DOI: 10.1002/adsc.200505197

Synthesis of Polymer Bound Azabis(oxazoline) Ligands and their Application in Asymmetric Cyclopropanations

Heiko Werner,[a] Clara I. Herrerías,[b] Michael Glos,[a] Anja Gissibl,[a] Jose M. Fraile,[b] Ignacio Pérez,[b] Jose A. Mayoral,[b,*] Oliver Reiser[a,*]

[a] Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany
Fax: (+49)-941-943-4121, e-mail: oliver.reiser@chemie.uni-regensburg.de
[b] Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón and Instituto Universitario de Catálisis Homogénea, Facultad de Ciencias, Universidad de Zaragoza-C. S. I. C., 50009 Zaragoza, Spain
E-mail: mayoral@unizar.es

Received: May 18, 2005; Revised: October 18, 2005; Accepted: November 7, 2005

Abstract: Aza(bisoxazoline) ligands were attached to various polymeric supports and the resulting immobilized ligands were evaluated in copper(I)-catalyzed asymmetric cyclopropanations. The efficiency of these transformations depends greatly on the polymeric support, on the protocol being applied for the immobilization of the ligands, and on the preparation of the catalysts.

Keywords: asymmetric cyclopropanation; azabis(oxazolines); copper; immobilization; N ligand; polymer-supported catalyst

Introduction

Azasemicorrins **1**[1] and bis(oxazolines) **3**[2] have proved to be privileged classes of chiral ligands, being able to form complexes with a broad variety of metals that are able to catalyze a great number of reactions with unparalleled enantioselectivity.

Recently, we introduced azabis(oxazolines)[3] **2** which can be viewed as structural hybrids of azasemicorrins **1** and bis(oxazolines) **3**. They combine the advantage of being accessible from the chiral pool like the bis(oxazolines) **3** and the structural variability of azasemicorrins **1** due to the possibility of functionalizing the central nitrogen atom. Therefore, an attractive feature of these ligands is their potential for attachment to polymeric supports through alkylation of the central nitrogen, thus arriving at recyclable catalysts. For example, **2c** could be attached to a polyethylene glycol support resulting in **4**, which represented the first example of a bis(oxazoline) ligand being covalently immobilized.[3] Subsequently, there have been many more reports elegantly demonstrating different strategies to attach bis(oxazoline) ligands of type **3** onto polymers.[4]

Since aza(bisoxazolines) **2** are considerably more electron-rich than the corresponding bis(oxazolines) **3**, metal complexes of **2** are less prone to dissociate, thus diminishing ligand leaching. Therefore such complexes can be immobilized in ionic liquids[5] and on nafion or clays by ion exchange[6] and employed as catalysts. On the other hand, metal-aza(bisoxazoline) complexes display a reduced Lewis acidity compared to their bis(oxa-

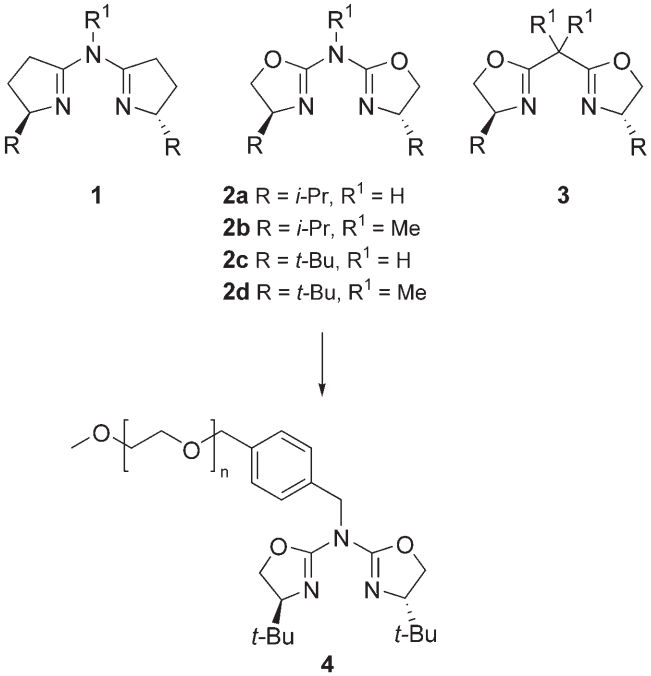


Figure 1. Chiral *N,N* ligands for asymmetric catalysis.

zoline) counterparts, as reflected, for example, in the inability of Cu(II)-aza(bisoxazoline) complexes to catalyze [4+2]-cycloadditions in sharp contrast[7] to their bis(oxazoline) analogues.

Immobilizing ligands on polyethylene glycol (MeO-PEG_{5000}) has the advantage that catalysts soluble in organic solvents such as dichloromethane are obtained. On the other hand, the low ligand loading that is achieved with this support (0.05–0.1 mmol ligand/g polymer) as well as the necessity of precipitating the catalyst by adding ether or pentane for its recovery makes the use of other polymers desirable. In this study we report the heterogenization of **2** on various polystyrene supports and evaluate the resulting ligands in copper(I)-catalyzed cyclopropanation reactions in comparison with the corresponding polyethylene glycol-supported or free ligands.

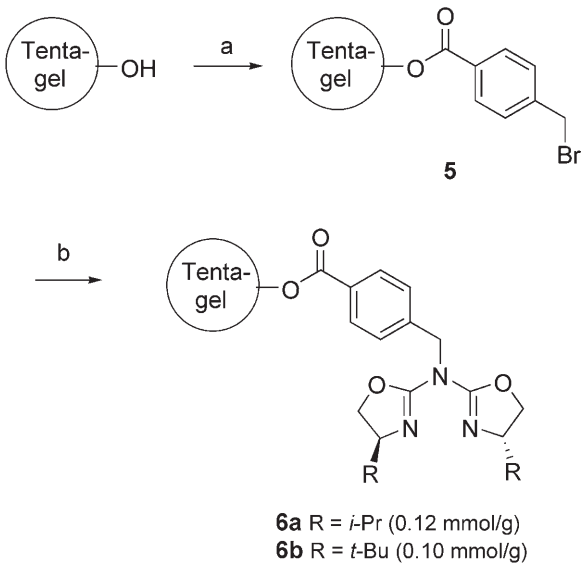
Results and Discussion

Preparation of Polystyrene-Bound Azabis(oxazolines)

Based on our work with MeOPEG-bound azabis(oxazolines), we chose as supports for this study (a) polystyrene, being cross-linked with divinylbenzene (DVB), and thus insoluble in organic solvents, and (b) Tentagel™, being a hybrid polymer consisting of a polystyrene backbone and a polyethylene glycol periphery, which displays, in spite of its heterogeneous character, homogeneous properties due to the solubility of the polar side chains to which the ligands will be attached. Two strategies, which were also previously successful for connecting bis(oxazoline) ligands with polystyrene supports,[8] were applied for the immobilization of **2**, i.e., the direct grafting of the ligand onto the polymer or the functionalization of the ligand with a styryl group which is subsequently polymerized.

Since azabis(oxazoline) ligands are readily benzylated on the central nitrogen, a benzyl moiety was chosen in all cases as linker between polymer and ligand. Thus, commercially available Tentagel™ (0.26 mmol theoretical loading capacity/g polymer) was converted to **5**, however, despite using the coupling reagent 4-(bromomethyl)-benzoyl chloride in a large excess the conversion could not be raised above 46% (Scheme 1). Subsequent reaction with the deprotonated azabox ligands **2** proceeded well (71–85% conversion) to give rise to the Tentagel™-bound ligands **6**. The loading (0.1–0.12 mmol/g polymer) onto the polymer was determined by elemental analysis, using the nitrogen content from the ligand as the indicative value for the ligand attachment.

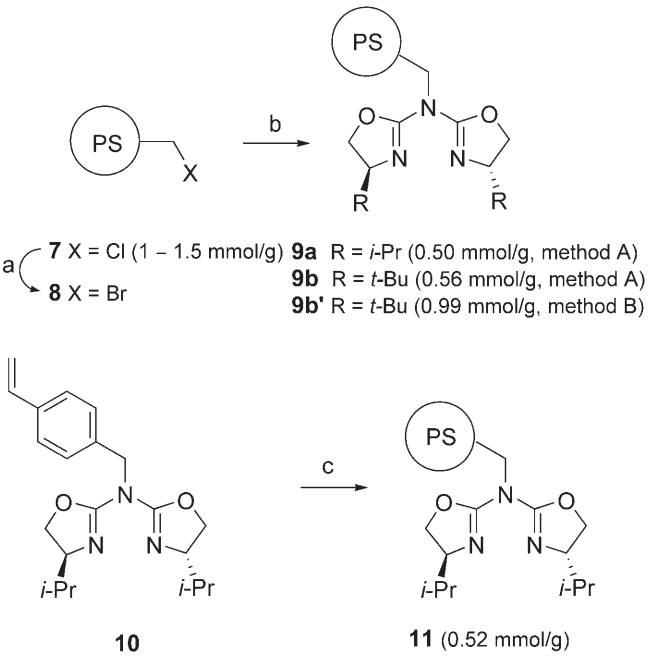
Likewise, the synthesis of polystyrene-bound azabis(oxazolines) could be achieved (Scheme 2). However, commercially available Merrifield resin proved not to be reactive enough to undergo coupling with deprotonated **2**. Therefore, conversion of the chloromethyl to the more reactive bromomethyl group was necessary, which could be readily achieved by treatment of **7** with $NaBr/NBu_4Br$. Subsequent coupling of **8** with **2** (Scheme 2, method A) proceeded cleanly to give rise to **9** with considerable higher ligand loading (0.5–0.56 mmol/g polymer) compared to **4** or **6**. Alternatively, **10** was copolymerized in the presence of styrene and divinylbenzene in a ratio aiming at a similar ligand loading in **11** as obtained previously in **9a**, using the protocol for the preparation of monolithic resins described by Fréchet and coworkers.[9]



Scheme 1. Synthesis of Tentagel™-bound azabis(oxazolines). *Reagents and conditions:* a) 4-(bromomethyl)benzoyl chloride (10 equivs.), pyridine (40 equivs.), CH_2Cl_2, room temperature, 48 h, 46%; b) i: 2 (3 equivs.), *n*-BuLi (3.3. equivs.), THF, −78 °C, 10 min; ii: 5 (1 equiv.), THF, room temperature, 72 h, 85% (**6a**), 71% (**6b**).

Asymmetric Cyclopropanations

The so prepared polymer-bound azabis(oxazoline) ligands were evaluated in copper(I)-catalyzed cyclopropanation reactions with ethyl diazoacetate and styrene or 1,1-diphenylethylene, a common test reaction for which also data from immobilized bis(oxazoline) ligands are available in the literature. Copper(II)-catalysts of Tentagel™-bound ligands **6** were prepared as previously reported for MeOPEG bound ligands **4**[3a] using an excess of ligand (2 equivs.). Employing ligand and metal in equimolar amounts led to inferior results in the subsequent catalysis experiments, which we attributed to undesired complexation of copper to the glycol chains in the polymer. In contrast, preparation of copper(II) complexes of polystyrene bound ligands **9** and **11** (~0.5 mmol/g polymer) were carried out with an excess

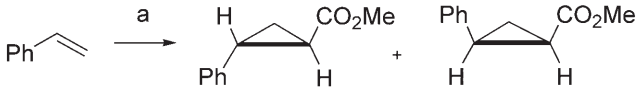


Scheme 2. Synthesis of polystyrene-divinylbenzene bound azabis(oxazolines). *Reagents and conditions:* a) Merrifield resin (loading 1–1.5 mmol/g), NaBr (~40 equivs.), NBu_4Br (~3 equivs.), H_2O/benzene, 5 d, 60 °C; b) Method A: *i*) **2a** or **2c** (7.5 equivs.), *n*-BuLi (8.25 equivs.), THF, −78 °C, 10 min; *ii*) **8** (1 equiv.), THF, room temperature, 72 h, 50% (**9a**), 58% (**9b**); Method B: *i*) **2c** (3.4 mmol), *n*-BuLi (3.7 mmol), THF, −78 to 0 °C, 10 min; *ii*) **8** (1 g), THF, reflux, 40 h; c) **10** (1 equiv.), styrene (6 equivs.), DVB (7.3 equivs.), cat. AIBN, toluene (monomers/toluene = 40/60 w/w), 80 °C, 24 h.

of metal (1.6 equivs.), since copper metal not bound to the ligand molecules could be readily removed by extraction with methanol, yielding catalysts with a copper content of 0.2–0.3 mmol/g polymer. The copper(II) complexes were reduced with phenylhydrazine prior to every catalysis run and could be easily recovered by simple filtration from the reaction mixture after completion of the reaction.

Cyclopropanations were performed with styrene (**12**, Table 1) and 1,1-diphenylethylene (**15**, Table 2), using 1–1.5 mol % catalyst in all cases. As benchmark, reactions with ligands **2b** and **2d** were also performed to allow a comparison between immobilized and non-immobilized ligands. The MeOPEG-bound azabis(oxazoline) ligand **4** gave very similar results (entry 3, Tables 1 and 2) as compared to the free ligand **2d** (entry 2, Tables 1 and 2), giving consistently high selectivities and good yields, and multiple sequential reactions could be carried out without a noticeable loss of catalyst performance. Moving to the polystyrene bound catalysts, we found that ligands **9** and **11** were considerably less active (entries 6–8, Table 1; entries 9–11, Table 2), as reflected by the long reaction time necessary for decomposition of the diazoacetates, but also by the increased amounts of

Table 1. Cu(I)-catalyzed cyclopropanation of **12** in the presence of various azabis(oxazoline) ligands.[a]

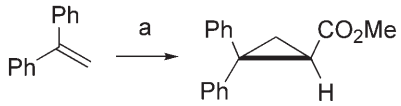


12 **13** **14**

Entry	Ligand	Run	Time [h]	Yield [%]	**13**:**14**[b]	% ee **13**[c]
1	**2b**[d]	1	8	78	64:36	66
2	**2d**[d]	1	8	82	73:23	92
3	**4**[d]	1–15	8	70–85	70:30	86–91
4	**6a**	1	48	51	64:34	62
5	**6b**	1	48	35	64:34	47
6[e]	**9a**	1–2	96	29–32	70:30	70–72
7[e]	**9b**	1	96	28	70:30	88
8[e]	**11**	1	96	28	67:37	58

[a] *Reagent and conditions*: **12** (6 equivs.), methyl diazoacetate (1 equiv.), catalyst (1.5 mol %), $PhNHNH_2$ (1.8 mol %).
[b] Determined by GC using a DB 1301 column.
[c] Determined by GC using a CP-Chiralsil DEX CB column.
[d] Ethyl diazoacetate was employed.
[e] 3 equiv of styrene, 1 mol % of ligand and 1.2 mol % of $PhNHNH_2$ were employed.

Table 2. Cu(I)-catalyzed cyclopropanation of **15** in the presence of various azabis(oxazoline) ligands.[a]



15 **16**

Entry	Ligand	Run	Time [h]	Yield [%][b]	% ee **16**[c]
1	**2b**[d]	1	8	49	56
2	**2d**[d]	1	8	41	83
3	**4**[d]	1–6	8	36–80[e]	83–90
4	**6a**	1	72	83	66
5	**6b**	1	48	70	60
6	**6b**	2	48	76	71
7	**6b**	3	72	78	67
8	**6b**	4	72	85	69
9	**9b**	1	96	34	84
10	**9b**	2	96	28	77
11	**9b**	3	96	30	79

[a] *Reagent and conditions*: **12** (6 equivs.), methyl diazoacetates (1 equiv.), catalyst (1 mol %), $PhNHNH_2$ (1.2 mol %).
[b] Determined by GC using a DB 1301 column.
[d] Determined by GC using a CP-Chiralsil DEX CB column.
[d] 3 equivs. of styrene, 1 mol % of ligand and 1.2 mol % of $PhNHNH_2$ were employed.
[e] Run 1: 80%, Run 2: 78%, Run 3: 36%, Run 4: 50%, Run 5: 80%, Run 6: 61%.

maleate and fumarate formed as by-products. Nevertheless, the enantioselectivity observed with these ligands compared reasonably well with the non-immobilized counterparts. Moreover, we found that the immobilized azabis(oxazoline) ligands **9** obtained by direct grafting onto the Merrifield resin gave better results than **11**, which was obtained by copolymerization of styrene and DVB with the monomer **10**. Consistent with the medium degree of heterogenization, the Tentagel™-bound ligands **6** displayed higher reactivity than the polystyrene-supported ligands **9** and **11**, but less activity than the polyethylene glycol-supported ligand **4**. However, the enantioselectivities obtained with **6** were comparatively low, suggesting, that copper ions, not being bound to the aza(bisoxazoline) ligands but possibly to the polyethylene glycol chains, could not be completely removed in the course of the catalyst preparation. A similar effect has been observed also with bis(oxazoline) ligands attached to polystyrene being cross-linked with bis(*p*-vinylbenzyl) poly(ethylene glycol).[10] In agreement with this analysis, in sequential reactions the enantioselectivity improved to some degree after the initial first cycle, which could be rationalized in that copper ions not being bound to the chiral ligand are removed within the washing cycles upon recovery of the catalyst. It is worth noting that this complication is not encountered with polyethylene glycol-bound aza(bisoxazoline) or bis(oxazoline) ligands but seems to be a particular problem of insoluble supports.

Comparing these results with the ones obtained for Cu(I)-catalyzed cyclopropanations using polystyrene-immobilized bis(oxazolines)[10] attached *via* a benzyl linker, it becomes evident that azabis(oxazolines) are advantageous over bis(oxazolines) regarding immobilization on such supports (Figure 2). When copper complexes of **17** and **19** are used to promote the reaction of styrene (**12**) with ethyl diazoacetate, both grafted or copolymerized catalysts led to greatly reduced enantioselectivities in comparison to the corresponding non-immobilized ligand. The best results were obtained with homopolymers **17** (no cross-linking agent used) but even with these supports enantioselectivities for the cyclopropane **21** did not exceed 78% ee[10] [> 99% ee with non-immobilized *t*-Bu-bis(oxazoline) ligands[2b]], clearly worse than 88% ee for **13** obtained with **9b** [92% ee with non-immobilized *t*-Bu-azabis(oxazoline) ligands[3a]]. We attribute the difference in the performance of polystyrene-bound bis(oxazoline) and azabis(oxazoline) ligands to the higher binding affinity of the latter towards copper, thus reducing leaching and consequently catalysis by non-ligand-bound metal centers during the reaction. However, another important factor has also to be taken into account, which was pointed out by Salvadori and co-workers,[11] i.e., the change of the optimal ligand geometry imposed by the *gem*-dimethyl substitution in the bis(oxazoline) bridge by sterically more bulky groups being used as linkers. Indeed, using **18** having a

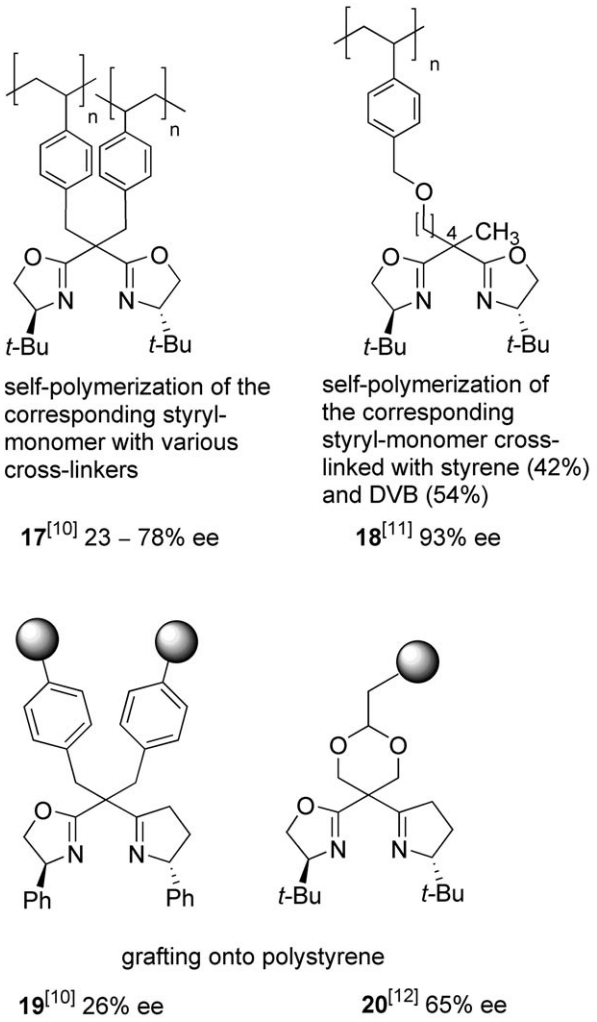
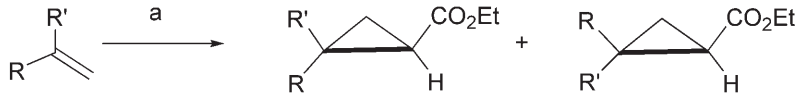


Figure 2. Enantioselectivities of the major *trans*-diastereomer **21** obtained for the cyclopropanation of styrene (**12**) with ethyl diazoacetate with polystyrene-immobilized bis(oxazoline) ligands.[10–12]

substitution pattern that was assumed to mimick best the *gem*-dimethyl substitution in the box-bridge, gave **21** in 93% ee, being the highest selectivity reported for the title reaction with polymer-bound box ligands to date. The same argument could also explain the better selectivity obtained with **20**[12] in comparison to **19**.

The best enantioselectivities, in some cases even slightly higher than in the homogeneous phase, are obtained with the ligands **9** grafted on a Merrifield resin. In spite of the higher selectivity, these PS-DVB-immobilized catalysts as well as the corresponding bis(oxazoline)-based catalysts **17**–**18** suffer from a low catalytic activity and a poor chemoselectivity as evidenced by the formation of considerable amounts of fumarate and maleate as by-products, resulting in longer reaction times and lower yields of cyclopropanes. This can be due to the low loading of copper catalyst onto the polymer, given that the content Cu(I)·**9** prepared by method A

Table 3. Consecutive cyclopropanation reactions catalyzed by **9b′**-Cu(I) prepared by method B.[a]



trans *cis*

12 R = Ph, R' = H	**21**	**22**
15 R = R' = Ph	**23**	**24**
25 R = Ph, R' = Me	**26**	**27**
28 R = *n*-C_6H_{13}, R' = H	**29**	**30**

Entry	Alkene	Run	% yield	*trans/cis*	% ee *trans*[b]	% ee *cis*[b]
1	**12**	1	94	74:26	99	90
2	**12**	2	87	74:26	96	90
3	**25**	3	74	55:45	91	81
4	**15**	4	96	–	75	–
5	**28**	5	26	65:35	64	67
6	**12**	6	3	n.d.	n.d.	n.d.
7[c]	**12**	7	2	n.d.	n.d.	n.d.
8	**28**	1	32	60:40	90	82
9	**12**	2	70	70:30	76	67

[a] *Reagent and conditions*: alkene (1 equiv.), ethyl diazoacetate (1 equiv.), **9b′**-Cu(OTf)$_2$ (1 mol %), 24 h.
[b] Determined by GC using a CP-Chiralsil DEX CB column or HPLC using a Chiralpack AD-H column.
[c] Polymer treated again with Cu(OTf)$_2$.

(Scheme 2) was only 0.2 mmol/g. Although employing a larger amount of polymer **9** can increase the number of catalytic sites, the possible diffusion limitations imposed by the high dispersion of the catalytic sites would not be avoided.

Consequently, we tried to increase the degree of functionalization of the resin by changing the immobilization conditions (Scheme 2, method B). The loading of Cu(I)·**9b′** onto the resin could be increased three-fold (0.74 mmol/g) when the brominated resin **8** and the deprotonated chiral azabis(oxazoline) **2c** were reacted in THF under reflux and the complexation with Cu(OTf)$_2$ was carried out in methanol instead of dichloromethane. This new solid was tested under more exigent conditions, employing only stoichiometric amounts of alkene[13] and, moreover, leaving out the commonly employed activation of the catalyst with phenylhydrazine. In spite of these disadvantageous conditions the results were excellent (Table 3) leading to 94% yield with 99% ee for the major *trans* product **21** (entry 1) in the reaction of styrene with ethyl diazoacetate, which is the best performance of a heterogeneous catalyst ever described in this cyclopropanation but also exceeds the best results achieved with non-polymer-bound azabis(oxazolines).

Moreover, the catalyst could be recovered and reused in cyclopropanation reactions with various alkenes. In the second run with styrene (entry 2) the behavior was almost identical with respect to yield and enantioselectivity. Subsequently, the recovered catalyst was tested in the cyclopropanation of α-methylstyrene (**25**) (entry 3), comparing quite well even to the best results obtained for this substrate with homogeneous catalysts.[14] In the fourth run 1,1-diphenylethylene (**15**) was cyclopropanted in almost quantitative yield and good enantioselectivity, comparable with the homogeneous results obtained earlier (see Table 2). The situation was changed when an aliphatic alkene was tried. 1-Octene (**28**) is much less reactive and as a consequence dimerization (and probably polymerization) of diazoacetate interferes, leading to low yield and only moderate enantioselectivities. Furthermore, those by-products are known to poison the copper catalysts[8a] as is clearly shown by the results in the sixth run again with styrene. The catalyst was rendered completely inactive, which is not due to copper leaching as demonstrated by analysis of the solution and the lack of activity of the polymer recharged with copper (entry 7). Also carrying out the cyclopropanation of 1-octene (**21**) with freshly prepared catalyst (entry 8) gave low yields of cyclopropanation adducts, albeit with better selectivity compared to the reused catalyst (entry 5). Upon recyclization of the catalyst followed by a second cyclopropanation with styrene (entry 9) the catalyst was still active in contrast to the results obtained in entry 6, but nevertheless significant poisoning clearly had occurred when compared to the results obtained for entries 1–4. Consequently, it can be concluded that catalyst deactivation occurs also to some extent with aromatic substrates but, due to their high reactivity, catalyst recycling and multiple cycles

with such substrates are possible with similar performance in each run. In contrast, with the less reactive acyclic alkenes, significant amounts of by-products are produced that rapidly poison the catalyst.

Conclusion

Azabis(oxazolines) can be efficiently immobilized onto insoluble polymers by either grafting or copolymerization of vinylbenzyl-substituted ligands. Copolymerization does not show any advantage over grafting, whereas Merrifield resin clearly is a better support than TentaGel. The catalytic results greatly depend on the immobilization conditions and the complexation method. Moreover, due to the higher binding affinity towards copper immobilized azabis(oxazolines) are far superior compared to the corresponding bis(oxazolines). Under the optimal conditions, the immobilized azabis(oxazoline) **9b′** leads to the most effective immobilized catalyst described so far for enantioselective cyclopropanations of aromatic substrates, rivaling the best results obtained with homogeneous chiral catalysts.

Experimental Section

General Remarks

The copper analysis is carried out by plasma emission spectrometry measuring at 224.7 nm after dissolving completely a sample (25–50 mg) of the polymer in an acidic aqueous solution (nitric acid, sulfuric acid, HF) under microwave irradiation. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyzer. Compound **4** was prepared as described in ref.[3a]

Synthesis of 5

TentaGel-S-OH (2.0 g, loading 0.26 mmol/g) was suspended in dichloromethane (20 mL) and pyridine (2 mL). To this suspension 4-bromomethylbenzoyl chloride (1.2 g, 5 mmol) dissolved in dichloromethane (15 mL) was added dropwise. After shaking of the reaction mixture for two days at room temperature, the polymer was isolated by filtration, and washed with methanol, tetrahydrofuran and dichloromethane. The resulting colorless solid was dried under vacuum; yield: 2.06 g (loading = 0.12 mmol/g).

Synthesis of 6

Azabis(oxazoline) **2a** or **2**c (0.9 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to −78 °C. Via syringe *n*-BuLi (621 μL, 0.99 mmol, 1.6 M in hexane) was added dropwise and the mixture was allowed to warm to room temperature. After stirring for 2 h the reaction mixture was transferred slowly to a suspension of **5** (500 mg, loading 0.12 mmol/g) in tetrahydrofuran (15 mL). After shaking of the suspension for further 2 d the brown solid was filtered off, washed with tetrahydrofuran and dried to obtain TentaGel-bound-ligand **6a** (loading 0.12 mmol/g. as deduced from the elemental analysis taking into account the nitrogen content which is unique to the ligand: C 62.86%, H 9.04%, N 0.50%) and **6b** (loading 0.10 mmol/g, as deduced from the elemental analysis taking into account the nitrogen content which is unique to the ligand: C 62.99%, H 9.07%, N 0.42%).

Synthesis of $Cu(OTf)_2 \cdot 6$

Ligand **6** (0.1 g) was suspended in dichloromethane (15 mL) and a solution of $Cu(OTf)_2$ (0.48 equivs.) in dichloromethane (10 mL) was added. After shaking for 24 h the green solid was filtered, washed several times with methanol and tetrahydrofuran, and dried under vacuum to obtain $Cu(OTf)_2 \cdot$**6a** (loading 0.044 mmol/g, determined by plasma emission spectrometry) and $Cu(OTf)_2 \cdot$**6b** (loading 0.054 mmol/g, determined by plasma emission spectrometry).

Synthesis of $Cu(OTf)_2 \cdot 9$

Merrifield resin (1 g) was suspended in benzene and treated with a solution of NaBr (4.12 g, 40 mmol) and Bu_4NBr (0.97 g, 3 mmol) in water. The mixture was stirred at 60 °C for 5 days. The solid was filtered and washed with THF to yield the brominated resin **8**.

Method A: Azabis(oxazoline) **2a** or **2c** (0.375 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to −78 °C. Via syringe *n*-BuLi (258 μL, 0.412 mmol, 1.6 M in hexane) was added dropwise and the mixture was allowed to warm to room temperature. After stirring for 2 h the reaction mixture was transferred slowly to a suspension of **8** (500 mg) in tetrahydrofuran (8 mL). After shaking the suspension for further 2 d the solid was filtered off, washed with tetrahydrofuran and dichloromethane, and dried under vacuum at 50 °C overnight to obtain PS-bound-ligand **9a** (loading 0.50 mmol/g, as deduced from the elemental analysis taking into account the nitrogen content which is unique to the ligand: C 87.96%, H 6.73%, N 2.11%) and **9b** (loading 0.56 mmol/g, as deduced from the elemental analysis taking into account the nitrogen content which is unique to the ligand: C 87.35%, H 6.51%, N 2.38%).

The resins (0.1 g) were suspended in dichloromethane (15 mL) and a solution of $Cu(OTf)_2$ (0.18 mmol) in dichloromethane (300 mL) was added. After shaking for 24 h, the solid was filtered off, washed with dichloromethane, methanol and tetrahydrofuran, and dried under vacuum at 50 °C overnight to obtain $Cu(OTf)_2 \cdot$**9a** (loading 0.20 mmol Cu/g, determined by plasma emission spectrometry) and $Cu(OTf)_2 \cdot$**9b** (loading 0.22 mmol/g, determined by plasma emission spectrometry).

Method B: Azabis(oxazoline) **2c** (0.41 g, 1.7 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to −78 °C. Via syringe *n*-BuLi (1.17 mL, 1.87 mmol. 1.6 M in hexane) was added dropwise and the mixture was allowed to warm to room temperature. After stirring for 10 min the reaction mixture was slowly transferred to a suspension of **8** (500 mg) in tetrahydrofuran (8 mL) and the resulting mixture was heated under reflux for 40 h. The solid was filtered off, washed with tetrahydrofuran, dichloromethane and methanol, and dried under vacuum at 50 °C overnight to obtain PS-bound-ligand **9b** (loading

0.99 mmol/g as deduced from the elemental analysis taking into account the nitrogen content which is unique to the ligand: C 83.72%, H 6.33%, N 4.16%).

The resin (0.1 g) was suspended in a solution of $Cu(OTf)_2$ (0.1 mmol) in methanol (1.7 mL) and shake for 24 h at room temperature. After this time the solid was filtered off, washed with methanol, and dried under vacuum to yield $Cu(OTf)_2 \cdot$ **9b** (loading 0.73 mmol/g, determined by plasma emission spectrometry).

Immobilization by Polymerization

Azabis(oxazoline) **2a** (1.0 mmol) was dissolved in tetrahydrofuran (3 mL) and cooled to $-78\,^{\circ}C$. Via syringe *n*-BuLi (687 μL, 1.1 mmol, 1.6 M in hexane) was added dropwise and the mixture was allowed to warm to room temperature. After stirring for 2 h the reaction mixture was added to a solution of *p*-vinylbenzyl bromide (1.0 mmol) in tetrahydrofuran (3 mL) and the resulting mixture was stirred overnight. The solution was treated with saturated $NaHCO_3$ solution (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent eliminated under reduced pressure. A mixture of this residue with styrene and divinylbenzene (7:42:51 molar ratio) was dissolved in toluene (monomers:toluene ratio = 40:60 w/w), placed in a glass mold, and purged with N_2 in the presence of AIBN (1% w/w). The mold was closed and heated at $80\,^{\circ}C$ for 24 h. The mold was broken and the solid was extracted with THF in a Soxhlet apparatus. The ligand loading was 0.52 mmol/g. This polymer (0.5 g) was added to a solution of $Cu(OTf)_2$ (0.42 mmol) in THF (17 mL) and the mixture was shake for 3 days at room temperature. The solid was filtered off, washed with THF and methanol and dried under vacuum to yield $Cu(OTf)_2 \cdot$ **11** (0.31 mmol/g, determined by plasma emission spectrometry).

Representative Procedure for Cyclopropanations of Alkenes with MeOPEG-Bound Azabis(oxazolines) 4

Under a nitrogen atmosphere $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and **12** (200 mg, 0.02 mmol) were dissolved in dichloromethane (5 mL). Phenylhydrazine (22 μL of a 5% solution in dichloromethane) and styrene (312 mg, 3 mmol, 345 μL) were added. Methyl diazoacetate (1 mmol, 8 mL of a 1% solution in dichloromethane) was added over 8 h using a syringe pump. Stirring was continued for 3 h and the reaction mixture was transferred via cannula to a 250-mL septum-capped flask. The reaction vessel was rinsed with 3 mL dry dichloromethane. The volume of the solvent was reduced to approximately 5 mL by applying vacuum and 100 mL of dry diethyl ether were added to precipitate the polymer-supported catalyst. After cooling with ice for 15 min the catalyst was separated from the products by filtration through a sintered glass funnel under a nitrogen atmosphere. The filtrate was evaporated under vacuum to give a slightly yellow oil, which was purified by chromatography on silica (3×25 cm silica, 9:1 hexanes/EtOAc as eluant). The products **13** and **14** were obtained as clear oils showing identical spectroscopic properties as described in the literature.[2b] For the following reaction cycle the catalyst was dissolved in 10 mL dry dichloromethane, transferred into a new reaction vessel, and activated by addition of phenylhydrazine (22 μL of a 5% solution in dichloromethane). Styrene (312 mg, 3 mmol, 345 μL) and methyl diazoacetate (1 mmol, 1 mL of an 8% solution in dichloromethane diluted with 7 mL dichloromethane) were added for the next cycle as described above.

Representative Procedure for Cyclopropanations of Alkenes with Tentagel-Bound Azabis(oxazolines) 6

$Cu(OTf)_2 \cdot$ **6a** (35 mg, 0.015 mmol) was mixed with dichloromethane (3 mL) and shaken for 2 h. Phenylhydrazine (33 μL of a 5% solution in dichloromethane) and, after 15 min, styrene (**12**) (625 mg, 6 mmol, 690 μL) were added. Methyl diazoacetate (1 mmol, 8 mL of a 1% solution in dichloromethane) was added over 8 h using a syringe pump. Stirring was continued for 40 h (total reaction time 48 h). The catalyst was filtered off, the filtrate was concentrated, and the residue was purified on silica (3×25 cm silica, 9:1 hexanes/EtOAc as eluant). The products **13** and **14** were obtained as clear oils showing identical spectroscopic properties as described in the literature.[2b]

Representative Procedure for Cyclopropanations of Alkenes with Merrifield-Bound Azabis(oxazolines) 9

$Cu(OTf)_2 \cdot$ **9b** (70 mg, 0.015 mmol) was mixed with dichloromethane (3 mL) and shaken for 2 h. Phenylhydrazine (33 μL of a 5% solution in dichloromethane) and, after 15 min, styrene (**12**) (625 mg, 6 mmol, 690 μL) were added. Methyl diazoacetate (1 mmol, 8 mL of a 1% solution in dichloromethane) was added over 8 h using a syringe pump. Stirring was continued for 40 h (total reaction time 88 h). The catalyst was filtered off, the filtrate was concentrated, and the residue was purified on silica (3×25 cm silica, 9:1 hexanes/EtOAc as eluant). The products **13** and **14** were obtained as clear oils showing identical spectroscopic properties as described in the literature.[2b]

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie, the DAAD (Accion Integrada HA2001–0096), the C.I.C.Y.T. (project PPQ2002–04012), the DGA, and through generous chemical gifts by Degussa AG. I.P. is indebted to the MEC for a grant.

References and Notes

[1] A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339.

[2] a) R. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005; b) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726; c) for a recent review see: H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151.

[3] a) M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045; b) H. Werner, R. Vicha, A. Gissibl, O. Reiser, *J. Org. Chem.* **2003**, *68*, 10166; c) C. Geiger, P. Kreitmeier, O. Reiser,

Adv. Synth. Catal. **2005**, *347*, 249–254; d) A. Gissibl, M. G. Finn, O. Reiser, *Org. Lett.* **2005**, *7*, 2325.

[4] Reviews: a) D. Rechavi, M. Lemaire, *Chem. Rev.* **2002**, *102*, 3467; b) O. Reiser, *Chimica Oggi* **2002**, *20*, 73–77; representative examples: c) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160–3166; d) S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2519–2521; K. Hallman, C. Moberg, *Tetrahedron: Asymmetry* **2001**, *12*, 1475–1478; e) D. Rechavi, M. Lemaire, *Org. Lett.* **2001**, *3*, 2493–2496; f) A. Mandolini, S. Orlandi, D. Pini, P. Salvadori, *Tetrahedron: Asymmetry* **2004**, *15*, 3233–3244; g) D. Rechavi, M. Lemaire, *J. Mol. Catal. A* **2002**, *182*, 239–247.

[5] J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, M. Vaultier, *Tetrahedron Lett.* **2004**, *45*, 6765.

[6] a) J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, A. Socuellamos, H. Werner, *Chem. Eur. J.* **2004**, *10*, 2997; b) J. M. Fraile, J. I. García, M. A. Harmer, C. I. Herrerías, J. A. Mayoral, O. Reiser, H. Werner, *J. Mater. Chem.* **2002**, *12*, 3290.

[7] D. A. Evans, S. J. Miller, T. M. P. von Lectka, *J. Am. Chem. Soc.* **1999**, *121*, 7559.

[8] a) M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, S. V. Luis, J. A. Mayoral, *Org. Lett.* **2000**, *2*, 3905; b) S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem.* **2001**, *113*, 2587.

[9] a) F. Svec, J. M. J. Fréchet, *Chem. Mater.* **1995**, *7*, 707; b) F. Svec, J. M. J. Fréchet, *Science* **1996**, *273*, 205; c) S. Xie, F. Svec, J. M. J. Fréchet, *Chem. Mater.* **1998**, *10*, 4072; d) F. Svec, J. M. J. Fréchet, *Ind. Eng. Chem. Res.* **1999**, ***38***, 34; e) N. Hird, I. Hughes, D. Hunter, M. G. J. T. Morrison, D. C. Sherrington, L. Stevenson, *Tetrahedron* **1999**, *55*, 9575.

[10] M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, C. I. Herrerías, S. V. Luis, J. A. Mayoral, *J. Org. Chem.* **2001**, *66*, 8893.

[11] A. Mandoli, S. Orlandi, D. Pini, P. Salvadori, *Chem. Commun.* **2003**, 2466–2467.

[12] J. G. Knight, P. E. Belcher, *Tetrahedron: Asymmetry* **2005**, *16*, 1415.

[13] The standard protocol used almost uniformly in the literature reports calls for 3–6 equivs. of alkene, also employed initially by us (*cf.* Tables 1 and 2).

[14] Review: H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050.

