Synthesis and asymmetric hydrogenation of (3*E*)-1-benzyl-3-[(2-oxopyridin-1(2*H*)-yl)methylidene]piperidine-2,6-dione

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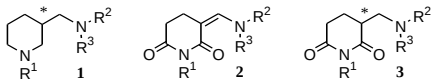
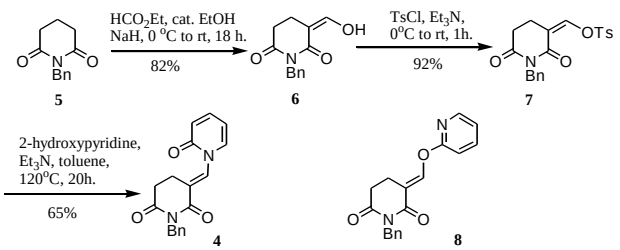
The synthesis of (3*E*)-1-benzyl-3-[(2-oxopyridin-1(2*H*)-yl)methylidene]piperidine-2,6-dione 4 from N-benzylglutarimide was achieved in three steps. The asymmetric hydrogenation of 4 gave either the product of partial reduction (10) or full reduction (13), depending on the catalyst which was employed, in high ee in each case. Attempts at asymmetric transfer hydrogenation (ATH) of 4 resulted in formation of a racemic product.

Chiral diamines of general structure **1** have valuable biological properties and represent useful synthetic building blocks.[1] Alkenes of type **2**, containing a (1-aminomethylene) function at the 3 position of a six-membered imide, are potential precursors to structure **1**, via reduction to **3**. In this paper we report the synthesis and reduction of a derivative of **2**, including studies of its asymmetric reduction.



We found that **4** could be prepared via the sequence shown in Scheme 1.[2,3] Starting with N-benzylglutarimide **5**, addition of a hydroxymethylene group was achieved through the use of sodium hydride followed by ethyl formate to form **6**.[2] Tosylation of **6** to give **7** was completed using TsCl and triethylamine.[2]

Scheme 1. Synthesis of (3*E*)-1-benzyl-3-[(2-oxopyridin-1(2*H*)-yl)methylidene]piperidine-2,6-dione **4**.



The reaction of **7** with 2-hydroxypyridine at reflux in toluene led to a substitution to form **4**, together with a quantity of the O-linked by-product **8**. However it was found that **8** isomerised to **4** upon extended heating, and that **4** could be formed in higher yields using longer reaction times. In one example, after 10h **4** and **8** were formed in isolated yields of 32% and 12% respectively, however by running the same reaction for 20h under reflux, **4** was formed exclusively in 62 % yield.[2f,g,4] Both **4** and **8** , which had formed as single diastereoisomers, were fully characterised and their structures were confirmed by X-ray crystallography (Figures 1 and 2 respectively) confirming an E-geometry of the double bond in each case. This geometry may be favoured in order to minimize unfavourable steric interactions. The geometries of **6** and **7** are not known however both are formed as single diastereoisomers, in the former case due to stabilization by an internal hydrogen bond.

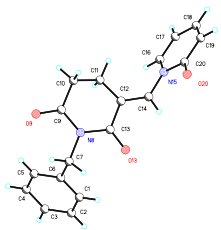


Figure 1. X-ray crystallographic structure of **4**.

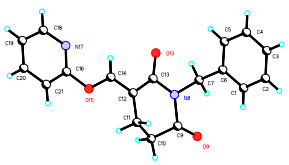


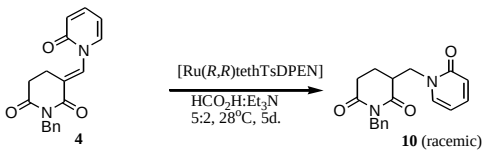
Figure 2. X-ray crystallographic structures of **8**.

The reduction of **4** using transfer hydrogenation was investigated, using Ru/arene complexes **9a/b**, together with formic acid/triethylamine (FA/TEA) as the hydrogen source.[5] Although these catalysts have been most commonly applied to C=O and C=N reduction, some examples have been reported of asymmetric C=C reduction.[6] The racemic catalyst **9a** successfully reduced **4** to 1-benzyl-3-[(2-oxopyridin-1(2*H*)-yl)methyl]-piperidine-2,6-dione **10** with full chemoselectivity for the C=C bond over any of the C=O bonds. Racemic **10** was additionally prepared by Pd/C reduction of **4** (1 atm, rt, 30 min.). The reduction was also successful using 3 mol% of homochiral catalyst **9b** in a range of solvents (Table 1).[5] However the product was racemic (determined by HPLC analysis of **10**), indicating a mechanism in which conjugate reduction of the C=C bond (possibly assisted by protonation of the imide C=O) initially leads to formation of enamine **11**, which subsequently protonates non-enantioselectively at the 3-position. An alternative explanation is that an initial product of high ee may be racemised under the reaction conditions. This possibility was eliminated in a separate experiment, in which a sample of enantiomerically-enriched **10**

(vide infra, 95% ee) did not exhibit significant racemisation after stirring in FA/TEA/methanol at rt for 5 days.

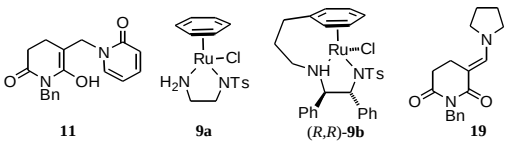
Better results were achieved in asymmetric hydrogenation reactions of substrate **4**.[7,8] Initial studies using [Rh((*R*,*R*)-EtDuPHOS)COD]BF_4 **12** led to full reduction in over 90% ee, predominantly to **10** although over-reduction to 1-benzyl-3-[(2-oxopiperidin-1-yl)methyl]piperidine-2,6-dione **13** was observed in some cases (Table 2). The highest ee of 94.5% was recorded under conditions where some 11% over-reduction to **13** was observed. A product of 90% ee was obtained in a case where no over-reduction was seen. The method for the determination of the absolute configuration is described later in this paper.

Table 1 Reduction of **4** by Ru(II)-catalysed transfer hydrogenation.[a]



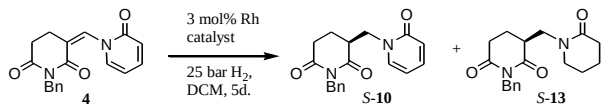
Entry	Cat /mol%	solvent	T	Conv./Yield [b]
1	**9a** 2 mol%	EtOH	28 °C	>99% conv. 89% yield.
2	(*R*,*R*)-**9b** 2 mol%	MeOH	rt	>99% conv.
3	(*S*,*S*)-**9b** 3mol%	EtOH	rt	>99% conv. 81% yield.
4	(*S*,*S*)-**9b** 3mol%	tBuOH	30 °C	>99% conv.
5	(*S*,*S*)-**9b** 3mol%	iPrOH	30 °C	>99% conv.
6	(*R*,*R*)-**9b** 3mol%	EtOH	rt	>99% conv.

[a] [S] = 0.06 M, [b] Product was not isolated in all cases.



11 **9a** (*R*,*R*)-**9b** **19**

Table 2 Asymmetric hydrogenation of**4** using Rh(I) complexes.



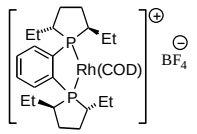
Entry	Catalyst	T	Conv./ ratio **10:13**	Ee/% **10/13** (*R/S*)
1	[Rh((*R*,*R*)-EtDuPHOS) COD]BF_4 **12**	30 °C	100% conv. 89:11	94.5 (*S*)[a] (**10**)
2	[Rh((*R*,*R*)-EtDuPHOS) COD]BF_4 **12**	rt	100% conv. 100:0 96% yield.	90 (*S*)[b] (**10**)
3	$[Rh(COD)Cl]_2$/SL-J001-1 Josiphos **14**	rt	42% conv. 42:0	76 (*R*)[b] (**10**)
4	$[Rh(COD)Cl]_2$/SL-J003-1 Josiphos **15**	rt	56% conv. 56:0	87 (*S*)[b] (**10**)
5	$[Rh(COD)Cl]_2$/SL-M001-1 Mandyphos **16**	rt	100% conv. 40:60	17 (*R*)[a] (**13**)
6	$[Rh(COD)Cl]_2$/SL-TOO2-1 Taniaphos **17**	rt	100% conv. 0:100	98 (*R*)[c] (**13**)
7	$[Rh(COD)Cl]_2$/SL-W001-1 Walphos **18**	rt	47% conv. 27:20	13 (*R*)[a] (**13**)

[a] Indirect determination of ee of **10** *via* Pd/C reduction of mixture to **13**. [b] Direct ee determination of **10**. [c] Direct ee determination of **13**.

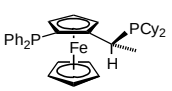
The use of dichloromethane (DCM) as solvent was compatible with the formation of **10**; an attempt to perform hydrogenations in methanol resulted in over-reduction to **13**.

A series of ligands, **14-18**, supplied by Solvias, were evaluated in complexes formed upon their in situ combination with $[Rh(COD)Cl]_2$. These gave varying degrees of reduction to **10** and **13.** In the case of Taniaphos **17**, a very high ee of 98% was recorded for the fully reduced product **13**, the sole product. The ee of **13** was determined by chiral HPLC, against an authentic racemic sample prepared by direct hydrogenation of **4** to **13** using Pd/C as a catalyst (5 atm, rt, 12h). Compound **10** could also be hydrogenated to **13** using Pd/C as catalyst, and this method was used in cases where inseparable mixtures of **4** and **10** were formed, in order to obtain an indirect measure of the ee of **10.**

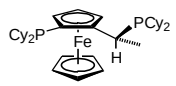
The pyrrolidine-substituted product **19** was formed from tosylate **7** in 35% yield Attempts to reduce the double bond in **19** using Rh/phosphine catalysts were unsuccessful, indicating that the heterocyclic group in **4** performs an important directing role in the reaction, analogous to the directing effect of the acylamino function in α-acylamino acrylate precursors of α-amino acids.[7-9] However the electron-donating nature of the pyrrolidine may also have an influence on the reactivity of this derivative.



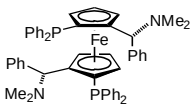
12 [Rh((*R*,*R*)-EtDuPHOS) COD]BF_4.



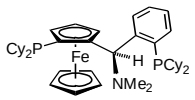
14 Josiphos SL-J001-1



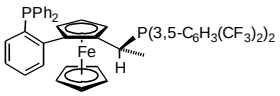
15 Josiphos SL-J003-1



16 Mandyphos SL-M001-1

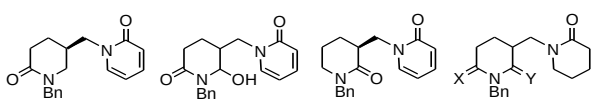


17 Taniaphos SL-T002-1



18 Walphos SL-W001-1

Confirming the absolute configuration of **10** (and **13**) was achieved by reduction of a sample of **10** prepared using the DuPHOS catalyst **12** (Table 2, entry 2, 90% ee) to known amide **20**[4] *via* intermediate **21** in ca. 3:1 regioselectivity over its regioisomer **22**.[10] Comparison of the optical rotation of our sample of **20** to that reported[4] allowed its configuration to be assigned as *R*. Hence the precursor imide of this sample, **10**, was of *S* configuration. This sequence was accompanied by partial racemisation, confirmed by reduction of our sample of **20** to the saturated compound **23** which was shown to be of 20% ee by chiral HPLC. A standard of racemic **23** was prepared by reducing racemic **13** through the same sequence as for **10**; 28% of the required regioisomer **23** was obtained, along with 20% of the minor isomer **24**.



20 (20% ee) **21** **22** **23** (X=O, Y-H,H) **24** (X=H.H, Y=O)

In conclusion, we have developed a concise route to either racemic or enantiomerically-enriched N-benzyl-(3-aminomethyl glutarimide) derivatives starting from N-benzylglutarimide using a selective condensation/reduction strategy.

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Notes and references

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