

# Catalytic, enantioselective synthesis of Boc-protected 1,2-amino alcohols through aminolysis of *meso*-epoxides with benzophenone imine

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**Dedicated to Prof. Johann Mulzer on the occasion of his 65th anniversary**

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## Abstract

Aromatic *meso*-epoxides **3** have been ring-opened with benzophenone imine (**2**) using catalytic quantities of the chiral scandium bipyridine complex **1a** to furnish Boc-protected 1,2-amino alcohols **5** in good yields and enantioselectivities after acidic hydrolysis and Boc-protection.

**Keywords:** Asymmetric catalysis, desymmetrization, *meso*-epoxide, benzophenone imine, 1,2-amino alcohol, scandium

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## Introduction

The catalytic, enantioselective ring-opening of *meso*-epoxides is a valuable strategy for the asymmetric synthesis of 1,2-difunctionalized fine chemicals.<sup>1</sup> In the past this strategy has been widely employed for the synthesis of 1,2-azido alcohols,<sup>2</sup> 1,2-halohydrins,<sup>3</sup> 1,2-cyano alcohols,<sup>4</sup> 1,2-diol monoester and monoethers,<sup>5</sup> and 1,2-mercapto alcohols<sup>6</sup> many of which have been obtained thus far in good to excellent enantioselectivities.

The nucleophilic addition of amines to epoxides catalyzed by Lewis acids typically suffers from compatibility problems between the Lewis basic amine and the Lewis acid catalyst which tend to coordinate to one another irreversibly. A solution to this problem was first shown in the work of Crotti who found that lanthanide triflates such as Yb(OTf)<sub>3</sub> are effective catalysts for the aminolysis of 1,2-epoxides, presumably because they are able to exert their exceptional Lewis acidity even in the presence of the amine.<sup>7</sup>

Following this precedence Hou et al. discovered a Yb(OTf)<sub>3</sub>-*R*-BINOL-catalyst for the first catalytic, enantioselective aminolysis of cyclohexene oxide with aniline.<sup>8</sup> Inaba et al. utilized a chiral titanium catalyst made from equimolar amounts of Ti(OiPr)<sub>4</sub> and (*S*)-BINOL (1 mol-%) for the addition of benzyl amine to a seven-membered cyclic epoxide containing a ketal moiety

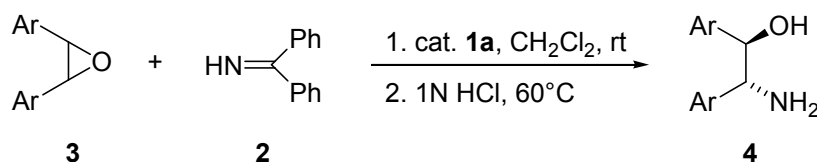


acidic hydrolysis in good yields and enantioselectivities when catalyzed with our scandium bipyridine catalyst **1a**.

## Results and Discussion

Based upon the well-known capacity of benzophenone imine to act as an ammonia surrogate in Buchwald-Hartwig amination reactions<sup>17</sup> we investigated its use as nucleophile in our scandium-bipyridine-catalyzed epoxide-opening process. We started our studies with the reaction of *cis*-stilbene oxide (**3a**) and benzophenone imine (**2**) (2 eq.) in dichloromethane (0.2 M) catalyzed through 10 mol% of the scandium bipyridine catalyst **1a**. After 3 d at rt we stopped the reaction by adding 1 N HCl-solution and heated the mixture to 60°C for 4 h to effect hydrolysis of the imine. Upon basification the desired 1,2-amino alcohol **4a** was obtained in 36% yield and 88% ee as determined by HPLC-analysis along with 45% of the starting epoxide **3a** which reflects the attenuated nucleophilicity of the ketimine relative to anilines (table 1, entry 1).

**Table 1.** Optimization studies for the addition benzophenone imine (**2**) to *cis*-stilbene oxide (**3**)



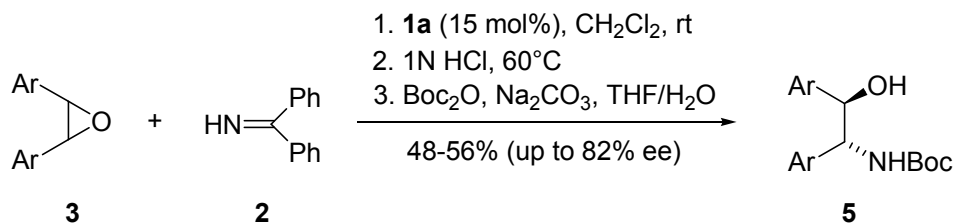
entry	epoxide	Ar	equiv. of <b>2</b>	conc. [M]	<b>1a</b> [mol%]	yield [%] <sup>a</sup>	ee [%] <sup>b</sup>
1	<b>3a</b>	Ph	2.0	0.2	10	36	88
2	<b>3a</b>	Ph	4.0	0.2	10	59	43
3	<b>3a</b>	Ph	2.0	0.5	15	75	80
4	<b>3b</b>	4-Me-Ph	2.0	0.5	15	84	66
5	<b>3c</b>	4-Cl-Ph	2.0	0.5	15	66	82

<sup>a</sup> Isolated yield of purified material. <sup>b</sup> Determined by HPLC-analysis on a chiral stationary phase.

In an attempt to increase conversion we doubled the amount of the nucleophile from 2 to 4 eq. of benzophenone imine (**2**) under otherwise identical reaction conditions. Indeed, 1,2-amino alcohol **4a** was now obtained in 59% yield, but with a diminished 43% ee indicating a detrimental effect of the imine on the enantioselectivity of the reaction (entry 2). In a further attempt the overall concentration of the mixture was increased from 0.2 M to 0.5 M and the catalyst amount was increased from 10 mol% to 15 mol%. Gratifyingly, these changes led to the isolation of **4a** in 75% yield and 80% ee after 5 d at rt (entry 3). Two other aromatic *meso*-epoxides **3b** and **3c** were subsequently converted into the corresponding 1,2-amino alcohols **4b**

and **4c**, respectively, in good overall yields and enantioselectivities according to this protocol (entries 4 and 5).

**Table 2.** Sequential epoxide-opening and Boc-protection to furnish Boc-protected 1,2-amino alcohols **5** in a one-pot operation



entry	epoxide	Ar	yield [%] <sup>a</sup>	ee [%] <sup>b</sup>
1	<b>3a</b>	Ph	51	80
2	<b>3b</b>	4-Me-Ph	48	66
3	<b>3c</b>	4-Cl-Ph	56	82

<sup>a</sup> Isolated yield of purified material. <sup>b</sup> Determined by HPLC-analysis on a chiral stationary phase.

In some experiments it turned out, however, that the highly polar 1,2-amino alcohols **4** were frequently difficult to isolate. Accordingly, we developed an alternate procedure which involved the *in situ* protection of the amino group with the butyloxycarbonyl(Boc)-group. When we followed the sequence comprising the enantioselective ring-opening of *meso*-epoxides **3** with benzophenone imine (**2**), imine hydrolysis and Boc-protection we were able to obtain the Boc-protected 1,2-amino alcohol **5a-c** in 48-56% overall yields and up to 82% ee (table 2). This procedure had the advantage that we could more reliably obtain the products in the indicated yields.

## Conclusions

We have developed a novel protocol for the scandium-bipyridine-catalyzed, enantioselective aminolysis of aromatic *meso*-epoxides with benzophenone imine as ammonia surrogate. Upon imine hydrolysis either the free or the Boc-protected 1,2-amino alcohols were obtained in good overall yields and enantioselectivities without the need to oxidatively cleave off a nitrogen substituent.

## Experimental Section

**General Procedures.** All reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. The following reaction solvents were distilled from the indicated drying agents: dichloromethane (CaH<sub>2</sub>), tetrahydrofuran (LiAlH<sub>4</sub>, triphenylmethane), diethyl ether (Na, benzophenone), toluene (Na, benzophenone), *N,N*-dimethylformamide (Acros ACS grade), acetonitrile (Acros ACS grade), chloroform (Acros ACS grade). Diethyl ether, petroleum ether and ethyl acetate for chromatography were technical grade and distilled from KOH or CaCl<sub>2</sub>. All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel SIL G/UV254 plates (Machery, Nagel & Co.); spots were visualized by treatment with a solution of vanillin (0.5 g), conc. acetic acid (10 mL), and conc. H<sub>2</sub>SO<sub>4</sub> (5 mL) in methanol (90 mL) or molybdophosphoric acid (5 g) in ethanol (250 mL). Flash column chromatography was performed by using Merck silica gel 60 230-400 mesh. The *meso*-epoxides **3b** and **3c** were prepared according to the method of Burk et al.<sup>18</sup> The chiral bipyridine was best prepared according to the protocol developed by Kobayashi.<sup>19</sup> All other chemicals were used as received from commercial suppliers. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with VARIAN Gemini 200 (200 MHz), VARIAN Gemini 300 (300 MHz) spectrometers or an Bruker Avance DRX 400 (400 MHz) spectrometer in CDCl<sub>3</sub> at 25°C with TMS as internal standard. IR spectra were obtained with a FTIR spectrometer (Genesis ATI, Mattson/Unicam). UV spectra were obtained with a Beckmann DU-650 spectrometer. Melting points are uncorrected. Optical rotations were measured using a Polarotronic polarimeter (Schmidt & Haensch). HPLC analyses were performed on a JASCO MD-2010 plus instrument with a chiral stationary phase column (Chiralcel AD-H column purchased from Daicel Co., Ltd.). Mass spectra were measured at 70 eV (EI) with a Finnigan MAT 95 A spectrometer. High-resolution mass spectra (HRMS; ESI/Na) were measured with a Bruker Daltonics APEX II FT-ICR spectrometer.

### General procedure for the one-pot synthesis of Boc-protected 1,2-amino alcohols

38 mg (0.075 mmol) of Sc(OTf)<sub>3</sub> and 30 mg (0.08 mmol) of chiral bipyridine were stirred in CH<sub>2</sub>Cl<sub>2</sub> (1 ml, 0.5 M final solution relative to epoxide) for 5 min at rt whereupon 0.50 mmol of *meso*-epoxide **3** and 181 mg (1.00 mmol) of benzophenone imine (**2**) were added. The mixture was stirred at rt for 5 d. Subsequently, 1 N HCl solution was added and the mixture heated to 60°C for 4 h. After cooling to rt the phases were separated, the aqueous layer was extracted with dichloromethane (3 x 10 ml) and subsequently made alkaline through addition of 6 N NaOH solution. The basic solution was extracted with EtOAc (4 x 50 ml), the combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and evaporated in vacuo. The crude product was dissolved in 2 ml of THF/H<sub>2</sub>O (3:1) and 106 mg (1.00 mmol) of Na<sub>2</sub>CO<sub>3</sub> and 130 mg (0.55 mmol) of Boc<sub>2</sub>O were added at 0°C. After 6 h stirring at rt 2 ml of water were added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 ml). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and evaporated in vacuo. The crude products were purified through column

chromatography over silica gel with ethyl acetate/hexane (1:4) to yield typically crystalline products **5**.

**N-Boc-1,2-amino alcohol 5a.**<sup>20</sup>Yield: 51% (80% ee); mp. 114-116°C;  $\alpha_D^{20} = +5.3^\circ$  ( $c = 1.26$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.33 (brs, 9 H, Boc), 2.73 (brs, 1 H, NH or OH), 4.81 (brs, 1 H, NH or OH), 4.98 (brs, 1 H, CH), 5.42 (d,  $J = 7.5$  Hz, 1 H, CH), 7.21- 7.35 (m, 10 H, aromatic-H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  28.20, 60.73, 77.32, 79.79, 126.3, 126.9, 127.5, 127.6, 128.1, 128.5, 139.9, 140.8, 156.0; IR (KBr)  $\nu = 1170, 1520, 1667, 2929, 2977, 3411$  cm<sup>-1</sup>; ESI-MS:  $m/z = 336.1$  (M + Na<sup>+</sup>), 648.9 (2M + Na<sup>+</sup>); HPLC (AD-H column, 85:15 hexane/iPrOH, 0.8 ml/min)  $t_{R\text{minor}} = 26.35$  min,  $t_{R\text{major}} = 33.10$  min.

**N-Boc-1,2-amino alcohol 5b.** Yield: 48% (66% ee); mp. 95-98°C;  $\alpha_D^{20} = +14.2^\circ$  ( $c = 0.66$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.34 (brs, 9 H, Boc), 2.32 (s, 6 H, 2x Me), 2.61 (brs, 1 H, NH or OH), 4.84 (brs, 1 H, NH or OH), 4.89 (brs, 1 H, CH), 5.36 (d,  $J = 8.0$  Hz, 1 H, CH), 7.09-7.19 (m, 8 H, aromatic-H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  21.06, 21.09 (2x Me), 28.23, 60.47, 77.21, 79.69, 126.2, 126.8, 128.8, 129.2, 137.1, 137.2, 137.8, 156.0; IR (KBr)  $\nu = 1172, 1523, 1670, 2920, 2977, 3413$  cm<sup>-1</sup>; ESI-HRMS:  $m/z = 364.18826$  (M + Na<sup>+</sup>), 705.38718 (2M + Na<sup>+</sup>); HPLC (AD-H column, 85:15 hexane/iPrOH, 0.8 ml/min)  $t_{R\text{minor}} = 16.92$  min,  $t_{R\text{major}} = 29.20$ . Anal. calcd. for C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub>: C 73.87, H 7.97, N 4.10; found C 74.15, H 7.83, N 4.05.

**N-Boc-1,2-amino alcohol 5c.** Yield: 56% (82% ee); mp. 161-164°C;  $\alpha_D^{20} = +70.6^\circ$  ( $c = 0.27$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.33 (brs, 9 H, Boc), 2.76 (brs, 1 H, NH or OH), 4.79 (brs, 1 H, NH or OH), 4.86 (brs, 1 H, CH), 5.34 (d,  $J = 7.5$  Hz, 1 H, CH), 7.13- 7.29 (m, 8 H, aromatic-H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  28.20, 60.30, 77.20, 80.24, 127.7, 128.3, 128.4, 128.7, 133.5, 133.6, 138.2, 139.0, 155.0; IR (KBr)  $\nu = 1168, 1412, 1516, 1672, 2919, 2965, 3415$  cm<sup>-1</sup>; ESI-HRMS:  $m/z = 404.07914$  (M + Na<sup>+</sup>), 787.16643 (2M + Na<sup>+</sup>); HPLC (AD-H column, 85:15 hexane/iPrOH, 0.8 ml/min)  $t_{R\text{minor}} = 14.77$  min,  $t_{R\text{major}} = 27.93$ . Anal. calcd. for C<sub>19</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>3</sub>: C 59.70, H 5.54, N 3.66; found C 59.85, H 5.43, N 3.60.

## Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (Schn 441/3-2) for the generous support of this project.

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