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Tetrahedron Letters 45 (2004) 535–537
Tetrahedron Letters

Transfer hydrogenation of activated ketones using novel chiral Ru(II)-*N*-arenesulfonyl-1,2-diphenylethylenediamine complexes

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Received 28 September 2003; revised 27 October 2003; accepted 31 October 2003

Abstract—A series of α-keto esters and α,α,α-trifluoromethyl ketones were reduced in high yields and excellent enantioselectivities under Ru-catalysed transfer hydrogenation using novel chiral *N*-arenesulfonyl-1,2-diphenylethylenediamine ligands.

Chiral α-hydroxy esters are important pharmaceutical intermediates and can be obtained through bioreduction or catalytic hydrogenation of the corresponding ketones.[1] Few literature examples of their preparation involving asymmetric transfer hydrogenation have been described.[2]

Asymmetric transfer hydrogenation using chiral Ru(II)-complexes with nitrogen-based chiral ligands proved to be a powerful method for the preparation of optically active α-arylated and α,β-acetylenic alcohols.[3] Such technology uses stable organic molecules such as 2-propanol or the formic acid–triethylamine azeotrope as hydrogen source. Amongst the various types of chiral nitrogen-based ligands, *N*-sulfonyl 1,2-diphenylethylenediamines (RSO_2-DPENs) with R = Ar,[4–8] R_F,[9] or R'_2N[10] in combination with Ru(II)Cl(η^6-arene) exhibit high enantiofacial discrimination ability. As proposed by Noyori and co-workers, the reduction takes place via a pericyclic mechanism involving an Ru hydride.[11] The RSO_2 functionality in the DPEN series is crucial in the reduction affecting the nucleophilicity of the neighbouring nitrogen and of the NH_2 in the Ru complex.

We disclose herein the preparation of a novel series of chiral $ArSO_2$-DPEN ligands and their use in the Ru(II)-catalysed transfer hydrogenation of a series of α-keto esters and α,α,α-trifluoromethyl ketones.

Chiral Ru(II)-complexes were prepared in situ at 80 °C in DMF[10] by reacting $[RuCl_2(p\text{-cymene})]_2$ with (1*S*,2*S*)-*N*-$ArSO_2$-DPEN ligands **1a**–**f**, which were prepared in turn in DCM from the corresponding arenesulfonyl chloride and (1*S*,2*S*)-DPEN followed by chromatographic purification. These catalysts were used to reduce a variety of activated ketones[12] at room temperature using the formic acid–triethylamine azeotrope (Fig. 1, Table 1).

Methyl mandelate was obtained within 4 h in up to 96% ee using 0.5 mol % of the Ru-precursor and ligand **1e** or **1f** compared to 59% ee using Ts-DPEN. Similar results were obtained for ethyl mandelate. Whether in the presence of a Ru/ligand ratio of 1:1 or 2:1, complex of **1f** led to equivalent results. Ethyl 4′-fluoromandelate was

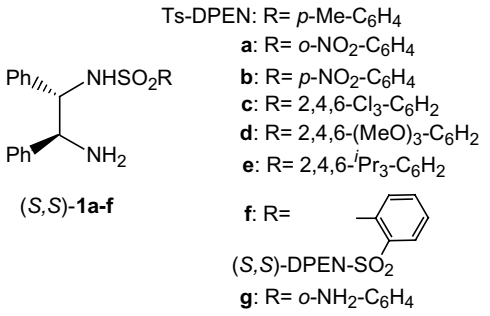

Figure 1. Novel series of (1*S*,2*S*)-*N*-arenesulfonyl-1,2-diphenylethylenediamine ligands based on Ts-DPEN.

Keywords: Asymmetric catalysis; Ketones; Ligands; Ruthenium; Transfer hydrogenation.
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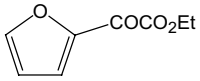
doi:10.1016/j.tetlet.2003.10.201

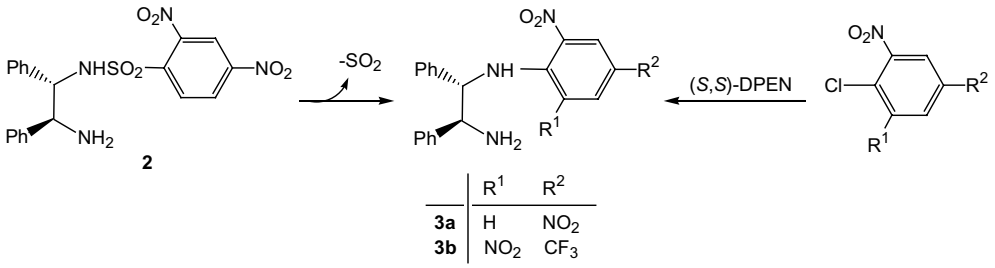
Table 1. Asymmetric transfer hydrogenation of ketones[a]

Ketone	Ligand	Substrate/catalyst ratio	Time (h)	Conversion (%)[b]	Ee (%)[b]
$C_6H_5COCO_2Me$	Ts-DPEN	200	4	100	59
	1a	200	4	90	85
	1b	200	4	100	71
	1c	200	4	100	93
	1d	200	4	100	76
	1e or **1f**	200	4	100	96
p-F-$C_6H_5COCO_2Et$	Ts-DPEN	200	4	100	28
	1b	200	8	100	27
	1c or **1f**	200	4	100	77
	1d	200	8	100	70
	1e	200	4	100	84
p-MeO-$C_6H_5COCO_2Et$	Ts-DPEN	200	24	34	73
	1b	200	24	44	75
	1c	200	24	58	95
	Ts-DPEN	40	36	100	82
	1b or **1e**	40	36	100	84
	1c or **1f**	40	36	100	94
	1d	40	36	100	87
$C_6H_5(CH_2)_2COCO_2Et$	Ts-DPEN	40	24	100	80
	1b	40	24	100	76
	1c	40	24	100	68
	1e or **1f**	40	24	100	74
CH_3COCO_2Et	Ts-DPEN	40	24	100	86
	1b	40	24	100	86
	1c or **1e**	40	24	100	78
	1d	40	24	85	74
	1f	40	24	100	83
$(CH_3)_2CHCOCO_2Et$[c]	Ts-DPEN	200	24	100	9
	1c	200	24	100	20
	1f	200	24	100	44
$MeO_2C(CH_2)_2COCO_2Me$	Ts-DPEN	200	4	100	65
	1b	200	4	100	63
	1c or **1f**	200	4	100	60
	1d	200	4	50	65
	1e	200	4	100	58
$C_6H_5COCF_3$	Ts-DPEN	100	24	100	42
	1a	100	24	100	42
	1c or **1f**	100	24	100	25
$C_6H_5CH_2COCF_3$	Ts-DPEN	100	1	100	95
	1b or **1c**	100	1	100	96
	1d or **1e**	100	1	100	97
	1f	100	1	100	98

[a] Reactions were carried out with HCO_2H/Et_3N 5:2 in DMF at 25 °C.
[b] Determined by GC analysis using Chirasil-DEX CB (25 m) unless otherwise stated.
[c] % Conversion and % ee determined by GC analysis using Chirasil-L-Val (25 m).

obtained in up to 84% ee using **1e** compared to 28% ee using Ts-DPEN. With an electron-donating group on the aromatic ring, the reduction was slower and ethyl 4′-methoxymandelate was obtained in 95% ee using **1c** compared to 73% ee using Ts-DPEN. The reduction of ethyl 2-furoylformate was sluggish requiring 2.5 mol% of Ru catalyst and led, after 36 h, to the corresponding α-hydroxyester in up to 94% ee using **1c** or **1f** compared to 82% ee employing Ts-DPEN. An ACE inhibitor intermediate, ethyl 2-hydroxy-4-phenylbutanoate, was obtained in up to 76% ee compared to 80% ee using Ts-DPEN. The same enantioselectivity (86% ee) was obtained for ethyl lactate using **1b** or Ts-DPEN. However, up to 44% ee was obtained in the reduction of ethyl ketovalinate using **1f** compared to 9% ee using Ts-DPEN. Moderate enantioselectivity (65% ee) was obtained in the reduction of dimethyl 2-oxoglutarate using **1d** or Ts-DPEN.

In the reduction of other activated ketones such as 2,2,2-trifluoroacetophenone, up to 42% ee was attained with **1a** or Ts-DPEN after 24 h. By contrast, the reduction of 1,1,1-trifluoro-3-phenyl-2-propanone took place within 1 h and led to 98% ee using **1f**.



Scheme 1. Synthesis of (1*S*,2*S*)-*N*-aryl-1,2-diphenylethylenediamine ligands.

Attempting to prepare *N*-(2,4-dinitrophenylsulfonyl)-DPEN ligand **2** following the standard procedure resulted, during purification, in the formation of *N*-(2,4-dinitrophenyl)-DPEN **3a** (Scheme 1).[13] No activity was observed for the corresponding Ru-complex under the standard conditions in the reduction of methyl benzoylformate as well as using the complex derived from *N*-(2,6-dinitro-4-trifluoromethylphenyl)-DPEN **3b**, which was prepared subsequently.

In addition, no reduction of methyl benzoylformate occurred using the *N*-(*o*-aminophenylsulfonyl)-DPEN ligand **1g** prepared by hydrogenation of the corresponding *N*-(*o*-nitrophenylsulfonyl)-DPEN ligand **1a**.

In summary, novel chiral *N*-arenesulfonyl-1,2-diphenylethylenediamine ligands were prepared and excellent enantioselectivities were obtained in the Ru(II)-catalysed transfer hydrogenation of α-keto esters and α,α,α-trifluoromethyl ketones. Enhanced enantioselectivity was reached by switching the tosyl group of Noyori's Ts-DPEN ligand with other arenesulfonyl groups and, in general, hindered ligands such as **1f** performed better.

Acknowledgements

We thank the Ministry of Education, Science and Technology of Slovenia for research grant Z1-3374-0104.

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13. Proven by ^1H NMR spectroscopy before and after purification and also by its independent preparation using 1-chloro-2,4-dinitrobenzene; (1*S*,2*S*)-*N*-(2,4-dinitrophenyl sulfonyl)-1,2-diphenylethylenediamine (**2**): ^1H NMR δ 4.40 (d, 1H, C*H*NH_2; *J* 3.2 Hz), 4.76 (d, 1H, C*H*NH; *J* 3.2 Hz), 6.98–7.42 (m, 10H, 2×Ph), 7.64 (d, 1H, H-3; *J* 8.6 Hz), 8.08 (dd, 1H, H-5; *J* 8.6, 2.1 Hz), 8.45 (d, 1H, H-6; *J* 2.1 Hz).