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Easy Routes towards Chiral Lithium Binaphthylamido Catalysts for the Asymmetric Hydroamination of Amino-1,3-dienes and Aminoalkenes

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The preparation of chiral lithium salts of *N*,*N*′-disubstituted binaphthyldiamines and their use as catalysts for asymmetric hydroamination/cyclisation of amino-1,3-dienes and aminoalkenes are reported. Several straightforward methods involving the combination of ligand with solutions of methyl- or [(trimethylsilyl)methyl]lithium ($LiCH_2TMS$) by ex situ or in situ preparation have been investigated. The use of $LiCH_2TMS$ in an in situ procedure was revealed as the easiest for carrying out reactions with reliable results by fine-tuning the quantity of base. Screening of a variety of ligands led to the selection of binaphthyldiamines modified by benzyl, pyridyl or naphthyl groups for the cyclisation of conjugated aminodienes in pyrrolidine or piperidine with the highest stereo- and enantioselectivities described to date (up to 61 and 72% *ee*, respectively). Primary and secondary aminoalkenes are efficiently cyclised at room temperature, but with poor enantioselectivities.

Introduction

Amines constitute a key scaffold of a variety of natural and synthetic organic molecules with diverse applications, such as pharmaceuticals, fine and bulk chemicals, and catalysts. The quest for the development of sustainable, more efficient and selective processes for their syntheses has never been as high as in recent years and will undoubtedly increase exponentially in the near future. Amongst the plethora of synthetic routes, the direct addition of an amine onto an unactivated carbon–carbon double bond, the so-called hydroamination reaction,[1] represents a very promising research field towards the development of an economical and environmentally benign synthetic method. Indeed, this reaction offers a waste-free process with 100% atom efficiency from relatively inexpensive and ubiquitous olefins and amines. Nevertheless, this seemingly simple transformation suffers from a high activation barrier caused by an unfavourable interaction between the nitrogen lone pair of the amine and the electron-rich double bond of the incoming olefin. Moreover, the negative reaction entropy impedes the use of higher reaction temperatures. Catalysis may yet afford a general answer to this intricate problem by lowering the reaction barrier. In addition, a metal-catalysed process brings the opportunity to control the regio- and stereoselectivities of the transformation by the appropriate metal–chiral ligand(s) synergy. Recent years have witnessed the emergence of manifold chiral catalytic systems based on late-transition metals,[2] group IV metals,[3] rare-earth elements[4] and alkali metals,[5] for the regio- and enantioselective hydroamination of unactivated olefins either in an inter- or in an intramolecular fashion.[6] Despite major breakthroughs in this area, some advances in terms of activity, enantioselectivity and substrate scope are still needed to bring this attractive alternative up to the requirements of a truly efficient and low-environmental-impact methodology.

In this context, we have recently reported the use of simple diaminobinaphthyl dilithium salts as efficient and easily accessible lithium-based (pre)catalysts for asymmetric intramolecular hydroamination (AIH) of amino-1,3-dienes with outstanding activities, high diastereoselectivities and moderate enantiomeric excess (*ee*) values.[5d] Although the era of alkali-metal-catalysed hydroamination reaction originated in the early 1950s, only limited studies were devoted to the hydroamination of truly unactivated alkenes under harsh conditions of pressure and temperature.[7,8] Most of the reports focused on the alkali-metal-catalysed hydroamination of vinylarenes[9,10] and 1,3-dienes[11,12] as activated alkene surrogates under gentler reaction conditions. It was only in 2006 that the potential of an asymmetric variant of a base-catalysed hydroamination reaction was demonstrated.[5a] In this seminal work by Hultzsch et al., a well-defined, dimeric, chiral, diamidobinaphthyl dilithium salt was elegantly exploited as an efficient chiral (pre)catalyst for the 5-*exo* cyclisation of primary amines tethered to unactivated alkenes. Pyrrolidines were quantitatively accessed

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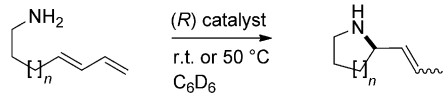
under mild conditions with *ee* values up to 75%.[5a] One year later, the group of Tomioka reported that the combination of butyllithium, diisopropylamine and a chiral bis(oxazoline) ligand was a competent in situ generated catalyst for the synthesis of enantioenriched *N*-methylisoquinoline and -isoindoline up to 91% *ee* by lithium-catalysed AIH.[5b] To the best of our knowledge, these two reports were, at the time, the sole contributions to the field of alkali-metal-catalysed asymmetric hydroamination.

Herein, we unveil a more complete study of our work on the hydroamination/cyclisation of amino-1,3-dienes catalysed by chiral dilithium diamides[5d] and disclose an extension of this methodology to AIH of primary amines tethered to unactivated alkenes.

Results and Discussion

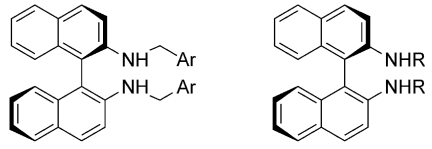
Hydroamination/Cyclisation of Amino-1,3-dienes

We describe herein our attempts to optimise the preparation of chiral lithium amides as efficient asymmetric catalysts to promote the AIH of primary amino-1,3-dienes. Hepta-4,6-dienylamine (**1a**) and octa-5,7-dienylamine (**1b**) were used as test substrates to afford the corresponding unsaturated pyrrolidine **2a** and piperidine **2b** as potentially valuable synthons for the preparation of biologically active molecules (Scheme 1). Binaphthylamine-based ligands were chosen as asymmetric scaffolds, since, when associated with rare-earth precatalysts, they allowed the preparation of highly enantioenriched N-containing heterocycles from primary or secondary aminoalkenes.[4j–4n,13] Delightfully, a catalyst preparation arising from dropwise addition of 2 equiv. of a solution of MeLi in diethyl ether to a solution of (*R*)-H_2**L**^{1} (Figure 1) in THF and subsequent solvent evaporation, afforded an active species for the enantioselective cyclisation of **1a** in deuterated benzene. 2-Propenylpyrrolidine **2a** was indeed formed with complete conversion within a very short time; the major (*E*) diastereomer [(*E*)/(*Z*) = 84:16] was isolated with 51% *ee* (Table 1, entry 1). With the aim of optimising these values, the amount of base was increased up to 6 equiv. (Table 1, Entries 2 and 3), allowing a slight increase in the *ee* values accompanied, however, with a decrease of the (*E*)/(*Z*) ratio. On the other hand, the use of diethyl ether as a solvent for the preparation of the catalyst did improve both the activity and selectivity of the transformation. The best conditions were achieved with 4 equiv. of MeLi to give the most rapid reaction and the synthesis of the major (*E*) diastereomer of **2a** [(*E*)/(*Z*) = 92:8] in 51% *ee* (Table 1, Entries 4–6). Interestingly, the minor diastereomer was also synthesised under those conditions with 50% *ee*. Very similar results were obtained with a solution of MeLi in diethoxymethane (Table 1, Entry 7). Furthermore, the precatalytic mixture obtained from MeLi in diethyl ether proved to be stable as a powder stored under anaerobic conditions and after storage led to the same values (Table 1, Entry 8). It is important to note that the transformation could also be run in the absence of a ligand. A blank experiment was thus conducted in the presence of a catalytic amount of MeLi (in diethyl ether, 0.2 equiv.) added to the substrate in solution in benzene. Interestingly, the transformation was considerably slower, and complete conversion took 4 h. The diastereomeric ratio was reversed with the formation of the (*Z*) diastereomer as the major species [(*E*)/(*Z*) = 20:80] and a non-negligible amount of the pyrrolidine containing a terminal olefin was detected by NMR spectroscopy. Hence, the ligand-accelerating effect is significant for this transformation.



1a: *n* = 1 **2a**: *n* = 1
1b: *n* = 2 **2b**: *n* = 2

Scheme 1. Asymmetric hydroamination of amino-1,3-dienes.



(*R*)-H_2**L**^{1}: Ar = C_6H_5 (*R*)-H_2**L**^{5}: R = cyclopentyl
(*R*)-H_2**L**^{2}: Ar = 2,4,6-$Me_3C_6H_2$ (*R*)-H_2**L**^{6}: R = *t*$BuCH_2$
(*R*)-H_2**L**^{3}: Ar = 2-pyridyl (*R*)-H_2**L**^{7}: R = cyclohexyl
(*R*)-H_2**L**^{4}: Ar = 2-naphthyl (*R*)-H_2**L**^{8}: R = *i*Pr

Figure 1. Chiral (*R*)-*N*-substituted binaphthyldiamine ligands.

Moreover, the structure of the base influenced the course of the transformation. The use of *n*BuLi lowered the diastereomeric ratio and more importantly afforded a nearly racemic (*Z*) compound (Table 1, entry 9). Although $LiCH_2SiMe_3$ as a solution in pentane (2 equiv.) led to a satisfyingly efficient catalyst (Table 1, Entry 10), it surprisingly completely lost its activity when it was exactly weighed from an isolated powder and dissolved in diethyl ether (Table 1, Entries 10 and 11). From this screening study, the best conditions for the catalyst preparation imply the use of a solution of both MeLi (4 equiv.) and ligand in diethyl ether. This methodology was chosen as a standard for the continuation of the study (Method A).

The effect of the catalytic ratio on the course of the reaction was then studied (Table 2), indicating that the stoichiometric reaction also occurred smoothly and led to the target products with similar selectivities as those reported for the catalyst used in a 10 mol-% ratio (Table 2, Entries 1 and 2).[14] Decreasing the catalyst amount to 5 mol-% required a longer reaction time to reach complete conversion and led to poorer stereo- and enantiodifferentiation. It was possible to run the reaction with a catalyst ratio of 2 mol-%, but similarly the trends in terms of activity and selectivity were not positive (Table 2, Entries 3 and 4). The use of 10 mol-% catalyst was thus chosen as the best compromise for short reaction times and optimised selectivities.

Table 1. Effect of the method of catalyst preparation[a] from (*R*)-H_2**L**^{1} on the asymmetric hydroamination reaction of **1a**.[b]

Entry	Alkyllithium reagent	Solvent	Equiv.	Time [h]	Conversion[c] [%]	Ratio[d] (*E*)/(*Z*)	*ee*(*E*)[d] [%] (config.[e])	*ee*(*Z*)[d] [%] (config.[e])
1	MeLi[f]	THF	2	0.33	>95	84:16	51 (*S*)	3
2	MeLi[f]	THF	4	0.33	>95	77:23	52 (*S*)	0
3	MeLi[f]	THF	6	0.50	>95	72:28	57 (*S*)	4
4	MeLi[f]	Et_2O	2	0.25	>95	92:8	49 (*S*)	47 (*S*)
5	MeLi[f]	Et_2O	4	0.17	>95	92:8	51 (*S*)	50 (*S*)
6	MeLi[f]	Et_2O	6	0.25	>95	85:15	50 (*S*)	6 (*S*)
7	MeLi[g]	Et_2O	4	0.17	>95	92:8	47 (*S*)	47 (*S*)
8[h]	MeLi[f]	Et_2O	4	0.17	>95	92:8	51 (*S*)	58 (*S*)
9	*n*BuLi[i]	Et_2O	3	0.25	>95	85:15	58 (*S*)	6
10	$LiCH_2SiMe_3$[j]	Et_2O	2	0.50	>95	93:7	49 (*S*)	40 (*S*)
11	$LiCH_2SiMe_3$[k]	Et_2O	2	1	0	–	–	–

[a] Catalyst preparation was performed by dropwise addition of a solution of the corresponding alkyllithium reagent to a solution of (*R*)-H_2**L**^{1} in solvent (c = 0.02–0.03 M) at room temp., followed by stirring for 10 min and concentration in vacuo. [b] Reactions were carried out in C_6D_6 at room temp. under argon with 10 mol-% of catalyst. [c] The configuration was determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis of the product following derivatisation with 2-benzoyl chloride. [e] See the Supporting Information for details. [f] MeLi in diethyl ether (1.6 M). [g] MeLi in diethoxymethane (3 M). [h] Catalyst powder used after 4 d of storage at room temp. under argon. [i] *n*BuLi in hexanes (1.6 M). [j] $LiCH_2SiMe_3$ in pentane (1 M). [k] $LiCH_2SiMe_3$ as an isolated powder.

Table 2. Effect of the catalyst ratio[a] on the asymmetric hydroamination reaction of **1a**.[b]

Entry	Catalyst ratio [%]	Time [h]	Ratio[c] (*E*)/(*Z*)	*ee*(*E*)[c] [%](config.[d])	*ee*(*Z*)[c] [%] (config.[d])
1	100	0.33	92:8	52 (*S*)	56 (*S*)
2	10	0.17	92:8	51 (*S*)	50 (*S*)
3	5	0.40	88:12	48 (*S*)	42 (*S*)
4	2	3	84:16	46 (*S*)	29 (*S*)

[a] Catalyst preparation was performed by dropwise addition of a solution of MeLi in diethyl ether (1.6 M, 4 equiv.) to a solution of (*R*)-H_2**L**^{1} in Et_2O (c = 0.02–0.03 M) at room temp., followed by stirring for 10 min and concentration in vacuo. [b] Reactions were carried out in C_6D_6 at room temp. under argon and went into completion (conversion >95%, as measured by ^{1}H NMR spectroscopy). [c] Determined by HPLC analysis of the product following derivatisation with 2-benzoyl chloride. [d] See the Supporting Information for details.

With the aim of optimising and facilitating catalyst preparation, another procedure was developed (see Method B in Table 3) for which the addition of MeLi in diethyl ether as a base was directly performed in a solution of the considered ligand in deuterated benzene. The resulting mixture was briefly stirred at room temperature before the substrate was added directly without any previous removal of the solvent. Both catalyst preparation procedures were then compared for the transformation of the two aminodienes **1a** and **1b** and in the presence of structurally different ligands (Table 3). Satisfyingly, in situ Method B, applied to the synthesis of the amide ligand arising from (*R*)-H_2**L**^{1}, afforded product **2a** with the same results as those obtained by applying stepwise Method A (compare Entries 1 and 2 in Table 3). Thus, simplified Method B demonstrated its practicability and was also applied for the synthesis of different catalysts from various ligands. The use of the bulkier ligand (*R*)-H_2**L**^{2} allowed the preparation of less active catalysts (Table 3, Entries 3 and 4), which furthermore showed a reverse selectivity for the favoured formation of the (*Z*) diastereomer for **2a**. Both procedures afforded, however, catalysts that were poorly enantioselective.

A similar trend was obtained for the use of the pyridyl-derived ligand (*R*)-H_2**L**^{3}. The stepwise preparation of the amide salt by using diethyl ether as the solvent (Table 3, Entry 5) afforded, after 2 h of reaction time, the (*Z*) product as the main compound with 26% *ee*, and a configuration reversed relative to that obtained with ligand (*R*)-H_2**L**^{1} as the precursor. Interestingly, the in situ preparation (Table 3, Entry 6) gave a more active and enantioselective catalyst, and the (*Z*) isomer could be isolated in up to 65% *ee* (*R*), which was the highest value obtained for this series. Modified binaphthyldiamine ligand (*R*)-H_2**L**^{4}, with naphthyl groups on the nitrogen atoms, behaved analogously to ligand (*R*)-H_2**L**^{1} as the catalyst precursor and, in particular, Method B allowed the formation of a selective catalyst that promoted the formation of the (*E*) isomer as the main product with up to 55% *ee* (*S*) (Table 3, Entries 7 and 8). Finally, two binaphthyldiamine ligands substituted with bulky alkyl groups on the nitrogen atoms were prepared, but they afforded less active and stereoselective catalysts (Table 3, Entries 9–12). Both isomers of product **2a** were formed in a nearly equimolar mixture, and the enantioselectivities were notably diminished compared with those obtained by the catalysts containing benzyl-like substituents. The highest values were obtained by using ligand (*R*)-H_2**L**^{5}, with cyclopentyl substituents, and reached only 43% *ee* (*S*) for the (*E*) isomer and 32% *ee* (*S*) for the (*Z*) isomer (Table 3, Entry 9).

These catalysts were then evaluated for the intramolecular hydroamination of substrate **1b**, leading to the formation of piperidine **2b**. As expected for the formation of six-membered heterocycles, the reaction proved to be trickier and had to be conducted at 50 °C to afford good conversions in reasonable reaction times. Satisfyingly, benzyl-modified ligand (*R*)-H_2**L**^{1} afforded an active catalyst that provided the expected compound **2b** in high yield after 21 h of reaction time and a high (*E*)/(*Z*) selectivity in favour of the (*E*) isomer. This catalyst gave the (*E*) isomer with up to 72% *ee* (*S*) and the (*Z*) compound with up to 55% *ee* (*S*);

Table 3. Asymmetric hydroamination of amino-1,3-dienes **1a** and **1b**[a] catalysed by the 1:4 (*R*)-H_2**L**/MeLi precatalyst system prepared according to Method A[b] or Method B.[c]

Entry	Substrate	Product	(*R*)-H_2**L**	Method	Time [h]	Conversion[d] [%]	Ratio[e] (*E*)/(*Z*)	*ee*(*E*)[e] [%] (config.[f])	*ee*(*Z*)[e] [%] (config.[f])
1	**1a**	**2a**	(*R*)-H_2**L**^{1}	A	0.17	>95 (68)[g]	92:8	51 (*S*)	50 (*S*)
2	**1a**	**2a**	(*R*)-H_2**L**^{1}	B	0.17	>95	92:8	52 (*S*)	53 (*S*)
3	**1a**	**2a**	(*R*)-H_2**L**^{2}	A	3	>95	25:75	9 (*S*)	2
4	**1a**	**2a**	(*R*)-H_2**L**^{2}	B	1	>95[h]	28:72	10 (*S*)	6
5	**1a**	**2a**	(*R*)-H_2**L**^{3}	A	2	89	22:78	2	26 (*R*)
6	**1a**	**2a**	(*R*)-H_2**L**^{3}	B	0.5	>95[h]	15:85	8	65 (*R*)
7	**1a**	**2a**	(*R*)-H_2**L**^{4}	A	0.25	>95	75:25	49 (*S*)	8 (*S*)
8	**1a**	**2a**	(*R*)-H_2**L**^{4}	B	0.25	>95[h]	91:9	55 (*S*)	36 (*S*)
9	**1a**	**2a**	(*R*)-H_2**L**^{5}	A	2	>95	47:53	43 (*S*)	32 (*R*)
10	**1a**	**2a**	(*R*)-H_2**L**^{5}	B	1	>95[h]	41:59	37 (*S*)	23 (*R*)
11	**1a**	**2a**	(*R*)-H_2**L**^{6}	A	2	>95	55:45	30 (*S*)	10 (*R*)
12	**1a**	**2a**	(*R*)-H_2**L**^{6}	B	1	>95[h]	58:42	35 (*S*)	8 (*R*)
13	**1b**	**2b**	(*R*)-H_2**L**^{1}	A	21	>95 (62)[g]	89:11	72 (*S*)	55 (*S*)
14	**1b**	**2b**	(*R*)-H_2**L**^{1}	B	17	>95	91:9	71 (*S*)	51 (*S*)
15	**1b**	**2b**	(*R*)-H_2**L**^{2}	A	46	>95	80:20	9 (*S*)	23 (*R*)
16	**1b**	**2b**	(*R*)-H_2**L**^{2}	B	42	>95[h]	51:49	13 (*S*)	8 (*R*)
17	**1b**	**2b**	(*R*)-H_2**L**^{4}	A	4	92	86:14	67 (*S*)	15 (*S*)
18	**1b**	**2b**	(*R*)-H_2**L**^{4}	B	4	>95	91:9	62 (*S*)	57 (*S*)
19	**1b**	**2b**	(*R*)-H_2**L**^{5}	A	27	>95	66:34	56 (*S*)	9 (*S*)
20	**1b**	**2b**	(*R*)-H_2**L**^{5}	B	20	>95[h]	61:39	56 (*S*)	2
21	**1b**	**2b**	(*R*)-H_2**L**^{6}	A	27	>95	86:14	51 (*S*)	5
22	**1b**	**2b**	(*R*)-H_2**L**^{6}	B	22	>95[h]	85:15	45 (*S*)	11 (*R*)

[a] Reactions were carried out in C_6D_6 at room temp. (**1a**) or 50 °C (**1b**) with 10 mol-% of precatalyst. [b] Method A: catalyst preparation was performed by dropwise addition of 4 equiv. of a solution of MeLi in diethyl ether (1.6 M) to a solution of the ligand (*R*)-H_2**L** in diethyl ether (c = 0.025 M) at room temp., followed by stirring for 10 min and concentration in vacuo. [c] Method B: catalyst preparation was performed by dropwise addition of 4 equiv. of a solution of MeLi in diethyl ether (1.6 M) to a solution of the ligand (*R*)-H_2**L** in C_6D_6 (c = 0.025 M) at room temp. After stirring for 10 min, the substrates were directly added to this catalyst solution. [d] Measured by ^{1}H NMR spectroscopy. [e] Determined by HPLC analysis of the product following derivatisation with 2-benzoyl chloride. [f] See the Supporting Information for details. [g] Isolated yield of **2a**·HCl and **2b**·HCl. [h] 10% of the product containing a terminal double bond was detected by ^{1}H NMR spectroscopy.

these were the highest values reported for compound **2b**. The in situ procedure yielded an even more active catalyst possessing similar selectivities (Table 3, Entries 13 and 14). In accordance with the results obtained for the previous transformation, the use of the analogous mesityl-substituted ligand (*R*)-H_2**L**^{2} was detrimental to both the activity and the selectivities (Table 3, Entries 15 and 16). Ligand (*R*)-H_2**L**^{4}, with naphthyl groups, gave rise to the most active catalysts of the series, since complete conversions were reached in 4 h when using both preparation methods (Table 3, Entries 17 and 18). Enantioselectivities, however, did not reach those obtained with precursor (*R*)-H_2**L**^{1}. In this case again, the use of the ligands with alkyl groups, (*R*)-H_2**L**^{5} and (*R*)-H_2**L**^{6}, led to active catalysts that were both less stereo- and enantioselective (Table 3, Entries 19–22). As already described for the transformation of aminodiene **1a**, a blank reaction was conducted with substrate **1b** in C_6D_6 in the presence of 20 mol-% of a solution of MeLi in diethyl ether. The reaction went to completion at 50 °C, but the mixture had to be stirred for more than 2 d and afforded product **2b** in an (*E*)/(*Z*) ratio of 78:22, providing additionally a non-negligible amount of a product containing a terminal double bond (20%). Again in this case, the preparation of chiral amide derivatives led to an important rate enhancement for hydroamination/cyclisation.

It should be noted, that for each ligand and considering both substrates **1a** and **1b**, when it was technically possible to make a difference, the in situ amide preparation led to far more active catalysts. Method B, as a straightforward in situ methodology, allowed the rapid preparation of active and selective catalysts for the cyclisation of aminodienes. Corresponding N-heterocycles could be isolated in good yields and with the highest enantioselectivities reported to date for such substrates.

To obtain more insight into the structure of the obtained pre-catalysts, attempts were devoted to the preparation of crystals suitable for X-ray analysis. This turned out to be successful by the use of racemic ligand H_2**L**^{1} mixed together with 2 equiv. of MeLi, as we previously reported.[5d] The catalytic activity of this isolated species was evaluated for the transformation of substrate **1a** at room temperature, but the use of 10 mol-% of catalyst did not show any activity, even after prolonged reaction times. The catalyst synthesis procedure was thus slightly modified, and ligand (±)-H_2**L**^{1} was treated with 4 equiv. of MeLi in diethyl ether and stirred for 10 min. This procedure also led to the isolation of crystals suitable for X-ray analysis, giving rise to exactly the same structure as that prepared with 2 equiv. of MeLi. The resulting crystals were further used to promote the cyclisation of **1a** (10 mol-%), which, interestingly, rapidly occurred within 15 min to yield the expected heterocycle **2a** with the same diastereoselectivity as that observed when using the corresponding (*R*)-H_2**L**^{1} ligand as the precursor [(*E*)/(*Z*) = 92:8]. Finally, we proved that the same efficiency

(i.e., both activity and selectivity) could be restored to the crystals issued from the precise stoichiometric preparation [1:2 (±)-H_2**L**^{1}/MeLi mixture] by adding a small amount of MeLi (one drop) to the reaction mixture. These experiments clearly indicated that a small excess of base was essential for the reaction to be successful, but this had to be precisely controlled to avoid the competitive racemic transformation, although we demonstrated that the latter was far more sluggish. Accordingly, the use of a solution of MeLi is not always straightforward, and we looked for other bases that could allow the fine-tuning of a simpler protocol and the precise control of the amount of base. $LiCH_2SiMe_3$ as a solution in pentane afforded interesting results for the transformation of **1a** associated with (*R*)-H_2**L**^{1} as the ligand (see Table 1, Entry 10). This base can be stored as a powder under an inert gas after removal of the solvent, and a precise amount can thus be weighed. A 1:2 mixture of (*R*)-H_2**L**^{1}/$LiCH_2SiMe_3$ was thus prepared and stirred in diethyl ether for 10 min, before the solvent was removed. The transformation of **1a** was then attempted in C_6D_6 with 10 mol-% of this complex, but no reaction occurred (see Table 1 Entry 11 and Table 4, Entry 1). According to the observations made by using MeLi as the base, an analogous catalyst was prepared, but 4 equiv. of $LiCH_2SiMe_3$ as a powder was added in the procedure instead of the exact stoichiometry (Table 4, Entry 2). The activity was restored, and results similar to those obtained with MeLi as base were observed, except that the (*Z*) compound was isolated in its nearly racemic form (Table 3 Entries 1 and 2 and Table 4, Entry 2).

Table 4. Use of $LiCH_2TMS$ as a base[a] for the asymmetric hydroamination reaction of **1a**.[b]

Entry	Solvent	Equiv. of base	Time [h]	Ratio[c] (*E*)/(*Z*)	*ee*(*E*)[c] [%] (config.[d])	*ee*(*Z*)[c] [%] (config.[d])
1	Et_2O	2	1	–	–	–
2	Et_2O	4	0.25	90:10	47 (*S*)	6
3	C_6D_6	4	0.25	80:20	53 (*S*)	5
4	C_6D_6	2.5	0.16	92:8	50 (*S*)	14 (*S*)
5[e]	C_6D_6	5 mol-%	1	33:67	–	–

[a] Catalyst preparation was performed by the addition of $LiCH_2SiMe_3$ as an isolated powder to a solution of (*R*)-H_2**L**^{1} in solvent (*c* = 0.02–0.03 M) at room temp., followed by stirring for 10 min and concentration in vacuo (for Et_2O solution) or direct use (for C_6D_6 solution). [b] Reactions were carried out in C_6D_6 at room temp. under argon with 10 mol-% of catalyst and went to completion (conversion >95%, measured by ^{1}H NMR spectroscopy). [c] Determined by HPLC analysis of the product following derivatisation with 2-benzoyl chloride. [d] See the Supporting Information for details. [e] Reaction run without ligand, and 24% of a product containing a terminal double bond was detected by ^{1}H NMR spectroscopy.

A simplified procedure was further developed by directly using the reaction solvent (i.e., C_6D_6) for the preparation of the catalyst, thus avoiding the intermediary evaporation step. This procedure afforded an active species, since the expected product was isolated after 15 min with complete conversion of substrate **1a** in 53% *ee* (*S*) for the main (*E*) isomer of **2a**; the (*E*)/(*Z*) selectivity, however, reached only 80:20 (Table 4, Entry 3). Decreasing the quantity of $LiCH_2SiMe_3$ to 2.5 equiv., as a slight excess of base only, gave rise to the preparation of the most active (10 min to completion) and selective catalyst [(*E*)/(*Z*) = 92:8] for the preparation of the (*E*) isomer of product **2a** in up to 50% *ee* (*S*) (Table 4, Entry 4). The use of $LiCH_2SiMe_3$ as a base without a ligand was also investigated as a potential catalyst, and analogously to MeLi, this base promoted a transformation, albeit at a slower rate and with a reversed selectivity, leading to the (*Z*) compound, as the major isomer (Table 4, Entry 5). The new procedure involving the use of 2.5 equiv. of $LiCH_2SiMe_3$ as an isolated powder with the appropriate ligand dissolved in C_6D_6 (Method C) was thus chosen as the easiest methodology, leading to very reproducible results, for preparing a chiral catalyst for the intramolecular hydroamination of aminodienes. This procedure was thus applied to the transformation of both substrates **1a** and **1b** in the presence of different binaphthyldiamine chiral ligands. The results are gathered in Table 5. The catalyst prepared with the bulky ligand (*R*)-H_2**L**^{2}, with mesityl substituents on the nitrogen groups, allowed the cyclisation of **1a** with the major isomer of product **2a** as the (*Z*) isomer [(*E*)/(*Z*) = 30:70] in nearly racemic form (Table 5, Entry 2), a very similar result to that obtained when employing MeLi as the base (Table 3, Entry 4). The absence of enantioselection and the reversal in stereoselectivity in this case could be explained by competitive cyclisation with $LiCH_2SiMe_3$ (Table 4, Entry 5). The pyridine-substituted ligand (*R*)-H_2**L**^{3} also gave pyrrolidine **2a** with a good selectivity for isomer (*Z*) [(*E*)/(*Z*) = 24:76] and 61% *ee* (Table 5, Entry 3). These values are very similar to those obtained by Method B using MeLi, albeit with small differences in the rate of the reaction and enantioselectivity for the minor stereoisomer (*E*) (Table 3, Entry 6). The enantioselectivity slightly increased when using $LiCH_2SiMe_3$, whereas the rate of the reaction decreased. The catalyst prepared from ligand (*R*)-H_2**L**^{4}, with naphthyl groups on the nitrogen atoms, afforded pyrrolidine **2a** with the same (*E*)/(*Z*) ratio and the same *ee* value for isomer (*E*) (51%) as those given by (*R*)-H_2**L**^{1} (Table 5, Entries 1 and 4). The similar behaviour of these two ligands had already been observed in reactions run with catalysts prepared according to Method B. Remarkably, for both ligands, the replacement of MeLi by $LiCH_2SiMe_3$ in the procedure led to a decrease in the *ee* value of isomer (*Z*) (compare Table 3, Entries 2 and 8 with Table 5, Entries 1 and 4). The lithium amide catalysts prepared from (*R*)-H_2**L**^{5} or (*R*)-H_2**L**^{6} and $LiCH_2SiMe_3$ led to product **2a** with or without low stereoselectivities and low values for the *ee* of both isomers (Table 5, Entries 5 and 6), as similarly observed when MeLi was employed as the base (Table 3, Entries 9–12). The cyclisation of substrate **1b** was further investigated by using catalysts prepared from different ligands according to Method C. Interestingly, ligand (*R*)-H_2**L**^{1} led to the preparation of piperidine **2b** within 18 h with high stereoselectivity for isomer (*E*) [(*E*)/(*Z*) = 90:10] and 72 and 58% *ee* for isomers (*E*) and (*Z*), respectively

Table 5. Asymmetric hydroamination of amino-1,3-dienes **1a** and **1b**[a] catalysed by the 1:2.5 (*R*)-H_2**L**/$LiCH_2SiMe_3$ precatalyst system[b] (Method C).

Entry	Substrate	Product	(*R*)-H_2**L**	Time [h]	Conversion[c] [%]	Ratio[d] (*E*)/(*Z*)	*ee*(*E*)[d] [%] (config.[e])	*ee*(*Z*)[d] [%] (config.[e])
1	**1a**	**2a**	(*R*)-H_2**L**^{1}	0.25	>95	92:8	50 (*S*)	14 (*S*)
2	**1a**	**2a**	(*R*)-H_2**L**^{2}	1	>95	30:70	6	1
3	**1a**	**2a**	(*R*)-H_2**L**^{3}	3	>95	24:76	18 (*S*)	61 (*R*)
4	**1a**	**2a**	(*R*)-H_2**L**^{4}	0.25	>95	92:8	51 (*S*)	13 (*S*)
5	**1a**	**2a**	(*R*)-H_2**L**^{5}	2	>95	51:49	35 (*S*)	18 (*R*)
6	**1a**	**2a**	(*R*)-H_2**L**^{6}	1	>95	58:42	20 (*S*)	9 (*R*)
7	**1b**	**2b**	(*R*)-H_2**L**^{1}	18	>95	90:10	72 (*S*)	58 (*S*)
8	**1b**	**2b**	(*R*)-H_2**L**^{4}	4	>95	90:10	73 (*S*)	42 (*S*)
9	**1b**	**2b**	(*R*)-H_2**L**^{5}	19	>95	64:36	51 (*S*)	2

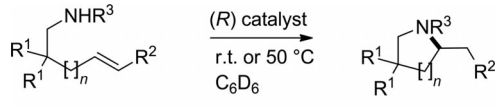
[a] Reactions were carried out in solution in C_6D_6 at room temp. (**1a**) or 50 °C (**1b**) with 10 mol-% of precatalyst. [b] Catalyst preparation was performed by the addition of 2.5 equiv. of $LiCH_2SiMe_3$ as an isolated powder to a solution of (*R*)-H_2**L** in C_6D_6 (*c* = 0.02–0.03 M) at room temp. After stirring for 10 min, substrates were directly added to this catalyst solution. [c] Measured by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis of the product following derivatisation with 2-benzoyl chloride. [e] See the Supporting Information for details.

(Table 5, Entry 7). Thus, the use of $LiCH_2SiMe_3$ resulted in the same *ee* value of isomer (*E*) and a slightly higher value for isomer (*Z*) than when Method B employing MeLi was used (Table 3, Entry 14). These enantioselectivities are the best reported to date for this piperidine.[15] A comparison of catalysts prepared from benzyl- and naphthyl-substituted binaphthyldiamines (*R*)-H_2**L**^{1} and (*R*)-H_2**L**^{4} revealed an increased reaction rate with the latter with the same stereo- and enantioselectivities for isomer (*E*) (Table 5, Entries 7 and 8) as observed with Method B (Table 3, Entries 14 and 18). Indeed, with a catalyst prepared from (*R*)-H_2**L**^{4} and $LiCH_2SiMe_3$, transformation of **1b** in piperidine **2b** was achieved with a ratio of (*E*)/(*Z*) = 90:10 and 73% *ee* for isomer (*E*). Catalysts resulting from ligand (*R*)-H_2**L**^{5}, either according to Method C (Table 5, Entry 9) or according to Method B (Table 3, Entry 20), led to similar results with lower reaction rates.

A comparison of the three methods did not reveal strong differences in stereo- and enantiodifferentiation for the cyclisation of 1,3-aminodienes in pyrrolidine **2a** or piperidine **2b**. Method C is a straightforward, in situ methodology that allows better tuning of the quantity of base and the simplest protocol for the preparation of the catalyst. The screening of different *N*-substituted binaphthyldiamines led to the selection of (*R*)-H_2**L**^{1} and (*R*)-H_2**L**^{4}, with benzyl and naphthyl groups, respectively, as ligands that provided the highest stereo- and enantioselectivities. For the synthesis of both products **2a** and **2b**, they allowed the selective formation of (*E*) isomers, with the highest enantioselectivity values. Noteworthy is the ability of ligand (*R*)-H_2**L**^{3} to promote the cyclisation of **1a** with a reversed stereoselectivity, leading preferentially to the (*Z*) isomer with a high *ee* value of 61%.

Hydroamination/Cyclisation of Aminoalkenes

Since only rare examples of asymmetric hydroamination/cyclisation of aminoalkenes promoted by lithium base catalysts have been reported,[5a–5c] our next goal was to study the efficiency of the diaminobinaphthyllithium salts described above for such reactions (Scheme 2). Catalysts prepared according to Methods A, B and C were first compared for the cyclisation of two substrates. We focused on aminoalkene **1c**, which was used as a test substrate in our former studies, and **1d**, which usually cyclised with a high rate due to a strong Thorpe–Ingold effect. Ligands (*R*)-H_2**L**^{1}, which led to the most enantioselective lithium-catalysed cyclisation of aminodienes **1a**–**b**, and (*R*)-H_2**L**^{5}, which led to the most enantioselective rare-earth-catalyzed cyclisations of aminoalkenes **1c** and **1d**, were selected as the most promising ligands for preparing the catalysts.[13b] The results are gathered in Table 6.



1c: *n* = 1, R^1 = –$(CH_2)_5$–, R^2 = R^3 = H
1d: *n* = 1, R^1 = Ph, R^2 = R^3 = H
1e: *n* = 1, R^1 = CH_3, R^2 = R^3 = H
1f: *n* = 1, R^1 = R^2 = Ph, R^3 = H
1g: *n* = 1, R^1 = –$(CH_2)_5$–, R^2 = H, R^3 = CH_3
1h: *n* = 1, R^1 = –$(CH_2)_5$–, R^2 = CH_3, R^3 = H
1i: *n* = 2, R^1 = –$(CH_2)_5$–, R^2 = R^3 = H

Scheme 2. Asymmetric hydroamination of aminoalkenes with chiral lithium amide derivatives.

Substrate **1c** could be cyclised with low *ee* values with catalysts prepared from (*R*)-H_2**L**^{1}, according to the three above-mentioned procedures (Table 6, Entries 1–3). Deceptively, the use of ligand (*R*)-H_2**L**^{5} did not result in an improvement in enantioselectivities regardless of the methodology employed for the catalyst preparation (Table 6, Entries 4–6). Notably, the highest reaction rates were observed with catalysts prepared with both ligands according to Method C. Pyrrolidine **2c** was thus obtained at room temperature within 2 h (Table 6, Entries 3 and 6). Conversely, a blank experiment conducted with 10 mol-% $LiCH_2TMS$ as the catalyst allowed the cyclisation of **1c**, but the reaction was considerably slower, indicating that this transformation

Table 6. Asymmetric hydroamination of aminoalkenes **1c**–**d**[a] catalysed by the 1:4 (*R*)-H_2**L**/MeLi precatalyst system (Methods A[b] or B[c]) or 1:2.5 (*R*)-H_2**L**/$LiCH_2TMS$ precatalyst system (Method C).[d]

Entry	Ligand	Substrate	Method	Time [h]	Conv. [%][e]	*ee*(**2**) [%][f,g]
1	(*R*)-H_2**L**^{1}	**1c**	A	4	>95	12
2	(*R*)-H_2**L**^{1}	**1c**	B	17	>95	10
3	(*R*)-H_2**L**^{1}	**1c**	C	2	>95	7
4	(*R*)-H_2**L**^{5}	**1c**	A	20[h]	>95	10
5	(*R*)-H_2**L**^{5}	**1c**	B	19	>95	11
6	(*R*)-H_2**L**^{5}	**1c**	C	2	>95	9
7	(*R*)-H_2**L**^{7}	**1c**	C	8	92	<5
8	(*R*)-H_2**L**^{8}	**1c**	C	4	90	11
9	(*R*)-H_2**L**^{1}	**1d**	A	4	92	9
10	(*R*)-H_2**L**^{1}	**1d**	B	17	>95	5
11	(*R*)-H_2**L**^{1}	**1d**	C	19	90	18
12	(*R*)-H_2**L**^{5}	**1d**	A	20	>95	58
13	(*R*)-H_2**L**^{5}	**1d**	B	19	>95	51
14	(*R*)-H_2**L**^{5}	**1d**	C	2	90	56
15	(*R*)-H_2**L**^{7}	**1d**	C	24	87	48
16	(*R*)-H_2**L**^{8}	**1d**	C	4	75	55

[a] Reactions were carried out in C_6D_6 at room temp. with 10 mol-% of precatalyst. [b] Method A: catalyst preparation was performed by dropwise addition of 4 equiv. of a solution of MeLi in diethyl ether (1.6 M) to a solution of the ligand (*R*)-H_2**L** in diethyl ether (c = 0.025 M) at room temp., followed by stirring for 10 min and concentration in vacuo. [c] Method B: catalyst preparation was performed by dropwise addition of 4 equiv. of a solution of MeLi in diethyl ether (1.6 M) to a solution of the ligand (*R*)-H_2**L** in C_6D_6 (c = 0.025 M) at room temp. After stirring for 10 min, substrates were directly added to this catalyst solution. [d] Method C: catalyst preparation was performed by addition of 2.5 equiv. of $LiCH_2SiMe_3$ as isolated powder to a solution of (*R*)-H_2**L** in C_6D_6 (c = 0.02–0.03 M) at room temp. After stirring for 10 min, substrates were directly added to this catalyst solution. [e] Measured by ^{1}H NMR spectroscopy. [f] Determined by HPLC analysis of the product following derivatisation with 2-benzoyl chloride. [g] See the Supporting Information for details. [h] Reaction was performed at 50 °C.

was not competing with the asymmetric cyclisation. The dimeric chiral diaminobinaphthyl dilithium salt reported by Hultzsch et al. was far more enantioselective, since **2c** was isolated under these conditions with 75% *ee*.[5a] The hydroamination of substrate **1d** catalysed by lithium amide prepared from (*R*)-H_2**L**^{1} by any of the three methods afforded pyrrolidine **2d** with small *ee* values (Table 6, Entries 9–11). The binaphthyldiamine with cyclopentyl groups on the nitrogen atoms, (*R*)-H_2**L**^{5}, afforded more enantioselective catalysts regardless of the base used. Pyrrolidine **2d** was obtained with 51–58% *ee* (Table 6, Entries 12–14), and the shortest reaction time was again observed for the catalyst prepared in situ by using $LiCH_2SiMe_3$ as the base (Table 6, Entry 14). In this case, the chiral lithium amide prepared from (*R*)-H_2**L**^{5} afforded pyrrolidine **2d** with an improved *ee* than that reported in the literature, which was obtained under comparable conditions.[5a] An analogous blank experiment was run with **1d** ($LiCH_2SiMe_3$ in catalytic amount in the absence of ligand), leading to similar results as those observed for the cyclisation of **1c**. A ligand-accelerating effect is thus clearly observed for the hydroamination of aminoalkenes **1c** and **1d**. The simple Method C, involving in situ preparation of catalyst with $LiCH_2SiMe_3$, is the most efficient for the cyclisation of aminoalkenes **1c** and **1d** and is thus employed for the following studies. Since ligand (*R*)-H_2**L**^{5}, as the sterically most hindered ligand on the nitrogen atoms, led to interesting results in terms of enantioselectivity, at least for substrate **1d**, two analogous ligands with cyclohexyl and isopropyl substituents, respectively, (*R*)-H_2**L**^{7} and (*R*)-H_2**L**^{8}, were tested in these transformations. The corresponding chiral lithium amide derivatives were prepared according to Method C and were used to promote cyclisation of both substrates (Table 6, Entries 7, 8, 15 and 16). The reactions were, in all cases, completed in longer reaction times than those with ligand (*R*)-H_2**L**^{5}. Pleasingly, however, the use of these ligands afforded 2-methyl-4,4-diphenylpyrrolidine with up to 55% *ee* (Table 6, Entry 16).

Hydroamination of more demanding substrates **1e**–**i** catalysed by lithium amides prepared with $LiCH_2SiMe_3$, according to Method C, were next examined. These results are reported in Table 7. For aminoalkene **1e** substituted by a *gem*-dimethyl group, cyclisation could be achieved at room temperature, and pyrrolidine **2e** was obtained, albeit with a low *ee* value, using ligand (*R*)-H_2**L**^{1} (Table 7, Entry 1). The same transformation was run in the presence of ligand (*R*)-H_2**L**^{5}, but the enantioselectivity was not improved, and the reaction times were longer than those with (*R*)-H_2**L**^{1} (Table 7, Entry 2). Noticeable is the absence of conversion into pyrrolidine **2e** in a blank experiment with 20 mol-% $LiCH_2TMS$ in the absence of ligand. The transformation of 1,2-disubstituted aminoalkene **1f** was very fast with both catalysts prepared from ligands (*R*)-H_2**L**^{1} and (*R*)-H_2**L**^{5}, but the product was obtained as a racemic form (Table 7, Entries 3 and 4). Interestingly, secondary aminoalkene **1g** could be transformed into pyrrolidine **2g** with catalysts prepared from ligands (*R*)-H_2**L**^{1} and (*R*)-H_2**L**^{5} with $LiCH_2SiMe_3$, either at room temperature or 50 °C (Table 7, Entries 5–8), although the products were nearly racemic. This cyclisation could not be performed by a catalytic amount of $LiCH_2SiMe_3$ in the absence of ligand. The more demanding 1,2-disubstituted aminoalkene **1h**, which has been cyclised only at elevated temperature with rare-earth-based catalysts,[4m,16] could not be transformed into the corresponding pyrrolidine **2h** at 50 °C by using the catalyst prepared from benzyl-substituted binaphthyldiamine (*R*)-H_2**L**^{1} (Table 7, Entry 9). Under similar conditions, aminoalkene **1i** was not cyclised to the corresponding piperidine, but transformed into a product resulting from the isomerisation of the double bond (Table 7, Entry 10). The chiral lithium amide prepared from *N*,*N*′-dibenzylbinaphthyldiamine [(*R*)-H_2**L**^{1}] and $LiCH_2SiMe_3$ was thus revealed as a very efficient catalyst for the transformation of primary or secondary aminoalkenes, despite not being active for the most demanding olefins, such as amino-tethered 1,2-dialkyl-substituted alkenes, or for the preparation of piperidines. Whereas this catalyst afforded the highest enantioselectivity for the hydroamination/cyclisation of amino-1,3-dienes, it conversely proved to be poorly enantioselective for the transformation of aminoalkenes. Ligand (*R*)-H_2**L**^{5},

substituted by cyclopentyl groups on the nitrogen atoms, gave promising *ee* values (up to 58% *ee*) for pyrrolidine **2d**, which contained a *gem*-diphenyl group.

Table 7. Asymmetric hydroamination of aminoalkenes **1e**–**i**[a] when using Method C as the procedure for catalyst preparation.[b]

Entry	Ligand	Substrate	Time [h]	Conv. [%][c]	*ee*(**2**) [%][d,e]
1	(*R*)-H_2**L**^{1}	**1e**	44	92	4
2	(*R*)-H_2**L**^{5}	**1e**	60	>95	7
3	(*R*)-H_2**L**^{1}	**1f**	0.33	>95	2
4	(*R*)-H_2**L**^{5}	**1f**	0.33	>95	0
5	(*R*)-H_2**L**^{1}	**1g**	16	>95	5
6	(*R*)-H_2**L**^{1}	**1g**	2[f]	>95	9
7	(*R*)-H_2**L**^{5}	**1g**	24	>95	5
8	(*R*)-H_2**L**^{5}	**1g**	2[f]	>95	2
9	(*R*)-H_2**L**^{1}	**1h**	19[f]	0	
10	(*R*)-H_2**L**^{1}	**1i**	19[f]	–[g]	

[a] Reactions were carried out in C_6D_6 at room temp. or 50 °C with 10 mol-% of the precatalyst. [b] Catalyst preparation was performed by the addition of 2.5 equiv. of $LiCH_2SiMe_3$ as an isolated powder to a solution of (*R*)-H_2**L** in C_6D_6 (c = 0.02–0.03 M) at room temp. After stirring for 10 min, substrates were directly added to this catalyst solution. [c] Measured by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis of the product following derivatisation with 2-benzoyl chloride. [e] See the Supporting Information for details. [f] Reaction was performed at 50 °C. [g] A total conversion was observed in the product that resulted in isomerisation of the double bond.

Conclusions

Substituted chiral binaphthyldiamine-based ligands were thus used as precursors for the formation of the corresponding lithium amide salts to promote the hydroamination/cyclisation of amino-1,3-dienes and aminoalkenes efficiently. Various catalyst preparation procedures were investigated, which allowed the fine-tuning of a straightforward protocol, resulting in an easy procedure for the formation of active catalysts for both substrates types. In particular, stereodefined 2-propenylpyrrolidine **2a** or -piperidine **2b** were prepared within short reaction times and with a level of enantioselection that competed well with the rare examples described in the literature.[15] Although aminoalkenes could be rapidly cyclised with this system, the corresponding products were obtained in only low to moderate enantioselectivities.

We have previously reported the description of the lithium amide complex arising from the use of ligand (±)-H_2**L**^{1} in the presence of 2 equiv. of base (MeLi), obtained by X-ray analysis.[5d] It was characterised as a monomeric species and showed no activity as a catalyst precursor for intramolecular hydroamination. We have demonstrated herein that, in all cases, a slight excess of base (relative to the ligand) was necessary to conduct the catalytic transformation. Mechanistic investigations are needed to propose some intermediates in the catalytic cycle, but we assume that the excess of base induces the deprotonation of a small amount of substrate to increase the nucleophilicity of the nitrogen atom. The role of the chiral lithium ligand could be to activate the double bond in a stereodefined environment.

Experimental Section

General Procedure for NMR-Scale Asymmetric Intramolecular Hydroamination of Amino-1,3-Dienes 1a and 1b and Aminoalkenes 1c–i by Method C: A solution of $LiCH_2SiMe_3$ (20 mg, 0.20×10^{-3} mol) in [D_6]benzene (0.6 mL) was added dropwise to a solution of the appropriate ligand (*R*)-H_2**L** (0.08×10^{-3} mol) in [D_6]benzene (1.8 mL) in an argon-filled Schlenk tube at room temperature. The homogeneous yellow reaction solution was then stirred at ambient temperature for 15 min. In an argon-filled glovebox, an aliquot (600 μL) of the homogeneous reaction mixture was removed by a micropipette and transferred to a vial containing the corresponding substrate (0.20×10^{-3} mol). The reaction mixture was then introduced into a screw-cap or a J-Young NMR tube. After the appropriate time, the reaction was quenched by the addition of a small amount of dichloromethane.

Procedure for Asymmetric Intramolecular Hydroamination of 1a to 2a by Method A: Table 3, Entry 1. A 1.6 M solution of MeLi (200 μL, 0.32×10^{-3} mol) in diethyl ether was added dropwise to a solution of (*R*)-*N*,*N*′-bis(benzyl)-1,1′-binaphthyl-2,2′-diamine (*R*)-H_2**L**^{1} (37 mg, 0.08×10^{-3} mol) in diethyl ether (5 mL) in an argon-filled Schlenk tube equipped with an O-ring tap (J. Young) at room temperature. The homogeneous yellow reaction solution was then stirred at ambient temperature for 10 min and concentrated in vacuo. In an argon-filled glovebox, the corresponding residue was dissolved in [D_6]benzene (2 mL), and the mixture was removed by a micropipette and transferred to a vial containing the substrate **1a** (88 mg, 0.80×10^{-3} mol). The reaction mixture was then introduced into a Schlenk tube equipped with an O-ring tap (J. Young). After 15 min, the reaction was quenched by the addition of a small amount of dichloromethane, and the mixture was distilled under reduced pressure. A solution of hydrogen chloride in methanol (1.25 M; 2 mL) was added dropwise to the colourless solution. The mixture was stirred at room temperature for 1 h and was then concentrated in vacuo to afford **2a**·HCl as a pale yellow solid (80 mg, 68%). $[a]_D^{25}$ = +84.0 (c = 0.70, CH_3OH). IR (neat): $\tilde{\nu}$ = 3407, 3050, 2917, 2740, 2558, 2480, 1632, 1587, 1451, 1422, 1310, 1069, 1021, 969 cm^{-1}. ^{1}H NMR (360 MHz, D_2O): δ = 6.05 (dq, J = 15.2 and 6.6 Hz, 1 H, H$^{2'}$), 5.63 (ddd, J = 15.2 and 8.2 and 1.6 Hz, 1 H, H$^{1'}$), 4.12 (q, J = 8 Hz, 1 H, H^2), 3.38–3.34 (m, 2 H, H^5), 2.44–2.08 (m, 3 H, H^3 and 2H^4), 1.80–1.77 (m, 1 H, H^3), 1.78 (dd, J = 6.6 and 1.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz; D_2O): δ = 134.3, 124.4, 62.1, 44.6, 29.9, 23.2, 17.1 ppm. MS (ESI): *m*/*z* (%) = 112 (100) [M]$^+$. HRMS: calcd. for $C_7H_{14}N$ [M]$^+$ 112.1121; found 112.1126.

Procedure for Asymmetric Intramolecular Hydroamination of 1b to 2b by Method A: Table 3, Entry 13. A 1.6 M solution of MeLi (200 μL, 0.32×10^{-3} mol) in diethyl ether was added dropwise to a solution of (*R*)-H_2**L**^{1}(37 mg, 0.08×10^{-3} mol) in diethyl ether (5 mL) in an argon-filled Schlenk tube equipped with an O-ring tap (J. Young) at room temperature. The homogeneous yellow reaction solution was then stirred at ambient temperature for 10 min and concentrated in vacuo. In an argon-filled glovebox, the corresponding residue was dissolved in [D_6]benzene (2 mL), and the mixture was removed by a micropipette and transferred to a vial containing the substrate **1b** (100 mg, 0.80×10^{-3} mol). The reaction mixture was then introduced into a Schlenk tube equipped with an O-ring tap (J. Young) and was heated at 50 °C. After 20 h, the reaction was quenched by the addition of a small amount of dichlorometh-

ane, and the mixture was distilled under reduced pressure. A solution of hydrogen chloride in methanol (1.25 M, 2 mL) was added dropwise to the colourless solution. The mixture was stirred at room temperature for 1 h and was then concentrated in vacuo to afford **2b**·HCl as a pale yellow solid (80 mg, 62%). $[\alpha]_D^{25}$ = +114.0 (c = 1.05, CH_3OH). IR (neat): $\tilde{\nu}$ = 3405, 3199, 2933, 2582, 2527, 2416, 1676, 1588, 1455, 1434, 1379, 1312, 1269, 1077, 1021, 967 cm^{-1}. ^1H NMR (360 MHz, D_2O): δ = 5.92 (dq, J = 15.5 and 6.9 Hz, 1 H , $H^{2'}$), 5.48 (ddd, J = 15.5 and 7.9 and 1.4 Hz, 1 H, $H^{1'}$), 3.62 (m, 1 H, H^2), 3.35 (d, J = 12 Hz, 1 H, H^{6b}), 2.97 (dd, J = 12 Hz, 1 H, H^{6a}), 1.93–1.82 (m, 3 H, H^{3b}, H^{4b} and H^{5b}), 1.68 (d, J = 6.8 Hz, 3 H, CH_3), 1.58–1.52 (m, 3 H, H^{3a}, H^{4a} and H^{5a}) ppm. ^{13}C NMR (62.5 MHz, D_2O): δ = 134.2, 127.2, 59.3, 45.4, 29.8, 22.7, 22.6, 18.3 ppm. MS (ESI): m/z (%) = 126 (100) $[M]^+$. HRMS: calcd. for $C_8H_{16}N$ $[M]^+$ 126.1277; found 126.1278.

Supporting Information (see footnote on the first page of this article): Complete experimental procedures, full characterisation and *ee* determinations.

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