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Recyclable diguanidinium-BINAP and PEG-BINAP supported catalysts: syntheses and use in Rh(I) and Ru(II) asymmetric hydrogenation reactions

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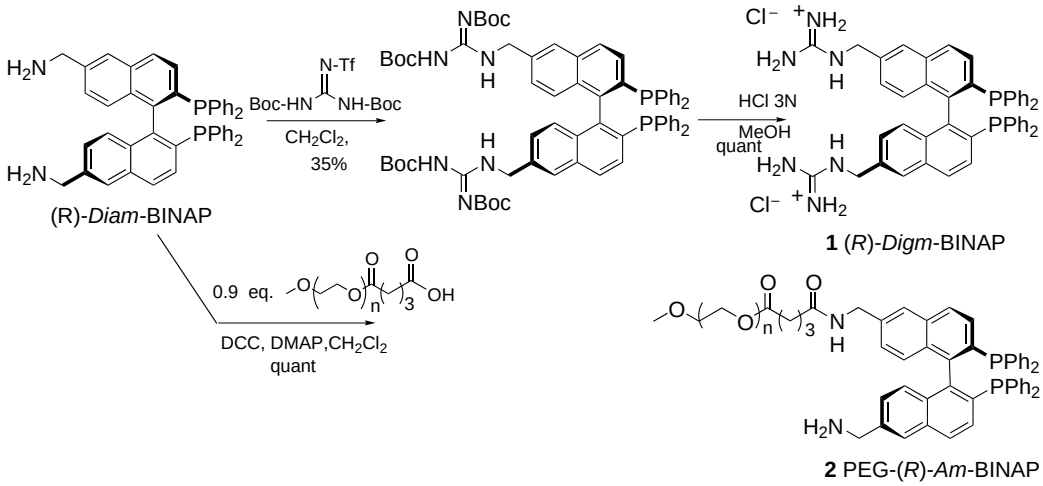
Abstract—The syntheses of new recyclable cationic BINAP type ligand diguanidinium **1** and PEG-bound BINAP ligand **2** are described. The use of ethylene glycol instead of water increased the enantioselectivity in the ruthenium-promoted hydrogenation reaction of functionalized ketones. These catalysts are highly active (catalyst/substrate ratio up to 1:10 000, up to 99% e.e.). The rhodium-mediated hydrogenation of acetamidoacrylic acid was also examined using **1** and **3** as chiral auxiliaries.

The development of water-soluble organometallic catalysis has expanded significantly.[1] One key challenge in the development of homogeneous catalysis[2] has always been the separation of product from the catalyst, the recycling and recovery of the expensive chiral catalyst. Since the early development of homogeneous biphasic catalysts,[3] increasing interest has been focused on asymmetric hydrogenation using water-soluble catalysts[4–7] including Rh[8] and Ru-based complexes.[9] Several successful approaches using the anionic phosphines TPPTS (e.g. triphenylphosphine trisulfonate) for the preparation of in situ water soluble palladium catalysts[10] and their use in a large number of C–C bond coupling reactions[11] have been demonstrated by our group. Some applications in the field of palladium-catalyzed cross coupling reactions using achiral cationic phosphi-



Scheme 1.

Keywords: asymmetric hydrogenation; polymer-supported catalyst; ruthenium; rhodium.

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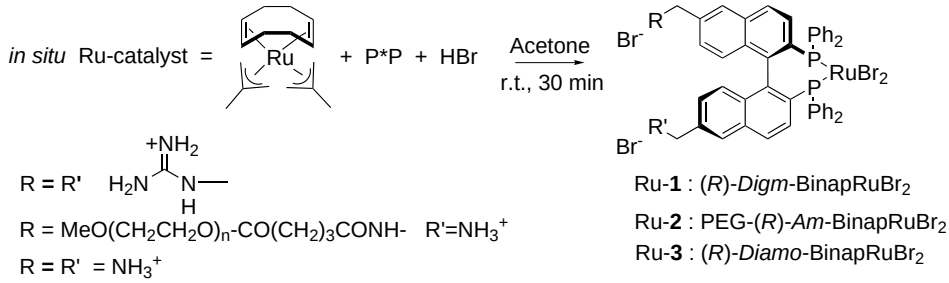


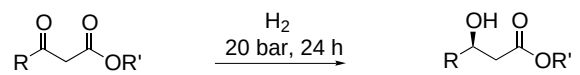
Scheme 2.

nes bearing quaternary ammonium[12] and more recently guanidinium[13] have been reported. Another approach for the separation of the product from the catalyst involves polymer supported catalysts.[14] Recently, a linear homopolymer polyethyleneglycol monomethylether (MeO-PEG) was attached first to an alkaloid[15] then to a pyrimidine and pyridazine ligand[16] and used for asymmetric dihydroxylation of olefins both in good yields and enantioselectivities. The use of highly efficient soluble chiral polyester-supported BINAP ligands obtained by polycondensation of 5,5′-diamino-BINAP was reported for the ruthenium-promoted asymmetric hydrogenation of 2-(6′-methoxy-2-naphtyl)acrylic acid.[17] In our continuous interest for the transition-metal catalyzed enantioselective hydrogenation reactions[18] and water-soluble catalysts[10,11] and due to the outstanding performances of various Rh and Ru-BINAP complexes,[19] we report here both the synthesis of recyclable BINAP-type ligands functionalized with guanidinium functions (*Digm*-BINAP **1**), and PEG-bound BINAP-type (PEG-*Am*-BINAP **2**) ligands and their use in ruthenium and rhodium-mediated hydrogenation. During this work, *Diam*-BINAP was simultaneously synthesized by Lemaire[20] and our group[21] using the same sequence. This group reported its use for the synthesis of heterogeneous enantioselective catalysts.[20] These reports prompted us to present our own results in this area (Scheme 1).

The guanidinium phosphine (*R*)-*Digm*-BINAP **1** was prepared in a two step sequence (35% yield) by reaction of (*R*)-*Diam*-BINAP with 2.5 equiv. of *N*,*N*′-di-Boc-*N*″-triflylguanidine[22] and triethylamine in CH_2Cl_2 at 50°C for 24 h followed by addition of a solution of 3N HCl in methanol. The commercially available poly(ethyleneglycol) methylether (MeO-PEG, M_n 5000) was acylated using glutaric anhydride in the presence of 4-*N*,*N*′-dimethylaminopyridine (DMAP) to provide the corresponding carboxylic acid. The (*R*)-*Diam*-BINAP reacted with 0.9 equiv. of the acid in CH_2Cl_2 at rt in the presence of dicyclohexylcarbodiimide and DMAP to afford quantitatively the monosubstituted PEG-(*R*)-*Am*-BINAP **2**. Only one of the amine functions of (*R*)-*Diam*-BINAP reacted with the solid support as shown by MALDI-TOF mass spectrometry.[23] The Ru(II)-catalysts containing the chiral auxiliaries **1**, **2** and (*R*)-*Diamo*-BINAPRuBr$_2$ Ru-**3** catalyst were prepared from [Ru(COD)(2-methylallyl)$_2$] and the corresponding ligand by addition of a methanolic solution of HBr in acetone using our in situ procedure[18a] (Scheme 2).

As a preliminary evaluation of the best experimental conditions, the hydrogenation was carried out using the standard methyl acetoacetate **4** as the substrate (Scheme 3) and (*R*)-*Diamo*-BINAPRuBr$_2$ Ru-**3** as the catalyst under 20 bar of hydrogen as shown in Table 1. In all cases, complete conversion was obtained. The homogeneous catalytic system based on (*R*)-*Diamo*-BINAPRuBr$_2$ Ru-**3** gave moderate e.e. when hydrogenation reaction was conducted in water, both at room temperature and 50°C (60 and 62% e.e., respectively, entries 1 and 2). By changing water to methanol, the e.e. increased to 80% (entry 3). The Ru-**3** catalyst containing *Diamo*-BINAP displayed the best catalytic activity at room temperature using ethylene glycol as the solvent affording (*R*)-3-hydroxybutyrate **7** in 96% e.e. (entry 4). Comparable catalytic activity was observed in ethylene glycol using (*R*)-*Digm*-BINAPRuBr$_2$ Ru-**1** (96% e.e., entry 5).

In the hydrogenation reaction of representative β-ketoesters such as *iso*butyrylacetate **5** and ethyl benzoylacetate **6**, promoted by the *Diamo*-BINAPRuBr$_2$ Ru-**3** and *Digm*-BINAPRuBr$_2$ Ru-**1** complexes, both the activity and e.e. were excellent, the β-hydroxyesters **8** and **9** being synthesized in 98 and 99% e.e., respectively (entries 6–8). On the other hand, PEG-(*R*)-*Am*-BINAPRuBr$_2$ Ru-**3** catalyst also promoted highly enantioselective hydrogenation of methyl acetoacetate **4** at 50°C in MeOH (99% e.e., entry 9). The advantage of MeO-PEG modification was that the hydrogenation was performed in the homogeneous phase. 3-Hydroxybutyrate **7** was easily separated from the supported catalyst by simple addition of ether, which allowed the precipitation of the enlarged catalyst. Thus, the polymer bound catalyst could be recycled four times, under 20 bar at 50°C, by adding 2 equiv. of a methanolic solution of bromhydric acid for each run (Table 2). The



4 R=R'=CH_3
5 R=*i*-Pr, R'=C_2H_5
6 R=C_6H_5, R'=CH_3

7
8
9

Scheme 3.

Table 1. Ruthenium-catalyzed hydrogenation of β-ketoesters **4–6**

Entry	Catalyst	Substrate[a]	Solvent	*T* (°C)	e.e. (%)[b] (*R*)
1	(*R*)-*Diamo*-BINAPRuBr$_2$	**4**	H_2O	Rt	60
2	(*R*)-*Diamo*-BINAPRuBr$_2$	**4**	H_2O[c]	50	62
3	(*R*)-*Diamo*-BINAPRuBr$_2$	**4**	MeOH	50	80
4	(*R*)-*Diamo*-BINAPRuBr$_2$	**4**	Ethylene glycol	Rt	96
5	(*R*)-*Digm*-BINAPRuBr$_2$	**4**	Ethylene glycol	Rt	96
6	(*R*)-*Diamo*-BINAPRuBr$_2$	**5**	Ethylene glycol	Rt	99
7	(*R*)-*Digm*-BINAPRuBr$_2$	**5**	Ethylene glycol	Rt	99
8	(*R*)-*Diamo*-BINAPRuBr$_2$	**6**	Ethylene glycol	Rt	98
9	PEG-(*R*)-*Am*-BINAPRuBr$_2$	**4**	MeOH	50	98

[a] Conversion rates were determined by ^{1}H NMR on the crude mixture.
[b] The enantiomeric excesses were determined by chiral GC on a Lipodex-A column.
[c] The corresponding acid was obtained.

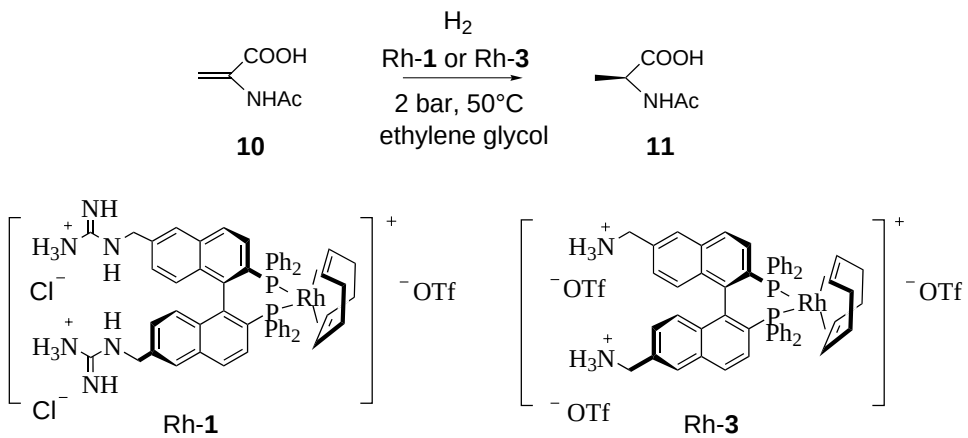
Table 2. Recycling of PEG-(*R*)-*Am*-BINAPRuBr$_2$ Ru-**3** and (*R*)-*Digm*-BINAPRuBr$_2$ Ru-**1** in the reduction of **4**

Run[a]	Catalyst	S/C	Solvent	Conv. (%)[b]	e.e. (%)[c]
1	Ru-**3**	100	MeOH	100	98
2	Ru-**3**	100	MeOH	100	98
3	Ru-**3**	100	MeOH	100	96
4	Ru-**3**	100	MeOH	100	95
1	Ru-**1**	1000	Ethylene glycol	100	97
2	Ru-**1**	1000	Ethylene glycol	100	93
3	Ru-**1**	500	Ethylene glycol	60	87

[a] Reaction time: 24 h.
[b] Conversion rates were determined by ^{1}H NMR on the crude mixture.
[c] The enantiomeric excesses were determined by chiral GC on a Lipodex-A column.

(*R*)-*Digm*-BINAPRuBr$_2$ Ru-**1** was recycled three times under 100 bar and 50°C (Table 2).

All hydrogenations in Table 1 have been preliminarily carried out on a 1 mmol scale and extended to preparative amounts (3.6 g) of methyl acetoacetate **4** in the case of PEG-(*R*)-*Am*-BINAPRuBr$_2$ Ru-**2** catalyst. Interestingly, this supported catalyst was efficient using a catalyst:substrate ratio up to 1:10 000 under 100 bar of hydrogen at 50°C.[24] Finally, the reactivity of some cationic rhodium complexes containing the ligands **1** and **3** was examined (Scheme 4). The rhodium catalysts such as Rh-**1** and Rh-**3** were prepared by stirring $[Rh(COD)_2]^+OTf^-$ and the chiral ligands in THF at room temperature for 30 min. We found that the hydrogenation of the standard substrate acetamidoacrylic acid **10** performed in ethylene glycol under 2 bar of hydrogen at 50°C using Rh-**1** and Rh-**3** as the catalyst occurred quantitatively with excellent enantiofacial discrimination leading to the (*S*)-*N*-acetylalanine **11** (94 and 95% e.e., respectively).



Scheme 4.

In summary, we have described the first chiral recyclable guanidinium-BINAP. Our preliminary experiments demonstrate the significant potential of the guanidinium-BINAP and PEG-*Am*-BINAP ligands both in the homogeneous ruthenium (e.e. up to 99%) and rhodium-mediated (e.e. up to 95%) hydrogenation reactions. After completion of this manuscript, hydrogenation of ethyl acetoacetate using the bromhydrate of *Diam*BINAP was reported.[25]

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