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Novel silica gel supported chiral biaryl-diphosphine ligands for enantioselective hydrogenation

Ivo Steiner,[a] Rhony Aufdenblatten,[a] Antonio Togni,[a,*] Hans-Ulrich Blaser[b] and Benoît Pugin[b,*]

[a]*Laboratory of Inorganic Chemistry, Swiss Federal Institute of Technology, ETH Hönggerberg, HCI, CH-8093 Zürich, Switzerland*
[b]*Solvias AG, R-1055.6, PO Box, 4002 Basel, Switzerland*

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Abstract—The synthesis of functionalized Biphemp and MeO-Biphep biaryl diphosphine ligands and their covalent attachment to silica gel are described. The catalytic performance of the immobilized ligands was tested in the asymmetric hydrogenation of methyl acetamidocinnamate (MAC) with Rh and of methyl phenylglyoxylate with Ru and compared with that of the homogeneous analogues. With the exception for a Rh catalyzed hydrogenation, where an increase of ee from 29% for the unfunctionalized ligand, to 40% for the functionalized ligand and 45% for the immobilized ligand was observed, functionalization and immobilization did not significantly affect the catalytic properties. The best ees of 90% were obtained for the Ru catalyzed hydrogenation of methyl phenylglyoxylate with the immobilized MeO-Biphep ligand and are comparable with those of the homogeneous catalyst. Recycling of the immobilized catalysts resulted in a significant drop in activity for the Rh catalysts, whereas the Ru catalysts were much more robust and could be used in >10 catalytic runs.

1. Introduction

Control of stereoselectivity is easier with homogeneous than with heterogeneous catalysts. On the other hand, soluble catalysts are more difficult to separate and to handle than the technically well-established heterogeneous catalysts. A promising strategy to combine the best properties of the two catalyst types is the immobilization of active metal complexes on supports or carriers. Indeed, a considerable amount of work has been carried out recently to test this strategy and many of the most successful homogeneous catalysts have been immobilized.[1] However, the catalytic properties of these immobilized catalysts have shown an enormous variation and in many cases were significantly below those of the homogeneous analogues. Since the reasons for these differences in performance are usually not understood, it is still of interest to test different immobilization methods and supports in order to get a systematic picture of positive and negative effects. Herein we describe two methods of functionalizing biaryl-type ligands, describe their first time attachment to silica gel and compare the performance of the various heterogeneous and homogeneous catalysts.

Since the first description of Binap as an effective ligand for enantioselective hydrogenation by Noyori and coworkers,[2] biaryl diphosphines have developed into one of the most important ligand classes[3] with several industrial applications.[3,4] The success of Binap has triggered the development of a large variety of related biphenyl ligands[5] and some of the most prominent examples are Biphemp[6] and the more electron rich MeO-Biphep[7] or Segphos,[8] which in some cases give superior catalytic performances.

While several publications describe the functionalization and immobilization of the parent Binap[9–13] with modest to very good catalytic properties for several ketone hydrogenation reactions, reports on the immobilization of biphenyl-type ligands are rather scarce and mostly restricted to patents.[14–16] Chapuis et al.[17] described the attachment of 6,6′-bis(diphenylphosphino)[1,1′-biphenyl]-2,2′-diol to tentagel via an ester or ether linkage and their application to the Rh catalyzed isomerization of geranyl and neryl derivatives. Both tentagel-bound

* Corresponding authors. Tel.: +41-61-686-6335; fax: +41-61-686-63-11; e-mail: benoit.pugin@solvias.com

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catalysts were much less active than the free catalyst or than a commercially available polystyrene Binap catalyst.[9] Interestingly, the ester-linked catalyst showed much lower ees than the ether-linked analogue, indicating that not only the support but also the linker can significantly affect the catalytic properties of covalently immobilized catalysts.

We have been interested in the effects of functionalization and immobilization on catalytic performance for many years and have worked with organic and inorganic supports.[18] In our experience both types of supports have their strengths and their weaknesses. Advantages of organic polymers are their large variety and the high loading capacities of functional groups. Disadvantages are the often high price and their restricted solvent compatibility, since they usually have to be used in a solvent in which they swell. In contrast, inorganic supports such as silica gels are relatively cheap, can be used in most organic solvents, but on the other hand loading capacities are lower than for organic polymers. Since we achieved very good results for several ligands attached to silica gel supports[18b] we decided to study the immobilization of two biaryl diphosphines on silica gel and test the resulting Rh and in Ru complexes standard hydrogenations.

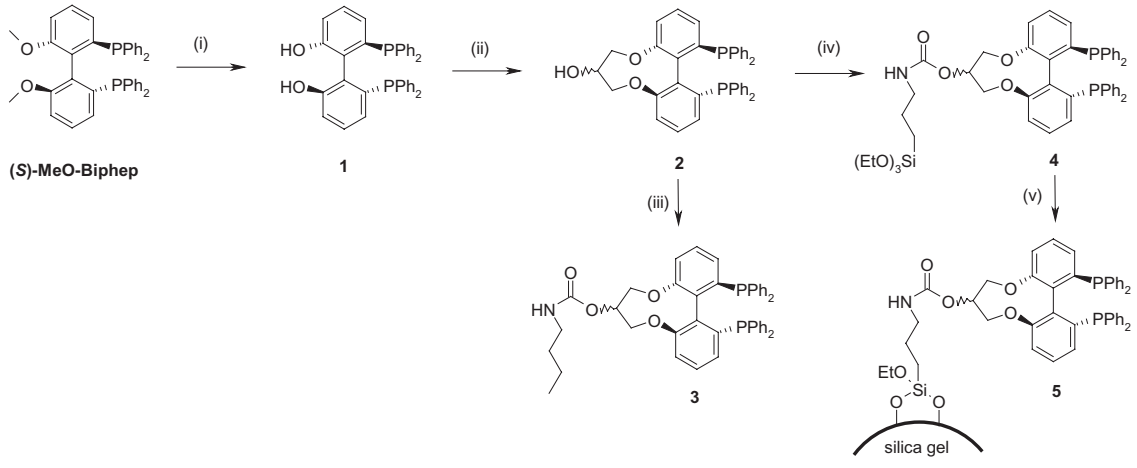
2. Results and discussion

2.1. Synthesis of the functionalized and silica gel bound ligands

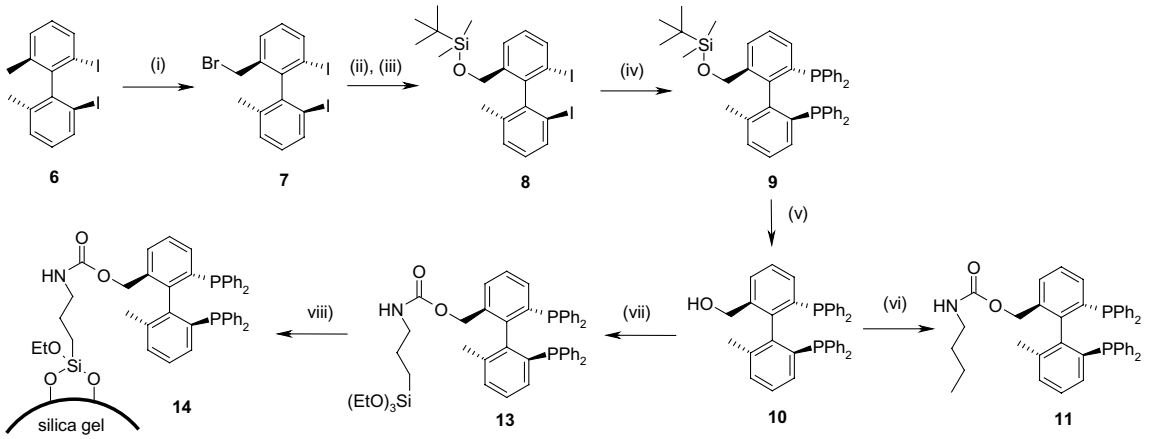
For the functionalization of the two ligands, we used different strategies, both based on chemistry developed for the synthesis of the parent MeO-Biphep and Biphemp ligands. In Scheme 1, the synthesis of the functionalized and immobilized MeO-Biphep is summarized. For this ligand, we chose a two point attachment, which leads to a quasi-C_2 symmetrical functionalized ligand.

The cleavage of the methyl groups of MeO-Biphep with BBr_3 was performed as described in the literature.[17,19] The cyclization of the resulting diol **1** to the functionalized ligand **2** proved to be critical and still needs to be optimized. So far, yields up to 36% were obtained when a mixture of **1** and epibromohydrin was slowly added to a slurry of Cs_2CO_3 in CH_3CN under reflux. Since the stereochemistry of the alcohol is not defined, compound **2** is a mixture of two diastereomers, which cannot be distinguished by standard NMR measurements. Reaction of **2** with butylisocyanate or with (3-isocyanatopropyl)-triethoxysilane gave the solid products **3** and **4** in good yields. The immobilization was performed by refluxing a mixture of **4** and dry silica gel in toluene. The immobilized ligand **5** had a loading 0.064 mmol ligand/g support. We used Grace 332, a commercial silica gel with a relatively homogeneous pore size (average 19 nm) and a high specific surface area of 320 m^2/g, which proved to be optimal with other ligands.[18a]

For the functionalization of Biphemp, we chose a different strategy with a linkage to only one of the methyl groups. Bromination of the enantiomerically pure 2,2′-diiodo-6,6′-dimethyl-biphenyl **6**[20] with NBS gave a mixture of 56% desired product **7**, 9% of a dibromo product where both methyl groups were brominated, 2% of another, where one methyl group is doubly brominated and some starting material **6**. After separation by chromatography, hydrolysis of **7** and protection with *tert*-butyl-dimethylchlorosilane gave **8** in almost quantitative yield. Lithiation of **8** at low temperature, addition of diphenylchlorophosphine and subsequent reflux gave the protected diphosphine **9**. Treatment with fluoride followed by recrystallization yielded the enantiomerically pure OH-functionalized diphosphine **10**, which was transformed to the two carbamates **11** and **13** by reaction with the corresponding isocyanates. Immobilization of **13** was performed as described for **4** and gave the immobilized ligand **14** with a loading of 0.063 mmol ligand/g support (Scheme 2).



Scheme 1. Synthesis of functionalized and immobilized MeO-Biphep. (i) BBr_3; (ii) epibromohydrin, Cs_2CO_3 in CH_3CN; (iii, iv) isocyanate, cat. $Bu_2Sn(laurate)_2$; (v) see text.

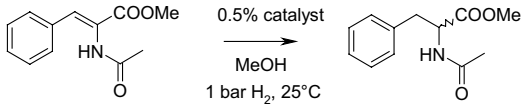


Scheme 2. Synthesis of functionalized and immobilized Biphemp. (i) NBS, cat. azoisobutyronitrile, CCl_4, reflux; (ii) aq KOH; (iii) *tert*-butyl-dimethylchlorosilane, imidazole, DMF; (iv) *n*-BuLi, diethylether −78 °C, Cl-PPh_2, then 20 h reflux; (v) Bu_4NF, THF (vi, vii) isocyanate, cat. $Bu_2Sn(laurate)_2$; (viii) see text.

2.2. Hydrogenations with the functionalized and immobilized ligands

One objective of this work was to study the influence of the functionalization and of the immobilization of the ligands/catalysts on their properties in catalysis. Since we wanted to be able to compare the results with other catalysts, we chose two assays where we had a broad experience. The Rh-catalyzed hydrogenation of methyl acetamidocinnamate (MAC) was chosen because it is probably the best known standard hydrogenation reaction, even though it was well known that usually low ees are obtained with biaryl diphosphines. This might even be regarded to be an advantage since small variations in activation energy are reflected in much larger ee changes. In addition, the Rh complexes are easy to prepare in situ and give relatively simple ^{31}P NMR spectra. We were indeed able to study the different homogeneous and heterogeneous catalyst species and could show that there are no significant differences between the soluble and immobilized Rh complexes. Details will be published elsewhere. The hydrogenation results are summarized in Table 1.

Table 1. Rh catalyzed hydrogenation of MAC



Entry	Ligand	TOF (h^{-1})	Ee (abs. conf.)	Comment
1	(*S*)-MeO-Biphep	200	29 (*S*)	
2	**2**	220	41 (*S*)	
3	**3**	240	41 (*S*)	
4	**4**	200	39 (*S*)	
5	**5**	200	45 (*S*)	
6	**5**	75	45 (*S*)	2nd run
7	(*R*)-Biphemp	240	27 (*R*)	
8	**10**	170	38 (*R*)	
9	**11**	300	35 (*R*)	
10	**13**	150	36 (*R*)	
11	**14**	150	40 (*R*)	
12	**14**	110	40 (*R*)	2nd run

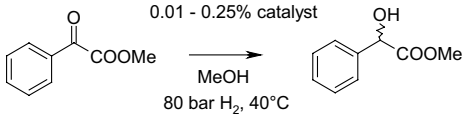
The results in Table 1 show that functionalization of both MeO-Biphep and Biphemp leads to a significant rise in ee. We assume that our modifications do not severely affect the electronic properties of the ligands and that it is more likely that steric effects are responsible for this outcome. In fact, several groups have prepared biaryl ligands with different substituents or bridging groups in 6,6′ position and found that the dihedral angle of biaryl ligands has an important influence on the catalytic properties.[8,21] It is interesting to note that immobilization leads to another small but significant increase of ee.

The activities of the rhodium catalysts with MeO-Biphep and Biphemp were estimated based on the rate of hydrogen uptake. All catalysts give only moderate TOFs in the range of 150–250 h^{-1}, no matter whether the ligands are unchanged, functionalized, or immobilized. We can therefore exclude mass transport effects from immobilization, which is in accordance with previous studies, where we achieved TOFs>1000 h^{-1} with other Rh complexes bound to Grace 332 under the same experimental conditions.[18a]

The immobilized catalysts can easily be separated after the reaction, either by filtration, sedimentation or centrifugation. The practically colorless reaction solutions indicate little if any catalyst leaching. Although great care was taken to avoid contact of the catalysts with air, re-use of the separated catalysts, for unknown reasons lead to a significant drop in TOF (entries 6 and 12).

The Ru-catalyzed hydrogenation of methyl phenylglyoxylate was chosen as a second test reaction. The Ru-catalysts were prepared in situ according to a protocol of Genet et al.[22] by replacement of 1,5-cyclooctadiene in [Ru(2-methylallyl)$_2$ (1,5-cyclooctadiene)] with the diphosphine ligand and exchange of the 2-methylallyl groups with an acid such as aqueous HBr. In order to be able to work in absence of water, we also tested mixtures of methanesulfonic acid and LiBr. Results with MeO-Biphep and the functionalized and immobilized derivatives are given in Table 2.

Table 2. Ru catalyzed hydrogenation of methyl phenylglyoxylate



Entry	Ligand	TOF (h^{-1})	Ee (%)	Additives (eq/Ru)
1	MeO-Biphep	10	55	None
2	MeO-Biphep	28	89	HBr (2.5)
3	MeO-Biphep	25	90	HBr (7.4)
4	MeO-Biphep	7	60	CH_3SO_3H (2.3)
5	MeO-Biphep	10	61	LiBr (2.3)
6	MeO-Biphep	30	88	CH_3SO_3H (2.3), LiBr (2.3)
7	MeO-Biphep	32	90	CH_3SO_3H (4.6), LiBr (4.6)
8	**2**	28	90	HBr (2.5)
9	**3**	>23	89	HBr (2.5)
10	**5** (1st run)	>18	86	HBr (3.4)
11	**5** (2nd run)	23	76	None
12	**5** (1st run)	>22	87	HBr (7.4)
13	**5** (2nd run)	~50	89	HBr (7.4)
14	**5** (3rd run)	~50	88	HBr (7.4)
15	**5** (1st run)	21	82	CH_3SO_3H (2.3), LiBr (4.6)
16	**5** (2nd run)	21	87	CH_3SO_3H (2.3), LiBr (4.6)
17	**5** (3rd run)	38	91	CH_3SO_3H (4.6), LiBr (4.6)
18	**5** (4th run)	48	87	CH_3SO_3H (2,3), LiBr (4.6)
19	**5** (7th run)	38	87	CH_3SO_3H (4.6), LiBr (4.6)
20	**5** (11th run)	17	74	CH_3SO_3H (4.6), LiBr (4.6)

As shown in Table 2, the addition of both acid and bromide ions is important to obtain a good catalytic performance. Without acid low activity and only 55% ee are obtained (entry 1). Addition of either only a non coordinating acid such as methanesulfonic acid or only LiBr does not give significant improvements (entries 4 and 5). Good results are obtained with aqueous HBr or with mixtures of methanesulfonic acid and LiBr. These conditions were subsequently used for the test of the immobilized ligands. Comparison of entries 2, 8, and 9 shows that in contrast to the Rh catalyzed reactions, functionalization of the MeO-Biphep ligand does not lead to a significant change in ee nor of the catalyst activity.

The performance of the immobilized catalyst in the first runs is slightly inferior to that of the free catalysts, but improves when the immobilized catalyst is re-used. Similar effects have been described for other immobilized catalysts[23] but the reasons for this behavior are not clear. The ee strongly depends on the amount and type of additives added and entry 11 shows that further addition of HBr is required to obtain good ees when re-using a catalyst. Possibly, Bayston et al.[9] who used the same Ru/HBr system for recycling a polymer-bound Binap might have prevented the significant drop in activity and ee if they had added some fresh HBr.

It is interesting to note that the immobilized Ru catalysts are much more robust than the corresponding Rh catalysts. They can be recycled many times and used over a long period of time without a severe drop in performance. Entries 15–20 describe the performance of a catalyst that was recycled 11 times in hydrogenations with s/c ratios between 400 and 1000. The experiments were performed over a period of 20 days during which the catalyst was operating for a total of almost 200 h. Although the last runs were carried out less carefully with respect to inert conditions the catalyst achieved a total of over 5000 TON before a strong drop in ee and activity was observed. Agitation with a magnetic stirring bar along with the long operating time caused the milling of the supported catalyst to a very fine powder. Catalyst separation therefore had to be performed by centrifugation. Preliminary investigations on leaching gave contradictory results. Although some of the hydrogenation solutions were slightly colored, indicating that some leaching occurred, ion selective mass spectroscopy indicated a loss of <0.2% of Ru per cycle. Further work to optimize the lifetime and performance of the immobilized catalysts is in progress.

3. Conclusion

The covalent immobilization of biaryl diphosphine ligands on silica gel leads to viable heterogeneous catalysts with similar or better catalyst performance compared to the homogeneous systems. While the rate in the Rh catalyzed MAC hydrogenation is reasonably high, enantioselectivities are too low to be of interest. The hydrogenation of methyl phenyglyoxylate can be carried out with good ees and TONS but at relatively low rates. The results confirm that silica gels like Grace 332 are suitable supports for the covalent immobilization of diphosphine-based hydrogenation catalysts.

4. Experimental

All manipulations of the phosphorus containing compounds were performed by standard Schlenk techniques under Argon. The synthesis and characterization of the functionalized and immobilized ligands is described in detail in Refs. 14 and 24.

Hydrogenation of methyl acetamidocinnamate: Methanol (2 mL) were added to 0.0125 mmol $[Rh(nbd)_2]BF_4$ and 0.015 mmol ligand in a Schlenk tube and the mixture was gently stirred for 10 min. The immobilized ligands thereby turned orange, while the solution became colorless. Then a solution of 2.5 mmol substrate in 8 mL methanol was added, the argon in the Schlenk tube replaced by hydrogen (1 bar) and the hydrogenation started by turbulent stirring. Conversion and ee were determined by GLC (CE Instruments MFC 800 equipped with a Chirasil-Val capillary column). To re-use the

solid catalyst, the reaction mixture was set under argon, the catalyst allowed to settle, then the solution was removed with a syringe and a new portion of substrate solution was added.

Hydrogenation of methyl phenylglyoxylate: Acetone (2 mL) were added to 0.013 mmol [Ru(2-methylallyl)$_2$(cyclooctadiene)] and 0.0143 mmol ligand. The required amounts of HBr or LiBr/methanesulfonic acid were added and the reaction mixture was stirred for 30 min before the acetone was removed under vacuum. After addition of a solution of 5 mmol methyl phenylglyoxylate in 5 mL methanol (s/c = 380) the reaction mixture was pressed with argon through a capillary into a 50 mL autoclave, which was flushed with argon. The autoclave was then sealed, heated to 40 °C, flushed with hydrogen and pressurized with hydrogen to 80 bar. The hydrogenation was started by switching on the stirrer. To re-use the solid catalyst, the autoclave was again set under argon and the reaction mixture transferred into a degassed flask with a syringe. After centrifugation the reaction solution was removed and replaced by a new portion of substrate solution and fresh HBr or LiBr/methanesulfonic acid. Conversion and ee were determined by GLC (DB17/30 w column for conversion; Lipodex A capillary column for ee).

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