Indium–Bipyridine Catalyzed, Enantioselective Aminolysis of *meso*-Epoxides

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Abstract: The enantioselective aminolysis of *meso*-epoxides is efficiently catalyzed by an indium(III)–bipyridine catalyst to furnish highly enantiomerically enriched 1,2-amino alcohols in good yields and up to 98% ee.

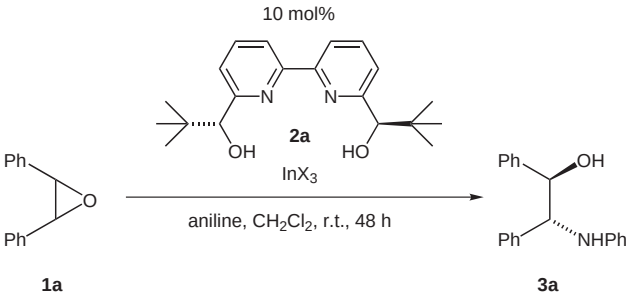
Key words: amine, asymmetric catalysis, bipyridine, epoxides, indium

The catalytic asymmetric ring opening of *meso*-epoxides has proven to be a valuable tool for the straightforward synthesis of enantiomerically highly enriched 1,2-difunctionalized fine chemicals.[1] In particular, chiral 1,2-azido alcohols,[2] 1,2-diol derivatives,[3] 1,2-cyano alcohols,[4] 1,2-mercapto alcohols,[5] and 1,2-halohydrins[6] have become available in partly excellent optical purity using this strategy. The direct nucleophilic addition of amines to *meso*-epoxides is complicated by compatibility problems between the Lewis basic amine and the typically Lewis acidic chiral catalyst. Therefore the azidolysis of *meso*-epoxides has been used extensively as a solution to this problem. There are, however, some protocols for the direct aminolysis of *meso*-epoxides giving rise to 1,2-amino alcohols in varying enantioselectivities and typically rather limited substrate scope.[7]

We have developed a highly enantioselective scandium–bipyridine-catalyzed process for the addition of alcohols and amines to *meso*-epoxides furnishing 1,2-diol monoethers and 1,2-amino alcohols in up to 97% ee.[8] In addition, we have recently shown that a highly enantioselective thiol addition to aromatic *meso*-epoxides takes place when the corresponding indium(III)–bipyridine complex was employed as chiral catalyst and 1,2-mercapto alcohols were obtained in excellent yields and enantioselectivities.[9]

We now report that a chiral indium(III)–bipyridine catalyst may also be employed for the highly enantioselective aminolysis of *meso*-epoxides.[10,11] In the model reaction of *cis*-stilbene oxide (**1a**) and aniline in CH_2Cl_2 various indium(III) salts were tested in combination with the bipyridine ligand **2a** (Table 1).[12] Whereas the $InCl_3$–bipyridine **2a** complex (10 mol% each) displayed only moderate catalytic activity (entry 1), the corresponding $InBr_3$–bipyridine and $In(OTf)_3$–bipyridine complexes were more reactive and furnished 1,2-amino alcohol **3a** in yields close to 50% yield and up to 91% ee (entries 2 and 3). When the latter reaction was run in more concentrated solution (0.50 M in CH_2Cl_2), the conversion was further improved and the product **3a** was obtained in 69% yield thereby slightly compromising the ee to 87% (entry 4). Interestingly, in the absence of the ligand or when bipyridine bis-*O*-methylether **2b** (Figure 1) was employed as chiral ligand a completely unreactive indium(III) catalyst was formed documenting the assistance of the hydroxyl protons in the catalytic cycle possibly by hydrogen bonding to the amine.[13]

Table 1 Indium–Bipyridine **2a** Catalyzed Aminolysis of *cis*-Stilbene Oxide (**1a**) with Aniline



Entry	InX_3	Concn (M)[a]	Yield (%)[b]	ee (%)[c]
1	$InCl_3$	0.25	34	82
2	$InBr_3$	0.25	50	85
3	$In(OTf)_3$	0.25	47	91
4	$In(OTf)_3$	0.50	69	87

[a] With respect to the epoxide.
[b] Isolated yield after chromatography.
[c] Determined by chiral HPLC analysis.

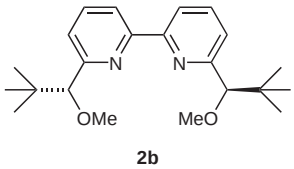


Figure 1

Under the optimized reaction conditions[14] a variety of aromatic amines was reacted with *cis*-stilbene oxide (**1**) and furnished 1,2-amino alcohols **3a**–**k** in typically good yields and enantioselectivities approaching and in many

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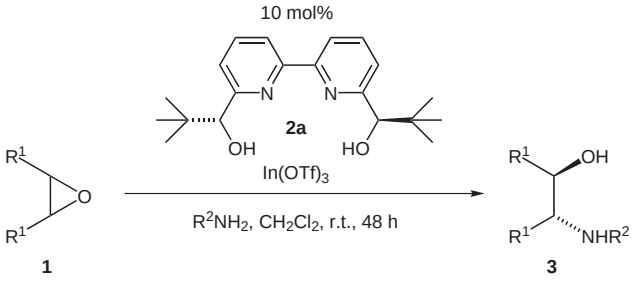
cases exceeding 90% (Table 2, entries 1–10). In particular, electron-deficient and sterically hindered anilines gave rise to very high enantioselectivities of up to 98% ee thereby maintaining the yields at a good level (entries 5–10). Other aromatic *meso*-epoxides were ring-opened with aniline in good yields and up to 95% ee (entries 11–13). Just as in the scandium–bipyridine-catalyzed process alkyl-substituted epoxides were ring-opened with only moderate enantioselectivities (entries 14 and 15).[8]

Table 2 Indium–Bipyridine **2a** Catalyzed Aminolysis of *meso*-Epoxides **1**



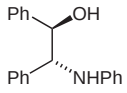
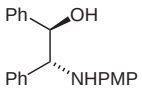
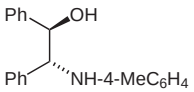
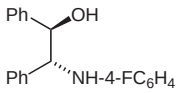
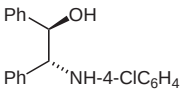
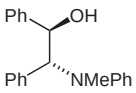
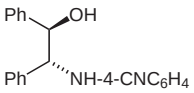
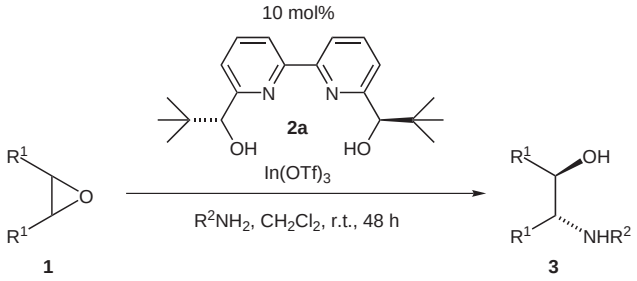
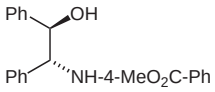
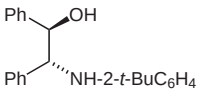
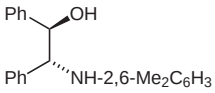
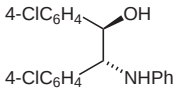
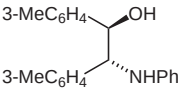
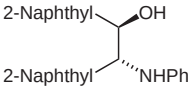
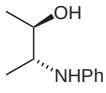
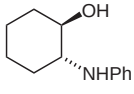
Entry	Product[a]	Yield (%)[b]	ee (%)[c]
1	 **3a**	69	87
2	 **3b**	83	72
3	 **3c**	89	88
4	 **3d**	86	88
5	 **3e**	95	90
6	 **3f**	80	92
7	 **3g**	80	97

Table 2 Indium–Bipyridine **2a** Catalyzed Aminolysis of *meso*-Epoxides **1** (continued)



Entry	Product[a]	Yield (%)[b]	ee (%)[c]
8	 **3h**	80	98
9	 **3i**	84	95
10	 **3k**	82	97
11	 **3l**	83	94
12	 **3m**	91	90
13	 **3n**	90	95
14	 **3o**	82	36
15	 **3p**	91	31

[a] The absolute configuration of the products was determined by comparison of the rotation values with literature values or by analogy.
[b] Isolated yield after chromatography.
[c] Determined by chiral HPLC analysis.

A crystal structure[9] of the related $InBr_3$–bipyridine **2a** catalyst revealed a pentagonal-bipyramidal coordination geometry around the metal center with the hydroxyl protons still attached to the complex which very closely resembles

the related scandium–bipyridine complex.[15] Consequently, the sense of asymmetric induction is identical in both processes furnishing the products with the same absolute configuration.

In conclusion, we have devised a novel chiral indium(III)-based catalyst for the aminolysis of *meso*-epoxides furnishing 1,2-amino alcohols in generally good yields and up to 98% ee at ambient temperature. Aromatic *meso*-epoxides were ring-opened with good to excellent enantioselectivity whereas alkyl-substituted epoxides underwent the aminolysis with only moderate selectivity. Work is currently being continued to further improve the efficiency and enantioselectivity of the process.

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(13) We have made the same observation in the related indium(III)–bipyridine **2a** catalyzed thiolysis of *meso*-epoxides (ref. 9).

(14) **Typical Experimental Procedure**
In an oven-dried flask and under inert atmosphere $In(OTf)_3$ (28 mg, 0.05 mmol) and bipyridine **2a** (20 mg, 0.05 mmol) were dissolved in CH_2Cl_2 (1 mL) and treated with epoxide (0.50 mmol) and amine (1.00 mmol) at r.t. The reaction mixture was stirred for 48 h at r.t. whereupon it was concentrated in vacuo and purified by silica gel chromatography. For analytical and spectroscopic details of the products, see ref. 8b.

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