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Hydrogenation of ethyl acetoacetate catalyzed by hydrosoluble BINAP derivatives

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Abstract—A new Ru hydrosoluble BINAP derivative has been synthesized. This water-soluble catalyst was revealed to be enantioselective up to 94% and recyclable (at least three times) for the asymmetric hydrogenation of ethyl acetoacetate in a biphasic system.

During the last 20 years, the synthesis of several chelating water-soluble organometallic complexes for asymmetric catalytic hydrogenation in aqueous/organic two-phase systems has been reported.[1] Among them, chiral phosphines were employed. Their water-solubilization is mainly due to either the introduction of a sodium sulfonate[2–4] or a quaternary ammonium[5] function into their backbone, or their grafting onto a water-soluble polymer such as polyacrylic acid sodium salt[6] or PEG.[7,8] The advantage of such a system towards homogeneous catalysis is easy catalyst separation, affording both economic and environmental benefits.[9–11]

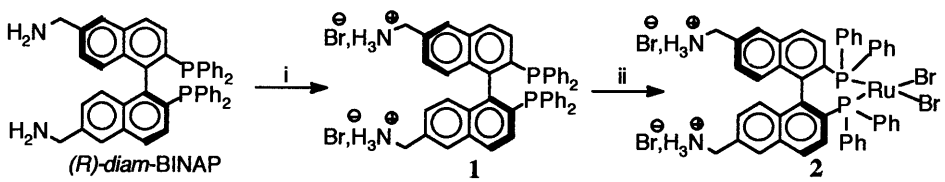
Recently, we have reported the synthesis of a BINAP derivative bearing two amine functions: the 6,6′-dimethylamino-BINAP (*diam*-BINAP).[12] We have shown that these amino groups could be used in order to introduce new functionalities. Thus, we have performed the heterogeneization of BINAP by polycondensation of *diam*-BINAP with diisocyanates.[12] In this paper, we describe some preliminary results on the synthesis of asymmetric water-soluble diphosphines derived from *diam*-BINAP and their use in hydrogenation of prochiral ketones.

First, we synthesized a water-soluble PEG derivative of *diam*-BINAP (number of PEG units: 110–113, $M=$ 5000 g mol^{-1}) according to the Veronese et al.[13] procedure. Unfortunately, a mixture of mono- and disubstituted PEG*diam*-BINAP derivatives (mono/di ratio 70/30) were formed, as shown by MALDI-TOF[14]

Table 1. Ruthenium catalyzed reduction of ethyl acetoacetate with complex **2**

Run	Reuse	Substrate/catalyst	Conversion[a] (%)	Ee[a] (%)
1		1000	100	94
2	1st	1000	97	91
3	2nd	1000	100	94
4	3rd	1000	100	83

[a] Conversion and enantioselectivity were determined on a lipodex A (25 m×0.25 mm) column.



Scheme 1. (i) 2 equiv. aq. HBr, CH_2Cl_2, rt, Ar, 1 h, 96%; (ii) [Ru-(2-methylallyl)$_2$(COD)], Me_2CO, Ar, rt, aq. HBr.

Keywords: asymmetric reactions; biphasic catalysis; hydrogenation; keto ester.

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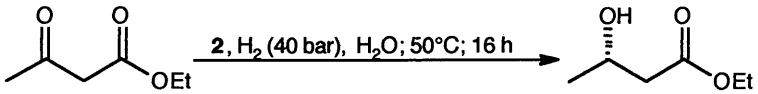

Scheme 2.

analysis. Their corresponding ruthenium complexes were synthesized from the $[RuCl_2(benzene)]_2$ precursor according to the Noyori et al.[15] procedure. The reduction of ethyl acetoacetate by this ruthenium complex mixture affords, after careful extraction of the water-soluble product with pentane, 100% of conversion and 75% ee and, after recycling, only 20% of conversion and 56% ee.

Then, we chose to synthesize the bromhydrate form of *diam*-BINAP (Scheme 1). The formation of ammonium salt **1** was easily performed with aqueous hydrobromic acid in CH_2Cl_2 solution with a 96% yield. The corresponding ruthenium complex was prepared from the $[Ru(\eta^3\text{-}2\text{-methylallyl})_2(\eta^2\text{-COD})]$ precursor according to the Genêt et al.[16] procedure.

Table 1 summarizes the results of the hydrogenation of ethyl acetoacetate using the water-soluble ruthenium complex **2** (Scheme 2). Catalyst **2** led to good enantioselectivity (run 1). The recycling of the catalyst **2** is also performed by careful extraction of the water-soluble product with pentane. From the first to the third recycling (runs 2–4), catalyst **2** showed no loss of activity but a slight decrease of enantioselectivity from 91 to 83% ee was observed.

We have demonstrated that little modification of *diam*-BINAP provides a water-soluble BINAP analog, such as the ammonium derivative, suitable for asymmetric biphasic catalytic hydrogenation of ethyl acetoacetate. The use of such a ligand is interesting because high conversions and attractive enantioselectivities were obtained. In addition, it allows easy separation of the catalyst from the reaction product by extraction. The reuse of ruthenium complex **2** is effective without any loss of either conversion or enantioselectivity.

Other substrates have to be tested in order to screen the scope and limitations of these new catalytic systems.

Experimental

*Synthesis of **1***: Under Ar, at 25°C, 8.4 μL of an aqueous HBr solution (0.05 mmol) was added to a stirred solution of (*R*)-*diam*-BINAP (17 mg, 0.025 mmol) in CH_2Cl_2 (1 mL). The reaction was allowed to stir for 1 h and the solvent was then removed to give **2** (96% yield). IR: 3500–2200; 2962; 2924; 1437; 1261; 803 cm^{-1}.

*Catalyst **2***: Under Ar, at 25°C, to a stirred solution of $Ru[(2\text{-methylallyl})_2(COD)]$ (7.5 mg, 0.024 mmol) and **1** (16 mg, 0.024 mmol) in acetone (1 mL) was added 8.4 μL of aqueous HBr (0.05 mmol). The reaction was allowed to stir for 0.5 h and the solvent was then removed.

Typical reduction procedure of ethyl acetoacetate: Under Ar, to the preceding catalyst **2** dissolved in H_2O (1 mL), the water-insoluble ethyl acetoacetate (2.2 mL) was added (substrate/catalyst: 1000). This biphasic mixture was allowed to stir and stand overnight in a stainless steel hydrogenation vessel at 50°C under 40 bar H_2. The resulting water-soluble reduced product was extracted twice with pentane (10 mL). The aqueous phase containing the catalyst was reused as previously described.

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