New catalysts for the epoxidation of olefins

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Abstract

New catalysts for the epoxidation of olefins

This thesis describes the development of inexpensive and practical iron catalysts for the environmentally benign epoxidation of olefins with hydrogen peroxide as terminal oxidant. Investigations on ruthenium complexes derived from *N,N,N*-tridentate ligands together with the co-ligand pyridine-2,6-dicarboxylic acid (H_2pydic) showed high catalytic activity in the epoxidation of various olefins. In order to develop an improved, environmentally benign and more economical procedure, these ruthenium catalysts were replaced by iron catalytic systems. By systematic variation of ligands, metal sources and reaction conditions, it was discovered that $FeCl_3 \cdot 6H_2O$ in combination with H_2pydic and various amines as bases and co-ligands shows high reactivity and good to excellent selectivity towards epoxidation of aromatic and aliphatic olefins. Excellent results were achieved in asymmetric epoxidation by the use of chiral diphenylethylene diamine derivatives.

Die vorliegende Dissertation beschäftigt sich mit der Entwicklung von kostengünstigen und praktischen Eisenkatalysatoren für die umweltfreundliche Epoxidation von Olefinen mithilfe von Wasserstoffperoxid als Oxidationsmittel. Bei Untersuchungen zu Rutheniumkomplexen mit *N,N,N*-tridentaten Liganden und Pyridin-2,6-dicarbonsäure (H_2pydic) als Coliganden wurde hohe katalytische Aktivität für die Epoxidation von verschiedenartigen Olefinen gefunden. Für die Entwicklung eines verbesserten, umweltfreundlicheren und ökonomischeren Verfahrens konnten diese Rutheniumkatalysatoren durch katalytische Eisen-Systeme ersetzt werden. Durch systematische Änderung der Liganden, Metallquellen und Reaktionsbedingungen wurde festgestellt, dass $FeCl_3 \cdot 6H_2O$ in Kombination mit H_2pydic und verschiedenen Aminen als Basen und Coliganden hohe Aktivität und exzellente Selektivität gegenüber der Epoxidation von aromatischen und aliphatischen Olefinen zeigt. Des Weiteren führte der Einsatz von chiralen Diphenylethylendiamin-Derivaten zu sehr guten Ergebnisse bei der asymmetrischen Epoxidation.

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Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
BPMCN	(*R,R*)-*N,N'*-bis-(2-pyridylmethyl)-*N,N'*-dimethyl-1,2-cyclohexane diamine
CD	circular dichroism
conv.	conversion
DFT	density functional theory
ee	enantiomeric excess
equiv.	equivalents
GC	gas chromatography
HPLC	high pressure liquid chromatography
L	ligand
m	meta
Me	methyl
MMO	methane monooxygenase
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
pybim	pyridine-2,6-bisimidazoline
pybox	pyridine-2,6-bisoxazoline
pyboxazin	pyridine-2,6-bisoxazine
pydic	pyridine-2,6-dicarboxylic acid
r.t.	room temperature
Ref.	reference
selec.	selectivity
temp.	temperature
tert	tertiary
TLC	thin layer chromatography
TON	turnover number
Ts	Tosyl, *p*-toluenesulfonyl

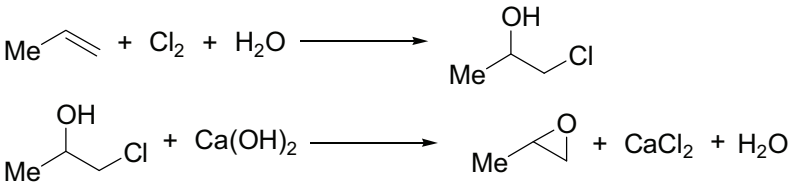
1. Introduction

Oxidation of olefins to obtain value-added products is of major importance in the chemical industry.[1] Among the various oxidation methods, epoxidation of olefins continues to be an interesting field of research in industry and academia. The formation of two C-O bonds in one reaction and the facile ring opening reactions make epoxides versatile building blocks for materials, bulk and fine chemicals as well as for agrochemicals and pharmaceuticals.[2] Despite all advancements in catalytic oxidations, epoxides are still often synthesized by stoichiometric reaction of olefins with peroxoacids generated from hydrogen peroxide and acids or acid derivatives.[3] A drawback of this convenient method is the limited use for acid labile olefins or epoxides and the generation of significant amounts of waste (salts). Obviously, in the context of more sustainable production processes reduction of waste by-products is highly desired.

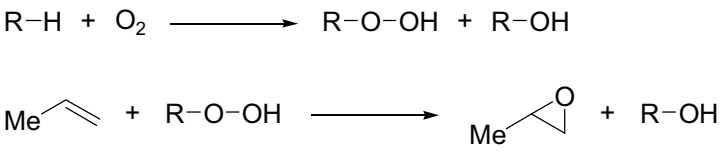
Among the different epoxides the industrially most important examples with respect to scale are ethylene oxide and propylene oxide. For example nowadays, approximately seven million tons of propylene oxide are produced annually and the demands grow steadily.[4] Three major routes are being used for this simple epoxide manufacturing: chlorohydrin process, propylene oxide/styrene monomer process and propylene oxide/*tert*-butyl alcohol process (Scheme 1). These processes produce various by-products and must be incorporated into other downstream treatment or production plants. These by-products can also be useful, such as *tert*-butanol and styrene and the price of the epoxide is often constricted when the by-product is over produced. With respect to environmental and economical considerations, the applied oxidant hence determines the value of the system to a significant extent.[5] It is apparent that molecular oxygen is the ideal oxidant for this transformation.[6] However, mostly only one oxygen atom of molecular oxygen is used productively for oxidation (50 % atom efficiency),[7] thus typically stoichiometric amounts of by-products is generated during the reactions. In spite of this, development of catalysts for the direct epoxidation of propylene using molecular oxygen with hydrogen as the co-reductant is still one of the “Holy Grail” reactions in this field.

Apart from molecular oxygen, hydrogen peroxide, H_2O_2, is an environmentally benign oxidant, which generates theoretically only water as co-product.[8] In this respect, BASF and Dow launched the construction of the first propylene oxide production plant using H_2O_2 as the oxidant recently (Scheme 1).[4] In future hydrogen peroxide will have more applications in the synthesis of fine chemicals, pharmaceuticals, agrochemicals and electronic materials owing to its characteristic physical properties. Hence, the discovery and advancement of new improved catalysts using H_2O_2 is an important and challenging goal in oxidation chemistry.[9]

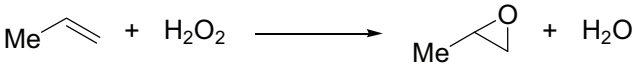
Chlorohydrin Process



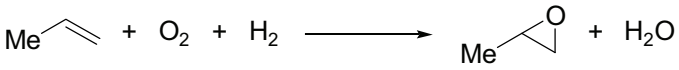
Peroxidation Process



Hydrogen Peroxide Process



Direct Oxidation Process



Scheme 1. Industrial processes for epoxidation of propylene.

1.1. Development of Epoxidation Catalysts Using H_2O_2

Excellent reviews appeared in recent years about the utilization of hydrogen peroxide as an epoxidation oxidant in the presence of various catalysts.[9,10] The combination of environmentally friendly H_2O_2 with non-toxic and inexpensive metal catalysts is undoubtedly an ideal system for epoxidation reactions.[11]

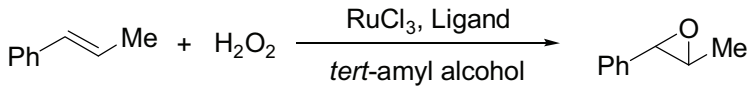
Among the various potential oxidation metals, iron-based catalysts are preferable because iron is the most abundant metal in the earth crust and is essential in nearly all organisms.[12] Many biological systems such as hemoglobin, myoglobin, cytochrome oxygenases, and non-heme oxgenases as well as [FeFe] hydrogenase are iron containing enzymes or co-enzymes.[13,14] Following natures path, biomimetic or bio-inspired approaches should be feasible to develop new synthetically useful epoxidation protocols with iron catalysts.[15]

The following chapters describe recent efforts on the development of novel ruthenium and iron epoxidation catalysts with hydrogen peroxide as oxidant.

1.1.1. Ruthenium catalyzed epoxidation

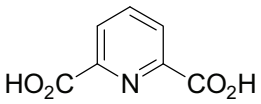
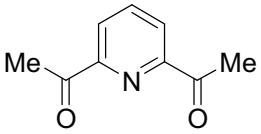
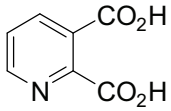
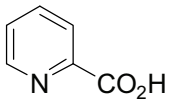
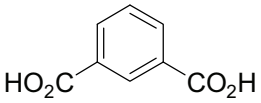
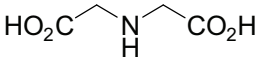
Ruthenium porphyrins have long been used as models for cytochrome P-450 for the epoxidation of olefins.[16] Pyridine *N*-oxides and iodosobenzenes have been usually used as the terminal oxidant. Comparably few examples showed epoxidation activity with H_2O_2 or oxygen in the presence of ruthenium catalysts. Most notably a sterically encumbered *trans*-dioxo ruthenium porphyrin complex showed catalytic activity towards epoxidation of olefins using both oxygen atoms of molecular oxygen.[17,18] Though this type of high valent ruthenium(VI) porphyrins are highly interesting epoxidation catalysts, their tedious synthesis hindered their further application, both in asymmetric and bulk chemical epoxidation.[13,19] Ruthenium(VIII) tetraoxide (RuO_4), which can be generated from $RuCl_3$ or RuO_2 with various oxidizing agents, is known to be a powerful oxidant. It has been applied for cleavage of olefins to aldehydes, ketones and carboxylic acids.[16] However, it is also possible to perform *cis*-dihydroxylation of olefins at low temperature in short time.[20] Under particular conditions, a-ketols can also be formed preferentially.[21] In literature relatively few examples described ruthenium-catalyzed epoxidations of olefins using H_2O_2.[22]

During the re-investigation on the ruthenium-catalyzed asymmetric epoxidation system of Nishiyama and co-workers using various oxidants,[23] it was discovered that slow addition of alkyl peroxides or hydrogen peroxide significantly improved the yield of chiral epoxides (vide infra).[24] Hence, the unproductive decomposition of H_2O_2 to O_2 is minimized. As model reaction the epoxidation of *trans*-ß-methylstyrene was studied (Scheme 2). It was shown that pyridine-2,6-dicarboxylic acid (H_2pydic) is an efficient and essential ligand for this reaction (Table 1). It is evident that the *O,N,O*-dianionic tridentate moiety is the origin of the catalyst activity. Removal of only one carboxylic group or the pyridine nitrogen gave inferior results. The developed reaction protocol is relatively general (Table 2). Both aliphatic and aromatic olefins can be oxidized to the corresponding epoxides in good to excellent yields. In most of the cases, 1 mol% of ruthenium is sufficient for high product yield. In some cases, as low as 0.01 mol% of ruthenium catalyzes the reaction efficiently. Hence, a maximum turnover number (TON) of 16,000 was achieved. The major drawback of this reaction is the necessity of a relatively high concentration of ligand loading (10 mol%).



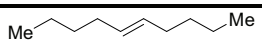
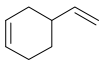
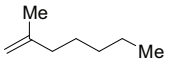
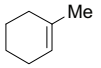
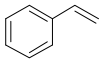
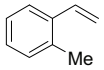
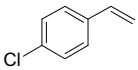
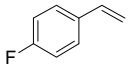
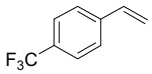
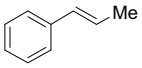
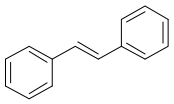
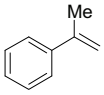
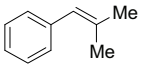
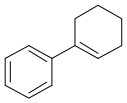
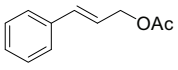
Scheme 2. Epoxidation of *trans*-ß-methylstyrene with H_2O_2.

Table 1. Ligand effects in the $RuCl_3 \cdot xH_2O$ catalyzed epoxidation of *trans*-ß-methylstyrene with H_2O_2.[a][24]

Entry	Ligand	Conv. [%]	Yield [%]	Selec. [%]
1	-	34	0	0
2		100	>99	>99
3		26	0	0
4		30	25	83
5		5	0	0
6		29	0	0
7		56	46	82

[a] General conditions: 0.5 mmol *trans*-ß-methylstyrene, 1 mol% $RuCl_3 \cdot xH_2O$ in 9 mL *tert*-amyl alcohol, 12 h slow addition of 3.0 equiv. 30 % H_2O_2 in 1 mL *tert*-amyl alcohol, room temperature, 10 mol% ligand.

Table 2. Ru-catalyzed epoxidation of different olefins with H_2O_2.[a][24]

Entry	Substrate	$RuCl_3 \cdot xH_2O$ [mol%]	Conv. [%]	Yield [%]	Selec. [%]
1		5	78	74	95
2		1[b]	100	90	90
3		0.1	79	66	83[c)]
4		0.1	100	95	95
5		0.01	100	>99	>99
6		1	100	71	71
7		1	100	70	70
8		1[b]	100	>99	>99
9		1	100	76	76
10		1[b]	49	46	93
11		0.01	100	96	96
12		0.1	100	93	93
13		0.1	100	90	90
14		0.1	100	96	96
15		0.01	100	97	97[d]
16		1	100	80	80

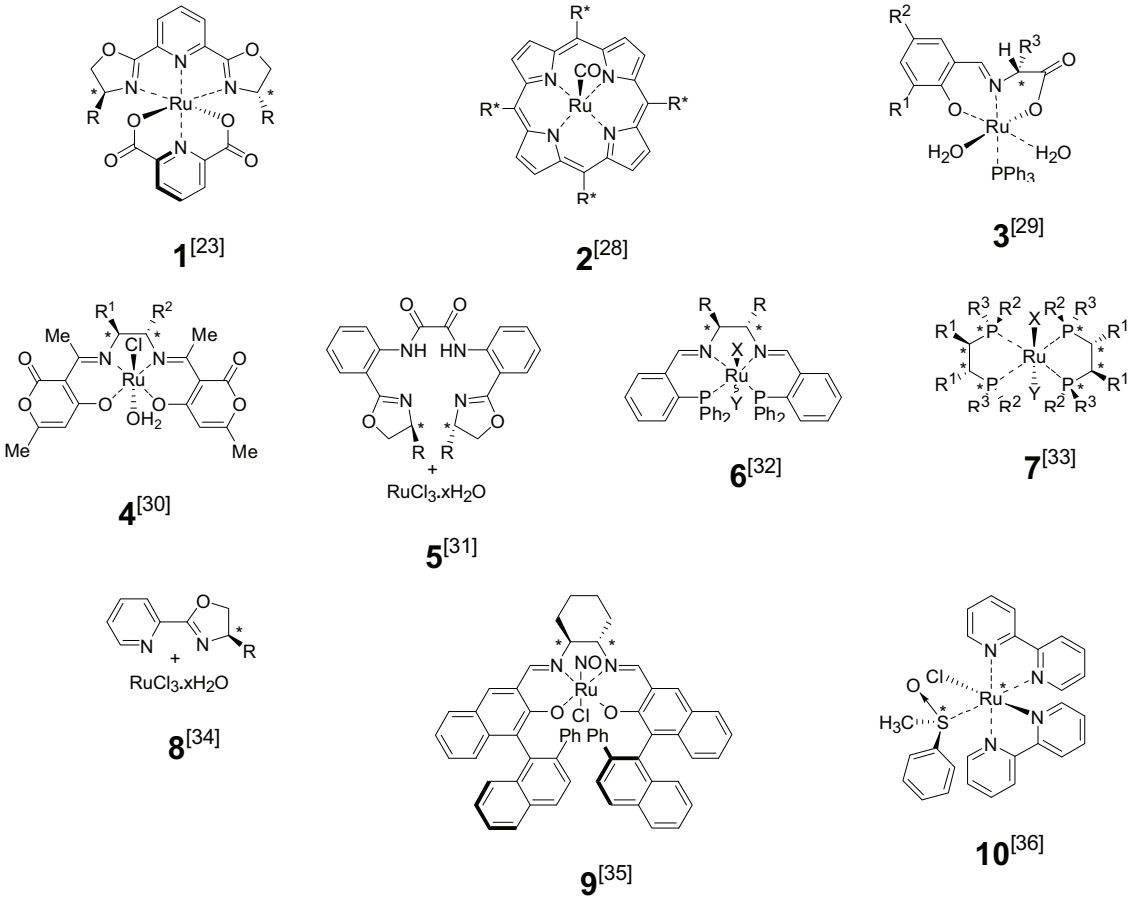
[a] General conditions: 0.5 mmol substrate, $RuCl_3 \cdot xH_2O$, 10 mol% pyridine-2,6-dicarboxylic acid in 9 mL *tert*-amyl alcohol, 12 h slow addition of 3 equiv. 30 % H_2O_2 in 1 mL *tert*-amyl alcohol, room temperature.

[b] 20 mol% pyridine-2,6-dicarboxylic acid.

[c] Product: 3-Vinyl-7-oxabicyclo[4.1.0]heptane.

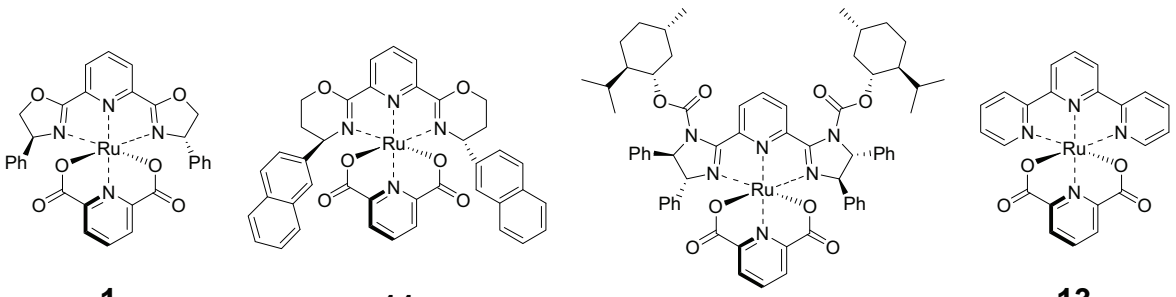
[d] Respective values for Ru-concentration of 0.001 mol%: conversion 16 %, yield 16 %, selectivity > 99 %.

With respect to asymmetric epoxidation a variety of chiral ruthenium catalysts have been developed (Scheme 3).[16] Mono-, bi-, tri- and tetradentate ligands as well as macrocyclic porphyrins have been demonstrated as selective ligands for this reaction. Moreover, various coordinating ligands including N, O, S or P donor centers can all be beneficial to these Ru catalysts. In some cases combination of ligands were advantageous. The coordinatively saturated ruthenium(II) complex, Ru(pyridine-2,6-bisoxazoline)(pyridine-2,6-dicarboxylate) **1**, which is composed of two different meridional ligands, was of particular interest.[23] Indeed **1** is a more practical epoxidation catalyst with $PhI(OAc)_2$ by adding a defined amount of water into the reaction mixture.[25] Later on, it was shown that alkyl peroxides[26] and hydrogen peroxide[27] can be used as oxidants. Applying complexes of type **1**, it seemed possible to tune up the reactivity and (enantio)selectivity by modifying the chiral (pybox) and the achiral (pydic) ligands separately.



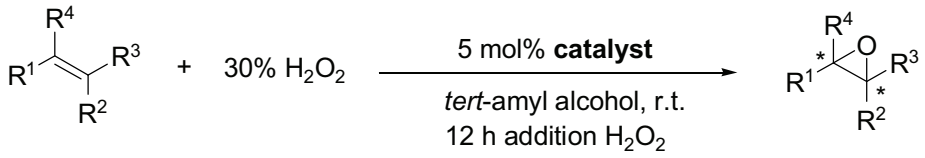
Scheme 3. Ruthenium catalysts for asymmetric epoxidation of olefins.

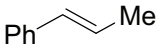
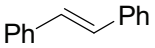
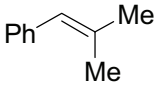
Based on this concept several ruthenium(II) pre-catalysts for epoxidation were synthesized (Scheme 4). They are all active oxidation catalysts towards various aromatic olefins and produce the corresponding epoxides in good to excellent yields (Table 3). With respect to the asymmetric induction, the complexes of pyridine-2,6-bisoxazoline (pybox) (**1**) and pyridine-2,6-bisimidazoline (pybim) (**12**) gave very similar results. The complex of pyridine-2,6-bisoxazine (pyboxazine) (**11**) gave the best stereoselective induction and up to 84 % *ee* were obtained. It was suggested that the 6-membered ring structure of the oxazine causes the chiral carbon center closer to the active metal center. This argument was supported by comparing the corresponding X-ray crystal structures of **1** and **11**.[27a b] With spectroscopic methods, independent synthesis and DFT calculations, mechanistic studies revealed an unusual pyridine *N*-oxide intermediate.[27b, 37] Particularly interesting is the ruthenium complex **13**. On one hand, it is a very general epoxidation catalyst. Both aliphatic and aromatic olefins can be epoxidized smoothly and all the 6 classes of substituted olefins work nicely.[27e] A turnover number (TON) of 8800 with high conversion (93 %) was also observed. On the other hand, **13** is also an excellent oxidation catalyst for naphthalene[38] and alcohol oxidation.[39] It is noteworthy that **13** reached a TON of 14,800 for alcohol oxidation with 30 % aqueous H_2O_2 in solvent-free and base-free conditions. The usefulness of this type of ruthenium catalysts is summarized in Scheme 5.

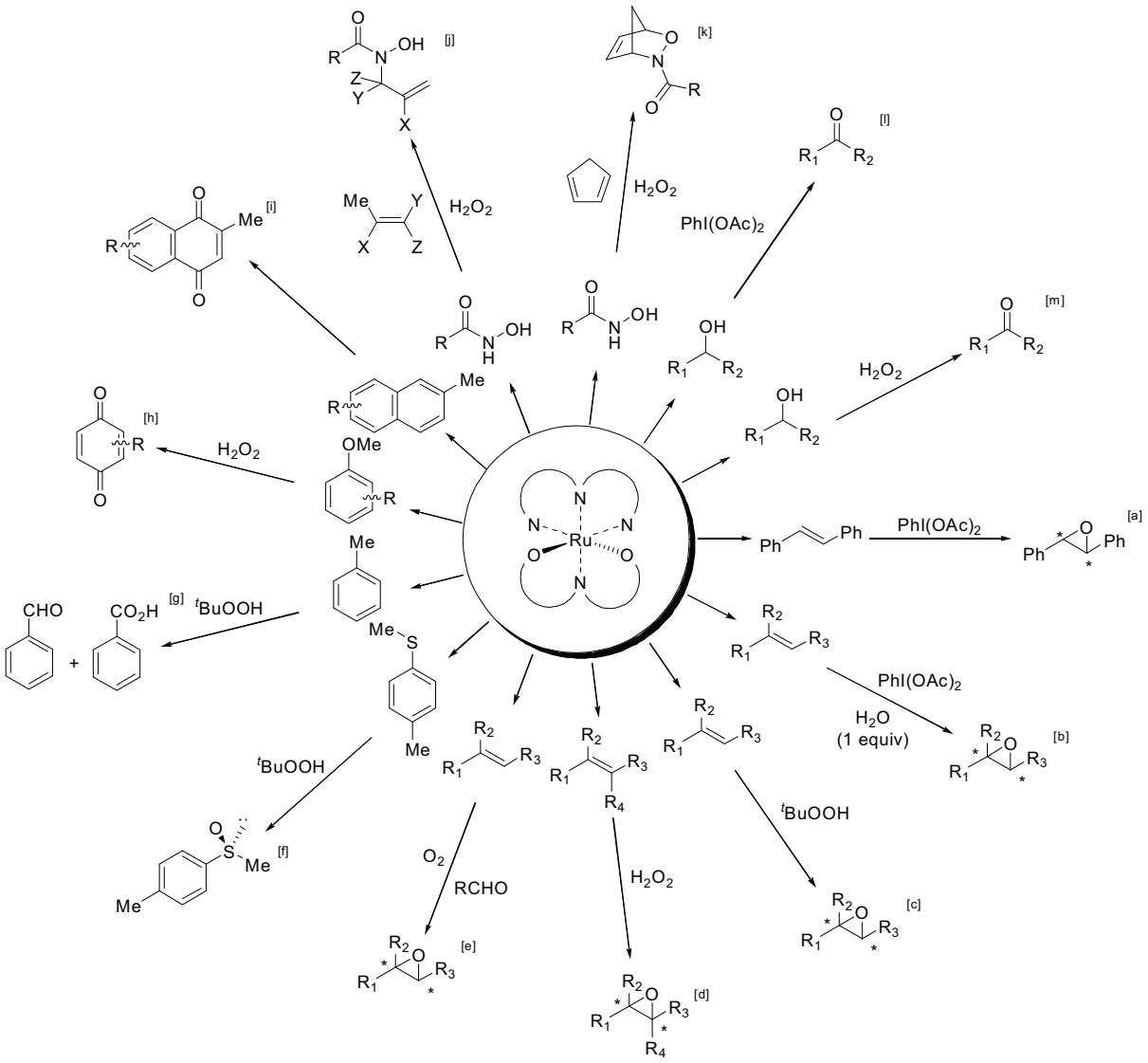


Scheme 4. Selected ruthenium(II) catalysts for epoxidation of aromatic olefins using 30 % H_2O_2.

Table 3. Epoxidation of aromatic olefins with ruthenium complexes **1** and **11**-**13** with 30 % H_2O_2.



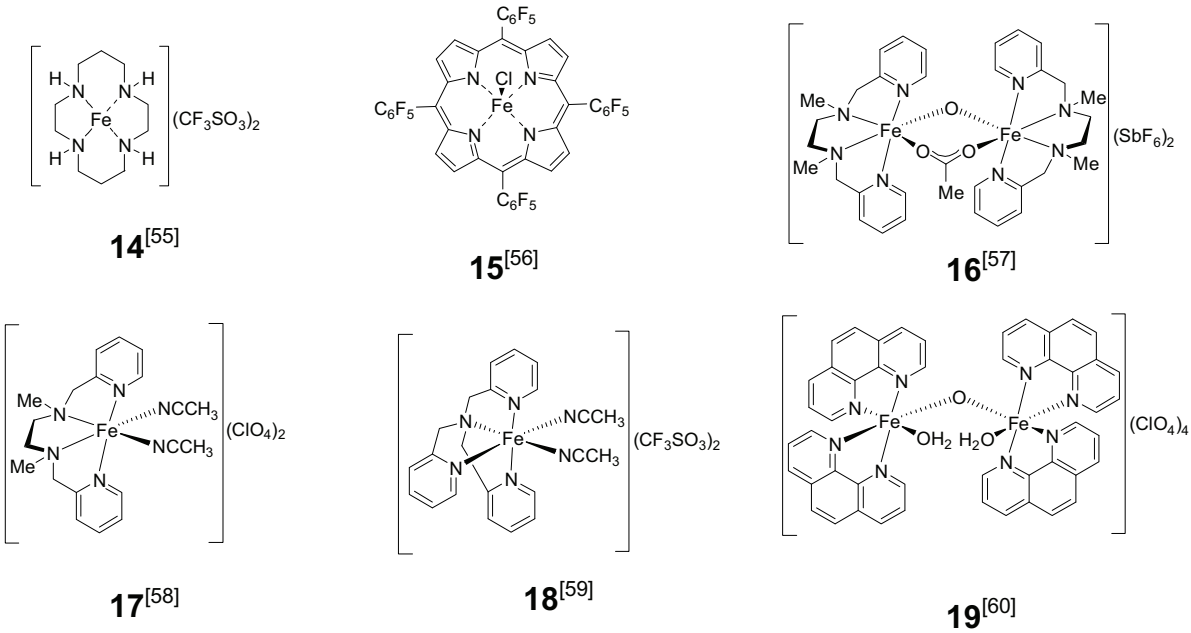
Entry	Substrate	Catalyst			
		1	**11**	**12**	**13**
1		75 % yield 42 % *ee*	85 % yield 59 % *ee*	76 % yield 42 % *ee*	71 % yield -
2		82 % yield 58 % *ee*	95 % yield 72 % *ee*	100 % 65 % *ee*	>99 % yield -
3		100 % yield 67 % *ee*	100 % yield 54 % *ee*	97 % yield 71 % *ee*	- -
4		91 % yield 72 % *ee*	91 % yield 84 % *ee*	82 % yield 68 % *ee*	>99 % yield -



Scheme 5. Use of Ruthenium catalysts ([a] see ref. [23]. [b] see ref. [25]. [c] see ref. [26]. [d] see ref. [27]. [e] see ref. [40]. [f] see ref. [41]. [g] see ref. [42]. [h] see ref. [43]. [i] see ref. [38]. [j] see ref. [44]. [k] see ref. [45]. [l] see ref. [46]. [m] see ref. [39]).

1.1.2. Biomimetic iron catalyzed epoxidation

Iron is the most abundant element by mass on the earth.[47] Due to its low cost, benignancy to the environment and biological relevance, there is an increasing interest to use iron complexes as catalysts for a wide range of reactions.[48] In this respect, iron catalysts for C-C [48a,49] and C-N [50] bond formation reactions, hydrogenations[51] as well as oxidations draw much attention.[9 10,15] However, the use of H_2O_2 in combination with simple iron complexes as oxidation catalysts is still limited.[52,53] It is partly because H_2O_2 decomposes vigorously in the presence of iron, which reduces the efficiency of the oxidant.[54] The generation of a highly reactive free hydroxyl radical by Fenton or Gif Chemistry induces the decomposition of the ligand and substrate as well as the product.[52d e] Hence, high substrate to hydrogen peroxide ratio is usually employed to solve these problems. In fact, only few examples of iron catalysts utilizing H_2O_2 as the oxidant are known (Scheme 6).



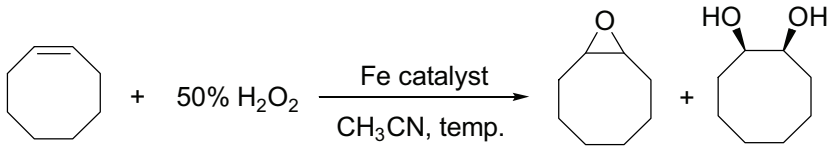
14[55] **15**[56] **16**[57]

17[58] **18**[59] **19**[60]

Scheme 6. Iron catalysts for epoxidation of olefins using H_2O_2.

Olefins can be oxidized in the presence of anhydrous $FeCl_3$ to a mixture of dimers, epoxides, aldehydes and others using 100 % H_2O_2 in anhydrous CH_3CN as the oxidant.[53] The exceptional oxidizing power of anhydrous H_2O_2 and the low selectivity of the reaction limit further applications of this system. Heme-models such as **14** and **15** have been reported to catalyze the epoxidation of olefins to the corresponding epoxides in good yield. The major drawback for these heme-model systems is the low tunability of the catalysts for different olefins. A number of non-heme models were reported recently. Of particular interest are complexes **16** and **17**, which were synthesized by Jacobsen's group and Que's group with the same parent ligand, respectively.[57,58] The self-assembling MMO-mimic **16** catalyzed the epoxidation of a range of aliphatic olefins. Even the relatively non-reactive substrate, 1-decene, can be oxidized to the corresponding epoxide in 85 % yield in 5 min. The presence of acetic acid not only affects the structure of the intermediate, but also the selectivity of the products (Table 4). A higher epoxide to *cis*-diol ratio was observed in the presence of HOAc. This effect is more significant when **18** was employed as the catalyst. *In-situ* generation of peracetic acid was thus suggested.[59b] Though these catalysts showed interesting selectivity towards epoxides and diols for aliphatic olefins, it decomposed aromatic olefins to unidentified products. This reduces the general application of this type of catalysts for synthetic purpose. Stacks catalyst derived from phenanthroline is synthetically more practical.[60] In spite of the fact that peracetic acid is used, a wide range of olefins can be oxidized to the corresponding epoxides with only 0.25 mol% of catalyst.

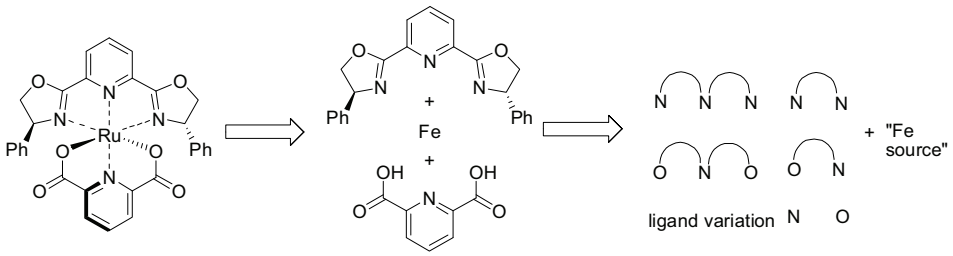
Table 4. Epoxidation of cyclooctene with **16** and **17** with 50 % H_2O_2.



Entry	Catalyst	:H_2O_2	Temp. [°C]	O a	HO OH a	Additive	Ref.
1	**16** 3 mol%	1:1.5	4	85 %	0 %	30 mol% HOAc	[57]
2	**17** 10 mol%	100:1	30	75 %	9 %	nil	[58b]
3	**17**[b] 7 mol%	100:2.8	r.t.	91 %	5 %	nil	[59b]
4	**17**[b] 7 mol%	100:2.8	r.t.	102 %[c]	3 %	34 mol% HOAc	[59b]
5	**18** 7 mol%	100:2.8	r.t.	30 %	41 %	29 mol% HOAc	[59b]
6	**18** 7 mol%	100:2.8	r.t.	88 %[c]	14 %	29 mol% HOAc	[59b]
7	**19** 0.25 mol%	1:2 CH_3CO_3H	0	100 %	0 %	nil	[60]

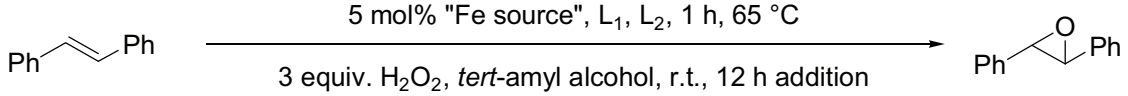
[a] Yield based on the limiting reagent.
[b] Trifluoromethansulfonate was the anion of the iron complex instead of perchlorate.
[c] A total yield over 100 % has been reported due to experimental error.

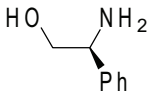
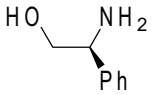
Despite these known works, Fe catalysts are still under development for a general epoxidation using aqueous H_2O_2 under neutral conditions. Instead of synthesizing molecularly well-defined iron complexes as epoxidation catalysts, this problem was tackled in another way. Based on the *in-situ* generation method from the ruthenium system,[25] the technology was transferred to simple iron systems using a combinatorial ligand strategy (Scheme 7).[61] It was found that $FeCl_3 \cdot 6H_2O$ can substitute the ruthenium source in the model reaction with 2,6-bis(4-phenyl-4,5-dihydrooxazol-2-yl)pyridine (Ph_2-pybox) and H_2pydic as ligands (Table 5). However, the synthesized iron(II) complex with the *N,N,N*-tridentate Ph_2-pybox is less active than the *in-situ* generated catalyst. Noteworthy evidence including mass spectrometric analysis and electronic absorption spectra suggests the pybox ligand was decomposed during the reaction and generated the active catalyst species. Combination of the fragments gave comparable result as the pybox ligand alone as well. With this information and the screening method in hand, the effect of base was demonstrated to be crucial in this system (Table 6).



Scheme 7. Iron catalyst modification strategy.

Table 5. Epoxidation of *trans*-stilbene with in-situ generated Fe catalysts.



Entry	Fe source	L_1	L_2	Conv.[a,b] [%]	Yield[b] [%]	Selec.[c] [%]
1	$FeCl_3 \cdot 6H_2O$	Ph_2-pybox[d]	H_2pydic	55	48	87
2	Fe(Ph_2-pybox)Cl_2	-	-	22	15	67
3	$FeCl_3 \cdot 6H_2O$	-	-	13	7	52
4	$FeCl_3 \cdot 6H_2O$	Ph_2-pybox	-	100	82	82
5	$FeCl_3 \cdot 6H_2O$	-	H_2pydic	69	53	77
6	$FeCl_3 \cdot 6H_2O$		H_2pydic	100	84	84
7	$FeCl_3 \cdot 6H_2O$		-	9	6	69

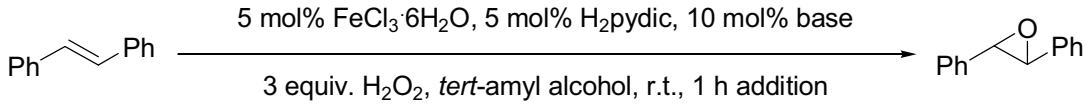
[a] Reaction conditions: In a 25 mL Schlenk tube, iron trichloride hexahydrate (0.025 mmol), Ph_2-pybox (0.025 mmol) and H_2pydic (0.025 mmol) were solved in *tert*-amyl alcohol (4 mL) and heated for 1 h at 65 °C. Afterwards *trans*-stilbene (0.5 mmol), *tert*-amyl alcohol (5 mL) and dodecane (GC internal standard, 100 µL) were added in sequence at r.t. in air. To this mixture, a solution of 30 % hydrogen peroxide (170 µL, 1.5 mmol) in *tert*-amyl alcohol (830 µL) was added over a period of 12 h at r.t. by a syringe pump.

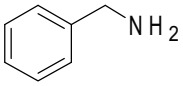
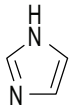
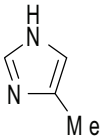
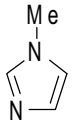
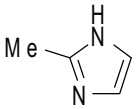
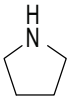
[b] Conversion and yield were determined by GC analysis.

[c] Selectivity refers to the ratio of yield to conversion in percentage.

[d] 2,6-bis(4-phenyl-4,5-dihydrooxazol-2-yl)pyridine = Ph_2-pybox.

Table 6. Epoxidation of *trans*-stilbene with different bases.



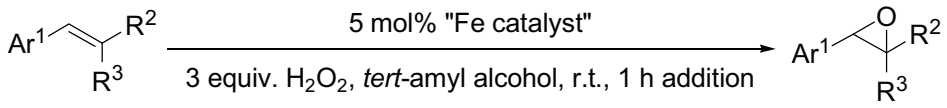
Entry	Base	Conv.[a,b] [%]	Yield [b] [%]	Selec.[c] [%]
1	KOH	33[d]	30	91
2	Et_3N	86	74	86
3		100	97	97
4		91	90	99
5		100[e]	97	97
6		78[e]	72	92
7		12[e]	11	92
8		56	50	89
9		100	97	97

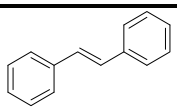
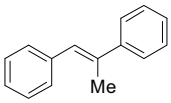
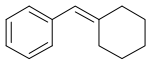
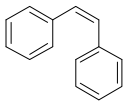
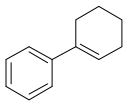
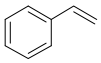
[a] Reaction conditions: In a 25 mL Schlenk tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), base (0.05 mmol), *trans*-stilbene (0.5 mmol) and dodecane (GC internal standard, 100 µL) were added in sequence at r.t. in air. To this mixture, a solution of 30 % hydrogen peroxide (170 µL, 1.5 mmol) in *tert*-amyl alcohol (830 µL) was added over a period of 1 h at r.t. by a syringe pump.
[b] Conversion and yield were determined by GC analysis.
[c] Selectivity refers to the ratio of yield to conversion in percentage.
[d] H_2O_2-addition over a period of 12 h.
[e] Addition of 2 equiv. of H_2O_2.

It is apparent that all organic bases form active species with $FeCl_3 \cdot 6H_2O$ and H_2pydic. Notably, excellent activity was found with pyrrolidine, benzyl amine and 4-methylimidazole. For some aromatic olefins, the reaction is finished in 5 minutes and slow dosage of H_2O_2 is not necessary. However, the structure of the base has dramatic effect to the system. Hence, it is evident that the organic base deprotonates the H_2pydic and acts as the ligand as well. As imidazole derivates also play an essential role as ligands or bases in enzymes,[62] this combinatorial-activity approach provides a general platform for searching functional mimics for iron enzymes. Understanding the fundamental aspects of these systems should allow developing synthetically more useful biomimetic iron catalyzed epoxidation systems. Hence, by fine tuning the imidazole ligand, a bio-inspired $FeCl_3$/imidazole-system was also developed for epoxidations of olefins using aqueous hydrogen peroxide as the oxidant. A wide range of imidazoles displayed good selectivity for epoxidation of *trans*-stilbene. With 15 mol% of 5-chloro-1-methylimidazole and 5 mol% $FeCl_3 \cdot 6H_2O$, 87 % yield of *trans*-stilbene oxide with 94 % selectivity is achieved.[63]

This system showed a more general activity and higher selectivity towards various olefins than that of the $FeCl_3 \cdot 6H_2O$/H_2pydic/pyrrolidine system (Table 7). However, the H_2pydic system has a higher activity for some substrates. Both reaction systems demonstrated that it is possible to perform epoxidations with hydrogen peroxide in the presence of easily manageable and simple Fe/Ligand catalysts. Reports of the efforts to examine the reaction mechanism and to realize an asymmetric version of these reactions are currently underway.

Table 7. Scope and limitations of $FeCl_3 \cdot 6H_2O/H_2$pydic/pyrrolidine and $FeCl_3 \cdot 6H_2O$/5-chloro-1-methylimidazole systems.

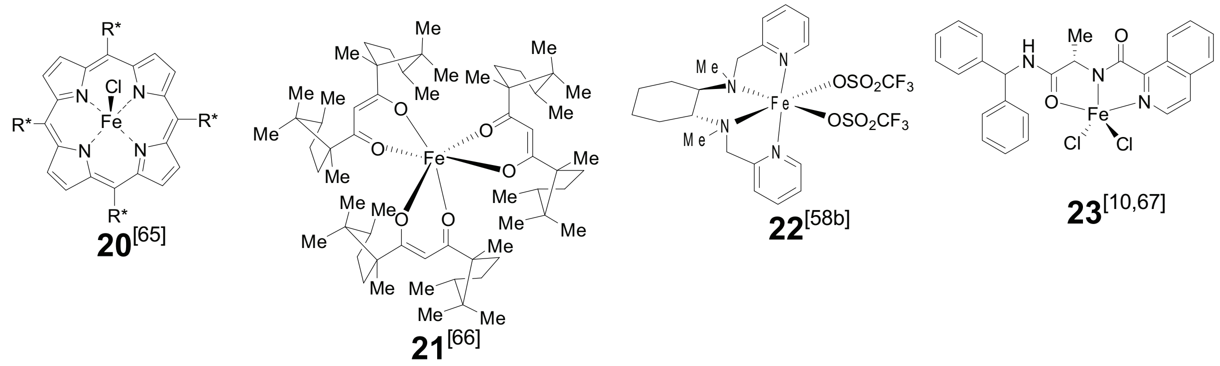


Entry	Substrate	$FeCl_3 \cdot 6H_2O/H_2$pydic/pyrrolidine[61]			$FeCl_3 \cdot 6H_2O$/5-chloro-1-methylimidazole[63]		
		Conv.[a,b] [%]	Yield[b] [%]	Selec.[c] [%]	Conv.[a,b] [%]	Yield[b] [%]	Selec.[c] [%]
1		100	97	97	92	87	94
2		40[d]	21	53	46	41	88
3		25[d]	11	44	39	25	64
4		22[d]	8	36	34	24[e]	71
5		85[d]	21	25	52	36	68
6		94[d]	93	99	74	70	95

[a] Reaction conditions: In a 25 mL Schlenk tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), base (0.05 mmol), *trans*-stilbene (0.5 mmol) and dodecane (GC internal standard, 100 µL) were added in sequence at r.t. in air. To this mixture, a solution of 30 % hydrogen peroxide (170 µL, 1.5 mmol) in *tert*-amyl alcohol (830 µL) was added over a period of 1 h at r.t. by a syringe pump.
[b] Conversion and yield were determined by GC analysis.
[c] Selectivity refers to the ratio of yield to conversion in percentage.
[d] Addition of 2 equiv. of H_2O_2.
[e] Additionally 3 % *trans*-stilbene oxide and *trans*-stilbene were observed.

Until very recently relatively few examples on asymmetric epoxidations using iron-based catalysts were reported in the literature (Scheme 8). This can be partly attributed to the rapid decomposition of H_2O_2 with iron catalysts. The other reason possibly comes from inferior activity of iron porphyrins compared to their manganese counterparts in the early studies of heme-models. Thus, researchers concentrated on the development of manganese catalysts in the 90s.[64] As a result, only handful of asymmetric epoxidation systems using iron porphyrin heme-mimics are known and merely iodosobenzene was successfully applied as oxidant.[65] Electron deficient polyfluorinated porphyrins catalyze epoxidation of olefins with H_2O_2.[56] However, the synthesis of chiral porphyrins with electron withdrawing groups has still not yet been realized because of their notorious reputation for labour-intensive and expensive syntheses.[13,19] Aerobic epoxidation of styrene derivatives with an aldehyde as co-reductant catalyzed by tris(δ,δ-dicampholylmethanato) iron(III) complex **21** was also reported.[66] In spite of the encouraging results, more environmentally benign oxidant and solvent are still to be developed. Notably, in the dihydroxylation of of *trans*-2-heptene with H_2O_2 using biomimetic non-heme Fe-catalysts, [Fe(BPMCN)$(CF_3SO_3)_2$] **22**, 58 % of the epoxide with 12 % *ee* was obtained.[58b] By elaborating 5760 metal-ligand combinations, Francis and Jacobsen identified three Fe-complexes with peptide-like ligands, which gave the epoxide in 15 – 20 % *ee* in the asymmetric epoxidation of *trans*-ß-methylstyrene utilizing 30 % H_2O_2. The homogeneous catalyst **23** derived from this study gave 48 % *ee* with 100 % conversion of *trans*-ß-methylstyrene. It is clear in this example that a combinatorial ligand approach can lead to promising new bio-inspired iron epoxidation catalysts.

The first breakthrough in non-porphyrin iron-catalyzed asymmetric epoxidation of aromatic alkenes using hydrogen peroxide has been reported by us very recently.[68] Here, good to excellent isolated yields of aromatic epoxides were obtained with *ee*-values up to 97 % for stilbene derivatives.

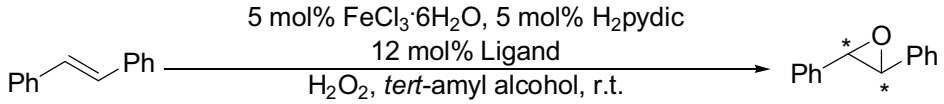


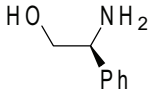
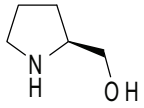
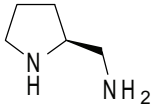
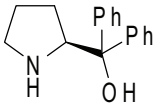
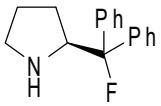
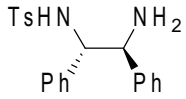
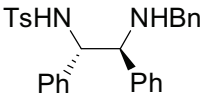
Scheme 8. Iron catalysts for asymmetric epoxidation of olefins.

In these investigations, *trans*-stilbene was used as the model substrate (Table 8).[68] In earlier studies of non-asymmetric iron catalyzed epoxidations decomposition of the Ph_2-pybox ligand was observed. [61] Comparable activity was obtained with H_2pydic and phenylglycinol as ligand and base. However, only less than 5 % *ee* was observed with the enantiomerically pure aminoalcohol. Further investigation of other optically pure amines showed high yield of the epoxide, albeit with low enantioselectivity. As ligands with a *p*-tolylsulfonamide substituent gave significantly higher *ee*-values and good activity, formation of hydrogen bonds as the key chiral information transferring step is suggestive. Optimization by ligand modification showed that *N*-((*1R,2R*)-2-(benzylamino)-1,2-diphenylethyl)-4-methyl-benzenesulfonamide (Table 8, entry 7) is the best ligand in terms of enantio-selectivity (42 % *ee*).

It has been demonstrated that *trans*-1,2-disubstituted aromatic olefins gave excellent activity with moderate to excellent *ee*'s (Table 9). It is mentionable that the activity of substituted *trans*-stilbenes is in the order: *para* > *meta* > *ortho*, presumably due to steric reasons. The higher steric bulkiness of the 4,4'-dialkyl substituted *trans*-stilbenes, the higher is the enantiomeric excess (^{t}Bu > Me > H). The highest *ee*-value was achieved with 2-(4-*tert*-butylstyryl)naphthalene as the substrate in the presence of 10 mol% of the iron catalyst (Table 9, entry 9). 91 % *ee* and 46 % isolated yield were obtained with the corresponding epoxide. By slightly lowering the reaction temperature to 10 °C, 97 % *ee* was reached with complete substrate conversion within one hour (Table 9, entry 10).

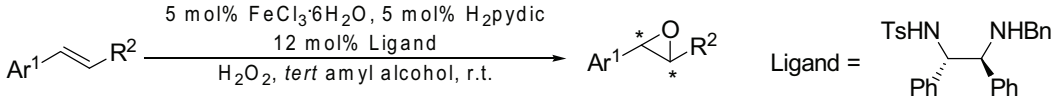
Table 8. Iron catalyzed asymmetric epoxidation of *trans*-stilbene.

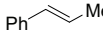
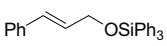
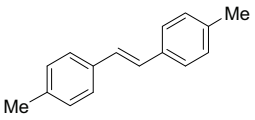
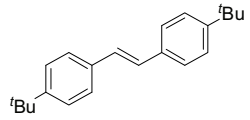
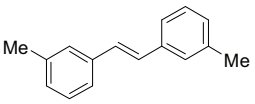
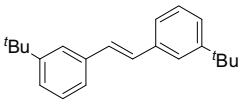
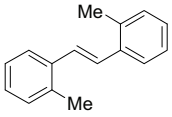
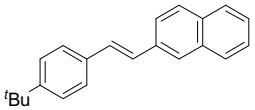
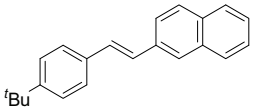


Entry	Ligand	Conv.[a] [%]	Yield[a] [%]	Selec.[c] [%]	*ee*[b] [%]	Ref.
1		100	84	84	<5	[61]
2		95	73	77	0	[68]
3[d]		60	58	97	1	[68]
4[d]		78	53	68	10	[68]
5[e]		100	98	98	17	[68]
6[f]		100	86	86	28	[68]
7[f]		100	87	87	42	[68]

[a] Reaction conditions: In a 25 mL Schlenk tube, iron trichloride hexahydrate (0.025 mmol), chiral ligand (0.060 mmol) and H_2pydic (0.025 mmol) and *trans*-stilbene (0.5 mmol) were dissolved in hot *tert*-amyl alcohol (9 mL). Dodecane (GC internal standard, 100 µL) were added in sequence at r.t. in air. To this mixture, a solution of 30 % hydrogen peroxide (170 µL, 1.5 mmol) in *tert*-amyl alcohol (830 µL) was added over a period of 1 h at r.t. by a syringe pump.
[b] Conversion and yield were determined by GC analysis.
[c] Selectivity refers to the ratio of yield to conversion in percentage.
[d] 36 h.
[e] 0 °C, 14 h.
[f] 1.0 mmol H_2O_2.

Table 9. Iron-catalyzed asymmetric epoxidation of various aromatic olefins.[68]



Entry	Substrate	Conv.[a] [%]	Yield[b] [%]	*ee*[c] [%], abs. conf.
1		100[d]	94[d]	28, (+)-(2*R*,3*R*)[e]
2		100	87	42, (+)-(2*R*,3*R*)
3		100	67	35, (+)-(2*R*,3*R*)[f]
4		100	92	64, (+)-(2*R*,3*R*)[g]
5		100	82	81, (+)-(2*R*,3*R*)[g]
6		>95	88	27, (+)-(2*R*,3*R*)[h]
7		>95	66	10, (–)-(2*S*,3*S*)[h]
8		60[i]	57[i]	55, (–)-(2*S*,3*S*)[h]
9[i]		100	46	91, (+)-(2*R*,3*R*)[h]
10[j,k]		100	40	97, (+)-(2*R*,3*R*)[h]

[a] Estimated by GC-MS and/or TLC which respectively showed absence of substrate peak and traces.
[b] Isolated yield of pure product.
[c] Determined by HPLC on chiral columns.
[d] Determined by GC.
[e] Assigned by comparing the retention times of the enantiomers on a chiral HPLC with that of an authentic sample of the (*S*,*S*)-enantiomer.
[f] Assigned by desilylation to the corresponding epoxy alcohol by analogy with literature protocol and comparing the sign of optical rotation of the resulting product with that of an authentic sample.[69]
[g] Determined by comparing the sign of the optical rotation of the major enantiomer on a chiral detector coupled with a chiral HPLC with known data, the CD spectra of these products are positive, opposite to those reported for the (*S*,*S*)-enantiomers.[70]
[h] Tentatively assigned by comparing the CD-spectrum with those of substituted *trans*-stilbene oxides.
[i] Determined after 24 h by ^{1}H NMR of crude product using an internal standard.
[j] 4 equiv. H_2O_2, 10 mol% H_2-pydic, 10 mol% $FeCl_3{\cdot}6H_2O$, 24 mol% ligand.
[k] Reaction at 10°C.

1.2. Conclusion

In summary, it has been demonstrated that high activity, chemoselectivity and even excellent enantioselectivity can be achieved in Fe-catalyzed epoxidations with hydrogen peroxide. This long standing goal in oxidation catalysis is realized by combining $FeCl_3$ with appropriately chosen ligands. Chiral diamines and pyridine-2,6-dicarboxylic acid as the ligand combination provide an excellent platform for further improvement of this up-rising bio-inspired oxidation chemistry. It is apparent that an advancement of the generality of these catalytic systems still awaits. Further work to extend the substrate scope and towards a mechanistic understanding of these new catalysts are underway.

1.3. References

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2. Objectives of this work

The epoxidation of olefins is an important synthetic method in organic chemistry as well as for the chemical industry. Recently, hydrogen peroxide has become one of the terminal oxidants of choice because it produces only water as by-product. Moreover, H_2O_2 is advantageous regarding costs, safety and storage. Hence developments on new catalytic systems using H_2O_2 are an important and challenging goal in oxidation chemistry. Based on successful projects in ruthenium-catalyzed oxidation reactions the Ru(pybox)(pydic) complex was chosen as starting point for different catalyst modifications. By variation of the ligands and metal sources the reactivity, (enantio)selectivity and generality should be possible to tune up.

During these studies a new chiral ligand library of *N,N,N*-tridentate pyridinebis-imidazolines, so-called pybims, was realized and applied in asymmetric ruthenium-catalyzed epoxidation (Publication 4.1., *Org. Lett.* **2005** and Publication 4.2., *Tetrahedron: Asymmetry* **2005**). The tunability of these ligands is much higher compared to the related pybox ligands. Scope and limitations were investigated for a variety of olefins. Furthermore these pybim ligands could be successfully applied in the asymmetric ruthenium catalyzed transfer hydrogenation of aliphatic and aromatic ketones (Publication 4.3., *Adv. Synth. Catal.* **2007**) Enantioselectivities up to > 99 % *ee* are achieved under optimized conditions.

To investigate the mechanistic aspects of the asymmetric ruthenium-catalyzed epoxidation reaction synthetic, spectral and catalytic activity studies of novel ruthenium(II) bipyridine and terpyridine complexes were established (Publication 4.3., *J. Organometallic Chem.* **2006**). Possible intermediates in the reaction pathway were suggested. Moreover, a simplified protocol for the epoxidation of olefins utilizing urea hydrogen peroxide complex was developed during these studies.

In order to develop a simple, environmentally benign and more economical procedure, the possibility of replacing Ru by Fe as the metal in the epoxidation of olefins with hydrogen peroxide was explored. The development of an efficient iron catalyst system starting from the previous work on Ruthenium catalyzed epoxidation should be very insightful.

By systematic variation of the reaction parameters, a new bio-inspired, convenient and fast epoxidation protocol using economical and environmentally friendly $FeCl_3 \cdot 6H_2O$ in combination with H_2O_2 was developed (Publication 3.5., *Chem. Commun.* **2006** and 3.6., *Asian J. Chem.* **2007**). Pyridine-2,6-dicarboxylic acid (H_2pydic) and pyrrolidine turned out to be the most effective ligands in this system. Mass spectrometric and UV-VIS spectroscopic measurements were used for an effective development and understanding of the catalyst system. The system showed excellent reactivity and selectivity towards terminal and 1,2-disubstituted aromatic olefins and moderate reactivity towards 1,3-dienes and aliphatic olefins. All the reagents used in the system are simple and commercially available and the reaction can be performed at room temperature and in air under mild conditions.

Unfortunately, aliphatic olefins and highly substituted aromatic olefins were less reactive and selective applying the previous system. Hence, an improved Fe-catalyzed epoxidation, which can be applied to all classes of olefins, was developed (Publication 3.7, *Eur. J. Org. Chem.* **2008**). This simple and practical catalyst system consists of $FeCl_3 \cdot 6H_2O$, H_2pydic and a benzylamine derivative. It was demonstrated that benzylamine is a preferred structural element for the co-ligand in this general epoxidation method. The system showed good to excellent reactivity to mono-, di-, and trisubstituted aromatic olefins as well as internal di-, tri-substituted and functionalized aliphatic olefins. Noteworthy, inactive aliphatic olefins can be oxidized in up to 96 % yield.

By studying the effect of the organic base in more detail, it was found that a combination of $FeCl_3 \cdot 6H_2O$ with simple imidazole derivatives without any H_2pydic could perform epoxidations. Difficult tri-substituted olefins and styrenes could be oxidized in good yields and selectivity (Publication 3.8., *Tetrahedron Lett.* **2007**).

Only a few examples on asymmetric epoxidations using iron-based catalysts were known in literature, hence the development of an asymmetric version still remains

a challenging task. This goal was realized by combining $FeCl_3 \cdot 6H_2O$ and H_2pydic with diamine ligands (Publication 3.9., *Angew. Chem.* **2007**). For the first time it was demonstrated that high enantioselectivity can be achieved in Fe-catalyzed epoxidation with hydrogen peroxide. Several *trans*-stilbene derivatives could be oxidized in excellent yields and up to 97 % *ee*.

α-Hydroxy-β-ketoester is an important scaffold found in numerous bioactive molecules. The hydroxylation of 1,3-dicarbonyl compounds is a straightforward approach to access these compounds. Based on the experience in iron-catalyzed epoxidation an easy and practical method for the hydroxylation of β-ketocarbonyl compounds with hydrogen peroxide was developed. Applying cheap iron chloride as catalyst system the α-oxidation of β-ketoesters proceeds smoothly in 75 - 90 % yield (Publication 3.10., submitted to *Tetrahedron Lett.* **2008**).

3. Publications

Publication 3.1.

Synthesis of a New Chiral N,N,N-Tridentate Pyridinebisimidazoline Ligand Library and Its Application in Ru-Catalyzed Asymmetric Epoxidation

Santosh Bhor, Gopinathan Anilkumar, Man Kin Tse, Markus Klawonn, Christian Döbler, Bianca Bitterlich, Anne Grotevendt, Matthias Beller

Org. Lett. **2005**, 7 (16), 3393-3396

Contributions:

In this paper, I contributed to a significant amount of the argumentation and I supported the synthetic work. I synthesized Pyridine-2,6-dicarboximidic acid dimethyl ester (**2**) and 2,6-Bis-([4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine (**4**) which serve as key-intermediates for the development of the ligand library. My contribution as co-author of this paper is approximately 15 %.

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Synthesis of a New Chiral *N,N,N*-Tridentate Pyridinebisimidazoline Ligand Library and Its Application in Ru-Catalyzed Asymmetric Epoxidation

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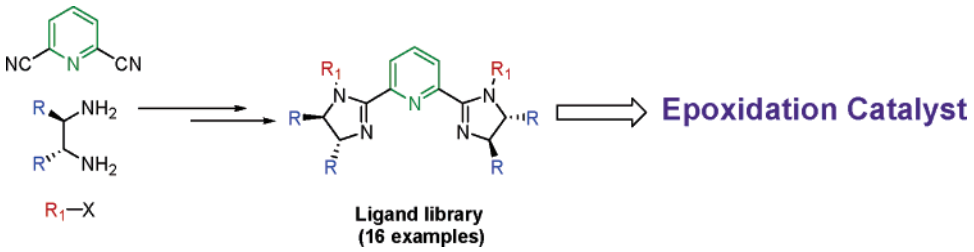
ABSTRACT



A small ligand library of chiral tridentate *N,N,N*-pyridinebisimidazolines have been synthesized for the first time. This new class of ligands can be easily tuned and synthesized on multi g-scale. The usefulness of the ligands is shown in the ruthenium-catalyzed asymmetric epoxidation with hydrogen peroxide as oxidant. Excellent yields (>99%) and good enantioselectivities (up to 71% *ee*) have been obtained for the epoxidation of aromatic olefins.

Transition metal-catalyzed asymmetric reactions offer an efficient and elegant possibility for the synthesis of enantiomerically pure compounds.[1] In general, the choice and synthesis of a suitable chiral controller ligand is the crucial step in the development of a new catalyst for stereoselective reactions. Clearly, a multitude of chiral mono-, bi- and multidentate ligands with P, N, O, and other coordinating atoms are known today and used extensively for all kinds of catalytic reactions. Prominent examples of so-called privileged ligand classes include the salens,[2] bisoxazolines,[3] phosphinooxazolines,[4] tartrate derivatives,[5] and cinchona alkaloids.[6] Nevertheless, there is still an increasing need for new and improved ligands. State-of-the-art chiral ligands[7]

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should offer the user a series of advantages: obviously, it should give highly selective and active as well as productive catalysts. In addition, the ligand should be conveniently prepared from mg- to kg-scale, and the synthesis should be economically feasible. Unfortunately, each catalytic reaction needs its own optimized ligand. To find the optimal catalyst for a certain substrate the preparation of ligand libraries with the same basic ligand skeleton should be possible without problems. However, the systematic modification of the structure of new ligands is often difficult and time-consuming.

Herein, we report a new class of chiral ligands, which is simply synthesized and can be easily varied by remote functionalizations to allow for the preparation of ligand libraries in a fast and practical manner.

The starting point of this work was our studies on ruthenium-catalyzed epoxidation of olefins with C_2-symmetric pyridinebisoxazolines (pybox) as the chiral ligand.[8] While synthesizing new pybox ligands, we realized that the preparation of such a ligand library is limited and time-consuming due to the difficulty of functionalizations of the ligand backbone and stepwise formation of the oxazoline moiety.[9]

We thought that introducing a second nitrogen atom in place of oxygen of pyridinebisoxazoline ligands would provide a more flexible ligand scaffold, which might be easily varied by *N*-alkylation, *N*-arylation, and *N*-acylation to tune the reactivity as well as stereoselectivity in catalytic asymmetric reactions (Figure 1).

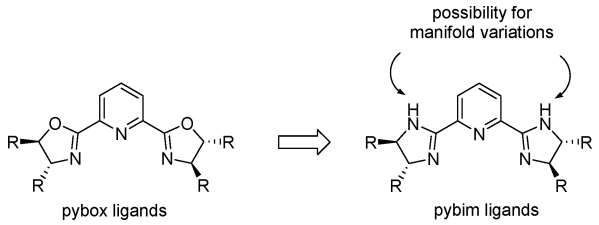

Figure 1. From pybox to pybim ligands.

Despite the importance of pybox ligands for numerous stereoselective reactions,[10] to the best of our knowledge similar chiral *pyridinebisimidazoline* ligands, here abbreviated as *pybim*, have not been synthesized and applied in asymmetric catalysis.

The synthesis of the pybim scaffold is easily done from commercially available 2,6-dicyanopyridine **1** in two steps. Treatment of **1** with a catalytic amount of sodium in anhydrous methanol followed by neutralization with acetic acid and removal of methanol under reduced pressure, afforded the bisimidate **2** as a pale yellow solid in quantitative yield.[11]

Condensation of **2** with chiral diamines such as *R,R*-1,2-diaminocyclohexane and *R,R*-1,2-diphenylethylene-diamine furnished the corresponding *pyridine bisimidazoline* ligands **3** and **4** in good to excellent yield. The pybims **3** and **4** are stable to air and moisture and offer numerous possibilities for further modification at the amine functionality. Noteworthy, the synthesis of **4** has been performed without problems on 10 *g*-scale.[12]

To demonstrate the usefulness of the concept a small library of 14 pybims was prepared from **3** and **4** (Table 1). Treatment with benzyl bromide in the presence of sodium hydride gave the corresponding ligands **5a** and **6a** in 68% and 65% yields respectively (Table 1, entry 1 and 3).

The reaction of tosyl chloride (Table 1, entry 2 and 4), carbonyl chlorides (Table 1, entry 5−10, and 13) and chloroformates (Table 1, entry 11, 12, and 14) with **3** or **4** gave the corresponding pybim ligands **5b, 6b−l** in moderate to very good yield (60 to 97%) by using DMAP in dichloromethane at 0 °C to room temperature.

For the preparation of **6k**, (*S*)-methoxy-α-methyl-2-naphthalene acetyl chloride was prepared by refluxing the corresponding acid in $CHCl_3$ with excess of thionyl chloride (Table 1, entry 13).

With the newly developed ligands in hand, we looked for a suitable test reaction to demonstrate that substitution of imidazoline NH group has a significant influence on catalysis. In principle, pybim-type ligands should be useful for any reaction, which use pybox ligands, e.g., aziridinations, epoxidations, carbene reactions, addition of nucleophiles to carbonyl groups, etc.[10] Among the various catalytic reactions known for pybox ligands asymmetric epoxidations with hydrogen peroxide are among the most challenging methods.[13] Therefore, we decided to study the behavior of the

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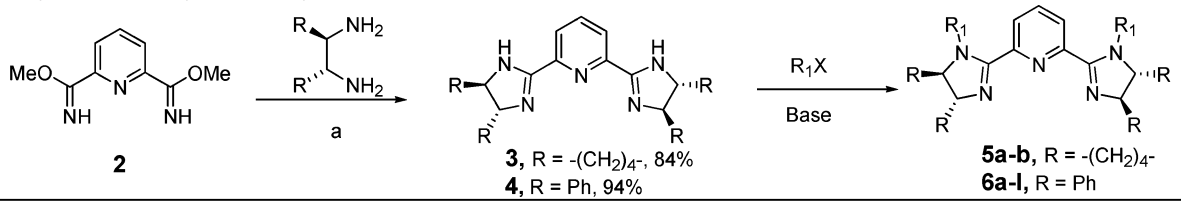
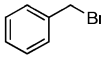
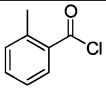
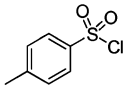
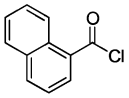
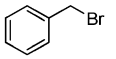
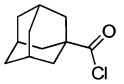
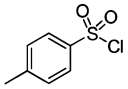
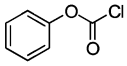
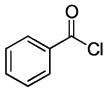
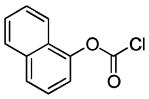
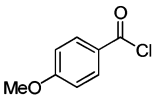
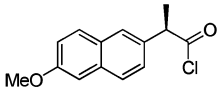
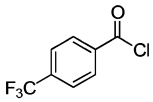
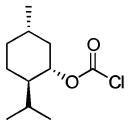
(12) A 100 mL pressure tube was charged with bis imidate **2** (4.55 g, 23.6 mmol), (*R, R*) 1, 2 diphenyl ethylenediamine (10.0 g, 47.1 mmol) and 75 mL of dichloromethane. The resulting mixture was stirred at reflux for 2 days. Then 50 mL of water was added and the phases were separated; the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo to give a light yellow solid, which was purified by crystallization (ether/ethyl acetate) to give **4** in 62% yields (7.6 g, 3.46 mmol).

(13) For reviews of H_2O_2 as epoxidation oxidant see: (a) Grigoropoulou, G.; Clark, J. H.; Elings, J. A. *Green Chem*. **2003**, *5*, 1−7. (b) Lane, B. S.; Burgess, K. *Chem. Rev*. **2003**, *103*, 2457−2473. For a commentary, see: (c) Beller, M. *Adv. Synth. Catal*. **2004**, *346*, 107−108.

Table 1. Synthesis of a Pybim Library



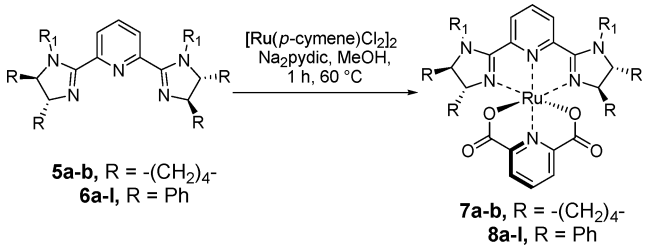
entry	R_1X	ligand	yield (%)	entry	R_1X	ligand	yield (%)
1		**5a**	68[b]	8		**6f**	99[c]
2		**5b**	93[c]	9		**6g**	94[c]
3		**6a**	65[b]	10		**6h**	96[c]
4		**6b**	85[c]	11		**6i**	98[c]
5		**6c**	96[c]	12		**6j**	84[c]
6		**6d**	87[c]	13		**6k**	62[c]
7		**6e**	97[c]	14		**6l**	90[c]

Reagents and conditions: [a] CH_2Cl_2, reflux, 2 d; [b] 2.5 equiv. NaH, THF, 0 °C to room temperature, 4 h; [c] 3.0 equiv. DMAP, CH_2Cl_2, 0 °C to room temperature, 5 h.

new ligands in the ruthenium-catalyzed asymmetric epoxidation[8,14] of stilbene with hydrogen peroxide. For this purpose, the pyridinebisimidazoline ligands **5a**−**b** and **6a**−**l** were transformed into the novel class of Ru(pybim)(pydic) complexes **7a**−**b** and **8a**−**l,** using disodium pyridine-2,6-dicarboxylate and $[Ru(p\text{-cymene})Cl_2]_2$ (Scheme 1).[15] The catalytic reactions were run at room temperature in the presence of 5 mol% of Ru-complex using 3 equiv. of H_2O_2 (30% in water), which was slowly dosed into the reaction mixture.

As shown in Table 2, all the Ru(pybim)(pydic) complexes catalyzed the epoxidation of *trans*-stilbene. It is important to note that the enantioselectivity and reactivity of the catalyst is largely dependent on the respective substituent on the nitrogen of the imidazoline ring (remote functionality) of Ru(pybim)(pydic) complex. This is a clear proof of our concept and by steric and electronic tuning at this position an optimization of the catalyst is possible. Similar effects

Scheme 1. Synthesis of Ru(pybim)(pydic) Complexes



Note: For R_1 substituent see Table 1.

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(15) Nishiyama, H.; Shimada, T.; Itoh, H.; Sugiyama, H.; Motoyama, Y. *Chem. Commun*. **1997**, 1863−1864.

Table 2. Ru(pybim)(pydic) Catalyzed Asymmetric Epoxidation of *trans* Stilbene Using H_2O_2 as Oxidant[a]

entry	catalyst	time (h)	conv. (%)	yield (%)[b]	*ee* (%)[c]
1	**7a**	16	85	79	1
2	**7b**	12	100	93	8
3	**8a**	16	90	79	11
4	**8b**	4	77	63	21
5	**8c**	12	100	90	34
6	**8d**	12	100	>99	38
7	**8e**	12	100	78	33
8	**8f**	12	100	>99	52
9	**8 g**	12	100	91	56
10	**8h**	12	100	97	28
11	**8i**	12	100	>99	60
12	**8j**	12	100	>99	71
13	**8k**	12	100	94	69
14	**8l**	12	100	97	71

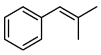
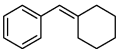
[a] Reaction conditions: In a 25 mL Schlenk tube Ru complex (0.025 mmol) and *trans* stilbene (0.5 mmol) were dissolved in *tert* amyl alcohol (9 mL). Dodecane (GC internal standard, 100 μL) was added. To this mixture a solution of hydrogen peroxide (170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added over a period of 12 h by a syringe pump. [b] Determined by comparing with authentic samples on GC FID. [c] Determined by HPLC and the major enantiomer of *trans* stilbene oxide had 1*R*,2*R* configuration.

might be expected for other catalytic reactions which proceed in the presence of pybox ligands, too.

More specifically the Ru(*R,R*-cyclohexyl-*N,N*′-Bn_2-pybim)(pydic) complex **7a** gave a racemic mixture of *trans*-stilbene oxide (79%) with low reactivity (Table 2, entry 1), while Ru-complexes which were synthesized from *tetra*-phenyl pybim ligands with *N*-benzoyl protection **8a**−**g** led to good to excellent yields (78 → 99%) and significant enantioselectivities (33−56% *ee*) (Table 2, entries 5−9). Best results for the epoxidation of *trans*-stilbene were obtained applying the carbamate-functionalized complexes **8j** and **8l**. Here, the enantioselectivity was increased up to 71% *ee* for *trans*-stilbene oxide (97 → 99% yield) (Table 2, entry 12 and 14). Interestingly, also **8k**, functionalized with the sterically bulky and flexible chiral (*S*)-2-(6-methoxynaphthyl)propionic acid gave 69% *ee* for *trans*-stilbene oxide (Table 2, entry 13).

Next, some preliminary substrate variation was done and catalyst **8l** was applied to different olefins (Table 3). To our delight, mono-, di-, and trisubstituted aromatic olefins gave good to excellent yields (76 → 99%) and moderate to good enantioselectivity (42−68%) (Table 3). Specifically, the result for styrene (Table 3, entry 1) is promising for further development of this type of catalyst since it is one of the most difficult substrates for epoxidation using hydrogen peroxide and often found in the literatures with low yields and enantioselectivity.[16] To the best of our knowledge, the maximum enantioselectivity is only 59% for styrene oxide using hydrogen peroxide as the oxidant.[8d]

Table 3. Catalyst Scope[a]

entry	substrate	conv. (%)[b]	yield (%)[b]	selec. (%)	*ee* (%)[c]
1		100	76	76	42
2		100	82	82	68
3		100	88	88	43
4		100	>99	>99	54

[a] Reaction conditions: In a 25 mL Schlenk tube Ru catalyst **8l** (0.025 mmol) and substrate (0.5 mmol) were dissolved in *tert* amyl alcohol (9 mL). Dodecane (GC internal standard, 100 μL) was added. To this mixture a solution of hydrogen peroxide (170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added over a period of 12 h by a syringe pump. [b] Determined by comparing with authentic samples on GC FID. [c] Determined by HPLC.

In summary, we have disclosed a novel class of chiral tridentate, pyridinebisimidazoline ligands (*pybims*). The key building blocks **3** and **4** are conveniently synthesized in two steps from commercially available starting materials. Similar compounds should be available by using other chiral 1,2-diamines.

Ru-complexes derived from most of the new ligands are effective catalysts for asymmetric epoxidation of alkenes with hydrogen peroxide. Advantageously, compared to the well-known pybox ligands systematic modification of the catalyst system is possible due to the presence of the imidazoline NH-groups. As proof of concept it is shown that these remote functionalizations have an important impact on the outcome of catalytic epoxidation reactions.

Acknowledgment. This work has been supported by the State of Mecklenburg−Western Pommerania. We thank Mrs. C. Mewes, Mrs. H. Baudisch, Mrs. A. Lehmann, and Mrs. S. Buchholz (all IfOK) for their excellent technical and analytical support. Dr. H. Hugl and Dr. W. Mägerlein (LANXESS) are thanked for general discussions.

Supporting Information Available: Experimental procedures and characterization of all ligands, complexes and epoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Stoop, R. M.; Mezzetti, A. *Green Chem.* **1999**, 39−41. (b) Stoop, R. M.; Bachmann, S.; Valentini, M.; Mezzetti, A. *Organometallics* **2000**, *19*, 4117−4126. (b) Bolm, C.; Kadereit, D.; Valacchi, M. *Synlett.* **1997**, 687−688. (c) Bolm, C.; Meyer, N.; Raabe, G.; Weyhermüller, T.; Bothe, E. *Chem. Commun.* **2000**, 2435−2436. (d) Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R.; Patel, S. T.; Jasra, R. V. *Tetrahedron: Asymmetry* **2001**, *12*, 433−437.

Publication 3.2.

Synthesis of a novel class of chiral *N,N,N*-tridentate pyridinebisimidazoline ligands and their application in Ru-catalzed asymmetric epoxidations

Gopinathan Anilkumar, Santosh Bhor, Man Kin Tse, Markus Klawonn, Bianca Bitterlich, Matthias Beller

Tetrahedron: Asymmetry **2005**, 16, 3536-3561

Contributions:

In this paper, I contributed to a significant amount of the argumentation and I supported the synthetic work. I synthesized Pyridine-2,6-dicarboximidic acid dimethyl ester (**2**) and 2,6-Bis-([4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine (**3**) which serve as key-intermediates for the development of the ligand library. My contribution as co-author of this paper is approximately 15 %.

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Synthesis of a novel class of chiral *N*,*N*,*N*-tridentate pyridinebisimidazoline ligands and their application in Ru-catalyzed asymmetric epoxidations

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Abstract A new class of easily tunable *N*,*N*,*N* pyridinebisimidazoline (pybim) ligands have been synthesized. The synthesis and tunability of these chiral tridentate ligands are much easier and flexible compared to the popular pyboxes, making the former a suit able ligand tool box for various asymmetric transformations. Ruthenium complexes of the new ligands were synthesized and applied in the asymmetric epoxidation of olefins using hydrogen peroxide as the oxidant. Excellent yields and moderate to good enantio selectivities were achieved in the epoxidation of aromatic olefins.

1. Introduction

Asymmetric synthesis continues to be an important area of research in organic chemistry due to the special properties of enantiomerically pure compounds, which are the focus of modern pharmaceutical industry.[1] Among the different methods available, transition metal-catalyzed asymmetric reactions offer an efficient and elegant way for the synthesis of pure enantiomers.[2] Generally, the design and synthesis of a chiral controller ligand is the most critical step in the development of a new catalyst for asymmetric reactions. A wide variety of chiral mono-, bi- and multidentate ligands with *P*, *N*, *O* and other coordinating atoms are now available and used extensively for all kinds of catalytic reactions. Prominent examples of the so-called privileged ligand classes include salens,[3] bisoxazolines,[4] phosphinooxazolines,[5] tartrate derivatives[6] and cinchona alkaloids.[7] However, there is still an increasing demand for new and improved ligands. State-of-the-art chiral ligands[8] should offer the user a series of advantages: obviously it should give a highly selective, active and productive catalyst. Moreover, the ligand should be prepared conveniently and economically from a mg- to kg-scale. Unfortunately, each catalytic reaction needs its own optimized ligand. To find a suitable optimal catalyst for a specific reaction, a library of ligands having a basic core skeleton amenable for easy functionalization should be conceivable without much difficulty. However, the systematic modification of a structure of new ligands is often difficult and time consuming.

In this context, we designed a new chiral ligand scaffold, which could be efficiently synthesized and easily functionalized.[9] Herein, we report the synthesis of a library of a new class of chiral ligands by easy functionalization of a basic skeleton, along with the application of these ligands in the Ru-catalyzed asymmetric epoxidation of olefins. The effect of acids as additives in these reactions is also demonstrated.

The starting point of this work was our studies on ruthenium-catalyzed epoxidation of olefins with C_2-symmetric pyridinebisoxazolines (pybox) as the chiral ligand.[10] During the study of the pybox ligands, we came to realize that the synthesis of a library of pybox ligands is limited and time consuming, due to the difficulty of functionalization of the ligand backbone and step-wise formation of the oxazoline moiety.[11]

To circumvent this problem, we thought of replacing the oxygen atoms in pybox by nitrogens, which gives the

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advantage of functionalization at nitrogen in an easy manner; thus allowing the synthesis of a library of ligands from a basic skeleton by N-alkylation, N-arylation, N-acylation, etc. to vary the reactivity as well as the selectivity in catalytic asymmetric reactions (Fig. 1). Although pyboxes are extensively used in stereoselective reactions,[12] to the best of our knowledge, analogous chiral pyridinebisimidazoline ligands, here abbreviated as pybim, have not been synthesized and applied in asymmetric catalysis prior to our work.[9]

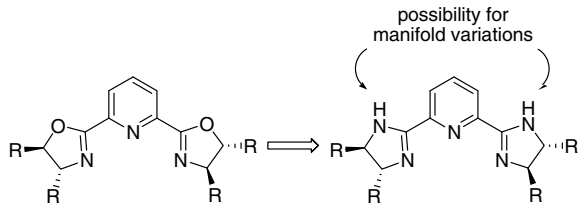


Figure 1. Design of pybim from pybox ligands.

2. Results and discussion

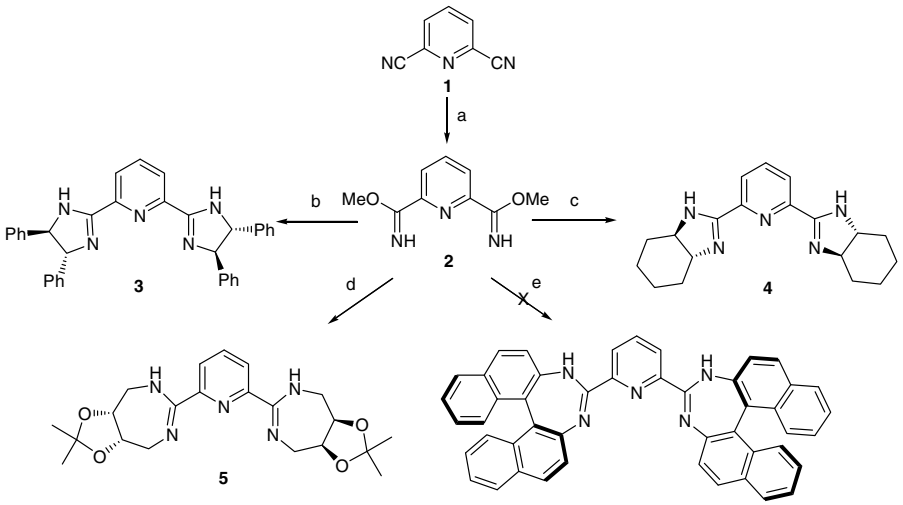
Bisimidate **2** was easily prepared by stirring the commercially available 2,6-pyridinedinitrile **1** with a catalytic amount of sodium in anhydrous methanol at room temperature, followed by neutralization with acetic acid and subsequent removal of the solvent (Scheme 1).[13] Reaction of bisimidate **2** with diamines should give the cyclic diimine derivatives. Thus, treatment of **2** with (*R*,*R*)-1,2-diphenylethylenediamine or (*R*,*R*)-1,2-diaminocyclohexane smoothly afforded the corresponding pyridine bisimidazoline derivatives (pybims) **3** and **4** in 84% and 95% yield, respectively, by refluxing in dichloromethane.

Interestingly, the related pyridinebisdiazepine **5** could be also synthesized by reaction of **2** with (4*S*,5*R*)-4,5-di-(aminomethyl)-2,2-dimethyl dioxolane. To the best of our knowledge, this is the first example of a chiral pyridinebisdiazepine. However, the preparation of the corresponding bisbinaphthyl derivative failed, presumably due to the greater strain in forming this benzoanellated seven-membered ring (see Scheme 1).

Next, pybims **3** and **4** were taken for further studies due to their stability in air and moisture, efficient formation and scope for easy derivatization. Notably, the synthesis of **3**, has been performed on 10 g scale without any problems and purification is possible by crystallization.[9,14] The presence of two secondary amino groups on the pybims, which are amenable for easy functionalization, allows for the formation of a library of compounds easily from a single basic skeleton, which is not possible in the popular pybox ligands. Thus, 29 ligands were prepared by coupling pybims **3** and **4** with a variety of reagents, such as acid chlorides, chloroformates and sulfonyl chlorides, etc.

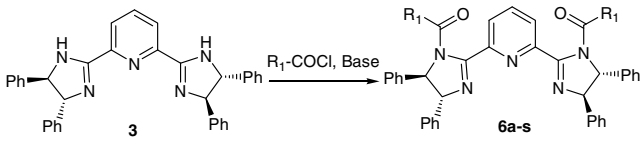
Initially, we prepared a series of amide derivatives of **3** by reaction with acid chlorides in the presence of a base in dichloromethane at room temperature (Table 1). After screening bases, such as NaH, KO^{t}Bu, triethylamine, pyridine, 4-dimethylaminopyridine (DMAP), etc., we found that DMAP was the most suitable for this reaction.

Hence, reaction of tetraphenyl pybim **3** with benzoyl chloride in the presence of DMAP in dichloromethane at room temperature furnished, after column chromatography, dibenzoyl pybim **6a** as a white solid in 96% yield. The ^{1}H NMR spectrum of **6a** showed doublets at δ 5.15 and 5.19 with a coupling constant of 3.40 Hz corresponding to the two pairs of mutually coupled vicinal protons on the imidazoline rings. The aromatic protons of the phenyl groups were observed at δ 7.02 7.43 as multiplets and those of the pyridine rings were observed at δ 7.73 as doublet of a doublet and at δ 7.83 as doublet.



Scheme 1. Reagents and conditions: (a) Na (10 mol %), MeOH, rt; (b) (1*R*,2*R*) diphenylethylenediamine, CH_2Cl_2, 50 °C; (c) (1*R*,2*R*) diaminocyclohexane, CH_2Cl_2, 50 °C; (d) (4*S*,5*S*) 4,5 diaminomethyl 2,2 dimethyldioxolane, CH_2Cl_2, 50 °C; (e) (*R*) 2,2 diamino 1,1 binaphthyl, CH_2Cl_2, 50 °C.

Table 1. Synthesis of *N* acyl protected pybims from acid chlorides



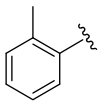
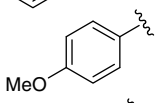
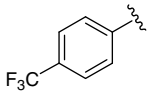
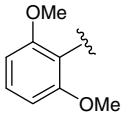
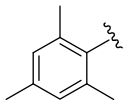
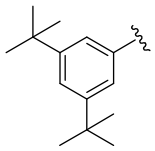
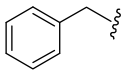
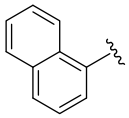
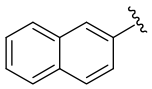
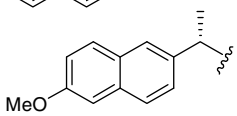
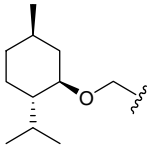
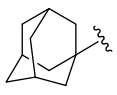
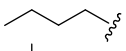
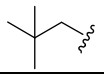
Entry	R_1	Ligand	Yield (%)[a]
1		**6a**	96
2		**6b**	99
3		**6c**	87
4		**6d**	97
5		**6e**	47
6		**6f**	45[b]
7		**6g**	32
8		**6h**	87
9		**6i**	100
10		**6j**	94
11		**6k**	76
12		**6l**	62
13		**6m**	92
14		**6n**	96
15		**6o**	86

Table 1 (*continued*)

Entry	R_1	Ligand	Yield (%)[a]
16		**6p**	93
17		**6q**	92
18		**6r**	93
19		**6s**	83

Reagents and conditions:
[a] DMAP (3 equiv), CH_2Cl_2, rt, 1 5 h.
[b] NaH (3 equiv), PhCl, reflux, 45 h.

The ^{13}C NMR spectra showed two peaks at δ 60.4 and 71.9, corresponding to the two pairs of symmetrical benzylic carbons on the imidazoline rings. The aromatic carbons and the imino carbon on the imidazoline were distributed from δ 125.5 139.4, while the amide carbon was observed at δ 169.3. The IR spectrum showed the characteristics of an amide carbonyl stretching vibration with an absorption at 1670 cm ^{1}. EI-MS showed a molecular mass peak at 728 (M^+), which was further supported by HRMS.

Using the above reaction conditions, ligands **6b s** were prepared with a variety of substitution pattern, such as mono-, di- and tri-substituted aryls, 1- and 2-naphthyls, adamantyl and various alkyl groups (see Table 1). In the case of the trimethylbenzoyl derivative **6f**, reacting the trimethylbenzoyl chloride with **3** in refluxing chlorobenzene in the presence of NaH was necessary to furnish the product in good yield (Table 1, entry 6). For the (*S*)-methoxy-α-methyl-2-naphthalene acetyl derivative **6l**, the chloride required for the reaction was prepared in situ from the corresponding acid with excess of thionyl chloride in refluxing chloroform (Table 1, entry 12).

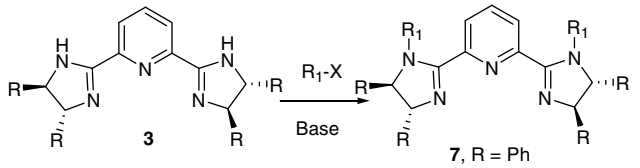
Next, we tried acylation with aliphatic carboxylic acid derivatives. Menthyl- and adamantyl-derived pybims **6m** and **6n** were formed in excellent yields. Less bulky aliphatic carboxylic acids formed the corresponding *N*-acyl pybims also in excellent yields (Table 1, entries 15 18). Protecting the NH groups of **3** with trimethylacetyl chloride met with defeat obviously due to steric reasons. However, *tert*-butylacetyl chloride reacted smoothly, affording **6s** in 83% yield (Table 1, entry 19).

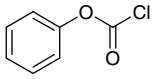
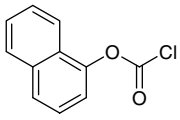
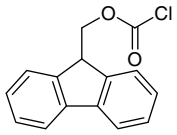
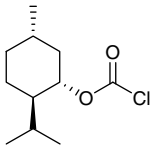
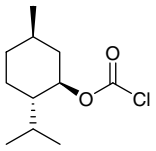
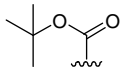
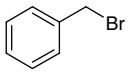
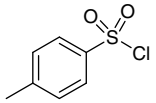
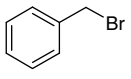
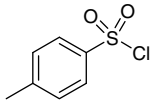
We then reacted **3** with chloroformates. Thus, by following the above procedure, a series of carbamates **7a f** was prepared in excellent yields (Table 2). The reaction was found to be fast compared to that of acid chlorides. In addition, **7f** was prepared by reaction of **3** with di-*tert*-butyldicarbonate in the presence of DMAP at room temperature (Table 2, entry 6). To vary the substituent pattern of the pybim scaffold further, we reacted benzyl bromide and tosyl chloride with **3**, which afforded **7g** and **7h** in 65% and 85% yield, respectively (Table 2, entries 7 and 8).

Similar to **3**, reaction of dicyclohexyl pybim **4** with benzyl bromide and *p*-tosyl chloride gave products **8a** and

8b in good yield (Table 2, entries 9 and 10). However, reactions of **4** with benzoyl chloride, *p*-methoxy benzoyl chloride and (−)-menthyl chloroformate were unsuccessful due to the instability of the products during column chromatography. The reason for this is not clear.

Table 2. Synthesis of N protected pybims from chloroformates and other halides



Entry	R_1 X	Ligand	Yield (%)[a]
1		**7a**	98
2		**7b**	84
3		**7c**	94
4		**7d**	90
5		**7e**	94
6		**7f**	91[b]
7		**7g**	65[c]
8		**7h**	85
9		**8a**	68[c]
10		**8b**	93

Reagents and conditions:
[a] DMAP (3 equiv), CH_2Cl_2, rt, 1 h.
[b] $(Boc)_2O$ (3 equiv), DMAP, (3 equiv), CH_2Cl_2, rt, 12 h.
[c] NaH (2.5 equiv), THF, rt, 4 h.

Attempts were also made to prepare urea derivatives of the pybim by reaction of **3** with phenylisocyanate in the presence of various bases and also using dibutyltindilaurate,[15] which resulted only in the trimerization of phenylisocyanate.

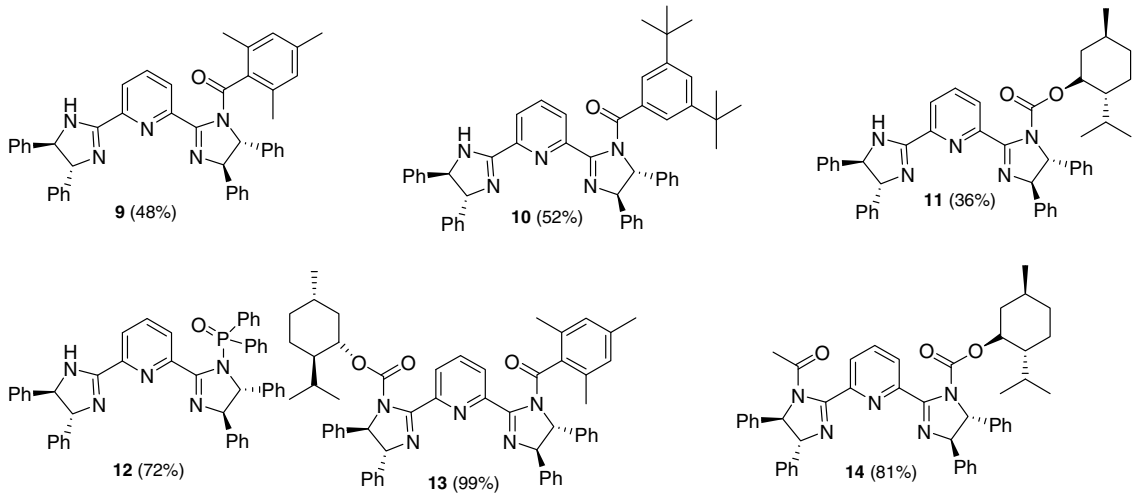
All new compounds shown were fully characterized (NMR, IR, MS and HRMS or EA) and gave satisfactory analytical data.

During the synthesis of trimethylbenzoyl pybim **6f**, we isolated a considerable amount of the mono-protected pybim **9** (Scheme 2). This prompted us to synthesize a few more mono-protected pybims **10** **12** by reaction of **3** with 1 equiv of a suitable acid chloride or chloroformate compound. The idea behind this was to also synthesize asymmetrically substituted pybims by reacting the free NH of the mono-protected pybim with a second different protecting group.

We presumed that an unsymmetrical complex prepared from such a ligand would direct the substrate (e.g., olefin in epoxidation) to occupy a specific orientation in the transition state and thereby induce selectivity during catalysis. With this in mind, compounds **13** and **14** were synthesized from the mono-protected pybims **9** and **11** with (+)-menthyl chloroformate and acetyl chloride, respectively. Unfortunately, an attempted one-pot sequential protection of the two amino groups of **3** by different protecting groups was unsuccessful since it produced an inseparable mixture of products.

With a library of pybims in hand, we searched for a suitable reaction to test the usefulness of these ligands in catalysis. Clearly, it was an objective to demonstrate that the substitution of an imidazoline NH group had a significant impact on catalysis. Due to the structural analogy of the pybim ligands to the pyboxes, it was reasonable to believe that any reaction that is catalyzed by metal pybox complexes should also be suitable for pybims as well. Hence, pybims should act as suitable ligands for aziridination, epoxidation, carbene reactions, addition of nucleophiles to carbonyl groups, etc.[12] Amongst the many catalytic reactions known for pyboxes, we selected asymmetric epoxidation using hydrogen peroxide for our studies since we were recently involved in investigating this type of reaction.[10d,16]

Consequently, we decided to investigate the behaviour of the new ligands in the Ru-catalyzed asymmetric epoxidation[9,17] of styrene and *trans*-stilbene with H_2O_2. For this purpose, ligand **6a** was reacted with $[Ru(p\text{-cymene})Cl_2]_2$ and disodium pyridine-2,6-dicarboxylate (pydic) in MeOH H_2O mixture at 65 °C to afford, after purification by column chromatography, the dark brown solid **15a** in good yield (Table 3, entry 1).[18] The ^1H NMR of **15a** showed two doublets at δ 4.42 and 5.15 for two protons each corresponding to the mutually coupled protons of the imidazoline rings. The aromatic protons of the four phenyl groups and those from the pyridine dicarboxylate ring were distributed from δ 6.56 7.65. The three mutually coupled protons of the pyridine ring of the pybim moiety resonated at δ 7.73 as a triplet and at δ 8.22 as a doublet (J 8.10 Hz).



Scheme 2. Unsymmetrical pybim ligands.

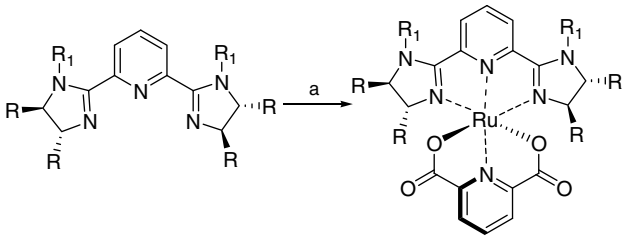
In the ^{13}C NMR, the two symmetrical benzylic carbon atoms on the imidazoline rings were seen at δ 74.1 and 77.5 while the two carbonyls were observed at δ 170.2 and 170.4. Mass spectrum and elemental analysis were in agreement with the structure assigned.

In a similar manner, Ru (pybim)(pydic) complexes **15b s**, **16a h** and **17a**,**b** were prepared in good to excellent yields (Table 3). All compounds were fully characterized and gave satisfactory spectral and analytical data. Due to the presence of a large hydrocarbon skeleton, the di-*tert*-butylbenzoyl ligand **6g** and the Fmoc-derived ligand **7c** were sparingly soluble in MeOH and therefore modification of the general reaction condition was needed to prepare the corresponding ruthenium complexes **15g** and **16c**. Thus, in the case of **6g**, the complexation was performed in a mixture of 12:5:1 *tert*-amyl-OH/MeOH/H_2O, which afforded complex **15g** in acceptable yields (Table 3, entry 7). Formation of **16c** was achieved in 59% yield by using a mixture of 4:4:1 *n*-BuOH/MeOH/H_2O as the solvent system. Unsymmetrical ligands **12 14** were also transformed into their respective ruthenium complexes **18 20** by following the general complexation procedure in good yields without any difficulty (Scheme 3).

We mentioned earlier that the synthesis of pybim ligands **4** is sometimes difficult due to their unstable nature during purification by silica gel and alumina column chromatography. We circumvented this problem by reacting **4** with the appropriate acid chlorides or chloroformates and subjecting the crude product directly to complexation with a ruthenium source and Na_2pydic. In this way, we were able to prepare ruthenium complexes **21 23** (Scheme 4).

With a number of Ru(pybim)(pydic) complexes in hand, we tested the asymmetric epoxidation of styrene and *trans*-stilbene using H_2O_2 as the oxidant. For the catalysis experiments, we chose the reaction conditions, which we developed earlier for the epoxidation of olefins using pybox ligands (rt, 3 equiv of H_2O_2 (30% in water) were slowly dosed into the reaction mixture by a syringe pump).[10d]

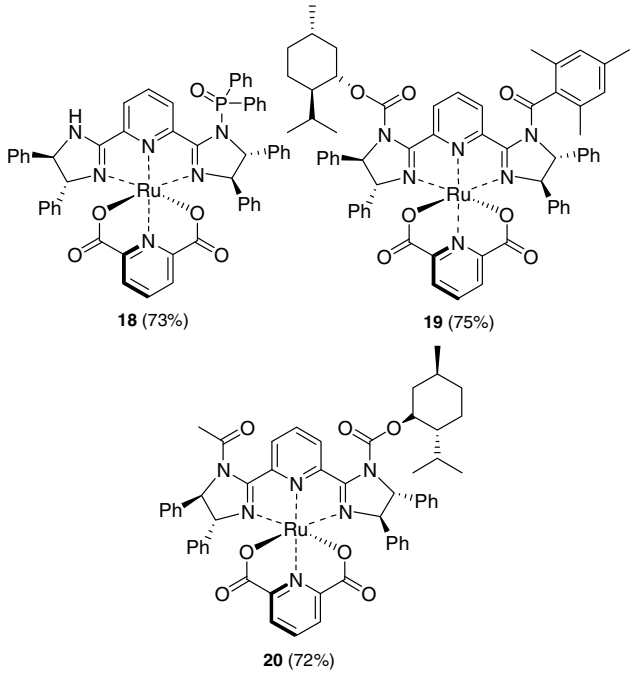
Table 3. Synthesis of Ru(pybim)(pydic) complexes



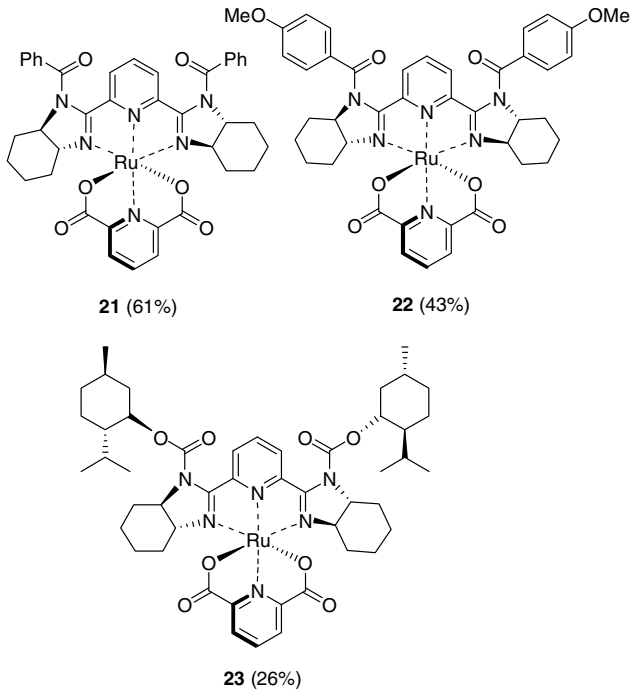
6a-s: R = Ph, For R_1 seeTable 1 — **15a-s**
7a-h: R = Ph, For R_1 seeTable 2 — **16a-h**
8a, b: R = -$(CH_2)_4$-, For R_1 seeTable 2 — **17a, b**

Reagents and conditions: (a) [Ru(*p*-cymene)$Cl_2]_2$, Na_2pydic, MeOH, H_2O, 65 °C, 1 h.

Entry	Ligand	Complex	Yield (%)
1	**6a**	**15a**	56
2	**6b**	**15b**	93
3	**6c**	**15c**	75
4	**6d**	**15d**	71
5	**6e**	**15e**	42
6	**6f**	**15f**	59
7	**6g**	**15g**	43
8	**6h**	**15h**	30
9	**6i**	**15i**	49
10	**6j**	**15j**	40
11	**6k**	**15k**	64
12	**6l**	**15l**	78
13	**6m**	**15m**	46
14	**6n**	**15n**	66
15	**6o**	**15o**	68
16	**6p**	**15p**	75
17	**6q**	**15q**	98
18	**6r**	**15r**	77
19	**6s**	**15s**	77
20	**7a**	**16a**	52
21	**7b**	**16b**	33
22	**7c**	**16c**	60
23	**7d**	**16d**	52
24	**7e**	**16e**	58
25	**7f**	**16f**	77
26	**7g**	**16g**	45
27	**7h**	**16h**	50
28	**8a**	**17a**	55
29	**8b**	**17b**	55



Scheme 3. Unsymmetrical Ru(pybim)(pydic) complexes.



Scheme 4. In situ generation of ruthenium complexes **21** **23**.

To find the optimum catalyst concentration, the epoxidation of styrene was performed using **16d** with varying catalyst loading. It was observed that full conversion and best yield were obtained in the presence of 5 mol % of catalyst (Fig. 2). This catalyst loading was used throughout our studies.

Next, all the complexes prepared were screened for the asymmetric epoxidation of styrene and *trans*-stilbene

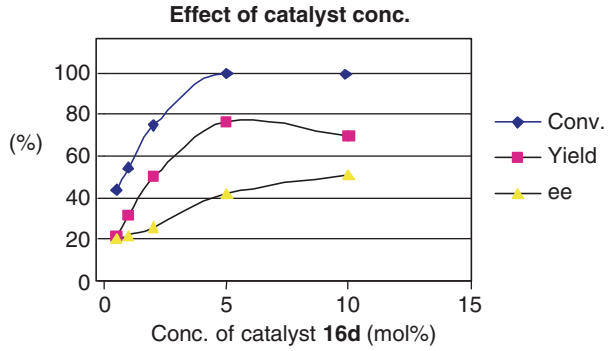


Figure 2. Effect of concentration of catalyst **16d** on the epoxidation of styrene.

and the results are shown in Table 4. Almost all complexes studied gave full conversion. However, it is important to note that the chemo- and enantioselectivity of the catalyst are dependent on the respective substituent on the nitrogen of the imidazoline ring (remote functionality) of the Ru(pybim)(pydic) complex. Although a rationalization on the electronic and/or steric influence of the substituent at the nitrogen of the imidazoline ring is difficult on the basis of the catalysis results depicted in Table 4, certain groups such as the 2-naphthyl, menthyl, etc. can be identified as potential substituents for the control of enantioselectivity.

In the case of styrene epoxidation, the yield of the product varied from 65% to 75% for benzoyl-protected pybims **15a l**, while that for aliphatic *N*-acyl-protected pybims **15n s** showed a small increment (80 85%) (Table 4, entries 1 12 and 14 19). The carbamate complexes **16a f** showed similar reactivities towards styrene (70 80%) and *trans*-stilbene (87 100%); but the enantioselectivities varied. To our delight, the dimethoxybenzoyl pybim complex **15e** and the menthyl carbamate complex **16d** showed the highest enantioselectivities (45% and 43%) for styrene (Table 4, entries 5 and 23), which is one of the most difficult substrates for epoxidation using H_2O_2 and often found in the literature with low yields and enantioselectivities.[19]

Due to the better reactivity of *trans*-stilbene, most of the complexes gave excellent yields with this substrate. Moreover, the enantioselectivities observed were also good. Notable are the performances of **15e**, **15i** and **15j** in the category of benzoyl-derived pybims and **16b**, **16d** and **16e** in the category of carbamate-functionalized pybims (Table 4, entries 5, 9, 10, 21, 23 and 24). In general, the carbamate-derived complexes gave better enantioselectivities both in styrene and *trans*-stilbene epoxidation.

All the complexes derived from **4** showed poor performances in both reactivity and enantioselectivity (Table 4, entries 28, 29, and 31 35). The unsymmetrical pybim complex **19**, which had a menthyl group on one side of the pybim and a trimethylbenzoyl group at the other, showed enantioselectivities comparable to those observed for complex **16d** (Table 4, entry 31 vs 23). The enantioselectivities observed for **15e** for styrene (45%)

Table 4. Ru(pybim)(pydic) catalyzed asymmetric epoxidation of styrene and *trans* stilbene using H_2O_2 as the oxidant[a]

Entry	Catalyst	Ph				Ph Ph			
		Time (h)	Conv. (%)	Yield (%)	ee (%)	Time (h)	Conv. (%)	Yield (%)	ee (%)
1	**15a**	12	100	64	15	12	100	90	34
2	**15b**	12	100	75	25	12	100	99	52
3	**15c**	12	100	78	1	12	100	99	38
4	**15d**	12	100	63	7	12	100	78	33
5	**15e**	12	100	77	**45**	16	92	84	46
6	**15f**	16	84	63	22	16	46	32	45
7	**15g**	12	100	67	18	12	100	96	40
8	**15h**	12	100	74	16	16	88	87	34
9	**15i**	12	100	70	32	12	100	95	70
10	**15j**	16	100	67	21	12	100	91	56
11	**15k**	12	100	76	6	12	100	99	43
12	**15l**	16	100	71	29	12	100	94	69
13	**15m**	12	100	67	23	12	100	90	39
14	**15n**	12	100	83	8	12	100	97	28
15	**15o**	12	100	84	20	12	100	97	51
16	**15p**	12	100	80	26	12	100	100	54
17	**15q**	12	100	85	28	12	100	100	52
18	**15r**	16	96	80	31	12	100	90	61
19	**15s**	12	100	80	30	12	100	100	66
20	**16a**	12	100	71	15	12	100	95	60
21	**16b**	12	100	77	26	12	100	99	**71**
22	**16c**	12	100	78	34	12	100	97	59
23	**16d**	12	100	72	**43**	12	100	97	**71**
24	**16e**	12	92	78	37	12	100	97	69
25	**16f**	12	100	77	13	16	94	87	59
26	**16g**					16	90	79	11
27	**16h**	12	100	73	17	16	77	63	21
28	**17a**	12	81	55	2	16	85	79	1
29	**17b**	12	100	63	31	12	100	93	8
30	**18**	12	100	70	6	12	100	93	39
31	**19**	12	100	68	**42**	12	100	93	**71**
32	**20**	12	100	86	34	12	100	100	57
33	**21**	16	87	67	3	16	98	93	5
34	**22**	16	88	64	3	12	100	93	7
35	**23**	16	94	61	9	16	94	90	7

[a] Reaction conditions: 0.5 mmol of olefin in *tert* amyl alcohol (9 mL) was oxidized in the presence of 5 mol % Ru catalyst using 1.5 mmol (170 μL) of H_2O_2 (30% in water) in *tert* amyl alcohol (830 μL) by a syringe pump over a period of 12 h.

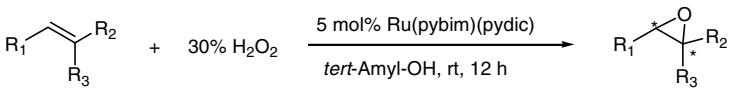
and **16d** for *trans*-stilbene (71%) are comparable to the highest values reported so far in the literature for the asymmetric epoxidation using H_2O_2 as oxidant.[10d] In addition, the reactivities of pybim complexes are comparable to that of pyboxes in the epoxidation of styrene and *trans*-stilbene. Interestingly, the sterically bulky and flexible (*S*)-methoxy-α-methyl-2-naphthalene acetyl complex **15l** gave 69% ee for *trans*-stilbene epoxide (Table 4, entry 12).

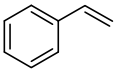
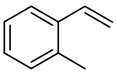
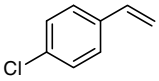
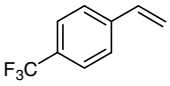
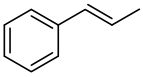
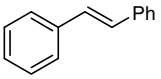
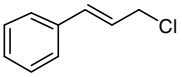
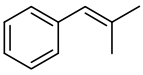
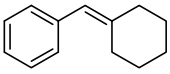
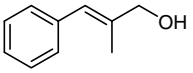
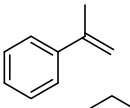
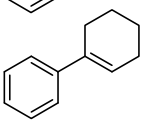
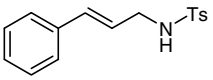
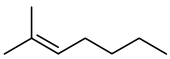
Next, we tested the scope of the catalysts in the epoxidation of other olefins. For this purpose, we selected complexes **16b** and **16d**, and applied them in the epoxidation of a variety of substrates. The results are shown in Table 5. To our delight, mono-, di- and tri-substituted aromatic olefins gave excellent yields (up to 100%) and moderate to good enantioselectivities (see Table 5). Electron donating/withdrawing groups on the aromatic ring of styrene did not influence much either the reactivity or enantioselectivity (Table 5, entries 1–4). Excellent reactivities and enantioselectivities were obtained with both complexes **16b** and **16d** when β-substituted styrenes were used as the substrates (Table 5, entries 5, 6, 8 and 9). However, α-substituted styrenes gave poor enantioselectivities (entries 11 and 12). Epoxidation of *N*-tosylcinnamylamine (Table 5, entry 13) using catalysts **16b** and **16d** gave very low ee (1–3%) and the epoxide was found to be unstable in the GC column and thus a reliable data on yield and selectivity could not be obtained.

Finally, we studied the epoxidation of styrene with **16d** in the presence of varying concentrations of acetic acid as the additive. The use of acids for the enhancement of efficiency of metal-catalyzed reactions is known in the literature and the reason for such enhancements can be attributed to the stabilization of the complex under the reaction conditions.[20] However, the results revealed that acetic acid had no significant influence on the conversion, yield or ee of the epoxidation of styrene (Table 6).

Other carboxylic acids, such as trifluoroacetic acid, benzoic acid, *p*-methoxy- and *p*-chloro-benzoic acids, were also tested. Trifluoroacetic acid showed a marginal

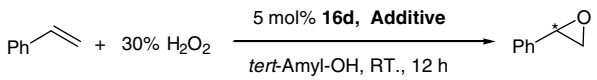
Table 5. Scope and limitations of the Ru(pybim)(pydic) catalysts in asymmetric epoxidation



Entry	Substrate	16b				16d			
		Conv. (%)	Yield (%)	Selec.[a] (%)	ee (%)	Conv. (%)	Yield (%)	Selec.[a] (%)	ee (%)
1		100	77	77	26	100	76	76	42
2		100	68	68	23	100	88	88	43
3		100	72	72	31	100	68	68	50
4		78	50	64	28	68	60	88	42
5		100	100	100	56	100	100	100	65
6		100	100	100	71	100	97	97	71
7		70	52	74	23	90	71	79	23
8		100	79	79	62	100	82	82	68
9		100	100	100	58	100	100	100	54
10		100	47	47	11	100	47	47	7
11		100	69	69	2	100	55	55	1
12		100	73	73	3	100	72	72	0
13		100			5	100			2
14						100	76	76	n.d.

[a] Selectivity refers to the ratio of yield to conversion in percentage.

Table 6. Effect of additives on the epoxidation of styrene



HOAc (mol%)	Conv. (%)	Yield (%)	ee (%)	Additive (20 mol %)	Conv. (%)	Yield (%)	ee (%)
0	100	76	42	CH_3COOH	100	76	42
2.5	100	71	45	CF_3COOH	100	54	32
5.0	100	72	43	PhCOOH	100	72	43
10.0	100	72	44	4 MeO $C_6H_4CO_2H$	100	71	44
20.0	100	73	42	4 Cl $C_6H_4CO_2H$	100	75	42

decrease in yield and ee while all other acids showed no appreciable influence.

Considering the parallels between pyboxes and pybims in their structure, reactivity and enantioselectivity in epoxidation reactions, a mechanistic pathway similar to that proposed for Ru(pybox)(pydic) involving a ruthenium dioxocomplex[10d] as the active species was envisaged for the pybim-catalyzed epoxidation.

3. Conclusion

We have designed and synthesized a new class of easily tunable pyridinebisimidazoline ligands (pybim). The tunability of these ligands is much higher compared to that of the structurally related pybox ligands. The ligands were easily transformed into Ru(pybim)(pydic) complexes and applied in the catalytic asymmetric epoxidation of styrene and *trans*-stilbene. The newly developed pybim complexes showed comparable reactivities and enantioselectivities to those obtained by using pybox complexes. The scope and limitations of the complexes were investigated on the asymmetric epoxidation of a variety of olefins.

The facile synthesis of the pybim ligands together with their easy tunability makes them a suitable toolbox for application to numerous other catalytic asymmetric reactions.

4. Experimental

4.1. General

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. Melting points were determined on a Leica galen III melting point apparatus and were uncorrected. Optical rotations were measured with a Perkin Elmer (model 241MC) polarimeter. Column chromatography was carried out using silica gel from Fluka. TLC was performed on Merck 60 F_{254} silica gel plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 spectrometer using the solvent as the internal reference. Data are reported as follows: chemical shifts (δ) in parts per million, coupling constants (J) in hertz. Mass spectra were recorded with an AMD 402/3 mass spectrometer. GC analyses were performed with a Hewlett Packard HP 6890 model spectrometer and UV vis spectra were recorded with a Shimadzu (model UV-1601) spectrophotometer. HPLC analyses were performed with a Hewlett Packard HP 1090 instrument using Chiralcel AD, Chiralcel OB H, Chiralcel OD, Chiralcel OD-H or Whelk chiral column. Elemental analyses were performed on a CHNS 932 analyzer from Leo company.

4.2. Pyridine-2,6-dicarboximidic acid dimethyl ester 2

To pyridine-2,6-carbodinitrile **1** (5.35 g, 41.5 mmol) in anhydrous MeOH (100 mL), was added metallic Na (120 mg, 5.20 mmol). After stirring for 40 h at room temperature, AcOH (300 μL, 5.25 mmol) was added and the solvent removed under reduced pressure to give **2** as a pale yellow powder (8.50 g, 100 %), which was used without further purification.

4.3. 2,6-Bis-([4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 3

In a 50 mL oven dried pressure tube, **2** (455 mg, 7.06 mmol) and (*R*,*R*)-1,2-diphenylethylene diamine (1.00 g, 4.70 mmol) were dissolved in dichloromethane (30 mL). The resulting mixture was stirred at refluxing temperature for two days. Then, water (20 mL) was added, the phases separated and the aqueous phase extracted with dichloromethane (2×20 mL). The combined organic layer was dried over Na_2SO_4 and the solvent removed in vacuo to give a light yellow solid, which was purified by silica gel column chromatography to give **3** as a white solid (1.15 g, 95%). R_f 0.52 (CH_2Cl_2/MeOH 10:1); mp 123 126 °C; $[\alpha]_D^{20} = +112.4$ (c 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90 (br s, 4H), 7.22 7.31 (m, 20H), 7.89 (t, J 7.8, 1H), 8.46 (d, J 7.8, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.9, 125.5, 127.1, 128.3, 129.2, 136.1, 138.2, 142.9, 162.1; EI-MS: m/z 519 (M^+); Anal. Calcd (%) for $C_{35}H_{29}N_5$: C, 78.19; H, 5.81; N, 13.03. Found: C, 78.20; H, 5.58; N, 13.20.

4.4. 2,6-Bis-([4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 3

A 100 mL pressure tube was charged with **2** (4.55 g, 23.6 mmol), (*R*,*R*)-1,2-diphenylethylenediamine (10.0 g, 47.1 mmol) and 75 mL of dichloromethane. The resulting mixture was stirred at reflux for two days. To the reaction mixture, 50 mL of water was added and the phases separated; the aqueous phase was extracted with dichloromethane (2×50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo to give a light yellow solid, which was purified by crystallization (ether/ethyl acetate) to give **3** (7.62 g, 62%).

4.5. 2,6-Bis-([3*aR*,7*aR*]-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine 4

A 50 mL oven dried pressure tube was charged with **2** (804 mg, 4.17 mmol), (*R*,*R*)-1,2-diaminocyclohexane (1.00 g, 8.75 mmol) and dichloromethane (40 mL). After the resulting mixture was stirred at refluxing temperature for two days, water (20 mL) was added and the phases separated. The aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic layer was dried over Na_2SO_4 and the solvent removed in vacuo to give a light yellow solid, which was purified by crystallization (ethyl acetate) to give **4** as a white solid (1.12 g, 84%). mp 320 322 °C; $[\alpha]_D^{20} = +242.4$ (c 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (1.34m, 4H), 1.55 (m, 4H), 1.83 (m, 4H), 2.28 (m, 4H), 3.36 (m, 4H) 7.81 (t, J 7.3, 1H), 7.21 (d, J 7.3, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 21.6, 22.9, 30.7, 23.5, 137.3, 147.8, 164.6;

EI-MS: *m*/*z* 323 (M^+); Anal. Calcd (%) for $C_{19}H_{25}N_5$: C, 70.76; H, 7.79; N, 21.65. Found: C, 70.32; H, 7.81; N, 21.59.

4.6. (3*aR*,6*Z*,8*aS*)-4,5,8,8a-tetrahydro-6-(6-((*Z*,3*aR*,8*aS*)-4,5,8,8a-tetrahydro-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*e*]-[1,3]diazepin-6-yl)pyridin-2-yl)-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-e][1,3]diazepine 5

Compound **5** was prepared as described for the synthesis of **3** using **2** (292 mg, 1.50 mmol), (4*S*,5*R*)-4,5-di-(aminomethyl)-2,2-dimethyl dioxolane (500 mg, 3.10 mmol) and 15 mL of dichloromethane in a pressure tube at 50 °C. After 2 days, the solvents were removed in vacuo to give a light yellow oil, which was purified by column chromatography on neutral alumina to give a white solid (100 mg, 16%). R_f 0.75 (CH_2Cl_2/MeOH 10:1, neutral alumina); mp 232 234 °C; $[\alpha]_D^{20} = +32.7$ (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 12H), 3.18 (br s, 4H), 3.68 (m, 4H), 3.85 (br s, 4H), 7.77 (t, *J* 7.9, 1H), 8.29 (d, *J* 7.9, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 78.8, 80.4, 111.1, 122.4, 137.7, 151.3, 151.9; EI-MS: *m*/*z* 415 (M^+); HRMS (ESI+): calcd for $C_{21}H_{29}N_5O_4$: 415.2219. Found: 415.2213.

4.7. General procedure for the synthesis of *N*-acyl-protected pybim ligands (procedure A)

A 50 mL oven dried one necked round bottom flask fitted with a magnetic stirring bar was charged with **3** (208 mg, 0.4 mmol) and DMAP (147 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (15 mL). The mixture was cooled to 0 °C and then acid chloride or chloroformate (1.2 mmol) added dropwise. The cooling bath was removed and the reaction mixture stirred at rt and the progress of the reaction was monitored by TLC. The reaction mixture was then washed with water (2 × 20 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent.

4.8. 2,6-Bis-(1-benzoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6a

Prepared according to general procedure A using **3** (200 mg, 0.38 mmol), DMAP (140 mg, 1.15 mmol), benzoyl chloride (134 μL, 1.15 mmol) and dichloromethane (8 mL). The residue was purified by silica gel column chromatography to give **6a** as a white solid (270 mg, 96%). R_f 0.27 (CH_2Cl_2/MeOH 100:5); mp 110 113 °C; $[\alpha]_D^{20} = -68.1$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 5.15 (d, *J* 3.4, 2H), 5.19 (d, *J* 3.4, 2H), 7. 02 7.06 (m, 4H), 7.11 7.13 (m, 6H), 7.25 7.29 (m, 6H), 7.33 7.36 (m, 6H), 7.39 7.43 (m, 8H), 7.73 (dd, *J* 6.7, 8.7, 1H), 7.83 (d, *J* 7.1, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 60.4, 71.9, 125.5, 126.3, 126.7, 126.9, 127.3, 127.4, 127.4, 128.0, 128.1, 128.3, 128.4, 129.1, 131.9, 134.6, 137.7, 139.4, 169.3; IR (KBr): ν 3060, 1670, 1358 cm^{-1}; EI-MS: *m*/*z* 728 (M^+); HRMS (ESI+): calcd for $C_{49}H_{38}N_5O_2$: 728.3025. Found: 728.3016.

4.9. 2,6-Bis-(1-(2-methyl-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6b

Prepared according to general procedure A using **3** (208 mg, 0.4 mmol), DMAP (147 mg, 1.2 mmol) and *o*-toluoyl chloride (160 μL, 1.2 mmol) in anhydrous CH_2Cl_2 (15 mL) for 12 h followed by column chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to give pale yellow crystals (304 mg, 100%). R_f 0.80 (CH_2Cl_2/MeOH 100:5); mp 116 118 °C; $[\alpha]_D^{20} = -115.7$ (*c* 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 2.08 (s, 6H), 5.22 (br d, *J* 2.43, 4H), 6.77 (t, *J* 7.53, 2H), 6.89 6.96 (m, 4H), 7.03 (t, *J* 7.92, 2H), 7.02 7.29 (m, 6H), 7.37 7.58 (m, 17H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 19.4, 70.6, 78.4, 124.3, 124.9, 125.3, 126.3, 127.1, 127.8, 128.1, 129.1, 129.2, 129.9, 130.5, 135.0, 137.1, 140.7, 141.8, 149.9, 168.8; IR (KBr): ν 3061, 3027, 1675, 1625, 1331 cm^{-1}; HRMS: calcd for $C_{51}H_{41}N_5O_2{\cdot}H^+$: 756.3339. Found: 756.3326; Anal. Calcd (%) for $C_{51}H_{41}N_5O_2{\cdot}2H_2O$: C, 77.35; H, 5.73; N, 8.84. Found: C, 78.02; H, 5.44; N, 8.68.

4.10. 2,6-Bis-(1-(4-methoxy-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6c

Prepared according to general procedure A using **3** (400 mg, 0.77 mmol), DMAP (206 mg, 1.69 mmol), 4-methoxybenzoyl chloride (260 μL, 1.92 mmol) and dichloromethane (10 mL). The residue was purified by silica gel column chromatography using MeOH CH_2Cl_2 as the gradient eluent to give **6c** as a white solid (527 mg, 87%). R_f 0.48 (CH_2Cl_2/MeOH 100:5); mp 191 193 °C; $[\alpha]_D^{20} = -86.4$ (*c* 0.41, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 3.66 (s, 6H), 5.08 (d, 2H), 5.10 (d, 2H), 6.53 (d, *J* 8.9, 4H), 7.04 7.12 (m, 6H), 7.26 7.40 (m, 18H), 7.81 (dd, *J* 6.9, 8.3, 1H), 7.92 (d, *J* 7.5, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 56.1, 72.6, 79.9, 113.9, 125.2, 126.1, 127.2, 128.1, 128.3, 128.7, 129.7, 131.3, 138.1, 141.1, 142.5, 150.2, 161.6, 163.1, 169.9, 193.6; EI-MS: *m*/*z* 787 (M^+); HRMS: calcd for $C_{51}H_{42}N_5O_4{\cdot}H^+$: 788.3238. Found: 788.3240.

4.11. 2,6-Bis-(1-(4-trifluoromethyl-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6d

Prepared according to general procedure A using **3** (400 mg, 0.77 mmol), DMAP (281 mg, 2.31 mmol), 4-trifluoromethylbenzoyl chloride (286 μL, 1.92 mmol) and dichloromethane (10 mL). The residue was purified by silica gel column chromatography using MeOH CH_2Cl_2 as the gradient eluent to give **6d** as a white solid (600 mg, 97%). R_f 0.55 (CH_2Cl_2/MeOH 100:5); mp 114 117 °C; $[\alpha]_D^{20} = -41.9$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 5.13 (d, *J* 3.5, 2H), 5.22 (d, *J* 3.5, 2H), 7.09 7.18 (m, 6H), 7.30 7.38 (m, 20H), 7.15 7.38 (m, 20H), 7.41 7.45 (m, 4H), 7.85 (dd, *J* 6.7, 8.5, 1H), 7.94 (d, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 72.4, 79.9, 125.6, 125.7, 125.8, 126.1, 127.0, 128.7, 128.9, 129.3, 129.8, 138.6, 139.2, 140.7, 141.8, 149.8, 160.3, 168.7; EI-MS: *m*/*z* 864 (M^+); Anal. Calcd (%) for $C_{51}H_{35}N_5F_6O_2$: C, 70.91; H, 4.08; N, 8.11. Found: C, 70.77; H, 3.85; N, 8.05.

4.12. 2,6-Bis-(1-(2,6-dimethoxy-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6e

Prepared according to general procedure A using **3** (208 mg, 0.4 mmol), DMAP (147 mg, 1.2 mmol) and 2,6-dimethoxybenzoyl chloride (245 mg, 1.2 mmol) in refluxing 1,2-dichloroethane (15 mL) for 24 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (167 mg, 47%). R_f 0.25 (CH_2Cl_2/MeOH 100:5); mp 135 138 °C; $[\alpha]_D^{20} = -86.1$ (*c* 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 6H), 3.83 (s, 6H), 5.02 (d, *J* 2.82, 2H), 5.65 (d, *J* 2.56, 2H), 6.04 (d, *J* 8.52, 2H), 6.16 (d, *J* 8.52, 2H), 6.57 (d, *J* 8.52, 2H), 6.85 (t, *J* 8.32, 2H), 7.05 (d, *J* 7.72, 2H), 7.33 7.55 (m, 15H), 7.56 (d, *J* 7.12, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 58.4, 59.2, 104.5, 124.7, 125.5, 127.2, 127.5, 128.1, 128.5, 128.7, 129.3, 129.9, 130.9, 139.2, 148.9, 157.9, 164.1, 167.1; IR (KBr): ν 2934, 1674, 1628, 1596, 1112 cm ^{1}; FAB-MS: *m*/*z* 848 (M^+); HRMS: calcd for $C_{53}H_{46}N_5O_6$: 848.3448. Found: 848.3437.

4.13. 2,6-Bis-(1-(2,4,6-trimethoxy-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6f

Prepared according to general procedure A using **3** (415 mg, 0.8 mmol), NaH (64 mg, 2.4 mmol) and 2,4,6-trimethylbenzoyl chloride (448 mg, 2.4 mmol) in refluxing chlorobenzene (20 mL) for 45 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (296 mg, 45%). R_f 0.30 (CH_2Cl_2/MeOH 100:5); mp 96 98 °C; $[\alpha]_D^{20} = -49.2$ (*c* 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 2.13 (br s, 18H), 4.82 (d, *J* 8.52, 2H), 5.13 (d, *J* 8.52, 2H), 7.30 7.44 (m, 27H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 18.5, 19.2, 19.9, 69.1, 77.8, 122.9, 125.3, 126.1, 126.3, 126.5, 126.6, 127.6, 127.9, 128.2, 128.9, 129.4, 138.8, 141.5, 142.8; IR (KBr): ν 2921, 1673, 1629, 1330 cm ^{1}; HRMS: calcd for $C_{55}H_{50}N_5O_2$: 812.3964. Found: 812.3965.

4.14. 2,6-Bis-(1-(3,5-di-*tert*-butylbenzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6g

Prepared according to general procedure A using **3** (363 mg, 0.7 mmol), DMAP (244 mg, 2.0 mmol) and 3,5-di-*tert*-butylbenzoyl chloride (524 mg, 2.0 mmol) in dichloromethane (20 mL) for 12 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (216 mg, 32%). R_f 0.30 (CH_2Cl_2/MeOH 100:5); $[\alpha]_D^{20} = -93.3$ (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.00 (s, 36H), 5.18 (br s, 2H), 5.44 (d, *J* 4.96, 2H), 7.12 7.30 (m, 10H), 7.38 (t, *J* 7.12, 4H), 7.43 7.50 (m, 12H), 7.72 7.75 (m, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 30.7, 34.6, 71.0, 78.8, 124.3, 125.0, 126.3, 127.8, 128.1, 129.1, 129.3, 134.9, 135.8, 137.4, 141.9, 169.6; IR (KBr): ν 2963, 1673, 1364 cm ^{1}; HRMS: calcd for $C_{65}H_{69}N_5O_2{\cdot}H^+$: 952.5529. Found: 952.5536; Anal. Calcd (%) for $C_{65}H_{69}N_5O_2{\cdot}3H_2O$: C, 77.58; H, 7.51; N, 6.95. Found: C, 77.72; H, 7.04; N, 6.67.

4.15. 2,6-Bis-(1-phenylacetyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6h

Prepared according to general procedure A using **3** (208 mg, 0.4 mmol), DMAP (147 mg, 1.2 mmol) and phenylacetyl chloride (159 μL, 1.5 mmol) in dichloromethane (15 mL) for 1.5 h at rt followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (246 mg, 87%). R_f 0.30 (CH_2Cl_2/MeOH 100:5); mp 83 84 °C; $[\alpha]_D^{20} = +27.4$ (*c* 0.23, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 3.57 (s, 4H), 5.15 (d, *J* 2.64, 2H), 5.39 (d, *J* 2.82, 2H), 6.84 6.89 (m, 4H), 7.13 7.44 (m, 22H), 7.54 7.59 (m, 4H), 7.92 8.04 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 43.3, 70.1, 78.1, 124.9, 125.1, 126.3, 127.0, 128.1, 128.5, 129.0, 129.4, 133.8, 138.2, 140.7, 141.7, 150.5, 158.6, 169.0; HRMS: calcd for $C_{51}H_{41}N_5O_2{\cdot}H^+$: 756.3338. Found: 756.3333; Anal. Calcd (%) for $C_{51}H_{41}N_5O_2{\cdot}H_2O$: C, 79.15; H, 5.60; N, 9.05. Found: C, 79.15; H, 5.85; N, 8.37.

4.16. 2,6-Bis-(1-(diphenylacetyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6i

Prepared according to general procedure A **3** (208 mg, 0.4 mmol), DMAP (147 mg, 1.2 mmol) and diphenylacetyl chloride (310 μL, 1.4 mmol) in 1,2-dichloromethane (20 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (366 mg, 100%). R_f 0.50 (CH_2Cl_2/MeOH 100:5); mp 108 109 °C; $[\alpha]_D^{20} = -29.6$ (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 5.00 (br s, 2H), 5.10 (d, *J* 2.80, 2H), 5.37 (br s, 2H), 6.80 (d, *J* 7.32, 4H), 6.99 7.33 (m, 32H), 7.57 (dd, *J* 3.96, 7.36, 4H), 7.74 (d, *J* 7.76, 2H), 7.93 (t, *J* 7.72, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 40.1, 57.1, 116.5, 125.1, 126.3, 127.1, 127.3, 127.9, 128.1, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.4, 135.8, 138.3, 140.7, 154.8, 169.7; IR (KBr): ν 1686, 1366, 1152 cm ^{1}; FAB-MS: *m*/*z* 908 (M^+); HRMS: calcd for $C_{63}H_{49}N_5O_2{\cdot}H^+$: 908.3964. Found: 908.4009; Anal. Calcd (%) for $C_{63}H_{49}N_5O_2{\cdot}2H_2O$: C, 80.15; H, 5.65; N, 7.42. Found: C, 80.57; H, 5.01; N, 6.98.

4.17. 2,6-Bis-(1-naphthoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6j

Prepared according to general procedure A using **3** (400 mg, 0.77 mmol), DMAP (281 mg, 2.31 mmol) and 1-naphthoyl chloride (255 μL, 1.69 mmol) in dichloromethane (16 mL). The residue was purified by silica gel column chromatography using MeOH CH_2Cl_2 as the gradient eluent to give **6j** as a white solid (600 mg, 94%). R_f 0.37 (CH_2Cl_2/MeOH 100:5); mp 130 132 °C; $[\alpha]_D^{20} = -104.3$ (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 5.17 (unresolved d, 2H), 5.51 (unresolved d, 2H), 6.98 (m, 4H), 7.15 (m, 2H), 7.34 7.70 (m, 31H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 70.2, 77.7, 116.6, 123.6, 123.6, 125.2, 126.2, 126.4, 126.9, 128.0, 128.1, 129.1, 129.2, 130.4, 132,8, 132.9, 135.6, 135,8, 137.5, 137.5, 140.8, 141.9, 149.2, 149.3, 156.2; EI-MS: *m*/*z* 828 (M^++1), 827 (M^+); HRMS: calcd for $C_{57}H_{42}N_5O_2{\cdot}H^+$: 828.3338. Found: 828.3355.

4.18. 2,6-Bis-(2-naphthoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6k

Prepared according to general procedure A using **3** (260 mg, 0.5 mmol), DMAP (180 mg, 1.5 mmol) and 2-naphthoyl chloride (294 mg, 1.5 mmol) in 1,2-dichloroethane (15 mL) for 2 h at rt followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (326 mg, 76%). R_f 0.60 (CH_2Cl_2/MeOH 100:5); mp 129 130 °C; $[\alpha]_D^{20} = +39.1$ (*c* 0.39, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 5.16 (br s, 4H), 6.99 7.05 (m, 6H), 7.22 7.58 (m, 24H), 7.68 7.75 (m, 5H) 7.87 (d, *J* 7.71, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 72.1, 79.0, 124.3, 124.8, 125.4, 126.4, 126.6, 127.5, 127.6, 127.8, 127.9, 128.0, 128.7, 129.0, 129.1, 131.7, 132.2, 134.5, 137.3, 140.2, 141.7, 149.2, 160.5, 169.6; IR (KBr): ν 1669, 1358, 1321, 1136 cm^{-1}; HRMS: calcd for $C_{57}H_{41}N_5O_2{\cdot}H^+$: 828.3338. Found: 828.3340; Anal. Calcd (%) for $C_{57}H_{41}N_5O_2{\cdot}H_2O$: C, 80.92; H, 5.12; N, 8.27. Found: C, 80.72; H, 4.29; N, 7.90.

4.19. 2,6-Bis-(1-[(2*S*)-2-(6-methoxy-naphthalen-2-yl)-propionyl]-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6l

Prepared according to general procedure A using **3** (400 mg, 0.77 mmol), DMAP (281 mg, 2.31 mmol), (*S*)-2-(6-methoxy-naphthaten-2-yl)-propionyl chloride (574 mg, 2.31 mmol) and dichloromethane (10 mL). The residue was purified by silica gel column chromatography using MeOH CH_2Cl_2 as the gradient eluent to give **6l** as a white solid (450 mg, 62%). R_f 0.75 (CH_2Cl_2/EtOAc 8:2); mp 115 118 °C; $[\alpha]_D^{20} = -46.6$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.31 (d, 6H), 3.73 (q, 2H), 3.91 (s, 6H), 4.95 (d, *J* 4.8, 2H), 5.18 (d, *J* 4.8, 2H), 6.93 7.17 (m, 16H), 7.33 7.35 (m, 6H), 7.44 (m, 2H), 7.52 7.54 (m, 4H), 7.57 7.60 (m, 4H) 7.83 (d, *J* 7.6, 2H), 7.98 (t, *J* 7.6, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 20.5, 45.6, 55.3, 68.4, 78.9, 105.5, 116.7, 118.7, 123.7, 125.3, 125.5, 126.0, 126.1, 127.6, 127.7, 128.1, 128.9, 129.3, 129.4, 133.7, 135.2, 137.5, 140.6, 141.7, 151.1, 157.8, 159.2, 171.3; EI-MS: *m*/*z* 944 (M^+); HRMS: calcd for $C_{63}H_{53}N_5O_4$: 944.4176. Found: 944.4167.

4.20. 2,6-Bis-(1-(2-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy-acetyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6m

Prepared according to general procedure A using **3** (416 mg, 0.8 mmol), DMAP (294 mg, 2.4 mmol) and (−)-menthoxyacetyl chloride (540 μL, 2.4 mmol) in dichloromethane (20 mL) for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (673 mg, 92%). R_f 0.75 (CH_2Cl_2/MeOH 100:5); mp 60 61 °C; $[\alpha]_D^{20} = -21.8$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.54 (d, *J* 6.92, 6H), 0.72 (d, *J* 6.52, 6H), 0.79 (d, *J* 7.12, 6H), 0.80 1.23 (m, 8H), 1.49 1.68 (m, 10H), 2.87 (dt, *J* 4.16, 10.68, 2H), 3.85 (d, *J* 14.64, 2H), 4.03 (d, *J* 14.68, 2H), 5.15 (d, *J* 2.56, 2H), 5.42 (d, *J* 2.56, 2H), 7.24 7.49 (m, 20H), 8.03 8.12 (m, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 15.6, 20.8, 21.8, 22.9, 25.2, 31.5, 34.3, 39.9, 48.1, 69.5, 70.1, 77.7, 80.8, 124.8, 125.0, 126.5, 127.8, 128.0, 129.0, 129.2, 137.8, 140.8, 141.7, 150.1, 158.6, 169.5; IR (KBr): ν 2954, 2924, 1680, 1617, 1383 cm^{-1}; HRMS: calcd for $C_{59}H_{69}N_5O_4{\cdot}H^+$: 912.5428. Found: 912.5410; Anal. Calcd (%) for $C_{59}H_{69}N_5O_4{\cdot}H_2O$: C, 76.18; H, 7.69; N, 7.53. Found: C, 76.18; H, 8.21; N, 6.46.

4.21. 2,6-Bis-(1-adamantoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6n

Prepared according to general procedure A using **3** (200 mg, 0.38 mmol), DMAP (206 mg, 1.69 mmol) and adamantoyl chloride (260 μL, 1.92 mmol) in dichloromethane (10 mL). The residue was purified by silica gel column chromatography using MeOH CH_2Cl_2 as the gradient eluent afforded **6n** as a white solid (310 mg, 96%). R_f 0.53 (CH_2Cl_2/MeOH 100:5); mp 132 135 °C; $[\alpha]_D^{20} = -22.0$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.43 1.46 (m, 6H), 1.52 1.60 (m, 14H), 1.77 1.80 (m, 12H), 5.16 (d, *J* 4.2, 2H), 5.29 (d, *J* 4.2, 2H), 7.24 7.26 (m, 4H), 7.32 7.42 (m, 16H), 7.95 (dd, *J* 6.8, 8.6, 1H), 8.03 (d, *J* 6.8, 1H), 8.03 (d, *J* 8.6, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 28.1, 36.2, 39.0, 43.7, 71.3, 81.6, 124.2, 126.1, 126.5, 127.9, 127.9, 128.9, 129.2, 137.1, 141.1, 142.2, 150.7, 163.7, 181.3; EI-MS: *m*/*z* 844 (M^+); HRMS: calcd for $C_{57}H_{58}N_5O_2$: 844.4590. Found: 844.4574.

4.22. 2,6-Bis-(1-acetyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6o

Prepared according to general procedure A using **3** (420 mg, 0.81 mmol), DMAP (296 mg, 2.42 mmol) and acetyl chloride (178 μL, 2.42 mmol) in dichloromethane (20 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded a pale yellow solid (419 mg, 86%). R_f 0.45 (CH_2Cl_2/MeOH 100:5); mp 108 109 °C; $[\alpha]_D^{20} = -24.5$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.93 (s, 6H), 5.14 (d, *J* 2.64, 2H), 5.34 (d, *J* 2.64, 2H), 7.29 7.55 (m, 20H), 8.07 8.09 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 24.5, 70.0, 78.0, 78.1, 124.7, 125.0, 126.3, 128.0, 128.1, 129.1, 129.3, 138.3, 140.8, 141.8, 150.4, 158.8, 168.0; IR (KBr): ν 2929, 1727, 1405, 1210 cm^{-1}; EI-MS: *m*/*z* 603 (M^+); HRMS: calcd for $C_{39}H_{33}N_5O_2{\cdot}H^+$: 604.2707. Found: 604.2704.

4.23. 2,6-Bis-(1-pentanoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6p

Prepared according to general procedure A using **3** (520 mg, 1.00 mmol), DMAP (367 mg, 3.00 mmol) and valeryl chloride (358 μL, 3.00 mmol) in dichloromethane (25 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded a pale yellow solid (637 mg, 93%). R_f 0.30 (CH_2Cl_2/MeOH 100:5); mp 50 51 °C; $[\alpha]_D^{20} = -9.6$ (*c* 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.68 (t, *J* 7.35, 6H), 0.89 1.12 (m, 4H), 1.29 1.59 (m, 4H), 1.98 2.29 (m, 4H), 5.15 (d, *J* 2.82, 2H), 5.32

(unresolved d, 2H), 7.29 7.56 (m, 20H), 8.02 8.09 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 13.4, 22.1, 26.7, 36.0, 69.9, 78.1, 124.4, 125.1, 126.2, 127.9, 128.1, 129.1, 129.3, 138.1, 141.0, 142.0, 150.8, 159.1, 171.1; IR (KBr): ν 2957, 2931, 1685 (br), 1453, 1380 cm ^{1}; EI-MS: m/z 687 (M^+); HRMS: calcd for $C_{45}H_{45}N_5O_2$: 687.3568. Found: 687.3593; Anal. Calcd (%) for $C_{45}H_{45}N_5O_2{\cdot}H_2O$: C, 76.57; H, 6.71; N, 9.92. Found: C, 76.79; H, 6.76; N, 9.36.

4.24. 2,6-Bis-(1-(2-methyl propanoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6q

Prepared according to general procedure A using **3** (520 mg, 1.00 mmol), DMAP (367 mg, 3.00 mmol) and isobutyryl chloride (315 μL, 3.00 mmol) in dichloromethane (25 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded a pale yellow solid (607 mg, 92%). R_f 0.45 (CH_2Cl_2/MeOH 100:5); mp 86 87 °C; $[\alpha]_D^{20} = -34.8$ (c 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.87 (d, J 6.78, 6H), 0.93 (d, J 6.78, 6H), 2.37 2.45 (m, 2H), 5.14 (d, J 2.82, 2H), 5.27 (d, J 2.82, 2H), 7.30 7.54 (m, 20H), 7.99 8.10 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 18.6, 19.8, 33.9, 70.1, 78.4, 124.3, 125.2, 126.2, 127.9, 128.1, 129.1, 129.3, 137.9, 141.1, 142.2, 151.1, 159.4, 175.8; IR (KBr): ν 2973, 1691 (br), 1618, 1466, 1388 cm ^{1}; EI-MS: m/z 659 (M^+); HRMS: calcd for $C_{43}H_{41}N_5O_2$: 659.3255. Found: 659.3263; Anal. Calcd (%) for $C_{43}H_{41}N_5O_2{\cdot}H_2O$: C, 76.19; H, 6.39; N, 10.33. Found: C, 76.19; H, 6.18; N, 9.96.

4.25. 2,6-Bis-(1-(3-methyl butanoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6r

Prepared according to general procedure A using **3** (520 mg, 1.00 mmol), DMAP (367 mg, 3.00 mmol) and isovaleryl chloride (367 μL, 3.00 mmol) in dichloromethane (25 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded a pale yellow solid (638 mg, 93%). R_f 0.35 (CH_2Cl_2/MeOH 100:5); mp 59 60 °C; $[\alpha]_D^{20} = -21.7$ (c 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.68 (d, J 6.39, 6H), 0.71 (d, J 6.39, 6H), 1.89 2.00 (m, 2H), 2.05 2.16 (m, 4H), 5.15 (d, J 2.82, 2H), 5.30 (d, J 2.82, 2H), 7.31 7.55 (m, 20H), 8.01 8.10 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 22.1, 25.5, 45.0, 70.0, 68.2, 124.4, 125.1, 126.2, 127.9, 128.1, 129.1, 129.3, 138.0, 141.0, 142.0, 150.9, 159.2, 170.6; IR (KBr): ν 2958, 1691 (br), 1466, 1375 cm ^{1}; EI-MS: m/z 687 (M^+); HRMS: calcd for $C_{45}H_{45}N_5O_2$: 687.3568. Found: 687.3553; Anal. Calcd (%) for $C_{45}H_{45}N_5O_2{\cdot}H_2O$: C, 76.57; H, 6.71; N, 9.92. Found: C, 76.51; H, 6.54; N, 9.33.

4.26. 2,6-Bis-(1-(3,3-dimethyl butanoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 6s

Prepared according to general procedure A using **3** (520 mg, 1.00 mmol), DMAP (367 mg, 3.00 mmol) and *tert*-butylacetyl chloride (417 μL, 3.00 mmol) in dichloromethane (25 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded a pale yellow solid (595 mg, 83%). R_f 0.25 (CH_2Cl_2/MeOH 100:5); mp 74 75 °C; $[\alpha]_D^{20} = -35.4$ (c 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.81 (s, 18H), 1.93 (d, J 15.24, 2H), 2.08 (d, J 15.24, 2H), 5.15 (d, J 2.82, 2H), 5.28 (d, J 2.82, 2H), 7.30 7.56 (m, 20H), 7.99 8.12 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 29.3, 31.3, 47.9, 70.1, 78.1, 124.2, 125.2, 126.3, 127.9, 128.0, 129.0, 129.3, 138.0, 141.1, 142.1, 151.2, 159.4, 170.0; IR (KBr): ν 2954, 1691 (br), 1466, 1361 cm ^{1}; EI-MS: m/z 715 (M^+); HRMS: calcd for $C_{47}H_{49}N_5O_2$: 715.3881. Found: 715.3872; Anal. Calcd (%) for $C_{47}H_{49}N_5O_2{\cdot}H_2O$: C, 76.91; H, 7.00; N, 9.54. Found: C, 76.98; H, 6.61; N, 8.96.

4.27. 2,6-Bis-(1-(phenoxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 7a

Prepared according to general procedure A using **3** (260 mg, 0.5 mmol), DMAP (184 mg, 1.5 mmol) and phenyl chloroformate (190 μL, 1.5 mmol) in dichloromethane (20 mL) for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (387 mg, 98%). R_f 0.65 (CH_2Cl_2/MeOH 100:5); mp 90 91 °C; $[\alpha]_D^{20} = +8.4$ (c 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (d, J 3.96, 2H), 5.63 (d, J 3.76, 2H), 6.96 6.99 (m, 4H), 7.24 7.34 (m, 6H), 7.46 7.52 (m, 6H), 7.60 7.72 (m, 10H), 7.76 7.79 (m 4H), 8.19 8.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.5, 78.3, 121.0, 124.6, 125.3, 126.2, 127.9, 128.1, 129.0, 129.1, 129.2, 137.3, 140.7, 141.4, 149.6, 150.2, 158.4; IR (KBr): ν 1744, 1631, 1493, 1355, 1201, 1328 cm ^{1}; FAB-MS: m/z 759 (M^+); HRMS: calcd for $C_{49}H_{37}N_5O_4{\cdot}H^+$: 760.2924. Found: 760.2927.

4.28. 2,6-Bis-(1-(1-naphthyloxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 7b

Prepared according to general procedure A using **3** (260 mg, 0.5 mmol), DMAP (184 mg, 1.5 mmol) and 1-naphthyl chloroformate (240 μL, 1.5 mmol) in dichloromethane (20 mL) for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (369 mg, 84%). R_f 0.60 (CH_2Cl_2/MeOH 100:5); mp 104 106 °C; $[\alpha]_D^{20} = -7.2$ (c 0.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (d, J 3.76, 2H), 5.70 (d, J 3.76, 2H), 7.07 (dd, J 1.00, 7.72, 2H), 7.18 7.31 (m, 6H), 7.38 7.43 (m, 6H), 7.50 (m, 3H), 7.58 7.67 (m, 9H), 7.73 (d, J 8.12, 2H), 7.79 7.81 (m, 4H), 7.87 (d, J 8.32, 2H), 8.10 (m, 1H), 8.21 (d, J 7.56, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.7, 78.3, 117.8, 120.8, 124.8, 125.1, 125.5, 125.8, 126.1, 126.2, 126.5, 127.6, 128.0, 128.2, 129.2, 129.4, 134.3, 137.2, 140.9, 141.6, 145.9, 149.5, 149.7, 158.7; IR (KBr): ν 1749, 1335, 1224, 1153 cm ^{1}; FAB-MS: m/z 860 (M^+); Anal. Calcd (%) for $C_{57}H_{41}N_5O_4{\cdot}H_2O$: C, 77.97; H, 4.94; N, 7.98. Found: C, 77.88; H, 4.93; N, 7.54.

4.29. 2,6-Bis-(1-(9-fluorenylmethyloxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 7c

Prepared according to general procedure A using **3** (208 mg, 0.4 mmol), DMAP (147 mg, 1.2 mmol) and

9-fluorenylmethyl chloroformate (315 mg, 1.2 mmol) in dichloromethane (20 mL) for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (367 mg, 94%). R_f 0.40 (CH_2Cl_2/MeOH 100:5); mp 115 116 °C; $[\alpha]_D^{20} = +21.7$ (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 3.87 (t, *J* 6.12, 2H), 4.07 (dd, *J* 7.92, 10.48, 2H), 4.33 (dd, *J* 5.68, 10.52, 2H), 5.08 (d, *J* 3.36, 2H), 5.15 (d, *J* 3.16, 2H), 6.88 (dd, *J* 1.00, 7.52, 2H), 7.00 (dt, *J* 1.20, 7.52, 2H), 7.04 (d, *J* 7.36, 2H), 7.09 7.19 (m, 8H), 7.27 7.35 (m, 8H), 7.38 7.49 (m, 10H), 7.67 (t, *J* 6.76, 4H), 7.89 7.96 (m, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 46.7, 68.1, 69.7, 78.6, 119.8, 119.9, 124.0, 124.7, 125.0, 125.1, 126.3, 127.1, 127.6, 127.7, 127.9, 128.0, 129.1, 129.2, 137.4, 141.0, 141.1, 141.2, 142.1, 143.1, 143.9, 149.9, 151.6, 158.5; IR (KBr): ν 1731, 1395, 1327, 1135 cm $^{-1}$; HRMS: calcd for $C_{65}H_{49}N_5O_4{\cdot}H^+$: 964.3857. Found: 964.3869; Anal. Calcd (%) for $C_{65}H_{49}N_5O_4{\cdot}2H_2O$: C, 78.06; H, 5.34; N, 7.00. Found: C, 78.69; H, 5.06; N, 6.91.

4.30. 2,6-Bis-(1-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy carbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 7d

Prepared according to general procedure A using **3** (400 mg, 0.77 mmol), DMAP (281 mg, 2.31 mmol) and (+)-menthyl chloroformate (364 μL, 1.69 mmol) in dichloromethane (10 mL). The residue was purified by silica gel column chromatography using MeOH CH_2Cl_2 as the gradient eluent to give a white solid (610 mg, 90%). R_f 0.34 (CH_2Cl_2/MeOH 100:2); mp 88 90 °C; $[\alpha]_D^{20} = -1.1$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.37 (d, 6H), 0.55 (d, 6H), 0.53 0.59 (m, 6H), 0.63 (d, *J* 8.12, 6H), 0.74 0.88 (m, 2H), 1.05 (m, 2H), 1.34 1.41 (m, 6H), 1.75 (m, 2H), 4.22 (unresolved ddd, *J* 4.36, 2H), 5.04 (d, *J* 3.16, 2H) 5.24 (d, *J* 3.16, 2H), 7.24 7.37 (m, 12H), 7.41 7.45 (m, 4H), 7.56 7.58 (m, 4H), 7.84 (d, *J* 7.16, 1H), 7.84 (d, *J* 8.12, 1H), 7.96 (dd, *J* 7.12, 8.12, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 16.9, 21.0, 22.0, 24.1, 26.8, 31.8, 34.6, 40.8, 47.2, 69.9, 77.7, 79.1, 124.1, 125.8, 126.9, 128.4, 128.7, 129.7, 129.8, 137.8, 142.2, 143.1, 151.6, 151.8, 159.1; EI-MS: *m*/*z* 884 (M^+); Anal. Calcd (%) for $C_{57}H_{65}N_5O_4$: C, 77.43; H, 7.41; N, 7.92. Found: C, 77.04; H, 7.63; N, 7.85.

4.31. 2,6-Bis-(1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy carbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 7e

Prepared according to general procedure A using **3** (400 mg, 0.77 mmol), DMAP (281 mg, 2.31 mmol) and (−)-menthyl chloroformate (364 μL, 1.69 mmol) in dichloromethane (10 mL). The residue was purified by silica gel column chromatography using MeOH CH_2Cl_2 as the gradient eluent to give a white solid (640 mg, 94%). R_f 0.34 (CH_2Cl_2/MeOH 100:2); mp 88 90 °C; $[\alpha]_D^{20} = -48.7$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.67 (d, 6H), 0.76 (d, 6H), 0.70 0.79 (m, 2H), 0.95 1.13 (m, 6H), 1.39 1.46 (m, 2H), 1.60 1.69 (m, 6H), 1.86 1.90 (m, 2H), 4.58 (unresolved ddd, *J* 4.36, 2H), 5.28 (d, *J* 3.48, 1H), 5.40 (d, *J* 3.48, 1H), 7.43 7.62 (m, 12H), 7.58 7.62 (m, 4H), 7.71 7.73 (m, 4H), 8.03 (d, *J* 6.93, 1H), 8.03 (d, *J* 8.32, 1H), 8.14 (dd, *J* 6.95, 8.32, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 16.3, 21.2, 22.3, 23.6, 26.7, 31.9, 34.7, 41.3, 47.6, 70.5, 77.3, 79.3, 124.4, 125.9, 127.0, 128.3, 128.7, 129.7, 129.8, 137.6, 142.1, 143.2, 151.5, 152.3, 159.6; EI-MS: *m*/*z* 884 (M^+); Anal. Calcd (%) for $C_{57}H_{65}N_5O_4$: C, 77.43; H, 7.41; N, 7.92. Found: C, 77.50; H, 7.65; N, 7.79.

4.32. 2,6-Bis-(1-(1,1-dimethylethyloxy carbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1-*H*-imidazol-2-yl)-pyridine 7f

Prepared according to general procedure A using **3** (260 mg, 0.5 mmol), DMAP (184 mg, 1.5 mmol) and di-*tert*-butyldicarbonate (760 μL, 1.5 mmol) in dichloromethane (20 mL) for 12 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent afforded pale yellow crystals (337 mg, 91%). R_f 0.40 (CH_2Cl_2/MeOH 100:5); mp 84 85 °C; $[\alpha]_D^{20} = -17.1$ (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 18H), 5.39 (d, *J* 3.60, 2H), 5.54 (d, *J* 3.36, 2H), 7.48 7.57 (m, 6H), 7.64 7.76 (m, 10H), 7.86 (m, 4H), 8.21 (m, 2H), 8.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 69.4, 77.9, 82.4, 123.4, 124.9, 126.2, 127.6, 128.0, 129.0, 129.2, 137.3, 141.1, 142.2, 150.0, 151.0, 158.9; IR (KBr): ν 2976, 1718, 1630, 1368, 1138 cm $^{-1}$; HRMS: calcd for $C_{45}H_{45}N_5O_4{\cdot}H^+$: 720.3550. Found: 720.3530.

4.33. 2,6-Bis-(1-benzyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 7g

To a solution of **3** (434 mg, 0.83 mmol) in anhydrous THF (15 mL) was added sodium hydride (80.2 mg, 3.34 mmol) at 0 °C. After 15 min, benzyl bromide (298 μL, 1.85 mmol) was slowly added and the reaction mixture stirred at room temperature for 4 h. Then, the reaction mixture was quenched with water and the aqueous phase extracted with dichloromethane (2 × 20 mL). The organic layer was dried over Na_2SO_4 and the solvents removed in vacuo to give pale yellow oil, which was further purified by column chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **7g** as a white solid (380 mg, 65%). R_f 0.57 (CH_2Cl_2/MeOH 100:5); mp 75 78 °C; $[\alpha]_D^{20} = +33.7$ (*c* 0.14 $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.02 (d, *J* 15.5, 2H), 4.38 (d, *J* 9.1, 2H), 4.92 (d, *J* 9.1, 2H), 5.60 (d, *J* 15.5, 2H), 7.02 (m, 4H), 7.11 (m, 4H), 7.19 7.29 (m, 22H), 8.04 (dd, *J* 7.5, 8.1, 1H), 8.31 (d, *J* 7.9, 2H); ^{13}C NMR (400 MHz, CD_2Cl_2): δ 50.0, 74.4, 78.5, 126.9, 127.6, 127.9, 127.9, 128.4, 128.9, 129.1, 129.2, 129.6, 136.5, 138.1, 138.6, 142.4, 144.6, 150.7, 163.2; EI-MS: *m*/*z* 699 (M^+); Anal. Calcd (%) for $C_{49}H_{41}N_5{\cdot}0.5H_2O$: C, 83.02; H, 5.97; N, 9.88. Found: C, 82.68; H, 5.49; N, 9.62.

4.34. 2,6-Bis-(1-[toluene-4-sulfonyl]-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine 7h

A 50 mL Schlenk tube was charged with **3** (400 mg, 0.77 mmol), DMAP (281 mg, 2.31 mmol) and dichloromethane

(15 mL). The resulting mixture was cooled to 0 °C, and tosyl chloride (323 mg, 1.69 mmol) added neat at once. The ice bath was removed, and the reaction mixture was stirred at room temperature for 5 h. The solvent was removed under vacuo, the residue partitioned between saturated NH_4Cl (25 mL) and ethyl acetate (25 mL), and the aqueous phase re-extracted with ethyl acetate (2×25 mL). The combined organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. The residue was crystallized from ethyl acetate/hexane to give **7h** as a white solid (635 mg, 99%). R_f 0.50 (CH_2Cl_2/MeOH 100:1); mp 105 107 °C; $[\alpha]_D^{20} = -29.6$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 2.11 (s, 6H), 5.18 (d, 2H), 5.37 (d, 2H), 7.85 (d, *J* 8.1, 4H), 7.15 7.38 (m, 20H), 7.47 (d, *J* 8.1, 4H), 8.12 (dd, *J* 6.5, 8.6, 1H), 8.18 (d, *J* 6.5, 1H), 8.18 (d, *J* 8.6, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 20.7, 71.0, 78.8, 125.5, 125.8, 125.9, 127.4, 127.5, 127.6, 128.3, 128.5, 129.2, 134.5, 136.4, 140.8, 140.9, 143.9, 149.4, 156.9; EI-MS: *m*/*z* 827 (M^+); Anal. Calcd (%) for $C_{49}H_{41}N_5O_4S_2 \cdot (C_2H_5)_2O \cdot H_2O$: C, 69.18; H, 5.81; N, 7.61; S, 6.97. Found: C, 69.36; H, 5.53; N, 7.37; S, 7.28.

4.35. 2,6-Bis-(1-benzyl-[3*aR*,7*aR*]-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine 8a

To a solution of **4** (200 mg, 0.62 mmol) in anhydrous THF (15 mL) was added sodium hydride (59 mg, 2.47 mmol) at 0 °C. After 15 min, benzyl bromide (220 μL, 1.85 mmol) was slowly added and the reaction mixture stirred at room temperature for 4 h. Then, the reaction mixture was quenched with water and the aqueous phase extracted with dichloromethane (2×20 mL). The organic layer was dried over Na_2SO_4 and the solvents were removed in vacuo to give a light yellow solid, which was purified by column chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to give **8a** as a white solid (213 mg, 68%). R_f 0.50 (CH_2Cl_2/MeOH 9:1); mp 183 185 °C; $[\alpha]_D^{20} = +191.2$ (*c* 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.07 1.18 (m, 2H), 1.24 1.41 (m, 6H), 1.67 1.85 (m, 6H), 2.25 2.29 (m, 2H), 2.66 (ddd, *J* 3.3, 11.4, 14.7, 2H), 3.05 (ddd, *J* 3.3, 11.4, 14.7, 2H), 4.54 (d, *J* 15.6, 2H), 4.64 (d, *J* 15.6, 2H), 7.05 (m, 4H), 7.18 (m, 6H), 7.80 (dd, *J* 7.3, 8.4, 1H), 7.93 (d, *J* 7.3, 1H), 7.93 (d, *J* 8.4, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 25.2, 26.3, 30.5, 31.9, 51.3, 71.2, 71.4, 125.7, 127.6, 128.7, 138.1, 139.1, 151.1, 165.9; EI-MS: *m*/*z* 503 (M^+); Anal. Calcd (%) for $C_{33}H_{37}N_5 \cdot H_2O$: C, 75.97; H, 7.53; N, 13.42. Found: C, 76.07; H, 7.26; N, 13.21.

4.36. 2,6-Bis-(1-[toluene-4-sulfonyl]-[3*aR*,7*aR*]-3a,4,5,-6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine 8b

A 50 mL Schlenk tube was charged with **4** (323 mg, 1.00 mmol), DMAP (366 mg, 3.00 mmol) and dichloromethane (15 mL). The resulting mixture was cooled to 0 °C, and tosyl chloride (476 mg, 2.50 mmol) added neat at once. The ice bath was removed, and the reaction mixture stirred at room temperature for 5 h. The solvent was removed under vacuo, the residue partitioned between saturated NH_4Cl (25 mL) and ethyl acetate (25 mL), and the aqueous phase re-extracted with ethyl acetate (2×25 mL). The combined organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was crystallized from ethyl acetate/hexane to give **8b** as a white solid (585 mg, 93%). R_f 0.45 (CH_2Cl_2/MeOH 100:6); mp 254 255 °C; $[\alpha]_D^{20} = +60.4$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ (1.59 1.76m, 6H), 1.9 2.1 (m, 2H), 2.13 2.21 (m, 4H), 2.60 (s, 6H), 2.66 (m, 2H), 2.90 (m, 2H), 3.50 (ddd, *J* 3.0, 10.9, 13.7, 2H), 3.58 (ddd, *J* 3.0, 10.9, 13.7, 2H), 7.38 (d, *J* 8.4, 4H), 7.82 (d, *J* 8.4, 4H), 7.88 (d, *J* 7.9, 2H), 8.12 (dd, *J* 7.5, 8.1, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 22.1, 25.4, 26.0, 31.5, 31.7, 70.1, 72.7, 125.5, 128.6, 130.2, 136.2, 137.1, 144.8, 151.0, 158.9; EI-MS: *m*/*z* 631 (M^+); Anal. Calcd (%) for $C_{33}H_{37}N_5O_4S_2$: C, 62.73; H, 5.90; N, 11.08; S, 10.15. Found: C, 62.77; H, 5.94; N, 10.99; S, 10.24.

4.37. 1-((4*R*,5*R*)-4,5-dihydro-2-(6-((4*R*,5*R*)-4,5-dihydro-4,5-diphenyl-1*H*-imidazol-2-yl)pyridin-2-yl)-4,5-diphenylimidazol-1-yl)(mesityl)methanone 9

Prepared according to general procedure A using **3** (415 mg, 0.8 mmol), NaH (64 mg, 2.4 mmol) and 2,4,6-trimethyl benzoyl chloride (448 mg, 2.4 mmol) in refluxing chlorobenzene (20 mL) for 45 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford pale yellow crystals (255 mg, 48%). R_f 0.20 (CH_2Cl_2/MeOH 100:5); mp 96 98 °C; $[\alpha]_D^{20} = +47.8$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.96 (s, 3H), 2.01 (s, 6H), 4.43 (m, 1H), 5.25 (d, *J* 4.16, 2H), 5.62 (m, 2H), 6.35 (s, 1H), 6.37 (s, 1H); 6.97 7.18 (m 3H), 7.26 7.58 (m, 18H), 7.69 (d, *J* 7.32, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 19.2, 20.6, 69.1, 77.8, 116.7, 122.9, 125.3, 126.2, 126.5, 126.6, 127.2, 127.9, 128.5, 128.8, 129.0, 129.3, 129.4, 142.9, 149.2, 168.7; IR (KBr): ν 3423, 2921, 1679, 1430, 1328 cm^{-1}; FAB-MS: *m*/*z* 664 (M^+); Anal. Calcd (%) for $C_{45}H_{38}N_5O_1 \cdot H_2O$: C, 79.15; H, 5.90; N, 10.25. Found: C, 79.78; H, 6.29; N, 9.69.

4.38. 1-(3,5-Di-*tert*-butylphenyl)((4*R*,5*R*)-4,5-dihydro-2-(6-((4*R*,5*R*)-4,5-dihydro-4,5-diphenyl-1*H*-imidazol-2-yl)-pyridin-2-yl)-4,5-diphenylimidazol-1-yl)methanone 10

Prepared according to general procedure A using **3** (363 mg, 0.7 mmol), DMAP (244 mg, 2.0 mmol) and 3,5-di-*tert*-butyl benzoyl chloride (524 mg, 2.0 mmol) in dichloromethane (20 mL) for 12 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford pale yellow crystals (335 mg, 52%). R_f 0.20 (CH_2Cl_2/MeOH 100:5); mp 97 99 °C; $[\alpha]_D^{20} = -2.9$ (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.13 (s, 18H), 4.77 (d, *J* 8.52, 1H), 5.06 (d, *J* 9.32, 1H), 5.26 (d, *J* 4.56, 1H), 5.31 (unresolved d, 1H), 7.23 7.45 (m, 23H), 7.81 (t, *J* 7.92, 1H), 7.93 (dd, *J* 1.16, 7.72, 1H), 8.19 (dd, *J* 1.20, 7.92, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 30.9, 34.6, 70.3, 72.6, 78.8, 81.1, 122.4, 123.5, 125.5, 125.9, 126.2, 126.5, 126.6, 127.2, 128.0, 128.5, 128.7, 128.9, 129.2, 134.9, 137.2, 140.8, 141.6, 147.9, 149.6, 150.8, 160.3, 161.7, 170.6; IR (KBr): ν 3414, 2962, 1673, 1332 cm^{-1}; HRMS: calcd for $C_{50}H_{49}N_5O \cdot H^+$: 736.4015. Found:

736.3992; Anal. Calcd (%) for $C_{50}H_{49}N_5O_1 \cdot H_2O$: C, 79.65; H, 6.82; N, 9.29. Found: C, 80.10; H, 6.71; N, 8.88.

4.39. 1-((1*R*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxycarbonyl)(4*R*,5*R*)-4,5-dihydro-2-(6-((4*R*,5*R*)-4,5-dihydro-4,5-diphenyl-1*H*-imidazol-2-yl)pyridin-2-yl)-4,5-di-phenylimidazole-1-carboxylate 11

Prepared according to general procedure A using **3** (260 mg, 0.50 mmol), DMAP (61 mg, 0.5 mmol) and (+)-menthyl chloroformate (90 μL, 0.42 mmol) in dichloromethane (20 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford pale yellow crystals (126 mg, 36%); R_f 0.20 (CH_2Cl_2/MeOH 100:5); mp 72 73 °C; $[\alpha]_D^{20} = +60.6$ (*c* 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.43 (d, *J* 6.94, 3H), 0.56 (d, *J* 6.98, 3H), 0.71 0.83 (m, 4H), 0.84 (d, *J* 6.52, 3H), 1.46 1.68 (m, 5H), 1.94 (br d, 1H), 4.33 (dt, *J* 4.16, 10.68, 1H), 4.85 (br d, *J* 7.92, 1H), 5.11 5.17 (m, 3H), 7.31 7.44 (m, 20H), 7.87 (dd, *J* 1.2, 7.76, 1H), 7.99 (t, *J* 7.72, 1H), 8.42 (dd, *J* 1.2, 7.92, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 15.4, 20.6, 21.8, 22.8, 25.4, 31.3, 34.0, 40.8, 46.8, 70.2, 76.8, 78.4, 123.4, 125.1, 125.7, 126.3, 127.9, 128.9, 129.1, 137.0, 141.7, 142.6, 147.9, 158.6, 162.1; IR (KBr): *v* 3421 (br), 2955, 1726, 1433 cm $^{-1}$; EI-MS: *m*/*z* 701 (M^+); HRMS: calcd for $C_{46}H_{47}N_5O_2 \cdot H^+$: 702.3777. Found: 702.3808.

4.40. 1-((4*R*,5*R*)-4,5-Dihydro-2-(6-((4*R*,5*R*)-4,5-dihydro-4,5-diphenyl-1*H*-imidazol-2-yl)pyridin-2-yl)-4,5-diphenylimidazol-1-yl)(diphenyl)phosphine oxide 12

Prepared according to general procedure A using **3** (208 mg, 0.4 mmol), DMAP (147 mg, 1.2 mmol) and diphenylphosphinyl chloride (230 μL, 1.2 mmol) in 1,2-dichloromethane (20 mL) for 8 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford pale yellow crystals (218 mg, 72%). R_f 0.20 (CH_2Cl_2/MeOH 100:5); mp 121 122 °C; $[\alpha]_D^{20} = +53.1$ (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.59 (t, *J* 2.76, 1H), 4.89 (d, *J* 8.32, 1H), 5.11 (d, *J* 8.52, 1H), 5.16 (d, *J* 2.16, 1H), 7.08 7.13 (m, 6H), 7.21 7.34 (m, 13H), 7.39 7.50 (m, 1H), 7.79 (t, *J* 7.72, 1H), 8.12 (dd, *J* 1.00, 7.72, 1H), 8.26 (dd, *J* 1.20, 7.92, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 70.0, 74.8, 78.2, 78.8, 124.1, 125.3, 125.8, 126.2, 126.9, 127.1, 127.8, 127.9, 128.1, 128.2, 128.3, 128.8, 129.0, 131.2, 131.6, 131.8, 131.9, 135.8, 137.4, 142.2, 142.7, 147.3, 147.9, 154.8, 160.9, 161.7; IR (KBr): *v* 3422 (br), 1605, 1451, 1209 (P=O), 1122 cm $^{-1}$; HRMS: calcd for $C_{47}H_{38}N_5PO \cdot H^+$: 720.2852. Found: 720.2868; Anal. Calcd (%) for $C_{47}H_{38}N_5PO \cdot H_2O$: C, 76.50; H, 5.46; N, 9.49. Found: C, 76.05; H, 4.96; N, 9.13.

4.41. 2-(1-(2,4,6-Trimethyl-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-6-(1-((1*R*,2*R*,5*S*)-2-iso-propyl-5-methylcyclohexyl-3-oxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine 13

Prepared according to general procedure A using **9** (193 mg, 0.28 mmol), DMAP (70 mg, 0.57 mmol) and (+)-menthyl chloroformate (130 μL, 0.57 mmol) in dichloromethane (10 mL) for 6 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford pale yellow crystals (247 mg, 99%). R_f 0.80 (CH_2Cl_2/MeOH 100:5); mp 94 96 °C; $[\alpha]_D^{20} = -23.9$ (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.44 (d, *J* 6.52, 3H), 0.51 (d, *J* 6.92, 3H), 0.57 (d, *J* 7.12, 3H), 0.59 0.95 (m, 5H), 1.16 1.46 (m, 4H), 2.02 (s, 6H), 2.08 (s, 3H), 4.21 (dt, *J* 4.36, 10.68, 1H), 5.15 (d, *J* 3.16, 1H), 5.20 (d, *J* 4.52, 1H), 5.24 (d, *J* 4.36, 1H), 5.72 (d, *J* 3.20, 1H), 6.38 (s, 1H), 6.47 (s, 1H), 7.31 7.58 (m, 21H), 7.74 (d, *J* 7.12, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 15.9, 19.4, 19.9, 20.3, 20.6, 21.4, 23.0, 25.8, 31.1, 33.8, 40.0, 46.1, 68.5, 69.7, 77.0, 77.5, 78.4, 122.7, 123.5, 125.2, 125.3, 125.4, 126.3, 126.4, 127.3, 127.8, 127.9, 128.0, 128.3, 128.9, 129.1, 129.4, 132.8, 135.8, 136.6, 139.1, 141.1, 142.5, 142.7, 149.8, 151.2, 157.8, 168.5; IR (KBr): *v* 2954, 2926, 1716, 1673, 1334 cm $^{-1}$; HRMS: calcd for $C_{56}H_{57}N_5O_3 \cdot H^+$: 848.4540. Found: 848.4515; Anal. Calcd (%) for $C_{56}H_{57}N_5O_3 \cdot H_2O$: C, 77.66; H, 6.67; N, 8.08. Found: C, 77.22; H, 7.15; N, 7.58.

4.42. 2-(1-((4*R*,5*R*)-(1*R*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl-3-oxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-6-(1-(acetyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)pyridine 14

Prepared according to general procedure A using **11** (220 mg, 0.31 mmol), DMAP (116 mg, 0.94 mmol) and acetyl chloride (69 μL, 0.94 mmol) in dichloromethane (10 mL) for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford a pale yellow solid (189 mg, 81%). R_f 0.50 (CH_2Cl_2/MeOH 100:5); mp 73 74 °C; $[\alpha]_D^{20} = -11.1$ (*c* 0.23, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.42 (d, *J* 6.57, 3H), 0.55 (d, *J* 6.99, 3H), 0.67 (d, *J* 7.14, 3H), 0.61 0.96 (m, 4H), 1.39 1.46 (m, 2H), 1.61 1.73 (m, 3H), 1.90 (s, 3H), 4.28 (dt, *J* 4.35, 10.74, 1H), 5.08 (d, *J* 2.64, 1H), 5.14 (d, *J* 3.39, 1H), 5.25 (d, *J* 3.39, 1H), 5.36 (d, *J* 2.64, 1H), 7.28 7.47 (m, 17H), 7.56 7.58 (m, 3H), 7.90 (dd, *J* 1.86, 6.78, 1H), 8.03 (d, *J* 2.07, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 16.0, 20.4, 21.3, 23.1, 24.5, 25.9, 31.1, 33.9, 40.3, 46.6, 69.5, 69.8, 76.9, 78.1, 78.4, 124.0, 124.1, 125.1, 126.3, 127.8, 128.0, 129.1, 129.3, 137.8, 141.0, 141.4, 141.7, 142.5, 150.5, 151.2, 158.4, 158.7, 167.9; IR (KBr): *v* 2955, 1717, 1627, 1453, 1373 cm $^{-1}$; EI-MS: *m*/*z* 743 (M^+); HRMS: calcd for $C_{48}H_{49}N_5O_3 \cdot H^+$: 744.3908. Found: 744.3897.

4.43. General procedure for the preparation of Ru(pybim)(pydic) complexes (procedure B)

A 25 mL oven dried Schlenk tube was charged with [Ru(*p*-cymene)Cl_2]$_2$ (306 mg, 0.5 mmol) and pybim (1 mmol) in 10 mL methanol. In another 25 mL Schlenk tube 2,6-pyridinedicarboxylate disodium salt (211 mg, 1 mmol) was dissolved in a mixture of water (5 mL) and methanol (5 mL). The solution was purged with argon for ca. 10 min and then transferred via a cannula into the Schlenk tube containing the ruthenium source

at rt. The mixture was then heated at 65 °C for 1 h, cooled to rt and then diluted with CH_2Cl_2 (30 mL). The mixture was washed with water (2 × 20 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to give the Ru(pybim)(pydic) complex as a dark brown solid after crystallization from CH_2Cl_2 hexane.

4.44. Ruthenium{2,6-bis-(1-benzoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15a

Prepared according to general procedure B using **6a** (100 mg, 0.14 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (42 mg, 0.070 mmol) and Na_2pydic (29 mg, 0.140 mmol) to give **15a** as a dark brown solid (78 mg, 56%). R_f 0.37 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.42 (d, J 4.1, 2H), 5.16 (d, J 4.6, 2H), 6.56 (d, J 7.7, 4H), 6.92 (d, J 7.3, 4H), 7.03 7.06 (m, 4H), 7.17 (t, J 7.5, 4H), 7.23 7.29 (m, 10H), 7.42 7.50 (m, 8H), 7.61 7.65 (m, 1H), 7.73 (t, J 8.1, 1H), 8.22 (d, J 8.1, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 74.1, 77.5, 125.9, 126.2, 126.3, 126.4, 128.5, 128.7, 128.7, 128.8, 129.2, 129.4, 132.7, 133.6, 134.9, 135.8, 136.3, 140.3, 149.0, 150.3, 163.1, 170.2, 170.4; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 374 (4.00), 493 (4.26); FAB-MS: m/z 994 (M^+); Anal. Calcd (%) for $C_{56}H_{40}N_6O_6$-Ru·0.5H_2O: C, 65.47; H, 3.99; N, 8.11. Found: C, 65.60; H, 4.09; N, 8.06.

4.45. Ruthenium{2,6-bis-(1-(2-methylbenzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}-{pyridine-2,6-dicarboxylate} 15b

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (80 mg, 0.13 mmol), pybim **6b** (206 g, 0.26 mmol) and disodium 2,6-pyridinedicarboxylate (55 mg, 0.26 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using 3% MeOH CH_2Cl_2 to afford **15b** as a dark brown powder (258 mg, 93%). R_f 0.25 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 6H), 4.69 (d, J 4.36, 2H), 5.08 (d, J 3.96, 2H), 6.84 (d, J 6.92, 4H), 6.89 (d, J 7.16, 4H), 7.15 7.23 (m, 3H), 7.31 7.51 (m, 19H), 7.74 7.83 (m, 3H), 8.02 (t, J 8.12, 1H), 8.80 (d, J 8.12, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 31.5, 73.6, 125.3, 125.9, 126.1, 126.9, 127.0, 127.3, 128.8, 128.9, 129.2, 129.3, 130.8, 130.9, 133.6, 134.3, 136.4, 139.7, 148.6, 150.6, 162.6, 169.4, 170.5; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 491 (4.30), 365 (3.98); FAB-MS: m/z 1023 (M^++1); HRMS: calcd for $C_{58}H_{44}N_6O_6Ru{\cdot}H^+$: 1023.2444. Found: 1023.2422. Anal. Calcd (%) for $C_{58}H_{44}N_6O_6Ru{\cdot}H_2O$: C, 66.98; H, 4.46; N, 8.08. Found: C, 66.50; H, 4.01; N, 7.67.

4.46. Ruthenium{2,6-bis-(1-(4-methoxy-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}-{pyridine-2,6-dicarboxylate} 15c

Prepared according to general procedure B using **6c** (200 mg, 0.25 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (78 mg, 0.13 mmol) and Na_2pydic (54 mg, 0.25 mmol) to give **15c** as a dark brown solid (200 mg, 75%). R_f 0.34 (CH_2Cl_2/MeOH 20:1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 3.97 (s, 6H), 4.40 (d, J 4.0, 2H), 5.20 (d, J 4.0, 2H), 6.56 (dd, J 8.1, 1.2 Hz, 4H), 6.77 (unresolved dd, 4H), 7.98 (m, 4H), 7.17 (tt, J 1.0, 7.4, 2H), 7.25 7.31 (m, 6H), 7.45 7.50 (m, 6H), 7.62 (dd, J 7.1, 8.1, 1H), 7.70 (d, J 8.1, 1H), 8.12 (d, J 8.1, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 55.6, 74.4, 77.5, 113.8, 125.5, 125.9, 125.9, 125.9, 126.3, 126.3, 128.6, 128.8, 129.1, 129.4, 131.2, 134.7, 136.4, 140.6, 149.1, 150.3, 163.5, 163.5, 170.1, 170.2; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 372 (3.99), 491 (4.23); FAB-MS: m/z 1055 (M^++1); Anal. Calcd (%) for $C_{58}H_{44}N_6O_8Ru{\cdot}2H_2O$: C, 63.90; H, 4.44; N, 7.71. Found: C, 63.96; H, 4.39; N, 7.52.

4.47. Ruthenium{2,6-bis-(1-(4-trifluoromethyl-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15d

Prepared according to general procedure B using **6d** (200 mg, 0.25 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (76 mg, 0.12 mmol) and Na_2pydic (53 mg, 0.25 mmol) to give **15d** as a dark brown solid (200 mg, 71%). R_f 0.40 (CH_2Cl_2/MeOH 100:6); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.45 (d, J 4.2, 2H), 5.10 (d, J 4.2, 2H), 6.55 (dd, J 8.1, 0.9, 4H), 6.88 (unresolved dd, 4H), 7.04 (unresolved dd, 4H), 7.18 (unresolved tt, 2H), 7.24 7.33 (m, 6H), 7.48 (d, J 7.5, 2H), 7.51 7.55 (m, 8H), 7.63 (dd, J 7.8, 7.6, 1H), 7.82 (t, J 8.1, 1H), 8.35 (d, J 8.1, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 74.1, 77.7, 125.5, 126.5, 125.9, 126.0, 126.3, 126.4, 126.5, 128.8, 128.9, 129.1, 129.3, 129.6, 133.9, 135.1, 136.0, 137.0, 139.8, 148.8, 150.1, 162.5, 169.0, 170.1; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 376 (4.00), 494 (4.25); FAB-MS: m/z 1130 (M^+); Anal. Calcd (%) for $C_{58}H_{38}N_6O_6$-$F_6Ru{\cdot}H_2O$: C, 60.68; H, 3.51; N, 7.32. Found: C, 60.51; H, 3.38; N, 7.12.

4.48. Ruthenium{2,6-bis-(1-(2,6-dimethoxybenzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15e

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (55 mg, 0.09 mmol), **6e** (156 mg, 0.17 mmol) and disodium 2,6-pyridinedicarboxylate (36 mg, 0.17 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using 2.5% MeOH CH_2Cl_2 to give **15e** as a dark brown powder (84 mg, 42%). R_f 0.25 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 3.15 (s, 6H), 3.60 (s, 6H), 4.26 (d, J 3.56, 2H), 4.91 (br s, 2H), 6.24 (d, J 6.76, 2H), 6.47 6.64 (m, 10H), 7.03 7.26 (m, 14H), 7.48 (d, J 7.52, 2H), 7.62 (t, J 7.36, 1H), 7.86 (br s, 1H), 9.03 (br s, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 55.6, 72.2, 78.5, 103.3, 103.8, 113.9, 125.8, 126.0, 126.5, 128.3, 128.5, 128.7, 128.9, 131.5, 133.8, 137.2, 140.1, 148.6, 150.7, 164.5; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 488 (4.65); FAB-MS: m/z 1116 (M^++2); HRMS: calcd for $C_{60}H_{48}N_6O_{10}Ru{\cdot}H^+$: 1115.2554. Found: 1115.2559. Anal. Calcd (%) for $C_{60}H_{48}N_6O_{10}Ru{\cdot}2H_2O$: C, 62.66; H, 4.56; N, 7.31. Found: C, 62.79; H, 4.94; N, 7.01.

4.49. Ruthenium{2,6-bis-(1-(2,4,6-trimethylbenzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15f

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (98 mg, 0.16 mmol), **6f** (266 mg, 0.33 mmol) and disodium 2,6-pyridinedicarboxylate (70 mg, 0.33 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15f** as a dark brown powder (217 mg, 59%). R_f 0.40 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.56 (s, 6H), 1.99 (s, 6H), 2.25 (s, 6H), 4.50 (d, J 3.16, 2H), 4.62 (unresolved d, 2H), 6.46 (d, J 7.52, 4H), 6.61 (m, 6H), 6.80 (s, 2H), 7.05 7.26 (m, 12H), 7.44 (d, J 7.52, 2H), 7.55 (t, J 7.76, 1H), 7.91 (t, J 8.12, 1H), 8.92 (d, J 7.72, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 18.3, 19.0, 20.9, 72.9, 76.0, 125.8, 126.1, 126.4, 127.7, 128.2, 128.4, 128.6, 128.9, 129.1, 132.2, 132.9, 135.0, 135.4, 135.8, 136.6, 139.8, 148.7, 150.8, 162.6, 169.2, 170.3; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 763 (3.28), 489 (4.32), 356 (4.03); HRMS: calcd for $C_{62}H_{52}N_6O_6Ru{\cdot}H^+$: 1079.3070. Found: 1079.3099. Anal. Calcd (%) for $C_{62}H_{52}N_6O_6Ru{\cdot}H_2O$: C, 67.19; H, 4.91; N, 7.58. Found: C, 67.25; H, 4.96; N, 7.28.

4.50. Ruthenium{2,6-bis-(1-(3,5-bis-(1,1-dimethylethyl)-benzoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15g

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (49 mg, 0.08 mmol), **6g** (164 mg, 0.17 mmol) and disodium 2,6-pyridinedicarboxylate (36 mg, 0.17 mmol) in a mixture of *tert*-amylalcohol/MeOH/H_2O (12:5:1 mL) at 65 °C for 2 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15g** as a dark brown powder (96 mg, 43%). R_f 0.35 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.12 (s, 36H), 4.33 (d, J 3.96, 2H), 5.19 (d, J 3.96, 2H), 6.56 (d, J 7.16, 4H), 6.97 (m, 4H), 7.04 (t, J 7.92, 4H), 7.14 7.19 (m, 2H), 7.26 7.30 (m, 10H), 7.47 7.52 (m, 4H), 7.62 (t, J 7.92, 1H), 7.77 (t, J 8.12, 1H), 8.28 (d, J 8.32, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 30.8, 34.7, 73.9, 77.8, 122.7, 125.6, 125.9, 126.1, 126.3, 126.4, 127.2, 128.7, 129.2, 129.6, 132.9, 134.8, 136.3, 140.4, 149.0, 150.4, 151.5, 163.3, 170.1, 171.5; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 595 (3.64), 491 (4.32), 371 (4.02); HRMS: calcd for $C_{72}H_{72}N_6O_6Ru{\cdot}H^+$: 1219.4635. Found: 1219.4702. Anal. Calcd (%) for $C_{72}H_{72}N_6O_6Ru{\cdot}H_2O$: C, 69.94; H, 6.03; N, 6.80. Found: C, 69.96; H, 5.75; N, 6.64.

4.51. Ruthenium{2,6-bis-(1-(2-phenylacetyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15h

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (107 mg, 0.17 mmol), **6h** (264 mg, 0.35 mmol) and disodium 2,6-pyridinedicarboxylate (74 mg, 0.35 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15h** as a dark brown powder (54 mg, 30%). R_f 0.25 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 3.68 (s, 4H), 4.28 (d, J 3.76, 2H), 5.28 (d, J 3.76, 2H), 6.44 (d, J 7.32, 4H), 6.96 7.02 (m, 6H), 7.07 7.15 (m, 8H), 7.21 7.25 (m, 6H), 7.31 7.44 (m, 6H), 7.56 7.66 (m, 3H), 7.76 (t, J 8.32, 1H), 8.65 (d, J 8.32, H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 42.3, 71.2, 76.8, 125.4, 125.9, 126.1, 127.4, 127.8, 128.6, 128.8, 129.1, 129.2, 129.9, 132.9, 134.8, 135.8, 136.6, 140.0, 140.4, 152.5, 161.7, 170.1, 172.5; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 488 (4.32); HRMS: calcd for $C_{58}H_{44}N_6O_6Ru{\cdot}H^+$: 1023.2442. Found: 1023.2456.

4.52. Ruthenium{2,6-bis-(1-(2,2-diphenylacetyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}-{pyridine-2,6-dicarboxylate} 15i

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (73 mg, 0.12 mmol), **6i** (215 mg, 0.23 mmol) and disodium 2,6-pyridinedicarboxylate (49 mg, 0.23 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15i** as a dark brown powder (137 mg, 49%). R_f 0.45 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.21 (d, J 3.56, 2H), 5.01 (s, 2H), 5.18 (d, J 3.60, 2H), 6.28 (d, J 7.92, 4H), 6.87 (t, J 7.72, 4H), 6.93 6.95 (m, 4H); 7.05 7.27 (m, 22H), 7.39 7.42 (m, 8H), 7.58 (t, J 7.32, 1H), 7.72 (t, J 8.32, 1H), 8.61 (d, J 8.32, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 56.7, 70.7, 76.7, 125.1, 125.9, 126.7, 127.5, 127.8, 127.9, 128.3, 128.4, 128.9, 129.1, 129.3, 129.4, 130.0, 134.9, 136.0, 136.5, 138.8, 140.1, 148.6, 150.3, 161.9, 170.0, 170.3; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 488 (4.32), 356 (4.04); HRMS: calcd for $C_{70}H_{52}N_6O_6Ru$: 1175.3118. Found: 1175.3105. Anal. Calcd (%) for $C_{70}H_{52}N_6O_6Ru{\cdot}2H_2O$: C, 69.47; H, 4.66; N, 6.94. Found: C, 69.12; H, 4.40; N, 6.73.

4.53. Ruthenium{2,6-bis-(1-naphthoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15j

Prepared according to general procedure B using **6j** (500 mg, 0.60 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (184 mg, 0.30 mmol) and Na_2pydic (126 mg, 0.60 mmol) to afford **15j** as a dark brown solid (262 mg, 40%). R_f 0.31 (CH_2Cl_2/MeOH 100:6); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.43 (d, J 3.9, 2H), 4.90 (d, J 3.9, 2H), 6.61 (m, 8H), 7.02 7.24 (m, 16H), 7.39 7.42 (m, 2H), 7.45 49 (m, 4H), 7.60 (dd, J 7.1, 8.1, 1H), 7.82 7.90 (m, 7H), 7.95 (d, J 8.1, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 73.8, 76.9, 116.7, 124.2, 124.5, 125.9, 125.9, 126.2, 126.6, 126.6, 126.7, 127.1, 127.6, 128.4, 128.7, 129.1, 129.1, 129.6, 131.2, 130.7, 133.5, 135.0, 136.3, 140.0, 148.8, 150.5, 162.7, 169.1, 170.2; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 492 (4.26); FAB-MS: m/z 1094 (M^+); Anal. Calcd (%) for $C_{64}H_{44}N_6O_6Ru{\cdot}2H_2O$: C, 68.01; H, 4.28; N, 7.44. Found: C, 67.94; H, 4.00; N, 7.22.

4.54. Ruthenium{2,6-bis-(2-naphthoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15k

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (104 mg, 0.17 mmol), **6k** (286 mg, 0.34 mmol) and disodium 2,6-pyridinedicarboxylate (72 mg, 0.34 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using 2% MeOH CH_2Cl_2 to afford **15k** as a dark brown powder (247 mg, 64%). R_f 0.30 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (d, J 4.16, 2H), 5.40 (d, J 4.16, 2H), 6.88 (d, J 7.16, 4H), 7.16 (d, J 6.96, 4H), 7.37 (t, J 7.72, 4H), 7.47 7.59 (m, 10H), 7.76 7.86 (m, 10H), 8.55 (d, J 8.12, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.83, 74.35, 124.6, 125.9, 126.1, 126.7, 127.0, 127.7, 128.4, 128.5, 128.8, 128.9, 129.3, 129.6, 130.2, 131.7, 134.2, 135.0, 136.2, 140.6, 148.8, 150.5, 163.4, 170.5, 170.7; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 495 (4.37), 378 (4.05); FAB-MS: m/z 1095 (M^++1); HRMS: calcd for $C_{64}H_{44}N_6O_6Ru$: 1094.2366. Found: 1094.2395. Anal. Calcd (%) for $C_{64}H_{44}N_6O_6Ru{\cdot}2H_2O$: C, 68.02; H, 4.28; N, 7.44. Found: C, 68.20; H, 4.88; N, 7.01.

4.55. Ruthenium{2,6-bis-(1-[(2*S*)-2-(6-methoxy-naphthalen-2-yl)-propionyl]-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15l

Prepared according to general procedure B using **6l** (150 mg, 0.16 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (49 mg, 0.080 mmol) and Na_2pydic (34.0 mg, 0.16 mmol) to afford **15l** as a dark brown solid (150 mg, 78%). R_f 0.45 (CH_2Cl_2/MeOH 100:6); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.50 (d, J 6.5, 6H), 3.80 (q, J 6.5, 2H), 3.86 (s, 6H), 4.05 (d, J 3.1, 2H), 5.18 (d, J 3.1, 2H), 6.02 (d, J 7.7, 2H), 6.46 (t, J 7.6, 4H), 6.72 (t, J 7.4, 2H), 7.01 (unresolved d, 2H), 7.07 7.10 (m, 6H), 7.24 (unresolved dd, 2H), 7.33 (d, J 7.8, 2H), 7.37 (m, 6H), 7.50 (t, J 7.8, 1H), 7.59 (t, 6H), 7.93 (*t*, J 8.3 Hz, 1H), 8.86 (d, J 8.3, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 20.8, 45.6, 55.3, 69.9, 76.5, 78.8, 105.5, 116.9, 119.2, 125.2, 125.4, 125.5, 125.6, 125.8, 127.9, 127.9, 128.1, 128.5, 129.0, 129.1, 129.3, 129.9, 133.8, 134.1, 136.1, 140.2, 148.6, 150.6, 158.0, 162.3, 169.9, 171.9; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 333 (3.65), 488 (4.27); FAB-MS: m/z 1211 (M^+); Anal. Calcd (%) for $C_{70}H_{56}N_6O_8Ru$: C, 69.47; H, 4.66; N, 6.94. Found: C, 69.96; H, 4.49; N, 6.64.

4.56. Ruthenium{2,6-bis-(1-(2-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-3-oxy-acetyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15m

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (168 mg, 0.27 mmol), **6m** (500 mg, 0.55 mmol) and disodium 2,6-pyridinedicarboxylate (116 mg, 0.55 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15m** as a dark brown powder (297 mg, 46%). R_f 0.30 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.69 (d, J 6.92, 6H), 0.81 (d, J 6.92, 6H), 0.84 (d, J 6.56, 6H), 0.87 0.95 (m, 4H), 1.00 1.07 (m, 2H), 1.21 1.31 (m, 4H), 1.52 1.60 (m, 4H), 1.81 1.84 (m, 2H), 2.03 2.09 (m, 2H), 3.08 (dt, J 3.96, 10.52, 2H), 3.95 (d, J 14.68, 2H), 4.17 (d, J 14.68, 2H), 4.32 (d, J 3.96, 2H), 5.42 (d, J 3.96, 2H), 6.54 (d, J 7.12, 4H), 7.02 7.10 (m, 8H), 7.17 7.21 (m, 2H), 7.32 7.34 (m, 6H), 7.45 (d, J 7.52, 2H), 7.61 (t, J 8.32, 1H), 7.83 (t, J 8.32, 1H), 8.73 (d, J 8.36, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 15.9, 20.7, 21.9, 23.1, 25.5, 31.4, 34.3, 39.8, 47.9, 68.2, 70.6, 77.2, 80.8, 125.4, 125.9, 126.2, 127.7, 128.7, 129.1, 129.2, 129.7, 136.7, 140.1, 148.8, 150.4, 162.0, 168.6, 170.1; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 352 (3.92), 488 (4.28); HRMS: calcd for $C_{66}H_{72}N_6O_8Ru$: 1178.4456. Found: 1178.4506. Anal. Calcd (%) for $C_{66}H_{72}N_6O_8Ru{\cdot}H_2O$: C, 66.26; H, 6.23; N, 7.02. Found: C, 66.57; H, 6.36; N, 6.78.

4.57. Ruthenium{2,6-bis-(1-adamantoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15n

Prepared according to general procedure B using **6n** (150 mg, 0.18 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (54 mg, 0.09 mmol) and Na_2pydic (37 mg, 0.18 mmol) to afford **15n** as a dark brown solid (130 mg, 66%). R_f 0.35 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.56 (m, 6H), 1.65 (m, 8H), 1.82 1.85 (m, 6H), 1.90 1.96 (m, 12H), 4.26 (d, J 2.7, 2H), 5.53 (d, J 2.7, 2H), 6.52 (m, 4H), 7.04 7.08 (m, 8H), 7.19 (m, 2H), 7.29 7.33 (m, 6H), 7.48 (d, J 7.5, 2H), 7.64 (dd, J 8.1, 7.3, 1H), 7.83 (dd, J 8.7, 7.5, 1H) 7.96 (d, J 7.7, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 28.1, 36.1, 39.4, 44.2, 71.5, 78.8, 125.1, 125.2, 125.8, 126.2, 126.6, 128.6, 128.7, 129.2, 129.5, 134.6, 136.1, 140.6, 149.1, 150.7, 165.1, 170.0, 181.1; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 458 (3.96), 487 (4.22); FAB-MS: m/z 1111 (M^++1); Anal. Calcd (%) for $C_{64}H_{60}N_6O_6Ru{\cdot}H_2O$: C, 68.13; H, 5.54; N, 7.45. Found: C, 67.65; H, 5.59; N, 7.14.

4.58. Ruthenium{2,6-bis-(1-acetyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15o

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (152 mg, 0.25 mmol), **6o** (300 mg, 0.50 mmol) and disodium 2,6-pyridinedicarboxylate (105 mg, 0.50 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15o** as a dark brown powder (292 mg, 68%). R_f 0.35 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 2.15 (s, 6H), 4.31 (d, J 3.75, 2H), 5.22 (d, J 3.78, 2H), 6.56 (d, J 7.17, 4H), 7.03 7.23 (m, 10H), 7.36 (t, J 3.75, 6H), 7.44 (d, J 7.53, 2H), 7.60 (t, J 7.14, 1H), 7.83 (t, J 8.10, 1H), 8.74 (d, J 8.28, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 23.7, 72.0, 76.6, 125.4, 125.8, 126.1, 126.5, 127.8, 128.6, 129.1, 129.2, 129.7, 134.7, 136.8, 140.1, 148.7, 150.4, 162.2, 168.7, 170.2; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 487 (4.29); HRMS: calcd for $C_{46}H_{36}N_6O_6Ru$: 870.1740, Found:

870.1730. Anal. Calcd (%) for $C_{46}H_{36}N_6O_6Ru{\cdot}4H_2O$: C, 58.65; H, 4.71; N, 8.92. Found: C, 59.08; H, 4.25; N, 8.82.

4.59. Ruthenium{2,6-bis-(1-pentanoyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15p

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (133 mg, 0.22 mmol), **6p** (300 mg, 0.44 mmol) and disodium 2,6-pyridinedicarboxylate (92 mg, 0.44 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15p** as a dark brown powder (310 mg, 75%). R_f 0.10 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.80 (t, J 7.35, 6H), 1.21 1.32 (m, 4H), 1.56 1.64 (m, 4H), 2.20 2.31 (m, 2H), 2.37 2.47 (m, 2H), 4.31 (d, J 3.78, 2H), 5.23 (d, J 3.78, 2H), 6.56 (d, J 7.17, 4H), 7.03 7.22 (m, 10H), 7.34 (t, J 3.00, 6H), 7.45 (d, J 7.56, 2H), 7.60 (t, J 7.17, 1H), 7.83 (t, J 8.28, 1H), 8.68 (d, J 8.28, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 13.5, 22.1, 26.7, 35.2, 71.5, 76.7, 125.3, 125.8, 126.1, 126.5, 127.6, 128.6, 129.0, 129.2, 129.7, 134.7, 136.9, 140.3, 148.7, 150.5, 162.4, 170.2, 171.8; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 487 (4.35); HRMS: calcd for $C_{52}H_{48}N_6O_6Ru$: 954.2679. Found: 954. 2654. Anal. Calcd (%) for $C_{52}H_{48}N_6O_6Ru{\cdot}H_2O$: C, 64.25; H, 5.18; N, 8.65. Found: C, 64.43; H, 5.23; N, 8.34.

4.60. Ruthenium{2,6-bis-(1-(2-methyl propanoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15q

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (139 mg, 0.23 mmol), **6q** (300 mg, 0.45 mmol) and disodium 2,6-pyridinedicarboxylate (95 mg, 0.45 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15q** as a dark brown powder (406 mg, 98%). R_f 0.15 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.00 (d, J 6.78, 6H), 1.12 (d, J 6.78, 6H), 2.59 2.68 (m, 2H), 4.33 (d, J 3.78, 2H), 5.27 (d, J 3.75, 2H), 6.56 (d, J 6.96, 4H), 7.03 7.23 (m, 10H), 7.32 7.35 (m, 6H), 7.45 (d, J 7.35, 2H), 7.61 (t, J 6.96, 1H), 7.82 (t, J 8.28, 1H), 8.52 (d, J 8.31, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 18.8, 19.8, 33.8, 71.4, 76.9, 125.3, 125.8, 126.1, 126.5, 127.2, 128.7, 129.0, 129.3, 129.7, 134.7, 136.7, 140.3, 148.8, 150.5, 162.6, 170.2, 176.6; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 352 (3.92), 488 (4.30); HRMS: calcd for $C_{50}H_{44}N_6O_6Ru{\cdot}H^+$: 927.2444. Found: 927.2419. Anal. Calcd (%) for $C_{50}H_{44}N_6O_6Ru{\cdot}H_2O$: C, 63.61; H, 4.91; N, 8.90. Found: C, 63.49; H, 4.74; N, 8.52.

4.61. Ruthenium{2,6-bis-(1-(3-methyl butanoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}-{pyridine-2,6-dicarboxylate} 15r

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (133 mg, 0.22 mmol), **6r** (300 mg, 0.44 mmol) and disodium 2,6-pyridinedicarboxylate (92 mg, 0.44 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15r** as a dark brown powder (320 mg, 77%). R_f 0.10 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.84 (d, J 6.39, 6H), 0.90 (d, J 6.42, 6H), 2.09 2.19 (m, 4H), 2.28 2.34 (m, 2H), 4.31 (d, J 3.57, 2H), 5.24 (d, J 3.57, 2H), 6.56 (d, J 7.17, 4H), 7.03 7.23 (m, 10H), 7.35 (t, J 3.21, 6H), 7.45 (d, J 7.32, 2H), 7.61 (t, J 7.14, 1H), 7.85 (t, J 8.28, 1H), 8.65 (d, J 8.28, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 21.9, 22.3, 25.6, 44.1, 71.4, 76.8, 125.3, 125.8, 126.1, 126.6, 127.5, 128.6, 129.0, 129.2, 129.7, 134.7, 136.8, 140.3, 148.7, 150.5, 162.5, 170.2, 171.3; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 350 (3.92), 487 (4.30); HRMS: calcd for $C_{52}H_{48}N_6O_6Ru$: 954.2679. Found: 954.2660. Anal. Calcd (%) for $C_{52}H_{48}N_6O_6Ru{\cdot}H_2O$: C, 64.25; H, 5.18; N, 8.65. Found: C, 64.62; H, 5.31; N, 8.33.

4.62. Ruthenium{2,6-bis-(1-(3,3-dimethylbutanoyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 15s

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (128 mg, 0.21 mmol), **6s** (300 mg, 0.42 mmol) and disodium 2,6-pyridinedicarboxylate (88 mg, 0.42 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **15s** as a dark brown powder (315 mg, 77%). R_f 0.10 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.96 (s, 18H), 2.26 (d, J 7.35, 4H), 4.33 (d, J 3.60, 2H), 5.22 (d, J 3.57, 2H), 6.56 (d, J 7.14, 4H), 7.03 7.24 (m, 10H), 7.35 (t, J 3.03, 6H), 7.45 (d, J 7.32, 2H), 7.60 (t, J 7.17, 1H), 7.85 (t, J 8.28, 1H), 8.58 (d, J 8.28, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 29.4, 31.8, 47.1, 71.8, 76.7, 125.5, 125.8, 126.1, 126.6, 127.2, 128.6, 129.0, 129.2, 129.7, 134.7, 136.8, 140.4, 148.7, 150.6, 162.7, 170.2, 171.0; UV vis (CH_2Cl_2: λ_{max}/nm, logε): 354 (3.97), 488 (4.34); HRMS: calcd for $C_{54}H_{52}N_6O_6Ru$: 982.2992. Found: 982.2984. Anal. Calcd (%) for $C_{54}H_{52}N_6O_6Ru{\cdot}H_2O$: C, 64.85; H, 5.44; N, 8.40. Found: C, 64.69; H, 5.64; N, 8.01.

4.63. Ruthenium{2,6-bis-(1-(benzyloxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}-{pyridine-2,6-dicarboxylate} 16a

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (80 mg, 0.13 mmol), **7a** (206 mg, 0.26 mmol) and disodium 2,6-pyridinedicarboxylate (55 mg, 0.26 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using 2.5% MeOH CH_2Cl_2 to afford **16a** as a dark brown powder (147 mg, 52%). R_f 0.10 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.48 (d, J 4.96, 2H), 5.58 (d, J 5.16, 2H), 6.65 (d, J 8.32, 4H), 7.02 (m, 4H), 7.11 (m, 4H), 7.20 7.41 (m, 18H), 7.51 (d, J 8.12, 2H), 7.65 (t, J 7.32, 1H) 7.75 (t, J 8.32, 1H), 9.01 (d, J 8.32, 2H); ^{13}C NMR

(100 MHz, CD_2Cl_2): δ 72.6, 75.9, 121.2, 126.0, 126.1, 126.3, 126.4, 126.5, 127.7, 128.7, 128.9, 129.3, 129.4, 134.9, 136.8, 140.4, 148.7, 150.1, 150.2, 160.3, 170.4; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 486 (4.32); FAB-MS: *m/z* 1026 (M^+); HRMS: calcd for $C_{56}H_{40}N_6O_8Ru$: 1026.1951. Found: 1026.1991. Anal. Calcd (%) for $C_{56}H_{40}N_6O_8Ru{\cdot}2H_2O$: C, 63.33; H, 4.18; N, 7.91. Found: C, 63.45; H, 3.59; N, 7.65.

4.64. Ruthenium{2,6-bis-(1-(1-naphthyloxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 16b

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (86 mg, 0.14 mmol), **7b** (258 mg, 0.29 mmol) and disodium 2,6-pyridinedicarboxylate (61 mg, 0.29 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using 2% MeOH CH_2Cl_2 to afford **16b** as a dark brown powder (118 mg, 33%). R_f 0.10 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.53 (d, *J* 4.92, 2H), 5.75 (d, *J* 4.96, 2H), 6.71 (d, *J* 3.00, 4H), 7.12 7.17 (m, 6H), 7.20 (dd, *J* 1.00, 7.72, 2H), 7.24 7.33 (m, 8H), 7.35 7.40 (m, 6H), 7.44 7.53 (m, 6H), 7.64 (t, *J* 6.96, 1H) 7.65 (t, *J* 7.16, 1H), 7.77 (d, *J* 8.32, 2H), 7.86 (d, *J* 8.32, 2H), 9.03 (d, *J* 8.32, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 72.7, 76.0, 118.1, 120.6, 125.3, 126.1, 126.2, 126.3, 126.4, 126.7, 126.8, 127.9, 128.0, 128.8, 129.3, 129.5, 134.6, 135.1, 136.9, 140.5, 145.9, 148.7, 150.1, 150.2, 160.3, 170.4; FAB-MS: *m/z* 1128 (M^++2); HRMS calcd for $C_{64}H_{44}N_6O_8Ru{\cdot}H^+$: 1127.2342. Found: 1127.2326. Anal. Calcd (%) for $C_{64}H_{44}N_6O_8Ru$: C, 66.14; H, 4.16; N, 7.23. Found: C, 66.64; H, 4.71; N, 6.85.

4.65. Ruthenium{2,6-bis-(1-(9-fluorenylmethyl-oxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 16c

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (80 mg, 0.13 mmol), **7c** (264 mg, 0.27 mmol) and disodium 2,6-pyridinedicarboxylate (57 mg, 0.27 mmol) in a mixture of *n*-BuOH/MeOH/H_2O (16:8:4 mL) at 65 °C for 2 h followed by chromatography on silica gel using EtOAc hexane as the gradient eluent to afford **16c** as a dark brown powder (195 mg, 60%). R_f 0.40 (EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.16 (d, *J* 4.36, 4H), 4.57 (dd, *J* 5.36, 10.92, 2H), 4.76 (d, *J* 4.36, 2H), 4.88 (dd, *J* 5.16, 10.92, 2H), 6.37 (dd, *J* 1.00, 7.92, 4H), 6.71 (d, *J* 6.92, 4H), 7.01 7.08 (m, 6H), 7.14 7.27 (m, 14H), 7.31 7.38 (m, 4H), 7.42 (d, *J* 7.52, 2H), 7.54 7.58 (m, 3H), 7.64 (d, *J* 7.56, 2H), 7.69 (t, *J* 8.32, 1H), 8.78 (d, *J* 8.32, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 42.0, 68.1, 71.8, 75.7, 119.9, 120.1, 124.5, 125.7, 125.8, 126.1, 127.2, 127.5, 127.9, 128.4, 128.6, 129.1, 135.8, 136.9, 140.7, 141.1, 141.4, 142.9, 143.3, 148.7, 150.1, 160.6, 170.3; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 486 (4.35); FAB-MS: *m/z* 1230 (M^+); HRMS: calcd for $C_{72}H_{52}N_6O_8Ru{\cdot}H^+$: 1231.3028. Found: 1231.3035. Anal. Calcd (%) for $C_{72}H_{52}N_6O_8Ru{\cdot}3H_2O$: C, 67.33; H, 4.55; N, 6.54. Found: C, 67.14; H, 4.30; N, 6.35.

4.66. Ruthenium{2,6-bis-(1-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-3-oxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 16d

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (416 mg, 0.68 mmol), **7d** (1200 mg, 1.36 mmol) and disodium 2,6-pyridinedicarboxylate (287 mg, 1.36 mmol) in MeOH/H_2O (35:10 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **16d** as a dark brown powder (814 mg, 52%). R_f 0.40 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.57 (d, *J* 6.92, 6H), 0.60 (d, *J* 6.76, 6H), 0.73 0.87 (m, 4H), 0.89 (d, *J* 6.52, 6H), 0.92 1.16 (m, 10H), 1.43 1.52 (m, 4H), 4.27 (d, *J* 5.12, 2H), 4.68 (dt, *J* 4.36, 10.88, 2H), 5.28 (d, *J* 5.16, 2H), 6.54 (dd, *J* 1.00, 8.12, 4H), 7.01 7.09 (m, 8H), 7.17 (t, *J* 7.52, 2H), 7.25 7.29 (m, 6H), 7.42 (d, *J* 7.52, 2H), 7.56 (t, *J* 7.16, 1H), 7.76 (t, *J* 8.32, 1H), 9.08 (d, *J* 8.32, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 20.6, 21.7, 22.9, 25.3, 31.5, 34.0, 41.0, 47.0, 72.2, 75.7, 78.2, 125.8, 125.9, 126.4, 127.9, 128.4, 128.5, 129.1, 134.5, 135.8, 137.4, 141.1, 148.8, 150.4, 151.5, 160.9, 170.4; HRMS: calcd for $C_{64}H_{68}N_6O_8Ru{\cdot}H^+$: 1151.4220. Found: 1151.4206.

4.67. Ruthenium{2,6-bis-(1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-3-oxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 16e

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (69 mg, 0.11 mmol), **7e** (200 mg, 0.23 mmol) and disodium 2,6-pyridinedicarboxylate (48 mg, 0.23 mmol) in MeOH/H_2O (35:10 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **16e** as a dark brown powder (214 mg, 81%). R_f 0.22 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.68 (m, 2H), 0.75 (d, *J* 6.9, 6H), 0.78 (d, *J* 6.9, 6H), 0.85 (d, *J* 6.5, 6H), 0.99 1.08 (m, 2H), 1.24 1.31 (m, 4 H), 1.40 1.49 (m, 2H), 1.64 1.77 (m, 6 H), 1.85 1.88 (m, 2H), 4.34 (d, *J* 4.8, 2H), 4.74 (unresolved ddd, *J* 4.4, 2 H), 5.33 (d, *J* 4.8, 2H), 6.55 (dd, *J* 8.2, 1.1, 4H), 7.03 7.10 (m, 8H), 7.10 (*tt*, *J* 7.4, 1.1, 2H), 7.27 7.31 (m, 6H), 7.50 (d, *J* 8.3, 1H), 7.50 (d, *J* 7.1, 1H), 7.63 (dd, *J* 8.3, 7.1, 1H), 7.75 (t, *J* 8.2, 1H), 8.94 (d, *J* 8.3, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 15.9, 20.5, 21.7, 23.1, 26.5, 31.4, 33.9, 40.3, 47.2, 72.2, 75.4, 78.1, 125.9, 126.1, 126.2, 127.7, 128.5, 128.6, 129.1, 129.1, 134.5, 135.8, 137.2, 140.7, 148.9, 150.3, 151.4, 161.1, 170.3; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 371 (3.58), 486 (4.26); FAB-MS: *m/z* 1151 (M^++1); Anal. Calcd (%) for $C_{64}H_{68}N_6O_8Ru{\cdot}H_2O$: C, 65.79; H, 6.04; N, 7.19. Found: C, 66.02; H, 6.28; N, 6.96.

4.68. Ruthenium{2,6-bis-(1-(1,1-dimethylethyloxy carbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 16f

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (92 mg, 0.15 mmol), **7f** (227 mg,

0.30 mmol) and disodium 2,6-pyridinedicarboxylate (63 mg, 0.30 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using 2.5% MeOH CH_2Cl_2 to afford **16f** as a dark brown powder (208 mg 77%). R_f 0.25 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.39 (s, 18H), 4.27 (d, J 5.16, 2H), 5.26 (d, J 5.36, 2H), 6.54 (dd, J 1.43, 7.92, 4H), 7.01 7.08 (m, 8H), 7.15 7.19 (m, 2H), 7.27 7.28 (m, 6H), 7.43 (d, J 7.52, 2H), 7.56 (t, J 7.16, 1H), 7.75 (t, J 8.32, 1H), 8.89 (d, J 8.12, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 72.6, 75.7, 84.3, 125.7, 125.9, 126.0, 126.4, 127.6, 128.4, 128.5, 129.1, 134.4, 137.4, 141.2, 148.8, 150.5, 150.6, 161.2, 170.4; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 486 (4.27), 373 (3.71); HRMS: calcd for $C_{52}H_{48}N_6O_8Ru{\cdot}H^+$: 987.2575. Found: 987.2581. Anal. Calcd (%) for $C_{52}H_{48}N_6O_8Ru{\cdot}H_2O$: C, 62.20; H, 5.02; N, 8.37. Found: C, 62.12; H, 5.36; N, 8.12.

4.69. Synthesis of ruthenium{2,6-bis-(1-benzyl-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}-{pyridine-2,6-dicarboxylate} 16g

Prepared according to general procedure B using **7g** (61 mg, 0.09 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (27 mg, 0.04 mmol) and Na_2pydic (18 mg, 0.09 mmol) to afford **16g** as a dark brown solid (46 mg, 55%). R_f 0.29 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.45 (br, 2H), 4.82 (br, 2H), 5.10 (br, 2H), 5.36 (br, 2H), 6.48 (d, J 7.3, 4H), 6.89 (m, 4H), 7.03 (t, J 7.2, 2H), 7.10 7.12 (m, 4H), 7.20 7.40 (m, 22H), 7.86 (br, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 50.4, 75.9, 77.3, 116.6, 125.4, 126.9, 127.3, 127.7, 127.8, 127.9, 128.6, 128.7, 129.0, 129.1, 132.9, 135.8, 138.3, 138.9, 148.7, 166.1; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 386 (sh) (3.52), 499 (4.33); FAB-MS: m/z 966 (M^+); HRMS (ESI+): calcd for $C_{56}H_{44}N_6O_4{}^{102}Ru$: 966.2434. Found: 966.2468.

4.70. Ruthenium{2,6-bis-(1-[toluene-4-sulfonyl]-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}-{pyridine-2,6-dicarboxylate} 16h

Prepared according to general procedure B using **7h** (54 mg, 0.06 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (20 mg, 0.03 mmol) and Na_2pydic (14 mg, 0.06 mmol) to afford **16h** as a dark brown solid (39 mg, 55%). R_f 0.39 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 2.45 (s, 6H), 4.12 (d, J 5.7, 2H), 4.98 (d, J 5.7, 2H), 5.66 (d, J 7.5, 4H), 6.67 (m, 4H), 6.95 (t, J 7.4, 2H), 7.12 (d, J 7.9, 2H), 7.17 7.19 (m, 4H), 7.27 7.31 (m, 5H), 7.34 7.38 (m, 6H), 7.55 (d, J 8.3, 4H), 8.00 (t, J 8.3, 1H), 9.41 (d, J 8.3, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 21.5, 73.6, 76.1, 125.5, 126.0, 126.1, 127.0, 127.5, 128.3, 128.8, 129.3, 130.8, 132.0, 135.1, 135.8, 136.7, 140.6, 146.6, 148.1, 150.5, 156.1, 159.7, 170.2; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 352 (sh) (3.90), 490 (4.22), 587 (sh) (3.55); FAB-MS: m/z 1094 (M^+); HRMS (ESI+): calcd for $C_{56}H_{44}N_6O_8{}^{102}RuS_2$: 1094.2122. Found: 1094.1705.

4.71. Ruthenium {2,6-bis-(1-benzyl-[3*aR*,7*aR*]-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 17a

Prepared according to general procedure B using **8a** (100 mg, 0.20 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (61 mg, 0.10 mmol) and disodium pyridine-2,6-dicarboxylate (42 mg, 0.20 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using 2.5% MeOH CH_2Cl_2 to afford **17a** as a dark brown powder (70 mg, 45%). R_f 0.17 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.92 0.94 (m, 2H), 1.05 1.11 (m, 6H), 1.38 1.43 (m, 2H), 1.53 1.55 (m, 2H), 1.68 1.70 (m, 4H), 1.94 1.97 (m, 2H), 3.70 (br, 4H), 4.72 (br, 2H), 5.47 (br, 2H), 7.16 (t, J 7.9, 1H), 7.30 7.34 (m, 2H), 7.39 7.45 (m, 10H), 8.04 8.07 (m, 1H), 8.14 (d, J 7.4, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 23.9, 24.7, 28.9, 50.8, 70.1, 72.9, 78.8, 116.6, 126.4, 126.6, 127.6, 129.0, 133.7, 135.8, 150.4, 168.8; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 321 (3.72), 394 (3.48), 498 (4.30); FAB-MS: m/z 770 (M^+); Anal. Calcd (%) for $C_{40}H_{40}N_6O_4Ru{\cdot}H_2O$: C, 60.98; H, 5.37; N, 10.67. Found: C, 60.95; H, 5.30; N, 10.79.

4.72. Ruthenium {2,6-bis-(1-[toluene-4-sulfonyl]-[3*aR*,7*aR*]-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 17b

Prepared according to general procedure B using **8b** (100 mg, 0.16 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (48 mg, 0.08 mmol) and Na_2pydic (33 mg, 0.16 mmol) to afford **17b** as a brown solid (72 mg, 50%). R_f 0.24 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.67 0.70 (m, 2H), 0.82 0.88 (m, 2H), 1.05 1.14 (m, 2H), 1.26 (m, 2H), 1.45 1.48 (m, 2H), 1.69 1.71 (m, 4H), 2.39 (s, 6H), 2.47 2.50 (m, 4H), 3.67 3.73 (m, 2H), 7.30 (d, J 8.2, 4H), 7.44 (d, J 8.2, 4H), 7.77 (t, J 8.1, 1H), 8.02 (d, J 7.7, 1H), 8.19 (d, J 7.7, 2H), 8.77 (d, J 8.1, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.7, 24.3, 24.4, 27.4, 27.8, 29.6, 69.1, 71.8, 126.7, 127.2, 127.3, 127.9, 130.6, 135.8, 136.8, 145.6, 150.0, 151.2, 164.1, 170.9; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 307 (sh) (4.01), 368 (sh) (3.65), 491 (4.17); FAB-MS: m/z 898 (M^+); Anal. Calcd (%) for $C_{40}H_{40}N_6O_8RuS_2$: C, 53.50; H, 4.49; N, 9.36; S, 7.14. Found: C, 53.16; H, 4.86; N, 8.94; S, 6.70.

4.73. Ruthenium{(2-(1-(diphenylphosphinyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl))-6-([4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 18

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (43 mg, 0.07 mmol), **12** (127 mg, 0.17 mmol) and disodium 2,6-pyridinedicarboxylate (30 mg, 0.14 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **18** as a dark brown powder (96 mg, 73%). R_f 0.10 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 4.20 (d, J 3.56, 2H), 5.01 (br s, 2H), 5.18 (d, J 3.60, 2H), 6.28 (d, J 7.92, 4H), 6.87 (t, J 7.72, 4H), 6.93 6.95 (m, 4H); 7.05 7.13 (m, 8H), 7.16 7.27 (m,

6H), 7.57 (t, *J* 7.32, 1H), 7.72 (t, *J* 8.32, 1H), 8.61 (d, *J* 8.32, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 56.6, 70.7, 76.7, 125.1, 125.9, 126.7, 127.5, 127.8, 127.9, 128.3, 128.4, 128.9, 129.1, 129.3, 129.4, 130.0, 134.9, 136.0, 136.5, 138.8, 140.1, 148.6, 150.3, 161.9, 170.1, 170.3; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 489 (4.17); HRMS: calcd for $C_{54}H_{41}N_6PO_5Ru{\cdot}H^+$: 986.2008. Found: 986.2004.

4.74. Ruthenium{(2-(1-(2,4,6-trimethyl-benzoyl))-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-6-(1-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-3-oxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 19

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (67 mg, 0.11 mmol), **13** (195 mg, 0.22 mmol) and disodium 2,6-pyridinedicarboxylate (46 mg, 0.22 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **19** as a dark brown powder (185 mg, 75%). R_f 0.40 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.57 (d, *J* 6.92, 3H), 0.61 (d, *J* 6.92, 3H), 0.91 (d, *J* 6.56, 3H), 0.74 1.69 (m, 5H), 1.21 1.34 (m, 2H), 1.42 1.55 (m, 2H), 1.94 (s, 6H), 2.24 (s, 3H), 4.38 (d, *J* 2.96, 1H), 4.40 (d, *J* 5.36, 1H), 4.55 (br s, 1H), 4.70 (dt, *J* 4.36, 10.72, 1H), 5.35 (d, *J* 5.56, 1H), 6.40 (d, *J* 7.52, 2H), 6.54 6.63 (m, 5H), 6.77 (s, 1H), 7.02 7.13 (m, 8H), 7.15 7.31 (m, 6H), 7.41 (dd, *J* 1.20, 7.56, 1H), 7.44 (dd, *J* 1.20, 7.92, 1H), 7.56 (t, *J* 7.72, 1H), 7.84 (t, *J* 8.12, 1H), 8.83 (d, *J* 7.92, 1H), 9.19 (d, *J* 8.32, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 15.5, 18.3, 18.9, 20.6, 20.9, 21.7, 22.8, 25.3, 31.5, 34.0, 41.0, 47.0, 72.3, 72.9, 75.7, 75.9, 78.3, 125.7, 125.8, 126.0, 126.3, 126.5, 127.8, 128.2, 128.5, 128.9, 129.0, 129.1, 129.2, 132.3, 132.9, 134.7, 135.3, 136.4, 137.5, 139.7, 141.1, 148.7, 150.3, 151.5, 154.7, 161.1, 169.0, 170.4; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 487 (4.30); HRMS: calcd for $C_{63}H_{60}N_6O_7Ru{\cdot}H^+$: 1115.3645. Found: 1115.3668. Anal. Calcd (%) for $C_{63}H_{60}N_6O_7Ru{\cdot}H_2O$: C, 66.83; H, 5.52; N, 7.42. Found: C, 66.63; H, 5.95; N, 7.03.

4.75. Ruthenium{(2-(1-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-3-oxycarbonyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-6-(1-acetyl)-[4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 20

Prepared according to general procedure B using [Ru(*p*-cymene)Cl_2]$_2$ (72 mg, 0.12 mmol), **14** (175 mg, 0.24 mmol) and disodium 2,6-pyridinedicarboxylate (50 mg, 0.24 mmol) in MeOH/H_2O (15:5 mL) at 65 °C for 1 h followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **20** as a dark brown powder (171 mg, 72%). R_f 0.20 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.57 (d, *J* 6.96, 3H), 0.60 (d, *J* 6.96, 3H), 0.85 1.12 (m, 5H), 1.25 1.27 (m, 2H), 1.54 1.61 (m, 2H), 2.14 (s, 3H), 4.26 (d, *J* 3.78, 1H), 4.31 (d, *J* 5.28, 1H), 4.69 (dt, *J* 4.35, 10.74, 1H), 5.19 (d, *J* 3.78, 1H), 5.30 (d, *J* 5.28, 1H), 6.53 6.57 (m, 4H), 7.00 7.44 (m, 16H), 7.58 (t, *J* 7.35, 1H), 7.79 (t, *J* 8.28, 1H), 8.71 (d, *J* 7.89, 1H), 9.12 (d, *J* 7.89, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 15.4, 20.6, 21.7, 22.8, 23.7, 25.3, 31.5, 34.0, 41.0, 46.9, 72.0, 72.2, 75.7, 76.6, 78.2, 125.4, 125.7, 125.8, 125.9, 126.1, 126.2, 126.4, 127.7, 128.0, 128.4, 128.5, 128.6, 129.1, 129.2, 129.3, 129.7, 134.6, 136.8, 137.4, 140.1, 141.1, 148.7, 148.8, 150.2, 150.7, 151.4, 161.0, 162.1, 168.6, 170.3; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 486 (4.30); HRMS: calcd for $C_{55}H_{52}N_6O_7Ru$: 1010.2941. Found: 1010.2927; Anal. Calcd (%) for $C_{55}H_{52}N_6O_7Ru{\cdot}H_2O$: C, 64.25; H, 5.29; N, 8.17. Found: C, 64.22; H, 5.71; N, 7.96.

4.76. General procedure for the preparation of Ru(dicyclohexylpybim)(pydic) complexes via in situ generation (procedure C)

In a 50 mL oven dried one necked round bottom flask fitted with a magnetic stirring bar under argon, **4** (130 mg, 0.4 mmol) and DMAP (147 mg, 1.2 mmol) were dissolved in anhydrous CH_2Cl_2 (15 mL). The mixture was cooled to 0 °C and then the corresponding acid chloride or chloroformate (1.2 mmol) added dropwise. The cooling bath was removed and the reaction mixture was stirred at rt and the progress of the reaction monitored by TLC. After full conversion, the reaction mixture was washed with water (2 × 20 mL), dried over Na_2SO_4, concentrated and transferred into a 25 mL Schlenk tube and dried in vacuum. To the remaining product methanol (10 mL) and [Ru(*p*-cymene)Cl_2]$_2$ (306 mg, 0.5 mmol) were added. Another 25 mL Schlenk tube was charged with disodium 2,6-pyridinedicarboxylate (211 mg, 1 mmol) and dissolved in a mixture of water (5 mL) and methanol (5 mL). The solution was purged with argon for ca. 10 min and then transferred via a cannula into the Schlenk tube containing the ruthenium source at rt. The mixture was then heated at 65 °C for 1 h, cooled to rt and diluted with CH_2Cl_2 (30 mL). The mixture was washed with water (2 × 20 mL), dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to give the Ru(dicyclohexylpybim)(pydic) complex as a dark brown solid after crystallization from CH_2Cl_2 hexane.

4.77. Ruthenium{2,6-bis-(1-benzoyl-[3*aR*,7*aR*]-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 21

Prepared according to general procedure C using **4** (320 mg, 1 mmol), DMAP (269 mg, 2.2 mmol), benzoyl chloride (0.29 mL, 2.5 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (306 mg, 0.5 mmol) and disodium 2,6-pyridinedicarboxylate (211 mg, 1 mmol) followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **21** as a dark brown crystalline product (484 mg, 61%). R_f 0.25 (CH_2Cl_2/MeOH 100:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 1.32 (m, 10H), 1.51 1.59 (m, 6H), 3.52 (dt, *J* 3.56, 12.48, 2H), 3.91 (dt, *J* 2.96, 11.68, 2H), 7.35 (t, *J* 8.08, 1H), 7.46 (t, *J* 7.96, 4H), 7.56 (t, *J* 6.36, 2 H), 7.66 7.68 (m, 4 H), 7.72 (d, *J* 8.12, 2H), 8.08 (t, *J* 7.52, 1H), 8.28 (d, *J* 7.72, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2, 24.9, 28.2, 30.0, 71.4, 73.5, 125.0, 127.5. 127.7,

129.3, 129.5, 133.6, 135.0, 135.7, 136.1, 150.6, 151.1, 164.6, 168.1, 172.2; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 492 (4.33), 379 (3.95); FAB-MS: *m*/*z* 798 (M^+); Anal. Calcd (%) for $C_{40}H_{36}N_6O_6Ru{\cdot}3H_2O$: C, 56.40; H, 4.97; N, 9.86. Found: C, 56.49; H, 4.64; N 9.53.

4.78. Ruthenium{2,6-bis-(1-(4-methoxybenzoyl)-[3*aR*, 7*aR*]- 3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 22

Prepared according to general procedure C using **4** (323 mg, 1 mmol), DMAP (276 mg, 2.2 mmol), 4-methoxy benzoyl chloride (514 mg, 3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (306 mg, 0.5 mmol) and disodium 2,6-pyridinedicarboxylate (211 mg, 1 mmol) followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **22** as a dark brown crystalline product (376 mg, 43%). R_f 0.40 (CH_2Cl_2/MeOH 100:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 1.31 (m, 10H), 1.50 1.61 (m, 4H), 1.76 1.79 (m, 2H), 3.49 (dt, *J* 3.16, 12.08, 2H), 3.83 (s, 6H), 3.96 (dt, *J* 2.96, 11.48, 2H), 6.91 (d, *J* 8.72, 4H), 7.28 (t, *J* 8.12, 1H), 7.60 (d, *J* 8.12, 2H), 7.64 (d, *J* 9.12, 4H), 8.07 (t, *J* 7.52, 1H), 8.27 (d, *J* 7.72, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 23.7, 24.5, 27.7, 29.4, 31.5, 55.5, 71.1, 72.9, 114.2, 124.3, 126.6, 127.1, 135.0, 150.1, 150.6, 163.5, 164.2, 167.1, 171.7; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 492 (4.37), 380 (4.01); FAB-MS: *m*/*z* 858 (M^+); Anal. Calcd (%) for $C_{42}H_{40}N_6O_8Ru{\cdot}H_2O$: C, 57.59; H, 4.83; N, 9.59. Found: C, 57.82; H, 4.68; N, 9.08.

4.79. Ruthenium{2,6-bis-(1-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy-carbonyl)-[3*aR*,7*aR*]-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazol-2-yl)-pyridine}{pyridine-2,6-dicarboxylate} 23

Prepared according to general procedure C using **4** (320 mg, 1 mmol), DMAP (269 mg, 2.2 mmol), (−)-menthyl chloroformate (0.64 mL, 3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (306 mg, 0.5 mmol) and disodium 2,6-pyridinedicarboxylate (211 mg, 1 mmol) followed by chromatography on silica gel using MeOH CH_2Cl_2 as the gradient eluent to afford **23** as a dark brown crystalline product (246 mg, 26%). R_f 0.50 (CH_2Cl_2/MeOH 100:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 0.94 (m, 18H), 0.95 1.26 (m, 10H), 1.37 1.98 (m, 18H), 2.13 (d, *J* 8.92, 2H), 2.60 (dd, *J* 2.96, 12.28, 2H), 3.28 (m, 2H), 3.64 (m, 2H), 4.81 (dt, *J* 4.36, 10.92, 2H), 7.53 (t, *J* 8.32, 1H), 8.05 (t, *J* 7.92, 1H), 8.25 (d, *J* 7.72, 2H), 8.45 (d, *J* 8.32, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 20.7, 21.9, 23.6, 24.1, 24.5, 26.5, 27.8, 30.3, 31.4, 31.5, 34.0, 40.8, 47.2, 69.1, 71.6, 126.3, 127.1, 135.7, 150.6, 150.8, 151.3, 162.9, 171.7; UV vis (CH_2Cl_2: λ_{max}/nm, log ε): 485 (4.32), 381 (3.64); FAB-MS: *m*/*z* 954 (M^+); Anal. Calcd (%) for $C_{48}H_{64}N_6O_8Ru{\cdot}2H_2O$: C, 58.22; H, 6.92; N, 8.49. Found: C, 58.39; H, 6.63; N, 8.25.

4.80. General procedure for asymmetric epoxidation with hydrogen peroxide

In a 25 mL Schlenk tube, the ruthenium catalyst (0.025 mmol) was stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. Olefin (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added. To this mixture, a solution of 30% hydrogen peroxide (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) was added over a period of 12 h by syringe pump. After the addition, aliquots were taken from the reaction mixture and subjected to GC analysis for the determination of yield and conversion. Finally, the reaction mixture was quenched with saturated Na_2SO_3 solution (10 mL), extracted with dichloromethane (2 × 10 mL) and washed with water (20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude epoxides. A solution of the crude product in hexane was used for the determination of the ee by HPLC.

4.81. Phenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (dd, *J* 5.6, 2.6, 1H), 3.06 (dd, *J* 5.6, 4.2, 1H), 3.78 (dd, *J* 4.2, 2.6, 1H), 7.16 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.3, 52.5, 125.6, 128.3, 128.6, 137.7; EI-MS: *m*/*z* 120 (M^+, 41), 119 (65), 92 (37), 91 (100), 90 (64), 89 (79); HPLC (Chiralcel OD-H (02), hexane/EtOH 99.95:0.05, flow rate 0.5 mL/min): t_R 6.27 min, 7.13 min.

4.82. 2-Tolyloxirane

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.14 7.22 (m, 4H), 3.98 (dd, *J* 3.97, 2.58, 1H), 3.13 (dd, *J* 5.75, 3.97, 1H), 2.65 (dd, *J* 5.75, 2.58, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 136.4, 136.2, 129.8, 127.6, 126, 124, 50.3, 50.1; EI-MS: *m*/*z* 134 (M^+, 53), 119 (44), 118 (42), 117 (64), 105 (100), 103 (48), 91 (52), 78 (33), 77 (35); HPLC (Chiralpak AD-H, hexane/EtOH, 99.95:0.05, flow rate 1.5 mL/min): t_R 16.70 min, 19.84 min.

4.83. 4-Chlorophenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (dd, *J* 5.6, 2.6, 1H), 3.07 (dd, *J* 5.6, 4.0, 1H), 3.76 (dd, *J* 4.0, 2.6, 1H), 7.12 7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.4, 51.9, 127.0, 128.8, 134.1, 136.3; EI-MS: *m*/*z* 156 (M^++2, 9), 155 (M^++1, 10), 154 (M^+, 28), 153 (M^+-1, 23), 125 (53), 119 (74), 89 (106); HPLC (Chiralcel OB H, hexane, flow rate 1.0 mL/min): t_R 14.47 min, 17.18 min.

4.84. 4-Trifluoromethylphenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (dd, *J* 5.6, 2.6, 1H), 3.19 (dd, *J* 5.6, 4.0, 1H), 3.92 (dd, *J* 4.0, 2.6, 1H), 7.4 (d, *J* 8.1, 2H), 7.6 (d, *J* 8.1, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.4, 51.6, 125.4 (q, *J* 3.8), 125.9, 141.9; EI-MS: *m*/*z* 188 (M^+, 14), 187 (20), 159 (49), 158 (48), 119 (100), 91 (37); HPLC (Chiralcel AD-151, hexane, flow rate 0.5 mL/min): t_R 12.30 min, 13.40 min.

4.85. *trans*-2-Methyl-3-phenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, *J* 5.2, 3H), 3.03 (dq, *J* 2.0, 5.2, 1H), 3.57 (d, *J* 2.0, 1H), 7.23 7.4

(m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 59.2, 59.6, 125.7, 128.1, 128.5, 137.9; EI-MS: 134 (M^+, 52), 133 (65), 105 (51), 91 (42), 90 (100), 89 (77), 77 (23); HPLC (Chiralcel OD-H (069), hexane/EtOH, 99.95:0.05, flow rate 1.0 mL/min): t_R 11.90 min (2*S*,3*S*), 13.48 min (2*R*,3*R*).

4.86. *trans*-2,3-Diphenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.31 (m, 10H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 128.6, 128.6, 125.5, 62.8; EI-MS: *m*/*z* 197 (M^++1, 18), 196 (M^+, 100), 195 (72), 178 (28), 167 (85), 90 (66), 89 (65); HPLC (Chiralcel OD-H, hexane/EtOH, 98:2, flow rate 0.5 mL/min): t_R 14.10 min (2*S*,3*S*), 4.79 min (2*R*,3*R*).

4.87. *trans*-2-Chloromethyl-3-phenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (ddd, *J* 5.8, 4.8, 1.9, 1H), 3.66 (dd, *J* 11.8, 5.8, 1H), 3.72 (dd, *J* 11.8, 4.8, 1H), 3.82 (d, *J* 1.9, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.3, 58.5, 60.9, 116.6, 125.6, 128.6, 135.9; GC-MS: *m*/*z* 168 (M^+); HPLC (Chiralpak AD-H, hexane/EtOH, 95:5, flow rate 1.0 mL/min): t_R 7.62 min, 9.09 min.

4.88. 2,2-Dimethyl-3-phenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.45 (s, 3H), 3.83 (s, 1H), 7.21–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 24.7, 61.0, 64.5, 126.3, 127.3, 128, 136.6; EI-MS: *m*/*z* 148 (M^+); HPLC (Chiralcel OD-H, hexane/EtOH, 99.95:0.05, flow rate 0.5 mL/min): t_R 11.78 min (3*S*), 18.63 min (3*R*).

4.89. 2-Phenyl-1-oxaspiro[2.5]octane

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.31 (m, 2H), 1.37–1.85 (m, 8H), 3.85 (s, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 25.3, 25.5, 28.4, 35.4, 64.5, 65.5, 126.3, 127.2, 127.9, 136.3; GC-MS: *m*/*z* 188 (M^+); HPLC (Chiralpak AD-H, hexane/EtOH, 90:10, flow rate 1.0 mL/min): t_R 4.34 min, 4.72 min.

4.90. (2-Methyl-3-phenyl-oxiranyl)-methanol

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 3H), 2.17 (dd, *J* 8.7, 4.3 Hz, 1H), 3.74 (dd, *J* 12.5, 8.7 Hz, 1H), 3.84 (dd, *J* 12.5, 4.3 Hz, 1H), 4.20 (s, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.41, 60.13, 63.66, 64.90, 126.36, 127.52, 128.06, 135.54; EI-MS: *m*/*z* 164 (M^+); HPLC (Chiralcel AD-H, hexane/EtOH, 99.5:0.5, flow rate 0.5 mL/min): t_R 12.24 min, 12.86 min.

4.91. 2-Methyl-2-phenyloxirane

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.73 (d, *J* 5.4, 1H), 2.90 (d, *J* 5.4, 1H), 7.17–7.31 (m, 5H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.9, 57.2, 125.4, 127.6, 128.5, 141.3; EI-MS: *m*/*z* 134 (M^+, 35), 133 (87), 105 (100), 104 (41), 103 (58), 91 (23), 79 (37), 78 (54), 77 (49); HPLC (Chiralcel OD-H, hexane/*iso*-propanol, 99.95:0.05, flow rate 1.0 mL/min): t_R 9.78 min, 12.77 min.

4.92. 1,2-Epoxy-1-phenylcyclohexane

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.32 (m, 4H), 7.15–7.2 (m, 1H), 2.99 (m, 1H), 2.16–2.25 (m, 1H), 2.00–2.09 (m, 1H), 1.87–1.95 (m, 2H), 1.44–1.58 (m, 2H), 1.34–1.44 (m, 1H), 1.18–1.3 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 128.4, 127.3, 125.4, 62.1, 60.3, 29, 24.8, 20.2, 19.9; EI-MS: *m*/*z* 175 (M^++1, 10), 174 (M^+, 82), 173 (100), 159 (21), 145 (40), 129 (50), 117 (47), 115 (58), 105 (68), 91 (58), 77 (43). HPLC (Chiralcel AD-H, hexane/EtOH, 99.95:0.05, flow rate 1.0 mL/min): t_R 8.35 min, 9.07 min.

4.93. 4-Methyl-*N*-(*trans*-3-phenyl-oxiranylmethyl)-benzenesulfonamide

Mp 128–131 °C; R_f 0.23 (hexane/ethyl acetate 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.10 (ddd, *J* 2.0, 3.4, 4.6, 1H), 3.23 (ddd, *J* 4.6, 6.8, 14.1, 1H), 3.38 (ddd, *J* 3.4, 6.0, 14.1, 1H), 3.74 (d, *J* 2.0, 1H), 4.82 (unresolved dd, 1H), 7.14–7.17 (m, 2H), 7.28–7.31 (m, 5H), 7.74 (d, *J* 8.3, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.51, 43.70, 55.55, 60.12, 125.66, 127.06, 128.51, 128.88, 129.84, 131.04, 135.69, 135.89, 136.71, 143.75; EI-MS: *m*/*z* 303 (M^+); HRMS: calcd for $C_{16}H_{17}NO_3S$: 303.0929. Found 303.0939; HPLC (Whelk01 [*R*,*R*], hexane/EtOH, 90:10, flow rate 1.0 mL/min): t_R 10.01 min, 11.38 min.

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Publication 3.3.

New Ruthenium Catalysts for Asymmetric Transfer Hydrogenation of Prochiral Ketones

Stephan Enthaler, Bernhard Hagemann, Santosh Bhor, Gopinathan Anilkumar, Man Kin Tse, Bianca Bitterlich, Kathrin Junge, Giulia Erre, Matthias Beller

Adv. Synth. Catal. **2007**, 349, 853-860

Contributions:

In this paper, I contributed to a significant amount of the argumentation and I supported the synthetic work on *N,N,N*-pyridinebisimidazoline ligands. I synthesized 2,6-Bis-([4*R*,5*R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine (**3a**) which serves as ligand and as key-intermediate for the synthesis of ligands **3b** - **3e**. My contribution as co-author of this paper is approximately 15 %.

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New Ruthenium Catalysts for Asymmetric Transfer Hydrogenation of Prochiral Ketones

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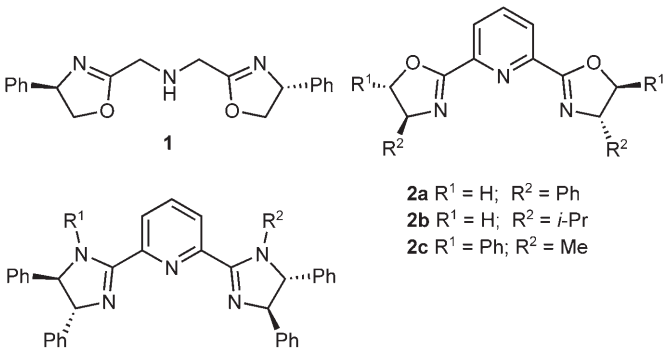
Abstract: Tridentate *N,N,N*-pyridinebisimidazolines have been studied as new ligands for the enantioselective transfer hydrogenation of prochiral ketones. High yields and excellent enantioselectivity up to >99% *ee* have been achieved with an *in situ* generated catalytic system containing dichlorotris(triphenylphosphine)ruthenium and 2,6-bis-([*4R,5R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine (**3a**) in the presence of sodium isopropoxide.

Keywords: asymmetric transfer hydrogenation; ketones; phosphines; ruthenium; tridentate nitrogen ligands

Enantiomerically pure alcohols have a wide range of applications, for example, building blocks and synthons for pharmaceuticals, agrochemicals, polymers, syntheses of natural compounds, auxiliaries, ligands and key intermediates in organic syntheses.[1] Within the different molecular transformations to chiral alcohols, transition metal-catalyzed reactions offer efficient and versatile strategies, such as addition of organometallic compounds to aldehydes, hydrosilylation, and hydrogenation of prochiral ketones.[2] From an economic and environmental point of view the asymmetric hydrogenation, in particular the transfer hydrogenation, represents a powerful tool for their synthesis because of its high atom economy and safety advantages.[3] Here, Noyori's ruthenium-based catalysts comprising chiral tosylated diamines constitute state-of-the-art transfer hydrogenation systems.[3d,4] Based on this seminal work an increasing number of ruthenium catalysts with chiral bidentate *N,N*-ligands were developed in the last decade.[3] Significantly fewer systems are known in which transfer of chiral information is promoted by tridentate ligands.[5,6] Up to now only a limited number of auspicious tridentate nitrogen-containing *N,N,N* ligands were established in the field of transfer hydrogenation. For example (*R*)-phenyl-ambox (**1**)[5] and different pyridinebisoxazoline (pybox) ligands (**2**)[6] have been applied for the reduction of acetophenone (Scheme 1).



Scheme 1. *N,N,N* Tridentate ligands.

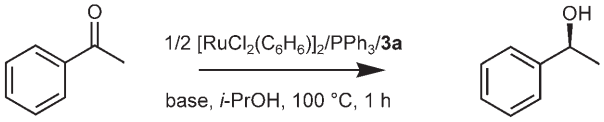
Recently, we reported the synthesis of a new class of chiral tridentate amines.[7] The preparation and tunability of these pyridinebisimidazolines (**3**) (so-called pybim ligands, Scheme 1) are easier and more flexible compared to the popular pyboxes, making the former a suitable ligand tool box for various asymmetric transformations. To date there is no report on the performance of these ligands in hydrogenation reactions. The resemblance between pybim (**3**) and pybox (**2**) stimulated our research to study the potential of this class of ligands in the transfer hydrogenation of aromatic and aliphatic ketones.

In exploratory experiments, isopropyl alcohol-based transfer hydrogenation of acetophenone was examined using a simple *in situ* catalyst system composed of $[RuCl_2(C_6H_6)]_2$, 2,6-bis-([*4R,5R*]-4,5-diphenyl-4,5-

dihydro-1*H*-imidazol-2-yl)-pyridine (**3**) and triphenylphosphine. To ensure complete formation of the active catalyst and avoid an induction period the reaction mixture was heated for 10 min at 100 °C in the presence of base followed by addition of acetophenone. First, studies for optimizing the reaction conditions were carried out with 1 mol% of pre-catalyst and 5 mol% of base. It is well-known that transfer hydrogenations are sensitive to the nature of the base. Thus, the influence of different bases on selectivity and conversion was investigated initially (Table 1). Best results were obtained for sodium isopropoxide and K_2CO_3 with conversions up to 95% and enantiomeric excesses up to 94% (Table 1, entries 1 and 8). Interestingly, NaOH and KOH the most commonly used bases for transfer hydrogenations gave only moderate enantioselectivity (78% and 80%, Table 1, entries 3 and 4). In addition, we tested some organic nitrogen-containing systems such as DBU, DABCO, NEt_3, $N(i\text{-}Pr)_2Et$ and pyridine, but only with $N(i\text{-}Pr)_2Et$ did we obtain significant amounts of product in a reasonable time (Table 1, entry 10). Next, the concentration of sodium isopropoxide was varied at different temperatures. As expected, the increase of the amount of base led to an acceleration of reaction rate; however, this was accompanied by an unacceptable decrease of enantioselectivity (Table 1, entries 13–15). In contrast, improved *ee* is obtained by reducing the amount of base to a ruthenium-to-base ratio of 1 to 0.5 (Table 1, entries 16 and 17). Notably, in the absence of base the transfer of hydrogen did not occur. Based on these results we investigated the behavior of the metal precursor.

Applying different ruthenium sources such as $[RuCl_2(PPh_3)_3]$, $[RuHCl(PPh_3)_3]$,[8] $RuCl_3 \cdot x\,H_2O$, $Ru_3(CO)_{12}$ and $Ru(cod)(methylallyl)_2$, lower conversion and/or poor selectivity were achieved. Nevertheless, $[RuCl_2(PPh_3)_3]$ showed an enantiomeric excess of >99%, which is to our knowledge the highest enantioselectivity in this model reaction for a chiral tridentate ligand (Table 1, entry 17). However, a slight excess of pybim **3a**, 3 equivs. with respect to 1 equiv.

Table 1. Transfer hydrogenation of acetophenone in the presence of pybim ligand **3a** and different bases.[a]



Entry	Base	Base:Metal	Temp. [°C]	Conv. [%][b]	*ee* [%][b]
1	NaO *i* Pr	5	100	80	**94 (*S*)**
2	KO *t* Bu	5	100	99	9 (*S*)
3	NaOH	5	100	79	78 (*S*)
4	KOH	5	100	85	80 (*S*)
5	LiOH	5	100	72	80 (*S*)
6	K_3PO_4	5	100	65	70 (*S*)
7	K_2HPO_4	5	100	19	96 (*S*)
8	K_2CO_3	5	100	95	93 (*S*)
9	Cs_2CO_3	5	100	45	67 (*S*)
10	$N(i\ Pr)_2Et$	5	100	18	90 (*S*)
11	NaO *i* Pr	5	60	93	84 (*S*)[c]
12	NaO *i* Pr	5	80	91	83 (*S*)[d]
13	NaO *i* Pr	5	90	91	88 (*S*)
14	NaO *i* Pr	50	90	98	87 (*S*)
15	NaO *i* Pr	250	90	99	44 (*S*)
16	NaO *i* Pr	0.5	100	88	95 (*S*)
17	NaO *i* Pr	0.5	100	96	**>99 (*S*)**[e]
18	NaO *i* Pr	0.5	110	58	84 (*S*)

[a] *Reaction conditions: in situ* catalyst **A** {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol ligand **3a**, 3.8×10^{-6} mol PPh_3}; addition of the corresponding base: entries 1–13: 1.9×10^{-5} mol, entry 14: 1.9×10^{-4} mol, entry 15: 9.5×10^{-4} mol and for entries 16–18: 1.9×10^{-6} mol in 2.0 mL isopropyl alcohol, 10 min at corresponding temperature then addition of 3.8×10^{-4} mol acetophenone, 1 h at corresponding temperature.

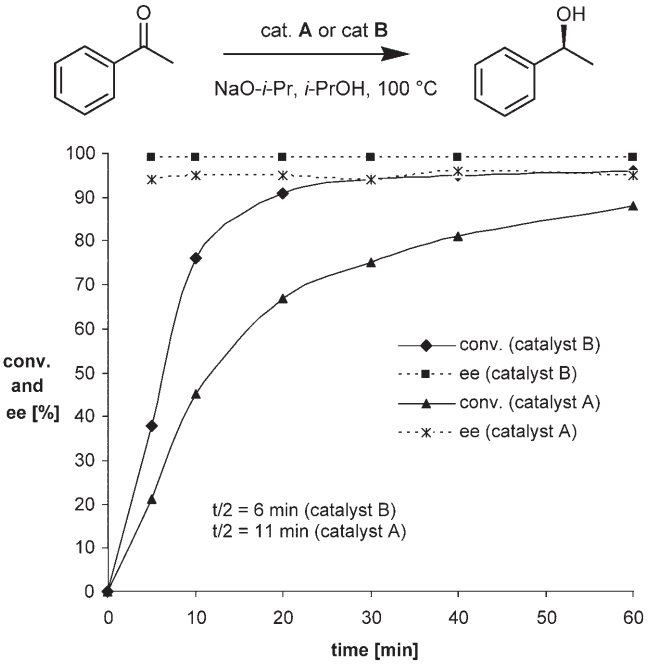
[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95–200 °C) analysis with diglyme as internal standard.

[c] Reaction time 14 h.

[d] Reaction time 4 h.

[e] *In situ* catalyst **B** {3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**}. Conversion was determined by GC (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard and *ee* was determined by chiral HPLC (Chiralcel OB H, eluent: *n* hexane/ethanol, 99:1, flow rate: 2 mL min^{-1}) analysis.

of ruthenium, was necessary to achieve high enantioselectivity. To compare the difference of catalyst system **A** and catalyst system **B**, we investigated the conversion-time and the enantioselectivity-time dependency (Scheme 2). No significant change of enan-



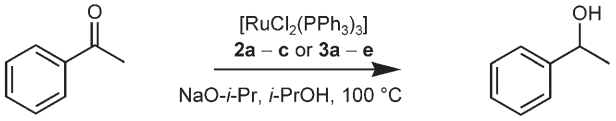
Scheme 2. Conversion time and enantioselectivity time behavior of catalyst **A** and catalyst **B**. *Reaction conditions: in situ* catalyst **A** (1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol ligand **3a**, 3.8×10^{-6} mol PPh_3) or *in situ* catalyst **B** (3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**); addition of sodium isopropoxide (1.9×10^{-6} mol) in 2.0 mL 2 propanol, 10 min at 100 °C then addition of 3.8×10^{-4} mol acetophenone, reaction temperature: 100 °C. Conversion was determined by GC (30 m HP Agilent Technologies 50 300 °C) with diglyme as internal standard and *ee* was determined by chiral HPLC (Chiralcel OB H, eluent: *n* hexane/ethanol, 99:1, flow rate: 2 mL min^{-1}) analysis.

tioselectivity was observed in the shown time frame, while after 24 h full racemization occurred with catalyst **A**. Noteworthy, the analysis of the conversion-time behavior proved a higher catalyst activity for catalyst **B**, while for catalyst **A** a slight deceleration was monitored. We assume a better stabilization of the active species by an excess of **3a** and PPh_3.

As shown in Table 2 we also examined different pybox ligands (**2a–c**), but only unsatisfying results were obtained demonstrating the advantage of **3a** (Table 2, entries 1–3).

Noyori et al. proposed a metal-ligand bifunctional mechanism for the hydride transfer process ("NH effect").[4,13b] Hence, the NH group of the imidazoline rings could be involved in the selectivity transfer and increase the coordination affinity between substrate

Table 2. Transfer hydrogenation of acetophenone in the presence of different pybox and pybim ligands.[a]



Entry	Ligand	Time [h]	Conv. [%][b]	*ee* [%][b]
1	**2a**	1	6	11 (*R*)
2	**2b**	1	10	18 (*S*)
3	**2c**	1	22	8 (*R*)
4	**3a**	1	83	**98 (*S*)**
5	**3b**	2	95	26 (*R*)
6	**3c**	2	74	29 (*S*)
7	**3d**	1	4	7 (*R*)
8	**3e**	1	77	7 (*S*)

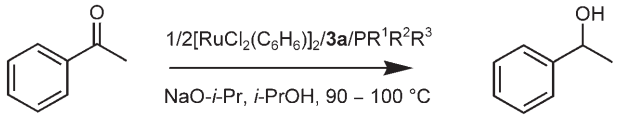
[a] Reaction conditions: 3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol ligand, 3.8×10^{-6} mol PPh_3, 1.9×10^{-6} mol NaO *i* Pr, 2.0 mL isopropyl alcohol, 10 min at 100 °C then addition of 3.8×10^{-4} mol acetophenone.

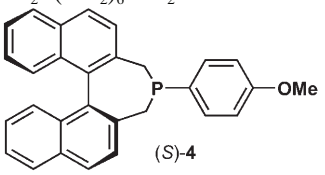
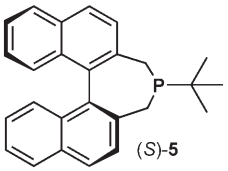
[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95 200 °C) analysis with diglyme as internal standard.

and catalyst. Due to the formation of a second binding site, a more favorable position for transferring the chiral information is attained.[5,9,13]

In order to understand the role of the free NH functionality for our pybim ligand **3a**, different substitutions at the imidazoline units were carried out. The corresponding monoprotected ligands **3b**, **c** were synthesized by reaction of **3a** with one equivalent of 3,5-di-*tert*-butylbenzoic acid chloride or $Ph_2P(O)Cl$. We presumed that the resulting unsymmetrical complexes would direct the substrate to occupy a specific orientation in the transition state and thereby induce increased selectivity during catalysis. However, 3,5-(*t*-Bu)$_2$C$_6$H$_3$)CO (**3b**) or Ph_2PO substitution (**3c**) decreased the enantioselectivity in the model reaction significantly (Table 2, entries 5 and 6). To confirm the results of the monosubstituted ligands an exchange of both hydrogens with Boc (**3d**) or Bz (**3e**) protecting groups was carried out. A further decrease of enantioselectivity was observed (Table 2, entries 7 and 8). Thus, there is a crucial necessity of both NH functionalities for obtaining high enantioselectivity in the transfer hydrogenation of acetophenone. Interestingly, the NH group is not necessary to achieve significant conversions (Table 2, entry 8), which is in contrast to previous reports by Noyori et al., for example catalysts containing *N*-dimethylamino alcohols are completely inactive compared to their *N*-monomethyl counterparts.[3d,13b] To estimate the influence of the ligands in more detail we varied also the phosphorus ligand part (Table 3). Among the different achiral ligands best results were obtained with PPh_3, (*p*-MeO-C$_6$H$_4$)$_3$P and (*p*-Me-C$_6$H$_4$)$_3$P (Table 3, entries 1, 3 and

Table 3. Influence of different phosphorus ligands on the trans fer hydrogenation of acetophenone.[a]



Entry	P Ligand	Temp. [°C]	Conv. [%][b]	*ee* [%][b]
1	Ph_3P	100	80	**94 (*S*)**
2	without	100	61	7 (*S*)
3	(*p* MeO $C_6H_4)_3P$	90	91	**87 (*S*)**[c]
4	(*o* Me $C_6H_4)_3P$	100	20	*rac*
5	(*p* Me $C_6H_4)_3P$	100	41	**97 (*S*)**
6	[3,4 $(CF_3)_2$ $C_6H_3]_3P$	90	24	66 (S)[c]
7	(*p* F $C_6H_4)_3P$	100	53	76 (*S*)
8	Cy_3P	90	2	15 (*S*)[c]
9	*t* Bu_3P	100	1	12 (*S*)
10	*n* $BuPAd_2$	100	4	5 (*S*)
11	(*i* $PrO)_3P$	100	28	75 (*S*)
12	$Ph_2P(CH_2)PPh_2$	100	37	*rac*
13	$Ph_2P(CH_2)_2PPh_2$	100	43	*rac*
14	$Ph_2P(CH_2)_5PPh_2$	100	43	6 (*S*)
15	$Ph_2P(CH_2)_6PPh_2$	100	15	37 (*S*)
16	 (*S*)-**4**	90	90	95 (*S*)[c]
17	 (*S*)-**5**	90	8	24 (*S*)

[a] *Reaction conditions: in situ* catalyst {1.9×10^{-6} mol [$RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol **3a**, 3.8×10^{-6} mol of the correspond ing P ligand}, 1.9×10^{-5} mol NaO *i* Pr, 2.0 mL isopropyl alco hol, 10 min at described temperature then addition of 3.8×10^{-4} mol acetophenone, 1 h at described temperature.

[b] Conversion and *ee* were determined by chiral GC (50 m Lip odex E, 95 200 °C) analysis with diglyme as internal stan dard.

[c] Experiments also performed at 100 °C, but only low enantio selectivities or conversions were obtained.

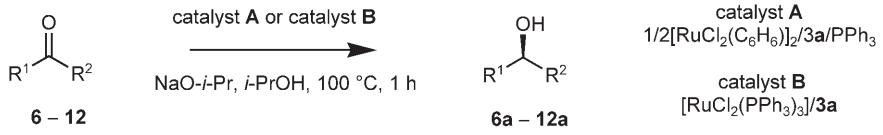
5). Methyl substitution in the *o*-position of arylphosphines decreased the enantioselectivity dramatically compared to that at the *p*-position (from 97% *ee* to *rac*, entries 4 and 5). Moderate conversion and selectivity were obtained for electron-poor substituted arylphosphines (Table 3, entries 6 and 7). Interestingly, also more basic and sterically hindered alkylphosphines such as PCy_3, $P(t\text{-}Bu)_3$, and *n*-$BuPAd_2$ showed only low activity (Table 3, entries 8–10).

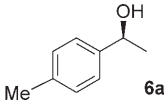
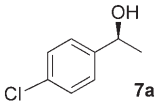
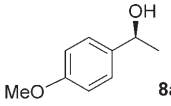
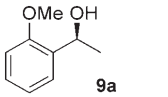
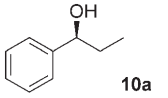
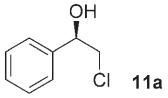
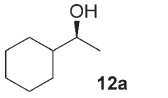
Furthermore, we applied chelating arylphosphine ligands. For bis(diphenylphosphino)methane (DPPM) only disappointing conversion and selectivity were obtained (Table 3, entry 12). By increasing the number of CH_2 groups in the bridge an increase of the enantiomeric excess was detected (Table 3, entries 13–15), probably due to a weaker coordination of the second phosphine group to the ruthenium. In addition, to improve the enantioselectivity and to increase the enantiomeric differentiation in the shape of the catalysts, we investigated the influence of chiral phosphines. Therefore, we tested chiral monodentate ligands (*S*)-**4** and (*S*)-**5** in the transfer hydrogenation of acetophenone in combination with pybim ligand **3a**. Recently, we have demonstrated the successful application of such chiral monodentate 4,5-dihydro-3*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]phosphepines in various asymmetric hydrogenations using molecular hydrogen.[10] Furthermore, Gladiali and co-workers reported previously the application of this ligand class in the rhodium-catalyzed asymmetric hydrogenation of C=C bonds.[21] However, only ligand (*S*)-**4** showed comparable enantioselectivity to PPh_3 of 95% *ee*, while (*S*)-**5** gave poor selectivity and conversion, due to a similar basicity to achiral alkylphosphines (Table 3, entry 16 and 17).

Next, we explored the influence of the concentration of PPh_3. The results indicated a necessity of 1 equiv. of PPh_3 relating to 1 equiv. of ruthenium, while the reaction with more than 1 equiv. of PPh_3 or in the absence of PPh_3 resulted in a decrease of enantioselectivity (Table 3, entries 1 and 2). Noteworthy, the use of an excess of PPh_3 has no disordered effect on selectivity while a negative influence was reported for other catalytic systems when PPh_3 was not removed.[5,6] In analogy to Gimeno et al.[6,11] and Yu et al.[12] we assume a *cis*-coordination of the phosphine with respect to the *N*-*N*-*N* plane, which forms after removal of the *cis*-coordinated chlorides (with respect to each other) a highly selective vacancy for substrate coordination and chirality transfer.

To demonstrate the usefulness of the novel catalysts we employed system **A** ($[RuCl_2(C_6H_6)]_2$/pybim/PPh_3) and **B** ($[RuCl_2(PPh_3)_3]$/pybim) in the asymmetric transfer hydrogenation of six aromatic and one aliphatic ketones (Table 4). In general, catalyst system **A** gave some higher enantioselectivities compared to catalyst **B**. Substituted acetophenones and propiophenone gave enantioselectivities up to 98% *ee* (Table 4, entries 1–5). In the case of methoxy-substitution the position of the substituent plays an important role, because *ortho*-substitution was favored (Table 4, entries 3 and 4). A chloro substituent in the α-position to the carbonyl group proved to be problematic and deactivated both catalysts (Table 4, entry 6). Compared to aromatic ketones, aliphatic ketones are more challenging substrates. Nevertheless, 1-cyclohexylethanone was reduced by catalyst **A** in good yield and enantioselectivity (Table 4, entry 7).

Table 4. Transfer hydrogenation of prochiral ketones.[a]



Entry	Alcohol	Catalyst **A**[b,c,d]		Catalyst **B**[b,c,d]	
		Conv. [%]	*ee* [%]	Conv. [%]	*ee* [%]
1	 **6a**	89	89 (*S*)	>99	85 (*S*)
2	 **7a**	84	94 (*S*)	>99	89 (*S*)
3	 **8a**	86[e]	72 (*S*)	68[f]	74 (*S*)
4	 **9a**	>99	98 ( )	99 [g]	70 ( )
5	 **10a**	>99	97 (*S*)	98[e]	87 (*S*)
6	 **11a**	12[g]	70 (*R*)	<2[f]	12 (*R*)
7	 **12a**	91	82 (*S*)	96[f]	72 (*S*)

[a] *Reaction conditions: in situ* catalyst **A** {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol **3a**, 3.8×10^{-6} mol PPh_3), 1.9×10^{-5} mol NaO *i* Pr, 2.0 mL isopropyl alcohol, 10 min at 100 °C then addition of 3.8×10^{-4} mol substrate, 1 h at 100 °C.

[b] Conversion and *ee* were determined by chiral GC (entry 1: 25 m Lipodex E, 80 180 °C; entry 2: 25 m Lipodex E, 100 °C; entry 3: 50 m Lipodex E, 90 105 °C; entry 4: 50 m Lipodex E, 90 180 °C; entry 5: 25 m Lipodex E, 90 180 °C; entry 6: 50 m Lipodex E, 95 180 °C; entry 7: 25 m Lipodex E, 100 °C) analysis with diglyme as internal standard.

[c] *In situ* catalyst **B** {3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**}.

[d] The absolute configurations were determined by comparing the sign of specific rotation with reported data.

[e] 4 h.

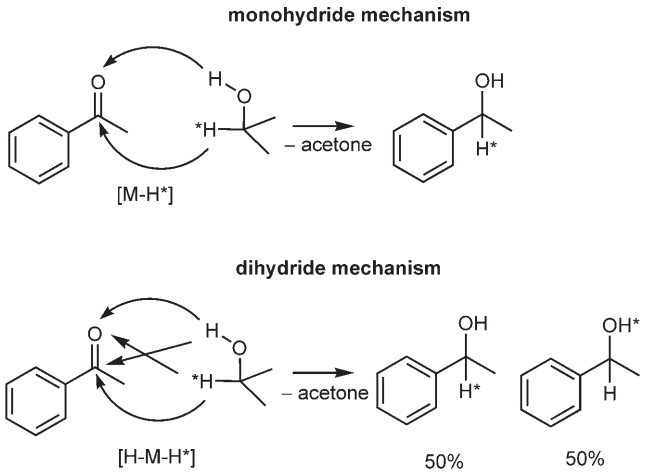
[f] 8 h.

[g] 24 h.

Various methods (^{1}H, ^{13}C, ^{31}P and ^{15}N NMR, COSY NMR, HMQC NMR and MS) were used for characterization of the pre-catalyst, but unfortunately no precise structure has been proven. The ^{31}P NMR spectrum of the pre-catalyst in $CDCl_3$ indicated a single compound, because a singlet appeared at 30 ppm (free PPh_3: −6 ppm and O=PPh_3: 27 ppm). Furthermore, the composition of the pre-catalyst was confirmed by HR-MS as $[RuCl_2(PPh_3)$(**3a**)] (calculated mass: 953.17549, detected mass: 953.17572). However, the coordination abilities of ligand **3a** are so far unclear, because a rapid exchange of NH protons was detected, which causes a broad signal in the ^{1}H NMR spectrum for the four protons adjacent to the nitrogen atoms and furthermore one signal for the corresponding carbons in the ^{13}C NMR spectrum.

Next, we focused our attention on a deeper comprehension of the reaction mechanism. For metal-catalyzed transfer hydrogenation two general mechanisms are accepted, designated as direct hydrogen transfer *via* formation of a six-membered cyclic transition state composed of metal, hydrogen donor and acceptor, and the hydridic route, which is subdivided into two pathways, the monohydride and dihydride mechanism (Scheme 3). More specifically, the formation of monohydride-metal complexes promotes an

exclusive hydride transfer from carbon (donor) to carbonyl carbon (acceptor) (Scheme 3), whereas a hydride transfer *via* dihydride-metal complexes leads to



Scheme 3. Monohydride and dihydride mechanisms for transfer hydrogenations.

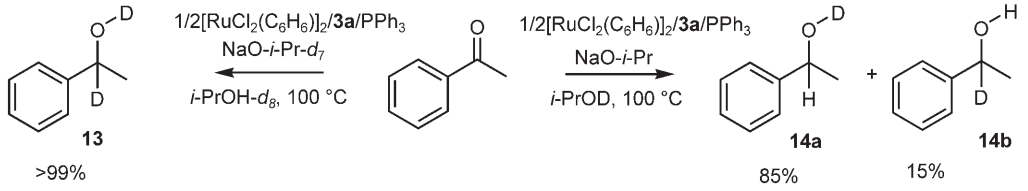
no accurate prediction of hydride resting state, because the former hydride was transferred to the carbonyl carbon (acceptor) as well as to the carbonyl oxygen (acceptor) (Scheme 3). Indications for both pathways (hydridic route) have been established by various research groups, when following the hydride transfer catalyzed by metal complexes, e.g., Ru, Rh or Ir.[13]

Reaction of cyclopropyl phenyl ketone ("radical clock"-substrate) with isopropyl alcohol in the presence of 1 mol% catalyst **A** gave exclusively the corresponding cyclopropylphenyl alcohol (>99% by ^{1}H NMR). Apparently there is no radical reduction induced by the transition metal or by sodium alkoxides.[14] The second assumption is also confirmed by performing the reduction of acetophenone in the presence of base and in the absence of the ruthenium catalyst. Here, no product at all was detected.

Next, we followed the incorporation of hydrogen from the donor molecule (isopropyl alcohol) into the product by applying a deuterated donor.[15] The precatalyst (1 mol%) is generated by stirring a solution of isopropyl alcohol-d_8, 0.5 equivs. of $[RuCl_2(C_6H_6)]_2$, ligand **3a** and PPh_3 for 16 h at 65 °C. Then, sodium isopropoxide-d_7 was added and the solution was stirred for 10 min at 100 °C. The reaction mixture was charged with acetophenone and after 1 h compound **13** was observed as main product (>99%) by ^{1}H NMR (Scheme 4).[16] The result proved an exclusive transfer of the deuterium into the carbonyl group, therefore a C–H activation of the substrate/product under the described conditions did not occur. Furthermore, this result rules out an enol formation in the catalytic cycle.[17]

To specify the position and the nature of the transferred hydride, the reaction was performed with isopropyl alcohol-d_1 (hydroxy group deuterated) as solvent/donor and sodium isopropoxide as base under identical reaction conditions. In the transfer hydrogenation of acetophenone we obtained a mixture of two deuterated 1-phenylethanols (Scheme 4, **14a** and **14b**).The ratio between **14a** and **14b** (85:15) indicated a specific migration of the hydride, albeit some scrambling was detected.[18] This was probably caused by rearrangement of the hydride complex, starting from HN–Ru–D *via* N=Ru(HD) to DN–Ru–H and subsequent transfer process into acetophenone yielding **14b**. In conclusion the incorporation is in agreement with the monohydride mechanism, implying the formation of a metal hydride species in the catalytic cycle (Scheme 3). Furthermore, this indication is confirmed by the above-mentioned influence of the NH groups. In conclusion, the transfer of hydrogen, in the case of catalyst **A**, is subdivided into the hydride transfer by the metal and the proton transfer by the NH group in analogy to the metal-ligand bifunctional catalysis.[13r]

We demonstrated for the first time the successful application of chiral tridentate pyridinebisimidazoline ligands in the asymmetric ruthenium-catalyzed transfer hydrogenation of aliphatic and aromatic ketones. Enantioselectivities up to >99% *ee* were obtained under optimized reaction conditions. Comparison experiments of **3a** with monoprotected pybims and pybox ligands displayed the crucial influence of the free NH functionality. Mechanistic experiments indicated the transfer of hydrogen from the donor molecule into the substrate *via* a metal-ligand bifunctional mechanism.



Scheme 4. Deuterium incorporation into acetophenone catalyzed by catalyst system **A**.

Experimental Section

General Remarks

All manipulations were performed under an argon atmosphere using standard Schlenk techniques. Isopropyl alcohol was used without further purification (purchased from Fluka, dried over molecular sieves). Sodium isopropoxide was prepared by reacting sodium with isopropyl alcohol under an argon atmosphere (stock solution). All ketones were dried over CaH_2, distilled in vacuum and stored under argon, except 4′ methoxyacetophenone and phenacyl chloride, which were used without further purification. $BuP(Ad)_2$[19] and *N* phenyl 2 (di *tert* butylphosphino) pyrrole[20] were synthesized according to literature protocols.

General Procedure for the Transfer Hydrogenation of Ketones

In a 10 mL Schlenk tube, the *in situ* catalyst was prepared by stirring a solution of $[RuCl_2(C_6H_5)]_2$ (1.9×10^{-6} mmol), ligand **3a** (3.8×10^{-6} mmol) and PPh_3 (3.8×10^{-6} mmol) in 1.0 mL isopropyl alcohol for 16 h at 65 °C. To this mixture sodium isopropoxide (1.9×10^{-5} mmol in 0.5 mL isopropyl alcohol (stock solution)) was added and the solution stirred at 100 °C for 10 min. After addition of the corresponding ketone (0.38 mmol in 0.5 mL isopropyl alcohol (stock solution)) the reaction mixture was stirred for 1 h at 100 °C. The solution was cooled to room temperature and filtered over a plug of silica. The conversion and *ee* were measured by GC without further manipulations.

Acknowledgements

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Synthetic, spectral and catalytic activity studies of ruthenium bipyridine and terpyridine complexes: Implications in the mechanism of the ruthenium(pyridine-2,6-bisoxazoline)(pyridine-2,6-dicarboxylate)-catalyzed asymmetric epoxidation of olefins utilizing H_2O_2

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Synthetic, spectral and catalytic activity studies of ruthenium bipyridine and terpyridine complexes: Implications in the mechanism of the ruthenium(pyridine-2,6-bisoxazoline)(pyridine-2,6-dicarboxylate)-catalyzed asymmetric epoxidation of olefins utilizing H_2O_2

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Abstract

Various $Ru(L_1)(L_2)$ (**1**) complexes (L_1 = 2,2′ bipyridines, 2,2′:6′,2″ terpyridines, 6 (4*S*) 4 phenyl 4,5 dihydro oxazol 2 yl 2,2′ bipy ridinyl or 2,2′ bipyridinyl 6 carboxylate; L_2 = pyridine 2,6 dicarboxylate, pyridine 2 carboxylate or 2,2′ bipyridinyl 6 carboxylate) have been synthesized (or in situ generated) and tested on epoxidation of olefins utilizing 30% aqueous H_2O_2. The complexes containing pyr idine 2,6 dicarboxylate show extraordinarily high catalytic activity. Based on the stereoselective performance of chiral ruthenium com plexes containing non racemic 2,2′ bipyridines including 6 [(4*S*) 4 phenyl 4,5 dihydro oxazol 2 yl] [2,2′]bipyridinyl new insights on the reaction intermediates and reaction pathway of the ruthenium catalyzed enantioselective epoxidation are proposed. In addition, a sim plified protocol for epoxidation of olefins using urea hydrogen peroxide complex as oxidizing agent has been developed.

Keywords: Ruthenium; Olefin; Epoxidation; Homogeneous catalysis; Mechanism

1. Introduction

Oxidation reactions constitute one of the core technologies which convert simple bulk raw materials, such as alkanes and olefins, to value-added products in higher oxidation states [1]. However, in the area of fine chemicals and pharmaceuticals they are less established on industrial scale compared to reductions and CC coupling reactions. For a more general application of oxidation reactions, the "ideal" oxidant should be in high atom-economy, environmentally benign, readily available and safe as well [2]. Air (molecular oxygen) is undoubtedly the perfect oxidant of choice for a number of oxidation reactions. However, only one oxygen atom of O_2 is productive for most oxidations (50% atom efficiency), thus such processes produce significant amount of waste from the co-reductant [3,4]. Apart from molecular oxygen, hydrogen peroxide (H_2O_2) has been shown to be a useful oxidant with respect to the criteria mentioned above [5,6]. Due to its handling and price it is particularly useful for liquid-phase oxidations for the synthesis of fine chemicals, pharmaceuticals, agrochemicals and electronic materials. Hence, developments on new catalytic systems using H_2O_2 are an important and challenging goal in oxidation chemistry [7,8].

With regard to enantioselective epoxidations of olefins, titanium (Sharpless epoxidation) [9] and manganese (Jacobsen Katsuki epoxidation) [10] based catalysts are still in the state-of-the-art. Very recently Katsuki et al. demonstrated that a titanium schiff base catalyst showed very good activity and excellent ee in asymmetric epoxidation utilizing aqueous H_2O_2 [11]. In the last decade significant

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progress using organic catalysts based on chiral ketones (Shi, Yang and other's ketone catalysts) [12,13] has also been reported. Besides, the polypeptide-catalyzed stereoselective epoxidation of enones under phase transfer conditions seems to be an industrially applicable process [14]. Chiral Lewis acids [15] and chiral amines [16] catalyzed epoxidation of α,β-unsaturated olefins also have been demonstrated.

Generally, there are several problems associated with the use of H_2O_2 in asymmetric epoxidations [8]. For instance H_2O_2 usually decomposes to O_2 in the presence of transition metal catalysts. Over stoichiometric amount of H_2O_2 is often employed to solve this problem. However, the stability of the catalyst in high concentration of H_2O_2 as well as the selectivity, especially enantioselectivity, in the presence of water obviously could be problematic. It is also apparent that oxidative cleavage of the olefin competes with the productive epoxidation. Therefore, even after decades of extensive research efforts, the development of general and catalytic asymmetric epoxidation methods using H_2O_2 is still underway [16,11,17].

Our interest has been aroused by ruthenium-catalyzed oxidation reactions with its wide range of applicability and broad variation of ligand type especially in asymmetric epoxidation of olefins [18]. In this regard, we chose Ru(pyridine-2,6-bisoxazoline)(2,6-pyridinedicarboxylate) (**1**) as our starting point as it contains two different meridional ligands [19]. It is patently advantageous that by modifying the chiral (pybox) and the achiral (pydic) ligands separately, the reactivity and (enantio)selectivity should be possible to tune up easily. Applying this concept, we were able to make **1** to become a more practical epoxidation catalyst by adding a controlled amount of water to the reaction mixture [20a]. This also led to the development of enantioselective epoxidation protocols applying alkyl peroxides [20b] and hydrogen peroxide [20d,20e,20f]. Noteworthy, highly productive and robust ruthenium catalysts with turnover number (TON) up to 10 000 have also been developed for non-asymmetric epoxidation with 30% aqueous H_2O_2 [20c,20e]. Most recently, a ligand library of *N*,*N*,*N*-tridentate pyridinebisimidazolines, so-called pybim ligands, was also realized during the course of these studies [20f,21]. Fig. 1 shows four of more than 70 catalysts which we have tested in the epoxidation of olefins with H_2O_2.

In this paper, we describe our work on the synthesis of novel ruthenium(II) bipyridine and terpyridine complexes. Spectral and catalytic activity studies using these complexes shed light on the mechanism of the ruthenium-catalyzed asymmetric epoxidation. Besides a simplified protocol for the epoxidation of olefins utilizing urea hydrogen peroxide complex has been developed.

2. Results and discussion

In our previous studies, we have shown that various ruthenium complexes, such as **1** and **2** allow for the epoxidation of aromatic olefins with high selectivity (chemoselectivity up to 99%; enantioselectivity up to 85%) [22]. With regard to the mechanism of this novel asymmetric epoxidation, we have established the role of the protic solvent, the effect of acid additives, and the relative rate of different catalysts. In addition, competitive reactions with different olefins suggested an unsymmetric oxo-transfer transition state [22b]. Modelling studies on the reactivity of the core structure **1′** at the B3LYP/LANL2DZ density functional level of theory showed that an *N*-oxide coordinating intermediate is likely to be the most thermodynamically stable isomer of all possible intermediates. Scheme 1 shows a preliminary mechanistic picture of the reaction.

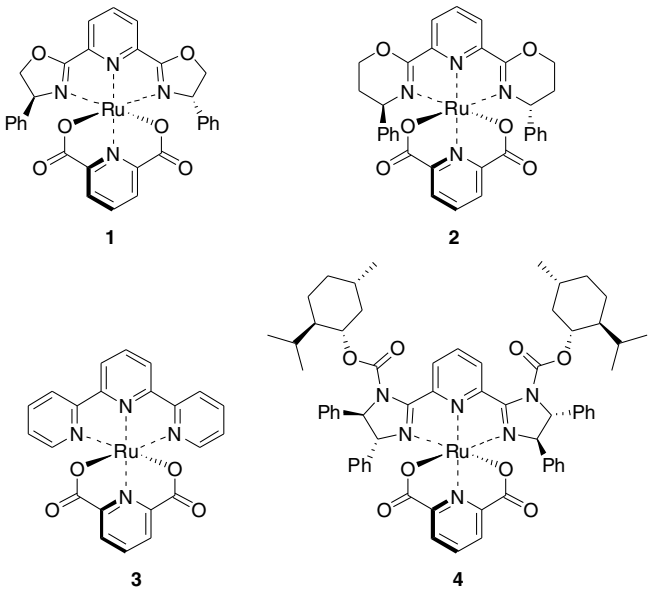
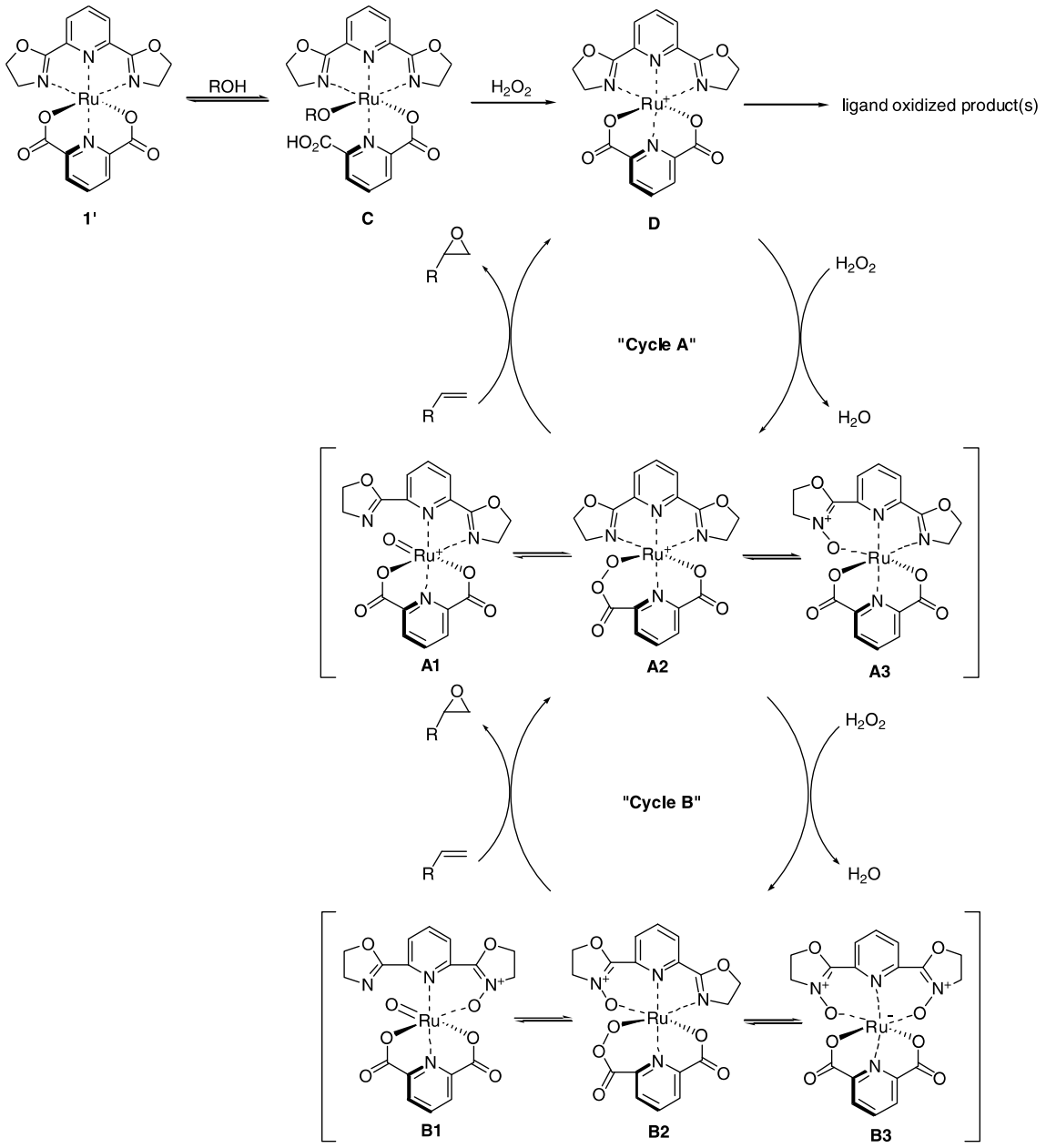


Fig. 1. Ruthenium catalysts for epoxidation of olefins with H_2O_2.

Initially, the carboxylate on **1′** dissociates in a protic solvent and makes the oxidation of the ruthenium center much faster. Hence, the ruthenium(III) species **D** forms, which is further oxidized to intermediates **A**. **A3** is the most stable one suggested by theoretical calculation. However, from the evidence of kinetic studies, **A1** is suspected to be the active oxo-transfer intermediate [23]. After epoxidation of the olefin **D** is regenerated (cycle A). Alternatively, intermediates **A** can be further oxidized to complexes **B** which transfer the oxygen atom to the olefin and regenerate intermediates **A** (cycle B).

Unfortunately, so far any isolation of ruthenium intermediates in higher oxidation state was not successful. Also initial attempts to synthesize the mono- or di-*N*-oxide of 2,6-bis-[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]pyridine (*S*,*S*-Ph_2-pybox) by oxidation with *m*-CPBA [24] or cyclization of (*S*)-2-hydroxy-amino-2-phenylethanol with dimethyl pyridine-2,6-dicarboximidate [25] did not yield the desired *N*-oxide ligands. Apparently *S*,*S*-Ph_2-pybox and its *N*-oxides are not stable in strong oxidizing and acidic conditions.

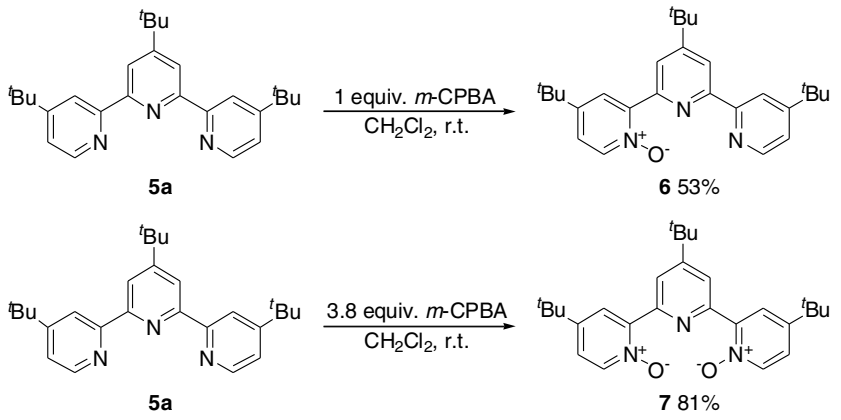
Therefore, we chose the more robust 2,2′:6′,2″-terpyridines as our model ligand system. Though the turnover



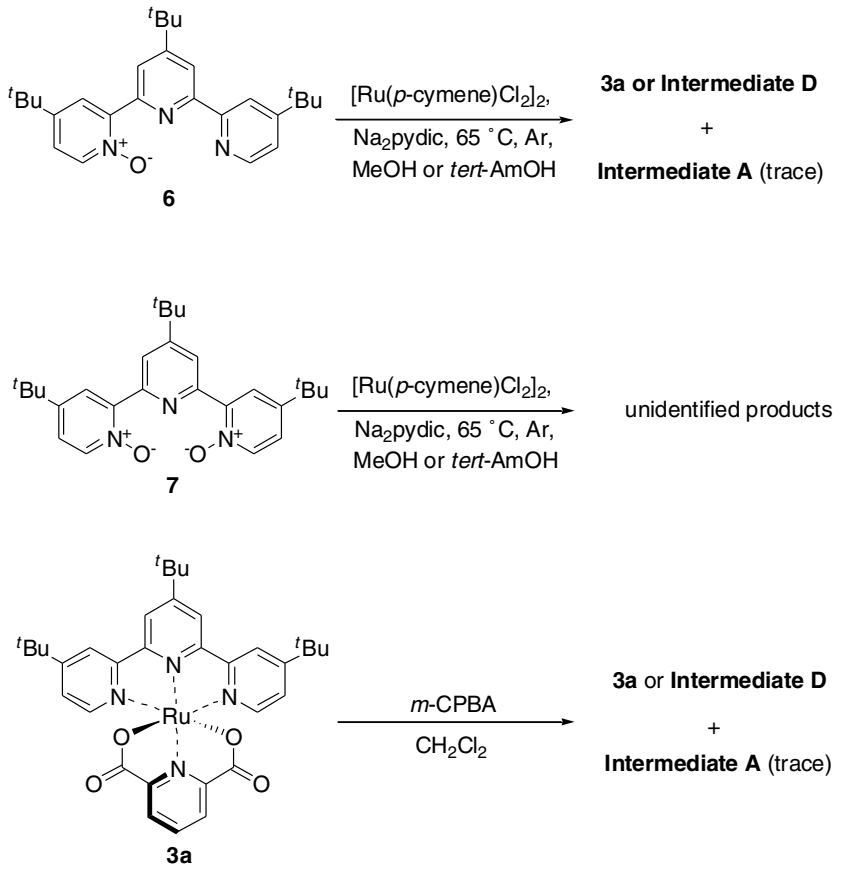
Scheme 1. Proposed mechanism for the Ru(pybox)(pydic) catalyzed epoxidation of olefins.

number (TON) of the ruthenium terpyridine complex **3** is around 40 times larger than that of **1** (TON of **1** and **3** are ~200 and ~8000, respectively) [20d,20e], competition reactions showed that the relative rate of **3** is only 1.8 2.4 times faster than that of **1** [22b]. This shows good agreement with our hypothesis that the high productivity of **3** is due to its robustness and not electronic or steric reasons. Owing to better solubility, 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2′-terpyridine **5a** was subjected to selective oxidation with *m*-CPBA to yield **6** and **7** in 53% and 81%, respectively (Scheme 2) [26].

Next, **6** and **7** were reacted with $[Ru(p\text{-cymene})Cl_2]_2$ as illustrated in Scheme 3. In case of **6** only metal species with a molecular weight similar to **3a** have been observed in the electrospray ionization mass spectrometry (ESI-MS) after removal of solvent. Moreover, unidentified products were observed in the ESI-MS when **7** was used in the complexation reaction. Direct oxidation of **3a** with *m*-CPBA in CH_2Cl_2 turned the solution from violet to brown instantaneously. However, after removal of solvent, only a purple solid with molecular mass as **3a** was observed. Hence, titration of **3a** with *m*-CPBA monitored by UV Vis spectroscopy in CH_2Cl_2 at 25 °C was then performed. As shown in Fig. 2 the absorption maxima at 526, 329, 321 nm were gradually decreased and the shoulder at 337 nm was increased when portions of *m*-CPBA solution was added (see Section 4). Isosbestic points were observed at 354 and 327 nm. This phenomenon indicates that a single



Scheme 2. Synthesis of terpyridine *N* oxides.



Scheme 3. Attempts to synthesize catalytic intermediates A.

product was formed preferentially [27]. The ratio of **3a** to *m*-CPBA determined by the titration was approximately 1:1 in three different concentrations of **3a**.

The ESI-MS of the **3a**:*m*-CPBA 1:1 solution showed only the molecular ion peak similar to **3a**. No epoxide was observed even in the presence of a 10-fold excess of styrene. Reacting an excess of *m*-CPBA with **3a** in CH_2Cl_2 or CH_3CN gave only a weak molecular ion peak of $[(\mathbf{3a} + O + H)^+]$ and high intensity of $[(\mathbf{3a})^+]$ in the ESI-MS. Noteworthy, the molecular ion peak of $[(\mathbf{3a} + 2O)^+]$ has never been observed. In addition, there was no observable change in the UV Vis spectrum when benzoic acid was added to the solution of **3a**. Hence, the UV Vis absorption spectrum shift is not due to the formation of intermediate **A** nor protonation. Instead, we propose that **3a** is easily oxidized by *m*-CPBA to intermediate **D**. This is in agreement with the previous observation that **3** can be oxidized to a paramagnetic Ru(III) state in solution [28]. However, we could not exclude that intermediate **A** is generated in low concentration or it decomposed back

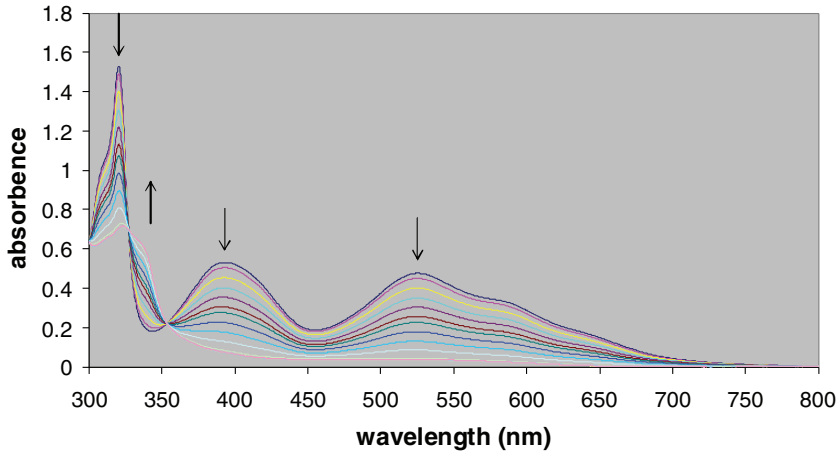


Fig. 2. UV Vis titration of **3a** with *m* CPBA.

to **3a** or intermediate **D**. In fact ruthenium (IV) oxo porphyrin has been reported to undergo disproportionation to give a ruthenium (II) porphyrin and a ruthenium (VI) dioxo porphyrin complex [29].

Thus, we computed the possible key intermediates aiming to have further insight about the decomposition pathways of the oxidized complex **3** (Scheme 4 and Table 1). All calculations were carried out by using the GAUSSIAN 03 program [30]. Structures were optimized at the B3LYP [31] density functional level of theory with the LANL2DZ basis set [32], and the nature of the optimized structures on the potential energy surface (PES) was characterized by the calculated number of imaginary frequency (NImag) at the same level of theory (B3LYP/LANL2DZ), i.e.; minimum structures without (NImag 0) [33]. The corresponding frequency calculations provide also the thermal corrections to Gibbs free energies at 298 K. The energies for discussion and interpretation are the Gibbs free energies (ΔG $\Delta H - T\Delta S$). At B3LYP/LANL2DZ, the parent complex **3** has C_2 symmetry, and the mono- and di-oxidized species **3**(**O**) and **3**(**O**)$_2$ are C_1 and C_2 symmetrical, respectively. All three structures are energy minimums on the PES.

From the Gibbs free energy, both the bimolecular decomposition of mono-oxo complex **3**(**O**) to **3** and O_2 and self decomposition of di-oxo ruthenium complex **3**(**O**)$_2$ to **3** and O_2 are highly thermodynamically favourable

Table 1
B3LYP/LANL2DZ total electronic energies (E_{tot}, au) and total Gibbs free energies (G_{tot}, au, at 298 K) and number of imaginary frequencies (NImag)

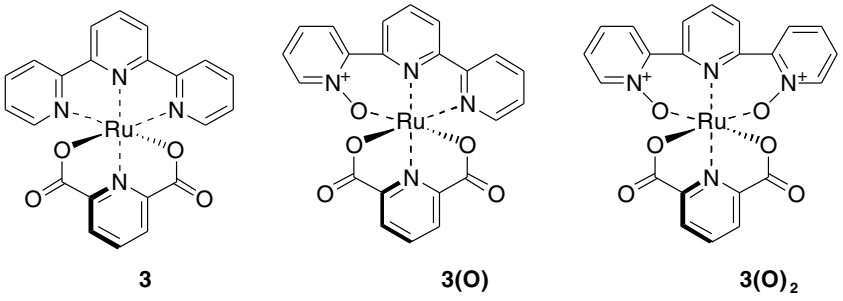
	E_{tot}	G_{tot}	NImag
3/C_2	1460.51505	1460.23975	0
3(**O**)/C_1	1535.65806	1535.38146	0
3(**O**)$_2$/C_2	1610.79774	1610.51774	0

$$2[\mathbf{3}(\mathbf{O})] \rightarrow 2[\mathbf{3}] + O_2 \quad \Delta G = -30.0 \text{ kcal mol}^{-1} \tag{1}$$

$$[\mathbf{3}(\mathbf{O})] \rightarrow 2[\mathbf{3}] + O_2 \quad \Delta G = -33.6 \text{ kcal mol}^{-1} \tag{2}$$

$$2[\mathbf{3}(\mathbf{O})] \rightarrow [\mathbf{3}] + [\mathbf{3}(\mathbf{O})_2] \quad \Delta G = +3.4 \text{ kcal mol}^{-1} \tag{3}$$

(about -30 kcal mol ^{1}). Disproportionation of **3**(**O**) to **3** and **3**(**O**)$_2$ is also not likely ($+3.4$ kcal mol ^{1}). The calculations suggest that the ruthenium oxo-transfer species is not **3**(**O**)$_2$ due to insufficient stability, though the rate of this decomposition is not so clear. Moreover, since the decomposition of **3**(**O**) is bimolecular, when the concentration of **3**(**O**) is low (as in the catalytic reaction conditions: H_2O_2 is dosed to the catalytic reaction slowly in 12 h and pre-catalyst is only in catalytic amount), the olefin acts as a good trap and epoxide forms. The bimolecular decomposition of two **3**(**O**) to molecular oxygen also explain the observation in the ESI-MS [very low intensity of **3**(**O**)] and the

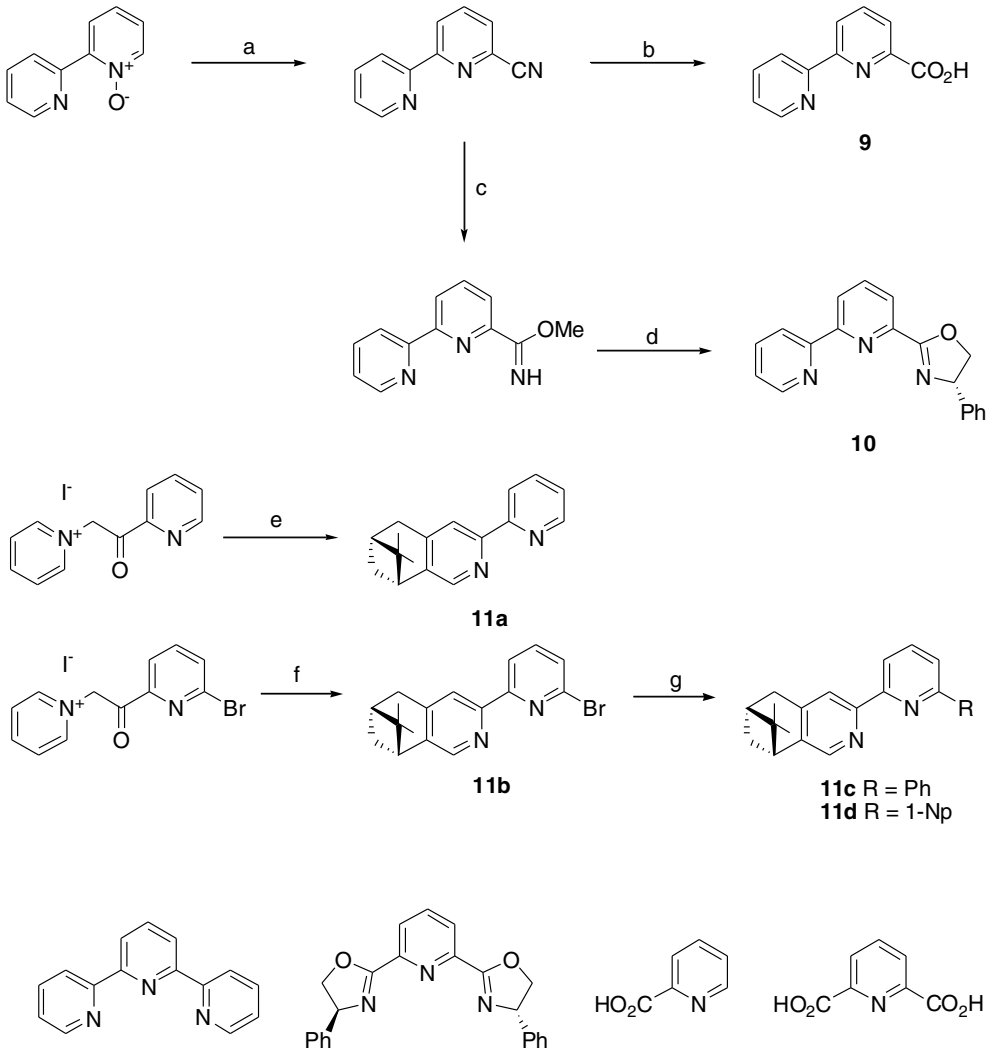


Scheme 4. Modeling of the decomposition reactions of **3**, **3**(**O**) and **3**(**O**)$_2$.

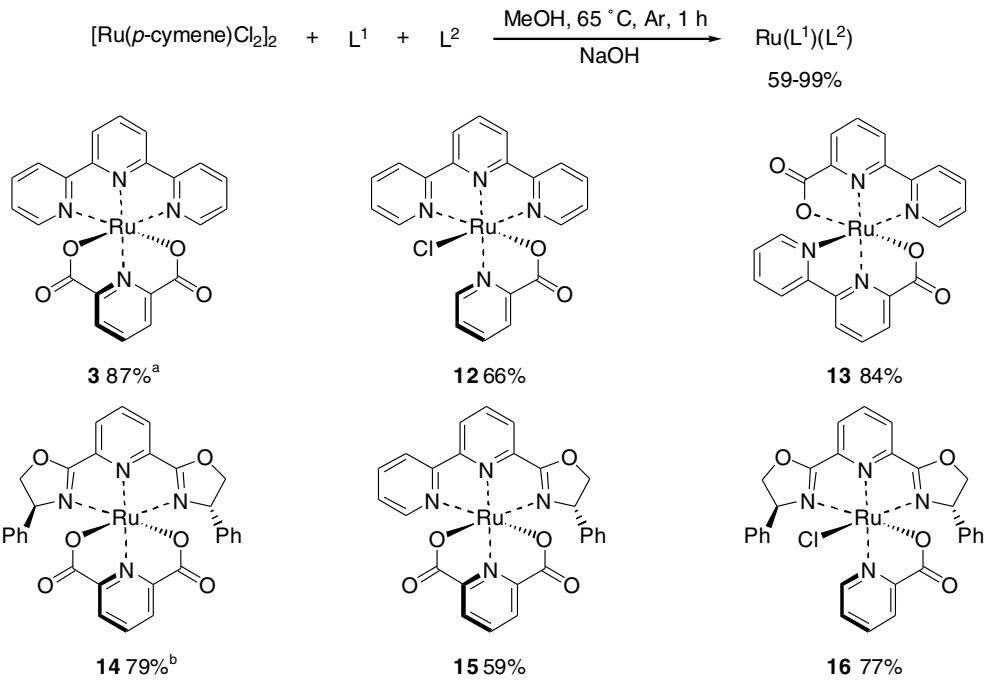
negative results in the attempts of isolating **3**(**O**) since concentrating of the solution of **3**(**O**) favours the bimolecular decomposition of **3**(**O**) to **3** and O_2 (infra supra).

In order to have a better understanding of the reactivity and transfer of chirality, we used the fragment-based approach to address the essential part of the catalysts. These C_2 symmetric catalysts contain two meridional ligands. Each of them contains four pyridine nitrogen and two carboxylate oxygen atoms. We decided to synthesize and test new catalysts with similar coordinating groups according to their possibility of modification, the availability of starting materials, and the ease of synthesis. Hence, different 2,2′-bipyridines functionalized in the 6-position were synthesized (Scheme 5). 2,2′-Bipyridine *N*-oxide was treated with TMSCN and benzoyl chloride at 0 °C to room temperature for 18 h to yield 2,2′-bipyridine-6-carbonitrile in 90% [34]. Hydrolysis of 2,2′-bipyridine-6-carbonitrile with HCl gave 2,2′-bipyridine-6-carboxylic acid in good yield (77%) [35].

Direct cyclization of unsymmetrical 6-[(4*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl]-[2,2′]bipyridinyl (**10**) with (*S*)-2-amino-2-phenylethanol and 2,2′-bipyridine-6-carbonitrile in refluxing anhydrous chlorobenzene using anhydrous $ZnCl_2$ as the catalyst showed inferior result and gave only a trace of the desired product. To our delight, **10** was obtained in good yield when methyl 2,2′-bipyridine-6-carboxyimidate was refluxed with (*S*)-2-amino-2-phenylethanol in CH_2Cl_2 for 48 h. Chiral non-racemic 2,2′-bipyridine (**11a**) was reported to induce good enantioselectivity in epoxidation of styrene with $PhI(OAc)_2$, though with low reactivity [36]. Therefore, we were interested to test this type of ligands in our reaction conditions [20d]. Hence, **11a** and **11b** were synthesized by Kröhnke condensation [37]. Subsequently, **11c** and **11d** were obtained in good yields using the Suzuki Miyaura cross coupling reaction [37b]. Other commercially available ligands and co-ligands used in this study are also shown in Scheme 5.



Scheme 5. Synthesis of ligands and commercially available ligands in this study. Reagents and conditions: (a) TMSCN, PhCOCl, CH_2Cl_2, 0 °C to r.t., 18 h, 90%; (b) 37% HCl, reflux, 2 h, 77%; (c) Na, anhy. MeOH, Ar, r.t., 4 days, 99%; (d) (*S*) 2 amino 2 phenylethanol, anhy. CH_2Cl_2, Ar, reflux, 48 h, 92%; (e) (1*R*) ( ) myrtenal, NH_4OAc, formamide, 75 °C, 6 h, 53%; (f) (1*R*) ( ) myrtenal, NH_4OAc, HOAc, reflux, 6 h, 42%; (g) 0.2 mol% $Pd(PPh_3)_4$, $RB(OH)_2$, toluene/H_2O, K_2CO_3, 120 °C, 13 h, **11c**: 99%, **11d**: 84%.



Scheme 6. Synthesis of ruthenium catalysts: [a]Ref. [20e]; [b]Ref. [22a].

Scheme 7. Ruthenium catalyzed epoxidation of styrene and *trans* stilbene.

Next, six different ruthenium complexes have been synthesized in moderate to good yields by heating [Ru(*p*-cymene)Cl_2]$_2$ with the corresponding ligand in MeOH at 65 °C under Ar in the presence of NaOH (1 equiv. per carboxylic acid) for 1 h (see Section 4) (Scheme 6). All pre-catalysts were well characterized and subjected to two prototypical epoxidation reactions. The results are summarized in Scheme 7 and Table 2. In case of complexes with 2,2′-bipyridines

Table 2
Ruthenium catalyzed epoxidation of styrene and *trans* stilbene with H_2O_2[a]

Entry	Catalyst	Ph		Ph Ph	
		Yield (%)	Ee (%)	Yield (%)	Ee (%)
1	0.5 mol% **3**[a]	71		96	
2	0.5 mol% **12**[b]	0		0	
3	0.5 mol% **13**	9		26	
4	5 mol% **14**[c]	70	+31[d]	100	67[e]
5	5 mol% **15**	68	1	>99	0
6	5 mol% **16**	18	n.d.[f]	14	n.d.
7	2.5 mol% [Ru(*p* cymene)Cl_2]$_2$, 5 mol% **11a**, 5 mol% H_2pydic, 12 mol% Et_3N	67	+4	84	0
8	2.5 mol% [Ru(*p* cymene)Cl_2]$_2$, 5 mol% **11b**, 5 mol% H_2pydic, 12 mol% Et_3N	40	2	28	0
9	2.5 mol% [Ru(*p* cymene)Cl_2]$_2$, 5 mol% **11c**, 5 mol% H_2pydic, 12 mol% Et_3N	29	4	19	3
10	2.5 mol% [Ru(*p* cymene)Cl_2]$_2$, 5 mol% **11d**, 5 mol% H_2pydic, 12 mol% Et_3N	77	0	69	0

[a] Ref. [20e].
[b] See Section 4.
[c] Ref. [22b].
[d] "+" sign means (*R*) (+) styrene oxide is the major enantiomer.
[e] " " sign means (*S*,*S*) ( ) *trans* stilbene oxide is the major enantiomer.
[f] Not determined.

11a d and 2,6-pyridinedicarboxylic acid we used an in situ catalyst generation protocol [20a], due to the easy hydrolysis of the resulting complexes [36].

All catalytic experiments were run with 30% aqueous H_2O_2 at room temperature. Complex **3** has been shown to be a general and efficient catalyst because of its robustness [20e]. Surprisingly complexes **12** and **13**, which contain the same aromatic terpyridine unit as **3**, showed a drastic decrease of activity. Simply changing 2,6-pyridinedicarboxylate (pydic) to 2-pyridinecarboxylate, the resulting ruthenium complex **12** showed no reactivity at all. Even **13** containing four pyridine nitrogen and two carboxylate groups similar to **3** gave only poor yield for the epoxides [38]. Clearly, the chelating sub-unit "O N O" of pydic, which stabilizes the Ru(III) oxidation state by donating electron density to the metal center, plays a dominating role on the catalytic reactivity.

The importance of this "O N O" sub-unit is also reflected by the reduction and oxidation potentials of different ruthenium complexes (Table 3). It is with good agreement that the higher the oxidation potential of Ru^{2+}/Ru^{3+}, the lower the reactivity in the epoxidation reaction. On the other hand, the higher the $E_{1/2}$ (reduction potential) the higher the stability of the ligands towards reduction. Hence, **3** showed the highest reduction potential on terpyridine. Moreover, no reduction potential of pydic was observed [39]. As both terpyridine and "pydic" are more stable, the whole catalytic system becomes more robust.

Attempts to isolate catalysis intermediates from epoxidation reactions in the presence of Ru(*S*,*S*-Ph_2-pybox)(pydic) (**14**) resulted in the isolation of suspected Ru(*S*,*S*-Ph_2-pybox)(pydic)(O) complexes in low yield (<10%). The ^1H NMR spectrum of the isolated product showed diamagnetic behaviour and was not explainable. A careful analysis of the ultra high resolution mass spectrum showed three major peaks at *m*/*z* 636.05765 ($C_{30}H_{22}N_4O_6Ru^+$), 650.03980 ($C_{30}H_{20}N_4O_7Ru^+$), and 652.05383 ($C_{30}H_{22}N_4O_7Ru^+$). We believe that **14** is oxidized to a Ru(III) species together with two Ru complexes with one oxygen atom more, in which one of them has an aromatized oxazoline ring. Catalytic tests with the chiral catalyst **15** demonstrated that even one aromatized oxazoline ring on the catalyst may lead to a total loss of enantioselectivity. In agreement with this observation, the suspected Ru(*S*,*S*-Ph_2-pybox)(pydic)(O) mixture gave a significantly lower enantioselectivity compared with the original catalyst **14**. The testing of in situ generated catalysts with chiral bipyridines **11a d** resulted in 29 77% of *trans*-stilbene oxide, however none of the catalysts gave any reasonable ee (0 4%) (Scheme 8).

Finally, we were interested in improving our general epoxidation protocol. In our original procedure, 30% aqueous H_2O_2 was delivered to the olefin in *tert*-amyl alcohol in the presence of 0.5 mol% of **3** for 12 h by a syringe pump to prevent unproductive decomposition of H_2O_2.

For a laboratory procedure, it is advantageous to apply a solid oxidizing agent which can be dosed to the reaction mixture without any additional equipment. In case of a lower solubility of the solid oxidant in *tert*-amyl alcohol, unwanted decomposition of H_2O_2 to O_2 should be minimized. Hence, we tested common solid oxidants for the epoxidation of *trans*-stilbene (Table 4). To our delight, urea hydrogen peroxide complex deserves our hypothesis and gave an excellent yield of epoxide (>99%) in our model reaction in only 1 h. Next, we tested this simplified protocol and the results are shown in Table 5. UPH oxidized aromatic olefins in the presence of 0.5 mol% **3** with moderate to very good selectivity. Compared to the original proce-

Table 3
Redox potentials of various ruthenium terpyridine and pydic complexes

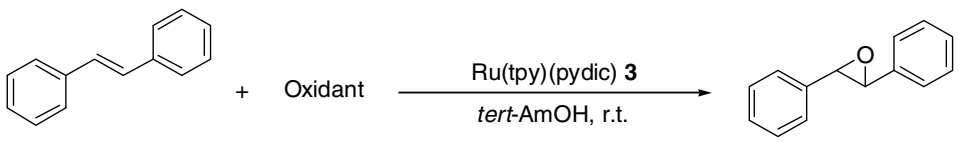
Complex	$E_{1/2}$ (oxidation) [V]	$E_{1/2}$ (reduction) [V]		Ref.
		1	2	
$Ru(tpy)^{2+}$	+1.31[a]	1.24	1.49	[38]
[Ru(tpy)(pic)][PF_6]	+0.88[b]	1.39	2.12	[39]
Ru(tpy)(bpyCO_2)	+0.90	1.36	1.63	[38]
Ru(tpy)(pydic) (**3**)	+0.60	1.53	not observed	[39]
Ru(bpyCO_2)$_2$ (**13**)	+0.52	1.49	1.79	[38]
K$Ru(pydic)_2$	+0.21[c]	n.d.	n.d.	[40]

n.d., Not determined.
[a] Reduction potential vs. SCE.
[b] Initial reported reduction potentials were referenced to Fc/Fc^+ which is taken as +0.48 V here.
[c] Determined by potentiometric titration at pH 7.

Table 4
Screening of various solid oxidant for epoxidation of *trans* stilbene

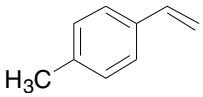
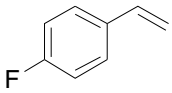
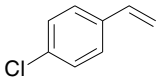
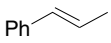
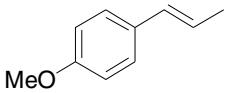
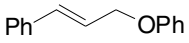
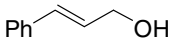
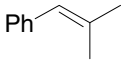
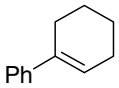
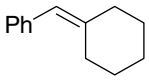
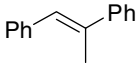
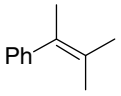
Entry	Oxidant	Time (h)	Conv. (%)	Yield (%)	Selec. (%)[a]
1	30% H_2O_2	12	100	96	96
2	UHP[b]	1	100	>99	>99
3	$Na_2CO_3 \cdot 1.5H_2O_2$	16	0	0	0
4	Oxone®[c]	16	9	4	44
5	$Ca(OCl)_2$	16	14	0	0

[a] Selectivity towards epoxide.
[b] Urea hydrogen peroxide complex.
[c] $2KHSO_4 \cdot KHSO_4 \cdot K_2SO_4$.



Scheme 8. Screening of various solid oxidant for epoxidation of *trans* stilbene.

Table 5
Scope and limitations of Ru(tpy)(pydic) **3** catalyzed epoxidation of olefin with UHP

Entry	Olefin	Time (h)	Conv. (%)	Yield (%)[a]	Selec. (%)[b]
1		3	41	39	95
2		3	81	74	91
3		3	49	39	80
4		3	40	28	71
5		3	100	>99	>99
6		3	100	95	95
7		3	100	92[c]	92
8		3	100	63	63
9		3	65	59	91
10		3	67	51	76
11		3	100	83	83
12		3	99	95	96
13		3	99	92	93
14		3	100	96[d]	96
15		3	53	48	91

[a] GC yields.
[b] Chemoselectivity towards epoxide.
[c] Isolated yield.
[d] NMR yield.

dure the reaction time is shortened. Mono-, 1,1-di, *trans*- and *cis*-1,2-di-, tri- and even tetra-substituted olefins all have good to excellent selectivity towards the corresponding epoxides. Functional groups like alcohol and halogens are tolerant in the reaction system. Clearly, slow dosage of the oxidant is no longer needed for this method.

3. Conclusion

In summary, mechanistic studies of ruthenium-catalyzed epoxidations of olefins were performed experimentally and theoretically with high level density functional theory calculations. Mono-*N*-oxide **A3** and active oxo-transfer catalyst **A1** are possible intermediates in the reaction pathway. A fragment-based catalyst design showed that the 2,6-pyridinedicarboxylic acid ligand is essential for the reactivity. Moreover, a C_2 symmetric chiral ligand provides the necessary chiral induction. Hence, catalyst **15** gave no ee for the epoxidation of *trans*-stilbene and styrene. This suggests that a partial ligand oxidation of the catalyst is possibly one of the non-productive asymmetric epoxidation pathways. Moreover, a general simplified and more active ruthenium-catalyzed epoxidation procedure of olefins utilizing urea hydrogen peroxide complex has been developed. Further development towards asymmetric epoxidation reactions are under investigation in our laboratory.

4. Experimental

4.1. General

Unless specified, all chemicals are commercially available and used as received. Ru(tpy)(pydic) (**3**) [19], Ru(^{t}Bu$_3$-tpy)(pydic) (**3a**) [20e], bpyCO$_2$H (**9**) [32], 2,2′-bipyridines (**11a d**) [37], Ru(bpyCO$_2$)$_2$ (**13**) [38], and Ru(*S*,*S*-Ph$_2$-pybox)(pydic) (**14**) [19], are synthesized according to the literature procedures. Qualitative analysis of reaction products was done on a gas chromatograph HP 5890 with mass selective detector HP 5989A (Hewlett-Packard) and a capillary column of type HP 5 was used for separation. For quantitative analysis of reaction mixture, the measurement was performed on a HP 6890 gas chromatograph (Hewlett-Packard) with flame ionization detector. The separation is obtained on a capillary column of type HP 5 (5% phenylmethylsiloxane, length 30 m, inner diameter 250 μm, film thickness 0.25) with argon as flowing gas. Enantiomeric excess of epoxides were determined with HP 1090 liquid chromatography (Hewlett-Packard) equipped with a DAD detector. UV Vis spectroscopic measurements were performed with a Shimadzu UV-1601 spectrophotometer. Nuclear magnetic resonance spectra were recorded on Bruker ARX300 or ARX400 spectrometers. All NMR spectra were taken in pure deuteriated solvents, such as $CDCl_3$, CD_2Cl_2, etc. Chemical shifts (δ) are given in ppm and refer to residual solvent as internal standard. Signal multiplicity and coupling constants (J in Hz) are shown in the parentheses. For multiplicity the following abbreviations are used: s, singlet; d, duplet; dd, duplet of duplet; t, triplet and m, multiplet.

4.2. Ligand synthesis

4.2.1. Synthesis of 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine 1-N-oxide (6)

To the solution of 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (**5a**) (300 mg, 0.75 mmol) in CH_2Cl_2 (7.5 ml), *m*-CPBA (77%, 167 mg, 0.75 mmol) in CH_2Cl_2 (7.5 ml) was added dropwise. The reaction mixture was stirred at r.t. for 15 h. It was then diluted with CH_2Cl_2 (10 ml) and washed with $NaHCO_3$ (10 ml × 3). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel (70 230 mesh) using ethyl acetate:Et_3N:MeOH 100:1:0 to 100:1:1 as the gradient eluent. An off-white solid was obtained after removal of solvent (165 mg, 53%). **6**: R_f 0.60 (ethyl acetate:Et_3N:MeOH 100:1:10); ^1H NMR (400.1 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.38 (s, 9H), 1.42 (s, 9H), 7.25 (dd, J 6.9, 3.0 Hz, 1H), 7.35 (dd, J 5.4, 2.0 Hz, 1H), 8.23 (d, J 6.9 Hz, 1H), 8.47 (d, J 3.0 Hz, 1H), 8.53 (d, J 2.0 Hz, 1H), 8.57 (d, J 1.7 Hz, 1H), 8.62 (d, J 5.4 Hz, 1H), 9.17 (d, J 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.46, 30.67, 34.65, 35.08, 35.44, 116.29, 118.51, 118.95, 121.89, 122.37, 123.12, 124.86, 140.06, 146.35, 148.18, 148.93, 150.12, 154.52, 155.50, 161.82; IR (KBr) 1588, 1546, 1480, 1377, 1261, 1192, 1067, 895, 831; 728, 609; EI-MS m/z 417 (M^+); FAB-MS m/z 418 ($M + H^+$); HRMS Calc. for $C_{27}H_{36}ON_3$: 418.28583. Found: 418.28564.

4.2.2. Synthesis of 4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine 1,1″-di-N-oxide (7)

To the solution of 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (**5a**) (100 mg, 0.25 mmol) in CH_2Cl_2 (2.5 ml), *m*-CPBA (77%, 210 mg, 0.94 mmol) in CH_2Cl_2 (2.5 ml) was added in one portion. The reaction mixture was stirred at r.t. for 15 h. It was then diluted with CH_2Cl_2 (15 ml) and washed with $NaHCO_3$ (10 ml × 3). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel (70 230 mesh) using ethyl acetate:Et_3N:MeOH 100:1:0 to 100:1:3 as the gradient eluent. A white solid was obtained after removal of solvent (88 mg, 81%). **7**: R_f 0.23 (ethyl acetate:Et_3N:MeOH 100:1:10); ^1H NMR (400.1 MHz, $CDCl_3$): δ 1.34 (s, 18H), 1.39 (s, 9H), 7.29 (dd, J 6.9, 3.0 Hz, 2H), 8.18 (d, J 3.0 Hz, 2H), 8.29 (d, J 6.9 Hz, 2H), 8.96 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.44, 30.56, 34.76, 35.38, 122.62, 123.71, 125.02, 139.94, 146.48, 149.23, 151.57, 160.87; IR (KBr) 1590, 1547, 1476, 1383, 1255, 1193, 887, 827; 709, 617, 604; EI-MS m/z 433 (M^+); FAB-MS m/z 434 ($M + H^+$); HRMS Calc. for $C_{27}H_{35}O_2N_3$: 433.27292. Found: 433.27271.

4.2.3. Synthesis of 6-[(4S)-4-phenyl-4,5-dihydro-oxazol-2-yl]-[2,2′]bipyridinyl (10)

4.2.3.1. Synthesis of 2,2′-bipyridine-6-carbonitrile. 2,2′-Bipyridine *N*-oxide (300 mg, 1.74 mmol) was dissolved in anhydrous CH_2Cl_2 (5 ml) under Ar. It was then cooled to 0 °C and TMSCN (1.0 ml, 8.71 mmol) was added. Benzoyl chloride (404 μl, 3.48 mmol) was added dropwise. The reaction mixture was stirred overnight. Then 10% Na_2CO_3 (10 ml) was added and the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml × 3). The combined organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel (70 230 mesh) using CH_2Cl_2 to CH_2Cl_2:ethyl acetate (10:1) as the gradient eluent. An off-white solid was obtained after removal of solvent (285 mg, 90%). 2,2′-bipyridine-6-carbonitrile: R_f 0.68 (CH_2Cl_2:ethyl acetate 6:1); ^1H NMR (400.1 MHz, $CDCl_3$): δ 7.37 (ddd, J 7.5, 4.8, 1.2 Hz, 1H), 7.68 (dd, J 7.6, 0.9 Hz, 1H), 7.85 (unresolved ddd, 1H), 7.93 (unresolved dd, 1H), 8.45 (d, J 7.9 Hz, 1H), 8.66 8.68 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 117.33, 121.65, 124.27, 124.80, 128.17, 133.18, 137.41, 137.92, 149.09, 153.82, 157.44; MS (EI, 70 eV) m/z 181 (M^+).

4.2.3.2. Synthesis of methyl 2,2′-bipyridine-6-carboxyimidate. 2,2′-Bipyridine-6-carbonitrile (1.0 g, 5.5 mmol) was dissolved in anhydrous MeOH with gentle heating under Ar. After it was cooled to r.t., Na (13 mg, 0.58 mmol) was added. The reaction mixture was stirred for four days at r.t. HOAc (33 μl, 0.58 mmol) was then added. The solvent was removed under reduced pressure to give an off-white solid (1.17 g, 99%). Methyl 2,2′-bipyridine-6-carboxyimidate: m.p. 69.4 69.7 °C; ^1H NMR (300.1 MHz, d^7-DMF): δ 3.99 (s, 3H), 7.52 (ddd, J 7.5, 4.8, 1.3 Hz, 1H), 7.91 (dd, J 7.6, 1.0 Hz, 1H), 8.02 (ddd, J 7.7, 7.7, 1.9 Hz, 1H), 8.13 8.19 (unresolved dd, 1H), 8.59 (dd, J 7.9, 1.1 Hz, 1H), 8.67 8.70 (unresolved ddd 1H), 8.74 (ddd, J 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (75.5 MHz, d^7-DMF): δ 53.94, 121.62, 121.67, 123.06, 124.31, 125.29, 138.03, 139.74, 147.37, 150.10, 155.51, 156.24, 166.61; MS (EI, 70 eV) m/z 213 (M^+); IR (KBr, cm ^{1}): 3290, 3050, 3002, 2951, 1976, 1654, 1185, 1099, 784, 748, 709; HRMS Calc. for $C_{19}H_{15}N_3O$ m/z: 213.0897. Found: 213.08844.

4.2.3.3. Synthesis of 6-[(4S)-4-phenyl-4,5-dihydro-oxazol-2-yl]-[2,2′]bipyridinyl (10). Methyl 2,2′-bipyridine-6-carboxyimidate (400 mg, 1.88 mmol) and (*S*)-2-amino-2-phenylethanol (257 mg, 1.88 mmol) were dissolved in anhydrous CH_2Cl_2 (8 ml) under Ar in a pressure tube. The mixture was then heated at 60 °C for three days. After removal of solvent, the crude product was chromatographed on silica gel (70 230 mesh) using CH_2Cl_2:Et_3N:-MeOH 100:1:0 to 100:1:2 as the gradient eluent. A pale yellow solid was obtained after removal of solvent (519 mg, 92%). Analytically pure product was obtained by slow evaporation of the etherate solution of **10** to yield an off-white product (310 mg, 55%). **10**: R_f 0.22 (CH_2Cl_2: Et_3N: MeOH 100:1:5); m.p. 108.0 111.8 °C; ^1H NMR (300.1 MHz, $CDCl_3$): δ 4.37 4.42 (unresolved dd, 1H), 4.91 (dd, J 10.2, 8.6 Hz, 1H), 5.46 (dd, J 10.2, 8.5 Hz, 1H), 7.25 7.37 (m, 6H), 7.79 (ddd, J 7.8, 7.8, 1.8 Hz, 1H), 7.88 7.93 (unresolved dd, 1H), 8.17 (dd,

J 7.7, 1.1 Hz, 1H), 8.52 (ddd, *J* 7.9, 2.5, 1.1 Hz, 2H), 8.66 (ddd, *J* 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 70.31, 75.36, 121.64, 123.11, 124.04, 124.31, 126.81, 127.71, 128.76, 136.97, 137.55, 141.84, 146.13, 149.09, 155.30, 156.22, 164.04; MS (EI, 70 eV) *m*/*z* 301 (M^+); $[\alpha]_D$ −115.1° (*c* 0.50, $CHCl_3$); IR (KBr, cm ^{1}): 3069, 3032, 2972, 2897, 1643, 1263, 1114, 787, 749, 700. Elementary analysis Calc. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.69; H, 4.62; N, 14.03%.

4.3. Synthesis of ruthenium complexes

4.3.1. Synthesis of chloro-ruthenium (2,2′:6′,2″-terpyridine) (pyridine-2-carboxylate) complex (**12**)

[Ru(*p*-cymene)Cl_2]$_2$ (131 mg, 0.21 mmol) and 2,2′:6′,2″-terpyridine (100 mg, 0.43 mmol) were dissolved in MeOH (7 ml) at r.t. under Ar to form a deep violet solution. Sodium 2-pyridinecarboxylate (62 mg, 0.43 mmol) was dissolved in H_2O (3 ml) and MeOH (4 ml) was added. This solution was purged with Ar for ~15 min and then added dropwise to the reaction mixture via a cannular. The whole reaction mixture was heated at 70 °C for 1 h. It turned to deep purple in ~15 min at 70 °C. After the reaction mixture was cooled to r.t., CH_2Cl_2 (25 ml) and H_2O (25 ml) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml × 3). The combined organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. It was then chromatographed on silica gel (70 230 mesh) using CH_2Cl_2:MeOH 100:1 to 100:5 as the gradient eluent. After removal of solvent, a purple solid was obtained (140 mg, 66%). The product can be further purified by recrystallization in CH_2Cl_2/hexane to give a deep purple solid. The product was not soluble enough to give satisfactory ^{1}H and ^{13}C spectra. **12**:R_f 0.15 (CH_2Cl_2/MeOH 100:5); UV Vis (CH_2Cl_2, λ_{max}/nm, log ε) 326 (4.40), 402 (3.94), 551 (3.82). HRMS Calc. for ($C_{21}H_{15}ClN_4O_2{}^{96}Ru$) *m*/*z*: 485.99611. Found: 485.99540. Elementary analysis Calc. $C_{21}H_{15}ClN_4O_2Ru{\cdot}CH_2Cl_2$ (%) C, 45.81; H, 2.97; N, 9.71. Found: C, 45.87; H, 3.21; N, 10.17.

4.3.2. Synthesis of ruthenium bis-(2,2′-bipyridine-6-carboxylate) complex (**13**) [38]

[Ru(*p*-cymene)Cl_2]$_2$ (46 mg, 0.075 mmol) and 2,2′-bipyridine-6-carboxylic acid (60 mg, 0.30 mmol) were dissolved in anhydrous MeOH (10 ml) under Ar at r.t. and Et_3N (42 μl, 0.30 mmol) was then added. The reaction mixture was heated at 65 °C for ~13 h and turned from pale orange to deep orange in color. After the reaction mixture was cooled to r.t., a purple solid precipitated with a clear orange solution. The purple solid was filtered, washed with MeOH and dried under high vacuum (63 mg, 84%). **13**: R_f 0.57 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, d^6-DMSO, ppm) δ 7.10 (d, *J* 5.1 Hz, 1H), 7.19 7.21 (m, 1H), 7.77 7.82 (m, 1H), 8.10 8.14 (m, 2H), 8.69 (d, *J* 7.2 Hz, 1H), 8.91 8.97 (m, 1H); UV Vis (EtOH:MeOH 4:1, λ_{max}/nm, log ε) 298 (4.69), 369 (3.89), 511 (4.11). HRMS Calc. for ($C_{22}H_{14}N_4O_4{}^{96}Ru$) *m*/*z*: 499.00868. Found: 499.008554.

4.3.3. Synthesis of ruthenium {6-[(4S)-4-phenyl-4,5-dihydro-oxazol-2-yl]-[2,2′]bipyridinyl} (2,6-pyridinedicarboxylate) complex (**15**)

[Ru(*p*-cymene)Cl_2]$_2$ (102 mg, 0.17 mmol) and **10** (100 mg, 0.33 mmol) were dissolved in MeOH (2 ml) at r.t. under Ar to form a deep violet solution. Disodium 2,6-pyridinedicarboxylate (70 mg, 0.33 mmol) was dissolved in H_2O (1 ml) and MeOH (1 ml) was then added. This solution was purged with Ar for ~15 min and then added dropwise to the reaction mixture via a cannular. The whole reaction mixture was heated at 65 °C for 1 h. It turned to deep red in ~5 min at 65 °C. After the reaction mixture was cooled to r.t., CH_2Cl_2 (50 ml) and H_2O (25 ml) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml × 3). The combined organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. It was then chromatographed on silica gel (70 230 mesh) using CH_2Cl_2:MeOH 100:3 to 100:7 as the gradient eluent. After removal of solvent, a purple solid was obtained (111 mg, 59%). The product can be further purified by recrystallization in CH_2Cl_2/hexane to give a deep purple solid. R_f 0.09 (CH_2Cl_2/MeOH 100:5); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 4.63 (dd, *J* 10.6, 8.9 Hz, 1H), 4.81 4.88 (unresolved dd, 1H), 5.17 5.23 (unresolved dd, 1H), 6.78 (d, *J* 7.2 Hz, 2H), 7.07 7.22 (m, 4H), 7.35 (d, *J* 5.3 Hz, 1H), 7.55 7.68 (m, 3H), 7.81 (t, *J* 7.7 Hz, 1H), 8.04 (d, *J* 7.7 Hz, 1H), 8.09 8.22 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, ppm) δ 67.91, 78.18, 121.12, 121.90, 123.76, 126.10, 126.71, 126.90, 127.25, 127.98, 128.59, 129.18, 134.01, 134.81, 136.42, 146.70, 149.40, 150.23, 151.09, 158.32, 167.67, 171.40, 171.92; UV Vis (CH_2Cl_2, λ_{max}/nm, log ε) 399 (3.94), 514 (4.10). HRMS Calc. for ($C_{26}H_{18}N_4O_5{}^{102}Ru + H^+$) *m*/*z*: 569.03989. Found: 569.03990. Elementary analysis Calc. $C_{26}H_{18}N_4O_5Ru \cdot H_2O$: C, 53.33; H, 3.44; N, 9.57. Found: C, 52.89; H, 3.00; N, 9.35%.

4.3.4. Synthesis of chloro-ruthenium {bis[(4S)-4-phenyl-4,5-dihydro-oxazol-2-yl]-pyridine}(2,6-pyridinedicarboxylate) complex (**16**)

[Ru(*p*-cymene)Cl_2]$_2$ (83 mg, 0.14 mmol) and bis[(4*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl]-pyridine (100 mg, 0.27 mmol) were dissolved in MeOH (2 ml) at r.t. under Ar to form a deep red solution. Disodium 2,6-pyridinedicarboxylate (70 mg, 0.33 mmol) was dissolved in H_2O (1 ml) and MeOH (1 ml) was then added. This solution was purged with Ar for ~15 min and then added dropwise to the reaction mixture via a cannular. The whole reaction mixture was heated at 65 °C for 1 h. It turned first to orange then brownish orange in color at 65 °C. After the reaction mixture was cooled to r.t., CH_2Cl_2 (20 ml) and H_2O (20 ml) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml × 3). The combined organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. It was then chromatographed on silica gel (70 230 mesh) using CH_2Cl_2:MeOH 100:1 to 100:5 as the gradient eluent. After

removal of solvent, a purple solid was obtained (131 mg, 77%). The product can be further purified by recrystallization in CH_2Cl_2/hexane. R_f 0.20 (CH_2Cl_2/MeOH 100:5); ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 4.49 4.69 (m, 3H), 4.93 5.00 (unresolved dd, 1H), 5.09 5.26 (m, 2H), 6.75 (d, J 7.0 Hz, 2H), 6.89 7.16 (m, 9H), 7.38 7.39 (m, 2H), 7.58 (t, J 7.8 Hz, 1H), 7.75 7.80 (m, 2H), 8.96 (d, J 5.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, ppm) δ 68.35, 68.69, 78.22, 78.43, 123.23, 123.25, 124.99, 125.21, 127.01, 127.32, 127.99, 128.13, 128.32, 128.68, 134.24, 136.27, 136.80, 150.12, 150.16, 150.52, 150.80, 167.21, 167.64, 172.48; MS (EI 70 eV) m/z 627 (M^+). UV Vis (CH_2Cl_2, λ_{max}/nm, $\log\varepsilon$) 378 (3.45), 506 (4.11). Elementary analysis Calc. $C_{29}H_{23}ClN_4O_4Ru{\cdot}H_2O$: C, 53.91; H, 3.90; N, 8.67. Found: C, 54.24; H, 4.21; N, 8.52%.

4.4. UV Vis spectroscopic titration

Ru(^{t}Bu$_3$-tpy)(pydic) **3a** (2.70 mg, 4.04×10^{-3} mmol) was dissolved in CH_2Cl_2 (100.00 ml) in a volumetric flask. *m*-CPBA was purified according to literature before use [41]. *m*-CPBA (10.51 mg, 6.09×10^{-3} mmol) was dissolved in CH_2Cl_2 (10.00 ml) in a volumetric flask. A solution of **3a** (3.00 ml) was transferred to a Teflon stoppered 1.0 cm quartz cell. Then the initial UV Vis spectrum was recorded. Next *m*-CPBA solution (2.0 μl) was added to the solution of **3a** and the reaction was monitored by UV Vis spectroscopy. When there was no further change indicated by the absorption spectrum, further portions of *m*-CPBA solution (2.0 μl each) were given. The ratio between **3a** and *m*-CPBA was determined at different wave lengths (at least 5) other than the isosbestic points.

4.5. Catalytic reactions

All olefins and epoxides are known compounds. The conversions and yields were determined by comparing the authentic samples with an internal standard on GC-FID. The identities of the products were further confirmed by GC MS.

4.5.1. Screening of different oxidants

4.5.1.1. General procedure for non-asymmetric epoxidation with hydrogen peroxide. In a 25 ml Schlenk tube, the catalyst (0.0025 mmol) and *trans*-stilbene (90.1 mg, 0.50 mmol) were stirred with gentle heating in *tert*-amyl alcohol (9 ml) until all *trans*-stilbene was dissolved. After the reaction mixture was cooled to r.t., dodecane (GC internal standard, 100 μl) was added. To this reaction mixture, a solution of 30% hydrogen peroxide (170 μl, 1.5 mmol) in *tert*-amyl alcohol (830 μl) was added over a period of 12 h by a syringe pump. After the addition, aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion data.

4.5.1.2. General procedure for asymmetric epoxidation with hydrogen peroxide. In a 25 ml Schlenk tube, the catalyst (0.025 mmol) and *trans*-stilbene (90.1 mg, 0.50 mmol) were stirred with gentle heating in *tert*-amyl alcohol (9 ml) until all *trans*-stilbene was dissolved. After the reaction mixture was cooled to r.t., dodecane (GC internal standard, 100 μl) was added. To this reaction mixture, a solution of 30% hydrogen peroxide (170 μl, 1.5 mmol) in *tert*-amyl alcohol (830 μl) was added over a period of 12 h by a syringe pump. After the addition, aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion data. The reaction mixture was then quenched with Na_2SO_3solution (~10 ml) and extracted with dichloromethane (10 ml × 2) and washed with water (~20 ml). The combined organic layer was dried over $MgSO_4$ and evaporated to give the crude epoxide. It was then dissolved in *n*-hexane for HPLC measurement.

4.5.1.3. General procedure for in situ generation of catalyst in asymmetric epoxidation with hydrogen peroxide. In a 25 ml Schlenk tube, [Ru(*p*-cymene)Cl_2]$_2$ (7.7 mg, 0.013 mmol) and the chiral ligand (0.025 mmol) were dissolved in *tert*-amyl alcohol (2 ml) under Ar. To this solution, H_2pydic (4.2 mg, 0.025 mmol) and Et_3N (8.4 μl, 0.060 mmol) in *tert*-amyl alcohol (2 ml) were added dropwise via a cannular. The reaction mixture was heated at 65 °C for 1 h. *trans*-Stilbene (90.1 mg, 0.50 mmol) and *tert*-amyl alcohol (5 ml) were added and the whole reaction mixture was heated until all *trans*-stilbene was dissolved. After the reaction mixture was cooled to r.t., dodecane (GC internal standard, 100 μl) was added. To this mixture, a solution of 30% hydrogen peroxide (170 μl, 1.5 mmol) in *tert*-amyl alcohol (830 μl) was added over a period of 12 h by a syringe pump. After the addition, aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion data. The reaction mixture was then quenched with Na_2SO_3 solution (~10 ml), extracted with dichloromethane (10 ml × 2) and washed with water (~20 ml). The combined organic layer was dried over $MgSO_4$ and evaporated to give the crude epoxide. It was then dissolved in *n*-hexane for HPLC measurement.

4.5.1.4. General procedure for screening of solid oxidants. In a 25 ml Schlenk tube, Ru(tpy)(pydic) (**3**) (0.0025 mmol) and *trans*-stilbene (90.1 mg, 0.50 mmol) were stirred with gentle heating in *tert*-amyl alcohol (10 ml) until all *trans*-stilbene was dissolved. After the reaction mixture was cooled to r.t., dodecane (GC internal standard, 100 μl) was added. To this reaction mixture, the solid oxidant (1.5 mmol) was added. After the addition, aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion data.

4.5.1.5. General procedure for epoxidation with urea hydrogen peroxide complex for solid olefins. In a 25 ml Schlenk tube, Ru(tpy)(pydic) **3** (0.0025 mmol) and olefin (0.50 mmol) were stirred with gentle heating in *tert*-amyl alcohol (10 ml) until it was dissolved. After the reaction mixture was cooled to r.t., dodecane (GC internal stan-

dard, 100 μl) was added. Urea hydrogen peroxide complex (47 mg, 0.50 mmol) was added in three portions at 0, 1, and 2 h as a total of (141 mg, 1.5 mmol). The reaction mixture was stirred at r.t. for an additional hour. Aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion data.

4.5.1.6. General procedure for epoxidation with urea hydrogen peroxide complex for liquid olefins. In a 25 ml Schlenk tube, Ru(tpy)(pydic) (**3**) (0.0025 mmol) was stirred with gentle heating in *tert*-amyl alcohol (10 ml). After the reaction mixture was cooled to r.t., olefin (0.50 mmol) and dodecane (GC internal standard, 100 μl) were added. Urea hydrogen peroxide complex (47 mg, 0.50 mmol) was added in three portions at 0, 1 and 2 h as a total of (141 mg, 1.5 mmol). The reaction mixture was stirred at r.t. for an additional hour. Aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion data.

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An efficient biomimetic Fe-catalyzed epoxidation of olefins using hydrogen peroxide

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Contributions:

In this paper, I contributed to a significant amount of the argumentation and the synthetic work. I developed the *in-situ* iron catalyst system and found the reaction conditions and I was involved in the study design. My contribution as co-author of this paper is approximately 50 %.

An efficient biomimetic Fe-catalyzed epoxidation of olefins using hydrogen peroxide†

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A new, environmentally benign and practical epoxidation method was developed using inexpensive and efficient Fe catalysts. $FeCl_3 \cdot 6H_2O$ in combination with commercially available pyridine-2,6-dicarboxylic acid and amines showed excellent reactivity and selectivity towards aromatic olefins and moderate reactivity towards 1,3-cyclooctadiene utilizing H_2O_2 as the terminal oxidant.

Nature utilizes iron proteins such as hemoglobin, myoglobin, and cytochrome oxygenases for vital biochemical processes such as transport of oxygen and electron transfer reactions in plants, animals and microorganisms.[1–3] Understanding such mechanisms may lead to new insights in biocatalysis and drug design as well as the development of new industrial catalysts.

Following nature's path, numerous reports on biomimetic oxidation of olefins using metalloporphyrins are known at present; a major problem curtailing these catalysts for use in industry is their difficult multi step synthesis.[4] Among the various oxidation methods, epoxidation of olefins continues to be an important field of research in industry and academia due to the formation of two C O bonds in one reaction and the facile opening of the epoxide ring to useful synthons.[5]

With respect to the oxidants[6] commonly used, molecular oxygen[7] and H_2O_2[8] are the reagents of choice. The latter is more convenient to use and produces only water as the by product. Thus, a combination of H_2O_2 with a catalytic amount of cheap and relatively non toxic metals such as Mn or Fe would be an ideal system for large scale production in industry. However, the use of H_2O_2 in combination with simple non heme manganese[9] or iron[10] is limited, since H_2O_2 is well known to decompose vigorously in the presence of these metals.[11] Consequently, iron catalyzed epoxidation using non heme complexes and H_2O_2 are scant in the literature.[12] For example, the Jacobsen's Fe mep catalyst[13] is known to epoxidize aliphatic olefins in the presence of acetic acid.[14] However, to the best of our knowledge there is no Fe catalyst known which allows for a general epoxidation under neutral conditions.[12c]

In this context, we were interested in exploring the possibility of Fe catalyzed epoxidation using H_2O_2, since iron and H_2O_2 are cheap, environmentally benign and reactive. As a starting point of our work on Fe catalysts, we tried to extrapolate our previously developed Ru reaction protocols[15–18] with Fe. Not surprisingly, initial attempts with pre made Fe complexes resulted in low yield and selectivity. Therefore *in situ* generated iron complexes, which are more easily tuned, were used for the epoxidation of *trans* stilbene at room temperature.[19]

A screening of different iron sources of Fe^{2+} and Fe^{3+} in the presence of acid or base revealed that complete conversion was observed only in the case of $FeCl_3 \cdot 6H_2O$. Hence, our further investigations focused on this iron source. While studying various nitrogen ligands, it was observed that simply pyridine 2,6 dicarboxylic acid (H_2pydic) is sufficient to form an active Fe epoxidation catalyst! Advantageously, the *in situ* formation of the active complex with H_2pydic and Fe occurs at rt. The combination of $FeCl_3 \cdot 6H_2O$, H_2pydic, and an organic base, such as benzylamine, 4 methylimidazole and pyrrolidine, leads to an active and highly selective epoxidation catalyst (see ESI†).

Unlike the corresponding Ru complexes, the use of disodium pyridine 2,6 dicarboxylate or using H_2pydic with 10 mol% of inorganic base was not effective in the case of Fe. To our delight, the addition of organic bases, such as benzylamine, 4 methylimi dazole and pyrrolidine, gave full conversion and almost quanti tative yield and selectivity. It is envisaged that one of the roles of the base is to deprotonate the pyridine 2,6 dicarboxylic acid; however reports on the influence of base on the stability of the catalyst and selectivity of the oxidation are known.[20] When the NH group of imidazole was substituted with an alkyl group, the reactivity remained. However, the reactivity dropped signifi cantly when 2 methylimidazole was used (12% conv., 11% yield). In comparison with the reactivity of pyridine (56% conv., 50% yield) and pyrrolidine (100% conv., 97% yield), this effect must be attributed to coordination effects to some extent. This is not the case with 4 methylimidazole, which led to full conversion with excellent yield (97%) of *trans* stilbene oxide. In order to explain the observed ligand effects, gelicification and redissolution of the ligand or catalyst should be considered, too. Such effects were reported during the deprotonation of the pyridine 2,6 dicarboxylic acid in aqueous alkaline solution due to pH dependent electrostatic interactions and hydrogen bonding between the polar species and water.[21] We have not noticed any such process in our reactions, obviously due to the less polar nature of *tert* amyl alcohol compared to water. Importantly, the formation of *trans* stilbene oxide was not observed when pyrrolidine, pyridine 2,6 dicar boxylic acid or the iron source was not used in the reaction. It is remarkable that the epoxidation reaction is quite fast and an optimum yield can be achieved by addition of the oxidant (H_2O_2)

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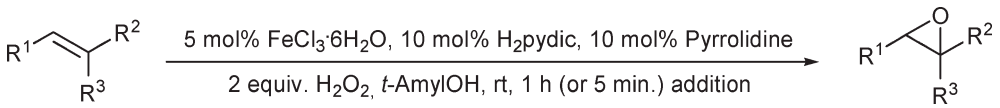
over a period of one hour using a syringe pump. Even an addition of hydrogen peroxide within 5 minutes showed no decrease in reactivity and selectivity for *trans* stilbene.

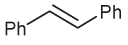
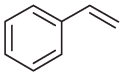
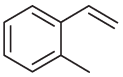
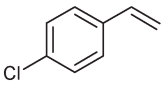
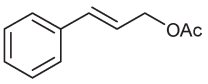
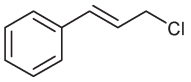
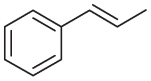
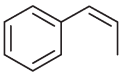
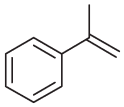
Next, different substrates were tested in these optimized reaction conditions (Table 1). Styrene, generally known as a difficult substrate for epoxidation, afforded excellent yield and selectivity of styrene oxide (Table 1, entries 3 4). The reaction also performed well for *ortho* and electron donating/withdrawing substituted styrenes (Table 1, entries 5 8). Cinnamyl acetate, cinnamyl chloride, and *cis* as well as *trans* β methyl styrene gave good to excellent yields (Table 1, entries 9 13). In the case of α methyl styrene, in addition to the epoxide, a small amount of 2 phenylpropanal was also formed, presumably by the iron promoted rearrangement of the epoxide *via* a stable benzyl carbocation.

To further extend the scope of the reaction 1,3 cyclooctadiene was tested. Here, the corresponding mono epoxide is obtained in 65% yield with 84% selectivity (Table 1, entry 14). To understand the mechanism of the reaction in more detail, *trans* stilbene was subjected to epoxidation using the new protocol in the presence of a radical scavenger (2,6 di *tert* butyl 4 methoxyphenol), which afforded the epoxide in very low yield (<10%) suggesting a selective radical pathway occurring as the major process in this reaction. Although to date we have no direct structural evidence of the active catalyst species, and discussions on the nature of the intermediate are so far speculative,[22] non heme dioxygenases, such as TauD,[23] TfdA[24] and NDO,[25] which contain carboxylate and histidine on their coordination sphere, may give us some insights.[26]

In conclusion, we have developed a new biomimetic, convenient and fast epoxidation protocol using a cheap and environmentally friendly iron source in combination with H_2O_2. The system showed excellent reactivity and selectivity towards terminal and 1,2 disubstituted aromatic olefins, and moderate reactivity towards 1,3 dienes. Unlike previous procedures, our protocol is much simpler and demands no pre made catalyst, acetic acid or freezing reaction temperature. Gratifyingly, all the reagents used in our

Table 1 Scope and limitations of the reaction



Entry	Substrate	Conv. (%)[a,b]	Yield (%)[b]	Selectivity (%)[c]
1		100	97	97
2		98[d]	96[d]	98[d]
3		94	93	99
4		88[d]	69[d]	78[d]
5		100	97	97
6		88[d]	87[d]	99[d]
7		100	77	77
8		100[d]	79[d]	79[d]
9		71	69	97
10		77	63	82
11		100	95	95
12		75	56[e]	75
13		93	64	69
14		77	65	84

[a] Reaction conditions: in a 25 mL Schlenk tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert* amyl alcohol (9 mL), pyrrolidine (0.05 mmol), olefin (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added in sequence at rt in air. To this mixture, a solution of 30% H_2O_2 (114 μL, 1.0 mmol) in *tert* amyl alcohol (886 μL) was added over a period of 1 h (or 5 min) at rt by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Selectivity refers to the ratio of yield to conversion as percentage. [d] The oxidant was added over a period of 5 min. [e] 19% *trans* β methylstyrene oxide was observed.

system are simple and commercially available and the reaction can be performed at rt. To the best of our knowledge, the system described here is the simplest and most practical iron catalyzed epoxidation procedure available for olefins today. Efforts are underway in our group aimed at realizing the asymmetric version of this reaction.

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Publication 3.6.

Development of a General and Efficient Iron-Catalyzed Epoxidation with Hydrogen Peroxide

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Contributions:

In this paper, I contributed to a significant amount of the argumentation and the synthetic work. I developed and performed most of the catalytic reactions and wrote the manuscript. My contribution as co-author of this paper is approximately 80 %.

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Development of a General and Efficient Iron-Catalyzed Epoxidation with Hydrogen Peroxide as Oxidant

Bianca Bitterlich,[a] Gopinathan Anilkumar,[a] Feyissa Gadissa Gelalcha,[a] Björn Spilker,[a] Anne Grotevendt,[a] Ralf Jackstell,[a] Man Kin Tse,[a, b] and Matthias Beller*[a, b]

Abstract: The development of inexpensive and practical iron catalysts for the environmentally benign epoxidation of olefins with hydrogen peroxide as terminal oxidant is described. By systematic variation of ligands, metal sources, and reaction conditions, it was discovered that $FeCl_3 \cdot 6H_2O$ in combination with pyridine 2,6 dicarboxylic acid and different amines shows high reactivity and excellent selectivity towards the epoxidation of aromatic olefins and moderate reactivity towards that of aliphatic olefins.

Keywords: alkenes · epoxidation · homogeneous catalysis · hydrogen peroxide · iron

Introduction

Many essential biological processes, such as the transport and storage of oxygen, oxidation, and electron transfer reactions, depend on iron containing enzymes.[1,2] New insight in the fields of biocatalysis, drug design, and even development of industrial processes is expected to arise from a more detailed understanding of the mechanism of these processes and the development of novel iron catalysts. To date, numerous reports have dealt with biomimetic oxidation reactions involving metalloporphyrins, but the complex multistep synthesis of these catalysts obstructs further applications.[3] Therefore, the search for easily available and more effective ligands is a major goal in current research with respect to Fe catalysts.[4]

Among the different feedstocks, olefins are one of the most important starting materials for organic synthesis. Their oxidation leads to various value added products such as epoxides, alcohols, diols, aldehydes, ketones, and carboxylic acids, which are important building blocks for the production of bulk and fine chemicals as well as for the synthesis of pharmaceuticals.[5] The formation of two C O bonds from olefins in one reaction and subsequent facile ring opening make epoxides particularly crucial as key intermediates.[6] For these reasons, we are interested in developing novel epoxidation catalysts.[7] From ecological and economic points of view, molecular oxygen[8] and hydrogen peroxide are the oxidants of choice. In general, hydrogen peroxide is easier to handle. Furthermore, it is cheap and produces only water as by product.[9] The combination of hydrogen peroxide with catalytic amounts of a cheap and less toxic metal such as Mn or Fe would lead to an ideal system for environmentally benign oxidations. Unfortunately, the use of H_2O_2 in combination with simple non heme manganese[10] or iron[11] is limited as H_2O_2 is well known to decompose vigorously in the presence of these metals.[12] Hence, only a handful of examples of non heme iron catalyzed epoxidations with H_2O_2 are known.[13] Of note are the Jacobsen Fe catalyst[14] derived from *N*,*N*′ dimethyl *N*,*N*′ bis(2 pyridylmethyl)ethane 1,2 diamine (the so called mep ligand) and the Stack catalyst[15] derived from phenanthroline. However, both catalysts are only active in the presence of large amounts of acetic acid. In case of the Stack catalyst, H_2O_2 is used to generate peracetic acid, which then acts as the "real" oxidant. Thus, acid labile epoxides cannot be prepared by this route. To the best of our knowledge, there is no Fe catalyst known that allows for the epoxidation of aliphatic and aromatic olefins under neutral conditions with H_2O_2 as the terminal oxidant.

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In earlier investigations, we showed the utility of Ru complexes derived from N,N,N tridentate ligands such as pyridinebisoxazolines (pyboxes),[16] pyridinebisoxazines (pyboxazines),[17] terpyridines,[18] and pyridinebisimidazolines (pybims),[19] together with the coligand pyridine 2,6 dicarboxylic acid (H_2pydic), in the epoxidation of various olefins.[20] To develop an improved, environmentally benign, and more economical procedure, we were interested in replacing the central metal Ru in these complexes by Fe. In an initial communication, we reported the influence of different bases on the reactivity and selectivity of Fe epoxidation catalysts.[21] Herein, we report the successive development of novel iron catalysts and their behavior in the epoxidation of olefins with hydrogen peroxide.

Results and Discussion

Our general catalyst modification strategy started with the simple idea of replacing Ru with Fe, followed by variation of bi and tridentate nitrogen ligands (Figure 1). Various

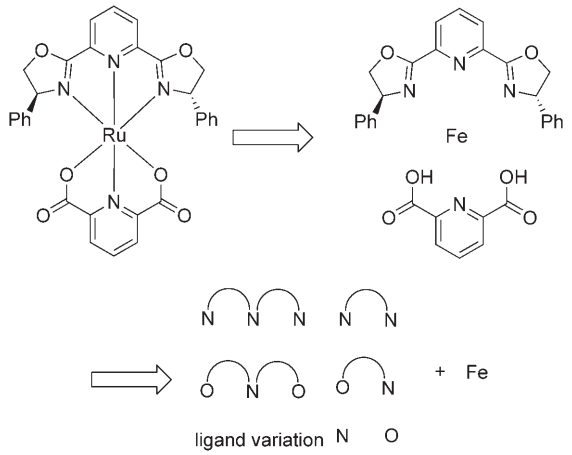


Figure 1. Catalyst modification strategy.

iron(II) complexes were initially synthesized and tested in the epoxidation of *trans* stilbene with 3 equivalents of hydrogen peroxide at room temperature. Similar reaction conditions were chosen as in our previously developed ruthenium catalyzed epoxidation reactions.[17] Tridentate nitrogen ligand derivatives of pybox, pybim, and terpyridine were examined (Figure 2). Selected results from this study are shown in Table 1. Notably, all the iron complexes tested exhibited some activity towards the formation of *trans* stilbene oxide. Typically, with pybox and terpyridine ligands, *trans* stilbene oxide was obtained in 15 30% yield and with 67 69% selectivity.

The high activity of the chiral terpyridine Fe complex (96% conversion) is also remarkable, although the chemoselectivity was low. In the presence of the pybim ligand, only poor conversion was observed. Although the yields were not satisfactory, the results are promising as significant conversion and selectivity were achieved. For a more efficient and convenient testing of various catalytic systems with versatile ligands, we decided to apply Fe complexes prepared in situ. We assumed that Fe^{II} was oxidized during the reaction with hydrogen peroxide and decided to use Fe^{III} sources instead. From our previous studies of the Ru catalyzed epoxidation, H_2pydic is known to enhance the stability and reactivity of the catalyst.[22] Thus, commercially available H_2pydic and 2,6 bis[(*S*) 4 phenyl 4,5 dihydrooxazol 2 yl]pyridine (Ph_2pybox) together with $FeCl_3{\cdot}6H_2O$ were tested in the model reaction (Table 2).

Notably, the combination of these easily available components is sufficient to form an active and selective Fe epoxidation catalyst. To our surprise, the metal to ligand ratio has a significant influence on the reactivity and selectivity. The best result was obtained with an $FeCl_3{\cdot}6H_2O/Ph_2$pybox ratio of 1:1; 100% conversion and 82% yield of stilbene oxide were observed (Table 2, entry 3). With these results in hand, we investigated the influence of different iron sources (Table 3). Importantly, only the hydrate of iron trichloride gave complete conversion and high yield of the corresponding epoxide. Apparently, the presence of chloride ions is

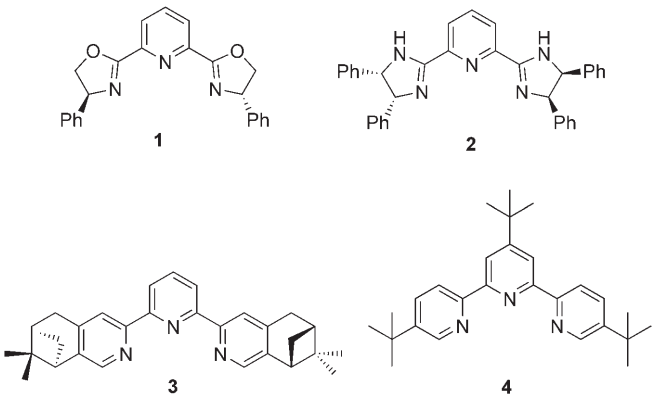
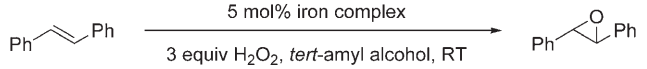


Figure 2. Different ligands for the epoxidation of olefins.

Table 1. Epoxidation of *trans* stilbene with different iron complexes.



Entry	Iron cat.	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]	*ee* [%][d]
1	$FeCl_2$+**1**	22	15	67	0
2	$FeCl_2$+**2**	7	4	62	n.d.[f]
3	$FeCl_2$+**3**	30	20	69	n.d.[f]
4	$FeCl_2$+**4**	96	30	31[e]	0

[a] Reaction conditions: Iron complex (0.025 mmol), *tert* amyl alcohol (9 mL), *trans* stilbene (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of hydrogen peroxide (30%, 170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added to this mixture over a period of 12 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage. [d] Determined by HPLC analysis. [e] Side products: diol, benzil, benzoin. [f] Not determined.

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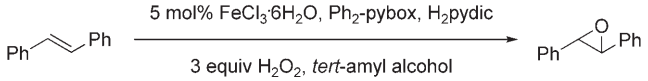
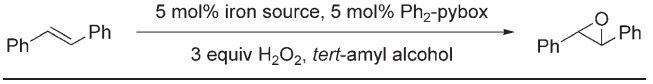
Table 2. Epoxidation of *trans* stilbene with H_2pydic, Ph_2 pybox, and $FeCl_3{\cdot}6H_2O$.



Entry	Mole ratio $FeCl_3{\cdot}6H_2O$	Ph_2 pybox	H_2pydic	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1	1	1	1	55	48	87
2	1			13	7	52
3	1	1		100	82	82
4	1	2		70	55	78
5	1		1	69	53	77
6	1		2	32	18	55
7	1	2	1	63	52	83
8	2	1		85	61	72

[a] Reaction conditions: Iron trichloride hexahydrate (0.025 mmol), Ph_2 pybox (0.025 mmol), and H_2pydic (0.025 mmol) were dissolved in *tert* amyl alcohol (4 mL) in a 25 mL Schlenk tube and heated for 1 h at 65 °C. Afterwards, *trans* stilbene (0.5 mmol), *tert* amyl alcohol (5 mL), and dodecane (GC internal standard; 100 μL) were added in sequence at room temperature in air. A solution of hydrogen peroxide (30 %, 170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added to this mixture over a period of 12 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage.

Table 3. Epoxidation of *trans* stilbene in the presence of different iron sources.



Entry	Iron source	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1	$FeCl_3{\cdot}6H_2O$	100	82	82
2	$FeCl_2{\cdot}4H_2O$	33	22	66
3	$FeCl_3$ (anhydrous)	21	13	62
4	$FeCl_2$ (anhydrous)	36	15	42
5	$Fe(acac)_3$	11	5	44
6	$Fe(NO_3)_3{\cdot}9H_2O$	7	0	0
7	$Fe(ClO_4)_3{\cdot}xH_2O$	1	0	0
8	$Fe(BF_4)_2{\cdot}6H_2O$	0	0	0

[a] Reaction conditions: The iron source (0.025 mmol) and Ph_2 pybox (0.025 mmol) were dissolved in *tert* amyl alcohol (4 mL) in a 25 mL Schlenk tube and heated for 1 h at 65 °C. Afterwards, *trans* stilbene (0.5 mmol), *tert* amyl alcohol (5 mL), and dodecane (GC internal standard; 100 μL) were added in sequence at room temperature in air. A solution of hydrogen peroxide (30 %, 170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added to this mixture over a period of 12 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage.

necessary for the reaction (Table 3, entries 5–8). The difference in the results with anhydrous iron trichloride (Table 3, entry 3) can be explained by the lower solubility of the latter, which inhibits complex formation. Interestingly, during the formation of the active iron complex in situ, a red precipitate was observed in the reaction mixture (Table 3, entry 1). This precipitate was then filtered off, and both the filtrate and precipitate were tested in the epoxidation of *trans* stilbene. Unexpectedly, they gave similar results (precipitate: 70 % conversion and 37 % yield; filtrate: 71 % conversion and 36 % yield). Mass spectrometric investigations (ESI MS) of both fractions showed unambiguously that decomposition of the pybox ligand into H_2pydic and phenyl glycinol occurred during the formation of the active catalyst in situ (Figure 3). The ESI MS spectrum of the precipitate showed various peaks that were assigned to different decomposition fragments of the ligand, whereas those in the ESI MS spectrum of the solution were assigned to the amino alcohol.

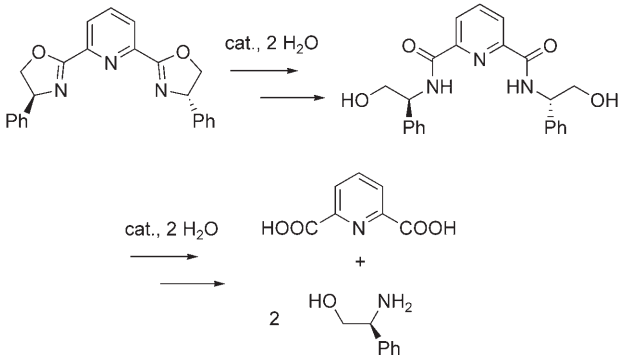
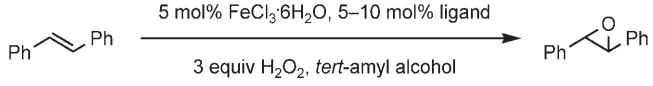
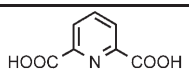
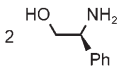
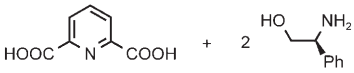
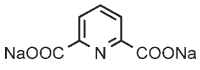


Figure 3. Decomposition of the ligand.

Owing to the similar catalytic activity of filtrate and precipitate, it is likely that the active catalyst contains fragments of the completely decomposed ligand as well as Fe. To confirm this assumption, we performed the epoxidation of *trans* stilbene with 5 mol % $FeCl_3{\cdot}6H_2O$ and possible decomposition fragments of the ligand (Table 4). The application of H_2pydic and phenyl glycinol, which could be formed by acidic hydrolysis of the pybox ligand (Figure 2), gave similar results to the case of pybox as the only ligand (Table 4,

Table 4. Epoxidation of *trans* stilbene with different ligands.



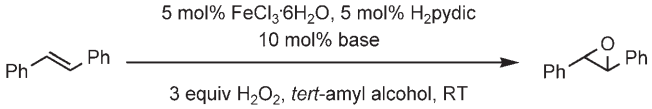
Entry	Ligand	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1		69	53	77
2		9	6	69
3		100	84	84
4		73	44	61

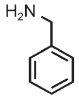
[a] Reaction conditions: Iron trichloride hexahydrate (0.025 mmol) and the ligands (0.025 mmol) were dissolved in *tert* amyl alcohol (4 mL) in a 25 mL Schlenk tube and heated for 1 h at 65 °C. Afterwards, *trans* stilbene (0.5 mmol), *tert* amyl alcohol (5 mL), and dodecane (GC internal standard; 100 μL) were added in sequence at room temperature in air. A solution of hydrogen peroxide (30 %, 170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added to this mixture over a period of 12 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage.

entry 3; see also Table 2, entry 3). This result confirms our hypothesis of ligand degradation. Notably, the catalyst system without any phenyl glycinol showed lower reactivity.[23] The application of the sodium salt of H_2pydic led to 73% conversion and 44% yield (Table 4, entry 4). This can be attributed either to the low solubility of Na_2pydic in *tert* amyl alcohol or the possibility that the amino alcohol acts as a coligand in the active catalyst system.[24] Control experiments of the epoxidation of *trans* stilbene showed that iron is essential in the reaction.[21] Unfortunately, none of our reactions showed significant enantioselectivity, so we concentrated on nonchiral reagents in subsequent reactions.

Next, we studied the effect of the amine in detail (Table 5). Hence, 12 different nitrogen ligands were tested in the model reaction. Most importantly, the combination of $FeCl_3{\cdot}6H_2O$, H_2pydic, and organic bases such as benzylamine, 4 methylimidazole, and pyrrolidine led to active and highly selective epoxidation catalysts (Table 5, entries 5, 7, and 12). The NH group is beneficial to the reactivity. This is shown clearly from the activities of substituted imidazoles and pyridine (Table 5, entries 6–11). The reactivity dropped significantly when 2-methylimidazole was used (Table 5, entry 9). In comparison with the reactivity of pyridine, 4-methylimidazole, and pyrrolidine (Table 5, entries 7, 9, and 12), this effect must, to some extent, be attributed to coordination effects.

Table 5. Epoxidation of *trans* stilbene with different bases.



Entry	Base	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1	KOH	33[d]	30	91
2	DMAP	19[d]	16	84
3	DABCO	40	33	82
4	Et_3N	86	74	86
5		100	97	97
6		91	90	99
7		100[e]	97	97
8		78[e]	72	92
9		12[e]	11	92
10		95[e]	85	89
11		56	50	89
12		100	97	97
13		61	59	97

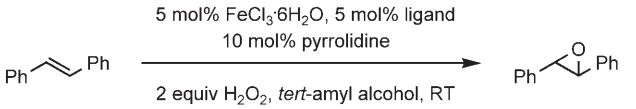
[a] Reaction conditions: $FeCl_3{\cdot}6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert* amyl alcohol (9 mL), base (0.05 mmol), *trans* stilbene (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of hydrogen peroxide (30%, 170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added to this mixture over a period of 1 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage. [d] H_2O_2 addition over a period of 12 h. [e] Addition of 2 equivalents of H_2O_2.

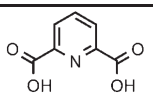
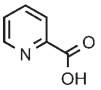
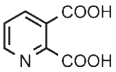
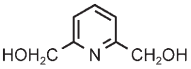
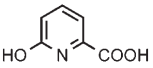
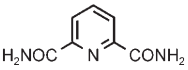
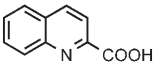
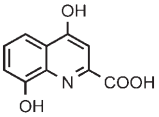
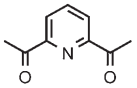
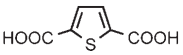
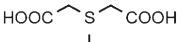
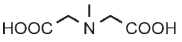
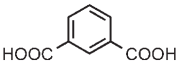
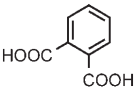
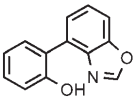
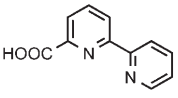
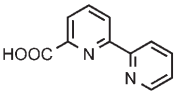
By changing the amount of hydrogen peroxide, we found that no more than 2 equivalents are necessary to achieve high conversion and yield (>90%). Advantageously, the time for H_2O_2 addition could be decreased from 12 to 1 h. In fact, the model reaction is so fast that full conversion was obtained after 5 min. However, for better comparison, we continued to add the oxidant over 1 h.

For a better understanding of the catalytic system and further improvement of the selectivity, we varied systematically the pyridine 2,6-dicarboxylic acid component. Hence, various ligands with a similar structure to H_2pydic were investigated (Table 6). The pyridine nitrogen atom and the carboxylic acid in the 2 position are clearly needed for high reactivity (Table 6, entries 1, 2, and 7). By omitting or changing these functional groups, the reactivity decreased significantly except in the case of 2,6-pyridinedimethanol (Table 6, entry 4). This can be attributed to the oxidation of this ligand during the reaction, which generated the H_2pydic ligand in situ. Also, scrambling of a second carboxylic acid group (Table 6, entry 3), introduction of phenoxy groups (Table 6, entries 5 and 8), or addition of an amide group (Table 6, entry 6) resulted in decreased conversion.

To understand of the active catalyst further, UV/Vis spectroscopic investigations with $FeCl_3{\cdot}6H_2O$, H_2pydic, and pyrrolidine were performed (Figures 4 and 5). Owing to the strong absorbance of *tert* amyl alcohol (TAA), the measurements were analyzed at above 225 nm.[25] In the absence of Fe, the curve of pyrrolidine and H_2pydic showed only a small difference to the calculated curve of the individual components (Figures 4 and 5, curve b). This indicates that no strong interaction between the ligands is present in solution. In contrast, the UV/Vis spectra of pyrrolidine or H_2pydic in the presence of $FeCl_3{\cdot}6H_2O$ showed a significant difference to the calculated curves (Figures 4 and 5, curves c and d). This clearly suggests that the metal interacts with the corresponding ligands and supports the assumption that pyrrolidine acts also as a ligand in the system. Consequently, there is also a difference between the measured and calculated curves for the whole catalyst system (Figure 6, curves d and e). The calculated addition curve, which includes individual interactions, shows that there has to be an additional interaction when the two ligands are present at the same time (Figure 7, curves c and d).[26] For comparison, UV/Vis measurements with an inactive catalytic system were performed. Hence, 2,6-pyridine dicarboxamide (PDCA) instead of H_2pydic was chosen as the ligand, and it showed no significant reactivity in the catalytic test reaction (Table 6, entry 6).

Table 6. Epoxidation of *trans* stilbene with different H_2pydic like structures.



Entry	Ligand	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1		96	84	87
2		52	43	83
3		9	4	38
4		77	69	90
5		20	18	86
6		1	0	0
7		70	65	93
8		3	0	0
9		8	5	63
10		3	2	65
11		7	2	26
12		6	4	67
13		5	2	43
14		13	4	29
15		14	9	65
16		37[d]	37	100
17		33[e]	24	74

[a] Reaction conditions: $FeCl_3·6H_2O$ (0.025 mmol), ligand (0.025 mmol), *tert* amyl alcohol (9 mL), pyrrolidine (0.05 mmol), *trans* stilbene (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of hydrogen peroxide (30%, 114 μL, 1.0 mmol) in *tert* amyl alcohol (886 μL) was added to this mixture over a period of 1 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage. [d] Addition of 1 equivalent of pyrrolidine. [e] Addition of 2 equivalents of pyrrolidine.

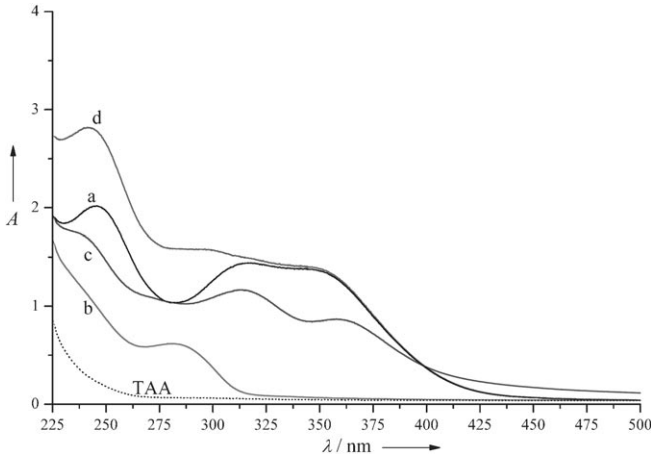


Figure 4. UV/Vis spectra of $FeCl_3·6H_2O$ and pyrrolidine in *tert* amyl alcohol. a) 0.25 mM $FeCl_3·6H_2O$; b) 0.6 mM pyrrolidine; c) 0.25 mM $FeCl_3·6H_2O$ + 0.6 mM pyrrolidine; d) curves (a + b − TAA).

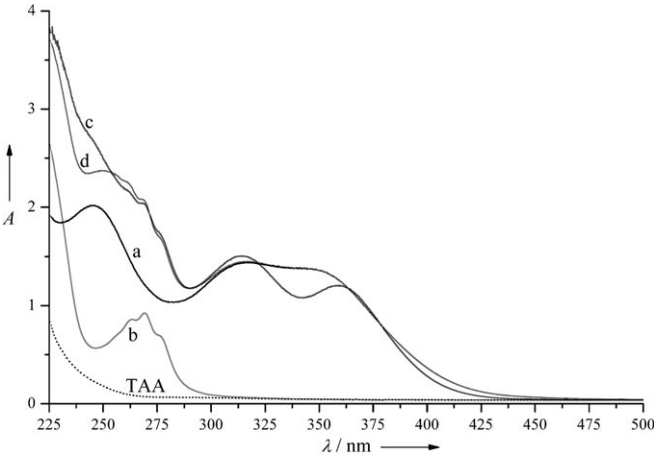


Figure 5. UV/Vis spectra of $FeCl_3·6H_2O$ and H_2pydic in *tert* amyl alcohol. a) 0.25 mM $FeCl_3·6H_2O$; b) 0.25 mM H_2pydic; c) 0.25 mM $FeCl_3·6H_2O$ + 0.25 mM H_2pydic; d) curves (a + b − TAA).

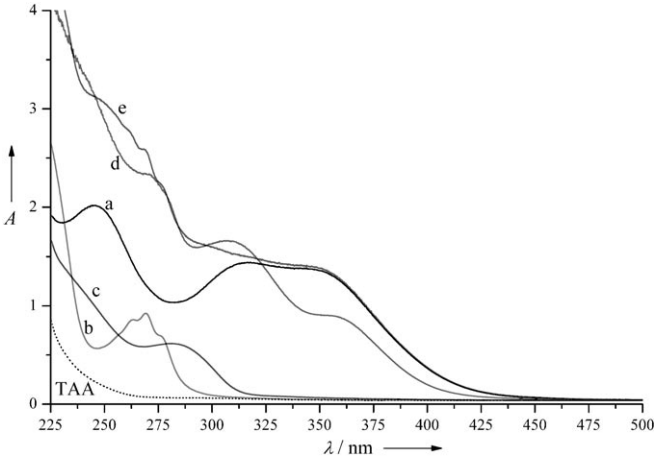


Figure 6. UV/Vis spectra of $FeCl_3·6H_2O$, pyrrolidine, and H_2pydic, part 1. a) 0.25 mM $FeCl_3·6H_2O$; b) 0.25 mM H_2pydic; c) 0.6 mM pyrrolidine; d) 0.25 mM $FeCl_3·6H_2O$ + 0.25 mM H_2pydic + 0.6 mM pyrrolidine; e) curves (a + b + c − 2 TAA).

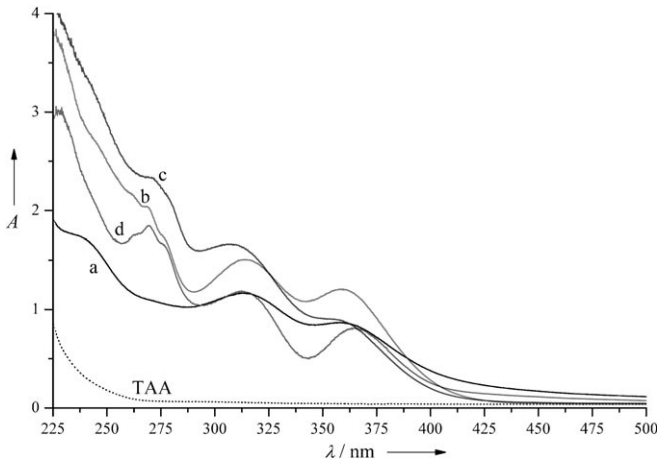


Figure 7. UV/Vis spectra of $FeCl_3{\cdot}6H_2O$, pyrrolidine, and H_2pydic, part 2. a) 0.25 mM $FeCl_3{\cdot}6H_2O$ + 0.6 mM pyrrolidine; b) 0.25 mM $FeCl_3{\cdot}6H_2O$ + 0.25 mM H_2pydic; c) 0.25 mM $FeCl_3{\cdot}6H_2O$ + 0.25 mM H_2pydic + 0.6 mM pyrrolidine; d) curves (a + b $FeCl_3{\cdot}6H_2O$ (curve a, Figure 6)).

As expected, no additional change in the UV/Vis spectrum by adding PDCA to a solution of $FeCl_3{\cdot}6H_2O$ and pyrrolidine in *tert* amyl alcohol could be observed (Figure 8,

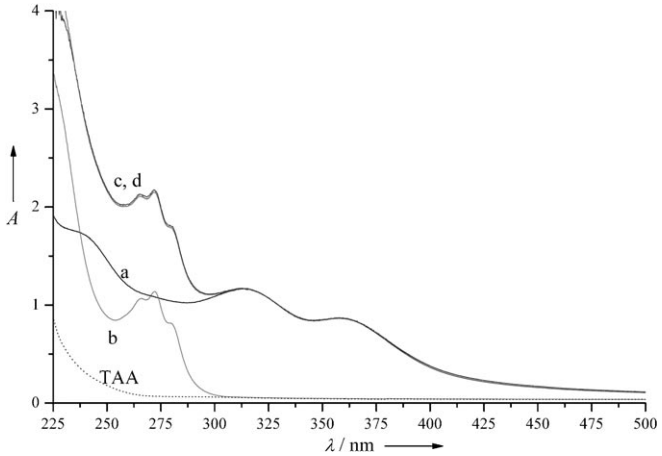


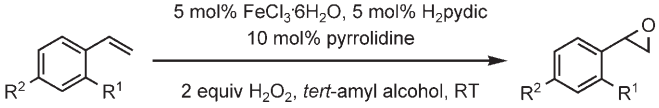
Figure 8. UV/Vis spectra of $FeCl_3{\cdot}6H_2O$, pyrrolidine, and PDCA. a) 0.25 mM $FeCl_3{\cdot}6H_2O$ + 0.6 mM pyrrolidine; b) 0.25 mM PDCA; c) 0.25 mM $FeCl_3{\cdot}6H_2O$ + 0.25 mM PDCA + 0.6 mM pyrrolidine; d) curves (a + b TAA).

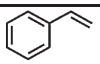
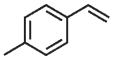
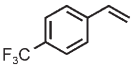
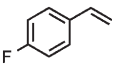
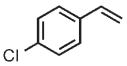
curves c and d). Apparently, there is no interaction between the metal and ligands that causes a change in the UV/Vis spectrum. UV/Vis spectra of the catalyst together with *trans* stilbene and hydrogen peroxide did not give interpretable results due to the strong absorbance of *trans* stilbene.

The change in the curves was so imprecise that conclusive results cannot be deduced. From the accumulated results, it is clear that the complexity of this Fe catalytic system presents a challenge for catalytic and mechanistic chemists and will require further scrutiny.

Next, we tested different aromatic and aliphatic olefins in the presence of $FeCl_3{\cdot}6H_2O$, pyrrolidine, and H_2pydic (Tables 7–10). Styrene, which is generally known as a difficult substrate for epoxidation, afforded excellent yield and selectivity of styrene oxide (Table 7, entry 1). The reaction also performed well for *o* and *p* substituted styrenes as well

Table 7. Scope and limitations of the Fe catalyzed epoxidation: styrenes.

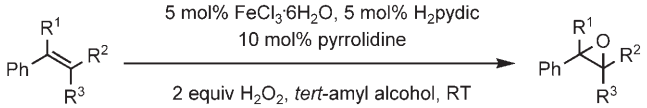


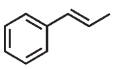
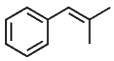
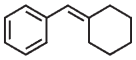
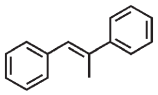
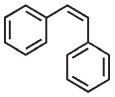
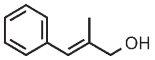
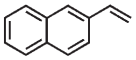
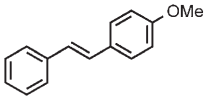
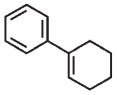
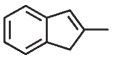
Entry	Olefin	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1		94	93	99
2		100	97	97
3		100	75	75
4		57	52	91
5		100	70	70
6		95	77	81
7		73	43	59

[a] Reaction conditions: $FeCl_3{\cdot}6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert* amyl alcohol (9 mL), pyrrolidine (0.05 mmol), olefin (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of H_2O_2 (30%, 114 μL, 1.0 mmol) in *tert* amyl alcohol (886 μL) was added to this mixture over a period of 1 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage.

as those with electron donating and withdrawing substituents (Table 7, entries 2–7). Substitution at the α or β *trans* positions led to good results (Table 8, entries 1 and 2), whereas β *cis* substitution gave only poor to moderate results (Table 8, entries 6 and 7). Presumably, β *cis* substitution inhibits the coordination of these substrates to the catalyst because of steric hindrance. With *p* methoxy substituted *trans* stilbene and 2 vinylnaphthalene, moderate yields were obtained (Table 8, entries 9 and 10). Notably, functionalized olefins such as cinnamyl acetate, cinnamyl alcohol, and even cinnamyl chloride gave good to excellent yields of the corresponding epoxides (Table 9, entries 1–3). However, ethers of cinnamyl alcohol led to moderate or poor yields (Table 9, entries 4–6). Aliphatic olefins and 1,3 cyclooctadiene also gave moderate to good yields (Table 10, entries 1–3).

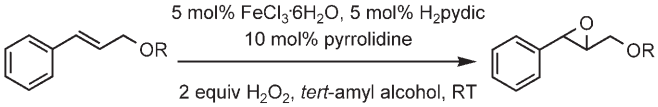
Table 8. Scope and limitations of the Fe catalyzed epoxidation: aromatic olefins.

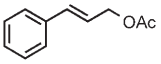
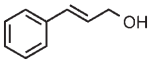
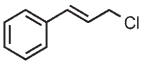
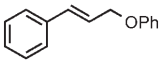
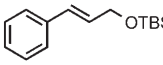
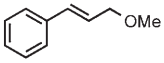


Entry	Olefin	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1		93	64	69
2		100	95	95
3		44	16	36
4		25	11	44
5		40	21	53
6		22	8	36
7		75	56	75
8		91	38	42
9		100	40	40
10		78	40	51
11		85	21	25
12		94	26	28

[a] Reaction conditions: $FeCl_3{\cdot}6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert* amyl alcohol (9 mL), pyrrolidine (0.05 mmol), olefin (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of H_2O_2 (30%, 114 μL, 1.0 mmol) in *tert* amyl alcohol (886 μL) was added to this mixture over a period of 1 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage.

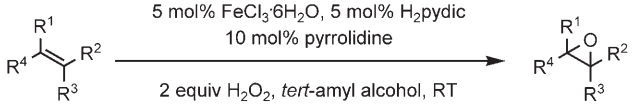
Table 9. Scope and limitations of the Fe catalyzed epoxidation: cinnamyl alcohol derivatives.

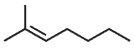
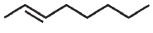


Entry	Olefin	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1		71	69	97
2		100	74	74
3		90	61	68
4		100	18	18
5		90	33	37
6		100	15	15

[a] Reaction conditions: $FeCl_3{\cdot}6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert* amyl alcohol (9 mL), pyrrolidine (0.05 mmol), olefin (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of H_2O_2 (30%, 114 μL, 1.0 mmol) in *tert* amyl alcohol (886 μL) was added to this mixture over a period of 1 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage. TBS = *tert* butyldimethyl silyl.

Table 10. Scope and limitations of the Fe catalyzed epoxidation: aliphatic olefins.



Entry	Olefin	Conv. [%][a,b]	Yield [%][b]	Selectivity [%][c]
1		63	32	51
2		48	36	75
3		77	65	84

[a] Reaction conditions: $FeCl_3{\cdot}6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert* amyl alcohol (9 mL), pyrrolidine (0.05 mmol), olefin (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of H_2O_2 (30%, 114 μL, 1.0 mmol) in *tert* amyl alcohol (886 μL) was added to this mixture over a period of 1 h at room temperature by a syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Ratio of yield to conversion as a percentage.

Conclusions

We have developed a convenient epoxidation protocol by using economical and environmentally friendly iron catalysts in combination with H_2O_2. 2,6 Pyridine dicarboxylic acid and pyrrolidine turned out to be the most effective ligands in this system. The system showed excellent reactivity and selectivity towards terminal and 1,2 disubstituted aromatic olefins, and moderate reactivity towards 1,3 dienes and aliphatic olefins. All the reagents used in our system are commercially available, and the reaction can be performed at room temperature in air under very mild conditions. To the best of our knowledge, the system described herein is the simplest and most practical iron catalyzed epoxidation procedure available for olefins today. Effort is underway in our group to realize the asymmetric version of this reaction.

Experimental Section

General

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. Mass spectra were recorded with an AMD 402/3 mass spectrometer. GC analysis was performed with a Hewlett Packard HP 6890 model spectrometer. Elemental analysis was performed on a CHNS 932 analyzer from Leco Company. To determine the amount of metal, a Type A Analyst 300 atom absorbance spectrometer from Perkin Elmer was used.

Syntheses

All manipulations of air and moisture sensitive compounds were performed by using standard Schlenk or cannula techniques under an argon atmosphere. THF and diethyl ether were heated at reflux and distilled from sodium/benzophenone under argon atmosphere. Complexes were prepared by the reaction of dry $FeCl_2$ with the corresponding ligand in THF. The solution was stirred for several hours and filtered to separate the product from the unreacted metal chloride. The volume of the filtrate was decreased and diethyl ether was added. The resulting solid was dried under vacuum.

2,6 Bis(4 phenyl 4,5 dihydrooxazol 2 yl)pyridineiron(II) chloride: Preparation proceeded as described above. 2,6 Bis(4 phenyl 4,5 dihydrooxazol 2 yl)pyridine (0.295 g, 0.8 mmol) and $FeCl_2$ (0.1 g, 0.79 mmol) reacted to give a magenta solid in 80% yield. MS (EI, 70 eV): *m/z* (%) = 495 (<1) $[M]^+$, 459 (<1) [*M* Cl], 369 (70.64) [L], 337 (12.87), 265 (16.84), 219 (41.92), 192 (29.84), 131 (28.82), 118 (47.44), 104 (100), 89 (67.54); MS (FAB, pos., NBA): *m/z* (%) = 794 [FeL_2] (30.6), 460 [*M* Cl] (51), 424 [*M* Cl_2] (29.75).

5,4′,5″ Tri *tert* butyl 2,2′;6′,2″ terpyridineiron(II) chloride: Preparation proceeded as described above. 5,4′,5″ Tri *tert* butyl 2,2′;6′,2″ terpyridine (0.321 g, 0.8 mmol) and $FeCl_2$ (0.1 g, 0.79 mmol) reacted to give a black solid in 85% yield. MS (ESI+): *m/z* (%) = 893.47283 (4.38) [FeL_2Cl], 492.18770 (3.28) [*M* Cl], 429.25030 (100), 143.09015 (12.66).

2,6 Bis (4,5 diphenyl 4,5 dihydro 1*H* imidazol 2 yl)pyridineiron(II) chloride: Preparation proceeded as described above. 2,6 Bis (4,5 diphenyl 4,5 dihydro 1*H* imidazol 2 yl)pyridine (0,353 g, 0.68 mmol) and $FeCl_2$ (0,085 g, 0.67 mmol) reacted to give a blue solid in 98% yield. MS (ESI+, CapExit 240 eV): *m/z* (%) = 1092.40498 (100) [FeL_2], 604.14556 (20), 576.17158 (8) [FeL], 520.25121 (46) [L].

Terpyridinemyrtanaliron(II) chloride: Preparation proceeded as described above. Terpyridinemyrtanal (0.18 g, 0.43 mmol) and $FeCl_2$ (0.053 g, 0.042 mmol) reacted to give a dark brown solid in 80% yield. MS (ESI+, CapExit 240 eV): *m/z* (%) = 547.12926 (32.76) $[M]^+$, 512.16012 (100) [*M* Cl], 391.14395 (26.15), 376.12027 (25.76), 363.11249 (18.07).

Epoxidation of trans Stilbene with Iron(II) Complexes

The iron complex (0.025 mmol), *tert* amyl alcohol (9 mL), *trans* stilbene (0.5 mmol), and dodecane (GC internal standard; 100 μL) were added in sequence to a 25 mL Schlenk tube at room temperature in air. A solution of hydrogen peroxide (30%, 170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added to this mixture over a period of 12 h at room temperature by a syringe pump.

Epoxidation of Olefins In Situ

The iron source (0.025 mmol) and ligands (each 0.025 mmol) were dissolved in *tert* amyl alcohol (4 mL) in a 25 mL Schlenk tube and heated for 1 h at 65 °C. Afterwards, the olefin (0.5 mmol) in *tert* amyl alcohol (5 mL) and dodecane (GC internal standard; 100 μL) were added in sequence at room temperature in air (in experiments without 1 h of heating at 65 °C, the iron source, ligands, olefin, and dodecane were dissolved at once in 9 mL *tert* amyl alcohol). A solution of hydrogen peroxide (30%, 170 μL, 1.5 mmol or 116 μL, 1.0 mmol) in *tert* amyl alcohol (830 or 884 μL) was added to this mixture over a period of 12 or 1 h at room temperature by a syringe pump.

UV/Vis Spectroscopic Measurements

UV/Vis spectra were recorded on a Cary 1 E UV/Vis spectrophotometer (Varian) in double beam mode with zero/baseline (empty cuvette) correction (40 nm min^{-1}, 0.2 nm data interval, 2 nm spectral bandwidth). Measurements were performed in a UV quartz cuvette (Hellma GmbH, QS 110, path length 10 mm) at room temperature and after the measuring solutions were filtered, if necessary. To obtain lower absorbance, solutions of tenfold dilution (relative to reaction solutions) were used.

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An Improved Iron-Catalyzed Epoxidation of Aromatic and Aliphatic Olefins with Hydrogen Peroxide as Oxidant

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Contributions:

In this paper, I contributed to a significant amount of the argumentation and the synthetic work. I developed and performed almost all of the catalytic reactions and wrote the manuscript. My contribution as co-author of this paper is approximately 80 %.

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An Improved Iron-Catalyzed Epoxidation of Aromatic and Aliphatic Olefins with Hydrogen Peroxide as Oxidant

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Keywords: Epoxidation / Alkenes / Iron / Hydrogen peroxide / Homogeneous catalysis

A convenient and practical method for the iron-catalyzed epoxidation of aromatic and aliphatic olefins is described. The iron catalyst system is generated in situ from iron trichloride hexahydrate, pyridine-2,6-dicarboxylic acid (H_2pydic), and benzylamines. By variation of the benzylamine ligand, a variety of aliphatic and aromatic olefins were oxidized in high yield (up to 96 %) and good-to-excellent selectivity in the presence of hydrogen peroxide as the terminal oxidant.

Introduction

The epoxidation of olefins is an important synthetic method in organic chemistry as well as for the chemical industry. With respect to generality, it still remains challenging to discover catalytic epoxidations that allow efficient and selective reactions for both aromatic and aliphatic olefins.[1,2] In general, state-of-the-art epoxidations should run under environmentally benign reaction conditions with inexpensive catalysts by using sustainable terminal oxidants and simple operation protocols.[3] Traditionally, stoichiometric oxidants such as organic peracids have been applied in epoxidation reactions.[4] More recently, hydrogen peroxide has become one of the terminal oxidants of choice, because it produces only water as a byproduct and is advantageous regarding costs, safety, and storage.[5] With regard to catalysts, the use of Fe- or Mn-based complexes is attractive due to their price and low toxicity.[6,7] On the basis of ruthenium-catalyzed epoxidation of olefins with hydrogen peroxide,[8] we found that $FeCl_3 \cdot 6H_2O$ in combination with pyridine-2,6-dicarboxylic acid and pyrrolidine shows high reactivity and selectivity towards the epoxidation of mono- and disubstituted aromatic olefins.[9] Unfortunately, aliphatic olefins and highly substituted aromatic olefins were less reactive and selective under the conditions of our previous system. Hence, we are interested in improved Fe-catalyzed epoxidations, which can be applied to all classes of olefins.

Herein, we report the development of a general method for the epoxidation of a broad scope of olefins with hydrogen peroxide.

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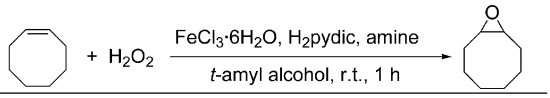
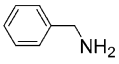
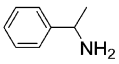
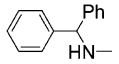
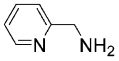
Results and Discussion

The key to the success of the Fe-catalyzed epoxidation is the use of pyridine-2,6-dicarboxylic acid (H_2pydic) as ligand. By studying the effect of the organic coligand on the epoxidation of cyclooctene as a model substrate, we observed a strong influence on the reactivity.

In Table 1 a small selection of the tested amines is shown. To our delight, the yield of cyclooctene oxide is improved from 4% (without ligand) up to 89% in the presence of *N*-(diphenylmethyl)methylamine (Table 1, entries 1 and 7). Notably, also our standard base pyrrolidine gave a significantly lower yield (16%) and selectivity with respect to epoxidation (Table 1, entry 2). Interestingly, in comparison to previous investigations the epoxidation of *trans*-stilbene with these amines did not display apparent differences in reactivity.[10] This can be attributed to the high reactivity of *trans*-stilbene. Hence, differences in the amine coligands did not show a significant influence on the reactivity. De novo analysis of the structural motif indicates that benzylamine is the important element in order to achieve high conversion. Strong coordinative 2-picolylamine gave inferior results as compared to benzylamine (Table 1, entries 5 and 8).[6a,6b,6d,6e] Slow dosing of hydrogen peroxide to the system increased the yield but is not the crucial factor. In fact, the addition of hydrogen peroxide can be performed within seconds, and cyclooctene oxide is obtained in 75% yield at 88% conversion. Further investigations on the concentration of the ligands showed 10 to 15 mol-% of the amine to be optimum. For better comparison and general applicability, the H_2O_2 addition time (1 h) and the amine concentration (12 mol-%) were maintained for all experiments. Replacement of H_2pydic with picolinic acid or quinaldic acid or the use of other iron sources resulted in a total loss of reactivity. Apparently, the H_2pydic component is essential in this system.[11]

Table 1. Effect of the amine coligand on the epoxidation of cyclooctene.[a]

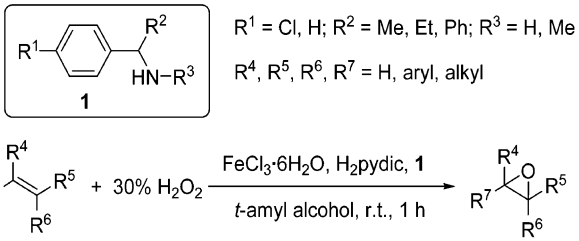


Entry	Amine	Conversion[b] [%]	Yield[b] [%]	Selectivity[c] [%]
1	–	7	4	57
2		23	16	70
3		33	21	64
4		44	32	73
5		56	43	77
6		65	51	78
7		100 (88)[d]	89 (75)	89 (85)
8		28	16	58

[a] Reaction conditions: In a test tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), amine (0.060 mmol), cyclooctene (0.50 mmol), and dodecane (GC internal standard, 100 μL) were added in sequence at r.t. in air. To this mixture was added a solution of 30% hydrogen peroxide (114 μL, 1.0 mmol) in *tert*-amyl alcohol (886 μL) over a period of 1 h at r.t. by syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Selectivity refers to the chemoselectivity of epoxide from olefin. [d] Addition of hydrogen peroxide within some seconds.

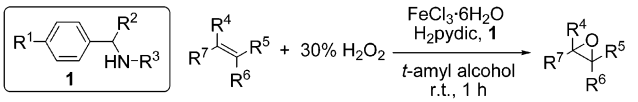
As shown in Table 1, it appears that benzylamine is a preferred structural element for the epoxidation of cyclooctene (Table 1, entries 5 to 7). For this reason we tested a selection of various commercially available benzylamines for the epoxidation of different classes of aromatic and aliphatic olefins (Scheme 1). Table 2 shows the epoxidation results for different substituted aromatic olefins. By applying the novel protocol, we could maintain the high reactivity and selectivity toward *trans*-stilbene and styrene as compared to our previous pyrrolidine system (Table 2, entries 1 and 3). Even though active catalysts for aliphatic olefins often lead to subsequent over oxidation reactions of the much-more reactive aromatic olefins, the benzylamine/H_2pydic/$FeCl_3$ system gives a general activity and good selectivity with respect to epoxidation in both of these classes of olefins.

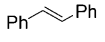
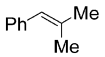
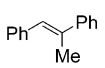
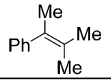
Epoxidation of *cis*-stilbene proceeded in 24% yield in comparison to 8% yield with the pyrrolidine-based system.[10] In addition, we could also increase the yields for trisubstituted aromatic olefins such as *trans*-β-methylstilbene (Table 2, entry 5; from 21 to 68% yield, respectively)



Scheme 1. Epoxidation of olefins with benzylamine derivatives **1**.

Table 2. Epoxidation of aromatic olefins with benzylamine derivative **1**.[a]



Entry	Substrate	R^1	R^2	R^3	Conversion[b] [%]	Yield[b] [%]	Selectivity[c] [%]
1		Cl	Me	H	100	84	84
2		Cl	Me	H	48	24	50
3		Cl	Me	H	100	91	91
4		H	Ph	H	68	37	54
5		H	Ph	Me	95	68	72
6		H	Ph	Me	0	0	–

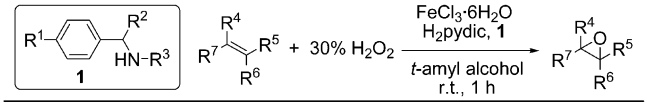
[a] Reaction conditions: In a test tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), amine (0.060 mmol), olefin (0.50 mmol), and dodecane (GC internal standard, 100 μL) were added in sequence at r.t. in air. To this mixture was added a solution of 30% hydrogen peroxide (114 μL, 1.0 mmol) in *tert*-amyl alcohol (886 μL) over a period of 1 h at r.t. by syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Selectivity refers to the chemoselectivity of epoxide from olefin.

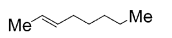
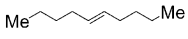
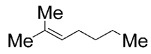
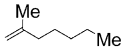
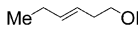
and 2-methyl-1-phenyl-1-propene (Table 2, entry 4; from 16 to 37% yield, respectively) in comparison to our previous system. However, the tetrasubstituted olefin 2-methyl-3-phenyl-2-butene gave no corresponding epoxide (Table 2, entry 6).

Aliphatic olefins work particularly well with the new catalyst system (Table 3). Internal olefins like *trans*-2-octene (Table 3, entry 1) and *trans*-5-decene (Table 3, entry 2) were oxidized in high yield and selectivity. Trisubstituted 2-methyl-2-heptene (Table 3, entry 3) and cyclic olefins (Table 3, entries 4 and 5) gave the corresponding epoxides in good yield. Terminal olefins are intrinsically poorly reactive substrates and catalytic methods for their epoxidation are limited.[6,7,12] Our system afforded 32% yield of 1-octene oxide, whereas 2-methyl-2-heptene was oxidized in 58% yield (Table 3, entries 6 and 7). Moreover, the iron cat-

alyst system showed good chemoselectivity towards olefins in the presence of hydroxy and carboxyl groups (Table 3, entries 8 and 9).

Table 3. Fe-catalyzed epoxidation of aliphatic olefins with benzylamine derivative **1**.[a]



Entry	Substrate	R^1	R^2	R^3	Conversion[b] [%]	Yield[b] [%]	Selectivity[c] [%]
1		Cl	Me	H	100	87	87
2		H	Et	H	96	96	99
3		H	Et	H	100	58	58
4		H	Et	H	77	48	62
5		H	Ph	Me	100	89	89
6		Cl	Me	H	45	32	71
7		H	Ph	Me	67	58	87
8		Cl	Me	H	84	80	85
9	Elaidic acid	H	Et	H	82	80	98

[a] Reaction conditions: In a tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), amine (0.060 mmol), olefin (0.50 mmol), and dodecane (GC internal standard, 100 μL) were added in sequence at r.t. in air. To this mixture was added a solution of 30% hydrogen peroxide (114 μL, 1.0 mmol) in *tert*-amyl alcohol (886 μL) over a period of 1 h at r.t. by syringe pump. [b] Conversion and yield were determined by GC analysis. [c] Selectivity refers to the chemoselectivity of epoxide from olefin.

Acetic acid is a well-known additive for the epoxidation of olefins with hydrogen peroxide by in situ formation of peracetic acid.[13] In contrast, addition of certain amounts of acetic acid to our catalyst system inhibited the conversion of 1-octene. Furthermore, to exclude the possibility of in situ formation of the alkyl hydroperoxide from *tert*-amyl alcohol, we used *tert*-BuOOH (70% aqueous) as an oxidant instead of hydrogen peroxide. Again no reactivity was observed for the epoxidation of cyclooctene. This indicates that *tert*-amyl hydroperoxide is not likely to be involved in the reaction and hydrogen peroxide is the only terminal oxidant in our system.

Conclusions

In conclusion, we developed an improved iron-catalyzed epoxidation, which can be performed under mild conditions with hydrogen peroxide as the terminal oxidant. The simple and practical catalyst system consists of iron trichloride hexahydrate, pyridine-2,6-dicarboxylic acid, and a benzylamine derivative. It was demonstrated that benzylamine is a preferred structural element for the coligand in this general epoxidation of aromatic and aliphatic olefins. The system showed good-to-excellent reactivity to mono-, di-, and trisubstituted aromatic olefins, as well as to internal di- and trisubstituted and functionalized aliphatic olefins. Noteworthy is that inactive aliphatic olefins can be oxidized in up to 96% yield. Currently, further efforts are underway to improve the protocol for tetrasubstituted aromatic and monosubstituted terminal aliphatic olefins and to investigate the mechanistic aspects of this reaction.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers (Aldrich, Fluka, Merck, etc.) without further purification. 2-Methyl-3-phenyl-but-2-ene (Table 2, entry 6) was synthesized according to literature procedures.[14] "30%" aqueous H_2O_2 from Merck was used as received. The peroxide content varied from 30% to 40% as determined by titration. GC analyses were performed with a Hewlett Packard HP 6890 model spectrometer. GC calibrations for alkenes and epoxides were carried out with authentic samples and dodecane as an internal standard.

General Procedure for the Epoxidation of Olefins: In a test tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), H_2pydic (0.025 mmol), *tert*-amyl alcohol (9 mL), amine (0.060 mmol), olefin (0.50 mmol) and dodecane (GC internal standard, 100 μL) were added in sequence at r.t. in air. To this mixture was added a solution of 30% hydrogen peroxide (aqueous, 114 μL, 1.0 mmol) in *tert*-amyl alcohol (886 μL) over a period of 1 h at room temperature by syringe pump. Conversion and yield were determined by GC analysis without further manipulations.

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Novel biomimetic iron-catalysts for environmentally benign epoxidations of olefins

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Contributions:

In this paper, I contributed to a significant amount of the argumentation and was involved in the study design. The new catalyst system is based on my previously developed *in situ* iron catalyst system and I supported the interpretation of the experimental data. My contribution as co-author of this paper is approximately 10 %.

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Novel biomimetic iron-catalysts for environmentally benign epoxidations of olefins

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Abstract A new selective and easily manageable epoxidation method is presented using an inexpensive and efficient $FeCl_3 \cdot 6H_2O$ and imidazole derivatives as catalysts. Aqueous hydrogen peroxide as an environmentally benign oxidant is utilized. This novel Fe/imidazole system gives moderate to excellent yields toward aromatic mono , di , and tri substituted olefins.

Epoxides play an important role in industry as intermediates for the production of fine chemicals as well as pharmaceuticals. With respect to environmental and economical considerations, the applied oxidant determines to a significant extent the value of the system.[1] Thus, the combination of hydrogen peroxide with a non-toxic and inexpensive metal source constitutes an ideal system for epoxidation reactions, especially in liquid phase processes in industry.[2,3] Among the various metals iron is the most abundant metal in nature and is indispensable in nearly all organisms.[4] Many biological systems such as hemoglobin, myoglobin, cytochrome oxygenases, and non-heme oxygenases are iron containing enzymes or co-enzymes.[5,6]

Due to its low cost and biological relevance there is an increasing interest to use iron complexes as catalysts for a wide range of reactions.[7] In this respect, recently we developed iron catalysts for C C-coupling reactions,[8] transfer hydrogenations[9] as well as epoxidations.[10,11] Based on the latter work, we report here a novel biomimetic $FeCl_3$/imidazole-system for epoxidations of olefins using aqueous hydrogen peroxide as the oxidant.[12]

Imidazole derivates play a fundamental role as ligands or base in enzymes.[13] For instance, the imidazole part of histidine often acts as a ligand in metalloenzymes, for example, hemoglobin.[14] With regard to epoxidations it is noteworthy that 1-sulfonylated imidazoles and hydrogen peroxide are known as powerful oxidant in stoichiometric amount for the reactions.[15] Besides, imidazoles and pyrazoles are widely employed as additives in epoxidation systems, such as iron[16] and manganese[17] porphyrins, manganese salen complexes,[18] methyltrioxorhenium,[19] and manganese schiff bases.[20]

Recently, we demonstrated that a combination of $FeCl_3 \cdot 6H_2O$, pyridine-2,6-dicarboxylic acid (H_2pydic) and an organic base like pyrrolidine catalyzes the epoxidation of *trans*-stilbene with 30% H_2O_2 to *trans*-stilbene oxide in high yield within 1 h.[11] Key to the success of this reaction is the use of pyridine-2,6-dicarboxylic acid as ligand. By studying the effect of the organic base in more detail, we found that a combination of $FeCl_3 \cdot 6H_2O$ with simple imidazole *without any* pyridine-2,6-dicarboxylic acid gave also *trans*-stilbene oxide in 38% yield with 90% selectivity (Table 1, entry 1).[21] Further investigations showed that the activity and selectivity of the catalytic system can be improved by varying the imidazole ligands (Table 1).

The influence of the substitution pattern of the imidazole ligands reveals some interesting aspects. Substitution

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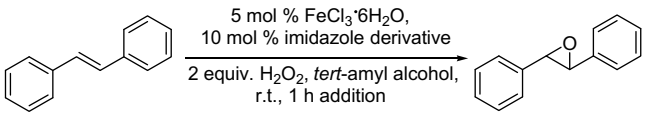
Table 1. Reactivity of different imidazole derivatives



Entry	Imidazole derivative	Conv.[a,b] (%)	Yield[b] (%)	Selectivity[c] (%)
1		43	38	90
2		47	39	83
3		**83**	**80**	**97**
4		69	69	100
5		40	39	99
6		5	4	90
7		39	36	93
8		5	5	87

[a] Reaction conditions: in a 25 mL Schlenk tube, $FeCl_3{\cdot}6H_2O$ (0.025 mmol), imidazole derivative (0.05 mmol), *tert* amyl alcohol (9 mL), *trans* stilbene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added in sequence at rt in air. To this mixture, a solution of 30% H_2O_2 (115 μL, 1.0 mmol) in *tert* amyl alcohol (885 μL) was added over a period of 1 h at rt by a syringe pump.
[b] Conversion and yield were determined by GC analysis.
[c] Selectivity refers to the ratio of yield to conversion in percentage.

at the 2-position of the imidazole gave inferior results (Table 1, entries 1, 2, 6, and 8). Furthermore, N-substitution of the 5-bromoimidazole led to a higher yield and conversion (Table 1, entries 4 and 7). In addition, 5-halo-*N*-methylimidazoles enhanced the yield significantly. In fact 5-chloro-1-methylimidazole (Table 1, entry 3) gave the best result (80% yield; 97% selectivity). It is noteworthy that 5-chloro-1-methylimidazole (5-Cl-1-MeIm) is a near-optimal imidazole activity enhancing additive with balanced steric and electronic factors in an iron porphyrin system.[16]

Next, we tried to find out more about the mechanism of this novel epoxidation catalyst. One of the possibilities for the effectiveness of these imidazole ligands might be the participation of a carbene type ligand in the reaction system due to their outstanding σ-donor strength.[22]

However, replacement of the imidazole derivative with 1,3-dimesityl-2,3-dihydro-1*H*-imidazol-2-ide gave no conversion at all. Besides, in the presence of the radical trap TEMPO (2,2,6,6-tetramethyl-piperidine-1-oxyl; 1.5 equiv), the reaction showed insignificant conversion and yield. This suggests the participation of a radical in the catalytic cycle in this epoxidation system. Control experiments indicated that all the components are essential for the activity and selectivity. Indeed, in the presence of 10 mol % of 5-Cl-1-MeIm without $FeCl_3{\cdot}6H_2O$ no product formation is observed. On the other hand 5 mol % of $FeCl_3{\cdot}6H_2O$ without 5-Cl-1-MeIm gave only 5% yield. These results exclude the possibility of organocatalysis.

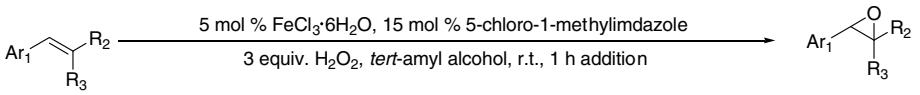
Further optimization showed that a higher yield (84% yield and 99% selectivity) can be reached when 3 equiv of 30% hydrogen peroxide is used.[23] The yield was maintained with a slight drop of selectivity when 4 equiv of hydrogen peroxide was added. Applying a higher amount of the ligand 5-Cl-1-MeIm gave slightly better results. Hence, with 15 mol % of 5-Cl-1-MeIm and 5 mol % $FeCl_3{\cdot}6H_2O$, the product yield reached 86% with 97% selectivity. No further significant improvement is observed with higher ligand loading.

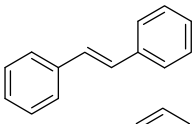
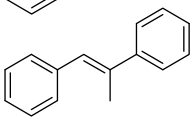
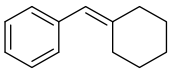
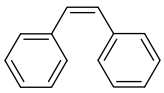
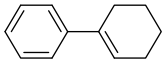
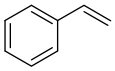
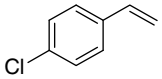
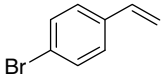
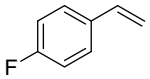
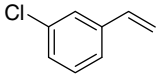
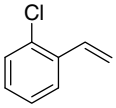
Next, various olefins were applied to the reaction under the optimized reaction conditions (3 equiv H_2O_2, 5 mol % $FeCl_3{\cdot}6H_2O$, and 15 mol % 5-Cl-1-MeIm) (Table 2).

In the presence of Fe/imidazole catalyst mono-, di-, and tri-substituted olefins can be epoxidized in moderate to excellent yield with high selectivity (Table 2). Compared with our previously reported first generation iron catalyst, this reaction system improved both the yield and selectivity especially for trisubstituted olefins.[11] For example, epoxidation of (cyclohexylidenemethyl)-benzene gave 25% yield with 64% selectivity in the new protocol (Table 2, entry 3) while the old system gave only 11% yield with 39% selectivity. Furthermore, all halogen-substituted styrenes gave improved selectivity compared to the first generation catalysts (up to 91%).

In conclusion, we have developed a novel, biomimetic and easily manageable epoxidation reaction. For the first time it is possible to perform epoxidations with hydrogen peroxide in the presence of simple Fe/imidazole catalysts. Compared to our previous catalyst system the newly developed iron catalyst does not need any pyridine-2,6-dicarboxylic acid and gave improved yield and selectivity for more difficult tri-substituted olefins and styrenes.[24] Efforts to examine the reaction mechanism and to realize an asymmetric version of this reaction are going on in our group.

Table 2. Scope and limitations of the reaction[25]



Entry	Substrates	Conv.[a,b] (%)	Yield[b] (%)	Selectivity[c] (%)
1		92	87	94
2		46	41	88
3		39	25	64
4		34	24[d]	71
5		52	36	68
6		74	70	95
7		90	79	88
8		91	82	90
9		73	62	86
10		74	67	91
11		55	46	84

[a] Reaction conditions: in a 25 mL Schlenk tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), 5 chloro 1 methylimidazole (0.075 mmol), *tert* amyl alcohol (9 mL), *trans* stilbene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added in sequence at rt in air. To this mixture, a solution of 30% H_2O_2 (170 μL, 1.5 mmol) in *tert* amyl alcohol (830 μL) was added over a period of 1 h at rt by a syringe pump.

[b] Conversion and yield were determined by GC analysis.

[c] Selectivity refers to the ratio of yield to conversion in percentage.

[d] Additionally 3% *trans* stilbene oxid and *trans* stilbene were observed.

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22. Hermann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290 1309.
23. Aqueous H_2O_2 (30%) from Merck was used as received. The peroxide content varied from 33% to 40% as deter mined by titration.
24. Side products are rearrangement products of the corre sponding epoxide.
25. Most of the substrates and epoxides for GC FID calibration are commercially available. The others were synthesized according to literature methods and deter mined by NMR and GC MS. In addition, authentic samples of the commercial products were analyzed by GC MS and GC FID.

Publication 3.9.

Iron Catalyzed Asymmetric Epoxidation of Aromatic Alkenes Using Hydrogen Peroxide

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Contributions:

In this paper, I contributed to a significant amount of the argumentation and the synthetic work. I was involved in the development of the catalyst system, the synthesis of ligands, the interpretation of the results and the study design. I developed the *in situ* iron catalyst system and synthesized a library of approximately 20 ligands containing chiral prolinol and diphenylethylene diamine as key structures. My contribution as co-author of this paper is approximately 45 %.

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Epoxidation

Iron-Catalyzed Asymmetric Epoxidation of Aromatic Alkenes Using Hydrogen Peroxide

*Feyissa Gadissa Gelalcha, Bianca Bitterlich, Gopinathan Anilkumar, Man Kin Tse, and Matthias Beller**

Dedicated to Süd Chemie on the occasion of its 150th anniversary

Optically active oxiranes are key building blocks for the synthesis of fine chemicals and pharmaceuticals.[1] They are available from resolution processes[2] and more interestingly from catalytic asymmetric epoxidations. State of the art pro tocols are the Sharpless epoxidation of allylic alcohols,[3] the Katsuki Jacobsen epoxidation of unfunctionalized alkenes using chiral Mn(salen) catalysts (salen = *N*,*N*′ bis(salicylide ne)ethylenediamine),[4] and organocatalytic methods using chiral ketones and oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).[5] Despite the usefulness of the known procedures, the develop ment of less expensive and environmentally more benign catalysts and oxidant systems is a major goal for organic synthesis.

Among the various oxidants, hydrogen peroxide is one of the most practical reagents (second only to air) in terms of cost and atom efficiency. In recent years hydrogen peroxide has become increasingly important not only for bulk epox idations but also for asymmetric catalyis.[6] In this respect the work of Katsuki and co workers, who developed convenient Ti catalysts for asymmetric alkene epoxidation with hydrogen peroxide, is most notable.[7] In addition, also Pt[8] and Ru catalysts[9] have been reported for asymmetric epoxidations of olefins. While these systems give high enantioselectivity, the catalysts involved are relatively expensive.

Nature relies on various iron containing enzymes for the oxidative degradation of a number of xenobiotics often with exceptional selectivities. Iron is not only ubiquitous but also one of the most versatile transition metals.[10] Hence, it is surprising that research on epoxidations using iron based catalysts has largely been neglected. Only recently, a success ful biomimetic approach was reported with iron porphyrin complexes for the epoxidation of styrene derivatives applying iodosobenzene as oxidant.[11] Unfortunately, the synthesis of the required chiral porphyrin ligands is notoriously diffi cult,[12] and the oxidant is not environmentally friendly. Moreover, Cheng et al. reported recently the aerobic epox idation of styrene derivatives catalyzed by tris(*d*,*d* dicampho lylmethanato) iron(III) complex, $[Fe(dcm)_3]$.[13] Although encouraging results were achieved, a drawback of this method is the need to employ an excess of aldehyde as sacrificial reductant and dichloroethane as the solvent.

To the best of our knowledge there is no Fe based asymmetric epoxidation catalyst known that gives more than 20% enantiomeric excess when hydrogen peroxide is used as the oxidant. This currently highest *ee* value was reported by Francis and Jacobsen, who used an elaborate combinatorial screening of 5760 metal ligand combinations to identify three Fe complexes with peptide like ligands suitable for asym metric epoxidation of *trans* β methylstyrene.[14] Using bio mimetic non porphyrin Fe catalysts, Costas et al. reported the $[Fe(bpmcn)(CF_3SO_3)_2]$ catalyzed dihydroxylation of of *trans* 2 heptene with hydrogen peroxide which gave the epoxide as a by product with 12% *ee* (bpmcn = *N*,*N*′ bis(2 pyridyl methyl) *N*,*N*′ dimethyl 1,2 cyclohexanediamine).[15] Clearly, it has not yet been possible to replace the established epoxidation catalysts with iron complexes.

For some time we have been interested in Ru catalyzed epoxidations with hydrogen peroxide in the presence of nitrogen ligands such as 2,6 di(4,5 dihydro 1,3 oxazol 2 yl)pyridine (pybox),[16a] 2,2′ (pyridine 2,6 diyl)bis(5,6 dihy dro 4*H* 1,3 oxazine) (pyboxazine),[16b] terpyridines,[16c] and pyridinebisimidazolines (pybims)[16d] together with the col igand pyridine 2,6 dicarboxylic acid (H_2pydic). Our initial approach to extend these Ru systems to Fe failed in terms of the stereoselectivity of the epoxidation. Nevertheless, a general racemic epoxidation of aromatic alkenes with hydro gen peroxide is possible with a convenient in situ catalyst consisting of ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), H_2pydic, and organic bases such as pyrrolidine.[17] Herein, we report the first genuinely promising iron catalyzed asym metric epoxidation of aromatic alkenes without porphyrin ligands and using hydrogen peroxide. This method not only gives good to excellent yields of isolated epoxides but also *ee* values up to 97%.

For our investigations we chose *trans* stilbene (**1a**) as the model substrate because of its nonvolatility and the stability of the product epoxide for reliable determination of con version, yield, and selectivity by gas chromatography. In testing a large number of commercially available optically pure amines we often obtained high conversions and excellent chemoselectivities. However, we could not obtain the corre sponding epoxide **2a** with enantioselectivities anywhere close to 10% *ee*. Among the ligands that gave small but reprodu cible enantioselectivities, we identified 2,2 diphenylprolinol (**3d**). A closer look at the effect of different chiral pyrrolidine derivatives **3** revealed a relationship between the type and

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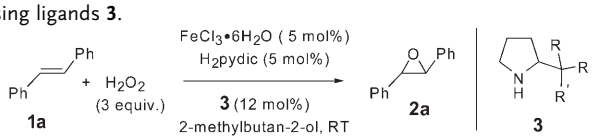
size of substituents adjacent to the chiral center and the *ee* values (Table 1). While prolinol (**3a**) gave the racemic product (Table 1, entry 1), the diphenyl substituted **3d** led

Table 1: Iron catalyzed asymmetric epoxidation of *trans* stilbene (**1a**) using ligands **3**.



Entry	Ligand, abs. config.	R	R′	*t* [h]	Conv.[a] [%]	Yield[a] [%]	*ee*(**2a**) [%],[b] abs. config.[c]
1	**3a**, (*S*)	H	OH	1	95	73	0
2	**3b**, (*S*)	H	NH_2	36	60	58	1, ( ) (2*S*,3*S*)
3	**3c**, (*S*)	Ph	H	60	61	45	0
4	**3d**, (*S*)	Ph	OH	36	78	53	10, (+) (2*R*,3*R*)
5	**3e**, (*R*)	Ph	F	1	100	90	16, ( ) (2*S*,3*S*)
6[d]	**3e**, (*R*)	Ph	F	14	100	98	17, ( ) (2*S*,3*S*)
7	**3f**, (*S*)	F	F	1	100	93	2, (+) (2*R*,3*R*)

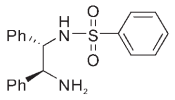
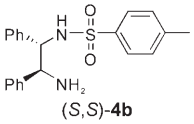
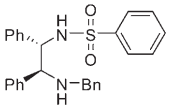
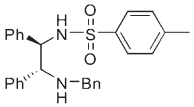
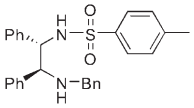
[a] Determined by gas chromatography using dodecane as the internal standard. [b] Determined by HPLC on a chiral column. [c] Determined by comparing the sign of the optical rotation of the major enantiomer on a chiral detector coupled to a chiral HPLC, with known data.[19] [d] Reaction at 0 °C.

to 10 % *ee* (Table 1, entry 4). Interestingly, maintaining the phenyl substituents and replacing the hydroxy group by fluoride led to a much more active catalyst (complete substrate conversion in less than 1 h at room temperature) and increased the *ee* value to 17 % (Table 1, entries 5 and 6). This suggested the importance of H bonding in addition to steric factors in the enantioselectivity determining step. Although, H bonding has also been implicated in asymmetric oxidations catalyzed by **3e** using oxone,[18] under our reaction conditions no epoxide is formed when the ligand is used without Fe.

Next, we extended our search to chiral amine ligands with a neighboring group capable of intramolecular H bonding such as carbonyl and sulfonyl groups. The required ligands are easily accessible by monoamidation or sulfonylation of optically pure C_2 symmetrical 1,2 diamines such as ( ) (*S*,*S*) 1,2 diphenylethylenediamine and N alkylation of the resulting products where necessary. In Table 2 the influence of ligands **4a**,**b** and **5a**,**b** on the enantioselectivity of the model reaction is summarized.

To our delight, application of this basic concept led to the identification of the commercially available ligand **4b**, which gave *trans* stilbene oxide ( ) (2*S*,3*S*) **2a** in 28 % *ee* under the standard reaction conditions (Table 2, entry 2). Interestingly this starkly contrasts with the nearly racemic product obtained when the unsubstituted ( ) (*S*,*S*) 1,2 diphenylethyl enediamine is used as the ligand. Among the modified ligands **5** the N benzyl substituted derivative (*S*,*S*) **5b** led to the most significant increase in *ee* values, giving (+) (2*R*,3*R*) **2a** in 42 % *ee* (Table 2, entry 5) at room temperature which improved to 47 % *ee* when the temperature was lowered to 8 °C (Table 2, entry 6). It is also striking that in the oxidation

Table 2: Iron catalyzed asymmetric epoxidation of *trans* stilbene (**1a**) using ligands **4** and **5**.[a]

Entry	Ligand	Conv.[b] [%]	Yield[b] [%]	*ee*(**2a**) [%][c], abs. conf.[d]
1	 (*S*,*S*)-**4a**	100	88	26, ( ) (2*S*,3*S*)
2	 (*S*,*S*)-**4b**	100	86	28, ( ) (2*S*,3*S*)
3	 (*S*,*S*)-**5a**	100	98	36, (+) (2*R*,3*R*)
4	 (*R*,*R*)-**5b**	100	92	41, ( ) (2*S*,3*S*)
5	 (*S*,*S*)-**5b**	100	87	42, (+) (2*R*,3*R*)
6[e]	(*S*,*S*) **5b**	100	97	47, (+) (2*R*,3*R*)

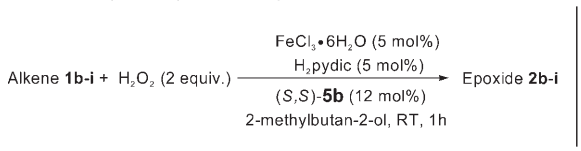
[a] Conditions: 0.5 mmol **1a**, 1 mmol H_2O_2, 5 mol %, $FeCl_3 \cdot 6H_2O$, 5 mol % H_2pydic, 12 mol % **4a**,**b**/**5a**,**b**, 2 methylbutane 2 ol, RT, 1 h. [b] Determined by gas chromatography using dodecane as the internal standard. [c] Determined by HPLC on a chiral column. [d] Determined by comparing the sign of the optical rotation of the major enantiomer on a chiral detector coupled with a chiral HPLC, with known data.[19] [e] Reaction at 8 to 10 °C, 24 h.

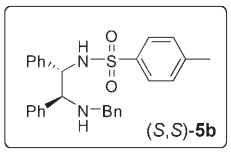
of *trans* stilbene, use of the mono(arenesulfonyl) protected ligands **4a**,**b** and the N benzylated ligands **5a**,**b** resulted in selectivity for enantiomers of **2a** with opposite absolute configurations (Table 2, entries 1 and 3). In general, manip ulations of the N benzyl substituent led to decreased reac tivity in the epoxidation reaction and did not improve results.

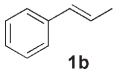
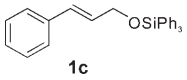
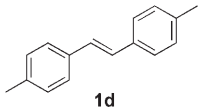
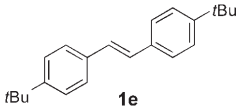
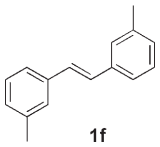
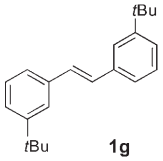
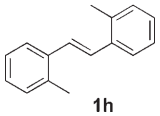
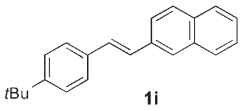
To explore the scope of the reaction, we epoxidized different aromatic olefins in the presence of **5b**, which was the best ligand in the model reaction in terms of costs, selectivity, and product yields (Table 3). The reaction performed well for β methylstyrene (**1b**), a cinnamyl alcohol derivative (**1c**), and various *trans* stilbenes (**1d h**). While **1b** furnished (+) (2*R*,3*R*) **2b** with 28 % *ee*, substrate **1c** was oxidized to (+) (2*R*,3*R*) **2c** with 35 % *ee* (Table 3, entries 1 and 2).

In reactions of *trans* stilbenes **1d h**, the substrates with substituents in the *para* position were more reactive than the analogous *ortho* or *meta* substituted compounds, presumably on steric grounds (Table 3, entries 3 7). Best enantioselectiv ities were obtained with sterically demanding 4,4′ dialkyl substituted stilbenes. Here, the enantioselectivity increases with steric bulk of the substituents, H < Me < *t*Bu, and reaches a maximum value for **1e**, which gave the correspond ing oxirane **2e** in 82 % yield and 81 % *ee* at room temperature within one hour (Table 3, entry 4). On the other hand, for 3,3′

Table 3: Fe catalyzed asymmetric epoxidation of different aromatic alkenes.





Entry	Alkene	Conv.[a] [%]	Yield[b] [%]	*ee*(**2**) [%],[c] abs. config.
1	 **1b**	100[d]	94[d]	28, (+) (2*R*,3*R*)[e]
2	 **1c**	100	67	35, (+) (2*R*,3*R*)[f]
3	 **1d**	100	92	64, (+) (2*R*,3*R*)[g]
4	 **1e**	100	82	81, (+) (2*R*,3*R*)[g]
5	 **1f**	>95	88	27, (+) (2*R*,3*R*)[h]
6	 **1g**	>95	66	10, ( ) (2*S*,3*S*)[h]
7	 **1h**	60[i]	57[i]	55, ( ) (2*S*,3*S*)[h]
8[j]	 **1i**	100	46	91, (+) (2*R*,3*R*)[h]
9[j,k]	**1i**	100	40	97, (+) (2*R*,3*R*)[h]

[a] Estimated by GC MS and/or TLC which indicated absence of substrate. [b] Yield of isolated pure product. [c] Determined by HPLC on chiral columns. [d] Determined by GC. [e] Assigned by comparing the retention times of the two enantiomers on a chiral HPLC with that of an authentic sample of the *S*,*S* enantiomer; [f] Assigned by desilylation to the corresponding epoxy alcohol by analogy with literature protocol[20] and comparing the sign of optical rotation of the resulting product with that of an authentic sample. [g] Determined by comparing the sign of the optical rotation of the major enantiomer on a chiral detector coupled with a chiral HPLC, with known data; the CD spectra of these products are positive, opposite to those reported for the *S*,*S* enantiomers.[19a] [h] Tentatively assigned by comparing the CD spectrum with those of **2a**,**d**,**e**. [i] Determined after 24 h by ^{1}H NMR spectrum of crude product using an internal standard. [j] 4 equiv H_2O_2, 10 mol% H_2pydic, 10 mol% $FeCl_3{\cdot}6H_2O$, 24 mol% (*S*,*S*) **5b**. [k] Reaction at 10°C.

dialkyl substituted stilbenes the *ee* values decrease with increasing size of the substituent. The highest *ee* value was achieved with **1i** as the substrate in the presence of 10 mol% of the iron catalyst (Table 3, entry 8). In this case oxirane **2i** was obtained with 91% *ee* and 46% yield. When the the reaction temperature was lowered slightly to 10°C, the *ee* value increased to 97% with complete substrate conversion within one hour (Table 3, entry 9).

In summary, we have demonstrated for the first time that high enantioselectivity can be achieved in Fe catalyzed epoxidations with hydrogen peroxide. This long standing goal in oxidation catalysis was realized by combining $FeCl_3$ with appropriately chosen chiral diamine ligands and pyridine 2,6 dicarboxylic acid. Clearly the cata lyst system has to be improved with respect to generality. Further work to extend the substrate scope and towards a mechanistic understand ing of this new catalyst are under way.

Experimental Section

General: Alkenes **1a**,**b**,**d**, ligands **3**, **4b**, (*S*,*S*) ( ) 1,2 diphenylethylenediamine, H_2pydic, $FeCl_3{\cdot}6H_2O$, and 2 methylbu tan 2 ol are commercially available. Monosufonylated ligand **4a** was pre pared by analogy with known proto cols.[21] Alkenes **1e h** were synthesized by McMurry[22] coupling of the corre sponding alkyl substituted benzalde hydes in high yields and purities. Ana lytical data are in accord with literature values. Alkene **1i** was synthesized by the Heck reaction of 4 *tert* butylbromoben zene with 2 vinylnaphthalene by modi fication of the method of Chandrasekhar et al.[23] Alkene **1c** was synthesized by silylation of *trans* cinamyl alcohol with triphenylsilylchloride in the presence of pyridine in 87% yield. All racemic epoxides **2** required as references for chiral HPLC data were synthesized by epoxidation with *meta* chloroperbenzoic acid (*m*CPBA): Typically 1 2 equiva lents of a solution of *m*CPBA were added dropwise to an ice cooled solu tion of the alkene in CH_2Cl_2. After stirring overnight at room temperature the solvent was removed and the residue purified by flash chromatography to furnish high yields (80 92%) of the corresponding epoxides.

Synthesis of (*S*,*S*) **5b**: Amine **4b** (2 g, 5.45 mmol) and freshly distilled benzaldehyde (582 µL, 5.81 mmol) were refluxed in 20 mL anhydrous eth anol for 2 h under Ar. The initially formed precipitate went into solution at 80°C bath temperature. The progress of the reaction was monitored by TLC. After complete consumption of **4b** the reaction vessel was cooled to room temper ature. An equal volume of ethanol was added and $NaBH_4$ (186.40 mg, 8.72 mmol) was introduced portionwise. The mixture was stirred at room temperature overnight. After the imine had been consumed completely (TLC), water was added dropwise until no more gas evolved. The gelatinous granules were filtered off and washed with ethanol. The filtrate was dried over $MgSO_4$ and filtered. The solvent

was removed by rotary evaporator and the residue purified by flash chromatography (silicagel 60, *n* hexane: ethyl acetate 3:1 (v/v), R_f 0.43) to give **5b** (2.33 g, 93%). M.p. 139.9°C; $[\alpha]_D^{25}$ +58.0 deg cm^3 g^{-1} dm^{-1} (*c* 0.72 g cm^{-3}, CH_2Cl_2); IR (KBr): $\tilde{\nu}$ 3338, 3305, 3086, 3064, 3028, 2788, 2713, 1599, 1494, 1453, 1348, 1324, 1152; ^{1}H NMR (400.13 MHz, CD_2Cl_2): δ 1.6 (br s, 1H, N*H*), 2.34 (s, 3H, CH_3), 3.42 (d, *J* 13.16 Hz, 1H, CH_2), 3.60 (d, *J* 13.16 Hz, 1H, CH_2). 3.74 (d, 7.80 Hz, 1H, C*H*Ph), 4.27 (dd, *J* 7.84 Hz, 1H, C*H*Ph), 6.21 (br s, 1H, N*H*), 6.95 7.00 (m, 4H, Ar), 7.05 7.13 (m, 5H, Ar), 7.15 7.19 (m, 5H, Ar), 7.22 7.32 (m, 3H, Ar), 7.37 7.39 ppm (m, 2H, Ar); ^{13}C NMR (75.47 MHz, CD_2Cl_2): δ 21.56 (*C*H$_3$), 51.16 (*C*H$_2$), 63.45 (*C*HPh), 67.22 (*C*HPh), 127.36, 127.48, 127.69, 127.92, 127.94, 128.04, 128.34, 128.40, 128.76, 128.77, 129.66, 137.21, 139.16, 139.33, 139.90, 143.49 ppm; elemental analysis calcd (%) for $C_{28}H_{28}N_2O_2S$: C 73.65, H 6.18, N 6.14, S 7. 02; found: C 73.60, H 6.44, N 6.01, S 7.24. MS (CI, positive mode, isobutane) *m*/*z*: 457.3 $[M+H]^+$(100), 349(15), 196 (40); HRMS (CI, negative mode, isobutane) *m*/*z*: calcd for $C_{28}H_{27}N_2O_2S$: 455.1788 $[M-H]^+$; found:455.1784.

General protocol for Fe catalyzed asymmetric epoxidation of alkenes: Pyridine 2,6 dicarboxylic acid (4.24 mg, 0.025 mmol), ferric chloride hexahydrate (6.76 mg, 0.025 mmol), ligand **3**, **4**, or **5** (0.06 mmol), and the corresponding alkene **1** (0.5 mmol) were mixed in 9 mL 2 methylbutane 2 ol and stirred at room temperature for ca. 30 min.[24] The resulting mixture usually assumes pale yellow color. When the yields and conversions were determined by GC, 100 μL dodecane was added as the internal standard. After samples were removed for GC analysis, 1 mmol of aqueous "30%" hydrogen peroxide[25] dissolved in 1 mL 2 methylbutane 2 ol was added to the reaction mixture over one hour using a syringe pump. In most cases complete conversion was achieved after this time (GC or TLC monitoring). For preparative purposes excess peroxide was destroyed by adding 1 mL of a saturated aqueous solution of sodium sulfite and shaking well. After addition of diethyl ether (10 mL) the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$. After filtration and solvent removal by rotary evaporator, the crude product was either directly analyzed by chiral HPLC or purified by silica gel chromatography on a short column (hexane/ethylacetate 20:1, 1% Et_3N) for full characterization.

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[24] The amounts of the iron salt, ligand (*S*,*S*) **5b**, H_2pydic, H_2O_2, and solvent were proportionately doubled for epoxidation of **1i** (Table 3, entries 8 and 9).

[25] We used "30%" aqueous H_2O_2 (Merck) as received; the peroxide content was determined by titration to range from 35% to 40%.

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Iron-catalyzed hydroxylation of β-ketoesters with hydrogen peroxide

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In this paper, I contributed to a significant amount of the argumentation and interpretation of experimental data within the preparation of the manuscript. My contribution as co-author of this paper is approximately 10 %.

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Iron-catalyzed hydroxylation of β-ketoesters with hydrogen peroxide as oxidant

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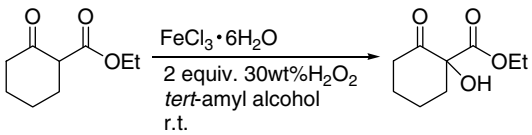
ABSTRACT

The hydroxylation of β ketoesters was studied using simple iron catalysts and 30 wt % hydrogen peroxide as the terminal oxidant. The highest activity and yield were achieved in the presence of iron(III) chloride. Cyclic β ketoesters could be smoothly hydroxylated in 75 90% yield. For linear β ketoester and β keto amide, the chloro substituted products were obtained.

α Hydroxy β ketoester is an important scaffold found in a lot of bioactive molecules.[1] The hydroxylation of 1,3 dicarbonyl com pounds is a straight forward important technique in organic syn thesis to access these compounds. A variety of reagents including hydrogen peroxide, *m* CPBA, molecular oxygen, and (camphor ylsulfonyl) oxaziridines were applied in the selective oxidation of β keto carbonyl compounds.[1d,2] Recently, it was reported that $CoCl_2$, $CeCl_3$, and $Mn(OAc)_2$ could be effective catalyst for this transformation using molecular oxygen as oxidant.[3] Noteworthy, the asymmetric hydroxylation of β ketoesters was also success fully demonstrated using a titanium TADOL based catalyst and up to 94% ee was achieved.[4] Hydrogen peroxide is known to be an environmentally benign oxidant with the ease of laboratory handling. The development of general, simple and efficient catalyst system using H_2O_2 is still a challenging goal for the hydroxylation of β keto carbonyl compounds.

Great progress has been advanced in iron catalysis in the last decade. Various reactions such as olefin hydroxylation,[5] sulfide oxidation,[6] cross coupling reactions,[7] heterolytic RO OH bond cleavage,[8] hydroamination,[9] allylic alkylation or amination,[10] and alcohol oxidation[11] were investigated. Based on our recent experi ence in iron catalyzed selective oxidation of olefin to epoxide and alcohol to aldehyde,[12] here we report our new findings about iron catalyzed selective hydroxylation of β ketoesters to the corres ponding α hydroxy β ketoesters. The selective hydroxylation of 2 ethoxycarbonyl 1 oxo cyclohexane (**1**) was used as the model reaction (Scheme 1).



Scheme 1. Selective hydroxylation of 2-ethoxycarbonyl-1-oxo-cyclohexane.

Initial screening of the reaction conditions, that is, different iron salts, organic solvents, and the amount of catalyst loading revealed that 1 mol % of iron(III) chloride hexahydrate, 2 equiv of hydrogen

Table 1
Catalyst screening using **1** as model substrate[a]

Entry	Iron salts	Con.[b] (%)	Yield[c] (%)	Sel.[d] (%)
1	$FeCl_3$	79	79	99
2	$FeCl_3 \cdot 6H_2O$	82	82	99
3	$FeCl_2$	80	80	99
4	$FeBr_3$	13	13	99
5	$Fe(OAc)_2$	7	7	99
6	$Fe(NO_3)_3 \cdot 9H_2O$	7	7	99
7	$Fe_2(SO_4)_3 \cdot 5H_2O$	13	13	99
8	$FePO_4 \cdot 4H_2O$	14	14	99

[a] 1 mmol (170 mg) **1**, 1 mol % iron salt, 2 equiv (0.20 mL) 30 wt % H_2O_2, and 25 mL *tert*-amyl alcohol were added into a 50 mL reaction tube, respectively. After being shaken, the reaction vessel was allowed to react at rt for 1 h without stirring. 1 mmol (170 mg) dodecane was added as an internal standard for quantitative analysis.[14]
[b] Conversion of **1**.
[c] Calibrated GC yield.
[d] Chemoselectivity toward the desired product with respect to consumed starting material.

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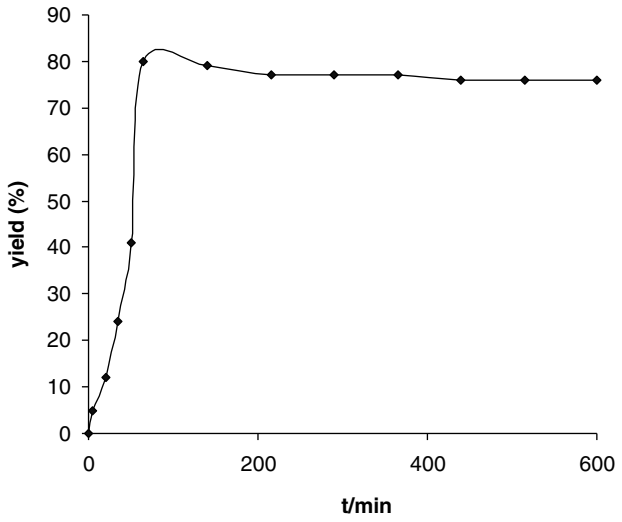
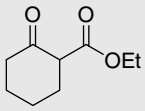
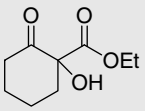
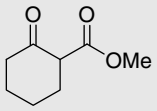
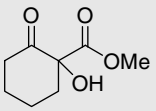
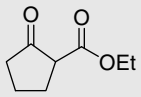
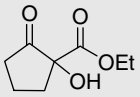
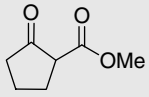
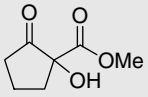
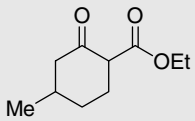
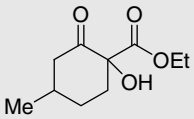
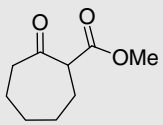
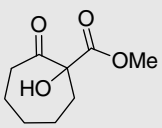


Figure 1. Yield of **1b** against time.

peroxide, and 25 mL of *tert* amyl alcohol were suitable for the hydroxylation of **1a**;[13] 86% conversion with 70% yield could be obtained with magnetic stirring in 1 h. The usage of other solvents, such as THF, dioxane, ethanol, acetonitrile, and *N* methyl 2 pyrro lidinone, caused lower selectivity. However, the yield of the reac tion varied significantly in some cases. With careful investigation of the possible factors, it was surprisingly found that the selectivity of the reaction significantly increased from 81% to >99% with sim ilar conversion without stirring. The addition of more iron chloride or hydrogen peroxide and with longer reaction time gave no improvement of the reaction but instead more byproducts. The re sults under the reaction conditions without stirring are highly reproducible, but the effect of stirring in this reaction is still not clear at this moment. Hence, all the following reactions were carried out without any stirring except specifically mentioned.

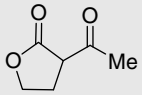
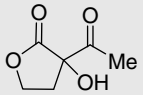
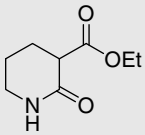
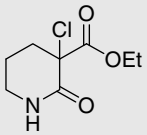
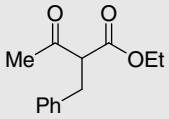
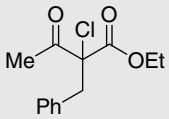
The catalytic activity of different iron salts was investigated in the presence of 1 mol % catalyst and 2 equiv, 30 wt % hydrogen per oxide (Table 1). The counter anions of iron salts highly affect the catalytic activity (Table 1, entries 1 8). The corresponding hydr oxylation product was obtained in high yield when using iron chlorides as the catalysts, no matter anhydrous or hydrated, Fe(II)

Table 2
Selective oxidation of diketone compounds catalyzed by iron(III) chloride[a]

Entry	Substrate	Product	*t* (h)	Conv.[b] (%)	Yield[c] (%)	Sel.[d] (%)
1	 **1a**	 **1b**	1	82	82	99
2	 **2a**	 **2b**	0.75	75	75	99
3	 **3a**	 **3b**	8	98	90	92
4	 **4a**	 **4b**	6	98	84	86
5	 **5a**	 **5b**	0.75	89	85[e]	96
6[f]	 **6a**	 **6b**	24	90	81	90

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	*t* (h)	Conv.[b] (%)	Yield[c] (%)	Sel.[d] (%)
7[g]	 **7a**	 **7b**	0.2	91	80	88
8[h]	 **8a**	 **8c**	4	57	38	67
9[i]	 **9a**	 **9c**	15	82	60	73

[a] The same reaction conditions as given in Table 1.
[b] Conversion of starting material.
[c] Calibrated GC yield.
[d] Chemoselectivity toward the desired product with respect to consumed starting material.
[e] A mixture of diastereomers in ~1:1 (GC–MS) was obtained.
[f] The substrates and 2 equiv 30 wt % H_2O_2 were dissolved in 5 mL *tert*-amyl alcohol, and 10 mol % $FeCl_3{\cdot}6H_2O$ (27 mg/20 mL *tert*-amyl alcohol) was added in 24 h.
[g] 10 mol % $FeCl_3{\cdot}6H_2O$.
[h] 1 mol % $FeCl_3{\cdot}6H_2O$, 2 equiv 30 wt % H_2O_2, and 15 mL *tert*-amyl alcohol were added initially. 19 mol % $FeCl_3{\cdot}6H_2O$ (51 mg/10 mL *tert*-amyl alcohol) and 6 equiv 30 wt % H_2O_2 were added in 4 h.
[i] 35 mol % $FeCl_3{\cdot}6H_2O$/20 mL *tert*-amyl alcohol and 6 equiv H_2O_2 were added in 15 h.

or Fe(III) (Table 1, entries 1 3). This small difference in all iron chloride catalysts indicates the reaction may be catalyzed by sim ilar intermediates as oxidation of iron(II) chloride to iron(III) chlo ride by hydrogen peroxide readily takes place. Noteworthy, this reaction is also easy to be scaled up in laboratory scale. ~80% yield and ~99% selectivity maintained when 13 mmol (2.21 g) **1a** was employed.[15]

An interesting phenomenon was also observed during the reac tion when using iron(III) chloride as catalyst. At the early stage of reaction, the color of the reaction mixture was yellow due to the color of $FeCl_3$ $6H_2O$. It turned brown immediately after the addi tion of β ketoester. This color stays during the reaction even after H_2O_2 has been added. When the conversion was above 80%, the reaction mixture changed back to yellow in color. This color change was not observed in the reactions with low conversion. Hence, the formation of a new iron complex from iron chloride and β ketoes ter is suspected. This phenomenon provides an opportunity to de velop high throughput screening methods with direct visual aids.

Close monitoring of the reaction showed that the reaction fin ished fast and smoothly in 1 h (Fig. 1). Although our reaction con ditions constitute typical Fenton reagent recipe,[16] the product is stable in our reaction system after its formation within 10 h.

The selective oxidation of other β ketocarbonyl compounds was further studied (Table 2). In most of the cases, the reaction can be finished overnight. However, shorter reaction time is also feasible. The time necessary to achieve high conversion is substrate depen dent, as also demonstrated in other reports.[3a,4] While **1a** and **2a**, gave higher than 75% conversion in less than 1 h, more than 6 h should be used in order to get high conversion and yield using **3a** and **4a** as starting materials (Table 2, entries 1 4). The reactivity of the preformed intermediate from iron chloride and β ketoesters (**1a** or **2a**) governs the productivity. More iron chloride (10 mol %) and longer reaction time (24 h) can be used to produce **6b** from unreactive **6a** in good yield (81%) (Table 2, entry 6). With higher catalyst loading (10 mol %), **7a** can be hydroxylated in 80% yield with 91% conversion (Table 2, entry 7).

It is interesting to note that chlorination occurred when the cat alyst loading increased. In the presence of 5 mol % iron chloride, the conversion of **8a** was ~20% with ~50% selectivity to the α hydroxylated **8b**. When the amount of iron chloride increased to 20 mol %, the conversion could reach to 57%. However, the major product under such conditions was α chloro β ketoester **8c** in 38% yield (Table 2, entry 8). For the non cyclic β ketoester **9a**, α chloro β ketoester **9c** was the main product even with only 10 mol % of $FeCl_3$ $6H_2O$. Up to 60% of **9c** could be obtained when 35 mol % of catalyst was used (Table 2, entry 9). Therefore, this system has potential to develop a new oxidative chlorination protocol for the synthesis of α chloro β ketocarbonyl compounds.

In summary, a simple and highly effective iron catalyst system was developed for the α oxidation of β ketoesters. 75 90% yield of the hydroxylation products could be obtained using cyclic β keto esters as starting material.

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Supplementary data

The detailed characterization results for all the products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.157.

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13. The effect of N-ligands, such as pyrrolidine and imidazoles, in Refs. 12a and 12b was also tested. No better activity and yield were obtained in comparison with the merely iron chloride addition system.
14. *Typical procedure for the hydroxylation of* **1**: 1 mmol (170 mg) of **1**, 1 mol % (2.7 mg) of iron(III) chloride hexahydrate, 2 equiv of (0.2 mL) 30 wt % H_2O_2 and 25 mL *tert*-amyl alcohol were added into a 50 mL reaction tube, respectively. After being sealed and shaken, the reaction was allowed to react at rt for 1 h without stirring. After the reaction, 1 mmol (170 mg) of dedecane was added as an internal standard for quantitative analysis. Then the solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the desired product. Compound **1b**: $R_f = 0.19$ (hexane/ethyl acetate = 90:10); colorless liquid; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 1.11–1.27$ (t, $J = 7.2$ Hz, 3H), 1.48–1.84 (m, 4H), 1.87–2.06 (m, 1H), 2.38–2.66 (m, 3H), 4.06–4.19 (q, $J = 7.2$ Hz, 2H), 4.19–4.28 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.3$, 22.2, 27.3, 38.0, 39.2, 62.3, 80.9, 170.4, 207.7; MS (EI): *m*/*z* (rel. int.) 186 (31), 168 (20), 142 (62), 140 (32), 130 (19), 114 (29), 113 (72), 112 (44), 111 (123), 101 (35), 95 (15), 86 (15), 85 (95), 84 (35), 83 (20), 73 (17), 68 (57), 67 (96), 57 (30), 56 (35), 55 (100), 45 (13), 43 (38), 42 (34), 41 (45), 39 (21), 29 (54), 27 (30); HRMS calcd for $C_9H_{14}O_4$ *m*/*z* 186.0887, found *m*/*z* 186.0890.
15. *Scaling up testing for the hydroxylation of* **1a**: 13 mmol (2.21 g) of **1a**, 1 mol % (35.1 mg) of iron(III) chloride hexahydrate, 2 equiv (2.6 mL) of 30 wt % H_2O_2 and 325 mL *tert*-amyl alcohol were added into a 500 mL round-bottomed bottle. After being sealed and shaken, the reaction was allowed to react at rt for 2 h without stirring. After the reaction, 13 mmol (2.2 g) of dodecane was added as an internal standard for quantitative analysis. The reactions were repeated two times. ~80% conversion, ~99% selectivity and ~80% yield were obtained. *Caution!* Although we have never faced any problem during our experiments, it needs to be mentioned that large scale usage of hydrogen peroxide may cause explosion.
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Eidesstattliche Erklärung

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, den 1. Juli 2008

Bianca Bitterlich