (Figure 1-29).

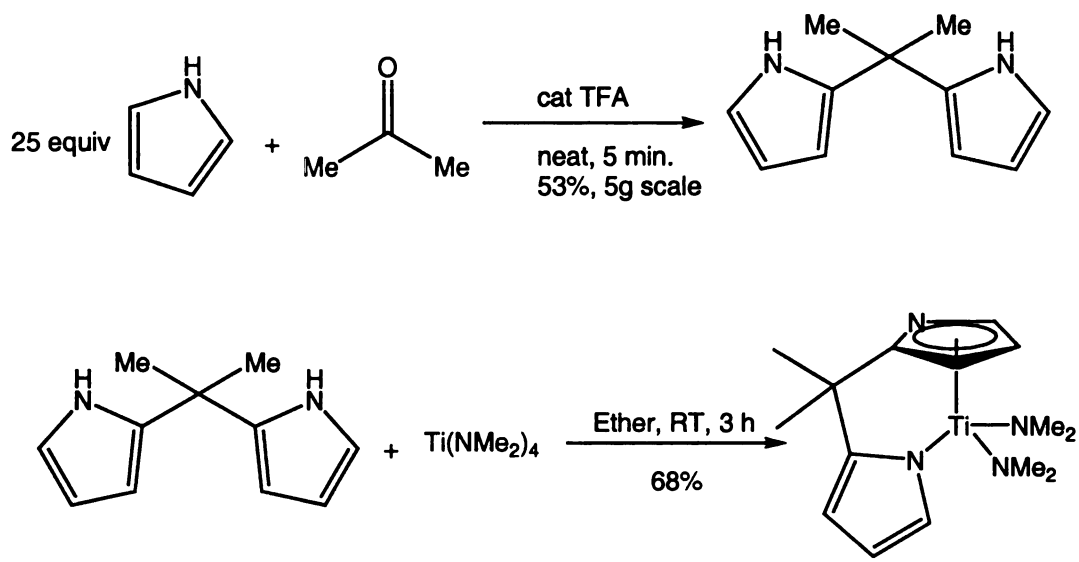


Figure 1-29. Synthesis of $Ti(dmpm)(NMe_2)_2$

Because of poor solubility of $Ti(dmpm)(NMe_2)_2$ in some common solvents, $Ti(dppm)(NMe_2)_2$ (H_2dppm is 5,5-di-*n*-propyldipyrrolylmethane) was also prepared from 5,5-di-*n*-propyldipyrrolylmethane and $Ti(NMe_2)_4$. The solid state structure of both $Ti(dppm)(NMe_2)_2$ and $Ti(dmpm)(NMe_2)_2$ has one η^5-pyrrolyl ligand, while the other is

an η^1-pyrrole. The hydroamination reaction of terminal alkynes with $Ti(dmpm)(NMe_2)_2$ as a catalyst yields the hydroaminated product in 5 minutes at room temperature in moderate yields of 50-80%. Internal alkynes like 3-hexyne and 1-phenylpropyne took longer times, usually around a day for completion. The Markovnikov product was selectively obtained for most of the cases, with more than 40:1 ratio of Markovnikov:anti-Markovnikov products. These catalysts obtained are an order of magnitude faster compared to the Cp_2Ti-($Me_3SiC{\equiv}CSiMe_3$) and $Ti(dpma)(NMe_2)_2$ catalysts.

Another application of alkyne hydroamination was investigated[51] wherein, 1,1-dialkyl-substituted hydrazines directly added across the multiple bond of unactivated alkynes to give a new catalytically transformed product. Due to effects associated with 1,1-disubstituted hydrazines, such as chelation effects with both nitrogens of the hydrazine bonding in the same complex, new catalysts were developed as the regular catalysts $Ti(NMe_2)_4$ and $Ti(dpma)(NMe_2)_2$ proved ineffective for hydrohydrazination (Figure 1-30).

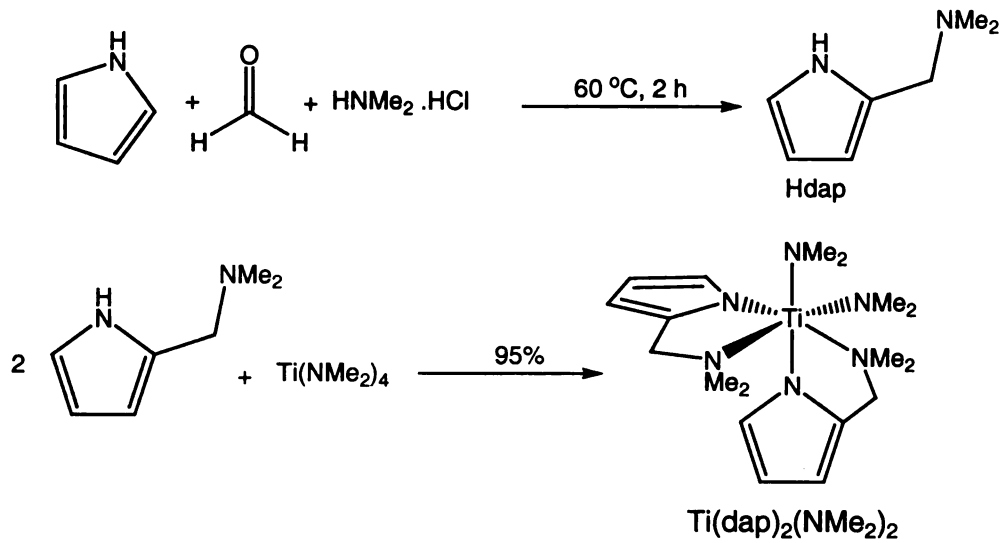


Figure 1-30. Synthesis of $Ti(dap)_2(NMe_2)_2$

The pyrrolyl titanium complex, $Ti(dap)_2(NMe_2)_2$ was prepared from two equivalents of α-(dimethylaminomethyl)pyrrole,[52] (Hdap) and $Ti(NMe_2)_4$. A second catalyst, five-coordinate $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$, was produced from two equivalents of commercially available pentaflurophenylthiol and $Ti(NMe_2)_4$ (Figure 1-31).

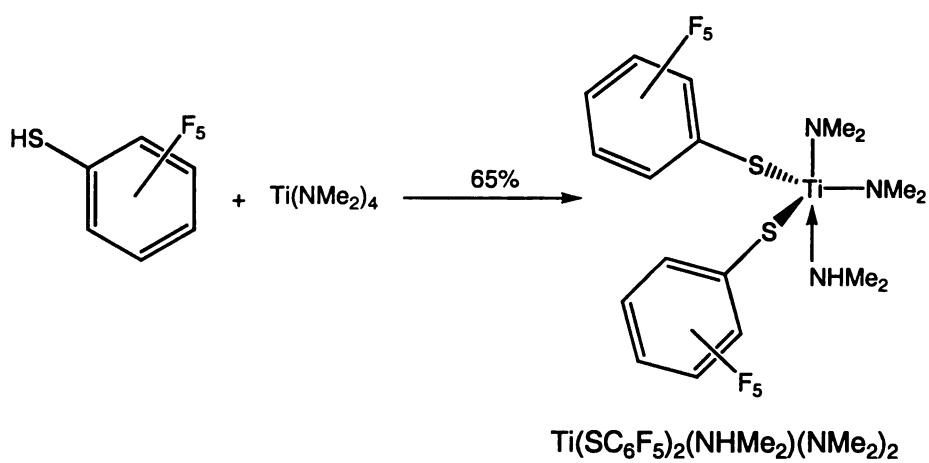


Figure 1-31. Synthesis of $Ti(SC_6F_5)_2(NHMe_2)(NMe_2)_2$

With $Ti(dap)_2(NMe_2)_2$ as the catalyst, hydroamination of terminal alkynes by 1,1-dimethylhydrazine proceeded to completion in a day at 100 °C to yield the imine in 75-80% yield. This catalyst fails to show any reactivity with symmetrical internal alkynes such as diphenylacetylene and 3-hexyne with 1,1-dimethylhydrazine although hydroamination was observed with 1-phenylpropyne. With $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$ as the catalyst for terminal alkynes such as 1-hexyne, the results were more or less consistent with those obtained by $Ti(dap)_2(NMe_2)_2$ (Figure 1-32).

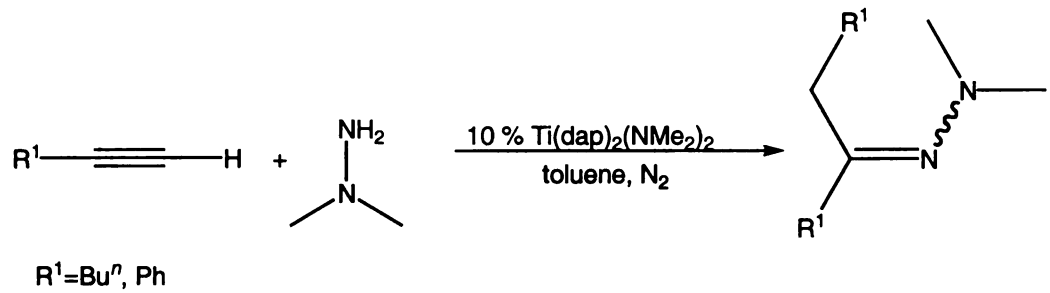


Figure 1-32. Hydroamination of hydrazines with $Ti(dap)_2(NMe_2)_2$

With $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$ as the catalyst, better reactivity is obtained with internal alkynes such as diphenylacetylene and 1-phenylpropyne, with yields of 90% and 22%, respectively. When aryl hydrazines were used, a modification of the Fischer indole synthesis,[53] occurred to give substituted indoles in moderate to high yield (Figure 1-33).

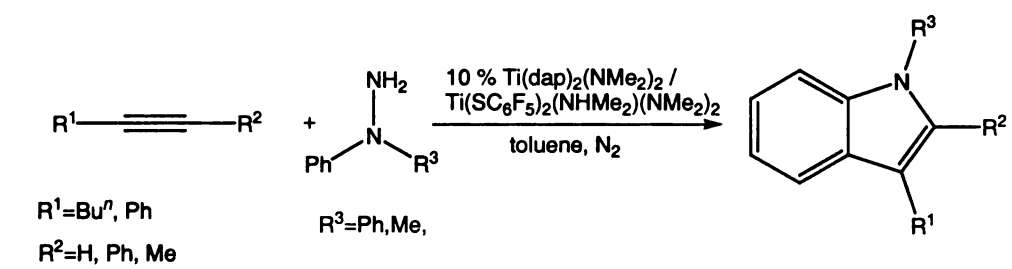


Figure 1-33. Hydroamination of alkynes and aryl hydrazines to give substituted indoles

To facilitate indole formation, $ZnCl_2$ was added to some reactions in a one-pot procedure. Also reported was acetylene hydroaminations by 1,1-disubstituted hydrazines. Acetylene hydroamination is extremely fast at room temperature, and the reactions were complete in less than two hours at room temperature.

As an extension of the current work, Odom reported[54] a titanium catalyzed three-component coupling between amines, alkynes, and isonitriles to generate α,β-unsaturated β-iminoamines in moderate to high yields (Figure 1-34).

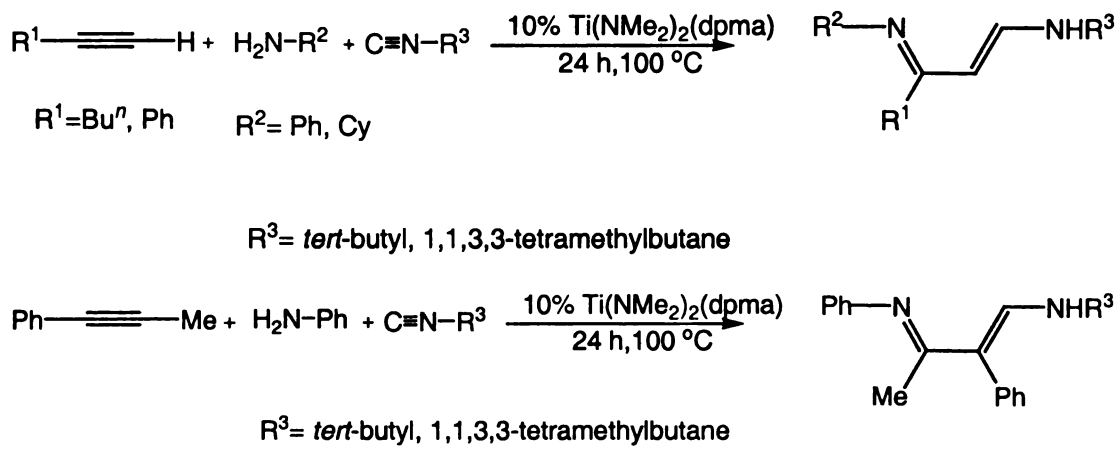


Figure 1-34. Titanium catalyzed 3-component coupling to give α,β-unsaturated β-iminoamines

Different isonitriles along with terminal and internal alkynes were tried for three-component coupling with aniline and cyclohexylamine. The major byproduct in some of the reactions was formamidine formation, which led to optimized conditions using 1.1 or 1.2 equivalents of isonitriles. The catalyst used for the three component coupling was $Ti(dpma)(NMe_2)_2$ which successfully catalyzed the reactions with aryl and alkyl amines,

terminal alkynes and internal alkynes with isonitriles bearing a quaternary alkyl group. Regioselectivities in the three-component coupling reactions using $Ti(dpma)(NMe_2)_2$ as catalyst yields results similar to hydroamination. Hydroamination of 1-hexyne by cyclohexylamine results in a 1.6:1 mixture of Markovnikov:anti-Markovnikov products. Three-component coupling between 1-hexyne, cyclohexylamine, and *tert*-butylisonitrile results in a 1.2:1 mixture of separable isomers.

Conclusion

A bunch of transition metals has been presented as catalysts for hydroamination of alkynes with amines in this chapter. Use of titanium as a catalyst for hydroamination offers several advantages over other transition metals.

a) Titanium catalysts are cheap and readily available.

b) They are nontoxic compared to some toxic metals like mercury.

c) Titanium catalysts can be readily prepared from existing literature procedures

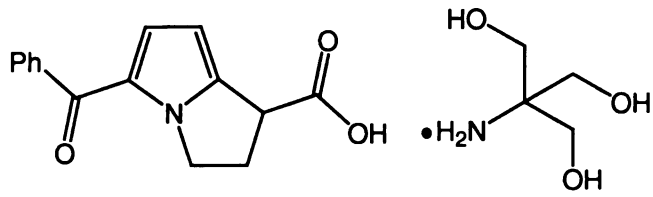
d) They are especially applicable to hydroamination of alkynes with primary amines.

Chapter 2

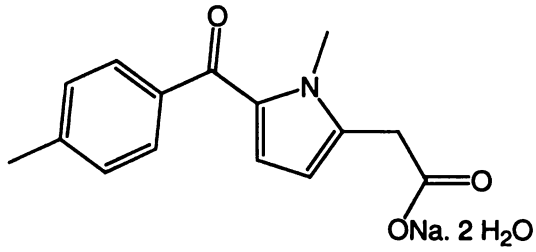
Hydroamination of diynes using a titanium catalyst to yield pyrroles has been reported by Odom.[55] Hydroamination of alkynes was discussed in the previous chapter along with some recent advances in this field by Odom group using inexpensive titanium-based catalysts. In this chapter, hydroamination of diynes will be presented as a one-pot synthesis of pyrroles.

Pyrroles are important biologically as they are present in many naturally occurring alkaloids and some NSAIDs (non-steroidal anti-inflammatory drugs) based on the pyrrole structure. The early impetus for the study of pyrroles came from degradative work relating to the structure of two pigments central to life processes: the blood respiratory pigment (heme) and, the green photosynthetic pigment of plants (chlorophyll).[56] Such degradation led to the formation of mixtures of alkylpyrroles.

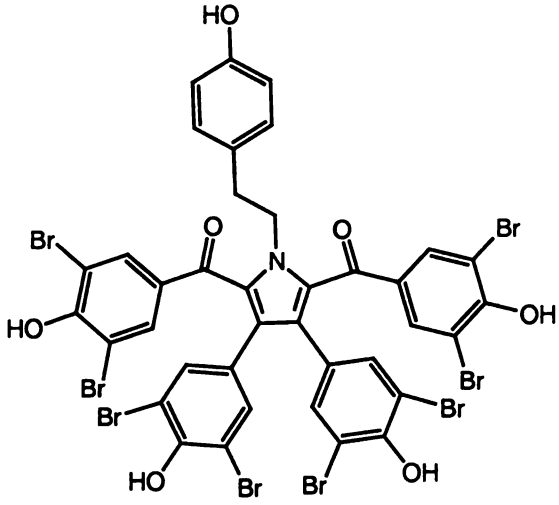
NSAIDs can be classified as COX-1 or COX-2 drugs (cyclooxygenase-1 or-2).[57] COX activities originate from these two distinct and independently regulated enzymes. COX-2 plays a major role in prostaglandin biosynthesis in inflammatory cells (monocytes/macrophages) and in the central nervous system.[58] Some of the NSAIDs that have a pyrrole as the core structure are Tolmetin Sodium (*Tolectin*) and Ketorolac Tromethamine ®(*Toradol*). Some natural products that include the pyrrole core are Polycitone A and B, Lamellarin O and Lukianol A (Figure 2-1a and b).



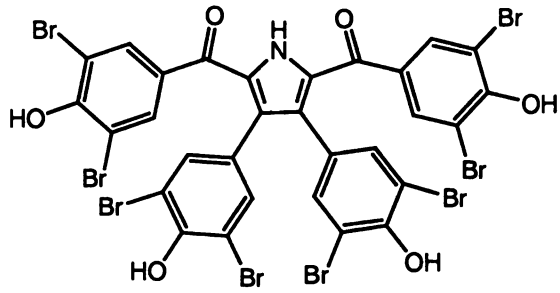
Ketorolac Tromethamine



Tolectin Sodium

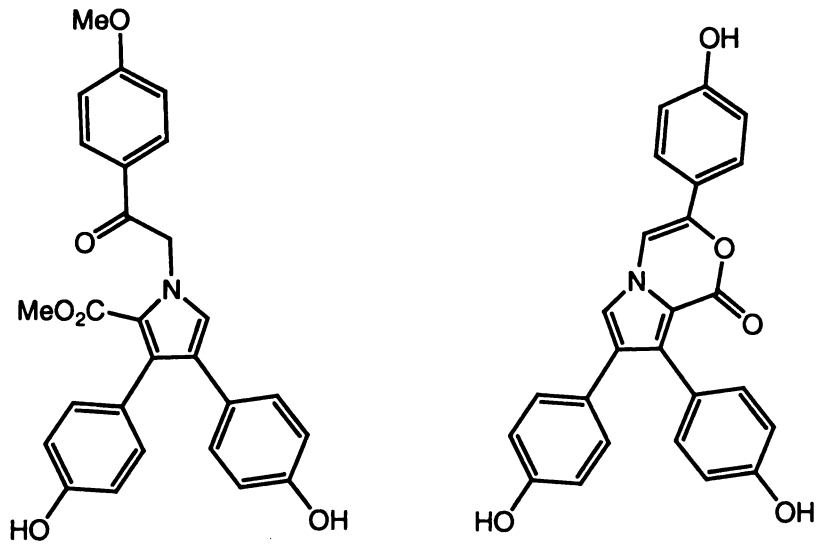


Polycitone A



Polycitone B

Figure 2-1a. Pyrrole core structure in NSAIDs and natural products



Lamellarin O Lukianol A

Figure 2-1b. Pyrrole core structure in natural products

2.1.2 Goal of this project

The primary goal of this project was to extend the hydroamination of alkynes to diynes using the titanium-based catalysts described in the previous chapter, followed by cyclization to give the hydroaminated product, i.e. a one-pot synthesis of pyrrole (Figure 2-2).

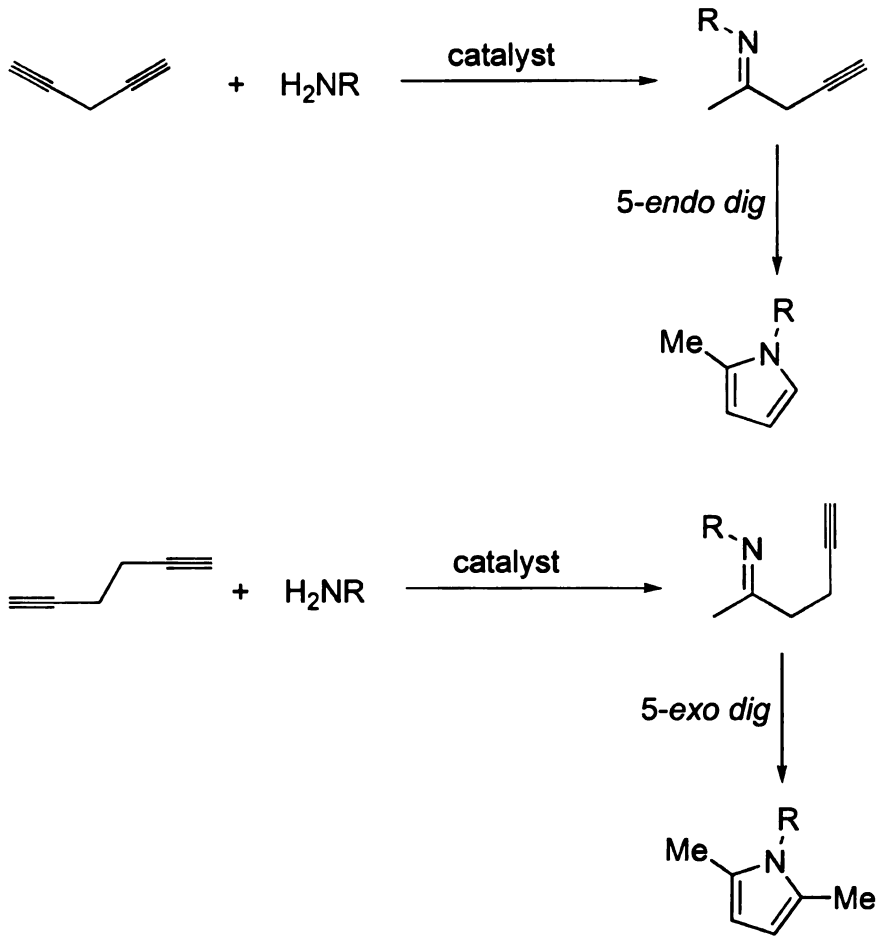


Figure 2-2. Hydroamination of 1,4 and 1,5-diynes

There have been quite a few reports in the literature of pyrrole syntheses from imino alkynes.[59-61] Some representative examples of these sorts of cyclizations are as follows. McDonald reported the use of Group VI carbenes for cycloisomerization, of terminal alkynes tethered to nitrogen nucleophiles. Reaction of *N*-(*t*-butoxycarbonyl)-3-butyn-1-amine with chromium hexacarbonyl/triethylamine *N*-oxide (*in situ* formation of triethylamine-chromium pentacarbonyl) yielded the cycloisomeric enecarbamate (Figure 2-3).

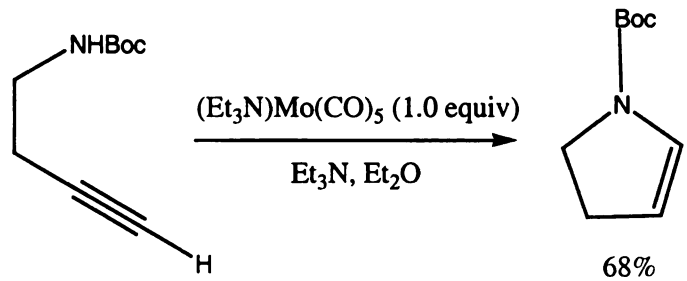


Figure 2-3. Hydroamination with molybdenum pentacarbonyl

Utimoto reported a palladium-catalyzed cyclization reaction of 1-amino-3-alkyn-2-ols to yield 2,4-disubtituted pyrroles in good yields (Figure 2-4).

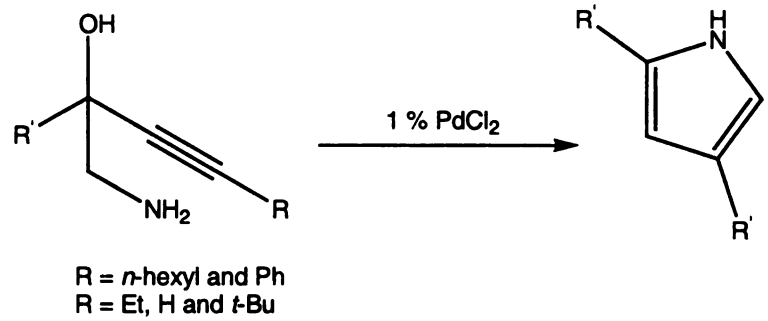


Figure 2-4. Palladium catalyzed intramolecular hydroamination and cyclization

Another palladium-catalyzed cycloisomerization reaction was reported by Gabriele and Salerno wherein catalytic amounts of $PdCl_2$ in conjunction with KCl at 25-100 °C cycloisomerized (*Z*)-(2-en-4-ynyl)amine to yield 2,3,4-trisubstituted pyrrole with DMA(*N*,*N*-dimethylacetamide) as the solvent (Figure 2-5).

The hydroamination of 1,4-diynes would yield the 4-iminoalkyne (Figure 2-2) which could undergo a 5-*endo dig* cyclization,[62] whereas the 1,5-diynes could undergo a 5-*exo dig* cyclization to yield the pyrrole.

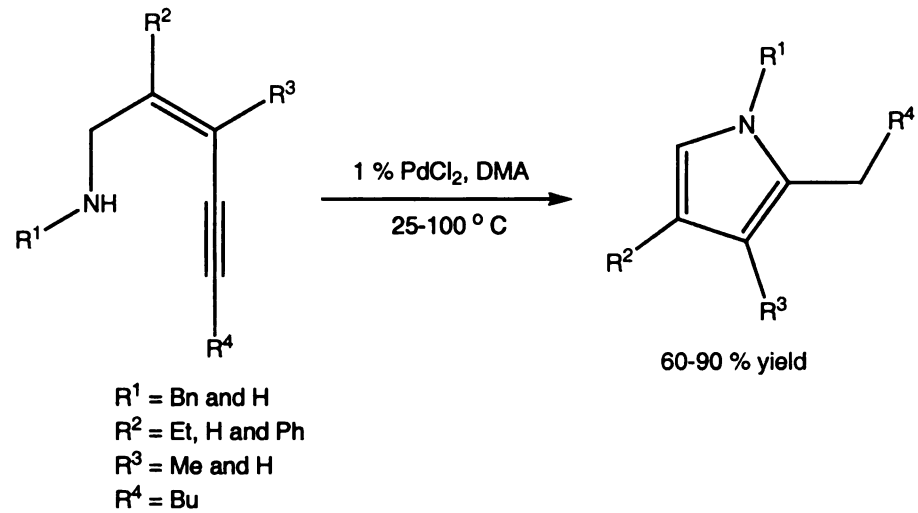


Figure 2-5. Another route for cyclization with Pd to yield pyrroles

2.1.3 Baldwin Rules for Ring Closure

Baldwin studied several types of cyclization reactions and categorized them as follows.

Baldwin's rules are for certain ring closings of 3- to 7-membered rings. These rules distinguish two types of ring closure, called *exo* and *endo*, and three kinds of atoms at the starred positions: *tet* for sp^3, *trig* for sp^2, and *dig* for *sp* (Figure 2-6).

Rule 1. Tetrahedral systems

(a) 3 to 7-*Exo-Tet* are favored

(b) 5 to 6- *Endo-Tet* are disfavored

Rule 2. Trigonal systems

(a) 3 to 7-*Exo-Trig* are favored

(b) 3 to 5-*Endo-Trig* are disfavored

(c) 6 to 7- *Endo-Trig* are favored

Rule 3. Digonal systems

(a) 3 to 4-*Exo-Dig* are disfavored

(b) 5 to 7- *Exo-Dig* are favored

(c) 3 to 7- *Endo-Dig* are favored

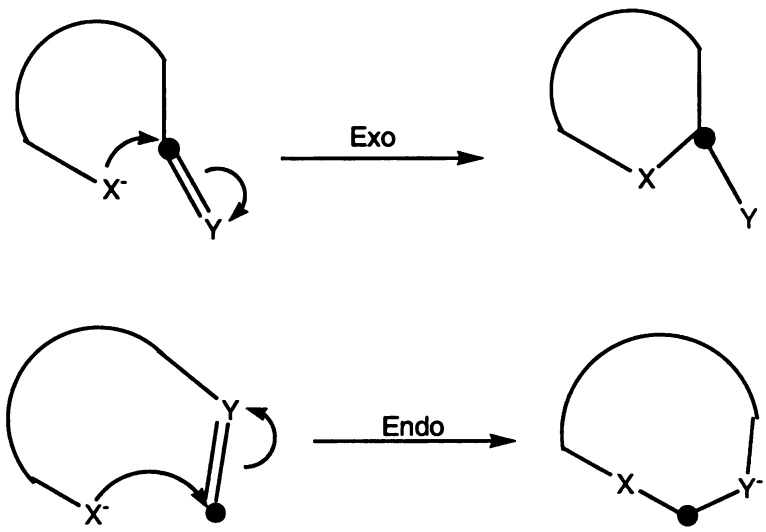


Figure 2-6. Baldwin's rules for ring closure in 3- to 7-membered rings

"Disfavored" does not mean it is not possible, it just means that it is more difficult than the favored ones. Some exceptions to this rule, have been reported by Trost, Auvray, and Torres.[63] From the Baldwin rules, we can conclude that the cyclization of the imino alkynes should be a favored process, since both 5-*endo dig* cyclization and 5-*exo dig* cyclization for 1,4-diynes and 1,5-diynes, respectively, are favored for the digonal systems.

2.1.4 Synthesis of 1,4-diynes

The substrates for the hydroamination, i.e. the diynes, were synthesized using Verkruijsse's procedure.[64,65] The unsymmetrical bis(internal)-1,4-diyne, 1-phenyl-1,4-hexadiyne was synthesized by the same procedure (Figure 2-7).

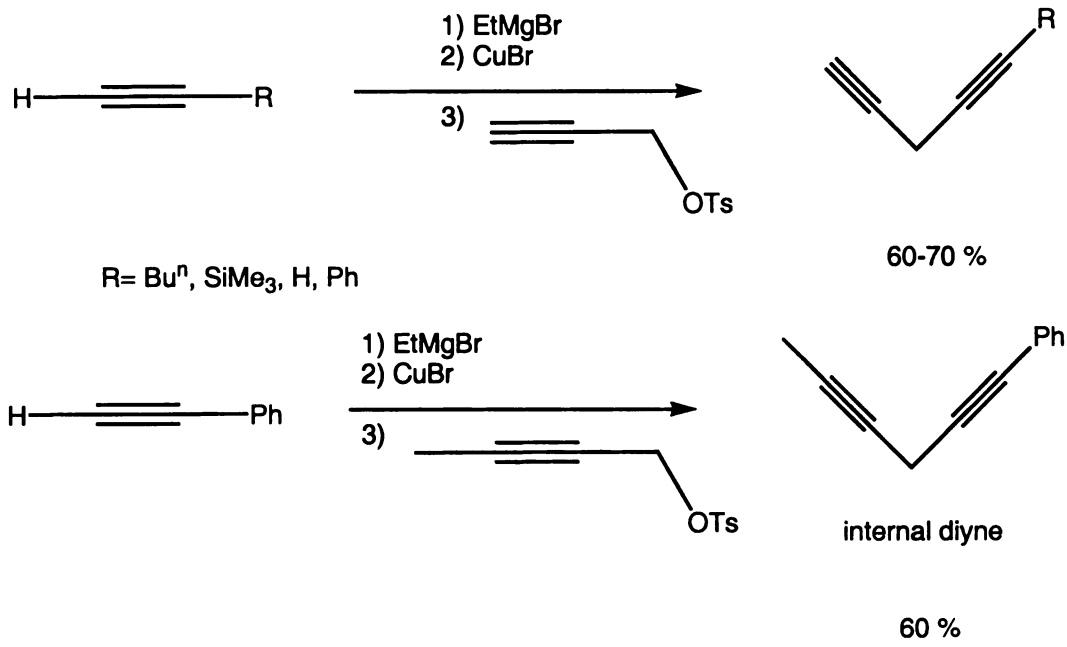


Figure 2-7. Synthesis of 1,4-diynes

2.1.5 Hydroamination of 1,4-Diynes

An attempt was made to hydroaminate 1,4-pentadiyne (**1a**) with 1 equivalent of aniline using Ti(dpma)(NMe_2)$_2$ (**A**) as the catalyst.[66] The major product obtained in the reaction had a mass consistent with double hydroamination of pentadiyne (Figure 2-8).

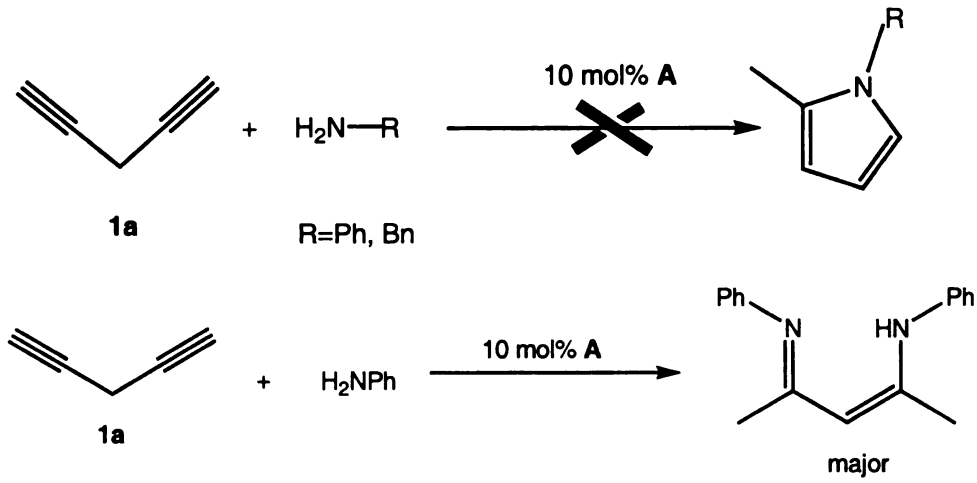
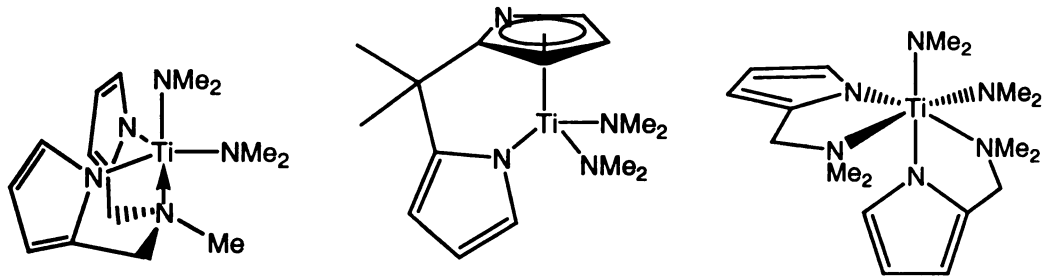


Figure 2-8. Hydroamination of 1,4-pentadiyne with aromatic amines

Data for the dihydroamination product matched an authentic sample of 2,4-bis(phenylimino)pentane, which was synthesized by the condensation of 2,4-pentanedione and aniline using catalytic *p*-toluenesulfonic acid. This result suggests that the second hydroamination was faster than both the mono-hydroamination and the 5-*endo dig* cyclization. Other catalysts like $Ti(dmpm)(NMe_2)_2$ (**B**) and $Ti(dap)_2(NMe_2)_2$ (**C**) were also used but to no avail. Increasing the temperature led to oligomerization of the diyne, and lowering the temperature led to dihydroamination. The structure of the catalysts is as shown in Figure 2-9.



$Ti(NMe_2)_2(dpma)$ **A**

$Ti(NMe_2)_2(dmpm)$ **B**

$Ti(dap)_2(NMe_2)_2$ **C**

Figure 2-9. Structure of catalysts used in hydroamination of diynes

Hydroamination of 1,4-nonadiyne (**1b**) with aniline and benzylamine at 100 ° C with **A** as the catalyst led to the corresponding pyrroles in moderate yields (Figure 2-10). Hydroamination of **1b** with aniline gave 1-phenyl-2-butyl-5-methylpyrrole (**3a**) in 55 % yield. Hydroamination with benzylamine took longer times and also gave a yield of only 35% of 1-benzyl-2-butyl-5-methylpyrrole (**3b**). The pyrrole product obtained from the imine cyclization is preferentially the Markovnikov product. Hydroamination of 1-hexyne with either benzylamine or aniline gives preferentially the Markovnikov product with **A** as the catalyst.[67] Considering the terminal alkynes used here are not sterically or electronically different from 1-hexyne, the major product expected in all the cases where a terminal alkyne was present, is the imine resulting from Markovnikov addition.

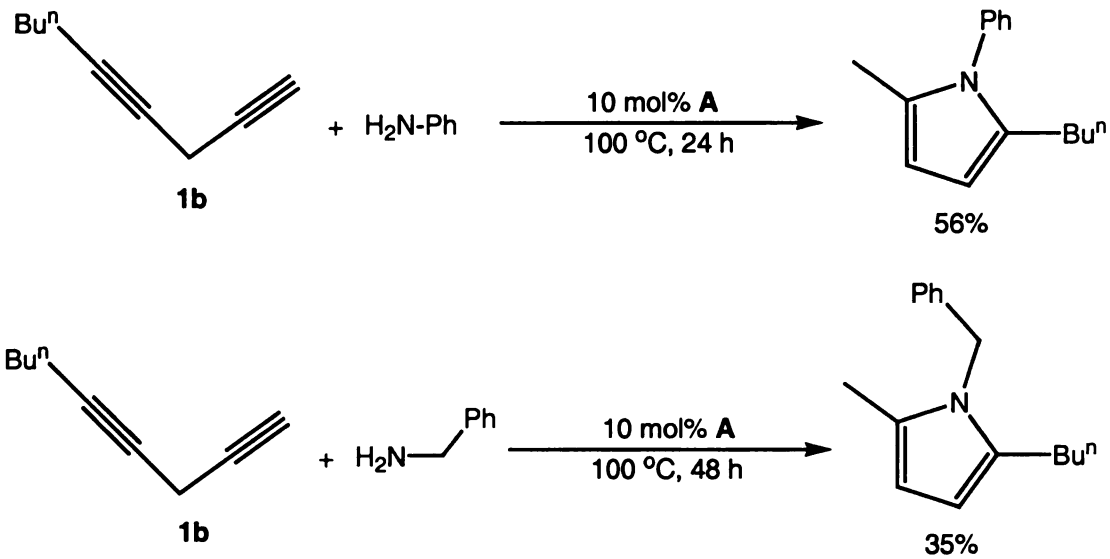


Figure 2-10. Hydroamination of 1,4-nonadiyne with aromatic amines

Hydroamination of 1-phenyl-1,4-pentadiyne with either aryl or alkyl amines did not yield the desired pyrrole with **A**, **B**, or **C** as catalyst (Figure 2-11). The problem could be a result of diyne oligomerization.

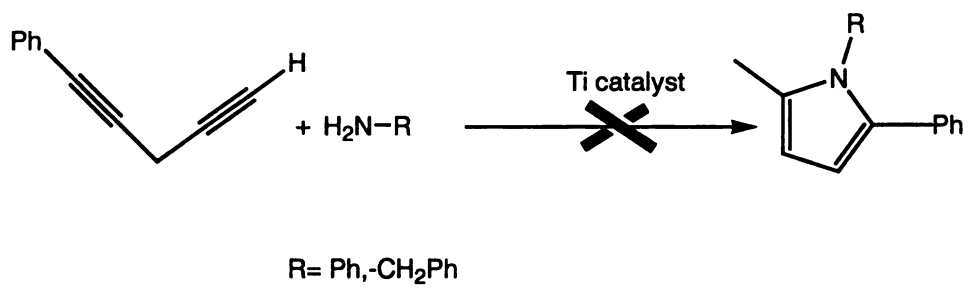


Figure 2-11. Hydroamination of 1-phenyl-1,4-pentadiyne with aromatic amines

Hydroamination of 1-trimethylsilyl-1,4-pentadiyne did not yield any pyrrole products (Figure 2-12).

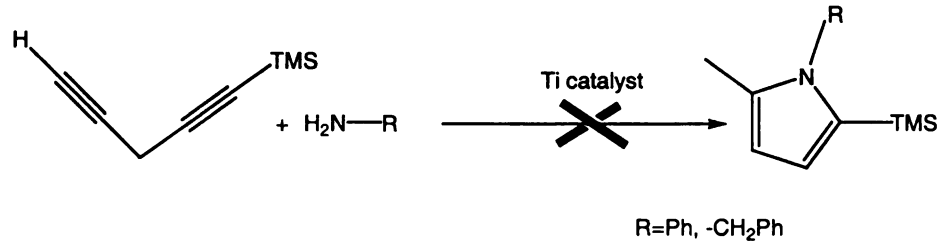


Figure 2-12. Hydroamination of 1-trimethylsilyl-1,4-pentadiyne with aromatic amines

Hydroamination reactions by titanium have been shown to be sensitive to the size of the alkyne substrate.[68] Hence, replacing the hydrogen on the terminal position of the diyne by alkyl or aryl groups should significantly slow down the second hydroamination reaction relative to the 5-*endo dig* cyclization as seen in the case of **1a**. We successfully demonstrated this by hydroaminating 1-phenyl-1,4-hexadiyne (**1c**) with **B** as the catalyst with aniline, benzylamine, and *p*-methoxybenzylamine yielding a single isomer (Figure 2-13). Hydroamination of **1c** with benzylamine gave 1,2-dibenzyl-5-methylpyrrole (**3d**) in 53% yield, while hydroamination of **1c** with *p*-methoxybenzylamine (PMB-NH_2) gave 1-(4-methoxy-benzyl)-2-benzyl-5-methyl pyrrole (**3e**). This is likely due to selective hydroamination of the phenyl-bearing alkyne. Hydroamination of similar substrates, e.g. 1-phenylpropyne, occurs with hydroamination β to the phenyl group, which is consistent with the observed regioselectivity for this diyne substrate. Also, hydroamination of 1-phenylpropyne is generally more facile than dialkyl substituted alkynes, e.g. 3-hexyne.

Consequently, it is likely that regioselectivity for this substrate is due to kinetically favored amination β to the phenyl group of 1-phenyl-1,4-hexadiyne.

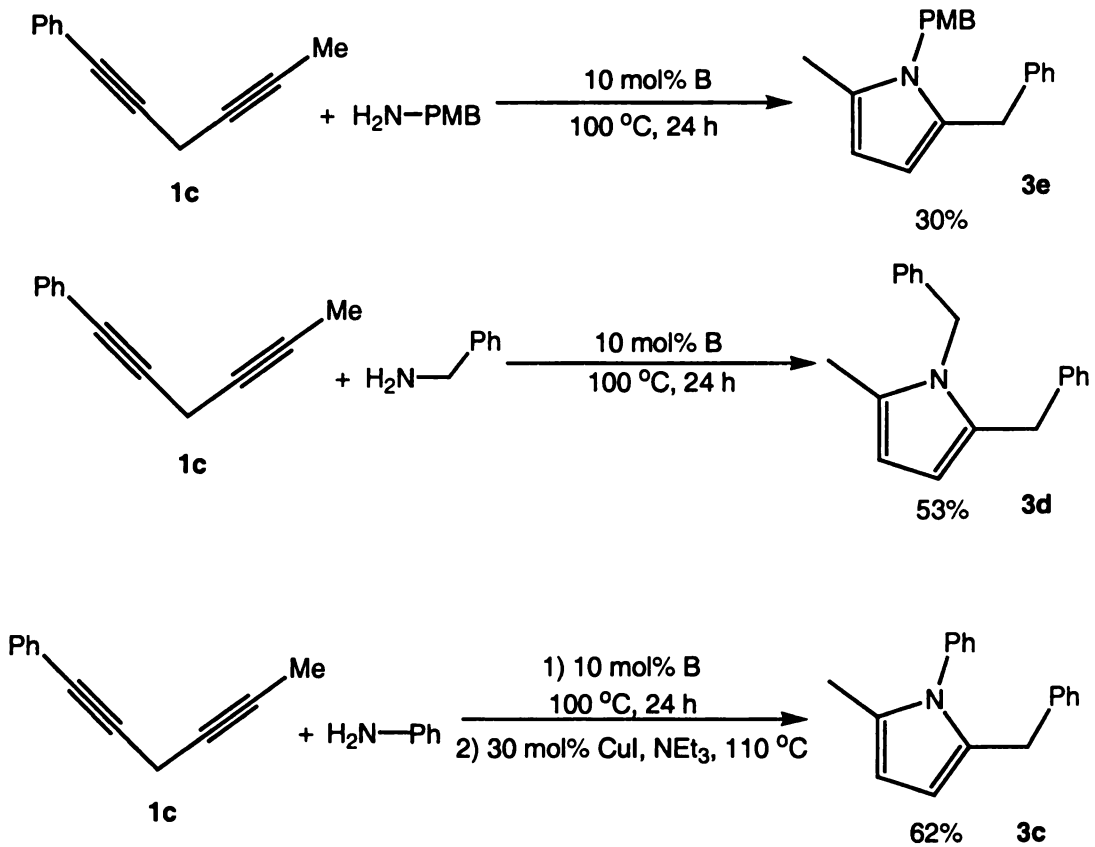


Figure 2-13. Hydroamination of 1-phenyl-1,4-hexadiyne with aromatic amines

The cyclization of the imine derived from **1c** was quite slow after titanium-catalyzed reaction when the amine substrate was aniline. To finish the cyclization, Gevorgyan's procedure using 30 mol% of CuI in the presence of triethylamine at 110 °C was employed prior to the work-up.[69] Interestingly, the addition of copper for the cyclization was only required for the aniline substrate to give 1-phenyl-2-benzyl-5-methyl pyrrole (**3c**) (Figure

2-13). The benzylamine and *p*-methoxybenzylamine (PMB-NH_2) hydroamination products underwent cyclization to the pyrrole structure in the absence of copper.

2.1.6 Synthesis of 1,5-diynes

1,5-hexadiyne (**2a**) was bought from GFS chemicals and was distilled and stored in the glove box prior to hydroamination. 1,6-diphenyl-1,5-hexadiyne (**2b**) was synthesized by the literature procedure[70] (Figure 2-14).

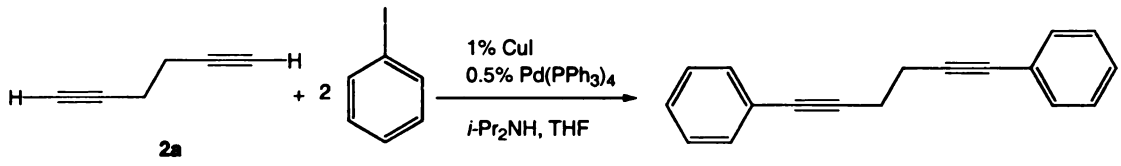


Figure 2-14. Synthesis of 1,6-diphenyl-1,5-hexadiyne

2.1.6 Hydroamination of 1,5-diynes

Hydroamination of **2a** proceeds smoothly with aniline using **1** as catalyst, at 75 °C in 6 h to give 1-phenyl-2,5-dimethylpyrrole (**3f**) (Figure 2-15). Hydroamination with benzylamine takes a longer time for completion and gives 1-benzyl-2,5-dimethylpyrrole (**3g**) with **A** as catalyst. The yields vary from 68% for hydroamination with aniline to 34% with benzylamine. The reaction is clean and does not yield any dihydroamination products, as is the case with **2a**.

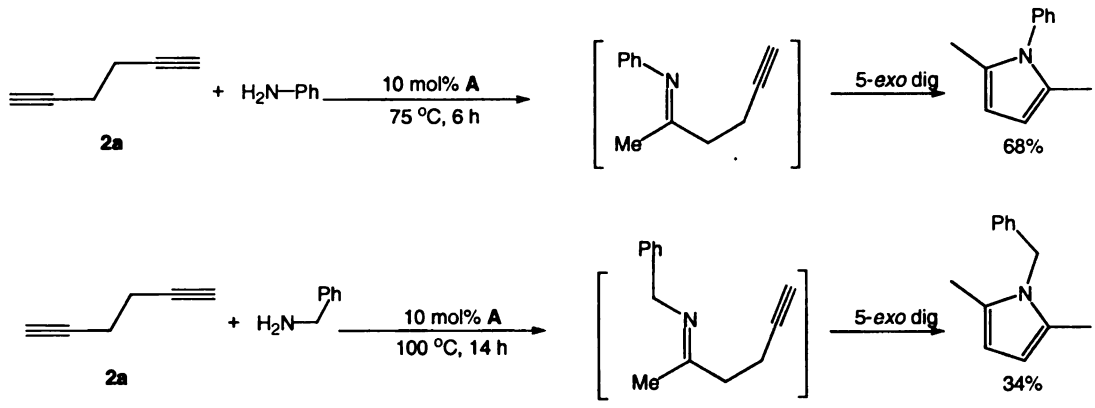


Figure 2-15. Hydroamination of 1,5-hexadiyne with aromatic amines

Hydroamination of **2b** with aniline at 150 °C using **A** as catalyst yields 1-phenyl-2,5-dibenzylpyrrole pyrrole (**3h**) in 90% yield after 26 h (Figure 2-16).

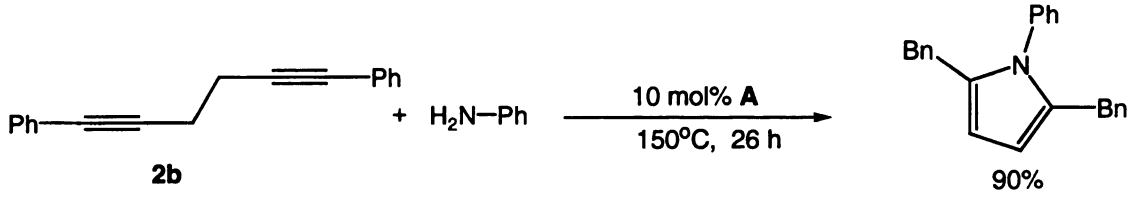


Figure 2-16. Hydroamination of 1,6-diphenyl-1,5-hexadiyne with aromatic amines

Treatment of **2b** with benzylamine gave no reaction with catalysts **A** and **B.** The lack of reaction with benzylamine probably represents a limitation to the activity of our current catalysts rather than an inherent problem with the substrate combination.

2.1.7 Cyclization of 1,4-diynes

The cyclizations of the imino alkyne to give the pyrrole can occur through several different routes: however, they are likely to occur through the Baldwin allowed 5-*endo dig* and 5-*exo dig* cyclizations It is unlikely that that allene intermediates were involved. The reason for this is that the 5-*endo trig* and 5-*exo trig* cyclizations required for the allene cyclizations are disfavored. Experimentally, it has been shown by Gevorgyan, that 1-imino-2-alkynes require copper catalysis to be cyclized, which has been suggested to occur through allene intermediates (Figure 2-17).

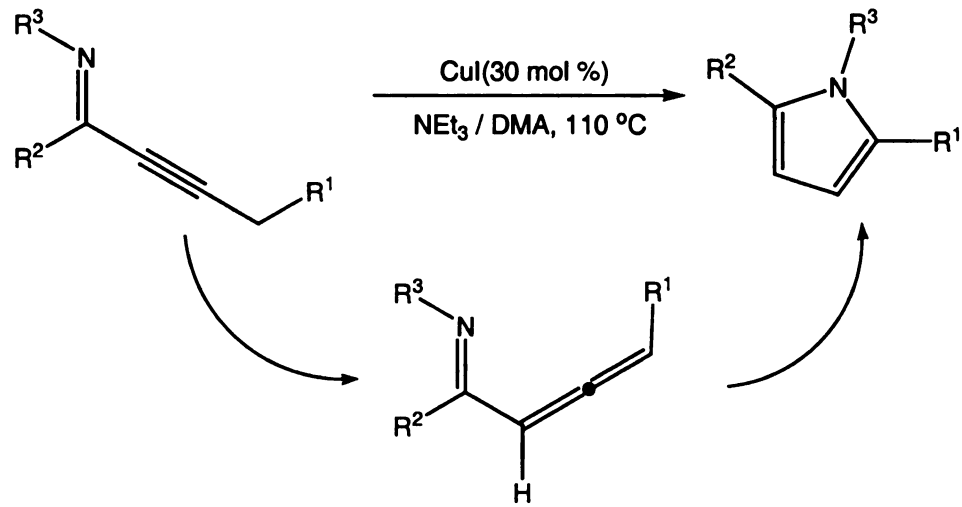


Figure 2-17. Gevorgyan's cyclization of 1-imino-2-alkynes catalyzed by copper

Our aim was to find out whether the cyclization of the iminoalkynes generated in 1,4- and 1,5-diyne hydroamination was mediated by titanium or was just a thermal process. Consequently, we sought to generate the imino alkyne in the absence of the transition metal compound to observe if cyclization would occur under those conditions.

The goal was to synthesize 4-nonyn-2-ol from propylene oxide, oxidize it to 4-nonyn-2-one and perform a schiff base reaction with aniline to give the imino alkyne (Figure 2-18).

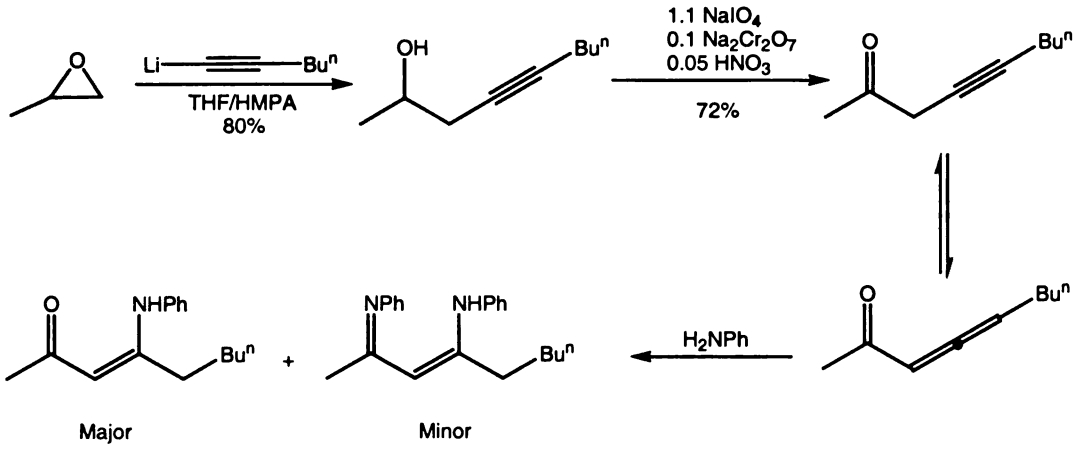


Figure 2-18. Reaction to verify if the cyclization is Ti mediated

The reaction did not work, as 4-nonyn-2-one undergoes isomerisation to the allene intermediate and then undergoes reaction to give the Michael-addition product and its schiff base analogue. All attempts to protect the alkyne with $Co_2(CO)_8$ and deprotect it later, after the condensation with aniline were unsuccessful. The deprotection step involves addition of an aqueous solution of ceric ammonium nitrate, [71] which seem to lead to complications. While we were not able to isolate the iminoalkyne in the absence of titanium, they were observed in several instances confirming their intermediacy in the reactions.

2.1.8 Cyclization of 1,5-diynes

Even though the imine product was not observed in the hydroamination of 1,5-hexadiyne (**2a**), it is still likely that the imine is an intermediate. The relevant ketone derivative of this intermediate, hex-5-yn-2-one (**2c**), was prepared according to the

literature procedure.[72] Reaction of the ketone with aniline (Figure 2-19) in the absence of titanium leads to formation of *N*-phenyl-2,5-dimethylpyrrole that is spectroscopically identical to the product of **2a** hydroamination with aniline.

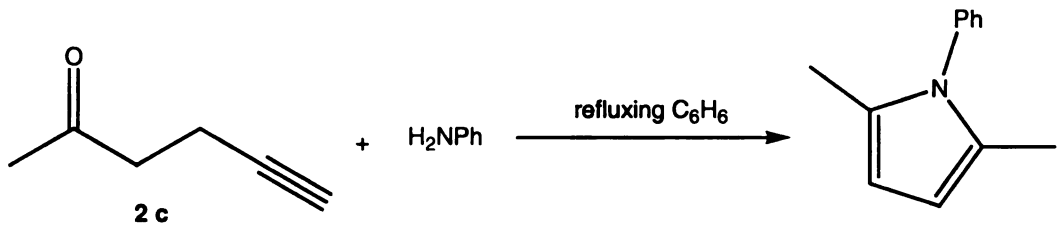


Figure 2-19. Condensation of hex-5-yn-2-one with aniline

2.1.8 3-Component coupling of diynes

Another application, which was attempted, was a multi-component reaction with diynes, in a similar vein as previously shown with alkynes, isonitriles, and amines[73] (Figure 2-20).

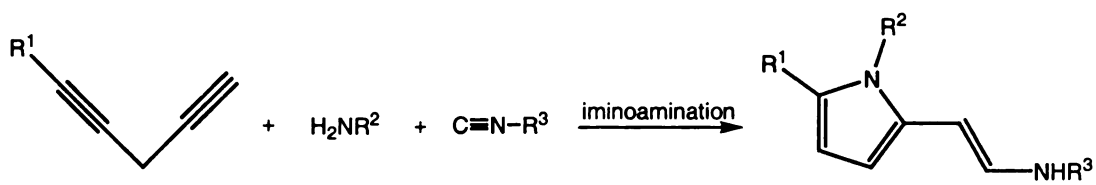


Figure 2-20 Three-component coupling of diyne with amine and isonitrile

The reaction did not afford the expected product with any of the 1,4 and 1,5-diynes attempted. Investigation is underway of new catalysts that might facilitate this transformation.

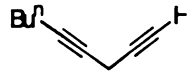
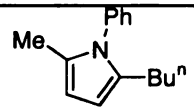
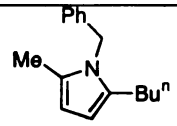
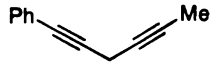
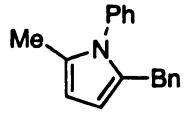
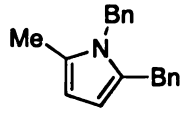
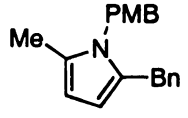
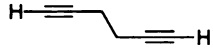
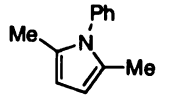
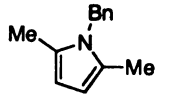
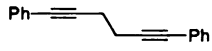
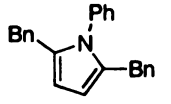
2.1.9 Summary

The results obtained for the hydroamination product are tabulated as follows. Applications of this new pyrrole synthesis based on alkyne hydroamination are currently under investigation. It is hoped that this new pyrrole synthesis will complement existing procedures such as the Paal-Knorr synthesis, at least in circumstances where unsymmetrical pyrroles are desired. Many unsymmetrical 1,4-diynes can be prepared in one or two steps from commercially available compounds and may be as or more accessible than the corresponding unsymmetrical 1,4-diones in some cases. The titanium-based pyrrole synthesis of 1,2-dibenzyl-5-methylpyrrole (**3d**) provides an interesting example for comparison with current and progressing ketone-based methodologies, e.g., Paal-Knorr synthesis. Generally, unsymmetrical 1,4-diketones are relatively difficult to access in a short symmetric sequence. However, the diketone needed for the synthesis of **3d** by Paal-Knorr synthesis and its reaction with benzylamine were recently reported.[76] The diketone was prepared using a novel Pd-catalyzed procedure from methyl vinyl ketone and benzylzinc chloride. Overall, **3d** was available in 54% yield over two steps. Using the procedure of Verkruijsse to generate the diyne and titanium hydroamination, we prepared the unsymmetrical pyrrole **3d** in the comparable yield of 41% in two steps.

In addition, we are investigating the use of this new methodology in the synthesis of pyrroles where application of the Paal-Knorr synthesis may lead to unwanted side reactions. For example, we are investigating the synthesis of α-vinylpyrroles using diyne hydroamination, which if prepared using α,β-unsaturated ketones may have problems with interfering Michael-addition side reactions.

Table 2.1

Tabulated results for hydroamination of 1,4 and 1,5-diynes with aromatic amines

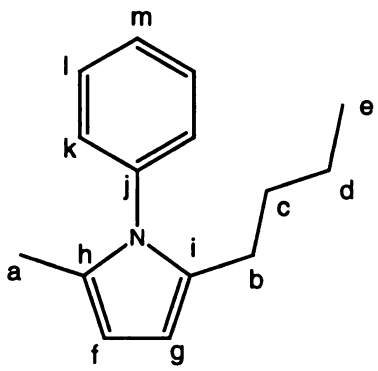
	diyne	amine	conditions[a] (%yield)	product[b,c]
1	 **1b**	H_2NPh	A, 24 h (56)	 **3a**
2		H_2NBn[b]	A, 48 h (35)	 **3b**
3	 **1c**	H_2NPh	B, 30h[d] (62)	 **3c**
4		H_2NBn[b]	B, 30h (53)	 **3d**
5		H_2NPMB[c]	B, 26h (30)	 **3e**
6	 **2a**	H_2NPh	A, 75 °C, 6 h, (68)	 **3f**
7		H_2NBn[b]	A, 14 h (34)	 **3g**
8	 **2b**	H_2NPh	B, 150 °C, 26 h (90)	 **3h**

a. Temperature is 100 °C unless otherwise stated. A = 10 mol% Ti(dpma)(NMe_2)$_2$, B = 10 mol% Ti(dmpm)(NMe_2)$_2$. b. Bn is benzyl. c. PMB is *p*-methoxybenzyl. d. CuI added to aid in cyclization.

General Procedures

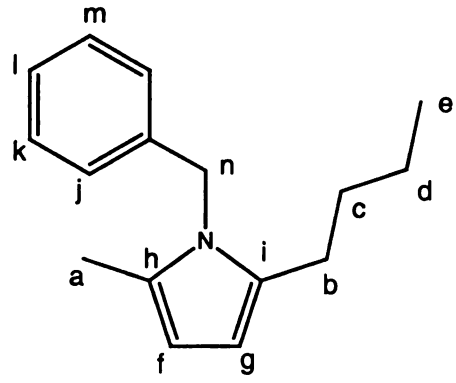
Unless otherwise stated, all manipulations were performed in an MBraun drybox under an atmosphere of purified nitrogen. All solvents were distilled and were stored in the drybox. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian Inova 300 spectrometer at room temperature unless otherwise stated. ^{1}H and ^{13}C NMR chemical shifts are reported with respect to internal solvent (7.21 ppm and 77.22 (t) ppm respectively for $CDCl_3$). Coupling constants could not measured for the pyrroles due to the complex nature of the spectra.

Experimental Section.



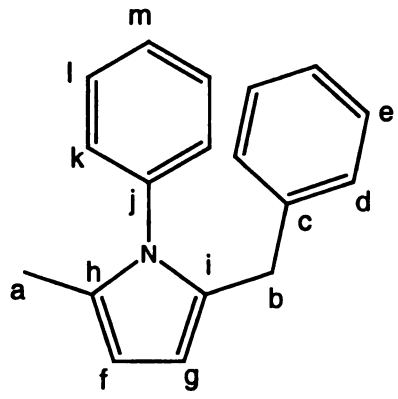
Preparation of 1-phenyl-2-butyl-5-methylpyrrole (**Entry 1**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with toluene (0.416 mL), Ti(dpma)(NMe_2)$_2$ (**A**) (0.269 g, 0.832 mmol), aniline (757.5 μL, 8.32 mmol), and 1,4-

nonadiyne (**1b**) (1.00 g, 8.32 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 100 °C for 22 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of alumina with 7:1 pentane:ether as the eluent. The product eluted in the first fractions in 55% yield (0.98 g, 4.56 mmol). The compound is a yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.2-7.6 (m, 5 H, **k, l** and **m**), 5.98 (s, 2 H, **f** and **g**), 2.06 (s, 3 H, **a**), 2.38 (t, 2 H, **b**), 1.44-1.54 (m, 2 H, **c**), 1.24-1.34 (m, 2 H, **d**), 0.84 (t, 3 H, **e**). ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 139.3 (**j**), 134.1 (**i**), 128.5 (**k**), 128.8 (**l**), 127.7(**m**), 122.8 (**h**), 105.6 (**f**), 104.6 (**g**), 31.2 (**b**), 13.0 (**a**), 26.8 (**c**), 22.4 (**d**), 13.9 (**e**). Elemental analysis; Experimental (Calc.), C: 84.01 (84.46); H: 9.17 (8.98); N: 6.53 (6.57). MS (EI) *m/z* = 213 (M^+).



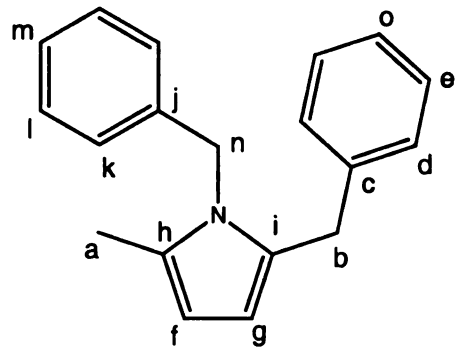
Preparation of 1-benzyl-2-butyl-5-methylpyrrole (**Entry 2**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with toluene (0.416 mL), Ti(dpma)(NMe_2)$_2$ (**A**) (0.269 g, 0.832 mmol), benzylamine (757.5 μL, 8.32 mmol), and 1,4-nonadiyne (**1b**) (1.00 g, 8.32 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 100 °C for 46 h. The volatiles were removed from the

reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of alumina with 7:1 pentane:ether as the eluent. The product eluted in the first fractions in 35% yield (0.66 g, 2.91 mmol). The compound is yellow viscous oil ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.8-7.4 (m, 5 H, **k, l** and **m**), 5.92 (s, 2 H, **f** and **g**), 5.06 (s, 2 H, **n**), 2.16 (s, 3 H, **a**), 2.48 (t, 2 H, **b**), 1.52-1.64 (m, 2 H, **c**), 1.30-1.42 (m, 2H, **d**), 0.84 (t, 3 H, **e**). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 138.8 (**j**), 133.1 (**i**), 128.7 (**l**), 128.0 (**h**), 126.3 (**m**), 125.6 (**k**), 105.5 (**f**), 104.4 (**g**), 46.6 (**n**), 31.1 (**b**), 26.5 (**c**), 22.6 (**d**), 14.0 (**e**), 12.5 (**a**). Elemental analysis; Experimental (Calc.), C: 85.07 (84.53); H: 9.67 (9.31); N: 6.00 (6.16). MS (EI) *m/z* = 227 (M^+).

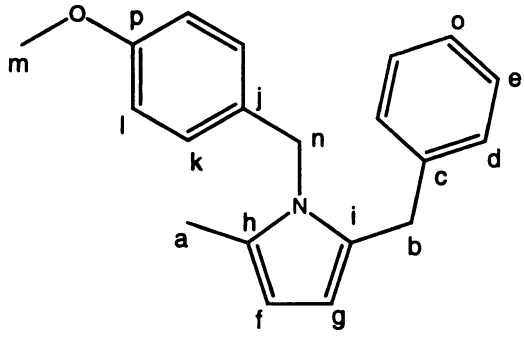


Preparation of 1-phenyl-2-benzyl-5-methylpyrrole (**Entry 3**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with chlorobenzene (0.324 mL), $Ti(dmpm)(NMe_2)_2$ (**B**) (0.20 g, 0.648 mmol), aniline (590.0 μL, 6.48 mmol), and 1-phenylhexa-1,4-diyne (**1c**) (1.00 g, 6.48 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 100 °C for 30 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to cyclization[69] with CuI (0.370 g, 1.945 mmol), anhydrous *N,N*-dimethylacetamide (28 mL) and Et_3N (14 mL).

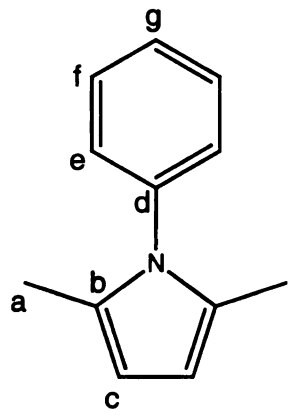
The mixture was stirred for 110 °C with protection from light for 7 h. The mixture was cooled to room temperature and poured into water (100 mL). After shaking with pentane (50 mL), a 3-layer system formed. The lower (water) phase and upper (organic) phase was thoroughly separated from the middle layer, which contained an emulsion of copper complexes. The emulsion and water phases were separately extracted with pentane (3 × 30 mL and 1 × 30 mL respectively). The combined pentane extracts were filtered over anhydrous Na_2CO_3. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography using 300 g of alumina with 7:1 pentane:ether as the eluent. The product eluted in the first fractions and was distilled at 200 °C (0.8 torr) to give yellow oil in 35% isolated yield (0.56 g, 2.27 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.9-7.4 (m, 10 H, **k**, **l**, **m**, **d**, **e**, and **o**), 5.89 (s, 1 H, **f** or **g**), 5.92 (s, 1 H, **f** or **g**), 1.99 (s, 3 H, **a**), 3.69 (s, 2 H, **b**). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 13.1 (**a**), 33.8 (**b**), 106.0 (**f** or **g**), 107.0 (**f** or **g**), 125-132 (**k**, **l**, **m**, **d**, **e**, **o**, **h**, and **i**), 139.0 (**j**), 140.2 (**c**). Elemental analysis; Experimental (Calc.), C: 86.60 (87.41); H: 6.93 (6.93); N: 5.68 (5.66). MS (EI) *m/z* = 247 (M^+).



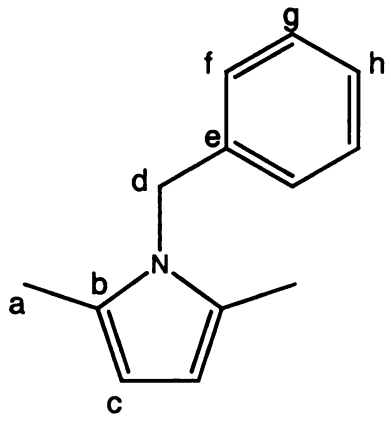
Preparation of 1,2-dibenzyl-5-methylpyrrole (**Entry 4**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with chlorobenzene (0.325 mL), Ti(dmpm)(NMe_2)$_2$ (**B**) (0.20 g, 0.65 mmol), benzylamine (708 μL, 6.49 mmol), and 1-phenylhexa-1,4-diyne (**1c**) (1.00 g, 6.49 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 100 °C for 30 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of alumina with 7:1 pentane:ether as the eluent. The product eluted in the first fractions to give brown oil in 53% (0.90 g, 3.45 mmol) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.8-7.4 (m, 10 H, **k**, **l**, **m**, **d**, **e**, and **o**), 5.89 (br s, 1 H, **f** or **g**), 5.84 (br s, 1 H, **f** or **g**), 4.90 (s, 2 H, **n**), 3.79 (s, 2 H, **b**), 2.12 (s, 3 H, **a**). ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 12.5 (**a**), 33.3 (**b**), 46.8 (**n**), 105.6 (**f** or **g**), 107.0 (**f** or **g**), 125-132 (**k**, **l**, **m**, **d**, **e**, **o**, **h**, and **i**), 138.5 (**j**), 139.7 (**c**). Elemental analysis (Calc.), C: 87.01 (87.31). H: 7.42 (7.33). N: 4.72 (5.36). MS (EI) *m/z* = 261 (M^+).



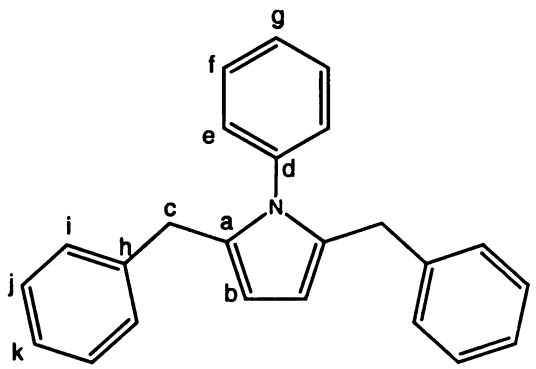
Preparation of 1-(4-methoxybenzyl)-2-benzyl-5-methyl pyrrole (**Entry 5**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with chlorobenzene (0.162 mL), Ti(dmpm)(NMe_2)$_2$ (**B**) (0.10 g, 0.32 mmol), 4-methoxybenzylamine (424 μL, 3.24 mmol), and 1-phenylhexa-1,4-diyne (**1c**) (0.50 g, 3.24 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 100 °C for 26 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of alumina with 7:1 pentane:ether as the eluent. The product eluted in the first fractions to give brown oil in 35% (0.33 g, 1.14 mmol) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.7-6.9 (m, 4 H, **k** and **l**), 7.2-7.4 (m, 5 H, **d**, **e** and **o**), 5.87 (s, 1 H, **f** or **g**), 5.89 (s, 1 H, **f** or **g**), 4.87 (s, 2 H, **n**), 2.16 (s, 3 H, **a**), 3.83 (s, 2 H, **b**), 3.80 (s, 3 H, **m**). ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 12.5 (**a**), 33.3 (**b**), 46.3 (**n**), 55.3 (**m**), 105.6 (**f** or **g**), 107.0 (**f** or **g**), 114.1 (**l**), 124-132 (**k**, **j**, **c**, **d**, **e**, **o**, **h**, and **i**), 139.8 (**c**), 158.6 (**p**). Elemental analysis; Experimental (Calc.), C: 82.25 (82.44); H: 7.67 (7.26); N: 4.46 (4.81). MS (EI) *m/z* = 291 (M^+).



Preparation of 1-phenyl-2,5-dimethylpyrrole (**Entry 6**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with toluene (6.4 mL), Ti(dpma)(NMe_2)$_2$ (**A**) (0.4135 g, 1.28 mmol), aniline (1,166 μL, 12.8 mmol), and 1,5-hexadiyne (**2a**) (1.00 g, 12.8 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 75 °C for 6 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of alumina and diethyl ether as the eluent. The product eluted in the first fractions in 68% isolated yield (1.50 g, 8.76 mmol). When solvent was removed, a colorless liquid was obtained, which solidified on standing. m.p. 45-46 °C (lit.[75] 50 °C). ^{1}H NMR[76] (300 MHz, $CDCl_3$): δ = 7.2-7.6 (m, 5 H, **d**, **e**, **f**, **g**), 5.93 (s, 2 H, **c**), 2.07 (s, 6 H, **a**). $^{13}C\{^1H\}$ NMR[77] (300 MHz, $CDCl_3$): δ = 139.3 (**d**), 129.3 (**f**), 129.0 (**b**), 128.5 (**e**), 127.9 (**g**), 105.9 (**c**), 13.2 (**a**). Elemental analysis; Experimental (Calc.), C: 84.37 (84.17); H: 8.22 (7.65); N: 7.54 (8.18). MS (EI) *m/z* = 171 (M^+).



Preparation of 1-benzyl-2,5-dimethylpyrrole (**Entry 7**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with toluene (6.4 mL), Ti(dpma)$(NMe_2)_2$ (**A**) (0.4135 g, 1.28 mmol), benzylamine (1390 μL, 12.7 mmol), 1,5-hexadiyne (**2a**) (1.00 g, 12.8 mmol). The tube was sealed with a Teflon cap and heated at 100 °C for 14 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 317 g of alumina with pentane, then ether as eluents. The product was isolated in 34 % yield (0.80 g, 4.32 mmol) as a colorless liquid that solidified on standing. m.p. 41-42 °C. ^{1}H NMR[78] (300 MHz, $CDCl_3$): δ = 7.5-7.3 (m, 3 H, **g** and **h**), 7.00-7.15 (m, 2 H, **f**), 6.03 (s, 2 H, **c**), 5.16 (s, 2 H, **d**), 2.30 (s, 6 H, **a**). $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$): δ = 138.7 (**e**), 128.9 (**f**), 128.1 (**b**), 127.2 (**h**), 125.8 (**g**), 105.6 (**c**), 46.8 (**d**), 12.6 (**a**). Elemental analysis; Experimental (Calc.), C: 83.82 (84.28). H: 8.28 (8.16). N: 7.22 (7.56). MS (EI) *m/z* = 185 (M^+).



Preparation of 1-phenyl-2,5-dibenzylpyrrole (**Entry 8**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with chlorobenzene (1.10 mL), Ti(dmpm)(NMe_2)$_2$ (**B**) (0.13 g, 0.43 mmol), aniline (600 μL, 6.58 mmol), and 1,6-diphenyl-1,5-hexadiyne[79] (**2b**) (1.00 g, 4.34 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 150 °C for 26 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of alumina with 1:1 pentane:ether as the eluent. The product was recovered in 90% (1.26 g, 3.90 mmol) isolated yield as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.6-7.6 (m, 15 H, **i**, **e**, **j**, **k**, **g** and **f**), 5.92 (s, 2 H, **b**), 3.70 (s, 2 H, **c**). ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 33.7 (**c**), 107.0 (**b**), 114.1 (**f**), 124-132 (**e**, **d**, **h**, **i**, **j**, **k**, and **a**), 139.8 (**h**), 158.6 (**g**). Elemental analysis (Calc.), C: 88.73 (89.12). H: 6.62 (6.54). N: 4.16 (4.33). MS (EI) *m/z* = 323 (M^+).

Chapter 3

Chapter 2 was an application of the hydroamination of alkynes, which our group has been pursuing for some years now. We showed an interesting application to the ever-expanding field of hydroamination of alkynes, by reporting a one-pot synthesis of substituted pyrroles using a titanium-based catalyst in moderate yields. In this chapter, a new application of hydroamination of diynes will be discussed, i.e. synthesis of vinylpyrroles from diynes along with some latest results that we have obtained in this pursuit. *C*-Vinylpyrroles, having the **A**, **B** structural element, (Figure 3-1) [80] have been extensively studied as building blocks for the synthesis of various representatives of the pyrrole family, especially condensed heterocycles related to pyrrole.[81]

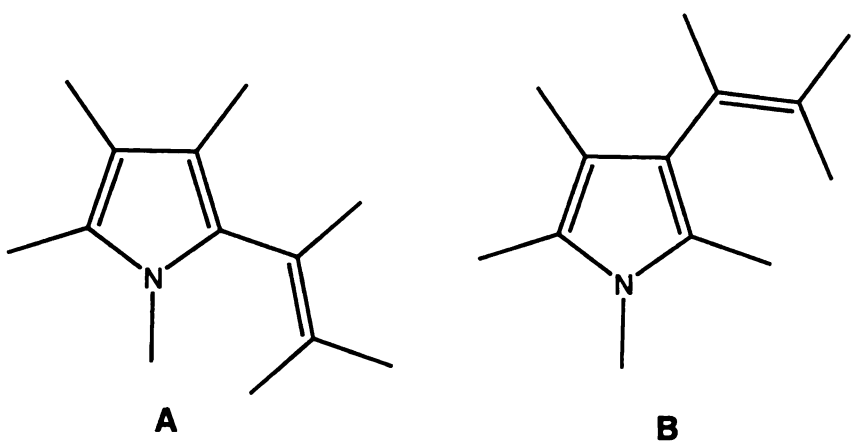


Figure 3-1. Structure of vinylpyrroles

2-Vinylpyrrole structure **A** is found in molecules of many vital natural compounds (porphyrins, chlorophylls, vitamin B12, prodigiosins, etc.). 3-Vinylpyrrole structural

elements **B** compose molecules of chlorophylls *a*, *b*, *c*, and *d* (which play a key role in photosynthesis processes, i.e., photocatalytic transformation of the solar energy) and haemoglobin (the compound responsible for oxygen transport in mammal organisms). *C*-Vinylpyrroles bearing functional groups on the double bond (or those without them) are highly reactive starting compounds for the targeted synthesis of conjugated and fused heterocycles similar to natural pyrrole assemblies. Over the past few years, functionalized *C*-vinylpyrroles started attracting attention as molecular optical switches, in particular, as ultra fast ones, for design of photo- and electroconducting materials, nanodevices[82] and also as ligands for new photocatalysts and biologically active complexes.[83]

3.1.1 Goal of this project

The aim of this project was to extend further the application of hydroamination of diynes to report one-pot syntheses of vinylpyrroles (Figure 3-2).

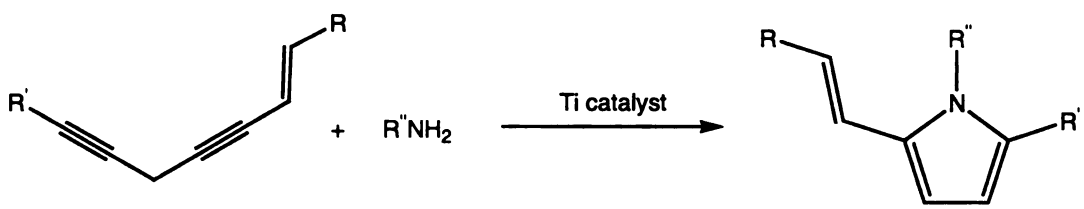


Figure 3-2. Proposed Figure for synthesis of 2-vinylpyroles

Further, the vinylpyrroles obtained can undergo Diels-Alder reaction to give fused heterocycles in 1-step (Figure 3-3)

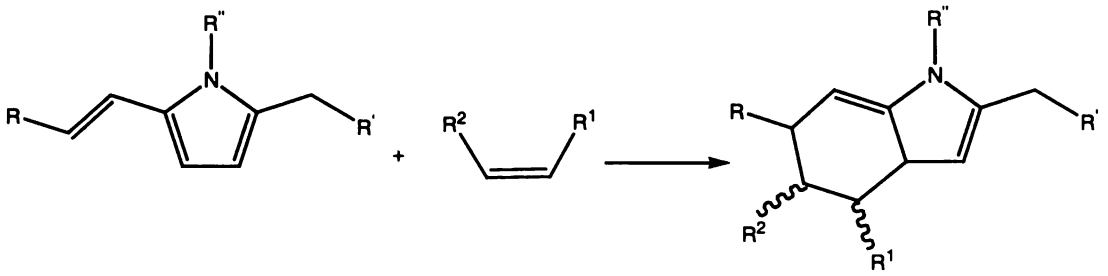


Figure 3-3. Proposed Figure for Diels-Alder reaction of vinylpyrroles

3.1.2 Synthesis of vinylpyrroles

a) Synthesis of 1-vinylpyrroles

The most extensively developed method for the preparation of 1-vinylpyrroles is based on the heterocyclization of ketoximes with acetylene in a strong base-DMSO system.[84] This reaction is called the "Trofimov reaction" and it requires no pyrrole precursors and starts from cheap and readily available ketones (Figure 3-4). The reaction allows the preparation of diverse 2-, 2,3- 2,5-, and 2,3,5- substituted 1-vinylpyrroles. The yields depend on the structure of reactants; with simple ketoximes and unsubstituted acetylene yields of 70-95% are attained under optimal conditions. General studies show that certain 1-vinylpyrroles are of interest as precursors of neurostimulators; 2-phenyl-1-(1-propargyloxyethyl)pyrrole derived from 2-phenyl-1-vinylpyrrole, for example, stimulates motor activity, and increases excitation. There have been some studies done regarding biological properties of 1-vinylpyrroles, which show promising results.[85]

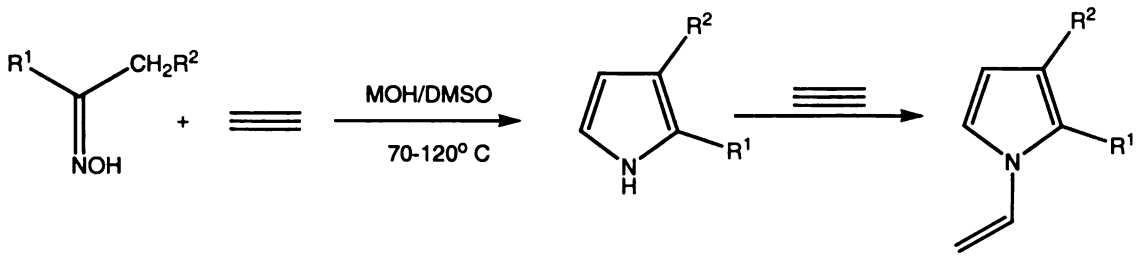
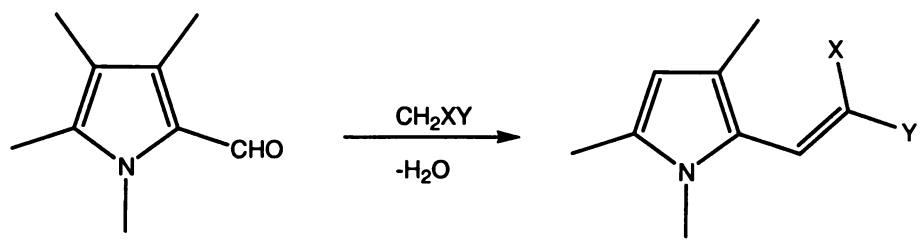


Figure 3-4. Synthesis of 1-vinylpyrroles

b) Synthesis of 2-vinylpyrroles

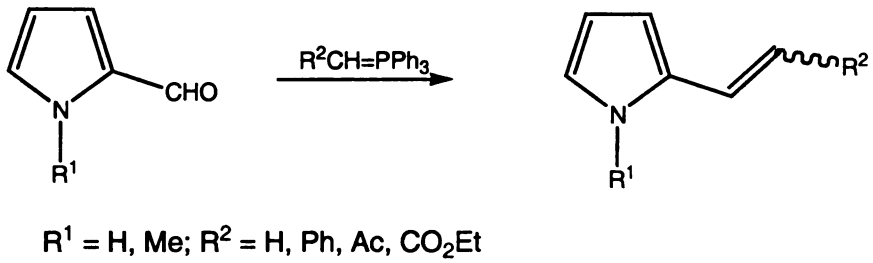
The general synthesis of 2-vinylpyrroles is the base catalyzed condensation of 2-formylpyrroles with activated methylene (or methyl groups (Figure 3-5). 2-Formylpyrroles undergo a normal base catalyzed aldol-type condensation with aliphatic, aromatic and heteroaromatic ketones to yield the correspondingly substituted 2-vinylpyrroles.[86]



X, Y = COR, CO_2R, CN, NO_2

Figure 3-5. Synthesis of 2-vinylpyrroles

Another common way to prepare 2-vinylpyrroles is via the Wittig reaction (Figure 3-6). The Wittig reaction is fairly efficient in conversion of formyl- and acylpyrroles to corresponding vinylpyrroles.[87]



R^1 = H, Me; R^2 = H, Ph, Ac, CO_2Et

Figure 3-6. Synthesis of 2-vinylpyrroles via Wittig reaction

In all the above-described synthesis the yields of the reaction is low and is in between 15-30%.

Some of the Diels-Alder chemistry of 2-vinylpyrroles is as follows. Facile cycloaddition of 2-vinylpyrroles with a range of dienophiles has been investigated [88] (Figure 3-7).

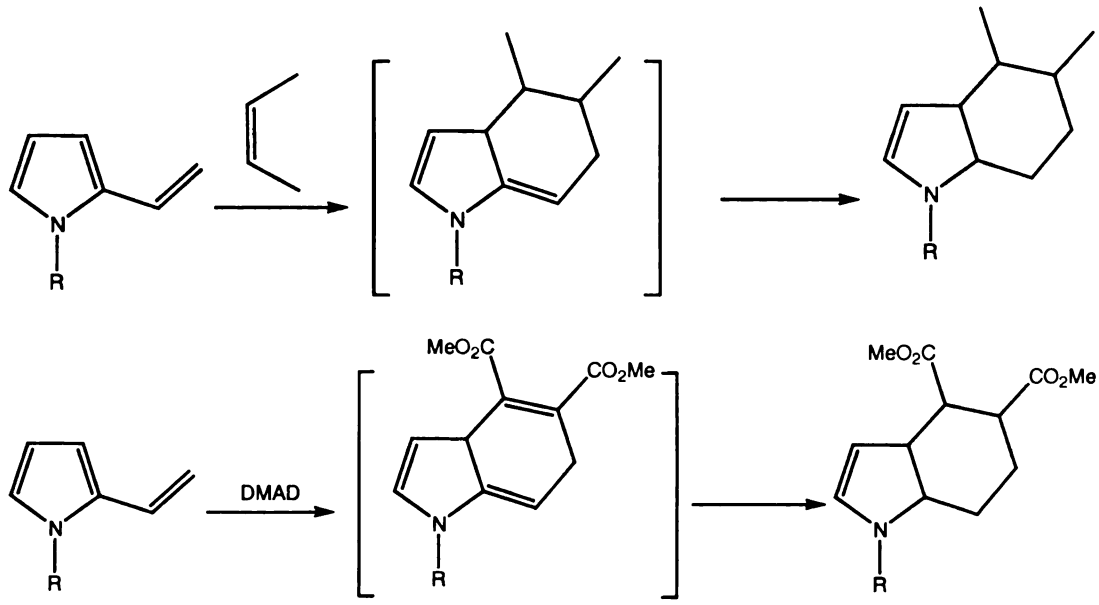


Figure 3-7. Diels-Alder chemistry of 2-vinylpyrroles

The products tetrahydroindoles and dihydroindoles are formed in a two-step process, the first being a [4π + 2π] addition and the second step being a [1,3]-sigmatropic reaction, which restores the aromaticity. The products are obtained in a moderate yield of 54-80%.

c) Synthesis of 3-vinylpyrroles

3-vinylpyrroles are important biologically as they are building blocks in the preparation of vinyl-substituted porphyrins (proto-, pento-, and spirographisporphyrins) and bile pigments (bilirubins, bileverdins, etc.) The synthesis of 3-vinylpyrroles is same as 2-vinylpyrroles, in most of the cases. The most common synthesis is from 3-formylpyrroles and CH acids (Figure 3-8).

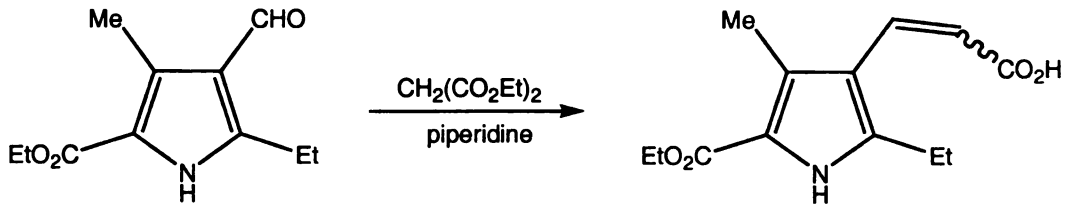


Figure 3-8. Synthesis of 3-vinylpyrroles

In the above example 3-formylpyrrole is condensed with malonic esters catalyzed by an amine yields the expected 3-[2,2-di(carbboxyvinyl]pyrroles at low temperature but, under more vigorous conditions, partial decarboxylation takes place to afford β-(3-pyrrolyl)acrylic acids.[89]

3.1.3 Synthesis of diynes

The diynes were synthesized using a modified literature procedure.[90] The diynes used for hydroamination were synthesized are as follows (Figure 3-9).

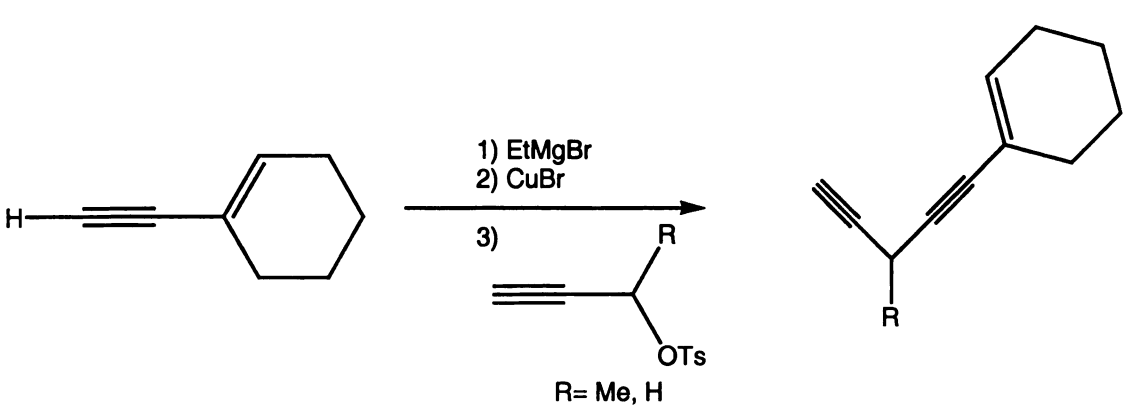


Figure 3-9. Synthesis of diynes for hydroamination

1-ethynylcyclohexene was prepared using standard literature procedures.[91]

3.1.4 Hydroamination of diynes

a) Hydroamination of 1-Cyclohexenyl-1,4-pentadiyne

Hydroamination of 1-cyclohexenyl-1,4-pentadiyne (**1a**) using $Ti(dpma)(NMe_2)_2$ (**A**) as the catalyst with aniline did not yield any 2-vinylpyrrole. Changing the conditions by increasing the temperature and by changing the catalyst to $Ti(dmpm)(NMe_2)_2$ (**B**), $Ti(dap)_2(NMe_2)_2$ (**C**) and $Ti(bap)(NMe_2)_3$ (**D**) also did not yield any products nor did changing the amine substrate (Figure 3-10).

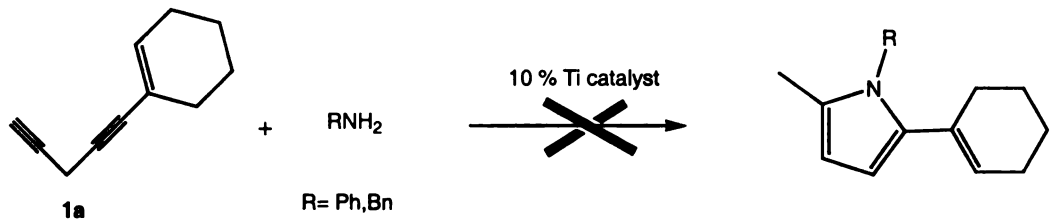


Figure 3-10. Hydroamination of 1-Cyclohexenyl-1,4-pentadiyne with aromatic amines

b) Hydroamination of 1-Cyclohexenyl-3-methyl-1,4-pentadiyne

We hoped that by introducing a substitution in the skipped position, the substrate might undergo hydroamination with diynes. Hydroamination of 1-cyclohexenyl-3-methyl-1,4-pentadiyne (**1b**) with aniline using **A** as the catalyst gave 1-phenyl-2,3-dimethyl-5-(1-cyclohexenyl)-pyrrole (**2a**) in only 23% yield. Reaction of **1b** with

benzylamine using **B** as the catalyst gave 1-benzyl-2,3-dimethyl-5-(1-cyclohexenyl)-pyrrole (**2b**) in a low yield of 8% (Figure 3-11).

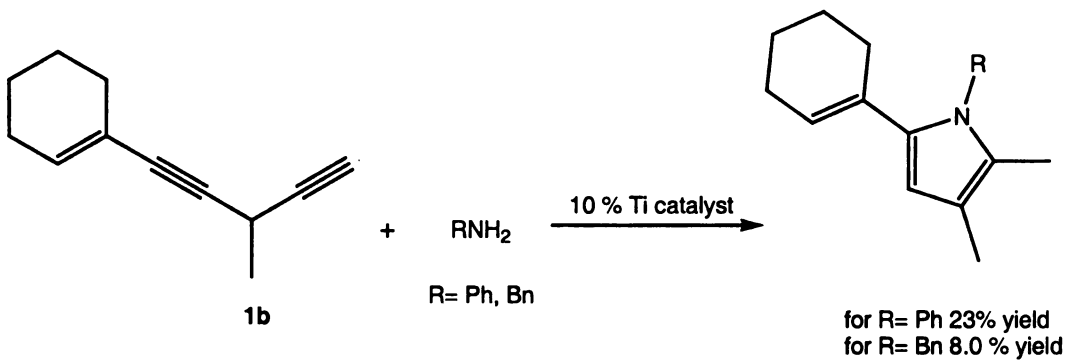


Figure 3-11. Hydroamination of 1-Cyclohexenyl-3-methyl-1,4-pentadiyne with amines

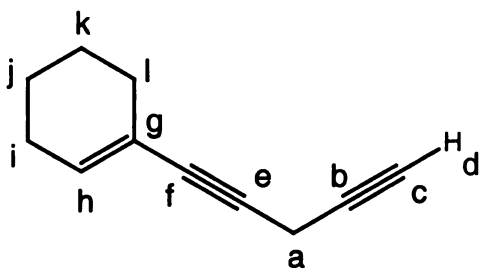
Conclusion

An attempt was made to extend the syntheses of pyrroles described in the previous chapter, to synthesize 2-vinylpyrroles. We have had limited success as far as this goal was achieved. Probably, we need some more variation in the catalysts that we are currently using for hydroamination. We have had some success with the 2-vinylpyrroles that we have synthesized so far. The yields of the reactions are not high and we are currently trying to optimize the yields. Also, testing of the Diels-Alder adducts for biological activity is under investigation.

General Procedures

Unless otherwise stated, all manipulations were performed in an Mbraun drybox under an atmosphere of purified nitrogen. All solvents were distilled and were stored in the drybox. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian Inova 300 spectrometer at room temperature unless otherwise stated. ^{1}H and ^{13}C NMR chemical shifts are reported with respect to internal solvent (7.21 ppm and 77.22 (t) ppm respectively for $CDCl_3$). Coupling constants could not be measured due to the complex nature of the spectra.

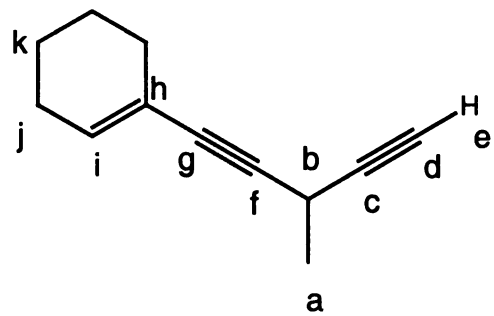
Experimental Section.



1-Cyclohexenyl-1,4-pentadiyne **(Entry 9)**

In a 1 L, 3-necked flask with a stir bar, reflux condenser and dropping funnel under nitrogen atmosphere were placed 1-ethynyl-1-cyclohexene (50.0 g, 0.472 mol) and THF (300mL). Under cooling in an ice bath, ethyl magnesium bromide (236 ml, 0.472 mol, 2M solution in THF) was added via a canula over a 45minute period. The solution was refluxed for 1 h. The reaction mixture was cooled in an ice bath. To this solution, copper (I) bromide (2.73 g) was added. 30 minutes after this addition. 1-Tosyloxy-2-butyne

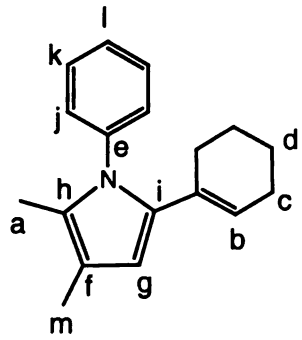
(105.73 g, 0.472 mol) in 150 mL THF was added with vigorous stirring over a period of 30 minutes at 0 °C. During this addition, the temperature of the reaction mixture was kept between 0 °C and +5 °C. The bath was then removed, and the reaction was stirred overnight at room temperature. The reaction was quenched with a solution made from 1 L of water and 100 g of ammonium chloride, and 10 g sodium cyanide. The mixture was stirred over a period 10 minutes. The organic phase was separated and aqueous phase was extracted with (4 × 50 mL) pentane. The combined organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by distillation 78 °C (1torr) to yield a pure product in 67% isolated yield (45.54 g, 316.2 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.00 (s, 1 H, **h**), 3.20 (s, 1 H, **a**), 1.60-2.10 (m, 8 H, **i**, **j**, **k**, and **l**), 2.03 (s, 1 H, **d**). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 10.35 (**a**), 21.73 (**i**), 22.51 (**k**), 25.79 (**j**), 29.35 (**l**), 68.86 (**c**), 78.66 (**f**), 80.00 (**b**), 82.95 (**e**), 120.52 (**g**), 135.02 (**h**).



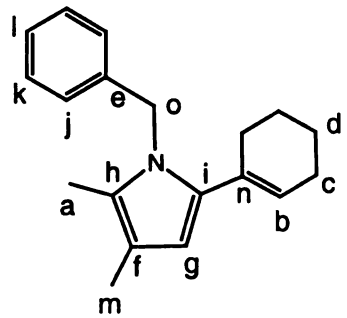
1-Cyclohexene-3-methyl-1,4-pentadiyne **(Entry 10)**

In a 1 L, 3-necked flask with a stir bar, reflux condenser and dropping funnel under nitrogen atmosphere were placed 1-ethynyl-1-cyclohexene (13.33 g, 0.126 mol) and THF (100mL). Under cooling in an ice bath to this solution was added benzyl magnesium chloride (63 mL, 0.126 mol, 2M solution in THF) with a dropping funnel over a 10-minute period. The solution was refluxed for 1 h. The reaction mixture was cooled in an

ice bath to 0 °C. To this solution, copper (I) bromide (0.73 g) was added. 30 minutes after this addition, 3-tosyl-1-butyne (28.17 g, 0.126 mol) in 40 ml THF was added 0 °C with vigorous stirring over a period of 15 minutes. During this addition, the temperature of the reaction mixture was kept between 0 °C and +5 °C. The bath was then removed, 150 mL of dry THF was added to the reaction mixture and was stirred overnight at room temperature. The reaction was quenched with a solution prepared from 500 mL of water and 55 g of ammonium chloride, and 10 g sodium cyanide. The mixture was stirred for 30 minutes. The organic phase was separated and aqueous phase was extracted with (2 × 200 mL) pentane. The combined organic phase was dried over MgSO4, and the solvent was removed under reduced pressure. The crude product was purified by distillation 65 °C (1 torr) to yield a pure product in 59% isolated yield (11.69 g, 74 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.08 (s, 1 H, **i**), 3.57 (d, 1 H, **b**), 1.60-2.10 (m, 8 H, **j**, **k**, **l** and **m**), 2.13 (d, 1 H, **e**), 1.48 (d, 3 H, **a**), 1.95 (s, 3 H, **m**). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ = 18.37 (**a**), 21.75 (**j**), 22.58 (**l**), 25.82 (**k**), 29.45 (**m**), 68.42 (**d**), 82.57 (**g**), 84.16 (**c**), 85.73 (**f**), 128.60 (**h**), 134.90 (**i**).



Preparation of 1-phenyl-2,3-dimethyl-5-(1-cyclohexenyl)-pyrrole (**Entry 11**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with toluene (3.17 mL), Ti(dpma)(NMe_2)$_2$ (**A**) (0.21 g, 0.63 mmol), aniline (576 μL, 6.33 mmol), and 1-cyclohexene-3-methyl-1,4-pentadiyne (**1b**) (1.00 g, 6.33 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 100 °C for 4 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of silica gel with 5:1 hexane:dichloromethane as the eluent. Product **2a** eluted in the first fractions in 23% (0.37 g, 1.45 mmol) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.0-7.3 (m, 5 H, **j**, **k** and **l**), 5.87 (s, 1 H, **b**), 5.25 (br s, 1 H, **g**), 2.16 (s, 3 H, **a**), 1.58-1.44 (m, 8 H, **c** and **d**), 1.95 (s, 3 H, **m**). ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 10.5 (**m**), 11.2 (**a**), 22.0-22.90 (**b**, **c** and **d**), 108.5 (**g**), 114.2 (**i**), 125-139 (**j**, **k**, **l**, **f**, **h**, **n** and **b**), 138.5 (**j**), 140.4 (**e**).



Preparation of 1-benzyl-2,3-dimethyl-5-(1-cyclohexenyl)-pyrrole (**Entry 12**): Under an atmosphere of dry nitrogen, a threaded-top pressure tube was loaded with toluene (6.33 mL), $Ti(dap)_2(NMe_2)_2$ (**C**) (0.48 g, 1.26 mmol), benzylamine (1380 μL, 12.65 mmol), and 1-cyclohexene-3-methyl-1,4-pentadiyne (**1b**) (2.00 g, 12.65 mmol). The tube was sealed with a Teflon cap, and the reaction mixture was heated at 60 °C for 19 h. The volatiles were removed from the reaction mixture in vacuo, and the residue was subjected to column chromatography using 300 g of alumina with 5:1 hexane:dichloromethane as the eluent. Product **2b** eluted in the first fractions in 8.3% (0.278 g, 1.05 mmol) isolated yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.80-7.25 (**m**, 5 H, **j**, **k** and **l**), 5.87 (s, 1 H, **b**), 5.45 (br s, 1 H, **g**), 4.99 (s, 2 H, **o**), 1.96 (s, 3 H, **a**), 1.58-1.44 (m, 8 H, **c** and **d**), 1.77 (s, 3 H, **m**). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 9.9 (**m**), 11.2 (a), 22.0-30.10 (**b**, **c** and **d**), 47.80 (**o**), 107.5 (**g**), 114.3 (**i**), 125-139 (**j**, **k**, **l**, **f**, **h**, **n** and **b**), 139.6 (**e**).

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