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Comparison of yttrium binaphthylamido alkyl and amide complexes for enantioselective intramolecular hydroamination

Isabelle Aillaud [a], Jacqueline Collin [a,b,*], Jérôme Hannedouche [a,b], Emmanuelle Schulz [a,b], Alexander Trifonov [c]

[a] Univ Paris-Sud, Laboratoire de Catalyse Moléculaire, ICMMO, UMR 8182, Orsay F-91405, France
[b] CNRS, Orsay F-91405, France
[c] G.A. Razuvaev Institute of Organometallic Chemistry of Russian Academy of Sciences, Tropinina 49, 603950 Nizhny Novgorod GSP-445, Russia

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ABSTRACT

A chiral trisamido yttrium complex Y[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$][N*i*Pr$_2$][THF]$_2$·LiCl coordinated by *N*-cyclopentyl binaphthylamine ligand has been prepared in situ and characterised by NMR spectroscopy. It has been revealed as an efficient catalyst for intramolecular hydroamination of aminoolefins. Comparison with neutral alkyl, ate alkyl or ate tetraamido complexes coordinated by the same ligand indicated that this complex was the most efficient catalyst of the series for its both activity and enantioselectivity values.

1. Introduction

Chiral nitrogen-containing molecules represent an important class of biologically active compounds. Catalytic asymmetric intramolecular hydroamination of aminoolefins, an atom-economical process which formally consists in the addition of an –NH unit on a non-activated carbon–carbon double-bond, is one of the most elegant procedures for the synthesis of nitrogen heterocycles.[1] In the first example of asymmetric cyclisation of aminoolefins, Marks and co-workers reported the use of chiral lanthanocenes for the preparation of several pyrrolidines with up to 74% ee.[2] Since the publication by Livinghouse of intramolecular hydroamination catalysed by rare-earth trisamides {Ln[N(SiMe$_3$)$_2$]$_3$},[3] chiral catalysts coordinated by a large variety of ligands such as binaphtholates,[4] aminobisphenolates,[5] aminobisthiolates,[6] bisoxazolinato[7] and bis-binaphthylamido[8] have been studied. Despite the increased number of catalysts, based on rare earth or more recently on lithium[9] or on group IV metals,[10] until now they have been used almost for the cyclisation of simple substrates only. Since only a few catalytic systems promoted this transformation with more than 90% ee the development of more active and enantioselective catalysts remains a challenging task. Research in our group has been focused on the study of chiral rare-earth hydroamination catalysts based on binaphthylamido ligands.[11–13] After studying a family of tetraalkyl amido ate complexes {Li(THF)$_4$}{Ln[(*R*)-$C_{20}H_{12}(NR)_2$]$_2$} we next found more active neutral [(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]LnCH$_2$SiMe$_3$(DME) and ate [(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]Ln[(μ-Me)$_2$Li(THF)$_2$(μ-Me)Li(THF)] alkyl complexes. We now aim to report the preparation of a neutral trisamido yttrium complex based on binaphthylamido ligand and the comparison of its activity in enantioselective intramolecular hydroamination of aminoalkenes with that of alkyl and amido ate and in neutral complexes coordinated with the same ligand.

We have previously synthesised a new family of rare-earth ate complexes {Li(THF)$_4$}{Ln[(*R*)-$C_{20}H_{12}(NR)_2$]$_2$} (**1**, Fig. 1) derived from various chiral disubstituted (*R*)-binaphthylamido ligands that proved to be efficient catalysts for the enantioselective intramolecular hydroamination of aminoolefins.[11] A large screening of alkyl substituents R and rare-earth atoms allowed us to prepare a spiropyrrolidine with up to 87% ee at room temperature in 20 h using {Li(THF)$_4$}{Yb[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]$_2$} as the catalyst. We also described the synthesis of neutral amido catalyst **2a** consisting in a unique *N*-isopropyl-bis-binaphthylamido ligand and a diisopropylamido moiety.[12] Higher enantiomeric excesses and/or higher rates of reaction were generally observed with **2a** than with chiral ate analogue **1a** for the formation of various pyrrolidines. With the aim of increasing both activity and enantioselectivity we recently reported the preparation and characterisation of new chiral binaphthylamido alkyl ate {[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]Ln[(μ-Me)$_2$Li(THF)$_2$(μ-Me)Li(THF)]} **3** and neutral {[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]LnCH$_2$SiMe$_3$(THF)$_2$} **4** yttrium

* Corresponding author. Tel.: +33 1 69154740.
E-mail address: jacqueline.collin@u-psud.fr (J. Collin).

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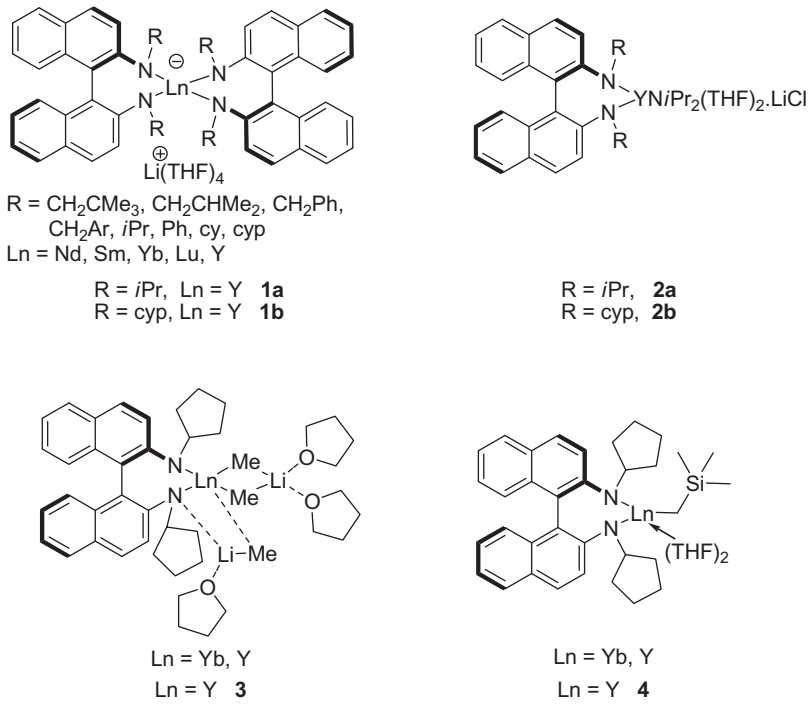
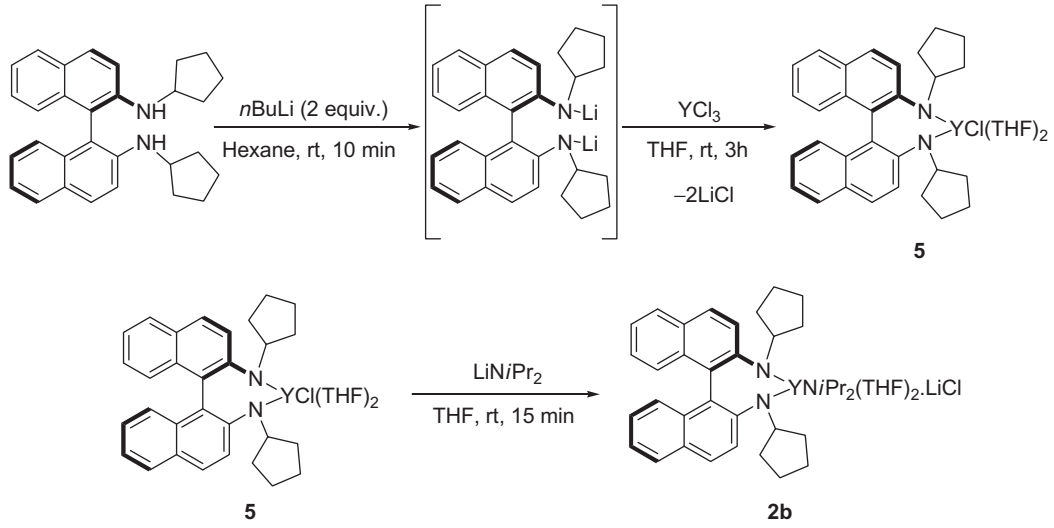


Figure 1. Structure of studied catalysts.

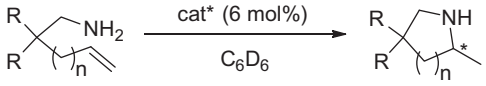


Scheme 1. Synthesis of yttrium amido complex {Y[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$][N*i*Pr$_2$][THF]$_2$[LiCl]} **2b**.

and ytterbium complexes, containing a unique *N*-cyclopentyl-bis-binaphthylamido ligand (Fig. 1).[13] Yttrium alkyl ate **3** and neutral **4** complexes turned out to be by far more active for this transformation than the yttrium ate tetraamido catalyst **1b** coordinated by the same *N*-cyclopentyl-bis-binaphthylamido ligand previously described. We thus focused on the preparation and the evaluation as hydroamination catalyst of an yttrium neutral trisamido complex **2b**, bearing the same *N*-cyclopentyl-binaphthylamido ligand for a comparison with neutral alkyl and amido yttrium catalysts in terms of activity and enantioselectivity.

Complex **2b** was prepared from an (*R*)-*N*,*N*′-dicyclopentyl-1,1′-binaphthyl-2,2′-diamido ligand, in three steps involving the formation of the chiral diamido yttrium chloride complex **5** (Scheme 1). The first step consisted in the formation of the bis lithium salt {Li$_2$[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]} using *n*BuLi at room temperature in hexane. The solvent was quickly removed in vacuo and the crude dilithium salt was used immediately after its preparation without further purification. Intermediate {Y[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]Cl(THF)$_2$} **5** was obtained by the salt metathesis reaction of anhydrous YCl_3 and 1 equiv of {Li$_2$[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$]}, in THF at room temperature. Complex **5** was purified after the evaporation of THF by extraction of the solid residue with toluene and subsequent recrystallisation from THF/hexane mixtures and characterised by ^{1}H and ^{13}C NMRs. The spectra showed the expected sets of resonances corresponding to the (*R*)-*N*,*N*′-dicyclopentyl-1,1′-binaphthyl-2,2′-diamido ligand and the coordinated THF molecules, similar to that obtained for the complex {Y[(*R*)-$C_{20}H_{12}$(N*i*Pr)$_2$]Cl(THF)$_2$} previ-

Table 1
Asymmetric intramolecular hydroamination catalysed by yttrium amido complexes



6a R,R = -$(CH_2)_5$-, n = 1 **7a**
6b R,R = Ph, n = 1 **7b**
6c R,R = -$(CH_2)_5$-, n = 2 **7c**

Entry	Substrate	Catalyst	Time (h)	Temperature (°C)	Conversion[a] (%)	ee[b] (%)
1	**6a**	**2b**	1.2	25	95	81
2		**2a**	4[c]	25	100	68[e]
3		**1b**	15	25	93	81[f]
4		**3**	2.3	25	90	75[g]
5		**4**	3.3	25	89	75[g]
6	**6b**	**2b**	1	25	92	72
7		**2a**	12	25	100	65[e]
8		**1b**	5	25	100	75[f]
9		**3**	1.9	25	100	72[g]
10		**4**	2.3	25	100	66[g]
11	**6c**	**2b**	19	60	100	34
12		**2a**	8[d]	60	100	18[e]
13		**1b**	24	60	100	41[f]
14		**3**	120	25	87	33[g]
15		**4**	27	60	100	25[g]

[a] Conversion was measured by ^{1}H NMR.
[b] ee was determined by GC analysis following derivatisation of the product with (*S*)-Mosher's acid chloride for products **7a** and **7b**, or by HPLC analysis of the product following derivatisation with 2-naphtoyl chloride for product **7c.**
[c] 4 mol % cat. ratio.
[d] 14 mol % cat. ratio.
[e] Ref. 12.
[f] Ref. 11d.
[g] Ref. 13.

ously described.[12] It should be noted that no trace of free ligand or ate complex {[Li(THF)$_4$]-[Y((*R*)-$C_{20}H_{12}(NC_5H_9)_2)_2$]} **1b** was observed in the NMR spectra.[11d] Complex **2b** was synthesised by a second metathesis reaction, from complex **5** and 1 equiv of Li*N*iPr_2 in THF at room temperature. After the evaporation of THF, ^{1}H NMR of the crude product revealed the presence of the diisopropylamido moiety coordinated to yttrium indicating the expected structure {Y[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$][*N*iPr_2][THF]$_2$[LiCl]}.[14] It is noticeable for this last step that it is required to use recrystallised complex **5** to get yttrium neutral amido complex **2b** in good yield and purity.

As products of ligand-redistribution reactions were observed when the analogous {Y[(*R*)-$C_{20}H_{12}(NiPr_2)_2$][*N*iPr_2][THF]$_2$[LiCl]} **2a** was extracted with toluene and recrystallised from THF/hexane mixture,[12] the new complex {Y[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$][*N*iPr_2][THF]$_2$[LiCl]} **2b** was not purified but used in situ immediately after its preparation and the evaporation of THF. In this case, crude complex {Y[(*R*)-$C_{20}H_{12}(NC_5H_9)_2$][*N*iPr_2][THF]$_2$[LiCl]} **2b** proved to be an efficient catalyst for the hydroamination/cyclisation of two aminopentenes and an aminohexene derivative (Table 1).

We first investigated the cyclisation of *C*-(1-allylcyclohexyl)-methyl amine **6a**. The corresponding spiropyrrolidine **7a** was obtained only after 1.2 h at room temperature and with 81% ee (Table 1, entry 1) using the new yttrium trisamido catalyst **2b**. The latter promoted this transformation in a shorter time and with higher enantioselectivity than the *N*,*N*′-diisopropyl-binaphthyl trisamido complex **2a** (68% ee in 4 h at 25 °C, entry 2). Similar differences in terms of enantioselectivity and activity for catalysts which differ only in N-substituents have already been observed with the ate tetraamido complexes series previously described, due to steric effects.[11,12] Moreover, catalyst **2b** proved to be more than 10 times active than the corresponding yttrium ate tetraamido complex **1b** to promote the intramolecular hydroamination of aminopentene **6a**. Catalyst **1b** afforded the spiropyrrolidine **7a** in 15 h at room temperature with an almost complete conversion and the same enantiomeric excess (entry 3). Gratifyingly, new yttrium trisamido catalyst **2b** appeared to be more reactive than yttrium alkyl ate **3** and neutral **4** complexes, which were up to now our most active well-defined complexes for the cyclisation of compound **6a**.[15,16] Using these catalysts, the spiropyrrolidine **7a** was obtained, respectively, in 2.3 h and 3.3 h with different values of enantiomeric excesses slightly lower (75% ee, entries 4 and 5). Similar trends were observed for the cyclisation of *gem*-diphenylaminopentene **6b**. The formation of *gem*-diphenylpyrrolidine **7b** was performed in an hour at room temperature and the cyclised product was obtained with 72% ee in the presence of catalyst **2b** (entry 6). Complex **2b** was thus the most active yttrium amido catalyst of our series for the preparation of those pyrrolidines (entries 6–10). For the cyclisation of the more challenging and demanding substrate **6c** the new complex **2b** was more active than complexes **1b** and **4** and that was the best compromise in terms of activity and enantioselectivity. (entries 11–15). Spiropiperidine **7c** was indeed obtained after 19 h at 60 °C with 34% ee using catalyst **2b** (entry 11). It is worth noting that in this case, the ate complex **1b** showed a slightly enhanced enantioselectivity (entry 13).

The new chiral yttrium trisamido complex **2b** afforded the hydroamination/cyclisation of several aminoolefins with the same level of enantioselectivity than yttrium ate tetraamido catalyst **1b** bearing the same N-substituents, but with a sharp increase in activity. Complex **2b** proved to be even more active than yttrium alkyl ate **3** and neutral **4** catalysts recently described. These differences both in terms of activity and enantioselectivity suggest that different active species are involved in this transformation, according to the complex used. If we assume for the neutral amido or alkyl precatalysts **2** and **4** a mechanism for the formation of the active species similar to that proposed by Marks,[17] the coordina-

tion of diisopropyl amine (arising from the protonolysis of the amido moiety by the substrate) to yttrium may not obviously explain the difference in reactivity between amido and alkyl complexes.[18] The second major difference between precatalysts **2** and **4** is the presence in the former of 1 equiv of LiCl.[19] Preliminary experiments emphasise the role of LiCl on the outcome of the reaction.[20] Although deeper investigations are definitely required to determine the exact role of LiCl on the structure and reactivity of precatalysts **2**, we might speculate coordination of the alkali-metal halide to the $\{Y[(R)\text{-}C_{20}H_{12}(NR)_2\ (R = C_5H_9,\ iPr_2)][NiPr_2]\}$ fragment of **2** during the second metathesis reaction (in a coordinating solvent) to afford a $(THF)_2$LiCl-adduct.[21,22] This difference in the precatalyst structure may account for the disparity in reactivity between **2** and **4**. Studies are ongoing to get the insights into the structure of these complexes for a better catalyst design.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.023.

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14. The ^{1}H NMR experiment did not allow to determine whether the THF molecules are coordinated to yttrium or lithium.
15. Spiropyrrolidine **7a** was obtained after 1 h at room temperature with 90% conv. and 71% ee using an yttrium precatalyst synthesised in situ in C_6D_6 from *n*BuLi, $YCl_3(THF)_{3.5}$ and the same ligand (see Ref. 16).
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18. As suggested by a referee, the catalytic amount of sterically bulky diisopropylamine ligand should be a much weaker ligand than the substrate (bearing a primary amine) or the cyclised product (bearing a secondary amine).
19. The authors would like to thank a referee for pointing out that complex **2b** is not a LiCl-free complex.
20. Indeed, the hydroamination reaction of **6a** and **6b** catalysed by a complex generated in situ by room-temperature combination of an alkali metal-free yttrium precurseur $Y(CH_2SiMe_3)_3(THF)_2$, (*R*)-*N*,*N*′-dicyclopentyl-1,1′-binaphthyl-2,2′-diamido ligand and diisopropylamine gives, respectively, the cyclised product **7a** and **7b** with low enantiomeric excess values. Addition of LiCl/THF during the preparative phase of the catalyst restores the enantiomeric excess values reported with complex **2b**.
21. For examples of salt coordination during the synthesis of rare-earth complexes: Colin, J.; van Mechelen, J. B. *Organometallics* **1991**, *10*, 1704–1709; Westerhausen, M.; Hartmann, M.; Pfitzner, A.; Schwarz, W. Z. *Anorg. Allg. Chem.* **1995**, *621*, 837–850.
22. As attempts to purify and recrystallise complex **2a** were unsuccessful (see Ref. 12), no efforts were engaged to obtain an alkali metal-free complex **2b**.