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Intramolecular hydroamination/cyclization of aminoalkenes catalyzed by diamidobinaphthyl magnesium- and zinc-complexes

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ABSTRACT

Reaction of 2 equiv of *n*-Bu_2Mg and Et_2Zn with the chiral L-proline-derived axial chiral tetraamines (*S*,*S*,*S*)-**1** and (*R*,*S*,*S*)-**1** gave the chiral bimetallic complexes [M_2{(*S*,*S*,*S*)-DABN(MeProline)$_2$}{R}$_2$] (M=Mg, R=*n*-Bu ((*S*,*S*,*S*)-**2**); M=Zn, R=Et ((*S*,*S*,*S*)-**3**)) and [M_2{(*R*,*S*,*S*)-DABN(MeProline)$_2$}{R}$_2$] (M=Mg, R=*n*-Bu ((*R*,*S*,*S*)-**2**)); M=Zn, R=Et ((*R*,*S*,*S*)-**3**)). The magnesium complexes showed moderate to high catalytic activity in the intramolecular hydroamination/cyclization of aminoalkenes, though enantiomeric excess was limited to 14% ee due to protolytic ligand exchange processes. The zinc complexes were less reactive and generally required higher reaction temperatures of 60–100 °C, but achieved slightly higher enantiomeric excess of up to 29% ee.

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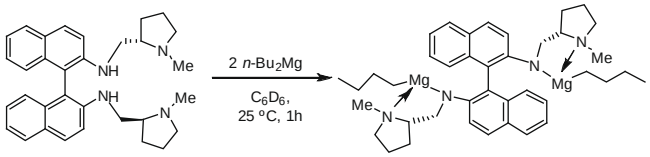
The importance of nitrogen-containing compounds, such as amines, enamines, and imines, as part of natural products and biological systems has sparked significant research efforts for their efficient synthesis. Their use is especially important in industrial basic and fine chemicals, where several million tons of amines are produced per year.[1] The addition of amines to unsaturated carbon–carbon bonds, the so-called hydroamination, generates amines in a waste-free, highly atom-economical manner, starting from simple and inexpensive precursors.[2,3] The hydroamination of alkenes, alkynes, and allenes has been studied using predominantly catalyst systems based on early[4] and late[5] transition metals. Alkali metal-based hydroamination catalysts have a long history going back more than 50 years,[6,7] but recent investigations have led to improved lithium-based catalysts for the hydroamination of alkenes.[8,9] However, the development of a generally applicable catalyst for the hydroamination of non-activated alkenes remains a pressing task.

While base-catalyzed hydroamination has been so far mostly studied using alkali metal-based catalysts, a few examples of alkaline earth metal-based (calcium and strontium)[10] and zinc-based[11] catalyst systems have emerged recently. Furthermore, (amido)magnesium (R_2NMgX, where X = organyl, amide, or alkoxide) chemistry is becoming an increasingly active area of study.[12] In part, this is due to the status gained by lithium amide reagents in synthesis.[13] Being lithium's diagonal neighbor, magnesium is clearly of interest since its complexes may offer differing selectivities and reactivities compared to the lithium derivatives.[14]

We had previously reported the first chiral lithium-based hydroamination catalyst system using L-proline-modified diamidobinaphthyl ligands.[8] Utilizing these ligands, we report herein the application of the novel chiral magnesium- and zinc complexes [M_2{(*S*,*S*,*S*)-DABN(MeProline)$_2$}{R}$_2$] (M=Mg, R=Bu ((*S*,*S*,*S*)-**2**); M=Zn, R=Et ((*S*,*S*,*S*)-**3**)) and [M_2{(*R*,*S*,*S*)-DABN(MeProline)$_2$}{R}$_2$] (M=Mg, R=*n*-Bu ((*R*,*S*,*S*)-**2**); M=Zn, R=Et ((*R*,*S*,*S*)-**3**)) as catalysts for the hydroamination/cyclization of non-activated aminoalkenes. To the best of our knowledge, magnesium has not been investigated as hydroamination catalyst yet. Also, asymmetric hydroamination of aminoalkenes is a field of intensive study currently,[15,16] but to date only achiral zinc catalysts have been investigated.

Addition of 1 equiv of *n*-Bu_2Mg or Et_2Zn to a solution of the L-proline-derived axial chiral tetraamines (*S*,*S*,*S*)-**1** and (*R*,*S*,*S*)-**1** (Scheme 1)[8] in a variety of aliphatic and aromatic solvents gave only complicated product mixtures. However, addition of 2 equiv of the dialkylmagnesium reagent or dialkylzinc reagent afforded well-defined species in both cases (Schemes 1 and 2). According to ^{1}H NMR spectroscopy, the complexes were formed as bimetallic compounds.[17]



(*S*,*S*,*S*)-**1**
(*R*,*S*,*S*)-**1**

(*S*,*S*,*S*)-**2** 61%
(*R*,*S*,*S*)-**2** 76%

Scheme 1.

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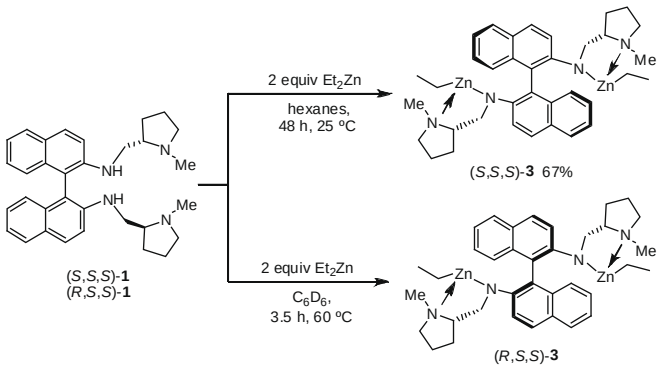


Scheme 2.

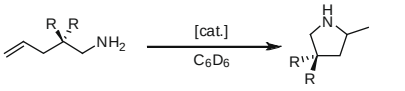
Formation of (*S*,*S*,*S*)-**2** and (*R*,*S*,*S*)-**2** was monitored by NMR spectroscopy. Completion of ligand complexation was indicated by the disappearance of the N–H signal at 4.30 ppm ((*S*,*S*,*S*)-**1**) and 3.94 ppm ((*R*,*S*,*S*)-**1**), and by the appearance of a new signal at 3.59 ppm ((*S*,*S*,*S*)-**2**) and 3.51 ppm ((*R*,*S*,*S*)-**2**), respectively, corresponding to the methylene group.[17] The α- and β-methylene groups of the butyl ligand are diastereotopic, giving two sets of multiplets each (–0.12 and –0.47 for β-CH_2, −1.43 and −1.60 for α–CH_2) in the case of (*S*,*S*,*S*)-**2**. Complexes (*S*,*S*,*S*)-**2** and (*R*,*S*,*S*)-**2** were isolated as yellow powders in 61% and 76% yield, respectively.[18]

Reaction of Et_2Zn with (*S*,*S*,*S*)-**1** in hexanes at room temperature for 48 h led to the zinc complex (*S*,*S*,*S*)-**3** as a fine yellow powder in 67% yield. Complexation of (*R*,*S*,*S*)-**1** required heating to 60 °C for 3.5 h to form (*R*,*S*,*S*)-**3** as a fine yellow powder after drying in vacuo; however, the isolated complex was only 86% pure according to ^{1}H NMR spectroscopy.

With the complexes in hand, we began to investigate their catalytic activity in the hydroamination/cyclization of aminoalkenes. Reaction of 2,2-dimethyl-4-pentene-1-amine (**4**) with 5 mol % (*S*,*S*,*S*)-**2** in C_6D_6 (100 °C, 22 h) produced **5** in 95% yield, but essentially in racemic form (Table 1, entry 1). In the case of (*R*,*S*,*S*)-**2**, 10 mol % catalyst was necessary to achieve full conversion of **5**, again, only the racemic product was obtained. The low enantioselectivities for the magnesium catalysts may be explained by a facile ligand exchange reaction and/or protolytic ligand cleavage upon addition of the substrate. Facile Schlenk equilibria have impeded attempts to perform asymmetric hydroamination using calcium-based catalysts.[10b] The observation of a N–H signal in the ^{1}H NMR spectrum of the reaction mixture indicates the presence of the protonated form of the ligand. Both magnesium complexes, (*S*,*S*,*S*)-**2** and (*R*,*S*,*S*)-**2**, showed better catalytic activities at room temperature when substrates with sterically more demanding *gem*-dialkyl groups[19] were used. Cyclization of 2,2-diphenyl-pent-4-enylamine (**6**) at room temperature rapidly formed pyrrolidine **7** in 6% ee using (*S*,*S*,*S*)-**2** and 14% ee using (*R*,*S*,*S*)-**2** (Table 1, entries 5 and 6), while cyclization of *C*-(1-allyl-cyclohexyl)-methylamine (**8**) proceeded significantly slower under the same conditions (Table 1, entries 5, 6 vs entries 10, 11). Overall, the reactivity of both magnesium catalysts is somewhat lower than that of calcium and strontium catalysts reported to date.[10] Interestingly, *n*-Bu_2Mg itself did not react with **8** after 2 h at 40 °C. This may indicate that the protonated diamidobinaphthyl ligand chelates the catalytically active magnesium species, thus preventing formation of unreactive higher aggregates.[20]

The zinc-based complexes (*S*,*S*,*S*)-**3** and (*R*,*S*,*S*)-**3** are less reactive than the analogous magnesium complexes. Complex (*S*,*S*,*S*)-**3** showed higher catalytic activity than (*R*,*S*,*S*)-**3**, and the reactions could be performed at lower temperatures (60–80 °C vs 100 °C). However, (*R*,*S*,*S*)-**3** gave the highest enantiomeric excess of 29% ee for the *gem*-diphenyl-substituted aminoalkene **6** (Table 1, entry 8), despite the high reaction temperature (100 °C) applied in this catalytic transformation. As with (*S*,*S*,*S*)-**2** and (*R*,*S*,*S*)-**2**, cyclization of **8** with the zinc-based catalysts produced essentially racemic pyrrolidine **9** (Table 1, entries 13 and 14). It is noteworthy that

Table 1
Magnesium- and zinc-catalyzed hydroamination/cyclization of non-activated aminoalkenes[a]



4 R = Me
6 R = Ph
8 R-R = -$(CH_2)_5$-

5 R = Me
7 R = Ph
9 R-R = -$(CH_2)_5$-

Entry	Substrate	Catalyst	[cat]/[S] (mol %)	*T* (°C)	*t* (h)	Conv.[b] (%)	ee[c] (%)
1	**4**	(*S*,*S*,*S*)-**2**	5	100	22	⩾99	4 (*S*)
2	**4**	(*R*,*S*,*S*)-**2**	10	100	21	⩾99	0
3	**4**	(*S*,*S*,*S*)-**3**	5	90	140	94	2 (*S*)
4	**4**	(*R*,*S*,*S*)-**3**	10	100[d]	89	⩾99	3 (*R*)
5	**6**[e]	(*S*,*S*,*S*)-**2**	4	22	0.33	⩾99	6 (*R*)
6	**6**[e]	(*R*,*S*,*S*)-**2**	10	22	0.17	⩾99	14 (*R*)
7	**6**	(*S*,*S*,*S*)-**3**	5	60	140	88	13 (*S*)
8	**6**	(*R*,*S*,*S*)-**3**	10	100	71	⩾99	29 (*R*)
9	**8**	*n*-Bu_2Mg	2	40	2	0	n/a
10	**8**	(*S*,*S*,*S*)-**2**	5	22	22	94	0
11	**8**[e]	(*R*,*S*,*S*)-**2**	10	22	3.5	80	6 (*R*)
12	**8**	Et_2Zn	10	60	100	⩾99	n/a
13	**8**[f]	(*S*,*S*,*S*)-**3**	5	80	50	97	5 (*S*)
14	**8**	(*R*,*S*,*S*)-**3**	10	100	20	⩾99	0

[a] Reaction conditions: 0.2 mmol substrate, 0.5 mL C_6D_6, Ar atm.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{19}F NMR spectroscopy of the Mosher amides at 60 °C.
[d] Reaction in toluene-d_8.
[e] 0.1 mmol substrate.
[f] 0.4 mmol substrate. n/a = not applicable.

Et_2Zn, which had been previously shown to mediate hydroamination/cyclization of aminoalkynes,[11c] catalyzes also the cyclization of **8** at 60 °C to give the desired pyrrolidine in quantitative conversion within 4 days.

The present study was aimed to ascertain the catalytic activity of magnesium-based hydroamination catalysts. While (*S*,*S*,*S*)-**2** and (*R*,*S*,*S*)-**2** displayed only poor enantioselectivities in asymmetric hydroaminations, they certainly show that magnesium-based catalysts are viable, and that the chelating nature of the diamidobinaphthyl ligands can enhance catalytic activity by prevention of aggregate formation. The catalytic activity of the magnesium complexes seems to be of similar order of magnitude, though somewhat reduced, in comparison to calcium- and strontium-based catalysts.[10] Facile ligand redistribution processes leading to achiral catalytic active species have thwarted our efforts to achieve appreciable enantioselectivities with these catalysts. The zinc-based catalysts show for the first time the feasibility of asymmetric hydroamination even under the harsh reaction conditions required for these catalysts, although the observed enantioselectivities are low. In order to improve catalyst efficiency and selectivity, we believe that it is imperative to utilize chiral ligands that will minimize ligand redistribution processes and provide a configurational stable coordination environment around the metal center under conditions of catalytic hydroamination.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.069.

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