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Asymmetric synthesis of benzofuryl β-amino alcohols by the transfer hydrogenation of α-functionalized ketones

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ABSTRACT

The asymmetric transfer hydrogenation of representative benzofuryl α-sulfonyloxy ketones and *N*-protected α-amino ketones with an azeotropic mixture of formic acid/triethylamine, catalyzed by RhCl[(*R*,*R*)-TsDPEN](C_5Me_5), afforded the corresponding 1,2-diol monosulfonates and *N*-substituted β-amino alcohols in high yields and with enantioselectivities up to 99%. Transformation of the reduction products to the chiral benzofuryl β-amino alcohols possessing a primary amine group is also described.

1. Introduction

Chiral amino alcohols represent useful structures in organic and medicinal chemistry. β-Amino alcohols are found in the structural units of many building blocks, chiral auxiliaries, and ligands.[1–5] Moreover, optically active β-amino alcohols containing heteroaryl moieties are of great importance as a key intermediates for the synthesis of physiologically active compounds.[6,7] Benzofuran is considered as an important structure due to its diverse biological profile.[8] There have been many reports on the synthesis of benzofuran derivatives because of their clinical importance.[9,10] For example, bufuralol (2-*tert*-butylamino-1-(7-ethylbenzofuran-2-yl)ethanol) is a potent non-selective β-adrenergic receptor antagonist of comparable potency to propranolol, an inhibitor of testosterone 6β-hydroxylase, and commonly used marker of hepatic CYP 2D6 activity.[11–15] 1-(3-Phenethylbenzofuran-2-yl)-2-propylaminoethanol, a propafenone analogue, shows antiarrhythmic activity with a lack of β-adrenoacceptor blocking activity.[16]

Various syntheses of enantiomerically pure β-amino alcohols including: the aminohydroxylation of olefins,[17] the reductive-amination of α-halo ketones,[5,18] the enzymatic resolution of racemic β-amino alcohols,[19] catalytic reduction of α-amino ketones,[20–24] and many others have been developed.[25–27] An attractive method for β-amino alcohol synthesis is the asymmetric transfer hydrogenation of α-functionalized ketones.[28–31] Asymmetric transfer hydrogenation (ATH) is established as an excellent reduction method due to its versatility, operational simplicity, avoidance of explosive hydrogen gas, catalyst robustness, and high stereoselectivity.[32–35]

In our previous asymmetric syntheses of benzofuryl β-amino alcohols, the transfer hydrogenation of α-halo ketones,[36] α-imino ketones,[37] and α-dialkylamino ketones[38] was a key step. Hereby, the corresponding β-amino alcohols possessing secondary and tertiary amine groups were obtained.

In continuation of our earlier efforts toward the preparation of chiral benzofuryl β-amino alcohols, we herein report the asymmetric transfer hydrogenation of α-sulfonyloxy, *N*-Cbz protected α-amino ketones, α-succinimido, and α-phthalimido ketones, and further transformations to afford β-amino alcohols with primary and secondary amine groups.

2. Results and discussion

2.1. Asymmetric transfer hydrogenation of benzofuryl α-sulfonyloxy ketones

The α-sulfonyloxy benzofuryl ketones **1**–**4** were readily prepared by sulfonyloxylation of the corresponding (benzofuran-2-yl)

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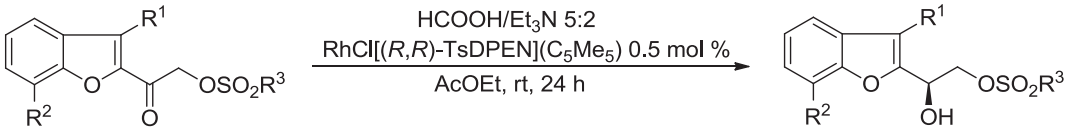
Table 1
Asymmetric transfer hydrogenation of benzofuryl α-sulfonyloxy ketones **1**–**4**.



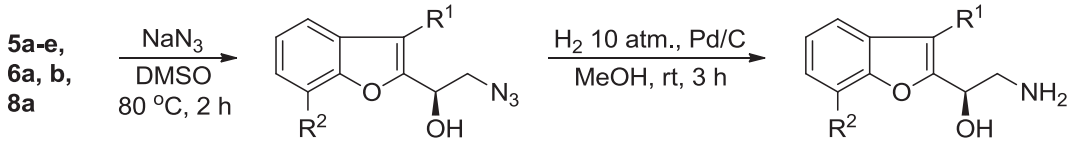
1-4 **5-8**

Ketone	R^1	R^2	R^3	Alcohol	Yield[a] (%)	ee[b] (%)
1a	H	H	4-Me-C_6H_4	**5a**	92	97
1b	H	Et	4-Me-C_6H_4	**5b**	93	90
1c	Me	H	4-Me-C_6H_4	**5c**	96	92
1d	Me	Me	4-Me-C_6H_4	**5d**	89	87
1e	$Ph(CH_2)_2$	H	4-Me-C_6H_4	**5e**	95	93
2a	H	H	4-Cl-C_6H_4	**6a**	84	98[c]
2b	H	Et	4-Cl-C_6H_4	**6b**	93	94[c]
2c	Me	H	4-Cl-C_6H_4	**6c**	96	90
3a	H	H	Ph	**7a**	99	97
3b	H	Et	Ph	**7b**	93	94
3c	Me	H	Ph	**7c**	93	92
4a	H	H	Me	**8a**	95	99
4b	H	Et	Me	**8b**	93	95
4c	Me	H	Me	**8c**	93	93
4e	$Ph(CH_2)_2$	H	Me	**8e**	96	93

[a] Isolated yield.
[b] Determined by HPLC analysis on a chiral column (Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm).
[c] Separation was not possible. Assignments based on the ee of β-azido alcohols **9** and **10**, respectively.

ethanones with [hydroxy(tosyloxy)iodo]benzene (PhI(OH)OTs),[39] [hydroxy(mesyloxy)iodo]benzene (PhI(OH)OMs),[40] [hydroxy(4-chloroben-zenesulfonyloxy)iodo]benzene (PhI(OH)OCs),[39] and [hydroxy(benzenesulfonyloxy)-iodo]benzene (PhI(OH)OSO_2Ph).[39] The α-sulfonyloxylation reactions were carried out in acetonitrile at reflux for 3 h,[41] and products were separated in moderate to good yields (45–79%). In general, the reaction products of ketones with PhI(OH)OCs were formed with lower yields than in other cases (see Experimental section). Moreover, in contrast to Lee and co-workers,[41] no problems with mesyloxylation and tosyloxylation of 1-(7-ethylbenzofuran-2-yl)ethanone were noticed; appropriate products were obtained in 57% and 76% yields, respectively. The transfer hydrogenation of **1**–**4** was carried out with the formic acid/triethylamine azeotrope (5:2), catalyzed by RhCl[(*R*,*R*)-TsDPEN](C_5Me_5), in ethyl acetate at room temperature. All 1,2-diol monosulfonates **5**–**8** were formed in very high yields (84–99%) and with enantioselectivities over 90% (Table 1). Only one product, 2-tosyloxy-1-(3,7-dimethylbenzofuran-2-yl)ethanol (**5d**), was obtained with lower ee, 87%. There was no significant influence of the sulfonyl group type on the yield and enantioselectivity of the reduction. 2-Sulfonyloxy-1-(benzofuran-2-yl)ethanols (**5**–**8**)**a** differing in the substituent of the sulfonyl group, were afforded with excellent ee, 97–99%. Derivatives of 3-methylbenzofuran (**5**–**8**)**c** were isolated with 90–93% ee, and 2-tosyloxy-1-(3-

Table 2
Asymmetric synthesis of benzofuryl β-amino alcohols.



9-13 **14-18**

No.	R^1	R^2	No.	Yield[a] (%)	ee (%)	No.	Yield[a] (%)
5a	H	H	**9**	84	97[b]	**14**	99
5b	H	Et	**10**	72	90[c]	**15**	97
5c	Me	H	**11**	62	92[c]	**16**	96
5d	Me	Me	**12**	53	87[b]	**17**	79
5e	$Ph(CH_2)_2$	H	**13**	50	93[b]	**18**	71
6a	H	H	**9**	77	98[b]	–[d]	–
6b	H	Et	**10**	88	94[c]	–[d]	–
8a	H	H	**9**	99	99[b]	–[d]	–

[a] Isolated yield.
[b] Determined by HPLC analysis on a chiral column (Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm).
[c] Determined by HPLC analysis on a chiral column (Daicel Chiralcel OJ, 250 × 4.6 mm, 10 μm).
[d] Not tested.