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COMMUNICATION

Planar-chiral [2.2]Paracyclophane-based Amides as Proligands for Titanium and Zirconium Catalyzed Hydroamination

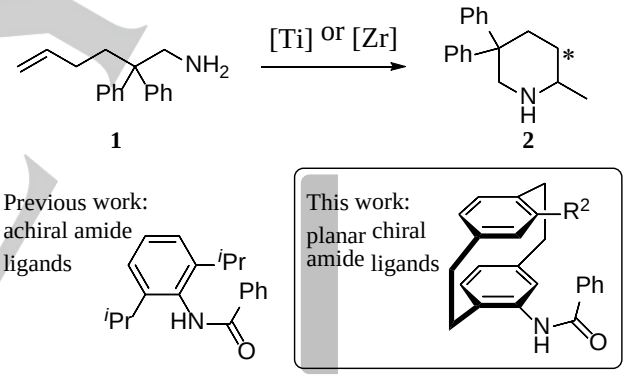
Carolin Braun,[a] Stefan Bräse,*[a,b] and Laurel L. Schafer*[c]

Dedication ((optional))

Abstract: A synthetic route to racemic and enantiopure planar chiral [2.2]paracyclophane containing amides was developed to combine the well-established reactivity of amides as *N,O*-chelating ligands in hydroamination reactions with the planar chirality of the [2.2]paracyclophane backbone. A mono- as well as a tethered bis(amide) were synthesized and investigated as ligands for titanium and zirconium. Hydroamination reactivity studies showed their ability to translate their planar chirality into central chirality in the product.

Introduction

Nitrogen containing compounds, such as amines and enamines, are widespread in nature and play a pivotal role not only as bulk chemicals, but also as fine chemicals, agrochemicals and pharmaceuticals. Therefore, an efficient and sustainable synthetic approach to these compounds is required. In this context, hydroamination[1] is the direct addition of an N–H bond across a C–C multiple bond. This transformation has garnered significant interest as it is 100% atom economic and uses simple starting materials such as amines and alkynes/alkenes without any further stoichiometric additives. The formation of pharmaceutical and agrochemical agents is of particular interest in the field. Interestingly, the formation of these products often requires a high level of enantioselectivity. Numerous examples using metals such as titanium[2], zirconium[2a, 2c-e, 3], lanthanides[3c, 4] and other early[2b, 2d, 3i, 5] or late[1c-e, 6] transition metals have been reported. However, the disclosed ligand systems for asymmetric hydroamination often usually central or axial chirality and amongst these reports there is no ligand system that possesses exclusively planar chirality. Although planar chirality is seldomly observed in classic organic chemistry, disubstituted ferrocene or substituted [2.2]paracyclophane derivatives are quite prominent representatives of this special type of chirality and have been exploited in other catalytic transformations such as hydrogenation or coupling reactions.[7] [2.2]Paracyclophanes indeed have an advantage over ferrocenes in that they are already chiral with only one substituent. Chiral resolution can be achieved by derivatization of the racemic [2.2]paracyclophane with an enantiopure compound to give a diastereomeric product, which can then be separated by column chromatography or fractional recrystallization.[8] To date there is no general route to access variously substituted [2.2]paracyclophanes in enantiopure form and often chiral resolutions result in a limited number of resolved, enantiopure derivatives.[8] However, they are a rigid ligand framework with immense stability and significant steric bulk.[7a, 9] Notably, reactivity and stereoselectivity in catalytic hydroamination has been shown to be sensitive to steric and electronic effects.



Scheme 1. Known achiral *N,O*-chelating amide[3j, 10] and new planar chiral [2.2]paracyclophane containing ligands for intramolecular hydroamination.

Therefore we combined the planar chirality of the [2.2]paracyclophane backbone with amides as potent *N,O*-chelating proligands[3l, 11] for titanium and zirconium catalyzed hydroamination (Scheme 1). These early transition metals are advantageous in that they are earth-abundant and inexpensive with low toxicity. Herein we report the racemic and enantiopure synthesis of [2.2]paracyclophane containing mono- and bisamides. Through catalytic investigation we have explored transfer of their planar chirality into central chirality in the hydroamination product.

Results and Discussion

First we explored the synthetic route towards the racemic [2.2]paracyclophanyl benzamides, using methods similar to those

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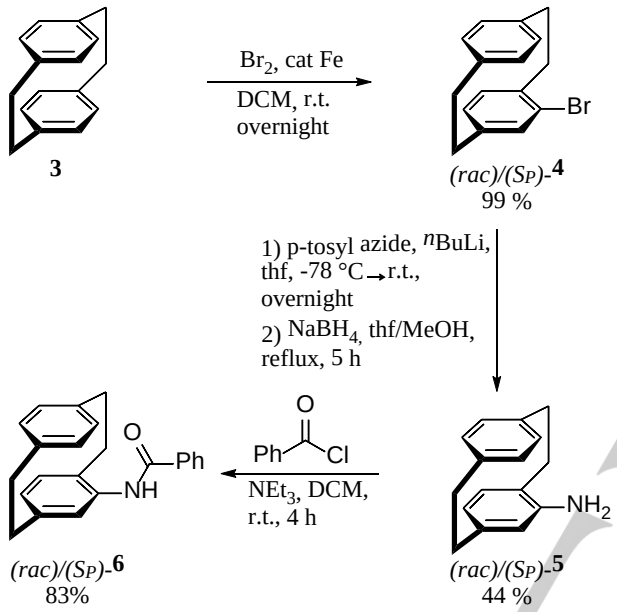
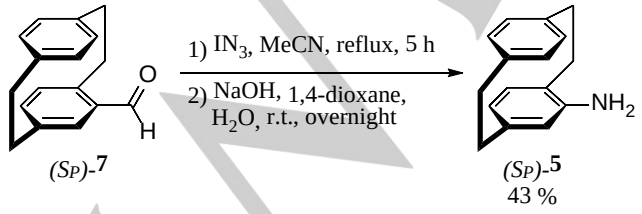
established for our achiral amide ligands[12] (Scheme 2). The racemic 4-amino[2.2]paracyclophane is accessible from the commercially available, unsubstituted parent compound **3** *via* iron-catalyzed bromination[13] to give **4** in excellent yield. Subsequent lithiation of bromide **4** and treatment with tosyl azide[14] gives the 4-azido[2.2]paracyclophane that can be reduced with $NaBH_4$ under slightly modified reaction conditions to give amine **5**[13c, 15] in an overall yield of 44% over three steps. The amine **5** can undergo a condensation reaction with benzoyl chloride to give the desired amide **6**[16], which can be recrystallized in high yield (83%).



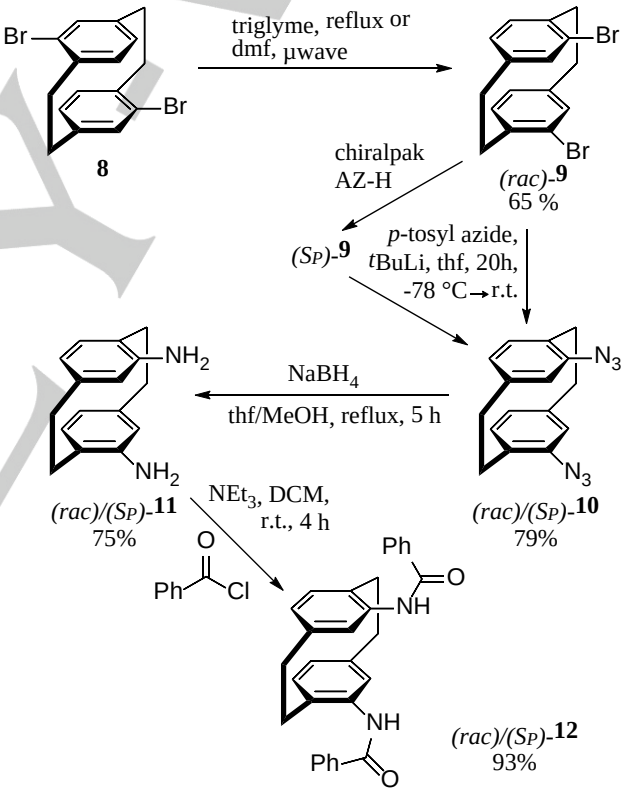
Scheme 2. Synthesis of the [2.2]paracyclophane containing benzamide **6** *via* amine **5**. For resolution, see text and supporting information.

With a synthetic procedure for the racemic proligand in hand, we wanted to extend this protocol to synthesize enantiopure, planar-chiral proligands. Our most reliable results for the chiral resolution were obtained with racemic formyl[2.2]paracyclophane **7**[17] *via* condensation reaction with enantiopure *(R)*-phenylethyl amine and fractional recrystallization of the resulting diastereomeric imines to get, after imine hydrolysis, the enantiopure *(SP)*-4-formyl[2.2]paracyclophane (**7**).[18]



Scheme 3. Radical azidonation of *(SP)*-4-formyl[2.2]paracyclophane to get the enantiopure amine *(SP)*-**5** as precursor for the enantiopure amide ligand *(SP)*-**6** (see supporting information for safety issues).

Fortunately we could develop a transformation of this enantiopure [2.2]paracyclophane derivative into the desired amide, although efficient transformations of benzaldehyde derivatives into aniline derivatives are rare. Nevertheless Bols *et al.* reported a radical azidonation to carbamoyl azides and subsequent hydrolysis as a route for accessing the appropriate amines.[19] We could use these conditions to access our desired, enantiopure [2.2]paracyclophane amine *(SP)*-**5** in 43% yield (Scheme 3, see supporting information for safety issues).Despite the common use of chiral resolution to access enantiopure [2.2]paracyclophanes, these protocols are expensive and time intensive and typically give access to only one enantiomer in pure form.[8] Therefore, we developed an alternative route based on preparative HPLC with commercially available chiral stationary phase (chiralpak® AZ-H column) to separate the two enantiomers of the racemic bromide **4**. Afterwards, the same synthetic route as for the racemic compound (Scheme 2) can be applied in the synthesis of the enantiopure ligand *(SP)*-**6**.



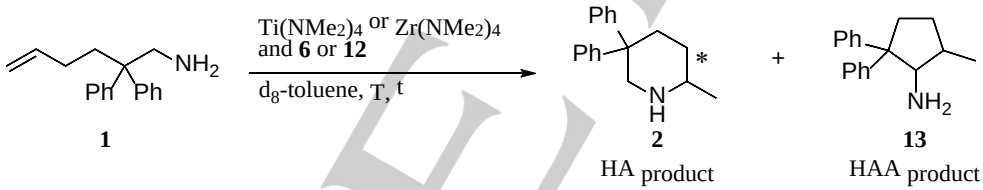
Scheme 4. Synthesis of the pseudo-*ortho* bisamide **12**.

Achiral amide proligands used in titanium or zirconium catalysed hydroamination catalysis have been prepared as bis(amidate) metal complexes.[11b, 11d, 20] Thus, the other targeted proligand structure was a tethered bisamide based on a pseudo-*ortho* disubstituted [2.2]paracyclophane backbone (Scheme 4). This substitution pattern[21] is well investigated in [2.2]paracyclophane chemistry in catalysis due to the well-established PhanePhos[22] ligand. The synthetic approach to those phosphine compounds is based on the unselective iron-

catalyzed double bromination of the [2.2]paracyclophane backbone which yields various regioisomers but has the advantage that the pseudo-*para* isomer **8** has the lowest solubility.[23] Afterwards, a thermal[23a, 23d, 23f, 24] or microwave-induced[25] isomerization reaction of **8** gives the desired racemic pseudo-*ortho* dibromide **9**. Separation of the enantiomers could be achieved by preparative HPLC using the commercially available chiralpak® AZ-H column. This strategy provides easy access to a homo-disubstituted [2.2]paracyclophane derivative with defined stereochemistry, which is not the case for the nitration[26] or acylation[27] approach from the unsubstituted [2.2]paracyclophane. The transformation to the bisamide **12** was performed following the same lithiation and reaction with tosyl azide strategy (Scheme 2). The bisazide **10** was then reduced with $NaBH_4$ in THF/methanol under reflux conditions to give the bisamine **11**[28] in good yield. The last step included condensation with benzoyl chloride to give the tethered desired bisamide **12** in excellent yield (93%) after recrystallization. This synthesis has the main advantage of giving a reliable access to the mono- as well as the homo-disubstituted amides **5** and **12**, which can sometimes be challenging for homo-disubstituted [2.2]paracyclophane derivatives due to solubility problems and low to modest yields. After the successful synthesis of our amide proligands, we tested them in the intramolecular alkene hydroamination.

Cyclohydroamination of aminoalkene **1** with bis-*N,O*-chelated complexes of Ti and Zr is well established,[3m, 10a, 29] with Zr complexes generally displaying shorter reaction times to give piperidine **2**. The enantioselective formation of **2** is known to be more challenging than the asymmetric synthesis of the related and more common five-membered pyrrolidine ring products, which are furnished in good *ee* (90 - 99%) with several group 4 catalysts.[2a, 3f, 3g, 3j] As an illustration of the challenge presented by substrate **1** only a few reported catalytic systems give approximately 25%*ee* for titanium[2c-e] and select systems with 21–82 %*ee* have been reported for zirconium.[2a, 2c-e, 2g, 3a-h, 3k-n] Furthermore, piperidine product formation often requires high reaction temperatures of over 100 °C and long reaction times of several days. Note that previously reported chiral catalysts are largely based upon the use of chelate ligands with axial chirality with a few examples incorporating point chirality into the ligand set.[2a, 3e, 3g, 3n] Furthermore, it has also been shown that catalysts are challenged by aminoalkene **1** in that a side reaction can occur under catalytic hydroamination conditions to give the hydroamino-alkylation[30] product **13** resulting from α-C–H-activation. Such reactivity has been observed with both titanium[30b-e] and zirconium[31] catalysts. The more commonly tested, shorter 2,2-disubstituted-pent-4-en-1-amine substrate readily undergoes hydroamination to give 5-membered pyrrolidine products and no hydroaminoalkylation side-products are observed. Substrate **1** allows for insights into relative reactivity, stereoselectivity and chemoselectivity (between hydroamination and hydroaminoalkylation) in one reaction that can be monitored by NMR spectroscopy. Thus substrate **1** is our preferred test substrate for catalyst development efforts.

Table 1 Results for the *in situ* intramolecular hydroamination reaction[a] of **1** to yield **2** (and **13**).



1 **2** HA product **13** HAA product

Entry	Ligand	Metal Precursor	M:lig ratio[b]	Temperature	Reaction Time	Conversion [d]	Yield **2**[e] (**13**)[d]	*ee*[f]
1	-	$Ti(NMe_2)_4$	-	55 °C	22 h	80%	72% (7%)	0
2	*(rac)*-**6**	$Ti(NMe_2)_4$	1:1	55 °C	22 h[c]	quant.	95%	0
3	*(S_P)*-**6**	$Ti(NMe_2)_4$	1:1	55 °C	22 h[c]	quant.	95%	9%*ee*
4	*(S_P)*-**6**	$Zr(NMe_2)_4$	1:1	55 °C	22 h	30%	29%	0
5	*(S_P)*-**6**	$Zr(NMe_2)$	1:2	55 °C	22 h	28%	26%	0
6	*(S_P)*-**12**	$Ti(NMe_2)_4$	1:1	55 °C	46 h	43%	36% (6%)	68%*ee*
7	*(S_P)*-**12**	$Zr(NMe_2)$	1:1	55 °C	22 h	44%	43%	33%*ee*
8	*(S_P)*-**12**	$Ti(NMe_2)_4$	1:1	100°C	12 h	90%	75% (12%)	15%*ee*
9	*(S_P)*-**12**	$Zr(NMe_2)$	1:1	100 °C	12 h	96%	95%	12%*ee*

[a] Reaction conditions: aminoalkene (1 equiv), $Ti(NMe_2)_4$ or $Zr(NMe_2)_4$ (10mol%), amide ligand (10 or 20 mol%), internal standard (250 µmol), d_8-toluene, T, t, N_2 atmosphere. [b] Metal precursor to ligand ratio. [c] Determined by ^{1}H NMR spectroscopy as time that was necessary for complete conversion. [d] Consumption of **1** and yield of **13** determined by ^{1}H NMR spectroscopy of the crude reaction mixture with an internal standard (1,3,5-trimethoxybenzene). [e] Isolated Yield. [f] Determined by analytical HPLC with chiral stationary phase.

For all hydroamination reactions, the catalyst system was prepared in situ via a protonolysis reaction by mixing the commercially available metal precursors $Ti(NMe_2)_4$ or $Zr(NMe_2)_4$ and the proligands **6** or **12** (Table 1). First, we tested our racemic ligand (*rac*)-**6** under our reaction conditions at 55 °C, a compromise between modest temperatures and reasonable reaction times. After 22 h full conversion was observed by 1H NMR spectroscopy with 95% isolated yield and without any detectable hydroaminoalkylation side product (Table 2, entry 2). Afterwards we wanted to clarify that in situ preparation of the metal complexes gave the same results compared to isolated compounds. Therefore we compared isolated racemic **6**-$Ti(NMe_2)_3$ as catalyst (see supporting information) with the in situ prepared example showing the same results and therefore the usefulness of the in situ screening. Unfortunately, use of enantiopure ligand imparts only a low *ee* of 9% (entry 3). This result cannot be improved upon by using $Zr(NMe_2)_4$ as metal precursor. On the contrary, the catalyst system comprised of $Zr(NMe_2)_4$ and *(S_P)*-**6**, prepared in situ with one or two equivalents of ligand (entries 4–5), shows a decreased reactivity of only 30% and 28% conversion, respectively, after the same reaction time, and gives racemic reaction products. Seemingly, the flexible ligand *(S_P)*-**6** is unable to give satisfying results, presumably due to the fact that the steric bulk of the [2.2]paracyclophane backbone can rotate freely even when the 1,3-*N,O*-ligand is chelated to the metal centre. It is noteworthy that we also tested the metal precursor $Ti(NMe_2)_4$ without any ligand as its activity for hydroamination reactions is known in literature.[1a, 32] (entry 1). Nevertheless, 7% of the hydroaminoalkylation side product **13** was detected by the characteristic doublet for the methyl substituent at 0.91 ppm showing that without a specific ligand, total chemoselectivity for hydroamination is not observed.

Next we tested our tethered bisamide *(S_P)*-**12** under the same reaction conditions with the two metal precursors (entries 6–9). With $Ti(NMe_2)_4$ and at 55 °C, the reaction runs significantly slower than with mono amidate **6** or without ligand. Even after prolonged reaction time of 2 d, only 43% conversion could be observed (entry 6). This behaviour can be easily explained regarding the increased steric bulk around the metal centre with this tethered ligand design. Despite the decreased reactivity and the fact that a significant amount of side product **13** was detected, this ligand is superior in terms of asymmetric induction, which is shown by 68%*ee*, which is a significant increase compared to other titanium catalysts.[2c-e] Superior reactivity was observed when $Zr(NMe_2)_4$ was used, showing 43% conversion after only 22 h without side product. This enhanced reactivity is consistent with previously reported group 4 catalysts for alkene hydroamination[10a] derived from the larger atomic radius of zirconium, which is less affected and sterically shielded by the tethered ligand **12**. Nevertheless, with 33%*ee* the *ee* is significantly decreased and follows the often observed trend that a higher reactivity goes hand in hand with a lower selectivity. Nevertheless, the obtained *ee* is in a comparable range with some other reported zirconium systems.[2a, 2c-e, 2g, 3a-c, 3f, 3k, 3l, 3n] With an increased temperature, that is often used for hydroamination catalysis,[3j, 3l, 11a, 29a] the reaction goes considerably faster (entries 8–9), but for both metals, the *ee*'s are drastically decreased.

Conclusions

In summary, we have explored the potential use of a planar chiral [2.2]paracyclophane system for asymmetric hydroamination. A synthetic route to racemic and enantiopure [2.2]paracyclophane containing amide proligands with different substitution patterns of the [2.2]paracyclophane backbone is shown. The enantiopure ligands are accessible *via* two different procedures, we demonstrated that both chiral resolution and separation of the enantiomers *via* preparative HPLC with chiral stationary phase, are powerful tools to gain access to enantiopure [2.2]paracyclophane derivatives with various substituents. Most importantly, we have demonstrated that these planar chiral ligand systems possess the ability to impart enantioselectvity to the respective central chiral products. Our preliminary results showed that mono-ligated Ti systems display desirable chemoselective reactivity giving uniquely the hydroamination product, making further exploration of other planar chiral systems attractive. These synthetic advances and reactivity insights provide a new platform for on-going catalyst development efforts.

Experimental Section

General procedure for NMR-tube scale intramolecular hydroamination. All NMR-tube scale reactions were prepared in an N_2-filled glove box. The amide ligand (37 µmol, 10 mol%) and $Ti(NMe_2)_4$ or $Zr(NMe_2)_4$ (37 µmol, 10 mol%) were dissolved in 300 µL d_8-toluene and stirred for 30 min. Then the internal standard (1,3,5-trimethoxybenzene) (250 µmol) and 2,2-diphenylhex-5-en-1-amine (375 µmol, 1 eq.) were added. The solution was transferred to a J.Young NMR-tube with a Teflon screw cap and the reaction vial was rinsed with 200 µL d_8-toluene. The tube was then heated to and maintained at the appropriate temperature for the stated duration of time. The NMR conversions and yields of **13** were determined by comparing the integration of the internal standard with a well-resolved signal for the starting material and the heterocyclic products. Afterwards, the crude reaction mixture was purified using column chromatography on silica.

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Keywords: [2.2]paracyclophanes; asymmetric intramolecular hydroamination; amidate ligands

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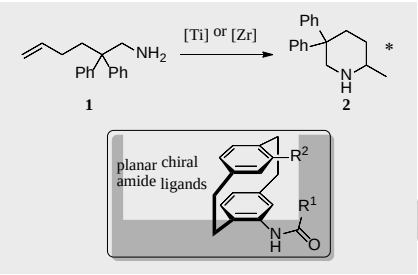

[2.2]paracyclophane, hydroamination

Carolin Braun, Stefan Bräse, and Laurel L. Schafer**

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Planar-chiral [2.2]Paracyclophane-based Amides as Proligands for Titanium and Zirconium Catalyzed Hydroamination