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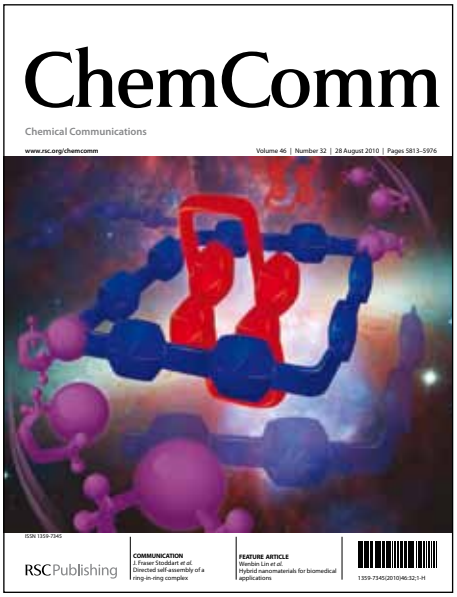


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# Highly diastereoselective cyclopropanation of α-methylstyrene catalysed by a $C_2$-symmetrical chiral iron porphyrin complex

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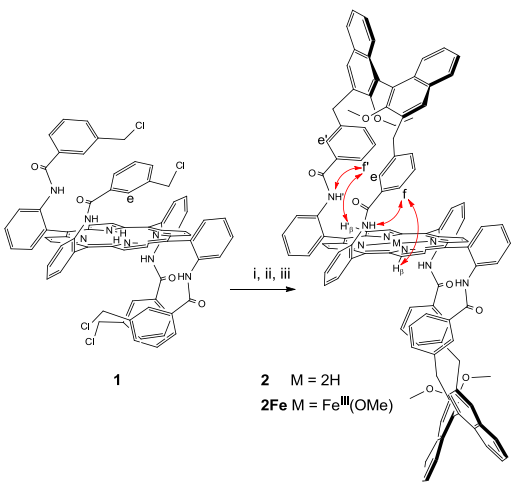
**A new chiral iron porphyrin-based catalyst performed α-methylstyrene stereoselective cyclopropanation with excellent yields (up to 99%), enantio- and diasteroselectivities ($ee_{trans}$ up to 87%, *trans/cis* ratios up to 99:1) and outstanding TON and TOF values (up to 20,000 and 120,000/h respectively).**

Compounds containing cyclopropane units play a crucial role in both synthetic and pharmaceutical chemistry due to high reactivity[1] and biological properties[2,3] of the three-membered ring. Consequently, the interest of the research community in developing new methodologies to synthesise cyclopropanes is strongly increasing.[4-6] Amongst the synthetic procedures available, the one-pot reaction of diazo compounds with olefins is a sustainable and atom-efficient strategy[7,8] due to the formation of $N_2$ as the only stoichiometric by-product.

Catalytic enantio- and diasteroselective olefin cyclopropanations[9-13] have been extensively explored and metal porphyrin complexes represent a very active and stereoselective class of catalysts.[14,15] Ruthenium,[16-18] osmium,[19,20] rhodium[21,22] and iridium[23] porphyrins show an excellent efficiency but their cost and toxicity prompted the scientific community to investigate the activity of the more eco-friendly first row transition metal porphyrin complexes, such as cobalt[15,24-26] and iron[27-29] derivatives. Iron porphyrins were employed for the first time in 1999[30] and since then their use in catalysis remains a challenge.

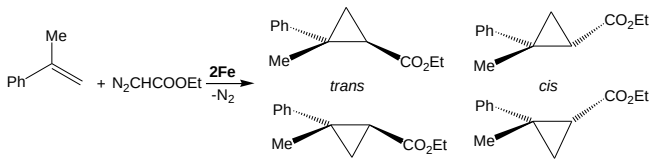
Some years ago we reported on the catalytic efficiency of chiral cobalt(II)-binaphthyl porphyrins in asymmetric cyclopropanations,[31] and recorded positive data encouraging us to synthesise the structurally related chiral porphyrin **2** (Scheme 1). Porphyrin **2** was obtained in one single Suzuki coupling step from previously reported porphyrin **1**[32] (35%) and fully characterised (see SI for the synthetic procedure and analytical data). Considering the structure of **1**, we assumed that a chiral moiety strapped on it would overhang above the coordination site[33,34] to induce a reaction stereoselectivity. Porphyrin **2** has one $C_2$ axis within the porphyrin plane and exhibits an open space on each side for substrate access and at the same time a steric chiral bulk surrounding the N-core. Furthermore, X-ray data of related ligands based on the same type of pickets indicate pre-organised yet flexible structures.[35,36] The $^1$H NMR analysis of **2** in $CDCl_3$ (see SI) revealed a well resolved spectrum with sharp signals for most protons indicating this pre-organisation. For instance, the eight benzylic protons appear as two AB systems between 3.5 and 4 ppm. The observed pattern for the β-pyrrolic protons composed of two typical doublets ($J$ = 4.7 Hz) and two singlets confirms the proposed symmetry in solution. In **2**, conversely to its diethylmalonate counterpart in which both pickets are bound on one carbon atom,[32] the quite large binap linker (*c.a.* 7.4 Å) was expected to reject the two pickets outside of the cavity. This outwards orientation of the pickets in **2** is reflected in the chemical shifts of the four protons $H_{e/e'}$ which resonate as two singlets at 7.19 and 7.32 ppm, where they appear at 6.19 ppm in **1** and 4.84 ppm in its diethylmalonate analogue. The proposed conformation of the straps drawn in Scheme 1 is deduced from the observed nuclear Overhauser effects between $H_f$ and both the amide protons and $H_\beta$ (SI).




**Scheme 1** Synthesis of $C_2$-symmetrical binap-*bis*-strapped porphyrin **2** and its iron(III) complex **2Fe**; i) (*R*)-(2,2'-dimethoxy-[1,1'-binaphthal-ene]-3,3'-diyl)diboronic acid, $(Ph_3P)_4Pd$, $K_2CO_3$ (35%); ii) $FeBr_2$/THF, reflux

overnight; iii) chromatographic purification using $CH_2Cl_2/CH_3OH$ as the eluent mixture (quantitative yield). Red arrows for significant NOE cross peaks in **2**.

Finally, the two signals from the binap methoxy groups (2.42 and 1.89 ppm) experience a shielding of 1.44 and 0.91 ppm relatively to 2,2'-dimethyl-3,3'-dimethyl-1,1'-binaphthalene as a reference, indicating that they are neither strongly differentiated nor very close to the porphyrin, but above the macrocycle as depicted in Scheme 1.
The reaction of **2** with $FeBr_2$ afforded **2Fe** (**Fe** = $Fe^{III}$(OMe)) by the initial formation of the iron (II) porphyrin complex which was oxidised by the atmospheric oxygen in the presence of $CH_3OH$ yielding the desired complex in a quantitative yield.[37,38] Complex **2Fe** was characterised by elemental analysis, $[\alpha]_D$,[20] IR, UV-Vis spectroscopies. The high resolution MS-ESI analysis revealed the presence of the methoxy ligand while the ESR spectroscopy confirmed the oxidation state of the iron (III) centre (S = 5/2) (see SI for details). The catalytic activity of **2Fe** was initially tested in the model reaction of α-methylstyrene with ethyl diazoacetate (EDA) (Scheme 2).




**Scheme 2** Cyclopropanation of α-methylstyrene by EDA

In order to optimise the experimental conditions we started screening several reaction solvents by using 1% of catalyst. As reported in Table 1, we have always obtained excellent *trans*-diasteroselectivities (94-99%) with the exception of DCM (Table 1, entry 3) in which no reaction was observed.

**Table 1**. Reaction solvent screening of the α-methylstyrene cyclopropanation by EDA[a]

| entry | T(°C) | solvent | *t*(min)[b] | yield(%)[c] | *trans/cis*[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|
| 1 | 25 | benzene | 5 | 87 | 96:4 | 72 |
| 2 | 25 | toluene | 5 | 85 | 99:1 | 75 |
| 3 | 25 | DCM | - | - | - | - |
| 4 | 25 | hexane | 120 | 70 | 94:6 | 40 |
| 5 | 0° | toluene | 5 | 89 | 99:1 | 75 |

[a]**2Fe**/EDA/α-methylstyrene = 1:100:250 (5.0 mg, $2.70x10^{-6}$mol of the catalyst in 5.0 mL of the desired solvent). [b]Time required for the complete EDA conversion monitored by IR spectroscopy. [c]Yields based on EDA and determined by $^1$H NMR (2,4-dinitrotoluene as the internal standard). [d]Enantiomeric excess of the *trans*(*R,R*) major diastereomer determined by HPLC analysis using a chiral column (DAI-CEL CHIRALCEL, IB, hexane/$^i$PrOH = 99.75:0.25).

A much lower *ee* value was obtained by using hexane as a solvent (Table 1, entry 4) whilst for toluene and benzene comparable results (Table 1, entries 1 and 2) were obtained. Surprisingly, we did not register any improvement in enantioselectivity by decreasing the temperature from room temperature to 0°C (compare entries 2 and 5, Table 1). Collected data suggested toluene as the best reaction solvent, thus it was employed to further optimise the catalytic conditions. Firstly, we performed the reaction without an olefin excess which is usually required to avoid the formation of side-products due to decomposition of the diazo compound. The use of an equimolar EDA/olefin ratio is of particular importance when expensive olefins are the substrates. Cyclopropanes were obtained in good yields also using a very low catalytic loading of 0.01% (Table 2, entries 3-8) and the catalytic efficiency was not improved by the slow addition of EDA to the reaction mixture (Table 1, entry 5 *vs* 4). Fumarate and maleate accounted for the rest of the mass balance according to NMR analyses.

**Table 2**. Optimisation of the catalyst loading and reaction temperature.

| entry | % cat. | T(°C) | *t* (min)[a] | yield (%)[b] | *trans/cis*[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| 1[d] | 1 | 25 | 5 | 75 | 99:1 | 73 |
| 2[e] | 0.1 | 25 | 5 | 75 | 97:3 | 68 |
| 3[e] | 0.01 | 25 | 5 | 72 | 94:6 | 58 |
| 4[e] | 0.01 | 0° | 5 | >99 | 98:2 | 78 |
| 5[f] | 0.01 | 0° | 36 | 83 | 99:1 | 74 |
| 6[e] | 0.01 | -15° | 420 | 72 | 99:1 | 79 |
| 7[e] | 0.01 | -20° | 540 | 70 | >99:1 | 79 |
| 8[e] | 0.01 | -78° | 600 | 70 | >99:1 | 87 |
| 9[e] | 0.005 | 25 | 480 | 55 | 95:5 | 57 |

[a]Time required for the complete EDA conversion monitored by IR spectroscopy. [b]Yields based on EDA and determined by $^1$H-NMR (2,4-dinitrotoluene as the internal standard). [c]Enantiomeric excess of the *trans*(*R,R*) major diastereomer determined by HPLC analysis using a chiral column (DAI-CEL CHIRALCEL, IB, hexane/$^i$PrOH = 99.75:0.25). [d]**2Fe** (5.0 mg, $2.70x10^{-6}$mol) was dissolved into 5.0 mL of toluene with an equimolar α-methylstyrene/EDA ratio. [e]145.0 μL of a **2Fe** toluene solution ($3.72x10^{-3}$ mol/L) was added to 2.0 mL of an equimolar α-methylstyrene/EDA toluene solution. [f]EDA was added dropwise by a syringe pump.

It should be noted that a catalyst loading of 0.005 % (TON of $2x10^4$, Table 2, entry 9) is one of the lowest observed for cyclopropanations[39,40] and to the best of our knowledge, leads to the highest reported TON for metallo porphyrin-based catalysts. To achieve the best catalyst loading/reaction time relationship, 0.01% of **2Fe** was employed to better investigate the effect of the temperature on the enantioselectivity. The best value of 87% *ee* was obtained at -78°C but unfortunately the reaction time greatly increased (Table 2, entry 8). Conversely, when the reaction was run at 0 °C very good diastero- and enantioselectivity (*trans*/*cis* = 98:2, $ee_{trans}$ = 78%) were observed with a complete EDA conversion in only 5 minutes (Table 2, entry 4). To our delight the consequent TOF of 120,000/h has never been reported for porphyrin-mediated cyclopropanations and it can be the starting point for an industrial application of this methodology.
In order to test the catalyst robustness, a reaction with 0.1% of **2Fe** (6.0 mg) was run at 0 °C by using 0.340 mL of EDA (3.24 mmol) and 0.421 mL of α-methylstyrene (3.24 mmol) in 17 mL of toluene. After complete EDA consumption, EDA and α-methystyrene were added again to the catalytic mixture for two more consecutive times (see SI for details). The three runs were completed in 5, 10 and then 10 minutes respectively. The NMR analyses of the crude at the end of the third run revealed 90% of global yield, 98% of *trans*-diastereoselectivity with 75% of $ee_{trans}$.
Considering that EDA is known to be a mild reducing agent[41] and it is important to avoid any oxidative degradation, we performed the cyclopropanation of α-methylstyrene with a catalyst/olefin/EDA ratio of 1:1000:1100.[42] The improvement of the reaction yield (from 75% to 85%) indicated a positive catalytic effect of the EDA excess.
Data collected up to now indicated that the best catalytic results were obtained in toluene at 0 °C with 0.01% of a catalyst loading and by

using a slight EDA excess. We are currently employing the optimised catalytic conditions to study the scope of the reaction.

In conclusion we have reported the synthesis of the new chiral porphyrin **2** and its iron (III) complex **2Fe** which promotes the cyclopropanation of α-methylstyrene by EDA with excellent *trans* diasteroselectivities (94-99%), and good enantioselectivities ($ee_{trans}$ up to 87%). To the best of our knowledge, the outstanding values of TON and TOF (20,000 and 120,000/h respectively) have never been reported for metallo-porphyrin catalysed cyclopropanations and the robustness of the catalyst under an inert atmosphere allowed three catalytic recycles. Finally, high cyclopropane yields were obtained without using an olefin excess in accordance with the industrial request for sustainable processes, especially when expensive olefins are involved. Studies are ongoing to expand the reaction scope, including testing the cyclopropanation of several olefins by differently substituted diazo derivatives.

## Notes and references

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42. 0.143 mL of a **2Fe** toluene solution ($3.81x10^{-3}$ mol/L) was added to 2.0 mL of a toluene solution containing α-methylstyrene/EDA = 1000:1100. The reaction was run at RT for 5 minutes. Then the $^1$H NMR analysis revealed 85% yield, a *trans*/*cis* ratio = 98:2 and an *ee* (*trans* isomer) = 70%.