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C_1-Symmetric Versus C_2-Symmetric Ligands in Enantioselective Copper–Bis(oxazoline)-Catalyzed Cyclopropanation Reactions

José M Fraile,[a] José I. García,*[a] Anja Gissibl,[b] José A. Mayoral,[a] Elísabet Pires,[a] Oliver Reiser,[b] Marta Roldán,[a] and Isabel Villalba[a]

Abstract: A thorough experimental and theoretical study of the enantioselective cyclopropanation of alkenes catalyzed by chiral bis(oxazoline)– and azabis(oxazoline)–copper complexes, which comprise a new family of ligands that lack C_2 symmetry, has been conducted. Surprisingly high enantioselectivities were observed with some of these ligands, which were rationalized on the basis of molecular modeling studies. The course of the asymmetric induction in connection with ligand symmetry and the implications for supported enantioselective catalysts are discussed.

Keywords: asymmetric catalysis · bis(oxazolines) · computational mechanistic models · copper · cyclopropanation

Introduction

Enantioselective homogeneous catalysis is one of the most efficient ways of introducing asymmetry in organic synthesis.[1] Although there are some significant exceptions,[2] C_2-symmetric ligands are usually preferred over C_1-symmetric (which are asymmetric in the sense that they lack any symmetry elements) ligands for catalytic enantioselective transformations. Those C_1-symmetric ligands that are successful in catalytic applications are generally both electronically and sterically asymmetric, for instance, salicylaldimines[2a] and phosphinooxazolines (Figure 1).[2b] There are evident advantages in using C_2-symmetric ligands: Arguably most importantly, fewer reaction channels are possible for the reaction, which simplifies the prediction of chiral induction. Furthermore, the synthesis of the ligands is often simpler.

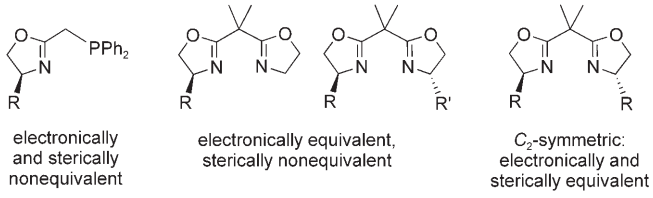

Figure 1. Some examples of chiral ligands based on the oxazoline motif with different degrees of electronic and steric asymmetry.

Oxazoline-based ligands, such as bis(oxazoline) (Box), azabis(oxazoline) (azaBox) and pyridinebis(oxazoline) (Pybox) ligands, have attracted much attention because they have been successfully used in many different enantioselective organic reactions.[3] In the vast majority of cases all of these ligands display C_2 symmetry. Given that all of these ligands have two electronically and sterically equivalent coordinating centers, there exists the possibility of modifying the steric surroundings in the proximity of one of these centers, thus leading to electronically equivalent, but sterically different coordinating points. These ligands would be "halfway" between the above-mentioned C_1-symmetric ligands and the usual C_2-symmetric ligands. Some illustrative examples based on the oxazoline motif are shown in Figure 1.

In general, in those cases in which C_2-symmetric ligands lead to good enantioselectivities, by using sterically nonequivalent but electronically equivalent (e.g., in the sense of a close similarity of the coordinating groups), analogues results in a dramatic worsening of the results. Analogously, the use of an asymmetric pyridine–oxazoline in the copper-

[a] Dr. J. M. Fraile, Prof. Dr. J. I. García, Prof. Dr. J. A. Mayoral, Dr. E. Pires, M. Roldán, I. Villalba
Departamento de Química Orgánica, ICMA
CSIC-Universidad de Zaragoza and IUCH
Universidad de Zaragoza
Pedro Cerbuna 12
50009 Zaragoza (Spain)
Fax: (+34) 976-762-077
E-mail: jig@unizar.es

[b] Dr. A. Gissibl, Prof. Dr. O. Reiser
Institut für Organische Chemie der Universität Regensburg
Universitätsstrasse 31, 93040 Regensburg (Germany)

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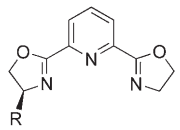
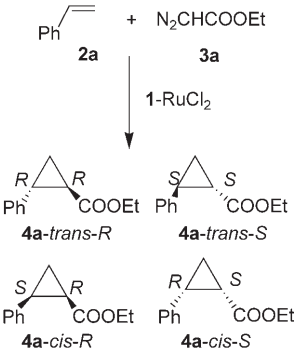


1a: R = *i*Pr
1b: R = *t*Bu

Figure 2. Structures of the Nishiyama asymmetric pybox ligands.

catalyzed cyclopropanation reaction of styrene with ethyl diazoacetate leads to virtually racemic products.[4] Similar observations have also been described for chiral unsymmetrical 2,2′-bipyridyl ligands in the same reaction.[5] However, there is at least one case in which the use of sterically nonequivalent ligands results in enantioselectivities that are comparable to those obtained with the corresponding C_2-symmetric analogues, namely, the so-called single-chiral Pybox ligands described by Nishiyama et al. (Figure 2).[6]

When these ligands are used in the ruthenium-catalyzed cyclopropanation reaction of styrene with alkyl diazoacetates (Scheme 1), very good enantioselectivities are obtained for the *trans*-cyclopropanes (up to 94% *ee*).[6]



Scheme 1. A typical cyclopropanation reaction.

We have recently studied this system from a theoretical point of view, and we have shown that the existence of two highly disfavored reaction channels out of a possible eight is sufficient to explain the unexpectedly high enantioselectivity observed.[7]

The aim of the work reported herein was to explore the enantioselection mechanisms in connection with ligand symmetry, which bears in mind the fact that the possibility of obtaining good enantioselectivities with electronically equivalent, but sterically nonequivalent, ligands would open the door to new strategies for supported chiral catalysts. For our study we chose chiral bis(oxazolines) (Box), a class of ligand that has been recognized as of the utmost importance in asymmetric catalysis. To expand the scope of these ligands, which have been applied almost exclusively in their C_2-symmetric versions to date, a thorough experimental and theoretical study has been carried out by using a completely new family of chiral C_1-symmetric Box ligands.

Results and Discussion

Computational methods: All QM calculations were carried out by using the B3LYP hybrid functional[8] because of the satisfactory performance of this technique in relation to the chemistry of transition metals,[9] particularly in the systems studied in this work.[10] Full geometrical optimizations using the 6-31G(d) basis set were carried out with the Gaussian 03 package.[11] Analytical frequencies were calculated at the same level as that used for the geometry optimizations and the nature of the stationary points was determined in each case according to the appropriate number of negative eigenvalues of the Hessian matrix. Scaled frequencies were not considered in full QM calculations because significant errors in the calculated thermodynamic properties are not found at this theoretical level.[12] Unless otherwise stated, only E_0+ ZPE energies (ZPE: zero-point energy) were used to discuss the relative stabilities of the chemical structures considered. Electronic energies, enthalpies, and Gibbs free energies of the different conformations of all the structures considered are available in the Supporting Information.

Experimental catalysis results: Figure 3 shows the structures of the asymmetric ligands used in the catalytic experiments. We have recently described a general method for the synthesis of C_1-symmetric bis(oxazoline) (Box) ligands[13] in connection with their possible use in supported asymmetric catalysis. Moreover, a strategy to synthesize a C_1-symmetric azabis(oxazoline) (azaBox) ligand has previously been described.[14] Following these strategies, the unsymmetrical ligands **5a–j** were synthesized. For comparison with the usual C_2-symmetric Box ligands, we included Box ligands in which one sterically demanding substituent was missing (**5a–c,g**), two different substituents were present that gave pseudo-C_2-symmetric-type ligands **5d–f**, and in which one side of the Box ligand was sterically blocked by introducing an achiral (**5h**) or chiral (**5i,j**) quaternary center. Some of the corresponding C_2-symmetric ligands have also been included in the study and are labeled with an additional "s" letter, for instance, **5as** for PhBox, **5bs** for IndanylBox, and **5cs** for *t*BuBox.

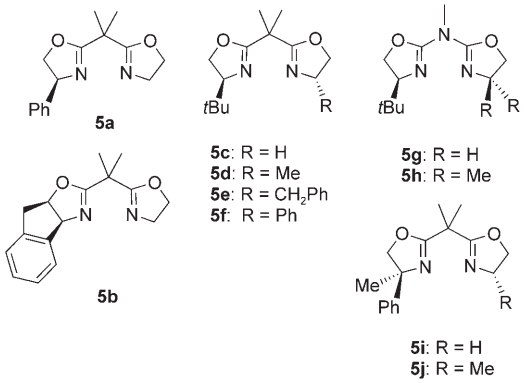


Figure 3. Structures of the asymmetric Box and azaBox ligands used in the catalytic experiments.

The benchmark reaction used throughout this work was the cyclopropanation of styrene (**2**) with ethyl diazoacetate

(**3a**, Scheme 1) catalyzed by **5**–Cu(OTf)$_2$ complexes in dichloromethane. A 1:1 molar ratio of **2** and **3** was used in all cases for the sake of comparison with previous mechanistic studies, which represented more challenging reaction conditions with respect to yields based on the diazo ester as the alkene is usually employed in large excess (5 equiv or more).

Table 1 summarizes the main results obtained in these cyclopropanation reactions. Some comparative results obtained by using analogous C_2-symmetric Box ligands have also been included.

Table 1. Results of the cyclopropanation reaction of styrene with ethyl diazoacetate catalyzed by chiral Box–CuOTf complexes.

Ligand	Yield [%][a]	*trans*/*cis*	*ee* (*trans*) [%][b]	*ee* (*cis*) [%][b]
5as	33	68:32	60	51
5a	42	71:29	20	8
5bs	69	60:40	85	81
5b	52	69:31	33	25
5cs	72	71:29	94	91
5c	58	68:32	29	8
5d	74	67:33	84	79
5e	73	64:36	83	75
5f	79	72:28	82	69
5gs	82	73:27	92	84
5g	65	73:27	23	9
5h	42	71:29	85	68
5is	72	60:40	−12	−31
5i	64	69:31	−8	−24
5j	69	70:30	48	31

[a] In all cases, the consumption of the diazo compound is the total yield, so the yield is also a measure of the chemoselectivity of the reaction. [b] Positive values indicate that (1*R*)-cyclopropanes are the major compounds.

The *trans*/*cis* diastereoselectivity values fall within a close range, between 60:40 and 73:27, irrespective of the symmetry of the chiral ligand and of the nature of the substitution of the oxazoline rings. This fact confirms that the *trans*/*cis* selectivity is mainly directed by the intermolecular steric interactions between the ester group of the carbene intermediate and the incoming alkene in the transition state and that it is basically unaffected by the nature of the chiral ligand.[15]

In contrast, large variations in enantioselectivity were observed when the results obtained with C_2-symmetric ligands were compared with those of ligands that bear a single substituent (**5as** with **5a**, **5bs** with **5b**, **5cs** with **5c**, and **5gs** with **5g**), except in the case of the ligands that bear quaternary stereogenic carbon atoms (**5is** and **5i**). In the former cases, a marked decrease in the enantioselectivity, in both the *trans*- and *cis*-cyclopropanes, was observed. However, note that the enantioselectivity in the *trans*-cyclopropanes was still significant (ca. 20–30% *ee*) when C_1-symmetric ligands that bear an unsubstituted oxazoline ring were used. This result is qualitatively analogous to that described by Nishiyama et al. in the case of Pybox ligands[6] and can probably be explained by the same mechanism, that is, the existence of particularly unfavorable reaction channels that lead to the formation of the minor enantiomer.[7] In a simple interpretation, the observed level of enantioselection would roughly correspond to one quarter of the possible reaction channels being disfavored and the rest being roughly equally favored (Figure 4).

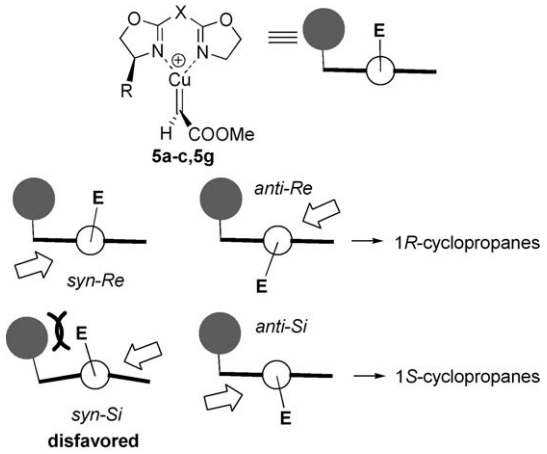


Figure 4. A possible mechanism to explain the low, but significant, enantioselectivities observed with monosubstituted bis(oxazoline) ligands. Only one of four possible reaction channels is disfavored.

In the case of C_1-symmetric ligands with two substituted oxazoline rings (**5d**, **5e**, **5f**, and **5h**) the enantioselectivities observed were closer to those obtained with the C_2-symmetric ligands (>80% *ee* for the *trans*-cyclopropanes and 70–80% *ee* in the case of the *cis*-cyclopropanes), even if the bis(oxazoline) ligand bears only one stereogenic center, as in the case of **5h**. We can conclude that when one of the oxazoline rings bears a *tert*-butyl group, any substitution on the second ring (even with a single methyl group) leads to good enantioselectivity levels in the benchmark cyclopropanation reaction. This result, apart from the mechanistic implications that we will discuss below, opens up the possibility of designing and synthesizing new asymmetric bis(oxazoline)-type ligands that are susceptible to being anchored to a support through a single substituent in the 4-position, an immobilization strategy not yet explored, without a foreseeable loss of enantioselectivity. Work in this direction is currently ongoing in our group.

Again, one possible explanation for these results comes from the existence of two *Si* reaction channels that are differently disfavored because of the different size of the bis(oxazoline) substituents (Figure 5).

We can see that these simple models may account for the experimental results observed, at least in a qualitative manner. However, if strict additivity (in energy terms) of steric effects (which has recently been reported for ligand **5is**[16]) is assumed, in the case of the aza-*t*BuMe$_2$Box (**5h**) ligand, a decrease in enantioselectivity should be expected with regard to the *t*BuMeBox (**5d**) ligand as the second methyl group in **5h** would disfavor one of the *Re* reaction channels to the same extent as the other methyl group disfavors one of the *Si* reaction channels. As shown in Table 1,

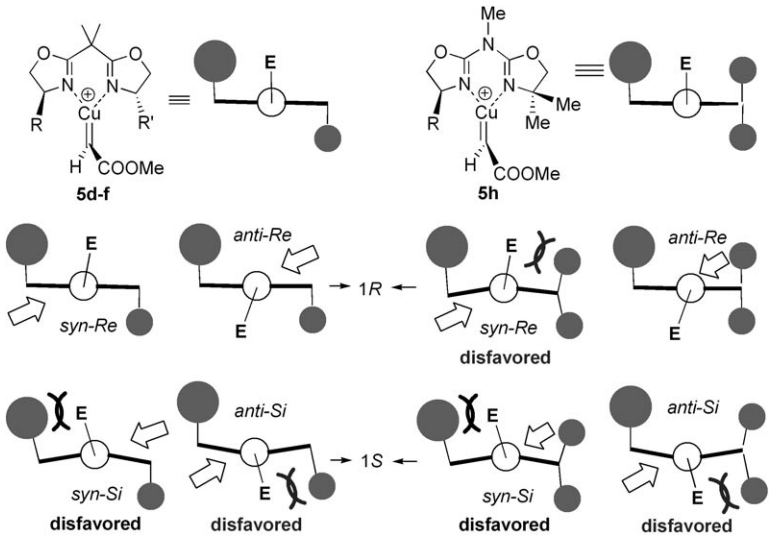


Figure 5. A schematic representation of the possible reaction channels in the case of chiral ligands substituted in both oxazoline rings, and the possible steric interactions that disfavor some of the corresponding TSs.

almost identical enantioselectivities in the major *trans*-cyclopropanes are observed with both chiral ligands. It is therefore clear that these models do not offer a complete view of the stereodifferentiation mechanism.

A special case is that of bis(oxazolines) that bear quaternary carbon stereogenic centers. Unlike the other ligands tested, in this case the presence or absence of C_2 symmetry (**5is** vs. **5i**) does not introduce significant changes in the enantioselectivies obtained.

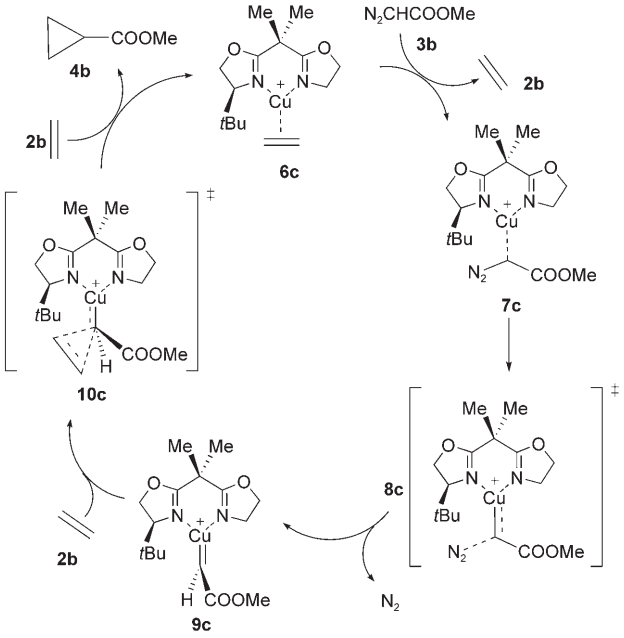
The question arises as to how the enantioselectivity depends on the substitution pattern of the asymmetric bis(oxazoline) ligands. Furthermore, the possible steric interaction between the incoming alkene and the Box substituent in the highly congested ligands cannot be discarded. To test the reliability of the aforementioned simple models and to better understand these systems, a thorough theoretical mechanistic study was therefore undertaken.

Theoretical results: Several computational mechanistic studies of the mechanism of copper-catalyzed cyclopropanation reactions have recently been published.[10,16–20] In particular, the enantiodifferentiation mechanism in the case of bis(oxazoline)–Cu catalysts has been studied by our group[10] and by Norrby and co-workers,[17] by using both QM and QM/MM methods to model the chiral ligand. It has been shown[16] that the enantioselection mechanisms can be appropriately studied by using simplified models in which the ethyl diazoacetate (**3a**) is substituted by methyl diazoacetate (**3b**) and the styrene (**2a**) is substituted by ethylene (**2b**) as the main steric interactions responsible for the enantioselection are retained in the simplified model, and consequently we adopted this approach in this study.

We recently reported[16] the results of a theoretical and experimental study of the prototypical C_2-symmetric *t*BuBox ligand (**5cs**). We have used these results as a reference for the results obtained with asymmetric ligands.

We started our theoretical study with the asymmetric ligand most dissimilar to C_2-symmetric *t*BuBox (**5cs**), namely, the *t*BuHBox (**5c**, Figure 3). With this ligand we considered the full catalytic cycle previously elucidated for this reaction and it is shown in Scheme 2.[10,16]

A fundamental difference exists between the reaction pathways that involve the C_1- and C_2-symmetric ligands. As noted previously by other authors,[6,19] there are two possible dispositions for the Cu–carbene intermediate, in our case **9c**, namely those with the ester



Scheme 2. Full catalytic cycle for the cyclopropanation reaction of ethylene (**2b**) with methyl diazoacetate (**3b**) catalyzed by the **5c**–Cu^I complex.

group and the bis(oxazoline) substituent either on the same side (*syn*) or on different sides (*anti*) of the chelate complex plane (Figure 6). This duplicates the number of possible reaction channels. In these conditions it is important to determine if Curtin–Hammett conditions apply to the systems. If the interconversion between the *syn* and *anti* forms of the Cu–carbene intermediate is faster than the addition of the carbene to the alkene double bond, then Curtin–Hammett conditions are met and the stereoselectivity of the reactions will only depend on the relative energies of the different addition transition states (TSs) **10c**. On the other hand, if the

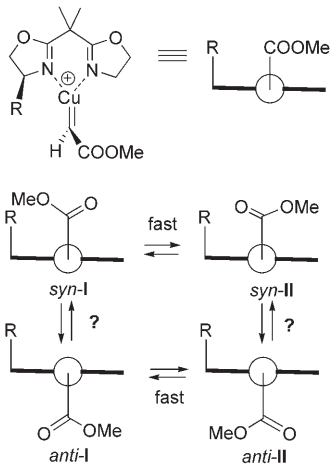


Figure 6. Different possible structures for the Box–Cu–carbene intermediates.

interconversion between the *syn* and *anti* forms is slower than the cyclopropanation step, then the stereoselectivity will depend on the detailed kinetics of the whole reaction, which include the nitrogen extrusion step via TS **8c**. Of course, when the ligand is C_2-symmetric, the *syn–anti* interconversion by Cu–$C_{carbene}$ rotation is equivalent to the half-rotation of the whole complex, thus leading to equivalent structures, and the above considerations do not apply.

To gain an insight into this reaction feature, we calculated all of the possible TSs **8c** and the subsequent Cu–carbene intermediates **9c**, the *syn–anti* rotation transition state **9cr**, and all the possible cyclopropanation TSs **10c**. In all cases, the two possible conformations of the ester group (labeled **I** and **II**) were taken into account. A scheme illustrating the possible reaction channels that lead to the cyclopropane product is shown in Figure 7. Of course, in the case of ethylene, no enantioselectivity is possible, but as mentioned before, we can take the *Re* and *Si* reaction channels as a measure of the enantioselectivity in real systems. Typical structures calculated for the different reaction intermediates and transition-state structures are shown in Figure 8 and the main energy results are gathered in Table 2.

Given that entropic effects are presumably more important in the bimolecular cyclopropanation reaction than in the carbene rotation around the Cu–C bond, we considered first the Gibbs free-energy surface. As can be seen in Table 2, the nitrogen extrusion step is the rate-determining step of the catalytic cycle, as previously described for other similar systems.[10,16,21] The calculated activation energies for the cyclopropanation step indicate a very fast reaction, and compare well with the experimental[22] and theoretical[23] values determined for the cyclopropanation reactions with electrophilic carbenes, as well as with the experimental value determined for the reaction of a neutral carbene complex derived from a less electrophilic diazo compound ($\Delta G^{\neq} = 20$ kcal mol^{-1}).[20] Concerning the mechanistic issue raised above, the results are not conclusive because the calculated carbene rotation barrier (14.5 kcal mol^{-1}), which

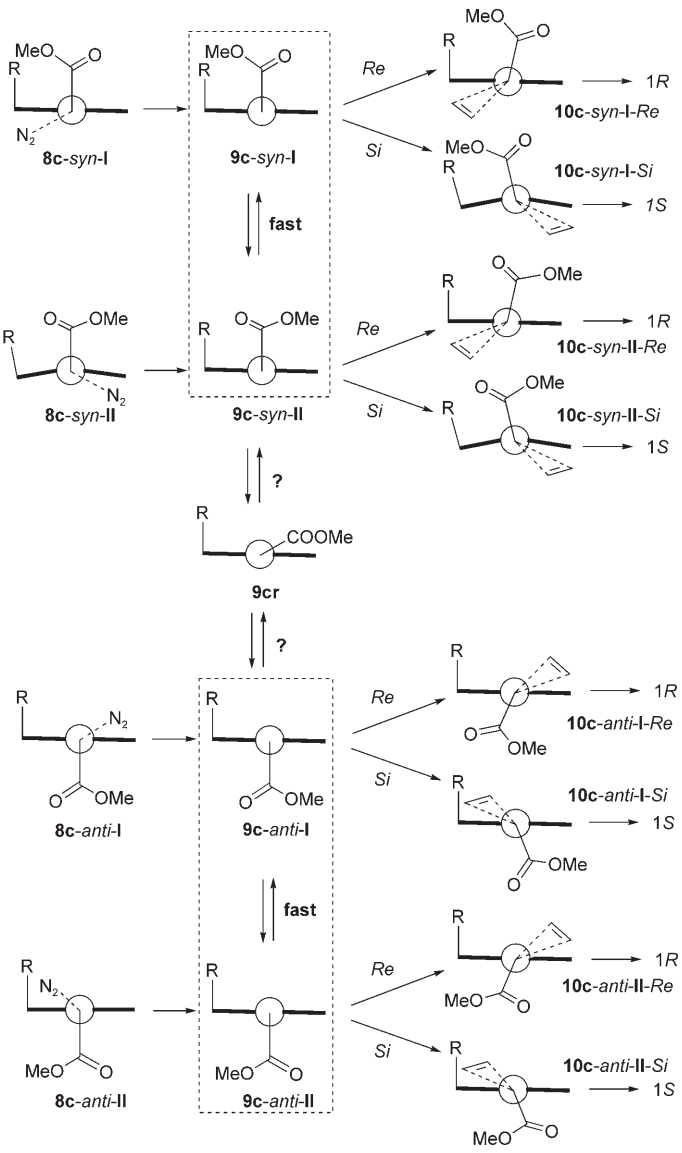


Figure 7. Possible reaction channels that lead to (1*R*)- and (1*S*)-cyclopropanes in the enantioselective reactions.

passes through TS **9cr**, is very similar to the cyclopropanation activation barriers (from 11.4 to 17.9 kcal mol^{-1}), similarly to that described for salicylaldimine–Cu^{I} systems.[19] Although these values point to a non-Curtin–Hammett behavior of the reaction, no clear conclusion can be made on the basis of these calculations given the limitations in accuracy that result from the theoretical level and the simplified model used. A possibility would lie in a comparison of the calculated enantioselectivities, by using each approximation, with the experimental values obtained for the reaction of styrene with ethyl diazoacetate catalyzed by the *t*BuHBox–Cu(OTf)$_2$ complex. As shown in Table 1, these values are 29% *ee* for the *trans*-cyclopropanes and 8% *ee* for the *cis*-cyclopropanes. By using the calculated Gibbs free energies, the values estimated for the "enantioselectivity" of the reaction of ethylene with methyl diazoacetate (taking into ac-

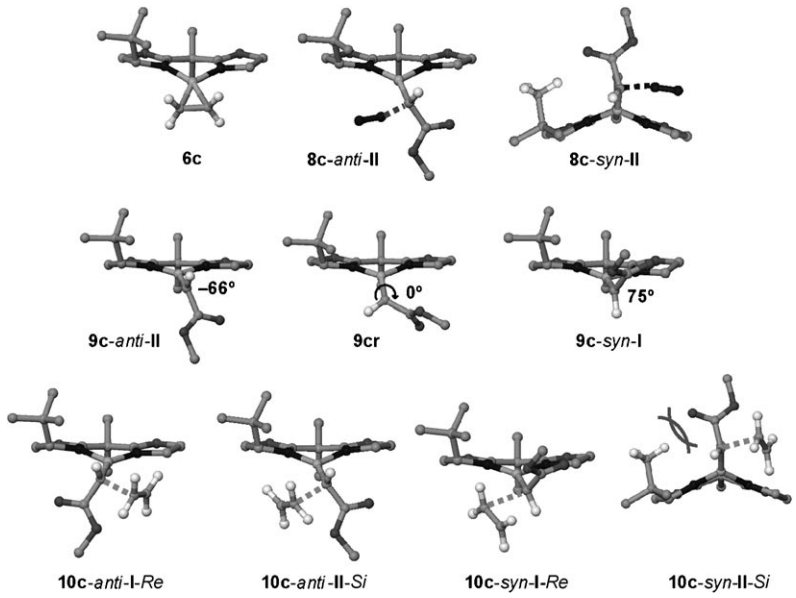


Figure 8. Some selected calculated (at the B3LYP/6-31G(d) theoretical level of theory) geometries of the main intermediates and transition-state structures of the reaction of ethylene with methyl diazoacetates, catalyzed by the *t*BuHBox–Cu^{I} (**5c**-Cu) complex.

count the *Re* and *Si* reaction channels) are 70% *ee* assuming Curtin–Hammett conditions and 66% *ee* assuming non-Curtin–Hammett behavior (i.e., that the carbene rotation is slower than the ethylene cyclopropanation) (Table 2).[24] In both approaches, the enantioselectivities are grossly overestimated and do not allow differentiation between the two mechanistic alternatives.

We have previously shown[16] that E_0+ZPE values often lead to calculated selectivities that are closer to the experimental values in similar systems, so we repeated our estimation of the enantioselectivity by using this parameter. The new calculated values are 8 and 18% *ee*, respectively, with and without assuming Curtin–Hammett condi-

Table 2. Calculated [B3LYP/6-31G(d)] relative energies[a] and activation barriers [kcal mol^{-1}] of the catalytic cycle of the cyclopropanation reaction of ethylene with methyl diazoacetate, catalyzed by the *t*BuHBox–Cu^{I} complex. Estimated % *ee* values with and without assuming Curtin–Hammett conditions.

Structure[b]	ΔE[c]	$\Delta\Delta E$	$\Delta E^{\neq}$	*ee* [%][d]		ΔG[c]	$\Delta\Delta G$	$\Delta G^{\neq}$	*ee* [%][d]	
				C–H	Non C–H				C–H	Non C–H
2b	0.0	–	–			0.0	–	–		
3b	0.0	–	–			0.0	–	–		
N_2	0.0	–	–			0.0	–	–		
6c	0.0	–	–			0.0	–	–		
8c-*anti*-**I**	20.4	1.0	20.4			20.7	1.0	21.1		
8c-*anti*-**II**	19.4	**0.0**	19.6			20.0	0.3	20.4		
8c-*syn*-**I**	19.6	0.2	19.4			19.7	**0.0**	20.1		
8c-*syn*-**II**	26.5	7.1	26.5			25.8	6.1	26.2		
9c-*anti*-**I**	6.8	0.6	–			−3.0	0.1	–		
9c-*anti*-**II**	6.2	**0.0**	–			−3.2	**0.0**	–		
9c-*syn*-**I**	6.7	0.5	–			−2.7	0.4	–		
9c-*syn*-**II**	7.0	0.8	–			−2.4	0.7	–		
9cr	20.9	–	14.7			11.4		14.5		
10c-*anti*-**I**-*Re*	6.6	0.4	0.4			8.8	0.6	12.0		
10c-*anti*-**II**-*Re*	8.2	2.1	2.1			9.8	1.6	13.0		
10c-*syn*-**I**-*Re*	6.4	0.2	0.2			8.2	**0.0**	11.4		
10c-*syn*-**II**-*Re*	8.3	2.1	2.1			9.7	1.4	12.8		
10c-*anti*-**I**-*Si*	8.6	2.4	2.4	8[e]	18[e]	10.4	2.1	13.5	70[e]	66[e]
10c-*anti*-**II**-*Si*	6.2	**0.0**	0.0			9.0	0.8	12.2		
10c-*syn*-**I**-*Si*	12.6	6.4	6.4			13.0	4.8	16.2		
10c-*syn*-**II**-*Si*	12.3	6.1	6.1			14.8	6.5	17.9		
4b	−55.3	–	–			−51.9	–	–		

[a] Energy values include ZPE corrections at the same theoretical level. [b] *syn* and *anti* stand for the relative positions of the *tert*-butyl and ester groups, *Re* and *Si* stand for the carbene carbon face approached by ethylene and **I** and **II** stand for the conformation of the ester group (see Figure 4). [c] The initial complex *t*BuHBox–Cu–ethylene (**6c**), ethylene (**2b**), methyl diazoacetate (**3b**), and dinitrogen have been arbitrarily chosen as the zero level in the relative energy calculations. [d] The experimental values for the reaction of styrene with ethyl diazoacetate using the same ligand are 29% *ee* (*trans*-cyclopropanes) and 8% *ee* (*cis*-cyclopropanes). [e] *Re* attack is favored (leading to (1*R*)-cyclopropanes in the case of a substituted alkene).

tions (Table 2). These values are, effectively, much closer to the experimental observations, but unfortunately, also do not allow discrimination between the two mechanistic alternatives. We realize that both mechanistic approaches lead to similar calculated enantioselectivities. This fact can be rationalized through the structural similarities of TSs **8** (governing the non-Curtin–Hammett behavior) and **10** (governing the Curtin–Hammett behavior) such that the steric interactions responsible for their relative stabilities should be similar in both cases (compare, for instance, the *anti*-**II** and *syn*-**II** structures for **8c** and **10c** in Figure 8 and their relative energies in Table 2). Therefore, in a first approach, we will henceforth assume Curtin–Hammett behavior for the catalytic systems to facilitate the calculation of the enantioselectivity.

Next, we considered two different substitution patterns in the second oxazoline ring, namely, the presence of a single methyl group (as in **5d**), and that of two methyl groups (as in **5h**), which lead to a nonstereogenic, quaternary carbon atom in the 4-position of the oxazoline ring. From an experimental point of view, both substitutions led to (unexpectedly) good enantioselectivities when the corresponding ligands were used in the benchmark cyclopropanation reaction.

Concerning the *t*BuMeBox ligand (**5d**), the relative energies of the corresponding cyclopropanation reactions are gathered in Table 3, as well as the estimated enantioselectivities assuming Curtin–Hammett behavior. Some representative structures are shown in Figure 9.

As can be seen, *Re* approaches of the alkene are always favored over the corresponding *Si* approach. In particular, and similarly to what happened in the case of the **5c** ligand, the *syn-Si* reaction channels are especially disfavored owing to the steric interaction between the ester group and the *tert*-butyl substituent of the ligand that results in an important deformation of the chelate complex (see the **10d**-*syn*-**II**-*Si* structure in Figure 9). A similar steric interaction exists between the ester and methyl groups in TS **10d**-*anti*-*Si*, which also leads to a deformation of the chelate complex. If we compare the relative energies of the TSs **10c** and **10d**, we realize that the main difference between the two sets of data indeed lies in the relative energy of **10c**-*anti*-**II**-*Si*, which is very low (even corresponding to the minimum value in the case of E_0+ZPE energies) and leads to an important reaction channel for the formation of (1*S*)-cyclopropanes, and hence, to a decrease in the global enantioselectivity of the reaction. In the case of the **5d** ligand, the two clearly favored reaction channels correspond to the **10d**-*syn*-**I**-*Re* and **10d**-*anti*-**I**-*Re* TSs, both leading to (1*R*)-cyclopropanes, in agreement with the experimental results. The estimated enantioselectivity for this ligand is around 90%, which is similar to the approximate 80% *ee* observed experimentally in the reaction of styrene and higher than the value calculated in the case of the **5c** ligand, that is again in complete agreement with experimental observations.

Concerning the aza-*t*BuMe$_2$Box ligand (**5h**), the relative energies of the corresponding cyclopropanation TSs are gathered in Table 3, as well as the estimated enantioselectivities assuming Curtin–Hammett behavior. Some representative structures are shown in Figure 9.

Table 3. Calculated [B3LYP/6-31G(d)] relative energies and activation barriers for the cyclopropanation transition-state structures of the reaction of ethylene with methyl diazoacetate, catalyzed by the **5d**–Cu^{I} and **5h**–Cu^{I} complexes.

TS[a]	$\Delta\Delta E^{\neq}$ [kcal mol^{-1}]	*ee* [%][b]	$\Delta\Delta G^{\neq}$ [kcal mol^{-1}]	*ee* [%][b]
10d-*anti*-**I**-*Re*	0.5	92	0.4	88
10d-*anti*-**II**-*Re*	2.4		2.2	
10d-*syn*-**I**-*Re*	0.0		0.0	
10d-*syn*-**II**-*Re*	1.7		1.7	
10d-*anti*-**I**-*Si*	1.8		2.1	
10d-*anti*-**II**-*Si*	2.3		1.5	
10d-*syn*-**I**-*Si*	5.3		4.9	
10d-*syn*-**II**-*Si*	5.0		4.2	
10h-*anti*-**I**-*Re*	0.8	94	0.3	90
10h-*anti*-**II**-*Re*	2.8		2.1	
10h-*syn*-**I**-*Re*	0.0		0.0	
10h-*syn*-**II**-*Re*	1.4		1.0	
10h-*anti*-**I**-*Si*	2.6		1.7	
10h-*anti*-**II**-*Si*	2.1		1.8	
10h-*syn*-**I**-*Si*	9.3		9.2	
10h-*syn*-**II**-*Si*	8.5		8.4	

[a] *syn* and *anti* stand for the relative positions of the *tert*-butyl and ester groups, *Re* and *Si* stand for the carbene carbon face approached by ethylene, and **I** and **II** stand for the conformation of the ester group (see Figure 4). [b] Estimated *ee* values assuming Curtin–Hammett conditions.

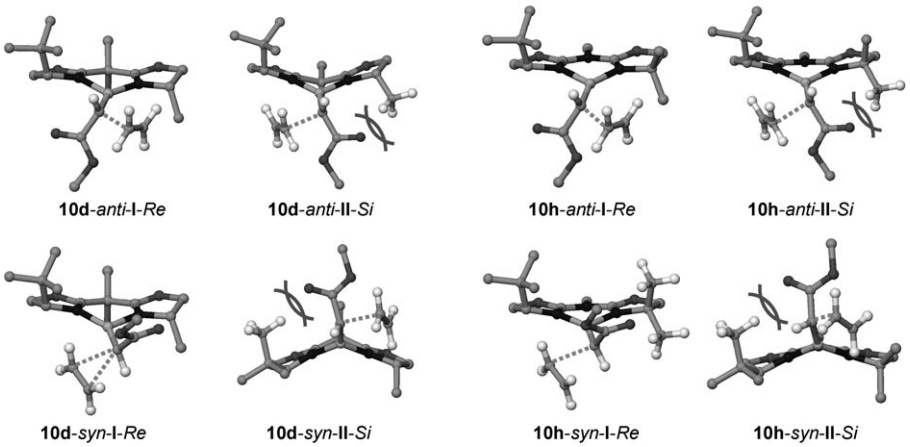


Figure 9. Some selected calculated (at the B3LYP/6-31G(d) theoretical level of theory) geometries of the transition-state structures of the reaction of ethylene with methyl diazoacetates, catalyzed by the *t*BuMeBox–Cu^{I} (**5d**-Cu) and the aza-*t*BuMe$_2$Box–Cu^{I} (**5h**-Cu) complexes.

Both *Re* approaches of the alkene are clearly favored over the *Si* approaches. Similarly to what happened in previous cases, the *syn-Si* reaction channel is highly disfavored (even more than for the rest of ligands investigated) owing to the steric interaction between the ester group and the *tert*-butyl substituent of the ligand. The presence of a second methyl group in the ligand does not appear to introduce new steric interactions that modify the enantioselection of the ligand (as assumed for the *syn-Re* TS in Figure 5), as is shown by comparing the relative energies of TSs *syn*-**I**-*Re*, *anti*-**I**-*Re*, and *anti*-**II**-*Si* for the **5d** and **5h** ligands (0.0, 0.4, and 2.1 vs. 0.0, 0.3, and 1.8 kcal mol^{-1} in the case of Gibbs free energies, and 0.0, 0.5, and 1.8 vs. 0.0, 0.8, and 2.1 kcal mol^{-1} in the case of E_0+ZPE energies). In fact, in **10h**-*syn*-**I**-*Re* it can be seen that the ester group adopts a position that is intermediate between the two methyl groups, which avoids the presumed steric interaction with the upper methyl group. This effect is probably favored by the lesser distortion of the azaBox ligand in adopting a boat conformation. Also, note that a steric interaction between the incoming alkene and the ligand substituents is not detected in any example, which is in agreement with previous computational studies.[10,16] These theoretical results are in excellent agreement with the similar enantioselectivities obtained experimentally in the reactions carried out by using the **5d** and **5h** ligands and highlight the excessive simplicity of the stereoselection models previously presented.

Conclusion

Experimental catalytic studies of the cyclopropanation reaction of styrene with ethyl diazoacetate catalyzed by a series of C_1-symmetric bis(oxazoline) ligands have shown that C_2 symmetry is not mandatory to obtain high levels of enantioselectivity. Even ligands that bear only one stereogenic center are able to induce stereoselectivity levels that are close to the best ones obtained with the classical C_2-symmetric ligands. This finding, apart from being of mechanistic interest, opens the door to new immobilization strategies through covalent bonding of the bis(oxazoline) ligand to the support through only one of the substituents in the 4-position, with no foreseeable loss of enantioselectivity. Work in this direction is currently ongoing in our group.

The computational mechanistic studies carried out do not allow a decision to be made as to whether or not Curtin–Hammett conditions are met in the catalytic reactions of asymmetric ligand complexes, but both approximations lead to sufficiently similar predictions that mechanistic issues can still be discussed. Thus, the theoretical calculations carried out on model systems show a very good agreement with experimental observations and have allowed us to gain an insight into the different systems investigated. In particular, enantioselectivity arises from differently favored reaction channels, which lead to the formation of one or other cyclopropane enantiomer depending on the steric interactions between the ester group and the bis(oxazoline) substituents. This agreement between experiment and theory will allow us to theoretically investigate the behavior of new ligands before their synthesis and testing, which facilitates the design of tailored catalytic systems for this reaction.

Experimental Section

General methods: All reactions were carried out under nitrogen or argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride. Ethanol was distilled from magnesium. Tetrahydrofuran was distilled from potassium and toluene was distilled from sodium. Amino acids were used as commercially available. ^{1}H and ^{13}C NMR spectra ($CDCl_3$, δ [ppm], J [Hz]) were obtained using a Bruker ARX-300 instrument with TMS as the standard. Quantitative elemental analyses were performed on a Perkin–Elmer 2400 instrument. Polarimetry was carried out using a Jasco P-1020 instrument. Mass spectra were carried out using a VG Autospec instrument.

Ligand synthesis: The asymmetric bis(oxazoline) ligands were prepared as previously described.[13a] The aminooxazolines[25] and ethoxyoxazolines[26,27] necessary for the azabis(oxazoline) syntheses were prepared according to literature procedures. The asymmetric azabis(oxazoline) ligands were prepared by the following general procedure: Ethoxyoxazoline (1.2 mmol), aminooxazoline (1.0 mmol), and a catalytic amount of *p*-toluenesulfonic acid (20 mg) were dissolved in toluene (20 mL) and heated at reflux for 24 h. After this period, the solution was concentrated in vacuo and purified by chromatography on silica gel by using ethyl acetate as the eluent to give the desired azabis(oxazolines) in a yield of 57 to 69%.

[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl](4,5-dihydrooxazol-2-yl)amine: According to the general procedure, reaction of 2-ethoxy-4,5-dihydrooxazole and (*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-ylamine gave the title compound as a colorless solid in a yield of 62%. M.p. 103–106°C; $[\alpha]_D^{20}$ (c = 1.0 in CH_3OH) = 75.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39–4.29 (m, 3H), 4.19 (dd, J = 8.8, 6.3 Hz, 1H; CH_2CH), 3.59–3.75 (m, 3H), 0.91 ppm (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.8 (NO*C*N), 165.8 (NO*C*N), 67.5 (*C*H$_2$CH$_2$), 67.3 (*C*HCH$_2$), 66.1 (CH*C*H$_2$), 49.1(CH$_2$*C*H$_2$), 33.6 (*C*(CH$_3$)$_3$), 25.3 ppm (C(*C*H$_3$)$_3$); IR: $\tilde{\nu}$ = 3199, 2961, 2894, 1625, 1592, 1479, 1439, 1385, 1250, 1058, 760 cm^{-1}; MS (CI-MS): m/z: 212.1 [MH$^+$]; elemental analysis calcd (%) for $C_{10}H_{17}N_3O_2$: C 56.85, H 8.11, N 19.89; found: C 56.55, H 7.85, N 19.89.

[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl](4,4-dimethyl-4,5-dihydrooxazol-2-yl)amine: According to the general procedure, reaction of 2-ethoxy-4,4-dimethyl-4,5-dihydrooxazole and (*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-ylamine gave the title compound as a colorless solid in a yield of 59%. M.p. 81–84°C; $[\alpha]_D^{20}$ (c = 1.0 in CH_3OH) = 73.8; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.34–4.32 (m, H), 4.22–4.12 (m, H), 4.01 (s, H), 4.84–3.72 (m, H), 1.32 (s, 3H), 1.30 (s, 3H), 0.89 ppm (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.7 (NO*C*N), 164.6 (NO*C*N), 77.8 (*C*CH$_2$), 67.5 (CH*C*H$_2$), 67.4 (*C*HCH$_2$), 62.0, 33.7 (*C*(CH$_3$)$_3$), 29.0 (C(*C*H$_3$)$_2$), 28.4 (C(*C*H$_3$)$_2$), 25.3 ppm (C(*C*H$_3$)$_3$); IR: $\tilde{\nu}$ = 2965, 2880, 1633, 1594, 1442, 1388, 1267, 1200, 1053, 999, 755 cm^{-1}; MS (CI-MS): m/z: 239.2 [$M^{\cdot+}$]; HRMS (EI-MS): m/z: calcd for [$M^{\cdot+}$]: 239.1634; found: 239.1636.

General procedure for the methylation of azabis(oxazolines): Azabis(oxazoline) (1 mmol) was dissolved in THF (10 mL), cooled to −78°C, and *n*-butyllithium (1.10 mmol, 690 μL of a 1.6 N solution in hexane) was added slowly. After stirring for 10 min, MeI (5.0 mmol, 710 mg) was added dropwise, the solution was slowly warmed to room temperature overnight and stirred for another 10 h. Then, aqueous Na_2CO_3 (5 mL) was added and the mixture concentrated. The residue was diluted with DCM (10 mL) and aqueous Na_2CO_3 (10 mL) and the phases were separated. The aqueous phase was extracted twice with DCM, the combined organic phases were dried with $MgSO_4$, and the solvent was evaporated to give the product in a yield of 98%.

[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl](4,5-dihydrooxazol-2-yl)methylamine (5g): According to the general procedure, reaction of [(*S*)-4-*tert*-

butyl-4,5-dihydro-oxazol-2-yl](4,5-dihydrooxazol-2-yl)amine with MeI gave the title compound as a clear oil in a yield of 98%. $[\alpha]_D^{20}$ (c = 1.0 in CH_3OH) = 15.7; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.27 (dd, J = 9.6, 8.5 Hz, 1H; CH_2CH), 4.13 (dd, J = 8.5, 7.4 Hz, 1H; CH_2CH), 3.92 (dd, J = 9.6, 7.4 Hz, 1H), 3.83–3.70 (m, 1H; OCH_2CH$_2$), 3.68–3.55 (m, 1H; OCH_2CH$_2$), 3.34–3.24 (m, 2H; OCH$_2$CH_2), 3.20 (s, 3H; CH_3), 0.89 ppm (s, 9H; CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.6 (NO*C*N), 157.7 (NO*C*N), 73.2 (*C*HCH$_2$), 70.5 (CH*C*H$_2$), 68.9 (*C*H$_2$CH$_2$), 52.8 (CH$_2$CH$_2$), 36.9 (NCH$_3$), 33.9 (*C*(CH$_3$)$_3$), 25.6 ppm (C(*C*H$_3$)$_3$); IR: $\tilde{\nu}$ = 3432, 2965, 2890, 1635, 1599 1479, 1395, 1255, 1058, 765 cm^{-1}; MS (CI-MS): m/z: 226.2 [MH$^+$]; HRMS (EI-MS): m/z: calcd for [$M^{\cdot+}$]: 225.1477; found: 225.1479.

[(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl](4,4-dimethyl-4,5-dihydrooxazol-2-yl)methylamine (5h): According to the general procedure, reaction of [(*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl](4,4-dimethyl-4,5-dihydrooxazol-2-yl)amine with MeI gave the title compound as a light yellow oil in a yield of 97%. $[\alpha]_D^{20}$ (c = 1.0 in CH_3OH) = 7.6; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.38–4.2 (m, 2H; CH_2CH), 4.08 (dd, J = 9.4, 7.9 Hz, 2H; CH_2C), 3.79 (dd, J = 9.5, 6.8 Hz, 1H; C*H*CH$_2$), 3.38 (s, 3H; NCH_3), 1.3 (s, 6H; CH$_3$), 0.88 ppm (s, 9H; C(CH_3)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.6 (NO*C*N), 156.6 (NO*C*N), 80.4 (*C*CH$_2$), 73.2 (*C*HCH$_2$), 70.5 (*C*CH$_2$), 64.9 (CH*C*H$_2$), 37.5 (NCH$_3$), 33.9 (*C*(CH$_3$)$_3$), 28.6 (C(*C*H$_3$)$_2$), 28.5 (C(CH$_3$)$_2$), 25.5 ppm (C(*C*H$_3$)$_3$); IR: $\tilde{\nu}$ = 3426, 2961, 1757, 1639, 1479, 1432, 1385, 1194, 952, 712 cm^{-1}; MS (EI-MS): m/z: 253.2 [$M^{\cdot+}$]; HRMS (EI-MS): m/z: calcd for [$M^{\cdot+}$]: 253.1790; found: 253.1794.

Cyclopropanation reactions: The bis(oxazoline)–copper complexes were prepared by dissolving the copper salt Cu(OTf)$_2$: (0.05 mmol) and the corresponding ligand (0.05 mmol) in anhydrous dichloromethane (1 mL). After stirring for 1 h, the insoluble materials were removed by microfiltration and the bluish-green solution was added to a 25 mL two-necked round-bottomed flask that contained styrene (520.75 mg, 5 mmol) and *n*-decane (100 mg) in CH_2Cl_2 (4 mL) under argon. Ethyl diazoacetate (570.5 mg. 5 mmol) diluted in anhydrous CH_2Cl_2 (1 mL) was slowly added (4 h) by using a syringe pump. The reaction was stirred at room temperature for 24 h. After this time the solution was diluted (5 mL CH_2Cl_2) and the results of the reaction were determined by gas chromatography. FID from Hewlett-Packard 5890II; cross-linked methyl silicone column: 25 m × 0.2 mm × 0.33 μm; helium as carrier gas: 20 psi; injector temperature: 230 °C; detector temperature: 250 °C; oven temperature program: 70 °C (3 min), 15 °C min^{-1} to 200 °C (5 min); retention times: ethyl diazoacetate 4.28 min, styrene 5.03 min, *n*-decane 6.93 min, *cis*-cyclopropanes 11.84 min, and *trans*-cyclopropanes 12.35 min. The asymmetric inductions of the reactions were also determined by gas chromatography. FID from Hewlett-Packard 5890II; Cyclodex B column: 30 m × 0.25 mm × 0.25 μm; helium as carrier gas: 20 psi; injector temperature: 230 °C; detector temperature: 250 °C; oven temperature program: 125 °C isotherm; retention times: (1*S*,2*R*)-cyclopropane 28.9 min, (1*R*,2*S*)-cyclopropane 29.8 min, (1*R*,2*R*)-cyclopropane 34.3 min, and (1*S*,2*S*)-cyclopropane 34.9 min.

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[24] The % *ee* in non-Curtin–Hammett conditions was estimated as follows: First, the percentage of the reaction going through the reaction channels that lead to *syn* and *anti* carbene intermediates was calculated on the basis of the relative energies of TS **8c**. Next, and considering that the ester rotation is faster than the carbene addition to ethylene, the percentage of the reaction going through the *Re* and *Si* reaction channels was calculated separately for the *syn* and *anti* reaction channels on the basis of the relative energies of TSs **10c**-*syn* and **10c**-*anti*. Finally, the percentage of *R* and *S* products, and hence the enantioselectivity, was estimated from the above percentages. For instance, in the case of the E_0+ZPE energies, 37.6% of the reaction occurs through the *syn* reaction channel and 62.4% through the *anti* reaction channel. 100% of the *syn* carbene intermediates give the *R* product, whereas only 34.6% of the *anti* carbene intermediates give the *R* product. This allows an estimate of $0.376\times1.00+0.624\times0.346=0.592$ (ca. 59%) for the *R* product, and hence 18% *ee*.

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