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Ruthenium-Catalyzed Asymmetric Epoxidation of Olefins Using H_2O_2, Part II: Catalytic Activities and Mechanism

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Abstract: Asymmetric epoxidation of olefins with 30% H_2O_2 in the presence of [Ru(pybox)(pydic)] **1** and [Ru(pyboxazine)(pydic)] **2** has been studied in detail (pybox = pyridine-2,6-bisoxazoline, pyboxazine = pyridine-2,6-bisoxazine, pydic = 2,6-pyridinedicarboxylate). 35 Ruthenium complexes with sterically and electronically different substituents have been tested in environmentally benign epoxidation reactions. Mono-, 1,1-di-, *cis*- and *trans*-1,2-di-, tri-, and tetra-substituted aromatic olefins with versatile functional groups can be epoxidized with this type of catalyst in good to excellent yields (up to 100%) with moderate to good enantioselectivies (up to 84% *ee*). Additive and solvent effects as well as the relative rate of reaction with different catalysts have been established. It is shown that the presence of weak organic acids or an electron-withdrawing group on the catalyst increases the reactivity. New insights on the reaction intermediates and reaction pathway of the ruthenium-catalyzed epoxidation are proposed on the basis of density functional theory calculation and experiments.

Keywords: asymmetric oxidation · epoxidation · homogeneous catalysis · mechanism · olefins · ruthenium

Introduction

One of the core technologies to convert bulk raw materials, such as alkanes and olefins, to value-added products is, undoubtedly, oxidation reactions.[1] On the one hand, high selectivity, broad substrate scope, and sufficient catalyst stability and productivity are in high priority of any chemical process. On the other, 100% atom-economy, usage of environmentally benign reagents, and minimizing or eliminating the use of dangerous chemicals are the major concerns for the general application of oxidation reactions.[2] Among the readily available oxidants, molecular oxygen seems to be the perfect reagent for an oxidation reaction. However, only one oxygen atom of an oxygen molecule is used productively for oxidation (this corresponds to only 50% atom efficiency) in most of the cases and 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 environmentally benign by a similar atom-economy with its side product being water. In addition, it is readily available, has a comparably low price ($< 0.6\,€\,kg^{-1}$ of 100% H_2O_2) and can be used safely without much precautions.[5,6] In general, it is particularly useful for liquid-phase oxidation for the synthesis of fine chemicals, pharmaceuticals, agrochemicals, and electronic materials. Clearly, the development of new catalytic systems using H_2O_2 is still an important and challenging goal in oxidation chemistry.[7,8]

With regard to enantioselective epoxidation of olefins, titanium (Sharpless epoxidation)[9] and manganese (Jacobsen–Katsuki epoxidation)[10] based catalysts are still in the state-of-the-art. Significant progress using organic catalysts based on chiral ketones has been reported by Shi, Yang, and others recently.[11,12] Besides, polypeptide-catalyzed epoxidation of enones under basic phase-transfer conditions is probably one of the most applicable processes in this context.[13]

Our interest in the past years has been aroused by ruthenium-catalyzed oxidation reactions with its wide range of applicability and broad variation of ligand type especially in the asymmetric epoxidation of olefins (**1**, **6**–**14**).[14] Mono-,

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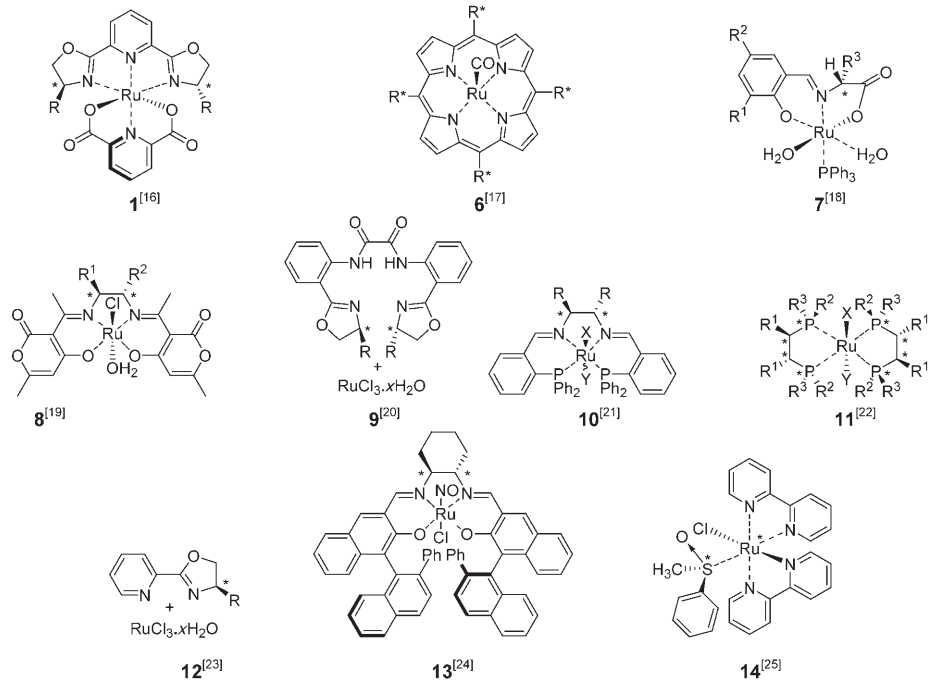
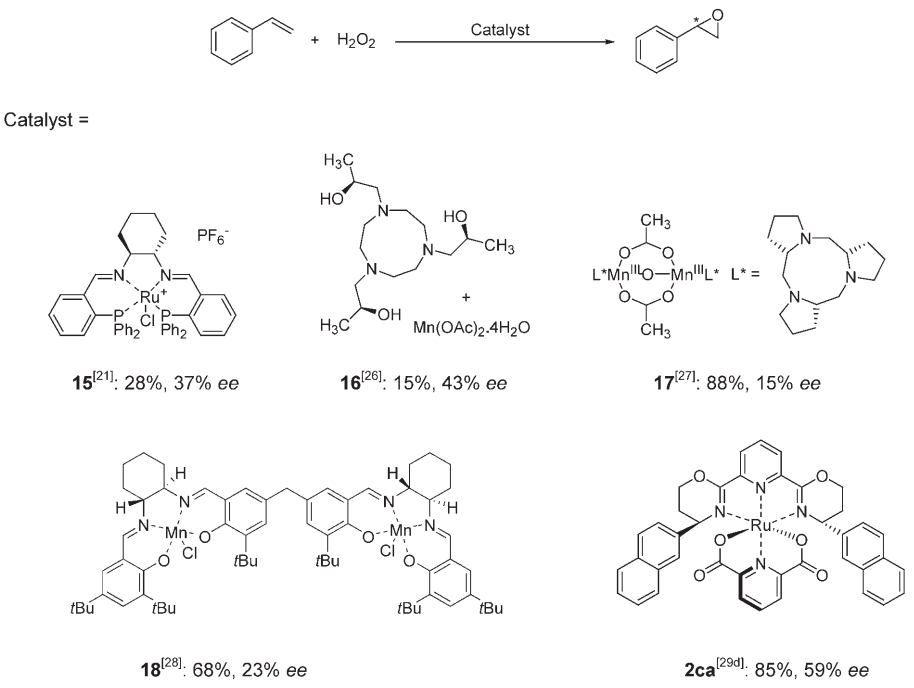


bi-, tri-, and tetradentate ligands as well as macrocyclic porphyrins have been found useful ligands for this reaction. Moreover, various coordinating atoms such as N, O, S, or P can all be beneficial for a given Ru catalyst. In some of the cases combination of ligands has also been applied. However, in spite of extensive research efforts, the development of a general and catalytic asymmetric epoxidation method with high enantioselectivity by using hydrogen peroxide has not yet been achieved.[15] Generally, there are several drawbacks in asymmetric epoxidation utilizing H_2O_2.[8] For instance more than the stoichiometric amount of H_2O_2 is needed to solve the problem of unproductive decomposition of H_2O_2 to O_2 by the used transition-metal catalyst.

Evidently, the stability of the catalyst and the ligands in high concentration of H_2O_2 as well as the selectivity, especially enantioselectivity, in the presence of water can be problematic. It is also not uncommon that oxidative cleavage of the olefin competes with the productive epoxidation. Therefore only a handful of examples of asymmetric epoxidation of simple styrene using H_2O_2 have been reported (Scheme 1).

We chose (pyridine-2,6-bisoxazoline)(2,6-pyridinedicarboxylate)ruthenium ([Ru(pybox)(pydic)] **1**) as the starting point for our research on novel epoxidation catalysts as it contains two different meridional ligands (see preceeding article).[16] It is apparent that by varying the chiral pybox and the achiral pydic separately, the reactivity as well as the (enantio)selectivity of the catalyst should be easily tuned.

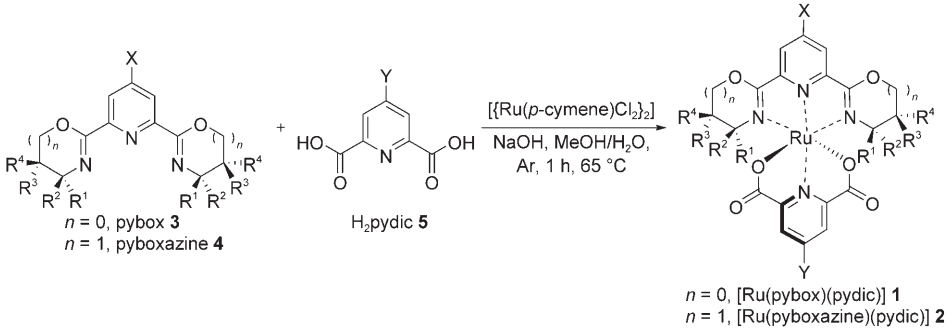
Initially, we demonstrated that **1** becomes a more practical oxidation catalyst by adding a defined amount of water to the reaction mixture.[29a] This also led to the development of enantioselective epoxidation protocols applying alkyl peroxides[29b] and hydrogen peroxide.[29d–g] In this paper we describe a full account of our work on ruthenium-catalyzed asymmetric epoxidation with H_2O_2 as the oxidant as well as the mechanistic studies. Systematic variation of the ligands led to the development of (pyridine-2,6-bisoxazine)(2,6-pyridinedicarboxylate)ruthenium ([Ru(pyboxazine)(pydic)] **2**) as novel epoxidation catalysts.



Scheme 1. Catalysts for asymmetric epoxidation of styrene.

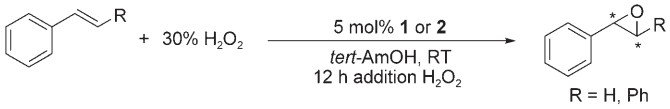
Results and Discussion

As a starting point for our systematic investigation, we synthesized and tested some [Ru(pybox)(pydic)] (**1aa**, **1na**, and **1pa**) complexes from commercially available chiral pybox ligands and found that the substitutions on the C4- and C5-positions of the oxazoline ring affect both the reactivity and selectivity of the catalyst.[29] We then identified the possibilities of variation of the catalyst according to the availability of starting materials, literature knowledge, and the ease of synthesis. These versatile electronic and steric substitution effects are valuable for a further development of the catalyst by rational design.[30] Hence, more than 30 different [Ru(pybox)(pydic)] **1** and [Ru(pyboxazine)(pydic)] **2** complexes were synthesized (Scheme 2) and tested in the asymmetric



Scheme 2. Synthesis of [Ru(pybox)(pydic)] **1** and [Ru(pyboxazine)(pydic)] **2**.[31]

epoxidation of styrene (Scheme 3, Tables 1 and 2).[31] For a better understanding of the generality of a specific catalyst, we also tested these catalysts with *trans*-stilbene as substrate (Scheme 3, Tables 1 and 2).



Scheme 3. [Ru(pybox)(pydic)] **1-** or [Ru(pyboxazine)(pydic)] **2**-catalyzed epoxidation of styrene and *trans*-stilbene.

The applied [Ru(pybox)(pydic)] **1** catalysts have a broad coverage of substitution pattern, including 4-, 5-, *cis*-4,5-di-, *trans*-4,5-di-, and 4,5,5-tri-substitution on the oxazoline ring; *para*-substitution on the pyridine ring on both pybox and pydic; *ortho*- or *meta*- substitution on the phenyl ring at the C4-position of the oxazoline; and a wide range of functional groups, such as halogen, alcohol, amine, silyl ether, ester, aryl, and alkyl groups. Complementary to [Ru(pybox)(pydic)] **1**, the six-membered pyboxazine derivatives **2** contain also aryl and alkyl group at the C4-positions and *para*-substitution on the phenyl ring at C4 as well.

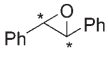
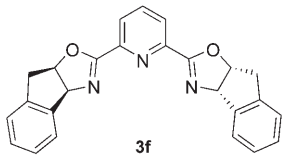
For convenience the catalytic reactions were run at room temperature in the presence of 5 mol% of Ru complex using three equivalents of H_2O_2 (30% in water), which was slowly dosed into the reaction mixture. In general, after 12 h of addition of H_2O_2 good yield for the epoxidation of styrene and an excellent yield for that of *trans*-stilbene are obtained. It is worth noting that aryl groups on the C4-position generally gave a better reactivity towards styrene than alkyl groups (Table 1, entries 1–16 and entries 18–22). When a highly sterically demanding group is introduced, either on the C4- or C5-position, the reactivity dropped tremendously (Table 1, entries 17 and 20). However, functional groups like amine, alkoxy, ester, halogen, hydroxy, and silylether did not affect the reactivity much (Table 1). In general, [Ru(pyboxazine)(pydic)] **2** were less reactive than its "pybox cousins" for *trans*-stilbene as well as styrene (Table 1, entries 1 and 19; Table 2, entries 1, 2, and 9).[32] From these initial reactivity patterns, we thought that modification of the catalysts should be possible to increase the *ee* without losing much reactivity.

Indeed, the substituents on both the C4- and C5-positions have a large influence on the *ee* of the prototypical reactions. The *ee* of styrene oxide ranged from 0–37% and 25–48% in **1** and **2**, respectively (Tables 1 and 2).[33] Aryl substituents on the C4-position generally gave higher *ee* than the alkyl groups (Table 1, entries 1, 12, and 18–22; Table 2, entries 1, 2, and 4–9). This positive effect is attributed to a π–π interaction between the ligand and the aryl substrates. Among the different aryl substituents, the larger 2-naphthyl group was beneficial in **1** with respect to a phenyl group (Table 1, entry 1 versus 12). However, a higher *ee* is not obtained in the case of **2** under standard reaction conditions (Table 2, entries 2, 5, vide infra). The more sterically hindered 1-naphthyl group in **2** turned out to be inferior to the *ee* (Table 2, entry 4). Furthermore, phenyl substitution on the C5-position in **1** has interesting effects on the enantioselectivity.

On the one hand it had no significant asymmetric induction to the product when there was no substituent at the C4-position (Table 1, entry 13). On the other hand it dominated the asymmetric induction when a methyl group is *trans* to it (Table 1, entries 18 and 21). However, when two phenyl groups were on both C4- and C5-positions, to our surprise, the *trans*-orientation gave a positive influence to the *ee* of styrene oxide, while the *cis*-orientation resulted in a reduction of *ee* (Table 1, entries 1, 14 and 15). This clearly is a cooperative effect and the reasons are difficult to understand. Evidently, one has to consider the effects of the substitution on the ligands as a whole rather than as single additive effects.

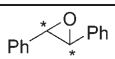
The influence of the size of the alkyl group at the C4-position to the *ee* of styrene oxide was not significant (10–19% *ee*; Table 1, entries 18, 19, and 22). The yield of styrene

Table 1. [Ru(pybox)(pydic)] **1**-catalyzed epoxidation of styrene and *trans*-stilbene with H_2O_2.[a]

		$n=0$, [Ru(pybox)(pydic)] **1**									
Entry		R^1	R^2	R^3	R^4	X	Y	Yield [%]	*ee*[b] [%]	Yield [%]	*ee*[c] [%]
1	**1aa**	H	Ph	H	H	H	H	70	+31	100	−67
2	**1ab**	H	Ph	H	H	H	OH	77	+27	100	−45
3	**1ac**	H	Ph	H	H	H	Cl	65	+43	93	−66
4	**1ad**	H	Ph	H	H	H	Br	65	+44	97	−66
5	**1ae**	H	Ph	H	H	H	OMe	62	+24	95	−52
6	**1af**	H	Ph	H	H	H	Ph	65	+36	97	−65
7	**1ba**	H	Ph	H	H	Cl	H	61	+23	93	−71
8	**1ca**	H	Ph	H	H	NMe_2	H	74	+26	99	−34
9	**1da**	H	Ph	H	H	Ph	H	64	+33	97	−69
10	**1ea**	H	Ph	H	H	1-Np	H	–	–	98	−63
11	**1fa**	 **3f**					H	59	+18	93	−46
12	**1ga**	2-Np	H	H	H	H	H	69	−37	99	+70
13	**1ha**	H	H	H	Ph	H	H	66	−3	93	−1
14	**1ia**	Ph	H	Ph	H	H	H	78	−18	100	+14
15	**1ja**	Ph	H	H	Ph	H	H	68	−35	94	+65
16	**1ka**	H	2-ClC_6H_4	H	H	H	H	59	+24	95	−50
17	**1la**	Ph	H	Me	Me	H	H	32	+12	29	−32
18	**1ma**	H	Me	H	H	H	H	52	+12	100	−51
19	**1na**	H	*i*Pr	H	H	H	H	45	+19	100	−54
20	**1oa**	H	*t*Bu	H	H	H	H	32	0	35	−29
21	**1pa**	H	Me	Ph	H	H	H	64	−14	94	+42
22	**1qa**	H	Bn	H	H	H	H	51	+10	87	−35
23	**1ra**	H	CH_2OH	H	H	H	H	48	−10	91	+25
24	**1sa**	CH_2OTBS	H	H	H	H	H	–	–	100	+50
25	**1ta**	H	$CH(CH_3)OTBS$	H	H	H	H	–	–	85	−36
26	**1ua**	CO_2Me	H	H	H	H	H	–	–	92	+25

[a] See Experimental Section. [b] "+" sign means (*R*)-(+)-styrene oxide is the major enantiomer. [c] "−" sign means (*S*,*S*)-(−)-*trans*-stilbene oxide is the major enantiomer.

Table 2. [Ru(pybox)(pydic)] **1**-catalyzed epoxidation of styrene and *trans*-stilbene with H_2O_2.[a]

		$n=1$, [Ru(pyboxazine)(pydic)] **2**									
Entry		R^1	R^2	R^3	R^4	X	Y	Yield [%]	*ee*[b] [%]	Yield [%]	*ee*[c] [%]
1	(*R*)-**2aa**	H	Ph	H	H	H	H	56	+48	93	-53
2	(*S*)-**2aa**	Ph	H	H	H	H	H	61	−46	86	+51
3	(*R*)-**2ac**	H	Ph	H	H	H	Cl	66	+47	49	−43
4	(*R*)-**2ba**	H	1-Np	H	H	H	H	65	+38	92	−30
5	(*S*)-**2ba**	1-Np	H	H	H	H	H	71	−44	95	+32
6	(*R*)-**2ca**	H	2-Np	H	H	H	H	59	+48	99	−54
7	(*S*)-**2da**	4-ClC_6H_4	H	H	H	H	H	69	−48	99	+51
8	(*S*)-**2ea**	4-$MeOC_6H_4$	H	H	H	H	H	54	−31	88	+52
9	(*R*)-**2fa**	H	*i*Pr	H	H	H	H	59	+25	60	−30

[a] See Experimental Section. [b] "+" sign means (*R*)-(+)-styrene oxide is the major enantiomer. [c] "−" sign means (*S*,*S*)-(−)-*trans*-stilbene oxide is the major enantiomer.

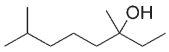
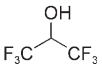
oxide and *ee* were both very low for the *tert*-butyl derivative **1oa**, possibly due to decomposition of the catalyst (Table 1, entry 20). The steric effect of the substituents on the catalysts to the *ee* in the case of *trans*-stilbene oxide follows the same trend as styrene oxide. However, the effect diminishes when the *ee* reached around 70% in **1**.

The *para*-positions of the pyridine ring of the pybox-(azine) and pydic ligands also influenced the *ee* of styrene oxide. Electron-deficient groups on pydic increased the *ee* up to 44%, while the electron-donating groups reduced the *ee* (Table 1, entries 1–5). The weak electron-withdrawing phenyl group has a positive effect to the *ee* as well possibly owing to additional π–π interactions with the substrate. However, the electronic effects on the pybox side seem to be controversial both in styrene and *trans*-stilbene cases (Table 1, entries 7–10). With a *para*-chloro group, the *ee* increased for *trans*-stilbene oxide and decreased for styrene oxide (Table 1, entry 7). However, in case of NMe_2 and Ph groups, the *ee* for *trans*-stilbene oxide and styrene oxide had the same trend (Table 1, entries 8, 9). Since the absolute

configuration of *trans*-stilbene oxide and styrene oxide are always the opposite with the same catalyst, we believe that the two test reactions pass through different major transition states. At this point we did not have any conclusive explanation of the electronic effects. But as we shall see below (mechanistic studies), it is suggested that the difference of *ee* is due to the difference of the rate of reaction and the influence of water content in the reaction mixture (vide infra).

Clearly, solvent effects plays an important role in asymmetric catalysis.[34] Therefore, we tested the asymmetric epoxidation of *trans*-stilbene in ten different reaction media. As shown in Table 3 protic solvents gave best results in this reaction (Table 3, entries 1–4). Hence, excellent yield and good *ee* have been achieved with tertiary alcohols. Use of the secondary alcohol 2-propanol gave a lower *ee*, since the competitive reaction of oxidation of 2-propanol occurred,[35] which increased the water content of the reaction mixture during the addition of H_2O_2. Previously, we have demonstrated that over-dosage of H_2O in the epoxidation of *trans*-stilbene catalyzed by **1aa** with $PhI(OAc)_2$ as the oxidant also decreased the *ee*.[29a] In the presence of the more acidic 1,1,1,3,3,3-hexafluoro-2-propanol high conversion of the olefin is observed, without any epoxide detected due to the decomposition of the stilbene oxide in the reaction medium (Table 3, entry 5). Other nonpolar solvents and one example of an ionic liquid showed to be inferior to the model reaction.

Table 3. Solvent effects in the [Ru(*S*,*S*-Ph_2-pybox)(pydic)] **1aa**-catalyzed epoxidation of *trans*-stilbene with H_2O_2.[a]

Entry	Solvent	Conversion [%][b]	Yield [%][b]	Selectivity [%][c]	*ee* [%][d]
1	*t*AmOH	100	100	100	−67[e]
2	*t*BuOH	100	93	93	−65
3	*i*PrOH	91	87	96	−57
4		83	80	96	−66
5		100	0	0	n.d.[f]
6	toluene	6	5	100	n.d.[f]
7	CH_3CN	100	86	86	−39
8	$[Bmim]PF_6$	trace	trace	–	n.d.[f]
9	1,4-dioxane	44	38	86	−28
10		trace	trace	–	n.d.[f]

[a] Reaction conditions: In a 25 mL Schlenk tube, **1aa** (0.025 mmol) was stirred at room temperature in the solvent (9 mL) for 10 min. *trans*-Stilbene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added. A solution of hydrogen peroxide (170 μL, 1.5 mmol) in the solvent (830 μL) was added over a period of 12 h by a syringe pump to this reaction mixture. [b] Determined by comparing with authentic samples on GC-FID. [c] Chemoselectivity for epoxide formation. [d] Determined by HPLC. [e] "−" sign means (*S*,*S*)-(−)-trans-stilbene oxide was the major enantiomer. [f] Not determined.

In addition to the variation of solvents we also tested 30 different additives to the epoxidation catalyzed by **1aa**. They included amines (four examples), pyridines (four examples), pyridine oxides (six examples), phosphine oxides (two examples), ammonium salts (four examples), and organic acids (ten examples). To our delight, organic acids generally increased the epoxide yield and the *ee* when a less reactive substrate is employed. In a typical reaction, when 20 mol% of HOAc was added, the epoxide yield increased from 71 to 75% and the *ee* increased from 31 to 42%. Further increasing the amount of HOAc did not give positive effects. When *para*-substituted benzoic acids with electron-donating or -withdrawing groups were used as the additives, similar results are obtained. It is questionable whether the acid is acting as a ligand in the reaction mixture in contrast to the iron-catalyzed sulfur oxidation demonstrated by Bolm and co-workers.[8k]

To understand the effect of the organic acid in more detail we traced the **1aa**-catalyzed epoxidation of *trans*-stilbene with 30% H_2O_2 with time in the presence and absence of 20 mol% HOAc (Figure 1). In the initial stage of the reaction, the conversion of *trans*-stilbene was more or less the same in both cases. As the reaction went further, the one with 20 mol% HOAc kept the rate of reaction, while the one without HOAc decelerated. This indicates that HOAc accelerates the reaction, possibly by slowing down the self-degradation of the active catalyst. Since the water content increases during the addition when H_2O_2 is used as the oxidant, the faster the reaction the higher the *ee* is.[29e] Thus, the positive effect of added carboxylic acid is the best applicable to a less reactive catalyst with less reactive substrates. Accordingly, this effect diminishes when electron-rich olefins are employed.

Next, we applied both **1aa** and (*R*)-**2ca** to 24 different olefins with versatile functional groups and substitution patterns (Table 4). In general, both catalysts showed good activ-

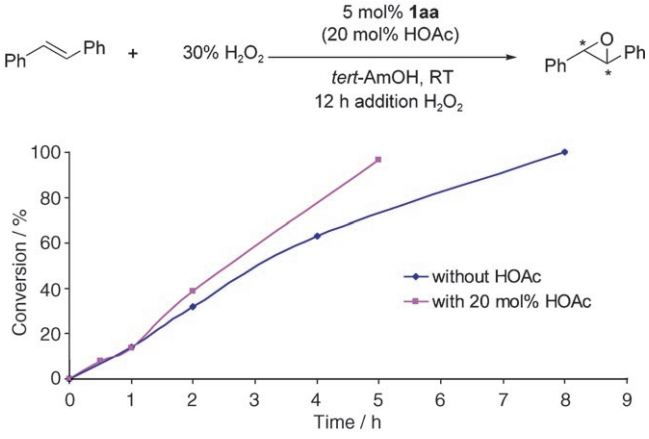
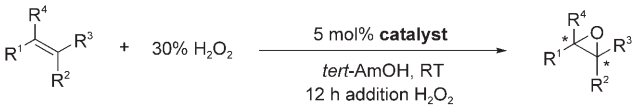
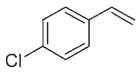
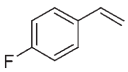
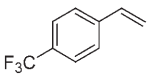
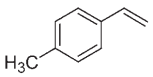
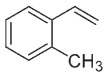
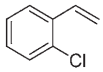
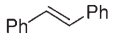
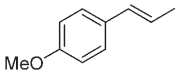
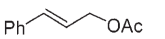
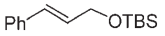
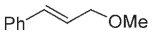
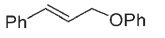
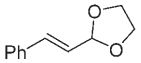
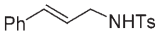
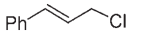
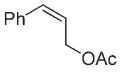
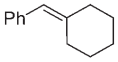
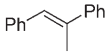


Figure 1. Conversion of *trans*-stilbene against time with 20 mol% HOAc (pink) and without HOAc (blue) in the epoxidation of *trans*-stilbene with H_2O_2 catalyzed by **1aa**.

Table 4. Scope of [Ru(*S*,*S*-Ph$_2$-pybox)(pydic)] **1aa**- and [Ru{(*R*,*R*)-(2-Np)$_2$-pyboxazine}(pydic)] (*R*)-**2ca**-catalyzed asymmetric epoxidation.[a]



		1aa				(*R*)-**2ca**			
Entry	Substrate	Conv. [%][b]	Yield [%][b]	Selec. [%]	*ee* [%][c]	Conv. [%][b]	Yield [%][b]	Selec. [%]	*ee* [%][c]
1		100	71	71	+31	82	59	72	+48[d]
2		100	75	75	+42[e]	100	85	85	+59[e]
3		–	–	–	–	100	76	76	54[e]
4		–	–	–	–	100	82	82	60[e]
5		–	–	–	–	65	57	88	55[e]
6		100	52	52	32[e]	100	80	80	58[e]
7		100	74	74	33	100	>99	99	64[e]
8		85	70	82	31[e]	86	78	91	58[e]
9		100	100	100	−67[f]	100	100	100	−54[f]
10		100	82	82	+58[g]	100	95	95	+72[g]
11		100	95	95	48	100	>99	>99	53
12		73	65	89	41	84	83	99	48[e]
13		100	72	72	42	97	79	81	41[e]
14		–	–	–	–	100	72	72	49
15		100	79	79	8[e]	100	77	77	6[e]
16		100	55	55	17	100	25	25	13[e]
17		100	71	71	32[e]	100	81	81	30[e]
18		66	56	85	21	79	68	86	28[e]
19		88	77	88	30[h]	100	96	96	60[e][h]
20		–	–	–	–	68	37	54	49[e]
21		100	52	52	13	100	65	65	13[i]
22		100	99	99	68	100	>99	>99	79
23		100	91	91	72	94	91	97	84[e][j]
24		–	–	–	–	100	100	100	10
25		–	–	–	–	100	92	92	52[e]

[a] Reaction conditions: In a 25 mL Schlenk tube, the 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. 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 to this reaction mixture. [b] Determined by comparing with authentic samples on GC-FID. [c] Determined by HPLC and absolute configurations were not determined unless mentioned. [d] (*R*)-(+)-styrene oxide was the major enantiomer. [e] 20 mol% of HOAc was added. [f] (*S*,*S*)-(−)-stilbene oxide was the major enantiomer. [g] (1*R*,2*R*)-(+)-1-Phenyl-1-propene oxide was the major enantiomer. [h] (1*R*,2*S*)-(−)-1-Phenyl-1-propene oxide was the major enantiomer. [i] (*S*)-**2aa** was used as the catalyst. [j] 0 °C, a solution of 50% hydrogen peroxide (51 μL, 0.75 mmol) in *tert*-amyl alcohol (949 μL) was added by a syringe pump.

ities under mild reaction conditions, but **1aa** was more reactive than (*R*)-**2ca** as shown in the conversion of less reactive substrates. However, (*R*)-**2ca** is more selective towards epoxide formation relative to **1aa**. Mono-, *cis*- and *trans*-di-, and trisubstituted olefins have been realized in **1aa** and (*R*)-**2ca** with good to excellent yields and moderate to good *ee*. A tetrasubstituted olefin also showed good reactivity towards epoxidation with good yield and moderate *ee* in the case of (*R*)-**2ca** (Table 4, entry 25). The best results were obtained with *trans*-disubstituted olefins and trisubstituted olefins. It is worth noting that our catalysts have been applied to all six classes of olefins in good yields, in which five of them gave moderate to good *ee* with (*R*)-**2ca.** By the introduction of the new pyboxazine ligands through systematic variation of ligands on **1**, a significant improvement of both chemoselectivity and enantioselectivity have been achieved. Hence, this type of catalyst is complementary to both Mn–salen[10] and chiral ketone[11] epoxidation catalysts in *trans*-disubstituted and monosubstituted olefins, respectively. Apart from different substituted aromatic olefins, functional groups such as amine, ether, halogens, silylether, allylic acetates, and even allylic chloride, could be epoxidized in high yields. However, high *ee*'s have not yet been obtained with 1,1-disubstituted olefins (Table 4, entry 21) and olefins with large substituents (Table 4, entries 21 and 24). Further improvement of the reaction through ligand modification is therefore still in progress.

For a more detailed understanding of this reaction, mechanistic studies were performed. We first addressed the effect of the solvent to this epoxidation reaction. ^{1}H NMR studies of **1na** in different solvents showed that a protic solvent is important to provide a vacant coordination site for the oxidation of the pseudo-octahedral 18-electron ruthenium complex. In $CDCl_3$, **1na** retained its C_2 symmetry in solution, while the *meta*-protons of the 2,6-pyridinedicarboxylate of **1na** splits into two sets of doublets and the *para*-proton into to a doublet of doublets in CD_3OD (Figure 2). However, when only a stoichiometric amount of MeOH (with respect to Ru) was added in the solution of **1na** in $CDCl_3$, no significant change in the ^{1}H NMR spectrum could be observed compared with Figure 2a. This implies that strong coordination of MeOH did not occur and the change of the ^{1}H NMR spectrum could be assigned to a polar solvent favourable equilibrium on the "open"-**1na** (Scheme 4). A closely related ruthenium complex with this "open" form has been reported.[36]

Clearly, all catalytic reactions reported here were started with a Ru^{II} pre-catalyst. However, in the active catalyst the central metal should be in a higher oxidation state. To determine the active species, [Ru(*S*,*S*-Ph_2-pybox)(pydic)] **1aa** was treated with 50% H_2O_2 in the presence and absence of *trans*-β-methylstyrene in *tert*-amyl alcohol in an NMR tube. Unfortunately, only paramagnetic species are observed. UV-visible spectroscopic studies of these reactions showed no isosbestic point in the spectra, indicating that more than one ruthenium complex is formed during the oxidation of **1aa** with H_2O_2. Indeed, when **1aa** was treated with ten equivalents of hydrogen peroxide in *tert*-amyl alcohol, after removal of solvent under reduced pressure, the residue showed molecular ion peaks for [Ru(*S*,*S*-Ph_2-pybox)(pydic)(O)] and [Ru(*S*,*S*-Ph_2-pybox)(pydic)$(O)_2$] along with some undefined peaks in the electrospray ionization mass spectra (ESI-MS). Isolation of the intermediates by crystallization or column chromatography were in vein. Hence, we tried to isolate the intermediate in the lower oxidation state by reacting [Ru(*S*,*S*-Ph_2-pybox)(pydic)] **1aa** with two equivalents of hydrogen peroxide in the presence of an excess of olefin (10 equiv). To our surprise, the ESI-MS of this reaction mixture showed also molecular ion peaks corresponding to [Ru(*S*,*S*-Ph_2-pybox)(pydic)(O)] and [Ru(*S*,*S*-Ph_2-pybox)(pydic)$(O)_2$]. From this mixture we were able to isolate one suspected [Ru(*S*,*S*-Ph_2-pybox)(pydic)(O)] complex in low yield (<10%). The ^{1}H NMR spectrum of this complex showed diamagnetic behaviour and is not explainable. The other complex was found to be unstable.

Next, the suspected [Ru(*S*,*S*-Ph_2-pybox)(pydic)(O)] was treated with *trans*-β-methylstyrene in *tert*-amyl alcohol at

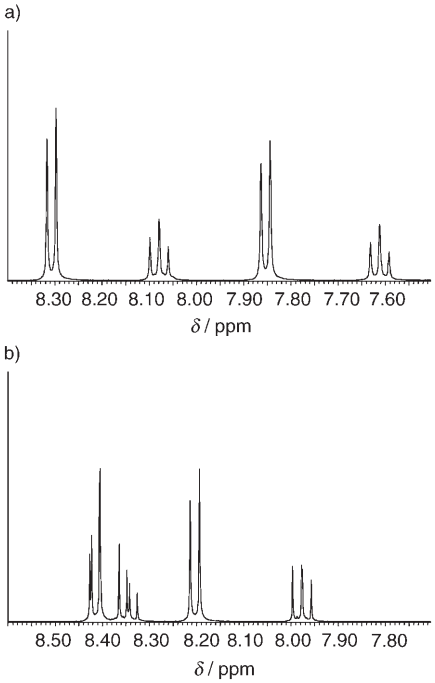
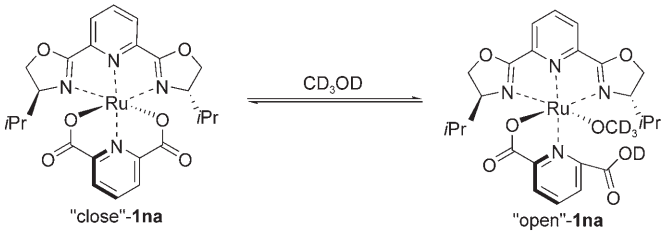
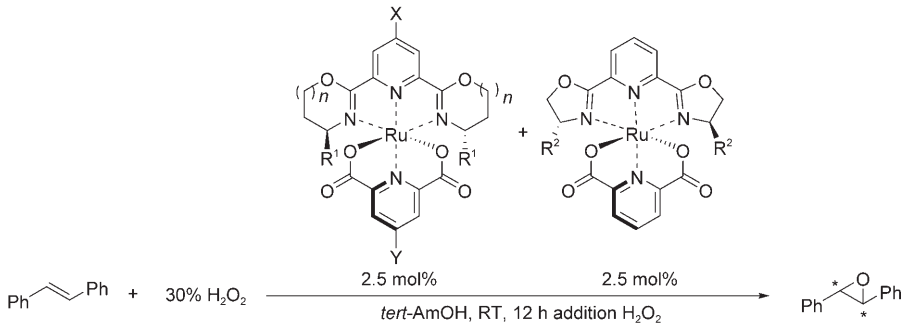


Figure 2. ^{1}H NMR spectra of **1na** a) in $CDCl_3$ and b) in CD_3OD.



Scheme 4. Proposed equilibrium between "close"-**1na** and "open"-**1na** in CD_3OD.

room temperature. Here, no oxygen transfer to the olefin is observed! This suggests that the [Ru(*S*,*S*-Ph_2-pybox)-(pydic)(O)] is not an active catalyst, but could be an intermediate in lower oxidation state. This assumption has been proven in a catalytic reaction of the [Ru(*S*,*S*-Ph_2-pybox)(pydic)(O)] with olefin (*trans*-β-methylstyrene) with hydrogen peroxide under standard reaction conditions and resulted in 100% conversion and 98% yield of the epoxide. However, compared with the original catalyst **1aa** (58% *ee*), a significantly lower enantioselectivity (19% *ee*) was obtained for *trans*-β-methylstyrene oxide. Thus, it is clear that the reaction pathway through this intermediate is not responsible for the major reaction and there should be at least two reaction pathways that give different enantioselectivity. So far we believe that the "[Ru(*S*,*S*-Ph_2-pybox)(pydic)(O)]" is a mixture of ligand-oxidized ruthenium(II) complexes (see modeling studies below).



Scheme 5. Competitive epoxidations of *trans*-stilbene with 30% H_2O_2.

As the active intermediates could not be isolated, we turned our interest to kinetic methods to probe the transition state of this reaction. There are some special features that standard kinetic techniques could not be easily applied to our epoxidation protocol.[37] Firstly, the rate of reaction depends on the amount of water in the reaction mixture.[29e] The rate of water production correlates not only with the olefin consumption with respect to a certain catalyst, but also the rate of H_2O_2 decomposition to oxygen by the catalyst. We solved this problem in the catalytic reaction by limiting the rate of addition of H_2O_2 with a syringe pump and this proved to be applicable. However, under these conditions the dosage of H_2O_2 turned out to be the limiting factor of the reaction rate. Moreover, high concentrations of H_2O_2 were counterproductive for epoxide formation and decomposition of the catalyst occurred. By using spectroscopic techniques such as UV-visible and NMR spectroscopy it was not possible to quantify the amount of the catalyst in the reaction mixture (vide supra). In spite of all these problems, we were able to establish a relative rate scale of our catalysts with the aid of catalyst competitive reactions.

We first confirmed that the *ee* of *trans*-stilbene oxide by epoxidation of *trans*-stilbene with 30% H_2O_2 was directly proportional to the optical purity of catalyst **1aa**. This suggests that a monomeric catalytic center dominates in the epoxidation of *trans*-stilbene.[38] Then, the relative activity of a given catalyst was determined by the *ee* of *trans*-stilbene oxide in the model catalytic reaction with this catalyst and the opposite isomer of **1aa** (Scheme 5). The relative activities of catalysts are shown in Table 5. In general, all the catalysts have activities within the same order of magnitude. Functional groups with different electronic properties on the *para*-position of "pydic" side show a more pronounced

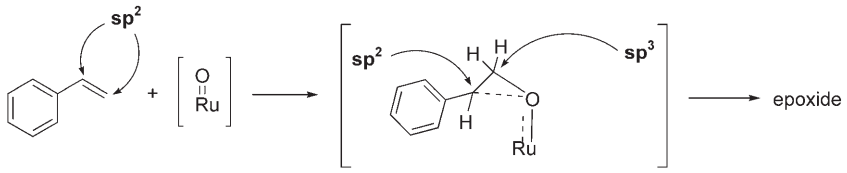
Table 5. Relative activity of [Ru(pybox)(pydic)] **1** and [Ru(pyboxazine)-(pydic)] **2**.

Entry	Catalyst	*n*	R^1	X	Y	Relative activity
1	**1aa**	0	Ph	H	H	1.00
2	**1ab**	0	Ph	H	OH	0.83
3	**1ac**	0	Ph	H	Cl	1.31
4	**1ad**	0	Ph	H	Br	1.41
5	**1ae**	0	Ph	H	MeO	1.01
6	**1af**	0	Ph	H	Ph	1.09
7	**1ba**	0	Ph	Cl	H	1.14
8	**1na**	0	*i*Pr	H	H	0.82
9	**2aa**	1	Ph	H	H	0.87
10	**2ba**	1	1-Np	H	H	2.00
11	**2ca**	1	2-Np	H	H	0.92
12	**2fa**	1	*i*Pr	H	H	0.93

effect to the activity (Table 5, entries 1–6). Normally, the faster the reaction, the higher the *ee* of stilbene oxide was, at least partially due to the effect of water content.[29e] It may also be attributed to electronic effects on the asymmetric induction.[39] A similar trend has been observed in a ruthenium–porphyrin-catalyzed asymmetric epoxidation with 2,6-dichloropyridine *N*-oxide.[17a] However, the trend observed here is reversed with respect to the well-known Mn–salen system, in which ligands with electron-deficient groups gave a higher *ee*.[39c]

Next, we evaluated the transition state by competitive epoxidations of styrene, α-deuteriostyrene, and β-dideuteriostyrene with H_2O_2 in the presence of **1aa**. An inverse secondary kinetic isotope effect (KIE) is observed for the β-olefinic carbon atom ($k_D/k_H = 0.87$), while the α-olefinic carbon atom showed no KIE ($k_D/k_H = 1.00$).[40] The observed values fall in good agreement with a nonsymmetric transition state and imply that C–O bond formation is more advanced at the β-carbon atom (sp^2 to sp^3) than the α-carbon atom (sp^2 to sp^2; Scheme 6).

Further investigation of competitive reactions of styrenes with electron-releasing or electron-withdrawing substituents revealed that the relative rates of the formation of styrene oxides catalyzed by **1aa** correlated with the Hammett σ^+ parameter (Figure 3).[41] This is contrary to the Hammett $\log k_{rel}$ versus $(\rho_{mb}\sigma_{mb}+\rho_{jj}^{\cdot}\sigma_{jj}^{\cdot})$ in $[Ru^{VI}(por)O_2]$ (H_2por = porphyrin),[39e,42] but coincides with $[Fe^{IV}(TMP^{\cdot+})O]$ (H_2TMP =



Scheme 6. Inverse secondary KIE for the epoxidation of styrene.

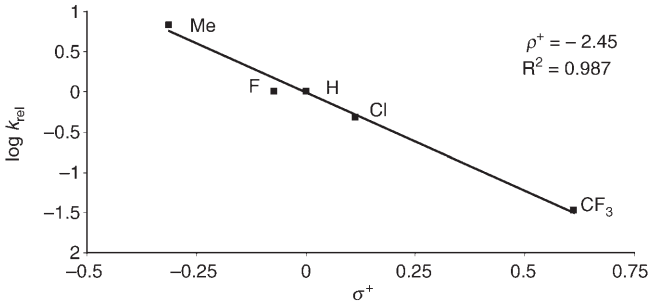


Figure 3. Hammett σ^+ correlation for the **1aa**-catalyzed epoxidation of *para*-substituted styrenes.

tetramesitylporphyrin),[43] $[Cr^{V}(Br_8TPP)(O)X]$ (H_2TPP = tetraphenylporphyrin),[44] and $[Ru^{VI}(N_4)O_2]^{2+}$ (N_4 = macrocyclic tertiary amines) complexes.[45] The ρ^+ (−2.45) found here is consistent with an initial charge transfer from the metal center. However, there was no KIE observed in the reported case.[43] Other electrophilic addition to styrenes showed even larger values of ρ^+ (−3.5 to −4.1).[46] It is worth noting that the σ^+ values also correlate well with radical type reactions when the polar effect dominates the spin effect or the radical coordinates to the metal center or metal ion.[47]

Because isolation of active catalyst species was unsuccessful we also performed modeling studies of potential intermediates. On the basis of the core structures of the pre-catalysts, there are several possibilities of the active catalyst for the oxygen-transfer reaction. The three thermodynamically most stable structures are shown in Figure 4. The first two are oxidation of pybox and pydic ligands by yielding new -NO (**C**) and -COOO (**A**) ligands, and the third one is the direct oxidation of metal center with the formation of Ru=O bond (**B**). The optimized structures are shown in Figure 4. At the B3LYP/LANL2DZ density functional level of theory, all four optimized structures are found to be energy minima on the potential-energy surface. Interestingly, structure **C** is the most stable oxidation product, while both **A** and **B** are higher in energy by ~20 kcal mol^{-1}. It should also be noted that **A** and **B** are close in energy (~0.3 kcal mol^{-1}).

Following the most popular oxidation reaction mechanism and our observed secondary kinetic isotope effect, it is most likely that structure **B** should be the active catalyst for epoxidation.[39c,e] Hence, we propose that the pre-catalysts in our catalytic reactions are initially oxidized to the Ru^{III} species **C**. This most stable complex **C** will isomerize subsequently into structure **B** by breaking the N–O bond. In structure **B**, the ruthenium center has a distorted octahedral conformation, and the oxazoline ring rotates away from the Ru=O group allowing thereby for further interaction of the upcoming olefin with the Ru=O bond. This proposal is further supported by the previously discussed ESI-MS studies, which showed that different [Ru(*S*,*S*-Ph_2-pybox)(pydic)(O)] complexes are present in the reaction mixture. In this context it is worth noting that the related ruthenium(II) complex [Ru(terpyridine)-(pydic)] oxidizes easily in solution to give a paramagnetic Ru^{III} species.[48] Also in NMR experiments **1** and **2** gave rise to paramagnetic metal complexes.

Regarding the origin of the enantioselectivity we believe that π–π interactions between the ligand and the substrate are the dominating factor for the asymmetric induction.[49] This is clearly shown in the epoxidations of styrene in the presence of [Ru{*S*,*S*-(*p*-$ClC_6H_4)_2$-pyboxazine}(pydic)] ((*S*)-**2da**) and [Ru{*S*,*S*-(*p*-$MeOC_6H_4)_2$-pyboxazine}(pydic)] ((*S*)-**2ea**) as catalysts (Table 2, entries 7 and 8). As the absolute configurations of styrene oxide and *trans*-stilbene oxide for **1aa** are *R* and *S* respectively, the major π–π interaction between the ligand and the substrate should be in different ge-

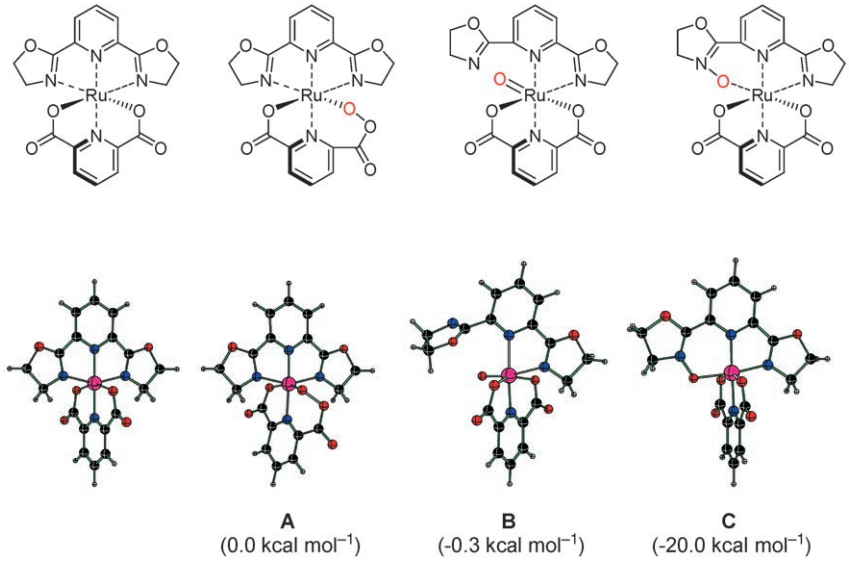


Figure 4. B3LYP/LANL2DZ structures and relative energies.

ometry in these cases. Further mechanistic studies on the asymmetric induction are under investigation.

In summary, a general ruthenium-catalyzed asymmetric epoxidation procedure of olefins with hydrogen peroxide has been developed. For the first time high yield and chemoselectivity have been obtained for all six classes of olefins by using hydrogen peroxide as oxidant. Enantioselectivities (typically in between 50–80%) up to 84% were observed by applying different aromatic olefins. It is worth noting that the usage of two different ligands significantly simplifies structural variations on the catalyst electronically and sterically. Mechanistic studies were performed experimentally and theoretically with high-level density functional theory calculations. Inverse secondary KIE suggested a nonsymmetric C–O bond formation, while the Hammett σ^+ relation showed the possibility of a charge-transfer complex or coordination of the respective radical. More insight into the nature of the active catalyst was revealed by DFT calculations. Instead of the normal preception of a metal–oxo complex perpendicular to the chiral C_2 pybox(azine) as in the case of *N*,*N*,*N*,*N*-porphyrin, a novel *N*-oxide type intermediate parallel to the pybox(azine) is suggested. Through the systematic catalyst variation, mechanistic studies, and calculations, a new generation of asymmetric epoxidation catalysts are under development.

Experimental Section

General procedure for asymmetric epoxidation with hydrogen peroxide: In a 25 mL Schlenk tube, the 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. 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 through a syringe pump to this reaction mixture. 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 aqueous Na_2SO_3 solution (~10 mL), extracted with dichloromethane (10 mL×2), and washed with water (~20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude epoxides. It was then dissolved in *n*-hexane for HPLC measurement.

General procedure for catalyst competitive asymmetric epoxidation with hydrogen peroxide: In a 25 mL Schlenk tube, catalyst A (0.0125 mmol) and the opposite isomer of **1aa** (0.0125 mmol) were stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. *trans*-Stilbene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added. 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 through a syringe pump to this reaction mixture. 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 aqueous Na_2SO_3 solution (~10 mL), extracted with dichloromethane (10 mL×2), and washed with water (~20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude epoxides. It was then dissolved in *n*-hexane for HPLC measurement.

General procedure for *para*-substituted styrene competitive asymmetric epoxidation with hydrogen peroxide: In a 25 mL Schlenk tube, **1aa** (0.025 mmol) was stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. Styrene (0.5 mmol), *p*-methylstyrene (0.5 mmol), and dodecane (GC internal standard, 100 μL) were added. A solution of 30% hydrogen peroxide (57 μL, 0.5 mmol) in *tert*-amyl alcohol (276 μL) was added over a period of 12 h through a syringe pump to this reaction mixture. After the addition, aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion data.

General procedure for deuterated styrene competitive asymmetric epoxidation with hydrogen peroxide: In a 25 mL Schlenk tube, **1aa** (0.025 mmol) was stirred at room temperature in *tert*-amyl alcohol (9 mL) for 10 min. Styrene (2.5 mmol), β-[D_2]styrene (2.5 mmol), and dodecane (GC internal standard, 100 μL) were added. A solution of 30% hydrogen peroxide (57 μL, 0.5 mmol) in *tert*-amyl alcohol (276 μL) was added over a period of 12 h through a syringe pump to this reaction mixture. 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 aqueous Na_2SO_3 solution (~10 mL), extracted with dichloromethane (10 mL×2), and washed with water (~20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude epoxides. These were then subjected to chromatography on silica gel (70–230 mesh, neutralized with 1% Et_3N) with hexane to hexane/ethyl acetate 100:3 as the gradient eluent. The selectivity was determined by ^{1}H NMR spectroscopy.

Phenyloxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=2.72 (dd, J=5.6, 2.6 Hz, 1H), 3.06 (dd, J=5.6, 4.2 Hz, 1H), 3.78 (dd, J=4.2, 2.6 Hz, 1H), 7.16–7.29 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=51.3, 52.5, 125.6, 128.3, 128.6, 137.7 ppm; MS (EI, 70 eV): *m*/*z* (%): 120 (41) $[M]^+$, 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^{-1}): t_R=6.27, 7.13 min.

4-Chlorophenyloxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=2.68 (dd, J=5.6, 2.6 Hz, 1H), 3.07 (dd, J=5.6, 4.0 Hz, 1H), 3.76 (dd, J=4.0, 2.6 Hz, 1H), 7.12–7.26 ppm (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=51.4, 51.9, 127.0, 128.8, 134.1, 136.3 ppm; MS (EI, 70 eV): *m*/*z* (%): 156 (9) $[M+2]^+$, 155 (10) $[M+1]^+$, 154 (28) $[M]^+$, 153 (23) $[M-1]^+$, 125 (53), 119 (74), 89 (106); HPLC (Chiralcel OB-H, hexane, flow rate 1.0 mL min^{-1}): t_R=14.47, 17.18 min.

4-Fluorophenyloxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=2.67 (dd, J=5.6, 2.6 Hz, 1H), 3.04 (dd, J=5.6, 4.0 Hz, 1H), 3.75 (dd, J=4.0, 2.6 Hz, 1H), 6.91- 6.96 (m, 2H), 7.12–7.17 ppm (m, 2H), ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=51.6, 52.2, 115.9 (d, J=20 Hz), 127.6 (d, J=7 Hz), 133.7 (d, J=2 Hz), 163.1 ppm (d, J=24 Hz); MS (EI, 70 eV): *m*/*z* (%): 138 (34) $[M]^+$, 137 (48) $[M-1]^+$, 122 (86), 109 (100), 96 (31); HPLC (Chiralcel AD-151, hexane/EtOH, 99:1, flow rate 1.1 mL min^{-1}): t_R=15.31, 18.08 min.

(4-Trifluoromethyl)phenyloxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=2.77 (dd, J=5.6, 2.6 Hz, 1H), 3.19 (dd, J=5.6, 4.0 Hz, 1H), 3.92 (dd, J=4.0, 2.6 Hz, 1H), 7.4 (d, J=8.1 Hz, 2H), 7.6 ppm (d, J=8.1 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=51.4, 51.6, 125.4 (q, J=3.8 Hz), 125.9, 141.9 ppm; MS (EI, 70 eV): *m*/*z* (%): 188 (14) $[M]^+$, 187 (20), 159 (49), 158 (48), 119 (100), 91 (37); HPLC (Chiralcel AD-151, hexane, flow rate 0.5 mL min^{-1}): t_R=12.30, 13.40 min.

2-(*p*-Tolyl)oxirane: ^{1}H NMR (400.1 MHz, CD_2Cl_2): δ=2.33 (s, 3H), 2.77 (dd, J=5.5, 2.6 Hz, 1H), 3.09, (dd, J=5.5, 4.1 Hz, 1H), 3.79, (dd, J=4.1, 2.6 Hz, 1H), 7.06–7.26 ppm (m, 5H); ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ=20.9, 50.9, 52.1, 125.5, 129.2, 134.8, 138.1 ppm; GC-MS: *m*/*z*: 134 $[M]^+$; HPLC (Chiralpak AD-H, hexane/EtOH, 99.95:0.05, flow rate 1.5 mL min^{-1}): t_R=4.53, 4.79 min.

2-(*o*-Tolyl)oxirane: ^{1}H NMR (400.1 MHz, CD_2Cl_2): δ=7.14–7.22 (m, 4H), 3.98 (dd, J=3.97, 2.58 Hz, 1H), 3.13 (dd, J=5.75, 3.97 Hz, 1H), 2.65 (dd, J=5.75, 2.58 Hz, 1H), 2.42 ppm (s, 3H); ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ=136.4, 136.2, 129.8, 127.6, 126, 124, 50.3, 50.1 ppm; MS (EI, 70 eV): *m*/*z* (%): 134 (53) $[M]^+$, 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^{-1}): t_R=16.70, 19.84 min.

2-(2-Chlorophenyl)oxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=2.67 (dd, J=5.6, 2.6 Hz, 1H), 3.20 (dd, J=5.6, 4.1 Hz, 1H), 3.20 (dd, J=4.1, 2.6 Hz, 1H), 7.21–7.28 (m, 3H), 7.35–7.38 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=50.00, 50.68, 125.64, 127.03, 128.88, 129.10, 133.24, 135.56 ppm; MS (EI, 70 eV): *m*/*z*: 154 $[M]^+$; HPLC (Chiralpak

AD-H [126], hexane/EtOH, 99.95:0.05, flow rate 0.5 mL min^{-1}): t_R = 12.49, 13.18 min.

***trans*-2,3-Diphenyloxirane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.24–7.31 (m, 10H), 3.87 ppm (s, 2H); ^{13}C NMR (100.6, MHz, $CDCl_3$): δ = 137.1, 128.6, 128.6, 125.5, 62.8 ppm; MS (EI, 70 eV): *m*/*z* (%): 197 (18) $[M+1]^+$, 196 (100) $[M]^+$, 195 (72), 178 (28), 167 (85), 90 (66), 89 (65); HPLC (Chiralcel OD-H, hexane/EtOH, 98:2, flow rate 0.5 mL min^{-1}): t_R = 14.10 (2*S*,3*S*), 4.79 min (2*R*,3*R*).

***trans*-2-Methyl-3-phenyloxirane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 5.2 Hz, 3H), 3.03 (dq, *J* = 5.2, 2.0 Hz, 1H), 3.57 (d, *J* = 2.0 Hz, 1H), 7.23–7.4 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.0, 59.2, 59.6, 125.7, 128.1, 128.5, 137.9 ppm; MS (EI, 70 eV): *m*/*z* (%): 134 (52) $[M]^+$, 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^{-1}): t_R = 11.90 (2*S*,3*S*), 13.48 min (2*R*,3*R*).

***trans*-2-(*p*-methoxyphenyl)-3-methyloxirane:** ^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.41 (d, *J* = 5.2 Hz, 3H), 3.01 (qd, *J* = 5.2, 2.0 Hz, 1H), 3.50 (d, *J* = 2.0 Hz, 1H), 3.79 (s, 3H), 6.87 (d, *J* = 8.9 Hz, 2H), 7.17 ppm (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ = 18.0, 58.9, 59.5, 114.1, 127.2, 130.3, 160.0 ppm; MS (EI, 70 eV): *m*/*z* (%): 165 (7) $[M+1]^+$, 164 (57) $[M]^+$, 121 (47), 120 (82), 105 (31), 91 (100), 77 (55), 51 (37); HPLC (Chiralpak AD-H, hexane/EtOH, 99.95:0.05, flow rate 1.5 mL min^{-1}): t_R = 16.70, 19.84 min.

***trans*-3-Phenyloxiranylmethyl acetate:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 3.18–3.20 (m, 1H), 3.73 (d, *J* = 2.0 Hz, 1H), 4.02 (dd, *J* = 12.3, 6.0 Hz, 1H), 4.41 (dd, *J* = 12.3, 3.4 Hz, 1H), 7.17–7.32 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.7, 56.4, 59.2, 64.2, 125.6, 128.4, 128.5, 136.1, 170.7 ppm; MS (EI, 70 eV): *m*/*z* (%): 192 (2) $[M]^+$, 150 (10), 149 (79), 133 (26), 107 (95), 105 (67), 91 (54), 90 (45), 89 (42), 79 (31), 77 (31), 43 (100); HPLC (Chiralcel OD-H, hexane/EtOH, 95:5, flow rate 1.0 mL min^{-1}): t_R = 4.64, 5.88 min.

***trans*-2-[(*tert*-Butyldimethylsiloxy)methyl]-3-phenyloxirane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 3.12–3.13 (ddd, *J* = 4.4, 2.8, 1.9 Hz, 1H), 3.79 (d, *J* = 1.9 Hz, 1H), 3.81 (dd, J = 12.0, 4.4 Hz, 1H), 3.95 (dd, J = 12.0, 2.8 Hz, 1H), 7.24–7.35 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = −5.3, 18.4, 25.9, 55.9, 62.7, 64.0, 125.7, 128.1, 128.4, 137.2 ppm; MS (EI, 70 eV): *m*/*z*: 249 $[M-CH_3]^+$; HPLC (Whelk01 [R,R], hexane/2-propanol, 99:1, flow rate 0.5 mL min^{-1}): t_R = 6.30, 8.19 min.

***trans*-2-Methoxymethyl-3-phenyloxirane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.19 (ddd, *J* = 5.2, 3.1, 2.1 Hz, 1H), 3.43 (s, 3H), 3.52 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.76 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.78 (d, *J* = 2.1 Hz, 1H), 7.25–7.35 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.7, 59.2, 60.9, 72.1, 125.6, 128.2, 128.4, 136.8 ppm; MS (EI, 70 eV): *m*/*z*: 164 $[M]^+$; HPLC (Chiralcel OD-H, hexane/EtOH, 98:2, flow rate 1.0 mL min^{-1}): t_R = 4.53, 5.53 min.

***trans*-2-Phenoxymethyl-3-phenyloxirane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.40 (ddd, *J* = 5.2, 3.2, 2.0 Hz, 1H), 3.91, (d, *J* = 2.0 Hz, 1H), 4.14 (dd, *J* = 11.2, 5.2 Hz, 1H), 4.32 (dd, *J* = 11.2, 3.2 Hz, 1H), 6.94–7.00 (m, 3H), 7.27–7.38 ppm (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 56.4, 60.2, 67.8, 114.7, 121.3, 125.7, 128.4, 128.5, 129.5, 136.5, 158.4 ppm; MS (EI, 70 eV): *m*/*z*: 226 $[M]^+$; HPLC (Chiralcel OD-H, hexane/EtOH, 98:2, flow rate 1.0 mL min^{-1}): t_R = 5.98, 6.89 min.

***trans*-2-(3-Phenyloxiranyl)-[1,3]dioxolane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.13 (dd, *J* = 3.8, 2.0 Hz, 1H), 3.89 (d, *J* = 2.0 Hz, 1H), 3.89–3.97 (m, 2H), 4.00–4.06 (m, 2H), 5.00 (d, *J* = 3.8, 1H), 7.25–7.35 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.2, 61.3, 65.3, 65.5, 102.3, 125.7, 128.3, 128.4, 136.2 ppm; GC-MS: *m*/*z*: 192 $[M]^+$; HPLC (Chiralpak AD-H, hexane/EtOH, 95:5, flow rate 1.0 mL min^{-1}): t_R = 25.57, 28.44 min.

4-Methyl-*N*-(*trans*-3-phenyl-oxiranylmethyl)benzenesulfonamide: M.p. 128–131 °C; R_f = 0.23 (hexane/ethyl acetate = 3:1); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 3.10 (ddd, *J* = 4.6, 3.4, 2.0 Hz, 1H), 3.23 (ddd, *J* = 14.1, 6.8, 4.6 Hz, 1H), 3.38 (ddd, *J* = 14.1, 6.0, 3.4 Hz, 1H), 3.74 (d, *J* = 2.0 Hz, 1H), 4.82 (unresolved dd, 1H), 7.14–7.17 (m, 2H), 7.28–7.31 (m, 5H), 7.74 ppm (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100.6 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 ppm; MS (EI, 70 eV): *m*/*z*: 303 $[M]^+$; HRMS calcd for $C_{16}H_{17}NO_3S$: 303.09293; found: 303.09398; HPLC (Whelk01 [*R*,*R*], hexane/EtOH, 90:10, flow rate 1.0 mL min^{-1}): t_R = 10.01, 11.38 min.

***trans*-2-Chloromethyl-3-phenyloxirane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.28 (ddd, *J* = 5.8, 4.8, 1.9 Hz, 1H), 3.66 (dd, *J* = 11.8, 5.8 Hz, 1H), 3.72 (dd, *J* = 11.8, 4.8, Hz, 1H), 3.82 (d, *J* = 1.9 Hz, 1H), 7.26–7.38 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 44.3, 58.5, 60.9, 116.6, 125.6, 128.6, 135.9 ppm; GC-MS: *m*/*z*: 168 $[M]^+$; HPLC (Chiralpak AD-H, hexane/EtOH, 95:5, flow rate 1.0 mL min^{-1}): t_R = 7.62, 9.09 min.

***cis*-2-Methyl-3-phenyloxirane:** ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 5.4 Hz, 3H), 3.33 (dd, *J* = 5.4, 4.3 Hz, 1H), 4.05 (d, *J* = 4.3 Hz, 1H), 7.25–7.36 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.5, 55.1, 57.5, 126.5, 127.4, 128.0, 135.5 ppm; MS (EI, 70 eV): *m*/*z*: 134 $[M]^+$; HPLC (Chiralcel OD-H, hexane/EtOH, 99.95:0.05, flow rate 1.0 mL min^{-1}): t_R = 11.64 (2*S*,3*R*), 15.56 min (2*R*,3*S*).

3-Phenyl-allyl ester of acetic acid: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 4.83 (dd, *J* = 6.6, 1.7 Hz, 2H), 5.80 (dt, *J* = 11.8, 6.6 Hz, 1H), 6.65 (d, *J* = 11.8 Hz, 1H), 7.20–7.22 (m, 2H), 7.24–7.28 (m, 1H), 7.32–7.36 ppm (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.94, 61.47, 125.75, 127.50, 128.36, 128.69, 132.95, 135.99, 170.88 ppm; MS (EI, 70 eV): *m*/*z*: 176 $[M]^+$.

2-Methyl-2-phenyloxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.65 (s, 3H), 2.73 (d, *J* = 5.4 Hz, 1H), 2.90 (d, *J* = 5.4 Hz, 1H), 7.17–7.31 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 56.9, 57.2, 125.4, 127.6, 128.5, 141.3 ppm; MS (EI, 70 eV): *m*/*z* (%): 134 (35) $[M]^+$, 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^{-1}): t_R = 9.78, 12.77 min.

2-Phenyl-1-oxaspiro[2.5]octane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.22–1.31 (m, 2H), 1.37–1.85 (m, 8H), 3.85 (s, 1H), 7.23–7.34 ppm (m, 5H); ^{13}C NMR (100.6 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 ppm; MS (EI, 70 eV): *m*/*z*: 188 $[M]^+$; HPLC (Chiralpak AD-H, hexane/EtOH, 90:10, flow rate 1.0 mL min^{-1}): t_R = 4.34, 4.72 min.

2,2-Dimethyl-3-phenyloxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.04 (s, 3H), 1.45 (s, 3H), 3.83 (s, 1H), 7.21–7.33 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.9, 24.7, 61.0, 64.5, 126.3, 127.3, 128, 136.6 ppm; MS (EI, 70 eV): *m*/*z* (%): 148 $[M]^+$; HPLC (Chiralcel OD-H, hexane/EtOH, 99.95:0.05, flow rate 0.5 mL min^{-1}): t_R = 11.78 (3*S*), 18.63 min (3*R*).

2-Methyl-2,3-diphenyloxirane: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.48 (s, 3H), 3.98 (s, 1H), 7.30–7.34 (m, 2H), 7.37–7.42 (m, 6H), 7.45–7.48 ppm (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.7, 63.0, 67.1, 125.1, 126.5, 127.5, 127.6, 128.2, 128.4, 135.9, 142.3 ppm; MS (EI, 70 eV): *m*/*z*: 210 $[M]^+$; HPLC (Whelk 0.1 [*R*,*R*], hexane/EtOH, 99:1, flow rate 0.6 mL min^{-1}): t_R = 5.33, 5.97 min.

2,2,3-Trimethyl-3-phenyloxiranе: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.95 (s, 3H), 1.46 (s, 3H), 1.61 (s, 3H), 7.20–7.23 (m, 1H), 7.27–7.33 ppm (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.7, 21.3, 21.7, 63.7, 66.5, 126.0, 126.7, 128.0, 142.2 ppm; MS (EI, 70 eV): *m*/*z*: 162 $[M]^+$; HPLC (Chiralpak AD-H, hexane, flow rate 1.0 mL min^{-1}): t_R = 6.23, 6.74 min.

Computation: All calculations were carried out by using the Gaussian 98 program.[50] All structures were optimized at B3LYP density functional level of theory with the LANL2DZ[51] basis set, and characterized as energy minimum structures without imaginary number of frequencies at the same level of theory (B3LYP/LANL2DZ).[52]

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