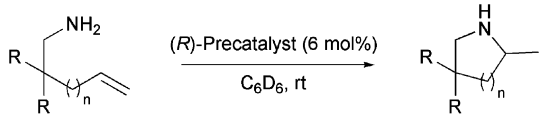
Convenient method for the rapid generation of highly active and enantioselective yttrium catalysts for asymmetric hydroamination†

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

Received (in Cambridge, UK) 19th March 2008, Accepted 22nd April 2008
First published as an Advance Article on the web 2nd June 2008
DOI: 10.1039/b804745f

A facile method for the preparation of highly active and enantioselective yttrium precatalysts for asymmetric hydroamination of *gem*-disubstituted aminoalkenes, from the combination of YCl_3 or $YCl_3(THF)_{3.5}$ with ligand (*R*)-L_1 and *n*-BuLi is described.

Asymmetric catalytic hydroamination of alkenes has recently emerged as potentially a powerful atom-economic tool for the stereoselective generation of C–N bond found in numerous chiral key building blocks and pharmaceutically active compounds.[1] Despite time and efforts dedicated to the development of efficient chiral catalysts over the last decade, there is to date, no "universal" chiral catalyst able to promote this transformation inter- and intramolecularly and in a highly enantioselective manner. Chiral late transition metal catalysts are by far the most suitable to promote the enantioselective intermolecular addition of amines to alkenes and excellent results were achieved for the addition of aromatic amines to vinylarenes, diene or norbornene.[2,3] Chiral group IV[4] and rare-earth metal complexes[5–7] afford the most active catalysts for the asymmetric intramolecular hydroamination[8] (AIH) of primary/secondary amines[9] and so have attracted the attention of a large scientific community. However despite intensive research in this field, only a few catalytic systems accomplish the hydroamination/cyclisation process with enantioselectivity >90% and in only a few cases.[4b,c,5k,8b] Furthermore, these systems involve either the use of homoleptic tris(organo or amido) rare-earth complexes in conjunction with sophisticated chiral ligands and thus require additional synthetic steps, or need harsh reaction conditions to afford an acceptable rate.



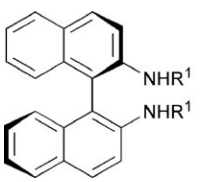
1a-d **2a-d**

We are interested in developing a convenient route to access efficient rare-earth catalysts for AIH that overcomes these constraints and does not involve prior metathetical synthesis of homoleptic lanthanide precursors in an independent step. Herein we disclose our current studies toward this goal and report the first example of *in situ* generated active and enantioselective yttrium catalyst from commercially available anhydrous YCl_3[10] for AIH of unactivated olefins.

Recently we described a new family of easily prepared lanthanide ate complexes from $LnCl_3$ and chiral (*R*)-1,1′-binaphthyl-2,2′-diamine (BINAM) ligand derivatives as novel catalysts for AIH reaction. These ate complexes were synthesised by the combination of 2 equiv. of dilithium salt of the corresponding ligand with 1 equiv. of $LnCl_3$.[6] Despite enantioselectivities up to 87%, moderate activities were observed for the catalysed intramolecular cyclisation of *gem*-disubstituted aminoalkenes.[6d]

As part of these ongoing studies to the development of efficient chiral catalysts for AIH, we further prepared a neutral heteroleptic tris(amido)yttrium complex bearing a chiral biaryl-based diamido ligand derived from (*R*)-$\mathbf{L_3}$ (Fig. 1) and a diisopropylamido entity.[7] This neutral complex was synthesised *via* a stepwise procedure involving 2 consecutive salt metathesis reactions of YCl_3 with respectively the dilithium salt of (*R*)-$\mathbf{L_3}$ and Li*N*iPr_2. Although this neutral complex afforded a better activity for AIH than our previous reported ate complexes,[6] this sequential approach suffered from practicability issues and turned out to be highly sensitive to the nature of the R^1 substituent of the ligand (Fig. 1).[7,11] On a course to find an alternative strategy to this two-step process, we wondered if chiral active (pre)catalysts for AIH might be generated directly from the reaction of anhydrous $LnCl_3$ with chiral BINAM-based ligand and *n*-BuLi in a single one-pot procedure and additionally reducing the number of preparative steps.[12]

To initially probe the feasibility of such approach, a preliminary experiment was performed on the model substrate **1a** (n = 1, R, R = $-(CH_2)_5-$). To our delight, in the presence of 6 mol% of precatalyst prepared from (*R*)-$\mathbf{L_1}$,[13] YCl_3,[14] and *n*-BuLi in a molar ratio of 1 : 1 : 3, the reaction of **1a** was almost complete (91% conv.) in 5 h at r.t. affording regioselectively the cyclised product **2a** in 75% enantiomeric excess (e.e.) (Table 1, entry 1).



(*R*)-$\mathbf{L_1}$ R^1 = Cyp
(*R*)-$\mathbf{L_2}$ R^1 = Cy
(*R*)-$\mathbf{L_3}$ R^1 = *i*Pr

Fig. 1 Chiral (*R*)-*N*-substituted binaphthyldiamine ligands. (Cyp = cyclopentyl).

[a] *Equipe de Catalyse Moléculaire, ICMMO, UMR CNRS 8182, Université Paris Sud 11, Bat 420, 91405 Orsay Cedex, France. E-mail: jacollin@icmo.u-psud.fr; jerome.hannedouche@icmo.u-psud.fr; Fax: 33(0)169154680; Tel: 33(0)169154740*
[b] *G. A. Razuvaev Institute of Organometallic Chemistry of Russian Academy of Sciences, Tropinia 49, 603600 Nizhny Novgorod GSP-445, Russia*

† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b804745f

Table 1 Precatalyst stoichiometry (**L** : Ln : *n*-BuLi) effect on the asymmetric hydroamination reaction of **1a** (n = 1, R, R = –$(CH_2)_5$–)[a]

Entry	Precatalyst[b]	**L** : Ln : *n*-BuLi	*t*/h	Conv.[c] (%)	e.e.[d] (%)
1	(*R*)-**L$_1$**/YCl_3/*n*-BuLi	1 : 1 : 3	5	91	75
2	(*R*)-**L$_1$**/YCl_3/*n*-BuLi	1 : 1 : 4	2	94	75
3	(*R*)-**L$_1$**/*n*-BuLi	1 : 0 : 4	24	0	—
4	YCl_3/*n*-BuLi	0 : 1 : 4	24	57	—
5	*n*BuLi	0 : 0 : 4	24	0	—
6	(*R*)-**L$_1$**/YCl_3/*n*-BuLi	1 : 1 : 2	24	99	60
7	(*R*)-**L$_1$**/YCl_3/*n*-BuLi	1 : 0.5 : 2	5	94	75
8	(*R*)-**L$_2$**/YCl_3/*n*-BuLi	1 : 1 : 4	5	92	63
9	(*R*)-**L$_3$**/YCl_3/*n*-BuLi	1 : 1 : 4	3.5	96	67

[a] Reactions were carried out in solution (c = 0.33 M) in C_6D_6 at r.t. with 6 mol% of precatalyst. [b] Precatalyst preparation was performed by dropwise addition of a hexanes solution of *n*-BuLi to a suspension of YCl_3 and (*R*)-**L** in THF (c = 0.03 M) at r.t., stirring for 10 min and concentration *in vacuo*, unless otherwise stated. [c] Measured by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis of the product following derivatisation with 2-naphthoyl chloride.

The precatalyst was prepared in a 10 min reaction after dropwise addition of a hexanes solution of *n*-BuLi to a suspension of YCl_3 and (*R*)-**L$_1$** in THF at ambient temperature and concentration *in vacuo*. Increasing the amount of *n*-BuLi to 4 equiv. (relative to YCl_3 and (*R*)-**L$_1$**) had a significant and beneficial effect on the reactivity of the AIH reaction of **1a**, while maintaining the same level of enantioselectivity (Table 1, entry 2). Control experiments emphasised that the chiral ligand, YCl_3 and *n*-BuLi were essential in the preparative stage of the catalyst to achieve high activity and enantioselectivity in this transformation (Table 1, entries 3–5).[8,15]

A short tuning of the molar ratio of the (*R*)-**L$_1$**/YCl_3/*n*-BuLi precatalyst was then surveyed on our model reaction.† No improvement in terms of activity and asymmetric induction was observed by increasing or decreasing the relative stoichiometry of each component of the precatalyst system (entries 6, 7 and ESI†).[16] Consequently, the 1 : 1 : 4 (*R*)-**L$_1$**/YCl_3/*n*-BuLi precatalyst system was set as the standard condition.

Regardless of a slight decrease in enantioselectivity, it is worth noting that the precatalyst prepared from (*R*)-**L$_1$**, YCl_3 and *n*-BuLi in a ratio 1 : 0.5 : 2 (entry 7) using this one-pot procedure has a superior activity to the one synthesised by metathesis reaction of YCl_3 (0.5 equiv.) with the dilithium salt of (*R*)-**L$_1$** (1 equiv.) that we previously reported.[17] With this observation in hand, the method of preparation of the standard precatalyst system was investigated. However, varying the amount of THF during the preparative phase of the precatalyst or changing the order of addition of the reagents had hardly any influence on the reactivity and enantiocontrol of the hydroamination/cyclisation of **1a**.†[18] We subsequently varied the R^1 substituent of the chiral BINAM ligand skeleton. Despite good conversions and moderate e.e. values, we observed no improvement on the reaction efficiency of the model substrate by the use of (*R*)-**L$_2$** or (*R*)-**L$_3$** ligands (Fig. 1) instead of (*R*)-**L$_1$** in the standard condition (entries 8, 9 *vs.* 2).

We were next pleased to find that the 1 : 1 : 4 (*R*)-**L$_1$**/YCl_3/*n*-BuLi precatalyst system was also efficient for the catalysed intramolecular cyclisation of other *gem*-disubstituted aminoalkenes (Table 2, entries 1–5). In fact, this system promoted the cyclisation of **1b** and **1c** into, respectively the corresponding pyrrolidine **2b** and **2c** without loss of efficiency and enantiocontrol (entries 3, 4).[6d] A more pronounced Thorpe–Ingold effect for geminal diphenyl substitution compared to dimethyl might explain the relative variation in reaction rate (entry 3 *vs.* 4). As previously observed,[6d,7] higher reaction time was needed for the formation of six-membered ring compound **2d** and with lower enantioselectivity (entry 5). The precatalyst loading could also be reduced to 3 mol% for the cyclisation of **1a** with no deterioration of conversion and e.e. value (entry 2). Under these conditions, cyclised product **2a** was isolated in 72% yield and with 73% e.e.

To gain preliminary insight into the structure of the precatalyst complex, ^{1}H NMR spectroscopy was performed on the *in situ* generated yttrium complex. This experiment revealed a set of signals in the upfield region between δ −0.07 and −0.95 ppm (in C_6D_6) characteristic of methylene protons bound to yttrium metal that disappeared in the presence of substrate.[19,20] Although deeper investigations are needed to determine the exact structure of the precatalyst, we might speculate the formation of a (diamido)alkyl yttrium ate complex under the standard condition of catalyst preparation.

Table 2 Asymmetric hydroamination of *gem*-disubstituted aminoalkenes **1a–d** catalysed by 1 : 1 : 4 (*R*)-**L$_1$**/YCl_3/*n*-BuLi or (*R*)-**L$_1$**/$YCl_3(THF)_{3.5}$/*n*-BuLi precatalyst system[a]

Entry	Method[b]	Substrate	R, R	*n*	Product	*t*/h	Conv.[c] (%)	e.e.[d] (%)
1	**A**	**1a**	–$(CH_2)_5$–	1	**2a**	2	94	75
2[e]		**1a**	–$(CH_2)_5$–	1	**2a**	3	92(72[f])	73
3		**1b**	Me, Me	1	**2b**	24	83	76
4		**1c**	Ph, Ph	1	**2c**	0.75	>95	75
5		**1d**	–$(CH_2)_5$–	2	**2d**	139	84	36
6[g]	**B**	**1a**	–$(CH_2)_5$–	1	**2a**	17	95	65
7		**1a**	–$(CH_2)_5$–	1	**2a**	1	90	71
8		**1b**	Me, Me	1	**2b**	23[h]	85	76
9		**1c**	Ph, Ph	1	**2c**	0.6	90	77
10		**1d**	–$(CH_2)_5$–	2	**2d**	96	95	38

[a] Reactions were carried out in solution (c = 0.33 M) in C_6D_6 at r.t with 6 mol% of precatalyst. [b] Preparation of the precatalyst: method **A**: ((*R*)-**L$_1$**/YCl_3/*n*-BuLi) (1 : 1 : 4) in THF, stirring for 10 min and concentration *in vacuo*); method **B**: ((*R*)-**L$_1$**/$YCl_3(THF)_{3.5}$/*n*-BuLi) (1 : 1 : 4) stirring for 10 min in C_6D_6. [c] Measured by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis of the product following derivatisation with 2-naphthoyl chloride. [e] 3 mol% of precatalyst. [f] Isolated yield. [g] YCl_3 is used instead of $YCl_3(THF)_{3.5}$. [h] Unoptimised reaction time.

To circumvent the need to remove the THF solvent during the phase of catalyst preparation and so improving the synthetic usefulness of this methodology, the AIH reaction of **1a** was tested in the presence of 6 mol% of precatalyst generated *in situ* in d^6-benzene from (*R*)-$\mathbf{L_1}$, YCl_3 and *n*-BuLi (Table 2, entry 6). As expected, the activity of the (pre)catalyst was diminished by contrast to that prepared in THF (entry 1 *vs*. 6). To restore the high activity previously observed, we turned our attention to the use of easily accessible $YCl_3(THF)_{3.5}$ as a substitute to anhydrous YCl_3.[21] Gratifyingly, intramolecular cyclisation of **1a** catalysed by yttrium complex (6 mol%) generated *in situ* from the 1 : 1 : 4 molar ratio combination of (*R*)-$\mathbf{L_1}$, $YCl_3(THF)_{3.5}$ and *n*-BuLi in d^6-benzene attained 90% conversion in 1 h giving pyrrolidine **2a** as sole product (entry 7). Enhanced activity was also noted for the hydroamination/cyclisation reaction of other substrates **1b–d** catalysed by the *in situ* generated precatalyst (method B) compared to that prepared in THF (method A) (entries 8–10). To our delight, no noticeable loss in asymmetric induction was observed with this *in situ* methodology.

In conclusion, we have developed a new strategy for the rapid preparation of efficient chiral yttrium precatalysts for asymmetric intramolecular hydroamination. This approach that relies on the combination of an yttrium chloride precursor, a chiral diamine ligand and *n*-BuLi in a "single pot", avoids the requirement of prior synthesis of homoleptic tris(organo or amido) rare-earth complexes. To our knowledge, this is the first example of the use of such a strategy to easily access rare-earth (pre)catalysts for asymmetric hydroamination. Studies are currently underway to define the structure and scope of the precatalyst formed under these conditions, and results will be reported in due course.

We are grateful to the CNRS for financial support and the Conseil Général de L'Essonne for a PhD grant for I. A. We are indebted to Ms Emilie Kolodziej for her HPLC technical assistance.

Notes and references

1. (*a*) I. Aillaud, J. Collin, J. Hannedouche and E. Schulz, *Dalton Trans*., 2007, 5105; (*b*) K. C. Hultzsch, *Adv. Synth. Catal*., 2005, **347**, 367; (*c*) S. Hong and T. J. Marks, *Acc. Chem. Res*., 2004, **37**, 673.
2. (*a*) R. Dorta, P. Egli, F. Zürcher and A. Togni, *J. Am. Chem. Soc*., 1997, **110**, 10857; (*b*) M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc*., 2000, **122**, 9546; (*c*) O. Löber, M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc*., 2001, **123**, 4366; (*d*) K. Li, P. N. Horton, M. B. Hursthouse and K. K. (M.) Hii, *J. Organomet. Chem*., 2003, **665**, 250; (*e*) A. Hu, M. Ogasawara, T. Sakamoto, A. Okada, K. Nakajima, T. Takahashi and W. Lin, *Adv. Synth. Catal*., 2006, **348**, 2051.
3. Other examples of chiral late transition metal-catalysed asymmetric hydroamination: (*a*) L. M. Lutete, I. Kadota and Y. Yamamoto, *J. Am. Chem. Soc*., 2004, **126**, 1622; (*b*) R. L. Lalonde, B. D. Sherry, E. J. Kang and F. D. Toste, *J. Am. Chem. Soc*., 2007, **129**, 2452; (*c*) Z. Zhang, C. F. Bender and R. A. Widenhoefer, *Org. Lett*., 2007, **9**, 2887; (*d*) Z. Zhang, C. F. Bender and R. A. Widenhoefer, *J. Am. Chem. Soc*., 2007, **129**, 14148.
4. (*a*) P. D. Knight, I. Munslow, P. N. O'Shaughnessy and P. Scott, *Chem. Commun*., 2004, 894; (*b*) A. L. Gott, A. J. Clarke, G. J. Clarkson and P. Scott, *Organometallics*, 2007, **26**, 1729; (*c*) M. C. Wood, D. C. Leitch, C. S. Yeung, J. A. Kozak and L. L. Schafer, *Angew. Chem., Int. Ed*., 2007, **46**, 354; (*d*) D. A. Watson, M. Chiu and R. G. Bergman, *Organometallics*, 2006, **25**, 4731.
5. (*a*) M. A. Giardello, V. P. Conticello, L. Brard, M. Sabat, A. L. Rheingold, A. L. Stern and T. J. Marks, *J. Am. Chem. Soc*., 1994, **116**, 10212; (*b*) M. R. Douglass, M. Ogasawara, S. Hong, M. V. Metz and T. J. Marks, *Organometallics*, 2002, **21**, 283; (*c*) S. Hong, S. Tian, M. V. Metz and T. J. Marks, *J. Am. Chem. Soc*., 2003, **125**, 14768; (*d*) J.-S. Ryu, T. J. Marks and F. E. McDonald, *J. Org. Chem*., 2004, **69**, 1038; (*e*) P. N. O'Shaughnessy, P. D. Knight, C. Morton, K. M. Gillespie and P. Scott, *Chem. Commun*., 2003, 1770; (*f*) P. N. O'Shaughnessy, K. M. Gillespie, P. D. Knight, I. J. Munslow and P. Scott, *Dalton Trans*., 2004, 2251; (*g*) J. Y. Kim and T. Livinghouse, *Org. Lett*., 2005, **7**, 1737; (*h*) H. Kim, Y. K. Kim, J. H. Shim, M. Kim, M. Han, T. Livinghouse and P. H. Lee, *Adv. Synth. Catal*., 2006, **348**, 2609; (*i*) N. Meyer, A. Zulys and P. W. Roesky, *Organometallics*, 2006, **25**, 4179; (*j*) K. C. Hultzsch, D. V. Gribkov and F. Hampel, *J. Organomet. Chem*., 2005, **690**, 4441; (*k*) D. V. Gribkov, K. C. Hultzsch and F. Hampel, *J. Am. Chem. Soc*., 2006, **128**, 3748.
6. (*a*) J. Collin, J.-C. Daran, E. Schulz and A. Trifonov, *Chem. Commun*., 2003, 3048; (*b*) J. Collin, J.-C. Daran, O. Jacquet, E. Schulz and A. Trifonov, *Chem. Eur. J*., 2005, **11**, 3455; (*c*) D. Riegert, J. Collin, A. Meddour, E. Schulz and A. Trifonov, *J. Org. Chem*., 2006, **71**, 2514; (*d*) I. Aillaud, J. Collin, C. Duhayon, R. Guillot, D. Lyubov, E. Schulz and A. Trifonov, *Chem. Eur. J*., 2008, **14**, 2189; (*e*) I. Aillaud, K. Wright, J. Collin, E. Schulz and J.-P. Mazaleyrat, *Tetrahedron: Asymmetry*, 2008, **19**, 82.
7. D. Riegert, J. Collin, J.-C. Daran, T. Fillebeen, E. Schulz, D. Lyubov, G. Fukin and A. Trifonov, *Eur. J. Inorg. Chem*., 2007, 1159.
8. Lithium metal-based catalysts for asymmetric intramolecular hydroamination of alkenes were also reported: (*a*) P. Horrillo Martinez, K. C. Hultzsch and F. Hampel, *Chem. Commun*., 2006, 2221; (*b*) T. Ogata, A. Ujihara, S. Tsuchida, T. Shimizu, A. Kaneshige and K. Tomioka, *Tetrahedron Lett*., 2007, **48**, 6648.
9. A highly promising rhodium-catalysed intramolecular hydroamination of primary (and secondary) amines was recently reported: Z. Liu and J. F. Hartwig, *J. Am. Chem. Soc*., 2008, **130**, 1570.
10. For examples of *in situ* generated chiral catalysts using tris(organo or amido) rare-earth precursors for AIH: see refs. 5*c*,*f*,*g*,*k*.
11. This sequential metathetic route was also not suitable for the preparation of chiral diamido alkylyttrium complexes, see ref. 7.
12. Indeed, all lithium salts mentioned above were prepared by deprotonation of the related amine or diamine with *n*-BuLi in an individual reaction.
13. (*R*)-$\mathbf{L_1}$ was the ligand of choice in terms of activity and enantioselectivity for AIH catalysed by our previously reported lanthanide ate complexes.[6d].
14. Anhydrous YCl_3 was chosen for its tendency to afford stable neutral alkyl complexes. For examples of isolated chiral neutral bis(amido) alkyl yttrium bearing a methyl, ethyl or 1-hexyl group, see: T. I. Gountchev and T. D. Tilley, *Organometallics*, 1999, **18**, 2896.
15. For *n*-BuLi-catalysed intramolecular hydroamination of unactivated olefins: (*a*) A. Ates and C. Quinet, *Eur. J. Org. Chem*., 2003, 1623; (*b*) C. Quinet, P. Jourdain, C. Hermans, A. Ates, I. Lucas and I. E. Markó, *Tetrahedron*, 2008, **64**, 1077.
16. Review on rare-earth/alkali metal heterobimetallic complexes that catalyse various asymmetric reactions: M. Shibasaki and N. Yoshikawa, *Chem. Rev*., 2002, **102**, 2187.
17. Indeed, AIH reaction of **1a** catalysed by 6 mol% of fully characterised ate complex prepared by metathesis reaction of YCl_3 (0.5 equiv.) with the dilithium salt of (*R*)-$\mathbf{L_1}$ (1 equiv.) was complete (93% conv.) in 15 h affording **2a** in 81% e.e.[6d].
18. For convenience, addition of the solution of *n*-BuLi to a suspension of YCl_3 and ligand in THF was chosen as the standard procedure.
19. For typical chemical shifts of methylene protons bound to yttrium, see ref. 14.
20. No trace of yttrium amide ate complex bearing two chiral ligands per yttrium as previously described was observed in the spectrum[6d].
21. For examples of the influence of THF or thiophene on the preparation of rare-earth metal catalysts for AIH, see, respectively refs. 5*k* and *g*.

