Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1475–1478

TETRAHEDRON:
ASYMMETRY

Polymer-bound bis(oxazoline) as a chiral catalyst

Kristina Hallman and Christina Moberg*

Department of Chemistry, Organic Chemistry, Royal Institute of Technology, SE-100 44 Stockholm, Sweden

Received 7 May 2001; accepted 24 May 2001

Abstract—A chiral bis(oxazoline) was grafted on ArgoGel and used in the palladium-catalysed substitution of (±)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The enantioselectivity was the same as that observed when the analogous monomeric catalyst was used (94–95% e.e.), despite the fact that the C_2 symmetry of the ligand was affected when coupled to the polymer. The polymer-supported catalyst could be recycled several times after removal of precipitated Pd(0). The polymer-bound bis(oxazoline) was also applied in a zinc-catalysed Diels–Alder reaction but lower selectivity and reactivity than the monomer was observed. © 2001 Elsevier Science Ltd. All rights reserved.

---

1. Introduction

Immobilised chiral ligands as catalysts for asymmetric synthesis have in recent years attracted renewed interest.[1] The major advantages of solid-supported ligands are the facile removal of the ligand after the reaction and the possibility of recycling the catalyst. The use of supported catalysts also opens up the possibility for use in continuous flow reactions. Polymer-supported chemistry in general has also been advancing rapidly as a result of developments in combinatorial chemistry.[2]

In a previous study we have shown that catalytically, chiral pyridinooxazolines grafted to TentaGel and ArgoGel were as efficient as a similar monomeric catalyst in the palladium-catalysed substitution reaction of (±)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate, affording products with up to 80% e.e.[3] TentaGel and ArgoGel are graft-copolymers of gel-type polystyrene and polyoxyethylene.[4] Catalysts bound to these supports behave like homogenous rather than heterogeneous catalysts because of the long, flexible poly(ethyleneglycol) linkers. Additionally, compared to the traditionally used polystyrene-divinylbenzene resins, they can be used in solvents with a wider polarity range and they are also more easily analysed by spectroscopic methods in the solvent-swollen state.

Chiral C_2-symmetric bis(oxazolines) have been shown to serve as successful ligands in several catalytic processes including Diels–Alder,[5,6] aldol,[6,7] aziridination,[6] allylic alkylation[6,8] and cyclopropanation[6,8,9] reactions. Several approaches for the immobilisation of these ligands have been investigated. The methodology chosen may affect the activity and selectivity of the catalytic reaction. In some approaches the ligand has been attached via non-covalent bonds and the resulting polymers have been assessed in cyclopropanation and aziridination reactions.[10,11] In some cases re-use of the catalyst was possible, but problems with leaching and decreased selectivity were occasionally seen. Recently a covalently bonded bis(oxazoline) was prepared using a central methylene bridge with polymerisable groups.[12] This ligand was successfully used and recycled in the copper-catalysed cyclopropanation of styrene with ethyl diazoacetate. The morphology of the polymer had important effects on the activity and selectivity of the catalyst. Ligands from a related ligand family, aza-bis(oxazolines), were attached to a soluble polymeric support.[13] These soluble catalysts were designed for palladium-catalysed allylic alkylations and copper-catalysed cyclopropanations. The monomer had reduced reactivity in the allylic alkylation of 1,3-(diphenyl)allyl acetate, but the results from the polymer-bound catalysts were not reported. Re-use of the cyclopropanation catalyst after precipitation in ether was possible affording 80–39% yield and 87–90% e.e. for the *trans* product and 81–85% e.e. for the *cis* product in 10 cycles.

The heterogeneous Pd-catalysed allylic alkylation using polymerised chiral diamino ligands was reported in 1995. The enantioselectivity was 80% for the most selective polymer but the conversion was only 38%.[14] A

---

* Corresponding author. Fax: +46-8-7912333; e-mail: kimo@kth.se

0957-4166/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(01)00245-2

chiral resin-bound *P*,*N* ligand was used in the same reaction in aqueous medium, affording product in 86% yield with 91% e.e. with the benchmark substrates (±)-1,3-diphenyl-2-propenyl acetate and dimethyl malonate, as well as affording high yields and high enantioselectivities (up to 94% yield and 98% e.e.) with cyclic substrates.[15]

We demonstrate herein that it is possible to attach a chiral bis(oxazoline) covalently to an ArgoGel resin and to use the resulting polymer as a catalyst in allylic alkylation reactions to afford products with high e.e.s. We also show that it is possible to re-use the polymer-bound ligand after removal of precipitated palladium black by washing the polymer with saturated KCN in DMSO.

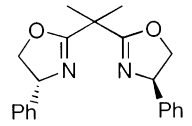
2. Results and discussion

2.1. Synthesis of polymer-supported bis(oxazoline)

The polymer-supported bis(oxazoline) **2** was synthesised from **1**[16] and ArgoGel-Wang-Cl in DMF in the presence of K_2CO_3 (Scheme 1). Both ^{13}C NMR spectroscopy and elemental analysis were used to analyse compound **2**, showing the degree of functionalisation to be 0.071 mmol/g.

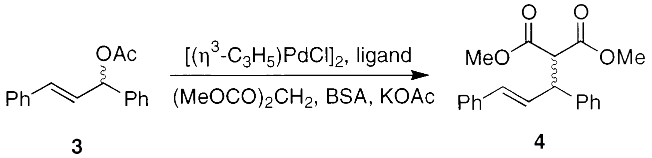
2.2. Allylic substitution

The polymer-bound bis(oxazoline) **2** was tested in the allylic substitution of (±)-1,3-diphenyl-2-propenyl acetate **3** with dimethyl malonate **4** (Scheme 2). This substrate was chosen since it serves as a benchmark substrate to compare the outcome of different ligands. The reaction was performed in dichloromethane at room temperature. The catalytic complex was generated from 2 mol% of bis[(π-allyl)palladium chloride] and 6 mol% of the ligand.[8] The nucleophile was generated in situ from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc. To study whether the polymer had a positive or negative effect on the selectivity and activity, the commercially available (*R*)-(+)-2,2′-isopropylidene bis(4-phenyl-2-oxazoline) **5** was used as a reference ligand. The reaction was repeated three times with the polymer-bound catalyst and two times with the monomeric catalyst. The yields varied from time to time, whereas the enantioselectivity remained essentially constant. The reason for the variation in yield is not known. The yield after 4 days was 67–95% when ligand **5** was used and the (*R*)-enantiomer formed predominantly with e.e.s of 95–96%. When the polymer-bound bis(oxaxoline) **2** was used as the ligand, the yields after 4 days were 28–70% and the e.e. was 94–95% (*R*)-enantiomer. It is interesting to note that the selectivity remained essentially the same despite the fact that ligand **2** has C_1 symmetry, whereas ligand **5** is C_2-symmetric.



5

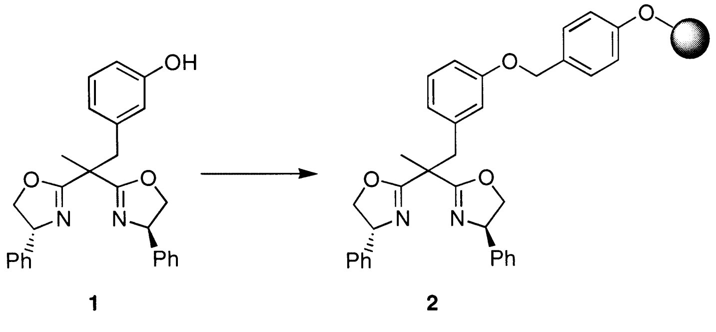
Palladium(0) precipitated during the reaction, thus preventing recycling of the polymer. However, after removal of palladium with saturated potassium cyanide in DMSO[17] the polymer-bound ligand could be re-used without any loss in selectivity (recycling up to five times was performed). The yields varied between 29 and 93% in the cycles and the trend in the yields indicated an increase in activity of the catalyst.



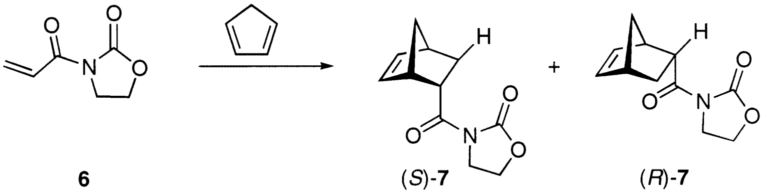
Scheme 2.

2.3. Diels–Alder reaction

The zinc-catalysed Diels–Alder cyclisation of 3-(2-propenoyl)-2-oxazolidone **6** and cyclopentadiene (Scheme 3) was attempted with ligands **2** and **5** (Scheme 3). Ligand **5** was used as a reference catalyst to compare monomer with polymer and also to compare with already published results (values within parentheses). The catalytic complex was prepared from 10 mol% ZnI_2, 11 mol% ligand and 20 mol% $AgSbF_6$ in dichloromethane at room temperature and the reaction was performed at −78°C, as described in the literature.[5a] The reaction was extremely slow at this tempera-



Scheme 1.



Scheme 3.

ture (traces of product were formed after 48 h) when ligand **2** was used, whereas full conversion was observed after 15 h with ligand **5**. Ligand **5** gave the *endo* product with 85% e.e. (*R*) (literature value: 92% e.e.[5a]) and the *endo*:*exo* ratio was 94:6 (literature value: 49:1[5a]). At room temperature both ligands catalysed the reaction to completion but the polymer-supported ligand gave racemic product, whereas ligand **5** gave the *endo* product 57% e.e. (*R*). The reaction employing **2** as a catalyst was still very slow at −40°C resulting in merely 13% conversion overnight. This low reactivity might be explained by the fact that the polymer is probably more rigid and less swollen at lower temperatures, causing the surface area of the polymer to be decreased, and thereby preventing exposure of a large fraction of the ligands.

When the polymer-bound catalyst was used the salts formed were not possible to filter off from the catalytic complex. To study whether the presence of salts might have a detectable effect, the reaction with the monomeric catalyst was performed without filtration. The salts were found not to have any negative effect on the conversion at −40°C, but the e.e. of the *endo* product decreased from 71 to 63%. The formation of the racemic product cannot thus be explained by the presence of salts.

3. Conclusion

The results presented show that it is possible to synthesise a polymer-supported bis(oxazoline) **2**. In the palladium-catalysed allylic alkylation the polymer had no negative effect on the selectivity and activity despite the reduction in symmetry of the ligand. The ligand could be re-used several times without significant losses in selectivity or reactivity after removal of palladium(0) by washing with a saturated solution of KCN in DMSO. In the zinc-catalysed Diels–Alder reaction, the polymer seems to inhibit the reaction at lower temperatures. At room temperature reaction occurred, but a racemic product was obtained.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100.6 MHz, respectively. Enantiomeric excesses were determined by HPLC using a chiral column (Chiracel OD-H). For the analysis of **4** a wavelength of 254 nm, a flow of 0.5 mL/min and a solvent composition of 99:1 hexane:propan-2-ol were used. For the analysis of **7** a wavelength of 240 nm, a flow of 0.5 mL/min and a solvent composition of 90:10 hexane:propan-2-ol were used. ArgoGel-Wang-Cl was purchased from Aldrich (bead size ca 170 μm).

4.2. Polymer-supported (*R*)-bis(4-phenyl-2-oxazoline) 2

K_2CO_3 (42 mg, 0.31 mmol) was added in one portion to a suspension of ArgoGel-Wang-Cl (0.35–0.45 mmol/g, 0.486 g, 0.17 mmol) and **1**[16] (87 mg, 0.20 mmol) in dry DMF (3.4 mL) in a dry flask. The reaction mixture was stirred overnight under a nitrogen atmosphere at 60°C. The polymer was filtered off and washed successively with MeOH (2 mL), THF:H_2O 1:1 (2 mL), H_2O (2 mL), acetone (2 mL), CH_2Cl_2 (2mL) and MeOH (2 mL). The polymer was dried at room temperature in vacuo overnight, resulting in **2** (0.616 g) containing 0.20% N (corresponding to 0.071 mmol of ligand/g polymer); ^{13}C NMR: δ 169.27, 169.11, 158.73, 158.24, 142.31, 142.15, 128.76, 128.67, 128.49, 127.65, 127.51, 126.76, 123.36, 117.31, 114.76, 114.62, 113.84, 113.29, 75.45, 75.34, 71.40, 69–73 (several signals), 67.53, 64.53, 43.80, 42.80, 42.21, 30.99, 21.72.

4.3. General procedure for removal of precipitated Pd(0)

After the allylic alkylation ligand **2** contaminated with Pd(0) was filtered off and washed with dichloromethane and ether to collect the product **4**. Ligand **2** was regenerated by washing the polymer with ca. 5 mL each of the following solvents: H_2O, CH_2Cl_2, DMF, satd KCN/DMSO, MeOH, H_2O, MeOH, CH_2Cl_2. The light yellow polymer was dried under vacuum and could be used again as ligand in the catalytic reaction.

Acknowledgements

This work was supported by the Swedish Research Council for Engineering Sciences.

References

1. De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinheim, 2000.
2. (a) von dem Bussche-Hünnefeld, C.; Balkenhohl, F.; Lansky, A.; Zechel, C. *Fresenius J. Anal. Chem.* **1997**, *359*,

3–9; (b) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18–26.

3. Hallman, K.; Macedo, E.; Nordström, K.; Moberg, C. *Tetrahedron: Asymmetry* **1999**, *10*, 4037–4046.
4. (a) Barany, G.; Albericio, F.; Kates, S. A.; Kempe, M. *ACS Symp. Ser.* **1997**, *680* (poly(ethylene glycol)), 239–264; (b) Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 113–129; (c) Li, W.; Yan, B. *J. Org. Chem.* **1998**, *63*, 4092–4097.
5. (a) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573; (b) Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721–15730; (c) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895–4896; (d) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372–3375; (e) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460–6461; (f) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594; (g) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099–6110.
6. Recent reviews: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335; (b) Ghosh, A. K.; Mathivanan, P.; Capiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; (c) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000.
7. (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1999**, 71–72; (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894; (c) Matsunaga, H.; Yamada, Y.; Ide, T.; Ishizuka, T.; Kunieda, T. *Tetrahedron: Asymmetry* **1999**, *10*, 3095–3098.
8. Leutenegger, U.; Umbricht, G.; Fahrni, C.; Von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143–2156.
9. Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919–7946.
10. Langham, C.; Piaggio, P.; Bethell, D.; Lee, D. F.; McMorn, P.; Bulman Page, P. C.; Willock, D. J.; Sly, C.; Hancock, F. E.; King, F.; Hutchings, G. J. *Chem. Commun.* **1998**, 1601–1602.
11. (a) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Tarnai, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3997–4008; (b) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Tarnai, T.; Harmer, M. A. *J. Catal.* **1999**, *186*, 214–221.
12. Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Luis, S. V.; Mayoral, J. A. *Org. Lett.* **2000**, *2*, 3905–3908.
13. Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045–2048.
14. Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1109–1116.
15. Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919–2920.
16. The procedure for the preparation of **1** will be published elsewhere.
17. (a) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306–3307; (b) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219–8222.