Asymmetric synthesis of 4*H*-1,3-dioxins and investigations in the metal catalyzed aziridination: aziridination versus insertion and stereoselective course

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Dedicated to Prof. Alain Krief on his 65th birthday

Abstract

The asymmetric synthesis of highly enantiomerically enriched 5-methyl-4*H*-1,3-dioxins by DIOP- and DuPHOS-modified nickel complexes via double-bond isomerization and metal catalyzed nitrogen transfer reactions to the resulting dioxins are reported. While Rh catalysis in the reaction of dioxins with nitrenes generated from PhI=NTs afforded insertion products **5**, the Cu(I) catalyzed reactions led to 4-methyl-1,3-oxazolidine-4-carbaldehydes **4** in an aziridination-rearrangement process with diastereoselectivities up to 73% de. Enantiomerically pure aldehydes **4** were obtained by crystallization of the diastereomeric mixture from TBME. A method for the determination of the diastereomeric excess in the intermediate aziridination step is described, and the absolute configurations of the (*S*,*S*)- and (*R*,*R*)-isomer, respectively, were established by X-ray crystallography.

Keywords: Asymmetric catalysis, isomerization, dioxins, aziridination, rearrangement, oxazolidinecarbaldehydes

Introduction

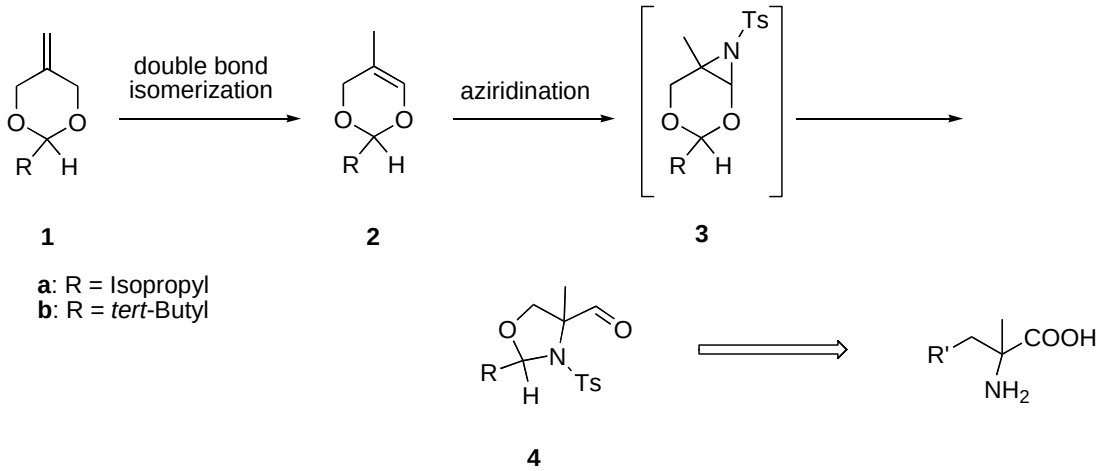
Aziridines, nitrogen analogues of epoxides,[1] have attracted great interest to chemists for years because of their easy transformation into pharmacological and biological active compounds,[2] their appearance as structural subunits in naturally occurring substances,[3] their antitumor and antibiotic activity,[4] or their use as precursors for chiral ligands, building blocks etc.[5]

A variety of methods have been developed for the synthesis of aziridines.[6] Among them, metal catalyzed nitrogen transfer processes to alkenes,[7,8] particularly metal catalyzed aziridinations using [*N*-(arenesulfonyl)imino]phenyliodinanes as nitrogen sources,[9] have intensively been studied.[10] To obtain optimal yields, these reactions are often performed with a

large excess of alkenes, and they are also often accompanied by insertion of a nitrene into activated C-H bonds.[8q,11] More recently, the in situ generation of PhI=NTs and [*N*-(alkenesulfonyl)imino]phenyliodinanes have been reported, which avoid the tedious preparation of PhI=NTs[12] and extend the scope of this type of aziridination.[13]

In contrast to the aziridination of substituted alkenes, less is known about metal catalyzed nitrogen transfer processes to functionalized alkenes, e.g. enol ethers, glucals, silylketene acetals and others.[14] In this case, the substrates are usually the limiting components of the reactions, and aziridines are often formed as intermediates, which directly rearrange to give aminated products. Only a few reports detail the isolation of aziridines derived from functionalized alkenes.[15]

We have previously reported the copper catalyzed aziridination of *rac*-5-methyl-4*H*-1,3-dioxin **1a** (R = isopropyl) with [*N*-(4-methylbenzenesulfonyl)imino]phenyliodinane, which leads to a diastereomeric mixture of *N*,*O*-protected α-methylserinal derivatives **4a** in a single step.[16] We assume, that the aziridination of **2** intermediately affords an aziridine **3**, which immediately rearranges via ring opening / ring contraction to give diastereomeric oxazolidinecarbaldehydes **4** (Scheme 1).



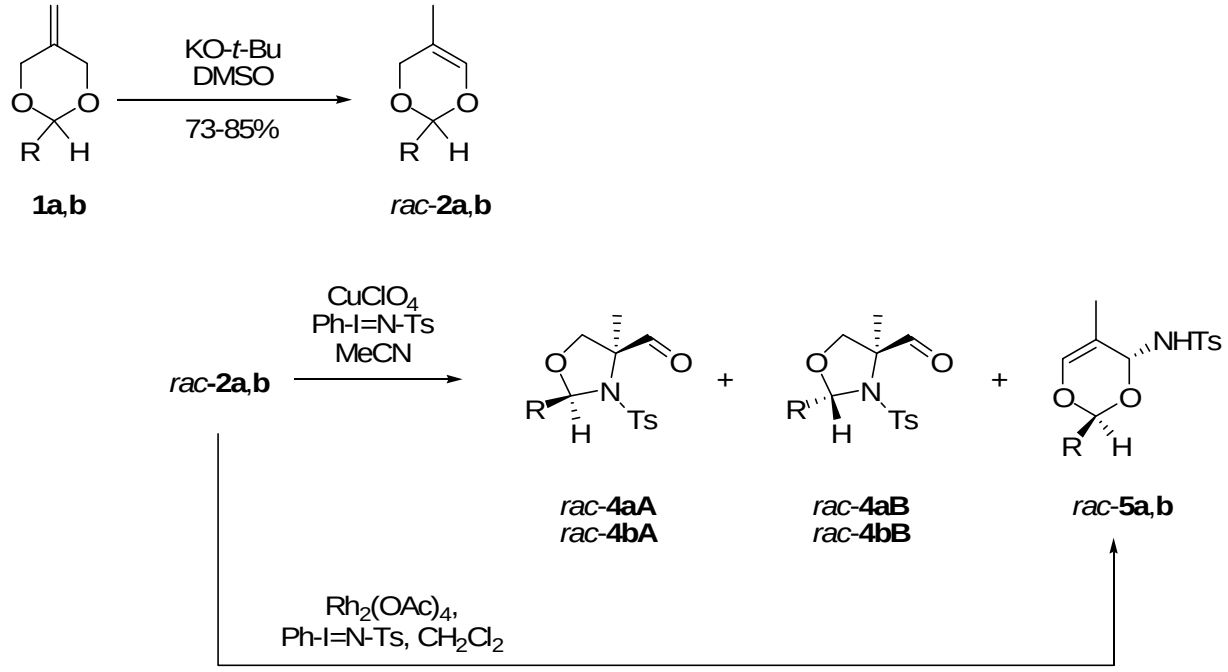
Scheme 1

Since serinal derivatives **4** are useful precursors for the synthesis of α-alkylated α-amino acids bearing a quarternary chiral center attached to nitrogen, we investigated the stereochemical course of the aziridination of **2** starting with enantiomerically enriched compounds. In this context we also studied the asymmetric double bond isomerization of **1** using DIOP- and DuPHOS-modified nickel complexes.

Results and Discussion

As already reported, the Cu(I) catalyzed reaction of 2-isopropyl-5-methyl-4*H*-1,3-dioxin *rac*-**2a** with [*N*-(4-methylbenzenesulfonyl)imino]phenyliodinane (tosyliminophenyliodinane, PhI=NTs)

in acetonitrile afforded a 90:10 mixture of diastereomers *rac*-**4aA** and *rac*-**4aB** in 60% isolated yield (Scheme 2; Table 1, entry 1).[16] Besides of small amounts of insertion product **5a,** *p*-toluenesulfonamide was found as the only byproduct.



Scheme 2

For the stereoselective synthesis of oxazolidinecarbaldehydes **4** starting with optically active dioxins **2**, however, only the *tert*-butyl derivative **2b** was available so far with high enantiomeric excess (92% ee).[17] Therefore, we first studied the aziridination of the *tert*-butyl derivative **2b**.

In contrast to the aziridination of **2a**, the reaction of **2b** proceeded very sluggishly. Diastereomers **4bA** and **4bB** were formed in < 10% yield, and only small amounts of insertion product **5b** could be isolated as a single diastereomer from the crude reaction mixture. (Scheme 2; Table 1, entry 2).

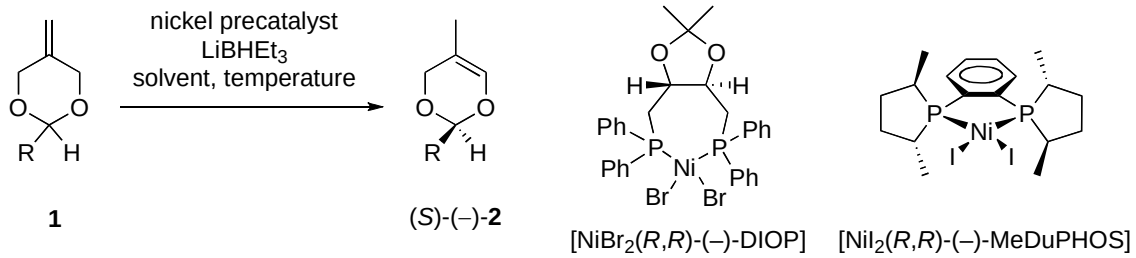
Table 1. Aziridination of *rac*-**2a** and *rac*-**2b** with PhI=NTs at room temperature

Entry	Compound	Catalyst	Solvent	Time [h]	Ratio **4A**:**4B** [a]	Ratio **4**:**5** [a]	Yield **4** [%]	Yield **5** [%]
1	*rac*-**2a**	$CuClO_4$ [b]	MeCN	2	90 : 10	98 : 2	60 [c]	[d]
2	*rac*-**2b**	$CuClO_4$ [b]	MeCN	2	51 : 49	70 : 30	9 [c]	[d]
3	*rac*-**2a**	$Rh_2(OAc)_4$ [e]	CH_2Cl_2	12	[f]	[f]	[f]	79
4	*rac*-**2b**	$Rh_2(OAc)_4$ [e]	CH_2Cl_2	12	[f]	[f]	[f]	83

[a] Ratios determined by GC. [b] 5 Mol%, calculated for $Cu(MeCN)_4ClO_4$. [c] Dioxin **2a** was the limited compound. [d] Yield not determined. [e] 2.5 Mol%. [f] Aldehydes **4** not detected by GC.

To get more information about the product formation, we also investigated the aziridination of both **2a** and **2b** using rhodium catalysts.[18] These reactions proceeded very smoothly, but only insertion products **5a**,**b** were formed in good yields (79 – 83%) as single diastereomers (Table 1, entries 3, 4).[19] The reason for the high selectivity is still unclear.[19]

Then we turned our attention back again to the copper catalyzed aziridination and the asymmetric synthesis of the isopropyl derivative **2a**. First, we investigated the asymmetric double-bond isomerization of **1a** with DIOP-modified nickel complexes (Scheme 3).[20] Under optimized conditions, the DIOP-modified nickeldibromo complex proved to be superior to the dichloro complex. [NiI_2DIOP] exhibited no catalytic activity after activation with lithium triethylborohydride, probably due to the insolubility of the catalyst precursor in diethyl ether at –70°C. However, the [$NiBr_2$(–)-DIOP]/$LiBHEt_3$ catalyzed isomerization of **1a** in diethyl ether at –70°C afforded (*S*)-(–)-**2a** only with 30% ee (Table 2, entry 1).



Scheme 3

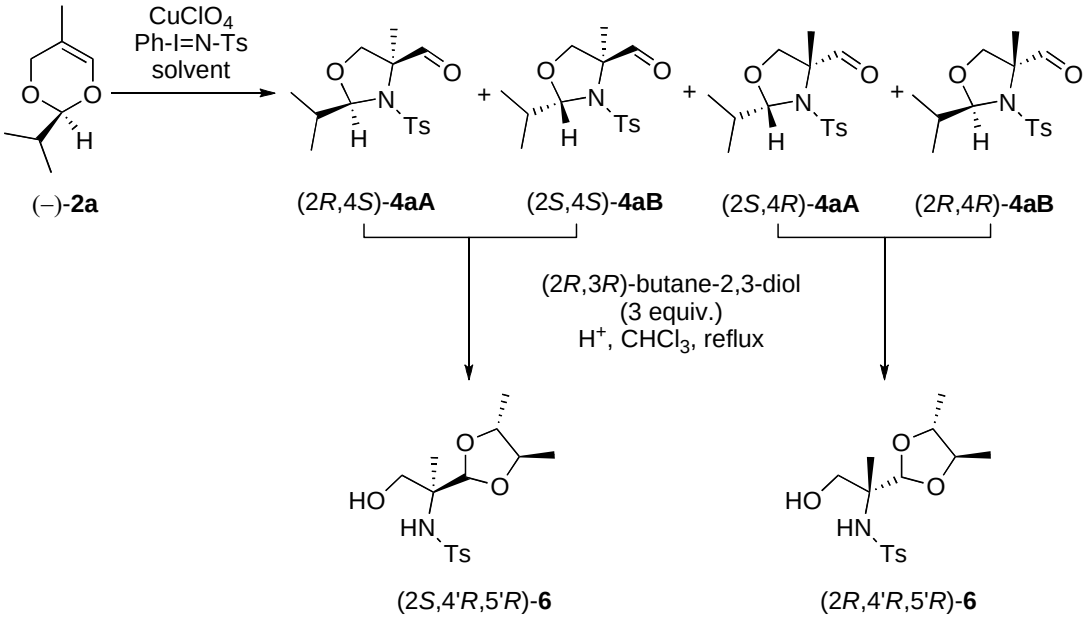
On the other hand, our findings in the asymmetric double bond isomerizations of dioxepins revealed, that improved enantioselectivities can be obtained using [NiI_2(MeDuPHOS)][21,22] instead of [$NiBr_2$DIOP] as catalyst precursor.[23] In fact, a significant improvement of the enantiomeric excess was achieved for the isomerization of **1a** with [NiI_2(MeDuPHOS)] in toluene at –20°C (Table 2, entry 2), and a slight enhancement of the enantiomeric excess was also observed for the isomerization of **1b** under the same reaction conditions (Table 2, entry 5 and 6).

Table 2. Nickel catalyzed double-bond isomerization of **1a** and **1b**

Entry	Product	Catalyst [a]	Solvent	Temperature [°C]	Time	Yield [%]	Ee [%] [d]
1	(–)-**2a**	[$NiBr_2$(*R*,*R*)-(–)-DIOP] [b]	Et_2O	–70	9d	83	30.0
2	(–)-**2b**	[$NiBr_2$(*R*,*R*)-(–)-DIOP] [b]	Et_2O	–70	9d	85	91.7
3	(–)-**2a**	[NiI_2(*R*,*R*)-(–)-MeDuPHOS] [b]	THF	–20	72h	81	90.0
4	(–)-**2a**	[NiI_2(*R*,*R*)-(–)-MeDuPHOS] [c]	toluene	–20	72h	79 [e]	92.7
5	(–)-**2b**	[NiI_2(*R*,*R*)-(–)-MeDuPHOS] [c]	toluene	–20	72h	83 [e]	95.1
6	(+)-**2b**	[NiI_2(*S*,*S*)-(+)-MeDuPHOS] [c]	toluene	–20	72h	83 [e]	94.7

[a] Activated with $LiBHEt_3$. [b] 5 Mol%. [c] 10 Mol%. [d] Determined by GC. [e] Yields after distillation using a spinning band column.

The copper(I) catalyzed aziridination of (*S*)-(–)-**2a** with (PhI=NTs) in acetonitrile at room temperature again afforded a 90:10 mixture of diastereomers **4aA** and **4aB**, but with respect to the diastereostereoselectivity of the intermediate nitrogen transfer step, the reaction proved to be unselective (Scheme 4; Table 3, entry 1).



Scheme 4

The stereochemical outcome was determined by treatment of **4a** with 3 equivalents of (2*R*,3*R*)-2,3-butanediol in the presence of catalytic amounts of *p*-toluenesulfonic acid, which led to a 1:1 mixture of dioxolanes (2*S*,4'*R*,5'*R*)-**6** and (2*R*,4'*R*,5'*R*)-**6**. As the stereocenters in the 2-position of oxazolidinecarbaldehydes **4** are destroyed by transacetalization, the diastereomeric ratio of (2*S*,4'*R*,5'*R*)-**6** and (2*R*,4'*R*,5'*R*)-**6** together with the enantiomeric ratio of the starting material reflects the diastereomeric ratio of the intermediate aziridination step of **2** → **3**.

We also investigated the aziridination of (*S*)-(–)-**2a** with PhI=NTs in different solvents (Table 3, entries 2-11). In dichloromethane, increasing amounts of insertion product **5a** are formed, particularly at lower temperatures and low catalyst concentrations (Table 3, entry 3). With higher catalyst concentration at ambient temperatures the formation of **5a** can be completely suppressed (Table 3, entry 11). With respect to the stereoselectivity of the aziridination step, no selectivity was observed. The reaction in acetone afforded nearly the same result as in acetonitrile (Table 3, entry 12). THF, which proved to be superior to other solvents in the epoxidation of dioxins **2**,[24] is excluded because of preferred insertion of PhI=NTs into an activated C–H bond and formation of **7** (Scheme 5).[8q]

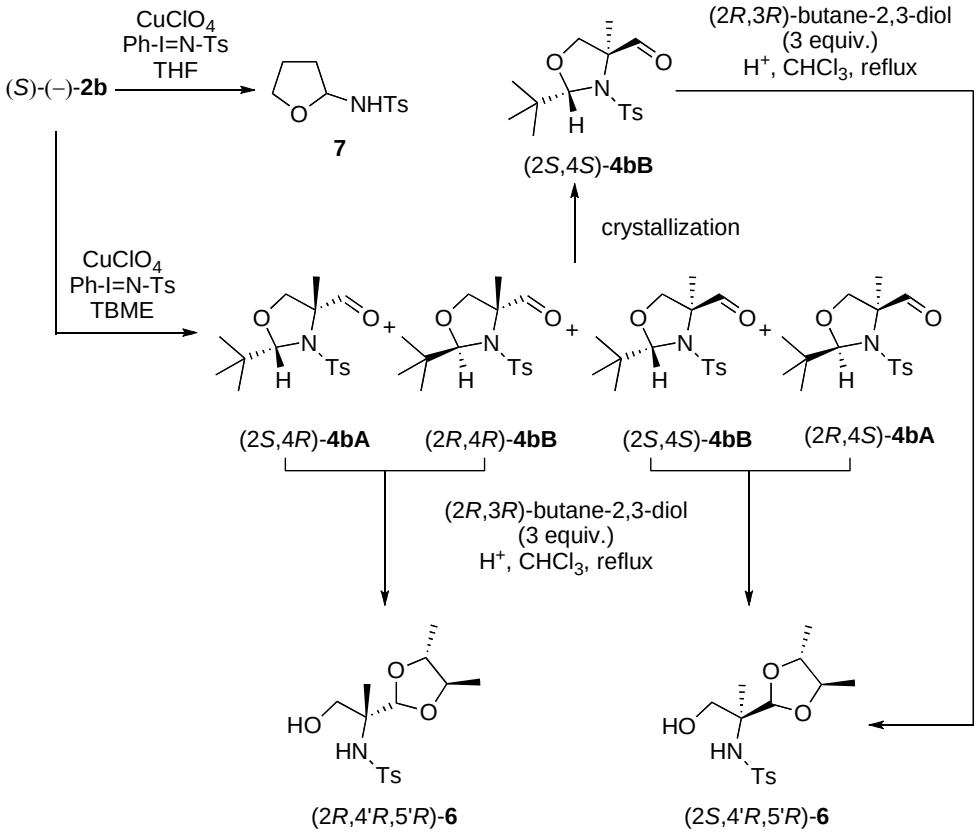
Table 3. Aziridination of (*S*)-(–)-**2a** and (*S*)-(–)-**2b** in different solvents

Entry	Comp.	Catalyst	Catalyst [Mol%]	Solvent	Temp.	Time	Ratio **4A**:**4B** [a]	Ratio **4**:**5** [a]	Yield **4** [b]	De% [%] [c]
1	(–)-**2a**	$CuClO_4$	5 [d]	MeCN	rt	2h	90 : 10	98 : 2	60 [e]	0
2	(–)-**2a**	$CuClO_4$	5 [d]	CH_2Cl_2	rt	3h	71 : 29	84 :16	51 [e]	0
3	(–)-**2a**	$CuClO_4$	2 [d]	CH_2Cl_2	–20°C	9 d	70 : 30	33 : 67	16	[f]
4	(–)-**2a**	$CuClO_4$	10 [d]	CH_2Cl_2	–20°C	7 d	70 : 30	80 : 20	24	[f]
5	(–)-**2a**	$CuClO_4$	20 [d]	CH_2Cl_2	–20°C	7 d	74 : 26	87 : 13	29	[f]
6	(–)-**2a**	$CuClO_4$	2 [d]	CH_2Cl_2	0°C	24 h	66 : 34	23 : 77	24	[f]
7	(–)-**2a**	$CuClO_4$	10 [d]	CH_2Cl_2	0°C	12 h	71 : 29	73 : 27	34	[f]
8	(–)-**2a**	$CuClO_4$	20 [d]	CH_2Cl_2	0°C	12 h	71 : 29	90 : 10	42	0
9	(–)-**2a**	$CuClO_4$	2 [d]	CH_2Cl_2	rt	16 h	68 : 32	71 : 29	36	[f]
10	(–)-**2a**	$CuClO_4$	10 [d]	CH_2Cl_2	rt	4 h	71 : 29	96 : 4	52	0
11	(–)-**2a**	$CuClO_4$	20 [d]	CH_2Cl_2	rt	4 h	70 : 30	>99	54	0
12	(–)-**2a**	$CuClO_4$	20 [d]	acetone	rt	3 h	87 : 13	>99	58	0
13	(–)-**2a**	$CuClO_4$	20 [d]	TBME	rt	18 h	65 : 35	[h]	51	30
14	(–)-**2b**	$CuClO_4$	20 [d]	TBME	rt	18 h	35 : 65	[h]	45	70
15	(–)-**2b**	CuOTf	20 [g]	TBME	rt	18 h	33 : 67	[h]	45	70
16	(–)-**2b**	CuOTf	20 [g]	TBME	0°C	18 h	40 : 60	[h]	41	73

[a] Determined by GC. [b] Yields are calculated for consumed PhI=NTs (limited compound), determined by isolated Ts-NH_2 (column chromatography). [c] Calculated as described in the text. [d] Calculated for $Cu(MeCN)_4ClO_4$. [e] Dioxin **2a** is the limited compound. [f] Not determined. [g] Insertion product **5** < 10%. [h] Calculated for CuOTf · $^1/_2$ C_6H_6.

However, we found that *tert*-butylmethyl ether (TBME) is a suitable substitute for THF. The Cu(I) catalyzed reaction of (*S*)-(–)-**2a** (92.7% ee) with PhI=NTs in TBME proceeded slower than in dichloromethane or acetonitrile, and increasing amounts of the minor diastereomer **4B** were found, but for the first time we observed a moderate diastereoselectivity for the intermediate step (Table 3, entry 13).

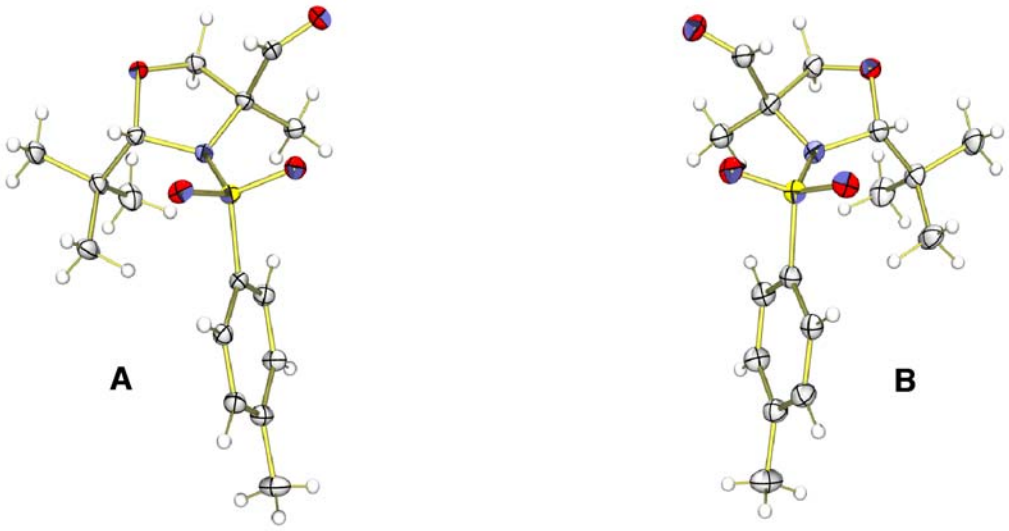
The reaction of (*S*)-(–)-**2b** (95% ee) in TBME at room temperature and 0°C, respectively, in the presence of a Cu(I) catalyst afforded a mixture of diastereomers **4b** together with small amounts of *p*-toluenesulfonamide, but with a reversed A / B ratio (Table 3, entries 14 – 16). After separation of the catalyst and byproduct by flash chromatography and treatment of the resulting amorphous solid with (2*R*,3*R*)-2,3-butanediol, a 85:15 ratio of compounds (2*S**,4'*R*,5'*R*)-**6** and (2*R**,4'*R*,5'*R*)-**6** was obtained (Table 3, entry 16). From this result the diastereoselectivity of the aziridination of (*S*)-(–)-**2b** was calculated to 73% de.



Scheme 5

Diastereomers **4bA** and **4bB** were separated by column chromatography, and each of the diastereomers was separately reacted with butanediol to give dioxolane derivatives **6**. As indicated by the NMR spectra, these compounds **6** comprised both diastereomers (2*S**,4'*R*,5'*R*)-**6** and (2*R**,4'*R*,5'*R*)-**6** also in a 85:15. The relative configurations could not be determined by NMR spectroscopy.

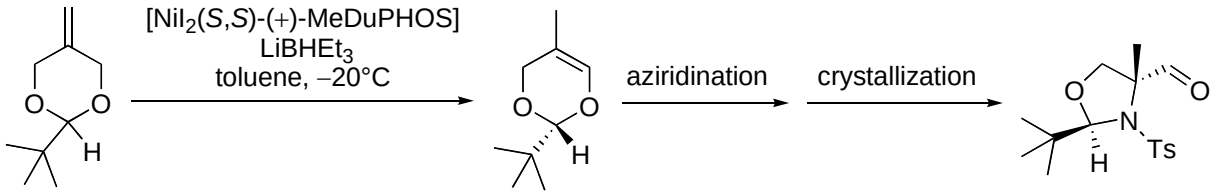
On the other hand, recrystallization of diastereomer **4bB** from TBME led to a crystalline material exhibiting a higher optical rotation than the starting material. After conversion of the crystalline solid into **6**, only one diastereomer could be detected in the NMR spectra. The same crystalline material was also obtained by recrystallization of the amorphous solid of **4b** from TBME. Obviously, (2*S*,4*S*)-**4bB** crystallizes from the diastereomeric mixture in an enantiomerically pure form. The enantiomeric purity was confirmed by X-ray crystallography, and the absolute configuration was established as the (2*S*,4*S*)-configuration (Figure 1**A**).[25]



(2*S*,4*S*)-(–)-**4bB** (2*R*,4*R*)-(+)-**4bB**

Figure 1. A: Crystal structure of (2*S*,4*S*)-(–)-**4bB**; **B**: Crystal structure of (2*R*,4*R*)-(+)-**4bB.**

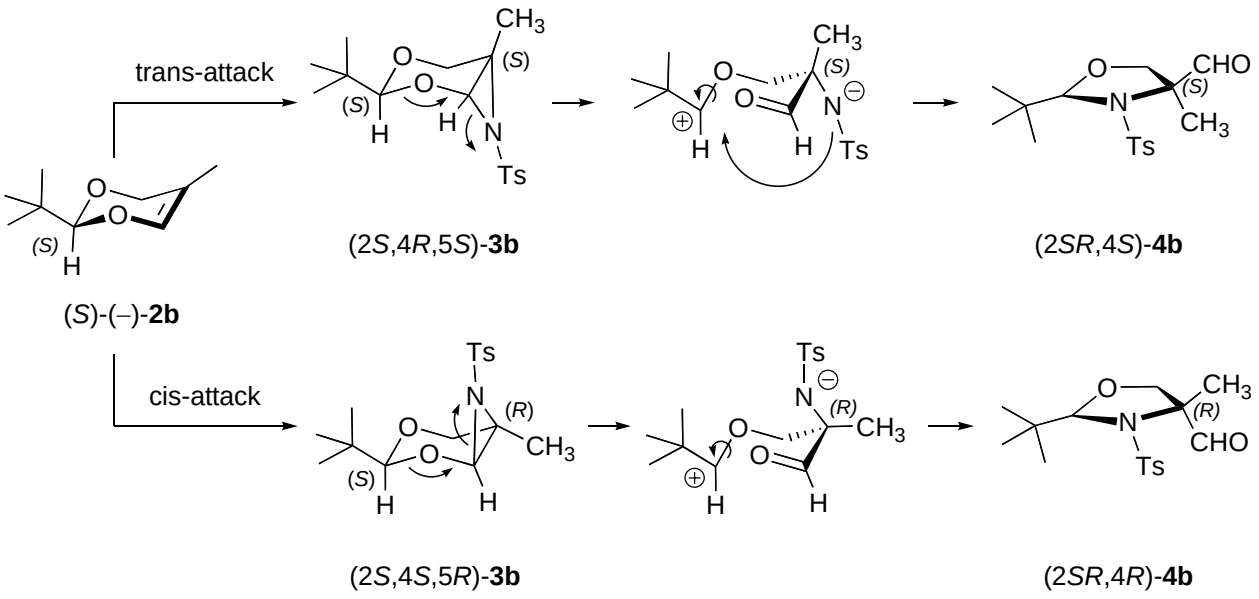
The enantiomer (2*R*,4*R*)-(+)-**4bB** was readily prepared by isomerization of **1b** using [NiI_2(*S*,*S*)-(+)-MeDuPHOS)] as a precatalyst, Cu(I) catalyzed aziridination of (*R*)-(+)-**2b** with PhI=NTs in TBME and crystallization from TBME after separation of the catalyst, iodobenzene and byproducts by flash chromatography (Scheme 6). The absolute configuration of (2*R*,4*R*)-**4bB** was also confirmed by X-ray crystallography (Figure 1**B**).[25] The optical purity again emerged from transformation of (2*R*,4*R*)-(+)-**4bB** into (2*R*,4'*R*,5'*R*)-**6**, which in the NMR-spectra only showed signals of a single diastereomer.



1b (*R*)-(+)-**2b** (2*R*,4*R*)-(+)-**4bB**

Scheme 6

From the results described above we conclude, that attack of a nitrene or nitrenoid species derived from PhI=NTs preferentially attacks dioxin (*S*)-**2b** in TBME *trans* to the *tert*-butyl group in the 2-position (Scheme 7). The enhanced diastereoselectivity of the aziridination of *tert*-butyl substituted dioxin **2b** may be reasoned by a more rigid conformation in comparison to isopropyl substituted dioxin **2a**.



Scheme 7

We also assume, that the reversed **A**/**B** diastereomeric ratio results from the fact, that aziridination reactions of dioxins **2** in TBME occure at a slower rate than in acetonitrile or the other described solvents giving rise for prolonged times for rotation of the intermediate carboxonium ion.

In summary, diastereomers of oxazolidinecarbaldehydes **4b** are prepared from readily available 5-methylene-1,3-dioxanes **1** in two simple steps: asymmetric double-bond isomerization and Cu(I) catalyzed aziridination in TBME. Enantiomerically pure compounds **4bB** are obtained by recrystallization of the diastereomeric mixture from TBME. The diastereomeric excess of the intermediately formed aziridine (up to 73% de) can be determined by transformation of aldehydes **4b** into the ring-opened acetals **6**. Further investigations in the stereoselective course of the formation of insertion products **5** are in progress.

Experimental Section

General Procedures. Solvents were purified according to standard procedures. Analytical TLC was performed using silica gel 60 F254 plates. Column chromatography was performed using silica gel 60 (0.063-0.200 mm). Melting points are uncorrected and were measured in open glassware. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity INOVA 500 spectrometer. Chemical shifts are reported in ppm, coupling constants in Hz. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in 1 cm or 10 cm cells. Microanalyses were carried out on a Vario El analyzer and were in good agreement with the calculated values. IR spectra were recorded on a Bio-Rad FTS 40a spectrometer. Mass spectra and high-resolution mass spectra were measured on a Finnigan LCQ Deca (ThermoQuest, San José, USA) and a micrOTOF (Bruker Daltonics, Bremen, D) with an Apollo^{TM} "Ion Funnel" ESI-ion source, respectively. GC

analysis for reaction control: Star 3400C (Varian), column 25 m x 0,25 mm, ID FS-OV-1-CB; GC analysis of the enantiomeric excess of **2a** and **2b**: GC 8000 Top Serie (CE Instruments), column 30 m x 0.32 mm ID, Rt-βDEXcst^{TM} (Restek GmbH).

General procedure for [NiI$_2$MeDuPHOS] catalyzed double bond isomerization of dioxanes (1)

[NiI$_2$MeDuPHOS] (1.98 g, 3.2 mmol) was dissolved in anhydrous solvent at room temperature and activated with LiBHEt$_3$ (3.2 mmol, 3.2 mL, 1M in THF). After cooling (reaction temperature is given in Table 2), a solution of **1** (32 mmol) in anhydrous solvent (25 mL) was added, and the mixture was left at this temperature in a deep freezer. The conversion of **1** was monitored by GC. After complete conversion, the mixture was allowed to warm up to room temperature and quenched with saturated NH_4Cl solution (50 mL). The organic layer was separated and the aqueous layer was extracted 3 times with diethyl ether. The combined organic layers were dried ($MgSO_4$). After removal of the solvent, the residue was distilled *in vacuo*. Absolute configuration of the precatalyst, yields, sign of the optical rotation and enantiomeric excess of **2** are given in Table 2.

(–)-2-Isopropyl-5-methyl-4*H*-1,3-dioxin [(–)-2a]. Colorless liquid; bp 52°C/13 Torr; $[\alpha]^{20}_D$ = –102.28 (*neat*); 92.7 % ee (GC) (Table 2, entry 4).

(–)-2-*tert*-Butyl-5-methyl-4*H*-1,3-dioxin [(–)-2b]. Colorless liquid; bp 56°C/12 Torr; $[\alpha]^{20}_D$ = –94.4 (*neat*); 95.1 % ee (GC) (Table 2, entry 5).

(+)-2-*tert*-Butyl-5-methyl-4*H*-1,3-dioxin [(+)-2b]. Colorless liquid; bp 56°C/12 Torr; $[\alpha]^{20}_D$ = +94.0 (*neat*); 94.7 % ee (GC) (Table 2, entry 6).

The isomerization of **1a** was performed according to the procedure for the [NiBr$_2$(–)-DIOP] catalyzed isomerization of **1b** (Table 2, entry 2).[17] Yields and enantiomeric excess are given in Table 2 (entry 1).

General procedure for the reaction of dioxins (2) and PhI=NTs in the presence of Cu-catalysts

Under an inert atmosphere [*N*-(4-methylbenzenesulfonyl)imino]phenyliodinane (PhI=NTs) (3.73 g, 10 mmol) was added in small portions over a period of 3 h to a solution of dioxin **2** (15 mmol) and Cu(I) catalyst in anhydrous solvent (25 mL). After complete conversion (monitored by GC) the solvent was evaporated under reduced pressure, and the oily residue was purified by column chromatography on silica gel [light petroleum–diethyl ether (5:1)]. Diastereomeric ratios and yields of **4** are listed in Table 3.

(2*R,4*S**)-2-Isopropyl-4-methyl-3-(toluene-4-sulfonyl)-1,3-oxazolidine-4-carbaldehyde (4aA).** Colorless solid; mp 121°C; *Anal*. Calcd. $C_{15}H_{21}NO_4S$ (311.4): C, 57.86; H, 6.80; N, 4.50. Found: C, 57.37; H, 6.60; N, 4.51. IR (ATR, cm^{-1}) 2975, 2879, 2829, 1736, 1598, 1467, 1401, 1341, 1305, 1188, 1157, 1084, 1066, 933, 864, 821, 709, 665. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, d, *J* = 6.9), 1.02 (3H, d, *J* = 6.9 Hz), 1.43 (3H, s), 2.34 (1H, dqq, *J* = 6.9, 6.9, 2.8 Hz), 2.45 (3H, s), 3.48 (1H, d, *J* = 8.8 Hz), 4.18 (1H, d, *J* = 8.8 Hz), 5.00 (1H, d, *J* = 2.8 Hz), 7.34 (2H, m), 7.74 (2H, m), 9.74 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 16.9, 18.7, 21.6, 32.0,

71.2, 73.2, 96.3, 127.5, 129.8, 137.6, 144.2, 198.5. MS *m/z*: 312 [M^++1, 90%], 294 (53%), 240 (100 %). HRMS Calcd. $C_{15}H_{21}NNaO_4S$: 334.1089. Found: 334.1084.

(2*S,4*S**)-2-Isopropyl-4-methyl-3-(toluene-4-sulfonyl)-1,3-oxazolidine-4-carbaldehyde (4aB).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.64 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 1.54 (3H, s), 2.11 (1H, dqq, *J* = 6.8, 6.8, 2.8 Hz), 2.44 (3H, s), 3.78 (1H, d, *J* = 9.3 Hz), 4.02 (1H, d, *J* = 9.3 Hz), 5.29 (1H, d, *J* = 2.5 Hz), 7.32 (2H, m), 7.74 (2H, m), 9.78 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 18.3, 18.5, 21.5, 31.3, 71.5, 74.1, 97.2, 127.4, 129.7, 138.0, 144.0, 197.4.

(2*R,4*S**)-2-*tert*-Butyl-4-methyl-3-(toluene-4-sulfonyl)-1,3-oxazolidine-4-carbaldehyde (4bA).** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.39 (3H, s), 2.45 (3H, s), 3.52 (1H, dd, *J* = 8.7, 0.8 Hz), 4.37 (1H, d, 1H, *J* = 8.7 Hz), 5.29 (1H, s), 7.34 (2H, m), 7.80 (2H, m), 9.72 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 21.5, 27.0, 38.2, 73.1, 75.9, 101.0, 127.5, 129.9, 138.0, 144.0, 199.4.

(2*S*,4*S*)-2-*tert*-Butyl-4-methyl-3-(toluene-4-sulfonyl)-1,3-oxazolidine-4-carbaldehyde [(–)-4bB]. Starting from (–)-**2b** (95.1 % ee); colorless crystals from TBME; mp 125-126°C; $[\alpha]^{20}_D$ = –76.1 (c = 2.95, $CHCl_3$). IR (ATR, cm^{-1}) 2962, 2927, 2852, 1737, 1451, 1334, 1259, 1160, 1090, 1012, 812, 705; 665, 594, 547. *Anal*. Calcd. $C_{16}H_{23}NO_4S$ (325.42): C, 59.05; H, 7.12; N, 4.30. Found: C, 59.03; H, 7.07; N, 4.28. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.63 (3H, s), 2.44 (3H, s), 4.04 (1H, d, *J* = 10.0 Hz); 4.10 (1H, d, *J* = 10.0 Hz); 5.44 (1H, s), 7.32 (2H, m), 7.76 (2H, m), 9.87 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.5, 26.3, 38.0, 71.9, 73.2, 100.5, 127.5, 129.9, 138.0, 144.0, 198.4. MS *m/z*: 380 [$(M+Na+MeOH)^+$, 100%], 348 [$(M+Na)^+$, 40%]; HRMS Calcd. $C_{16}H_{23}NNaO_4S$: 348.1245. Found: 348.1243.

(2*R*,4*R*)-2-*tert*-Butyl-4-methyl-3-(toluene-4-sulfonyl)-1,3-oxazolidine-4-carbaldehyde [(+)-4bB]. Starting from (+)-**2b** (94.7 % ee,); colorless crystals from TBME; mp 125-126°C; $[\alpha]^{20}_D$ = +73.03 (c = 1.65, $CHCl_3$).

General procedure for the reaction of dioxins (2) and PhI=NTs catalyzed by $Rh_2(OAc)_4$

Under an inert atmosphere [*N*-(4-methylphenylsulfonyl)imino]phenyliodinane (PhI=NTs) (3.73 g, 10 mmol) was added in small portions over a period of 3 h to a solution of dioxin **2** (10 mmol) and $Rh_2(OAc)_4$ (110 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (25 mL). After complete conversion (monitored by GC) the solution was filtered through a plug of silica (washed with 200 mL CH_2Cl_2) and recrystallized from light petroleum–diethyl ether (4:1).

***N*-(2-Isopropyl-5-methyl-4*H*-1,3-dioxin-4-yl)-4-methyl-benzenesulfonamide (5a).** 2.46 g (7.9 mmol, 79%); colorless solid; mp 111-113°C. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.59 (3H, d, *J* = 6.9 Hz), 0.67 (3H, d, *J* = 6.9 Hz), 1.51 (3H, dd, *J* = 0.8, 1.3 Hz), 1.53 (1H, dqq, *J* = 6.9, 6.9, 4.7 Hz), 2.39 (3H, s), 4.26 (1H, d, *J* = 4.7 Hz), 5.23 (1H, dq, *J* = 9.4, 0.8 Hz), 5.78 (1H, d, *J* = 9.4 Hz), 6.37 (1H, q, *J* = 1.3 Hz), 7.29 (2H, m), 7.76 (2H, m). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 13.8, 16.1, 16.2, 21.4, 31.5, 79.1, 96.1, 107.5, 127.2, 129.9, 139.2, 142.0, 144.0. MS *m/z*: 645 [$(2M+Na)^+$, 100%], 334 [$(M+Na)^+$, 65%]. HRMS Calcd. $C_{15}H_{21}NNaO_4S$: 334.1089. Found: 334.1091.

***N*-(2-*tert*-Butyl-5-methyl-4*H*-1,3-dioxin-4-yl)-4-methyl-benzenesulfonamide (5b).** 2.70 g (8.3 mmol, 83%); colorless solid; mp 115-117°C. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.63 (9H, s), 1.53 (3H, dd, *J* = 1.0, 1.4 Hz), 2.38 (3H, s), 4.15 (1H, s), 5.24 (1H, ddq, *J* = 9.5, 1.4, 1.9 Hz), 5.69

(1H, dq, *J* = 9.5, 0.6 Hz), 6.38 (1H, ddq, *J* = 1.9, 1.1, 0.6 Hz), 7.28 (2H, m), 7.75 (2H, m). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 13.7, 21.4, 23.9, 33.9, 79.3, 98.1, 107.4, 127.2, 129.9, 139.2, 142.0, 144.0. IR (ATR, cm^{-1}) 3256; 2963; 2871; 1726; 1678; 1441; 1329; 1159; 1071; 1029; 912; 893; 864; 808; 671; 570; 548. MS *m/z*: 689 [$(2M+K)^+$, 25%], 673 [$(2M+Na)^+$, 100%], 364 [$(M+K)^+$, 32%], 348 [$(M+Na)^+$, 60%].

(*S*,*R*)-2-[(4*R*,5*R*)-4,5-Dimethyl-1,3-dioxolan-2-yl]-2-(tosylamino)propan-1-ol (6). Aldehydes **4** (0.352 mmol) and (2*R*,3*R*)-(–)-2,3-butanediol (95 mg, 1.056 mmol) were dissolved in 15 mL anhydrous $CHCl_3$. *p*-toluene sulfonic acid (6 mg, 0.032 mmol) was added and the solution was heated to reflux in a Dean-Stark trap (filled with activated molsieve 4Å). After complete conversion (monitored by gas chromatography) the reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (85 mL) and washed with K_2CO_3 (aqueous solution, 10%). The organic layer was dried (K_2CO_3), concentrated under reduced pressure and dried *in vacuo*. The crude product was analyzed by NMR without further purifying steps. (2*R*,4'*R*,5'*R*)-**6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (3H, s), 1.12 (3H, d, *J* = 5.9 Hz), 1.21 (3H, d, *J* = 5.9 Hz), 2.36 (3H, s); 2.87 (1H, dd, *J* = 8.4, 5.2 Hz), 3.45 (1H, dd, *J* = 12.0, 8.4 Hz), 3.53 (2H, m), 3.66 (1H, dd, *J* = 12.0, 5.2 Hz), 4.87 (1H, s, 1H), 5.30 (1H, s), 7.23 (2H, m), 7.75 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 16.4, 17.0, 21.5, 60.9, 65.6, 78.9, 80.1, 104.6, 127.0, 129.5, 139.9, 143.2. (2*S*,4'*R*,5'*R*)-**6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, s), 1.19 (3H, d, *J* = 5.7 Hz), 1.26 (3H, d, *J* = 5.7 Hz), 2.42 (3H, s), 2.92 (1H, dd, *J* = 8.4, 5.0 Hz), 3.49 (1H, dd, *J* = 11.8, 8.4 Hz), 3.58 (2H, m, *J* = 5.7 Hz), 3.74 (1H, dd, *J* = 11.8, 5.0 Hz), 4.96 (1H, s), 5.35 (1H, s), 7.29 (2H, m), 7.80 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 16.5, 17.0, 21.4, 60.9, 65.4, 79.2, 80.0, 104.5, 127.0, 129.4, 139.9, 143.1.

Supplementary Information Available

Complete spectroscopic material is available as an attachment.

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