DOI: 10.1002/ejoc.201100781

Covalent and Noncovalent Immobilization of Arylid-BOX Ligands and Their Derivatives: Evaluation in the Catalytic Asymmetric Cyclopropanation of Styrenes

Elisabete P. Carreiro,[a,b] Nuno M. M. Moura,[a,b] and Anthony J. Burke*[a,b]

Keywords: Heterogeneous catalysis / Supported catalysts / Asymmetric catalysis / Asymmetric synthesis / Arylid-BOX

The aim of this work was to immobilize an Arylid-BOX ligand on solid supports either by covalent attachment (to Wang resin) or by noncovalent attachment (on MK10 and SiO_2) and to evaluate the products in the catalytic asymmetric cyclopropanation (CACP) of styrene in the presence of Cu^I and Cu^{II}. The synthetic strategy used to obtain the target functionalized Arylid-BOX furnished a new, partially hydrogenated, Arylid-BOX derivative. Evaluation of this ligand in the catalytic asymmetric cyclopropanation of styrene in the presence of Cu^I gave a highest *ee* of 68 %, a result better than that obtained for the nonhydrogenated Arylid-BOX ligand. The new ligand was grafted to Wang resin; a loading of 0.321 mmol of ligand per gram of polymer could be obtained. $[Cu(CH_3CN)_4]PF_6$ or $Cu(OTf)_2$ were used in the CACP of styrene with CH_2Cl_2 or toluene as solvents. A highest *ee* of 71 % was obtained and the catalyst could be recycled and reused up to four times. In the case of the heterogeneous CACP in the presence of $[Cu(CH_3CN)_4]PF_6$ and toluene, the yields, *ee*s, des, and selectivities were maintained over the four cycles. This heterogeneous catalyst was shown to be very similar to the homogeneous catalyst with regard to selectivity and activity. In the case of noncovalent immobilization, both Cu^I and Cu^{II} Arylid-BOX complexes were immobilized on Montmorillonite K10 (MK10) and silica gel through noncovalent interactions. The obtained results depended on the natures both of the chiral ligand and of the support. In the case of MK10, enantioselectivities of 62 % *ee* (*trans*-cyclopropane) and 65 % *ee* (*cis*-cyclopropane) could be achieved, whereas in the case of the silica-gel-supported catalyst, enantioselectivities of 50 % *ee* (*trans*-cyclopropane) and 43 % *ee* (*cis*-cyclopropane) were obtained.

Introduction

Heterogeneous asymmetric catalysis is a field of great interest both in academic and in industrial circles.[1] The principle reason for this, and perhaps the most enduring, is the importance of producing enantiomerically pure compounds in the most efficient and cost-effective way possible. By this technique it is possible to isolate and to recycle the catalyst easily, thus reducing costs.[2] Through the choice of a suitable support – organic and inorganic materials, for example – a heterogeneous catalyst can be modified to give high selectivities and activities. The role of the support has changed from being that of an appendage to that of a well defined material that can be used to influence the outcome of the catalyzed reaction beneficially. For a long time now, covalent immobilization of chiral complexes has been unequaled, due to the stabilities and recyclabilities of the resulting immobilized catalysts. Besides this technique, though, noncovalent immobilization has become quite sophisticated and highly promising.[3]

[a] Centro de Química de Évora, Universidade de Évora, 59, Rua Romão Ramalho, 7000 Evora, Portugal
E-mail: ajb@uevora.pt
[b] Departamento de Química, Universidade de Évora, 59, Rua Romão Ramalho, 7000 Evora, Portugal
Fax: +351-266745303

Bis(oxazoline) ligands have been shown to be very important in a wide range of catalytic asymmetric reactions,[4] and as a consequence their immobilization has became an important challenge over the last 10 years.

Several strategies have been used for covalent immobilization of bis(oxazoline) ligands.[1–3] The first was developed by Burguete et al.[5] and consisted of the polymerization of bis(oxazoline) ligands (**1** and **2**, Figure 1) bearing vinylbenzyl groups. The heterogeneous ligands were then evaluated in the catalytic asymmetric cyclopropanation reaction, giving low selectivities and enantioselectivities. Some disadvantages were: i) that some ligands remained in inaccessible positions on the support, and ii) that there was unwanted steric hindrance at the C_1 bridge with the oxazoline rings. Mandoli et al.[6] used systems with less steric hindrance in the C_1 bridge (ligand **3**) thus ensuring more favorable binding with the metal. The results obtained in the CACP were very good. Knight and Belcher[7] developed the new bis(oxazoline) **4**, containing a 1,3-dioxane unit to restrict the conformational mobility of the oxazoline units on the C_1 bridge. This ligand was grafted onto a Wang resin and used in the CACP. The enantioselectivities were lower than those achieved in the homogeneous reaction. Later, Rieser and Mayoral[8] attached the AzaBOX ligands **5** to a Tentagel resin. Some good results were obtained in the

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

CACP reaction. These ligands were easier to attach to the support through the amine group, which is a good attachment point. Recently, Aranda et al. have immobilized copper–pyridine–oxazoline catalysts on a polymeric support; the resulting systems showed good efficiency in the heterogeneous CACP.[9]

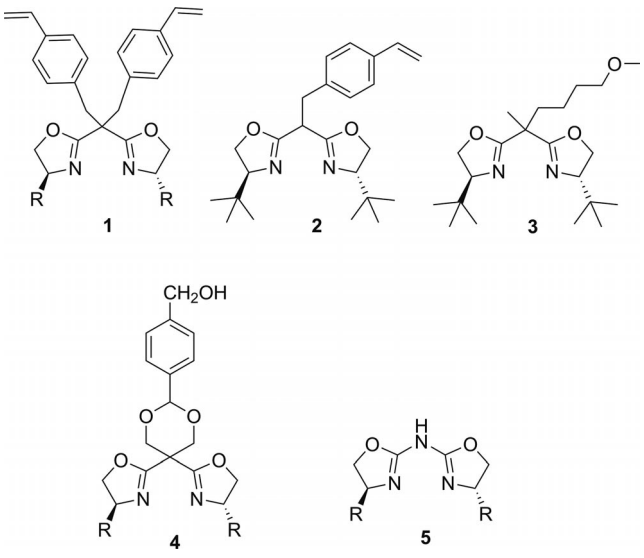


Figure 1. Functionalized BOX ligands for immobilization on organic supports.

In 1997, Mayoral and co-workers immobilized some BOX-copper complexes noncovalently through ion-exchange on laponite and bentonite supports.[10] Testing in the catalytic asymmetric cyclopropanation showed low selectivities and enantioselectivities. Mayoral and Reiser in 2004 immobilized the AzaBOX **5** copper complexes on laponite and Nafion-silica supports and the resulting systems were used for the catalytic asymmetric cyclopropanation reaction.[11] Three cycles were conducted, but both the yields and the enantioselectivities dropped considerably from the first cycle to the third.

BOX-copper complexes can also be immobilized on silica gel supports through electrostatic interactions; this method was introduced by van Koten's group[12] and employed by the same group in the heterogeneous catalytic Diels–Alder reaction and by McDonagh and O'Leary in the carbonylene reaction.[13] The catalyst showed activity and enantioselectivity similar to that observed in the homogeneous phase for both reactions. However, a reversal of selectivity was observed, due to a change in the conformation of the catalyst on immobilization.

The Arylid-BOX family **6** of chiral nonracemic pseudo-C_2-symmetric bidentate bis-oxazoline ligands was introduced by us in 2006 (Figure 2).[14] They have shown significant applicability in some asymmetric catalytic reactions, such as styrene cyclopropanations,[15,16] the Friedel–Crafts alkylation of indole with phenylidenemalonates,[17a] and the Henry reaction between nitromethane and benzaldehyde.[17b] The synthetic strategy to obtain these Arylid-BOX ligands **6** is a versatile one and highly modular in nature.

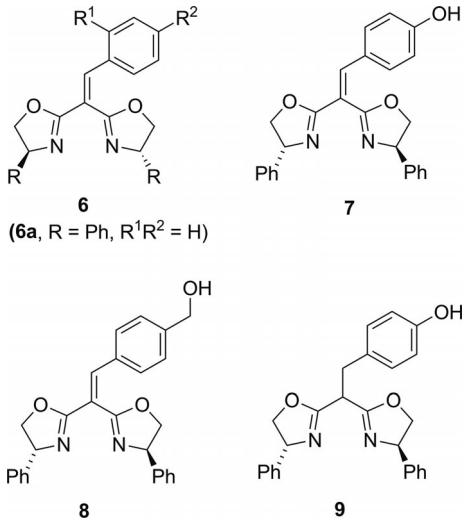


Figure 2. Arylid-BOXs **6**–**8** and the arylid-BOX derivative **9**.

We decided to immobilize our rigid Arylid-BOX family of ligands **6**[14,15] on a Wang resin, expecting their inherent rigidity to lead to good levels of metal binding within the support.

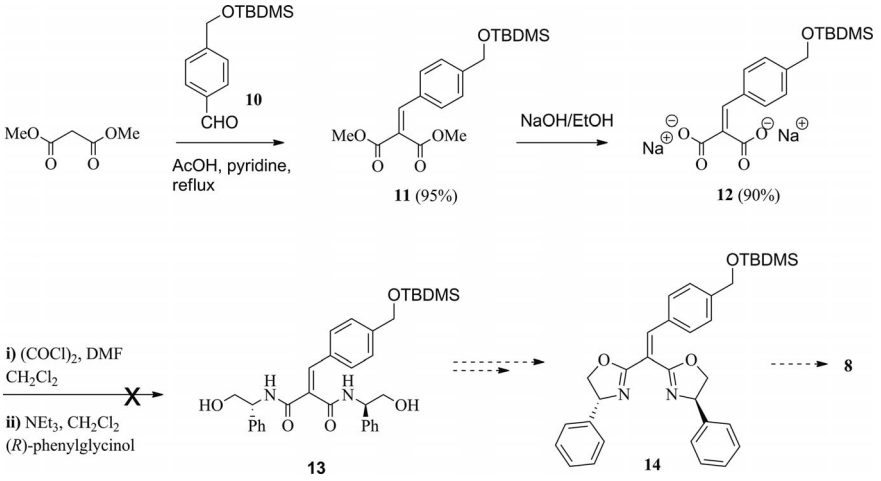
Here we describe for the first time our efforts with both covalent and noncovalent immobilization of Arylid-BOX ligands (Figure 2) and their corresponding Cu^{I} catalysts on solid supports and their evaluation as catalysts for asymmetric catalysis by the simple CACP benchmark reaction, which has become a standard preliminary screening reaction in our laboratory.

Results and Discussion

Covalent Immobilization

Our key objective was the immobilization of the BOX **7** (Figure 2) on a polymeric support. For this reason an unsuccessful attempt to convert 2-(4-hydroxybenzylidene)-malonic acid (not shown) into the corresponding bis-amide by our standard method[14–16] was made.[18] It was assumed that the free hydroxy group was interfering with the reaction. In order to advance rapidly with this work, we attempted the synthesis of the analogous Arylid-BOX **8** (Figure 2) by the method shown in Scheme 1. Although the TBDMS-protected dimethyl malonate ester **11** was successfully prepared from the *p*-TBDMS-protected hydroxymethylbenzaldehyde derivative **10**,[7] transformation into the corresponding protected diamide alcohol **13** proved impossible despite our best efforts. Acid hydrolysis of the diester **11** by the standard procedure[14–16] proved difficult, so we used

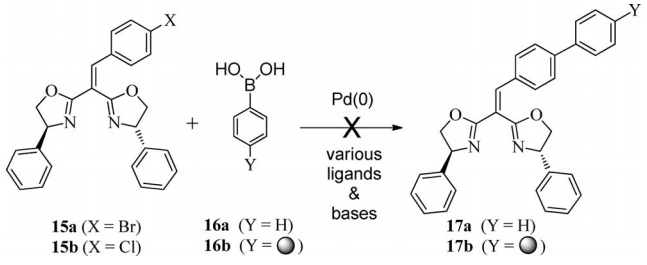
 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Attempted synthesis of **8**.[19]

basic hydrolysis, leading to the disodium salt **12**. Unfortunately this intermediate failed to afford the diamide-alcohol **13** (Scheme 1), so the synthesis of **8** was abandoned.

Another approach was to attach the Aylid-BOX ligand to a polymeric support by some elegant Suzuki–Miyaura chemistry with the commercially available polystyrene-immobilized phenylboronic acid **16b** (Scheme 2). Study of the conditions for this Suzuki–Miyaura reaction was first carried out with a homogeneous model system involving the *p*-halo-Arylid-BOX ligands **15** and phenylboronic acid (**16a**, Scheme 2). The *p*-bromo-Arylid-BOX **15a** and *p*-chloro-Arylid-BOX **15b** were prepared under our standard conditions.[14,15] Unfortunately, after much experimentation with a variety of sets of conditions – which included the use of various palladium catalysts [e.g. $Pd(OAc)_2$, $Pd(dba)_2$, $Pd(dppf)_2$, $Pd(PPh_3)_4$], bases, and ligands – it was not possible to obtain the phenylated Arylid-BOX **17a**.[19]



Scheme 2. Suzuki–Miyaura coupling strategy to immobilize the arylid-BOX ligand.

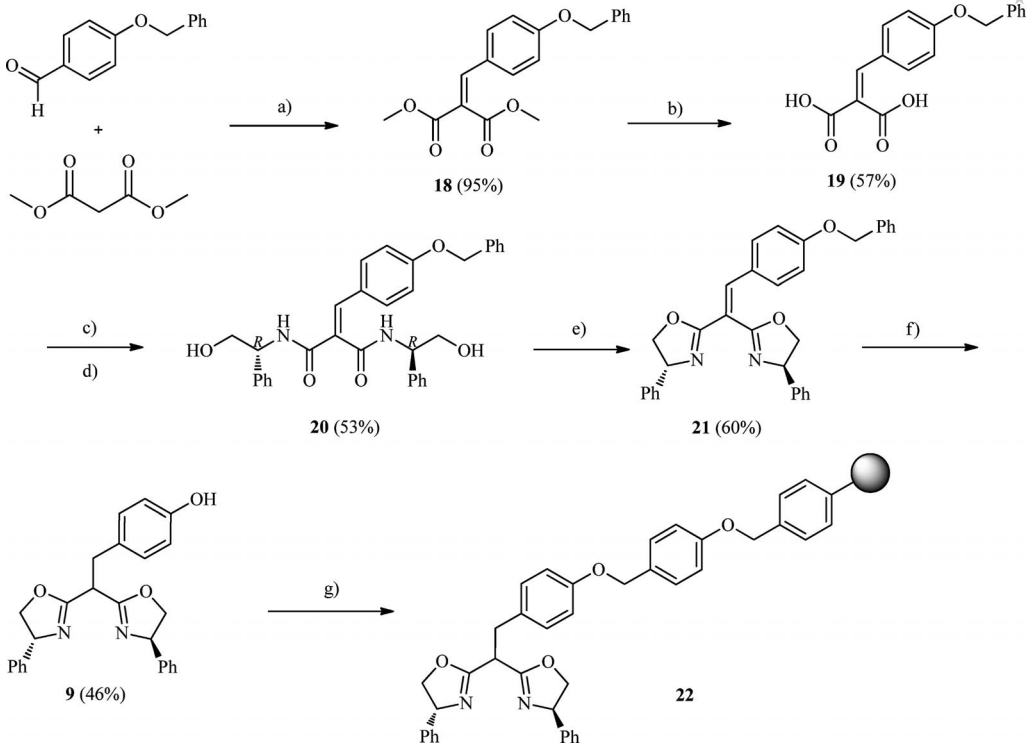
We decided in the end to return to our initial strategy and to obtain ligand **7** from the benzyloxy-protected precursor **21** (Scheme 3). The Arylid-BOX **21** was prepared in a good yield by our established method for the synthesis of Arylid-BOX ligands (Scheme 3).[14–16]

Compound **20** (Scheme 3) was obtained by the procedure reported by Evans et al.,[20] through a simple Knoevenagel condensation with dimethyl malonate and 4-benzyloxybenzaldehyde. Hydrolysis of **18** with NaOH in ethanol furnished the diacid **19**.

The synthesis of **21** was achieved through two important steps: formation of the malonamide **20** and subsequent cyclization to afford **21** (Scheme 3). In order to deprotect **21** and to convert it into **9** (Figure 2) we chose a palladium-catalyzed debenzylation strategy as the method of choice, even though many other methods exist for this transformation (such as the use of Lewis acids), due to it being an efficient, clean, and simple method. Catalytic hydrogenation with Pd on activated charcoal was the method of choice.[21] It was assumed that the olefin unit would remain unsaturated, due to its high degree of conjugation with the two oxazoline rings.[15] However, only starting material was recovered, as indicated by ^1H NMR spectroscopy. The reaction was repeated with heating at 50 °C, but, unexpectedly for us, the partially hydrogenated Arylid-BOX derivative **9** (Figure 2 and Scheme 3) was obtained, as was confirmed by ^{13}C NMR (presence of C=N peaks at δ = 166.1 and 165.9 ppm) and high-resolution mass spectrometry. Other hydrogenation methods were conducted, including the method of Felix et al.,[22] involving a catalytic transfer hydrogenation with cyclohexa-1,4-diene as the hydrogen donor at room temperature (25 °C) in the presence of Pd/C (10%). However, the initial Arylid-BOX **21** was obtained in all cases.

With this unexpected route to **9** now available to us, however, we decided to immobilize this ligand on Wang resin. Immobilization of **9** on Wang resin (benzyloxybenzyl bromide, 0.5–1 mmol Br per gram resin) was carried out with NaH in DMF followed by addition of Br-Wang resin to give the immobilized ligand **22** (Scheme 3). Microanalysis of **22** indicated a loading of 0.321 mmol of ligand per gram of resin. We chose Wang resin as the support because it is

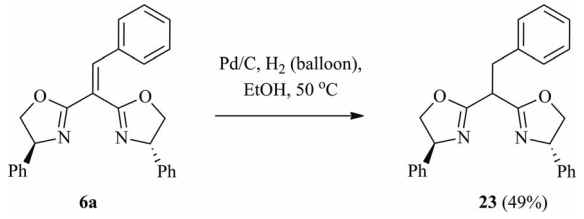
 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Reaction conditions: a) piperidine (5 mol-%), acetic acid (5 mol-%), benzene, Δ; b) NaOH (2.5 equiv.), EtOH, 0 °C. c) $(COCl)_2$, DMF, CH_2Cl_2; d) (*R*)-phenylglycinol, NEt_3, CH_2Cl_2; e) MsCl, NEt_3, CH_2Cl_2; f) Pd/C (10%), H_2 (balloon), EtOH at 50 °C, 24 h; g) Wang resin, NaH, DMF, 50 °C.

a well defined polymeric resin and because the active catalytic sites on the resin were expected to be more accessible during the reaction.

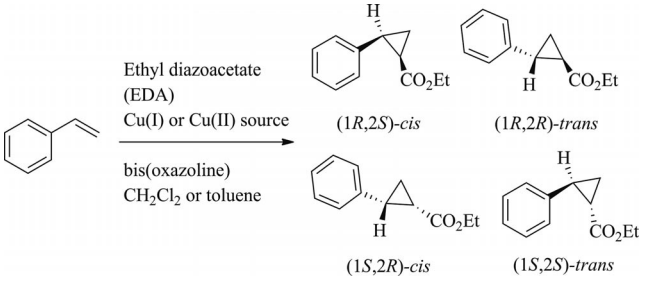
We also used our new procedure to convert the Arylid-BOX **6a** into the corresponding partially hydrogenated derivative **23** (Scheme 4). Compound **23** was used as a reference to establish the efficiency of the immobilized Arylid-BOX **22** in the CACP of styrenes.



Scheme 4. Synthesis of the arylid-BOX derivative **23**.

Catalytic Asymmetric Cyclopropanation of Styrene

The polymer-supported Arylid-BOX-derivative **22** was evaluated in the benchmark CACP of styrene. Three studies were carried out with $[Cu(MeCN)_4]PF_6$ and two different solvents: CH_2Cl_2 and toluene, and $Cu(OTf)_2$ with CH_2Cl_2 (Scheme 5 and Table 1). The objective was to compare these reactions with those performed with the homogeneous system and to verify which precatalyst was more suitable for the heterogeneous reaction.



Scheme 5. Asymmetric cyclopropanation of styrene – the benchmark reaction for this study.

The Arylid-BOX-derivatives **9** and **23** were also evaluated in the CACP of styrene (Scheme 4). The best enantioselectivities were obtained with the ligand **9** – 68% *ee* for *cis*-cyclopropane and 64% *ee* for the *trans*-cyclopropane – but the yield and diastereoselectivity were inferior to those obtained with ligand **23**. The enantioselectivities were slightly higher for the *cis*-cyclopropane (68% *ee*) than for the *trans*-cyclopropane (64% *ee*), in a result that was the opposite of that obtained with the Arylid-BOX ligand.[14,15] CACP with the ligand **9** gave better enantioselectivities than those obtained with the Arylid-BOX ligand **6a** (Figure 2).[15] These results seem to indicate some inductive effect by the hydroxy group in ligand **9**. It should be noted that the reaction in the presence of **6a** had also been carried out in toluene, giving enantioselectivities of 54% and 47% *ee* for the *trans* and *cis* isomers, respectively and a diastereoselectivity of 30% *de*, with a yield of 20%.[14]

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1. Catalytic asymmetric cyclopropanation of styrene.[a].

Entry	Precatalyst	Ligand	Solvent	Cycle	Yield[b] [%]	*cis*/*trans*[c]	*ee*[c] *cis* [%]	*ee*[c] *trans* [%]	Products/ dimers[c]
1[14]	$[Cu(MeCN)]_4PF_6$	**6a**	CH_2Cl_2	–	30	35:65	45	57	n.d.
2[14]	$[Cu(MeCN)]_4PF_6$	**6a**	toluene[d]	–	20	35:65	47	54	n.d.
3	$Cu(OTf)_2$	**6a**	CH_2Cl_2	–	5	27:73	53	63	n.d.
4	$[Cu(MeCN)]_4PF_6$	**23**[e]	CH_2Cl_2	–	63	29:71	52	59	92:8
5	$[Cu(MeCN)]_4PF_6$	**9**	CH_2Cl_2	–	31	37:63	68	64	93:7
6	$[Cu(MeCN)]_4PF_6$	**22**	CH_2Cl_2	first	61	32:68	45	68	99:1
7			CH_2Cl_2	second	38	30:70	50	67	89:11
8			CH_2Cl_2	third	57	32:68	44	69	97:3
9[f]			CH_2Cl_2	fourth	44	32:68	36	47	97:3
10	$[Cu(MeCN)]_4PF_6$	**22**	toluene[d]	first	30	33:67	62	71	98:2
11			toluene[d]	second	26	33:67	61	71	91:9
12			toluene[d]	third	36	36:64	58	66	91:9
13[g]			toluene[d]	fourth	33	36:64	57	64	90:10
14	$Cu(OTf)_2$	**22**	CH_2Cl_2	first	5	32:68	52	68	76:24
15			CH_2Cl_2	second	47	31:69	47	70	95:5
16			CH_2Cl_2	third	19	28:72	13	36	72:28
17[h]			CH_2Cl_2	fourth	24	30:70	17	22	81:19

[a] Styrene (4 equiv.), $[Cu(MeCN)_4]PF_6$ or $Cu(OTf)_2$ (0.027 mmol, 2 mol-%), ligand (2.2 mol-%), EDA (1 equiv.), solvent (5 mL), room temp., 48 h. [b] Calculated by determining the product weight. [c] Determination by GC analysis; n.d. = not determined. [d] Temperature was 40 °C. [e] Determined with use of an internal standard. [f] ICP-OES 0.204 mmol Cu g^{-1} after the fourth cycle (before the first cycle 0.265 mmol Cu g^{-1}). [g] ICP-OES 0.137 mmol Cu g^{-1} after the fourth cycle (before the first cycle 0.265 mmol Cu g^{-1}). [h] ICP-OES 0.109 mmol Cu g^{-1} after the fourth cycle (before the first cycle 0.266 mmol Cu g^{-1}).

The polymeric ligand **22** was complexed with both Cu^I and Cu^{II} precatalysts. The results obtained in the heterogeneous CACP of styrene in the presence of $[Cu(MeCN)]_4PF_6$ with EDA and CH_2Cl_2 showed that the enantioselectivity for production of the *cis*-cyclopropane decreased, but that for the *trans*-cyclopropane remained the same as that obtained in the homogeneous CACP with **9** (Table 1, Entries 5 and 6). The diastereoselectivity increased in the heterogeneous system. In the second cycle the *ee* of the *cis*-cyclopropane was increased as well as the diastereoselectivity, but the yield was less, due to a decrease in selectivity (i.e., the amounts of maleate/fumerate side products increased due to increased dimerization under these conditions). This behavior could imply reduced levels of or no free copper in the mixture. In the third cycle, the enantioselectivity of the *cis*-cyclopropane production had decreased, but the yield and selectivity had increased. These results were very similar to those encountered in the first cycle. In the fourth cycle both the enantioselectivities and the yield had decreased, particularly for the *trans*-cyclopropane. The diastereoselectivity and selectivity remained constant. After the last cycle the supported-ligand **22**-$[Cu(MeCN)_4]PF_6$ complex was analyzed by ICP-OES, and it was determined to have a loading of 0.204 mmol Cu g^{-1}, this result indicating only 23% leaching of Cu^I over the four reaction cycles.

Toluene was used as the solvent in the CACP of styrene in the presence of $[Cu(MeCN)_4]PF_6$-polymer supported ligand **22** and the reactions were carried out at 50 °C. In terms of enantioselectivity, the results were better than in the homogeneous case (vide supra).[14] They were also better than when CH_2Cl_2 was used (vide infra). Heating was necessary to activate the catalyst.[13] The results obtained for the first and second cycles (*cis* isomer 61% *ee* and *trans* *isomer* 71% *ee*) were very similar, although there were slight decreases in the yield and the selectivity. In the third cycle there were also slight decreases in the enantioselectivities and the diastereoselectivity, but the yield was larger by 10%. The results obtained in the fourth cycle were closer to those of the third cycle. The supported Cu^I complex isolated after the fourth cycle was analyzed by ICP-OES and a loading of 0.137 mmol Cu g^{-1} was determined; 48% of the Cu^I had leached out over the four cycles. This was probably due to the higher temperature used.

On comparing the results obtained for the CACP in toluene and in CH_2Cl_2, it was toluene that gave the more consistent enantioselectivities over the four cycles. In the case of CH_2Cl_2 the enantioselectivities became progressively lower with the number of cycles.

For the CACP of styrene with **22**-$Cu(OTf)_2$, EDA, and CH_2Cl_2 the enantioselectivities and diastereoselectivities remained almost constant between the first (*cis* isomer 52% *ee* and *trans* isomer 68% *ee*) and the second cycles (*cis* isomer 47% *ee* and *trans* isomer 70% *ee*), but the yield and the selectivity significantly increased. After the second cycle the enantioselectivities, yield, and selectivity decreased more than half.

On comparison of the results obtained for Cu^{II} with Cu^I in CH_2Cl_2, the yields and enantioselectivities (after the second cycle) were in general lower for the Cu^{II} catalyst. It is not known for sure why this was the case.

Noncovalent Immobilization

Arylid-BOX-Copper Complexes Immobilized by Ion Exchange on MK10

The Arylid-BOXs **6a** and **6b** were prepared by our procedure.[15,16] Some of the chiral complexes were obtained

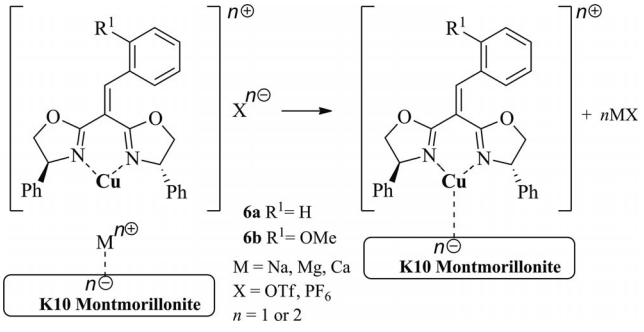
 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 2. Catalytic asymmetric cyclopropanation of styrene in the presence of **6a**-$Cu^{II}(OTf)_2$ and **6b**-$[Cu^{I}(MeCN)_4]PF_6$ immobilized on MK10.

Catalyst type	Cycle	Solvent	Cu[a] [mmol g^{-1}]	Yield[b] [%]	*ee*[c] *cis* [%]	*ee*[c] *trans* [%]	*cis*/*trans*[c] [%]	Products/ dimers[c] [%]
Homogeneous	n.a.	DCM	–	5	53	63	27:73	n.d.
Heterogeneous	first		–	19	46	38	34:66	80:20
Heterogeneous	second		–	30	45	46	36:64	87:13
Heterogeneous	third		0.053	37	35	23	40:60	91:9
Homogeneous[d][15,16]	n.a.	toluene	–	25	39	47	35:65	n.d.
Heterogeneous[d]	first		–	25	43	50	41:59	86:14
Heterogeneous[d]	second		0.045	11	43	19	39:61	85:15

[a] Determined by ICP-OES analysis after the corresponding run. [b] Determined by mass isolation. [c] Determined by GC analysis. [d] The temperature was 40 °C. n.a.: not applied. n.d.: not determined.

with use of equimolecular amounts of $Cu(OTf)_2$ and **6a** in dry CH_2Cl_2. The ion exchange was carried out by stirring a suspension of non-activated MK10 (used without any acid treatment) in CH_2Cl_2 (Scheme 6). The quantity of Cu immobilized in the MK10 was analyzed by ICP-OES. The quantity of ligand immobilized in MK10 was also analyzed by microanalysis. In the case of ligand **6b**, it was complexed with $[Cu(MeCN)_4]PF_6$ in CH_2Cl_2. The ion exchange was carried out with MK10 (Scheme 6). From the analysis of the immobilized Cu in the MK10 support, the immobilization of **6b**-$[Cu(MeCN)_4]PF_6$ was more effective than that for the **6a**-$Cu(OTf)_2$ complex, despite the fact that the same amount of complex was immobilized in 50 mg less MK10 support. The catalysts **6a**-$Cu(OTf)_2$ and $[Cu(MeCN)_4]PF_6$ cannot be compared, however, because the ligands used were different, but are compared with the homogeneous systems. Both **6a**-$Cu(OTf)_2$ MK10 and **6b**-$[Cu(MeCN)_4]$-PF_6 MK10 were screened in the heterogeneous benchmark cyclopropanation of styrene with EDA (Scheme 5 and Table 2). We conducted four cycles in each case, but only the first two cycles were of significance and are listed in Table 2. In terms of enantioselectivity, it is obvious from these results that immobilized **6a** gives results closer to those seen with the homogeneous phase. On going from the first cycle to the second cycle, there were significant drop-offs both in the enantioselectivities and in the yield. This we believe to be a consequence of leaching of the catalyst from the support, because ICP analysis of the recovered supported catalyst after the fourth cycle revealed a 35% loss of catalyst. The quantity of nitrogen in the **6a**-$Cu(OTf)_2$ on MK10 recovered after the fourth cycle was determined by elemental analysis and implied that it was only the Cu that was being leached out and not the full catalyst, because the quantity of nitrogen remained constant. We cannot explain this result, but it might be because the copper is not bound to the BOX ligand, and can be removed easily. Curiously, the *cis*-cyclopropane was obtained with better enantioselectivity than the *trans*-cyclopropane in these reactions. Mayoral's group has reported a similar result in the case of analogous BOX-derived Cu catalysts on other clay supports.[23] To explain this phenomenon Mayoral and coworkers have proposed a working model involving key stereochemical interactions between the catalyst and the reagents.[24] It was hypothesized that potentially important steric effects between the surface and the incoming alkene enable the transition state leading to the *cis*-cyclopropane product to be freer from steric interactions. In the case of the immobilized **6b** the *ee* values are similar but rather inferior in the first cycle and decreased in the second cycle. The catalytic asymmetric cyclopropanation with the heterogeneous catalyst **6b**-$Cu^{I}(MeCN)_4$ and styrene was carried out with 2.05 mol-% catalyst, practically the same amount that was used in the original homogeneous catalysis (2 mol-%).[14,15] The enantioselectivity obtained with this immobilized catalyst was lower than for the homogeneous catalytic system. The results obtained for the first cycle were very close to those obtained in the homogeneous reaction, the main difference being the higher yield obtained in the heterogeneous phase, which is accounted for on the basis of the reduced level of maleate/fumarate side-product formation in the case of the heterogeneous reaction. With this immobilized catalyst we observed once again that the yield and the stereoselectivities drop from one cycle to the next.



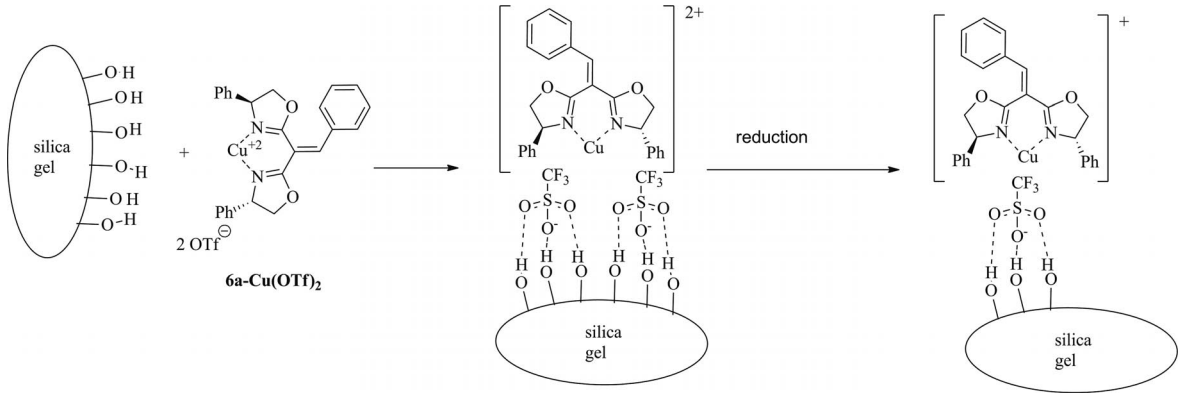
Scheme 6. Ion-exchange of the Cu complexes on MK10.

There was also a gradual increase in the proportion of *cis*-cyclopropane produced on going from the first to the second cycle.

Arylid-BOX-$Cu^{II}(OTf)_2$ Complex Immobilized by Hydrogen Bonding with SiO_2

The **6a**-$Cu(OTf)_2$ complex in dichloromethane was immobilized on silica gel by the rapid method introduced by van Koten[12] (Scheme 7). The electrostatically immobilized

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 7. Representation of the immobilization of **6a**-Cu(OTf)$_2$ on silica gel and its subsequent reduction to Cu^{I}.

Table 3. Catalytic asymmetric cyclopropanation of styrene in the presence of complex **6a**-Cu(OTf)$_2$ immobilized on silica gel.

Catalyst type	Run	Complex	Cu [mmol g^{-1}]	*t* [h]	Yield[a] [%]	*ee*[b] *cis* [%]	*ee*[b] *trans* [%]	*cis*/*trans*[b] [%]	Products/ dimers[b] [%]
Homogeneous	n.a.	**6a**-Cu(OTf)$_2$	–	20	5	53	63	27:73	n.d.
Heterogeneous	first		0.133[c]	45	31	65	62	32:68	94:6
Heterogeneous	second		–	45	18	47	46	38:62	87:13
Homogeneous[16]	n.a.	**6b**-[Cu(MeCN)$_4$]PF$_6$	–	24	100	41	50	31:69	95:5
Heterogeneous	first		0.171[c]	45	22	39	45	34:66	83:17
Heterogeneous	second		–	45	14	26	37	40:60	82:18

[a] Determined by GC with use of di-*n*-butyl ether as the internal standard. [b] Determined by chiral GC analysis. [c] Determined by ICP-OES analysis before the first run. n.d.: not determined.

catalyst was tested in the benchmark catalytic asymmetric cyclopropanation (Scheme 5) in both CH_2Cl_2 and toluene as solvents (Table 3).

In the case of the reactions run in CH_2Cl_2, the enantioselectivities were lower in the case of the supported reactions, although the yields increased from the first to the third cycles. There were also gradual increases in the amounts of *cis*-cyclopropane produced on going from the homogeneous phase to the last cycle. In this case, the quantities of maleate/fumarate side-product decreased on going from the first to the third cycles. There was also significant leaching in this case, of approximately 81% in immobilized Cu from the first to the third cycles (it was estimated on the basis of the quantity of ligand and catalyst used that there was initially approximately 0.28 mmol of Cu immobilized on the support).

With regard to the copper oxidation state, because the catalyst is constantly maintained under anhydrous conditions, it is assumed that it remains in the Cu^{I} oxidation state throughout. The color of the solid was always green.

When toluene was used, the enantioselectivity achieved in the first run was slightly better than that obtained with the homogeneous phase. Although the enantioselectivities and the yields for the *cis*-cyclopropane were constant in the first and second cycles, the enantioselectivities for the *trans*-cyclopropane and the yields dropped drastically in the second cycle. Once again there was significant leaching, of the order of 84%, indicating that this method of weak immobilization with this catalytic system is not very applicable for catalyst reuse. There was, yet again, a preference for the formation of the *cis*-cyclopropane with this support.

Conclusions

The covalent immobilization method described in this paper is a simple way to immobilize bis(oxazoline) ligands on polymeric supports. Evaluation of the polymeric ligand **22** in the CACP showed that the activity of the Cu^{I} catalyst and its selectivity remained constant over four cycles, achieving similar results to the homogeneous system. This was one of the advantages of this system over the Knight and Belcher[7] system.

The covalent immobilization method described in this paper has many advantages over the grafting technique by polymerization documented in the literature.[5] Burguete et al.[5b] could only obtain a highest enantioselectivity of 33% *ee* (in relation to our highest of 71% *ee*) with their immobilized ligand **2** (Figure 1). The immobilized catalyst gave results similar to those achieved with the non-immobilized catalyst in the CACP of styrene with [Cu(MeCN)$_4$]-PF$_6$.

If the results obtained for the noncovalent immobilized Arylid-BOX catalysts and for the covalently immobilized catalyst are compared, the latter was superior in all aspects: activity, selectivity, and recycling. Leaching of the catalyst was less than that observed in the noncovalent immobilization process.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Experimental Section

General Remarks: 2-Phenyl-1,1-bis[(*S*)-4-phenyloxazoline-2-yl]ethene (**6a**),[15] 2-(2-methoxyphenyl)-1-[(*S*)-4-phenyloxazoline-2-yl]ethane (**23**)[21] and the α-amino alcohol (*R*)-phenylglycinol[25] were prepared by previously described methods. Solvents were dried by common laboratory methods. All reagents were obtained from Aldrich, Fluka, Alfa Aesar, or Acros. Column chromatography was carried out on silica gel (sds, 70–200 μm), as was flash column chromatography (Merck, 40–63 μm and sds, 40–63 μm). TLC was carried out on aluminium-backed Kieselgel plates (Merck, 60 F254). Plates were visualized either under UV light or by use of phosphomolybdic acid in ethanol. The melting points were recorded with a Barnstead Electrothermal 9100 apparatus and are uncorrected. The NMR spectra were recorded either with a Bruker AMX 300 (^{1}H: 300.13 MHz and ^{13}C: 75 MHz) instrument or with a Bruker Avance instrument (^{1}H: 400 MHz and ^{13}C: 100 MHz) in $CDCl_3$ or [D_6]DMSO as solvents. Mass spectra were recorded with a Waters-Micromass GC-TOF and a MicroTOF Focus (Bruker Daltonics) instrument by the TOF technique and electron spray ionization (ESI) mass spectra were recorded with a Bruker Daltonics Apex-Qe instrument. Infrared spectra were measured with a Perkin–Elmer Paragon 1000 model. Gas chromatographic (GC) analyses of the products were performed with a Hewlett–Packard (HP) 6890 series instrument and a flame ionization detector (FID). The chromatograph was fitted with a cyclosil-B capillary column (30 m, 250 μm, 0.25 μm, Agilent 112–2532). ICP-OES analyses were performed with a Perkin–Elmer Optima 4300 DV instrument at CACTI, Universidad de Vigo. Elemental analysis was performed with an EA 1108 CHNS-O Fisons instrument. Specific rotations were measured with a Perkin–Elmer 241 polarimeter.

Dimethyl 2-[4-(*tert*-Butyldimethylsilanoxy)benzylidenemethyl]malonate (11): A dry round-bottomed flask fitted with a Dean–Stark trap and condenser and containing a magnetic stirring bar was charged with acetic acid (0.4 mL, 5 mol-%), piperidine (0.6 mL, 5 mol-%), dimethyl malonate (1.58 mL, 0.024 mol), 4-[(*tert*-butyldimethylsilyl)methoxy]benzaldehyde (**10**)[7] (3.5 g, 0.014 mol), and benzene (60 mL). The solution was stirred at reflux. The cooled reaction mixture was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo to give **11** as a yellow solid (4.83 g, 95%); m.p. 59–60 °C. ^{1}H NMR (300 MHz): δ = 7.77 (s, 1 H, ArC*H*=CR_2), 7.41–7.33 [m, 4 H, C*H*(Ar)], 4.76 (s, 2 H, OCH_2-OTBDMS), 3.85 (s, 6 H, –CO_2CH_3), 0.95 [s, 9 H, –C(CH_3)$_3$], 0.11 [s, 6 H, Si(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz): δ = 167.4, 164.7, 144.7, 143.0, 131.5, 129.6, 126.4, 125.1, 64.6, 52.7, 26.1, 18.5, –5.2 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2955, 1733, 1702, 1631, 1440, 1230, 1100, 838, 774 cm^{-1}.

Dimethyl 2-[4-(Benzyloxy)benzylidene]malonate (18): A dry round-bottomed flask fitted with a Dean–Stark trap and condenser and containing a magnetic stirring bar was charged with acetic acid (0.068 mL, 1.2 mmol, 5 mol-%), piperidine (0.11 mL, 1.2 mmol, 5 mol-%), dimethyl malonate (2.7 mL, 0.024 mol), 4-(benzyloxy)-benzaldehyde (5 g, 0.024 mol), and benzene (60 mL). The solution was stirred at reflux until 0.43 mL of H_2O had been removed. The cooled reaction mixture was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo to give **18** as a pale yellow solid (8.13 g, 95%); m.p. 54–55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (s, 1 H, ArC*H*=CR_2), 7.39–6.83 [m, 9 H, C*H*(Ar)], 4.50 (s, 2 H, OCH_2Ph), 3.87 (s, 3 H, –CO_2CH_3), 3.84 (s, 3 H, –CO_2CH_3) ppm. ^{13}C NMR (100 MHz): δ = 167.7, 164.9, 142.6, 136.3, 131.6, 128.7, 128.3, 127.5, 125.6, 123.0, 115.3, 70.2, 52.7, 52.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3004, 2952, 1712, 1598, 1380, 1228, 1181, 1063, 147 cm^{-1}. MS (ESI-TOF): *m*/*z* = 327.05 [M + H]$^+$.

2-(4-Benzyloxybenzylidene)malonic Acid (19): A solution of **18** (6.580 g, 0.020 mol) in ethanol (50 mL) was added to a solution of NaOH (2.016 g, 0.050 mol) in ethanol (150 mL) and the mixture was stirred for 4 d at 0 °C. The ethanol was removed under reduced pressure and the residue was dissolved in H_2O (until the solution became clear), allowed to cool, and cautiously acidified with concd. HCl to a pH of 3.0. The acid was extracted with EtOAc (3 × 75 mL), and the organic layers were dried ($MgSO_4$), filtered, and concentrated to afford the **19** as a pale yellow solid (3.410 g, 57%); m.p. 186 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 7.56 [d, *J* = 8.7 Hz, 2 H, C*H*(Ar)], 7.47–7.33 [m, 6 H, C*H*(Ar), RC*H*=CR_2], 7.07 [d, *J* = 8.4 Hz, 2 H, C*H*(Ar)], 5.15 (s, 2 H, OCH_2Ph) ppm. ^{13}C NMR (100 MHz): δ = 168.3, 165.5, 160.1, 138.4, 136.6, 131.3, 128.5, 128.0, 127.8, 125.8, 125.4, 115.3, 69.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3346, 2979, 1728, 1665, 1514, 1436, 1280, 1217, 1067, 1174, 837 cm^{-1}. MS (ESI-TOF): *m*/*z* = 299.10 [M + 1]$^+$.

2-(4-Bromophenyl)-1,1-bis[(*S*)-4-phenyloxazolin-2-yl]ethene (15a): A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with malonic acid (3.0 g, 28.8 mmol) and *p*-bromobenzaldehyde (5.3 g, 28.8 mmol). The mixture was heating at 80 °C for 24 h. The mixture was allowed to cool to room temperature and extracted with Et_2O (15 mL) and NaOH (1 M, 25 mL). The aqueous layer was washed with Et_2O (10 mL), a solution of concd. HCl was added until pH 1, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layer was collected, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum to give 2-(4-bromobenzylidene)malonic acid as a white solid (1.8 g, 24%). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 7.87 (s, 1 H, ArC*H*=CR_2), 7.72–7.65 [m, 2 H, C*H*(Ar)], 7.52–7.49 [m, 2 H, C*H*(Ar)] ppm.

The 2-(4-bromobenzylidene)malonic acid (1.8 g, 6.6 mmol) was placed in a dry 25 mL two-necked round-bottomed flask containing a magnetic stirring bar, dimethylformamide (0.06 mL, 0.86 mmol), and CH_2Cl_2 (20 mL). The solution was cooled to 0 °C, oxalyl chloride (1.5 mL, 16.6 mmol) was added dropwise over 30 min, and the solution was then stirred at room temperature until the evolution of gas had ceased. The solution was concentrated in vacuo to give the 4-bromobenzylidenemalonyl chloride intermediate as a yellow semi-solid (2.0 g, 97%). A 25 mL two-necked round-bottomed flask containing a magnetic stirring bar was charged with a solution of (*S*)-phenylglycinol (0.6 g, 4.4 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C with an ice bath. Dry triethylamine (0.92 mL, 6.6 mmol) was added by syringe. A solution of crude 2-(4-bromobenzylidene)malonyl chloride (0.85 g, 2.78 mmol) in CH_2Cl_2 (5 mL) was slowly added by syringe to the vigorously stirred reaction mixture over 30 min. The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was washed with HCl (2 M, 12 mL) and saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give (*S*,*S*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-(4-bromobenzylidene)malonamide as a yellow solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford the amide as a white solid (0.46 g, 41%); m.p. 86–87 °C. $[a]_D^{24}$ = –66 (*c* = 0.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8 Hz, 1 H, N*H*), 7.85 (d, *J* = 8 Hz, 1 H, N*H*), 7.42 (s, 1 H, ArC*H*=CR_2), 7.31–7.25 [m, 10 H, C*H*(Ar)], 7.13 [d, *J* = 8 Hz, 2 H, C*H*(Ar)], 7.00 [d, *J* = 8 Hz, 2 H, C*H*(Ar)], 5.30–2.25 (m, 1 H, C*H*), 5.21–5.16 (m, 1 H, C*H*), 3.88–3.69 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 164.7, 138.4,

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

138.3, 137.6, 132.0, 131.9, 131.8, 131.0, 129.0, 128.9, 128.2, 128.0, 127.2, 126.7, 124.3, 66.2, 65.7, 56.4, 56.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3271, 2929, 1737, 1662, 1531, 1261, 1073, 819, 757, 700 cm^{-1}. MS (ESI-TOF): *m*/*z* = 509.1052 $[M + 1]^+$. HRMS (ESI): calcd. for $C_{26}H_{26}BrN_2O_4$ $[M + H]^+$ 509.10522; found 509.10705.

A solution of methanesulfonyl chloride (0.14 g, 1.25 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise over 20 min to a solution of the malonamide (0.25 g, 0.5 mmol) and dry triethylamine (0.42 mL, 3.0 mmol) in dry CH_2Cl_2 (20 mL) and the solution was stirred between –5 and –10 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 d. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude product. The crude product was purified by column chromatography (silica gel, EtOAc/hexane 1:1) to give bis[(*S*)-4-phenyloxazoline-2-yl]-2-(4-bromophenyl)ethene (**15a**) as a yellow solid (0.07 g, 30%); m.p. 134–135 °C. $[\alpha]_D^{24}$ = +42.7 (*c* = 0.93, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (s, 1 H, ArC*H*=CR_2), 7.46–7.26 [m, 14 H, Ar(*H*)], 5.44–5.36 (m, 2 H, –CH_2–), 4.3 (t, *J* = 8.4 Hz, 1 H, –C*H*–), 4.22 (t, *J* = 8.4 Hz, 1 H, –C*H*–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 161.6, 142.1, 141.8, 140.6, 133.1, 132.0, 131.0, 128.8, 128.7, 127.7, 127.0, 126.8, 124.3, 119.5, 75.1, 75.0, 70.4, 70.3 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2869, 1672, 1634, 1615, 1182, 1024, 760, 702 cm^{-1}. MS (ESI-TOF): *m*/*z* = 473.09 $[M + 1, Br^{79}]^+$, 474.09 $[M + 2, Br^{79}]^+$, 475.09 $[M + 1, Br^{81}]^+$, 476.09 $[M + 2, Br^{81}]^+$. HRMS (ESI): calcd. for $C_{26}H_{22}BrN_2O_2$ $[M + H]^+$ 473.08538; found 473.08592.

(*R*,*R*)-2-(4-Benzyloxybenzylidene)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)malonamide (20): A dry 25 mL two-necked round-bottomed flask containing a magnetic stirring bar was charged with 2-(4-benzyloxybenzylidene)malonic acid (**19**) (1 g, 3.35 mmol), dimethylformamide (0.03 mL, 0.44 mmol), and CH_2Cl_2 (10 mL). The solution was cooled to 0 °C, oxalyl chloride (0.73 mL, 8.38 mmol) was added dropwise over 30 min, and the solution was stirred at room temperature until the evolution of gas had ceased. The solution was evaporated in vacuo to give 4-benzyloxybenzylidenemalonyl chloride as a yellow semi-solid (because of the unstable nature of this compound it was stored in the freezer at –10 °C). A 25 mL two-necked round-bottomed flask containing a magnetic stirring bar was charged with a solution of (*R*)-phenylglycinol (1.22 g, 8.88 mmol) and dry CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C with an ice bath. Dry triethylamine (1.24 mL, 8.88 mmol) was added by syringe. A solution of crude 2-(4-benzyloxybenzylidene)malonyl chloride (1.28 g, 3.35 mmol) in CH_2Cl_2 (5 mL) was slowly added to the vigorously stirred reaction mixture by syringe over 30 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was washed with HCl (2 M, 12 mL) and saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (15 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give (*R*,*R*)-*N*,*N*′-bis(2-hydroxy-1-phenylethyl)-2-(4-benzyloxybenzylidene)malonamide (**20**) as a yellow solid. The crude product was purified by column chromatography (silica gel, EtOAc) to afford the amide **20** as a white solid (0.955 g, 53%); m.p. 90–91 °C. $[\alpha]_D^{20}$ = +62.2 (*c* = 1.03, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.9 Hz, 1 H, N*H*), 7.84 (d, *J* = 8.4 Hz, 1 H, N*H*), 7.41–7.30 [m, 6 H, R_2C=C*H*R, C*H*(Ar)], 7.26–7.18 [m, 10 H, C*H*(Ar)], 7.03 [d, *J* = 8.8 Hz, 2 H, C*H*(Ar)], 6.52 [d, *J* = 8.8 Hz, 2 H, C*H*(Ar)], 5.39–5.37 (m, 1 H, C*H*), 5.23–5.22 (m, 1 H, C*H*), 4.91 (s, 2 H, –OCH_2Ph), 3.86–3.79 (m, 2 H, CH_2), 3.66 (dd, *J* = 9.7, 11.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 165.3, 159.8, 139.3, 138.3, 137.6, 136.3, 131.7, 128.7, 128.6, 128.1, 128.1, 127.7, 127.7, 127.4, 127.3, 126.5, 125.4, 114.5, 69.7, 65.7, 65.5, 56.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3274, 2930, 1736, 1659, 1602, 1511, 1177, 1026, 829, 753, 699 cm^{-1}. MS (ESI-TOF): *m*/*z* = 537.24 $[M + H]^+$. HRMS (ESI): calcd. for $C_{33}H_{33}N_2O_5$ $[M + H]^+$ 537.23696; found 537.23840.

2-(4-Benzyloxyphenyl)-1,1-bis[(*R*)-4-phenyloxazoline-2-yl]ethane (21): A solution of methanesulfonyl chloride (0.166 g, 1.45 mmol) in dry dichloromethane (1 mL) was added dropwise over 20 min to a solution of the malonamide **20** (0.354 g, 0.66 mmol) and dry triethylamine (0.55 mL, 3.96 mmol) in dry dichloromethane (20 mL) and the solution was stirred between –5 and –10 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 d. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford the crude product. The crude product was purified by column chromatography [silica gel, EtOAc/hexane 1:1] to give bis[(*R*)-4-phenyloxazoline-2-yl]-2-(4-benzyloxyphenyl)ethane (**21**) as a white solid (0.11 g, 60%); m.p. 68 °C (decomposition). $[\alpha]_D^{20}$ = +50.3 (*c* = 1.89, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1 H, R_2C=C*H*R), 7.50 [d, *J* = 8.8 Hz, 2 H, C*H*(Ar)], 7.42–7.23 [m, 15 H, C*H*(Ar)], 6.93 [d, *J* = 8.7 Hz, 2 H, C*H*(Ar)], 5.43 (dd, *J* = 9 Hz, 2 H, 2× C*H*H), 5.08 (s, 2 H, –OCH_2Ph), 4.88 (dd, *J* = 9, 10 Hz, 1 H, C*H*H), 4.81 (dd, *J* = 9, 12 Hz, 1 H, CH*H*), 4.31 (t, *J* = 8.4 Hz, 1 H, C*H*), 4.20 (t, *J* = 8.2 Hz, 1 H, C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 162.2, 160.2, 142.3, 141.9, 141.4, 136.4, 131.5, 128.7, 128.6, 128.6, 128.2, 127.5, 127.0, 126.8, 126.7, 74.9, 74.8, 70.2, 70.1, 70.0 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2958, 1739, 1670, 1633, 1601, 1509, 1250, 1173, 1013, 741, 699 cm^{-1}. MS (ESI-TOF): *m*/*z* = 501.22 $[M + H]^+$. HRMS (ESI): calcd. for $C_{33}H_{29}N_2O_3$ $[M + H]^+$ 501.21786; found 501.21727.

2-(4-Hydroxyphenyl)-1,1-bis[(*R*)-4-phenyloxazoline-2-yl]-ethane (9): A dry 50 mL round-bottomed flask containing a magnetic stirring bar was charged with the Arylid-BOX **21** (0.371 g, 0.74 mmol), dry ethanol (25 mL), and Pd on activated carbon (0.186 g, 0.5 equiv.). The mixtures were warmed to 50 °C and a balloon filled with hydrogen was attached to the flask. The mixture was stirred for 24 h and then allowed to cool to room temp., filtered through a celite filter, and washed with CH_2Cl_2 (30 mL), and the solvent was removed under vacuum. The crude product was purified by column chromatography (silica gel, EtOAc/hexane 91:9) to give **9** as a colorless semi-solid (0.14 g, 46%). $[\alpha]_D^{25}$ = –177 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.23 [m, 10 H, C*H*(Ar)], 6.98–6.93 [m, 2 H, C*H*(Ar)], 6.29 [d, *J* = 8.3 Hz, 2 H, C*H*(Ar)], 5.21 (dd, *J* = 9, 18 Hz, 2 H, 2× C*H*H), 4.7 (dd, *J* = 8.6, 10 Hz, 2 H, 2× C*H*), 4.24 (t, *J* = 8 Hz, 1 H, C*H*), 4.17–4.09 (m, 2 H, 2× C*H*H), 3.34–3.28 (m, 1 H, C*H*H), 3.27–3.22 (m, 1 H, CH*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 165.9, 155.9, 141.6, 141.4, 129.7, 128.7, 127.8, 127.7, 127.7, 126.9, 126.6, 126.4, 115.6, 75.5, 75.4, 69.3, 68.9, 41.9, 34.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3200, 2925, 1736, 1657, 1613, 1516, 1239, 994, 823, 761, 700 cm^{-1}. MS (ESI-TOF): *m*/*z* = 413.19 $[M + H]^+$. HRMS (ESI): calcd. for $C_{26}H_{25}N_2O_3$ $[M + H]^+$ 413.18625; found 413.18597.

Wang-Resin-Supported 2-(4-Hydroxyphenyl)-1,1-bis[(*R*)-4-phenyloxazoline-2-yl]ethane (22): The bis(oxazoline) **9** (130 mg, 0.315 mmol) was dissolved in dry DMF (5 mL), and NaH (60%,

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

27 mg, 0.63 mmol) was added in one portion. The mixture became yellow and the suspension was stirred for 30 min at room temp. Wang-Br resin (0.5–1 mmol g^{-1}, 0.630 g, 0.315 mmol) was added to the reaction mixture, which was stirred under nitrogen overnight at 50 °C. The resin was filtered off and washed successively with MeOH (3 mL), THF/H_2O (1:1, 3 mL), H_2O (3 mL), CH_2Cl_2 (3 mL), and MeOH (3 mL). The supported ligand **22** was dried at 40 °C under vacuum for several hours, giving a final mass of 0.598 g, with a loading of 0.321 mmol of ligand per gram polymer.

Catalytic Asymmetric Cyclopropanation of Styrene

[Cu(MeCN)$_4$]PF$_6$ as Precatalyst

Representative Asymmetric Cyclopropanation of Styrene: The immobilized catalyst **22** (92 mg, 0.029 mmol, 2.2 mol-%) was added to a suspension of [Cu(MeCN)$_4$]PF$_6$ (10 mg, 0.027 mmol, 2 mol-%) in solvent (4 mL). After 1 h, styrene (0.58 mL, 5.6 mmol, 4 equiv.) was added to the resulting green solution. A solution of ethyl diazoacetate (159 mg, 1.4 mmol, 1.0 equiv.) in solvent (1 mL) was added to the reaction vessel by syringe pump over 8 h. The reaction mixture was stirred at room temperature for 40 h and was filtered off and washed with CH_2Cl_2 to collect the products. The yellow solid was dried under vacuum and used again in subsequent catalytic cycles. The crude product was analyzed by GC. For the other runs the same procedure was used, but because of the powdery nature of the supported catalyst some of the immobilized catalyst was inevitably lost. Although the quantity of supported catalyst used in the subsequent cycles was reduced, however, the proportions were always the same. In order to conduct these catalytic reactions rapidly it was assumed that there was negligible catalyst leaching. All cyclopropane products were obtained as mixtures of *cis* and *trans* diastereomers, and the ratios were determined by GC analysis. Isolated yields, diastereoselectivities, and enantioselectivities are given in Table 1.

Cu(OTf)$_2$ as a Precatalyst

Representative Asymmetric Cyclopropanation of Styrene: Ethyl diazoacetate (EDA, 0.032 mg, 0.28 mmol) was added under nitrogen to a suspension of Cu(OTf)$_2$ (9.6 mg, 0.027 mmol, 2 mol-%) in CH_2Cl_2 (4 mL) together with immobilized catalyst **22** (92 mg, 0.029 mmol, 2.2 mol-%) in dry CH_2Cl_2 (4 mL). This was followed by the addition of styrene (580 mg, 5.6 mmol). The reaction mixture was stirred for 15 min, followed by the addition of EDA (0.159 mg, 1.4 mmol) in CH_2Cl_2 (1 mL) by syringe pump over 6 h. The reaction mixture was stirred under nitrogen for 48 h. The solid was filtered off and washed with CH_2Cl_2, and the volatiles were then removed in vacuo. The crude product was analyzed by GC. All cyclopropane products were obtained as mixtures of *cis* and *trans* diastereomers, the ratios of which were determined by GC analysis. Isolated yields, diastereoselectivities, and enantioselectivities are given in Table 1.

Immobilization of the Cu Catalysts on MK10

Immobilization of (6a)-Cu(OTf)$_2$: The Arylid-BOX **6a** (20 mg, 0.05 mmol), Cu(OTf)$_2$ (18 mg, 0.05 mmol), and dry CH_2Cl_2 (3 mL) were placed in a flask under nitrogen. The mixture was stirred for 2 h. The solvent was removed. Montmorillonite K10 (300 mg) was added to the complex (38 mg, 0.05 mmol) together with dry CH_2Cl_2 (5 mL). The resulting suspension was stirred for 24 h. The solid was filtered, washed with CH_2Cl_2, and dried under vacuum. Immobilized catalyst (279 mg) was obtained and was calculated (ICP-OES analysis) to contain Cu (0.133 mmol per gram support) and N (0.296 mmol per gram support) (as determined by EA).

Immobilization of (6b)-[Cu(MeCN)$_4$]PF$_6$: By the same procedure as described previously, the Arylid-BOX **6b** (25.5 mg, 0.06 mmol) and [Cu(MeCN)$_4$]PF$_6$ (22.51 mg, 0.06 mmol) were dissolved in CH_2Cl_2 (3 mL). The resulting complex (36 mg, 0.05 mmol) was immobilized in MK10 (250 mg), and after washing the immobilized catalyst, it was dried thoroughly, giving a final mass of 227 mg. It was calculated to contain Cu (0.171 mmol per gram support) and N (0.419 mmol per gram support) (as determined by EA).

Heterogeneous Catalytic Asymmetric Cyclopropanation with the MK10-Supported Catalysts

Application of (6a)-Cu(OTf)$_2$ MK10: Ethyl diazoacetate (EDA, 0.032 mg, 0.28 mmol) was added under nitrogen to a mixture containing the immobilized (**6a**)-Cu(OTf)$_2$ catalyst (0.172 g, 0.0228 mmol, 1.6 mol-%) in dry CH_2Cl_2 (4 mL). This was followed by the addition of styrene (580 mg, 5.6 mmol). The reaction mixture was stirred for 15 min, followed by the addition of EDA (0.159 mg, 1.4 mmol) in CH_2Cl_2 (1 mL) by syringe pump over 6 h. It was found that the color of the insoluble supported catalyst changed from grey to greenish. The reaction mixture was stirred under nitrogen for 45 to 47 h. The solid was filtered off and washed with CH_2Cl_2 and EtOAc, and the volatiles were then removed in vacuo. The crude product was analyzed by GC with di-*n*-butyl ether as an internal standard (Table 2). For the other runs the same procedure was used, but because of the powdery nature of the supported catalyst some of the immobilized catalyst was inevitably lost. However, although the quantity of supported catalyst used in the subsequent cycles was reduced, the proportions were always the same. In order to conduct these catalytic reactions rapidly it was assumed that there was negligible catalyst leaching.

Application of (6b)-[Cu(MeCN)$_4$]PF$_6$ MK10: Styrene (580 mg, 5.6 mmol) was added under nitrogen to a mixture containing the immobilized (**6b**)-[Cu(MeCN)$_4$]PF$_6$ catalyst (0.168 g, 0.0287 mmol, 2.05 mol-%) in dry CH_2Cl_2 (4 mL). The reaction mixture was stirred for 15 min, followed by the addition of EDA (0.159 mg, 1.4 mmol) in CH_2Cl_2 (1 mL) by syringe pump over 6 h. The reaction mixture was stirred under nitrogen for 45 to 47 h. The solid was filtered off and washed with CH_2Cl_2 and EtOAc, and the volatiles were removed in vacuo. The crude product was analyzed by GC with di-*n*-butyl ether as an internal standard (Table 2). For the other runs the same procedure was used.

Heterogeneous Catalytic Asymmetric Cyclopropanation with Catalysts Supported on Silica Gel: A mixture of the Arylid-BOX **6a** (11.8 mg, 0.03 mmol) and Cu(OTf)$_2$ (10.1 mg, 0.028 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under nitrogen in a Schlenk tube and stirred for 30 min at room temp. The catalyst complex solution was filtered and the filtrate was added under nitrogen to pre-dried silica gel (100 mg, 63–20 μm, dried for 1 h under vacuum at 70 °C) in a dry Schlenk tube. The mixture was stirred until the color had disappeared from the solution. The silica gel (which was now colored) was allowed to settle and washed with dry dichloromethane (2 mL) and then left under the appropriate dry reaction solvent (2 mL) and nitrogen. EDA (0.032 mg, 0.28 mmol) was added under nitrogen to the mixture containing the immobilized catalyst complex, along with more dry solvent (1 mL), followed by styrene (580 mg, 5.6 mmol). The reaction mixture was stirred for 15 min, followed by the addition of EDA (0.159 mg, 1.4 mmol) in an appropriate dry reaction solvent (1 mL) by syringe pump over 6 h. The reaction mixture was stirred under nitrogen for 91.5 h. The solvent layer was removed with a Pasteur pipette and filtered through Celite, the remaining solid was then washed with dry solvent (2 × 5 mL), and the washings were filtered through Celite under reduced pressure. The silica gel catalyst was left under a dry solvent (1 mL) and nitrogen for subsequent catalytic runs. The combined extracts were concentrated under reduced pressure to give the crude

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

product as a colorless oil, which was purified by silica gel chromatography, (hexane/EtOAc 9:1). The product mixture was analyzed by GC (Table 3).

Acknowledgments

We are grateful for financial support from the Fundação para a Ciência e a Tecnologia (FCT) (project; PPCDT/QUI/55779/2004) through POCI 2010, supported by the European community, Fundo Europeu de Desenvolvimento Regional (FEDER). FCT is also acknowledged for the award of a PhD grant to E. P. C. (SFRH/BD/277688/2006). The staff from CACTI (University of Vigo, Spain) are gratefully acknowledgment for the ICP analysis.

[1] a) M. Lemaire, *Pure Appl. Chem.* **2004**, *76*, 679; b) G. J. Hutchings, *Annu. Rev. Mater. Res.* **2005**, *35*, 143; c) J. Gladysz, *Pure Appl. Chem.* **2001**, *73*, 1319; d) J. M. Fraile, J. I. García, M. A. Harmer, C. I. Herrerías, J. A. Mayoral, E. Pires, *Chem. Soc. Rev.* **2009**, *38*, 695–706.

[2] a) B. Kerler, R. E. Robinson, A. S. Borovik, B. Subramaniam, *Appl. Catal. B* **2004**, *49*, 91; b) V. S. Gerard, F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry*, Elsevier, **2000**.

[3] a) D. Rechavi, M. Lemaire, *Chem. Rev.* **2002**, *102*, 3467; b) J. M. Fraile, J. I. García, J. A. Mayoral, *Coord. Chem. Rev.* **2008**, *252*, 624–646; c) J. M. Fraile, J. I. García, J. A. Mayoral, *Chem. Rev.* **2009**, *109*, 360–417.

[4] a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1; b) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561, and references cited thereinc) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151; d) G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505, and references cited therein.

[5] 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) 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; c) M. I. Burguete, E. Díez-Barra, J. M. Fraile, J. I. García, E. García-Verdugo, R. González, C. I. Herrerías, S. V. Luis, J. A. Mayoral, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1821.

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

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

[8] a) H. Werner, C. I. Herrerías, M. Glos, A. Gissibl, J. M. Fraile, I. Pérez, J. A. Mayoral, O. Reiser, *Adv. Synth. Catal.* **2006**, *348*, 125; b) J. M. Fraile, I. Pérez, J. A. Mayoral, O. Reiser, *Adv. Synth. Catal.* **2006**, *348*, 1680.

[9] C. Aranda, A. Cornejo, J. M. Fraile, E. Garcia-Verdugo, M. J. Gil, S. V. Luís, J. A. Mayoral, V. Martinez-Merino, Z. Ochoa, *Green Chem.* **2011**, *13*, 983.

[10] J. M. Fraile, J. I. Garcia, J. A. Mayoral, T. Tarnai, *Tetrahedron: Asymmetry* **1997**, *8*, 2089–2092.

[11] J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, O. Reiser, A. Scuéllamos, H. Werner, *Chem. Eur. J.* **2004**, *10*, 2997.

[12] P. O'Leary, N. P. Krosveld, K. P. De Jong, G. van Koten, R. Gebbink, *Tetrahedron Lett.* **2004**, *45*, 3177.

[13] a) C. McDonagh, P. O'Leary, *Tetrahedron Lett.* **2007**, *50*, 979; b) C. McDonagh, P. O'Leary, *Tetrahedron Lett.* **2009**, *50*, 979–982.

[14] E. P. Carreiro, S. Chercheja, N. M. M. Moura, C. S. C. Gertrudes, A. J. Burke, *Inorg. Chem. Commun.* **2006**, *9*, 823–826.

[15] A. J. Burke, E. P. Carreiro, S. Chercheja, N. M. M. Moura, J. P. P. Ramalho, A. I. Rodrigues, C. I. M. Santos, *J. Organomet. Chem.* **2007**, *692*, 4863–4874.

[16] E. P. Carreiro, J. P. P. Ramalho, A. I. Rodrigues, A. J. Burke, *Tetrahedron: Asymmetry* **2009**, *20*, 1272–1278.

[17] a) Y.-J. Sun, N. Li, Z.-B. Zheng, L. Liu, Y.-B. Yu, Z.-H. Qin, B. Fu, *Adv. Synth. Catal.* **2009**, *351*, 3113–3117; b) R. Yuryev, A. Liese, *Synlett* **2009**, *16*, 2589.

[18] S. C. Gertrudes, A. J. Burke, unpublished results.

[19] N. M. M. Moura, *B.Sc. Thesis*, Universidade de Évora, Portugal, **2006**.

[20] D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134.

[21] E. P. Carreiro, *Ph.D. Thesis* (European), Universidade de Évora, Portugal, **2010**.

[22] A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, J. Meienhofer, *J. Org. Chem.* **1978**, *43*, 4194.

[23] a) A. I. Fernandez, J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, L. Salvatella, *Catal. Commun.* **2001**, *2*, 165; b) J. I. García, B. López-Sánchez, J. A. Mayoral, E. Pires, I. J. Villalba, *J. Catal.* **2008**, *258*, 378.

[24] a) J. M. Fraile, J. I. García, V. Martínez-Merino, J. A. Mayoral, L. Salvatella, *J. Am. Chem. Soc.* **2001**, *123*, 7616; b) J. I. García, G. Jiménez-Osés, V. Martínez-Merino, J. A. Mayoral, E. Pires, I. Villalba, *Chem. Eur. J.* **2007**, *13*, 4064.

[25] M. J. McKennon, A. I. Meyers, K. Drauz, M. Schwarm, *J. Org. Chem.* **1993**, *58*, 3568.

Received: June 1, 2011
Published Online: November 30, 2011

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim