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Aza-bis(oxazolines): New Chiral Ligands for Asymmetric Catalysis†

Martin Glos and Oliver Reiser*

Institut für Organische Chemie der Universität Regensburg, Universitätsstrasse 31, D-93040 Regensburg, Germany

oliver.reiser@chemie.uni-regensburg.de

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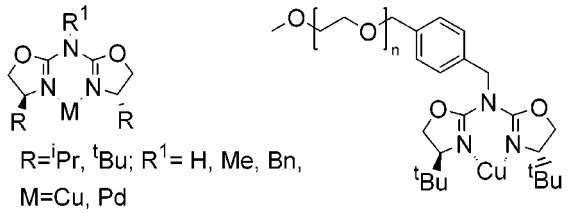
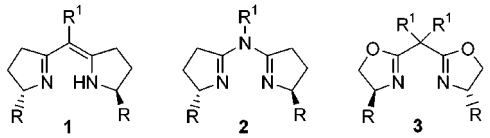
ABSTRACT



Aza-bis(oxazolines) are introduced as chiral ligands for asymmetric catalysis combining the advantages of easy availability of bis(oxazolines) and backbone variability of aza-semicorrins. Especially, the title ligands could be attached to a polymeric support, which allowed the development of easily recoverable copper(I)-catalysts for asymmetric cyclopropanation reactions.

Among the most successful developments in the area of chiral ligands for asymmetric catalysis is the introduction of C_2-symmetrical semicorrins **1**,[1,2] aza-semicorrins **2**,[1,2] and bis(oxazolines) **3**.[1,3] These ligands form superior catalysts



with a broad variety of metals to promote a number of transformations, including copper-catalyzed cyclopropanations,[2b,c,3a−f,p] aziridinations,[3c,g] Diels−Alder[3h−m] or aldol reactions,[3n−o] ruthenium-catalyzed oxidations,[3p−q] palladium-

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(1) Reviews: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (b) Pfaltz A. *Synlett* **1999**, 835−842. (c) Pfaltz A. *Heterocycl. Chem.* **1999**, *36*, 1437−1451. (d) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339−345. (e) Doyle, M. P.; Protopova, M. N. *Tetrahedron* **1998**, *54*, 7919−1946. (f) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, 991−1002. (g) Meyers, A. I.; Price, A. *J. Org. Chem.* **1998**, *63*, 412−413. (h) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297−2360. (i) Reiser, O. *Nachr. Chem. Technol. Lab.* **1996**, *44*, 744−750. (j) Bolm, C. *Angew. Chem.* **1991**, *103*, 556−558.

(2) (a) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A.; Keller, W.; Kratky, C. *Helv. Chim. Acta* **1988**, *71*, 1541−1552. (b) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553−1565. (c) Leutenegger, U.: Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143-2156. (d) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem.* **1989**, *101*, 61−62; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 60−61.

(3) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005−6008. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373−7376. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (d) Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073−4076. (e) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518−2526. (f) Boulch, R.; Scheurer, A.; Mosset, P.; Saalfrank, R. W. *Tetrahedron Lett.* **2000**, *41*, 1023−1026. (g) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329. (h) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807−6810. (i) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573. (j) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7482−7594. (k) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem.* **1998**, *110*, 3554−3557. (l) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (m) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321−7328. (n) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (o) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. (p) End, N.; Pfaltz, A. *Chem. Commun.* **1998**, 589−590. (q) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818−824. (r) Müller, K.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232−240. (s) Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K, *Tetrahedron: Asymmetry* **1993**, *4*, 143−150. (t) Hishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846−848. (u) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453−2462. (v) Lee, S.; Lim, C. W.; Song, C. E.; Kim, I. O.; Jun, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2927−2932. (w) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831−1834. (x) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945−2948.

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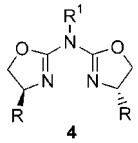
catalyzed allylations,[2c,3r] cobalt-catalyzed reductions,[2d] rhodium-catalyzed hydrosilylations,[3s−v] and copper-catalyzed allylic oxidations.[3w,x]

Of the three types of ligands, the bis(oxazolines) **3** are in general the easiest to prepare using readily available amino alcohols **5** as the source of chirality. Aza-semicorrins **2**, however, offer a greater structural flexibility than bis(oxazolines), because the central nitrogen atom can be functionalized by alkylating reagents. Moreover, they display a more rigid conformation due to the planar bridging nitrogen functionality.

We would like to report aza-bis(oxazolines)[4] **4** as a new class of chiral ligands which combine the advantages of easy accessibility of **3** and the structural flexibility of **2**.



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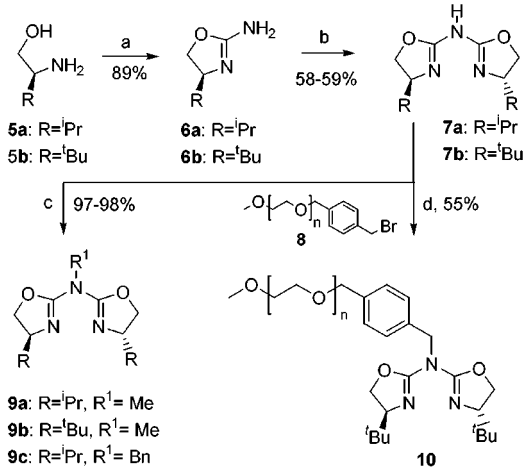
A distinct advantage of these ligands is that they can be attached to methoxypoly(ethylene glycol)e (MeOPEG 5000) as a soluble support, giving rise to the immobilized aza-bis(oxazoline) **10**, which could be successfully applied in asymmetric catalysis.

Aminooxazolines **6** (Scheme 1) serve as the key building blocks for the assembly of aza-bis(oxazolines). The aminooxazoline attached were readily synthesized from amino alcohols **5** following literature procedures.[5] Upon heating in toluene in the presence of *p*-toluenesulfonic acid and benzaldehyde, **6** underwent condensation with formal loss of ammonia to give **7** in good yields. In the absence of benzaldehyde, the yield of **7** decreased significantly and, as already noted by Kampe,[6] complex mixtures of products were obtained.

Scheme 1[a]



[a] (a) BrCN, CH_3OH, 0 °C; (b) *p*TsOH·H_2O (5%), PhCHO, Tol, △; (c) *n*BuLi, MeI, THF (**6a**−**b**); *n*BuLi, BnBr, THF (**6c**); (d) *n*-BuLi, THF, −78 to 0 °C, 44 h (**6b**).

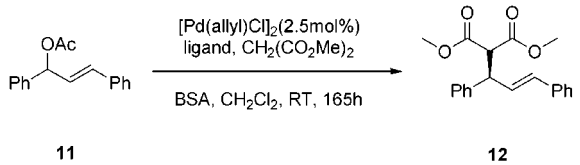
In contrast to the aza-semicorrins **2**,[2c] **7** could not be alkylated directly by simply stirring with alkyl iodides. Deprotonation of **7** with *n*-butyllithium readily occurred, however, and the resulting anion could be cleanly trapped with alkyl halides to give rise to **9**.

The development of polymer-bound ligands and catalysts is an important new goal for increasing the efficiency of organic reactions. Apart[7,8] from semicorrins **1** and **2** and bis(oxazolines) **3**, several other classes of chiral ligands including binaphthyls,[9] salens,[10] TADDOLs,[11] or the ligands[12] for the Sharpless dihydroxylation and aminohydroxylation have been attached to different polymers to arrive at easily manageable and reusable catalysts.[13]

We therefore investigated the possibility of immobilizing aza-bis(oxazolines) **4** on supports. An attractive polymeric support for catalysts is methoxypolyethylene glycole (MeOPEG), because it is soluble in many organic solvents but can be precipitated with diethyl ether.[14] Various attempts to attach MeOPEG directly to **7b** failed, but **8** which contains a benzylidene spacer linked to MeOPEG could be successfully coupled with the conjugate base of **7b** to yield **10** in 55% yield as determined by ^{1}H NMR spectroscopy.

To benchmark our new ligands in their ability to promote asymmetric reactions, we carried out palladium-catalyzed allylic alkylations (Table 1) and copper-catalyzed cyclopropanations of alkenes (Tables 2 and 3). Using the nonalkylated ligand **7** in the palladium-catalyzed reaction between dim-

Table 1. Enantioselective Allylic Substitution of 1,3-Diphenylallyl Acetate[a]



11 **12**

entry	ligand	% yield	% ee of **12**[b]
1	**7**	0	
2	**9a**	66	97
3	**9b**	38	97
4	**2**[d]	99	95

[a] All reactions were carried out under nitrogen. [b] Determined by HPLC using a Chiralpak AD column. [c] Entry taken from ref 2c. [d] R = CH_2OSiMe_2t-Bu, R^1 = Me.

(4) Rational name: bis[4,5-dihydro-1,3-oxazole-2-yl)amines.

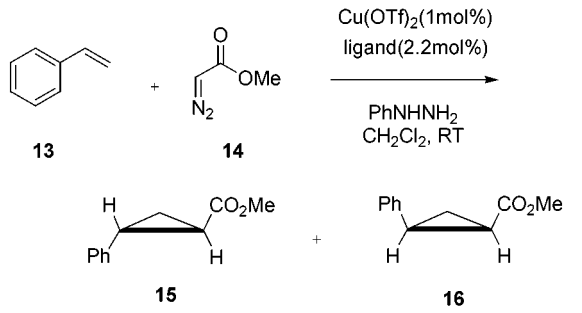
(5) (a) Wittekind, R. R.; Rosenau, J. D.; Poos, G. I. *J. Org. Chem.* **1961**, *26*, 444−446. (b) Poos, G.; Carson, J.; Rosenau, J.; Roszkowski, A.; Kelley, N.; McGowin, J. *J. Med. Chem.* **1963**, *6*, 266−272.

(6) Kampe, K.-D. *Liebigs Ann. Chem.* **1974**, 593−607.

(7) Polymer-supported pyridineoxazolines have been reported: (a) Hallmann, K.; Macedo, E.; Nordström, K.; Moberg, C. *Tetrahedron: Asymmetry* **1999**, *10*, 4037−4046. (b) Brunner, H.; Brandl, P. *Z. Naturforsch.* **1992**, *47b*, 609−613.

(8) Achiral dendritic bis(oxazoline)copper(II) catalysts have been reported: Chow, H.-F.; Mak, C. C. *J. Org. Chem.* **1997**, *62*, 5116−5127.

Table 2. Enantioselective Cyclopropanation of Styrene[a]



entry	ligand	% yield	**15**:**16**[b]	% ee of **15**[c]	% ee of **16**[c]
1	**7a**	85	62:38	56	42
2	**9a**	78	66:34	66	44
3	**9c**	44	64:36	62	47
4	**7b**	75	67:33	87	80
5	**9b**	82	73:27	92	84
6	**10**	69	71:29	91	87
7[d]	**2**[e]	45 (ent-)	75:25	95	90
8[f]	**3**[g]	77	73:27	99	97

[a] All reactions were carried out under nitrogen. [b] Determined by GC using DB 1301 column. [c] Determined by GC using a CP-Chiralsil DEX CB column. [d] Entry taken from ref 2c. [e] R = CMe_2OSiMe_2*t*-Bu, R^1 = Me. [f] Entry taken from ref 3c. [g] R = *t*-Bu, R^1 = Me.

ethylmalonate and 1,3-diphenylallyl acetate (**11**), no product was obtained (entry 1). With **9a** (entry 2) and **9b** (entry 3), high enantioselectivity was achieved, although the reaction was considerably slower than the reaction with aza-semicorrin **2**[2c] (entry 4) as catalyst. These results indicate that aza-bis(oxazolines) **4** form more electron-rich palladium allyl complexes compared to the aza-semicorrins **2** and therefore display a lower reactivity toward nucleophiles.

Cyclopropanation reactions using aza-bis(oxazolines) **4** were initially conducted following either the procedure of Evans et al.[3c] using copper(I) triflate directly or the procedure described by Masamune et al.[3a] in which the active copper(I) complex was generated in situ using copper(II) triflate, ligand, and phenylhydrazine for reduction. Both procedures gave almost identical results, so that for reasons of convenience we used the latter one in general.

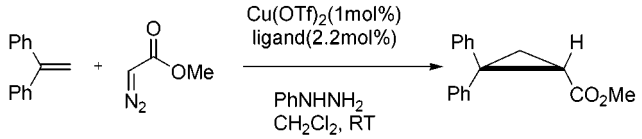
Consistent with the reported results for the copper-catalyzed cyclopropanation of styrene (**13**) (Table 2) using **2** or **3**, the most effective aza-bis(oxazoline) turned out to be **9b** bearing the sterically demanding *tert*-butyl groups. This ligand compared well in terms of selectivity and yield (entry 5) to the best reported results of **2** (entry 7) and **3** (entry 8), although somewhat lower enantioselectivities were obtained. Furthermore, it is interesting to note that catalysis also proceeded well with the nonalkylated ligand **7b** (entry 4), since only alkylated aza-semicorrins **2** have been reported as ligands for asymmetric catalysis to date. Most importantly, the polymer-bound ligand **10** gave similar yields and selectivities compared to **9b** (entry 6), indicating that the immobilization of aza-bis(oxazolines) has no detrimental effects on their ability to serve as catalysts.

Similar results were obtained in the cyclopropanation of 1,1-diphenylethylene **17** (Table 3); this time, however, the nonalkylated aza-bis(oxazoline) **7b** (entry 3) was superior to the alkylated derivative **9b** both in terms of yield and selectivity (entry 4). In accord with our expectations that polymer-bound catalysts would improve the efficiency of these reactions, the polymeric catalyst derived from **10** gave the best results of all aza-bis(oxazolines) (entry 5).

To examine the possibility of reusing **10**, we repeated the cyclopropanation of styrene (**13**) several times. A total of 13 cycles were conducted (Figure 1). During the first 10 cycles, no copper salts were added nor was activation of the catalyst with phenylhydrazine necessary. When the yield dropped to 39% in the 10th cycle phenylhydrazine was added in the following cycles and the yield increased. Throughout all 13 cycles the enantiomeric excess was 87−90% for the *trans*-product **15** and 81−85% for the *cis*-product **16**.[15]

In conclusion, aza-bis(oxazolines) are efficient ligands for enantioselective catalysis. In particular, these ligands open

Table 3. Enantioselective Cyclopropanation of 1,1-Diphenylethene[a]



17 **14** **18**

entry	ligand	% yield	% ee of **18**[b]
1	**7a**	70	47
2	**9a**	49	56
3	**7b**	63	86
4	**9b**	41	83
5	**10**	78	90
6[c]	**3**[d]	70	99

[a] All reactions were carried out under nitrogen. [b] Determined by HPLC using a Chiralpak AD column. [c] Entry taken from ref 3c. [d] R = *t*-Bu, R^1 = Me.

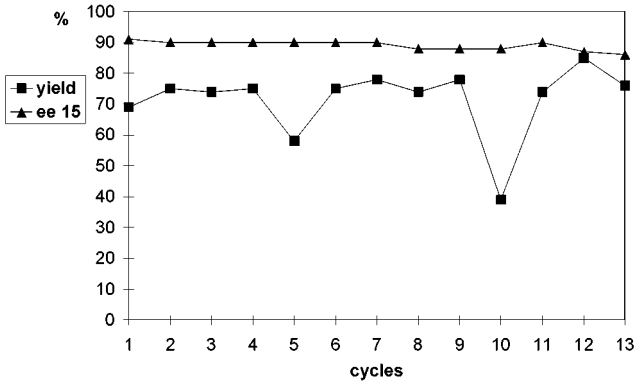


Figure 1. Copper-catalyzed cyclopropanation of styrene (**13**) with **14** using Cu(I)·**10** (cf. Table 2).

up the possibility to readily attach bis(oxazolines)—being among the most versatile ligands for asymmetric catalysis—to a polymer support, as was demonstrated by the preparation of polyethylene glycole bound aza-bis(oxazoline) **10**. Copper-(I) complexes of **10** turned out to be highly effective and easily recyclable catalysts in cyclopropanation reactions.

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Supporting Information Available: ^{1}H NMR spectra and experimental procedures of all new ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005947K

(9) (a) Bayston, D. J.; Fraser, J. L.; Ashton, M. R.; Baxter, A. D.; Polywka, E. C.; Moses, E. *J. Org. Chem.* **1998**, *63*, 3137−3140. (b) Fan, Q.; Ren, C.; Yeung, C.; Hu, W.; Chan, A. S. C. *J. Am. Chem. Soc.* **1999**, *121*, 7407−7408. (c) Xiao-Wu Yang, X. W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295−296. (d) Huang, W.-S.; Hu. Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940−7956. (e) Pu, L. *Chem. Rev.* **1998**, *98*, 2405−2494.

(10) (a) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147−4154. (b) Peukert, S.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1245−1248.

(11) (a) Altava, B.; Burguete, I.; Escuder, B.; Luis, S. V.; Salvador, R. V.; Fraile, J. M.; Mayoral, J. A.; Royo, A. J. *J. Org. Chem.* **1997**, *62*, 3126−3134. (b) Sellner, H.; Seebach, D. *Angew. Chem.* **1999**, *111*, 2039−2041. (c) Heckel, A.; Seebach, D. *Angew. Chem.* **2000**, *112*, *165−167*.

(12) (a) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632−7633. (b) Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527−1530. (c) Lohray, B. B.; Nandanan, E.; Bushan, V. *Tetrahedron: Asymmetry* **1996**, *7*, 2805−2808. (d) Nandandan, E.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1997**, *38*, 2577−2580. (e) Bolm, C.; Gerlach, A. *Angew. Chem.* **1997**, *109*, 773−775. (f) Bolm, C.; Maischak, A.; Gerlach, A. *Chem. Commun.* **1997**, 2353−2354. (g) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1956**, *21*, 1−27. (h) Salvadori, P.; Pini, D.; Petri, A. *J. Am. Chem. Soc.* **1997**, *119*, 6929−6930. (i) Salvadori, P.; Pini, D.; Petri, A. *Synlett* **1999**, 1181−1190.

(13) (a) Smith, K. *Solid Supports and Catalysts in Organic Chemistry*; Ellis Horwood Limited: 1993. (b) Shuttleworth. S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217−1239.

(14) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509.

(15) **Cyclopropanation of styrene using 10:** Under a nitrogen atmosphere $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and **10** (200 mg, 0.02 mmol) were dissolved in dichloromethane (5 mL). Phenylhydrazine (22 μL of a 5% solution in dichloromethane) and styrene (**13**) (312 mg, 3 mmol, 345 μL) were added. Methyl diazoacetate (**14**) (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 of dry dichloromethane. The volume of the solvent was reduced to approximately 5 mL by applying vacuum, and 100 mL of dry diethyl ether was 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 in vacuo to give a slightly yellow oil, which was purified by chomatography on silica gel (3 × 25 cm silica, 9:1 hexanes/EtOAc). The products were obtained as a clear oil showing spectroscopical properties identical to those described in the literature.[3c] For the following reaction cycle the catalyst was dissolved in 10 mL of dry dichloromethane and transferred into a new reaction vessel. Styrene (**13**) and methyl diazoacetate (**14**) were added as described above.