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Synthesis of enantiopure (*R*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoic acid—a key intermediate for the preparation of Aliskiren

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ABSTRACT

The enantioselective hydrogenation of (*E*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzylidene)-3-methylbutanoic acid (**1**) to (*R*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoic acid (**2**)—a key intermediate in the synthesis of the pharmacologically important renin inhibitor Aliskiren—is described. The stereochemistry of the catalytic transformation has been studied using a number of homogeneous chiral Rh(I) and Ru(II) complexes bearing ferrocene-based phosphine ligands. The highest enantioselectivity for the homogeneous hydrogenation of **1** (up to 95% ee) was achieved with a $[Rh(NBD)_2]BF_4$ pre-catalyst (substrate/catalyst ratio 100:1, 10 bar H_2, 40 °C, in MeOH). To bring the enantioselectivity to perfection an effective method for the isolation of the enantiopure carboxylic acid is suggested likewise.

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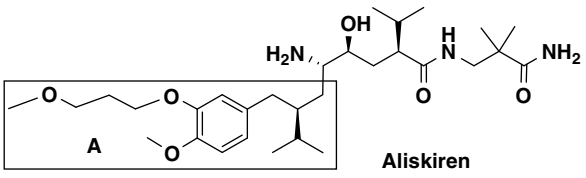
Aliskiren (trade-names Tekturna®, Rasilez®) represents the first drug on the market being constituent of a novel class of renin inhibitors with a huge potential for treatment of hypertension and related cardiovascular diseases.[1] Renin is an important enzyme at the beginning of the renin angiotensin system (RAS), one of the key regulators of blood pressure. Efficient renin inhibitors decrease the plasma renin activity and reduce the production of angiotensin I from angiotensinogen. In this view, Aliskiren is a highly efficient, nonpeptidic, orally administered drug. Currently, the development of more efficient and alternative methods for the synthesis of this compound is in the focus of several pharmaceutical companies. One of the key steps is the stereoselective generation of the enantiopure building block **A**.



In this connectivity, herein we describe our results for the production of enantiopure (*R*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoic acid (**2**) by asymmetric hydrogenation of (*E*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzylidene)-3-methylbutanoic acid (**1**) (Scheme 1). The chiral acid can be employed for the synthesis of Aliskiren. The hydrogenation was already investigated by some other research groups.[2,3] In best cases up to 95% ee at S/C ratios of >5000 were reported. However, the broad application of these protocols is hampered by the inaccessibility of some chiral ligands used. Moreover, the frequently faced problem how to proceed with hydrogenation products of low enantioselectivity is not clear.

In order to identify efficient hydrogenation conditions we screened the reaction in the presence of a set of rhodium and ruthenium catalysts bearing several commercially available chiral ferrocene-based phosphine ligands (**I**–**XII**). The results of the hydrogenation are summarized in Table 1. Most reactions were conducted by using a commercially available $[Rh(NBD)_2]BF_4$ complex as a precursor. It was mixed with 1.2 equiv of the chiral diphosphine prior to the hydrogenation.

The hydrogenation catalyzed by these Rh-catalysts proceeded smoothly at 40 °C in MeOH with an initial H_2-pressure of 10 bar. Remarkably, other Rh-precursors like $[RhI_2(p\text{-cymene})]_2$ or related Ru-complexes provided low ee (<42%). Moreover, catalysts were less active. The most efficient system for the production of optically pure (*R*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoic acid was noted in the reaction with a Rh-complex based on (*R*)-(*R*)-PPPhFCHCH$_3$P((3,5-CF$_3$)$_2$Ph)$_2$ (**I**) as chiral

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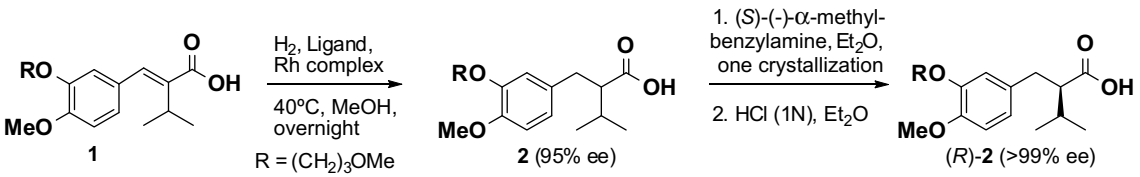
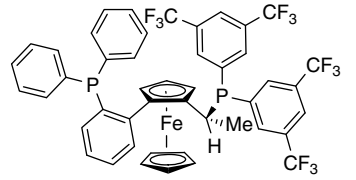
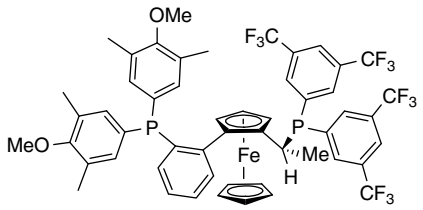


Scheme 1. Asymmetric hydrogenation and kinetic resolution.



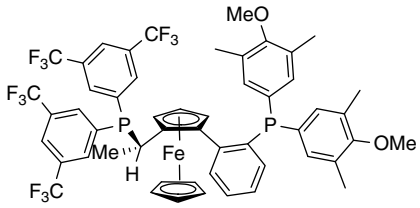
(*R*)-(*R*)-PPPhFCHCH$_3$P((3,5-CF$_3$)$_2$Ph)$_2$

I



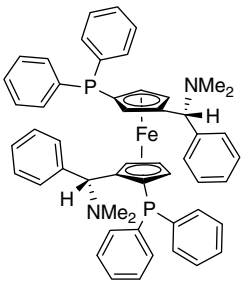
(*R*)-(*R*)-(3,5-Me-4-MeOPh)$_2$PPhFCHCH$_3$P(3,5-CF$_3$Ph)$_2$

II



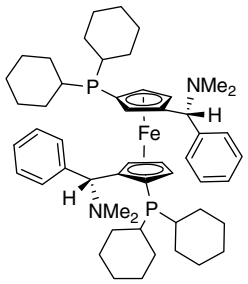
(*S*)-(*S*)-(3,5-Me-4-MeOPh)$_2$PPhFCHCH$_3$P-(3,5-CF$_3$Ph)$_2$

III



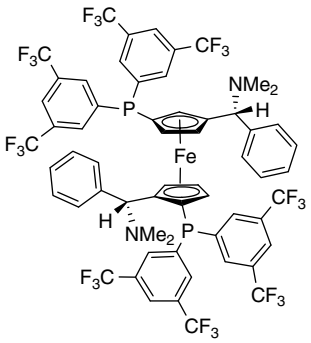
(*R*)-(*S*)-NMe$_2$-PPh$_2$-Mandyphos

IV



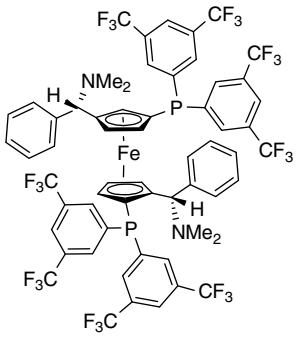
(*R*)-(*S*)-NMe$_2$-PCy$_2$-Mandyphos

V



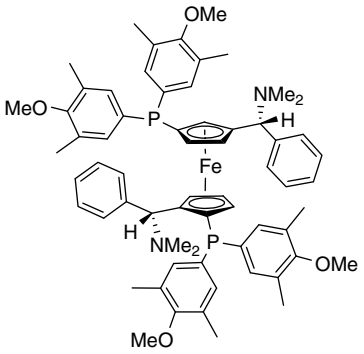
(*R*)-(S)-NMe$_2$-P(3,5-CF$_3$Ph)$_2$-Mandyphos

VI



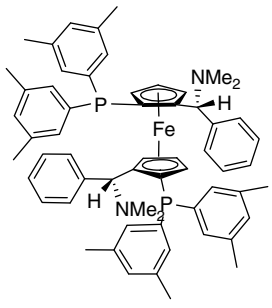
(*S*)-(*R*)-NMe$_2$-P(3,5-CF$_3$Ph)$_2$-Mandyphos

VII



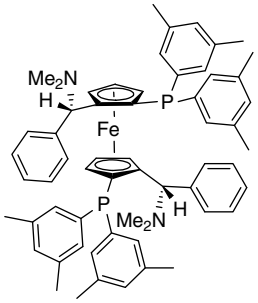
(*R*)-(*S*)-NMe$_2$-P(3,5-Me-4-MeOPh)$_2$-Mandyphos

VIII



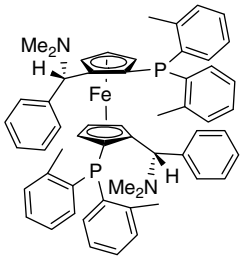
(*R*)-(*S*)-NMe$_2$-PXyl$_2$-Mandyphos

IX



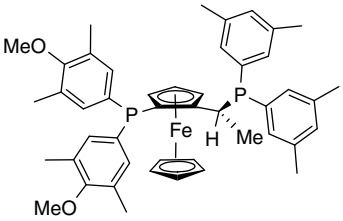
(*S*)-(*R*)-NMe$_2$-PXyl$_2$-Mandyphos

X



(*S*)-(*R*)-NMe$_2$-P(*o*-Tol)$_2$-Mandyphos

XI



(*R*)-(*S*)-(3,5-Me$_2$-4-MeOPh)$_2$PFPXyl$_2$

XII

Table 1
Asymmetric hydrogenation of (*E*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzylidene)-3-methylbutanoic acid according to Scheme 1

Ligand	Metal complex	Metal:ligand:substrate ratio	Pressure (bar)	Conc. (mol/l)	Conv.[a] (%)	ee[b] (%), Conf.
I	$[Rh(NBD)_2]BF_4$	1:1.2:25	10	0.1	100	91(*R*)
I	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	94(*R*)
I	$[Rh(NBD)_2]BF_4$	1:1.2:500	10	0.1	100	94(*R*)
I	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.2	100[c]	95(*R*)
I	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.5	100	90(*R*)
I	$[Rh(NBD)_2]BF_4$	1:1.2:500	10	0.2	72	77(*R*)
II	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	90(*R*)
III	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	94(*S*)
IV	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	66	27(*R*)
V	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	3(*R*)
VI	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	24	68(*R*)
VII	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	22	49(*S*)
VIII	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	69(*R*)
VIII	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.2	24	61(*R*)
IX	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	66(*R*)
X	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	65(*S*)
XI[c]	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	100	61(*R*)
XII	$[Rh(NBD)_2]BF_4$	1:1.2:100	10	0.1	24	8(*R*)
VIII	$[RhI_2(p\text{-cymene})]_2$	1:1.2:25	10	0.1	62	16(*S*)
VIII	$[RhI_2(p\text{-cymene})]_2$	1:1.2:25	50	0.1	100	42(*S*)

[a] Conversion was detected by ^1H NMR.
[b] Ratio of enantiomers was estimated by using HPLC.
[c] The reaction was completed within 1 h.

Table 2
Enantiomeric enrichment of acid **2**

ee of the crude hydrogenation product (%)	Times of recrystallization[a]	Yield after recrystallization (%)
95	1	90
90	2	75
70	3	38

[a] In order to achieve >99% ee.

ligand. At a preparative substrate/catalyst ratio of 100:1 an ee by up to 95% was achieved, and the reaction was complete within 1 h.[4]

In order to enhance the optical purity of the reaction product the crude hydrogenation product was recrystallized with (*S*)-(−)-α-methyl benzylamine as a base.[5] Already one crystallization is sufficient to provide the free carboxylic acid **2** with >99% ee (Table 2) after acidification of the salt derived from a hydrogenation product of 95% ee. Two crystallizations are required for a mixture of 90% ee of stereoisomers **2** in order to obtain perfect enantioselectivity, for a hydrogenation product of 60–70% ee three crystallizations were required.[6] The acidification reaction with hydrochloric acid proceeded fast, smoothly, and without prior purification of the salt.[7]

In conclusion a new protocol for the preparation of enantiomeric pure (*R*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoic acid was found based on the enantioselective Rh-catalyzed hydrogenation or/and the subsequent enantiomeric enrichment of a product with poor enantioselectivity.

Acknowledgments

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4. Under argon a 25 ml flask was charged with $[Rh(NBD)_2]BF_4$ (3.0 mg, 0.008 mmol), 4 ml of methanol, and (*R*)-(*R*)-$PPPhFCHCH_3P((3,5\text{-}CF_3)_2Ph)_2$ (8.96 mg, 0.0096 mmol). The resulting mixture was vigorously stirred for 30 min at room temperature and then was added to a solution of (*E*)-2-(4-methoxy-3-(3-methoxypropoxy)-benzylidene)-3-methylbutanoic acid. (246.7 mg, 0.8 mmol) in 4 ml of methanol. The reaction mixture was placed into a 12 ml autoclave equipped with a magnetic stirring bar. The autoclave was flushed 3 times with H_2 and pressurized to 10 bar. The reaction mixture was stirred at 40 °C for 1 h. After cooling to rt and releasing of the excess H_2, the solvent was evaporated and 2-(4-methoxy-3-(3-methoxypropoxy)-benzyl)-3-methylbutanoic acid (95% ee) was obtained.
5. A similar method was applied in a preparative scale for the purification of *R*-(−)-ibuprofen: Trung, T. Q.; Kim, J. M.; Kim, K. H. *Arch. Pharm. Res.* **2006**, *29*, 108–111.
6. To the solution of acid **2** (95% ee) (235 mg, 0.76 mmol) in 3 ml of diethyl ether was added at room temperature dropwise a solution of (*S*)-(−)-α-methyl benzylamine (96.3 mg, 0.8 mmol) in 2 ml of diethyl ether. The solution was cooled and allowed to stand in the fridge overnight. Crystals formed were filtered off and dried.
7. To the salt (100 mg, 0.23 mmol) in 4 ml of diethyl ether was added 1 N aqueous HCl, and the mixture was vigorously shaken. Then the organic layer was separated and three times extracted with diethyl ether. Combined organic extracts were dried with $MgSO_4$, filtered off, and evaporated.