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Enantioselective catalytic asymmetric hydrogenation of ethyl acetoacetate in room temperature ionic liquids

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Abstract—Ethyl acetoacetate was chosen to evaluate the efficiency of hydrosoluble derivatives of 4,4′- and 5,5′-*diam*BINAP in enantioselective catalytic asymmetric hydrogenation in various room temperature ionic liquids (RTILs). Complete conversion and good selectivity were obtained. Recycling by simple extraction with pentane was also possible.

1. Introduction

Room temperature ionic liquids (RTILs) are emerging as excellent alternatives to toxic, volatile and/or inflammable organic solvents in homogeneous and biphasic processes.[1] Inert ionic liquids with counter anions such as tetrafluoroborate, hexafluorophosphate or bis(trifluoromethylsulfonyl)imide have been used as catalyst supports in biphasic processes for a wide range of reactions.[2] Today, many examples of hydrogenation in RTILs are known and, in most cases, good results obtained with recycling often possible.[3,4] More specifically Ru-BINAP or Ru-tolBINAP catalysts have been immobilized in many RTILs for asymmetric hydrogenation.[5] The organic products from these reactions were separated by decantation or supercritical CO_2 extraction while the ionic liquid phase containing the active catalysts could be reused several times without significant deterioration in activity and selectivity. However supercritical fluids cannot dissolve all substrates and decantation can not be done in all cases; in these two studies the ratio of substrate/catalyst was only between 40 and 80. To the best of our knowledge, very few BINAP derivatives have been used for such an application. The only example we found was BINAP functionalized by phosphonic acid.[6] In this example, polar derivatives of Ru-BINAP precatalysts permitted easy recycling and reuse of the catalyst in RTILs. Recently, we have described the synthesis of two new polar BINAP derivatives, 4,4′- and the 5,5′-*diam*BINAP.[7] These ligands were used as hydrosoluble chiral ligands in the biphasic asymmetric hydrogenation of various β-keto-esters in a water/organic solvent media. Herein we report our preliminary results on the use of RTILs for asymmetric hydrogenation of ethyl acetoacetate with the ammonium salt of 4,4′- and 5,5′-Ru-*diam*BINAP. In order to compare the role of the nature of the solvent, various RTILs such as immidazolium, pyridinium and phosphonium salts were tested (Scheme 1).

2. Results and discussion

4,4′- and 5,5′-*diam*BINAP **7** and **8**, respectively, were synthesized in five steps from enantiomerically pure BINAP as previously described.[7] The ammonium salt catalysts **9** and **10** were then prepared in situ from the bromohydrates and $[Ru(\eta^3\text{-2-methylallyl})_2(\eta^2\text{-COD})]$ according to the reported procedure (Scheme 2).[8]

The catalysts were used immediately by dissolving in the appropriate ionic liquid with the substrate then added (substrate/catalyst = 1000). The biphasic mixture was allowed to react in an autoclave at 50 °C and 40 bar of

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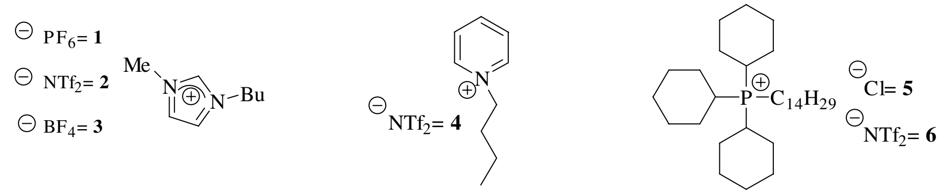
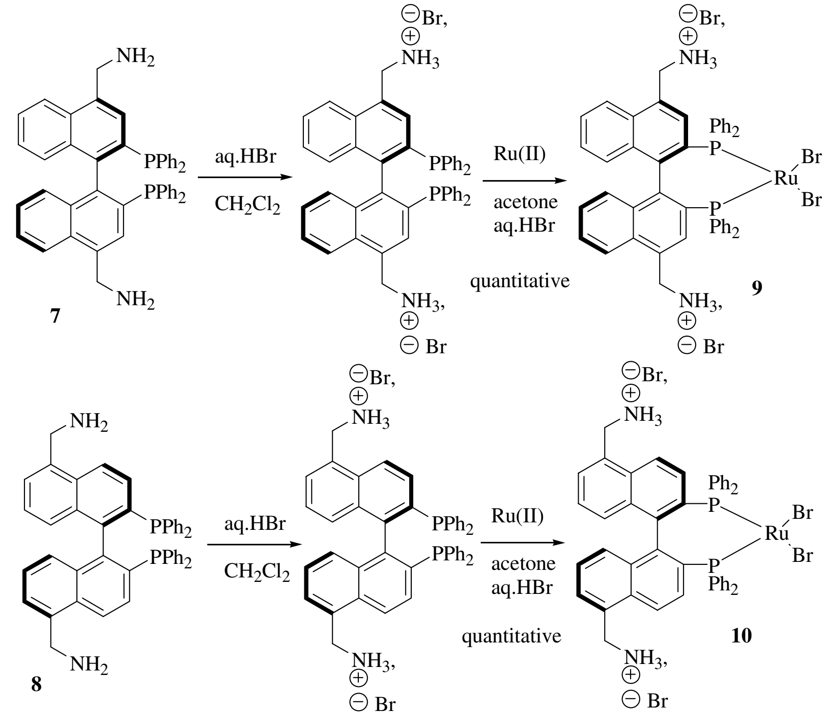


Scheme 1. Room temperature ionic liquids tested.



Scheme 2. Preparation of the hydrosoluble catalysts.

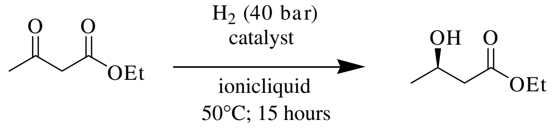
hydrogen for 20 h. The resulting homogeneous mixture was then cooled, extracted with pentane and analyzed by gas chromatography and high pressure liquid chromatography (Table 1).

Catalysts **9** and **10** led to good conversion and good enantioselectivity (entries 1 and 8). The influence of the cation seems to be important. No significant ees were observed with the phosphonium salt (entries 5 and 6).

This observation could be ascribed to problems of solubility and complexation competition. Both ILs, which had imidazolium and pyridinium cations gave good results. The tetrafluoroborate counter-ion gave better results than the other with the same cation (entries 3 and 8). All the selectivities obtained with the RTILs were lower than those obtained in water (entry 10). This effect has been studied by Dyson et al.[10] and was due to impurities (chloride) in the ionic liquid that deactivated the catalyst. The recycling of **9** was also performed by extraction of the ionic liquid phase by pentane (Table 2).

Recycling occurred with no loss in activity and an increase in selectivity. The catalyst became more selec-

Table 1. 4,4′- and 5,5′-Ru-*diam*BINAP catalyzed hydrogenation of ethyl acetoacetate in ionic liquid



Entry	Catalyst	Ionic liquid	Conversion (%)[a]	Ee (%)[b]
1	**9**	**1**[c]	100	75
2	**9**	**2**[c]	100	78
3	**9**	**3**[c]	100	86
4	**9**	**4**[c]	100	85
5	**9**	**5**[d]	80	2
6	**9**	**6**[c]	30	3
7	**10**	**2**	100	71
8	**10**	**3**	100	80
9	**10**	**4**	100	83
10	**9**	H_2O	100	95
11	**9**	**1** + H_2O	100	13

[a] Conversion was determined by GC/MS.

[b] Ee was determined by HPLC with a CHIRALCEL® OD column.

[c] Prepared according to method described in Ref. 9.

[d] Commercially available at Cytec Canada Inc.

Table 2. Recycling in ionic liquid

Entry	Reuse	Catalyst	Ionic liquid	Conversion (%)[a]	Ee (%)[b]
1		**9**	**3**	100	76
2	1st	**9**	**3**	100	90
3		**9**	**4**	100	85
4	1st	**9**	**4**	100	90

[a] Conversion was determined by GC/MS.

[b] Ee was determined by HPLC with a CHIRALCEL® OD column.

tive after recycling but no explanation could be put forward for this observation. Finally we were surprised to observe a large decrease in selectivity when small amounts of water (10%) were added in the ionic liquid layer. We have no explanation for this but this effect has already been observed at high hydrogen pressure in the hydrogenation of tiglic acid in **4**.[4]

We have demonstrated that minor modification of 4,4′- and 5,5′-*diam*BINAP provides a polar and ionic liquid-soluble BINAP analogue suitable for asymmetric biphasic catalytic hydrogenation of ethyl acetoacetate in RTILs. The use of such a media is not just interesting for this substrate, which was hydrogenated in water/organic solvent biphasic mixture with perfect conversion and excellent ee. This paper shows the use of certain BINAP derivatives is possible with more atypical media. This could be extremely interesting for substrates or catalysts, which need specific conditions.

3. Experimental

Under Ar, to the catalyst **9** or **10** (0.024 mmol) dissolved in ionic liquid (1 mL), the 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 bars H_2. The resulting homogeneous mixture was extracted twice with pentane (10 mL). The ionic liquid phase containing the catalyst was reused as previously described.

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