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# Yttrium(III)-Catalyzed Intramolecular Alkyne Hydroaminations

Hyunseok Kim,[a] Tom Livinghouse,[b,*] Jun Hwan Shim,[a] Seong Guk Lee,[a] Phil Ho Lee[a,*]

[a] Department of Chemistry, Kangwon National University, Chunchon 200-701, Republic of Korea
Fax: (+82)-33-253-7582, e-mail: phlee@kangwon.ac.kr
[b] Department of Chemistry, Montana State University, Bozeman, MT 59717, U.S.A.
Fax: (+1)-406-994-5407, e-mail: livinghouse@chemistry.montana.edu

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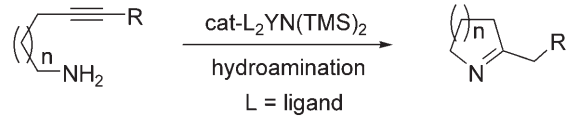
This paper is dedicated to Professor Sunggak Kim on the occasion of his 60th birthday.

**Abstract:** The neutral Y(III) complex **4** has been shown to be an effective precatalyst for intramolecular alkyne hydroaminations that provide cyclic amines in good to excellent yields.

**Keywords:** alkynes; catalysis; cyclization; hydroamination; yttrium



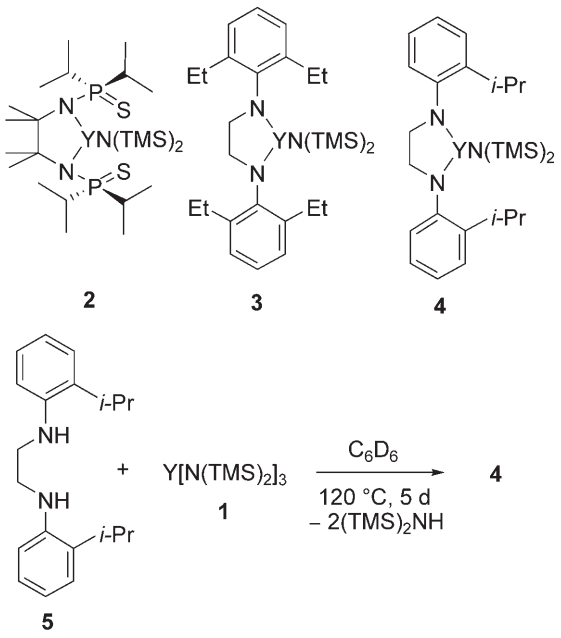

**Scheme 1.**

Catalytic N–H addition reactions to C–C multiple bonds are among the most important methods for the synthesis of azacycles common to naturally occurring alkaloids.[1] Of the variety of early transition metal-based catalysts for this transformation, complexes of the lanthanides appear uniquely well suited for alkene and alkyne hydroaminations under mild reaction conditions.[2] The majority of the complexes that have found utility for this purpose are comparatively air- and moisture-sensitive metallocene derivatives.[3] In addition to the metallocene versions of these catalysts, very effective non-metallocene lanthanide and group 3 catalysts have been reported for alkene and alkyne hydroamination reactions.[4] Recently, Livinghouse and co-workers disclosed that simple amido derivatives of the group 3 metals corresponding to the formula $M[N(TMS)_2]_3$ and $[L_2YN(TMS)_2$ (L = ligand)] are competent catalysts for intramolecular alkene hydroamination.[4a,5] Herein we show that $L_2YN(TMS)_2$ obtained from coordination of the active metal center to simple chelating diamide ligands can be efficiently used for intramolecular alkyne hydroamination (Scheme 1).

As part of our previous study,[4a] we demonstrated that the addition of a variety of aminoalkenes to catalytic amounts of $Y[N(TMS)_2]_3$ (**1**) in $C_6D_6$ at 24 °C resulted in generation of the corresponding amine-ligated[6] amido complexes with concomitant immediate liberation of $(TMS)_2NH$. It is well established that the catalytic activity of group 3 metallocenes in alkyne hydroamination is influenced by steric hindrance about the metal center.[3o,7] Although we set out to determine the role that sterically hindered chelating ligands might play in changing the reactivity of group 3 amido complexes, we cannot draw a conclusion about the relationship of catalyst reactivity and structure of ligands because ligand exchange of *N*,*N*′-bis(2,6-diethylphenyl)ethylenediamine with $Y[N(TMS)_2]_3$ was not completed even after 10 days. However, attachment of the ligand **5** to Y was quantitatively achieved by direct metalation with 1 equivalent of $Y[N(TMS)_2]_3$ in $C_6D_6$ (120 °C, 5 days) to afford complex **4** *via* elimination of $(TMS)_2NH$ (Scheme 2). Ligand exchange of *N*,*N*′-bis(*P*,*P*-diisopropylthiophosphinyl)-2,3-dimethyl-2,3-butanediamine with $Y[N(TMS)_2]_3$ proceeded to give precatalyst **2** in $C_6D_6$ (120 °C, 10 days) *via* smooth elimination of bis(trimethylsilyl)amine.

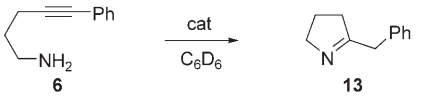
At the outset, the catalytic activity of these complexes (**1**, **2**, and **4**) was examined in the intramolecular hydroamination of 5-phenyl-4-pentyn-1-amine (**6**). The results are summarized in Table 1. Treatment of **6** with 5 mol % $Y[N(TMS)_2]_3$ or **4** in a J. Young NMR tube ($C_6D_6$, 0.46 M) produced the desired product **13** in 90% *via* 5-*exo*-*dig* intramolecular hydroamination (25 °C, 480 h) and 67% (25 °C, 330 h) yields, respectively (entries 1 and 3). Heating the reaction mixture at 60 °C with 5 mol % $Y[N(TMS)_2]_3$ accelerated the reaction to give **13** in 90% yield after 89 h (entry 2). Subjecting 5 mol % **4** to **6** afforded azacycles in 94% yield (entry 6). Although reaction of **2** with **6** (60 °C, 1.5 h, $C_6D_6$, 1.0 M) afforded **13** in 96% yield (entry 5), internal aminoal-




**Scheme 2.** *In situ* generation of the yttrium precatalyst for hydroamination.

**Table 1.** Optimization of intramolecular alkyne hydroamination catalyzed by yttrium.[a]



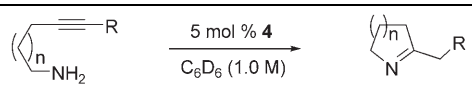

| Entry | Cat. | Conc. [M] | Temp. [°C] | Time [h] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | **1** | 0.46 | 25 | 480 | 90 |
| 2 | **1** | 0.46 | 60 | 89 | 90 |
| 3 | **4** | 0.46 | 25 | 330 | 67 |
| 4 | **1** | 1.0 | 60 | 80 | 96 |
| 5 | **2** | 1.0 | 60 | 1.5 | 96 |
| 6 | **4** | 1.0 | 60 | 9 | 94 (85)[c] |

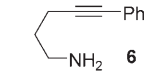
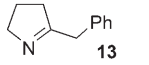
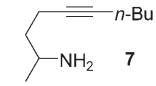
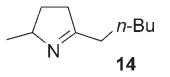
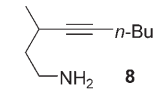
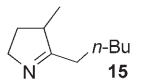
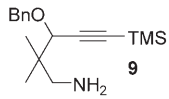
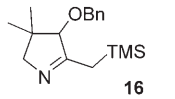
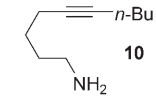
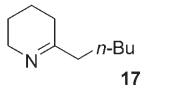
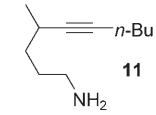
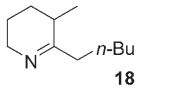
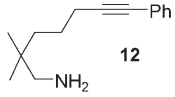
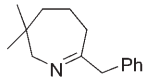
[a] Reaction performed in the presence of 5 mol % catalyst in $C_6D_6$.
[b] NMR yields based on *p*-xylene as an internal standard.
[c] Isolated yield.

kynes lacking an aryl substituent did not give rise to the desired product.[8] Therefore, we examined the precatalyst **4** for intramolecular alkyne hydroamination. Moreover, it could be readily scaled up (3.0 mmol of aminoalkyne **6**) with the same efficiency (5 mol % of **4**, 85% isolated yield, 406.0 mg).

To demonstrate the efficiency and scope of the present method, we applied the optimum conditions to a variety of aminoalkynes. The results are summarized in Table 2. Addition of **9** to **4** (5 mol %) provided **16** in 98% yield (by NMR) after 0.2 h at 25 °C (entry 4).[9] Also, aminoalkyne **7** having a methyl group at the carbon adjacent to

**Table 2.** Intramolecular alkyne hydroamination catalyzed by yttrium.




| Entry | Reactant | Temp. [°C] | Time [h] | Product | Yield [%][a] |
|---|---|---|---|---|---|
| 1 |  **6** | 60 | 9 |  **13** | 94 (85)[b] |
| 2 |  **7** | 25 | 1.5 |  **14** | 95 |
| 3 |  **8** | 120 | 13 |  **15** | 81 |
| 4 |  **9** | 25 | 0.2 |  **16** | 98 |
| 5 |  **10** | 150 | 71 |  **17** | 93 |
| 6 |  **11** | 150 | 18 |  **18** | 92 |
| 7 |  **12** | 120 | 158 |  **19** | 48 |

[a] NMR yields based on *p*-xylene as an internal standard.
[b] Isolated yield.

nitrogen was smoothly cyclized to give **14** in 95% yield (25 °C, 1.5 h, entry 2). These results imply that cyclization of these substrates is facilitated by the Thorpe–Ingold effect.[4a] Reaction of **8** with **4** at 120 °C for 13 h produced the desired product **15** in 81% yield (entry 3). Although treatment of **10** with **4** (5 mol %) furnished the cyclized product **17** in 93% yield in $C_6D_6$ at 150 °C for 71 h (entry 5), hydroamination of **11**, having a methyl group at the carbon adjacent to the triple bond, was accelerated to afford **18** in 92% yield $C_6D_6$ at 150 °C for 18 h (entry 6). Exposure of **12** to **4** (5 mol %) resulted in the production of **19** in 48% yield, albeit under harsh conditions ($C_6D_6$, 120 °C, 158 h) (entry 7).

In conclusion, we have shown that the neutral Y-diamine complex **4** is a competent precatalyst for intramolecular alkyne hydroaminations involving primary amines. Complex **4** was quantitatively generated *in situ* by direct metalation reaction of the ligand **5** with 1 equivalent of $Y[N(TMS)_2]_3$ (**1**) in $C_6D_6$ (120 °C, 5 days) *via* elimination of $(TMS)_2NH$. 5-*exo*-, 6-*exo*-, and 7-

*exo-dig* intramolecular hydroaminations were found to proceed smoothly in all cases. These results should immediately provide more opportunities for the elucidation of efficient and selective new catalytic C–N bond forming reactions by way of neutral catalyst development. Further studies to expand the utility of this reaction are underway.

## Experimental Section

### Preparation of *N,N′*-Bis(2-isopropylphenyl)ethane-1,2-diamine (5)

To a solution of 2-isopropylaniline (2.35 g, 17.4 mmol) and triethylamine (2.64 mL, 19.0 mmol) in THF(60 mL) at 0 °C was added dropwise oxalyl chloride (1.0 g, 7.9 mmol). The reaction mixture was stirred overnight, then refluxed for 1 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 mL), and then washed with $H_2O$ (20 mL), 1 N HCl (10 mL), and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated under vacuum to provide *N,N′*-bis(2-isopropylphenyl)oxalamide as a white solid; yield: 2.5 g (97%); mp 179–181 °C.

*N,N′*-Bis(2-isopropylphenyl)oxalamide (2.0 g, 6.16 mmol) was reduced by addition to $LiAlH_4$ (0.47 g, 12.3 mmol) in THF (30 mL) at room temperature and then heating the resulting mixture at reflux overnight. The reaction mixture was cooled to 0 °C and carefully quenched *via* sequential addition of $H_2O$ (0.5 mL), 15% aqueous NaOH (0.5 mL) and $H_2O$ (1 mL). The mixture was stirred at room temperature for 2 h, and anhydrous $MgSO_4$ (1.0 g) was added. After filtration, the solvent was evaporated under vacuum. The residue was purified by bulb-to-bulb distillation (160–165 °C at 0.5 mmHg) to afford *N,N′*-bis(2-isopropylphenyl)ethane-1,2-diamine (**5**) as a white solid; yield: 1.0 g (55%); mp 47–48 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$ (m, 4H, ArH), 6.76 (m, 4H, ArH), 4.03 (bs, 2H, NH), 3.50 (s, 4H, $CH_2$), 2.85 (septet, $J =$ 6.9 Hz, 2H, CH), 1.22 (d, $J = 6.9$ Hz, 12H, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 144.6$, 132.8, 126.8, 125.1, 118.0, 110.8, 43.5, 27.2, 22.3; IR (KBr): $\nu = 3421.3$, 2959.5, 2867.5, 1602.3, 1582.1, 1504.7, 1449.1, 1305.6, 1256.8, 744.7 cm$^{-1}$; HR-MS (CI, $NH_3$): $m/z = 297.2368$, calcd. for $C_{20}H_{28}N_2H$ [$M^+$]: 297.2331,

### Typical Experimental Procedure

In an argon-filled glove box, $Y[N(TMS)_2]_3$ (11.4 mg, 0.02 mmol) and *N,N′*-bis(2-isopropylphenyl)ethane-1,2-diamine (**5**) (5.93 mg, 0.02 mmol) in $C_6D_6$ (0.4 mL) were introduced sequentially into a J. Young NMR tube with Teflon screw cap (purchased from Aldrich or J. Young Ltd.). The reaction mixture was stirred at 120 °C for 5 days until ligand attachment was judged to be complete by the disappearance of the $Y[N(TMS)_2]_3$ with concomitant generation of the free $(TMS)_2NH$. The appropriate aminoalkyne (0.4 mmol) and *p*-xylene (4.9 μL, 0.04 mmol) were added to the resulting complex *via* a microsyringe and the reaction mixture was subsequently heated at the corresponding temperature (25, 60, 120, or 150 °C) in an oil bath until hydroamination was judged complete by disappearance of the starting material in the $^1$H-NMR relative to the aromatic resonance of the internal standard *p*-xylene.

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[8] Treatment of **8** with catalyst **2** did not produce the desired product **15**.
[9] J. Young NMR tubes, purchased from Aldrich or J. Young Ltd, were used under refluxing conditions (bath temperature, 120 °C or 150 °C) without any special precautions.

  