VIP Asymmetric Catalysis

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Chiral Neutral Zirconium Amidate Complexes for the Asymmetric Hydroamination of Alkenes**

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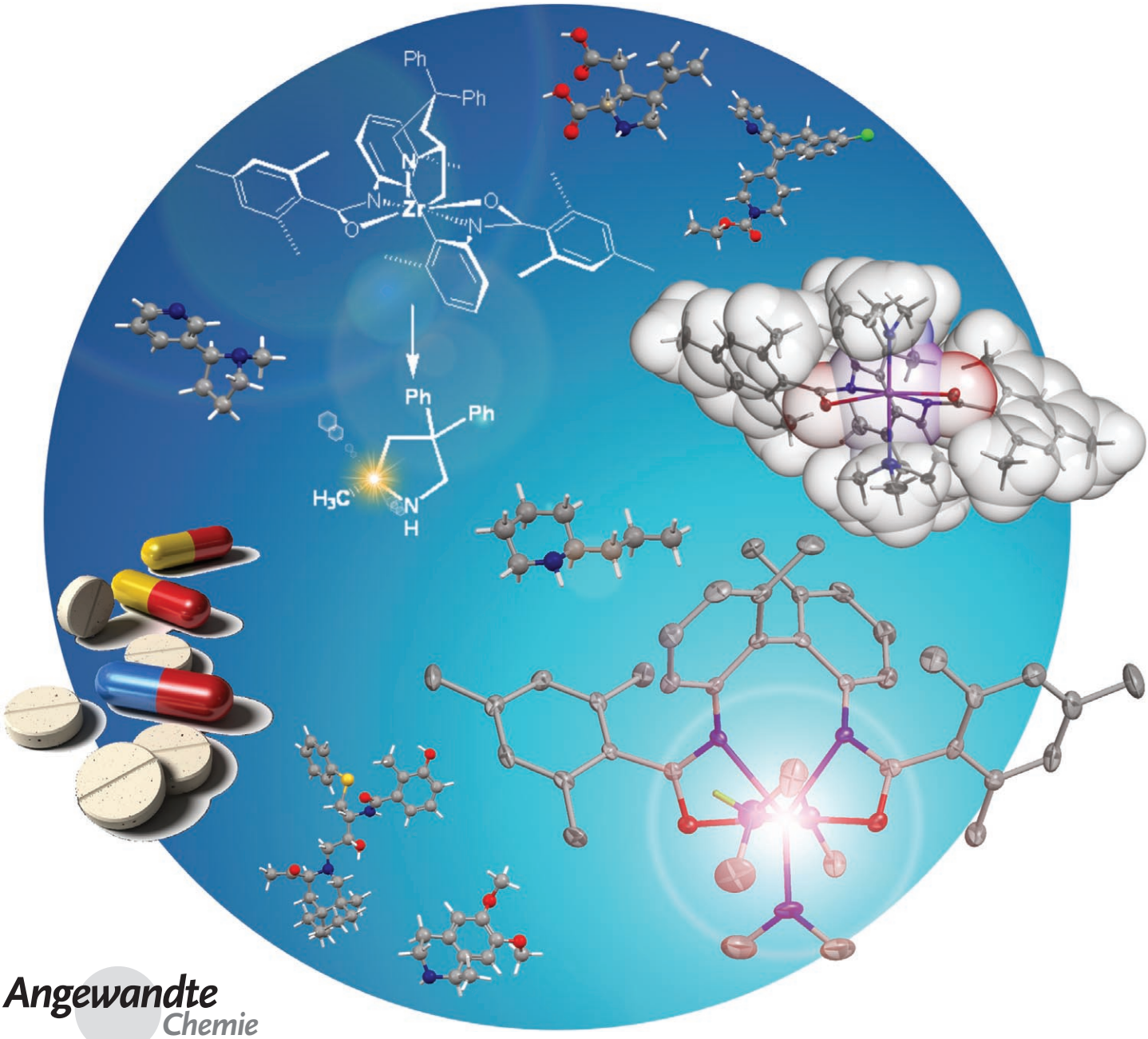
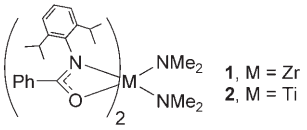
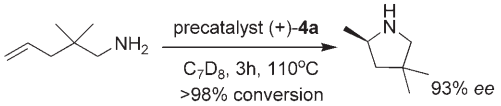


The formation of C–N bonds in an enantioselective fashion is a significant challenge in the synthesis of pharmaceuticals and fine chemicals. The generation of a stereogenic center by the selective addition of N–H to C=C bonds is efficiently accomplished by catalytic asymmetric hydroamination, which is a stereoselective, atom-economic transformation for the generation of enantioenriched α-chiral amines.[1] Despite intense investigation, to date, there are no general catalysts for this demanding synthetic transformation.[2] Most breakthroughs in this area have been accomplished using rare-earth-metal catalysts.[3] However, Group 4 metal catalysts are particularly attractive owing to their low cost, low toxicity, high reactivity, and established utility in asymmetric catalysis.[4] An important advancement in enantioselective hydroaminations catalyzed by Group 4 metals was a cationic zirconium complex developed by Scott and co-workers[5] for the asymmetric hydroamination of select secondary aminoalkenes.[5,6] Also, some chiral late-transition-metal complexes have been investigated for enantioselective intermolecular hydroamination, with good results obtained for activated alkene and alkyne substrates.[7] Certainly, the development of easily prepared catalysts for general use in the enantioselective hydroamination of a broad range of alkenes remains a critical goal.



1, M = Zr
2, M = Ti

As an entry into developing new catalysts for this challenging reaction, our group has been investigating a family of modular titanium and zirconium bis(amidate) precatalysts for the catalytic hydroamination of alkynes,[8] allenes,[9] and alkenes.[10] Recently, we showed that the Zr and Ti bis(amidate) complexes **1** and **2** can be used for the preparation of 2,4,4-trimethylpyrrolidine as a racemate, with Zr complex **1** being the most active catalyst [Eq. (1)].[10]



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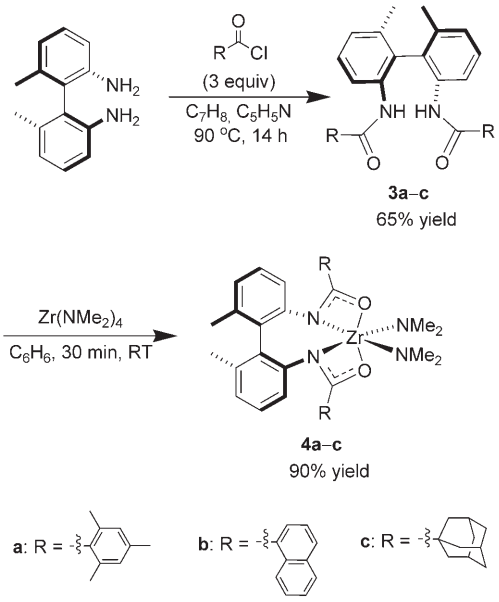
Supporting information for this article (including all crystallographic and experimental details) is available on the WWW under http://www.angewandte.org or from the author.

Herein, we disclose the first chiral neutral amidate zirconium complexes that can be used for enantioselective cyclohydroamination of primary aminoalkenes with up to 93% *ee*, which is, to the best of our knowledge, the highest reported enantioselectivity for this typical test substrate.[3]

The auxiliary amide proligands used for our systems were easily prepared from amines and acid chlorides, resulting in proligands with varying steric and electronic properties.[8a,b] In an effort to control both coordination isomerism and chirality at the metal center, the known rigid and axially chiral 2,2′-diamino-6,6′-dimethylbiphenyl backbone[11] was used in combination with three different sterically demanding acid chloride reagents to prepare tethered bis(amide) proligands **3a–c** (see Scheme 1). It is known that amidate ligands can



Scheme 1. Facile preparation of chiral Zr bis(amidate) complexes.

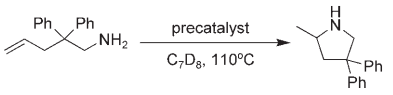
adopt multiple bonding motifs,[12] and, importantly, Arnold and co-workers previously reported the application of a tethered amide proligand for the preparation of bimetallic titanium complexes.[13] However, in our case, the orientation of the amine groups in the selected chiral backbone in combination with the steric bulk imposed by the carbonyl substituents was anticipated to both favor the formation of monomeric complexes and impose a well-defined chiral environment about the reactive metal center.

The axially chiral diamine was prepared as a racemate and subsequently resolved by using a modified published protocol.[11] Preliminary efforts focused on the preparation of the (+) enantiomer of the proligands for an initial catalyst screen. Reaction of the (+)-diamine with three equivalents of mesitoyl chloride (**a**), naphthoyl chloride (**b**), or adamantoyl chloride (**c**) in toluene, with pyridine as base, resulted in the preparation of microcrystalline proligands that could be purified by recrystallization in good yield (Scheme 1). These new chiral proligands were fully characterized, including determination of their specific rotations (e.g. for (+)-**3a**: $[\alpha]_D^{20} = +139°$). The purified proligand was then dried under

vacuum and treated with one equivalent of $Zr(NMe_2)_4$ in benzene as solvent. The solvent and dimethyl amine by-product were removed under vacuum to give (+)-**4a**–**c** as light yellow, highly soluble materials in over 90% yield (Scheme 1). These solid crude materials were then screened for catalyst activity and enantioselectivity in the cyclohydroamination of 2,2-diphenyl-4-pentenamine in [D_8]toluene on a small scale at 110°C (Table 1).

Complex (+)-**4a** showed high efficiency in the cyclohydroamination reaction (Table 1, entry 1), with complete conversion of the starting material to product occurring within 75 min. The steric bulk imposed by the mesityl group was the most significant in this series of amidate complexes, and consequently the observed enantioselectivity of 74% *ee* was the highest for this catalyst screen. Complex (+)-**4b** (Table 1, entry 2) shows somewhat reduced reactivity, and at present we attribute this to the comparably reduced steric congestion imposed by the naphthyl substituent, which may permit equilibria with aggregate species that are catalytically inactive. Furthermore, the enantioselectivity imparted by this catalyst system is somewhat reduced at 31% *ee*. Finally, complex (+)-**4c** with the bulky adamantyl substituent revealed good catalytic activity (Table 1, entry 3), requiring 3 h for the reaction to go to completion. The steric bulk imposed by the adamantyl group is significant, yet this bulk lies removed from the reactive metal center and may explain the modest enantioselectivity of 39% *ee*. Thus, by taking advantage of the modular nature of the amidate ligands, a rapid screen was used to identify the first neutral Zr complexes that mediate enantioselective alkene hydroamination of primary aminoalkenes.[4b] Most importantly, the mesityl-substituted complex (+)-**4a** was found to impart the highest enantioselective control. The enantiomer obtained using (−)-**4a** was achieved with comparable enantioselectivity (Table 1, entry 4). Finally, the catalyst loading of (+)-**4a** could be reduced to 5 mol% with no detectable loss in enantioselectivity (Table 1, entry 5), although the reaction required double the time to reach complete conversion.

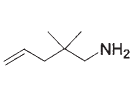
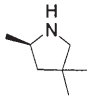
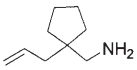
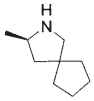
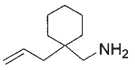
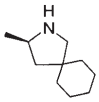
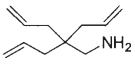
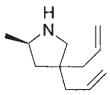
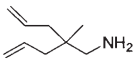
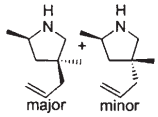
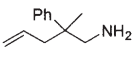
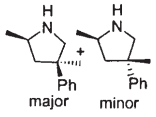
Table 1: Screening of asymmetric hydroamination with precatalysts **4a**–**c**.



Entry	Precat.	Loading [mol%]	*t* [h]	Conv. [%][a]	*ee* [%][b]
1	(+)-**4a**	10	1.25	>98 (93)[c]	74 (*R*)[d]
2	(+)-**4b**	10	18	>98	31
3	(+)-**4c**	10	3	>98	39
4	(−)-**4a**	10	1.25	>98 (93)[c]	72 (*S*)[d]
5	(+)-**4a**	5	2.5	>98	74

[a] Measured by ^{1}H NMR spectroscopy. [b] Enantiomeric excess based on ^{1}H NMR spectroscopy of the product following derivatization with (+)-(*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride. [c] Yield of isolated product. [d] Absolute stereochemistry assigned based on ^{19}F NMR spectroscopy of the (+)-(*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride derivative[12]

Table 2: Asymmetric hydroamination using precatalysts (+)-**4a** or (−)-**4a** (10 mol%) at 110°C in toluene.[a]

Entry	Precat.	Aminoalkene	Product	*t* [h]	Yield [%][a]	*ee* [%]
1	(+)-**4a**			3	80[b]	93[c]
2	(−)-**4a**			3	>98[d]	93[b]
3	(+)-**4a**			5	91	88[b]
4	(+)-**4a**			3	96	82[e]
5	(+)-**4a**			4.5	88	74[e]
6	(+)-**4a**		 major minor	2	82 (2.3:1)[f]	92:88[e]
7	(+)-**4a**		 major minor	12	94 (1.9:1)[f]	62:86[b]

[a] Yield of isolated product unless otherwise noted. [b] Yield of isolated product following derivatization with benzoyl chloride. [c] Enantiomeric excess based on ^{1}H NMR spectroscopy of the product following derivatization with (+)-(*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride. [d] Yield based on ^{1}H NMR spectroscopy. [e] Enantiomeric excess based on ^{19}F NMR spectroscopy of the (+)-(*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride derivative[3] [f] Diastereomeric ratio.

With catalyst (+)-**4a** in hand, investigations of its application in the preparation of isolable *gem*-substituted heterocyclic products were undertaken (Table 2). Reported *ee* values were determined by integration of ^{1}H and/or ^{19}F NMR spectra of the (*S*)-Mosher's acid derivatives of at least two independent experiments. Remarkably, the smaller *gem*-dimethyl-substituted substrate was used with (+)-**4a** (Table 2, entry 1) and the benzoyl-derivatized pyrrolidine product was isolated in good yield with 93% *ee*. To the best of our knowledge, this is the highest enantioselectivity reported for this typical test substrate. Furthermore,

we confirmed that the opposite enantiomer could be prepared in 93% *ee* also by using (−)-**4a** (Table 2, entry 2). Precatalyst (+)-**4a** efficiently formed spiro-pyrrolidine products in excellent yield and with good enantioselectivity (Table 2, entries 3 and 4). Only the *gem*-disubstituted product was isolated in good yield and no bicyclic products resulted from a second intramolecular alkene hydroamination (Table 2, entry 5).[1a] Good to excellent enantioselectivities were observed in the preparation of diastereomeric products (Table 2, entries 6 and 7).[1a,14] While pyrrolidine products were formed with excellent enantioselectivities in this first example of asymmetric neutral Group 4 metal catalyzed alkene hydroaminations, piperidine products were noted to be formed in excellent yields (e.g. 91%) although with substantially reduced enantioselectivies (e.g. 29% *ee*).[15] The lower *ee* values observed in the formation of piperidines are consistent with a larger, less-organized eight-membered transition state that would be required in the metal-mediated formation of the six-membered ring product (see below).

The most active and enantioselective catalyst **4a** was fully characterized. Amorphous samples of (+)-**4a** isolated from the reaction mixture gave ^{1}H and ^{13}C NMR spectra and elemental analysis data that were consistent with the formulation shown in Scheme 1.[15] The specific rotation of the metal complex was determined as $[\alpha]_D^{20} = +422°$ in benzene. Unfortunately, attempts to grow X-ray quality crystals of this material from noncoordinating solvents failed. From a sample of incompletely dried crude product, X-ray quality crystals of the $HNMe_2$ adduct of complex (+)-**4a** were obtained by recrystallization from a pentane solution at room temperature. The solid-state molecular structure (Figure 1) confirmed a monomeric species that is seven-coordinate, with a distorted pentagonal-bipyramidal geometry. In the crystalline material, a neutral dimethylamine ligand (N5) occupies an axial position to give a coordinatively saturated 18-electron complex. The tethered amidate ligand is in the equatorial plane with the rigid chiral backbone defining a slight canting of the auxiliary ligand.

Preliminary efforts to probe the mechanism of this important reaction confirmed that the activity and selectivity of the catalyst remain unaffected by the presence of 2,6-di-*tert*-butyl-4-methylpyridine (a bulky noncoordinating base) thereby negating the possibility of proton-mediated catalysis.[16] Furthermore, this precatalyst was tested with the secondary-amine derivative of the most reactive substrate (Scheme 2) and no heterocyclic product was observed by ^{1}H NMR spectroscopy, despite prolonged reaction times (up to 4 days) and elevated reaction temperatures (up to 140 °C). This is in contrast to the cationic catalysts with Group 4 metals that are unable to mediate the hydroamination of primary aminoalkenes, but work efficiently with a range of secondary aminoalkenes.[5,6] The lack of reactivity in our case suggests that alkene hydroamination is mediated by the in situ formation of a catalytically viable Zr imido complex, which then undergoes a [2+2] cycloaddition reaction with the alkene through a chairlike transition state. The proposed cycloaddition reaction results in the formation of an azametallacyclobutane intermediate. This imido-based mechanism is well established for alkyne hydroaminations catalyzed by

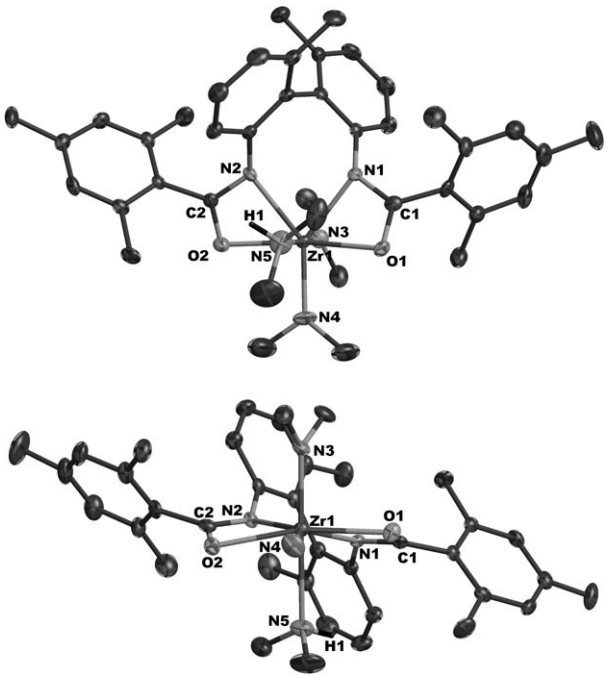
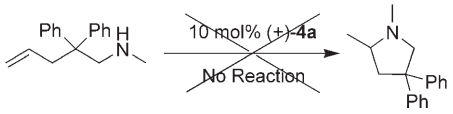


Figure 1. Two views of an ORTEP diagram (ellipsoids shown at 50% probability level) of the dimethylamine adduct of (+)-**4a** (CH_3 substituents omitted from N4 dimethylamido ligand for clarity in the top view). Selected interatomic distances [Å] and angles [°]: Zr1–O1 2.2802(35), Zr1–O2 2.2890(37), Zr1–N1 2.3134(43), Zr1–N2 2.3468(33), Zr1–N3 2.0651(41), Zr1–N4 2.0694(43), Zr1–N5 2.5357(53); O1-Zr1-O2 166.68(0.13), N1-Zr1-N2 74.87(0.16), O1-Zr1-N1 56.81(0/13), O2-Zr1-N2 56.21(0.13), N3-Zr1-N5 177.95(0.17), O1-C1-N1 144.52(0.41), O2-C2-N2 113.47(0.42). Biphenyl torsion angle [°]: 68.28(0.65).



Scheme 2. Substrate scope test reaction which suggests that the mechanism involves a Zr imido complex.

Group 4 metals[8c,17] and has been postulated for alkene hydroamination by ourselves and others.[14,18] Additionally, we recently reported the first example of an isolable bis-(amidate)Zr imido complex (with the amidates bound in the equatorial plane and the imido group bound axially), which was also a competent precatalyst for the hydroamination of primary aminoalkenes.[10] Thus, by combining our mechanistic rationale with structural data obtained for the precatalyst, we propose the preferred formation of one of the diastereomeric azametallacyclic intermediates as a result of steric interactions with the geminal substituents, as shown in Figure 2. Further experiments to study the substrate scope and kinetic mechanistic investigations are underway to probe this working hypothesis.

In summary, we have illustrated the ease of synthesis and flexibility afforded by the modular amidate ligand set and the potential of this variable class of complexes in enantioselective cyclohydroaminations catalyzed by Group 4 metals.

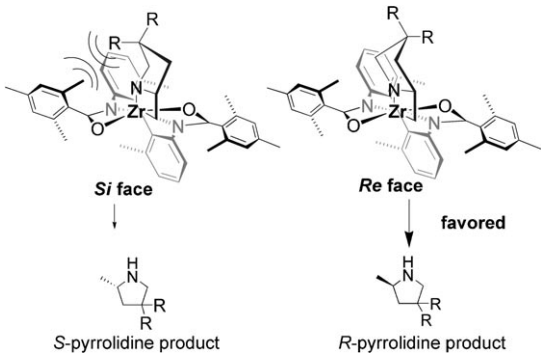


Figure 2. Suggested intermediates in the enantioselective aminoalkene hydroamination using precatalyst (+)-**4a** in which the alkene can approach from the *Re* face or the *Si* face.

These modular amidate complexes are easily prepared from commercially available chiral diamines, acid chlorides, and $Zr(NMe_2)_4$ to yield precatalysts that can be isolated on the gram scale. Most importantly, these first examples of neutral chiral zirconium precatalysts for enantioselective intramolecular hydroamination show promising preliminary results, providing *ee* values of up to 93%. Ongoing efforts are focused on mechanistic investigations and on broadening the scope of reactivity and selectivity of this class of complexes.

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