Pergamon

Tetrahedron Letters, Vol. 37, No. 45, pp. 8165-8168, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01853-9

New Efficient Catalysts for Enantioselective Transfer Hydrogenations

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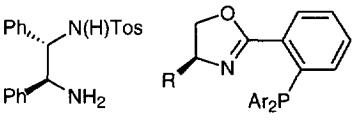
*Summary: New C_2-symmetrical diaminoferrocenyl derivatives **3** and 2-amino(sulfonamido)cyclohexanes **4** were found to be highly active ligands for the ruthenium catalyzed asymmetric transfer hydrogenation of ketones. Contrary to many existing catalytic systems, the ligands **3** show a high activity 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.



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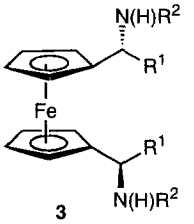

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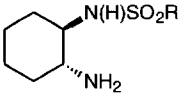

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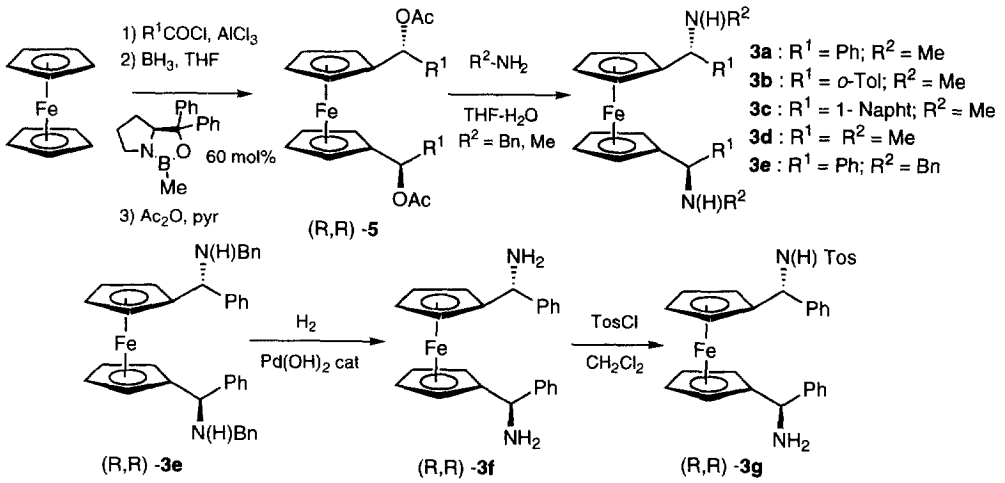
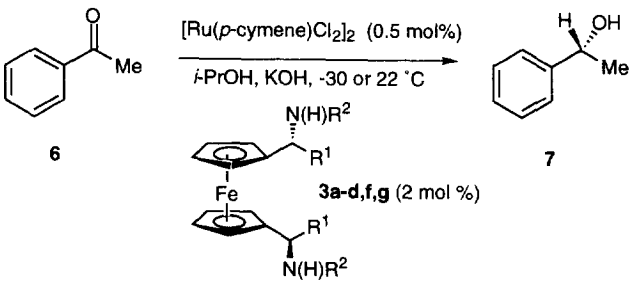
Herein we report our preliminary results with the new chiral ligand system as well as a highly enantioselective transfer hydrogenation using *N*-monosulfonylated 1,2-diaminocyclohexane derivatives of type **4**.
The ferrocenes **3** were prepared from ferrocene in four steps (Scheme 1). Acylation of 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.

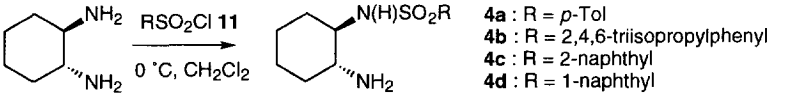
Table 2. Enantioselective transfer hydrogenation of ketones **6**, **8** and **12** in *i*-PrOH or $HCOOH/Et_3N$ in the presence of 0.5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ and 2 mol % of the aminosulfonamides **4a-d**.

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.

Acknowledgment: We thank the DFG (SFB 260), Fonds der Chemischen Industrie, BASF AG, Witco AG, Chemetall, Sipsy, Bayer AG and Chiroscience for generous financial support and gift of chemicals.

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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.

(*Received in Germany* 30 *August* 1996; *accepted* 17 *September* 1996)