Base-catalysed asymmetric hydroamination/cyclisation of aminoalkenes utilising a dimeric chiral diamidobinaphthyl dilithium salt†

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A dimeric proline derived diamidobinaphthyl dilithium salt represents the first example of a chiral main group metal based catalyst for asymmetric hydroamination/cyclisation reactions of aminoalkenes.

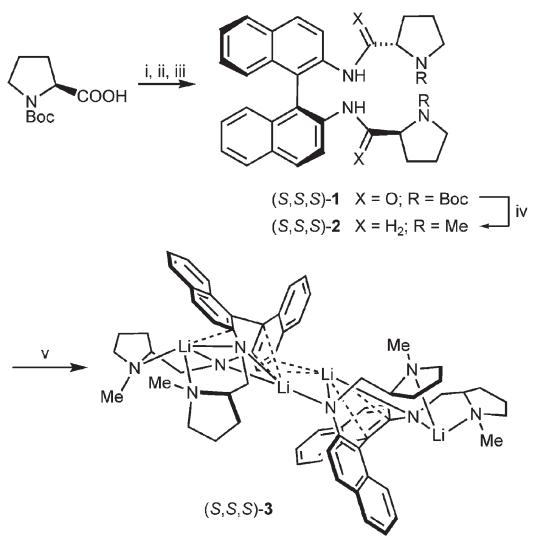
The high importance of nitrogen containing compounds in biological systems and industrial relevant basic and fine chemicals has sparked significant research efforts for their efficient synthesis. Although many synthetic methods have been devised over the last century, one of the simplest synthetic approaches, hydroamination, has become only the focus of attention with the advent of transition metal catalysts. The addition of amine N–H functionalities to unsaturated carbon–carbon bonds generates amines in a waste-free, highly atom-economical manner starting from simple and inexpensive precursors.[1]

Because of the chirality of many hydroamination products, asymmetric hydroamination of alkenes (AHA) carried out with chiral catalysts is an attractive, but highly challenging task.[2] Recent interest has focused on the development of chiral early[1e,3] and late[1f,4] transition metal catalysts. Although alkali metals are known hydroamination catalysts for more than fifty years,[5] the overall number of reports is limited.[1a–c] Many investigations have focused on the hydroamination of activated alkenes, such as vinyl arenes and 1,3-dienes.[6] Most noteworthy, base catalysed hydroamination has been utilised in the industrial scale synthesis of (−)-menthol.[6b,7] The base catalysed hydroamination of non-activated alkenes is significantly less developed,[5b,c,8] and (non-asymmetric) hydroamination/cyclisation of aminoalkenes utilising *n*-BuLi,[9] or β-diketiminato calcium complexes[10] has been reported only recently. Despite the high potential of the hydroamination reaction, to the best of our knowledge no base catalysed asymmetric hydroamination of non-activated alkenes using a main group metal has been reported.[11,12] In this communication we present an asymmetric hydroamination catalyst system based on a chiral diamidobinaphthyl dilithium salt.

The L-proline derived axial chiral tetraamines **2** were prepared in two steps through coupling of BOC-L-proline and racemic diaminobinaphthyl (*rac*-DABN) followed by $LiAlH_4$ reduction (Scheme 1). The diastereomeric BOC-L-proline substituted diaminobinaphthyls (*R*,*S*,*S*)-**1** and (*S*,*S*,*S*)-**1** could be seperated *via* column chromatography or preparative HPLC.[13] Subsequent lithiation of (*S*,*S*,*S*)-**2** in hexanes generated the dilithium salt (*S*,*S*,*S*)-**3** as a yellow–orange powder. (*S*,*S*,*S*)-**3** possesses a dimeric structure, as revealed by X-ray crystallographic analysis (Fig. 1).‡

All four lithium atoms are situated in different coordination environments. The terminal lithium atom Li2 is coordinated to two amine nitrogen atoms of pyrrolidine donor groups (av. Li–N 2.10 Å) and one amido nitrogen atom (Li2–N120 1.992(4) Å). Li1 is stabilized by two amine (av. Li–N 2.19 Å) and two amido nitrogen ligands. While Li1–N20 is rather short (1.975(4) Å), Li1–N10 is significantly elongated (2.264(4) Å) due to a η^2 binding mode of the naphthyl amido moiety (Li1–C31 2.448(5) Å).[14] The interior lithium atoms Li1a and Li2a are significantly stabilized by π-interaction with the aromatic rings[15] of the diamidobinaphthyl ligands. Li1a is coordinated to three amido nitrogen atoms (Li–N 1.936(4)–2.104(4) Å), with one amido ligand, consisting of N20, C41 and C50, being bound in a η^3 mode. Li2a is bound only to two amido nitrogens and displays a similar η^3 coordination mode to N120, C141 and C150 as observed for Li1a. Additionally, Li2a is stabilized by a η^2 π interaction with C42 and C43 (av. Li–C 2.45 Å).

Initial catalytic experiments revealed that (*S*,*S*,*S*)-**3** is a suitable catalyst for asymmetric hydroamination/cyclisation reactions of various aminopentene derivatives (Table 1). For example, cyclisation of **5** proceeded using 5 mol% (*S*,*S*,*S*)-**3** (= 20 mol% Li) within 42 h in 86% isolated yield and 68% ee at 22 °C (Table 1, entry 2).



Scheme 1 *Reagents and conditions*: i, $ClCO_2Et$, Et_3N, THF, −15 °C, 1 h; ii, *rac*-DABN, THF, −15 °C, 1 h, then 25 °C overnight; iii, chromatographic diastereomer separation; iv, $LiAlH_4$, Et_2O, 0 °C, then 7 h reflux; v, 2 equiv. *n*-BuLi, hexanes/benzene, 0 °C, then 1 h at 25 °C.

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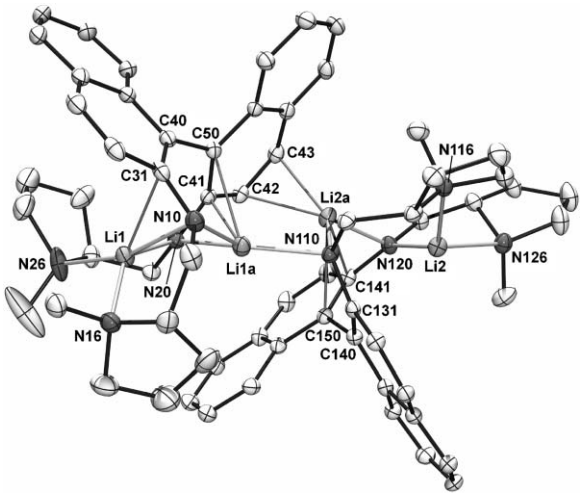
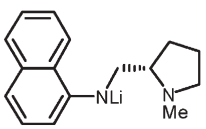


Fig. 1 Molecular structure of (*S*,*S*,*S*)-**3** with thermal ellipsoids at 30% probability level. Selected bond lengths (Å) and dihedral angles (°): Li1–N10 2.264(4), Li1–N16 2.204(4), Li1–N20 1.975(4), Li1–N26 2.174(4), Li1–C31 2.448(5), Li1a–N10 1.936(4), Li1a–N20 2.104(4), Li1a–N110 2.070(4), Li1a–C41 2.253(4), Li1a–C50 2.489(4), Li2–N116 2.112(4), Li2–N120 1.992(4), Li2–N126 2.097(4), Li2a–N110 1.974(4), Li2a–N120 2.031(4), Li2a–C42 2.466(5), Li2a–C43 2.437(5), Li2a–C141 2.263(5), Li2a–C150 2.537(5); C31–C40–C50–C41 76.6(3), C131–C140–C150–C141 84.8(3).

Even at 2.5 mol% catalyst loading the reaction gave 93% yield (by NMR spectroscopy) in 67% ee after 45 h. Addition of THF (Table 1, entry 4) significantly reduced catalytic performance requiring elevated temperatures (80 °C) and resulted in a slight erosion in enantioselectivity.

The close proximity of at least two lithium atoms seems to be essential for catalyst performance, because simple lithium amides, such as $LiN(SiMe_3)_2$, required significant higher reaction temperatures (Table 1, entry 6). A catalyst system comprising of $LiN(SiMe_3)_2$ and (–)-sparteine[12b] resulted in improved rate of cyclisation (Table 1, entry 7),[16] but no enantiomeric excess in the pyrrolidine product was observed. Also, the chiral mono(lithium) amide (*S*)-**4**[17] was inferior in reactivity and selectivity (Table 1, entries 5 and 10).

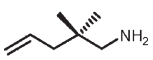
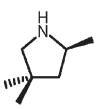
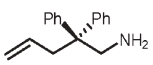
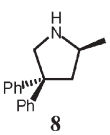
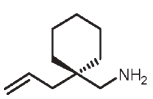
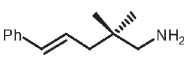
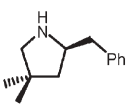
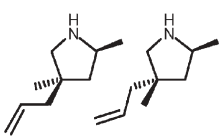


(*S*)-**4**

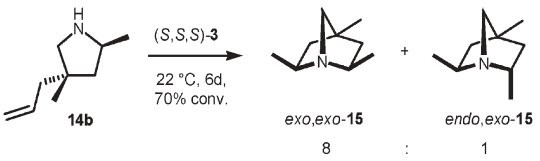
Cyclisation of sterically more demanding aminoalkenes **7** and **9** proceeded significantly faster thanks to the increased *gem*-dialkyl effect.[18] While diphenyl-substituted **7** was cyclised in only 31% ee using (*S*,*S*,*S*)-**3** at 22 °C, substrate **9** showed the highest selectivity of 75% ee. The 1,2-disubstituted aminoalkene **11** was cyclised very rapidly within 5 min at 22 °C due to the activating effect of the electron-withdrawing phenyl-substituent, though enantioselectivity was low.

The first cyclisation of aminodialkene **13** proceeded also rapidly at 22 °C within 2 h, yielding the allyl-substituted pyrrolidines **14a** and **14b** in good enantioselectivity (72% ee for the minor diastereomer **14b**), but only low diastereoselectivity. The minor diastereomer **14b**, presumably the isomer with a *cisoid*

Table 1 Hydroamination/cyclisation reactions utilising lithium amide catalysts[a]

Entry	Substrate	Product	Cat.	[cat.]/[subst.][b]	*T*/°C	*t*/h	Yield[c] (%)	ee[d] (%) (config.)
1	 **5**	 **6**	(*S*,*S*,*S*)-**3**	7.5	22	9	96	64 (*S*)
2			(*S*,*S*,*S*)-**3**	5	22	42	96 (86)	68 (*S*)
3			(*S*,*S*,*S*)-**3**	2.5	22	45	93	67 (*S*)
4			(*S*,*S*,*S*)-**3**·4THF	5	80	407	66	53 (*S*)
5			(*S*)-**4**	10	120	333	56	2
6			$LiN(SiMe_3)_2$	10	90	38	98	—
7			$LiN(SiMe_3)_2$/(–)-sparteine	10	90	22	98	0
8	 **7**	 **8**	(*S*,*S*,*S*)-**3**	5	22	0.8	97	31 (*S*)
9			(*S*,*S*,*S*)-**3**·4THF	5	80	27	70	24 (*S*)
10			(*S*)-**4**	10	120	140	0	—
11	 **9**	 **10**	(*S*,*S*,*S*)-**3**	2.5	22	1.1	91	75 (*S*)
12			(*S*,*S*,*S*)-**3**	5[e]	20	2	98 (82)	74 (*S*)
13			(*S*,*S*,*S*)-**3**·4THF	5	60	91	64	69 (*S*)
14	 **11**	 **12**	(*S*,*S*,*S*)-**3**	5	22	0.08	98	17
15	 **13**	 **14a** **14b**	(*S*,*S*,*S*)-**3**	5	22	2	98 (79)	64, 72[f]

[a] *Reaction conditions*: C_6D_6, Ar atm. [b] Calculated for a dimeric species for (*S*,*S*,*S*)-**3** and (*S*,*S*,*S*)-**3**·4THF containing 4 Li atoms each. [c] NMR yield relative to ferrocene internal standard. Values given in parentheses are isolated yields from preparative scale reactions. [d] Enantiomeric excess was determined by ^{19}F NMR of the Mosher amides. [e] Reaction in toluene. [f] dr(**14a**:**14b**) = 1.2:1.



Scheme 2 Bicyclisation of **14b**.

arrangement of the two methyl substituents,[19] underwent slow bicyclisation at 22 °C (70% conv. of **14b** in 6 d) to give 2,4,6-dimethyl-1-azabicyclo[2.2.1]heptane (**15**) with 8:1 *exo*,*exo*:*endo*,*exo* diastereoselectivity (Scheme 2). The major diastereomer **14a** with a *transoid* arrangement of the two methyl substituents remained unaffected under these conditions.

Lithium amides are well known to form higher aggregates.[20] Although the molecularity of (*S*,*S*,*S*)-**3** under catalytic conditions is not known,[21] it seems obvious, though still speculative, that a dimeric structure similar to that observed in the solid state is pivotal for the catalytic process described herein. Preliminary experiments indicate a relative minor influence of catalyst loading or added THF on enantiomeric excess (Table 1, entries 1–4), while the effect on catalytic activity is more pronounced. With respect to the importance of the nuclearity of (*S*,*S*,*S*)-**3** for its catalytic activity it is also important to note that lithiation of (*R*,*S*,*S*)-**2** did not generate a well defined species, based on the broad and featureless NMR spectra, and no catalytic activity was observed.[22]

Further investigations are currently aimed at extending the scope of the catalyst to intermolecular hydroamination reactions. More detailed mechanistic and kinetic investigations are required in order to elucidate the catalytically active species and understand the factors which are responsible for the increased catalytic activity and enantioselectivity in the dimeric dilithium amide complex (*S*,*S*,*S*)-**3** relative to simple lithium amides, such as (*S*)-**4**.

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Notes and references

‡ *Crystallographic data* for (*S*,*S*,*S*)-**3**·C_6H_6: $C_{70}H_{78}Li_4N_8$, M_r = 1059.16, crystal size 0.15 × 0.10 × 0.10 mm, monoclinic, space group $P2_1$, a = 9.7704(1), b = 17.6269(3), c = 16.8330(2) Å, β = 93.335(1)°, V = 2894.10(7) Å^3, Z = 2, D_c = 1.215 g cm^{-3}, F(000) = 1132, Mo-Kα radiation (λ = 0.71073 Å), T = 173(2) K, μ = 0.070 mm^{-1}, 13208 independent reflections were measured on a Nonius KappaCCD system, R_1 ($I > 2\sigma(I)$) = 0.0542, wR_2 (all data) = 0.1438. The absolute configuration could not be determined (abs. struct. param. 0.30(16)), but the relative configuration was assigned based on the known (*S*) configuration of the BOC-L-proline ligand precursor. CCDC 297865. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b518360j

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21 The ^{7}Li NMR spectrum showed only a single resonance for (*S*,*S*,*S*)-**3** (C_6D_6, 60 °C).

22 No reaction was observed in the attempted cyclisation of **5** (90 h, 110 °C). The spectral features of this compound suggest an oligomeric structure, rather than a dimeric species similar to (*S*,*S*,*S*)-**3**.