

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Highly Enantioselective Iron(II)-catalyzed Opening Reaction of Aromatic *meso*-Epoxides With Indoles

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Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

A highly enantioselective method for the catalytic *cis*-stilbene oxide opening reaction with indole derivatives was developed. The scope of the reaction was studied with a selection of aromatic *meso*-epoxides and various indoles, and the desired β -hydroxy indole derivatives were obtained in good to excellent yields with excellent enantioselectivities (from 96 to > 99% ee).

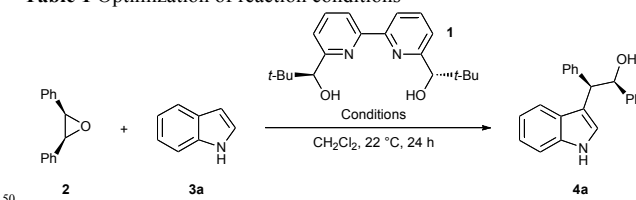
The *meso*-epoxide opening reaction is well-recognized as one of the most powerful, atom-economical bond-forming reactions.¹ In this reaction, a clean S_N2 addition of achiral nucleophiles allows the formation of two neighboring stereogenic centers in one straightforward operation. This transformation has been successfully realized using various nucleophiles, such as azides,² cyanides,³ amines,⁴ alcohols,⁵ water,⁶ thiols,⁷ selenols,⁸ halides,⁹ and indoles.¹⁰ The *meso*-epoxide opening reaction with indoles is certainly an essential achievement in the field. This route provides a rapid access to β -hydroxy indole derivatives, which have induced many synthetic efforts due to their motifs, often seen in natural products and bioactive molecules.¹¹ Nitrogen-containing heterocycles are essential cores in natural products and drugs. The synthesis of enantio-enriched *N*-heteroaromatic derivatives is therefore a major challenge.

The ring-opening reaction of *meso*-epoxides with indole derivatives has been reported to occur smoothly in water in the presence of Sc(III) and Cu(II) surfactant-type catalysts to afford the corresponding products in moderate to high yields with good to excellent enantioselectivities.^{10b-c} However, moderate yields and decreased enantioselectivities with some substrates and conversion problems when the reaction is performed in organic solvents, sometimes restrict their utilization.

From an environmental point of view, the development of new efficient benign chemical processes is in high demand. In connection with our ongoing studies involving C–C bond forming reactions using green Lewis acids,¹² we disclose herein our results using iron(II) perchlorate conjointly with Bolm's ligand **1**.¹³ To the best of our knowledge, iron has never been used as a catalyst for a highly enantioselective epoxide opening reaction with indoles. Iron is one of the most abundant metals on earth; it is inexpensive, environmentally benign, and relatively nontoxic in comparison with other metals.¹⁴

First, we screened various conditions for the *meso*-stilbene oxide

opening reaction with indole catalyzed by chiral iron complexes (Table 1).

Table 1 Optimization of reaction conditions^a


Entry	Conditions	Conc. (M)	Yield 4a (%)	ee 4a (%) ^b
1	5 mol % Fe(ClO ₄) ₂ ·6H ₂ O	0.5	50	98
2	10 mol % Fe(ClO ₄) ₂ ·6H ₂ O	0.5	50	99
3	10 mol % Fe(ClO ₄) ₂ ·6H ₂ O, 4Å MS	0.5	91	>99
4	10 mol % Fe(ClO ₄) ₂ ·6H ₂ O, 4Å MS	1.0	90	>99
5 ^c	10 mol % Fe(ClO ₄) ₂ ·6H ₂ O, 4Å MS	1.0	88	>99
6	10 mol % Fe(OTf) ₂ ·H ₂ O	1.0	76	92
7	10 mol % Fe(ClO ₄) ₃ ·6H ₂ O, 4Å MS	1.0	53	97
8 ^d	10 mol % Fe(ClO ₄) ₂ ·6H ₂ O, 4Å MS	1.0	27	99

^a Epoxide (1.0 equiv), indole (1.2 equiv), 1/[Fe] 1.2:1. ^b Determined by chiral HPLC analysis. ^c Reaction run at 0 °C, 48 h. ^d Reaction performed in *tert*-butyl methyl ether.

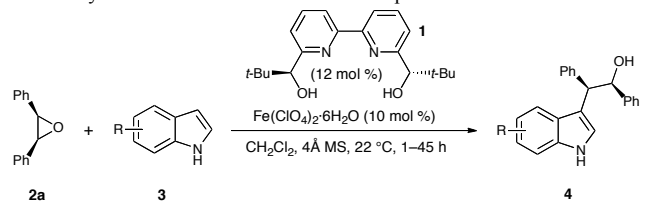
It was found that an iron(II) Lewis acid, such as Fe(ClO₄)₂, was an effective catalyst for the reaction and afforded the corresponding alcohol **4a** in moderate yield but high enantioselectivity (Table 1, entry 1). By using 10 mol % catalyst, an excellent enantioselectivity was achieved, but still in moderate yield (Table 1, entry 2). The use of molecular sieves in our reaction conditions allowed us to obtain an excellent yield and a near-complete enantioselectivity (Table 1, entry 3). Next, we demonstrated that the reaction could be run in more concentrated conditions (1.0 M vs. 0.5 M) without significant changes in the results (Table 1, entry 4). In terms of selectivity and yield, the reaction was as efficient at 0 °C as it was at room temperature, albeit with an extended reaction time (Table 1, entry 5). When Fe(OTf)₂ was used instead of Fe(ClO₄)₂, the enantioselectivity decreased (Table 1, entry 6). A Fe^{III} salt, such as Fe(ClO₄)₃, was not as effective as a Lewis acid when used in the same conditions since the product could only be isolated in lower yield and enantioselectivity (Table 1, entry 7).¹⁵ In our attempt to use greener solvents, the reaction was performed in *tert*-butyl methyl ether (Table 1, entry 8). Although the selectivity obtained in such solvent was very high, the yield remained low and




dichloromethane was kept as the solvent of choice. In our optimized conditions, the chiral catalyst is prepared by stirring a mixture of $\text{Fe}(\text{ClO}_4)_2$ with ligand **1** in a 1:1.2 ratio with powdered 4 Å molecular sieves at room temperature in dichloromethane for 0.5 h.

To the best of our knowledge, the enantioselectivity observed is the highest found with a chiral Lewis acid for this ring-opening model reaction. Moreover, this reaction has the advantage of using a cheap and environmentally benign Lewis acid. In comparison, Umani-Ronchi reported a good enantioselectivity for the reaction of epoxide **2a** with indole **3a** (93% ee), but using a chiral complex containing toxic chromium salts.^{10a} Kobayashi also reported the same reaction using Sc(III) and Cu(II)-based catalysts.^{10b-c} Enantioselectivities obtained were very good (92% and 96% ee respectively), but the scarcity and the increasing price of rare earth metals (Sc) restricts their use. Copper remains a good green alternative but a slight decrease in enantioselectivities and lower yields were observed when using substituted indoles.

Other examples of the ring-opening reaction are summarized in Table 2.

Table 2 Catalytic asymmetric *meso*-epoxide opening reaction with differently substituted indoles – substrate scope^a



Entry	Indole	R	Yield 4 [%]	ee 4 (%) ^b
1		H	90	>99
2		4-Cl	63	97
3		5-Me	99	>99
4		5-MeO	80	>99
5		5-Br	87	>99
6		5-NO ₂	64	99
7		6-F	86	98
8		7-MeO	89	98
9			82	96
10			79	>99
11			76	>99

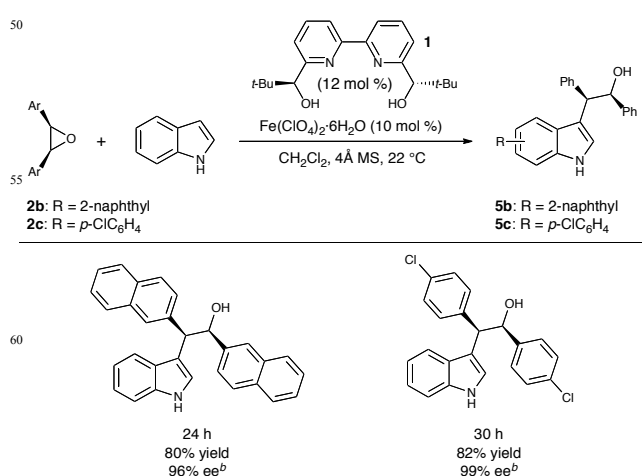
^a Epoxide (1.0 equiv), indole (1.2 equiv). ^b Determined by chiral HPLC analysis.

To further probe the generality and scope of the reaction, differently substituted indoles were examined (Table 2, entries 1–8). In all cases, good to excellent yields (63–99%) and very high enantioselectivities (97 to > 99% ee) were obtained. Electron-donating (Me, OMe) and -withdrawing (Br, Cl, F, NO₂) substituents, irrespective of their positions on the indole ring (4, 5, 6 or 7), had negligible influence on the enantioselectivity. *N*-methylated indole also proved to be an excellent substrate for this

reaction since the corresponding *N*-methylated product was obtained in good yield and excellent enantioselectivity (Table 2, entry 9). Di-substituted indoles were also used and the corresponding β -hydroxy indole derivatives were isolated with > 99% ee (Table 2, entries 10–11). The reaction with 5-bromo-7-iodoindole is of prime interest since the product could be further regioselectively functionalized.

Two other aromatic *meso*-epoxides were tested in the opening-reaction with indole (Scheme 1). The corresponding β -hydroxy indole derivatives were obtained in good yield and high enantioselectivity (ee \geq 96%). In preliminary experiments, decreased enantioselectivities were obtained using non aromatic *meso* epoxides (e.g. cyclohexene oxide, ee < 10%).

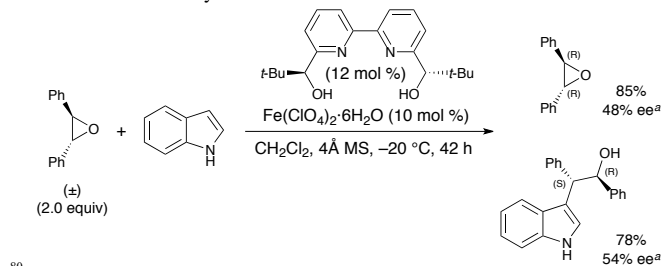
Scheme 1 Catalytic Asymmetric Aromatic *meso*-Epoxide Opening Reaction with Indole^a



^a Epoxide (1.0 equiv), indole (1.2 equiv). ^b Determined by chiral HPLC analysis.

Finally, we also tested our reaction conditions in the kinetic resolution of *trans*-stilbene oxide (Scheme 2). Under our standard conditions at –20 °C, indole **3a** reacted smoothly. The unreacted *trans*-stilbene oxide and the β -hydroxy indole derivative were isolated with good enantioselectivities (48% ee and 54% ee, respectively). The only precedents reported for the kinetic resolution of *trans*-stilbene oxide used chromium-derived catalysts.^{10a,16} Given the importance of the development of new methods for the production of enantio-enriched molecules using environmentally-benign iron(II) catalysts, these preliminary results are of prime importance.

Scheme 2 Kinetic Resolution of *trans*-Stilbene Oxide Using Fe(II)-derived Chiral Catalyst



^a Determined by chiral HPLC analysis.

To elucidate the pre-catalyst structure, we performed X-ray structure analysis of single crystals obtained from FeBr₂ and Bolm's ligand **1** (Figure 1).¹⁷

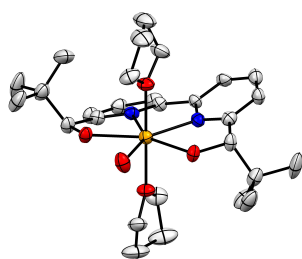


Fig. 1 ORTEP (50% ellipsoid) of [1-Fe·2THF·H₂O]²⁺·2Br⁻ complex. 2 Br⁻ and hydrogens are omitted for clarity.

The structure contains a discrete monomeric [1-Fe·2THF·H₂O]²⁺ cation and two Br⁻ anions. The complex adopts a pentagonal bipyramidal geometry. The structure of this complex is similar to those previously reported by Kobayashi with ScBr₃¹⁸ and BiBr₃¹⁹ or by Schneider with InBr₃.^{7c} The bipyridine ligand is coordinated to the metal center in a tetradentate manner. An additional water molecule in an equatorial position affords a slightly distorted pentagonal basis. Two THF molecules complete the structure of this heptacoordinated chiral Fe^{II} complex.

To sum up, the catalytic enantioselective ring-opening reaction of aromatic *meso*-epoxides with indole derivatives has been achieved by using iron perchlorate and a chiral bipyridine ligand. Differently substituted indoles have been used and proved to be excellent substrates for the ring-opening reaction with catalyst **1**-Fe(ClO₄)₂. To the best of our knowledge, the obtained enantioselectivities are the highest found with a Lewis acid catalyst for this type of ring-opening reaction with indoles. High enantioselectivities (ee up to > 99%) and very good yields have been obtained. Structural evidence of the pre-catalyst revealed a very rare heptacoordination around the metal center. Our method has the advantage of using a cheap and environmentally benign Lewis acid. In addition, the chiral ligand can be easily recycled at the end of the reaction. Further studies to clarify the precise mechanism are now in progress.

This work was financially supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Centre in Green Chemistry and Catalysis (CGCC), the Canada Foundation for Innovation (CFI), and Université Laval. We thank F. Bélanger-Gariépy (Université de Montréal) for X-ray analysis.

Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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