Aluminum-catalyzed intramolecular hydroamination of aminoalkenes†

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A new aluminium complex bearing a dianionic phenylene-diamine based ligand has been synthesized and shown to catalyze the intramolecular hydroamination of various aminoalkenes.

The formal addition of a N-H bond across an unsaturated C-C bond, also known as hydroamination, constitutes a highly efficient synthetic pathway towards formation of amines, enamines, and imines.¹ Formation of N-heterocycles, *via* the intramolecular hydroamination of aminoalkenes, is of particular interest due to the importance of N-containing cyclic compounds in biologically relevant systems. Although the overall reaction is thermodynamically favorable, the electrostatic repulsion between the electron-rich olefin and the amine nucleophile provides kinetic stability to the aminoalkenes, rendering uncatalyzed reactions exceedingly slow. The necessity of finding efficient catalysts for this transformation has spawned extensive research efforts resulting in the discovery of catalysts including early² and late³ transition metals as well as lanthanide/actinide complexes.⁴

Recently, main group catalysts have received increased attention.⁵ Although group 13 metals such as aluminum are exceedingly inexpensive and show similarities (e.g. electronegativity, atomic radii) to early transition metals such as Zr, catalytically active systems involving these metals have remarkably little precedent.⁶ Our goal was to establish the viability of well-defined organometallic Al complexes as active catalysts towards the hydroamination of aminoalkenes.

Phenylene-diamine (pda) ligands have been used extensively in organometallic coordination chemistry and after exploring a number of other ligands, these were ultimately chosen as a support for the Al metal center.⁷ The dianionic binding motif offers extensive kinetic stability towards protonolysis of the M-N bonds, which has been proposed as a problem in other catalytic systems involving primary amines as substrates.

Compound **1** was prepared in moderate yield by treating the

Scheme 1. Synthesis of **1**.

neutral protonated ligand with commercially available [Al(NMe₂)₃]₂ (Scheme 1). Despite the dimeric nature of the metal precursor, compound **1** was isolated as a monomer, most likely due to the sterically demanding 3,5-di-*tert*-butyl substituents on the flanking aryl-groups. Unsurprisingly, one equivalent of dimethylamine remains coordinated to the metal center to complete the preferred tetrahedral coordination sphere of Al, as evidenced by well separated signals for the amide (2.76 and 41.41 ppm) and amine (1.45 and 37.81 ppm) functionalities in both the ¹H and ¹³C NMR spectra, respectively.

To corroborate the monomeric nature of **1**, single-crystal X-ray diffraction studies were conducted which revealed the Al metal center in a distorted tetrahedral configuration as shown in Figure 1. The Al1A-N1A and Al1A-N2A bond distances of 1.849(3) and 1.830(3) Å, respectively, are similar to those in the only other example of a pda-ligand coordinated to Al.⁸ The observed large bite angle of 88.7° corresponds well with short Al-N bond distances in analogous transition metal complexes involving pda-ligands.^{7b,9} As expected, the Al1A-N3A bond (1.774(3) Å) of the amide functionality is significantly shorter than the Al1A-N4A bond (1.965(3) Å) of the coordinated amine, indicating considerable multiple bond character between the metal center and N3A.

Upon heating a solution of 2,2-diphenylpent-4-ene-1-amine in the presence of **1** (10 mol%), catalytic formation of the hydroamination product 2-methyl-4,4-diphenylpyrrolidine was observed. Although catalytic activity was evident at 135 °C (in C₆D₆), heating the solution at 150 °C resulted in more reasonable reaction times (Table 1, entry 1). Control experiments revealed that the reaction rates were not influenced by the presence of one or two catalytic equivalents of a sterically hindered non-coordinating base such as 1,2,2,6,6-pentamethylpiperidine, thus ruling out the possibility of acid catalysis.¹⁰ Additionally, reactions carried out in the absence of **1** did not yield the hydroamination products even after extended reaction times (>5 days at 150 °C).

Figure 1. ORTEP representation of **1**. Thermal ellipsoids are drawn at 40% probability. Hydrogen atoms (except H4A) are omitted for clarity.

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Table 1. Catalytic Hydroamination of Aminoalkenes using **1**.

Entry ^a	Substrate	Product	Time (h)	%Conv. ^b	%Yield ^b
1			38	91	81
2			12	90	87
3			90	72	63
4			123	67	58

^aAll reactions were carried out in C₆D₆ at 150 °C and 10 mol% catalyst loading. ^bDetermined by integration of ¹H NMR reactant and product signals versus an internal standard.

Decreasing the steric bulk at the geminal position resulted in slower conversion of the aminoalkene to the corresponding hydroamination product as has been observed with other catalytic systems (Thorpe-Ingold effect).^{5b} In the case of (1-allylcyclohexyl)-methanamine (Table 1, entry 3), extended reaction times were necessary to achieve moderate yields of the hydroamination product. Similarly, formation of larger heterocycles such as 2,5,5-trimethylpiperidine required much longer reaction times to achieve reasonable conversion (Table 1, entry 4), an observation consistent with Baldwin's guidelines for ring formation.¹¹

Methyl-substitution at the internal position of the olefin moiety had a significant positive impact on the reaction rate, resulting in near quantitative conversion of 4-methyl-2,2-diphenylpent-4-en-1-amine to 2,2-dimethyl-4,4-diphenylpyrrolidine in 12 h (Table 1, entry 2). Preliminary kinetic experiments revealed the rate of hydroamination of the methyl substituted substrate ($k_{\text{obs}} = 5.0 (\pm 0.3) \times 10^{-6} \text{ mol L}^{-1} \text{ s}^{-1}$) to be significantly faster than that of its unsubstituted counterpart ($k_{\text{obs}} = 1.5 (\pm 0.1) \times 10^{-6} \text{ mol L}^{-1} \text{ s}^{-1}$). A similar effect has been observed in lanthanide catalysis and was attributed to stabilization of the transition state (upon alkyl-substitution) during the rate determining olefin insertion into the M-N bond (Structure II, Figure 2).¹²

Figure 2. Proposed catalytic cycle.

To obtain some more insight into the reaction mechanism, a stoichiometric reaction of **1** with 2,2-diphenylpent-4-ene-1-amine on an NMR scale (in C₆D₆) was conducted to determine whether the resting state of the catalyst could be observed. The aminoalkene was consumed in less than 5 minutes at room temperature (determined by ¹H NMR), accompanied by the appearance of new signals. The emergence of a significantly upfield shifted N-H resonance (-0.26 ppm) as well as the convergence of the dimethyl-amine/-amide resonances are consistent with the formation of a new Al-amide species (Structure I, Figure 2) via the loss of dimethylamine. At elevated temperatures (>135 °C), disappearance of the olefin signals was observed, accompanied by the appearance of diagnostic alkyl-resonances consistent with the formation of ring-closed pyrrolidine (Structure III, Figures 2 and S2).

In conclusion, we have demonstrated the viability of an Al-complex supported by a pda-ligand as a catalyst for the intramolecular hydroamination of aminoalkenes. Compound **1** offers a cost-effective alternative to late transition metal and lanthanide based catalysts with the added benefit of facile synthesis.

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Notes and references

The synthesis was carried out under nitrogen using standard Schlenk and vacuum line techniques.

Synthesis of **1**: A Schlenk flask was charged with *N*¹,*N*²-bis(3,5-di-*tert*-butylphenyl)benzene-1,2-diamine (400 mg, 0.825 mmol), [Al(NMe₂)₃]₂ (131 mg, 0.416 mmol), and toluene (20 mL). The clear solution was heated at 100 °C for one hour. After cooling to ambient temperature, the solvent was removed *in vacuo* to yield crude **1** as an off-white solid. The crude product was recrystallized from 20 mL of toluene/diethyl ether (1:5) as colorless crystals at -35 °C. Yield after recrystallization: 229 mg (0.382 mmol, 46%). ¹H NMR (benzene-*d*₆, 298 K): δ 7.64 (m, 2H, Ph), 7.51 (m, 4H, Ph), 7.25 (m, 2H, Ph), 6.91 (m, 2H, Ph), 2.76 (s, 6H, N(CH₃)₂), 1.45 (s, 6H, HN(CH₃)₂), 1.44 (s, 36H, C(CH₃)₃), 1.08 (bs, 1H, HN(CH₃)₂). ¹³C NMR (benzene-*d*₆, 298 K): δ 152.26 (s, Ph), 148.71 (s, Ph), 142.06 (s, Ph), 118.80 (s, Ph), 117.98 (s, Ph), 115.26 (s, Ph), 111.04 (s, Ph), 41.41 (s, N(CH₃)₂), 37.81 (s, HN(CH₃)₂), 35.44 (s, C(CH₃)₃), 32.24 (s, C(CH₃)₃). Anal. Calcd for C₃₈H₅₉N₄Al: C, 76.21; H, 9.93; N, 9.36. Found: C, 75.89; H, 10.17; N, 9.57.

Crystal data for **1** with Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$): C_{39.50}H_{62.56}AlN₄O_{0.43}, $M = 627.33$, monoclinic, $a = 26.378(5)$, $b = 25.722(5)$, $c = 28.451(5) \text{ \AA}$, $V = 17202(6) \text{ \AA}^3$, $\alpha = 90^\circ$, $\beta = 116.980(3)^\circ$, $\gamma = 90^\circ$, $T = 183(2) \text{ K}$, space group $P2_1/n$ (no. 14), $Z = 16$, $D_c = 0.969 \text{ g/cm}^3$, $\mu = 0.067 \text{ mm}^{-1}$, 152676 reflections measured, 31601 unique ($R_{\text{int}} = 0.0916$) which were used in all calculations. Final R_i values were 0.0850 ($I > 2\sigma(I)$) and 0.1690 (all data). Final $wR(F^2)$ values were 0.2335 ($I > 2\sigma(I)$) and 0.2721 (all data). Data collection was performed on a Bruker APEX-I CCD instrument. The structure was solved by direct methods and refined by full matrix least squares method, SHELXTL6.¹³ SQUEEZE was used to partially remove solvent contribution from the overall intensity data.¹⁴ Complete crystal composition: **1***0.5Et₂O. CCDC reference number 765662. Refinement parameters including discussion of disorder can be found in the ESI file.

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