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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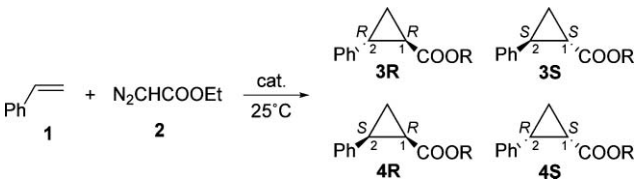
Aza-pyridinoxazoline ligands, a new class of C_1-symmetric ligands, are described and tested in the heterogeneous enantioselective catalysis of a cyclopropanation reaction, with the aim of improving surface confinement effects by the clay support on the reaction stereoselectivity. In the case of *trans*/*cis* 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 the origin of the enantioselectivity in the 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 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 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 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 as non-covalent immobilization strategies, such as entrapment, electrostatic or adsorptive methods.[3,4]

In this regard, the first unequivocally demonstrated confinement effect by the support surface on an enantioselective reaction concerns the cyclopropanation reaction of styrene with ethyl diazoacetate (Scheme 1),[5] catalyzed by the C_2-symmetric bis(oxazoline) ligand bearing phenyl groups.[6–8]

Complete reversal of stereoselectivities with regard to the homogeneous phase catalytic reaction was observed when the support was laponite, a synthetic clay with a lamellar structure.[9] A marked *cis* preference, in contrast to the *trans* preference observed in solution,[5] was observed, and the asymmetric 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 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[11–21] and the strong ion-pair interaction between the key copper-carbene intermediate 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 of the complex. Several 2-oxazolinylpyridine,[22–24] 8-oxazolinylquinoline,[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]



Scheme 1 Benchmark cyclopropanation reaction between styrene and ethyl diazoacetate.

From these studies, the enhancement of support confinement effects with C_1-symmetric ligands have been corroborated through the observation of 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

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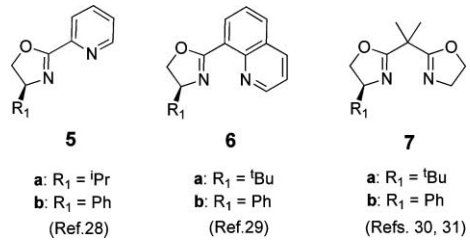
† Electronic supplementary information (ESI) available: Tables of electronic energies, as well as enthalpies, entropies, and Gibbs free energies (the last three data series at 25 °C) for the different conformations of the structures considered in this work. Calculated geometries of the structures discussed in this paper. NMR spectra of the chiral ligands described. See DOI: 10.1039/b919274c



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

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 combine 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.

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. Fig. 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**

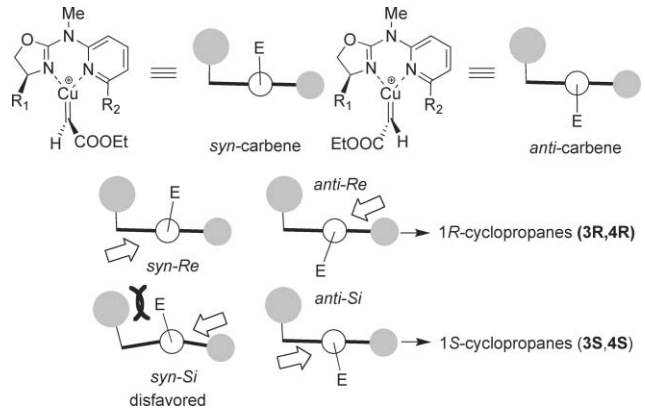


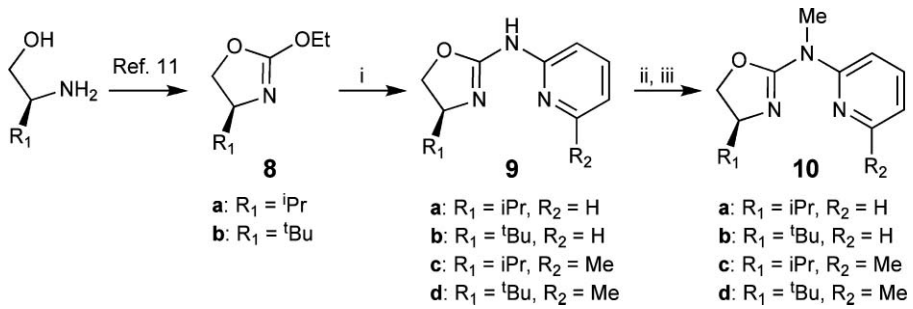
Fig. 1 A possible mechanism to explain the low, but yet significant enantioselectivities observed with C_1-symmetric ligands: only one of four main possible reaction channels is disfavored.

(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 the 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.

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 the 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 preferentially 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,



Scheme 3 Synthesis of chiral aza-pyridinoxazolines. (i) 2-aminopyridine (**a,b** compounds) or 2-amino-6-methylpyridine (**c,d** compounds), pTsOH, toluene, reflux, 48 h; (ii) *n*-BuLi, THF, –78 °C; 15 min; (iii) MeI, THF, rt, 10 h.

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

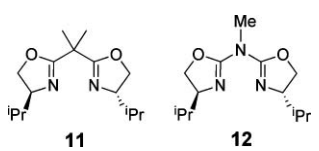
		Homogeneous (CH_2Cl_2 as solvent)					Heterogeneous (styrene as solvent)				
Entry	Ligand	Yield	**3**/**4**	%ee (**3**)[c]	%ee (**4**)[d]	1*R*/1*S*[e]	Yield	**3**/**4**	%ee (**3**)[f]	%ee (**4**)[f]	1*R*/1*S*[e]
1	**6a**[a]	65	68/32	48	28	71 : 29	59	23/77	24	33	65 : 35
2	**7a**[b]	58	68/32	29	8	61 : 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. [b] 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 1*S*-cyclopropanes (**3S**, **4S**) are the major enantiomers.

the enantioselectivity in the **4R**-cyclopropane goes from 8% ee in the homogeneous phase to 43% ee in the heterogeneous phase (Table 1, entry 4). Furthermore, cyclopropane **4R** becomes the major product in the heterogeneous phase, because of the above-mentioned *cis*-preference induced by the support.

Similarly, with **10c**, the enantioselectivity in the **4R**-cyclopropane goes from 29% ee in the homogeneous phase to 60% ee in the 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 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 the heterogeneous phase (**4S**) with regard to the catalytic result in the homogeneous phase, similar 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 to 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 (Fig. 2) were used in the same conditions. The corresponding results are presented in Table 1 (entries 7 and 8).



11 **12**

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 previously been 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 (as schematized in the upper part of Fig. 3). 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 in an attempt 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**, Fig. 3). Provided the negative charges on the support surface are placed at an adequate distance, di-copper-carbene complex of **13** should be preferentially fixed in the geometry allowing a better Coulombic interaction (as schematized in Fig. 3), hence diminishing the number of reactive approaches of styrene to this intermediate. We have recently described the synthesis and use of this kind of ditopic ligand, 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 collects the results obtained with these ditopic ligands both in homogeneous and heterogeneous catalysis experiments (entries 9 and 10).

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 (**13**) 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 Fig. 3, probably due to the fact that negative charge distribution on the support surface does not match with the distance between positive charges in the di-copper complexes, and also

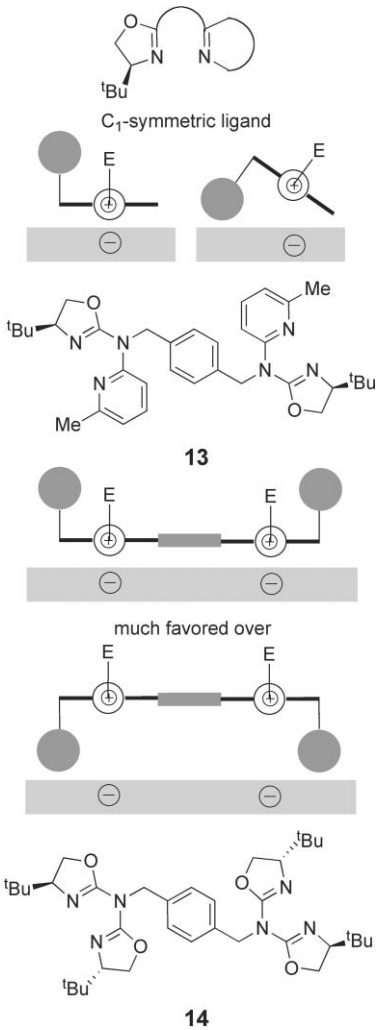


Fig. 3 C_1-symmetric aza-pyox and C_2-symmetric aza-bis(oxazoline) ditopic ligands. Proposed disposition of the copper complexes of ditopic ligand **13**, compared to a generic C_1-symmetric ligand, with regard to the laponite surface.

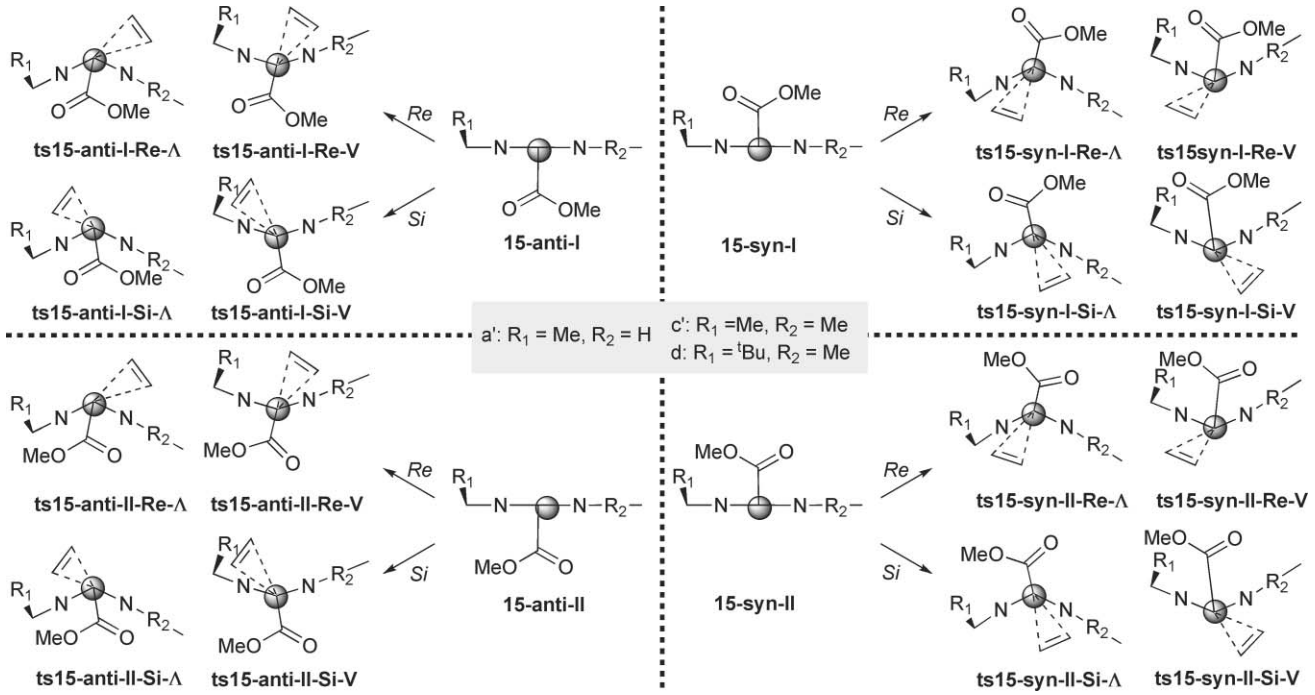
that the conformational flexibility of the latter is greater than supposed.[31]

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 performed. 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 the 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 *anti* and *syn* dispositions 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 recently developed 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 functionals in the field of transition metal thermochemistry, which is of particular interest in our theoretical study.[41–48] Fig. 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 presented in Table 2, together with the calculated enantioselectivities.

The first observation made from the energy values presented 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 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



Scheme 4

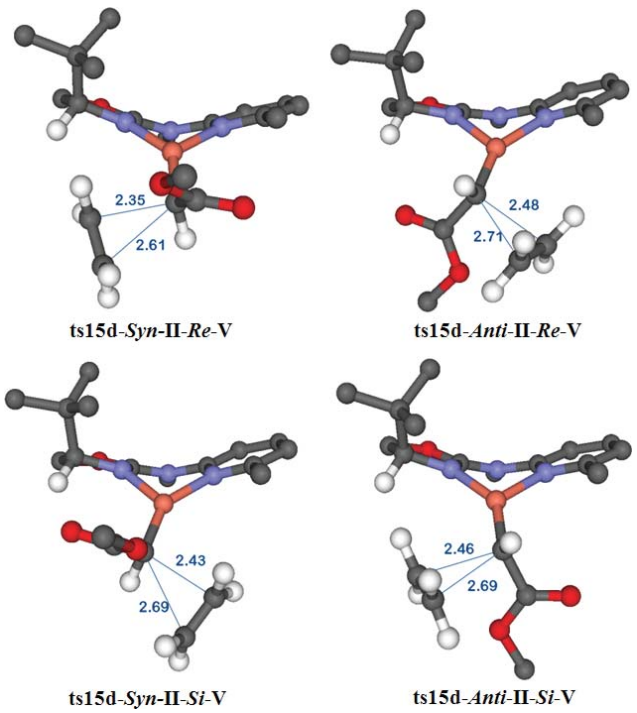


Fig. 4 Selected geometries of the lowest energy **ts15d** transition structures, leading to both enantiomeric cyclopropane products. Most hydrogen atoms are omitted for clarity.

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 $1R/1S = 33:67$ from aza-pyox(Me,Me)-Cu(I)-carbene complexes (**15c′**) and $1R/1S = 25:75$ with aza-pyox(^{t}Bu,Me)-Cu(I)-carbene complexes (**15d**) (see ESI†).

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 method-dependent 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 classical functionals like B3LYP. As a consequence, and despite the remarkable success of the B3LYP functional in classical organic and organometallic systems, this method has failed 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 are advantageous.

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,

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 **10a-d**-Cu(I) complexes

TS	$\Delta\Delta E^{\ddagger}$/ kcal mol^{-1} [a]	% mol	Cumulative % mol	Cyclopropane configuration
ts15a′-*anti*-I-*Re*-Λ	1.6	3.8	74.0	1*R*
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		
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	—	—	26.0	1*S*
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		
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	49.3	1*R*
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		
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	—	—	50.7	1*S*
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		
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	66.0	1*R*
ts15d-*anti*-I-*Re*-V	1.8	2.8		
ts15d-*anti*-II-*Re*-Λ	2.7	0.6		
ts15d-*anti*-II-*Re*-V	—	—		
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	34.0	1*S*
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		
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		

[a] Calculated ZPE-corrected energies with thermal corrections at 298.15 K.

similar 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 the homogeneous phase is also the lowest energy one in the heterogeneous phase. To shed some light on this point, we carried out some calculations taking into account the effect of the support. Given the huge size of such systems, we used a low theoretical level for geometry optimizations. Thus, we first selected the lowest energy calculated TS for the *Re* and *Si* approaches of the alkene, and reoptimized them in the presence of a model of the clay support at the ONIOM(PM6:[52]UFF) theoretical level. The inorganic support was left in the molecular mechanics part of the ONIOM calculation, and their atomic coordinates were kept fixed. Single point energy calculations were then carried out at the ONIOM(M05-2X/6-31G(d):UFF) level, to give better relative energy values. Fig. 5 shows the calculated geometries for the lowest energy *Re* and *Si* TS, in the case of **ts15d**. As can be seen, **ts15d-*syn*-II-*Re*-V** (Fig. 5a) allows a closer ion pair disposition between the copper complex and the negatively charged support, without significant geometry change. On the other hand, both the *anti* and *syn* TS in the *Si* approach (**ts15d-*anti*-II-*Si*-V** and **ts15d-*syn*-II-*Si*-V**, Fig. 5b and 5c, respectively) have problems in accommodating the surface. In the first case, the Cu–$C_{carbene}$ bond must be rotated to avoid steric interactions between the ester group and the surface. In the second one, the complex disposition results in a larger cation–anion separation. Both circumstances are reflected in the higher energy of the *Si* TS with respect to the *Re* TS (10.9 and 12.3 kcal mol^{-1}, respectively), in agreement with the experimental behavior observed. Of course, these results must be taken with caution, because of the simplicity of the model used, but they support at least qualitatively the connection between the TS-support geometrical disposition, and the resulting relative energies.

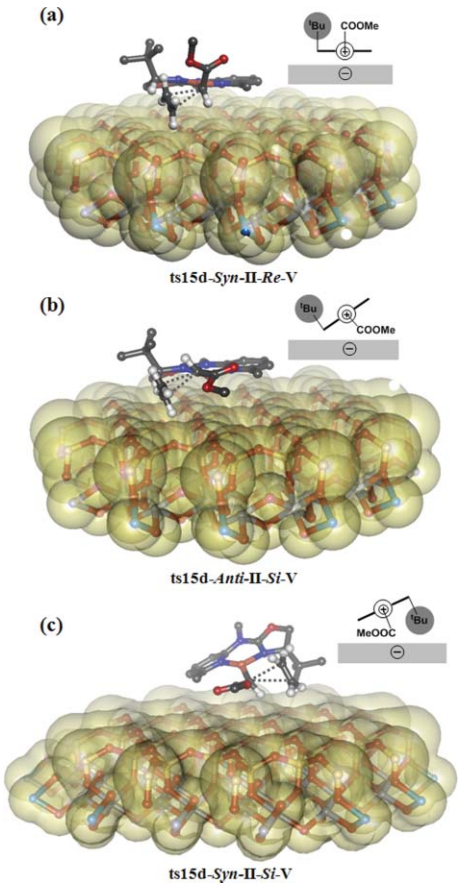


Fig. 5 Possible dispositions of the lowest energy **ts15d** transition structures with regard to the support surface, leading to both enantiomeric cyclopropane products. Most hydrogen atoms are omitted for clarity.

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 a 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 catalyst supports, 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 (1*R*)- or (1*S*)-*cis*-cyclopropanes can be selectively obtained in heterogeneous catalysis, illustrating the interplay between the chiral ligand structure and support confinement effects.

A theoretical mechanistic study has been carried out to explain the origin of the enantioselectivity in the homogeneous and heterogeneous phase at a molecular level. The theoretical study allows us 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 aid 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 increases the number of possible reaction channels, making the selective formation of a single cyclopropane enantiomer more difficult. However, as the lowest energy TS in the homogeneous phase is also the one displaying better accommodation with the support surface, no inversion in the absolute configuration of the major cyclopropane is observed, which is also corroborated by the molecular modelling studies.

Experimental

General methods

All reactions were carried out under an 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_3N 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 °C; $[\alpha]_D^{20}$ (*c* 0.99, CH_2Cl_2) +130.0; ^{1}H NMR (400 MHz, $CDCl_3$, 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 $C_{11}H_{15}N_3O$: 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 °C; $[\alpha]_D^{20}$ (*c* 0.90, CH_2Cl_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 $C_{12}H_{17}N_3O$: 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 °C; $[\alpha]_D^{20}$ (*c* 0.98, CH_2Cl_2) +128,2; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) δ 7.38 (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 $C_{12}H_{17}N_3O$: 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 °C; $[\alpha]_D^{20}$ (*c* 1.2, CH_2Cl_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 (1.5 N, 688 µL) was added at −78 °C. After stirring for 20 min iodomethane (2.5 mmol, 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_2Cl_2 (10 ml) and saturated $NaHCO_3$ (10 ml). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 ml) 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%.

$[\alpha]_D^{20}$ (*c* 0.81, CH_2Cl_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 $C_{12}H_{17}N_3O$: 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-dihydrooxazol-2-amine (10b)

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

$[\alpha]_D^{20}$ (*c* 1.05, CH_2Cl_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-dihydrooxazol-2-amine (10c)

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

$[\alpha]_D^{20}$ (*c* 0.90, CH_2Cl_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; $J = 8.1$ 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 $C_{13}H_{19}N_3O$: 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-dihydrooxazol-2-amine (10d)

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

$[\alpha]_D^{20}$ (*c* 0.90, CH_2Cl_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 $C_{14}H_{21}N_3O$: 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-dihydrooxazol-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 (1.5 N, 688 µL) was added at −78 °C. 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_2Cl_2 (10 ml) and saturated $NaHCO_3$ (10 ml). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 ml) and the combined organic phases dried over Na_2SO_4. After evaporation of the solvent, the product was purified by chromatography on neutral alumina using ethyl acetate–hexane 7/3 and 5% Et_3N as eluent to yield 70% of **13** as a yellow oil.

$[\alpha]_D^{20}$ (*c* 0.99, CH_2Cl_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 $C_{34}H_{44}N_6O_2$: 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 an 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 an 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): 25 m × 0.2 mm × 0.33 μm; 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 were also 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 ESI.† ONIOM calculations with the PM6 semiempirical method[52] were carried out with the Gaussian 09 package.[53]

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Notes and references

1 D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs, (ed.), *Chiral Catalysts Immobilization and Recycling*, Wiley-VCH, Weinheim, 2000.
2 J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral and E. Pires, *Chem. Soc. Rev.*, 2009, **38**, 695–706.
3 For a recent review on non-covalent immobilization of enantioselective catalysts, see: J. M. Fraile, J. I. García and J. A. Mayoral, *Chem. Rev.*, 2009, **109**, 360–417.
4 D. Rechavi and M. Lemaire, *Chem. Rev.*, 2002, **102**, 3467–3494.
5 For a review on stereoselective cyclopropanation reactions, see: H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977–1050.
6 G. C. Hargaden and P. J. Guiry, *Chem. Rev.*, 2009, **109**, 2505–2550.
7 R. Rasappan, D. Laventine and Oliver Reiser, *Coord. Chem. Rev.*, 2008, **252**, 702–714.
8 G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561–3651.
9 A. I. Fernández, J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral and L. Salvatella, *Catal. Commun.*, 2001, **2**, 165–170.
10 M. R. Castillo, L. Fousse, J. M. Fraile, J. I. García and J. A. Mayoral, *Chem.–Eur. J.*, 2007, **13**, 287–291.
11 Theoretical mechanistic studies: J. M. Fraile, J. I. García, V. Martínez-Merino, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, 2001, **123**, 7616–7625.
12 T. Rasmussen, J. F. Jensen, N. Èstergaard, D. Tanner, T. Ziegler and P.-O. Norrby, *Chem.–Eur. J.*, 2002, **8**, 177–184.
13 J. M. Fraile, J. I. García, M. J. Gil, V. Martínez-Merino, J. A. Mayoral and L. Salvatella, *Chem.–Eur. J.*, 2004, **10**, 758–765.
14 J. I. García, G. Jiménez-Osés, V. Martínez-Merino, J. A. Mayoral, E. Pires and I. Villalba, *Chem.–Eur. J.*, 2007, **13**, 4064–4073.
15 G. Drudis-Solé, F. Maseras, A. Lledós, A. Vallribera and M. Moreno-Mañas, *Eur. J. Org. Chem.*, 2008, 5614–5621.
16 Experimental mechanistic studies: B. F. Straub and P. Hofmann, *Angew. Chem., Int. Ed.*, 2001, **40**, 1288–1290.
17 B. F. Straub, I. Gruber, F. Rominger and P. Hofmann, *J. Organomet. Chem.*, 2003, **684**, 124–143.
18 X. Dai and T. H. Warren, *J. Am. Chem. Soc.*, 2004, **126**, 10085–10094.
19 Y. M. Badiei and T. H. Warren, *J. Organomet. Chem.*, 2005, **690**, 5989–6000.
20 P. Hofmann, I.V. Shishkov and F. Rominger, *Inorg. Chem.*, 2008, **47**, 11755–11762.
21 I.V. Shishkov, F. Rominger and P. Hofmann, *Organometallics*, 2009, **28**, 1049–1059.
22 G. Chelucci, S. Medici and A. Saba, *Tetrahedron: Asymmetry*, 1997, **8**, 3183–3184.
23 G. Chelucci, M. G. Sanna and S. Gladiali, *Tetrahedron*, 2000, **56**, 2889–2893.
24 K. Schwekendiek and F. Glorius, *Synthesis*, 2006, 2996–3002.
25 X.-Y. Wu, X.-H. Li and Q.-L. Zhou, *Tetrahedron: Asymmetry*, 1998, **9**, 4143–4150.
26 X.-G. Li, L.-X. Wang and Q.-L. Zhou, *Chin. J. Chem.*, 2002, **20**, 1445–1449.
27 J. I. García, J. A. Mayoral, E. Pires and I. Villalba, *Tetrahedron: Asymmetry*, 2006, **17**, 2270–2275.
28 A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, C. I. Herrerías, G. Legarreta, V. Martinez-Merino and J. A. Mayoral, *J. Mol. Catal. A: Chem.*, 2003, **196**, 101–108.
29 J. M. Fraile, J. I. García, G. Jiménez-Osés, J. A. Mayoral and M. Roldán, *Organometallics*, 2008, **27**, 2246–2251.
30 J. M. Fraile, J. I. García, A. Gissibl, J. A. Mayoral, E. Pires, O. Reiser, M. Roldán and I. Villalba, *Chem.–Eur. J.*, 2007, **13**, 8830–8839.

31 J. I. García, B. López-Sánchez, J. A. Mayoral, E. Pires and I. Villalba, *J. Catal.*, 2008, **258**, 378–385.
32 J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, A. Socuéllamos and H. Werner, *Chem.–Eur. J.*, 2004, **10**, 2997–3005.
33 H. Werner, R. Vicha, A. Gissibl and O. Reiser, O., *J. Org. Chem.*, 2003, **68**, 10166–10168.
34 For some examples of *cis*-selective cyclopropanation catalysts, see: M. L. Rosenberg, A. Krivokapic and M. Tilset, *Org. Lett.*, 2009, **11**, 547–550.
35 H. Suematsu, S. Kanchiku, T. Uchida and T. Katsuki, *J. Am. Chem. Soc.*, 2008, **130**, 10327–10337, and references therein.
36 C. Bonaccorsi and A. Mezzetti, *Organometallics*, 2005, **24**, 4953–4960.
37 M. M. Diaz-Requejo, T. R. Belderrain, S. Trofimenko and P. J. Pérez, *J. Am. Chem. Soc.*, 2001, **123**, 3167.
38 W. Hu, D. J. Simmons and M. P. Doyle, *Org. Lett.*, 2002, **4**, 901–904.
39 Isopropyl-substituted ligands were used instead of the *tert*-butyl-substituted ones because it is well-known that the copper complexes of the *tert*-butyl-bearing bis(oxazoline) ligand are more difficult to support, and decomplexation and loss of the chiral ligand is often observed. See Ref. 10 and: J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral and M. A. Harmer, *J. Catal.*, 2004, **221**, 532–540.
40 J. I. García, B. López-Sánchez and J. A. Mayoral, *Org. Lett.*, 2008, **10**, 4995–4998.
41 Y. Zhao, N. E. Schultz and D. G. Truhlar, *J. Chem. Theory Comput.*, 2006, **2**, 364–382.
42 Y. Zhao and D. G. Truhlar, *J. Phys. Chem. A*, 2006, **110**, 10478–10486.
43 Y. Zhao and D. G. Truhlar, *J. Phys. Chem. A*, 2006, **110**, 5121–5129.
44 Y. Zhao and D. G. Truhlar, *J. Chem. Theory Comput.*, 2006, **2**, 1009–1018.
45 Y. Zhao and D. G. Truhlar, *J. Org. Chem.*, 2007, **72**, 295–298.
46 Y. Zhao and D. G. Truhlar, *J. Chem. Theory Comput.*, 2007, **3**, 289–300.
47 Y. Zhao and D. G. Truhlar, *Org. Lett.*, 2006, **8**, 5753–5755.
48 Y. Zhao and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 157–167.
49 C. Lee, W. Yang and R. Parr, *Phys. Rev. B: Condens. Matter*, 1988, **37**, 785–789.
50 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652.
51 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *GAUSSIAN 03 (Revision E.01)*, Gaussian, Inc., Wallingford, CT, 2004.
52 J. J. P. Stewart, *J. Mol. Model.*, 2007, **13**, 1173–1213.
53 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *GAUSSIAN 09 (Revision A.2)*, Gaussian, Inc., Wallingford, CT, 2009.