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Asymmetric hydrogenation of methyl α-benzamido cinnamate in ionic liquid solvent

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Abstract—The room temperature ionic liquid EMIMOTf was employed as the sole reaction solvent for the asymmetric hydrogenation of methyl α-benzamido cinnamate. Under conditions of 60 psi hydrogen and 50 °C for 24 h, near quantitative conversions were observed using both the achiral DiPFc–Rh catalyst, and the chiral EtDuPHOS–Rh catalysts. Enantiomeric excess of 89% ee was observed for hydrogenations carried out with the chiral catalyst.

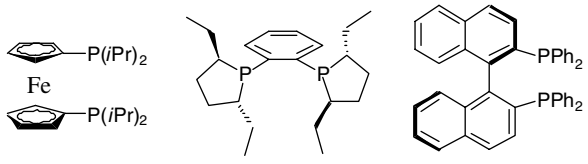
1. Introduction

The use of room temperature ionic liquids (RTILs) as more environmentally friendly alternatives to conventional organic solvents has exploded over the last decade.[1,2] While there are many classes of ionic liquids including pyridinium salts and quartenary ammonium salts, ionic liquids based on the imidazolium cation have received the most attention as reaction solvents. In particular, ethyl methyl imidazolium (EMIM) and butyl methyl imidazolium (BMIM) salts (Fig. 1) with a variety of anions including tetrafluoroborate (BF_4) and trifluoromethanesulfonate (OTf) have been used widely. The imidazolium RTILs act like moderately polar organic solvents with the ability to dissolve many common organic solutes, both polar and non-polar. The short chain imidazolium RTILs, in particular, have limited miscibility in organic solvents like hexanes, toluene, and ether.[3] This allows for ease of extraction of organic products from the RTIL. For these reasons, imidazolium ionic liquids have been investigated as reaction solvents for a variety of stoichiometric reactions such as Diels–Alder[4] and for numerous catalytic reactions including hydrogenation, hydroformylation, and Heck type couplings.[5]

The DuPHOS–Rh and BINAP–Ru catalyst systems (Fig. 2) have proven to be versatile and highly effective at asymmetric induction when used for hydrogenation of a wide variety of substrates including α-enamide esters,[6a,b] enol benzoates,[7] β-keto esters,[8a,b] and α-aryl enamides.[9] In addition, the achiral DiPFc[10] is a highly active catalyst useful for generating the racemic material necessary for development of the method for analysis of enantiomeric excess. These reactions are typically carried out in organic solvents such as methanol, 2-propanol, or even the more toxic THF and benzene. More recently, efforts have been made to use this type of catalyst in more 'green' solvents. In fact, the use of EtDuPHOS–Rh in supercritical CO_2 has been reported to catalyze the hydrogenation of α-enamide esters to the corresponding amino acid derivatives with levels of enantioselectivity that rival, and in some cases exceed those achieved in methanol and hexane.[11]

EMIMOTf BMIMBF$_4$

Figure 1. Structures of imidazolium ionic liquids.



DiPFc *(R,R)* EtDuPHOS *(R,R)* BINAP

Figure 2. Structure of DiPFc, EtDuPHOS, and BINAP ligands.

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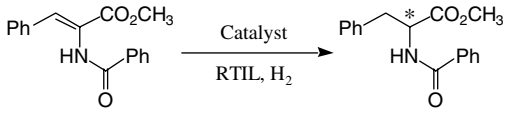
Asymmetric hydrogenations in which RTILs played the role of solvent or co-solvent for a variety of substrates have been reported in the literature. The substrates involved in these reactions include aromatic ketones,[12a,b] β-keto esters,[13a–c] and α-enamide esters.[14a–c] For example, the ionic liquid $BMIMPF_6$ was used in combination with 2-propanol for the hydrogenation of α-enamide esters[14a] and $BMIMBF_4$ was used with the co-solvents 2-propanol or water in a roughly one-to-one ratio for similar types of reactions.[14b] In fact, Wolfson et al. reported *no conversion* of methyl 2-acetamidoacrylate under homogenous conditions using EtDuPHOS–Rh in $BMIMPF_6$ ionic liquid as the only solvent at 5 bar H_2 pressure, whereas complete reaction and good enantiomeric excesses were achieved in a variety of co-solvent systems in which the ionic liquid was combined with another organic solvent.[14c] In contrast to that report, our studies presented here demonstrate near quantitative conversion of a similar substrate, methyl α-benzamido cinnamate, to the corresponding protected amino acid using the ionic liquid EMIMOTf as the sole reaction solvent (Scheme 1).

2. Results and discussion

Initial hydrogenations of methyl α-benzamido cinnamate carried out in the $BMIMBF_4$ ionic liquid showed very low conversion in the case of the DiPFc–Rh catalyst, and no product was observed with the two chiral catalysts (see Table 1). These results are in agreement with the recent report by Wolfson et al. in which no reaction of methyl 2-acetamidoacrylate was found under homogenous conditions using EtDuPHOS–Rh in either $BMIMPF_6$ or $BMIMBF_4$ ionic liquid as a single solvent at 5 bar H_2.[14c]



Scheme 1. Hydrogenation of methyl α-benzamido cinnamate.

Table 1. Results of hydrogenation reactions[a]

Catalyst	RTIL	Conversion[b] (%)	% ee[c]
DiPFc–Rh	$BMIMBF_4$	<2	—
	EMIMOTf	15	Racemic
	EMIMOTf[d]	100	Racemic
EtDuPHOS–Rh	$BMIMBF_4$	0	—
	EMIMOTf	15	85
	EMIMOTf[d]	95	89
	EMIMOTf[e]	80	62
BINAP–Ru	$BMIMBF_4$	0	—
	EMIMOTf	16	95

[a] Conditions: 1 mol % catalyst, 60 psi H_2, 24 h, room temperature, unless otherwise noted.
[b] Conversion determined by ^1H NMR.
[c] Enantiomeric excess determined by HPLC.
[d] Reaction carried out at 50 °C for 24 h.
[e] Reaction carried out at 1000 psi for 24 h.

A change from the $BMIMBF_4$ ionic liquid to the EMIMOTf ionic liquid was met with an improvement in conversion under the same reaction conditions (see Table 1). The conversion of methyl α-benzamido cinnamate with the chiral catalysts EtDuPHOS–Rh and BINAP–Ru as well as the achiral catalyst DiPFc–Rh was increased to about 15% in all cases. With the EMIMOTf solvent, dramatic improvement in conversion was observed both under increased hydrogen pressure of 1000 psi at room temperature (80% conversion) and under increased reaction temperature of 50 °C at 60 psi (95% conversion). The product from the high pressure reaction showed a respectable 62% ee while the product form the 50 °C reaction showed an outstanding 89% ee. In addition to increased conversion and excellent stereochemical induction, the use of EMIMOTf effected easier extraction of the organic products from the ionic liquid solvent. In our hands, the BMIM was somewhat miscible with virtually all extraction solvents. Thus, the EMIMOTf is the clear choice for ionic liquid as lone solvent for this type of hydrogenation reaction.

In summary, this study demonstrates that it is possible to achieve near quantitative conversion and high enantiomeric excesses in the asymmetric hydrogenation of methyl α-benzamido cinnamate using EMIMOTf RTIL as sole reaction solvent. With these promising results, we are in the process of evaluating other substrates such as benzamido acrylates and acetamido acrylates in an attempt to determine the scope and limitations of this solvent for asymmetric hydrogenation reactions.

3. Experimental details

3.1. Typical hydrogenation procedure

The reaction mixture consisting of methyl α-benzamido cinnamate (0.35 mmol) and the appropriate catalyst (3 μmol) along with degassed RTIL (4 mL) was added to an Andrews glass pressure reaction vessel (60 psi) or a Parr stainless steel reactor (1000 psi) in an inert atmosphere glove box. After removal and three vacuum-hydrogen flush cycles, the vessel was pressurized to either 60 psi or 1000 psi. After 24 h, the reaction was vented and the product extracted using three 5-mL portions of ether (EMIM) or three portions of hexanes (BMIM). The organic solvent was removed under reduced pressure and the remaining residue was analyzed for conversion by NMR and for stereochemistry by HPLC. The methyl α-benzamido cinnamate and the RTILs were prepared according to literature procedures.[3,15a,b]

3.2. Product analyses

Conversion was determined by integration of the methyl ester singlet in the ^1H NMR at δ 3.87 for the methyl α-benzamido cinnamate and δ 3.77 for the hydrogenated product. Determinations of enantiomeric excess were made using an Agilent 1100 Series HPLC equipped with a Chiralcel OD-H column and a flow rate of 1.0 mL/min of 90/10 hexanes/2-propanol and UV detection at

215 nm. Retention times of 11.5 and 14.8 min represented the two enantiomers of the hydrogenated product.

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