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Iron(II)-catalyzed enantioselective *meso*-epoxide-opening with anilines†

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A highly enantioselective method for the catalytic opening of aromatic *meso*-epoxides with aniline derivatives was developed. The desired chiral β-amino alcohols were obtained in mostly good to very good yields with excellent enantioselectivities. Structural evidence of the pre-catalyst revealed a scarcely disclosed heptadentate Fe(II) complex with the chiral bipyridine ligand.

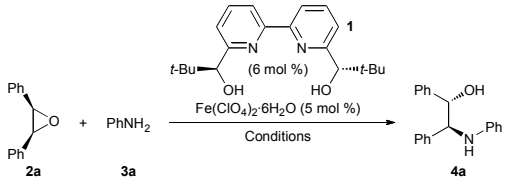
The opening of *meso*-epoxides is one of the most powerful and atom-economical bond-forming reactions.[1] By differentiating between the two enantiotopic carbons of the *meso*-epoxide using a chiral Lewis acid, S_N2 nucleophilic addition of achiral nucleophiles generates two neighboring stereogenic centers in one straightforward operation. Catalytic asymmetric ring-opening of *meso*-epoxides has been successfully performed with various nucleophiles such as azides,[2] cyanides,[3] alcohols,[4] water,[5] thiols,[6] selenols,[7] indoles,[8] or halides.[9] The asymmetric *meso*-epoxide-opening reaction with aniline derivatives is of prime interest since it allows the formation of chiral β-amino alcohol units, which are found in many biologically active compounds and auxiliaries used in asymmetric reactions.[10]

Few research groups have developed efficient asymmetric ring-opening reactions of *meso*-epoxides with aniline derivatives.[11] Generally, these reactions need the use of expensive and/or toxic catalysts that restrain their use. From an environmental point of view, the development of new efficient benign chemical processes is in high demand. Replacing expensive and toxic metals by cheap and environmentally benign elements is an essential concern nowadays. In this regard, we have developed an efficient iron(II)-catalyzed enantioselective *meso*-epoxide-opening reaction. Our method is on a par with the selectivities previously reported by other groups, with the added advantage of using a cheap and nontoxic catalyst in a low loading (5 mol %). Indeed, iron is one of the most abundant metals on earth; it is inexpensive, environmentally benign, and relatively nontoxic in comparison with other metals.[12]

The combination of Bolm's ligand **1** [13] with iron(II) salts has been recently demonstrated by our group to be a very efficient catalyst for highly enantioselective Mukaiyama aldol reactions in aqueous conditions.[14] The efficiency of this complex is now demonstrated for the opening of aromatic epoxides.

First, we screened different solvents for the reaction of *cis*-stilbene oxide **2a** with aniline **3a** catalyzed by complex **1**·$Fe(ClO_4)_2$ (Table 1). Among the various solvents tested, only dichloromethane furnished the desired product with a moderate yield at 0 °C. Acetonitrile, THF, 1,2-dimethoxyethane (DME) or diethyl ether led only to trace amounts of amino alcohol **4a** after 24 h (entries 1–5). The high enantioselectivity obtained with CH_2Cl_2 (entry 5) encouraged us to pursue our optimization process in order to improve the yield of this transformation. Increasing the catalyst loading to 10 mol % of $Fe(ClO_4)_2$ only led to a slight increase in enantioselectivity (entry 6) but still with a moderate yield. Using 2 equivalents of aniline gave almost exactly the same results as the reaction with equimolar amounts of both reagents (entry 7 *vs.* entry 5). However, a significant concentration effect was observed. In more concentrated reaction conditions (1.0 M *vs.* 0.3 M), a very good yield of **4a** was obtained, even with a slight increase in enantioselectivity. Finally, the temperature did not have a strong influence on the enantioselectivity, since the same high enantiomeric excess was obtained at room temperature (entry 9). In these conditions, the product could be obtained in a much shorter reaction time, with an improved chemical yield. Dichloroethane was also tested and comparable results were obtained (entry 10). CH_2Cl_2 was then kept as the solvent of choice in our optimized conditions.

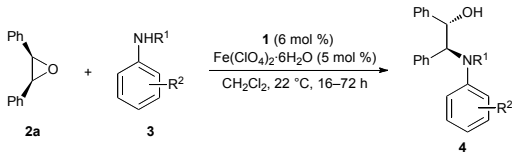
Table 1 Optimisation of reaction conditions[a]

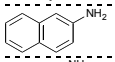


Entry	Solvent	*T* (°C)	Time (h)	Conc. (M)	Yield **4a** (%)	*ee* (%)[b]
1	MeCN	0	24	0.3	< 5	–
2	THF	0	24	0.3	< 5	–
3	DME	0	24	0.3	< 5	–
4	Et_2O	0	24	0.3	< 5	–
5	CH_2Cl_2	0	72	0.3	68	94
6[c]	CH_2Cl_2	0	72	0.3	60	95
7[d]	CH_2Cl_2	0	72	0.3	70	94
8	CH_2Cl_2	0	72	1.0	84	95
9	CH_2Cl_2	22	16	1.0	90	95
10	$(CH_2Cl)_2$	22	24	1.0	88	95

[a] Conditions: epoxide (1.0 equiv), aniline (1.0 equiv). [b] Determined by chiral HPLC analysis. [c] $Fe(ClO_4)_2$ (10 mol %), **1** (12 mol %). [d] Epoxide (1.0 equiv), aniline (2.0 equiv).

Table 2 Catalytic asymmetric *cis*-stilbene oxide-opening reaction with various aniline derivatives – substrate scope[a]



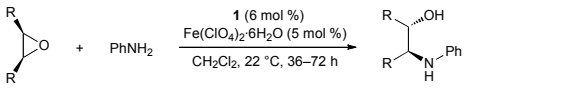
Entry	Aniline	R	Time (h)	Yield **4** (%)	*ee* (%)[b]
1		H	16	90	95
2		2-Me	72	78	92
3		2-OMe	72	70	82
4		4-Cl	16	90	94
5		2-Cl	48	78	90
6		4-Br	16	87	94
7		4-CF_3	24	90	96
8		4-CN	24	90	96
9			72	70	93
10			24	81	95
11			16	87	94
12		H	16	95	95
13		Br	16	88	96

[a] Conditions: epoxide (1.0 equiv), aniline (1.0 equiv). [b] Determined by chiral HPLC analysis.

Optimal conditions established for the enantioselective epoxide-opening reaction with aniline **3a** were applied to differently substituted anilines (Table 2). In all cases, the desired amino alcohol was obtained in high enantioselectivity. For mono-substituted anilines, electron-donating and -withdrawing substituents, in *ortho*- or *para*-positions, had negligible influence on the enantioselectivity (entries 1–8). Except for *o*-anisidine that gave a slightly lower enantioselectivity (entry 3),[15] other substituted anilines furnished the desired amino alcohol in ≥ 90% *ee*. Sterically hindered anilines, such as 2,6-dimethylaniline and *N*-methylaniline, maintained good yields and led to high enantioselectivities (entries 9–10). α- and β-Naphthylamines also reacted smoothly to provide the product in very good yields with high enantioselectivities (entries 11–12). Functionalized naphthylamine, such as 1-amino-4-bromonaphthalene, also led to a highly enantio-enriched amino alcohol, which could be further transformed to introduce other functional groups (entry 13). Two other aromatic *meso*-epoxides were tested in the opening-reaction with aniline (Table 3).[16] The corresponding amino alcohols were obtained in good yield and high enantioselectivity (*ee* ≥ 90%).

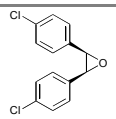
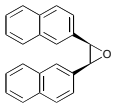
To obtain some information on the chiral Fe pre-catalyst, we performed an X-ray structure analysis of single crystals obtained from **1**–Fe(ClO_4)$_2$ complex (Figure 1).[17] The complex adopts a pentagonal bipyramidal geometry. The structure of this complex is similar to those previously reported by Kobayashi with $ScBr_3$ [18] and $BiBr_3$ [19] or by Schneider with $InBr_3$.[6c] The bipyridine ligand is coordinated to the metal center in a tetradentate manner. An additional water molecule in equatorial position affords a slightly distorted pentagonal basis. Two acetonitrile molecules in apical positions furnished an heptacoordinated chiral Fe^{II} complex. Additional HRMS measurements (ESI-TOF) corroborated the formation of the complex in solution. Both molecular peaks corresponding to the mono- and the bis-cationic complex were detected at 483.0978 $[M+ClO_4]^+$ and 192.0746 $[M]^{2+}$ respectively (Figure 2).

Table 3 Catalytic asymmetric aromatic *meso*-epoxide-opening reaction with aniline[a]



2b: R = *p*-ClC_6H_4
2c: R = 2-naphthyl

5b: R = *p*-ClC_6H_4
5c: R = 2-naphthyl

Entry	Epoxide	Time (h)	Yield **5** (%)	*ee* (%)[b]
1		72	79	90
2		36	80	95

[a] Conditions: epoxide (1.0 equiv), aniline (1.0 equiv). [b] Determined by chiral HPLC analysis.

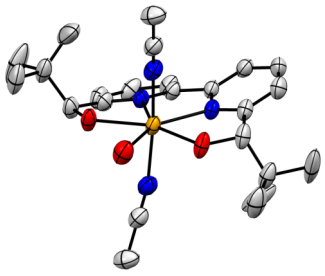


Fig. 1 ORTEP (50% ellipsoid) of [**1**·Fe·2MeCN·H_2O]$^{2+}$·2ClO_4^- complex. 2 ClO_4^- and hydrogens are omitted for clarity.

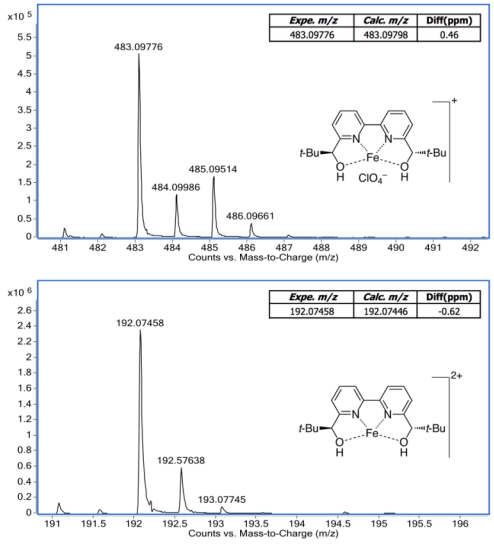


Fig. 2 High resolution ESI-MS measurements of complex **1**·Fe(ClO_4)$_2$.

In summary, the catalytic enantioselective opening of aromatic *meso*-epoxides with various aniline derivatives has been achieved with $Fe(ClO_4)_2$ and Bolm's bipyridine ligand. The desired chiral β-amino alcohols were obtained in mostly good to very good yields with excellent enantioselectivities (generally 90–96% *ee*). The chiral pre-catalyst structure was characterized both in solid state and in solution. Mono- and bis-cationic complexes were detected by high resolution ESI-MS and a crystal structure analysis revealed a scarcely disclosed heptacoordinated chiral Fe^{II} complex. Our method has the advantage of using a low catalyst loading of an environmentally benign Lewis acid and an equimolar amount of both reagents, allowing atom-economical synthesis. 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.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and full characterization data for all compounds are provided. See DOI: 10.1039/b000000x/

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