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Titanium Binolate Catalyzed Aminolysis of *meso* Aziridines: A Highly Enantioselective and Direct Access to 1,2-Diamines**

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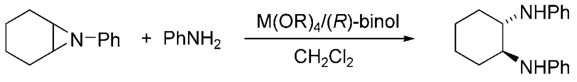
Dedicated to Professor Hans-Ulrich Reißig on the occasion of his 60th birthday

The asymmetric ring-opening of *meso* aziridines has only recently attracted attention within the chemical community and offers an elegant and direct synthesis of chiral, α-functionalized amines.[1] The groups of Jacobsen,[2] Shibasaki,[3] Antilla,[4] and most recently RajanBabu[5] have developed metal-based as well as organocatalytic processes for the synthesis of 1,2-azido amines and 1,2-cyano amines, which were obtained in excellent yields and enantioselectivities; these compounds constitute valuable synthetic precursors to optically pure 1,2-diamines and β-amino acids, respectively. Nucleophiles other than trimethylsilyl azide and trimethylsilyl cyanide have not yet been as successful used in aziridine ring-opening reactions. For the direct aminolysis of *meso* aziridines using anilines Kobayashi et al. developed a chiral niobium catalyst which furnished 1,2-diamines with 50–84 % *ee*.[6] Very recently, the same group described a chiral titanium catalyst which improved the enantioselectivity to above 90 % *ee* for a single substrate, whereas other substrates were converted with only 60–76 % *ee*.[7] Also, phase-transfer-catalyzed thiol additions to *meso* aziridines currently proceed only with moderate selectivities.[8] Additionally, all processes suffer from multistep syntheses of chiral ligands or catalysts and require the use of precious reagents and some special techniques (e.g., glovebox or a syringe pump).[5,7]

We have previously shown that chiral scandium– and indium–bipyridine complexes catalyze highly enantioselective ring-opening reactions of *meso* epoxides with various heteronucleophiles.[9] Accordingly, we investigated analogous reactions of *meso* aziridines with amines and thiols and were able to obtain 1,2-diamines and 1,2-amino sulfides in very good yields when catalyzed with just 1 mol % $Sc(OTf)_3$ and $InCl_3$, respectively.[10] All our efforts, however, to convert this process into an enantioselective reaction by attaching chiral ligands to the metal were unsuccessful.

We report herein that a chiral catalyst prepared in situ from the commercially available and cheap components $Ti(O\mathit{i}Pr)_4$ or $Ti(O\mathit{t}Bu)_4$ and (*R*)-binol effects the highly enantioselective ring-opening of *meso* aziridines using anilines to furnish 1,2-diamines in one step in very good yields and up to 99 % *ee*. By using the reaction of 7-phenyl-7-azabicyclo[4.1.0]heptane (**1a**) with aniline (**2a**) as a model reaction, the reaction conditions were optimized (Table 1). Whereas $Ti(O\mathit{i}Pr)_4$ alone displayed only little catalytic activity (Table 1, entry 1), the reaction conducted in the presence of a chiral catalyst prepared in situ from equimolar amounts of $Ti(O\mathit{i}Pr)_4$ and (*R*)-binol (10 mol %) in CH_2Cl_2 led to complete conversion within 30 minutes at room temperature and delivered 1,2-diamine **3a** in 83 % yield and 48 % *ee* (Table 1, entry 2). In contrast, zirconium binolate complexes displayed reduced catalytic activity and furnished **3a** with lower enantioselectivity (Table 1, entries 3 and 4).

Table 1: Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry[a]	M(OR)$_4$	M(OR)$_4$/ (*R*)-binol	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	Ti(O*i*Pr)$_4$	–	20	12	13	–
2	Ti(O*i*Pr)$_4$	1:1	20	0.5	83	48
3	Zr(O*i*Pr)$_4$	1:1	20	12	76	12
4	Zr(O*t*Bu)$_4$	1:1	20	12	95	28
5	Ti(O*i*Pr)$_4$	1:1	0	1	85	61
6	Ti(O*i*Pr)$_4$	1:1	−40	14	51	79
7	Ti(O*i*Pr)$_4$	1:2	0	0.5	81	69
8	Ti(O*i*Pr)$_4$	1:2	−20	1	88	80
9	Ti(O*i*Pr)$_4$	1:2	−40	5	81	97
10	Ti(O*t*Bu)$_4$	1:2	−40	5	92	98
11	Ti(OEt)$_4$	1:2	−40	5	91	87

[a] Reaction conditions: **1a** (1 equiv), **2a** (1.1 equiv), M(OR)$_4$ (10 mol %), (*R*)-binol (11 or 22 mol %, resp.), 0.25 M in CH_2Cl_2. [b] Yield of isolated product. [c] Determined by HPLC methods using chiral stationary phases (see the Supporting Information). [d] Without (*R*)-binol as the chiral ligand. (*R*)-binol = (*R*)-2,2′-dihydroxy-1,1′-binaphthyl.

Not unexpectedly, lowering the reaction temperature increased the enantioselectivity of the reaction albeit at the expense of the conversion (Table 1, entries 5 and 6). Eventually, the key to the success of this reaction was the carefully optimized preparation of the chiral catalyst in the correct titanium/binol stoichiometry. After $Ti(O\mathit{i}Pr)_4$ (10 mol %) and (*R*)-binol (22 mol %) had been premixed in CH_2Cl_2 (0.25 M)

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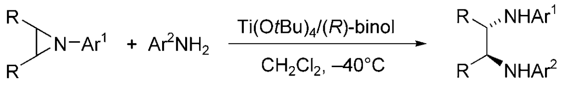
for 1 hour at room temperature, aniline (**2a**; 1.1 equiv) was then added, and the reaction mixture was stirred for an additional 30 minutes at room temperature. The solution was then cooled to the indicated temperature and aziridine **1a** was added, whereupon a rapid and highly enantioselective reaction commenced. The optimal reaction temperature was −40 °C, at which 1,2-diamine **3a** was obtained in 81 % yield and 97 % *ee* after 5 hours (Table 1, entry 9). With $Ti(OtBu)_4$ as the titanium source under otherwise identical reaction conditions, **3a** was isolated in 92 % yield and with 98 % *ee*, whereas the use of $Ti(OEt)_4$ led to a decrease in the enantioselectivity (Table 1, entries 10 and 11). The addition of activated 4 Å molecular sieves led to identical results; however, trace amounts of water present in the reaction mixture significantly deteriorated the enantioselectivity of the reaction.

By using the optimized reaction conditions anilines **2b–e** were reacted with *meso*-aziridine **1a** furnishing the corresponding *trans*-cyclohexane-1,2-diamines **3b–e** in good yields and high enantioselectivities of up to 99 % *ee* (Table 2, entries 2–5). To have the option to cleave off the N-aryl group and liberate the free amino group *N-para*-methoxyphenyl aziridine **1b** was submitted to the reaction with aniline (**2a**) and *para*-anisidine (**2c**), and delivered 1,2-diamines **3c** and **3f**, respectively, with 98 % *ee* in each case (Table 2, entries 6 and 7). The established protocol was successfully extended to other *meso* aziridines. In particular, the 6-phenyl- and 6-*para*-methoxyphenyl-6-azabicyclo[3.1.0]hexanes (**1c** and **1d**, respectively) proved to be highly suitable substrates for this process and delivered, even using $Ti(OiPr)_4$ as the titanium source, *trans*-cyclopentane-1,2-diamines **3g–l** in excellent yields and enantioselectivities (up to > 99 % *ee*; Table 2, entries 8–12). Even the unsaturated *meso*-aziridine **1e** successfully underwent ring-opening with various anilines and furnished the corresponding 1,2-diamines **3m–o** in good yields and high enantioselectivities (Table 2, entries 13–15). This process can also be applied to acyclic *meso* aziridines as was explicitly shown for *N*-phenyl-*cis*-2,3-dimethylaziridine (**1f**) which upon reaction with aniline gave rise to (2*S*, 3*S*)-2,3-bisphenyl aminobutane (**3p**) in 87 % yield and 90 % *ee* (Table 2, entry 16).

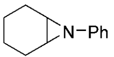
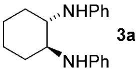
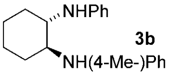
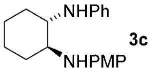
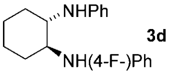
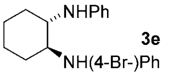
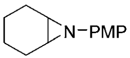
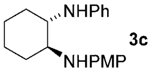
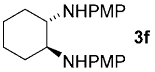
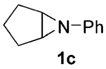
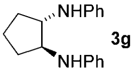
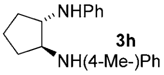
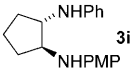
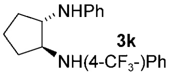
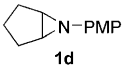
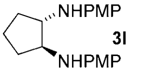
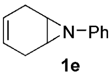
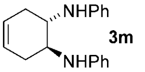
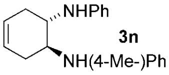
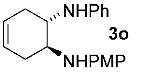
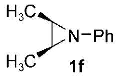
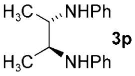
To explicitly demonstrate the selective removal of the PMP groups, 1,2-diamines **3c** and **3f** were first converted into the cyclic ureas **4a** and **4b**, respectively. Ceric ammonium nitrate oxidation of the electron-rich aryl groups and subsequent acidic hydrolysis of the urea moiety furnished *N*-phenyl-1,2-diamine **5a** and C_2-symmetrical 1,2-diamine **5b**, respectively, as their dihydrochloride salts in good overall yields (Scheme 1).

Titanium binolate complexes have been employed as chiral controllers for a broad range of different catalytic, asymmetric transformations and belong to the class of privileged chiral catalysts.[11] In particular, alkylations,[12] allylations,[13] aldol[14] and carbonyl-ene reactions[15] of aldehydes have been conducted in an asymmetric fashion using this catalyst system. It is remarkable, however, that the in situ preparation of the active chiral catalyst significantly differs from reaction to reaction with respect to titanium/binol stoichiometry, solvent, and the addition of water or molecular sieves. In spite of the frequent use of this metal–ligand combination in asymmetric catalysis, only very few detailed mechanistic investigations regarding the reaction course have

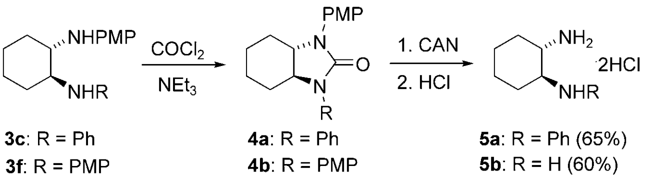
Table 2: Titanium binolate catalyzed ring-opening of *meso*-aziridines **1** with anilines **2**.[a]



1 **2** **3**

Entry	*meso*-Aziridine **1**	1,2-Diamine **3**	Yield [%][c]	*ee* [%][d,e]
1	 **1a**	 **3a**	92	98
2	**1a**	 **3b**	85	99
3	**1a**	 **3c**	86	98
4	**1a**	 **3d**	91	95
5	**1a**	 **3e**	91	91
6	 **1b**	 **3c**	89	98
7	**1b**	 **3f**	86	98
8[b]	 **1c**	 **3g**	90	99
9[b]	**1c**	 **3h**	83	99
10[b]	**1c**	 **3i**	96	99
11[b]	**1c**	 **3k**	71	94
12	 **1d**	 **3l**	75	99
13	 **1e**	 **3m**	78	89
14	**1e**	 **3n**	89	90
15	**1e**	 **3o**	78	87
16	 **1f**	 **3p**	87	90

[a] Reaction conditions: *meso*-aziridine **1** (1 equiv), aniline **2** (1.1 equiv), $Ti(OtBu)_4$ (10 mol %), (*R*)-binol (22 mol %), 0.25 M in CH_2Cl_2, −40 °C. [b] $Ti(OiPr)_4$ was employed as the titanium source. [c] Yield of isolated product. [d] Determined by HPLC methods using chiral stationary phases (see the Supporting Information). [e] The absolute configuration of the products was assigned by comparison of the optical rotation with the literature data, or by analogy. PMP = *para*-methoxyphenyl.



Scheme 1. Removal of the *para*-methoxyphenyl groups. CAN = ceric ammonium nitrate

been conducted[16] and there are few crystal structures of such complexes which are mainly oligonuclear in nature.[17]

In our case, two observations call for the existence of an oligomeric titanium complex as well. An ESI(+) MS measurement of a mixture of Ti(O*t*Bu)$_4$, (*R*)-binol, and aniline (1:2.2:10), which had been prepared in CH_2Cl_2 according to the general synthetic protocol, displayed a tetranuclear titanium cluster of the formal composition [Ti$_4$(O*t*Bu)$_3$((*R*)-binol)$_6$] ($m/z = 2115$) as a major component. Additionally, asymmetric aziridine ring-opening reactions conducted with binol ligands of varying enantiomeric excesses revealed a weak, but significant positive nonlinear effect (NLE), which indicates the involvement of more than one chiral ligand within the active metal catalyst; this data is in accord with the MS investigations (see the Supporting Information).[18] To rule out that the 1,2-diamines generated in this process act as chiral ligands themselves and affect the enantiomeric excess of the products, the enantioselectivity of the reaction to furnish **3a** was determined as a function of the conversion (Table 2, entry 1). In the course of the entire reaction, however, the *ee* value was constantly 97–98 %.

We have reported the first highly enantioselective ring-opening of *meso* aziridines using anilines to furnish valuable 1,2-diamines with excellent optical purities in just one step. As a chiral catalyst we have employed an extremely user friendly titanium complex, the preparation of which involves the commercially available components Ti(O*i*Pr)$_4$ and Ti(O*t*Bu)$_4$, respectively, and (*R*)-binol, thereby precluding any complicated ligand synthesis or special techniques. Investigations are currently ongoing to further elucidate the structure of the active catalyst and extend this process to other nucleophiles.

Experimental Section

General protocol: Ti(O*t*Bu)$_4$ (19 µL, 0.05 mmol) was added to a solution of (*R*)-binol (31.5 mg, 0.11 mmol) in 1 mL CH_2Cl_2 at RT, and the mixture was stirred for 1 h under argon atmosphere. Subsequently, aniline (50 µL, 0.55 mmol) was added to the deep red solution, which was then stirred for another 30 min at RT. The mixture was cooled to −40 °C whereupon *meso*-aziridine **1a** (87 mg, 0.50 mmol) was added dropwise. After the solution had been stirred for 5 h at −40 °C the reaction was quenched by the addition of NEt_3 (0.50 mL) at −40 °C, and then warmed to RT. The reaction mixture was directly purified by chromatography on silica gel (petroleum ether/ethyl acetate = 20:1 containing 1 % NEt_3). 1,2-diamine **3a** (122 mg; 92 %) was isolated with 98 % *ee*, which was determined by chiral HPLC methods (see the Supporting Information).

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Keywords: asymmetric catalysis · aziridines · desymmetrization · 1,2-diamines · titanium

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