

Asymmetric Homogeneous Hydrogenation of 2,5-Disubstituted Furans

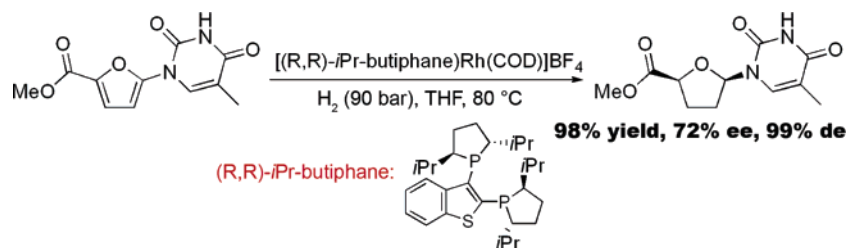
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ABSTRACT



A homogeneous catalyst system for the asymmetric *cis*-hydrogenation of 2,5-disubstituted furans leading to 2',3'-dideoxynucleoside analogues is described. Best enantioselectivities (ee values of up to 72%) were obtained with cationic rhodium complexes ligated by diphospholanes of the *butiphane* family. The selectivity of the hydrogenation was reversed by the addition of a base or a polar protic solvent in certain cases. Ferrocene- and proline-based systems gave significant, but lower, ee values.

For olefins with suitable substitution patterns, such as enolacetates, enamides, allylic alcohols, or enones, a plethora of powerful catalysts, which allow for an enantioselective hydrogenation, have been developed.¹ Though the asymmetric reduction of alkenes devoid of such a directing polar anchor group is more demanding, some efficient catalytic systems have been described in the literature.² In contrast,

the stereoselective reduction of asymmetrically substituted aromatic rings still represents a particular challenge, which is reflected by the small number of successful reports. Although the hydrogenation of aromatic compounds is considered to be rather a domain of heterogeneous catalysis, enantiodifferentiation upon reduction of appropriately substituted (hetero)arenes is more often achieved using structurally diverse homogeneous catalysts. Cinchona-modified heterogeneous Pt or Pd catalysts³ have been used for the reduction of ethyl nipecotinate,⁴ a series of 2-pyrans,⁵ and furan carboxylic acids⁶ with varying ee values. Recently, an efficient diastereoselective hydrogenation of chiral oxazo-

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lidinone-substituted pyridines with Pd(OH)₂/C as catalyst has been reported.⁷

A ferrocene-based homogeneous diphosphinerhodium complex was applied by Fuchs for the reduction of a 2-substituted pyrazine derivative yielding the corresponding piperazine with enantiomeric purities up to 78%.⁸ Studer et al. employed Rh(nbd)₂BF₄/(*S,S*)-DIOP for the reduction of a series of pyridines and furans with enantioselectivities up to 27%.⁹ 2-Methylquinoxaline was reduced to (–)-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline with ee's up to 90% by Bianchini and his group using an ortho-metalated dihydride Ir complex (*fac-exo*-(*R*)-[IrH₂{C₆H₄C*(H)(Me)N(CH₂CH₂PPh₂)₂}).¹⁰ Kuwano and co-workers reported on the efficient reduction of *N*-protected indoles catalyzed by [Rh(nbd)₂]SbF₆/(*S,S*)-(*R,R*)-PhTRAP¹¹ with very good enantioselectivities.¹² Substituted-quinolines were hydrogenated by [Ir(cod)Cl]₂ with (*R*)-MeO-Biphep¹³ or with (*R*)-P-PHOS as ligand with good to excellent ee values.¹⁴

Recently, we published a new diastereoselective route to 2',3'-dideoxynucleoside analogues¹⁵ from 2-substituted furans.¹⁶ In this short reaction sequence (Figure 1), planar, prochiral

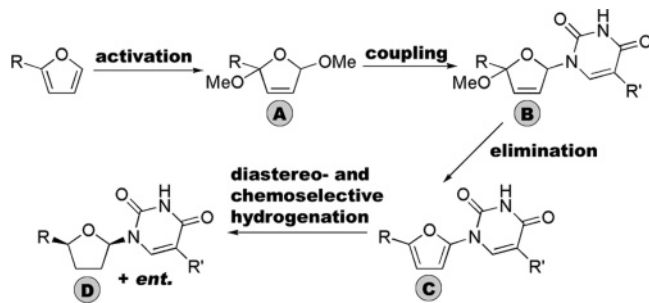


Figure 1. Reaction sequence for the synthesis of 2',3'-dideoxynucleosides.

furylnucleosides (C) served as key intermediates, which were subsequently transformed into the target compounds by a chemo- and diastereoselective heterogeneous hydrogenation using Pd/C or Rh/Al₂O₃ as catalysts. The required β -configuration is thereby established, and only two out of four possible diastereoisomers are formed. Since the separation of the enantiomers (the β -D- and β -L-nucleoside) is not a

trivial task, an enantioselective hydrogenation of the furan ring is highly desirable. In this paper, we want to communicate our results for the asymmetric hydrogenation of a selected furan derivative, leading to enantiomerically enriched 2',3'-dideoxynucleosides.

Furan **1**¹⁶ (Table 1) appeared to be a promising substrate for an asymmetric homogeneous hydrogenation for the

Table 1. Asymmetric Hydrogenation of **1** with Chiral Rh and Ru Catalysts

	catalyst (equiv)	conditions ^a	yield ^{b,c} / ee ^d (%)
1	[Rh(nbd) ₂]BF ₄ / 6 ^e (0.3)	THF/MeOH, H ₂ (80 bar), 80 °C	<5/0
2	[Rh(nbd)Cl] ₂ / 7 ^e (0.3)	THF, H ₂ (50 bar), rt	75/0
3	[Rh(nbd)Cl] ₂ / 7 ^e (0.3)	THF, Et ₃ N (0.1 equiv), H ₂ (50 bar), rt	73/10 (β -L- 2)
4	[Rh(nbd)(8)]ClO ₄ (0.3)	THF, H ₂ (50 bar), rt	65/0
5	[Ru(<i>p</i> -cymene)Cl ₂] ₂ / 9 ^e (0.2)	THF, H ₂ (50 bar), rt	56/0
6	[Ru(<i>p</i> -cymene)Cl ₂] ₂ / 9 ^e (0.2)	THF, Et ₃ N (0.1 equiv), H ₂ (50 bar), rt	77/26 (β -L- 2)
7	[Rh(cod)(10)]BF ₄ (0.2)	THF, H ₂ (80 bar), 80 °C	10/0
8	[Rh(cod)(10)]BF ₄ (0.2)	THF, Et ₃ N (0.1 equiv), H ₂ (80 bar), 80 °C	10/0
9	[Rh(cod)(11)]BF ₄ (0.3)	THF, H ₂ (80 bar), 80 °C	68/23 (β -D- 2)
10	[Rh(cod)(11)]BF ₄ (0.3)	MeOH, H ₂ (80 bar), 80 °C	10/23 (β -L- 2)
11	[Rh(cod)(11)]BF ₄ (0.1)	THF, H ₂ (80 bar), 80 °C	60/32 (β -D- 2)
12	[Rh(cod)(12)]BF ₄ (0.1)	THF, H ₂ (80 bar), 80 °C	98/72 (β -D- 2)
13	[Rh(cod)(12)]BF ₄ (0.2)	THF, NEt ₃ (0.2 equiv), H ₂ (80 bar), 80 °C	30/49 (β -L- 2)
14	[Rh(cod)(12)]BF ₄ (0.1)	THF, Cs ₂ CO ₃ (0.25 equiv), H ₂ (80 bar), 80 °C	10/29 (β -L- 2)
15	[Rh(cod)(12)]BF ₄ (0.01)	THF, H ₂ (80 bar), 80 °C	67/58 (β -D- 2)

^a Reaction time 22–24 h. ^b Isolated yield of **2**. ^c Compound **3** was detected in each run in low amounts. ^d Determined by HPLC. ^e Prepared in situ. ^f Compound **4** was detected as a side product.

following reasons: (i) furan as an electron-rich heterocycle with low aromatic character is reduced under mild conditions and (ii) the presence of anchor groups (methyl carboxylate

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and/or thymine) in the substrate might enable a precoordination with the catalyst, which should enhance the selectivity. The fully hydrogenated tetrahydrofuran derivative **5**, the selectively base-hydrogenated furan **4**, and nucleobase **3** formed upon hydrogenolytic C–N bond cleavage were expected as possible byproducts in the hydrogenation of **1**.

Table 1 summarizes our results obtained for the asymmetric hydrogenation of furan **1**. Emphasis in this catalyst screening study was put on commercially available ligands and recently published diphosphines. Depending on catalyst precursor, additives, solvent, and reaction conditions, marked differences within the individual systems have been observed. In this paper, only systems leading to hydrogenated products are disclosed. The yield always refers to isolated product **2**.

The amount and distribution of side products thymine (**3**) and **4**¹⁷ (Figure 2) was not accurately determined for each

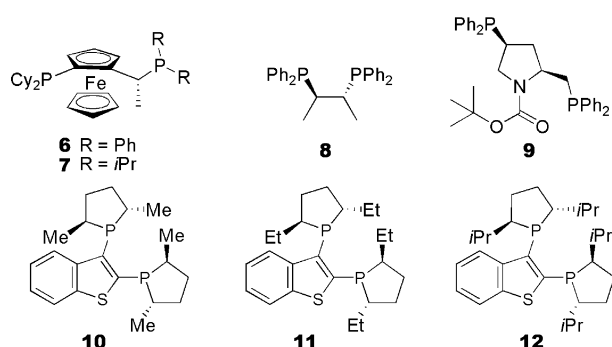


Figure 2. Ligands **6**–**12**.

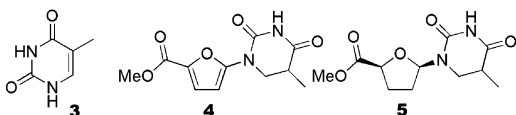
run. Surprisingly, the fully hydrogenated tetrahydrofuran **5**¹⁷ was not detected under conditions described in this paper. Products arising from trans-hydrogenations (de values >99%) were not observed in any of these experiments.

The reactivity of the cationic catalyst generated in situ from $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ and the bulky electron-rich ligand of the *Josiphos* family (*R*)-(*S*)-**6**¹⁸ was significantly lower than the one of the neutral Rh catalyst with the structurally similar ligand (*R*)-(*S*)-**7**.¹⁹ The latter afforded the desired product in good yields (73–75%, entries 1–3). The addition of a base

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(NEt_3) led to some enantioselectivity (10% ee; entry 3). The selectivity-enhancing effect of an admixed base has already been observed by Kuwano and co-workers, but to a much larger extent.¹² As expected, by using the mirror-imaged ligand (*S*)-(*R*)-**7** the β -D-nucleoside (65% yield, 8% ee) predominated.

The catalyst $[\text{Rh}(\text{nbd})(\mathbf{8})]\text{ClO}_4$ was unselective regarding enantiocontrol but exhibited a good reactivity (entry 4). *L*-Hydroxyproline-derived ligand **9**²⁰ with $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ provided racemic tetrahydrofuran **2** in 56% yield (entry 5). Again, addition of a base (0.1 equiv of NEt_3 , entry 6) significantly enhanced both yield and ee (77% and 26%, respectively). The benzothiophene-based catalyst $[\text{Rh}(\text{cod})((\text{R},\text{R})\text{-}\mathbf{10})]\text{BF}_4$ ²¹ performed rather disappointingly, giving **2** in only 10% yield without any detectable selectivity (entry 7). The addition of base only influenced the chemoselectivity of the hydrogenation, yielding side product **4** to a larger extent.

However, the increase of the steric bulk in the ligand sphere by switching from bis(dimethylphospholane) (*R,R*)-**10** to the bis(diethylphospholane) derivative (*S,S*)-**11**²¹ improved not only the activity but also the selectivity of the catalyst (68% yield and 23% ee (β -D-**2**), entry 9). MeOH instead of THF as solvent *reversed* the enantioselectivity of the hydrogenation. Though in low yield, β -L-**2** was preferentially obtained (23% ee; entry 10). A lower catalyst loading (from 0.3 to 0.1 equiv) led to a slightly decreased yield but increased the ee (32%; entry 11). By further increasing the steric demands of the catalyst, yields and enantioselectivities could be improved. Addition of 0.1 equiv of *butiphane*-type catalyst $[\text{Rh}(\text{cod})((\text{R},\text{R})\text{-}\mathbf{12})]\text{BF}_4$ ²¹ allowed for the reduction of **1** in 98% yield together with 72% enantiomeric purity (entry 12). The addition of a base (NEt_3 or Cs_2CO_3) reversed the stereoselectivity of the hydrogenation (entries 13 and 14), yielding predominantly β -L-**2** with 49% and 29% ee, respectively. The performance of $[\text{Rh}(\text{cod})((\text{R},\text{R})\text{-}\mathbf{12})]\text{BF}_4$ at a catalyst loading of 1% still gave β -D-**2** with 67% yield and 58% ee.

In the present paper, one of the highest enantioselectivities for a homogeneous hydrogenation of a furan derivative is reported.

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Supporting Information Available: Experimental procedures and selected spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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