VIP Asymmetric Hydroamination

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A Chiral Phenoxyamine Magnesium Catalyst for the Enantioselective Hydroamination/Cyclization of Aminoalkenes and Intermolecular Hydroamination of Vinyl Arenes**

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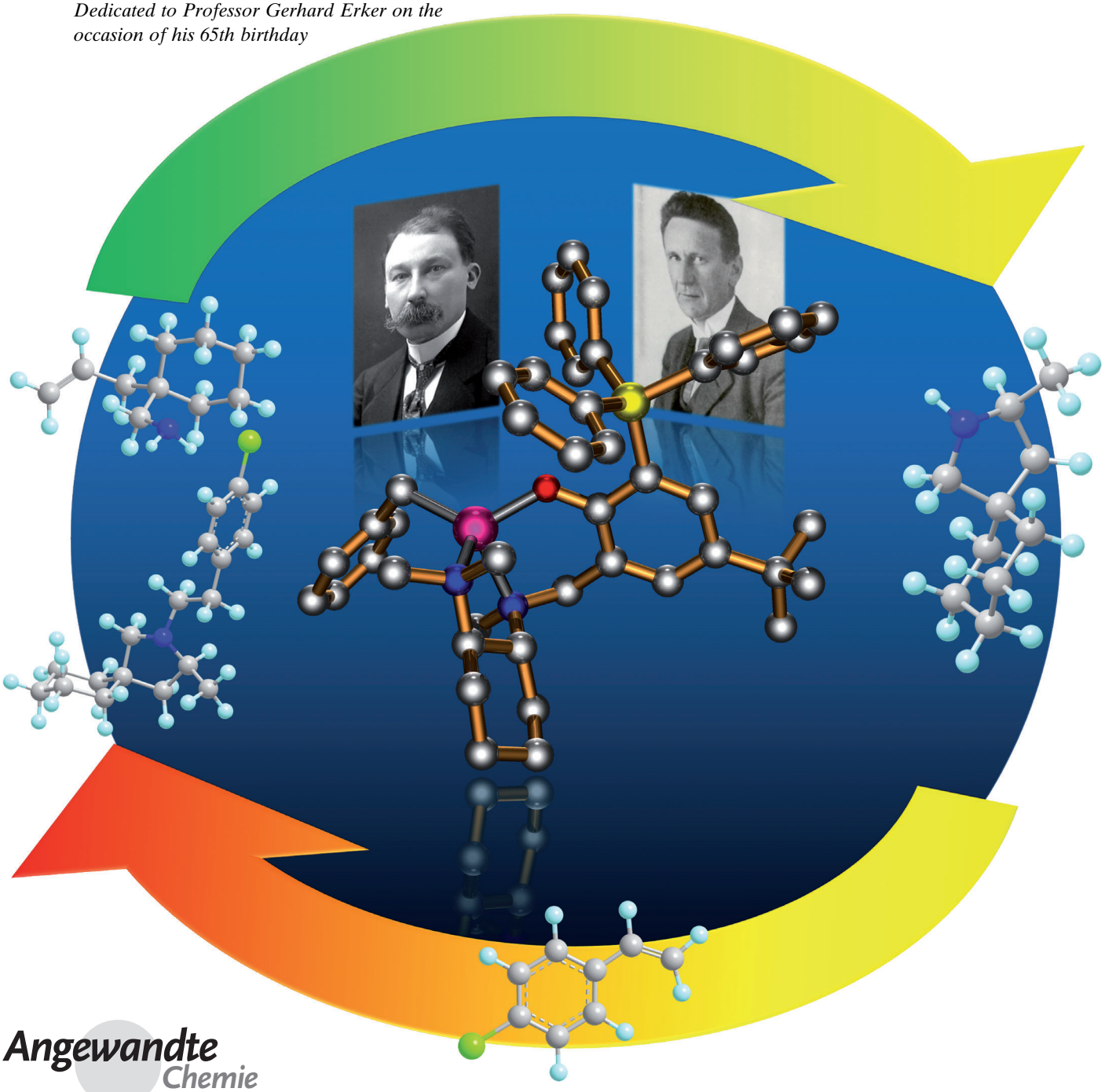
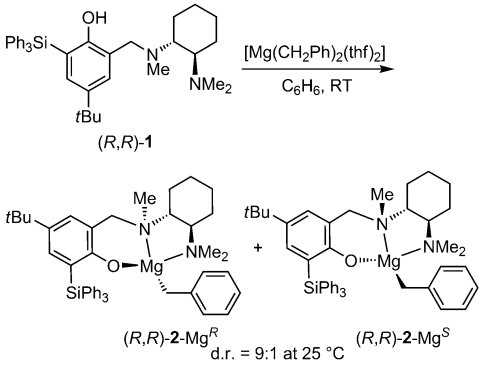
Dedicated to Professor Gerhard Erker on the occasion of his 65th birthday



The application of alkaline earth metal complexes as substitutes for transition-metal catalysts in alkene hydrofunctionalizations has drawn increasing attention in recent years owing to their abundance, biocompatibility, and chemical behavior, which resembles that of the rare-earth elements.[1] A number of magnesium, calcium, and strontium catalysts[2] have been shown to exhibit activity comparable to catalysts based on rare-earth metals[3] in the highly desirable hydroamination reaction.[4] Unfortunately, alkaline earth metal complexes are prone to facile Schlenk-type ligand redistributions[1,5] that can result in catalyst deactivation and hamper efforts to perform these transformations in a stereoselective[6] manner. Indeed, previous attempts to elaborate chiral alkaline earth metal catalysts for asymmetric hydroaminations have not produced enantioselectivities exceeding 36% *ee*.[7] In order to address this issue we have recently developed achiral phenoxyamine magnesium catalysts that resist ligand-redistribution reactions under the conditions of hydroamination catalysis.[8] Herein we disclose our findings on the development of a chiral magnesium catalyst for the enantioselective hydroamination which achieves—unprecedented for alkaline earth metal catalysts—enantioselectivities of up to 93% *ee*.[9] The high catalytic activity of this system permits reactions to be performed at or below room temperature in several cases, which is unprecedented in the chemistry of alkaline earth metal complexes as well.[10]

Chiral phenoxyamine ligands incorporating a chelating cyclohexyldiamine arm have been applied in indium-[11] and zinc-catalyzed[12] lactide polymerizations. We decided to utilize the related phenoxyamine ligand (*R*,*R*)-**1** in which the increased steric demand of the triphenylsilyl substituent should eliminate undesired ligand-exchange processes and improve stereoselectivity. Reaction of (*R*,*R*)-**1** with [Mg(CH$_2$Ph)$_2$(thf)$_2$] produced the phenoxyamine magnesium complex (*R*,*R*)-**2** as a 9:1 mixture of diastereomers (based on ^{1}H NMR spectroscopy) in 63% yield of crystallized product (Scheme 1).[13] The two diastereomers differ in the chirality at magnesium and the central *N*-methyl amine group.[12] A second recrystallization furnished pure (*R*,*R*)-**2**-Mg^R (Figure S1a in the Supporting Information).[14] A solution of pure (*R*,*R*)-**2**-Mg^R in [D$_6$]benzene slowly returned to the 9:1 equilibrium mixture of diastereomers within 5 h at 25 °C (Figure S1b).[14] The complex was stable at 80 °C for 12 h, and a mixture of both diastereomers was obtained in a 5:1 ratio (Figure S1c);[14] this composition was retained for 24 h when the mixture was allowed to cool to room temperature.[15] Higher temperatures (120 °C) resulted in decomposition of the precatalyst **2**, but a model complex for the catalytically active magnesium amide species was found to be stable under these conditions (vide infra).



Scheme 1. Synthesis of the chiral phenoxyamine magnesium complex (*R*,*R*)-**2**.

The X-ray crystallographic analysis of *rac*-**2** (Figure 1)[16] revealed the expected tetrahedral geometry around magnesium as seen in achiral phenoxyamine magnesium complexes[8,17] and related zinc complexes.[12] The methine proton on C15 is oriented *trans* to the *N*-methyl group at N2 which results in an *R*-configured magnesium stereocenter in the (*R*,*R*)-cyclohexyldiamine enantiomer.

With complex (*R*,*R*)-**2** in hand we were eager to evaluate its catalytic performance in intramolecular hydroaminations (Table 1). We were pleased to find that (*R*,*R*)-**2** displayed high catalytic activity as well as outstanding enantioselectivities in the cyclizations of aminopentenes **3a–d**. Reactions with 2–5 mol% catalyst were complete within 1.5–10 h at 22 °C. More intriguingly and unprecedented for alkaline earth metal catalysts, the cyclization of the more activated substrates **3a–c** proceeded also readily at −20 °C (Table 1, entries 2, 5, and 9) with the highest enantioselectivity of 90% *ee* observed

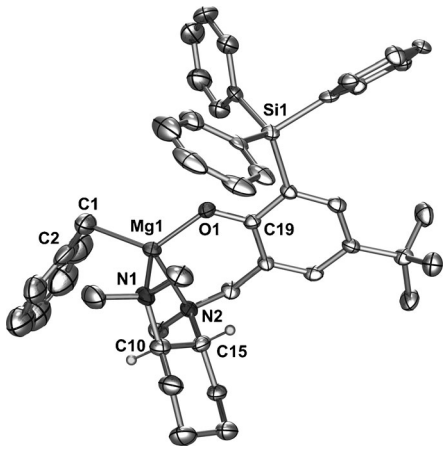


Figure 1. ORTEP diagram of the molecular structure of *rac*-**2**. Thermal ellipsoids are shown at the 50% probability level, and hydrogen atoms, except for those attached to C10 and C15, are omitted for clarity. Selected bond lengths [Å] and angles [°]: Mg1–O1 1.896(4), Mg1–N1 2.157(5), Mg1–N2 2.149(5), Mg1–C1 2.152(6); O1-Mg1-N1 111.22(18), O1-Mg1-N2 95.17(17), O1-Mg1-C1 121.9(2), N1-Mg1-C1 113.9(3), N2-Mg1-C1 124.2(2), N1-Mg1-N2 83.25(18), Mg1-O1-C19 129.1(3), Mg1-C1-C2 114.8(5).

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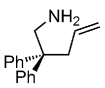
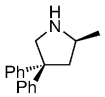
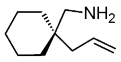
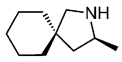
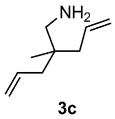
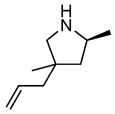
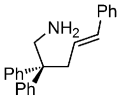
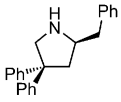
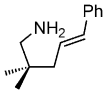
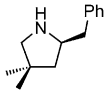
Table 1: Asymmetric intramolecular hydroamination/cyclization of aminoalkenes catalyzed by (*R*,*R*)-**2**.[a]

Entry	Substrate	Product	*T* [°C]; *t* [h][b]	*ee* [%][c]
1	 **3a**	 **4a**	22; 1.5[d]	74
2			−20; 12[d,e]	80
3	 **3b**	 **4b**	22; 2	84
4			22; 4.5[f]	85
5			−20; 48[e]	90
6			22; 2	84[g]
7			22; 2	83[h]
8	 **3c**	 **4c**	22; 3	76/76[i]
9			−20; 72[e]	82/82[i]
10	 **3d**	 **4d**	22; 10	79
11	 **3e**	 **4e**	80; 72[j,k]	51
12	 **3f**	 **4f**	22; 0.1	88
13			22; 0.2[f]	90
14			−20; 12[e,f]	93[l]
15	 **3g**	 **4g**	22; 2[m]	88
16			−20; 36[e]	92[l]
17			22; 3	86[h]

[a] Reaction conditions: 0.1 mmol substrate, 5 mol% (*R*,*R*)-**2** (d.r. = 9:1), 0.6 mL [D_6]benzene, Ar atmosphere. [b] Time required to achieve ≥95% yield (NMR analysis; ferrocene as internal standard). [c] Determined by ^{19}F NMR analysis of Mosher amides. [d] 3 mol% (*R*,*R*)-**2**. [e] Reaction in [D_8]toluene. [f] 2 mol% (*R*,*R*)-**2**. [g] Pure (*R*,*R*)-**2**-Mg^R. [h] (*R*,*R*)-**2** (d.r. = 5:1). [i] d.r. = 1.2:1. [j] 10 mol% (*R*,*R*)-**2**. [k] 81% yield (NMR analysis). [l] Enantiomeric excess was also confirmed by HPLC with a chiral stationary phase. [m] Preparative-scale reaction: 86% yield of isolated product.

in the cyclization of **3b**. The reaction of the unsubstituted aminopentene **3e** required heating to 80 °C and proceeded with a reduced selectivity of 51% *ee*.[18]

Substrates **3f** and **3g** containing an 1,2-disubstituted double bond were cyclized rapidly at 22 °C as a result of the activating effect of the electron-withdrawing phenyl substituent. Both substrates could also be cyclized at −20 °C to furnish the pyrrolidines **4f** and **4g** in 93 and 92% *ee* (Table 1, entries 14 and 16), respectively. The enantioselectivities obtained for **4b**, **4f**, and **4g** are among the highest published results so far.[19,20]

Overall, (*R*,*R*)-**2** exhibits at room temperature catalytic activity comparable to that of Hill's β-diketiminate magnesium complex,[2e,k] but it is more active than our achiral phenoxyamine complexes[8] and Sadow's tris(oxazolinyl)phenylborato magnesium complexes.[2l,7c]

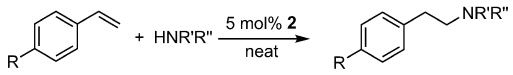
The presence of a mixture of diastereomers could pose a problem in obtaining reproducible selectivities with different batches of precatalyst. However, we were unable to find a significant difference in the selectivity when either diastereomerically pure (*R*,*R*)-**2**-Mg^R or a 5:1 diastereomeric mixture of the precatalysts were applied in the cyclization of **3b** and **3g** (Table 1, entries 6, 7, and 17). The stoichiometric reaction of (*R*,*R*)-**2** with 1–3 equiv of pyrrolidine in [D_6]benzene at various temperatures uniformly showed a 9:1 diastereomeric ratio and no decomposition became apparent after 3 h at 120 °C (Figures S2 and S3 in the Supporting Information).[14]

Kinetic studies show that the cyclization of **3b** is first-order in catalyst and substrate (Figures S8 and S9).[14] This contrasts our finding for related achiral triphenylsilyl-substituted phenoxyamine complexes that exhibited zero-order kinetics in substrate.[8] Certainly, the cyclohexyl ring side chain in (*R*,*R*)-**2** is significantly more rigid than the propylidene side chain in the achiral phenoxyamine complexes. The slow rate of diastereomer interconversion observed for (*R*,*R*)-**2**-Mg^R in [D_6]benzene indicates that dissociation of the side arm in (*R*,*R*)-**2** is hampered. The catalytic reaction proceeded also with a considerable primary kinetic isotope effect ($k_H/k_D = 3.6$, Figure S10),[14] but no significant change in enantioselectivity was observed (84% *ee* for **4b** vs. 82% *ee* for [D_2]**4b**). These findings suggest that the cyclization of aminoalkenes by (*R*,*R*)-**2** proceeds by means of a concerted alkene-insertion/protonolysis mechanism[21,22] analogous to that recently proposed by Hill et al.[2k] and Sadow et al.[2l]

In order to further exploit the catalytic activity of the magnesium catalyst **2** we decided to investigate the significantly more challenging intermolecular hydroamination of alkenes.[2f,3a,23] Hill and co-workers recently reported that homoleptic calcium and strontium amides catalyze the anti-Markovnikov addition of amines to vinyl arenes, but the corresponding magnesium amide was much inferior.[2f,24] Gratifyingly, complex **2** is also capable of catalyzing these transformations efficiently. The addition of pyrrolidine to styrene proceeded to 87% conversion with exclusive anti-Markovnikov regioselectivity within 16 h at 60 °C in neat solution using 5 mol% of (*R*,*R*)-**2** (Table 2, entry 1). The addition of pyrrolidine to the more-electron-deficient *p*-chlorostyrene required only 4 h at 60 °C to reach 89% conversion, and even at room temperature the reaction proceeded to 69% conversion in 48 h. The reaction of benzylamine required a higher reaction temperature of 80 °C to give 76% conversion in 8 h. Overall, the activity of the magnesium complex (*R*,*R*)-**2** seems to be of comparable magnitude to the calcium and strontium amides investigated by Hill et al.[2f]

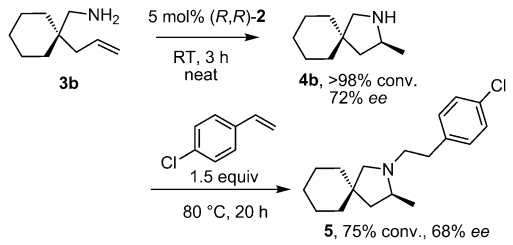
The potential of our magnesium catalyst was also demonstrated in a intramolecular/intermolecular tandem reaction (Scheme 2). Cyclization of **3b** (neat) with (*R*,*R*)-**2** at room temperature produced **4b** quantitatively in slightly lower selectivity than under more dilute conditions (cf.

Table 2: Catalytic intermolecular hydroamination of vinyl arenes with amines.[a]



Entry	R	Amine	*T* [°C]	*t* [h]	Conv. [%][b]
1	H	$(CH_2)_4NH$[c]	60	16	87
2	Cl	$(CH_2)_4NH$	60	4	89 (62)
3	Cl	$(CH_2)_4NH$	22	48	69
4	Cl	$PhCH_2NH_2$	80	8	76

[a] Reaction conditions: 0.24 mmol vinyl arene, 0.2 mmol amine, 5 mol% (*R*,*R*)-**2**, Ar atmosphere. [b] Determined by ^{1}H NMR spectroscopy. The value given in parenthesis is the yield of isolated product from a preparative-scale reaction. [c] Vinyl arene/amine = 3:2.



Scheme 2. Magnesium-catalyzed tandem intramolecular/intermolecular hydroamination.

Table 1, entry 3). Subsequently, the addition of **4b** to *p*-chlorostyrene proceeded at 80 °C in 20 h to 75% conversion to give the tertiary pyrrolidine **5** (56% yield of isolated product) in 68% *ee*.[25]

The results presented herein highlight the great potential of alkaline earth metal catalysts in the very challenging areas of asymmetric and intermolecular hydroamination. The suppression of Schlenk-type ligand-redistribution processes is an important prerequisite to achieve high enantioselectivities. With the catalyst system (*R*,*R*)-**2** presented herein we have successfully demonstrated that this goal is attainable utilizing a sterically demanding phenoxyamine ligand set. The enantioselectivities achieved with catalyst (*R*,*R*)-**2** in the cyclization of aminoalkenes significantly surpass all previous attempts reported for alkaline earth metal based catalysts. At the same time, complex (*R*,*R*)-**2** displays high catalytic activity and reactions have been carried out below room temperature for the first time using alkaline earth metal catalysts. Finally, we have shown that magnesium-based complexes can be viable catalysts for intermolecular hydroamination reactions (including tandem intramolecular/intermolecular processes) with activities comparable in magnitude to the usually much more reactive calcium- and strontium-based catalysts. Therefore, it can be anticipated that the corresponding phenoxyamine complexes of the heavier alkaline-earth metals will exhibit even greater catalytic performance.

Experimental Section

Typical catalytic intermolecular hydroamination reaction: A screw-cap vial was charged with the catalyst precursor (*R*,*R*)-**2** (6.9 mg, 0.01 mmol, 5 mol%), the olefin (0.24 mmol), and the amine (0.2 mmol). The vial was then placed in a preheated metal block (25–80 °C), and conversion was monitored by ^{1}H and ^{13}C NMR spectroscopy from samples taken from the reaction mixture. Final conversions were determined from the disappearance of characteristic olefinic signals. For a preparative-scale reaction see the Supporting Information.

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[13] The racemic complex *rac*-**2** was prepared in a similar manner and exhibits identical spectroscopic properties. See the Supporting Information.

[14] See the Supporting Information.

[15] This is in agreement with observations made for related phenoxyamine zinc complexes, see Ref. [12]. However, addition of 3 equiv of pyrrolidine to a 5:1 mixture of (*R*,*R*)-**2**-Mg^R and (*R*,*R*)-**2**-Mg^S produced a pyrrolidinide complex that equilibrated to a 10:1 mixture of diastereomers within 30 min.

[16] Crystal size 0.30 × 0.03 × 0.02 mm, trigonal, space group $P\bar{3}$, $Z = 6$; $a = 25.467(3)$, $b = 25.467(3)$, $c = 11.2793(15)$ Å, $V = 6335.5(14)$ Å^3, $d_{calcd} = 1.124$ g cm^{-3}, $T = 100(2)$ K, $1.8° < \theta < 20.8°$, ($Mo_{K\alpha}$ 0.71073 Å, $\mu = 0.106$ mm^{-1}), 34459 reflections measured, 4422 independent [$R_{int} = 0.2191$]. Cell parameters were obtained from 4693, reflections within the range $2.4 < \theta < 23.3°$. Lorentz, polarization, and empirical absorption corrections were applied. The space group was determined from systematic absences (XPREP program). The structure was solved by direct methods (SHELXS-97). All positional and atomic displacement parameters (ADP) were refined with all reflections data by full-matrix least squares on F^2 using SHELXL-97. Non-hydrogen atoms were refined anisotropically, 506 parameters, $R = 0.0723$, $wR_2 = 0.1990$, min./max. residual electron density 0.497/−0.366 e A^{-3}. CCDC 835382 (*rac*-**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] A. R. F. Cox, V. C. Gibson, E. L. Marshall, A. J. P. White, D. Yeldon, *Dalton Trans.* **2006**, 5014 – 5023.

[18] Enantioenriched 2-methylpiperidines can be prepared with slightly reduced rates and moderate enantioselectivities. For example, cyclization of 2,2-diphenylhex-5-en-1-amine is carried out with 5 mol% (*R*,*R*)-**2** at 22 °C within 6 h in 98% yield (NMR analysis) and 25% *ee*. Similarly, the cyclization of aminopentenes containing a secondary amino group requires elevated temperatures and provides moderate enantioselectivities. Thus, cyclization of *N*-benzyl-2,2-diphenylpent-4-en-1-amine proceeds at 70 °C using 10 mol% (*R*,*R*)-**2** within 15 h in 98% yield (NMR analysis) and 20% *ee*.

[19] Reported *ee* values in the literature: a) Ref. [9a]: **4b** 85%; **4g** 72%; b) Ref. [9b]: **4b** 82%; c) Ref. [9f]: **4b** 94%; d) Ref. [20a]: **4g** 82%; e) Ref. [20b]: **4b** 87%; f) Ref. [20c]: **4f** 55%.

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[21] a) This mechanism was first proposed by Marks for lanthanide-catalyzed hydroamination reactions as a rationale for the significant primary kinetic isotope effect observed in these transformations, see: M. R. Gagné, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 275 – 294; b) For a computational study of this mechanism for lanthanide-catalyzed aminodiene cyclizations see: S. Tobisch, *Chem. Eur. J.* **2010**, *16*, 13814 – 13824; c) A noninsertive mechanism was also proposed for group-4-metal-catalyzed hydroaminations of alkenes, see Ref. [9f] and L. E. N. Allan, G. J. Clarkson, D. J. Fox, A. L. Gott, P. Scott, *J. Am. Chem. Soc.* **2010**, *132*, 15308 – 15320.

[22] Owing to the catalytically active Mg – amide species, this mechanism differs from purely Lewis acid catalyzed hydroaminations, e.g. with $Zn(OTf)_2$, see: V. Neff, T. E. Müller, J. A. Lercher, *Chem. Commun.* **2002**, 906 – 907.

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[24] For alkali-metal-catalyzed hydroaminations of vinyl arenes, see: a) M. Beller, C. Breindl, T. H. Riermeier, M. Eichberger, H. Trauthwein, *Angew. Chem.* **1998**, *110*, 3571 – 3573; *Angew. Chem. Int. Ed.* **1998**, *37*, 3389 – 3391; b) K. Kumar, D. Michalik, I. G. Castro, A. Tillack, A. Zapf, M. Arlt, T. Heinrich, H. Böttcher, M. Beller, *Chem. Eur. J.* **2004**, *10*, 746 – 757; c) P. Horrillo-Martínez, K. C. Hultzsch, A. Gil, V. Branchadell, *Eur. J. Org. Chem.* **2007**, 3311 – 3325.

[25] The slight erosion of enantiomeric excess of the tandem hydroamination product **5** in comparison to intermediate **4b** presumably results from a weak kinetic discrimination of the two enantiomers of **4b** by the chiral catalyst (*R*,*R*)-**2** in the intermolecular hydroamination. Unreacted pyrrolidine **4b** was found to have a slightly increased enantiomeric excess of 75% *ee*.

