Zirconium Bis(Amido) Catalysts for Asymmetric Intramolecular Alkene Hydroamination

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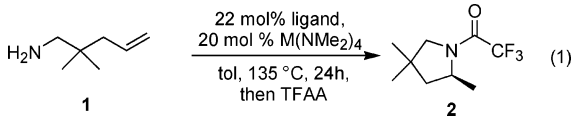
Summary: In situ combination of diphosphinic amides and $Zr(NMe_2)_4$ results in the formation of chiral zirconium bis-(amido) complexes. The complexes are competent catalysts for intramolecular asymmetric alkene hydroamintion, providing piperidines and pyrrolidines in up to 80% ee and high yield. This system utilizes an inexpensive precatalyst, readily prepared ligands and is the first asymmetric alkene hydroamination catalyst based upon a neutral zirconium bis(amido) complex.

The development of catalysts for intramolecular asymmetric alkene hydroamination has been the subject of intense investigation over the past 15 years.[1−5] While considerable advances have been made using catalysts containing a variety of metals, no general solution has emerged. To date, catalysts based on group 3 and lanthanide metals have shown the most promise for unactivated alkenes.[1−3] However, even within this class only a small number (4) of highly enantioselective reactions (>90% ee) have been reported.[3c] Thus, alkene hydroamination remains an open area of research.

Recently, Schafer[6] (and subsequently Livinghouse[7]) reported that neutral group IV bis(amido) complexes bearing achiral ligands are competent catalysts for intramolecular alkene hydroamination. Our group has previously reported that closely related catalysts containing chiral dialkoxide and diamide ligands are effective in intramolecular allene and alkyne hydroamination.[8] We decided to explore the possibility that these types of chiral complexes could be applied to asymmetric alkene hydroamination. Herein, we report the first examples of asymmetric, intramolecular alkene hydroamination catalyzed by group 4 bis(amido) complexes.[9] The reported catalysts employ readily available chiral ligands and provide enantioselectivities of up to 80% ee.

Having previously demonstrated that in situ combination of various diamines or diols and group IV tetrakis(dimethyl)amides provides competent hydroamination catalysts,[8] we screened various combinations of these compounds as catalysts in the cyclization of **1** (eq 1).[10,11] In an effort to develop a practical



(1)

catalyst, we focused exclusively on commercially available or readily prepared diols, diamines, and amino alcohols (Table 1; Figure 1).[12] Although enantioselective catalysts based on titanium and hafnium[13] were also identified, the zirconium catalyst prepared by combination of diphosphinic amide **3c**[12c] and $Zr(NMe_2)_4$ (entry 11) proved significantly more enantioselective than others that we studied. Under unoptimized conditions (see footnote, Table 1), pyrrolidine **2** was obtained in 67% ee and excellent yield. Given this initial result, we elected to explore additional ligands of the same general structure.

A series of diphosphinic amides was prepared using one of two short synthetic sequences.[14] These ligands were investigated in the cyclization of **1** (Table 2). Ligands containing the cyclohexanediamine backbone proved to be the most selective (entries 1−5). Variation of the phosphorus substituent (R) had

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(3) For recent reports of hydroaminations using lanthanum and group 3 metal complexes, see: (a) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737−1739. (b) Collin, J.; Daran, J.; Jacquet, O.; Schulz, E.; Trifonov, A. *Chem. Eur. J.* **2005**, *11*, 3455−3462. (c) Birkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748−3759. (d) Riegert, D.; Collin, J.; Meddour, A.; Schulz, E.; Trifonov, A. *J. Org. Chem.* **2006**, *71*, 2514−2517.

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(5) For examples of asymmetric hydroaminations using other metals, including cationic zirconium complexes, see: (a) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894−895. (b) Gribkov, D. V.; Hultzcsh, K. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5542−5546. (c) Martinez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221−2223.

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(9) There has been one report of an asymmetric intramolecular allene hydroamination catalyzed by neutral titanium bis(amido) complexes that employed chiral amino alcohol ligands. The maximum reported ee was 16%. See: Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614−4620.

(10) In screening efforts, ligand (22 mol %) and group IV tetrakis-(dimethylamide) (20 mol %) were combined in toluene and heated to 135 °C for 15 min to ensure formation of ligand/metal complex. Aminoalkene **1** was then introduced, and the reaction mixture was heated with stirring for 24 h. After acylation with trifluoroacetyl anhydride (TFAA), the product was analyzed by chiral GC.

(11) The absolute stereochemistry of amide **2** was established by determination of the des-acyl piperdine using the method reported by Livinghouse using *O*-acetylmandelatic acid; see ref 3a. The absolute stereochemistries of the remaining products have not been established.

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(13) To our knowledge, these are the first examples of hafnium-catalyzed hydroaminations.

(14) See Supporting Information for details.

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Table 1. Results from Initial Screen of Ligands for Conversion of 1 to 2[a]

		$M(NMe_2)_4$, % conversion(% ee)		
entry	ligand	Ti	Zr	Hf
1	none	97(0)	80(0)	88(0)
2	***R,R*-3a**	<5(n/a)	92(21)	94(13)
3	***R*-4a**	<5(n/a)	89(18)[b]	59(30)[b]
4	***R*-4b**	<5(n/a)	90(23)[b]	24(26)[b]
5	***S,S*-3b**	97(9)	94(20)	94(13)
6	***R*-4c**	88(<5)	87(<5)	87(<5)
5	***S*-4d**	<5(n/a)	97(<5)	63(19)
6	**5a**	59(13)	97(24)[b]	98(9)[b]
7	**5b**	52(6)[b]	98(27)[b]	99(12)[b]
8	**6**	84(26)	96(<5)	98(7)
9	**7**	<5(n/a)	<5(n/a)	<5(n/a)
10	**8**	95(15)[b]	99(34)[b]	73(18)[b]
11	***R,R*-3c**	8(<5)	96(67)	76(58)

[a] Conditions: 22 mol % ligand, 20 mol % $M(NMe_2)_4$, 135 °C, tol, 24 h; ligand and $M(NMe_2)_4$ were preheated to 135 °C for 15 min prior to introduction of **1**. Unless otherwise indicated, the *S*-enantiomer of product predominated. Conversion was determined using chiral GC by comparison of the sum of the enantiomers of product to the remaining starting material. [b] The *R*-enantiomer was predominant.

Table 2. Results from the Use of Diphosphinic Amide Ligands with $Zr(NMe_2)_4$ in the Conversion of 1 to 2[a]

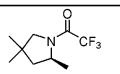
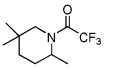
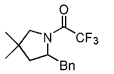
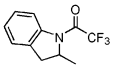
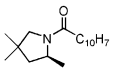
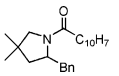
entry	ligand	R	% conversion	% ee
1	**3c**	Ph	98	67
2	**9**	Ph	96	50
3	**10**	Ph	95	55
4	**11**	Ph	<1	n/a
5	**12**	Ph	46	16
6	**13a**	*o*-tol	<1	n/a
7	**13b**	$3,5\text{-}C_6H_3(CF_3)_2$	decomp	n/a
8	**13c**	$3,5\text{-}C_6H_3F_2$	92	63
9	**13d**	$3,5\text{-}C_6H_3(OMe)_2$	99	68
10	**13e**	$p\text{-}C_6H_4(OMe)$	99	70
11	**13f**	$o\text{-}C_6H_4(OMe)$	95	76
12	**13g**	$3,5\text{-}C_6H_3Me_2$	99	75
13	**13h**	$3,5\text{-}C_6H_3(^tBu)_2$	98	62

[a] Conditions: 22 mol % ligand, 20 mol % $Zr(NMe_2)_4$, 135 °C, tol, 24 h; ligand and $Zr(NMe_2)_4$ were preheated to 135 °C for 15 min prior to introduction of **1**. In all cases, the ligand was the *R,R*-enantiomer and the *S*-enantiomer of **2** was predominant in the product. Conversion was determined using chiral GC by comparison of the sum of the enantiomers of product to the remaining starting material.

pronounced effects on catalytic activity. The *ortho*-tolyl-containing ligand **13a** gave catalytically inactive complexes (entries 6), while the 3,5-bis(trifluromethyl)phenyl-substituted ligand **13b** decomposed when exposed to $Zr(NMe_2)_4$. Ligands containing other electron-deficient arenes proved more stable to the reaction conditions, but did not provide improved catalysts (entries 9 and 10). The addition of electron-donating groups did improve catalyst performance in the cyclization of **1**. The *para*-methoxyphenyl-containing ligand **13e** provided slightly higher enantioselectivity. The more sterically demanding *ortho*-methoxyphenyl group in **13f** provided even higher selectivity, but at the cost of slightly diminished reactivity. Among the ligands screened, the best proved to be 3,5-dimethylphenyl-substituted ligand **13g** (entry 12). This ligand provided the best combination of reactivity and enantioselectivity, providing **2** in 75% ee and 99% conversion under these unoptimized conditions. Larger meta substituents did not improve catalyst performance (entry 13).

Having identified a promising ligand, we sought to further optimize the cyclization of **1** using the combination of **13g** and $Zr(NMe_2)_4$ as catalyst. Neither variation of the solvent (PhH, Ph-F, Ph-Cl, 1,4-dioxane, and pyridine) nor the addition of basic ($LiNMe_2$)[15] or acidic ($HEt_2O{\cdot}B(C_6F_5)_4$) additives affected the yield or ee of the product obtained in the reaction. Lowering the reaction temperature did improve the ee, and under optimized conditions, **2** was produced in 95% yield and 80% ee in 24 h using 20 mol % each of **13g** and $Zr(NMe_2)_4$ (Table 3). Lowering the catalyst loading to 10 mol % provided **2** in 91% yield and identical ee in 48 h.

Table 3. Substrate Scope under Optimized Conditions (reactions performed in toluene)

entry	product		mol% cat.[a]	temp (°C)/ time (h)	% yield (% ee)
1		**2**	20	115/24	95(80)[c]
			10	115/48	91(80)[c]
2		**14**	20[b]	85/24	99(51)[c]
			10[b]	85/48	91(51)[c]
3		**15**	20	135/72	33(62)[c,d]
4		**16**	10	135/24	79(33)[c]
5		**17**	20	135/24	93(62)[c]
6		**18**	20	115/48	93(70)[c]
			20	115/48	85(70)[e]
7		**19**	10	115/48	78(80)[f]
8		**20**	20	135/24	75(55)[f]

[a] Prepared in situ by combination of equimolar amounts of ligand and $Zr(NMe_2)_4$ in toluene and heating at the reaction temperature for 15 min prior to introduction of substrate. [b] Ligand and $Zr(NMe_2)_4$ preheated at 105 °C for 15 min. [c] GC yield determined using C_6Me_6 as an internal standard; ee determined by chiral GC. [d] 32% starting material remained in solution at the end of the reaction. [e] Isolated yield; ee determined by chiral GC. [f] Isolated yield as 2-naphthoyl amide; ee determined by chiral HPLC.

Table 3 illustrates the substrate scope of the asymmetric hydroamination reaction using the combination of **13g** and $Zr(NMe_2)_4$ as the catalyst. Formation of piperidine **14** (entry 2) proceeded in 99% yield and 51% ee using 20 mol % catalyst at 85 °C. Lowering the catalyst loading to 10 mol % provided **14** in slightly lower yield but without erosion of ee. Substrates lacking the geminal dimethyl group could also be cyclized, albeit in diminished yield and ee (entries 3 and 4). Substrates containing *trans*-disubstituted alkenes cyclized in high yield with moderate enantioselection (entry 5). Cyclization of 2-allylaniline provided **18** in 93% yield and 70% ee as determined by GC analysis (entry 5). On a larger scale, **18** could be isolated in 85% yield and identical ee. As a means of corroboration, we also wished to isolate other hydroamination products. 2-Naphthoyl chloride proved the most convenient derivitizing agent for this purpose, providing amides of sufficient molecular weight and stability for facile isolation. Isolated yields and enantioselectivities for amides prepared by this method (entries 7 and 8) are similar to those determined by the GC method.

Although we have not yet undertaken detailed mechanistic studies of this catalytic system, we have attempted to identify

(15) The fact that $LiNMe_2$ does not inhibit the reaction excludes the possibility that catalysis is due to trace acidic impurities.

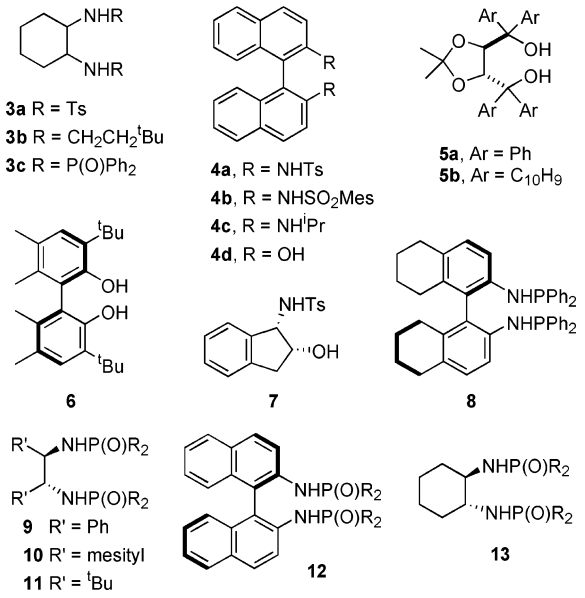
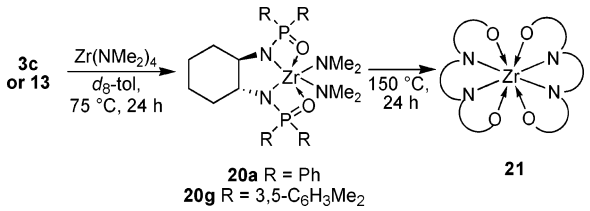


Figure 1. Structures of ligands examined.

Scheme 1. Products from the Reaction of Diphosphinic Amide Ligands and $Zr(NMe_2)_4$



the catalytically active species generated from the combination of the diphosphinic amide ligands and $Zr(NMe_2)_4$. Upon combination of either **3c** or **13g** and an equimolar amount of $Zr(NMe_2)_4$ in d_8-toluene at 25 °C, a complex mixture of compounds arose with 10 unassigned signals observed in the ^{31}P NMR spectrum. Heating this mixture at 75 °C for 24 h led to the clean formation of the expected 1:1 Zr:ligand adduct **20** (Scheme 1), along with traces of the 2:1 adduct **21**.[14] The structure of **20** was assigned by the indicative dimethylamide signals in the ^1H NMR spectrum at ca. 3.55 ppm and a single peak in the ^{31}P NMR spectrum at ca. 33 ppm. Addition of substrate to in situ generated **20** and subsequent heating provided product at a rate similar to the rates of the reactions reported in Table 1. Heating the solution of **20** at 135 °C (with or without substrate present) resulted in the slow formation of **21**. At 150 °C, in the absence of substrate, **20** was fully converted to **21** within 24 h. The structure of **21a** has been determined by X-ray crystallographic analysis (Figure 2). Both **21a** and **21g** were catalytically inactive.

Based upon these studies, and those previously reported by our group and others,[6−8] this reaction likely proceeds via a transient imidozirconium species according to the general mechanism presented in Scheme 2. Combination of **13** and $Zr(NMe_2)_4$ results in the formation of **20**. Addition of substrate allows the reversible loss of dimethylamine and the formation of the imidozirconium species **22**. Subsequent [2+2] cycloaddition and protonation of the resulting azametallocyclobutane **23** by substrate regenerates the imido species and delivers the cyclic amine product. Slow decomposition of **20** to **21** represents a pathway for catalyst decomposition. Further research designed

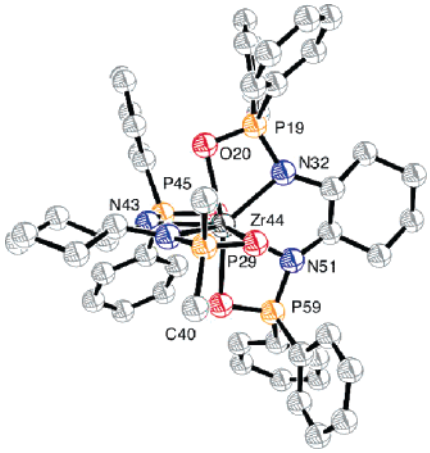
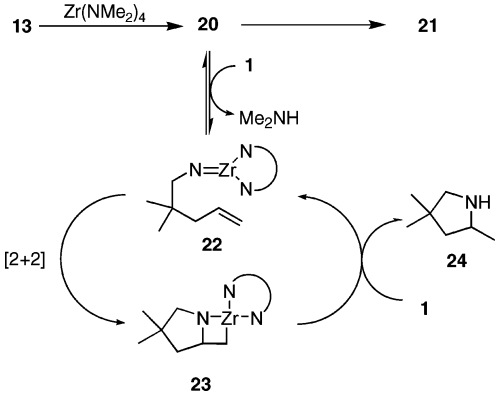


Figure 2. ORTEP representation of the solid-state structure of **21a**. Arenes connected to P29 have been truncated for clarity. Thermal ellipsoids are shown at 50% probability.

Scheme 2. Proposed Catalytic Cycle and Catalyst Decomposition



to inhibit the latter process represents a potential avenue for further optimization of this catalyst system.

In summary, we have developed the first asymmetric alkene hydroamination catalyst based upon a neutral zirconium bis(amido) complex. This system utilizes an inexpensive zirconium precatalyst and a readily prepared diphosphinic amide ligand and provides cyclic amines in high yields and up to 80% ee. In situ preparation of the active catalyst obviates the need to isolate moisture-sensitive compounds. Studies aimed at further optimization of the ligand architecture and full elucidation of the mechanism of this transformation are ongoing.

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Supporting Information Available: Complete experimental details for the preparation of diphosphinic amide ligands and cyclization experiments, copies of the ^1H and ^{13}C NMR spectra for **3c**, **9**−**12**, **13a**−**g**, and **17**−**21**, and chromatograms for ee analysis.

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