Stereoselectivity induced by Support Confinement Effects. Aza-pyridinoxazolines: A New Family of C_1-Symmetric Ligands for Copper-Catalyzed Enantioselective Cyclopropanation Reactions

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Aza-pyridinoxazoline ligands, a new class of C_1-symmetric ligands, are described and tested in the heterogeneous enantioselective catalysis of a cyclopropanation reaction, with the aim of improving
10 surface confinement effects by the clay support on the reaction stereoselectivity. In the case of *trans/cis* diastereoselectivity, these surface effects lead to a systematic reversal of selectivity, *cis*-cyclopropanes being favored. Regarding the enantioselectivities, support confinement has a positive effect in the case of major *cis*-cyclopropane products, leading to moderate enantioselectivity values (60% ee). A theoretical (DFT) mechanistic study is carried out to explain
15 the origin of the enantioselectivity in homogeneous phase at a molecular level, and to get insights on the geometries of the key intermediates and transition structures.
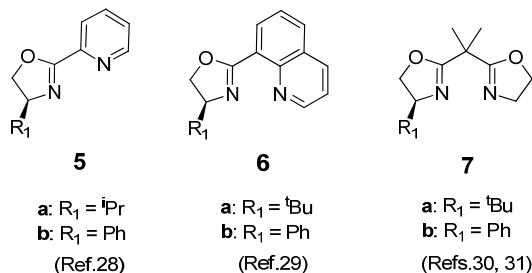
Introduction

Chiral catalysts immobilization is a powerful strategy to improve the performance of catalytic systems, as well as
20 separation and contamination issues.[1] It is usually thought that the interaction between the catalytic complex and the support may reduce stereoselectivities, and hence the placement of the catalytic complex far away from the surface is highly desirable in order to get a homogeneous-like environment
25 around the catalytic site. On the other hand, some recent observations of support-induced confinement effects on regio- and stereoselectivity of catalytic reactions have opened the door to a new viewpoint, *i.e.*, that steric support effects can be beneficial for improving the stereoselectivity of a reaction, or
30 even to obtain stereoselectivities difficult to obtain in homogeneous or traditional supported catalysis.[2] Most known examples of changes induced by support confinement effects are referred to non-covalent immobilization strategies, such as entrapment, electrostatic or adsorptive methods.[3,4]
35 In this regard, the first unequivocally demonstrated confinement effect by the support surface on an enantioselective reaction concerns to the cyclopropanation reaction of styrene with ethyl diazoacetate (Scheme 1),[5] catalyzed by the C_2-symmetric bis(oxazoline) ligand bearing
40 phenyl groups.[6–8]

homogeneous phase catalytic reaction was observed when the support was laponite, a synthetic clay with lamellar structure.[9] A marked *cis* preference, in contrast to the *trans* preference observed in solution,[5] was observed, and the asymmetric
50 induction for the major *cis* isomers was also reversed. As a consequence, the isomer *cis*-(1*S*,2*R*) (**4S**) was preferably obtained instead of the major *trans*-(1*R*,2*R*) (**3R**) obtained in solution. An extensive study on the importance of the nature of the support has been recently reported, confirming the need
55 of having a lamellar anionic support to observe such surface confinement effects.[10] A simple model has been proposed to explain those results, taking into account the known cyclopropanation reaction mechanism[11–20] and the strong ion-pair interaction between the key copper-carbene intermediate
60 and the support surface, as well as the steric constraints of the catalytic complex. From that model we proposed the synthesis of chiral ligands without C_2 symmetry as a method to enhance the surface-complex proximity and hence the support-complex interaction, allowing the surface to effectively shield one face
65 of the complex. Several 2-oxazolinylpyridine,[22–24] 8-oxazolinyl-quinoline,[25,26] and C_1-symmetric bis(oxazoline)[27] ligands have been prepared and tested as chiral ligands for immobilized copper complexes (Scheme 2).[28–31]

5

a: $R_1 = {}^i Pr$
b: $R_1 = Ph$
(Ref.28)

6

a: $R_1 = {}^t Bu$
b: $R_1 = Ph$
(Ref.29)

7

a: $R_1 = {}^t Bu$
b: $R_1 = Ph$
(Refs.30, 31)

Scheme 1 Benchmark cyclopropanation reaction between styrene and ethyl diazoacetate.

45 Complete reversal of stereoselectivities with regard to the

70

Scheme 2 C_1-symmetric ligands previously used in the heterogeneous catalysis of cyclopropanation reactions by copper complexes.

From these studies, the enhancement of support confinement effects with C_1-symmetric ligands have been corroborated through the observation higher *cis* preference (up to 92% in *cis*-cyclopropanes). However, changes in enantioselectivity were not so good (up to 48% ee in the major product).

In this paper we report the preparation of a new family of C_1-symmetric ligands bearing the oxazoline motif, namely aza-pyridinoxazolines (henceforth aza-pyox), their immobilized copper complexes, and the surface effect in the benchmark enantioselective cyclopropanation reaction of styrene with ethyl diazoacetate (Scheme 1), together with a molecular modeling study to explain the results obtained. The aim of this ligand design is to gather the good coordinating abilities of aza-bis(oxazoline) ligands[32] with the planarity and chemical stability of the pyridine ring, and a straightforward synthetic procedure.

Results and Discussion

Experimental Studies

Aza-pyox ligands were synthesized from 2-ethoxyoxazolines **8**, obtained from the corresponding amino alcohol by the method described by Reiser *et al.* (Scheme 3).[33] The coupling of each 2-ethoxyoxazoline with either 2-aminopyridine or 2-amino-6-methylpyridine in the presence of *p*-toluenesulfonic acid (pTsOH) and subsequent methylation at the aza bridge with *n*-BuLi/MeI afforded the desired *N*-methyl-4-alkyl-*N*-(pyridin-2-yl)-4,5-dihydrooxazol-2-amine ligands **10**, henceforth aza-pyox(R_1,R_2), R_1 and R_2 being the alkyl substituents at the oxazoline and pyridine rings, respectively.
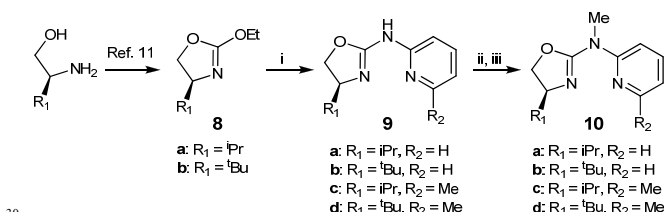
Scheme 3 Synthesis of chiral aza-pyridinoxazolines. i) 2-aminopyridine (**a,b** compounds) or 2-amino-6-methylpyridine (**c,d** compounds), pTsOH, toluene, reflux, 48h; ii) *n*-BuLi, THF, –78 ºC; 15 min; iii) MeI, THF, rt, 10 h.

According to previous results reported for 8-oxazolinyl-quinoline[29] and C_1-symmetric bis(oxazoline)[30,31] ligands, all the aza-pyox ligands show a very similar behavior in the homogeneous-phase cyclopropanation reactions (Table 1, entries 3–6, homogeneous phase results), achieving almost equal *trans/cis* ratios and low values of enantioselectivity (8–30%) as expected for chelating chiral ligands bearing only one stereocenter. These poor enantioselectivities can be easily explained by invoking only one disfavored reaction channel from four possible. Figure 1 illustrates this point, by showing the four main reaction channels possible for a C_1-symmetric ligand. Noteworthy, the presence of a methyl group at the 6-position of the pyridine ring in ligands **10c,d** (Table 1, entries 5 and 6) has a slight positive effect on the enantioselectivity

with respect to their unsubstituted counterparts **10a,b** (Table 1, entries 3 and 4). The next step was to test if steric effects from support can introduce changes in the stereochemical reaction course, leading to better results.

To this end, the copper complexes of ligands **10a–d** were prepared and immobilized onto laponite, following the same protocol previously described for other similar complexes.[28–31] Copper and nitrogen analyses, together with the IR spectra of adsorbed species, confirmed that the complexes remained intact after immobilization. These solids were tested as catalysts in the same benchmark cyclopropanation reaction (Scheme 1), using styrene as solvent. Table 1 gathers the most relevant results of these reactions.
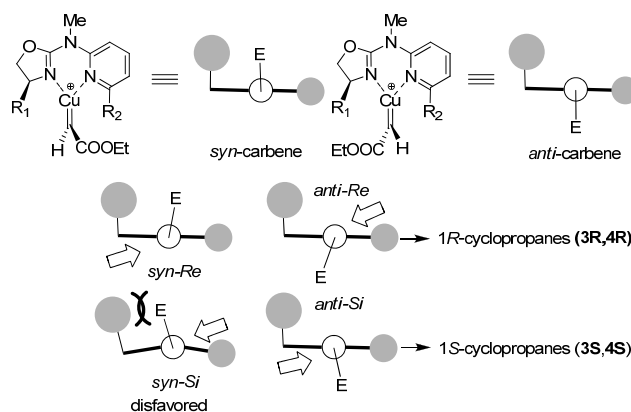

Fig. 1 A possible mechanism to explain the low, but yet significant enantioselectivities observed with C_1-symmetric ligands: only one of four main possible reaction channels is disfavored.

As can be seen, the reversal of *trans/cis* diastereoselectivity demonstrates that there are important support confinement effects in these catalytic systems. Thus, the *ca.* 70:30 *trans*-preference in homogeneous phase becomes *ca.* 20:80 *cis*-preference for ligands **10a,b**, and *ca.* 34:66 *cis*-preference for ligands **10c,d**. This is an interesting result from a synthetic point of view, since there are relatively few catalytic systems described able to lead preferently to *cis*-cyclopropanes,[34–38] and often they require the use of structurally quite complex ligands.[5,35]

Unfortunately, in most cases the support confinement effect does not have a strong effect on the enantioselectivities obtained with the aza-pyox ligands. The only remarkable effects are observed in the case of ligands **10b** and **10c**. With the former, the enantioselectivity in the **4R**-cyclopropane goes from 8% ee in homogeneous phase to 43% ee in heterogeneous phase (Table 1, entry 4). Furthermore, cyclopropane **4R** becomes the major product in heterogeneous phase, because of the above-mentioned *cis*-preference induced by the support.

Table 1 Results of the cyclopropanation between styrene and ethyl diazoacetate catalyzed by aza-pyox-copper complexes in homogeneous phase and supported on laponite

entry	Ligand	Homogeneous (CH$_2$Cl$_2$ as solvent)					Heterogeneous (styrene as solvent)				
		Yield	3/4	%ee (3)[c]	%ee (4)[d]	1R/1S[e]	Yield	3/4	%ee (3)[f]	%ee (4)[f]	1R/1S[e]
1	**6a**[a]	65	68/32	48	28	71:29	59	23/77	24	33	65:35
2	**7a**[b]	58	68/32	29	8	61:39	60	15/85	13	–48	31:69
3	**10a**	48	73/27	30	16	63:37	52	20/80	10	~0	51:49
4	**10b**	48	70/30	28	8	61:39	52	24/76	10	43	68:32
5	**10c**	48	63/37	29	35	66:34	53	32/68	23	60	74:26
6	**10d**	57	57/43	30	34	66:34	58	33/67	~0	59	70:30
7	**11**	53	70/30	72	63	85:15	88	22/78	19	–62	29:71
8	**12**	45	71/29	71	55	83:17	48	39/61	60	41	74:26
9	**13**	56	55/45	35	38	68:32	38	32/68	12	57	71:29
10	**14**	58	74/26	97	92	98:2	54	45/55	40	8	61:39

[a] Results from Ref. 29. [f] Results from Ref. 30,31. [c] **3R** was the major product. [d] **4R** was the major product. [e] (**3R**+**4R**)/(**3S**+**4S**) ratio. [f] Negative sign indicates that 1S-cyclopropanes (**3S**, **4S**) are the major enantiomers.

Similarly, with **10c**, the enantioselectivity in the **4R**-cyclopropane goes from 29% ee in homogeneous phase to 60% ee in heterogeneous phase (Table 1, entry 5). It is worth noting that this is the best enantioselectivity described to date for a support confinement effect enhanced by the C$_1$-symmetry of the ligand in the cyclopropanation reaction catalyzed by copper complexes, which validates the hypothesis that *ad hoc* ligand design can be used to take advantage of the steric effect of the support to obtain better stereoselectivities.

Another point deserves a particular comment. There is a significant difference in the behavior of ligands **6** and **10** with regard to ligand **7**. With the latter, there is a reversal of the absolute configuration of the major *cis*-cyclopropane obtained in heterogeneous phase (**4S**) with regard to the catalytic result in homogeneous phase, similarly to that described for C$_2$-symmetric bis(oxazoline) ligands.[9,10,27] This reversal is not observed neither for **6** nor for **10** ligands. This fact could be related with the different structural features of bis(oxazoline)-copper complexes, more prone to adopt boat-like geometries[14,30] than either aza-bis(oxazoline)- and 8-oxazolinylquinoline-copper complexes, which are much more rigid, leading to almost planar geometries.[14,29] In order to test this hypothesis, copper complexes of both isopropyl-substituted[39] C$_2$-symmetric bis(oxazoline) (**11**) and aza-bis(oxazoline) (**12**) chiral ligands (Figure 2) were used in the same conditions. The corresponding results are gathered in Table 1 (entries 7 and 8).
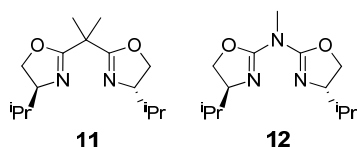
Fig. 2 C$_2$-symmetric bis(oxazoline) and aza-bis(oxazoline) ligands.

As can be seen, both C$_2$-symmetric ligands display a different behavior when used in supported catalysis. Whereas with the bis(oxazoline) ligand **11** a reversal in the absolute configuration of the major *cis*-cylopropane (**4S**) is observed, this reversal does not happen with the corresponding aza-bis(oxazoline) ligand **12**. This seems to indicate that both the geometrical constrains imposed by the ligand to the complex

and the support steric effects are important to determine the enantiodiscrimination of the different reaction pathways.

It has been previously proposed[29–31] that the origin of these moderate enantioselectivities probably lies in the existence of several reaction channels of similar energy, leading to different enantiomers, differing in the relative disposition of the copper complex with regard to the support surface. Some experiments conducted using reagents with different steric requirements have corroborated this explanation.[30,31] In order to obtain a more rigid disposition of the copper complex and trying to avoid turnarounds with regard to the support surface, we designed and synthesized a ditopic ligand, bearing two aza-pyox moieties, linked through a 1,4-phenylene bridge (**13**, Figure 3). We have recently described the synthesis and use of this kind of ditopic ligands, in their C$_2$-symmetric form, to obtain self-supported catalysts.[40] We also included a ditopic aza-bis(oxazoline) (DAX) ligand, **14**, for comparative purposes. Table 1 gathers the results obtained with these ditopic ligands both in homogeneous and heterogeneous catalysis experiments (entries 9 and 10).
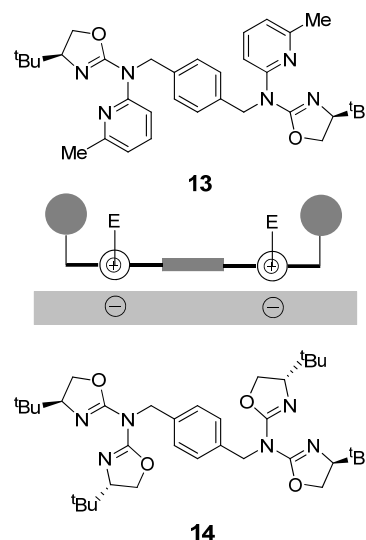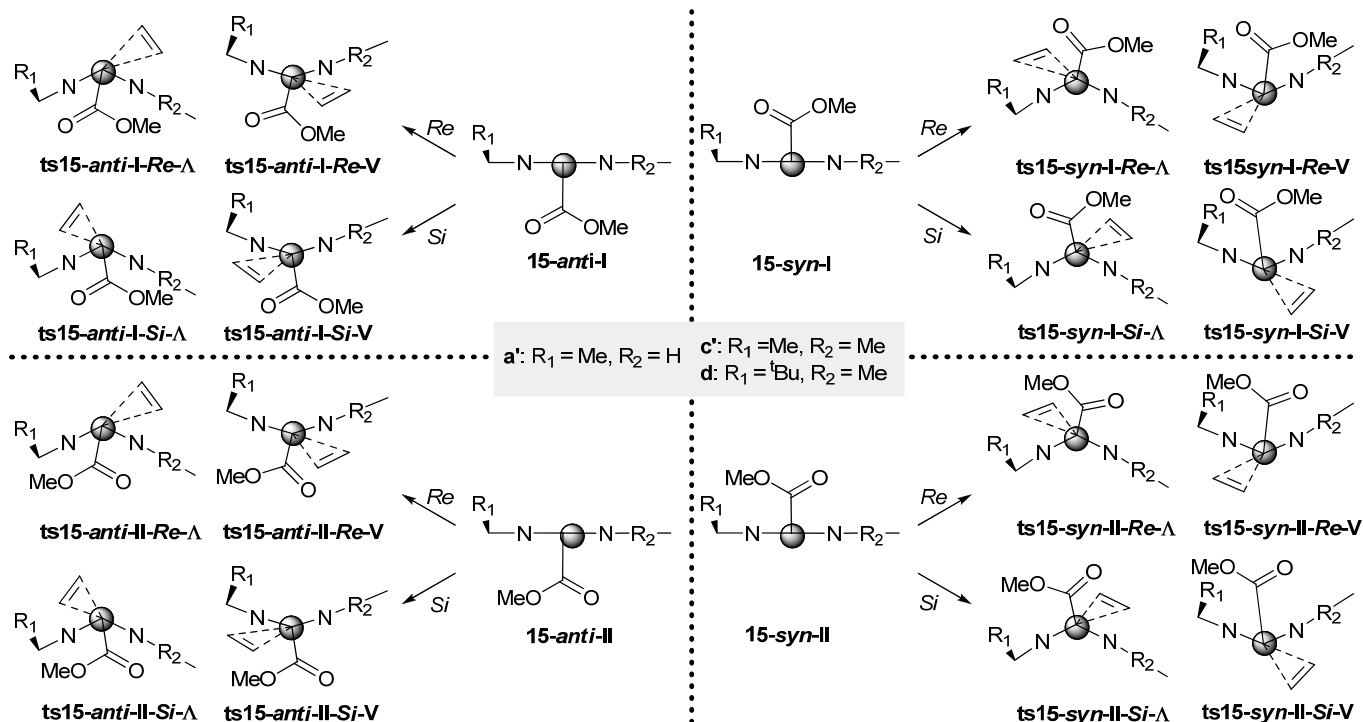
Fig. 3 C$_1$-symmetric aza-pyox and C$_2$-symmetric aza-bis(oxazoline) ditopic ligands. Proposed disposition of the di-copper complex of ligand **13** with regard to the laponite surface.

Scheme 4 Sixteen possible reaction trajectories for the approach of ethylene to the different conformers of the carbene in their *syn* and *anti* forms. *Re* approaches lead to 1*R*-cyclopropanes and *Si* approaches to 1*S*-cyclopropanes.

Clearly, the use of a ditopic ligand based on a starting C_2-symmetric building block (**14**) does not introduce any advantage over the traditional C_2-symmetric bis(oxazoline) and aza-bis(oxazoline) ligands (**11** and **12**, for instance). Similarly, the use of the ditopic aza-pyox derived ligand results in almost identical *trans/cis* diastereoselectivities and enantioselectivities of the major cyclopropanes. These results seem to point to a more complex situation than that ideally depicted in Figure 3.[31]

Theoretical Studies.

With the aim of rationalizing the experimental results described above, and to have a better understanding of the geometries of the key intermediates and transition structures (TS), a theoretical study of the different reaction channels of the copper-catalyzed cyclopropanation reaction with C_1-symmetric aza-pyox ligands was done. Apart from the well-known drawbacks in modeling the cyclopropanation reaction with styrene due to the flatness of the potential energy surface,[11–15] our main interest in this work was to evaluate the enantioselectivity of the process; therefore, all the calculations were carried out using ethylene as olefin. In addition, as in previous studies, methyl diazoacetate was used in the calculations instead of ethyl diazoacetate. The lack of symmetry of the ligand and, as demonstrated by preliminary calculations, the high flexibility of the Cu(I)-carbene complex increased significantly the number of reaction channels to be calculated: 1) the ester group of the carbene moiety can be placed in both an *anti* and *syn* disposition with respect to the alkyl group of the oxazoline ring; 2) two main rotamers arise from the ester group, one with the carbonyl pointing to the

alkyl group of the oxazoline ring (**I**) and the other with the carbonyl group oriented in the reverse direction (**II**); 3) the approach of the olefin to the copper-carbene intermediate bows the chelate Cu(I) complex to two different boat conformations, either towards the alkyl group of the oxazoline ring (**Λ**) or in the opposite direction (**V**); 4) finally, the nucleophilic attack of the incoming olefin can take place by the *Re* and *Si* faces of the Cu(I)-carbene plane, which determines the absolute configuration of the carbon bearing the ester group in the resulting cyclopropanes. Scheme 4 summarizes the different approximations of the olefin and conformers considered in the calculations, that is, four starting carbenes (**15**) and sixteen transition structures (**ts15**) overall for each aza-pyox(R_1,R_2) ligand.

The theoretical ratio of cyclopropane products was calculated through the energy of the different diastereomeric transition states using a Maxwell-Boltzmann distribution. It must be noted that the resulting cyclopropanes using ethylene as olefin are achiral, so the theoretical ratio of 1*R*/1*S* cyclopropanes is only an estimation of the hypothetical enantioselectivity that would be obtained with a substituted olefin (*i.e.* styrene) which, on the other hand, are the only experimental data available. As described later on, it was demonstrated that a proper selection of both the ligand models and the theoretical method is necessary to obtain reliable results. Thus, a methyl group in the oxazoline ring (ligand **10a'**) is enough to model the reaction experimentally carried out with **10a** and **10b**, but a bulkier *tert*-butyl group is necessary to account for the experimental behavior of **10c** and **10d** (ligand **10c'** bearing a methyl group gives worse results). From the methodological point of view, single-point energy calculations using the M05-

2X functional[41–48] carried out on B3LYP[49,50] optimized geometries led to much better relative energies, which is necessary to account for the subtle energy differences involved in enantioselective processes. It has been reported that the hybrid meta functional M05-2X shows a superior performance with respect to classical functional in the field of transition metal thermochemistry, which is of particular interest in our theoretical study.[41–48] Figure 4 shows some selected examples of calculated TS structures and the relative energies of all the calculated TS (a few structures could not be properly converged) are gathered in Table 2, together with the calculated enantioselectivities.
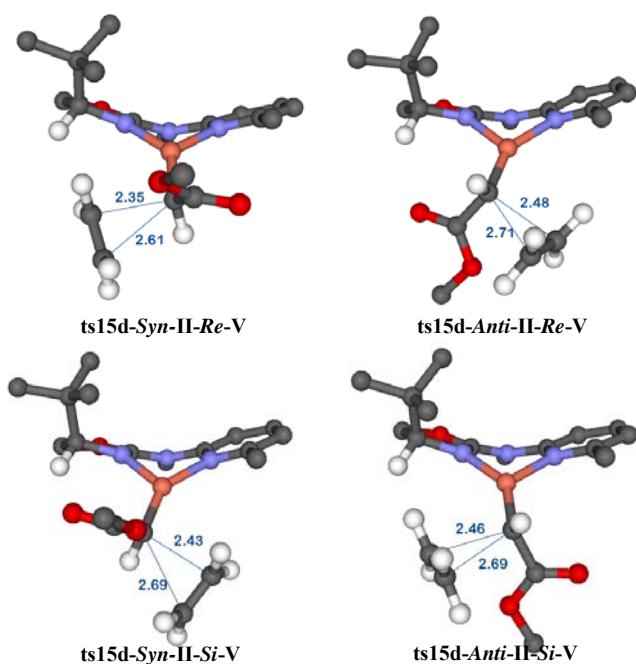

ts15d-*Syn*-II-*Re*-V **ts15d-*Anti*-II-*Re*-V**

ts15d-*Syn*-II-*Si*-V **ts15d-*Anti*-II-*Si*-V**

Fig. 4 Selected geometries of the lowest energy **ts15d** transition structures, leading to both enantiomeric cyclopropane products. Most hydrogen atoms are omitted for clarity.

The first observation made from the energy values in Table 2 is that conformations labeled as **Λ** are always less favored than the corresponding **V**. In addition, an inspection of the transition structures revealed that the lowest energy conformations are always associated to a distal disposition of the carbonyl group with regard to the incoming alkene. Regarding the enantioselectivity, it can be seen that the calculated ratio of cyclopropanes 1*R* and 1*S* are in good qualitative agreement with the experimental values (*ca.* 60:40, Table 1, entries 3–6) obtained in homogeneous conditions (Table 1). In particular, and although slightly overestimated, the enantioselectivity calculated from the aza-pyox(Me,H)-Cu(I)-carbene complexes (**15a'**) agrees quite well with that obtained experimentally with aza-pyox(*i*Pr,H) (**10a**) and aza-pyox(*t*Bu,H) (**10b**) ligands irrespective of the theoretical method used (calculated 1*R*/1*S* = 66:34 with B3LYP functional). In contrast, the addition of a methyl group in the 6-position of the pyridine made the calculations of the enantioselectivity fail when the B3LYP functional was used:

calculated 1*R*/1*S* = 33:67 from aza-pyox(Me,Me)-Cu(I)-carbene complexes (**15c'**) and 1*R*/1*S* = 25:75 with aza-pyox(*t*Bu,Me)-Cu(I)-carbene complexes (**15d**) (see Supporting Information).

Table 2 Calculated (M05-2X/6-31G(d)//B3LYP/6-31G(d)) relative energies[a] (kcal mol^{-1}) and enantioselectivities of the carbene addition step of the cyclopropanation reaction of styrene with methyl diazoacetate, catalyzed by the **8a-d**-Cu(I) complexes

TS	$\Delta\Delta E_{298}^{\ddagger}$ (kcal mol^{-1})[a]	% mol	cumulative % mol	cyclopropane configuration
ts15a'-*anti*-I-*Re*-Λ	1.6	3.8		
ts15a'-*anti*-I-*Re*-V	1.0	10.8		
ts15a'-*anti*-II-*Re*-Λ	4.3	0.0		
ts15a'-*anti*-II-*Re*-V	2.4	1.1	74.0	1*R*
ts15a'-*syn*-I-*Re*-Λ	–	–		
ts15a'-*syn*-I-*Re*-V	3.4	0.2		
ts15a'-*syn*-II-*Re*-Λ	--	--		
ts15a'-*syn*-II-*Re*-V	**0.0**	58.1		
ts15a'-*anti*-I-*Si*-Λ	–	–		
ts15a'-*anti*-I-*Si*-V	4.4	0.0		
ts15a'-*anti*-II-*Si*-Λ	1.2	7.7		
ts15a'-*anti*-II-*Si*-V	1.1	8.9	26.0	1*S*
ts15a'-*syn*-I-*Si*-Λ	2.6	0.8		
ts15a'-*syn*-I-*Si*-V	1.2	8.1		
ts15a'-*syn*-II-*Si*-Λ	3.9	0.1		
ts15a'-*syn*-II-*Si*-V	3.1	0.3		
ts15c'-*anti*-I-*Re*-Λ	2.4	0.6		
ts15c'-*anti*-I-*Re*-V	0.7	10.1		
ts15c'-*anti*-II-*Re*-Λ	5.6	0.0		
ts15c'-*anti*-II-*Re*-V	1.7	1.8	49.3	1*R*
ts15c'-*syn*-I-*Re*-Λ	2.0	1.1		
ts15c'-*syn*-I-*Re*-V	1.4	3.2		
ts15c'-*syn*-II-*Re*-Λ	1.9	1.2		
ts15c'-*syn*-II-*Re*-V	**0.0**	31.4		
ts15c'-*anti*-I-*Si*-Λ	–	–		
ts15c'-*anti*-I-*Si*-V	2.0	1.1		
ts15c'-*anti*-II-*Si*-Λ	2.2	0.8		
ts15c'-*anti*-II-*Si*-V	0.4	17.1	50.7	1*S*
ts15c'-*syn*-I-*Si*-Λ	2.3	0.6		
ts15c'-*syn*-I-*Si*-V	0.0	30.9		
ts15c'-*syn*-II-*Si*-Λ	4.1	0.0		
ts15c'-*syn*-II-*Si*-V	3.1	0.2		
ts15d-*anti*-I-*Re*-Λ	2.1	1.5		
ts15d-*anti*-I-*Re*-V	1.8	2.8		
ts15d-*anti*-II-*Re*-Λ	2.7	0.6		
ts15d-*anti*-II-*Re*-V	–	–	66.0	1*R*
ts15d-*syn*-I-*Re*-Λ	6.0	0.0		
ts15d-*syn*-I-*Re*-V	1.3	5.9		
ts15d-*syn*-II-*Re*-Λ	3.3	0.2		
ts15d-*syn*-II-*Re*-V	**0.0**	55.0		
ts15d-*anti*-I-*Si*-Λ	6.4	0.0		
ts15d-*anti*-I-*Si*-V	2.9	0.5		
ts15d-*anti*-II-*Si*-Λ	5.0	0.0		
ts15d-*anti*-II-*Si*-V	0.6	21.6	34.0	1*S*
ts15d-*syn*-I-*Si*-Λ	4.5	0.0		
ts15d-*syn*-I-*Si*-V	1.0	10.9		
ts15d-*syn*-II-*Si*-Λ	5.1	0.0		
ts15d-*syn*-II-*Si*-V	2.4	1.1		

This erroneous inversion of the calculated enantioselectivity with respect to the experimental values obtained with aza-pyox(*i*Pr,Me) (**10c**) and aza-pyox(*t*Bu,Me) (**10d**) ligands, is probably due to an incorrect evaluation by the B3LYP functional of relatively small steric interaction differences in the TS. Better values can be obtained by performing single-point energy calculations through the recently developed

M05-2X functional on the B3LYP optimized transition structures. Hence, the re-evaluation of the energies of transition structures **ts15d** through this methodology allowed an outstanding improvement on the calculated enantioselectivity towards values very close to the experimental ones (Tables 1 and 2).

The source of this reversal on the enantioselectivity calculated through 6-methylpyridine-derived catalysts was located on the overstabilization of the *syn*-I-*Si* reaction trajectories at the expense of the *syn*-II-*Re* ones. The origin of this special stability of the **ts15c,d**-*syn*-I-*Si*-**V** transition structures is not clear, moreover when large steric interactions between the 6-methyl group and the incoming alkene and between the ester moiety and the alkyl group of the oxazoline should take place; on the contrary, these interactions appear to be attractive under the B3LYP scheme. In this sense, the proper evaluation of dispersion forces is widely recognized as one of the more important drawbacks of classic functionals like B3LYP. As a consequence, and despite of the remarkable success of the B3LYP functional in classical organic and organometallic systems, this method has been found to fail when treating problems in which dispersion forces are relevant. In these cases, the use of new functionals like Truhlar's hybrid meta-GGA M05-2X results advantageous.

ts15d-*Syn*-II-*Re*-V

ts15d-*Anti*-II-*Si*-V

Fig. 5 Possible dispositions of lowest energy **ts15d** transition structures with regard to the support surface, leading to both enantiomeric cyclopropane products. Most hydrogen atoms are omitted for clarity.

Concerning support effects, the most significant feature, apart from the well-documented preference toward *cis*-cyclopropanes, is the lack of inversion in the absolute configuration of the major *cis*-cyclopropanes with regard to the homogeneous phase reactions, similarly to that observed for quinolinoxazoline ligands,[29] but opposite to that observed with bisoxazoline ligands.[31] This result can be rationalized if the lowest energy TS in homogeneous phase is also the lowest energy one in heterogeneous phase. Figure 5 shows several ideal dispositions for lowest energy Re and Si TS, in the case of ts15d. As can be seen, ts15d-Syn-II-Re-V allows a closer ion pair disposition between the copper complex and the negatively charged support, whereas the two possible dispositions of ts15d-Anti-II-Si-V result in larger cation-anion separation, so in higher relative energies. This situation is similar to that previously described for quinolinoxazoline ligands.[8] It is worth noting that, depending on the structure of the C_1-oxazoline-based ligand, coming from the same chiral aminoalcohol, either (1R)- or (1S)-*cis*-cyclopropanes can be selectively obtained in heterogeneous catalysis, which constitutes a nice example of interplaying between support confinement effect and chiral ligand design.

Conclusions

We have synthesized a series of chiral aza-pyridinoxazoline ligands, a new class of C_1-symmetric ligands with a single stereogenic center, through a general synthetic method. These ligands have been tested in the enantioselective supported catalysis of the cyclopropanation reaction of styrene with ethyl diazoacetate, with the aim to improve surface confinement effects of the clay support on the reaction stereoselectivity, due to the foreseeable better adaptation of the chiral complex to the surface. In the case of *trans/cis* diastereoselectivity, the support confinement effects result in a reversal of selectivity, leading to good *cis*-selectivity values. On the other hand, in general, the enantioselectivities do not display important variations upon catalysts supporting, except in the case of ligand **10c**, for which a fairly good enantioselectivity (60% ee) is obtained in the major *cis*-cyclopropane. These results suggest the existence of multiple dispositions of the complex reaction intermediates with regard to the support surface. As a consequence, more work is necessary to improve the ligand design to take advantage of surface confinement effects in the enantioselective catalysis of this reaction. As a general conclusion, it can be said that depending on the structure of the C_1-oxazoline-based ligand (bisoxazoline, quinolinoxazoline, aza-pyridinoxazoline), coming from the same chiral aminoalcohol, either (1R)- or (1S)-*cis*-cyclopropanes can be selectively obtained in heterogeneous catalysis, illustrating the interplay between chiral ligand structure and support confinement effects.

A theoretical mechanistic study has been carried out to explain the origin of the enantioselectivity in homogeneous phase at a molecular level. The theoretical study allows to conclude that steric interactions different from those originated at the stereogenic centers of the chiral ligand might also be important in determining the final enantioselectivity of the catalyst. This knowledge can help in the design of more efficient chiral ligands, lacking C_2 symmetry. The theoretical results also help to explain the low enantioselectivity values obtained in most cases with supported catalysts. The presence
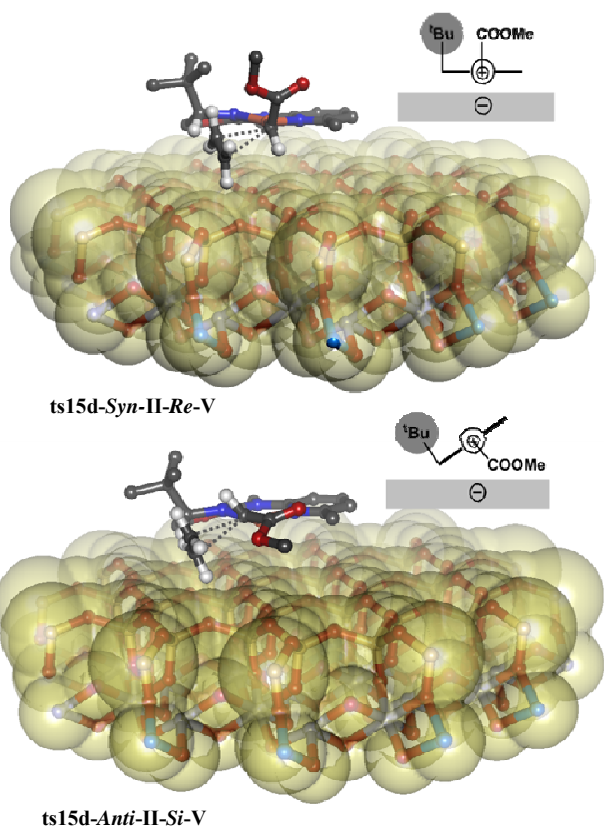
of different chelate complex conformations increase the number of possible reaction channels, making it more difficult the selective formation of a single cyclopropane enantiomer.

Experimental Section

General Methods

All reactions were carried out under argon atmosphere in oven-dried glassware. Dichloromethane, tetrahydrofuran and toluene were dried in an SPS-Device. Ethanol was distilled from magnesium. Amino acids were used as commercially available. 2-Ethoxyoxazolines (**8a,b**) were synthesized by the method described by Reiser et al.[33] Aminopyridines are commercially available, and were distilled prior use.

General procedure for the synthesis of the Aza-Pyridinoxazolines

Ethoxyoxazoline (7.5 mmol), aminopyridine (7.5 mmol) and a catalytic amount of *p*-toluensulfonic acid (20 mg) were dissolved in toluene (40 ml) and heated at reflux for 60 h. After this period, the solution was concentrated in vacuum and purified by chromatography on neutral alumina using ethyl acetate/hexane (7:3) and 5% Et$_3$N as eluent.

(*S*)-4-isopropyl-*N*-(pyridin-2-yl)-4,5-dihydrooxazol-2-amine (9a)

Prepared according to the general procedure, reaction of (*S*)-2-ethoxy-4-isopropyl-4,5-dihydrooxazol and 2-aminopyridine gave the title compound as a colorless solid in a yield after purification of 20%.
Mp: 116.5-117.6 [α]$_D^{20}$ (*c* 0.99, CH$_2$Cl$_2$) +130.0; ^{1}H NMR (400MHz, CDCl$_3$, δ ppm) δ 8.21 (ddd, 1H; *J* = 0.8 Hz, *J* = 2 Hz, *J* = 5.1 Hz), 7.54 (td, 1H; *J* = 2 Hz, 7.8 Hz), 6.95 (d, 1H; *J* = 7.8 Hz), 6.76(t, 1H; *J* = 5.2 Hz), 4.36(t, 1H; *J* = 8.5 Hz), 4.05 (dd, 1H; *J* = 6.2 Hz, 8.5 Hz), 3.76 (dd, 1H; *J* = 6.8 Hz, *J* = 14.7 Hz), 1.74(m, 1H), 0.95 (d, 3H; *J* = 6.7 Hz), 0.88 (d, 3H; *J* = 6.7 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ 146.0, 137.0, 120.0, 116.5, 112.5, 67.5, 61.0, 32.5, 31.0, 29.8, 18.5, 18.0; m/z (ESI+) 206 ; IR (cm^{-1}): 1587 Anal. Calcd. for C$_{11}$H$_{15}$N$_3$O: C, 64.3; H, 7.3; N, 20.5. Found: C, 63.7; H, 7.0; N, 19.8.

(*S*)-4-*tert*-butyl-*N*-(pyridin-2-yl)-4,5-dihydrooxazol-2-amine (9b)

Prepared according to the general procedure, reaction of (*S*)-2-ethoxy-4-*tert*-butyl-4,5-dihydrooxazol and 2-aminopyridine provided the title compound as a colorless solid in a yield after purification of 17%.
Mp: 93.3-94.1 [α]$_D^{20}$ (*c* 0.90, CH$_2$Cl$_2$) +121.3; ^{1}H NMR(400 MHz, CDCl$_3$, δ ppm) δ 8.2 (dd, 1H; *J* = 1.89 Hz, *J* = 5 Hz), 7.48(t, 1H; *J* = 7.58 Hz), 6.95 (d, 1H; *J* = 7.9 Hz), 6.76 (dd, 1H; *J* = 0.8 Hz, 11.75 Hz), 4.28 (t, 1H; *J* = 8.7 Hz), 4.15 (dd, 1H; *J* = 5 Hz, 8.8 Hz), 3.7 (dd, 1H; *J* = 5.4 Hz, *J* = 8.5 Hz), 0.9 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ 146.0, 137.5, 120.5, 116.5, 66.0, 64.2, 50.3, 35.1, 33.7, 25.1; m/z

(ESI+) 220; IR (cm^{-1}): 1587. Anal. Calcd. for C$_{12}$H$_{17}$N$_3$O: C, 65.75; H, 7.75; N, 19.18. Found: C, 66.88; H, 8.20; N, 17.81.

(*S*)-4-isopropyl-*N*-(6-methylpyridin-2-yl)-4,5-dihydrooxazol-2-amine (9c)

Prepared according to the general procedure, reaction of (*S*)-2-ethoxy-4-isopropyl-4,5-dihydrooxazol and 2-aminopycoline provided the title compound as a colorless solid in a yield after purification of 16%.
Mp: 83.6-84.3 [α]$_D^{20}$ (*c* 0.98, CH$_2$Cl$_2$) +128,2; ^{1}H NMR(400 MHz, CDCl$_3$, δ ppm) δ7.38 (t, 1H; J=7.7 Hz), 6.83 (d, 1H; J=7.7 Hz), 6.69 (d, 1H; *J* = 7.7 Hz), 4.43(t, 1H; *J* = 8.4 Hz), 4.04 (dd, 1H; J=6.4 Hz, J=8.4 Hz), 3.80 (dd, 1H; J= 7.4 Hz, J= 14.6 Hz), 2.38 (s, 3H), 1.79(m, 1H), 1.03 (d, 3H; J=6.6 Hz), 0.95 (d, 3H; J=6.6 Hz).^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ 137.5, 117.2, 115.7, 68.0, 61.0, 32.5, 24.5, 18.5, 18.2.; m/z (ESI+) 220; IR (cm^{-1}): 1648. Anal. Calcd. for C$_{12}$H$_{17}$N$_3$O: C, 65.75; H, 7.75; N, 19.18. Found: C, 63.54; H, 7.23; N, 19.24.

(*S*)-4-*tert*-butyl-*N*-(6-methylpyridin-2-yl)-4,5-dihydrooxazol-2-amine (9d)

Prepared according to the general procedure, reaction of (*S*)-2-ethoxy-4-*tert*-butyl-4,5-dihydrooxazol and 2-aminopycoline provided the title compound as a colorless solid in a yield after purification of 19%.
Mp: 74.5-75.6 [α]$_D^{20}$ (*c* 1.2, CH$_2$Cl$_2$) +121.6; ^{1}H NMR(400 MHz, CDCl$_3$, δ ppm) δ 7.45 (t, 1H; *J* = 7.7 Hz), 6.83 (d, 1H; *J* = 8.1 Hz), 6.69 (d, 1H; *J* = 7.3 Hz), 4.34 (t, 1H; *J* = 8.8 Hz), 4.20 (dd, 1H; *J* = 5.4 Hz, 8.9 Hz), 3.8 (dd, 1H; *J* = 5.4 Hz, *J* = 8.7 Hz), 2.44 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ 153.6, 137.0, 122.4,120.6, 114.9, 64.9, 44.5, 32.7, 30.0, 24.1, 23.5 m/z (ESI+) 234; IR (cm^{-1}): 1644. Anal. Calcd. for C$_{12}$H$_{17}$ON$_3$: C,66.95; H,8.15; N,18.03. Found: C, 57.23; H, 8.8; N, 12.78.

General Procedure for the methylation of Aza-pyridinoxazolines

The corresponding Aza-pyridinoxazoline (1 mmol) was dissolved in THF (10 ml) and a 15% solution of *n*-butyl lithium in hexane (1.5N, 688 μL) was added at –78ºC. After stirring for 20 min iodomethane (2.5mmol, 355 mg) was added. The cooling bath was removed and stirring at room temperature continued for 10 h. After evaporation of the solvent the residue was partitioned between CH$_2$Cl$_2$ (10 mL) and saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (2x5mL) and the combined organic phases dried over NaSO$_4$. Evaporation of the solvent yielded the corresponding products as yellow oils.

(*S*)-4-isopropyl-*N*-methyl-*N*-(pyridin-2-yl)-4,5-dihydrooxazol-2-amine (10a)

Prepared according to the general procedure using 220 mg of **9a** to yield 98%.
[α]$_D^{20}$ (*c* 0.81, CH$_2$Cl$_2$) –19.4; ^{1}H NMR (400 MHz, CDCl$_3$, δ ppm) δ 8.26 (ddd, 1H; *J* = 0.8 Hz, *J* = 1.9 Hz, *J* = 4.9 Hz), 7.8 (dt, 1H; *J* = 0.8 Hz, 8.5 Hz), 7.52 (ddd, 1H; *J* = 1.9 Hz, *J* =

6.9 Hz, J = 7.20 Hz), 6.84 (ddd, 1H; J = 0.9 Hz, J = 4.9 Hz, J = 7.2 Hz), 4.28 (dd, 1H; J = 8.2 Hz, J = 8.9 Hz), 4.01 (dd, 1H; J = 7 Hz, 8 Hz), 3.76 (td, 1H; J = 6.7 Hz, J = 9 Hz), 3.45 (s,3H), 1.7(m, 1H), 0.94 (d, 3H; J = 6.7 Hz), 0.85 (d, 3H; J = 6.7 Hz); ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ 147.3, 136.9, 124.9, 117.9, 116.9,70.7, 70.5, 33.3, 19.0, 18.0, 16.3; m/z (ESI+) 220; IR (cm^{-1}): 1650 Anal. Calcd. for C$_{12}$H$_{17}$N$_3$O: C, 65.7; H, 7.8; N, 19.2. Found: C, 63.7; H, 7.5; N, 17.3.

(*S*)-4-*tert*-butyl-*N*-methyl-*N*-(pyridin-2-yl)-4,5-dihydroooxazol-2-amine (10b)

Prepared according to the general procedure using 220 mg of **9b** to yield 98%.

$[α]_D^{20}$ (*c* 1.05, CH$_2$Cl$_2$) +12.5; ^{1}H NMR(400 MHz, CDCl$_3$, δ ppm) δ 8.3 (ddd, 1H; J = 0.76 Hz, J = 1.91 Hz, J = 4.89 Hz), 7.9 (d, 1H; J = 8.54 Hz), 7.5 (dd, 1H; J = 1.98 Hz, J = 7.18 Hz), 6.8 (ddd, 1H; J = 0.87 Hz, 4.92 Hz, J = 7.20 Hz), 4.2 (dd, 1H; J = 8.49 Hz, J = 9.30 Hz), 4.1 (dd, 1H; J = 6.54 Hz, 8.39 Hz), 3.78 (dd, 1H; J = 6.5 Hz, J = 9.4 Hz), 3.5 (s, 3H) 0.86 (s, 9H);(hacer); ^{13}C NMR (400 MHz, CDCl$_3$, δ ppm) δ 146.0, 137.5, 120.5, 116.5, 66.0, 64.2, 50.3, 35.1, 33.7, 25.1; m/z (ESI+) 234; IR (cm^{-1}): 1653. Anal. Calcd. for C$_{13}$H$_{19}$ON$_3$: C,66.9; H,8.2; N, 18.0. Found: C,67.3; H,7.9; N,17.6.

(*S*)-4-isopropyl-*N*-methyl-*N*-(6-methylpyridin-2-yl)-4,5-dihydroooxazol-2-amine (10c)

Prepared according to the general procedure using 220 mg of **9c** to yield 99%.

$[α]_D^{20}$ (*c* 0.90, CH$_2$Cl$_2$) −10.3; ^{1}H NMR(400 MHz, CDCl$_3$, δ ppm) δ 7.60 (d, 1H; J = 8.3 Hz), 7.50(t, 1H; J = 7.8 Hz), 6.80 (d, 1H; J = 7.3 Hz), 4.34 (dd, 1H; 8.1 Hz, 8.9 Hz), 4.09 (dd, 1H; J = 6.9 Hz, 8.0 Hz), 3.7 (td, 1H; J = 6.5 Hz, J = 8.9 Hz), 3.54 (s,3H), 2.49 (s,3H), 1.02 (d, 3H, J = 6.7 Hz), 0.93 (d, 3H, J = 6.7); ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ 156.3, 154.5, 137.2, 117.2, 113.7, 70.5, 70.4, 35.2, 33.3, 24.4, 18.9, 17.9; m/z (ESI+) 234; IR (cm^{-1}): 1648. Anal. Calcd. for C$_{13}$H$_{19}$N$_3$O: C, 66.9; H, 8.1; N, 22.8. Found: C, 65.7; H, 7.7; N, 21.2.

(*S*)-4-*tert*-butyl-*N*-methyl-*N*-(6-methylpyridin-2-yl)-4,5-dihydroooxazol-2-amine (10d)

Prepared according to the general procedure using 220 mg of **9d** to yield 98%.

$[α]_D^{20}$ (*c* 0.90, CH$_2$Cl$_2$) +15.1; ^{1}H NMR(400 MHz, CDCl$_3$, δ ppm) δ 7.61(t, 1H; J = 8.3 Hz),7.47 (dd, 1H; J = 7.4 Hz, 8.3 Hz), 6.76 (d, 1H; J = 7.3 Hz), 4.25 (dd, 1H; J = 8.5 Hz, 9.2 Hz), 4.17 (dd, 1H; J = 6.4 Hz, 8.4 Hz), 3.86 (dd, 1H; J = 6.4 Hz, J = 9.3 Hz), 3.5 (s,3H), 2.5 (s, 3H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ 156.3, 154.5, 137.2, 117.1, 113.5, 74.1, 68.9, 35.1, 34.1, 30.9, 25.7, 24.4 m/z (ESI+) 248; IR (cm^{-1}): 1654. Anal. Calcd. for C$_{14}$H$_{21}$N$_3$O: C, 71.8; H, 7.8; N,14.8. Found: C, 72.4; H, 7.5; N, 15.7.

(*S*)-*N,N*-(1,4-phenylenebis(methylene))bis(4-*tert*-butyl-*N*-(6-methyl-pyridin-2-yl)-4,5-dihydroooxazol-2-amine)(13)

248 mg (1 mmol) of **9d** was dissolved in tetrahydrofuran (10 ml) and a 15% solution of n-butyl lithium in hexane (1.5N, 688 µL) was added at -78ºC. After stirring for 20 min α,α′-Dibromo-*p*-xylene (0.45 mmol, 11.88 mg) was added. The cooling bath was removed and stirring at room temperature continued for 10 h. After evaporation of the solvent the residue was partitioned between CH$_2$Cl$_2$ (10 mL) and saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (2x5mL) and the combined organic phases dried over NaSO$_4$. After evaporation of the solvent, the product was purified by chromatography on neutral alumina using ethyl acetate/hexane 7/3 and 5% Et$_3$N as eluent to yield 70% of **13** as a yellow oil.

$[α]_D^{20}$ (*c* 0.99, CH$_2$Cl$_2$) +12.3; ^{1}H NMR(400 MHz, CDCl$_3$, δ ppm) δ 7.67 (d, 1H; J = 8.3 Hz), 7.47 (dd, 1H; J = 7.4 Hz, 8.3 Hz), 6.75 (d, 1H; J = 7.3 Hz), 5.3(q, 2H; J = 15.1 Hz), 4.15(m, 2H), 3.84 (dd, 1H; J = 6.2 Hz, 9.3 Hz), 2.42 (s, 3H), 0.85 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm) δ.158.6, 156.2, 153.6, 137.6, 137.3, 127.5, 117.2, 113.7, 74.2, 68.7, 49.9, 34.1, 30.9, 29.7, 25.6, 24.3; m/z (ESI+) 569; IR (cm^{-1}): 1649 Anal. Calcd. for C$_{34}$H$_{44}$N$_6$O$_2$: C, 71.8; H, 7.8; N,14.8. Found: C, 73.7; H, 6.7 ; N,15.3.

Preparation of Immobilized Catalysts

The complex for cationic exchange was prepared by mixing Cu(OTf)$_2$ (65.1 mg, 0.18 mmol) with a solution of the corresponding **10** ligand (0.20 mmol) in dichloromethane (2 mL). After stirring for 30 min under inert atmosphere, the solution was filtered through a syringe PTFE microfilter, and the solvent was evaporated under reduced pressure. The residue was redissolved in anhydrous methanol (3 mL), and dried laponite (500 mg) was added to this solution. The suspension was stirred at room temperature for 24 h, and the solid was filtered and washed with anhydrous methanol (7 mL) and dichloromethane (10 mL). The resulting freshly exchanged catalyst was dried under vacuum overnight. The catalysts were characterized by elemental analysis, copper analysis, and transmission FT-IR spectroscopy of self-supported wafers evacuated (<10^{-4} Torr) at 50 °C.

Catalytic Tests

Homogeneous Phase

The complex was prepared by mixing Cu(OTf)$_2$ (65.1 mg, 0.18 mmol) with a solution of the corresponding ligand (0.20 mmol) in dichloromethane (2 mL). After stirring for 30 min under inert atmosphere, the solution was filtered through a syringe PTFE microfilter and added to a solution of styrene (2 mL, 2.0 mmol) and *n*-decane (50 mg, internal standard) in anhydrous dichloromethane (1 mL). Ethyl diazoacetate (two additions of 2.5 mmol) was then slowly added with a syringe pump at room temperature. The reaction was monitored by gas chromatography. FID from Hewlett–Packard 5890-II, cross-linked methyl silicone column (SPB): 25m × 0.2mm × 0.33µm; helium as carrier gas. 20 psi; injector temperature: 230 °C; detector temperature: 250 °C; oven program: 70 °C (3 min), 15°C min^{-1} to 200 °C (5 min); retention times: ethyl diazoacetate 3.2 min, styrene 3.82 min, *n*-decane 5.47 min,

diethyl maleate 7.84 min, diethyl fumarate 8.02 min, *cis*-cyclopropanes 10.91 min, *trans*-cyclopropanes 11.41 min. The asymmetric inductions of the reactions also were determined by gas chromatography with a Cyclodex-*β* column. Oven temperature program: 125 °C isotherm; retention times: (1*S*,2*R*)-cyclopropane (**4S**) 28.9 min, (1*R*,2*S*)-cyclopropane (**4R**) 29.8 min, (1*R*,2*R*)-cyclopropane (**3R**) 34.3 min, (1*S*,2*S*)-cyclopropane (**3S**) 34.9 min.

Heterogeneous Phase

Ethyl diazoacetate (228 mg, 2.0 mmol) was slowly added with a syringe pump over 2 h to a suspension of laponite catalyst (150 mg) in styrene (2 mL, 2.0 mmol) containing *n*-decane (internal standard, 50 mg) at room temperature. The reaction was monitored by gas chromatography with SPB and Cyclodex-β columns. After total consumption of the diazoacetate the solid catalyst was filtered off. Additional ethyl diazoacetate (228 mg, 2.0 mmol) was slowly added to the filtrate, and the absence of reaction was tested by GC.

Theoretical Calculations

Quantum chemical calculations were carried out by means of the B3LYP[49,50] and M05-2X[41–48] hybrid functionals. Full geometrical optimizations using the 6-31G(d) basis set were carried out with the Gaussian 03 package.[51] Analytical frequencies were calculated at the same level used in the geometry optimization, and the nature of the stationary points was determined in each case according to the right number of negative eigenvalues of the Hessian matrix. Hard data on electronic energies, enthalpies, and Gibbs free energies of the different conformations of all structures considered are available as Supporting Information.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Tables of electronic energies, as well as enthalpies, entropies, and Gibbs free energies (the last three data series at 25 °C) for the different conformations of the structures considered in this work. Calculated geometries of the structures discussed in this paper. See DOI: 10.1039/b000000x/

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