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Polytopic Oxazoline-Based Chiral Ligands for Cyclopropanation Reactions: A New Strategy to Prepare Highly Recyclable Catalysts

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Abstract: New polytopic chiral copper complexes based on azabis(oxazoline) moieties have been synthesized and applied in cyclopropanation reactions of several alkenes. Excellent enantioselectivities have been obtained in all cases and additionally, the catalysts have been recovered in up to 14 cycles without noticeable loss of activity and selectivity. Analysis of the copper complexes by mass spectrometry suggests the formation of coordination polymers, representing the resting state of the catalysts.

Keywords: bis(oxazoline) ligands; catalyst recovery; cyclopropanation reaction; enantioselective catalysis; multitopic chiral ligands; self-assembled catalysts

Introduction

Enantioselective catalysis is a key strategy in order to obtain optically pure compounds.[1] In this respect, homogeneous catalysts have proved to exhibit high activity and selectivity in a great number of organic reactions.[2] However, this catalytic methodology is not always the most efficient one for large scale applications because of possible product contamination caused by incomplete separation of the catalyst, and the frequently encountered difficulties of recovery and reuse of the usually expensive chiral catalyst. This limitation can, in principle, be overcome by heterogeneous catalysts, which bear the promise of facile separation from a reaction mixture, in most cases by simple filtration, and their subsequent reuse.

Over the last decades several approaches have been developed for the successful immobilization of highly effective homogeneous catalysts.[3] The most common strategy consists in the covalent linkage of the catalyst onto a solid support. This approach usually needs a structural modification of the catalyst with the consequent increase in the number of steps for their synthesis. Nevertheless, the cost of that extra effort is not always rewarded since the activity of the catalyst, once immobilized, is usually lower and the selectivities can vary as well. These effects are also observed when the immobilization is performed by non-covalent methods due to diffusion limitations or to distortion in the geometry of the active sites in the solid matrix. These results stress the important role of the support for the catalyst performance, which still remains not well understood.[4]

However, in spite of the advantages of heterogeneous catalysts, homogeneous catalysis generally offers better values of TON per reaction and better enantioselectivities. In this context, it would be highly desirable to develop a strategy that allows us to join the best of both worlds, in other words, to combine the high activity and selectivity provided by homogeneous catalysis with the possibility of separation and recovery offered by heterogeneous catalysis.

An appealing possibility is the use of release-and-capture mechanisms, in which the catalyst remains heterogeneous when it is in its resting state at the end of the reaction, thus being easily recoverable and reusable. On the other hand, in the catalytically active state, the catalyst is dissolved in the reaction medium,

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so that catalysis is truly homogeneous. Some applications of this approach are based on catalyst microencapsulation in flexible polymer matrices, non-covalent immobilization on nanoparticles, or selective precipitation.[5]

Another possibility recently described for achiral catalysts is the use of insoluble self-assembled coordination polymers.[6] The strategy consists of the heterogenization of the homogeneous catalyst by the self-assembly of multitopic ligands and the corresponding metallic ions.

In a preliminary communication,[7] we described the application of this strategy to the enantioselective cyclopropanation reaction through the use of a new ditopic ligand **3**, coined as DAX. Herein, we describe protocols for the synthesis of new multitopic chiral ligands based on the azabis(oxazoline) moiety in order to form self-assembled coordination polymers with copper. The catalytic performance of these systems has been tested in the benchmark enantioselective cyclopropanation reaction between styrene and ethyl diazoacetate (Scheme 2), and has been extended to other cyclopropanation reactions.

In addition, structural characterization of the species involved in the formation of the coordination polymers has been done by means of mass spectrometry.

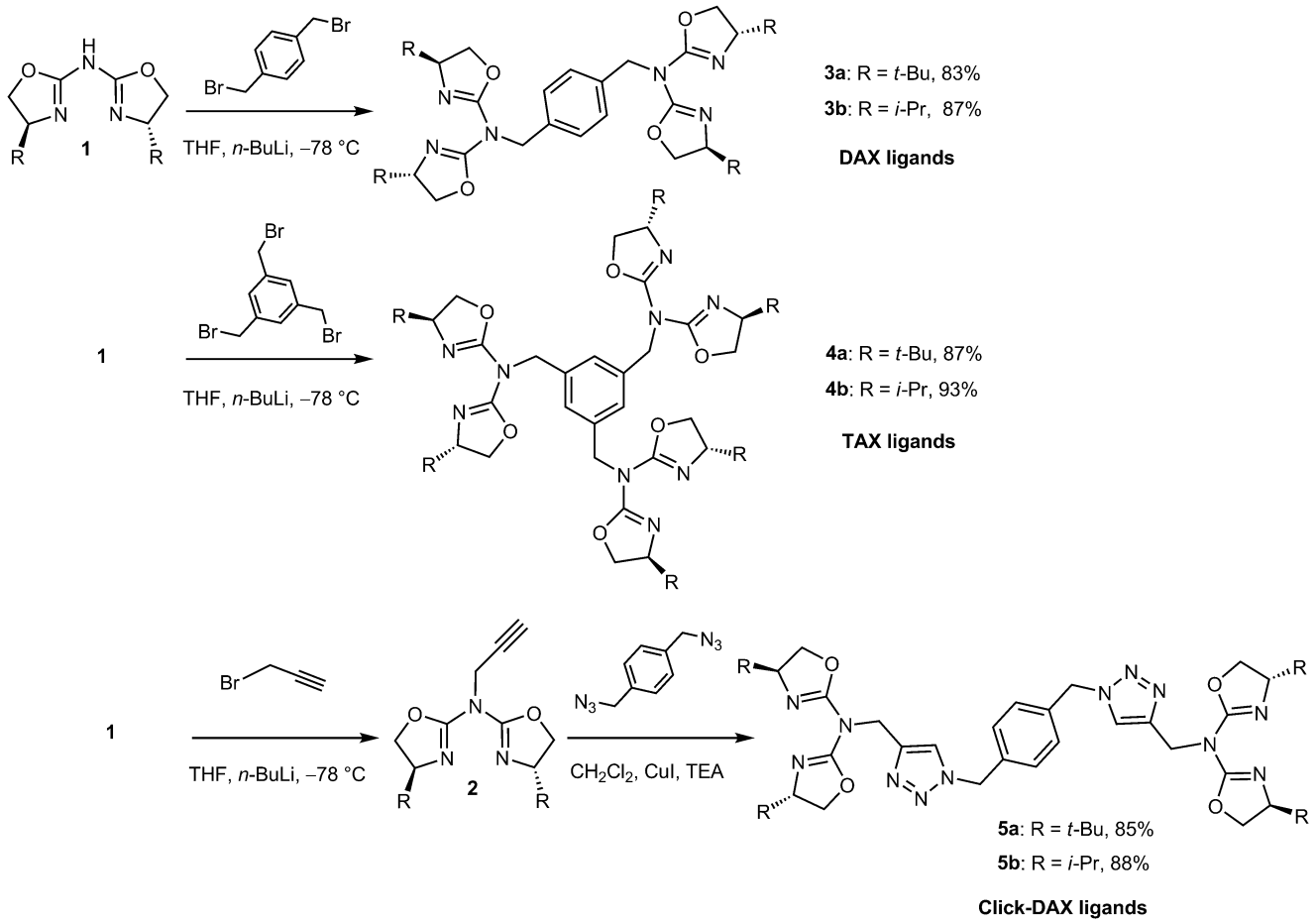
Results and Discussion

Design and Synthesis of the Ligands

The aim of synthesizing multitopic ligands based on the azabis(oxazoline) (AzaBox) moiety was to take advantage of its strong coordinating ability to copper together with its ease of preparation and functionalization.

Thus, different linkers between azabis(oxazolines) (Scheme 1) are readily introduced, which allows an effective screening of different systems with respect to their assembly, solubility and activity profile.

The synthesis of diazabis(oxazolines) (DAX) ligands was carried out following the methodology described in our previous work for *t*BuDAX.[7] Ligands **3** were obtained in high purity by metalation of aza-



Scheme 1. Synthesis of the different multitopic ligands: ***di****a*zabiso***x***azolines (DAX), ***t***ri***a***zabiso***x***azolines (TAX) and Click-***di****a*-zabiso***x***azolines (Click-DAX).

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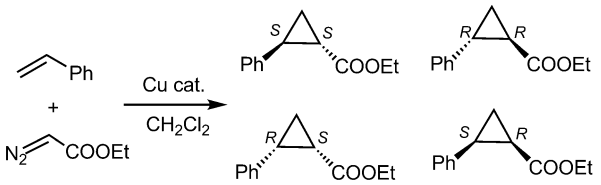

Scheme 2. Cyclopropanation reaction between styrene and ethyl diazoacetate.

bis(oxazoline) **1**[8] with butyllithium and subsequent trapping with α,α′-dibromo-*p*-xylene, followed by recrystallization in acetone (>80% yield).

Encouraged by these results, we decided to extend the procedure to the preparation of threefold ligands, namely triazabis(oxazoline) ligands **4** (TAX; Scheme 1). In this case, the linker between the azabis(oxazolines) was derived from 1,3,5-tris(bromomethyl)benzene giving rise to **4** in up to 93% yield.

It is noteworthy to point out that the total number of steps needed for the synthesis of DAX or TAX ligands is the same as those for simple alkylated azabis(oxazoline) ligands that are commonly employed as chiral ligands in homogeneous catalysts. In other words, no extra synthetic effort is required to prepare the polytopic ligands described in this study.

Alternatively ligands **5** were obtained following a click-synthetic strategy that had already been applied to link azabis(oxazolines) to polymeric, dendrimeric, and inorganic supports.[8] The same strategy has also been described for the immobilization of other chiral ligands.[9] Copper-catalyzed [3+2]cycloaddition[10] between **2** and two equivalents of 1,4-bis(azidomethyl)benzene were reacted to give rise to **5** in approximately 90% yield. Complete information on the characterization of all the new ligands prepared is available in the Supporting Information.

Formation of the Coordination Polymers

For the formation of coordination polymers based on azabis(oxazolines) **3–5** we chose copper as the ligand-connecting metal ion since monomeric copper-azabis(oxazoline) complexes have proved to be outstanding catalysts in several enantioselective reactions, including cyclopropanation reactions.[11] The copper salts to be employed must be chosen carefully because the coordination strength of the anions could prevent coordination polymers from forming. Strongly coordinating counter ions such as chloride prevent the recruiting of two AzaBox ligands by copper since the chloride anions remain in its coordination sphere.[8a] A similar consideration must be applied to the solvent: Those with strong coordinating ability, for example, methanol or acetonitrile, can compete for the copper and consequently impede the assembly of coordination polymers. Accordingly, the correct combination of anion salt and solvent was found to be critical to obtain the desired self-supported catalysts. The use of Cu(I) or Cu(II) triflate with dichloromethane turned out to be a perfect choice for obtaining the desired polymers (Figure 1). Hence, coordination polymers were formed by mixing the corresponding polytopic oxazoline ligands **3–5** with copper triflate salts in the appropriate L:Cu molar ratio in CH_2Cl_2 in all the cases. Both Cu(I) and Cu(II) are amenable for these processes.

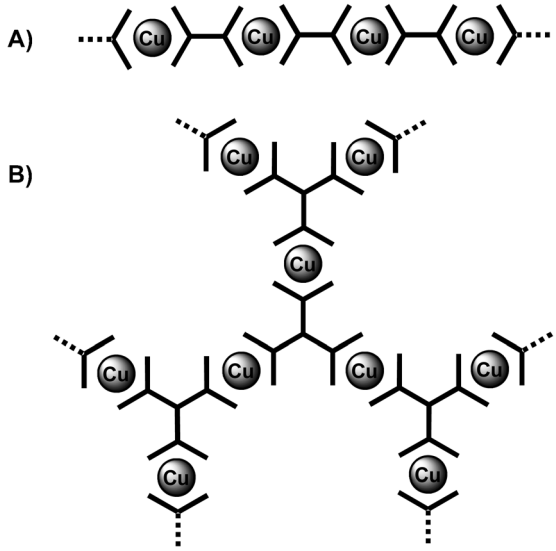

Figure 1. Schematic representation of the self-assembled catalysts from the coordination of copper cations with: **A**) DAX or Click-DAX ligands (chains) and **B**) TAX ligands (layers).

Structural Studies of the Catalysts by Mass Spectrometry

One of the most important features of a catalyst is its structure given that the catalytic performance and its recoverability are directly dependent on it. X-ray diffraction techniques have been profusely employed in the characterization of metal complexes acting as catalysts. Disappointingly, obtaining a single crystal with copper complexes of multitopic ligands **3–5** has proved to be not possible despite several crystallization techniques that have been tried.

In order to collect more information on the copper coordination polymers, some analyses were conducted by mass spectrometry. Even though those studies were carried out with most of the polymers obtained, the more detailed study was performed with the *t*BuDAX-Cu polymeric catalyst **[3a·Cu]$_n$** since it has shown the best performance in the promotion of the cyclopropanation reaction (*vide infra*).

The electrospray ionization technique calls for dissolving the sample in methanol or acetonitrile, both

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coordinating solvents. In these conditions the solvent would coordinate to the copper centers in the *t*BuDAX-Cu(I) complex, and polymeric or oligomeric species would disaggregate in monomers. Indeed, using electrospray ionization mass spectrometry (ESI-MS) carried out in a device with a single octupole solution of *t*BuDAX-Cu(I) **[3a·Cu]$_n$** in methanol the major species detected corresponds with 1:1 (or *n:n* oligomers) [*t*BuDAX-Cu(I)]$^+$ species at $m/z = 699.6$.[7] Other relevant species identified were 2:1 [DAX-Cu(I)-DAX]$^+$ at $m/z = 1336.1$ and 1:2 [Cu(I)-DAX-Cu(I)]$^{2+}$ species at $m/z = 381.4$, being in agreement with previously reported ESI mass spectra of monotopic Box and Azabox ligands, in which [L-Cu] and [L$_2$-Cu] species were found.[12]

In order to detect the presence of oligomers in the mass spectra, we therefore conducted experiments with saturated methanolic solutions of *t*BuDAX-Cu(OTf) complex **[3a·Cu]$_n$** in an ESI-MS device including an ion trap as analyzer. In its maximum resolution mode 1,650 u/sec, this device is able to resolve multicharged species up to 4+ ions. Under these conditions it was indeed possible to obtain spectra with resolved peaks, allowing their deconvolution based on isotopic patterns of the species. Thus, the presence of higher order copper-ligand species of **[3a·Cu]** could be unambiguously proved. Figure 2 shows a typical mass spectrum in which several characteristic peaks that are indicative for such higher order species appear with prominent intensity.

All the species observed in previous experiments in a standard ESI-MS-spectrometer were also detected using the spectrometer with the ion trap. In addition, peaks at $m/z = 1100.2$, 1247.3, and 1368.8 were detected, which could be assigned based on their isotopic patterns (for a detailed analysis see Supporting Information) as [*t*BuDAX$_3$-Cu$_4$Cl]$^{2+}$ (the presence of chloride is attributed to the complex formation being carried out in dichloromethane), [*t*BuDAX$_3$-Cu$_4$(OTf)$_2$MeOH]$^{2+}$ and [*t*BuDAX$_4$-Cu$_3$]$^{2+}$species, respectively.

Especially noteworthy, the peak at 700.4 displaying an isotopic distribution with a peak every third of a unit indicates the presence of a threefold-charged species that can be attributed as the [*t*BuDAX-Cu]$_3^{3+}$ ion. The signals of such multi-charged species result from superimposition of a mixture of species with the same *m/z* ratio but different *z* values. Thus, the isotopic distribution of the signal at $m/z = 700.4$, shown on the top of the Figure 3, is different from the one that would be theoretically expected for [*t*BuDAX-Cu]$_3^{3+}$ because the ions [*t*BuDAX-Cu]$_2^{2+}$ and [*t*BuDAX-Cu]$^+$ are contributing to the overall signal as well.

The detection of [*t*BuDAX-Cu]$_n^{n+}$ species ($n = 1$–3) by mass spectrometry strongly supports the hypothesis that the complexes formed in a non-coordinating solvent are indeed coordination polymers. The same conclusion is reached for the analysis of analogous MS-ESI experiments conducted for click-DAX **5a** (see Supporting Information).

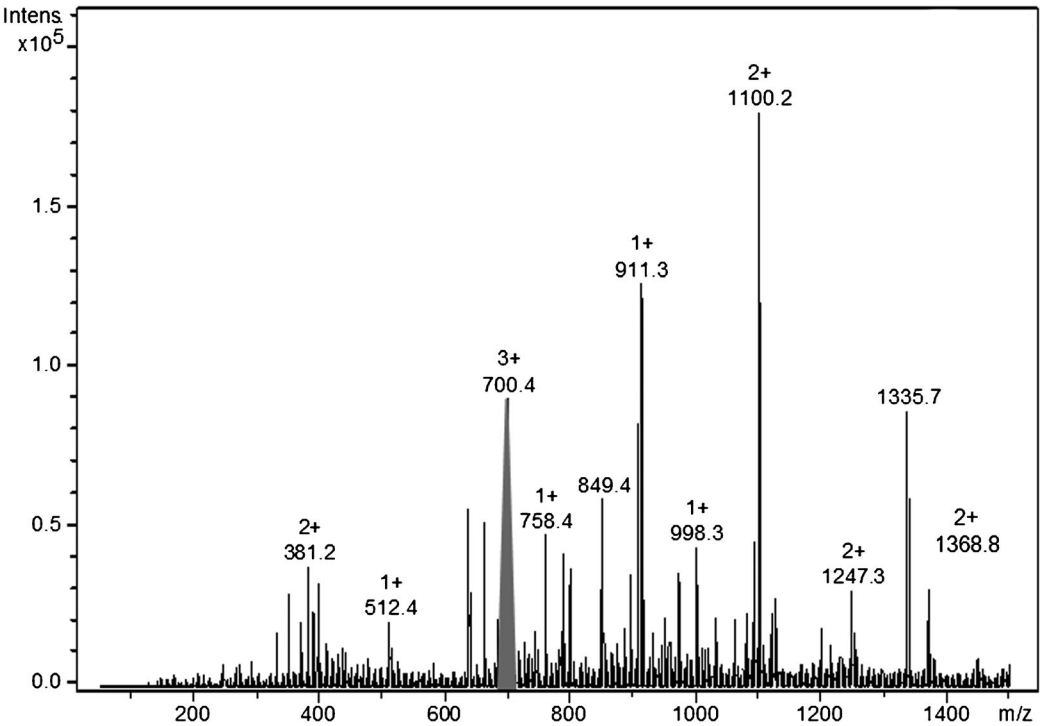

Figure 2. Infusion ESI-mass spectrum of the [*t*BuDAX-CuOTf] complex carried out in an ion trap spectrometer.

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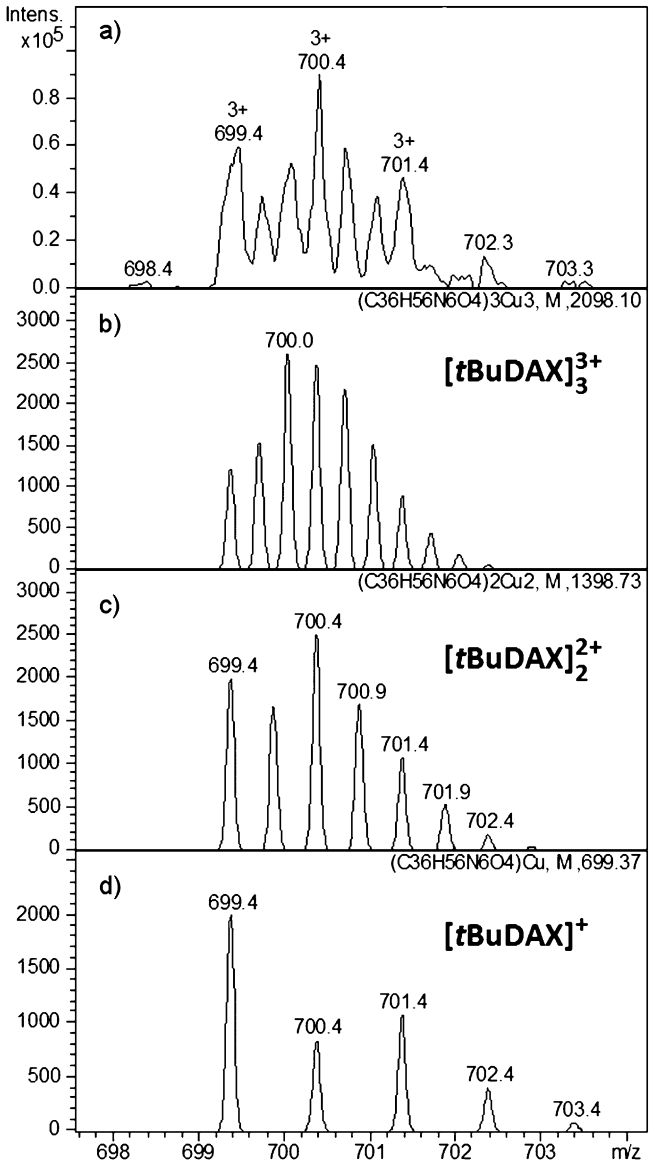

Figure 3. Enlargement of the signal at $m/z = 700.4$ (top) and theoretical simulated pattern for several $[t\text{BuDAX-Cu}]_n^{n+}$ species (below).

Catalytic Studies

Coordination polymers are attractive for applications in catalysis since they can represent the resting state of a catalyst that precipitates in the absence of reactants or by change of solvent.[13] In the presence of the latter the polymers disassemble due to competitive coordination of the reactants and thus become soluble and catalytically active. This concept is demonstrated for the copper-catalyzed cyclopropanation of styrene with ethyl diazoacetate (Scheme 2). The coordination polymer **[3a·Cu]$_n$** (obtained from mixing **3a** and $Cu(OTf)_2$ in a 1:1 ratio)[7] being insoluble in CH_2Cl_2, is broken up and thus solubilized in the presence of ethyl diazoacetate due to the formation of copper carbenoids, which are known to be decisive intermediates in the title reaction.[14] As a consequence soluble copper-DAX species are formed allowing the cyclopropanation to proceed in the homogeneous phase with similar high enantioselectivities and yields as are known from monomeric copper-bis(oxazoline) catalysts. After consumption of ethyl diazoacetate **[3a·Cu]$_n$** reassembles again and as a consequence precipitates from the reaction mixture, from which it can be recovered by filtration and subsequently reused. In all cases, we found that the first cyclopropanation reaction lasted 24 h from the end of the reagents addition until the final precipitation of the polymer, which agrees with the usual cyclopropanation reaction time. However, the formation of the copper polymer in the subsequent reactions required two to three days mainly because of the presence of by-products diethyl maleate and fumarate formed in the course of the reaction. This period can be considerably shortened by evaporating most of dichloromethane and extracting the reaction products with *n*-hexane, in which the coordination polymer is nearly insoluble. An additional advantage of using the latter strategy is the ability of dichloromethane to dissolve monomeric and oligomeric copper complexes (as indicated by the green color of the reaction solution), so it is impossible to avoid partial loss of catalytic species in the recovering procedure. We also tested the possible solubilization of catalytic species in *n*-hexane, leading to catalyst leaching. After carrying out a reaction with styrene and evaporating the dichloromethane, an extraction was performed with *n*-hexane. The hexane was subsequently removed and the sample redissolved in dichloromethane. Then, 1-octene and ethyl diazoacetate were added to the resulting solution. After four days of reaction, only a marginal activity of cyclopropanation (less than 0.5% yield) was observed, which indicates that the amount of complex lost during the recycling is almost negligible (see Supporting Information for details).

Maleate and fumarate are known to act as a catalyst poison in the title reaction by competing with ligands and substrates in coordination to copper, which has been recognized as a limiting factor for the reuse of conventional polymer-bound copper-box complexes. The ultimate formation of the insoluble coordination polymer **[3a·Cu]$_n$**, calling for coordination of copper by two ligand molecules, drives the equilibrium away from copper species being coordinated with maleate or fumarate, thus, allowing the reuse of **[3a·Cu]$_n$** for at least 14 runs without loss of activity of selectivity (Table 1, entries 3–16).

Notably, the catalysts with DAX ligands **[3a·Cu]$_n$** and **[3b·Cu]$_n$** compare well with the performance of their monomeric analogues **7a·Cu** and **7b·Cu**, respectively, both with respect to yields and selectivities. It became furthermore apparent that for the *tert*-butyl-

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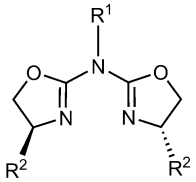
Table 1. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by *t*BuDAX-Cu and *i*PrDAX-Cu.[a]

Entry	Catalyst	Run	Yield [%]	% *ee trans*	% *ee cis*
1	**6a**·Cu	1	82	92	84
2	**7a**·Cu	1	54	98	90
3	**[3a·Cu]$_n$**	1	55	98	91
4		2	60	97	90
5		3	60	97	90
6		4	60	97	89
7		5	58	97	89
8		6	56	97	89
9		7	46	96	89
10		8	65	97	89
11		9	67	96	87
12		10	69	96	87
13		11	71	96	87
14		12	78	95	87
15		13	59	96	87
16		14	58	96	86
17	**6b**·Cu	1	45	71	55
18[b]	**6b**·Cu	1	78	66	44
19[b]	**7b·Cu**	1	44	62	47
20	**[3b·Cu]$_n$**	1	29	75	58
21		2	41	69	60
22		3	50	69	59
23		4	10	n.d.	n.d.

[a] *Reagents and conditions*: styrene (1 equiv.), ethyl diazoacetate (1 equiv.), DAX-Cu(OTf)$_2$ (1 mol%), CH_2Cl_2, room temperature. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1*R*,2*R*)-*trans*-cyclopropane and (1*R*,2*S*)-*cis*-cyclopropane are the major isomers. The *trans/cis* ratio is *ca.* 70:30 in all cases.

[b] Taken from ref.[5a], 3 equiv. of styrene were used.

substituted azabis(oxazoline) ligands a significant increase in enantioselectivity is achieved upon switching the alkyl substituent at the central nitrogen from methyl to benzyl (Table 1, entries 1–3),[15] which is nearly retained upon subsequent multiple reuse of catalyst **[3a·Cu]$_n$**. On the other hand, lower yields are obtained with **[3a·Cu]$_n$** compared to **6a·Cu**, whereas they are closer to those obtained with **7a·Cu** (Figure 4). These results suggest that, under identical conditions, catalysts with the N−Me motif lead to higher yields than those with the N−Bn motif. Similar conclusions can be reached by examining the results obtained with **6b·Cu**, **7b·Cu** and **[3b·Cu]$_n$**. (note that in the case of **7b·Cu**, in Table 1, entry 19, the yield corresponds to a reaction in which a 3:1 styrene:diazocompound ratio has been used).



6a: $R^1 = CH_3$, $R^2 = t$-Bu
6b: $R^1 = CH_3$, $R^2 = i$-Pr
7a: R^1 = Bn, $R^2 = t$-Bu
7b: R^1 = Bn, $R^2 = i$-Pr

Figure 4. Azabox ligands used in the homogeneous phase.

Concerning the erratic reaction yields observed along the recycling experiments, they could be attributed to an incomplete extraction of the products with hexane after some of the reactions. These products would accumulate in the reaction medium and subsequently, they would be extracted in the successive run. This particular behavior on the yields was also observed sometimes in the experiments with catalysts **[4a·Cu]$_n$** and **[5a·Cu]$_n$** (Table 2 and Table 3).

In agreement with previous studies on cyclopropanations with copper-box catalysts,[5] the *tert*-butyl substituted DAX ligand **[3a·Cu]$_n$** is superior in enantioselectivity than its isopropyl-substituted counterpart **[3b·Cu]$_n$**. Moreover, the possibility to reuse **[3b·Cu]$_n$** was by far inferior with respect to **[3a·Cu]$_n$**, which we attribute to a better solubility and thus less efficient precipitation of the former.

Since the recycling of the catalysts directly corresponds with the efficient formation and precipitation of their coordination polymers, we next studied the TAX-ligands **4a** that should be capable of forming two- rather than one-dimensional coordination polymers as described with DAX-ligands **3**. Copper complexes with **4a** were prepared by mixing Cu(OTf)$_2$ and **4a** in a ratio of 3:2.

Indeed, catalyst **[4a·Cu]$_n$** also performed well in the cyclopropanation of styrene, giving even higher enantioselectivities than previously obtained with **[3a·Cu]$_n$** (Table 2), which remained unaltered in eleven consecutive cycles. The catalyst recovery procedure was ex-

Table 2. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by *t*BuTAX-Cu **[4a·Cu]$_n$**.[a]

Entry	Run	Yield [%]	% *ee trans*	% *ee cis*
1	1	57	99	93
2	2	51	98	92
3	3	54	98	92
4	4	57	98	91
5	5	71	98	92
6	6	49	98	91
7	7	51	98	92
8	8	53	98	92
9	9	27	98	91
10	10	29	98	92
11	11	41	98	91

[a] *Reagents and conditions*: styrene (1 equiv.), ethyl diazoacetate (1 equiv.), *t*BuTAX-Cu(OTf)$_2$ (1 mol%), CH_2Cl_2, room temperature. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1*R*,2*R*)-*trans*-cyclopropane and (1*R*,2*S*)-*cis* cyclopropane are the major isomers. The *trans/cis* ratio is *ca.* 70:30 in all cases.

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actly the same as that used with **[3a·Cu]$_n$**, that is, partial evaporation of dichloromethane and extraction of the reaction products with several portions of *n*-hexane.

Azabis(oxazoline)-copper complexes containing triazole linkers have been found to be less soluble in organic solvents and to readily crystallize.[8a] Consequently, we synthesized ligands **5** of the DAX-type that were connected *via* additional triazole units rather than just xylyl linkers. By mixing **5a** and Cu(OTf)$_2$ again in a ratio of 1:1, the synthesis of the coordination polymer **[5a·Cu]$_n$** was attempted. As with **[3a·Cu]$_n$**, the combination of **5a** with Cu(OTf)$_2$ yielded an insoluble solid in CH_2Cl_2. In contrast to **[3a·Cu]$_n$**, the polymer **[5a·Cu]$_n$** precipitated considerably faster from CH_2Cl_2, moreover, the remaining solution was almost colorless, indicating indeed a lower solubility profile of **[5a·Cu]$_n$** with respect to **[3a·Cu]$_n$**.

Indeed, recovery of **[5a·Cu]$_n$** in cyclopropanation reactions proved to be exceptionally facile. Thus, in initially performed 10 cycles with styrene the catalyst readily precipitated at the end of the reaction and was reused. However, the enantioselectivities obtained with **[5a·Cu]$_n$** (Table 3) were somewhat lower and more erratic than those obtained with catalyst **[3a·Cu]$_n$**. This effect might be caused by the presence of the triazole rings in the ligand, which seem to be capable of coordinating copper,[8a,16] giving rise to non-enantioselective catalytic sites.

Having identified **[3a·Cu]$_n$** and **[5a·Cu]$_n$** to be most efficient in cyclopropanation reactions, we explored the scope of these catalysts, addressing especially the question if different substrates can be used with the catalyst used in a previous run with another substrate. 2,5-Dimethyl-2,4-hexadiene for its importance in the synthesis of pyrethroids, 1-octene as a linear and α-methylstyrene as a branched alkene with a larger steric hindrance on only one side of the double bond were chosen as representative substrates. After each reaction cycle, with one of these substrates the catalyst was reused in the reaction with styrene in order to assess its performance in the benchmark reaction initially studied. The results of these experiments are disclosed in Table 4 and Table 5.

Table 3. Cyclopropanation reactions between styrene and ethyl diazoacetate catalyzed by *t*Buclick-DAX-Cu **[5a·Cu]$_n$**.[a]

Entry	Run	Yield [%]	% *ee trans*	% *ee cis*
1	1	46	97	82
2	2	48	89	78
3	3	53	85	75
4	4	62	84	73
5	5	91	83	71
6	6	58	83	73
7	7	49	83	74
8	8	30	92	76
9	9	55	89	78
10	10	51	84	76

[a] *Reagents and conditions*: styrene (1 equiv.), ethyl diazoacetate (1 equiv.), *t*BuClick-DAX-Cu(OTf)$_2$ (1 mol%), CH_2Cl_2, room temperature. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1*R*,2*R*)-*trans*-cyclopropane and (1*R*,2*S*)-*cis* cyclopropane are the major isomers. The *trans/cis* ratio is *ca.* 70:30 in all cases.

Table 4. Cyclopropanation reactions of several alkenes with ethyl diazoacetate catalyzed by *t*BuDAX-Cu **[3a·Cu]$_n$**.[a]

Run	Alkene	Yield [%]	*trans/cis*	% *ee trans*	% *ee cis*
1	styrene	56	73/27	99	92
2	2,5-dimethyl-2,4-hexadiene	35	79/21	63	70
3	1-octene	75	68/32	93	93
4	α-methylstyrene	37	52/48	91	86
5	styrene	47	75/25	98	89
6	2,5-dimethyl-2,4-hexadiene	35	77/23	68	61
7	1-octene	52	68/32	95	92
8	α-methylstyrene	41	52/47	92	87
9	styrene	52	73/27	98	89

[a] *Reagents and conditions*: alkene (1 equiv.), ethyl diazoacetate (1 equiv.), *t*BuDAX-Cu(OTf)$_2$ (1 mol%), CH_2Cl_2, room temperature. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1*R*,2*R*)-*trans*-cyclopropane and (1*R*,2*S*)-*cis* cyclopropane are the major isomers. The *trans/cis* ratio is *ca.* 70:30 in all cases.

Table 5. Cyclopropanation reactions between several alkenes and ethyl diazoacetate catalyzed by *t*BuclickDAX-Cu **[5a·Cu]$_n$**.[a]

Run	Alkene	Yield [%]	*trans/cis*	% *ee trans*	% *ee cis*
1	styrene	58	74/26	94	89
2	2,5-dimethyl-2,4-hexadiene	31	78/22	66	65
3	1-octene	54	68/32	90	86
4	α-methylstyrene	66	52/48	92	88
5	styrene	41	74/26	97	84
6	1-octene	56	68/32	95	87
7	α-methylstyrene	68	51/49	93	88
8	styrene	60	73/27	93	84
9	α-methylstyrene	57	51/49	91	87
10	styrene	54	72/28	94	89

[a] *Reagents and conditions*: alkene (1 equiv.), ethyl diazoacetate (1 equiv.), *t*BuClickDAX-Cu(OTf)$_2$ (1 mol%), CH_2Cl_2, room temperature. Yield and selectivities were determined by gas chromatography (methyl silicone and cyclodex-β columns). (1*R*,2*R*)-*trans*-cyclopropane and (1*R*,2*S*)-*cis* cyclopropane are the major isomers

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For all alkenes employed, both with **[3a·Cu]$_n$** as well as with **[5a·Cu]** high enantioselectivites were achieved in all runs, comparing well with the commonly employed copper-azabox catalysts. The moderate enantioselectivities achieved with 2,5-dimethyl-2,4-hexadiene are typical for this substrate, in fact, this reaction is usually carried out with bulkier diazocompounds to achieve better enantioselectivities.[17]

Conclusions

We have described the synthesis of several coordination polymers based on the copper-azabis(oxazoline) moiety. The multitopic complexes were able to act as self-supported catalysts in cyclopropanation reactions through a capture-release mechanism, combining the advantages of both homogeneous and heterogeneous catalysis. Facile recovery of the catalysts by reforming its self-assembling polymeric structure which is insoluble in dichloromethane or hexane has been demonstrated in up to 14 cycles without a noticeable loss of activity or enantioselectivity. Structural information on the copper complexes was obtained by ESI-mass spectra, carried out in an ion trap spectrometer, proved the presence of oligomeric species, supporting the hypothesis that the solids formed in a non-coordinating solvent are coordination polymers.

Experimental Section

General Remarks

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. The starting azabis(oxazolines) and 1,4-bis(azidomethyl)benzene were prepared according to literature procedures.[8]

Synthesis of (4*S*,4′*S*)-*N*,*N*′-[1,4-Phenylenebis(methylene)]bis[4-*tert*-butyl-*N*-(4-*tert*-butyl-*N*-(4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4,5-dihydrooxazol-2-yl]amine (*t*BuDAX) (3a)

(*S*)-4-*tert*-Butyl-4,5-dihydro-oxazol-2-yl)-(4,5-dihydrooxazol-2-yl)-amine (1.00 mmol, 267 mg) was dissolved in tetrahydrofuran (10 mL) and a 15% solution of *n*-butyllithium in hexane (1.50 M, 688 μL) was added at −78 °C. After stirring for 20 min α,α′-dibromo-*p*-xylene (0.45 mmol, 11.9 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 were dried over $MgSO_4$. Evaporation of the solvent yielded the product as colorless solid which could be recrystallized from acetone; isolated yield: 87%; mp 198–199 °C; $[\alpha]_D^{20}$: −24.6 (*c* 0.85, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34 (s, 4H), 5.05 (d, 2H, *J*=15.2 Hz), 4.96 (d, 2H, *J*=15.2 Hz), 4.29 (dd, 4H, *J*=8.8, 9.2 Hz), 4.18 (dd, 4H, *J*=6.4, 8.4 Hz), 3.77 (dd, 4H, *J*=6.4, 9.2 Hz), 0.79 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.2, 136.5, 127.8, 73.4, 70.1, 52.9, 34.0, 25.5; MS (ESI+): *m/z*=637 $[M+H]^+$; IR (C=N): ν =1640 cm^{-1}; elemental Analysis: calcd. ($C_{36}H_{56}N_6O_4$): C 67.89, H 8.86, N 13.20, O 10.05; found: C 67.98, H 8.48, N 13.11, O 10.43.

Synthesis of (4*S*,4′*S*)-*N*,*N*′-[1,4-phenylenebis-(methylene)]bis{4-isopropyl-*N*-[4-isopropyl-*N*-(4-isopropyl-4,5-dihydrooxazol-2-yl]-4,5-dihydrooxazol-2-yl}amine (*i*PrDAX) (3b)

The procedure is the same as for the synthesis of **3a** using (*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-(4,5-dihydro-oxazol-2-yl)-amine (1.00 mmol, 239 mg); isolated yield: 83%; mp 114–116 °C; $[\alpha]_D^{20}$: −66.7 (*c* 0.99, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30 (s, 4H), 5.02 (d, 2H, *J*=15.2 Hz), 4.96 (d, 2H, *J*=15.2 Hz), 4.34 (dd, 4H, *J*=8.4, 9.2 Hz), 4.08 (dd, 4H, *J*=6.8, 8.4 Hz), 3.85 (m, 4H), 1.67 (m, 4H), 0.86 (d, 12H, *J*=6.8 Hz), 0.78 (d, 12H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.1, 136.5, 127.6, 71.3, 69.9, 52.6, 32.8, 18.6, 17.7; MS (ESI+): *m/z*=581 $[M+H]^+$; IR (C=N): ν=1641 cm^{-1}; elemental analysis: calcd. ($C_{32}H_{48}N_6O_4$): C 66.18, H 8.33, N 14.47, O 11.02, found: C 66.15, H 8.21, N 14.21, O 11.43.

Synthesis of (4*S*,4′*S*,4″*S*)-*N*,*N*′,*N*″-[Benzene-1,3,5-triyltris(methylene)]tris[4-*tert*-butyl-*N*-(4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4,5-dihydrooxazol-2-yl]amine (*t*BuTAX) (4a)

The procedure is the same as for the synthesis of **3a** using 1,3,5-tris(bromomethyl)benzene (0.34 mmol, 121 mg) instead of α,α′-dibromo-*p*-xylene to give **4a**; yield: 93%; mp 99–101 °C; $[\alpha]_D^{20}$: −16.0 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27 (s, 3H), 5.04 (d, 3H, *J*=15.1 Hz), 4.92 (d, 3H, *J*=15.1 Hz), 4.29 (dd, 6H, *J*=8.6, 9.3 Hz), 4.17 (dd, 6H, *J*=6.8, 8.4 Hz), 3.76 (dd, 6H, *J*=6.8, 9.4 Hz), 0.79 (s, 54H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.3, 137.4, 126.1, 73.3, 70.1, 52.9, 33.9, 25.5; MS (ESI+): *m/z*=917 $[M+H]^+$; IR (C=N): ν=1640 cm^{-1}; elemental analysis: calcd. ($C_{51}H_{81}N_9O_6$): C 66.85, H 8.91, N 13.76, O 10.48; found: C 67.30, H 8.41, N 13.64, O 10.71.

Synthesis of (4*S*,4′*S*,4″*S*)-*N*,*N*′,*N*″-[Benzene-1,3,5-triyltris(methylene)]tris[4-isopropyl-*N*-(4-isopropyl-4,5-dihydrooxazol-2-yl)-4,5-dihydrooxazol-2-yl]amine (*i*PrTAX) (4b)

The procedure is the same as for the synthesis of **3b** using 1,3,5-tris(bromomethyl)benzene (0.34 mmol, 121 mg) instead of α,α-dibromo-*p*-xylene as an oil; isolated yield: 93%; $[\alpha]_D^{20}$: −48.1 (*c* 0.95, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (s, 3H), 5.00 (d, 3H, *J*=15.1 Hz), 4.92 (d, 2H, *J*=15.1 Hz), 4.33 (dd, 6H, *J*=8.4, 9.2 Hz), 4.07 (dd, 6H, *J*=6.8, 8.4 Hz), 3.84 (m, 6H), 1.67 (m, 6H), 0.86 (d, 18H, *J*=6.8 Hz), 0.78 (d, 18H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.0, 137.3, 125.8, 71.2, 70.0, 52.7, 32.8, 18.7,

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17.7; MS (ESI+): $m/z = 833$ $[M+H]^+$; IR (C=N): $\nu = 1641\ cm^{-1}$; elemental analysis: calcd. ($C_{45}H_{69}N_9O_6$): C 64.95, H 8.36, N 15.15, O 11.54; found: C 65.10, H 8.48, N 14.95, O 11.47.

Synthesis of (4*S*,4′*S*)-*N*,*N*′-[1,1′-(1,4-Phenylenebis-(methylene)]bis[1*H*-1,2,3-triazole-4,1-diyl)]bis-(methylene)bis{4-*tert*-butyl-*N*-[(*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl]-4,5-dihydrooxazol-2-yl}amine (*t*Buclick-DAX) (5a)

(*S*)-4-*tert*-Butyl-*N*-[(*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl]-*N*-(prop-2-ynyl)-4,5-dihydrooxazol-2-amine (**2**) (2.00 mmol, 610 mg) and 1,4-bis(azidomethyl)benzene (1.00 mmol, 188 mg) were dissolved in 16 mL of CH_2Cl_2 and 4 mL of Et_3N. The mixture was stirred during 20 h at room temperature. After this time, the solvent was evaporated under reduced pressure and the residue partitioned between 10 mL of CH_2Cl_2 and a 1% EDTA (ethylenediaminetetraacetic acid) aqueous solution. The aqueous phases were extracted with CH_2Cl_2 and the combined organic phases dried over anhydrous Na_2SO_4 and subsequently, evaporated under vacuum. A recrystallization in acetone yielded dark brown crystals of the product; isolated yield: 85; mp 220–221 °C; $[\alpha]_D^{20}$: +46.6 (*c* 0.96, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$ (s, 2H), 7.22 (s, 4H), 5.46 (s, 4H), 5.12 (s, 4H), 4.30 (t, 4H, $J = 9.0$ Hz), 4.19 (t, 4H, $J = 7.6$ Hz), 3.76 (m, 4H), 0,76 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.9$, 145.0, 135.3, 128.7, 123.0, 73.4, 70.3, 53.5, 45.4, 33.9, 25.6; IR (C=N): $\nu = 1638\ cm^{-1}$; HR-MS (ESI+): $m/z = 799.5080$ $[MH^+]$, calcd. for $C_{42}H_{62}O_{12}N_4$: 799.5090.

Synthesis of (4*S*,4′*S*)-*N*,*N*′-(1,1′-[1,4-Phenylenebis-A(methylene)]bis(1*H*-1,2,3-triazole-4,1-diyl)bis(methylene)bis{4-isopropyl-*N*-[(*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl]}-4,5-dihydrooxazol-2-yl)amine (*i*Prclick-DAX) (5b)

The procedure is the same as for the synthesis of 5**a** using (*S*)-4-isopropyl-*N*-((*S*)-4-isopropyl-4,5-dihydrooxaz-ol-2-yl)-*N*-(prop-2-ynyl)-4,5-dihydrooxazol-2-amine (**2**) (2.00 mmol, 554 mg); isolated yield: 88%; mp 168–170; $[\alpha]_D^{20}$: −102.5 (*c* 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (s, 2H), 7.22 (s, 4H), 5.46 (s, 4H), 5.14 (d, 2H, $J = 15.3$ Hz), 5.06 (d, 2H, $J = 15.3$ Hz), 4.35 (t, 4H, $J = 8.8$ Hz), 4.09 (t, 4H, $J = 7.5$ Hz), 3.84 (m, 4H), 1.69–1.63 (m, 4H), 0.85 (d, 12H, $J = 6.5$ Hz), 0.77 (d, 12H, $J = 6.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.6$, 145.0, 135.0, 128.6, 123.1, 70.9, 70.0, 51.8, 45.1, 33.3, 19.3, 18.7; MS (ESI+): $m/z = 743$; IR (C=N): $\nu = 1640\ cm^{-1}$; HR-MS: $m/z = 743.4486$ $[MH^+]$, calcd. for $C_{38}H_{54}O_{12}N_4$: 743.4464.

General Procedure for the Preparation of the Copper(II)-Ligand Coordination Polymers

The ligand-copper coordination polymers were prepared by dissolving 0.02 mmol of $Cu(OTf)_2$ and either 0.02 mmol of the corresponding ditopic ligand or 0.013 mmol of TAX in 1 mL of anhydrous dichloromethane. The resulting clear solution was stirred for 15 min. After this time the corresponding coordination polymer formed appeared as a green solid precipitate, and could be used as in the catalytic tests without further treatment.

General Procedure for the Cyclopropanation Reactions

Ethyl diazoacetate (2.00 mmol) was slowly added *via* syringe pump to a solution of the corresponding alkene (2.00 mmol), *n*-decane (100 mg; internal standard) and the polymeric catalyst (0.02 mmol) in 2 mL of anhydrous dichloromethane at room temperature. During the addition of the ethyl diazoacetate the solid polymer disappeared and a clear solution appeared instead. After total consumption of the diazoacetate (approx. 24 h) the polymer catalyst precipitated again. The solution was concentrated to 0.5 mL and the solid washed with *n*-hexane and dried. In these conditions the catalyst was ready to be used again in a new reaction. Reactions were monitored by gas chromatography using an FID detector connected to a Hewlett–Packard 5890II chromatograph, using a cross-linked methyl silicone column: 25 m × 0.25 mm × 0.25 μm; helium was used as carrier gas. Column pressure: 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). The enantioselectivities of the reactions were also determined in all cases by gas chromatography using a Cyclodex-β column. Temperature program: 125 °C isotherm. Specific chromatographic conditions, retention times and some typical chromatograms are gathered in the Supporting Information.

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[13] One of the referees raised the question of the role of alkene coordination. From Kochi's seminal work it is well known that olefins have a high affinity for copper(I), so an 18-electron ligand-copper-olefin is usually proposed as the resting state of the catalyst. In our system, when pure styrene was added to the solid coordination polymer formed in dichloromethane, no appreciable changes were noticed (neither dissolution of the solid nor coloring of the liquid phase). On the other hand, when the same experiment was performed, but adding ethyl diazoacetate instead of styrene, a rapid dissolution of the solid, accompanied with color change and dinitrogen evolution, was observed. These experiments support our hypothesis that, in the case of ditopic ligands, the coordination polymer is the actual resting state of the catalyst. For the role of copper olefin complexes in the catalytic cycle, see: a) R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 3300–3310; b) M. M. Díaz-Requejo, T. R. Belderrain, M. C. Nicasio, F. Prieto, P. J. Pérez, *Organometallics* **1999**, *18*, 2601–2609.

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