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

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A) General

All manipulations were carried out under an argon atmosphere by using standard Schlenk or glove box techniques. THF was distilled from sodium benzophenone ketyl, degassed by freeze-pump-thaw method and stored over activated 4Å molecular sieves. d^6-Benzene, purchased from SDS, was dried with sodium benzophenone ketyl, transferred under vacuum and stored over 4Å molecular sieves. *n*-BuLi (1.6 M in hexanes), purchased from Acros Organics, was degassed by freeze-pump-thaw method. Titration of degassed *n*-BuLi was realised according to the method reported by Suffert.[1] Anhydrous YCl_3, (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine were respectively purchased from Alfa Aesar and Acros Organics and used without any further purification. Ligands (*R*)-**L**$_1$,[2] (*R*)-**L**$_2$,[3] (*R*)-**L**$_3$[4] and $Y(N(SiMe_3)_2)_3$[5] were prepared according to reported procedures. $YCl_3(THF)_{3.5}$ was prepared by stirring anhydrous YCl_3 in THF for 1 h and concentration under high vacuum until dryness. Substrates **1a**,[3] **1b**,[6] **1c**,[7] **1d**,[3] were prepared as reported and dried overnight on 4Å molecular sieves with a few drops of d^6-benzene prior to use. Bruker AM250, Bruker AV300 and AV360 NMR spectrometers, operating at 250, 300 and 360 MHz respectively, were used for recording the ^{1}H NMR spectra. Chemical shifts were referenced internally according to the residual solvent resonances.

B) Table 1 (continued): Precatalyst stoichiometry (L/Ln/n-BuLi) effect on the asymmetric hydroamination reaction of 1a (n = 1, R = -(CH$_2$)$_5$-)[a]

Entry	Precatalyst[b]	**L**/Ln/*n*-BuLi Molar ratio	*t* (h)	Conv.[c] (%)	E.e.[d] (%)
10	(*R*)-**L**$_1$+YCl_3+*n*-BuLi	(1:1:8)	24	84	10
11		(1:2:4)	24	97	69
12		(1:2:8)	24	94	64
13		(1:0.5:4)	18	95	59
14[e]	(*R*)-**L**$_1$+YCl_3+*n*-BuLi	(1:1:4)	2	90	75
15[f]		(1:1:4)	2	92	77

[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. [e] Addition of YCl_3, *n*-BuLi and (*R*)-**L**$_1$ successively. [f] Addition of (*R*)-**L**$_1$, *n*-BuLi and YCl_3 successively.

C) Influence of the amount of THF during the preparation stage of the 1:1:4 (*R*)-L1/YCl_3/n-BuLi precatalyst system[a] on the asymmetric hydroamination reaction of 1a[b]

Entry	Amount of THF (mL)	*c* x 10^{-2} (mol. L^{-1}) in yttrium	*t*(h)	Conv. (%)[c]	Ee (%)[d]
1	1	5.6	2	91	74
2	2	2.8	2	94	75
3[e]	4	1.4	2	94	73
4[f]	8	0.7	2	93	74

[a] 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 at r.t., stirring for 10 min and concentration *in vacuo*, unless otherwise stated. [b] Reactions were carried out in solution in C_6D_6 at r.t with 6 mol% of precatalyst. [c] Measured by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis of the product following derivatisation with 2-naphthoyl chloride. [e] Stirring of precatalyst preparation for 15 min. [f] Stirring of precatalyst preparation for 30 min.

D) General procedure for NMR-scale asymmetric intramolecular hydroamination–cyclisation of aminoalkenes (Method A)

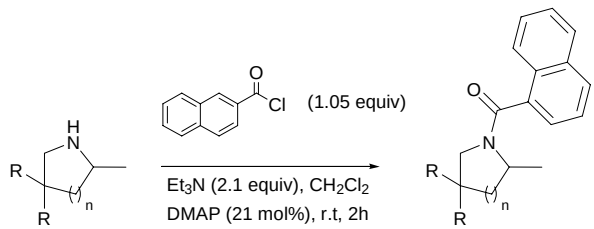
In the glovebox, a 1.6 M hexanes solution of *n*-BuLi (140 µL, 0.22 mmol) was dropwise added by micropipette to a suspension of YCl_3 (11 mg, 0.056 mmol) and the corresponding ligand (0.056 mmol) in THF (2 mL) at ambient temperature. As the lithium reagent was slowly added, the suspended YCl_3 gradually disappeared to give a clear light orange coloured solution at the end of the addition. The homogeneous reaction solution was then allowed to stir 10 min at ambient temperature and a 436 µL-aliquot of the mixture was taken off by a micropipette and introduced into a Schlenk tube equipped with a 'O' ring tap (J. Young). The Schlenk tube was next evacuated on a high vacuum line connected to the glovebox. The residue was dissolved in benzene-d^6 (0.6 mL) and transferred to a vial containing the substrate (0.19 mmol). The reaction mixture was then introduced into a screw-tap NMR tube. The conversion of the reaction was monitored by comparative integration of the signal relative to the olefinic protons of the substrate and the signal relative to the protons of the product. After the appropriate time, the reaction was quenched by addition of a small amount of CH_2Cl_2.

E) Procedure for preparative-scale asymmetric intramolecular hydroamination–cyclisation of 1a

In the glovebox, a 1.6 M hexanes solution of *n*-BuLi (140 µL, 0.22 mmol) was dropwise added by micropipette to a suspension of YCl_3 (11 mg, 0.056 mmol) and (*R*)-**L$_1$** (23 mg, 0.056 mmol) in THF (2 mL) in a Schlenk tube equipped with a 'O' ring tap (J. Young) at ambient temperature. As the lithium reagent was slowly added, the suspended YCl_3 gradually disappeared to give a clear light orange coloured solution at the end of the addition. The homogeneous reaction solution was then allowed to stir 10 min at ambient temperature and next concentrated until dryness on a high vacuum line connected to the glovebox. The residue was dissolved in benzene-d^6 (4 mL) and transferred to a vial containing the substrate **1a** (288 mg, 1.9 mmol). After stirring 3h at ambient temperature, the reaction was quenched by addition of CH_2Cl_2 (3 mL). After evaporation of solvents, the crude oil was distilled *in vacuo* to afford the product **2a** as a colorless oil (207 mg, 72%)(b.p. = 100 °C, 0.15 mBar). The spectroscopic data is in agreement with previously published data.[3] The enantiomeric excess of the product was determined as described below.

F) Determination of the enantiomeric excess values:

The enantiomeric excess values were determined by HPLC analysis of the derivatised product using a (*S*,*S*)-Whelk-O1 column (EtOH/hexane 25/75; 0.9 mL.min^{-1}, λ 254 nm): **Typical procedure of derivatisation:** To a solution of the corresponding cyclised product (0.19 mmol) in CH_2Cl_2 (4 mL) was added dimethylaminopyridine (6.0 mg, 0.04 mmol), triethylamine (55 mL, 0.40 mmol) and 1-naphthoyl chloride (29.5 mL, 0.20 mmol) at ambient temperature. After stirring for 2 h, a saturated aqueous solution of ammonium chloride (4 mL) was poured into the reaction mixture and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was then washed with a saturated aqueous solution of ammonium chloride (5 mL), dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC plate (silica gel) (EtOAc/cyclohexane 25/75).



2a n = 1 R = -$(CH_2)_5$-
b n = 1 R = Me
c n = 1 R = Ph
d n = 2 R = -$(CH_2)_5$-

3a n = 1 R = -$(CH_2)_5$-
b n = 1 R = Me
c n = 1 R = Ph
d n = 2 R = -$(CH_2)_5$-

Retention time of derivatised products 3a-d: Retention times were compared to racemic standard samples prepared by hydroamination reaction with $Y(N(SiMe_3)_2)_3$ as previously reported[3] followed by a derivatisation reaction as mentioned above. Absolute configuration was assigned from comparison of the elution order with literature data.[7]

Entry	Compound	Retention time t_1 (minor) *min* (abs. config)	t_2 (major) *min* (abs. config)
1	**3a**	6.7	17.3
2	**3b**	6.7 (*R*)	15.2 (*S*)
3	**3c**	9.3	17.6
4	**3d**	6.5	17.5

G) General procedure for NMR-scale asymmetric intramolecular hydroamination–cyclisation of aminoalkenes catalysed by *in situ* generated yttrium complex (Method B)

In the glovebox, a 1.6 M hexanes solution of *n*-BuLi (105 µL, 0.17 mmol) was dropwise added by micropipette to a solution of $YCl_3(THF)_{3.5}$ (19 mg, 0.042 mmol) and (*R*)-**L$_1$** (18 mg, 0.042 mmol) in d^6-benzene (2 mL) at ambient temperature. As the lithium reagent was slowly added, the colourless solution changed to a clear light orange solution. The reaction solution was then allowed to stir 10 min at ambient temperature and the appropriate substrate (0.7 mmol) was added. After stirring at ambient temperature the required reaction time, an aliquot of the reaction was introduced into a screw-tap NMR tube and ^{1}H NMR spectroscopy analysis was performed. The conversion of the reaction was monitored by comparative integration of the signal relative to the olefinic protons of the substrate and the signal relative to the protons of the product. The reaction was then quenched by addition of a small amount of CH_2Cl_2. The enantiomeric excess of the product was determined as mentioned above.

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