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ORGANOLANTHANIDE CATALYZED INTRAMOLECULAR 5-*ENDO-DIG* HYDROAMINATION: AN UNUSUAL ANTI-MARKOVNIKOV CYCLIZATION†

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Abstract – Intramolecular 5-*endo-dig* hydroaminations of homopropargylamine derivatives were efficiently catalyzed by the organolanthanide precatalyst, $Cp^*_2YbCH(TMS)_2$ ($Cp^* = C_5Me_5$), to give the endocyclic enamine products. The 5-*endo-dig* hydroamination was also preferred in the presence of another olefin that would afford a 6-*exo* cyclization.

INTRODUCTION

Carbon-nitrogen bond-forming reactions between unsaturated carbon-carbon bonds and amines represents one of the more challenging current themes in organic synthesis. Because both amines, and alkenes and alkynes, are electron rich, activation of the C-C multiple bond or the nitrogen center of an amine is necessary to induce such a coupling. Recently, organolanthanide-catalyzed hydroaminations have been developed as an attractive means to form C-N bonds.[1] The reaction has been principally used for intramolecular hydroamination with aminoalkynes,[2] aminoalkenes[3] and aminoallenes[4] to synthesize nitrogen containing heterocycles. Some applications of this method to natural product synthesis have also been reported.[5, 6]

In our laboratory, an asymmetric synthesis of the monocyclic alkaloid pinidinol using an organolanthanide catalyzed intramolecular hydroamination was accomplished and reported recently.[6]

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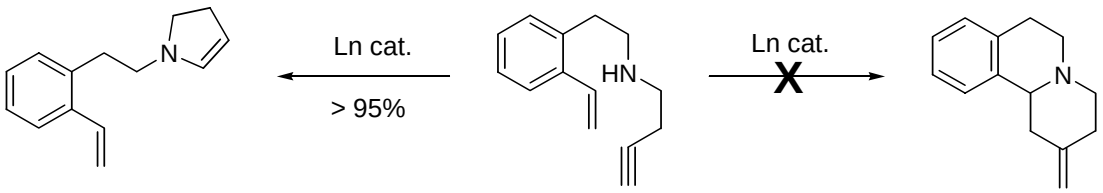
†Dedicated with great respect and admiration to Dr. Pierre Potier on his 70th birthday.

During the course of our investigations into the use of organolanthanide catalysts for polycyclic alkaloid synthesis,[7] a unique anti-Markovnikov intramolecular 5-*endo-dig* hydroamination was discovered (Scheme 1). Thus, the reaction of homopropargylamine substrate (**1**) using an organolanthanide catalyst afforded not the desired 6-*exo*, 6-*exo* tandem cyclic product (**2**), but rather led to 5-*endo* ring closure product (**3**) *via* an intramolecular anti-Markovnikov addition to the alkyne. Although there are examples of organolanthanide catalyzed hydroamination of aminoalkynes,[1,2] to the best of our knowledge this is the first example of a 5-*endo-dig* hydroamination. Herein we wish to report our preliminary studies of this unusual reaction.

Scheme 1



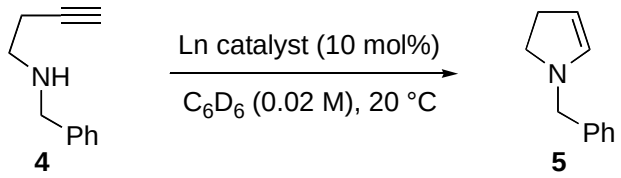
3 **1** **2**

RESULTS AND DISCUSSION

At the outset of our studies, several organolanthanide catalysts were tested for the intramolecular 5-*endo-dig* hydroamination, and a simple *N*-benzylhomopropargylamine (**4**)[8] was chosen as the amine substrate to optimize the reaction conditions. Ansa-bridged precatalyst $Me_2SiCp''_2NdCH(TMS)_2$ (Cp" = C_5Me_4), often employed as a good precatalyst for intramolecular hydroaminations,[9] was tested (Table 1). Thus, a solution of the homopropargylamine (**4**) (10 μmol) in C_6D_6 (0.02 M) was added to a sealable NMR tube in which was placed 1 μmol of the precatalyst. The reaction was monitored by ^{1}H NMR spectroscopy. However, this reaction did not proceed and only starting material was recovered (entry 1). Similar reactions using $Cp^*_2NdCH(TMS)_2$ and $Cp^*_2SmCH(TMS)_2$ gave many products, with a small amount of the 5-*endo* ring closure product (**5**) being detected in the latter case (entries 2 and 3). The $Cp^*_2YbCH(TMS)_2$ precatalyst, having a smaller ionic radius, was next utilized in conjunction with substrate (**4**). We were pleased to find that 5-*endo* hydroamination took place to give the desired enamine product (**5**) quantitatively (entry 4).[10] Other types of organolanthanide precatalysts (Cp^*_2YMe•THF and Cp^*_2LuMe•THF) were also employed under the same reaction conditions, although they were determined to be less efficient (entries 5 and 6). From these observations it was determined that organolanthanide catalysts possessing metals with a small ionic radius were more efficient for the 5-*endo* hydroamination of the homopropargylamine substrate, even though increasing the lanthanide ionic radius (Lu < Yb < Y < Sm < Nd)[11] and opening the metal coordination sphere, such as with the ansa-bridged precatalyst

$Me_2SiCp''NdCH(TMS)_2$, usually gave higher reactivity in intramolecular[9] as well as in intermolecular hydroaminations.[12]

Table 1. Screening of organolanthanide precatalysts for intramolecular 5-*endo-dig* hydroamination[a]



4 **5**

entry	Ln cat.	Time	Conv.%[b]	Yield%[b]
1	$Me_2SiCp''_2NdCH(TMS)_2$	3 d	N.R.[c]	-
2	$Cp^*_2NdCH(TMS)_2$	3 d	70	0[d]
3	$Cp^*_2SmCH(TMS)_2$	3 d	70	20[e]
4	$Cp^*_2YbCH(TMS)_2$	1 d	>95	>95
5	$Cp^*_2YMe•THF$	2 d	60	30[f]
6	$Cp^*_2LuMe•THF$	9 d	90	40[f]

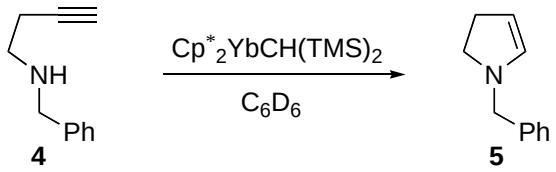
[a] The reaction was carried out in an NMR tube with 10 mol% of lanthanide catalyst.
[b] Conversion and yield were determined by ^1H NMR spectroscopy.
[c] No reaction. Only starting amine was recovered.
[d] Complex mixture.
[e] Other products were found by ^1H NMR spectroscopy.
[f] There were two other products.

The reaction conditions for the intramolecular 5-*endo* hydroamination were optimized using $Cp^*_2YbCH(TMS)_2$ (Table 2). The 5-*endo* hydroaminations of homopropargylamine (**4**) were carried out under several concentrations in C_6D_6 using 5 mol% of Yb precatalyst and were monitored by ^1H NMR. Increasing the concentration afforded faster reactions as is usual in hydroaminations (entries 1 to 4),[9] although some byproducts were generated under the higher concentration reaction conditions (entry 4). Competitive product inhibition,[13] which causes a decrease of the reaction rate, was noticed during the monitoring of these reactions. Indeed, this effect led to incomplete reaction when less Yb precatalyst was used (entries 5 and 6). Fortunately, a higher reaction temperature solved this problem and allowed the use of 3 mol% of Yb precatalyst to achieve satisfactory results (entry 7).

Unfortunately, all efforts to isolate the endocyclic enamine product (**5**) failed due to the instability of the product. However, enamine (**5**) was reduced to give the stable product, *N*-benzylpyrrolidine (**6**), according to the reported procedure (eq. 1).[14] Thus, after completion of the 5-*endo* hydroamination of homopropargylamine (**4**), the reaction solution was poured into a MeOH solution containing $NaBH_3CN$ (5 equiv.) and $ZnCl_2$ (2.5 equiv.). After stirring for 1 h and the proper workup, column purification of the

crude sample by basic Al_2O_3 gave *N*-benzylpyrrolidine (**6**), which was identified by comparison of its ^1H NMR and MS with an authentic sample.[15]

Table 2. Optimization of reaction conditions for intramolecular 5-*endo-dig* hydroaminations[a]

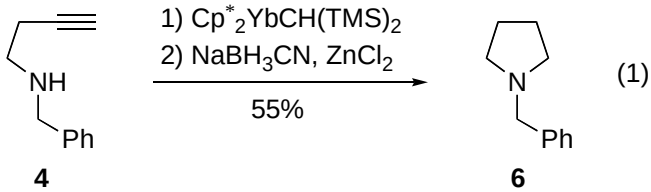


4 **5**

entry	Conc.[b]	mol%[c]	Temp.	Time	Conv.%[d]	Yield%[d]
1	0.02	5	20 °C	2 d	>95	>95
2	0.05	5	20 °C	2 d	>95	>95
3	0.1	5	20 °C	1 d	>95	90
4	0.2	5	20 °C	12 h	>95	85[e]
5	0.1	3	20 °C	1 d	80	80[e]
6	0.1	1	20 °C	3 d	50	80[e]
7	0.1	3	60 °C	<1 h	90	95
8	0.1	1	60 °C	6 h	90	90[e]

[a] The reaction was carried out in an NMR tube.
[b] Concentration (mol/L) of the starting amine in C_6D_6.
[c] Amount of lanthanide catalyst.
[d] Conversion and yield were determined by ^1H NMR spectroscopy.
[e] Byproducts were found by ^1H NMR spectroscopy.

The low isolated yield was caused not from the hydroamination but from generation of a byproduct under the reducing conditions. Thus, the dimerized product obtained from the enamine product and its iminium ion intermediate is generated in substantial quantities under these reaction conditions.[16]

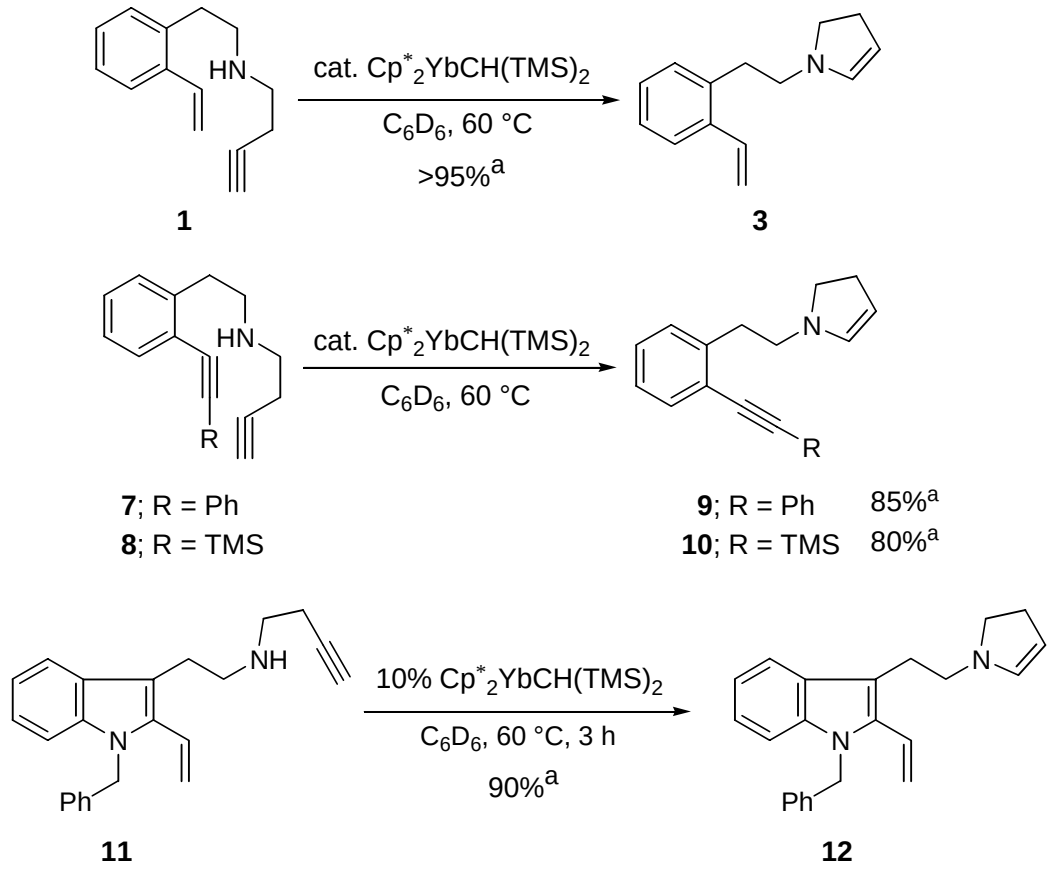


4 **6** (1)

Surprisingly, the 5-*endo* hydroamination product was formed in preference to the 6-*exo* hydroamination product (Scheme 2). Thus, the hydroamination of amine (**1**) under the optimized conditions (Table 2, entry 7) took place to give only 5-*endo* ring closure product (**3**). The starting amine was consumed in 1 h as determined by ^1H NMR spectroscopy. To the best of our knowledge, this is the first example of a 5-*endo-dig* hydroamination taking place in the presence of a second olefin positioned for 6-*exo* cyclization,

although there are many examples of 5-*endo-dig* cyclization catalyzed by transition metals.[17] This selectivity was also observed in the hydroamination of diyne substrates (**7**) and (**8**), even though the carbon-carbon triple bond, especially the alkyne substituted by the trimethylsilyl group, has a higher reactivity than a carbon-carbon double bond in organolanthanide catalyzed hydroaminations.[2] Similar selectivity was observed in the transformation of **11** to **12**.

Scheme 2. Intramolecular 5-*endo-dig* hydroamination of amine derivatives having another olefin at the 6-*exo* position.

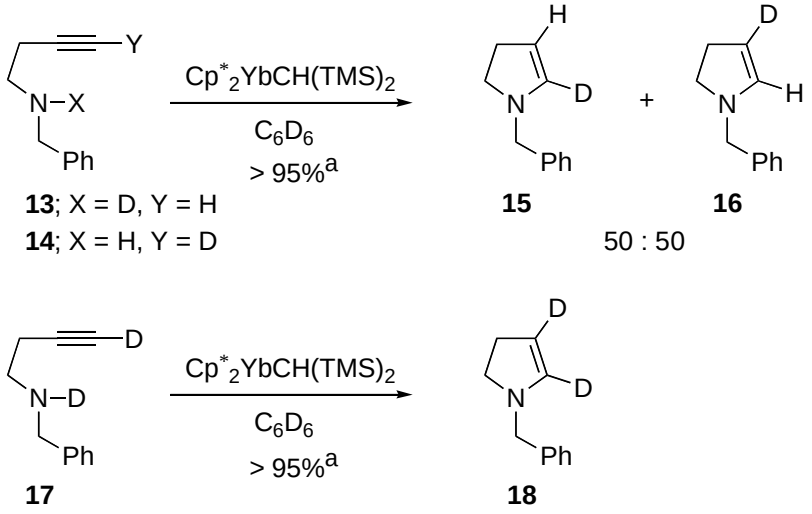


[a] Yields were determined by ^{1}H NMR spectroscopy.

The mechanism of organolanthanide catalyzed hydroamination has been proposed to occur through a four-centered transition structure involving insertion of a C-C multiple bond into the lanthanide-amide bond.[9,12,13] However, it is difficult to imagine this paradigm for the 5-*endo* hydroamination. In the hope of shedding some light on the mechanism of the current transformation, deuterated homopropargylamines were prepared and transformed with Cp*$_2$YbCH(TMS)$_2$ in reactions monitored by ^{1}H NMR spectroscopy (Scheme 3). Surprisingly, the ^{1}H NMR spectrum of the hydroamination of nitrogen-deuterated amine (**13**) showed two products (**15**) and (**16**). Integration of the 2- (δ = 5.87) and 3-position (δ = 4.75) enamine protons indicated 0.5 H protons at each position, and each of these integrated to one-fourth the amount of protons at the other methylene position (benzyl, 4- and 5-position, δ= 3.64, 2.34, 2.81 for 2H). A similar

result was obtained from the hydroamination of the amine deuterated at the terminal alkyne (**14**). Changing the reaction conditions (e.g., concentration and temperature) made no difference in the product ratio. Although there is an example of deuterium scrambling in a hydroamination catalyzed by a rhodium catalyst,[18] the current labeling studies have unfortunately provided few details on the mechanism of the reaction. As expected, the hydroamination of dideuterated amine (**17**) gave the dideuterated product (**18**).

Scheme 3. Hydroamination of deuterated amine substrates.



[a] Yields were determined by ^{1}H NMR spectroscopy.

CONCLUSIONS

The first example of organolanthanide catalyzed intramolecular 5-*endo-dig* hydroamination had been reported. It is noteworthy that $Cp^*_2YbCH(TMS)_2$, having a relatively small ionic radius, is a suitable catalyst for this reaction. More detailed experiments to determine the reaction mechanism and to apply the enamine products as intermediates in organic synthesis are being conducted in our laboratory.

EXPERIMENTAL

General Procedure. Preparation of homopropargylamine substrates for hydroamination. *N*-3-Butynyl-(2-ethenylphenyl)methylamine (1): To the solution of 2-ethenylbenezeneacetonitrile in Et_2O (0.3 M) was slowly added a solution of diisobutylaluminum hydride in hexane (2.5 equiv.) under an argon atmosphere at -78 °C. The reactant was allowed to warm to -40 °C and stirred for 3 h. The solution of 3-butynylamine hydrochloride (2.0 equiv.) in methanol (1.0 M) was then added into the reactant at –40 °C. After stirring for 2 h at rt, the reactant was quenched with saturated NH_4Cl aqueous solution. The precipitate was removed through a Celite pad and the aqueous solution was extracted with Et_2O. The ether solution was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude sample by SiO_2

column chromatography (10 : 1 EtOAc : *i*-PrOH as eluent) gave the title substrate. The amine substrate was further purified by recrystallization of its HCl salt from EtOH/1,2-dichloroethane.

Preparation of homopropargylamine solution in C_6D_6: The homopropargylamine HCl salt, which was prepared according to the above procedure or the known procedure for *N*-benzyl-3-butynylamine (**4**),[8] was neutralized with 2N NaOH in a small vial, and it was then extracted with C_6D_6 (*ca.* 2 mL) 3 times. The amine solution in C_6D_6 was placed into a Schlenk flask and dried over MS 4Å. After degassing of the solution, it was moved into a nitrogen-filled glove box and diluted with C_6D_6 to make the appropriately concentrated amine solution.

General procedure for hydroaminations: A solution of the homopropargylamine (10 μmol) in C_6D_6 (0.02 M) was added to a sealable NMR tube in which was placed 1 μmol of the precatalyst. The reaction was monitored by ^{1}H NMR spectroscopy. The yield was also determined by ^{1}H NMR spectroscopy.

Reduction of hydroamination product 5; **Preparation of *N*-Benzylpyrrolidine** (**6**)[10]: After completion of the hydroamination of homopropargylamine (**4**), the reaction solution was poured quickly into a MeOH solution containing $NaBH_3CN$ (5 equiv.) and $ZnCl_2$ (2.5 equiv.). After stirring for 1 h, the reaction was quenched with saturated NH_4Cl aqueous solution, and it was then extracted with Et_2O. Purification of the crude sample by basic Al_2O_3 column chromatography (30 : 1 hexane EtOAc as eluent) gave *N*-benzylpyrrolidine (**6**).

ACKNOWLEDGEMENTS

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