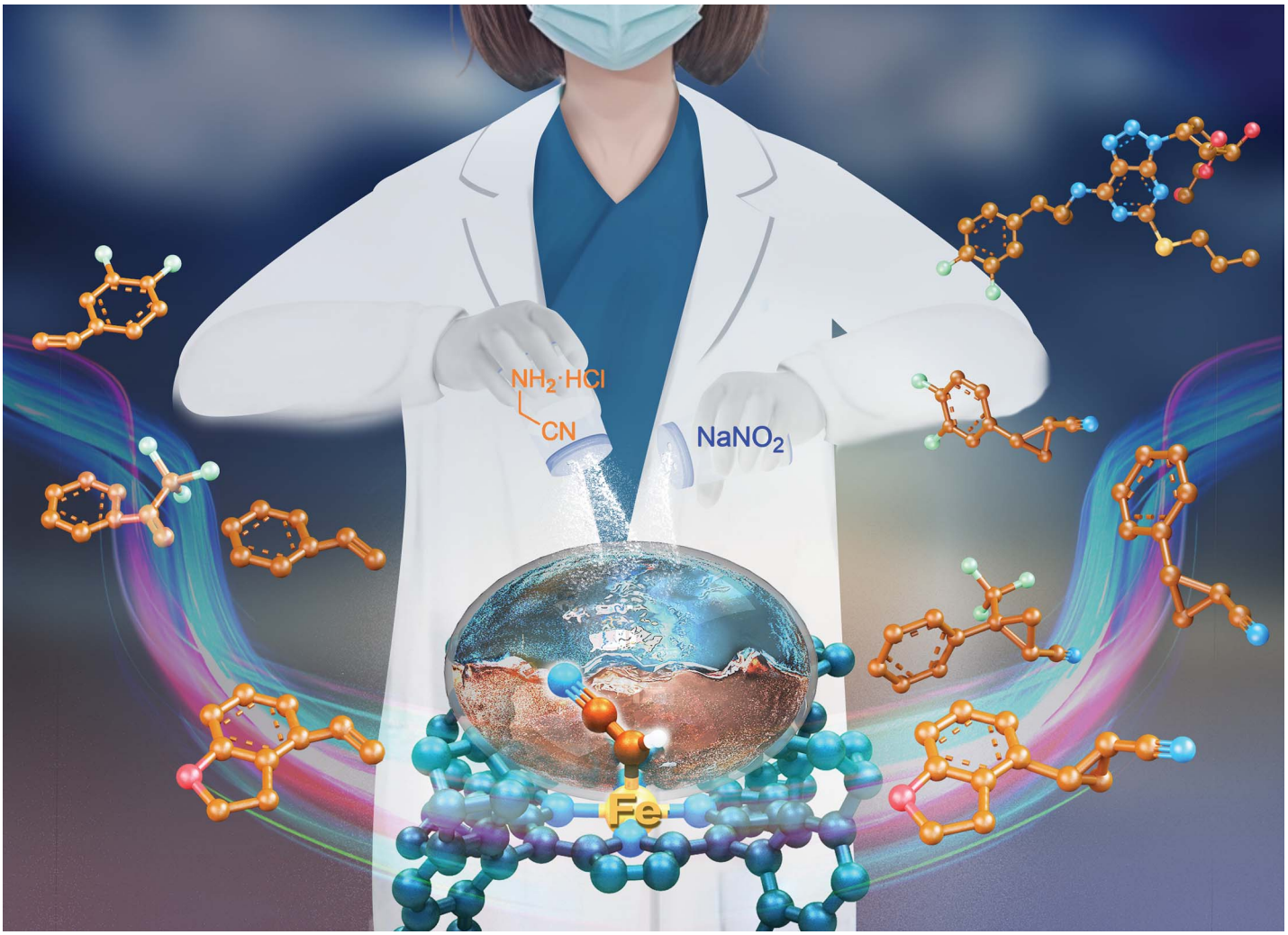

Showcasing research from Professor Che's laboratory, Department of Chemistry, Southern University of Science and Technology, Shenzhen, P. R. China.

Chiral iron porphyrin (+)-D_4-(por)FeCl catalyzes highly enantioselective cyclopropanation of alkenes using *in situ* generated diazoacetonitrile with up to 35000 product turnover

With α-diazoacetonitrile, *in situ* generated through the reaction of commercially available aminoacetonitrile hydrochloride with sodium nitrite, as carbene source, chiral iron porphyrin catalyzed asymmetric cyclopropanation reaction is applicable to a broad substrate scope (44 examples) with high enantioselectivity (up to 98% ee) and product turnover (up to 35000 TON). The reactive chiral iron-cyanocarbene intermediate has been characterized by spectroscopic methods.

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Chiral iron porphyrin (+)-D_4-(por)FeCl catalyzes highly enantioselective cyclopropanation of alkenes using *in situ* generated diazoacetonitrile with up to 35 000 product turnover†

Hao-Chong Tan,[a] Ka-Pan Shing,[bd] Hua-Hua Wang,[a] Yungen Liu [a] and Chi-Ming Che *[bcd]

Transition metal-catalyzed asymmetric cyclopropanation of alkenes is an important strategy to construct chiral cyclopropane skeletons of pharmaceutical interest, but highly enantioselective and practical carbene transfer reactions based on Earth abundant and bio-compatible metals are still a difficult challenge. In this work, we use a chiral iron porphyrin (+)-D_4-(por)FeCl catalyst and *in situ* generated α-diazoacetonitrile for highly enantioselective cyclopropanation of arylalkene. This reaction is applicable to a wide range of arylalkenes (44 examples) with yield up to 99%, diastereomeric ratio (dr) up to 93 : 7, and enantiomeric excess (ee) values up to 98%. Importantly, for the cyclopropanation reaction of 3,4-difluorostyrene (1.40 g, 10.0 mmol) with α-diazoacetonitrile in the presence of 0.002 mol% of (+)-D_4-(por)FeCl as a catalyst, the turnover number and enantioselectivity of the cyclopropyl nitrile product reached 31 000 and 88% ee, respectively. Using cyclopropyl nitriles as a starting material, downstream functionalization derivatives including cyclopropyl carboxylic acids, cyclopropylamines, and cyclopropylmethanamines can be produced as key intermediates for the preparation of a series of bioactive or drug-like molecules. In addition, the chiral Fe(II)porphyrin–cyanocarbene intermediate [(–)-D_4-(por)Fe^{II}(:CHCN)], which is directly responsible for the carbene transfer reaction, has been characterized by ^{1}H NMR, HR ESI-MS, UV-vis and ATR-FTIR spectroscopy.

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Introduction

Cyclopropane scaffolds are commonly found in many pharmaceuticals and bioactive natural products.[1,2] Typically, cyclopropane skeletons[3–5] are prepared by carbene transfer reactions using diazo compounds as precursors, especially in an asymmetric manner,[6] and noble metal catalysts of rhodium, ruthenium and iridium are often used in asymmetric carbene transfer reactions. In the context of developing sustainable catalysis, there has been great interest in developing iron catalysis for organic synthesis[7–10] due to iron's Earth abundance and biocompatibility.[11] Although iron carbene complexes have been reported for a long time,[12] the development of practical iron-catalyzed carbene transfer reactions has lagged behind.[13] Furthermore, there are few studies on the detection and reactivity of reactive iron–carbene intermediates involved in the catalytic cycle. In the literature, Woo,[14] Che,[15] Gross[16] and Carreira[17,18] reported iron macrocyclic complexes (porphyrin and corrole) as catalysts for carbene transfer reactions (cyclopropanation of alkenes). In most cases, high product yields and high stereoselectivities (mainly *trans*-configuration) are obtained. Asymmetric cyclopropanation of alkenes using synthetic chiral iron porphyrin catalysts has only been reported sporadically by Gross,[19] Woo,[20] Simonneaux,[21,22] Wong and Che,[23] Zhang,[24,25] and Gallo.[26,27] Although good to high product yields (>80%) and high diastereoselectivities (dr > 10 : 1, mainly *trans*-configuration) were obtained, the enantioselectivities were moderate (typically <80% ee, excluding Zhang's recent report[25]). When chiral non-heme iron complexes are used as catalysts, lower enantioselectivities are obtained[20,28,29] except for the intramolecular cyclopropanation of α-diazoesters or indoles catalyzed by iron bisoxazoline complexes.[30,31] So far, for iron-catalyzed carbene transfer reactions, only engineered iron enzymes (such as P450, P411 variants and myoglobins with iron

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra. CCDC 2349759 (**2g**), 2349760 (**2l**), 2349761 (**2z**), 2349764 (**2aa**), and 2351894 (**2ad**). For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5sc00461f

porphyrins as co-factors) have been reported to achieve excellent enantioselectivity and high product turnover numbers (TONs) (Fig. 1).[32–35] In the literature, a rhodium-catalyzed styrene cyclopropanation using a donor/acceptor diazo-compound (trichloroethyl *p*-bromophenyl diazoacetate) resulted in a product TON and enantioselectivity of 100 000 and 94% ee, respectively. However, when the catalyst loading was reduced, the enantioselectivity decreased (400 000 with 90% ee, Fig. 1).[36] In this context, metal porphyrin complexes may be a promising catalyst choice due to their excellent activity and stability. Taking the asymmetric cyclopropanation of styrene with ethyl diazoacetate (EDA) as an example, chiral ruthenium porphyrin catalyst (−)D_4-(por)Ru(IMe)$_2$ gave the *trans*-cyclopropane product with a TON of 23 750 and an ee of 95%;[37] The artificial metalloenzyme Ir(Me)-PIX (with iridium porphyrin as a co-factor) afforded a *cis*-cyclopropane product of 10 000 TON and 98% ee (Fig. 1).[38] Engineered iron enzymes (with iron porphyrins as cofactors) produced even more exciting results: Mb (H64V, V68A) (myoglobin variant) gave a *trans*-product TON of 46 800 with 99.9% ee,[39] and the P411$_{BM3}$-CIS variant achieved a *cis*-product TON of 67 800 with 99% ee (Fig. 1).[40]

Among various carbene precursors, diazo compounds are the most commonly used.[41] However, diazo compounds have inherent disadvantages in preparation and storage due to their potentially explosive properties. It is more applicable when diazo compounds can be generated and used *in situ*,[42,43] simplifying the reaction process and broadening the application scope of such reactions, especially when the reactions are carried out on a large scale.[17,18] In this context, α-diazoacetonitrile, which can be generated *in situ* through the reaction of commercially available aminoacetonitrile hydrochloride with sodium nitrite,[44] was studied (Scheme 1). Simonneaux and co-workers reported the asymmetric cyclopropanation of styrene catalyzed by (+)-D_4-(por)RuCO or polymer-supported (+)-D_4-(por)RuCO using α-diazoacetonitrile as a carbene precursor; cyclopropane products were obtained with ee up to 90% and dr up to 93 : 7.[45] Using *in situ* generated α-diazoacetonitrile as the carbene precursor, Koenigs and co-workers[46,47] reported the catalytic cyclopropanation of styrene by Fe(TPP)Cl in a slow-release protocol, providing the product in up to 89% yields and up to 7 : 1 dr.[48] Using *in situ* generated α-diazoacetonitrile as the carbene precursor, Fasan and co-workers reported that Mb variants (in whole cells) catalyzed the asymmetric cyclopropanation of alkenes to provide up to 99.9% ee and up to 500 : 1 dr of cyclopropane product.[49] In this work, we used *in situ*

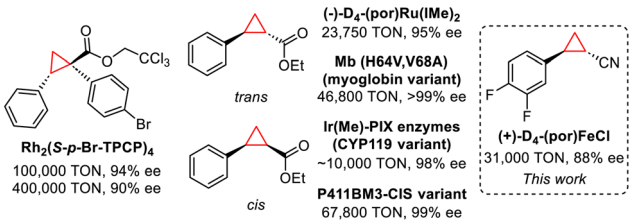
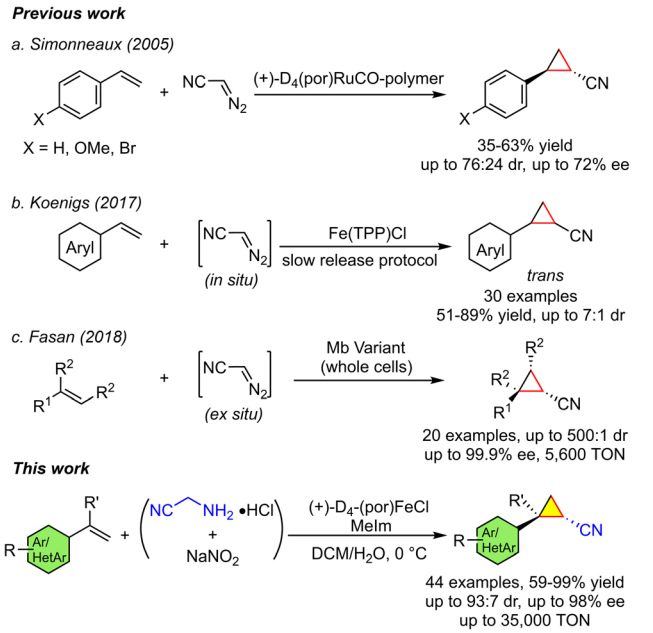


Fig. 1 Transition metal-catalyzed asymmetric cyclopropanation of alkenes.



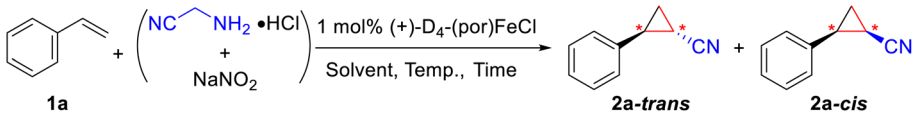
Scheme 1 Chiral iron porphyrin-catalyzed asymmetric cyclopropanation of alkenes.

generated α-diazoacetonitrile as the carbene precursor and chiral iron porphyrin (+)-D_4-(por)FeCl as the catalyst for the asymmetric cyclopropanation of aryl alkenes. Good product yields (up to 99%), high diastereoselectivities (up to >93 : 7 dr), high enantioselectivities (up to 99% ee) and high product TONs (up to 35 000 with 85% ee) were achieved (Scheme 1). This catalytic reaction has a broad substrate scope (44 examples) and can be used to prepare core scaffolds for the synthesis of bioactive or drug-like molecules. In addition, the chiral Fe(II)–porphyrin–cyanocarbene intermediate [Fe^{II}(por)(:CHCN)], which is directly responsible for the carbene transfer reaction, has been characterized by ^{1}H NMR, HR ESI-MS, UV-vis and ATR-FTIR spectroscopy.

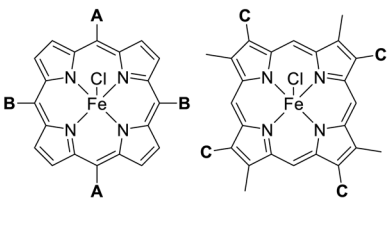
Results and discussion

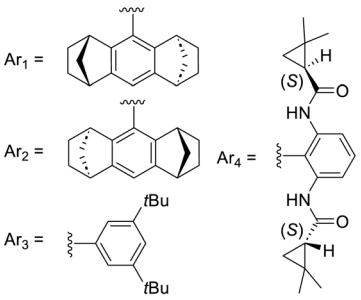
Similar to Koenigs's strategy, we used aminoacetonitrile hydrochloride to prepare α-diazoacetonitrile *in situ*.[48,50] Using (+)-D_4-(por)FeCl as a catalyst, it was found that 93% ee and 85 : 15 dr were obtained at room temperature using a slow-addition protocol[48] (Table 1, entry 1). For comparison, 84% ee and 81 : 19 dr were obtained *via* the one-pot addition method (Table 1, entry 2). There was a slight decrease in enantioselectivity when using other biphasic solutions (toluene/H_2O or $PhCF_3$/H_2O) (Table 1, entries 3 and 4). Higher enantioselectivities (88% ee) and diastereoselectivities (88 : 12 dr) were obtained when the one-pot reaction was performed at 0 °C (Table 1, entry 5). The best results were obtained with *N*-methyl imidazole (MeIm) as an additive (Table 1, entry 6, 91% yield, 97% ee and 90 : 10 dr).[23,51] Using (−)-D_4-(por)FeCl as a catalyst, the enantiomer of **2a** was obtained in 92% yield and −95% ee (Table 1, entry 7 *vs.* entry 6). Under optimized conditions, using other chiral iron

Table 1 Optimization of reaction conditions for (+)-D_4-(por)FeCl catalyzed asymmetric cyclopropanation of styrene[a]



Entry	Additive	Solvent	T (°C)	Time (h)	Yield[b] (%)	dr[b]	ee[c] (%)
1[d]	None	DCM/H_2O	r. t.	10 + 4[d]	82	85 : 15	93
2	None	DCM/H_2O	r. t.	14	85	81 : 19	84
3	None	Toluene/H_2O	r. t.	14	83	85 : 15	78
4	None	$PhCF_3$/H_2O	r. t.	14	81	81 : 19	79
5	None	DCM/H_2O	0	14	87	88 : 12	88
6	**MeIm (0.01 eq.)**	**DCM/H_2O**	**0**	**14**	**91**	**90 : 10**	**97**
7[e]	MeIm (0.01 eq.)	DCM/H_2O	0	14	92	89 : 11	−95
8[f]	MeIm (0.01 eq.)	DCM/H_2O	0	14	90	80 : 20	65
9[g]	MeIm (0.01 eq.)	DCM/H_2O	0	14	93	92 : 8	81
10[h]	MeIm (0.01 eq.)	DCM/H_2O	0	14	93	80 : 20	15
11[i]	MeIm (0.01 eq.)	DCM/H_2O	0	14	86	77 : 23	20
12[j]	MeIm (0.01 eq.)	DCM/H_2O	0	14	77	82 : 18	10
13[k]	None	DCM/H_2O	0	14	NR	—	—





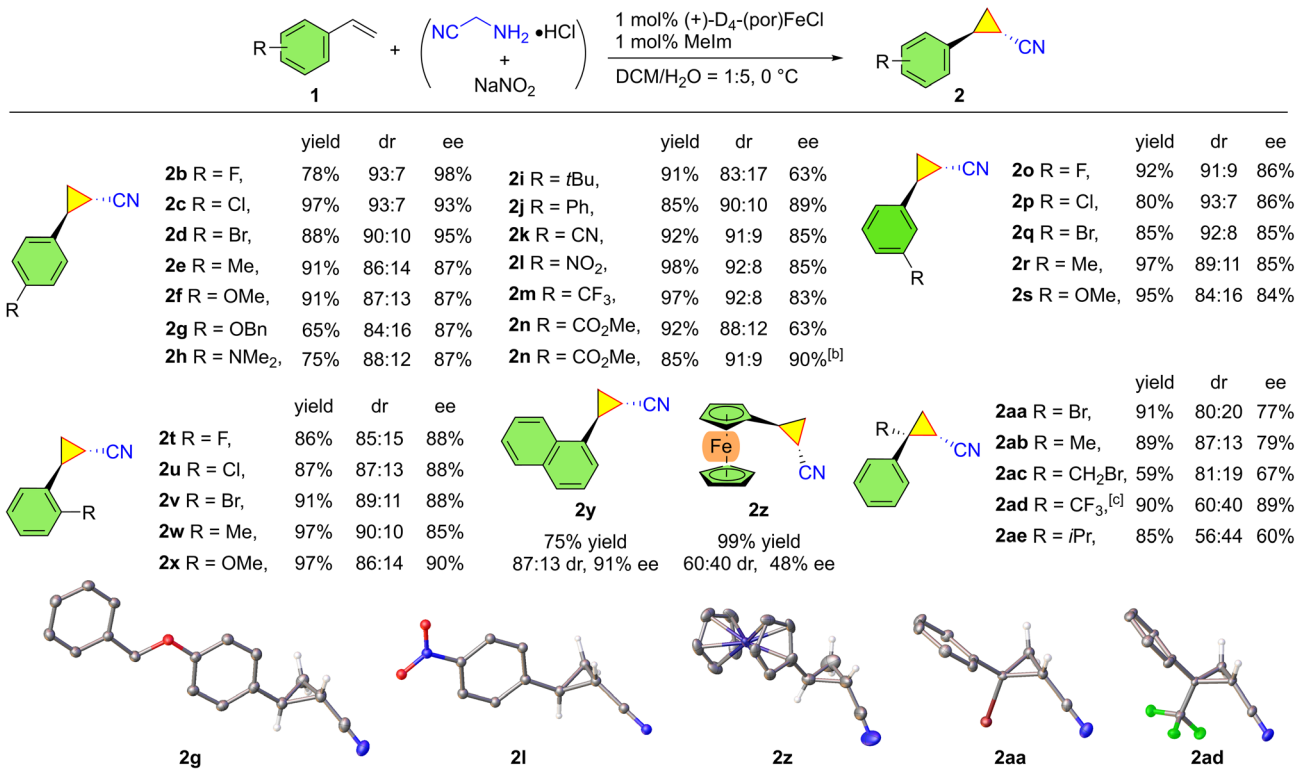
Entry		A	B
1-6	(+)-D4-porFeCl	Ar_1	Ar_1
7	(-)-D4-porFeCl	Ar_2	Ar_2
8	(*S*)-*t*Bu-chenporFeCl	Ar_3	Ar_4
9	(*S*,*S*)-cmcporFeCl	Ar_1	Ar_4
10	(*S*,*R*)-cmcporFeCl	Ar_2	Ar_4

Entry		C
11	β-(+)-D_4-porFeCl	Ar_1
12	β-(*S*)-chiral-porFeCl	Ar_4

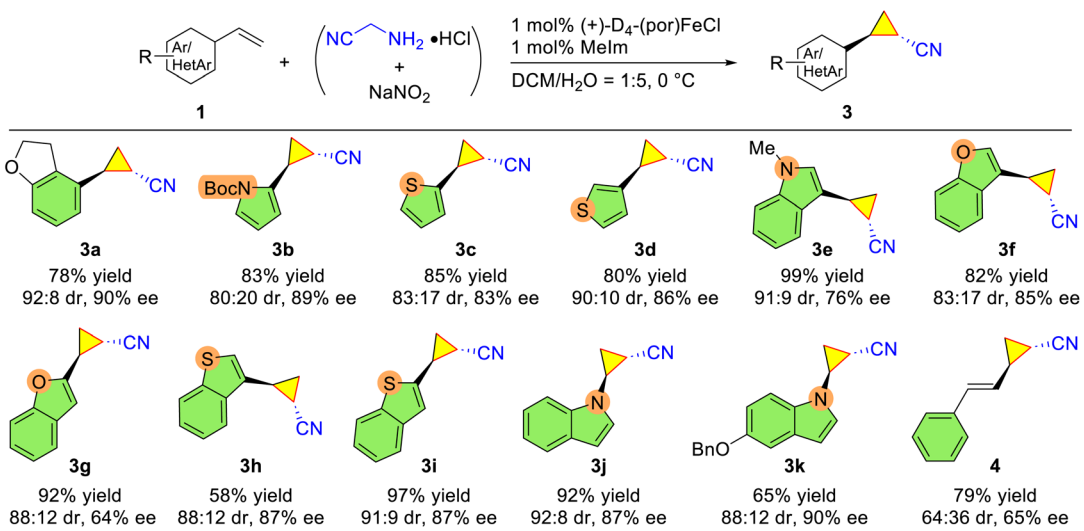
[a] Reaction conditions: **1a** (0.2 mmol) and catalyst (1 mol%) in 0.5 mL of DCM, diazo was generated *in situ* by one-pot reaction of amino-hydrochloride salt (0.4 mmol) with $NaNO_2$ (0.6 mmol) in 2 mL of degassed water. [b] Determined by ^{1}H NMR analysis of crude products. [c] Determined by HPLC. [d] Aminoacetonitrile hydrochloride (0.4 mmol, in 1 mL of degassed water) and sodium nitrite (0.6 mmol, in 1 mL of degassed water) were added dropwise using a syringe pump for 10 h and further reacted for 4 h. [e] (−)-D_4-(por)FeCl (1 mol%) was used. [f] (*S*)-*t*Bu-chenporFeCl (1 mol%) was used. [g] (*S*,*S*)-cmcporFeCl (1 mol%) was used. [h] (*S*,*R*)-cmcporFeCl (1 mol%) was used. [i] β-(+)-D_4-porFeCl (1 mol%) was used. [j] β-(*S*)-chiral-porFeCl (1 mol%) was used. [k] FeSalen(*S*,*S*)(3,5-*t*Bu)X (X = Cl or OTf) (10 mol%) was used. MeIm, methyl imidazole. NR, no reaction.

porphyrins such as (*S*)-*t*Bu-chenporFeCl, (*S*,*R*)-cmcporFeCl, (*S*,*S*)-cmcporFeCl, β-(+)-D_4-porFeCl and β-(*S*)-chiral-porFeCl,[52] cyclopropanation products were obtained with an ee of 10–81% (Table 1, entries 8–12). With FeSalen(*S*,*S*)(3,5-*t*Bu)X (Salen(*S*,*S*)(3,5-*t*Bu) = (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine, X = Cl or OTf) as a catalyst, no reaction was observed (Table 1, entry 13). Under optimal conditions (as those in Table 1, entry 6), we examined the scope of styrene derivatives (Scheme 2). In general, good enantioselectivities (up to 98% ee) and high diastereoselectivities (up to 93 : 7 dr) and high product yields (up to 97%) were obtained. For *para*-substituted styrene derivatives, strong electron-donating groups such as MeO (**2f**, 87% ee), Me_2N (**2h**, 87% ee) and strong electron-withdrawing groups such as CN (**2k**, 85% ee), NO_2 (**2l**, 85% ee), CF_3 (**2m**, 83% ee), CO_2Me (**2n**, 63% ee) and steric bulky groups (**2i**, *t*Bu, 63% ee) were found to slightly reduce the enantioselectivity of the product (Scheme 2). Lowering the temperature to −15 °C improved the enantioselectivity (to 90% ee for **2n**). When the substituent is located in the *meta*-position (**2o–2s**) or *ortho*-position (**2t–2x**), the enantioselectivity of the resulting cyclopropanation products decreases slightly (84–90% ee). This reaction is sensitive to substituents on disubstituted alkenes (Scheme 2). For α-substituted styrene derivatives (**2aa–2ae**), both diastereoselectivity and enantioselectivity decrease significantly with increasing α-substituent size. On the other hand, neither *cis*- nor *trans*-β-methylstyrene could be converted into the corresponding cyclopropanation products (Scheme 2). The *trans*-configurations of compounds **2g**, **2l**, **2z**, **2aa** and **2ad** were unambiguously determined by X-ray crystallography.

For alkenes tethered to aromatic heterocycles or benzo-heterocycles (Scheme 3, **3a–3i**), the yields of cyclopropanation products are 58–99%, ee is 76–91%, and dr is 80 : 20–92 : 8. *N*-Vinyl indoles also provided the corresponding cyclopropanation products (**3j**, **3k**) with 87% ee and 90% ee, respectively. The cyclopropanation product **4** was obtained from 4-phenyl-buta-



Scheme 2 (+)-D_4-(por)FeCl catalyzed cyclopropanation of styrene derivatives[a]. [a]Reaction conditions: **1** (0.2 mmol), MeIm (1.0 mol%) and (+)-D_4-(por)FeCl (1.0 mol%) in 0.5 mL of DCM, diazoacetonitrile (cacld 0.4 mmol) was *in situ* generated by reaction of aminoacetonitrile hydrochloride (0.4 mmol) with sodium nitrite (0.6 mmol) in 2.0 mL of degassed water. After 4 h under argon at 0 °C, another batch of aminoacetonitrile hydrochloride (0.4 mmol) and sodium nitrite (0.6 mmol) was added and further reacted for 14 h. [b]Replaced degassed water with saturated NaCl solution, reacted at −15 °C. [c]Two batches of aminoacetonitrile hydrochloride (0.4 mmol) and sodium nitrite (0.6 mmol) were added consecutively with an interval of 4 h. For the X-ray structure, H atoms are omitted for clarity, except for the H atoms from the cyclopropyl group.

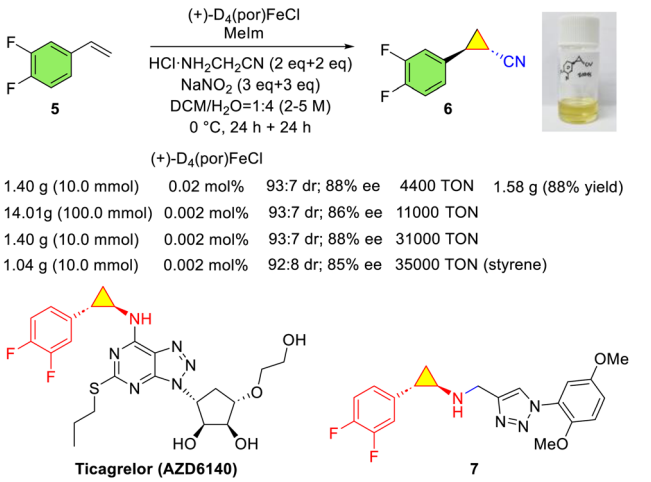


Scheme 3 (+)-D_4-(por)FeCl-catalyzed cyclopropanation of alkenes tethered to the heterocyclic ring and also an aryl 1,3-diene[a]. [a]Reaction conditions: **1** (0.2 mmol), MeIm (1.0 mol%) and (+)-D_4-(por)FeCl (1.0 mol%) in 0.5 mL of DCM, diazoacetonitrile (cacld 0.4 mmol) was generated *in situ* by reaction of aminoacetonitrile hydrochloride (0.4 mmol) with sodium nitrite (0.6 mmol) in 2.0 mL of degassed water. After 4 h under argon at 0 °C, another batch of aminoacetonitrile hydrochloride (0.4 mmol) and sodium nitrite (0.6 mmol) was added and further reacted for 14 h.

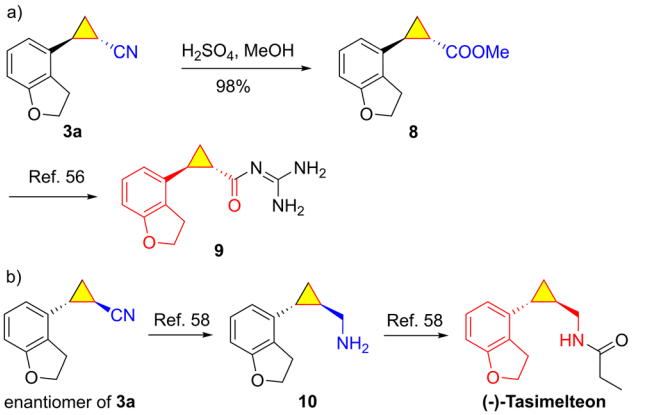
1,3-diene, with a dr of 64 : 36 and a yield of 79%; the ee values of the *trans*-isomer and *cis*-isomer are 65% and 8%, respectively (Scheme 3). No cyclopropanation reaction was observed using allylic benzene as a substrate.

Our catalytic cyclopropanation reaction is scalable and user-friendly (Scheme 4). In the presence of 0.02 mol% of (+)-D_4-(por)FeCl, 1.40 g of 3,4-difluorostyrene (**5**) was converted into 1.58 g of product **6** (88% yield, 88% ee, TON of 4400). For a batch reaction of 14.01 g of **5** in the presence of 0.002 mol% of (+)-D_4-(por)FeCl as a catalyst, a product TON of 11 000 (86% ee) was obtained. We attribute the slight erosion in enantioselectivity to inefficient mechanical stirring. Finally, the optimized conditions were: 1.40 g of **5** was reacted in the presence of 0.002 mol% of (+)-D_4-(por)FeCl to produce a cyclopropane product with a TON of up to 31 000 and 88% ee (Scheme 4). Under similar reaction conditions, styrene was used as the substrate (1.04 g scale) to give the corresponding cyclopropanation product with a TON of 35 000, an ee of 85% ee, and a dr of 92 : 8. Starting from **6**, Ticagrelor (AZD6140, antiplatelet agent)[53] and **7** (LSD1 inhibitor)[54] can be prepared. In the literature, for the cyclopropanation reaction of styrene/styrene derivatives and α-diazoacetonitrile, when Fe(F_{20}TPP)Cl is used as the catalyst, the obtained product TON is up to 2133 (using styrene as a substrate).[48] Using engineered myoglobin as the catalyst and *p*-chlorostyrene as the substrate, the product TON is reported to be as high as 5600.[49]

Chiral cyclopropyl nitrile can be easily converted into a variety of structurally diverse cyclopropane scaffolds including cyclopropylmethanamine, cyclopropylcarboxylic acid and cyclopropylamine, as valuable chiral building blocks for the preparation of bioactive or drug-like molecules.[55] For examples: (1) alcoholysis of **3a** gives the corresponding cyclopropyl carboxylic ester **8** with a yield of 98%, from which **9** (selective sodium hydrogen exchanger isoform-1 inhibitor) can be prepared (Scheme 5a; for the synthetic route,[56] see the ESI†). **(−)-Tasimelteon** (a melatonin receptor agonist)[57] can be synthesized from the enantiomer of **3a** (**3a** can be prepared by



Scheme 4 Gram-scale reactions catalyzed by chiral iron porphyrins and examples that can be prepared from **6**.

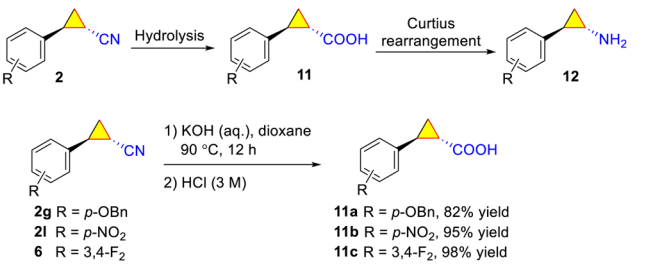


Scheme 5 (a) Preparation of **9** from **3a**. (b) Preparation of **(−)-Tasimelteon** from the enantiomer of **3a**.

using (−)-D_4-(por)FeCl as catalyst) according to literature methods (Scheme 5b).[58] This strategy is more step-economical[59] than similar approaches starting from EDA,[60] or *via* chiral epoxide intermediates.[61,62] Since our cyclopropanation reaction proceeds in an asymmetric manner, optical resolution of racemic amine **10** is unnecessary.[58]

(2) Hydrolysis of aryl cyclopropyl nitrile **2** under alkaline conditions gave the corresponding aryl cyclopropyl carboxylic acid (**11**) in high yield (Scheme 6).[49] Using acid **11** as the starting material, aryl cyclopropyl amines (**12**) were prepared in high yields *via* Curtius rearrangement.[63–66] A series of bio-active compounds containing a chiral cyclopropyl moiety such as **ST-161** (antiviral reagent against Lassa virus),[67] **VU0359595** (selective PLD1 inhibitor),[68] and **S 17092** (human proline endopeptidase inhibitor)[69] (Fig. 2) can be prepared from **2a** or its enantiomer. Our method is simpler[70] than the cyclopropanation of α,β-unsaturated carboxylic acid derivative of Oppolzer's chiral sultam (bornane[10,2]sultam, auxiliary) using diazomethane (used to construct the stereochemistry of the cyclopropyl moiety).[71]

(3) Phenylcyclopropylamine (tranylcypromine, **TCP**) and its derivatives are key and versatile intermediates in the preparation of bioactive or drug-like molecules (Fig. 2).[72,73] For examples, **Diprovocim-1** (toll-like receptor agonist)[74] can be prepared from **2a**. **RN-1** (LSD1 inhibitor)[75] and **ORY-2001** (Vafidemstat, LSD1 inhibitor)[76] can be prepared starting from **2g**. **MC2580** derivative (LSD1 inhibitor)[77] can be prepared starting from **2l**.



Scheme 6 Diversification of aryl cyclopropyl nitriles.

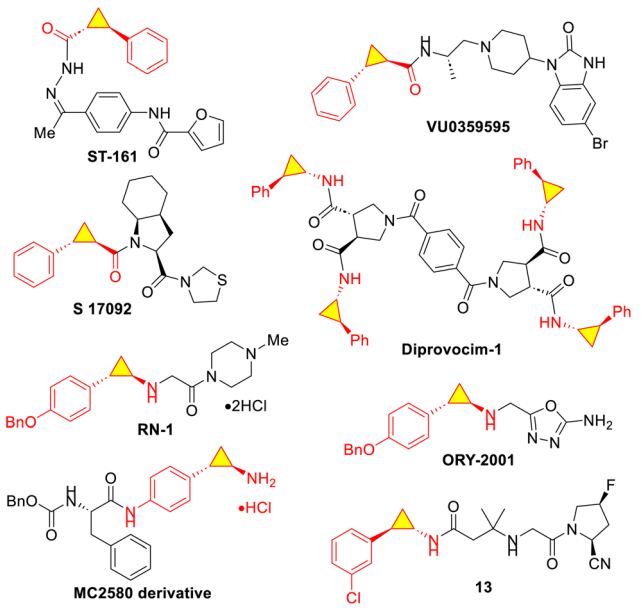


Fig. 2 Examples of cyclopropyl carboxamides and tranylcypromine derivatives.

Compound **13** (dipeptidyl peptidase IV inhibitor)[78] can be prepared starting from **2p**.

We performed time course experiments to gain a deeper understanding of the reaction mechanism (Fig. 3). There is a clear induction period before the reaction proceeds rapidly (Fig. 3a). Furthermore, MeIm shortened the induction period, possibly due to the *trans* effect *via* axial ligation to iron porphyrin. Under similar reaction conditions in the presence of MeIm, one-pot addition of diazoacetonitrile drastically shortened the induction period (<3 min) and the catalytic reaction was finished within 10 min (Fig. 3b). The reaction was found to be sensitive to O_2 (Fig. 3b). When carried out under O_2, the reaction slowed down significantly, and the product yield was only 29% in 60 min. In the presence of *N-tert*-butyl-2-phenylnitrone (PBN) or 2,2,6,6-tetramethyl-1-piperinedinyloxy (TEMPO), the cyclopropanation product was obtained in yield within 5% (Fig. 3c). However, the decrease in product yield in the presence of radical scavengers cannot exclude the interaction between free radical scavengers and metal catalysts, which can also lead to the loss of catalyst activity.[79] Butylated hydroxytoluene (BHT), which has weak interaction with metal catalysts, was used as a free radical scavenger, and the cyclopropanation product was obtained with a yield of 70%. The finding may differ from Zhang's recent report,[25] in which Fe(III)-based metalloradical species (α-Fe(IV)-alkyl and γ-Fe(IV)-alkyl radicals) were proposed. On the other hand, non-radical pathways in iron porphyrin-catalyzed carbene transfer reactions have also been proposed and supported by both experimental and computational results.[80]

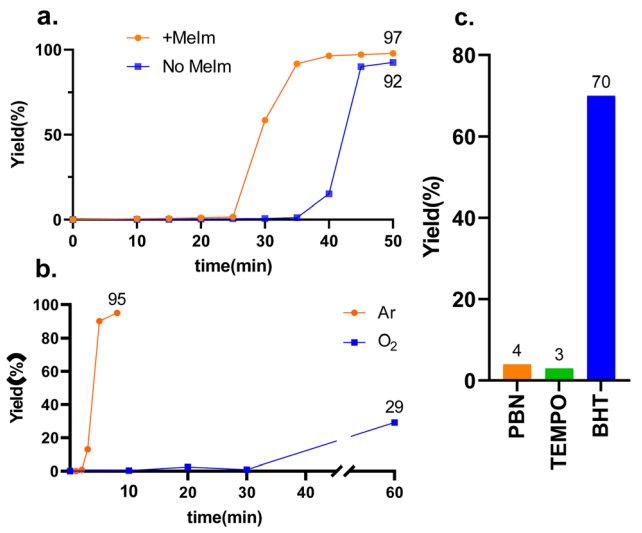
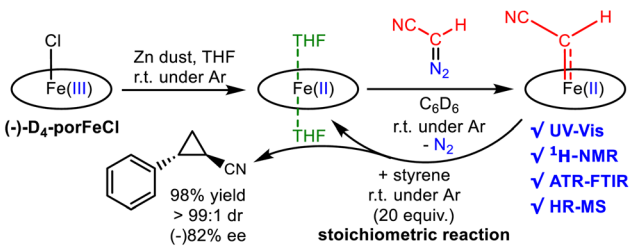


Fig. 3 Time course studies and the effect of radical scavengers. Reaction conditions: 0.8 mmol styrene, 1.6 mmol $HCl{\cdot}NH_2CH_2CN$, 2.4 mmol $NaNO_2$, 0.25 mol% (−)D_4-(por)FeCl, 1.6 mL DCM, 8 mL H_2O, 25 °C under argon, one-pot addition. (a) Effect of MeIm (in the presence or absence of 0.25 mol% of MeIm). (b) With 0.25% MeIm, used prepared diazoacetonitrile (0.4 mmol) under different atmospheres. (c) Reaction performed with different radical scavengers (1.2 eq. to diazoacetonitrile), 12 h at 25 °C.

We performed a series of experiments to characterize the reactive Fe(II) porphyrin cyanocarbene [(por)Fe(:CHCN)] intermediate (Scheme 7). [(−)-D_4-(por)Fe$(THF)_2$] was prepared by stirring (−)-D_4-(por)FeCl with Zn dust in degassed and anhydrous tetrahydrofuran (THF) overnight. [(−)-D_4-(por)Fe$(THF)_2$] can be characterized by ^{1}H NMR. All sharp resonance peaks appear within δ −1.8 to 12.5 ppm. It was found that [(−)-D_4-(por)Fe$(THF)_2$] reacted with an equimolar diazoacetonitrile (0.07 M solution in toluene) to immediately produce [(−)-D_4-(por)Fe(:CHCN)], as shown by using UV-vis (in benzene) and ^{1}H NMR spectroscopy. In a non-coordinating solvent (benzene), [(−)-D_4-(por)Fe(:CHCN)] has UV-vis absorption peaks at 417 and 509 nm (Fig. 4). Studies have found that [(−)-D_4-(por)Fe(:CHCN)] is unstable in benzene under aerobic conditions, producing a species with UV-vis absorption spectrum similar to Fe(III) porphyrin (spectral changes in benzene solution show isosbestic points at 387, 512 and 554 nm, see Fig. S2, ESI†). Comparing the UV-vis absorption spectra of [(−)-D_4-(por)Fe$(THF)_2$] and [(−)-D_4-(por)Fe(:CHCN)], the Soret and Q bands blue shift from 430 and 547 nm to 422 and 538 nm (solvent: THF), respectively (see Fig. S1, ESI†).



Scheme 7 Synthesis, characterization and reactivity studies of Fe(II) porphyrin–cyanocarbene.

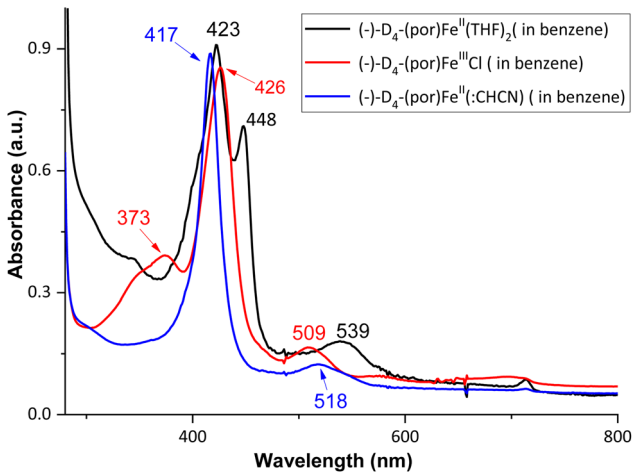


Fig. 4 UV-vis absorption spectrum of [(−)-D_4-(por)Fe(THF)$_2$], [(−)-D_4-(por)FeCl] and [(−)-D_4-(por)Fe(:CHCN)] in benzene-d_6.

The ^{1}H NMR spectrum (Fig. 5) of [(−)-D_4-(por)Fe(:CHCN)] in C_6D_6 shows characteristic peaks at δ 17.8 (s, 1H, [:C***H***CN]), 8.77–8.82 ($d\times$ 2, 8H, splitting *via* desymmetrization of the chiral Fe–carbene species) and 7.30 (s, 4H) ppm, consistent with diamagnetic Fe(II) carbene porphyrins.[81] The ^{1}H NMR chemical shifts fall into a similar range for typical terminal metal-carbene porphyrins containing [:C***H***(CN)] fragment such as [Fe(TTP)(:CHY)] (Y = mesityl, 19.71 ppm in C_6D_6),[82] [Ru(TTP)(:CHY)] (Y = CO_2Et, 13.43 ppm in C_6D_6),[83] [Ru(TMP)(:CHY)] (Y = CO_2Et, 13.79 ppm in C_6D_6)[84] and [Ru(TTPPP)(H_2O)(:CHY)] (Y = CO_2Et, 13.07 ppm in $CDCl_3$).[85] The highly de-shielded protons may originate from multiple bonding features between Fe and $C_{carbene}$, bringing the coordinated carbene group closer to the de-shielded zone around Fe porphyrin. The [(−)-D_4-(por)Fe(:CHCN)] intermediate was also characterized by HR-MS (Fig. 5). The experimental mass value ($C_{86}H_{77}FeN_5$, 1235.5517 m/z) and isotopic pattern of the spectrum match well with the theoretical values (1235.5523 m/z).

[(−)-D_4-(por)Fe^{II}(:CHCN)] was characterized based on the absorbance band of ν(C≡N) using ATR-FTIR spectroscopy (Fig. 6). The ν(C≡N) of [(−)-D_4-(Por)Fe^{II}(:CHCN)] is observed at 2178 cm^{-1}, which is different from the organic species NCCH=CHCN (*trans*) (2235 cm^{-1}) and CH(CN)N_2 (2100 cm^{-1}). This excludes the possibility that Fe(II) porphyrin is mixed with organic species after treatment with diazoacetonitrile and the possible dimeric byproduct NCCH=CHCN coordinated with the Fe(II)porphyrin.

Shortly after adding styrene (20 equiv.) to a solution of [(−)-D_4-(por)Fe^{II}(:CHCN)] in C_6D_6 at room temperature, the cyclopropanation product was obtained in 98% yield. This enantioselectivity (−82% ee) is in good agreement with the

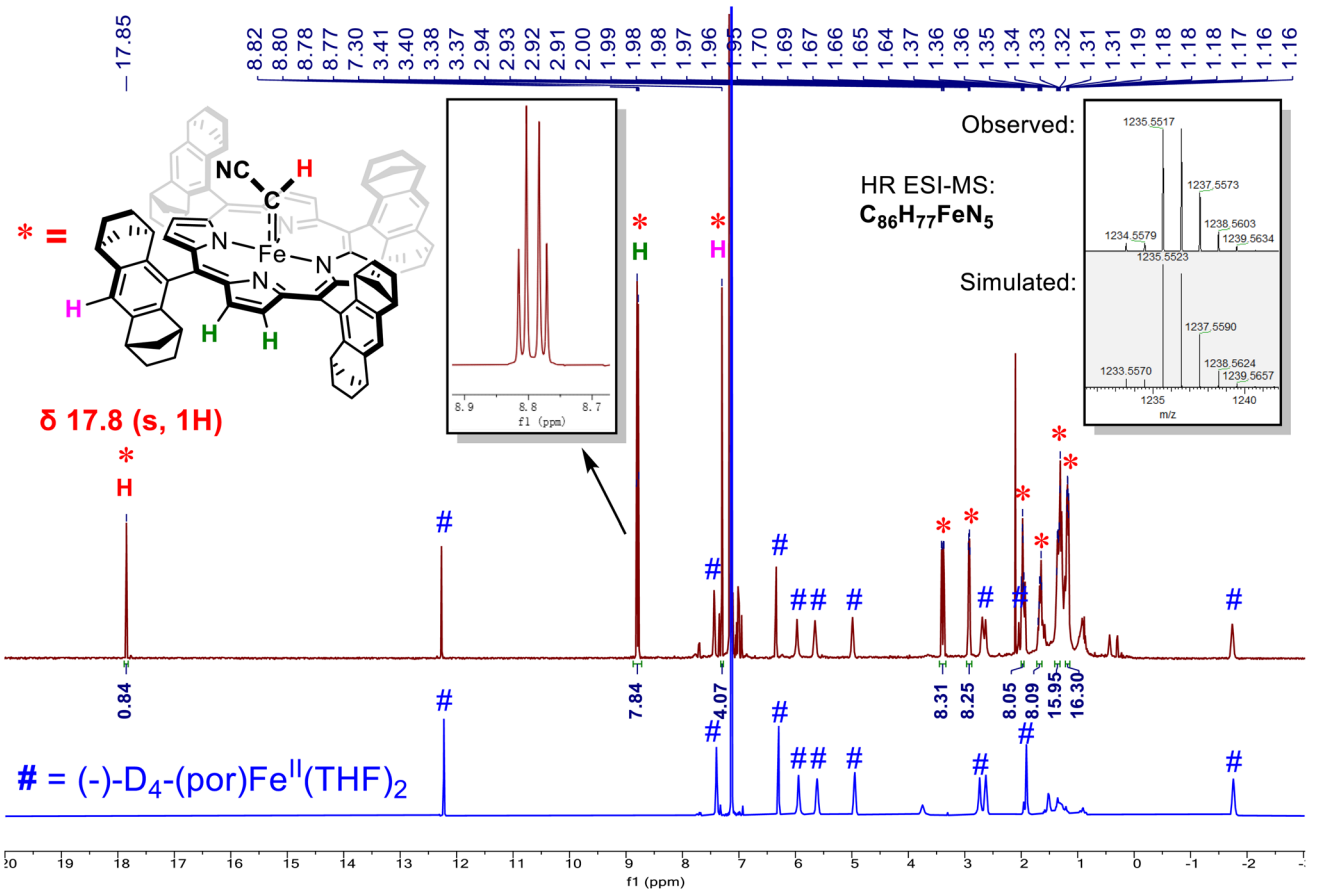


Fig. 5 ^{1}H NMR spectrum of [(−)-D_4-(por)Fe^{II}(:CHCN)] (in benzene-d_6).

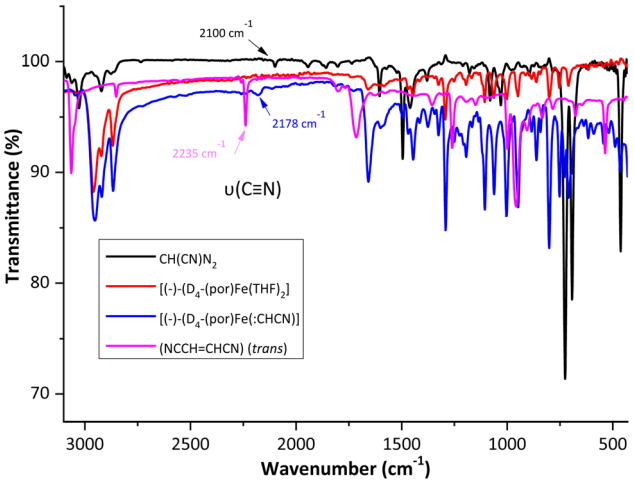


Fig. 6 ATR-FTIR spectroscopy for comparison of ν(C≡N).

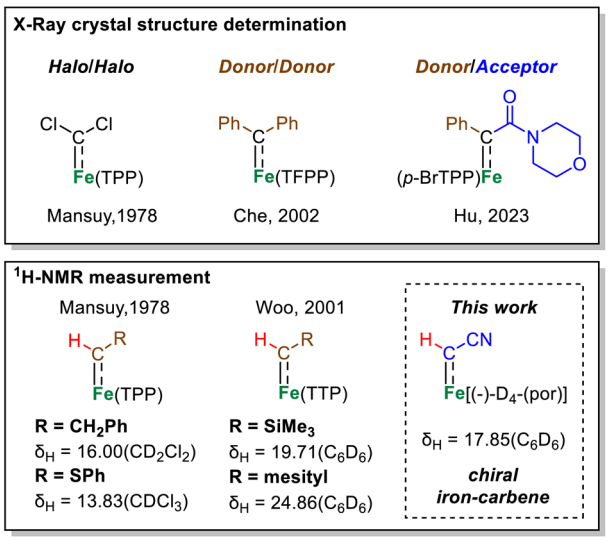
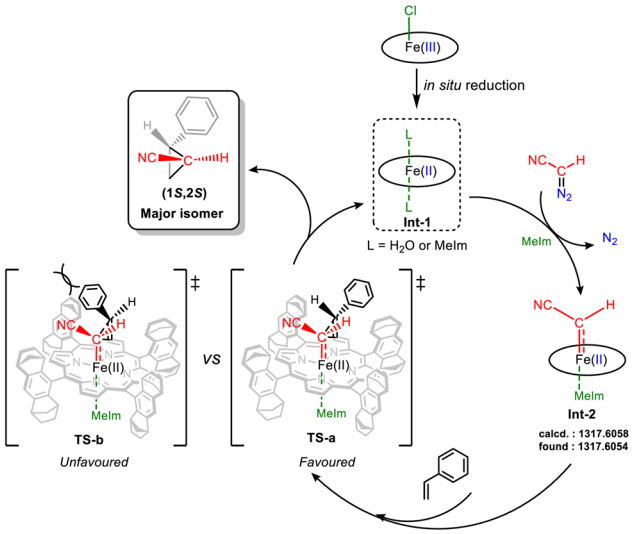


Fig. 7 Fe(porphyrin)–carbene complexes reported in the literature.

value determined under catalytic conditions (84% ee by (+)-D_4-(por)FeCl, Table 1, entry 2), showing that [(−)-D_4-(por)Fe^{II}(:CHCN)] is an active reaction intermediate directly involved in the cyclopropanation reaction.

In the literature, Mansuy,[86] Che[15] and Hu[87] reported the crystal structures of some Fe(porphyrin)–monocarbene complexes containing carbene moieties, such as [:CCl_2], [:CPh_2] and [:C(Ph)CO(morpholine)] (Fig. 7). On the other hand, the Fe(porphyrin)–carbene complex containing the [:C**H**R] carbene moiety was only characterized by ^{1}H-NMR.[82,88,89] In this work, we captured and characterized a highly reactive iron carbene containing a chiral porphyrin ligand and further performed the stoichiometric reaction of this chiral iron carbene intermediate with styrene. The enantioselectivity of the chiral cyclopropanation product was found to be comparable to that obtained under catalytic conditions, indicating that the chiral iron carbene intermediate is directly involved in and responsible for the asymmetric cyclopropanation reaction.



Scheme 8 Plausible mechanism of (+)-D_4-(por)FeCl-catalyzed asymmetric cyclopropanation.

Based on the above experimental results, a plausible mechanism for the asymmetric cyclopropanation of alkenes catalyzed by (+)-D_4-(por)FeCl was proposed (Scheme 8). Under the reaction conditions, (+)-D_4-(por)Fe(III)Cl is reduced *in situ* to give [(+)-D_4-(por)Fe(II)(L)] (L = H_2O or MeIm) (**Int-1**). After further reaction with diazoacetonitrile, the Fe(II)–carbene intermediate [(+)-D_4-(por)Fe^{II}(:CHCN)(MeIm)] (**Int-2**) was generated and detected by HR ESI-MS (cal. 1317.6058 *m*/*z*, found 1317.6054 *m*/*z*, Fig. S6†). The sterically bulky D_4-porphyrin ligand provides a chiral environment, resulting in enantioselectivity of the carbene transfer reaction. Styrene attacks the iron–carbene intermediate in different directions, producing two transition states, one of which is energetically unfavorable (**TS-a** *vs.* **TS-b**). The favorable conformation (**TS-a**) dominates during the reaction and produces the (1*S*,2*S*)-isomer as the major product.

Conclusions

In summary, by using chiral iron porphyrin (+)-D_4-(por)FeCl as the catalyst and diazoacetonitrile (*in situ* generated) as the carbene precursor, we have achieved the iron-catalyzed arylalkene cyclopropanation reaction with a broad substrate scope, excellent diastereoselectivity, high enantioselectivity, and good product yield. Reactive chiral Fe–carbene intermediates have been characterized by ^{1}H NMR, HR ESI-MS, UV-vis and ATR-FTIR spectroscopy. The scalable reaction and product TONs up to 35 000 demonstrate the versatility of our approach in preparing key intermediates for the synthesis of bioactive or drug-like molecules using chiral iron porphyrin catalysts.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data have been deposited at the

CCDC under 2349759 (**2g**), 2349760 (**2l**), 2349761 (**2z**), 2349764 (**2aa**), and 2351894 (**2ad**).

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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