Indium–bipyridine-catalyzed, enantioselective thiolysis of *meso*-epoxides†

Mecheril Valsan Nandakumar,[a] Andreas Tschöp,[a] Harald Krautscheid[b] and Christoph Schneider*[a]

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The indium–bipyridine-catalyzed, enantioselective ring-opening of *meso*-epoxides with aliphatic and aromatic thiols furnished 1,2-mercapto alcohols in good yields and excellent enantioselectivities; the crystal structure of the chiral catalyst reveals a pentagonal-bipyramidal coordination geometry around the indium center.

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-amino alcohols[2] and 1,2-azido alcohols,[3] 1,2-diol derivatives,[4] 1,2-cyano alcohols[5] and 1,2-halohydrins[6] have become available in excellent optical purities using this strategy. Among the processes reported for the addition of thiols to *meso*-epoxides,[7] a heterobimetallic gallium–lithium–BINOL complex has been established by Shibasaki *et al.* as the most enantioselective catalyst currently known for this reaction.[7a] Unfortunately, the use of *tert*-butyl thiol is mandatory here to avoid undesired ligand exchange on the metal center which significantly limits the applicability of this process.

We have reported recently a highly enantioselective catalyst for the alcoholysis and aminolysis of *meso*-epoxides composed of scandium triflate and bipyridine **1a** (Fig. 1).[8a,b] With just 5 mol% of the metal–ligand complex formed *in situ*, *meso*-epoxides were ring-opened with anilines and aliphatic alcohols to furnish 1,2-amino alcohols[8c] and 1,2-diol monoethers,[8d] respectively, in good yields and up to 97% ee. We have now extended this protocol to the enantioselective thiolysis of *meso*-epoxides and show here that an indium–bipyridine complex formed *in situ* from $InBr_3$ and bipyridine **1a** is an effective chiral catalyst for this endeavour.[9,10]

We started our investigations with the reaction of *cis*-stilbene oxide (**2a**) and benzylthiol (**3a**) and screened a broad range of Lewis acids and Lewis acid–chiral ligand combinations as catalysts for this reaction (Table 1). Eventually, we identified indium(III) halide–bipyridine **1a** complexes as the most suitable chiral catalysts which not only possessed sufficient Lewis acidity to activate the epoxide towards nucleophilic ring-opening but also readily tolerated the Lewis basic thiol. Thus, 10 mol% of $InCl_3$ and 11 mol% of bipyridine **1a** afforded 1,2-mercapto alcohol **4a** in 60% yield and 95% ee after 6 days at rt (entry 4). The reaction was markedly accelerated by employing 10 mol% of $InBr_3$ and 11 mol% bipyridine **1a**, which furnished **4a** in 80% yield and 92% ee after just 16 h at rt (entry 5). Interestingly, no product formation was observed in the absence of the chiral ligand or when the unsubstituted 2,2′-bipyridine, which lacks the additional hydroxyl groups, was employed as the ligand (entries 1–3). Also, the bis-*O*-methylated bipyridine **1b** failed to give a reactive indium(III) catalyst (entry 6). These results clearly indicate the combined effect of the metal center and the hydroxyl protons for the epoxide opening reaction, similar to what we had observed in the scandium–bipyridine-catalyzed alcoholysis and aminolysis of *meso*-epoxides.[8a]

Employing 10 mol% of $InBr_3$–bipyridine **1a** as catalyst, *cis*-stilbene oxide (**2a**) was ring-opened with various aromatic as well as aliphatic thiols, furnishing 1,2-mercapto alcohols **4a–f** in typically good to very good yields and excellent enantioselectivities of up to 96% ee (Table 2, entries 1–6). There appears to be no structural or electronic limitation in the thiol component and straight-chain aliphatic thiols even give rise to some of the most enantioselective reactions included in this study (entries 4–6). Other aromatic *meso*-epoxides were subsequently ring-opened with thiophenol and benzylthiol, and furnished the corresponding 1,2-mercapto alcohols **4g–m** in generally good yields and high

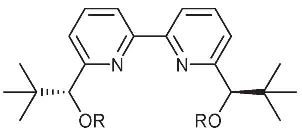
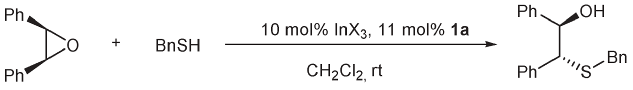


Fig. 1 **1a** R = H, **1b** R = CH_3.

Table 1 Optimization studies



Entry	Lewis acid	Ligand	Time	Yield (%)[a]	ee (%)[b]
1	$InCl_3$	—	48 h	—	—
2	$InBr_3$	—	48 h	—	—
3	$InBr_3$	2,2′-Bipyridyl	48 h	—	—
4	$InCl_3$	**1a**	6 d	60	95
5	$InBr_3$	**1a**	16 h	80	92
6	$InBr_3$	**1b**	6 d	—	—

[a] Isolated yields of chromatographed material. [b] Determined from chiral HPLC analysis (see supplementary information).

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[a] *Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany. E-mail: schneider@chemie.uni-leipzig.de; Fax: +49 341 9736599; Tel: +49 341 9736529*
[b] *Institut für Anorganische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany. E-mail: krautscheid@rz.uni-leipzig.de; Fax: +49 341 36199; Tel: +49 341 9736172*

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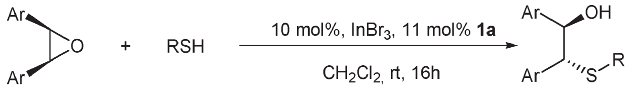
Table 2 Indium–bipyridine-catalyzed ring opening of *meso*-epoxides with thiols[a]



2a-e **3a-f** **4a-m**

Entry	Ar	R	Yield (%)[b]	ee (%)[c,d]
1	C_6H_5	$C_6H_5CH_2$	80 (**4a**)	92
2	C_6H_5	C_6H_5	81 (**4b**)	96
3	C_6H_5	4-Me-C_6H_4	79 (**4c**)	96
4	C_6H_5	CH_3CH_2	91 (**4d**)	>95
5	C_6H_5	n-Bu	90 (**4e**)	95
6	C_6H_5	$(CH_3)_2CH(CH_2)_2$	89 (**4f**)	96
7	2-Naphthyl	C_6H_5	79 (**4g**)	96
8	2-Naphthyl	$C_6H_5CH_2$	82 (**4h**)	96
9	3-Me-C_6H_4	C_6H_5	67 (**4i**)	91
10	4-Me-C_6H_4	C_6H_5	76 (**4j**)	85
11	4-Me-C_6H_4	$C_6H_5CH_2$	68 (**4k**)	92
12	4-Cl-C_6H_4	C_6H_5	84 (**4l**)[e]	92
13	4-Cl-C_6H_4	$C_6H_5CH_2$	67 (**4m**)[e]	93

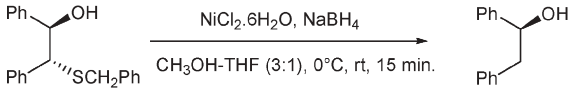
[a] Reaction conditions: 10 mol% $InBr_3$, 11 mol% bipyridine **1a**, 1.5 equiv. thiol, CH_2Cl_2, rt, 16 h. [b] Isolated yields of chromatographed material. [c] Determined from chiral HPLC analysis (see supplementary information). [d] The absolute configuration of **4b** was proven to be 1*R*,2*R* through conversion into the corresponding known sulfone;[11] the configurations of all other products were assigned by analogy. [e] Reaction time: 6 d.

enantioselectivities (entries 7–13). Unfortunately, aliphatic *meso*-epoxides currently give rise to only low enantioselectivity in the indium–bipyridine-catalyzed thiolysis.

The product 1,2-mercapto alcohols **4** may be employed as substrates for desulfurization reactions, furnishing chiral, highly enantiomerically enriched alcohols. Thus, nickel boride reduction[12] of **4a** afforded alcohol **5** in good yield and almost identical enantiomeric excess as **4a**, proving that the reaction had not affected the stereochemistry of the adjacent carbinol center (Scheme 1).

Accordingly, the sequential thiolysis–desulfurization of *meso*-epoxides constitutes an elegant alternative to the still elusive enantioselective hydride addition to epoxides.[13]

A single crystal of the indium(III)–bipyridine complex suitable for X-ray crystallography was obtained from tetrahydrofuran–H_2O solution.[14] The cationic $[InBr_2{\cdot}\mathbf{1a}{\cdot}H_2O]^+$ complex (the bromide counter anion is omitted for clarity) depicted in Fig. 2 is characterized with a pentagonal-bipyramidal coordination geometry around the indium(III) center, which is tetracoordinated by the bipyridine ligand **1a** through both nitrogen and oxygen atoms. Significantly, both hydroxyl protons are still attached to the catalyst. The crystal structure very closely resembles the structure of the scandium(III)–bipyridine catalyst,[15] and both catalysts also exhibit the same sense of asymmetric induction in epoxide-opening reactions.[8] Additional high resolution ESI-MS measurements gave a molecular peak at 602.9533 for $[M]^+$ which further corroborated the molecular formula $InBr_2C_{20}H_{28}N_2O_2$.



4a (92% ee) **5**

Scheme 1 Desulfurization of 1,2-mercapto alcohol **4a**.

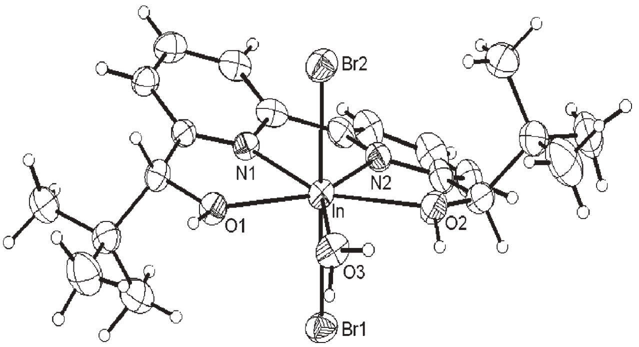


Fig. 2 ORTEP (50% ellipsoid) of the $[InBr_2{\cdot}\mathbf{1a}{\cdot}H_2O]^+$ moiety in the X-ray crystal structure of $[InBr_2{\cdot}\mathbf{1a}{\cdot}H_2O]Br{\cdot}THF{\cdot}4H_2O$.

Considering the failure of any indium(III)–bipyridine catalyst lacking the additional hydroxyl groups, it is most likely that the chiral catalyst exhibits a combined Lewis acid–Brønsted acid activity, with the Lewis acidic indium center activating the epoxide and the hydroxyl protons possibly forming a hydrogen bond to the incoming thiol, thereby guiding it to the epoxide.

In conclusion, we have devised a novel chiral catalyst for the highly enantioselective thiolysis of aromatic *meso*-epoxides, with aromatic as well as aliphatic thiols furnishing 1,2-mercapto alcohols in good yields and excellent enantioselectivities. Most importantly, there is no restriction to a specific thiol. A crystal structure analysis of the chiral catalyst reveals a pentagonal-bipyramidal coordination geometry around the indium center with both nitrogen and oxygen atoms coordinating to the metal. Additional hydrogen-bonding between the catalyst and the incoming nucleophile appears to activate and direct the incoming nucleophile to the indium-bound epoxide.

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