Enantioselective catalysis with *tropos* ligands in chiral ionic liquids

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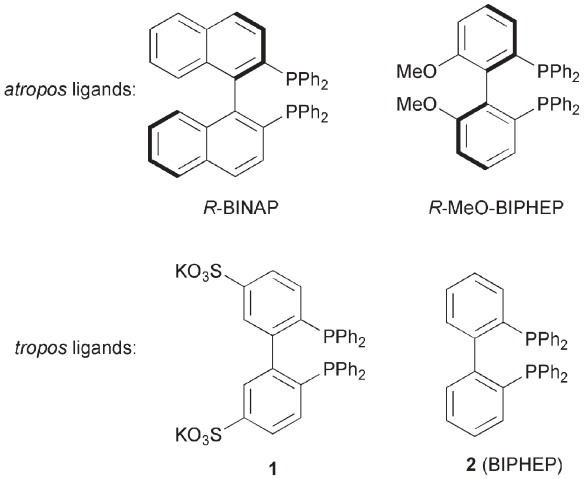
Enantioselective homogeneous rhodium-catalysed hydrogenation using tropoisomeric biphenylphosphine ligands was accomplished in readily available chiral ionic liquids and the catalytic system could be reused after extraction with *sc*CO_2.

Chiral transition metal catalysis is one of the key technologies for carrying out enantioselective transformations.[1,2] The utilised transition metal catalysts usually provide the necessary chiral information through the structure of the ligand backbone. In this respect, bidentate chelating phosphorus compounds based on atropoisomeric binaphthyl and biphenyl backbones like BINAP[3] or MeO-BIPHEP[4] are among the most effective chiral ligands for a broad variety of transformations. In contrast to the "locked" structure of these backbones, rapid rotation of the phenyl rings is typically observed in 2,2′-bis(diphenylphosphino)biphenyl ligands such as **1** or **2**, which lack substituents at the 6,6′ positions. These structures are referred to as pro-atropoisomeric or *tropos*;[5] they do not possess permanent chiral information and show no preference for a given conformation without an external chiral bias.



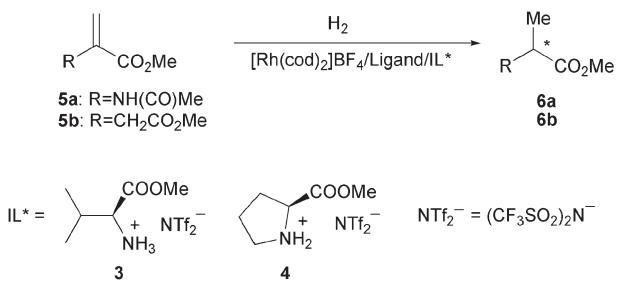
Flexible biphenyl units have been successfully incorporated into ligand frameworks containing a fixed element of chirality.[6,7] A second strategy combines the *tropos* ligands with another chiral ligand in the coordination sphere of a metal centre.[8–10] In the case of the biphenyl-based bidentate phosphorus ligand BIPHEP **2**, a resolution of the tropoisomeric backbone was achieved upon coordination to a metal centre (Rh,[11] Pd[12] or Pt[13]) bearing a chiral diamine, diene, aminoalcohol or diol as enantiopure co-ligand. After the removal of the chiral auxiliary, typically *via* protonation, the resulting chiral kinetically stable metal species can be used as a catalyst for asymmetric transformations. When the chiral co-ligand is part of the active catalysts, two diastereomeric complexes are usually present in solution. Using this approach, highly enantioselective Ru-catalysed asymmetric hydrogenations were carried out with the BIPHEP ligand.[14]

Very recently, specially designed chiral ionic liquids (ILs) have been used as solvents providing the only source of chirality for enantioselective transformations. This approach has already resulted in high enantioselectivities in organocatalytic reactions[15,16] and in the heterogeneous hydrogenation of keto-functionalities.[17] Furthermore, high enantioselectivities were obtained recently in the homogeneously catalysed Sharpless dihydroxylation using a quinic-based IL.[18]

Herein, we report the first example of asymmetric catalysis based on the use of a catalyst bearing tropoisomeric ligands and a chiral IL. The validity of this approach is demonstrated for the enantioselective Rh-catalysed hydrogenation of benchmark substrates using amino acid–based cation-chiral ionic liquids in combination with *tropos* biphenylphosphine ligands.

Ligands modified with sulfonato groups have already been used for reactions in ILs as they combine good solubility of the corresponding catalysts in the polar media and effective catalyst immobilisation for applications in multiphase systems.[19] We therefore started our investigations with the *tropos* ligand 5,5′-disulfonato-2,2′-bis(diphenylphosphino)-1,1′-biphenyl (**1**) which was synthesised according to a literature procedure.[20] Rh-catalysed hydrogenations of methyl 2-acetamidoacrylate (**5a**) and dimethyl itaconate (**5b**) were chosen as test reactions (Scheme 1).

In the course of our recent effort in the development and application of chiral ILs, we focused on systems based on amino acids for asymmetric transition metal catalysis. The cation-chiral ILs **3** and **4** are readily available starting from L-valine and L-proline, respectively, after esterification in the presence of



Scheme 1 Rh-catalysed hydrogenation in chiral ionic liquids.

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$SOCl_2$ and subsequent anion exchange with $LiNTf_2$ (NTf_2 = bis(trifluoromethylsulfonyl)amide).†[21]

Table 1 summarises the most important results.‡ Using ligand **1** and $[Rh(cod)_2]BF_4$ in combination with the chiral IL **3**, full conversion in the hydrogenation of methyl 2-acetamidoacrylate, **5a** (entry 1) was obtained. This reaction resulted in the formation of racemic product **6a**. In contrast, **5a** was hydrogenated quantitatively with a remarkable enantioselectivity of 49% *ee* (*S*) in the presence of the proline derived IL **4** (entry 2). Thus, chiral IL **4** was selected for further experiments.

In order to evaluate the influence of the ligand backbone in the catalytic reaction, hydrogenation experiments in the absence of phosphorus ligand (entry 3), with achiral bidentate 1,2-bis(diphenylphosphino)ethane (DPPE) (entry 4) and with monodentate bis(3-sulfonatophenyl)phenylphosphine (TPPDS) (entry 5) were performed. All these reactions yielded racemic products and similar results were obtained in previous attempts using TPPTS[22]-based Rh-catalysts having chiral "spectator" counter-anions.[23]

To further improve the performance of the system, various additives were tested. The deliberate introduction of a drop of water into the reaction system resulted in a comparable enantiomeric excess (entry 6 *vs.* entry 2). In contrast, the addition of 20 equiv. triethylamine with respect to the catalyst led to a remarkable increase of the enantioselectivity to 69% *ee* (*S*) in the hydrogenation of **5a** (entry 7), whereas the use of acetic acid as additive led to a sharp decrease of the enantioselectivity (entry 8).

In order to evaluate the recyclability of the catalytic system, the reaction mixture of entry 7 was extracted using *sc*CO_2[24] to isolate the product. Three consecutive hydrogenations of **5a** were carried out with some depletion of conversion and enantioselectivity in the third run (1st run: conv. >99%, 69% *ee*; 2nd run: conv. 98%, 63% *ee*; 3rd run: conv. 57%, 52% *ee*). This result shows a moderate stability of the immobilised catalyst and demonstrates the applicability in multiphase reaction systems.

The catalyst system $[Rh(cod)_2]BF_4$/**1**/**4** was also applied in the hydrogenation of dimethyl itaconate (**5b**) leading to only a modest enantioselectivity of 20% *ee* (entry 9). In this case, the addition of triethylamine improved the enantioselectivity slightly (29% *ee*) leading, at the same time, to a decrease of the catalyst activity (entry 10). A similar enantioselectivity was achieved by pre-treating the catalyst system with hydrogen (40 bar) in the presence of 2 equiv. of dimethyl itaconate over two days before adding a larger batch of the same substrate and pressurising again with hydrogen. Using this procedure, 27% *ee* was obtained in the hydrogenation of **5b** (entry 11 *vs.* entry 9). The reuse of the catalyst system after product extraction with *sc*CO_2 resulted in reduced conversion over three runs (1st run: conv. >99%, 20% *ee*; 2nd run: conv. 85%, 22% *ee*; 3rd run: conv. 69%, 16% *ee*).

Table 1 Rh-catalysed hydrogenation in chiral ionic liquids[a]

Entry	Ligand	IL	Substrate	Additive	*ee* [%]
1	**1**	**3**	**5a**	—	*rac*
2	**1**	**4**	**5a**	—	49 (*S*)
3	—	**4**	**5a**	—	*rac*
4	DPPE	**4**	**5a**	—	*rac*
5	TPPDS	**4**	**5a**	—	*rac*
6	**1**	**4**	**5a**	H_2O	47 (*S*)
7	**1**	**4**	**5a**	NEt_3	69 (*S*)
8	**1**	**4**	**5a**	CH_3COOH	7 (*S*)
9	**1**	**4**	**5b**	—	20 (*R*)
10[b]	**1**	**4**	**5b**	NEt_3	29 (*R*)
11[c]	**1**	**4**	**5b**	—	27 (*R*)
12	**2**	**4**	**5a**	—	28 (*S*)
13	**2**	**4**	**5a**	NEt_3	52 (*S*)
14	**2**	**4**	**5b**	—	3 (*S*)

[a] Substrate to rhodium ratio = 250, pH_2 = 40 bar. Full conversion was achieved in all experiments unless otherwise noted. Conversion and enantioselectivity were determined by GC (Lipodex E). [b] Conv. 87%. [c] Catalyst system was pre-treated with hydrogen over two days in the presence of two equivalents of substrate.

In the next experiments BIPHEP **2** was applied as a *tropos* ligand to investigate whether the sulfonate groups in **1** have an influence on the outcome of the catalytic transformation. Indeed, BIPHEP was less effective than **1** and lower enantioselectivities were obtained in the hydrogenation of **5a** (entry 12) to give the same preferred enantiomer. Again, in this system the addition of triethylamine resulted in a significant enhancement of the enantioselectivity to 52% *ee* (entry 13). Surprisingly, the hydrogenation of dimethyl itaconate **5b** in the presence of **2** yielded **6b** as an almost racemic mixture (entry 14).

In summary, significant enantioselectivities were obtained for the first time in a homogeneous transition metal-catalysed reaction using tropoisomeric ligands in a chiral ionic liquid as the exclusive source of chiral information. The reusability of the catalyst system was demonstrated using *sc*CO_2 as the extracting medium. The exact mechanism of the transfer of chiral information from the IL to the catalytically active centre is currently under investigation. Two possible alternatives include asymmetric activation[25] or poisoning processes[26,27] by interaction of the metal centre with the IL. Given the significant enantioselectivity obtained with ligand **2**, a direct interaction of the ligand backbone with the IL seems less likely, but cannot be excluded at present.

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Notes and references

† *Preparation of the L-proline methyl ester bis(trifluoromethylsulfonyl)amide ionic liquid*

To a solution of L-proline (34.5 g, 0.30 mol) in methanol (300 mL) thionyl chloride (78.0 mL, 1.03 mol) was added dropwise at −10 °C. The reaction mixture was warmed to room temperature and stirred for an additional 12 h. Then, all volatiles were removed *in vacuo* and the residue was dissolved in water. Lithium bis(trifluoromethylsulfonyl)amide (90.0 g, 0.31 mol) dissolved in water was added and the resulting mixture was stirred for an additional 30 min at room temperature. CH_2Cl_2 was added and the phases were separated. The organic phase was washed with water until no chloride was detected using $AgNO_3$. Afterwards, all volatiles were removed *in vacuo*. The product was obtained as a colourless liquid (87.3 g, 71.0%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.79 (s, 1H, NH_2), 7.33 (s, 1H, NH_2), 4.50 (m, 1H, CH), 3.88 (s, 3H, CH_3), 3.57 (m, 2H, CH_2), 2.43–2.55 (m, 1H, CH_2), 2.02–2.27 (m, 3H, CH_2) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 168.3, 119.6 (q, J(C–F) = 319 Hz), 60.3, 54.1, 47.7, 28.5, 23.8 ppm.

‡ *Procedure for a typical catalytic reaction*:

The catalyst was formed *in situ* by dissolving **1** (9.7 mg, 0.013 mmol) in **4** (0.8 mL) and then adding $[Rh(cod)_2]BF_4$ (4.7 mg, 0.012 mmol, cod = 1,5-cyclooctadiene) as a CH_2Cl_2 solution (2 mL). After ten minutes, the substrate **5a** (343 mg, 2.40 mmol) was added and the resulting solution was transferred into a stainless steel reactor (12 mL) equipped with thick-glass windows. CH_2Cl_2 was removed under vacuum and the reactor pressurised with hydrogen (40 bar). Although strong magnetic stirring-bars were used, only poor mixing of the highly viscous reaction mixture was achieved as

confirmed by visual control. After 16 h, a small sample of the reaction mixture was taken from the autoclave, diluted with CH_2Cl_2, and analysed *via* GC. It should be noted that although a 16 h standard reaction time was chosen, the reaction probably proceeds much more rapidly as constant pressure was usually observed within one hour.

Extraction procedure: After the reaction, the reactor was vented and a small sample was taken out for GC-analysis. The product was extracted by flushing $scCO_2$ through the reactor (260 bar, 40 °C) for 4 h with an exit flow of 1.5 L min^{-1}. The product was collected in a cold trap (dry ice–acetone) almost quantitatively (recovery between 80–95%). The *ee* measurements of crude mixture and of the extracted products were identical within the analytical error (discrepancy $< 0.4\%$), ruling out an enantioenrichment of the product in the extract or in the IL.

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