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C_2-Symmetric Zirconium Bis(Amidate) Complexes with Enhanced Reactivity in Aminoalkene Hydroamination

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Summary: Binaphthalenedicarboxamide zirconium complexes exhibit significantly enhanced catalytic activity in aminoalkene hydroamination reactions with respect to substrate scope (substrates without gem-dialkyl activation; cyclization of aminoheptenes), catalyst loading (as low as 0.5 mol %) and reaction temperatures (as low as 70 °C) compared to previous group 4 metal-based hydroamination catalyst systems.

The importance of nitrogen containing compounds in biological systems and industrially relevant basic and fine chemicals has sparked significant research efforts to develop efficient synthetic protocols.[1] One of the simplest approaches, the hydroamination, has found significant attention only in recent years with the development of more efficient transition metal-based catalyst systems.[2] The addition of amine N−H functionalities to unsaturated carbon−carbon bonds generates amines in a waste-free, highly atom-economical manner starting from simple and inexpensive precursors. An area of particular interest has been the generation of new stereogenic center during the hydroamination process, but the development of chiral catalysts for the asymmetric hydroamination of alkenes (AHA) has remained challenging.[3−5]

Group 4 metal-based catalyst systems have been studied intensively in the hydroamination of alkynes and allenes,[2i−o,6]

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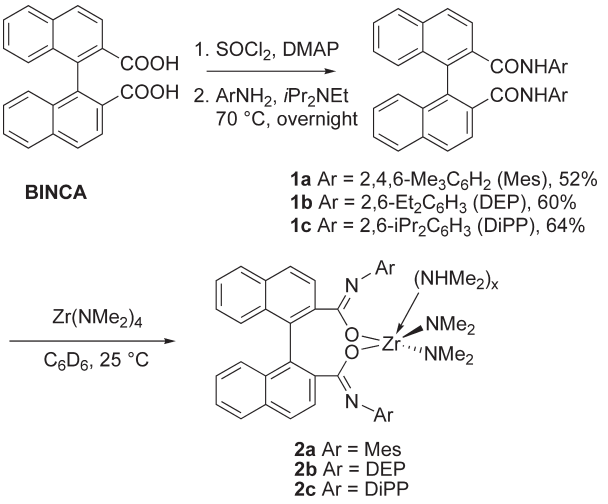
while reactions involving unactivated alkenes have emerged only in recent years.[7] Schafer[4c,6j,l,q,r,7d,g,8] has developed amidate titanium and zirconium hydroamination catalysts that exhibit promising hydroamination activity, including cyclization of primary aminoalkenes. Chiral variants of these catalysts developed in Schafer's[4c] and Scott's[4d] group have displayed enantioselectivities of up to 93% ee.

Alkene hydroamination with group 4 metal-based catalysts requires significant harsher reaction conditions (> 100 °C) and higher catalyst loadings (typically 5−10 mol %) in comparison to rare earth metal-based catalysts.[2h,5a,k,9] With a few exceptions,[4b,7c,k] neutral group 4 metal catalyst systems have been limited to gem-dialkyl-activated aminoalkenes. Cyclization of aminoheptenes led to the unexpected formation of the hydroaminoalkylation product rather than the anticipated 7-membered ring hydroamination product.[10−12] However, easier catalyst preparation and handling, as well as potential higher functional group tolerance, may compensate for this disadvantage.

We selected binaphthalenedicarboxylic acid (BINCA) as a key starting material for the preparation of novel bis(amidate) ligands, based on its readily availability and excellent configurational stability.[13] To our surprise, no bis(amidate) BINCA-based ligands have been reported so far.[14] For our initial study we selected a few aromatic amines with varying steric demand to synthesize corresponding zirconium bis(amidate) complexes.

The synthesis of the desired bis(amide) proligands proceeded in a convenient two-step, one-pot sequence (Scheme 1) in moderate yields. Subsequent reaction of the proligands **1b-c** with $Zr(NMe_2)_4$ led to well-defined C_2-symmetric species **2** (Scheme 1), which can be formulated as the amine adduct (**1**)$Zr(NMe_2)_2(NHMe)_2$.[15]

Scheme 1. Preparation of Binaphthalenedicarboxamide Ligands and Their Corresponding Zirconium Complexes



The observation of a single carbonyl signal for **2b**,**c** in the ^{13}C NMR spectrum at around 161 ppm is indicative of a κ^1-binding mode of the amidate ligand.[4d] The reaction of the least sterically demanding ligand **1a** led an unsymmetric species with two carbonyl signals at 160.8 and 178.6 ppm, which is indicative of different binding modes (κ^1/κ^2) of the two amidate moieties. The precatalysts **2a**,**b** may be isolated by removal of the solvent in vacuo with retention of two equivalents of dimethylamine. However, removal of solvent from the sterically most hindered complex **2c** produced the mono(amine) adduct (**1c**) $Zr(NMe_2)_2(HNMe_2)$ (**2c′**) with two κ^1 bound amidate moieties.[15] The catalysts exhibited the same reactivity independently of being isolated or generated in situ. Thus, for convenience the catalysts were generally prepared in situ and used as a standard solution.

A screening of complexes **2a**−**c** in various catalytic hydroamination/cyclization reactions revealed a remarkable increase in catalytic performance compared to previously studied group 4 alkene hydroamination catalyst systems. Most notably, reactions could be performed with catalyst loadings as low as 0.5 mol % (Table 1, entry 13) and reaction temperatures as low as 70 °C (Table 1, entry 5).

As anticipated, increasing steric bulk of the gem-dialkyl-substituent in aminopentenes **3a**−**d** resulted in higher rates of cyclization, allowing it to perform cyclizations with low catalyst loadings and lower reaction temperatures. In the absence of any gem-dialkyl-substituent the cyclization of **3e** required slightly higher reaction temperatures, higher catalyst loadings, and longer reaction times (Table 1, entries 16 and 17). However, there are only a limited set of group 4 metal catalysts capable to cyclize this substrate and they

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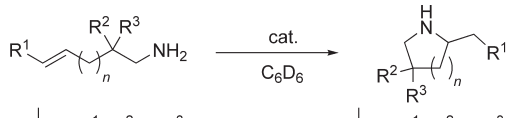
(14) Schafer and co-workers have reported recently related biphenyl-based bis(amidate) tantalum catalysts for hydroaminoalkylation, see ref 12e.

(15) The complexes were isolated as mono(amine) adduct (complex **2c′**, see Supporting Information) and bis(amine) adducts (complexes **2a** and **2b**) based on NMR spectroscopy. The reaction of the proligands **1** with $Ti(NMe_2)_4$ lead to a mixture of products and we are currently attempting to identify and separate these species.

(16) The only previous example of hydroamination/cyclization of an aminoheptene with a group 4 metal catalyst has been reported recently by Schafer while studying the hydroaminoalkylation reaction. The achiral bis(amidate) zirconium catalyst required forcing reaction conditions (20 mol % cat., 145 °C, 115 h, 55% conv), see ref 11a and 7o.

Table 1. Zirconium-Catalyzed Asymmetric Hydroamination of Aminoalkenes[a]



	n	R^1	R^2	R^3
3a	1	H	Me	Me
3b	1	H	-$(CH_2)_5$-	
3c	1	H	Ph	Ph
3d	1	H	Me	
3e	1	H	H	H
3f	1	Ph	Ph	Ph
5a	2	H	Ph	Ph
5b	2	H	Me	Me
7	3	H	Ph	Ph

	n	R^1	R^2	R^3
4a	1	H	Me	Me
4b	1	H	-$(CH_2)_5$-	
4c	1	H	Ph	Ph
4d	1	H	Me	
4e	1	H	H	H
4f	1	Ph	Ph	Ph
6a	2	H	Ph	Ph
6b	2	H	Me	Me
8	3	H	Ph	Ph

entry	subst	cat (mol %)	conditions[b]	% ee (config)
1	**3a**	(*S*)-**2a** (2)	100 °C, 26 h	23 (*R*)
2	**3a**	(*R*)-**2b** (2)	100 °C, 7 h	42 (*S*)[c]
3	**3a**	(*S*)-**2c** (5)	110 °C, 6 h	< 5% (*R*)
4	**3b**	(*S*)-**2a** (2)	100 °C, 12 h	14 (*R*)
5	**3b**	(*S*)-**2a** (6)	70 °C, 28 h	16 (*R*)
6	**3b**	(*R*)-**2b** (2.5)	90 °C, 7 h	27 (*S*)
7	**3b**	(*R*)-**2b** (1)	90 °C, 12 h	26 (*S*)
8	**3b**	(*S*)-**2c** (2)	110 °C, 3 h	11 (*S*)
9	**3c**	(*S*)-**2a** (2)	100 °C, 3 h	54 (*S*)
10	**3c**	(*S*)-**2a** (2)	80 °C, 14 h	52 (*S*)[d]
11	**3c**	(*R*)-**2b** (1)	100 °C, 2.5 h	36 (*R*)
12	**3c**	(*S*)-**2c** (2)	100 °C, 1.5 h	39 (*S*)
13	**3c**	(*rac*)-**2c** (0.5)	100 °C, 6 h	
14	**3d**	(*S*)-**2a** (2)	90 °C, 13 h	60/0[e]
15	**3d**	(*R*)-**2b** (2)	90 °C, 9 h	48/48[f]
16	**3e**	(*S*)-**2a** (8)	120 °C, 39 h	7 (*R*)
17	**3e**	(*R*)-**2b** (3)	110 °C, 72 h	6 (*S*)
18	**3f**	(*S*)-**2a** (6)	110 °C, 16 h	8
19	**5a**	(*S*)-**2a** (4)	100 °C, 3 h	33
20	**5a**	(*R*)-**2b** (2)	100 °C, 3 h	26
21	**5b**	(*S*)-**2a** (2)	100 °C, 7 h	7
22	**7**	(*S*)-**2a** (8)	120 °C, 51 h	60[g]
23	**7**	(*R*)-**2b** (10)	120 °C, 72 h	53

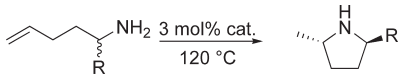
[a] Reaction conditions: C_6D_6, Ar atm. [b] Greater than 95% conv based on ^{1}H NMR spectroscopy using ferrocene as internal standard. [c] Isolated yield is 84%. [d] Isolated yield is 85%. [e] dr = 1.6:1. [f] dr = 1.8:1. [g] NMR yield is 94%.

typically require harsher reaction conditions (≥10 mol % catalyst loading, ≥120 °C).[4b,7c,k] Complexes **2** catalyze not only the cyclization of aminohexenes **5a**,**b**, they also facilitate formation of the azepane **8** (Table 1, entries 22 and 23),[16] which is the first example for an enantioselective 7-membered ring formation via catalytic hydroamination. This contrasts previous reported attempts of hydroamination/cyclization of aminoheptene derivatives that either gave no product[7b,e,l] or resulted in a hydroaminoalkylation process instead.[10−12] In fact, under the catalytic conditions employed in this study, we did not observe hydroaminoalkylation or olefin isomerization[4a,7a,b,11b] products in any of the catalytic reactions.

Although still speculative at this point, the significant higher reactivity of complexes **2** in comparison to previously studied group 4 metal alkene hydroamination catalysts (including amidate complexes) may be attributed to the

(17) As observed by Schafer in the crystal structure of a biphenyl-based bis(k^1-amidate) tantalum complex, see ref 12e. Coincidentally, the highest enantioselectivity achieved with this catalyst system in the hydroaminoalkylation of norbornene was 61% ee.

Table 2. Diastereoselective Hydroamination/Cyclization of α-Substituted Aminopentenes



9a R = Me
9b R = Bn
9c R = Cy

10a-c

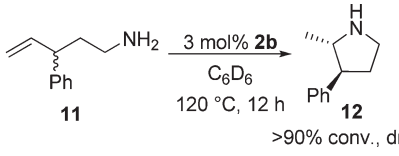
subst	cat	*t*, h	trans/cis	yield, %[a]
9a	**2b**	20	15:1	94
9b	**2b**	25	> 30:1	95
9c	**2a**	12	> 30:1	88[b]

[a] NMR yield based on ^{1}H NMR spectroscopy using ferrocene as internal standard. [b] Isolated yield.

κ^1 binding mode of the amidate moieties leading to a more electron deficient, thus more reactive metal center. On the other hand, this κ^1 binding mode puts the stereodirecting N-aryl substituents in a more remote position, pointing away from the metal center.[17] Therefore, it is not too astonishing that the enantioselectivities achieved with complexes **2** do not compare well with the highest selectivities achieved to date in group 4 metal catalyzed alkene hydroamination reactions.[4a−d] Nevertheless, it seems remarkable that the highest selectivity of 60% ee was observed in the formation of the azepane **8** using catalyst **2a**. Generally, the sterically less demanding mesityl substituent in **2a** resulted in higher enantioselectivities, which may be rationalized by a mixed κ^1/κ^2-binding mode of the two amidate moieties in this complex.

The scope of the reaction is not limited to terminal olefins, but also the internal olefin **3f** was cyclized efficiently. Cyclization of α-alkyl substituted aminopentenes proceeded with high trans/cis diastereoselectivities (Table 2), but no kinetic resolution of the starting material was observed.[5k,18,19]

Cyclization of **11** (eq 1) proceeded chemoselectively without any substrate isomerization, remarkably contrasting our observations with binaphtholate rare earth metal complexes[19] that are highly resistant to olefin isomerizations otherwise.



(1)

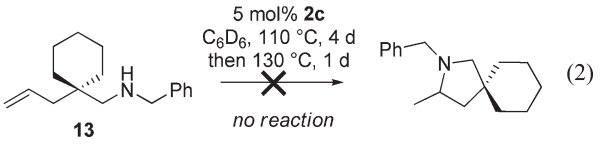
However, no reaction was observed for the *N*-benzyl aminopentene derivative **13** even under more forcing reaction conditions (eq 2), which is in agreement to

(18) The starting material remained racemic at conversions as high as 86%. It is conceivable that the zirconium catalysts may racemize the substrate, see: Pohlki, F.; Bytschkov, I.; Siebeneicher, H.; Heutling, A.; König, W. A.; Doye, S. *Eur. J. Org. Chem.* **2004**, 1967. However, cyclization of enantiomerically pure **9a** did not show any sign of racemization of the starting material.

(19) Reznichenko, A. L.; Hampel, F.; Hultzsch, K. C. *Chem.—Eur. J.* **2009**, *15*, 12819.

(20) A few neutral group 4 metal catalyst systems have been reported to catalyze the hydroamination/cyclization of secondary aminoalkenes, which has been interpreted in terms of an alternative lanthanide-like σ-bond metathesis mechanism, see refs 7h, 7k, and 7l.

most[20] previous studies on neutral group 4 metal based catalysts.[4c,7b,d]



(2)

This finding has been interpreted as an indicator for a [2 + 2]-cycloaddition mechanism analogous to group 4 metal-catalyzed alkyne and allene hydroaminations,[6a,b,d,21] as the secondary amine does not allow formation of a metal imido species required in this mechanism.[20]

Some initial kinetic studies[22] indicate that the reaction is first order in aminoalkene substrate and catalyst, which is in agreement to some studies,[7d,l] while others have observed a zero order rate dependence on substrate concentration.[4f,7h] Certainly, the reaction order in substrate depends on the underlying reaction mechanism and the structure of the catalytic active species. To that end, it is interesting to note that enantiopure and racemic catalysts **2** exhibited the same rate of cyclization, which is highly indicative (in conjunction with the first order rate dependence on catalyst concentration) that the resting state of the catalyst in this process is a monometallic species. A strong primary kinetic isotope effect of 4.2 in the cyclization of **3b** is in agreement to a previous study by Scott[4f] and the resulting pyrrolidine **4b**-d_2 shows deuteration exclusively at the α-methyl position (as well as at nitrogen).

We are currently performing further catalytic and mechanistic studies toward the scope and limitation of complexes **2** in order to improve enantioselectivity and improve our understanding of the increased reactivity of these new catalysts.

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Supporting Information Available: Experimental procedures and characterization data, NMR spectra of ligands **1a**−**c**, complexes **2a**−**c**, catalytic reactions and Mosher amides, kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) (a) Pohlki, F.; Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2305. (b) Straub, B. F.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4632.

(22) See Supporting Information for details.