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Enantioselective iron-catalysed O–H bond insertions

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The ready availability, low price and environmentally benign character of iron mean that it is an ideal alternative to precious metals in catalysis. Recent growth in the number of iron-catalysed reactions reported reflects an increasing demand for sustainable chemistry. Only a limited number of chiral iron catalysts have been reported and these have, in general, proven less enantioselective than other transition-metal catalysts, thus limiting their appeal. Here, we report that iron complexes of spiro-bisoxazoline ligands are highly efficient catalysts for asymmetric O–H bond insertion reactions. These complexes catalyse insertions into the O–H bond of a wide variety of alcohols and even water, with exceptional enantioselectivities under mild reaction conditions. The selectivities surpass those obtained with other transition-metal catalysts. This study should inspire and encourage the use of iron instead of traditional precious metals in the development of greener catalysts for catalytic asymmetric synthesis.

Many fundamental phenomena and laws of nature result from dissymmetry, which is exemplified as chirality or handedness in modern chemistry. In nature, the effective forms of many biological molecules such as amino acids, sugars or nucleic acids occur as only a single enantiomer, and the important differences in the physiological properties of enantiomers are now well known. To meet the rapidly increasing demand for chiral molecules in a single enantiomeric form, catalytic asymmetric synthesis has become an important topic of research for chemists in both academic laboratories and industry.

Three types of chiral catalysts—enzymes, transition-metal complexes and chiral organic molecules—have emerged as the most successful and efficient catalysts in asymmetric synthesis. Owing to the versatile activation modes of transition-metal complexes, transition-metal catalysis is still central to the investigations and applications of asymmetric synthesis[1]. A chiral transition-metal catalyst is generally composed of two parts: a chiral ligand and a central metal. The efforts to develop chiral transition metal catalysts have mainly focused on the design of the chiral ligands[2], with the central metals being predominately precious metals, such as palladium, platinum, rhodium, ruthenium, osmium, iridium and so on. However, these precious metals are too costly and may contaminate both the products and the environment, which restricts their wide application.

Iron, the second most abundant metal in the Earth's crust, has become the most common metal in everyday use[3]. Given its ready availability, low price and environmentally benign character, iron is an attractive and often advantageous alternative to other transition metals in the field of catalysis. In light of the increasing demand for sustainable chemistry, iron-catalysed reactions have drawn much attention and have undergone explosive growth[4–7]. Although transition-metal-catalysed asymmetric reactions have undergone great progress in the last several decades, only a handful of iron-catalysed asymmetric reactions have reached an enantiomeric excess (e.e.) beyond 90% (refs 4–13). Moreover, the iron-catalysed asymmetric reactions reported to date are less enantioselective than other metal-catalysed reactions, with the exception of a few special substrates.

Carbenes are among the most active and useful intermediates in organic reactions. However, their great reactivity makes it difficult to obtain reasonable selectivity in reactions involving a free carbene. Transition metals can stabilize carbenes by forming a metal–carbene complex[14]. Because they are easier to handle and are more selective than free carbenes, metal–carbene complexes have been widely applied in organic synthesis. Transition-metal-catalysed insertion of diazo compounds into the X–H (X=C, Si, O, N and so on) bond is a useful carbene transfer reaction[15] (Fig. 1a) and has become an efficient tool for the construction of C–X bonds under mild reaction conditions. The most successful catalysts in asymmetric insertion reactions have been rhodium and copper complexes[16–22]. Although iron carbene complexes have been known for several decades[23], an iron-catalysed asymmetric insertion reaction has not yet been realized[24]. Weak coordination between iron and the corresponding chiral ligands may account for the unsuccessful chiral induction of iron catalysts in insertion reactions. We considered that increasing the rigidity of the ligands might increase the stability of the iron complexes and thus improve chiral induction. We envisioned that the chiral bisoxazoline ligands **1** (Fig. 1b)[25] with an unusually rigid spiro scaffold that have been developed in our laboratory might coordinate tightly with iron and create an efficient chiral pocket for enantioselective control. Herein, we report an iron/spiro bisoxazoline-catalysed asymmetric O–H bond insertion of alcohols and water with exceptional enantioselectivities (up to 99% e.e.) (Fig. 1b). For the first time, the enantioselectivities accomplished in this O–H insertion reaction using iron catalyst unambiguously surpass those obtained with other transition-metal catalysts.

Results and discussion

The insertion reaction of methyl α-diazophenylacetate (**2a**) with *n*-butanol (**3a**) was performed in chloroform at 40 °C with 5 mol% iron catalyst prepared *in situ* from $FeCl_2 \cdot 4H_2O$ and various chiral spiro bisoxazoline ligands **1** (Table 1). A preliminary investigation revealed that the ligand **(S_a,S,S)-1c**, with 4-*iso*-propyl moieties on the dihydrooxazole rings, afforded the insertion product **4a** with excellent yield (93%) and extremely high enantioselectivity (98% e.e.) (Table 1, entry 4). Other chiral ligands, including bisoxazolines, phosphino-oxazolines and diphosphines, which were efficient in different catalytic asymmetric reactions, were also investigated in the O–H

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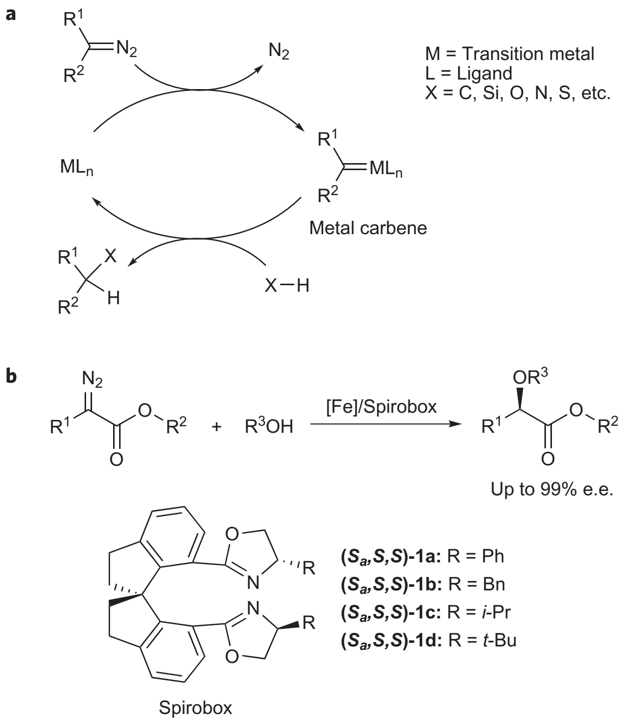
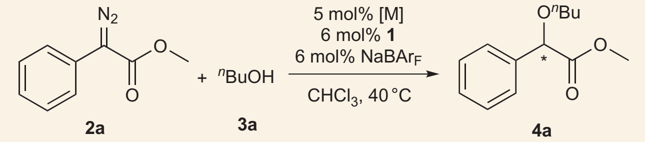


Figure 1 | Transition-metal-catalysed insertion reactions starting with diazo compounds. a, General catalytic cycle for transition-metal-catalysed insertion reactions via metal carbene *in situ*, generated from diazo compounds. Several transition metals, such as rhodium and copper, can decompose diazo compounds to generate metal carbenes, which readily undergo an insertion reaction with the X-H (X = C, Si, O, N and so on) bond to form a carbon–hydrogen bond and a carbon–carbon or carbon–heteroatom bond. This transition-metal-catalysed insertion reaction is an important carbene transfer reaction and has become an efficient tool for the construction of C–X bonds under mild reaction conditions. **b**, Enantioselective iron-catalysed O-H bond insertion reaction. Iron complexes of spiro-bisoxazoline ligands are highly efficient catalysts for asymmetric O-H bond insertion reactions. These complexes catalyse O-H insertion into a wide variety of alcohols and even water, with exceptional enantioselectivities under mild reaction conditions. The selectivities surpass those obtained with other transition-metal catalysts. Ph, phenyl; Bn, benzyl; *i*-Pr, isopropyl; *t*-Bu, tert-butyl.

Table 1 | Asymmetric catalytic O-H insertion of 2a with 3a: ligand and metal evaluation.



Entry	[M]	Ligand	Time (h)	Yield (%)	e.e. (%)*
1	$FeCl_2·4H_2O$	**(S_a,*S*,*S*)-1a**	15	87	86
2	$FeCl_2·4H_2O$	**(R_a,*S*,*S*)-1a**	8	86	38
3	$FeCl_2·4H_2O$	**(S_a,*S*,*S*)-1b**	24	86	88
4	$FeCl_2·4H_2O$	**(S_a,*S*,*S*)-1c**	15	93	98
5	$FeCl_2·4H_2O$	**(S_a,*S*,*S*)-1d**	30	63	50
6	$FeCl_2$	**(S_a,*S*,*S*)-1c**	15	90	98
7	$Fe(ClO_4)_2·xH_2O$	**(S_a,*S*,*S*)-1c**	40	68	95
8	$FeSO_4·7H_2O$	**(S_a,*S*,*S*)-1c**	40	85	92
9	$FeCl_3$	**(S_a,*S*,*S*)-1c**	15	93	76
10	CuCl	**(S_a,*S*,*S*)-1c**	1	90	80
11	$CoCl_2$	**(S_a,*S*,*S*)-1c**	48	23	82
12	$NiCl_2$	**(S_a,*S*,*S*)-1c**	48	3	81
13	AuCl	**(S_a,*S*,*S*)-1c**	48	NR[†]	—
14	AgOTf	**(S_a,*S*,*S*)-1c**	4	63	42
15	$[RhCl(CO)_2]_2$	**(S_a,*S*,*S*)-1c**	2	27	15
16	$[RuCl_2C_6H_6]_2$	**(S_a,*S*,*S*)-1c**	2	45	67

Reaction conditions: [M]/**1**/$NaBAr_F$/**2a**/**3a** = 0.015/0.018/0.018/0.3/0.45 mmol, in 4 ml $CHCl_3$ at 40 °C. $NaBAr_F$, sodium tetrakis[3,5-*bis*(trifluoromethyl)phenyl]borate.
*Determined by HPLC (high-performance liquid chromatography) using a Chiralcel OD-H column.
[†] NR, no reaction.

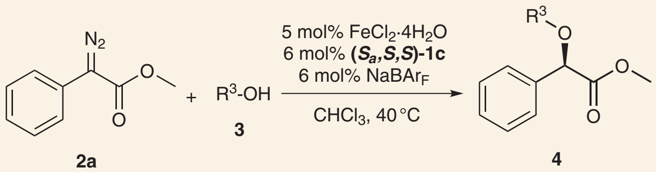
insertion reaction, but very low enantioselectivities (Supplementary Table S1) were observed. This result clearly revealed that the rigid spiro scaffold of ligand **1** is crucial for a high level of chiral induction. Various commercially available iron(II) salts were suitable precursors for the insertion reaction (Table 1, entries 4 and 6–8). $FeCl_2·4H_2O$ precursors from different sources gave the same level of reactivity and enantioselectivity (Supplementary Tables S5,S6). Competitive insertion of water was not detected in the reaction with $FeCl_2·4H_2O$ as catalyst. In view of its ready availability, ease of handling and low price, $FeCl_2·4H_2O$ was used for further investigation. It is worth mentioning that $FeCl_3$ can also catalyse the insertion reaction, giving high yield and moderate enantioselectivity (Table 1, entry 9). Other transition metals, including copper, cobalt, nickel, gold, silver, rhodium and ruthenium, were also evaluated under the standard reaction conditions and all gave markedly lower enantioselectivity (Table 1, entries 10–16) than the corresponding iron catalyst.

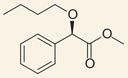
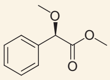
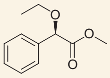
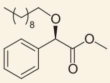
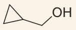
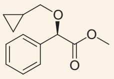
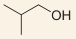
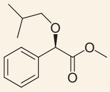
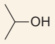
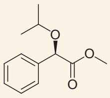
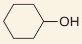
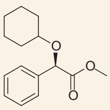
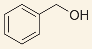
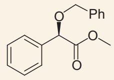
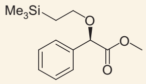
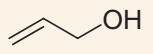
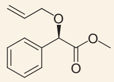
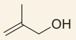
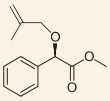
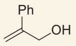
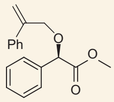
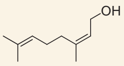
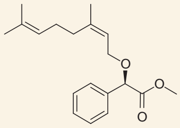
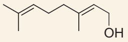
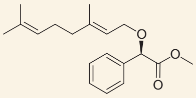
A broad range of alcohols was then investigated in the insertion reaction with methyl α-diazophenylacetate (**2a**) under standard reaction conditions (Table 2). All the tested saturated alcohols underwent the O–H insertion reaction smoothly to afford the corresponding α-alkoxy esters (**4a**–**4j**) with excellent yields (85–95%) and particularly high enantioselectivities (93–99% e.e.) (Table 2, entries 1–10). The only exception was the highly sterically hindered tert-butanol, which was unreactive. All the enantioselectivities of the iron-catalysed O–H insertion reactions remarkably surpassed previous records (Table 2, entries 2, 3, 7, 9 and 10) of this reaction.

Compared to the saturated alcohols, allylic alcohols are troublesome substrates for the catalytic asymmetric O–H insertion reaction. The instability of the carbon–carbon double bond of allylic alcohols dramatically lowers the reactivity and enantioselectivity of the O–H insertion reaction[18]. To our delight, the Fe/**(S_a,*S*,*S*)-1c** efficiently catalysed the insertion of allylic alcohols with α-diazophenylacetate (**2a**) to produce α-allyloxy phenylacetates (**4k**–**4o**) in high yields (86–92%) and with excellent enantioselectivities (89–95% e.e.) (Table 2, entries 11–15). The cyclopropanation is a major competitive reaction in the transition-metal-catalysed reactions of allylic alcohols with diazo compounds. However, we detected no cyclopropanation product in our reactions. The carbon–carbon double bond in the chiral α-allyloxy phenylacetates leaves potential functionalities for further transformation in organic synthesis. For instance, other investigators have applied the α-allyloxy phenylacetates in the synthesis of densely functionalized dihydropyran derivatives, pyrazole derivatives and 3-phenyl clavams (Fig. 2a)[26–29]. The present reaction provides one of the most efficient methods for the synthesis of chiral α-allyloxy phenylacetates[30].

The use of water in catalytic asymmetric O–H bond insertion reactions to produce synthetically useful alcohols is a more meaningful challenge. The iron-catalysed O–H bond insertion of water, to the best of our knowledge, has never been documented. Encouraged by our success with the insertion of alcohols, we studied the iron-catalysed asymmetric O–H insertion reaction between water and methyl α-diazophenylacetate (Table 3). A comparison of ligands showed that the ligand **(S_a,*S*,*S*)-1a**, with phenyl groups on the dihydrooxazole rings, was the most efficient for O–H insertion with water (Supplementary Table S4). With a 5 mol% iron complex of ligand **(S_a,*S*,*S*)-1a** as catalyst, the insertion of methyl α-diazophenylacetate with water proceeded successfully to give mandelate **5a** in high yield (90%) with excellent

Table 2 | Enantioselective iron-catalysed O-H insertion with alcohols.



Entry	R^3OH	Product	Time (h)	Yield (%)	e.e. (%)*
1	*n*BuOH, **3a**	 **4a**	15	93	98
2	MeOH, **3b**	 **4b**	10	85	96 (69)
3	EtOH, **3c**	 **4c**	10	88	95 (87)
4	$CH_3(CH_2)_8$ CH_2OH, **3d**	 **4d**	15	92	95
5	 **3e**	 **4e**	20	90	94
6	 **3f**	 **4f**	20	92	98
7	 **3g**	 **4g**	15	95	98 (68)
8	 **3h**	 **4h**	10	95	99
9	 **3i**	 **4i**	15	94	98 (77)
10	 **3j**	 **4j**	15	91	93 (90)
11	 **3k**	 **4k**	48	86	89 (27)
12	 **3l**	 **4l**	3	92	93
13	 **3m**	 **4m**	12	90	95
14	 **3n**	 **4n**	24	88	95
15	 **3o**	 **4o**	24	91	95

Reaction conditions and analysis were the same as those in Table 1, entry 4.
*The data in parentheses are the e.e. values obtained with copper catalysts (see ref. 18).

enantioselectivity (95% e.e.) (Table 3, entry 1). The catalyst is stable enough to handle in air without loss of either reactivity or enantioselectivity of the reaction. The catalyst Fe/(*S*ₐ,*S*,*S*)-**1a** was highly efficient for a wide range of α-diazoesters. In all reactions of α-diazophenylacetate derivatives (**5b**–**5n**), α-diazo-2-naphthylacetate (**5o**) and α-diazo-3-thienylacetate (**5p**), high enantioselectivities (88–95% e.e.) were achieved (Table 3, entries 2–17). The results gained with the catalyst Fe/(*S*ₐ,*S*,*S*)-**1a** were superior to those obtained with the copper counterpart[22]. In addition to α-diazoarylacetate substrates, α-diazopropionate (**2q**) can also undergo the insertion reaction with water to give benzyl 2-hydroxypropionate (**5q**) in 80% yield with 76% e.e. (Table 3, entry 18).

Notably, the reactions of α-diazo-(2-methoxyphenyl)acetate (**5j**) and α-diazo-(2-halophenyl)acetates (**5k**–**5n**), which have a

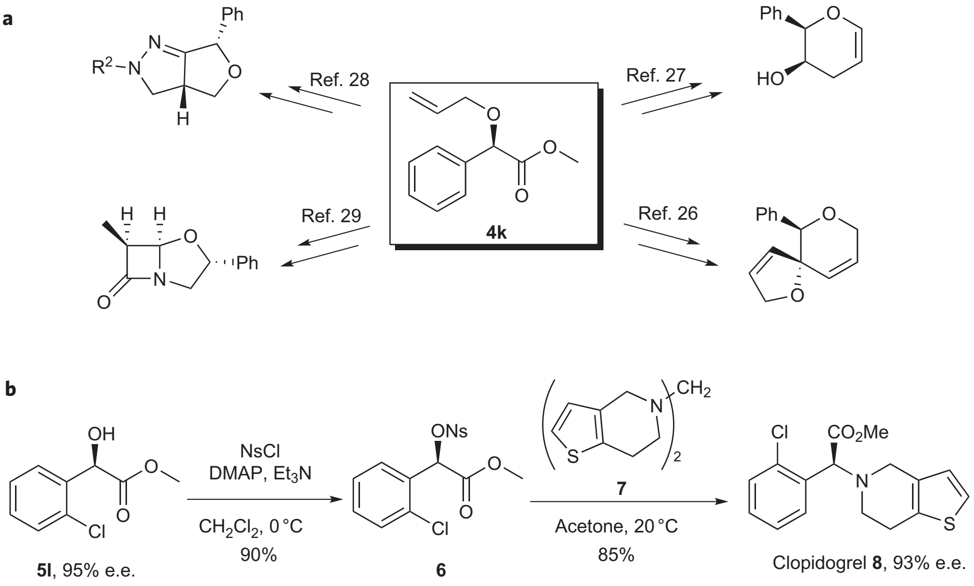
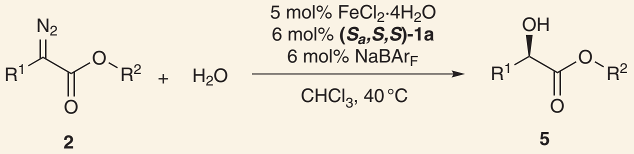
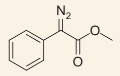
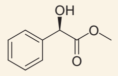
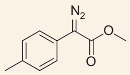
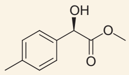
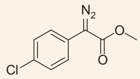
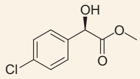
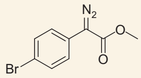
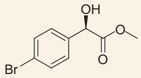
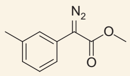
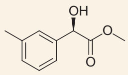
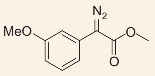
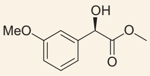
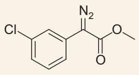
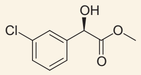
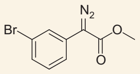
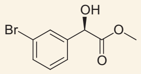
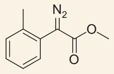
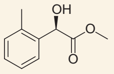
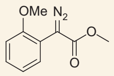
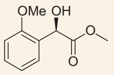


Figure 2 | Synthetic applications of the O–H insertion products. a, Transformations of 2-allyloxy-2-phenylacetate (**4k**). The iron-catalysed asymmetric insertion of the O–H bond of allylic alcohol provides one of the most efficient methods for the synthesis of chiral α-allyloxy phenylacetates, which have been applied by other investigators in the synthesis of chiral densely functionalized dihydropyran derivatives, pyrazole derivatives and 3-phenyl clavams.
b, Asymmetric synthesis of clopidogrel (**8**). The Fe/(***S**ₐ*,***S***,***S***)-**1a**-catalysed insertion reaction of methyl α-diazo-2-chlorophenylacetate with water produces methyl (*R*)-*o*-chloromandelate (**5l**) with an excellent e.e. value at low catalyst loading. (*R*)-**5l** is a key intermediate for the preparation of clopidogrel (**8**), a highly market-occupied platelet aggregation inhibitor. Iron-catalysed asymmetric insertion with water provides an efficient route for the preparation of this important drug. Ns, nitrobenzenesulphonyl; DMAP, *N*,*N*-dimethylpyridin-4-amine.

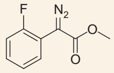
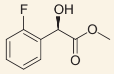
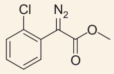
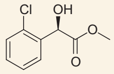
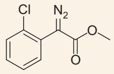
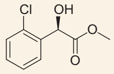
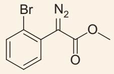
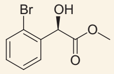
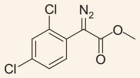
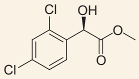
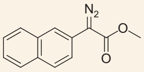
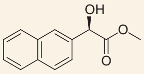
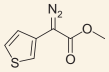
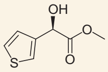
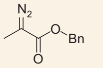
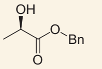
Table 3 | Enantioselective iron-catalysed O–H insertion with water.



Entry	2	Product	Time (h)	Yield (%)	e.e. (%)*
1	 2a	 5a	10	90	95
2	 2b	 5b	5	89	94
3	 2c	 5c	20	90	94
4	 2d	 5d	20	93	92
5	 2e	 5e	10	93	92
6	 2f	 5f	10	92	94
7	 2g	 5g	20	92	91
8	 2h	 5h	20	93	90
9	 2i	 5i	3	87	94
10	 2j	 5j	3	72	92

Continued

Table 3 | Continued

Entry	2	Product	Time (h)	Yield (%)	e.e. (%)*
11	 **2k**	 **5k**	3	91	90
12	 **2l**	 **5l**	2	92	95
13[†]	 **2l**	 **5l**	6	90	92
14	 **2m**	 **5m**	3	94	94
15	 **2n**	 **5n**	3	93	88
16	 **2o**	 **5o**	10	90	91
17	 **2p**	 **5p**	12	66	92
18	 **2q**	 **5q**	20	80	76

Reaction conditions: $FeCl_2 \cdot 4H_2O$/**(S_a,S,S)-1a**/$NaBAr_F$/**2**/H_2O = 0.015/0.018/0.018/0.3/1.5 mmol, in 4 ml $CHCl_3$ at 40 °C.
*Determined by HPLC or SFC (supercritical fluid chromatography) using a chiral column.
[†] 1 mol% catalyst was used.

coordinating group at the *ortho* position and were less enantioselective (<50% e.e.) in the reaction using our previously described copper catalysts, gave high enantioselectivities with the iron catalyst (Table 3, entries 10–15). For instance, in the insertion reaction of methyl α-diazo-2-chlorophenylacetate with water, the catalyst Fe/**(S_a,S,S)-1a** produced methyl (R)-*o*-chloromandelate (**5l**) with 95% e.e., while the analogous copper catalyst gave the same product with only 36% e.e. (ref. 22). The activity of the catalyst Fe/**(S_a,S,S)-1a** is remarkable in this reaction. The catalyst loading can be reduced to 1 mol% without a significant reduction in yield (90%) and enantioselectivity (92% e.e.) of the reaction (Table 3, entry 13). The product methyl (R)-*o*-chloromandelate (**5l**) is a key intermediate for the preparation of clopidogrel (**8**), a highly market-occupied platelet aggregation inhibitor (Fig. 2b)[31]. The facile conversion of **5l** to clopidogrel[32] demonstrated that this iron-catalysed asymmetric insertion with water was an efficient route for the preparation of this important drug.

In summary, we have developed a highly efficient iron-catalysed asymmetric O–H bond insertion reaction. Iron complexes containing chiral spiro bisoxazoline ligands proved to be the most enantioselective catalysts in asymmetric O–H bond insertion reactions, and should encourage the use of iron instead of precious metals for the development of greener catalysts for asymmetric procedures.

Methods

The general procedure for *in situ* catalyst preparation and catalytic asymmetric O–H insertion reaction is as follows. The powdered $FeCl_2 \cdot 4H_2O$ (3.0 mg, 0.015 mmol, 5 mol%), **(S_a,S,S)-1** (0.018 mmol, 6 mol%) and $NaBAr_F$ (16.9 mg, 0.018 mmol, 6 mol%) were added to an oven-dried Schlenk tube in an argon-filled glovebox. After $CHCl_3$ (4 ml) was injected into the Schlenk tube, the solution was stirred at room temperature under the argon atmosphere for 4 h. Alcohol (0.45 mmol) or water (1.5 mmol) was injected into the reaction mixture at 40 °C and stirred for a few seconds. Methyl 2-diazo-2-arylacetate (0.3 mmol) was then introduced into the reaction mixture. The resulting mixture was stirred at 40 °C for a specified time and the product was purified by flash chromatography. The enantiomeric purity of the product was determined by HPLC or SFC analysis in comparison with authentic racemic material.

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Author contributions

S.-F.Z., J.-H.X. and Q.-L.Z. designed the project. C.Y. and H.-X.M. carried out the experimental work. S.-F.Z. and Q.-L.Z. wrote the paper. All authors analysed the data, discussed the results and commented on the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/. Correspondence and requests for materials should be addressed to Q.L.Z.