ORIGINAL ARTICLE

A C G
publications

*Org. Commun.*10:2 (2017) 79-89

organic
communications

Asymmetric cyclopropanation of olefins catalyzed by a chiral cobalt(II) porphyrin

Albrecht Berkessel*, Erkan Ertürk and Jörg M. Neudörfl

Department für Chemie, Universität zu Köln, Greinstrasse 4, 50939 Köln, Germany

(Received April 15, 2017; Revised May 25, 2017; Accepted May 26, 2017)

Abstract: The cobalt(II) complex of the Halterman porphyrin, 5,10,15,20-tetrakis[(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-yl]porphyrinato cobalt(II) [Co(por*)], was synthesized and its structure was identified by X-ray analysis. Up to 80:20 *trans*:*cis* diastereomeric ratio and 82% *ee* were achieved in the cyclopropanation of styrene with ethyl diazoacetate by using this cobalt(II) porphyrin complex as catalyst.

Keywords: Asymmetric catalysis, cyclopropanation, cobalt, porphyrin, ethyl diazoacetate.

1. Introduction

Catalytic asymmetric cyclopropanation of prochiral olefins *via* carbene transfer reactions is one of the most frequently used synthetic technique for constructing chiral cyclopropane rings that are encountered in numerous biologically active compounds as well as natural products.[1] The majority of the methods employ a diazo reagent as the carbene precursor, and a chiral transition metal complex as the catalyst for generating the reactive carbene intermediate.[2] The catalysts that have been developed for this purpose so far mainly comprise copper(I),[3] rhodium(II)/(III),[4] ruthenium(II),[5] and cobalt (II)/(III)[6,7] complexes.[2c,d]

Since the work of Callot and Piechocki in 1980 in which a metal porphyrin complex, i.e. rhodium(III) tetraphenylporphyrin iodide, was for the first time reported to be capable of catalyzing cyclopropanation of alkenes with ethyl diazoacetate (EDA),[8] metal porphyrins have been shown to feature high catalytic turnover numbers (TONs) in alkene cyclopropanation using diazo reagents, due to their robustness. O'Malley and Kodadek then developed rhodium(III) complexes of "chiral wall" and "chiral fortress" porphyrins as the first enantioselective metal-porphyrin catalysts for cyclopropanation, and modest *cis*/*trans* diastereoselectivities and enantioselectivities were achieved.[9] Among the metal porphyrin complexes, such as iridium(III),[10] osmium(III),[11] iron(II)[12,13] ruthenium(II)[14] and cobalt(II)[15,16] porphyrin complexes, ruthenium(II) and iron(III) prophyrins have appeared to possess higher catalytic activities in cyclopropanation of olefins with diazo reagents. Thus, up to 7500 and 10000 TONs were observed for Ru(II)[14h] and Fe(III)[13c] porphyrins, respectively.

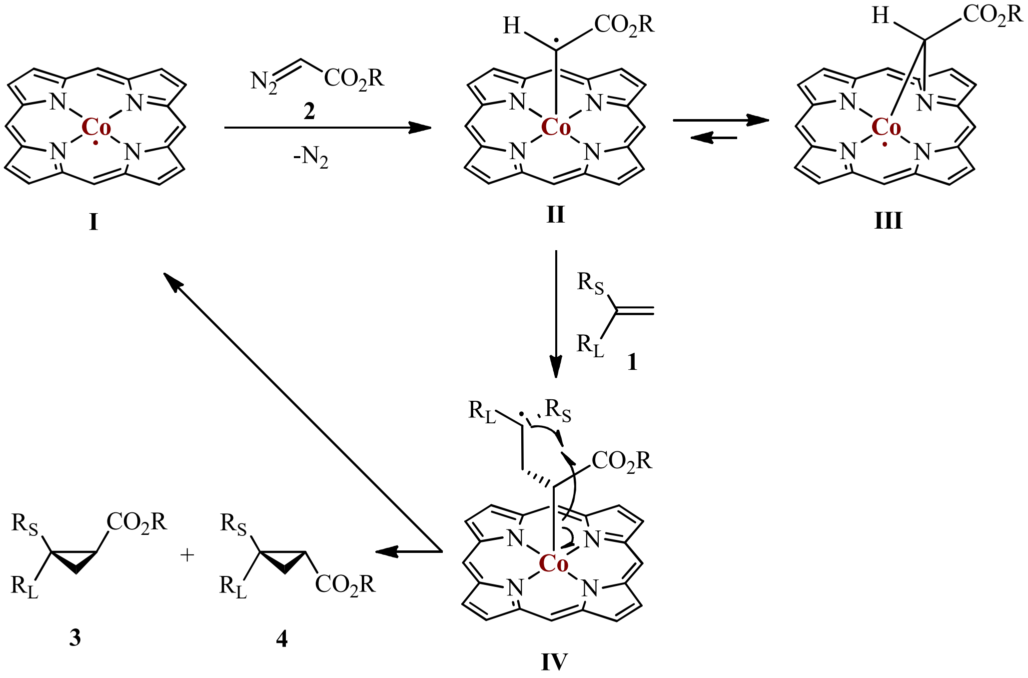
In spite of the fact that the stoichiometric condensation reaction of cobalt(II) porphyrin complexes with ethyl diazoacetates (EDA) was already disclosed by Johnson and co-workers in 1975,[15a] only recent years have witnessed significant impact of cobalt(II) porphyrins to the

---

[*] Corresponding authors: E-Mail: berkessel@uni-koeln.de; Tel: +49 (221) 470 3283; Fax: +49 (221) 470 5102

The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 05/29/2017 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.11.17.04.019

cyclopropanation of olefins with diazo reagents.[16-23] The EPR, ESI-MS as well as DFT studies revealed that the cobalt(II)-porphyrin-mediated cyclopropanation of olefins with diazoesters proceeds via the formation of the Fischer-type radical carbene **II** followed by a stepwise radical addition of an olefin (**1**) and cyclization cascade toward the corresponding cyclopropanes **3** and **4** (Scheme 1).[17,18] The "terminal radical carbene species" **II** and the "bridging carbene species" **III** were proposed to exist as redox isomers and in dynamic equilibrium with each other, although the latter was determined to be thermodynamically somewhat more stable according to DFT calculations.[18] While the dynamic equilibrium between the species **II** and **III** is expected to prevent the formation of dimerization by-products (e.g. diethyl fumarate and diethyl maleate in case of EDA) during olefin cyclopropanation, the existence of radical carbene moiety bound to d^6 Co^{III} center of the species **II** accounts for its more nucleophilic character, i.e. radical reactivity that is unusual for carbenes bound to other metal porphyrin complexes.[17,10] The nucleophilic character of the carbene radicals **II** enables cobalt(II) porphyrins to catalyze also the cyclopropanation of electron-deficient olefins such as methyl acrylate.[16e] Zhang and co-workers developed D_2-symmetric chiral porphyrin ligands bearing secondary amide functionality and their cobalt(II) complexes as cyclopropanation catalysts.[16c,16e16h,16i] Cobalt(II) porphyrins with amide functionality showed higher reactivities and diastereo- and enantioselectivities than those without amide functionality such as cobalt(II) tetraphenylporphyrin. This observation was attributed to the formation of a hydrogen bond between the carbonyl oxygen of the carbene moiety and the N-H hydrogen of the amide functionality. It should also be noted that the addition of 0.50 equivalents of 4-dimethylaminopyridine (DMAP) to the catalytic system for cyclopropanation, described by Zhang and co-workers, was found to be crucial for achieving high activity and stereoselectivity. This was ascribed to the so-called *trans* effect of DMAP. Thus, cobalt(II) complexes of Zhangs' chiral porphyrins having amide functionality have emerged as general and highly diastereo- and enantioselective catalysts for the cyclopropanation of olefins with diazo reagents.[19-23] All these developments, as well as our continuing interest in metal-porphyrins in asymmetric catalysis,[14c,14h,24] have prompted us to disclose our recent work on the synthesis of the cobalt(II) complex of the Halterman prophyrin, and its catalytic performance in the cyclopropanation of olefins with diazo esters.



Scheme 1. Stepwise radical mechanism for the Co^{II}(por)-catalyzed cyclopropanation of olefins.

2. Experimental

5,10,15,20-Tetrakismesitylporphyrin (**5**) was prepared from mesitaldehyde and pyrrole under Lindsey conditions.[25] Cobalt(II) tetramesitylporphyrin (CoTMP, **6**) was synthesized from the reaction of the porphyrin ligand **5** with excessive $Co(OAc)_2 \cdot 4H_2O$ in boiling mixture of $CHCl_3$-MeOH and it was purified via column chromatography (aluminum oxide, neutral, hexane/$CHCl_3$, gradient elution from 10:0.2 to 10:1).[26] The chiral Halterman porphyrin ligand (**7**) was prepared according to the literature.[27] Ethyl diazoacetate (EDA) was purchased from Aldrich and used as received. *tert*-Butyl diazoacetate (^{t}BDA) was prepared from *tert*-butyl glycinate hydrochloride according to the literature.[28] All reactions were carried out in oven-dried Schlenk tubes with magnetic stirring under a positive pressure of argon. Toluene and THF were freshly distilled from sodium/benzophenone prior to use under an argon atmosphere. Dichloromethane (DCM) was dried by distillation over calcium hydride under argon atmosphere. Dimethyl formamide (DMF) was dried over calcium hydride and distilled under reduced pressure under argon. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 instrument. The IR measurements were performed on a Perkin–Elmer Paragon 1000 spectrometer. UV-Vis spectra were obtained on a Beckman Coulter DU 800 spectrometer. EI mass spectra were provided on a Finnigan MAT 900. Optical rotations were measured on a Perkin–Elmer polarimeter 343 plus. The absolute configurations of the products were determined by comparison of their optical rotations with literature data, as well as by chiral GC or HPLC analysis.

*2.1. Synthesis of 5,10,15,20-tetrakis[(1S,4R,5R,8S)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimetha-noanthracene-9-yl]porphyrinato cobalt(II) (**8**):* The enantiomerically pure porphyrin ligand **7** (114 mg, 0.1 mmol, 1.00 equiv) was placed in an oven-dried round-bottomed two-neck flask equipped with a reflux condenser. The flask was evacuated for 15 min and back-filled with argon. After addition of 30 mL of dry $CHCl_3$ and 10 mL of dry DMF by means of gas-tight syringes, the resulting solution was heated to 65 °C (oil bath temperature) under Ar whereupon the reaction mixture became homogenous. $Co(OAc)_2 \cdot 4H_2O$ (150 mg, 0.6 mmol, 6.00 equiv) was added in one portion and the resulting reaction mixture was stirred at 65 °C for 12 h under Ar. After cooling to rt, the organic phase was washed several times with water (3×50 mL) in a separatory funnel, and dried over Na_2SO_4. All volatile components of the solution were removed under reduced pressure by rotary evaporation. The crude product was then purified by dry column chromatography on aluminum oxide (neutral, Fluka, Brockmann activity I) using *n*-hexane-chloroform (10:0.1) as eluent. 80 mg (67 μmol, 67%) of the chiral cobalt(II) porphyrin complex **8** were obtained as brick red powder. Remaining porphyrin ligand was also recovered in this way. Crystals suitable for X-ray analysis were grown from dichlormethane-acetonitrile mixture. Mp >250 °C, R_f=0.26 (aluminum oxide, neutral; *n*-hexane-chloroform, 10:0.1). UV-VIS: $\lambda_{(max)}$=413 nm ($CHCl_3$). FT-IR (CsBr): υ (cm^{-1})=2964 [s, (C-H) alkyl], 2921 [w, (C-H) alkyl], 2869 [m, ν(C-H) alkyl], 1473 [w, (C-H) alkyl], 1297,1104 [both m], 1009, 950, 864 [all w], 801 [m, (C-H) aryl], 756, 709 [both w] cm^{-1}. HR-MS (EI): *m/z* $[M]^+$ calcd for $C_{84}H_{76}N_4Co$: 1199.5402; found: 1199.5400. EA: Anal. Calcd. for $C_{84}H_{76}N_4Co$: C, 84.04; H, 6.38; N, 4.67. Found: C, 82.79; H, 6.57; N: 4.62.

*X-ray crystal structure analysis of (**8**)* : $C_{84}H_{76}CoN_4$, M = 1200.46, brick red crystals, 0.05 x 0.1 x 0.1 mm, monoclinic, a = 23.018(5), b = 17.890(5), c = 19.247(5) Å, β = 126.57(5)°, V = 6366(3) $Å^3$, T = 100(2) K, space group C2, Z = 4, d_{calcd} = 1.253 g/cm^3, μ = 0.321 mm^{-1}. A total of 5255 reflections were measured. Final residuals were R1 = 0.0533 and wR2 = 0.0978 (for 3755 observed reflections with I > 2σ(I), 802 parameters) with GOF 1.015 and largest residual peak 0.264 e $Å^{-3}$ and hole -0.317 e $Å^{-3}$.

All data were collected on an Nonius Kappa CCD diffractometer ($2\Theta_{max}$ = 50°,$Mo_{K\alpha}$ radiation(λ = 0.71073 Å), graphite monochromator, φ / ω - scans). The structure was solved using direct methods (SIR-97, Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.G.G.; Burla, M.C.; Polidori, G.; Camalli, M.; Spagna, R.), followed by full-matrix least squares refinement with anisotropic thermal parameters for C,N,O and F and fixed parameters for H (SHELXL-2014, Sheldrick, G. M.: Program for the Refinement of Crystal Structures. University of

Göttingen, Germany 2015). The crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1535476. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+ 44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

2.2. General procedure for the cobalt(II) porphyrin-catalyzed cyclopropanation:

A catalytic amount of the cobalt(II) porphyrin complex **6** or **8** (see Table 1) was placed in an oven-dried Schlenk tube and then the tube was capped with a glass stopper. The tube was evacuated for 15 min and back-filled with argon. The glass stopper was replaced with a rubber septum under positive pressure of argon. After addition of absolute solvent, olefin (1.00 equiv) was added which was succeeded by the addition of an additive, if necessary. The homogenous mixture was stirred for ca. 5 min at room temperature and then 1.20 equiv of ethyl diazoacetate (**2a**) or *tert*-butyl diazoacetate (**2b**) were added via syringe at once whereupon gas evolution was observed. After stirring the reaction mixture for a while at a certain temperature as indicated in Table 1 or Table 2, the yield of the reaction was determined by GC analysis or isolating the products by column chromatography.

*2.3. trans- and cis-Ethyl 2-phenylcyclopropanecarboxylate (**3a** and **4a**):* GC analysis (chiral): WCOT-FS, CP Chirasil-Dex CB, 25 m, 0.25 mm ID; inlet: 250 °C (split modus); det.: 250 °C (FID); He, 1.2 $\mathrm{mL\cdot min^{-1}}$ (constant flow modus); oven: 80 °C, 5 $\mathrm{°C\cdot min^{-1}}$, 115 °C (40 min), 4 $\mathrm{°C\cdot min^{-1}}$, 120 °C (5 min), 15 $\mathrm{°C\cdot min^{-1}}$, 160 °C (3 min). t_R=3.5 min (styrene), t_R=11.0 min (1,2-dibromobenzene as the internal standard), t_R=30.2 min (*ent*-**4a**), t_R=32.6 min (**4a**), t_R=34.4 min (**3a**), t_R=35.8 min (*ent*-**3a**).

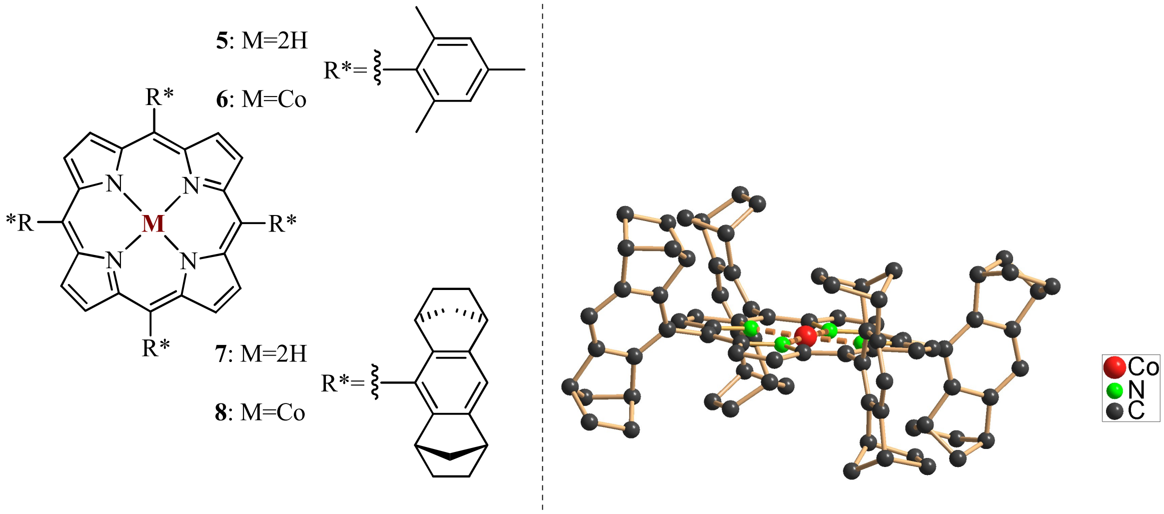
*2.4. trans-and cis-tert-Butyl 2-phenylcyclopropanecarboxylate (**3b** and **4b**):* GC analysis (chiral): WCOT-FS, CP Chirasil-Dex CB, 25 m, 0.25 mm ID; inlet: 250 °C (split modus); det.: 250 °C (FID); N_2, 12 psi column head pressure (constant pressure modus); oven: 80 °C, 5 $\mathrm{°C\cdot min^{-1}}$, 115 °C (40 min), 4 $\mathrm{°C\cdot min^{-1}}$, 130 °C (15 min), 15 $\mathrm{°C\cdot min^{-1}}$, 160 °C (3 min). t_R=51.8 min (**4b**), t_R=52.3 min (*ent*-**4b**), t_R=59.9 min (*ent*-**3b**), t_R=60.3 min (**3b**).

HPLC analysis (chiral): Chiralcel OD-H; eluent: *n*-hexane (100%), flow rate: 0.7 $\mathrm{mL\cdot min^{-1}}$, pressure: 23 bar; detection: 254 nm (UV). t_R=16.6 min (**3b**), t_R=20.0 min (*ent*-**3b**). No separation for the enantiomers **4b** and *ent*-**4b** was observed on this chiral column.

*2.5. Ethyl 2,2-diphenylcyclopropanecarboxylate (**3c**):*HPLC analysis (chiral): Chiralpak OJ; eluent: *n*-hexane/^{i}PrOH, 85:15; flow rate: 1.0 $\mathrm{mL\cdot min^{-1}}$, pressure: 27 bar; detection: 254 nm (UV). t_R=18.6 min (*ent*-**3c**), t_R=28.0 min (**3c**).

3. Results and Discussion

The cobalt(II) porphyrin **6** (TMPCo) was prepared according to the literature.[26] The chiral cobalt(II) porphyrin **8** (Co(por*)) was obtained by reacting the enantiomerically pure porphyrin ligand **7** with an excess of cobalt(II) acetate tetrahydrate ($Co(OAc)_2\cdot 4H_2O$) in $CHCl_3$-DMF solvent mixture (3:1) at 65 °C under Ar (Figure 1). The structure of the new cobalt complex of the Halterman porphyrin (**8**) was well identified by X-ray analysis. It should be noted that the cobalt complex **8** could not be formed when the Halterman porphyrin (**7**) was interacted with some selected cobalt sources, such as $CoCl_2$, $Co(OAc)_2$, in boiling DMF which is known to be the usual technique for the synthesis of cobalt(II) porphyrin complexes. Even in boiling DMF, the Halterman porphyrin (**7**) was found to be practically insoluble, which possibly hampered the cobalt insertion in DMF.



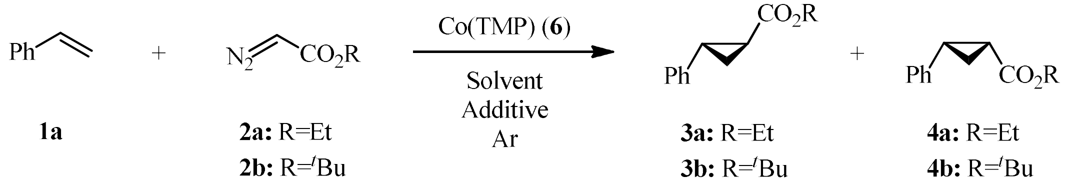
8

Figure 1. Cobalt(II) porphyrin complexes **6** [Co(TMP)] and **8** [Co(por*)] (left). The structure of Co(por*) (right). Hydrogen atoms were omitted for clarity.

We then revisited the catalytic cyclopropanation of styrene (**1a**) with EDA (**2a**) and ^{t}BDA (**2b**) in the presence of **6** (Table 1). Co(TMP) (**6**) was chosen as the model complex to find out the optimum reaction conditions because of its very close similarity to the our Co(por*) (**8**) in terms of its steric and electronic features as well as considering its ready availability. The results are summarized in Table 1. A vigorous reaction between **1a** and **2a** in toluene at rt was observed when 2 mol% of **6** was employed (Table 1, entry 1). The conversion was almost quantitative after 20 min. Then, the amount of **6** was reduced on 1.5 mol%, 1 mol%, and 0.5 mol%, successively (Table 1, entries 2, 3, and 4). Under these conditions, the reaction between **1a** and **2a** also smoothly took place, giving the same diastereomeric ratio (*trans*/*cis*, 70:30). However, 1 mol% of the Co(TMP) amount was determined to be optimal with regard to the reaction time (Table 1, entry 3). When the solvent was changed to THF, the reaction took more than one day, and did not go to completion even at 60 °C (Table 1, entry 5). Cobalt(III) tetramesitylporphyrin bromide (Co^{III}(TMP)Br) that was generated in situ by treating **6** with Br$_2$ (0.5 equiv. relative to **6**) before adding styrene and EDA to the reaction mixture was also tested as potential catalyst for cyclopropanation of styrene (**1a**) with EDA (**2a**). However, no conversion was detected in this case (Table 1, entry 6). ^{t}BDA (**2b**) was then used as carbene source. While the reaction of styrene (**1a**) with EDA (**2a**) in the presence of 1 mol% of Co(TMP) was proceeding very well giving the desired cyclopropanes in high yield, the reaction mixture of styrene (**1a**) and ^{t}BDA (**2b**) had to be heated up to 80 °C affording the corresponding cyclopropane products **3b** and **4b** in reasonable yield (85%) under the same conditions (Table 1, entries 3, 7, and 8). Changing the diazo ester from EDA to ^{t}BDA afforded higher diastereoselectivity, 70:30 vs. 90:10 *trans*:*cis* ratio, respectively, as expected (Table 1, entry 3 and 8). The effect of co-ligands was also investigated expecting to observe any co-ligand acceleration in the cyclopropanation of styrene (**1a**) with ^{t}BDA (**2b**) because of the somewhat slower reaction between **1a** and **2b**. For this purpose, 4-(dimethylamino)pyridine (DMAP) and *N*-methyl imidazole (NMI) were tested as coordinating co-ligand. However, in contrast to our expectations, an inhibition in the presence of NMI and a deceleration in the presence of DMAP of were observed (Table 1, entries 8, 9, and 10). After these screenings, the optimum conditions for the cyclopropanation of styrene were determined by using EDA and ^{t}BDA (Table 1, entries 3 and 8 respectively). Cyclopropanation of 1-octene and 1,2-dihydronaphthalene was also tried, by using 1 mol% **6** and EDA in toluene. However, no conversion was detected in both cases. These "negative" results are in line with the reactivity profiles for cobalt porphyrin-based radical carbenes in cyclopropanation observed previously: There has been no report on the cyclopropanation of aliphatic olefins and 1,2-dihydronaphthalene with EDA or ^{t}BDA, in the presence of Co(II) porphyrins.

Nonetheless, Zhang et al. demonstrated that 1-hexene could be cyclopropanated with α-nitrodiazoacetates, a special carbene source, in modest yield (43%) by using a bifunctional Co(II) porphyrin.[20] The inefficiency of Co(TMP) (**6**) in the cyclopropanation of 1-octene might be attributed to the stability of the cobalt porphyrin carbenes induced by the equilibrium between the "radical carbene" **II** and the "bridging carbene" **III** redox isomers. On the other hand, it can be expected that steric factors could prevent the cyclopropanation of 1,2-dihydronaphthalene. It is worthy to note that no dimerization by-products, i.e. maleate or fumarate esters, were detected during cyclopropanation of styrene with EDA and ^{t}BDA.

Table 1. Cyclopropanation of styrene (**1a**) with diazo esters **2a** and **2b** catalyzed by Co(TMP) (**6**).[a]



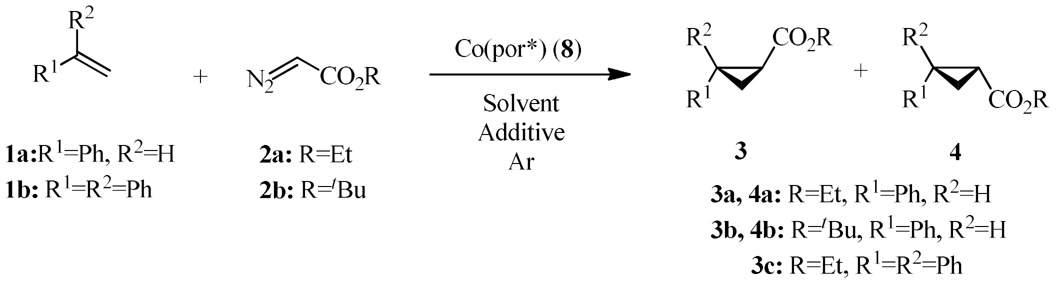
Entry	Co(TMP) (mol%)	**2**	Additive	*T* (°C)	Time (h)	Conversion (%)[b]	**3**:**4** *(trans/cis)*[c]
1	2.0	**2a**	–	rt	0.3	97	67:33
2	1.5	"	–	"	1.0	96	70:30
3	1.0	"	–	"	0.5	96	70:30
4	0.5	"	–	"	1.0	77	69:31
5[d]	1.0	"	–	60	20	87	72:28
6[e,f]	1.0	"	Br_2 (0.5%)	rt	44	6	–
7	1.0	**2b**	–	rt	24	<5	–
8	1.0	"	–	80	6	85	90:10
9	1.0	"	NMI (10%)	60	14	–	–
10	1.0	"	DMAP (10%)	60	24	30	87:13

[a] *Typical reaction conditions:* To the solution of styrene (315 μmol, 1.00 equiv) and **6** in dry toluene (0.4 mL) under Ar was added the diazo ester **2a** or **2b** via syringe at once. [b] Conversions of styrene (**1a**) to the product were determined by GC using 1,2-dibromobenzene as internal standard. [c] *trans*/*cis* ratios were determined by GC. [d] THF was used as the solvent. [e] DCM was used as the solvent. [f] This reaction was also run in the presence of 2 mol% MeOH to test $Co^{III}(TMP)(MeOH)_2Br$ as potential catalyst. However, no conversion was observed.

The asymmetric cyclopropanation using Co(por*) (**8**) was investigated next, under the optimized conditions determined with Co(TMP) (Table 2). A 76:24 *trans/cis* diastereomeric ratio and 77% *ee* (*trans*) and 22% *ee* (*cis*) for the cyclopropanation of styrene (**1a**) with EDA (**2a**) were observed (Table 2, entry 1). While the presence of NMI as co-ligand delivered significantly higher diastereomeric ratio in favor of the *trans*-diastereomer, and higher *ee* for the *cis*-diastereomer, but lower *ee* for the *trans*-diastereomer, the presence of MeOH as co-ligand afforded somewhat higher diastereomeric ratio in favor of *trans*-diastereomer and higher *ee* for *trans*-diastereomer but somewhat lower *ee* for *cis*-diastereomer (Table 2, entries 2 and 3) compared to no co-ligand (Table 2, entry 1). Thus, 87:13 *trans/cis* diastereomeric ratio, 65% *ee* for *trans*- (**3a**) and 43% *ee* for *cis*- diastereomer (**4a**) were observed with 95% total product yield in the presence of NMI (10 mol%). In the presence of MeOH (10 mol%), 80:20 *trans/cis* diastereomeric ratio, 82% *ee* for *trans*- (**3a**) and 19% *ee* for *cis*-diastereomer (**4a**) were attained with 96% total product yield within 1 h at room temperature. A 82:18 *trans/cis* diastereomeric ratio and 60% *ee* for *trans*-diastereomer (**3b**) and 32% *ee* for *cis*-diastereomer

(**4b**) were determined for the cyclopropanation products of styrene (**1a**) with ^{t}BDA (Table 2, entry 4). The diastereoselectivity and the enantioselectivity were slightly affected by the presence of MeOH (Table 2, entry 5). It is worthy to note that Co(TMP) furnished higher diastereoselectivity than Co(por*) in the cyclopropanation of styrene with ^{t}BDA, 90:10 and 82:18 *trans*/*cis* diastereomeric ratio, respectively (Table 1, entry 8 and Table 2, entry 4). The cyclopropanation of 1,1-diphenylethylene (**1b**) with EDA (**2a**) catalyzed by Co(por*) (**8**) gave the corresponding cyclopropane **3c** with moderate yield (62%) and enantiomeric excess (50% *ee*) (Table 2, entry 6). Previously, Ru(II) and Fe(III) complexes of the D_4-symmetric Halterman porphyrin were shown to catalyze asymmetric cyclopropanation of styrene derivatives with diazo esters.[14a-c,h,13b] While enantiomeric excesses that are herein presented with its Co(II) complex are comparable with those reported with its Fe(III) complex, they are lower than those achieved with its Ru(II) complex.

Table 2. Asymmetric cyclopropanation of olefins with diazo esters catalyzed by Co(por*) (**8**).[a]



Entry	1	2	Additive[b]	*T* (°C)	Time (h)	Yield (%)[c]	**3**:**4** (*trans*/*cis*)	*ee trans* (%)	*ee cis* (%)
1	**1a**	**2a**	–	rt	1	88	76:24[d]	77 (1*S*,2*S*)[e]	22 (1*R*,2*S*)[e]
2	**1a**	**2a**	NMI	rt	1	95	87:13	65 (1*S*,2*S*)	43 (1*R*,2*S*)
3	**1a**	**2a**	MeOH	rt	1	96	80:20	82 (1*S*,2*S*)	19 (1*R*,2*S*)
4[f]	**1a**	**2b**	–	70	6	85	82:18[g]	60 (1*S*,2*S*)[h,i]	32[h]
5	**1a**	**2b**	MeOH	70	3	87	83:17	61 (1*S*,2*S*)	32
6	**1b**	**2a**	MeOH	rt	5	62	–	50 (*S*)[j,i]	

[a] *Typical reaction conditions:* To the solution of olefin (315 μmol, 1.00 equiv) and **8** (1.0 mol%) in dry toluene (0.4 mL) under Ar was added the diazo ester **2a** or **2b** (1.20 equiv) via syringe at once. [b] 10 mol% of an additive was employed. [c] Isolated yield after column chromatography. [d] Determined by GC analysis by comparison with authentic sample and ^{1}H NMR spectroscopy. [e] Determined by GC analysis by using chiral column (WCOT-FS, CP Chirasil –Dex CB). The absolute configuration was determined by comparison with authentic sample. [f] 1.5 mol% of **8** was used. [g] Determined by ^{1}H NMR spectroscopy.[6d] [h] Determined by GC analysis by using chiral column (WCOT-FS, CP Chirasil –Dex CB). [i] The absolute configuration was determined by comparison of the sign of optical rotation using HPLC (Chiralcel OD-H) equipped with Chiralyser. [j] Enantiomeric excess was determined by HPLC analysis using chiral column (Chiralcel OJ).

4. Conclusion

In summary, the cobalt(II) complex (Co(por*)) of the Halterman porphyrin was synthesized and its single crystal X-ray analysis was provided. Diastereo- and enantioselective cyclopropanation of olefins with EDA and ^{t}BDA catalyzed by cobalt(II) porphyrins were revisited, and the effect of co-ligands was determined. While coordinating co-ligands, such as NMI and DMAP, were found to accelerate the cyclopropanation with EDA, they decelerated the cylopropanation with ^{t}BDA. However, the presence of MeOH affected positively the outcomes of the reactions in terms of diastereo- and enantioselectivity. In the presence of the chiral Co-porphyrin **8** as catalyst, high yields and stereoselectivities were achieved in the cyclopropanations investigated.

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie (Frankfurt, Germany).

References and Notes

[1] For the synthesis of biologically active compounds by cyclopropanation reactions, see: (a) Salaün, J. Optically active cyclopropanes. *Chem. Rev.* **1989**, *89*, 1247-1270. (b) Padwa, A.; Krumpe, K. E. Application of intramolecular carbenoid reactions in organic synthesis. *Tetrahedron* **1992**, *48*, 5385-5453. (c) Doyle, M. P.; Protopopova, M. N. New aspects of catalytic asymmetric cyclopropanation. *Tetrahedron* **1998**, *54*, 7919-7946. (d) Donaldson, W. A. Synthesis of cyclopropane containing natural products. *Tetrahedron* **2001**, *57*, 8589-8627. (e) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. Recent advances in the total synthesis of cyclopropane-containing natural products. *Chem. Soc. Rev.* **2012**, *41*, 4631-4642.

[2] In general, the uses of transition metal catalysts in catalytic asymmetric cyclopropanations, see: (a) Singh, V. K.; Gupta, A. D.; Sekar, G. Catalytic enantioselective cyclopropanation of olefins using carbenoid chemistry. *Synthesis* **1997**, 137-149. (b) Doyle, M. P.; Forbes, D. C. Recent advances in asymmetric catalytic metal carbene transformations. *Chem. Rev.* **1998**, *98*, 911-936. (c) Lebel, H.; Macoux, J.-F.; Molinaro, C.; Charette, A. B. Stereoselective cyclopropanation reactions. *Chem. Rev.* **2003**, *103*, 977-1050. (d) Pellissier, H. Recent developments in asymmetric cyclopropanation. *Tetrahedron* **2008**, *64*, 7041-7095.

[3] (a) Fritschi, H.; Leutenegger, U.; Pfaltz, A. Chiral copper-semicorrin complexes as enantioselective catalysts for the cyclopropanation of olefins by diazo compounds. *Angew. Chem. Int. Ed.* **1986**, *25*, 1005-1006. (b) Lo, M. M.-C.; Fu, G. C. A new class of planar-chiral ligands: Synthesis of a C_2-symmetric bisazaferrocene and its application in the enantioselective Cu(I)-catalyzed cyclopropanation of olefins. *J. Am. Chem. Soc.* **1998**, *120*, 10270-10271.

[4] (a) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. Dirhodium(II) tetrakis(carboxamidates) with chiral ligands. Structure and selectivity in catalytic metal-carbene transformations. *J. Am. Chem. Soc.* **1993**, *115*, 9968-9978. (b) Davies, H. M. L.; Venkataramani, C. Dirhodium tetraprolinate-catalyzed asymmetric cyclopropanations with high turnover numbers. *Org. Lett.* **2003**, *5*, 1403-1406. (c) Marcoux, D.; Azzi, S.; Charette, A. B. $TfNH_2$ as achiral hydrogen-bond donor additive to enhance the selectivity of a transition metal catalyzed reaction. Highly enantio- and diastereoselective rhodium-catalyzed cyclopropanation of alkenes using α-cyano diazoacetamide. *J. Am. Chem. Soc.* **2009**, *131*, 6970-6972.

[5] (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. New chiral ruthenium bis(oxazolinyl)pyridine catalyst. Efficient asymmetric cyclopropanation of olefins with diazoacetates. *J. Am. Chem. Soc.* **1994**, *116*, 2223-2224. (b) Chanthamath, S.; Iwasa, S. Enantioselective cyclopropanation of a wide variety of olefins catalyzed by Ru(II)–Pheox complexes. *Acc. Chem. Res.* **2016**, *49*, 2080-2090.

[6] For cobalt-Schiff base-catalyzed asymmetric cyclopropanation, see: (a) Fukuda, T.; Katsuki, T. Co(III)-salen catalyzed asymmetric cyclopropanation. *Synlett* **1995**, 825-826. (b) Fukuda, T.; Katsuki, T. Highly enantioselective cyclopropanation of styrene derivatives using Co(III)-salen complex as a catalyst. *Tetrahedron* **1997**, *53*, 7201-7208. (c) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. Co(II)–salen-catalyzed highly *cis*- and enantioselective cyclopropanation. *Tetrahedron Lett.* **2000**, *41*, 3647-3651. (d) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. Highly enantioselective cyclopropanation with Co(II)-salen complexes: Control of *cis*- and *trans*-selectivity by rational ligand-design. *Adv. Synth. Catal.* **2001**, *343*, 79-88. (e) Iwakura, I.; Ikeno, T.; Yamada, T. Proposal for the metallacycle pathway during the cyclopropanation catalyzed by cobalt−Schiff base complexes. *Org. Lett.* **2004**, *6*, 949-952. (f) Uchida, T.; Katsuki, T. α-Diazoacetates as carbene precursors: metallosalen-catalyzed asymmetric cyclopropanation. *Synthesis* **2006**, 1715-1723. (g) Shitama, H.; Katsuki, T. Synthesis of metal–(pentadentate-salen) complexes: Asymmetric epoxidation with aqueous hydrogen peroxide and asymmetric cyclopropanation (salenH_2: *N,N'*-bis(salicylidene)ethylene-1,2-diamine). *Chem. Eur. J.* **2007**, *13*, 4849-4858. (h) Morandi, B.; Mariampillai, B.; Carreira, E. M. Enantioselective cobalt-catalyzed preparation of trifluoromethyl-substituted cyclopropanes. *Angew. Chem. Int. Ed.* **2011**, *50*, 1101-1104. (i) White, J. D.; Shaw, S. A new

cobalt–salen catalyst for asymmetric cyclopropanation. Synthesis of the serotonin–norepinephrine re-uptake inhibitor (+)-synosutine. *Org. Lett.* **2014**, *16*, 3880-3883.

[7] For 3-oxobutylideneaminocobalt-catalyzed asymmetric cyclopropanation, see: (a) Ikeno, T.; Sato, M.; Yamada, T. Highly enantioselective cyclopropanation of styrenes with diazoacetates catalyzed by optically active *β*-ketoiminato cobalt(II) complexes. *Chem. Lett.* **1999**, 1345-1346. (b) Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. Highly enantioselective cyclopropanation in alcoholic and aqueous solvents catalyzed by optically active *β*-ketoiminato cobalt(II) complex. *Synlett* **2001**, 406-408. (c) Ikeno, T.; Iwakura, I.; Yamada, T. Cobalt−carbene complex with single-bond character: Intermediate for the cobalt complex-catalyzed cyclopropanation. *J. Am. Chem. Soc.* **2002**, *124*, 15152-15153.

[8] Callot, H. J.; Piechocki, C. Cyclopropanation using rhodium (III) porphyrins: Large *cis* vs *trans* selectivity. *Tetrahedron Lett.* **1980**, *21*, 3489-3492.

[9] (a) O'Malley, S.; Kodadek, T. Asymmetric cyclopropanation of alkenes catalyzed by a "chiral wall" prophyrin. *Tetrahedron Lett.* **1991**, *32*, 2445-2448. (b) Maxwell, J. L.; O'Malley, S.; Brown, K. C.; Kodadek, T. Shape-selective and asymmetric cyclopropanation of alkenes catalyzed by rhodium porphyrins. *Organometallics* **1992**, *11*, 645-652. (c) O'Malley, S.; Kodadek, T. Asymmetric cyclopropanation of alkenes catalyzed by a rhodium chiral fortress porphyrin. *Organometallics* **1992**, *11*, 2299-2302.

[10] For Ir(III) porphyrin-catalyzed cyclopropanation, see: Anding, B. J.; Ellern, A.; Woo, L. K. Olefin cyclopropanation catalyzed by iridium(III) porphyrin complexes. *Organometallics* **2012**, *31*, 3628-3635.

[11] For Os(III) porphyrin-catalyzed cyclopropanation, see: Che, C.-H.; Huang, J.-S. Ruthenium and osmium porphyrin carbene complexes: Synthesis, structure, and connection to the metal-mediated cyclopropanation of alkenes. *Coord. Chem. Rev.* **2002**, *231*, 151-164.

[12] For Fe(II) porphyrin-catalyzed non-asymmetric cyclopropanation, see: (a) Hamaker, C. G.; Mirafzal, G. A.; Woo, L. K. Catalytic cyclopropanation with iron(II) complexes. *Organometallics* **2001**, *20*, 5171-5176. (b) Morandi, B.; Carreira, E. M. Iron-catalyzed cyclopropanation with trifluoroethylamine hydrochloride and olefins in aqueous media: In situ generation of trifluoromethyl diazomethan. *Angew. Chem. Int. Ed.* **2010**, *49*, 938-941.

[13] For enantioselective cyclopropanation catalyzed by chiral Fe(II) porphyrins, see: (a) Du, G.; Andrioletti, B.; Rose, E.; Woo, L. K. Asymmetric cyclopropanation of styrene catalyzed by chiral macrocyclic iron(II) complexes. *Organometallics* **2002**, *21*, 4490-4495. (b) Lai, T.-S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. Alkene cyclopropanation catalyzed by Halterman iron porphyrin: Participation of organic bases as axial ligands. *Dalton Trans.* **2006**, 4845-4851. (c) Intrieri, D.; Le Gac, S.; Caselli, A.; Rose, E.; Boitrel, B.; Gallo, E. Highly diastereoselective cyclopropanation of α-methylstyrene catalysed by a C_2-symmetrical chiral iron porphyrin complex. *Chem. Commun.* **2014**, *50*, 1811-1813. (d) Rioz-Martínez, A.; Oelerich, J.; Ségaud, N.; Roelfes, G. DNA-accelerated catalysis of carbene-transfer reactions by a DNA/cationic iron porphyrin hybrid. *Angew. Chem. Int. Ed.* **2016**, *55*, 14136-14140.

[14] For Ru(II) porphyrin-catalyzed cyclopropanation of olefins, see: (a) Galardon, E.; Le Maux, P.; Simonneaux, G. Cyclopropanation of alkenes with ethyl diazoacetate catalysed by ruthenium porphyrin complexes. *Chem. Commun.* **1997**, 927-928. (b) Lo, W.-C.; Che, C.-M.; Cheng, K.-F.; Mak, T. C. W. Catalytic and asymmetric cyclopropanation of styrenes catalysed by ruthenium porphyrin and porphycene complexes. *Chem.Commun.* **1997**, 1205-1206. (c) Frauenkron, M.; Berkessel, A. A novel chiral ruthenium porphyrin as highly efficient and selective catalyst for asymmetric cyclopropanations. *Tetrahedron Lett.* **1997**, *38*, 7175-7176. (d) Galardon, E.; Roué, S.; Le Maux, P.; Simonneaux, G. Asymmetric cyclopropanation of alkenes and diazocarbonyl insertion into S-H bonds catalyzed by a chiral porphyrin Ru(II) complex. *Tetrahedron Lett.* **1998**, *39*, 2333-2334. (e) Gross, Z.; Galili, N.; Simkhovich, L. Metalloporphyrin catalyzed asymmetric cyclopropanation of olefins. *Tetrahedron Lett.* **1999**, *40*, 1571-1574. (f) Che, C.-M. ; Huang, J.-S.; Lee, F.-W.; Lai, T.-S.; Kwong, H.-L.; Teng, P.-F.; Lee, W.-S.; Lo, W.-C.; Zhou, Z.-Y. Asymmetric inter- and intramolecular cyclopropanation of alkenes catalyzed by chiral ruthenium porphyrins. Synthesis and crystal structure of a chiral metalloporphyrin carbene complex. *J. Am. Chem. Soc.* **2001**, *123*, 4119-4129. (g) Simonneaux, G.; Le Maux, P. Optically active ruthenium porphyrins: Chiral recognition and asymmetric catalysis. *Coor. Chem. Rev.* **2002**, *228*, 43-60. (h) Berkessel, A.; Kaiser, P.; Lex, J. Electronically tuned chiral ruthenium porphyrins: Extremely stable and selective catalysts for asymmetric epoxidation and cyclopropanation. *Chem. Eur. J.* **2003**, *9*, 4746-4756. (i) Ferrand, Y.; Le Maux, P.; Simonneaux, G. Highly enantioselective synthesis of cyclopropylphosphonates catalyzed by chiral ruthenium porphyrins. *Org. Lett.* **2004**, *6*, 3211-3214. (j)

Zhou, C.-Y.; Huang, J.-S.; Che, C.-M. Ruthenium-porphyrin-catalyzed carbenoid transfer reactions. *Synlett* **2010**, 2681-2700.

[15] For stoichiometric reactions of ethyl diazoacetate with cobalt(II) porphyrin complexes, see: (a) Johnson, A. W.; Ward, D.; Batten, P.; Hamilton, A. L.; Shelton, G.; Elson, C. M. Condensation of ethyl diazoacetate with cobalt porphyrins. *J. Chem. Soc., Perkin Trans.1* **1975**, 2076-2085. (b) Penoni, A.; Wanke, R.; Tollari, S.; Gallo, E.; Musella, D.; Ragaini, F.; Demartin, F.; Cenini, S. Cyclopropanation of olefins with diazoalkanes, catalyzed by Co^{II}(porphyrin) complexes − A synthetic and mechanistic investigation and the molecular structure of $Co^{III}(TPP)(CH_2CO_2Et)$ (TPP = dianion of *meso*-tetraphenylporphyrin). *Eur. J. Inorg. Chem.* **2003**, 1452-1460. (c) Iwakura, I.; Tanaka, H.; Ikeno, T.; Yamada, T. FT-IR and theoretical analysis of the characteristic bonding properties in the multiplet metal porphyrin carbene complexes. *Chem. Lett.* **2004**, *33*, 140-141.

[16] Asymmetric cyclopropanation of olefins with diazo esters catalyzed by cobalt(II) porphyrins, see: (a) Huang, L.; Chen, Y.; Gao, G.-Y.; Zhang, X. P. Diastereoselective and enantioselective cyclopropanation of alkenes catalyzed by cobalt porphyrins. *J. Org. Chem.* **2003**, *68*, 8179-8184. (b) Chen, Y.; Zhang, X. P. Vitamin B_{12} derivatives as natural asymmetric catalysts: Enantioselective cyclopropanation of alkenes. *J. Org. Chem.* **2004**, *69*, 2431-2435. (c) Chen, Y.; Fields, K. B.; Zhang, X. P. Bromoporphyrins as versatile synthons for modular construction of chiral porphyrins: Cobalt-catalyzed highly enantioselective and diastereoselective cyclopropanation. *J. Am. Chem. Soc.* **2004**, *126*, 14718-14719. (d) Chen, Y.; Gao, G.-Y.; Zhang, X. P. Palladium-mediated synthesis of novel *meso*-chiral porphyrins: Cobalt-catalyzed cyclopropanation. *Tetrahedron Lett.* **2005**, *46*, 4965-4969. (e) Chen, Y.; Ruppel, J. V.; Zhang, X. P. Cobalt-catalyzed asymmetric cyclopropanation of electron-deficient olefins. *J. Am. Chem. Soc.* **2007**, *129*, 12074-12075. (f) Fantauzzi, S.; Gallo, E.; Rose, E.; Raoul, N.; Caselli, A.; Issa, S.; Ragaini, F.; Cenini, S. Asymmetric cyclopropanation of olefins catalyzed by chiral cobalt(II)-binaphthyl porphyrins. *Organometallics* **2008**, *27*, 6143-6151. (g) Fields, K. B.; Engle, J. T.; Sripothongnak, S.; Kim, C.; Zhang, X. P.; Ziegler, C. J. Cobalt carbaporphyrin-catalyzed cyclopropanation. *Chem. Commun.* **2011**, *47*, 749-751. (h) Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; de Mesa, S. L.; Wojtas, L.; Zhang, X. P. Highly asymmetric intramolecular cyclopropanation of acceptor-substituted diazoacetates by Co(II)-based metalloradical catalysis: Iterative approach for development of new-generation catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 15292-15295. (i) Xu, X.; Zhu, S.; Cui, X.; Wojtas, L.; Zhang, X. P. Cobalt(II)-catalyzed asymmetric olefin cyclopropanation with α-ketodiazoacetates. *Angew. Chem. Int. Ed.* **2013**, *52*, 11857-11861.

[17] Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. 'Carbene radicals' in Co^{II}(por)-catalyzed olefin cyclopropanation. *J. Am. Chem. Soc.* **2010**, *132*, 10891-10902.

[18] (a) Intrieri, D.; Caselli, A.; Gallo, E. Cyclopropanation reactions mediated by group 9 metal porphyrin complexes. *Eur. J. Inorg. Chem.* **2011**, 5071-5081. (b) Intrieri, D.; Maria, D. M.; Gallo, E. The ligand influence in stereoselective carbene transfer reactions promoted by chiral metal porphyrin catalysts. *Dalton Trans.* **2016**, *45*, 15746-15761.

[19] Zhu, S.; Ruppel, J. V.; Lu, H.; Wojtas, L.; Zhang, X. P. Cobalt-catalyzed asymmetric cyclopropanation with diazosulfones: Rigidification and polarization of ligand chiral environment via hydrogen bonding and cyclization. *J. Am. Chem. Soc.* **2008**, *130*, 5042-5043.

[20] Zhu, S.; Perman, J. A.; Zhang, X. P. Acceptor/acceptor-substituted diazo reagents for carbene transfers: Cobalt-catalyzed asymmetric *Z*-cyclopropanation of alkenes with α-nitrodiazoacetates. *Angew. Chem. Int. Ed.* **2008**, *47*, 8460-8463.

[21] Ruppel, J. V.; Gauthier, T. J.; Snyder, N. L.; Perman, J. A.; Zhang X. P. Asymmetric Co(II)-catalyzed cyclopropanation with succinimidyl diazoacetate: General synthesis of chiral cyclopropyl carboxamides. *Org. Lett.* **2009**, *11*, 2273-2276.

[22] Zhu, S.; Xu, X.; Perman, J. A.; Zhang, X. P. A general and efficient cobalt(II)-based catalytic system for highly stereoselective cyclopropanation of alkenes with α-cyanodiazoacetates. *J. Am. Chem. Soc.* **2010**, *132*, 12796-12799.

[23] Cui, X.; Xu, X.; Lu, H.; Zhu, S. Wojtas, L.; Zhang, X. P. Enantioselective cyclopropenation of alkynes with acceptor/acceptor-substituted diazo reagents via Co(II)-based metalloradical catalysis. *J. Am. Chem. Soc.* **2011**, *133*, 3304-3307.

[24] (a) Berkessel, A.; Frauenkron, M. Catalytic asymmetric epoxidation with a chiral ruthenium porphyrin and N-oxides *J. Chem. Soc., Perkin Trans. 1* **1997**, 2265-2266. (b) Berkessel, A.; Ertürk, E.; Laporte, C. Chiral chromium(III) porphyrins as highly enantioselective catalysts for hetero-Diels–Alder reactions

between aldehydes and dienes. *Adv. Synth. Catal* **2006**, *348*, 223-228. (c) Berkessel, A.; Ertürk, E.; Kaiser, P.; Klein, A.; Kowalczyk, R. M.; Sarkar, B. On the redox states of ruthenium porphyrin oxidation catalysts. *Dalton Trans.* **2007**, 3427-3434.

[25] Li, F.; Yang, K.; Tyhonas, J. S.; MacCrum, K. A.; Lindsey, J. S. Beneficial effects of salts on an acid-catalyzed condensation leading to porphyrin formation. *Tetrahedron* **1997**, *53*, 12339-12360.

[26] Polam, J. R.; Shokhireva, T. Kh.; Raffii, K.; Simonis, U.; Walker, F. A. Rates of axial ligand rotation in diamagnetic d^6 Co(III) and Fe(II) porphyrinates. *Inorg. Chim. Acta* **1997**, *263*, 109-117.

[27] (a) Halterman, R. L.; Jan, S.-T. Catalytic asymmetric epoxidation of unfunctionalized alkenes using the first D4-symmetric metallotetraphenylporphyrin. *J. Org. Chem.* **1991**, *56*, 5253-5254. (b) Halterman, R. L.; Jan, S.-T.; Nimmons, H. L.; Standlee, D. J.; Khan, M. A. Synthesis and catalytic reactivity of D4-symmetric dinorbornabenzene-derived metallotetraarylporphyrins. *Tetrahedron* **1997**, *53*, 11257-11276.

[28] Searle, N. E. Ethyl diazoacetate. *Org. Synth.* **1956**, *36*, 25-27.

A C G
publications