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Donor ligand effects in group 3 metal-catalyzed hydroaminations

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ABSTRACT

A series of donor ligands were examined for their effect on group 3 metal-catalyzed intramolecular alkene hydroamination. The cyclization proved to be surprisingly tolerant to the presence of several coordinative functional groups suggesting more latitude with regard to reaction conditions of group 3 metal-catalyzed processes.

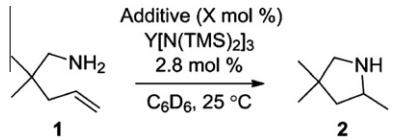
Due to their unique chemical properties, early transition metal and lanthanide catalysts possess exceptionally diverse catalytic applications.[1] The range of chemical transformations accessible to these catalysts spans the activation of inert small molecules[2] to olefin polymerization.[3] This wide spectrum of reactivity is a consequence of the unusual combination of large ion size, limited radial extension of valence orbitals, and high coordinative unsaturation of these metals. In this Letter, we present results concerning the extent to which common donor ligands affect the catalytic activity of amide complexes derived from these metals.

In order to probe additive effects on catalytic activity, we chose to apply these catalysts to a classical chemical transformation, aminoalkene hydroamination/cyclization. Hydroamination has been the focus of considerable research due to the importance of the resultant nitrogen-containing products.[4] Researchers in our group, and others, have successfully applied early transition metal catalysts to this transformation.[5]

In an initial study, a well-known intramolecular alkene hydroamination catalyzed by $Y[N(TMS)_2]_3$[6] was selected.[7] We began by examining the reaction progress of yttrium-catalyzed cyclizations in the presence of common ethereal ligands. Ethereal solvents are known to coordinate to oxophilic metal complexes and can suppress catalytic reactivity. In the present context, when used in small quantities, most ethers had a negligible effect (Table 1, entries 1–4).[8] Even the highly coordinative ether, THF, did not significantly impede the reaction progress. To determine if additional equivalents had a competitive effect, the quantity of THF was sequentially increased (entries 4–7). As anticipated, the reaction progress was slowed down somewhat in the presence of increasing quantities of THF, with the reaction time required for >95% conversion being markedly increased (2 weeks) when the cyclization was performed in neat THF. Although the aforementioned results are relevant in a preparative sense, we have observed that the overall rate of product formation is not linear, but decreases with time.[9a–g] Accordingly, selected time markers required to achieve ≈50% conversion were obtained for comparative purposes (entries 1 and 7), with the latter revealing a pronounced deceleration in neat THF.

Other donor ligands were subsequently assayed (Table 2). Among the neutral ligands, tetrahydrothiophene had no effect (entry 1) while 1-methylpyrrolidine slightly slowed the reaction progress (entry 2). Hydroamination reactions performed in the

Table 1
Additive effects of ethereal ligands



1 2

Entry	Additive	mol %	t_1[a]	t_2[b]
1	n/a	0	2.3 h	6 h
2	$(i\text{-Pr})_2O$	14	—	6 h
3	MTBE	14	—	6 h
4	THF	14	—	6 h
5	THF	28	—	8 h
6	THF	56	—	9 h
7	THF	Neat	12 h	336 h (2 weeks)

[a] Fifty percentage of conversion, monitored by ^1H NMR spectroscopy.
[b] >95% Conversion, monitored by ^1H NMR spectroscopy.

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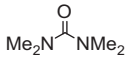
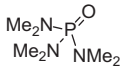
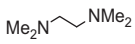
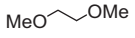
Table 2
Effect of a series of donor ligands on Y(III)-catalyzed hydroaminations

Entry	Additive[a]	t_1[b]	t_2[c]
1		—	6 h
2		—	6.5 h
3		3.5 d	19 d[d]
4		26 h	4 d[d,e]
5		—	6.5 h
6		—	7 h (no reaction[f])
7		(5.7 h[f])	7 h (24 h[f])
8	*t*BuOLi	25.3 h	4 d[e,g]
9	*t*BuONa	28.5 h	9 d[e,g]
10	$Bu_4N^+Cl^-$	24.7 h	3 d[g]

[a] 14 mol %.
[b] ⩾50% Conversion, monitored by ^{1}H NMR spectroscopy.
[c] Reactions were performed in C_6D_6 at 25 °C using $Y[N(TMS)_2]_3$ (2.8 mol %) and monitored by ^{1}H NMR spectroscopy.
[d] 2.8 mol % of additive.
[e] Double bond isomerization occurred in the presence of these additives (HMPA—<5%; *t*BuOLi—15%; *t*BuONa—21%.
[f] Reaction was performed in neat additive at 25 °C.
[g] Reaction was performed at 60 °C with only 2.8 mol % of additive.

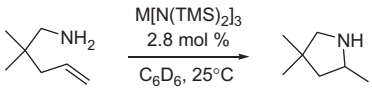
presence of 14 mol % of hexamethylphosphoramide (HMPA) completely inhibited hydroamination at 22 °C. However, in the presence of a lower concentration of HMPA, (e.g., 2.8 mol %), the reaction proceeded in 4 days at room temperature, with 50% conversion being realized after 26 h (entry 4).

Neutral, chelating donor ligands were surveyed and revealed moderate reaction inhibition. Tetramethylethylenediamine (TMEDA) slightly slowed the hydroamination as did the chelating ethers, dimethoxyethane (DME) and dioxane (entries 5–7). A comparison of the use of THF, DME, and dioxane as solvents provided an interesting set of results. When the reaction was performed in THF, hydroamination required two weeks to reach completion (Table 1, entry 6). Yet in DME the reaction failed to proceed altogether (Table 2, entry 6). Out of all the ethers, neat dioxane was the least inhibitive solvent, requiring only 5.7 h for 50% conversion with completion observed at 24 h. (Table 2, entry 7).

We subsequently probed the effects of a series of anionic donor ligands on catalysis (Table 2, entries 8–10). Due to the substantial rate of suppression resulting from the presence of these charged additives, hydroaminations were performed at 60 °C, using only 2.8 mol % additive. With lithium *tert*-butoxide the hydroamination reaction was completed in four days while the analogous sodium *tert*-butoxide reaction required nine days for completion. The coordinative behavior of chloride ions to the lanthanide species is well known,[10] and we found tetrabutylammonium chloride to be substantially inhibitive (3 days at 60 °C), with the times required for 50% conversion recorded in column 3. It is noteworthy that the presence of alkoxide additives and HMPA led to considerable amounts of double bond isomerization of **1** (21% with 2.8 mol % of *t*BuONa). However, no alkene isomerization occurred in the presence of anionic additives *or in the absence of the Y(III) catalyst*.

The comparatively mild effects of ethereal donor ligands on yttrium-catalyzed reactions motivated us to explore the effect of these additives on other group 3 metals (Nd, Lu, and Sc). The hydroamination/cyclization of **1** was initially performed in the presence of several homoleptic bis(trimethylsilyl)amides (Table 3). Of the metal complexes examined, $Nd[N(TMS)_2]_3$ and $Y[N(TMS)_2]_3$ most effectively catalyzed the reaction with overall reaction times of 4 and 6 h, respectively.[7] As expected, the reaction rate decreased as the ionic radius of the metal center decreased. Accordingly, the scandium tris(amide) was the least efficient catalyst (entry 4). In accord with the proceeding observations, the reaction progress was not linear and slowed considerably subsequent to 50% conversion.

Table 3
Additive-free hydroamination reactions[a]



1 **2**

Entry	Catalyst[b]	t_1[c]	t_2[d]
1	$Nd[N(TMS)_2]_3$	0.7 h	4 h
2	$Y[N(TMS)_2]_3$	2.3 h	6 h
3	$Lu[N(TMS)_2]_3$	30.7 h	96 h (4 d)
4	$Sc[N(TMS)_2]_3$[e]	90.1 h	360 h (15 d)

[a] Reactions were performed in C_6D_6 at 25 °C.
[b] 2.8 mol % of catalyst.
[c] ⩾50% Conversion, monitored by ^{1}H NMR spectroscopy.
[d] >95% Conversion by ^{1}H NMR spectroscopy.
[e] 5 mol % of catalyst.

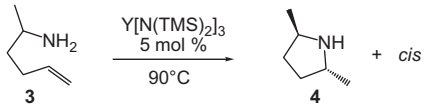
Table 4
Influence of donor ligands on Nd, Lu, and Sc metal precatalysts

Entry	Metal	Additive[a]	t_1[b]	t_2[c]
1	Nd	THF	1.0 h	6.0 h
2	Nd	DME	0.3 h	7.0 h
3	Lu	THF	25.6 h	2.6 d
4	Lu	DME	28.0 h	1.9 d
5	Sc[d]	THF	96.0 h	8.0 d
6	Sc[d]	DME	67.5 h	6.0 d

[a] 14 mol % of additive.
[b] ⩾50% Conversion, monitored by ^{1}H NMR spectroscopy.
[c] >95% Conversion by ^{1}H NMR spectroscopy.
[d] 5 mol % of catalyst.

As noted for the yttrium catalyst, small quantities of ethereal donor ligands had little influence on the reaction rate when $Nd[N(TMS)_2]_3$ was employed (Table 4). Surprisingly, for the lutetium and scandium tris(amide)s, small quantities of 1,2-DME or THF accelerated hydroamination. This beneficial effect of these ligands is possibly due to the inhibition of complex aggregation and is currently under investigation.

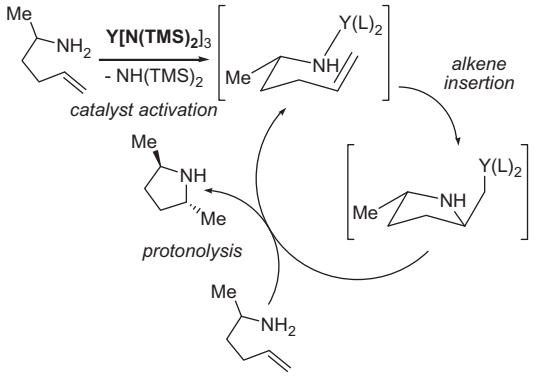
Table 5
Diastereoselectivity effects of ether ligands and alternative solvents



3 **4**

Entry	Additive	Quantity	t[a]	dr[b] (*t*/*c*)
1	None[c]	n/a	6.1 d	6:1
2	THF[c]	14 mol %	5.0 d	9:1
3	THF	Neat	8.7 d	5:1
4	Dioxane	Neat	9.8 d	6:1
5	MTBE	Neat	4.4 d	9:1
6	C_6H_5Cl	Neat	3.2 d	9:1
7	$C_6H_5(CF_3)$	Neat	2.2 d	8:1

[a] >95% Conversion by ^{1}H NMR spectroscopy.
[b] dr = diastereomeric ratio; *trans*:*cis*; determined by ^{1}H NMR spectroscopy.
[c] Reaction performed in C_6D_6.



Scheme 1. Simplified mechanism of yttrium-catalyzed intramolecular hydroamination.

In order to determine the impact of differing concentrations of THF and the influence of alternative solvents on the stereochemical aspects of this reaction, we subsequently examined the diastereoselectivity of hydroamination/cyclization of **5** in the presence of precatalyst **4** (Table 5). A small quantity of THF moderately increased *trans*/*cis* stereoselectivity with a slight increase in reaction efficiency (entry 2), while the use of either THF or 1,4-dioxane as the reaction solvent resulted in a marked suppression of the rate of hydroamination (entries 3 and 4). In this context it is noteworthy that the utilization of *t*-butyl methyl ether as the reaction solvent resulted not only in *an enhancement of rate but also diastereoselectivity* (entry 5). It is also of interest that the substitution of chlorobenzene or benzotrifluoride for C_6D_6 resulted in an appreciable improvement of the efficiency of cyclization and diastereoselectivity (entries 6 and 7).

Potent donor ligands can have a substantial effect on the progress of early transition metal-catalyzed hydroaminations. Since Lewis basic compounds are known to coordinate to group 3 metal complexes, the observed rate suppressions likely arise from additive-substrate competition during alkene insertion (Scheme 1).[11] The concomitant increase in diastereoselectivity is consistent with donor ligand coordination during the stereochemistry-determining insertion step, thereby enhancing the steric environment of the metal center.

In conclusion, the results presented here suggest considerable latitude with regard to the reaction conditions available for group 3 metal catalyzed processes. Significantly, in some instances small amounts of donor ligands (i.e., 1,2-DME, THF) accelerate hydroamination/cyclization (Table 4, Lu and Sc) and can also lead to an increase in diastereoselectivity (Table 5, entry 2). It is also of considerable interest that the use of alternative solvents (Table 5, entries 5–7) can result in synthetically beneficial enhancements in both the reaction rate and stereoselectivity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.019.

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