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# New Efficient Catalysts for Enantioselective Transfer Hydrogenations

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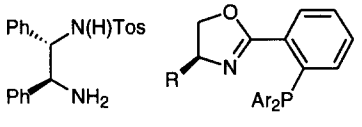
*Summary: New $C_2$-symmetrical diaminoferrocenyl derivatives **3** and 2-amino(sulfonamido)cyclohexanes **4** were found to be highly active ligands for the ruthenium catalyzed asymmetric transfer hydrogenation of ketones. Contrary to many existing catalytic systems, the ligands **3** show a high activity at 25 °C and operate even at -30 °C (up to 90 % ee). On the other hand, the slightly less active ligands **4** are very easily prepared and are highly enantioselective at 30 °C in HCOOH/$Et_3N$ (up to 96 % ee).*

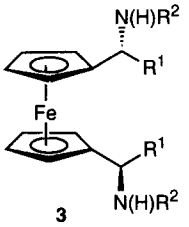

The catalytic enantioselective reduction of ketones has been extensively studied during the last decade.[1] A especially useful method is the catalytic transfer hydrogenation[2] using *i*-PrOH[3] or a HCOOH/$Et_3N$ mixture[4] as hydride source and a chiral ruthenium catalyst bearing ligands such as **1** or **2**. In the course of our work on the preparation of new chiral $C_2$-symmetrical ferrocenyl derivatives for asymmetric catalysis,[5] we have now discovered that the ruthenium complexes of the diaminoferrocenyl derivatives of type **3** are a new class of highly efficient transfer hydrogenation catalysts operating even at -30 °C with high conversion and good enantioselectivity.



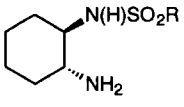

**1**




**2**

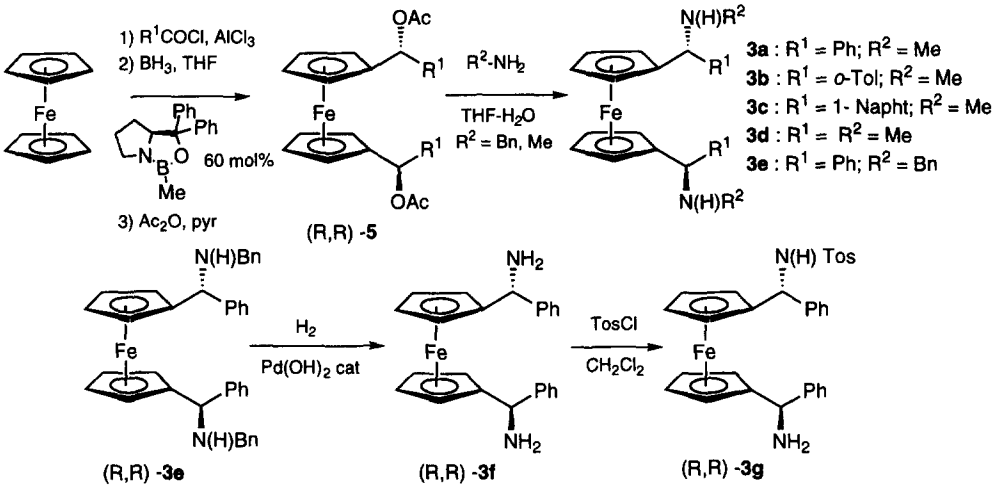



**3**



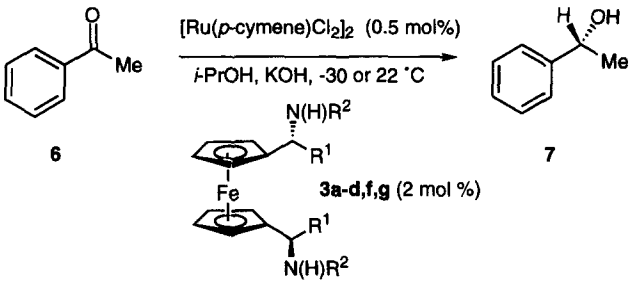

**4**

Herein we report our preliminary results with the new chiral ligand system as well as a highly enantioselective transfer hydrogenation using *N*-monosulfonylated 1,2-diaminocyclohexane derivatives of type **4**. The ferrocenes **3** were prepared from ferrocene in four steps (Scheme 1). Acylation of ferrocene ($R^1COCl$, $CH_2Cl_2$, $AlCl_3$, 0 °C to 25 °C, 4 h) provides ferrocenyldiketones (71 - 92 %) which were reduced enantioselectively with an oxazaborolidine catalyst (CBS-reduction) providing 1,1'-ferrocenyl diols in 90 % - 96 % yield and > 99 % *ee*.[5] Acetylation of these diols ($Ac_2O$, pyridine, 25 ° C, 12 h) gives quantitatively the corresponding diacetates **5** which undergo a substitution with an excess of primary amines (THF-$H_2O$, 25 °C, 12 h) furnishing the diaminoferrocenes **3a-e** ( 56 % - 93 %) with retention of configuration.[6] Hydrogenolysis of **3e** ($H_2$, $Pd(OH)_2$ cat) leads to the unprotected diaminoferrocene derivative **3f** (96 %).[7] Monotosylation of **3f** (TosCl (1 equiv), $CH_2Cl_2$, 0 °C, 1 h) affords the aminosulfonamide **3g** in 36 % yield.[8] The aminoferrocenes **3a-d,f,g** were tested in the catalytic reduction of acetophenone (**6**). Thus, a *i*-PrOH solution of the catalytic system prepared from the ferrocene derivatives **3a-d,f,g** (2 mol %) and




**Scheme 1**

[Ru(*p*-cymene)$Cl_2$]$_2$ (0.5 mol %) was treated at temperatures between -30 °C and 22 °C with a *i*-PrOH solution of acetophenone (**6**) in the presence of KOH (5 mol %) affording (*R*)-1-phenylethanol (**7**) with excellent conversions and enantioselectivities up to 80 % *ee* (Scheme 2 and Table 1).[9] *No decrease of the enantioselectivity is observed with time.*




**Scheme 2**

Similarly 1-acetylnaphthalene (**8**) is reduced to (*R*)-1-naphthyl-1-ethanol (**9**) with an enantioselectivity up to 90 % *ee*. Entries 1-6 of Table 1 compare the results of the different ligands **3a-d,f,g** at 22 °C. All except the monosulfonamido derivative **3g** are highly effective and high conversions are reached within a few minutes to a few hours at rt. The best enantioselectivities are obtained with **3a** and **3b**, both bearing an aryl substituent ($R^1$ = Ph or *o*-Tol) and a *N*-methylamino substituent. The free diaminoferrocene derivative **3f** shows a good catalytic activity but leads to a moderate enantioselectivity (52 % *ee*, see entry 5). The increase of the size of the aryl substituent $R^1$ (phenyl to 1-naphthyl) doubles the catalytic activity but lowers the enantioselectivity (71 % *ee* to 60 % *ee*, compare entries 1 and 3). Remarkably, the high activity of our catalytic system allows us to lower further the reaction temperature. Carrying out the acetophenone reduction at -14 °C with the ligand **3a** increases the enantioselectivity from 71 % *ee* to 79 % *ee*. Lowering the temperature further to -30 °C (120 h) furnishes the alcohol **7** with 80 % *ee* (compare entries 1, 7 and 8). A similar temperature effect is observed with 1-acetylnaphthalene (**8**). By using the most selective ligands **3a** and **3b**, enantioselectivities of 78 % *ee* and 85 % *ee* were obtained at rt. Lowering the reaction

Table 1. Enantioselective transfer hydrogenation of ketones **6** and **8** in *i*-PrOH in the presence of 0.5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ and 2 mol % of the aminoferrocenes **3a-d, f, g**.

| entry | ketone | ligand | T ( °C) | reaction time (h) | conversion (%)[a] | *ee* (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **6** | **3a** | 22 | 0.5 | 98 | 71 |
| 2 | **6** | **3b** | 22 | 1.5 | 97 | 80 |
| 3 | **6** | **3c** | 22 | 0.25 | 98 | 60 |
| 4 | **6** | **3d** | 22 | 3 | 94 | 62 |
| 5 | **6** | **3f** | 22 | 1 | 98 | 52 |
| 6 | **6** | **3g** | 22 | 24 | 97 | 56 |
| 7 | **6** | **3a** | -14 | 41 | 96 | 79 |
| 8 | **6** | **3a** | -30 | 120 | 95 | 80 |
| 9 | **6** | **3g** | 30 | 120 | 42 | 83[b] |
| 10 | **8** | **3a** | 22 | 1 | 99 | 78 |
| 11 | **8** | **3a** | -30 | 120 | 91 | 90 |
| 12 | **8** | **3b** | 22 | 1 | 97 | 85 |
| 13 | **8** | **3b** | 0 | 12 | 96 | 88 |

[a] Determined by GC analysis (Chirasil-DEX CB) [b] A HCOOH/$Et_3N$ mixture was used.

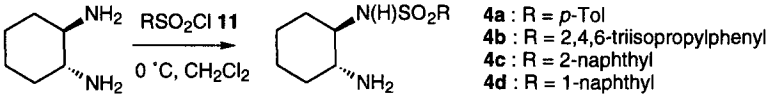
Table 2. Enantioselective transfer hydrogenation of ketones **6**, **8** and **12** in *i*-PrOH or HCOOH/$Et_3N$ in the presence of 0.5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ and 2 mol % of the aminosulfonamides **4a-d**.

| entry | ketone | ligand | T ( °C) | reaction time (h) | conversion (%)[a] | *ee* (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **6** | **4a** | 22 (30) | 24 | 97 (>99) | 89 (94) |
| 2 | **6** | **4b** | 22 (30) | 24 | 96 (>99) | 90 (89) |
| 3 | **6** | **4c** | 22 (30) | 24 | 97 (>99) | 90 (95) |
| 4 | **6** | **4d** | 22 (30) | 24 | 96 (>99) | 92 (96) |
| 5 | **8** | **4d** | 22 (30) | 36 | 99 (>99) | 92 (96) |
| 6 | **12** | **4d** | 22 (30) | 65 | 60 (54) | 23 (67) |

[a] Determined by GC analysis (Chirasil-DEX CB). Conversions and % *ee* in HCOOH-$Et_3N$ are indicated in parenthesis.

temperature with the ligand **3a** to -30 °C and for **3b** to 0 °C allows to increase the enantioselectivity respectively to 90 % *ee* and 88 % *ee* (compare entries 10 to 13). The high catalytic activity observed using the ligand **3a**, even allows the reduction of sterically hindered ketones. Thus *t*-butylphenylketone was reduced with high conversion (> 93 %) within 17 h at 22 °C leading to (*S*)-2,2-dimethyl-1-phenyl-1-propanol with 38 % *ee*. Interestingly, the less active transfer hydrogenation ligand the monosulfonamide **3g** reacts with high enantioselectivity by replacing the *i*-PrOH/KOH reaction medium by the solvent mixture HCOOH/$Et_3N$ (5:2). Under these conditions, a moderate conversion is obtained (42 %, 120 h) but the enantioselectivity increases from 56 % *ee* to 83 % *ee* (compare entries 6 and 9). This enantioselectivity increase

led us to prepare several monosulfonamides derived from the readily available (*1R,2R*)-1,2-diaminocyclohexane (**10**). Thus, treatment of commercially available **10** with various arylsulfonyl chlorides **11** (1 equiv, 0 °C, $CH_2Cl_2$) furnishes highly enantioselective transfer hydrogenation ligands **4a-d** (Scheme 3 and Table 2).[10]




**Scheme 3** **10** 55-65 %

The reduction of acetophenone (**6**) proceeds smoothly with the aminosulfonamides **4a-d**. High enantioselectivities (90-92 % *ee*) are obtained with **4a-d** in *i*-PrOH. Switching to the HCOOH/$Et_3N$ solvent system leads to a further increase of the enantioselectivity (94-96 % *ee*) and to almost quantitative conversions (see entries 1-4 of Table 2).[11] 1-Acetylnaphthalene (**8**) behaves as expected in the same way and furnishes the alcohol **9** in 96 % *ee* (see entry 5 of Table 2). Interestingly, the sterically hindered isopropylphenylketone **12** is reduced in 23 % *ee* using the *i*-PrOH/KOH system, whereas an enantioselectivity of 67 % *ee* is obtained with the HCOOH/$Et_3N$ system.

In summary, we have reported two new classes of highly active transfer hydrogenation catalysts derived from $C_2$-symmetrical diaminoferrocene derivatives or readily available 2-(sulfonamido)cyclohexanes. Extension of this work is currently underway.

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(8) **3a**: $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.30-7.15 (m, 10H), 4.33-4.30 (m, 2H), 4.28 (s, 2H), 4.08-4.05 (m, 4H), 4.00-3.99 (m, 2H), 2.36 (s, 6H), 2.0 (s, br, 2H). $[\alpha]_D$ +56 (*c* 0.55, $CHCl_3$). **3b**: $[\alpha]_D$ -34 (*c* 2.00, $CHCl_3$). **3c**: $[\alpha]_D$ -5 (*c* 2.33, $CHCl_3$). **3d**: $[\alpha]_D$ -6 (*c* 1.73, $CHCl_3$). **3e**: $[\alpha]_D$ -98 (*c* 0.71, $CHCl_3$). **3f**: $[\alpha]_D$ +30 (*c* 2.39, $CHCl_3$). **3g**: $[\alpha]_D$ -32 (*c* 2.52, $CHCl_3$).
(9) The experiments were carried out according to Noyori's procedure (ref. 2 h) using a 0.05 M solution of the ketone.
(10) Compounds **4a-d** were isolated as hydrochlorides. **4a**: $[\alpha]_D$ +57 (*c* 3.50, MeOH). **4b**: $[\alpha]_D$ +54 (*c* 0.98, MeOH). **4c**: $[\alpha]_D$ +31 (*c* 1.26, MeOH). **4d**: $[\alpha]_D$ +164 (*c* 0.98, MeOH).
(11) A mixture of $[Ru(p\text{-cymene})Cl_2]_2$ (4.5 mg, 7.3 μmol) and **4a** (7.9 mg, 29 μmol) was heated in MeOH at 80 °C for 30 min under an argon atmosphere. After the solvent had been removed, **6** (0.17 mL, 1.5 mmol) and HCOOH/$Et_3N$ (5:2) (0.73 mL) were added and the mixture stirred at 30 °C for 24 h.

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