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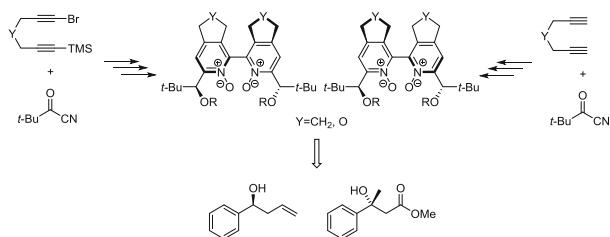
# Synthesis of new bipyridine *N,N'*-dioxides and their application in asymmetric allylation of benzaldehyde and aldol addition to acetophenone

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## Abstract

Two methods for the synthesis of new axially chiral bipyridine *N,N'*-dioxides based on catalytic [2+2+2] cyclootrimerization of diynes with nitriles were developed. The *N,N'*-dioxides were used as catalysts in enantioselective allylation of benzaldehyde with allyltrichlorosilane and aldol reaction of trichlorosilyl ketene acetal of methyl acetate with acetophenone.

## Graphical abstract



**Keywords** Cyclootrimerization · Catalysis · *N,N'*-Dioxides · Silicon compounds · Enantioselective synthesis

## Introduction

Chiral pyridine *N*-oxides and bipyridine *N,N'*-dioxides are an important class of heteroaromatic compounds with interesting chemical properties. Polarization of the N–O bond results in their electron-donation activity and makes them rather strong Lewis bases, which are able to activate Lewis acids such as trichlorosilanes. Therefore, they can catalyze a number of various reactions such as allylation and crotylation of aldehydes, aldol reactions, ring-opening of epoxides, and cyanosilylation of ketones and imides [1–10]. Due to the general high interest in the development of new Lewis basic chiral organocatalysts, synthetic approaches providing new chiral compounds possessing the pyridine *N*-oxide moiety are desirable.

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## Results and discussion

### Ligand design

We designed new types of bipyridine  $N,N'$ -dioxides with the C<sub>2</sub> symmetry (Fig. 1) which possess centers of chirality in the side chains. The pyridine cores are connected in positions 2 and 2'. In addition, the presence of two substituents in position 3 and 3' together with two oxygen atoms of the  $N$ -oxides should cause restricted rotation of the C<sub>2</sub>–C<sub>2'</sub> bond between the two pyridine rings, thus, to generate dynamic axial chirality [11] in the molecule.

Generally, there are two possible pathways of synthesis of these types of  $N,N'$ -dioxides (Scheme 1). The first approach (A) is based on the following retrosynthetic analysis: (i) oxidation of a bipyridine to a bipyridine  $N,N'$ -dioxide, (ii) reductive homocoupling of a 2-halopyridine that could be prepared by (iii) catalytic cyclotrimerization of a 1-halodiyne with a nitrile. In the second approach (B) is a bipyridine  $N,N'$ -dioxide synthesized by (i) oxidative dimerization of a pyridine  $N$ -oxide prepared by (ii) oxidation of a bicyclic pyridine and (iii) catalytic cyclotrimerization of an unsubstituted diyne with a nitrile.

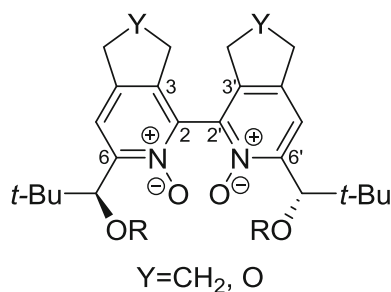


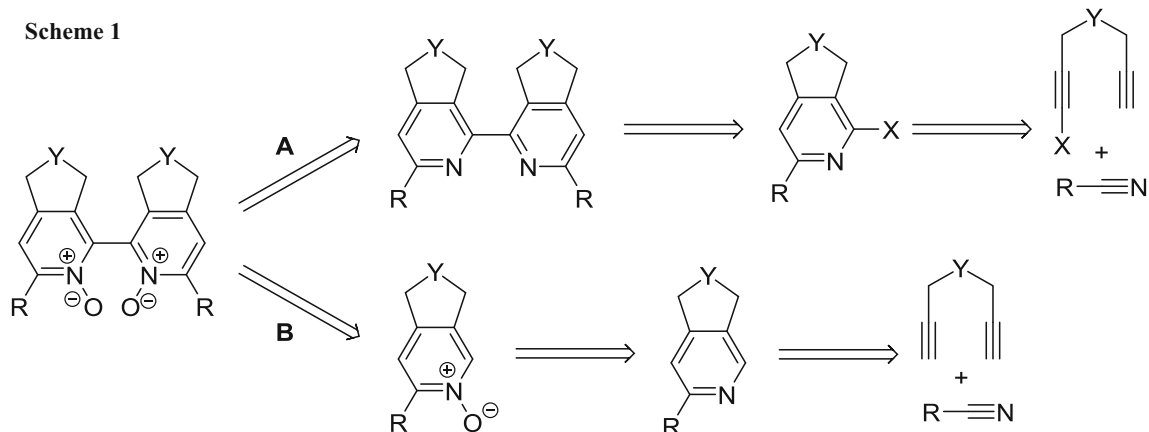
Fig. 1 Newly designed bipyridine  $N,N'$ -dioxide

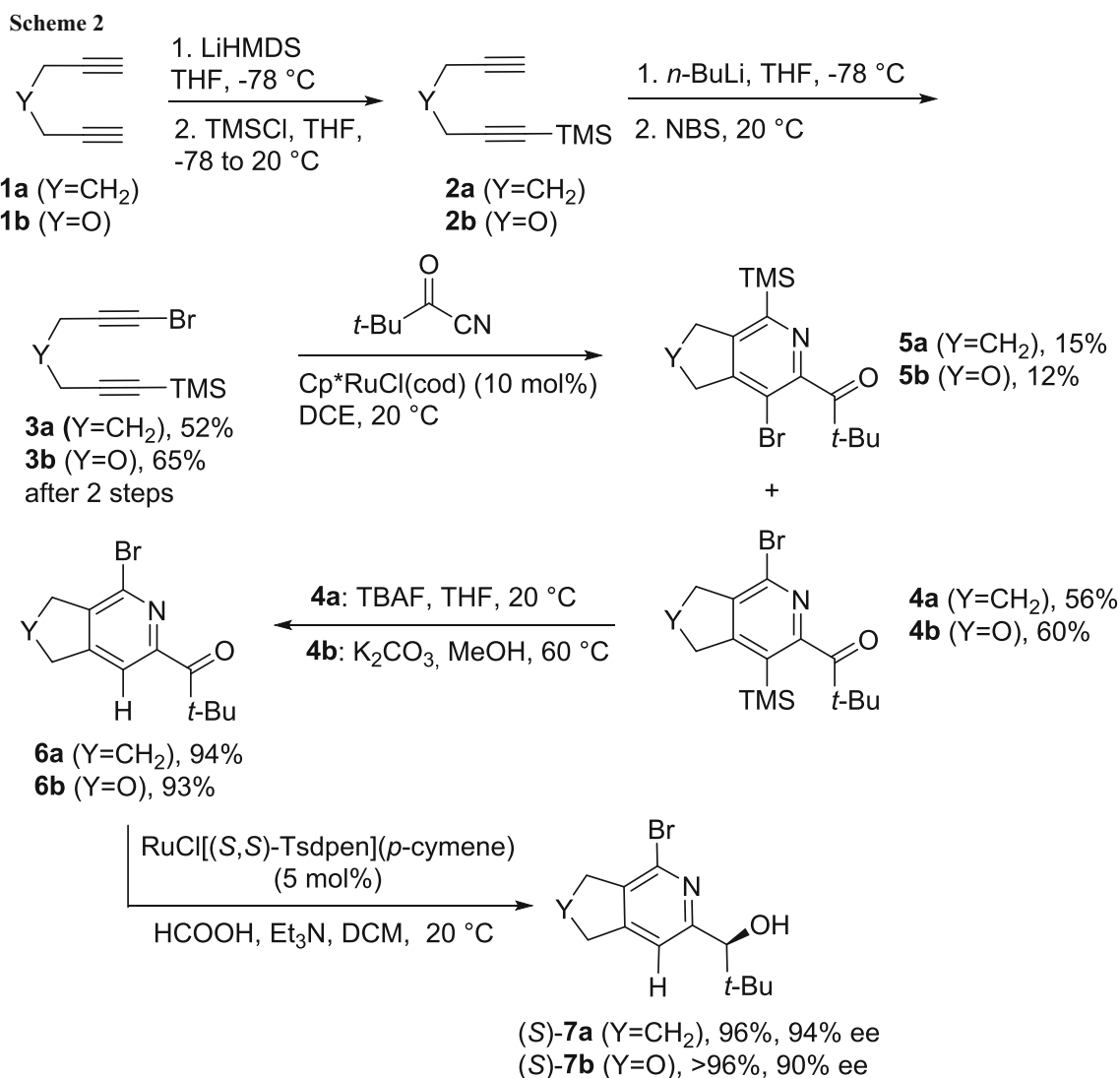
### Synthesis of bipyridine $N,N'$ -dioxides

#### Approach A

Synthesis of desired bipyridine  $N,N'$ -dioxides started with monolithiation of hepta-1,6-diyne (**1a**, Y=CH<sub>2</sub>) or propargyl ether (**1b**, Y=O) with LiHMDS followed by reactions with trimethylsilyl chloride (Scheme 2). Then the formed diynes **2a** and **2b** underwent bromination with NBS providing 1-bromodiyne **3a** and **3b** at isolated yields of 52% and 65% after two steps. The subsequent cyclotrimerization of **3a** and **3b** with pivaloyl cyanide under the standard condition developed in our group (Cp\**Ru*Cl(cod) (10 mol%), dichloroethane, 20 °C) [12] proceeded with the preferential formation of 2-bromopyridines **4a** and **4b** in both cases. Thus, in each case, mixtures of both possible regioisomers **4a** and **5a**, and **4b** and **5b** were obtained at high isolated yields (**4a** 56%, **5a** 15%; **4b** 60%, **5b** 12%). The TMS group of **4a** was then removed using tetrabutylammonium fluoride (TBAF) yielding ketone **6a** at 94% yield. In the case of **4b** it was necessary to use potassium carbonate and the deprotected ketone **6b** was obtained at 93% yield. It should be mentioned that deprotection with TBAF was not reproducible and intractable reaction mixtures were obtained, probably as a result of low stability of either the starting material or the product. Ketones **6a** and **6b** were then reduced by enantioselective *Ru*-catalyzed transfer hydrogenation to chiral alcohols **7a** and **7b** in quantitative yields and with excellent enantioselectivity of 94% and 90% ee, respectively [13]. *S* configuration of both alcohols **7a** and **7b** was unequivocally confirmed by a single-crystal X-ray analysis (for **7a**, see Ref. [14], for **7b**, see Fig. 2).

After protection of the free hydroxyls with the acetyl group, the pyridines **8a** and **8b** were dimerized using in situ-generated Ni(0) species in 68% and 62%,





respectively (Scheme 3). Surprisingly, deprotection of the acetyl groups in bipyridines **9a** and **9b** under the standard conditions (K<sub>2</sub>CO<sub>3</sub>, MeOH, 20 °C) resulted in different outcomes. Whereas the reaction with **9a** proceeded without any problems and provided pyridine **10a** at 96% yield as an optically pure compound, deprotection of **9b** produced an insoluble material, which we were not able to characterize and identify. Although a full consumption of the starting material and formation of monodeprotected species was observed using different deprotection conditions such as 4 Å MS in MeOH or NH<sub>3</sub> in MeOH, the same insoluble material was formed at the end of the reaction. Some of the aspects of the synthesis of bipyridine **10a** are discussed in detail in our recent report, where this chiral 2,2'-bipyridine was efficiently used as a ligand in metal-catalyzed reactions [14].

The reaction of bipyridine **10a** with methyl iodide formed bipyridine **11a** which was then oxidized with MCPBA to furnish the desired bipyridine *N,N'*-dioxide **12a** at 93% isolated yield (Scheme 4). Although formation of two atropoisomers of **12a** could have been expected, only one diastereoisomer was detected and isolated and its *aR* configuration was determined by the single-crystal X-ray analysis (Fig. 3).

Unsatisfactory result of the attempt to synthesize *N,N'*-dioxide bearing oxygen in the 5-membered ring resulted in invention of a new synthetic approach. As we were suspicious that our problems could originate in the presence of free hydroxyl groups in bipyridine **10b**, we tested the possibility to convert the OH groups to methyl ethers prior to dimerization. In addition, this pathway would also

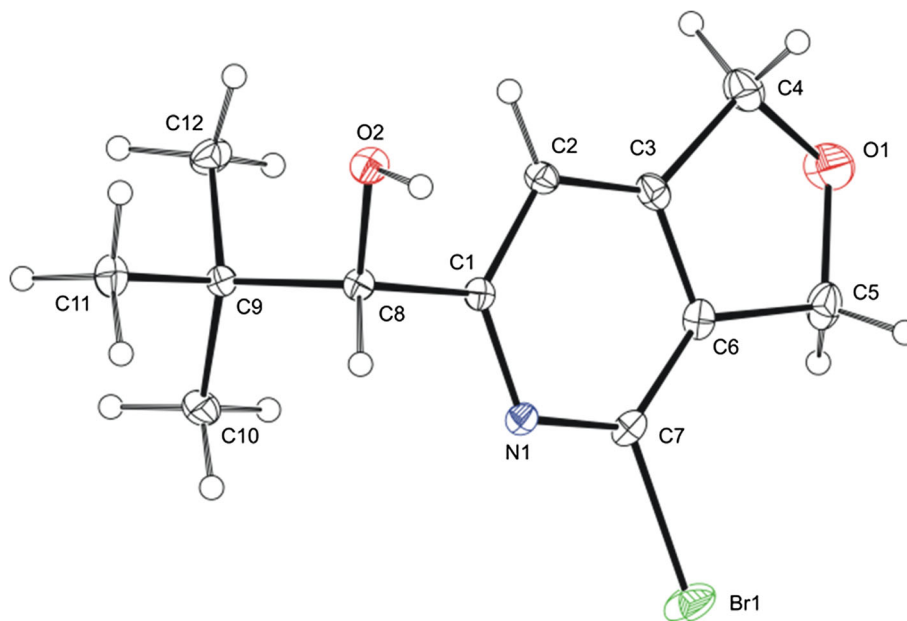
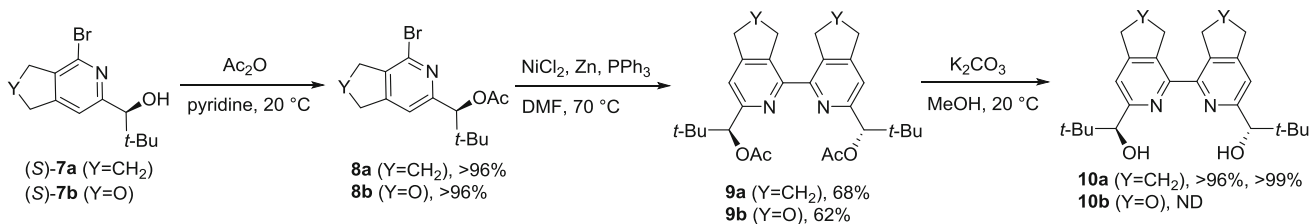
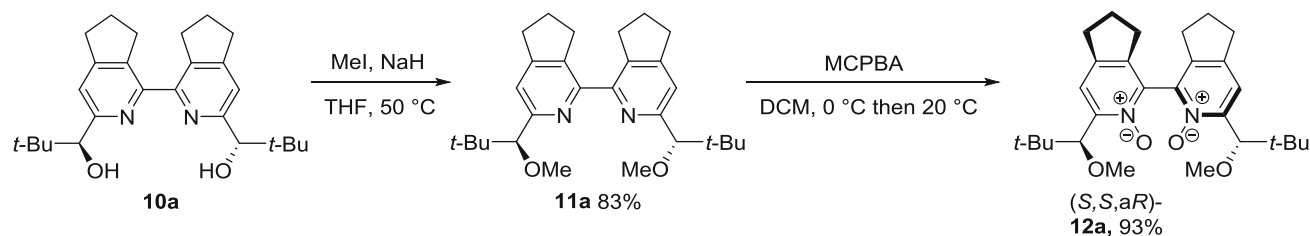


Fig. 2 ORTEP drawing of (*S*)-7b

### Scheme 3



### Scheme 4



shorten the synthesis of *N,N'*-dioxide by making the steps of protection and deprotection with acetyl groups obsolete.

We were pleased that treatment of chiral alcohols (*S*)-7a and (*S*)-7b with methyl iodide furnished pyridines 13a and 13b at 87% and almost quantitative yield, respectively.

They were afterwards successfully dimerized to bipyridines 11a and 11b at 68% and 78% isolated yields (Scheme 5). Surprisingly, oxidation of bipyridine 11b with MCPBA provided a complex mixture of products. The LC-MS analysis of the mixture detected the formation of other

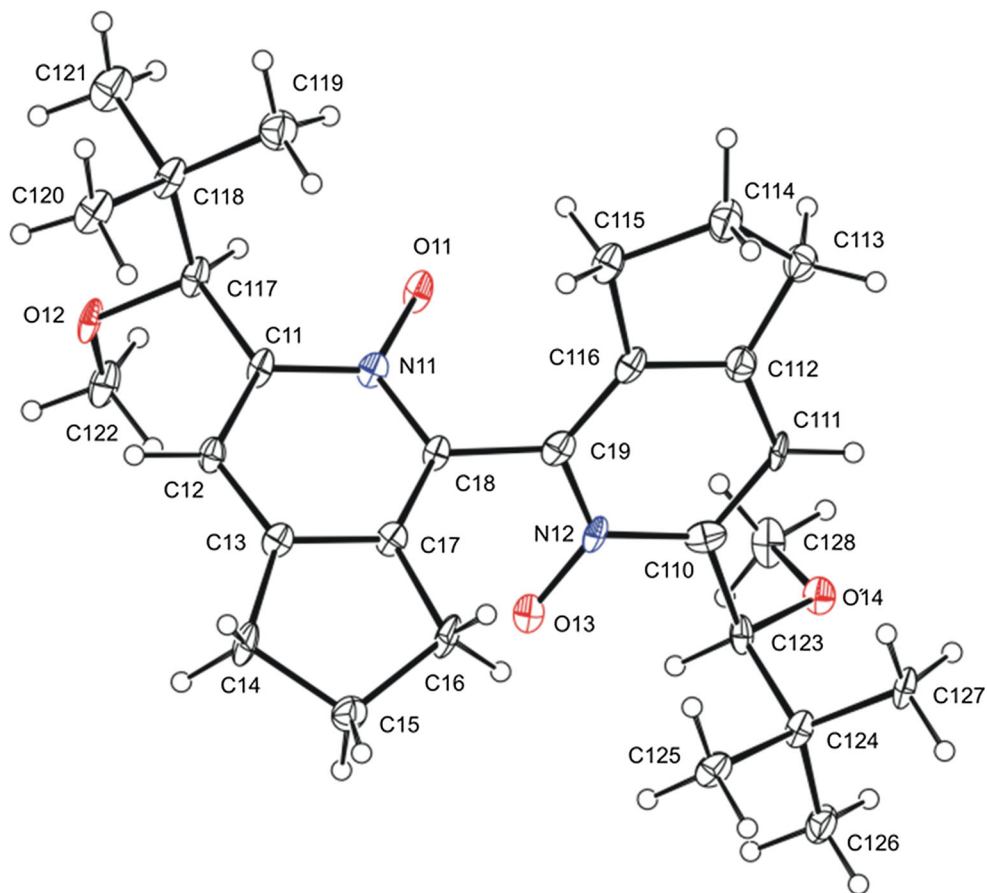
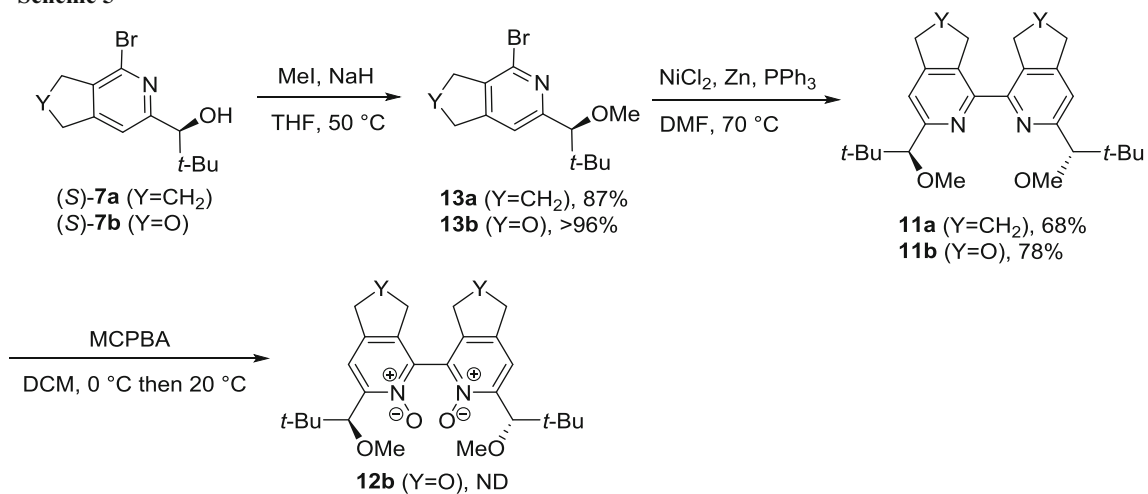


Fig. 3 ORTEP drawing of (*S,S,aR*)-**12a**

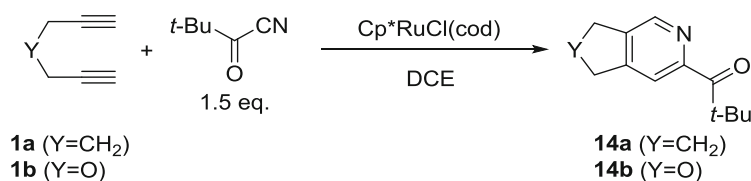
**Scheme 5**



products as cyclic lactones formed by oxidation of benzylic CH<sub>2</sub> groups in the five-membered ring. Unfortunately, also other oxidizing agents (other peroxides, percarbonate,

TEMPO, perruthenate, nitrite, oxaziridines, etc.) did not improve the selectivity of the reaction towards selective formation of *N,N'*-dioxide **12b**.



**Table 1** Cyclotrimerization of **1a** and **1b** with pivaloyl nitrile

Entry	Y	Diyne	[Ru]/mol% <sup>a</sup>	T/°C	Time/h	Pyridine	Yield/% <sup>b</sup>
1	CH <sub>2</sub>	<b>1a</b>	5	20 then 60	2.5	<b>14a</b>	44
2	O	<b>1b</b>	5	20 then 60	2.5	<b>14b</b>	58
3 <sup>c</sup>	CH <sub>2</sub>	<b>1a</b>	10	60	12	<b>14a</b>	70
4 <sup>c</sup>	CH <sub>2</sub>	<b>1a</b>	10	20	15	<b>14a</b>	75
5 <sup>c</sup>	O	<b>1b</b>	10	20	13	<b>14b</b>	89

<sup>a</sup>[Ru]—Cp\*RuCl(cod)<sup>b</sup>Isolated yield<sup>c</sup>Diyne was added slowly by a syringe pump

### Approach B

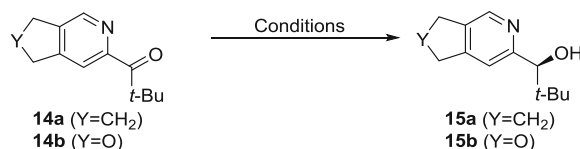
As we did not find a way for the synthesis of bipyridine *N,N'*-dioxide **12b** using approach **A** and as it would be convenient to prepare also the second atropoisomer (*S,S,aS*)-**12b** with the opposite chirality, we turned our attention to approach **B** described in Scheme 1. We started our synthesis with cyclotrimerization of hepta-1,6-diyne (**1a**) and propargyl ether (**1b**) with pivaloyl cyanide (Table 1). The original conditions developed by Yamamoto [15] for similar substrates provided desired products **14a** and **14b** at 44% moderate and 58% isolated yield, respectively (entries 1 and 2). Gratifyingly, optimization of reaction conditions comprising increase of the catalyst loading to 10 mol % and slow addition of diyne by a syringe pump resulted in increased yields of 75% and 89%, respectively (entries 4 and 5).

Reduction of the starting ketone **14a** with (–)-Ipc<sub>2</sub>BCl brought about no conversion (Table 2, entry 1). Its Ru-complex catalyzed transfer hydrogenation under the standard conditions (RuCl[(*S,S*)-Tsdpen](*p*-cymene), HCOOH/Et<sub>3</sub>N, 20 °C) [13] turned out to be very slow and, in addition, the required chiral alcohol **15a** was formed with moderate enantioselectivity: 47% yield, 55% ee after 12 days (entry 2). Increasing the temperature to 40 °C improved not only the rate of the reaction, the yield, but surprisingly also enantioselectivity (88% yield, 74% ee; entry 3). The rate of the reaction together with its yield was further improved by refluxing of the reaction mixture; unfortunately, a significant drop of enantioselectivity to 67% ee was observed (entry 4). Ketone **14b** was reduced under optimized conditions yielding alcohol **15b** in

quantitative yield and 89% ee (entry 5). In addition, after recrystallization from hexanes, the enantiomeric purity of both of the alcohols **15a** and **15b** was further improved. As a result, both compounds were obtained as optically pure compounds. *S* configuration of **15a** was unequivocally confirmed by a single-crystal X-ray analysis (Fig. 4).

Alcohols (*S*)-**15a** and (*S*)-**15b** were in the next step treated under basic conditions with methyl iodide to provide the corresponding methyl ethers **16a** and **16b** at 94% and the quantitative yield, respectively (Scheme 6). Their oxidation by MCPBA proceeded smoothly to furnish pyridine *N*-oxides **17a** and **17b** in quantitative yield without any sign of oxidation of benzylic CH<sub>2</sub> positions as was observed in the case of bipyridine **11b**. Ensuing oxidative dimerization using LiTMP and iodine furnished both atropoisomers of the target compounds (*S,S,aS*)-**12a** and (*S,S,aR*)-**12a** at 28% and 59% isolated yields, and (*S,S,aS*)-**12b** and (*S,S,aR*)-**12b** at 11% and 60% isolated yields.

Interestingly, our levels of selectivity in the last steps of approaches **A** and **B** are completely opposite to the observation reported by Denmark [16]. While we observed in approach **A** formation of only atropoisomer (*S,S,aR*)-**12b** by oxidation of bipyridine **11b** to *N,N'*-dioxide **12b**, Denmark described formation of both isomers (*R,R,aS*) and (*R,R,aR*) in 5/2 ratio when a structurally similar compound is oxidized. On the other hand, in the last step in approach **B**, the oxidative dimerization of a pyridine *N*-oxide to an *N,N'*-dioxide in the Denmark's case only (*R,R,aS*)-isomer was obtained, the same type of reaction in our hands furnished both (*S,S,aR*) and (*S,S,aS*) atropoisomers in 2/1 ratio for **12a** and 6/1 ratio for **12b**.

**Table 2** Chiral reduction of **14a** and **14b**

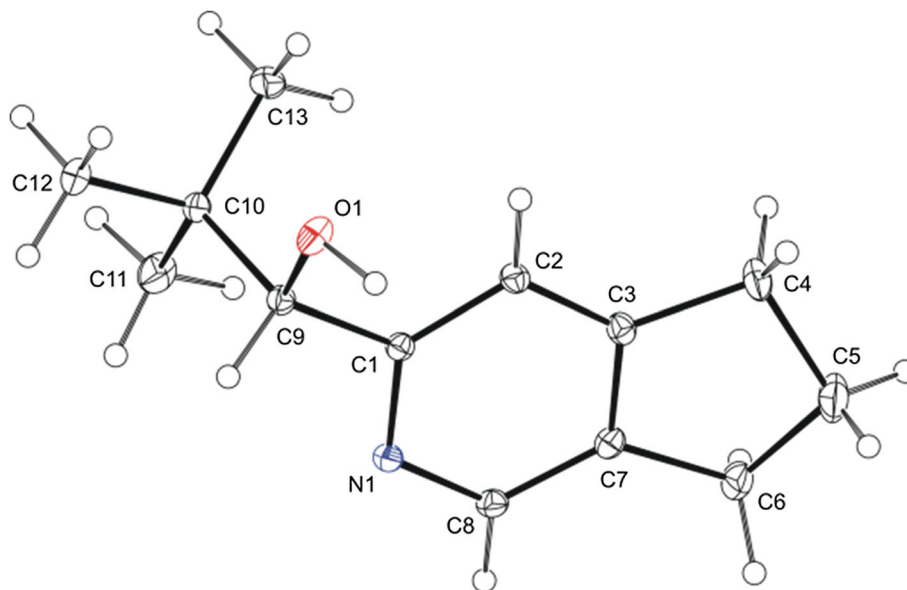
Entry	Y	Ketone	Catalyst <sup>a</sup>	Reductant	Solvent	<i>T</i> /°C	Time/d	Alcohol	Yield/% <sup>b</sup>	ee/% <sup>c</sup>
1	CH <sub>2</sub>	<b>14a</b>	–	(–)-Ipc <sub>2</sub> BCl	THF	20	2	<b>15a</b>	NR	–
2	CH <sub>2</sub>	<b>14a</b>	[Ru]	HCOOH, Et <sub>3</sub> N	DCM	20	12	<b>15a</b>	47	55
3	CH <sub>2</sub>	<b>14a</b>	[Ru]	HCOOH, Et <sub>3</sub> N	DCM	40	6	<b>15a</b>	88 (48) <sup>d</sup>	74 (> 99) <sup>d</sup>
4	CH <sub>2</sub>	<b>14a</b>	[Ru]	HCOOH, Et <sub>3</sub> N	DCM	reflux	0.5	<b>15a</b>	98	67
5	O	<b>14b</b>	[Ru]	HCOOH, Et <sub>3</sub> N	DCM	40	2	<b>15b</b>	98 (68) <sup>d</sup>	89 (> 99) <sup>d</sup>

<sup>a</sup>[Ru]—(RuCl[(*S,S*)-Tsdpen](*p*-cymene) (5 mol%)

<sup>b</sup>Isolated yield. *NR* no reaction

<sup>c</sup>Determined by HPLC with a chiral stationary phase

<sup>d</sup>Recrystallization from hexanes in parenthesis

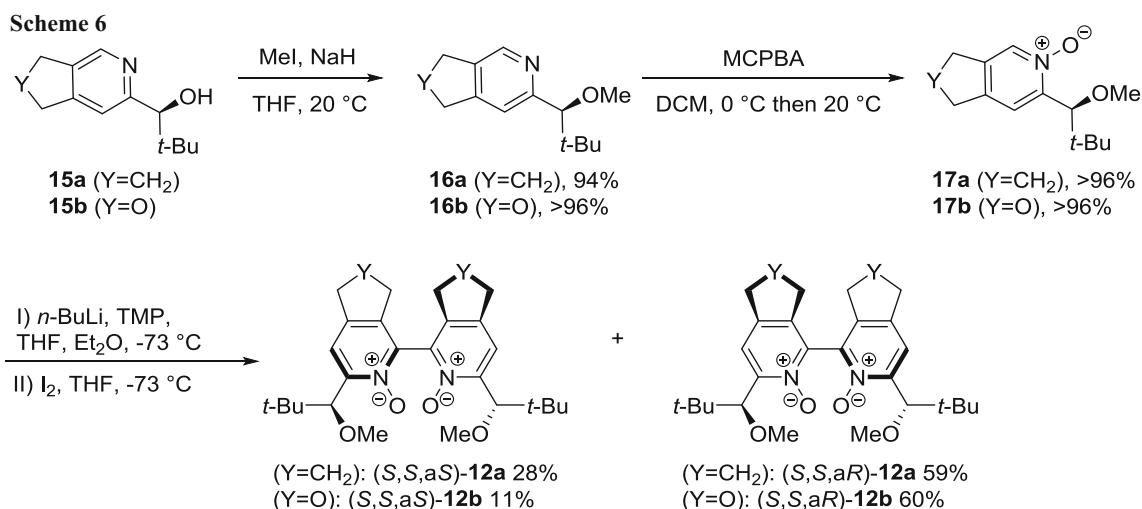
**Fig. 4** ORTEP drawing of (*S*)-**15a**

### Application of bipyridine *N,N'*-dioxide in organocatalytic reactions

Lewis base-catalyzed asymmetric allylation of benzaldehyde **18** with allyltrichlorosilane **19** has become the testing ground of the new *N*-oxide catalyst. For testing, we used all four of our newly prepared bipyridine *N,N'*-dioxide (*S,S,aS*)-**12a**, (*S,S,aR*)-**12a**, (*S,S,aS*)-**12b**, (*S,S,aR*)-**12b**, and *N,N'*-dioxide **20** (Fig. 5) derived from Bolm's 2,2'-bipyridine which possesses no axial chirality because of the lack of substituent in the positions 3 and 3' and which was

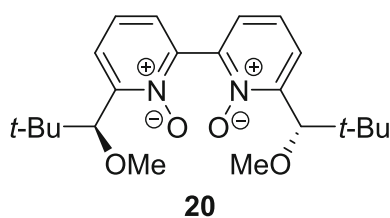
prepared following a slightly modified published procedure [17].

We started our study with conditions (0.5 mol% of the catalyst, 1.5 eq. of base, THF, – 78 °C, Table 3) that turned out to be optimal in our previous study of allylation of aldehydes using bipyridine *N,N'*-dioxide catalysts [18]. Unfortunately, only catalysts **20** and (*S,S,aR*)-**12a** turned out to be active providing allyl alcohol **21** at low yield and moderate to high enantioselectivity in the range of 0–69% ee (entries 1–5). Elevation of the reaction temperature to – 40 °C improved the yield but the enantioselectivity



noticeably dropped (entries 6–10). Increasing the amount of the base to 5 eq. caused the drop of both yield and ee (entries 11–15). A higher loading of the catalyst (1.5 mol %) improved the yield of the reaction but the change of enantioselectivity was marginal if any (entries 16–20). Although the use of acetonitrile notably improved the yields, the enantioselectivity remained moderate (entries 21–25). On the other hand, using DCM brought rise of enantioselectivity (entries 26–30) keeping the catalyst **20** the most active (76% yield, 82% ee). Increasing of the amount of the base as well as loading of the catalyst did not improve the results of the reaction (entries 31 and 32).

Generally, it can be stated that in most cases the *N,N'*-dioxide **20** without element of axial chirality provided allylic alcohol **21** in the best yields and enantioselectivity. Among the atropisomeric *N,N'*-dioxides, (*R*)-atropoisomers ((*S,S,aR*)-**12a** and (*S,S,aR*)-**12b**) provided the higher yield of alcohol **21** while the higher ee could be obtained using (*aS*)-isomers ((*S,S,aS*)-**12a** and (*S,S,aS*)-**12b**). Comparing *N,N'*-dioxides **12a** (Y = CH<sub>2</sub>) and **12b** (Y=O), the more selective were catalysts **12b** bearing the oxygen atom in the five-membered ring, whereas catalysts **12a** bearing all-carbon ring gave better enantioselectivity.

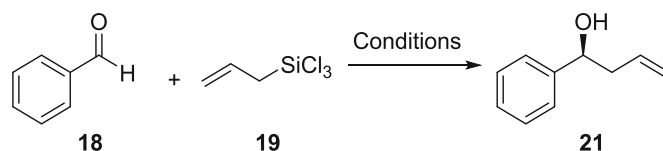


**Fig. 5** Structure of *N,N'*-dioxide **20**

Catalytic activity of the abovementioned *N,N'*-dioxides was then studied in aldolization reaction of acetophenone (**22**) with trichlorosilyl ketene acetal of methyl acetate (**23**) to tertiary alcohol **24** (Table 4). Despite its synthetic potential, the enantioselective variant of the aldol reaction is rather scarce. In 2002, Denmark et al. found out that the reaction can be catalyzed by bipyridine *N,N'*-dioxides of a similar structure to ours and they obtained the required alcohol **24** at 91% isolated yield and 87% ee, which has not been surpassed yet [17, 19]. For our study, we used Denmark's reaction conditions without any further optimization (10 mol % of the catalyst, DCM, -20 °C).

The use of (*S,S,aS*)-**12a** furnished (*S*)-**24** at 93% yield and 60% ee (entry 1), while utilization of the opposite atropoisomer (*S,S,aR*)-**12a** provided the desired product with the opposite stereochemistry, however, with low enantioselectivity (entry 2). On the other hand, using the atropoisomers (*S,S,aS*)-**12b** and (*S,S,aR*)-**12b**, the desired alcohol **24** was obtained with the same *R* configuration and quantitative yields with 57% and 78% ee, respectively (entries 3 and 4). Since Denmark et al. in their studies found that the *N,N'*-dioxides possessing 2,4,6-trimethylbenzyl (TMB) substituent instead of the methyl group in the etheric part of the catalysts provided the best results [17, 19], we synthesized new dioxides (*S,S,aS*)-**25b** and (*S,S,aR*)-**25b** (Fig. 6) following approach B. Using catalyst (*S,S,aS*)-**25b** alcohol (*S*)-**24** was formed at 67% yield with 24% ee (entry 5), while using catalyst (*S,S,aR*)-**25b**, alcohol **24** was obtained in 56% yield and 70% ee (entry 6) giving no advantage in use of *N,N'*-dioxide (*S,S,aR*)-**25b** instead of (*S,S,aR*)-**12b**.

The *N,N'*-dioxides (*R,aS*)-**26** and (*R,aR*)-**26**, which were previously developed in our group [20] (Fig. 6) and gave us the best results in allylation reactions, were studied as

**Table 3** Allylation of benzaldehyde **18** with allyltrichlorosilane **19**

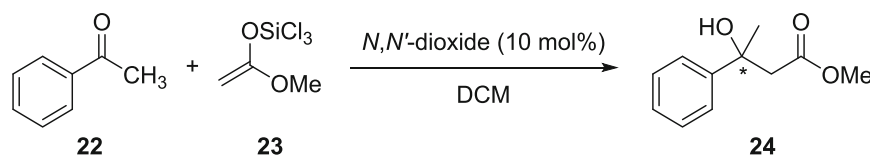
Entry	<i>N,N'</i> -Dioxide	Mol%	DIPEA/eq.	Solvent	<i>T</i> /°C	Time/h	Yield/% <sup>a</sup>	ee/% <sup>b,c</sup>
1	<b>20</b>	0.5	1.5	THF	− 78	13	17	69
2	( <i>S,S,aS</i> )- <b>12a</b>	0.5	1.5	THF	− 78	13	NR	−
3	( <i>S,S,aR</i> )- <b>12a</b>	0.5	1.5	THF	− 78	13	14	48
4	( <i>S,S,aS</i> )- <b>12b</b>	0.5	1.5	THF	− 78	13	NR	−
5	( <i>S,S,aR</i> )- <b>12b</b>	0.5	1.5	THF	− 78	13	NR	−
6	<b>20</b>	0.5	1.5	THF	− 40	13	40	21
7	( <i>S,S,aS</i> )- <b>12a</b>	0.5	1.5	THF	− 40	13	NR	−
8	( <i>S,S,aR</i> )- <b>12a</b>	0.5	1.5	THF	− 40	13	57	10
9	( <i>S,S,aS</i> )- <b>12b</b>	0.5	1.5	THF	− 40	13	NR	−
10	( <i>S,S,aR</i> )- <b>12b</b>	0.5	1.5	THF	− 40	13	NR	−
11	<b>20</b>	0.5	5	THF	− 78	15.5	18	47
12	( <i>S,S,aS</i> )- <b>12a</b>	0.5	5	THF	− 78	15.5	NR	−
13	( <i>S,S,aR</i> )- <b>12a</b>	0.5	5	THF	− 78	15.5	10	43
14	( <i>S,S,aS</i> )- <b>12b</b>	0.5	5	THF	− 78	15.5	NR	−
15	( <i>S,S,aR</i> )- <b>12b</b>	0.5	5	THF	− 78	15.5	NR	−
16	<b>20</b>	1.5	1.5	THF	− 78	12	27	70
17	( <i>S,S,aS</i> )- <b>12a</b>	1.5	1.5	THF	− 78	12	6	68
18	( <i>S,S,aR</i> )- <b>12a</b>	1.5	1.5	THF	− 78	12	42	49
19	( <i>S,S,aS</i> )- <b>12b</b>	1.5	1.5	THF	− 78	12	NR	−
20	( <i>S,S,aR</i> )- <b>12b</b>	1.5	1.5	THF	− 78	12	NR	−
21	<b>20</b>	0.5	1.5	ACN	− 40	13.5	93	54
22	( <i>S,S,aS</i> )- <b>12a</b>	0.5	1.5	ACN	− 40	13.5	11	40
23	( <i>S,S,aR</i> )- <b>12a</b>	0.5	1.5	ACN	− 40	13.5	96	33
24	( <i>S,S,aS</i> )- <b>12b</b>	0.5	1.5	ACN	− 40	13.5	39	51
25	( <i>S,S,aR</i> )- <b>12b</b>	0.5	1.5	ACN	− 40	15.5	93	45
26	<b>20</b>	0.5	1.5	DCM	− 78	15.5	76	82
27	( <i>S,S,aS</i> )- <b>12a</b>	0.5	1.5	DCM	− 78	15.5	NR	−
28	( <i>S,S,aR</i> )- <b>12a</b>	0.5	1.5	DCM	− 78	15.5	77	46
29	( <i>S,S,aS</i> )- <b>12b</b>	0.5	1.5	DCM	− 78	15.5	NR	−
30	( <i>S,S,aR</i> )- <b>12b</b>	0.5	1.5	DCM	− 78	15.5	27	72
31	<b>20</b>	0.5	1.5	DCM	− 78	17	40	83
32	<b>20</b>	1.5	5	DCM	− 78	17	73	81

<sup>a</sup><sup>1</sup>H NMR yield, *NR* no reaction<sup>b</sup>Determined by HPLC with a chiral stationary phase<sup>c</sup>*S* configuration in all cases

catalysts in aldolization reaction as well. Catalyst (*R,aS*)-**26** provided alcohol (*S*)-**24** in 86% and 40% ee; on the other hand, alcohol (*R*)-**24** was obtained using (*R,aR*)-**26** in 93% yield and 65% ee (entries 7 and 8).

Unfortunately, the most promising results with catalysts (*S,S,aR*)-**12b** and (*R,aR*)-**26** were not further improved by decrease of the reaction temperature to − 50 °C (entries 9

and 10). The replacement of DCM by THF, which revealed to be essential in allylation reaction with catalyst (*R,aR*)-**26** [20], caused the formation of opposite major enantiomer, however, with low selectivity (entry 11).

**Table 4** Aldol reaction of acetophenone **22** with trichlorosilyl ketene acetal **23**

Entry	<i>N,N'</i> -Dioxide	<i>T</i> /°C	Time/h	Yield/% <sup>a</sup>	ee/% <sup>b</sup>
1	( <i>S,S,aS</i> )- <b>12a</b>	− 20	18	93	60 ( <i>S</i> )
2	( <i>S,S,aR</i> )- <b>12a</b>	− 20	18	87	15 ( <i>R</i> )
3	( <i>S,S,aS</i> )- <b>12b</b>	− 20	18	> 96	57 ( <i>R</i> )
4	( <i>S,S,aR</i> )- <b>12b</b>	− 20	18	> 96	78 ( <i>R</i> )
5	( <i>S,S,aS</i> )- <b>25b</b>	− 20	18	67	24 ( <i>S</i> )
6	( <i>S,S,aR</i> )- <b>25b</b>	− 20	18	56	70 ( <i>R</i> )
7	( <i>R,aS</i> )- <b>26</b>	− 20	18	86	40 ( <i>S</i> )
8	( <i>R,aR</i> )- <b>26</b>	− 20	18	93	65 ( <i>R</i> )
9	( <i>S,S,aR</i> )- <b>12b</b>	− 50	36	81	75 ( <i>R</i> )
10	( <i>R,aR</i> )- <b>26</b>	− 50	36	81	68 ( <i>R</i> )
11 <sup>c</sup>	( <i>R,aR</i> )- <b>26</b>	− 50	36	42	9 ( <i>S</i> )

<sup>a</sup><sup>1</sup>H NMR yield<sup>b</sup>Determined by HPLC with a chiral stationary phase<sup>c</sup>THF was used as a solvent

## Conclusion

We have developed two new pathways for the synthesis of six axially chiral *N,N'*-dioxides based on catalytic [2+2+2] cyclootrimerization of diynes with nitriles. These two approaches differ in the dimerization method—while in approach A, the *N,N'*-dioxide was prepared by oxidation of a bipyridine, which is formed by reductive dimerization of 2-bromopyridine, approach B is based on oxidative dimerization of a pyridine *N*-oxide. While only one atropisomer of the desired *N,N'*-dioxide is formed selectively in approach A, approach B provides both the atropisomers. The utility of all six newly formed *N,N'*-dioxides was proved in asymmetric reactions, namely allylation of aldehydes and aldol addition to acetophenone.

## Experimental

All chemicals were purchased from common commercial sources—Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem chemicals and PENTA. Dry solvents for reactions were purified and dried by distillation from sodium/benzophenone (THF, Et<sub>2</sub>O), CaH<sub>2</sub> (DCM, DCE), or by standing over molecular sieves (DMF, ACN). For degassing the solvents, freeze–pump–thaw technique or

sonication with argon bubbling was used. Solvents for column chromatography were distilled prior to use. Benzaldehyde (**18**), acetophenone (**22**), tetrachlorosilane, diisopropylamine, *N,N*-diisopropylethylamine, and tributyltin chloride were purified by distillation prior to use. Other solvents and chemicals were used without any purification. Argon or nitrogen was used as an inert gas.

Silica gel 60 (0.040–0.063 mm) was used for column chromatography, TLC was performed on aluminum sheets with a layer of silica gel 60 F<sub>254</sub>, both purchased from MERCK. Spots on TLC plates were detected using UV lamp ( $\lambda = 254$  nm), basic permanganate solution or acidic *p*-anisaldehyde solution.

NMR spectra were recorded on Varian VNMRS 300 ( $\nu(^1\text{H}) = 299.94$  MHz,  $\nu(^{13}\text{C}) = 75.43$  MHz), on Bruker Avance III (400 MHz) ( $\nu(^1\text{H}) = 400.13$  MHz,  $\nu(^{13}\text{C}) = 100.61$  MHz), or on Bruker Avance III (600 MHz) ( $\nu(^1\text{H}) = 600.17$  MHz,  $\nu(^{13}\text{C}) = 150.04$  MHz) in deuterated chloroform and referenced to residual solvent peak (<sup>1</sup>H: 7.26 ppm, <sup>13</sup>C: 77.16 ppm). Chemical shifts are given in  $\delta$  scale; coupling *J* constants are given in Hz.

Mass spectra were recorded on VG-Analytical ZAB-SEQ and Synapt G2-S. Infrared spectra were recorded in KBr and measured on spectrometer Hermo Nicolet AVATAR 370 FT-IR. All melting points were determined on Kofler apparatus. Optical rotations were measured on automatic polarimeter Autopol III and are given in

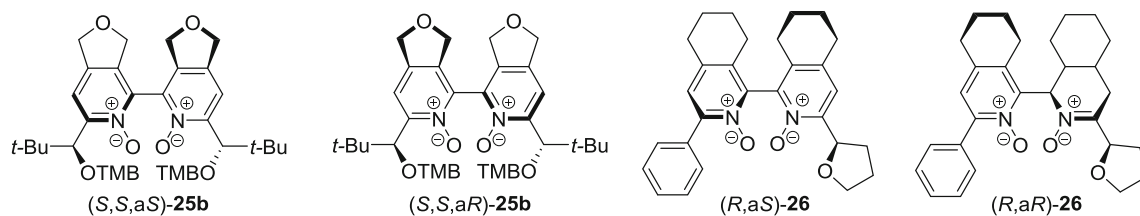


Fig. 6 Structure of *N,N'*-dioxides **25b** and **26**

deg cm<sup>3</sup> g<sup>-1</sup> dm<sup>-1</sup> with accuracy  $\pm 2$  and the mass concentrations in g/100 cm<sup>3</sup>. HPLC analyses of chiral products were done on Shimadzu chromatograph with Daicel Chiralpak<sup>®</sup> and Lux Columns.

Compounds **2a**, **2b**, **3a**, **3b**, **4a**, **5a**, **6a**, **7a**, **8a**, **9a**, **10a**,  $(R,aS)$ -**26**,  $(R,aR)$ -**26**, **27**, and pivaloyl cyanide were prepared according to the previously published procedures [12, 14, 20].

**1-[4-Bromo-7-(trimethylsilyl)-1,3-dihydrofuro[3,4-c]pyridin-6-yl]-2,2-dimethylpropan-1-one (4b, C<sub>14</sub>H<sub>20</sub>BrNO<sub>2</sub>Si)** and **1-[7-bromo-4-(trimethylsilyl)-1,3-dihydrofuro[3,4-c]pyridin-6-yl]-2,2-dimethylpropan-1-one (5b, C<sub>14</sub>H<sub>20</sub>BrNO<sub>2</sub>Si)** To a dry-argon-flushed 5-cm<sup>3</sup> Schlenk flask were added 9 mg of Cp<sup>\*</sup>RuCl(cod) (0.02 mmol), 1 cm<sup>3</sup> of DCE and 60 mm<sup>3</sup> of pivaloyl cyanide (0.5 mmol). Then 60 mg of diyne **3b** (0.25 mmol) dissolved in 2 cm<sup>3</sup> of DCE was added slowly by a syringe pump during the course of 1 h. The reaction mixture was stirred at 20 °C until **3b** was fully consumed (disappearance of the respective spot on TLC). Then volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradient 50/1 → 40/1 cyclohexane/EtOAc) provided 52 mg (60%) of **4b** and 10 mg (12%) of **5b** as colorless oils. **4b**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.23–5.20 (m, 2H, CH<sub>2</sub>), 5.06–5.03 (m, 2H, CH<sub>2</sub>), 1.41 (s, 9H, 3 × CH<sub>3</sub>), 0.27 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 208.84, 160.81, 156.96, 136.02, 132.71, 127.25, 74.99, 71.90, 43.26, 27.18, 0.29 ppm; IR (drift KBr):  $\bar{\nu}$  = 2956, 1693, 1541, 1241, 1050, 1009, 931, 846 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>14</sub>H<sub>21</sub>BrNO<sub>2</sub>Si ([M+H]<sup>+</sup>) 342.0525, found 342.0524; *R<sub>f</sub>* = 0.40 (10/1 hexane/EtOAc). **5b**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.27 (t, *J* = 2.1 Hz, 2H, CH<sub>2</sub>), 5.06 (t, *J* = 2.1 Hz, 2H, CH<sub>2</sub>), 1.33 (s, 9H, 3 × CH<sub>3</sub>), 0.29 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 211.31, 159.66, 157.34, 149.89, 143.85, 111.99, 75.90, 75.47, 46.16, 28.81, 0.00 ppm; IR (drift KBr):  $\bar{\nu}$  = 2966, 1704, 1249, 1057, 1013, 942, 895, 845 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>14</sub>H<sub>21</sub>BrNO<sub>2</sub>Si ([M+H]<sup>+</sup>) 342.0525, found 342.0524; *R<sub>f</sub>* = 0.31 (10/1 hexane/EtOAc).

**1-(4-Bromo-1,3-dihydrofuro[3,4-c]pyridin-6-yl)-2,2-dimethylpropan-1-one (6b, C<sub>12</sub>H<sub>14</sub>BrNO<sub>2</sub>)** To a solution of

3.27 g of **4b** (9.24 mmol) in 80 cm<sup>3</sup> of MeOH was added 1.3 g of K<sub>2</sub>CO<sub>3</sub> (9.4 mmol). After stirring at 60 °C for 10 h, the reaction mixture was quenched by addition of 30 cm<sup>3</sup> of water and extracted with 3 × 100 cm<sup>3</sup> of DCM. Combined organic fractions were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under the reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1 → 20/1) yielded 2415 mg (93%) of the title compound as colorless crystals. M.p.: 112.9 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.79 (s, 1H, Ar-H), 5.23–5.19 (m, 2H, CH<sub>2</sub>), 5.11–5.08 (m, 2H, CH<sub>2</sub>), 1.44 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 204.87, 154.44, 151.86, 139.84, 132.80, 116.21, 74.38, 73.41, 44.46, 27.59 ppm; IR (drift KBr):  $\bar{\nu}$  = 2973, 2959, 1679, 1550, 1281, 1191, 1127, 1049, 996, 910, 855 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>12</sub>H<sub>15</sub>BrNO<sub>2</sub> ([M+H]<sup>+</sup>) 284.0286, found 284.0288; *R<sub>f</sub>* = 0.23 (10/1 hexane/EtOAc).

**(S)-1-(4-Bromo-1,3-dihydrofuro[3,4-c]pyridin-6-yl)-2,2-dimethylpropan-1-ol (7b, C<sub>12</sub>H<sub>16</sub>BrNO<sub>2</sub>)** To a dry-argon-flushed 10-cm<sup>3</sup> flask with a solution of 270 mg of **6b** (0.95 mmol) and 34 mg of RuCl[(*S,S*)-Tsdpen](*p*-cymene) (0.05 mmol) in 2 cm<sup>3</sup> of DCM, 1.5 cm<sup>3</sup> of a mixture of Et<sub>3</sub>N/HCOOH (2/1) was added. After stirring for 17 h at 20 °C, the reaction mixture was quenched with 5 cm<sup>3</sup> of water and extracted with 3 × 20 cm<sup>3</sup> of EtOAc. The combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 7/1 → 4/1 hexanes/EtOAc) furnished 270 mg (99%, 90% ee) of the title compound as an amorphous solid. Optically pure compound could be obtained by recrystallization from CHCl<sub>3</sub> by slow evaporation of solvent. M.p.: 49.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.08 (s, 1H, Ar-H), 5.18–5.16 (m, 2H, CH<sub>2</sub>), 5.05 (t, *J* = 2.2 Hz, 2H, CH<sub>2</sub>), 4.35 (s, 1H, CH), 0.92 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 161.70, 151.05, 136.04, 133.60, 114.75, 80.77, 74.16, 73.15, 36.43, 25.97 ppm; IR (drift KBr):  $\bar{\nu}$  = 2955, 2867, 1607, 1556, 1364, 1051, 1016, 906 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>12</sub>H<sub>17</sub>BrNO<sub>2</sub> ([M+H]<sup>+</sup>) 286.04372, found 286.04381; *R<sub>f</sub>* = 0.30 (4/1 hexane/EtOAc);  $[\alpha]_D^{20}$  = + 2.58° (*c* = 2.7, CHCl<sub>3</sub>). HPLC



of **7b**: Daicel Chiralpak IA, *n*-heptane/IPA 98/2, 1 cm<sup>3</sup>/min, 207 nm, *t*<sub>S</sub> = 17.8 min (major), *t*<sub>R</sub> = 18.8 min (minor).

**(rac)-1-(4-Bromo-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropan-1-ol ((rac)-7b, C<sub>12</sub>H<sub>16</sub>BrNO<sub>2</sub>)** To a solution of 16 mg of **6b** (0.06 mmol) in 0.4 cm<sup>3</sup> of dry MeOH in 4 cm<sup>3</sup> vial, 3 mg of NaBH<sub>4</sub> (0.08 mmol) was added. After 3 h at 20 °C, the reaction mixture was quenched with 2 cm<sup>3</sup> of water and the mixture was extracted with 3 × 5 cm<sup>3</sup> of Et<sub>2</sub>O. The combined organic fractions were washed with 5 cm<sup>3</sup> of brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (5/1 hexanes/EtOAc) provided 15 mg (93%) of the title compound as an amorphous solid. All the spectral data were in agreement with the chiral product **7b**. HPLC of **(rac)-7b**: Daicel Chiralpak IA, *n*-heptane/IPA 98/2, 1 cm<sup>3</sup>/min, 207 nm, *t*<sub>S</sub> = 17.7 min, *t*<sub>R</sub> = 18.7 min.

**(S)-1-(4-Bromo-1,3-dihydrofuro[3,4-*c*]pyridin-6-yl)-2,2-dimethylpropyl acetate (8b, C<sub>14</sub>H<sub>18</sub>BrNO<sub>3</sub>)** To a cooled solution (ice–water) of 198 mg of **7b** (0.69 mmol) in 150 mm<sup>3</sup> of pyridine (1.7 mmol) in 10-cm<sup>3</sup> flask, 200 mm<sup>3</sup> of acetic anhydride (1.9 mmol) was added dropwise. After stirring at 20 °C for 16 h, the reaction mixture was quenched with 5 cm<sup>3</sup> of NaHCO<sub>3</sub> (sat. aq. solution) and extracted with 3 × 15 cm<sup>3</sup> of DCM. The combined organic fractions were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 6/1 → 5/1 hexanes/EtOAc) furnished 225 mg (99%) of the title compound as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.11 (s, 1H, Ar–H), 5.52 (s, 1H, CH), 5.19–5.14 (m, 2H, CH<sub>2</sub>), 5.06–5.01 (m, 2H, CH<sub>2</sub>), 2.13 (s, 3H, CH<sub>3</sub>), 0.97 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 170.34, 159.36, 151.07, 136.10, 133.85, 114.10, 82.89, 74.24, 73.27, 35.17, 26.22 ppm; IR (drift KBr):  $\bar{\nu}$  = 2968, 1371, 1240, 1201, 1051, 1027, 911 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>14</sub>H<sub>19</sub>BrNO<sub>3</sub> ([M+H]<sup>+</sup>) 328.0548, found 328.0552; *R*<sub>f</sub> = 0.50 (3/1 hexane/EtOAc).

**(S,S)-(1,1',3,3'-Tetrahydro[4,4'-bifuro[3,4-*c*]pyridine]-6,6'-diyl)bis(2,2-dimethylpropane-1,1-diyl) diacetate (9b, C<sub>28</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>)** To a dry-argon-flushed 100-cm<sup>3</sup> flask with 193 mg of NiCl<sub>2</sub> (1.5 mmol), dry degassed 5 cm<sup>3</sup> of DMF was added. The mixture was heated to 70 °C, then 1.53 g of PPh<sub>3</sub> (5.8 mmol) and 105 mg of Zn (1.6 mmol) were added. The reaction mixture was stirred at 70 °C for 1 h, then 400 mg of **8b** (1.2 mmol) in dry degassed 4 cm<sup>3</sup> of DMF was added. After stirring for 13 h at 70 °C, the reaction mixture was quenched with 10 cm<sup>3</sup> of water and extracted with 3 × 30 cm<sup>3</sup> of Et<sub>2</sub>O. The combined organic

fractions were washed with 20 cm<sup>3</sup> of brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 4/1 → 3/1 hexanes/EtOAc) furnished 187 mg (62%) of the title compound as a colorless solid. M.p.: 176.4 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.14 (s, 2H, 2 × Ar–H), 5.75 (dt, *J* = 14.6, 1.9 Hz, 2H, CH<sub>2</sub>), 5.62–5.53 (m, 2H, CH<sub>2</sub>), 5.55 (s, 2H, 2 × CH), 5.14–5.09 (m, 4H, 2 × CH<sub>2</sub>), 2.15 (s, 6H, 2 × CH<sub>3</sub>), 1.01 (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 170.47, 156.58, 150.72, 149.45, 133.95, 114.74, 83.76, 75.18, 72.36, 35.23, 26.46, 21.24 ppm; IR (drift KBr):  $\bar{\nu}$  = 2959, 2929, 2869, 1739, 1592, 1568, 1371, 1242, 1042, 1024, 902 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd. for C<sub>28</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 497.2652, found 497.2654; *R*<sub>f</sub> = 0.34 (3/1 hexane/EtOAc).

**3,3'-Bis((S)-1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-1,1'-bi(cyclopenta[*c*]pyridine)**

**(11a, C<sub>28</sub>H<sub>40</sub>N<sub>2</sub>O<sub>2</sub>)** Method A: To a suspension of 30 mg of NaH (60% w/w suspension in mineral oil, 0.73 mmol) in 1 cm<sup>3</sup> of THF in 10-cm<sup>3</sup> Ar-flushed flask, a solution of 100 mg of **10a** (0.25 mmol) in 4 cm<sup>3</sup> of THF was added slowly. Mixture was stirred at 20 °C for 30 min, then 124 mm<sup>3</sup> of MeI (3.0 mmol) was added slowly. After stirring at 50 °C for 24 h, the reaction mixture was quenched by addition of 2 cm<sup>3</sup> of water and extracted with 3 × 10 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1 → 20/1) yielded 89 mg (83%) of the title compound as a colorless solid.

Method B: To a dry-argon-flushed 5-cm<sup>3</sup> vial with 48 mg of NiCl<sub>2</sub> (0.36 mmol), dry degassed 2 cm<sup>3</sup> of DMF was added. The reaction mixture was heated to 70 °C, then 380 mg of PPh<sub>3</sub> (1.45 mmol) and 26 mg of Zn (0.39 mmol) were added. The reaction mixture was stirred at 70 °C for 1 h, then 90 mg of **13a** (0.30 mmol) in 2 cm<sup>3</sup> of dry degassed DMF was added. After stirring for 12 h at 70 °C, DMF was distilled off under the reduced pressure, the residue was suspended in 10 cm<sup>3</sup> of DCM and filtered through Celite®. Filtrate was washed with 5 cm<sup>3</sup> of NaHCO<sub>3</sub> (sat. aq. solution) and the aqueous phase was then washed with 2 × 15 cm<sup>3</sup> of DCM. The combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 100/1 → 12/1 hexanes/EtOAc) furnished 45 mg (68%) of the title compound as colorless crystals. M.p.: 199.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.27 (s, overlapping with CDCl<sub>3</sub>), 4.05 (s, 2H, 2 × CH), 3.44–3.33 (m, 2H, 2 × CH), 3.18 (s, 6H,

2 × CH<sub>3</sub>), 3.01–2.93 (m, 4H, 2 × CH<sub>2</sub>), 2.75–2.65 (m, 2H, 2 × CH), 2.23–2.11 (m, 2H, 2 × CH), 2.05–1.19 (m, 2H, 2 × CH), 0.96 (s, 18H, 9 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 157.67, 155.51, 152.50, 138.13, 117.66, 92.93, 57.77, 35.80, 33.13, 31.92, 26.66, 25.06 ppm; IR (drift KBr):  $\bar{\nu}$  = 2983, 2962, 2926, 2869, 2815, 1248, 1231, 1183, 1105, 973 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>2</sub> ([M+H]<sup>+</sup>) 437.31626, found 437.31570; *R<sub>f</sub>* = 0.48 (5/1 hexanes/EtOAc).

**6,6'-Bis((S)-1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro-4,4'-bifuro[3,4-*c*]pyridine (11b, C<sub>26</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>)** To a dry-argon-flushed 5-cm<sup>3</sup> vial with 80 mg of NiCl<sub>2</sub> (0.6 mmol), dry degassed 1.5 cm<sup>3</sup> of DMF was added. The reaction mixture was heated to 70 °C, then 630 mg of PPh<sub>3</sub> (2.4 mmol) and 43 mg of Zn (0.65 mmol) were added. The reaction mixture was stirred at 70 °C for 1 h, then 150 mg of **13b** (0.50 mmol) in dry degassed 2 cm<sup>3</sup> of DMF was added. After stirring for 12 h at 70 °C, DMF was distilled off under the reduced pressure; the residue was suspended in 15 cm<sup>3</sup> of DCM and filtered through Celite®. Filtrate was washed with 10 cm<sup>3</sup> of NaHCO<sub>3</sub> (sat. aq. solution) and the aqueous phase was then washed with 2 × 30 cm<sup>3</sup> of DCM. The combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1 → 18/1 hexanes/EtOAc) furnished 86 mg (78%) of the title compound as colorless crystals. M.p.: 215.0 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.26 (s, overlapping with CDCl<sub>3</sub>, 2 × Ar-H), 5.73 (dt, *J* = 14.5, 2.0 Hz, 2H, 2 × CH), 5.61 (dt, *J* = 14.6, 1.9 Hz, 2H, 2 × CH), 5.17–5.13 (m, 4H, 2 × CH<sub>2</sub>), 4.05 (s, 2H, 2 × CH), 3.23 (s, 6H, 2 × CH<sub>3</sub>), 0.96 (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 159.11, 150.72, 149.31, 133.49, 114.14, 92.98, 75.17, 72.49, 57.95, 35.25, 26.51 ppm; IR (drift KBr):  $\bar{\nu}$  = 2986, 2962, 2926, 2866, 1180, 1099, 1048, 964, 908 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>4</sub> ([M+H]<sup>+</sup>) 441.27478, found 441.27457; *R<sub>f</sub>* = 0.35 (10/1 hexanes/EtOAc).

**(S,S,aS)-3,3'-Bis((S)-1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((S,S,aS)-12a, C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>) and (S,S,aR)-3,3'-bis((S)-1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5H,5'H-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((S,S,aR)-12a, C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>)** Method A: To a solution of 60 mg of **11a** (0.14 mmol) in 4.5 cm<sup>3</sup> of DCM cooled down to 0 °C (ice-water) was added 90 mg of MCPBA (0.41 mmol) in six portions during 5 h. After stirring for 2 h at 20 °C, **11a** was fully consumed (disappearance the respective spot on TLC), the reaction was quenched by addition of 3 cm<sup>3</sup> of NaOH (40% aq. solution) and stirred for 1 h. The phases were separated and the aqueous phase was washed with

3 × 15 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 20/1 → 5/1 CHCl<sub>3</sub>/acetone) furnished 60 mg (93%) of (S,S,aR)-**12a** as a colorless solid.

Method B: To a solution of 273 mg of **17a** (1.16 mmol) in 5 cm<sup>3</sup> of Et<sub>2</sub>O cooled to –73 °C in 25-cm<sup>3</sup> Ar-flushed flask, freshly prepared solution of LiTMP (1.27 mmol) in 3.5 cm<sup>3</sup> of dry THF was added dropwise. Mixture was stirred at –73 °C for 16 h, then solution of 330 mg of I<sub>2</sub> (1.3 mmol) in 2.5 cm<sup>3</sup> of dry THF was added in two portions in 1 h. The reaction mixture was let to warm up to 20 °C during the period of 3 h, then it was quenched by addition of 5 cm<sup>3</sup> of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (sat. aq. solution) and extracted with 5 × 15 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 90/1/1 → 90/30/1 DCM/acetone/EtOH) furnished 75 mg (28%) of (S,S,aS)-**12a** and 160 mg (59%) of (S,S,aR)-**12a** as yellowish solids. (S,S,aS)-**12a**: M.p.: 210.6 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.28 (s, 2H, 2 × Ar-H), 4.98 (s, 2H, 2 × CH), 3.21 (s, 6H, 2 × CH<sub>3</sub>), 3.01 (ddd, *J* = 15.8, 8.6, 6.8 Hz, 2H, 2 × CH), 2.96 (t, *J* = 7.4 Hz, 4H, 2 × CH<sub>2</sub>), 2.54 (ddd, *J* = 16.5, 8.8, 5.7 Hz, 2H, 2 × CH), 2.26–2.03 (m, 4H, 2 × CH<sub>2</sub>), 0.96 (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 148.88, 142.36, 141.31, 139.17, 120.49, 83.35, 58.05, 37.29, 32.67, 30.90, 25.85, 25.19 ppm; IR (drift KBr):  $\bar{\nu}$  = 2965, 1290, 1263, 1248, 1225, 1174, 1096, 1066 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>28</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>4</sub> ([M+Na]<sup>+</sup>) 491.28803, found 491.28775; *R<sub>f</sub>* = 0.17 (60/1 DCM/MeOH); [α]<sub>D</sub><sup>20</sup> = –315.6° (*c* = 0.48, CHCl<sub>3</sub>); HPLC of (S,S,aS)-**12a**: Lux Columns—Lux Cellulose-1, *n*-heptane/IPA 99.5/0.5, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>S,S,aS</sub> = 13.2 min, *t*<sub>R,R,aR</sub> = ND. (S,S,aR)-**12a**: M.p.: 112.0 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.31 (s, 2H, 2 × Ar-H), 5.04 (s, 2H, 2 × CH), 3.22 (s, 6H, 2 × CH<sub>3</sub>), 3.07–2.95 (m, 4H, 2 × CH<sub>2</sub>), 2.90 (dt, *J* = 16.5, 8.3 Hz, 2H, 2 × CH), 2.45 (ddd, *J* = 16.5, 9.1, 5.0 Hz, 2H, 2 × CH), 2.28–2.15 (m, 2H, 2 × CH), 2.15–2.02 (m, 2H, 2 × CH), 0.98 (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 149.19, 142.30, 142.15, 139.35, 120.73, 82.68, 58.34, 37.23, 32.72, 30.68, 25.89, 24.86 ppm; IR (drift KBr):  $\bar{\nu}$  = 2971, 2953, 2926, 2908, 1392, 1293, 1248, 1210, 1102, 1072 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub> ([M+H]<sup>+</sup>) 469.30608, found 469.30599; *R<sub>f</sub>* = 0.36 (30/1 DCM/MeOH); [α]<sub>D</sub><sup>20</sup> = +36.7° (*c* = 0.15, CHCl<sub>3</sub>); HPLC of (S,S,aR)-**12a**: Lux Columns—Lux Cellulose-1, *n*-heptane/IPA 95/5, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>S,S,aR</sub> = 4.1 min, *t*<sub>R,R,aS</sub> = ND.



**Racemic (*S,S,aS*)-3,3'-bis(1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-12a<sub>1</sub>, C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>), racemic (*S,S,aR*)-3,3'-bis(1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-12a<sub>2</sub>, C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>), racemic (*S,R,aR*)-3,3'-bis(1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-12a<sub>3</sub>, C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>), and racemic (*S,R,aR*)-3,3'-bis(1-methoxy-2,2-dimethylpropyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-[1,1'-bi(cyclopenta[*c*]pyridine)] 2,2'-dioxide ((*rac*)-12a<sub>4</sub>, C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub>)** By approach B using racemic alcohol (*rac*)-15a were prepared products (*rac*)-12a<sub>1</sub> and (*rac*)-12a<sub>2</sub> and as well 50/50 mixture of (*rac*)-12a<sub>3</sub> and (*rac*)-12a<sub>4</sub>. Spectral data of products (*rac*)-12a<sub>1</sub> and (*rac*)-12a<sub>2</sub> were in agreement with chiral products (*S,S,aS*)-12a and (*S,S,aR*)-12a. HPLC of (*rac*)-12a<sub>1</sub>: Lux Columns—Lux Cellulose-1, *n*-heptane/IPA 99.5/0.5, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>S,S,aS</sub> = 13.6 min, *t*<sub>R,R,aR</sub> = 16.1 min. HPLC of (*rac*)-12a<sub>2</sub>: Lux Columns—Lux Cellulose-1, *n*-heptane/IPA 95/5, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>S,S,aR</sub> = 4.1 min, *t*<sub>R,R,aS</sub> = 5.4 min. (*rac*)-12a<sub>3</sub> + (*rac*)-12a<sub>4</sub>: M.p.: 234.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.30 (s, 2H, 2 × Ar-H), 7.29 (s, 2H, 2 × Ar-H), 5.02 (s, 2H, 2 × CH), 5.01 (s, 2H, 2 × CH), 3.26 (s, 6H, 2 × CH<sub>3</sub>), 3.20 (s, 6H, 2 × CH<sub>3</sub>), 3.13–2.89 (m, 12H, 6 × CH<sub>2</sub>), 2.49–2.33 (m, 4H, 4 × CH), 2.27–2.13 (m, 4H, 4 × CH), 2.13–1.99 (m, 4H, 4 × CH), 0.98 (s, 36H, 12 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 149.05 (2C), 142.78, 142.71, 142.00, 141.44, 139.22, 139.15, 120.66 (2C), 83.11, 82.79, 58.61, 57.97, 37.36, 37.12, 32.69, 32.64, 30.89, 30.76, 25.93, 25.92, 25.03, 24.99 ppm; IR (drift KBr):  $\bar{\nu}$  = 2965, 1296, 1251, 1225, 1210, 1180, 1150, 1093, 1069, 970, 937, 923 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>4</sub> ([M+H]<sup>+</sup>) 469.30608, found 469.30627; *R*<sub>f</sub> = 0.49 (30/1 DCM/MeOH).

**(*S,S,aS*)-3,3'-6,6'-Bis((*S*)-1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S,S,aS*)-12b, C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub>) and (*S,S,aR*)-3,3'-6,6'-bis((*S*)-1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S,S,aR*)-12b, C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub>)** To a solution of 163 mg of 17b (0.7 mmol) in 4 cm<sup>3</sup> of Et<sub>2</sub>O cooled to -73 °C in 25-cm<sup>3</sup> Ar-flushed flask, freshly prepared solution of LiTMP (0.76 mmol) in 1.4 cm<sup>3</sup> of dry THF was added dropwise. Mixture was stirred at -73 °C for 16 h, then solution of 191 mg of I<sub>2</sub> (1.3 mmol) in 2 cm<sup>3</sup> of dry THF was added in two portions in 2 h. The reaction mixture was let to warm up to 20 °C during the period of 3 h, then it was quenched by addition of 5 cm<sup>3</sup> of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (sat. aq. solution) and extracted with 5 × 15 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 90/1/

1 → 100/20/1 DCM/acetone/EtOH) furnished 18 mg (11%) of (*S,S,aS*)-12b and 97 mg (60%) of (*S,S,aR*)-12b as yellowish solids. (*S,S,aS*)-12b: M.p.: 205.0 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.36 (s, 2H, 2 × Ar-H), 5.29–5.22 (m, 2H, 2 × CH), 5.13–5.08 (m, 4H, 2 × CH<sub>2</sub>), 4.97 (s, 2H, 2 × CH), 4.73–4.66 (m, 2H, 2 × CH), 3.21 (s, 6H, 2 × CH<sub>3</sub>), 0.96, (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 150.82, 139.00, 136.31, 135.85, 118.14, 83.35, 73.13, 72.18, 58.21, 37.41, 25.79 ppm; IR (drift KBr):  $\bar{\nu}$  = 1260, 1198, 1186, 1099, 1075, 1048, 1033, 908 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>26</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>6</sub> ([M + Na]<sup>+</sup>) 495.24656, found 495.24652; *R*<sub>f</sub> = 0.20 (60/1 DCM/MeOH); [α]<sub>D</sub><sup>20</sup> = -393.4° (*c* = 0.24, CHCl<sub>3</sub>); HPLC of (*S,S,aS*)-12b: Lux Columns—Lux Cellulose-2, *n*-heptane/IPA 80/20, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>S,S,aS</sub> = 7.1 min, *t*<sub>R,R,aR</sub> = ND. (*S,S,aR*)-12b: M.p.: 180.7 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.36 (s, 2H, Ar-H), 5.25–5.20 (m, 2H, 2 × CH), 5.14–5.09 (m, 4H, 2 × CH<sub>2</sub>), 4.98 (s, 2H, 2 × CH), 4.64–4.60 (m, 2H, 2 × CH), 3.21 (s, 6H, 2 × CH<sub>3</sub>), 0.99 (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ = 150.84, 139.15, 136.46, 135.92, 118.14, 82.95, 73.17, 72.25, 58.48, 37.41, 25.79 ppm; IR (drift KBr):  $\bar{\nu}$  = 1260, 1201, 1183, 1102, 1096, 1078, 1048, 1033, 973, 914, 899 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 473.26461, found 473.26462; *R*<sub>f</sub> = 0.17 (60/1 DCM/MeOH); [α]<sub>D</sub><sup>20</sup> = +296.3° (*c* = 0.37, CHCl<sub>3</sub>); HPLC of (*S,S,aR*)-12b: Lux Columns—Lux Cellulose-4, *n*-heptane/IPA 90/10, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>R,R,aS</sub> = ND, *t*<sub>S,S,aR</sub> = 20.4 min.

**Racemic (*S,S,aS*)-3,3'-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-12b<sub>1</sub>, C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub>), racemic (*S,S,aR*)-3,3'-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-12b<sub>2</sub>, C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub>), racemic (*S,R,aS*)-3,3'-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-12b<sub>3</sub>, C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub>), and racemic (*S,R,aR*)-3,3'-6,6'-bis(1-methoxy-2,2-dimethylpropyl)-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*rac*)-12b<sub>4</sub>, C<sub>26</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub>)** By approach B using racemic alcohol (*rac*)-15b were prepared products (*rac*)-12b<sub>1</sub> and (*rac*)-12b<sub>2</sub> and as well 50/50 mixture of (*rac*)-12b<sub>3</sub> and (*rac*)-12b<sub>4</sub>. Spectral data of products (*rac*)-12b<sub>1</sub> and (*rac*)-12b<sub>2</sub> were in agreement with chiral products (*S,S,aS*)-12b and (*S,S,aR*)-12b. HPLC of (*rac*)-12b<sub>1</sub>: Lux Columns—Lux Cellulose-2, *n*-heptane/IPA 80/20, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>S,S,aS</sub> = 7.0 min, *t*<sub>R,R,aR</sub> = 28.2 min. HPLC of (*rac*)-12b<sub>2</sub>: Lux Columns—Lux Cellulose-4, *n*-heptane/IPA 90/10, 1 cm<sup>3</sup>/min, 254 nm, *t*<sub>R,R,aS</sub> = 9.7 min, *t*<sub>S,S,aR</sub> = 20.5 min. (*rac*)-12b<sub>3</sub> + (*rac*)-12b<sub>4</sub>: M.p.: 232.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.37 (s, 2H, 2 × Ar-H), 7.36 (s, 2H, 2 × Ar-H), 5.36–5.30 (m, 2H, 2 × CH), 5.29–

5.23 (m, 2H, 2 × CH), 5.13–5.08 (8H, 4 × CH<sub>2</sub>), 5.01 (s, 2H, 2 × CH), 4.95 (s, 2H, 2 × CH), 4.65–4.61 (m, 2H, 2 × CH), 4.61–4.57 (m, 2H, 2 × CH), 3.26 (s, 6H, 2 × CH<sub>3</sub>), 3.20 (s, 6H, 2 × CH<sub>3</sub>), 0.99 (s, 18H, 6 × CH<sub>3</sub>), 0.97 (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 150.89, 150.87, 139.41, 139.35, 136.63, 136.30, 135.89, 135.87, 118.18, 118.16, 83.19, 83.01, 73.09, 73.07, 72.48, 72.21, 58.74, 58.16, 37.52, 37.29, 25.83, 25.82 ppm; IR (drift KBr):  $\bar{\nu}$  = 1263, 1231, 1183, 1093, 1078, 1051, 1036, 1024, 970, 943, 899 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd. for C<sub>26</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>6</sub> ([M+Na]<sup>+</sup>) 495.24656, found 495.24612; *R<sub>f</sub>* = 0.53 (30/1 DCM/MeOH).

**(S)-1-Bromo-3-(1-methoxy-2,2-dimethylpropyl)-6,7-dihydro-5H-cyclopenta[c]pyridine (13a, C<sub>14</sub>H<sub>20</sub>BrNO)** To a cooled (ice water) suspension of 28 mg of NaH (60% w/w suspension in mineral oil, 0.70 mmol) in 2 cm<sup>3</sup> of THF in 25-cm<sup>3</sup> argon-flushed flask, a solution of 131 mg of **7a** (0.46 mmol) in 4 cm<sup>3</sup> of THF was added slowly. Mixture was stirred at 20 °C for 30 min, then 58 mm<sup>3</sup> of MeI (0.92 mmol) was added slowly to the cooled reaction mixture. After stirring at 20 °C for 2 h, the reaction mixture was quenched by addition of 5 cm<sup>3</sup> of water and extracted with 3 × 15 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1 → 20/1 hexanes/EtOAc) yielded 119 mg (87%) of the title compound as a colorless solid. M.p.: 113.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.19 (s, 1H, Ar-H), 3.96 (s, 1H, CH), 3.22 (s, 3H, CH<sub>3</sub>), 3.02 (t, *J* = 7.6 Hz, 2H, CH<sub>2</sub>), 2.93 (t, *J* = 7.6 Hz, 2H, CH<sub>2</sub>), 2.13 (p, *J* = 7.7 Hz), 0.89 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 160.07, 155.97, 140.32, 137.63, 117.47, 92.01, 58.00, 35.72, 34.04, 32.94, 26.24, 23.73 ppm; IR (drift KBr):  $\bar{\nu}$  = 2956, 2923, 2821, 1592, 1539, 1368, 1242, 1180, 1099, 976, 967, 917 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>14</sub>H<sub>20</sub>BrNNaO ([M+Na]<sup>+</sup>) 320.06205, found 320.06203; *R<sub>f</sub>* = 0.47 (20/1 hexanes/EtOAc).

**(S)-4-Bromo-6-(1-methoxy-2,2-dimethylpropyl)-1,3-dihydrofuro[3,4-c]pyridine (13b, C<sub>13</sub>H<sub>18</sub>BrNO<sub>2</sub>)** To a cooled (ice water) suspension of 130 mg of NaH (60% w/w suspension in mineral oil, 3.2 mmol) in 9 cm<sup>3</sup> of THF in 50-cm<sup>3</sup> argon-flushed flask, a solution of 630 mg of **7b** (2.14 mmol) in 17 cm<sup>3</sup> of THF was added slowly. Mixture was stirred at 20 °C for 10 min, then 270 mm<sup>3</sup> of MeI (4.3 mmol) was added slowly to the cooled reaction mixture. After stirring at 20 °C for 2 h, the reaction mixture was quenched by addition of 10 cm<sup>3</sup> of water and extracted with 3 × 30 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue

on silica gel (gradient 30/1 → 20/1 hexanes/EtOAc) yielded 622 mg (97%) of the title compound as a colorless solid. M.p.: 47.3 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.24 (s, 1H, Ar-H), 5.21–5.17 (m, 2H, CH<sub>2</sub>), 5.08–5.04 (m, 2H, CH<sub>2</sub>), 4.00 (s, 1H, CH), 3.23 (s, 3H, CH<sub>3</sub>), 0.90 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 162.08, 151.17, 135.68, 133.52, 113.93, 91.95, 74.34, 73.24, 58.16, 35.85, 26.20 ppm; IR (drift KBr):  $\bar{\nu}$  = 2974, 2959, 1380, 1242, 1189, 1099, 1054, 908, 860 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>13</sub>H<sub>18</sub>BrNNaO<sub>2</sub> ([M+Na]<sup>+</sup>) 322.04131, found 322.04140; *R<sub>f</sub>* = 0.42 (5/1 hexanes/EtOAc).

**1-(6,7-Dihydro-5H-cyclopenta[c]pyridin-3-yl)-2,2-dimethylpropan-1-one (14a, C<sub>13</sub>H<sub>17</sub>NO)** To a dry-argon-flushed 100-cm<sup>3</sup> flask were added 126 mg of Cp\*RuCl(cod) (0.33 mmol), 12 cm<sup>3</sup> of DCE and 0.60 cm<sup>3</sup> of pivaloyl cyanide (90% purity, 4.9 mmol). Then 310 mg of hepta-1,6-diyne **1a** (3.3 mmol) dissolved in 18 cm<sup>3</sup> of DCE was added slowly by a syringe pump during the course of 10 h. The reaction mixture was stirred at 20 °C for 5 h and then volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradient 50/1 → 40/1 hexanes/EtOAc) provided 499 mg (75%) of the title compound as colorless crystals. M.p.: 25.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.44 (s, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 2.99–2.90 (m, 4H, 2 × CH<sub>2</sub>), 2.12 (p, *J* = 7.5 Hz, 2H, CH<sub>2</sub>), 1.44 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 207.35, 154.32, 153.06, 143.68, 142.82, 120.01, 44.26, 32.77, 30.55, 27.75, 24.98 ppm; IR (drift KBr):  $\bar{\nu}$  = 3446, 3416, 2956, 2863, 1679, 1231, 1111, 985, 899, 884 cm<sup>-1</sup>; HRMS (ED): *m/z* calcd. for C<sub>13</sub>H<sub>17</sub>NO (M<sup>+</sup>) 203.1310, found 203.1306; *R<sub>f</sub>* = 0.61 (10/1 hexanes/EtOAc).

**1-(1,3-Dihydrofuro[3,4-c]pyridin-6-yl)-2,2-dimethylpropan-1-one (14b, C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>)** To a dry-argon-flushed 250-cm<sup>3</sup> flask were added 282 mg of Cp\*RuCl(cod) (0.73 mmol), 50 cm<sup>3</sup> of DCE and 1.35 cm<sup>3</sup> of pivaloyl cyanide (90% purity, 10.9 mmol). Then 770 mm<sup>3</sup> of propargyl ether **1b** (7.3 mmol) dissolved in 20 cm<sup>3</sup> of DCE was added slowly by a syringe pump during the course of 10 h. The reaction mixture was stirred at 20 °C for 3 h and then volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradient 20/1 → 8/1 hexanes/EtOAc) provided 1327 mg (89%) of the title compound as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.52 (d, *J* = 0.8 Hz, 1H, Ar-H), 7.82 (d, *J* = 0.8 Hz, 1H, Ar-H), 5.19–5.15 (m, 2H, CH<sub>2</sub>), 5.13–5.09 (m, 2H, CH<sub>2</sub>), 1.44 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 206.64, 153.92, 149.60, 140.77, 137.57, 116.71, 73.08, 71.86, 44.31, 27.63 ppm; IR (drift KBr):  $\bar{\nu}$  = 3482, 3422, 3402, 2968, 2956, 2926, 2863, 1688, 1272, 1189, 1147, 1123, 1048, 1003, 985, 899, 881 cm<sup>-1</sup>; HRMS

(ESI):  $m/z$  calcd. for  $C_{12}H_{15}NO_2$  ( $M^+$ ) 205.1103, found 205.1105;  $R_f = 0.46$  (5/1 hexanes/EtOAc).

**(S)-1-(6,7-Dihydro-5H-cyclopenta[c]pyridin-3-yl)-2,2-dimethylpropan-1-ol (15a,  $C_{13}H_{19}NO$ )** To a dry-argon-flushed 20-cm<sup>3</sup> vial with a solution of 498 mg of **14a** (2.45 mmol) and 86 mg of  $RuCl[(S,S)\text{-Tsdpen}](p\text{-cymene})$  (0.12 mmol) in 5 cm<sup>3</sup> of DCM, 4 cm<sup>3</sup> of a mixture of  $Et_3N/HCOOH$  (2/1) was added. After stirring for 6 days at 40 °C, the reaction mixture was quenched with 5 cm<sup>3</sup> of  $NaHCO_3$  (sat. aq. solution) and extracted with 3 × 15 cm<sup>3</sup> of DCM. The combined organic fractions were dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 5/2 → 2/1 hexanes/EtOAc) furnished 442 mg (88%, 74% ee) of the title compound as a colorless solid. By recrystallization from excess of hexanes was obtained 240 mg (48%, > 99% ee) of the title compound. M.p.: 93.2 °C; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta = 8.36$  (s, 1H, Ar-H), 7.05 (s, 1H, Ar-H), 4.40 (rs, 1H, OH), 4.29 (s, 1H, CH), 2.98–2.84 (m, 4H, 2 ×  $CH_2$ ), 2.19–2.03 (m, 2H,  $CH_2$ ), 0.90 (s, 9H, 3 ×  $CH_3$ ) ppm; <sup>13</sup>C NMR (100 MHz,  $CDCl_3$ ):  $\delta = 157.48, 153.68, 143.46, 139.11, 119.03, 80.44, 36.40, 32.71, 30.02, 26.07, 25.27$  ppm; IR (drift KBr)  $\bar{\nu} = 3264, 3246, 3210, 2974, 2953, 2902, 2872, 1344, 1296, 1072, 1018, 884$  cm<sup>-1</sup>; HRMS (ESI):  $m/z$  calcd. for  $C_{13}H_{20}NO$  ( $[M+H]^+$ ) 206.15394, found 206.15395;  $R_f = 0.32$  (2/1 hexanes/EtOAc);  $[\alpha]_D^{20} = -30.1^\circ$  ( $c = 0.38$ ,  $CHCl_3$ ); HPLC of **15a**: Daicel Chiralpak IA, *n*-heptane/IPA 80/20, 1 cm<sup>3</sup>/min, 208 nm,  $t_S = 6.3$  min,  $t_R = ND$ .

**(rac)-1-(6,7-Dihydro-5H-cyclopenta[c]pyridin-3-yl)-2,2-dimethylpropan-1-ol ((rac)-15a,  $C_{13}H_{19}NO$ )** To a solution of 153 mg of **14a** (0.75 mmol) in 3 cm<sup>3</sup> of dry MeOH in 25-cm<sup>3</sup> flask, 43 mg of  $NaBH_4$  (1.1 mmol) was added. After 1 h at 20 °C, the reaction mixture was quenched with 5 cm<sup>3</sup> of water and extracted with 3 × 15 cm<sup>3</sup> of DCM. The combined organic fractions were dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. Filtration of the residue through silica gel pad (1/1 hexanes/EtOAc) provided 152 mg (99%) of the title compound as an amorphous solid. All the spectral data were in agreement with the chiral product **15a**. HPLC of ((rac)-**15a**): Daicel Chiralpak IA, *n*-heptane/IPA 80/20, 1 cm<sup>3</sup>/min, 208 nm,  $t_S = 6.3$  min,  $t_R = 7.7$  min.

**(S)-1-(1,3-Dihydrofuro[3,4-c]pyridin-6-yl)-2,2-dimethylpropan-1-ol (15b,  $C_{12}H_{17}NO_2$ )** To a dry-argon-flushed 50-cm<sup>3</sup> flask with a solution of 1327 mg of **14b** (6.47 mmol) and 227 mg of  $RuCl[(S,S)\text{-Tsdpen}](p\text{-cymene})$  (0.32 mmol) in 7 cm<sup>3</sup> of DCM, 10 cm<sup>3</sup> of a mixture of  $Et_3N/HCOOH$  (2/1) was added. After stirring for 2 days at 40 °C, the reaction mixture was quenched with 10 cm<sup>3</sup> of  $NaHCO_3$  (sat. aq. solution) and extracted with 3 × 30 cm<sup>3</sup>

of DCM. The combined organic fractions were dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1 → 2/3 hexanes/EtOAc) furnished 1317 mg (98%, 89% ee) of the title compound as an amorphous solid. By recrystallization from excess of hexanes was obtained 909 mg (68%, > 99% ee) of the title compound. M.p.: 101.9 °C; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta = 8.45$  (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 5.18–5.03 (m, 4H, 2 ×  $CH_2$ ), 4.36 (s, 1H, CH), 4.21 (brs, 1H, OH), 0.91 (s, 9H, 3 ×  $CH_3$ ) ppm; <sup>13</sup>C NMR (100 MHz,  $CDCl_3$ ):  $\delta = 159.09, 148.82, 140.77, 134.34, 115.49, 80.69, 72.90, 71.59, 36.43, 26.00$  ppm; IR (drift KBr):  $\bar{\nu} = 3249, 2959, 2932, 2869, 1341, 1075, 1048, 1021, 902, 878$  cm<sup>-1</sup>; HRMS (ESI):  $m/z$  calcd. for  $C_{12}H_{18}NO_2$  ( $[M+H]^+$ ) 208.13321, found 208.13322;  $R_f = 0.11$  (2/1 hexanes/EtOAc);  $[\alpha]_D^{20} = -20.9^\circ$  ( $c = 0.31$ ,  $CHCl_3$ ); HPLC of **15b**: Daicel Chiralpak IC, *n*-heptane/IPA 80/20, 1 cm<sup>3</sup>/min, 207 nm,  $t_S = 7.4$  min,  $t_R = ND$ .

**(rac)-1-(1,3-Dihydrofuro[3,4-c]pyridin-6-yl)-2,2-dimethylpropan-1-ol ((rac)-15b,  $C_{12}H_{17}NO_2$ )** To a solution of 150 mg of **14b** (0.73 mmol) in 4 cm<sup>3</sup> of dry MeOH in 25-cm<sup>3</sup> flask, 41 mg of  $NaBH_4$  (1.1 mmol) was added. After 1.5 h at 20 °C, the reaction mixture was quenched with 5 cm<sup>3</sup> of water and extracted with 3 × 15 cm<sup>3</sup> of DCM. The combined organic fractions were dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. Filtration of the residue through silica gel pad (1/2 hexanes/EtOAc) provided 145 mg (96%) of the title compound as an amorphous solid. All the spectral data were in agreement with the chiral product **15b**. HPLC of ((rac)-**15b**): Daicel Chiralpak IC, *n*-heptane/IPA 80/20, 1 cm<sup>3</sup>/min, 207 nm,  $t_S = 7.5$  min,  $t_R = 11.0$  min.

**(S)-3-(1-Methoxy-2,2-dimethylpropyl)-6,7-dihydro-5H-cyclopenta[c]pyridine (16a,  $C_{14}H_{21}NO$ )** To a cooled (ice water) suspension of 80 mg of  $NaH$  (60% w/w suspension in mineral oil, 2.0 mmol) in 8 cm<sup>3</sup> of dry THF in 50-cm<sup>3</sup> argon-flushed flask, a solution of 259 mg of **15a** (1.26 mmol) in 8 cm<sup>3</sup> of dry THF was added slowly. Mixture was stirred at 20 °C for 30 min, then 160 mm<sup>3</sup> of MeI (2.5 mmol) was added slowly to the cooled reaction mixture. After stirring at 20 °C for 1 h, the reaction mixture was quenched by addition of 10 cm<sup>3</sup> of water and extracted with 3 × 30 cm<sup>3</sup> of DCM. Combined organic phases were dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexanes/EtOAc) yielded 259 mg (94%) of the title compound as a colorless solid. M.p.: 38.0 °C; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta = 8.36$  (s, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 3.92 (s, 1H, CH), 3.19 (s, 3H,  $CH_3$ ), 2.89 (t,  $J = 7.5$  Hz, 4H, 2 ×  $CH_2$ ), 2.08 (p,  $J = 7.5$  Hz, 2H,  $CH_2$ ), 0.88 (s, 9H, 3 ×  $CH_3$ ) ppm; <sup>13</sup>C

NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 157.79, 153.66, 144.11, 138.76, 118.16, 92.87, 57.80, 35.60, 32.81, 30.08, 26.36, 25.16 ppm; IR (drift KBr):  $\bar{\nu}$  = 2974, 2955, 2904, 1366, 1359, 1233, 1198, 1179, 1154, 1097, 1103, 1046, 973, 951, 900 cm<sup>-1</sup>; HRMS (ESI):  $m/z$  calcd. for C<sub>14</sub>H<sub>22</sub>NO ([M+H]<sup>+</sup>) 220.16959, found 220.16979;  $R_f$  = 0.43 (3/1 hexanes/EtOAc).

**(S)-6-(1-Methoxy-2,2-dimethylpropyl)-1,3-dihydrofuro[3,4-c]pyridine (16b, C<sub>13</sub>H<sub>19</sub>NO<sub>2</sub>)** To a cooled (ice water) suspension of 42 mg of NaH (60% w/w suspension in mineral oil, 1.1 mmol) in 3 cm<sup>3</sup> of THF in 50-cm<sup>3</sup> argon-flushed flask, a solution of 145 mg of **15b** (0.7 mmol) in 6 cm<sup>3</sup> of THF was added slowly. Mixture was stirred at 20 °C for 20 min, then 90 mm<sup>3</sup> of MeI (1.4 mmol) was added slowly to the cooled reaction mixture. After stirring at 20 °C for 2 h, the reaction mixture was quenched by addition of 6 cm<sup>3</sup> of water and extracted with 3 × 20 cm<sup>3</sup> of DCM. Combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 3/1 → 2/1 hexanes/EtOAc) yielded 150 mg (97%) of the title compound as a colorless solid. M.p.: 81.6 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.45 (s, 1H, Ar-H), 7.26 s, overlapping with CDCl<sub>3</sub>, Ar-H), 5.15–5.11 (m, 2H, CH<sub>2</sub>), 5.11–5.07 (m, 2H, CH<sub>2</sub>), 3.99 (s, 1H, CH), 3.21 (s, 3H, CH<sub>3</sub>), 0.89 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.54, 148.92, 141.27, 134.04, 114.71, 92.70, 73.07, 71.69, 57.96, 35.71, 26.30 ppm; IR (drift KBr):  $\bar{\nu}$  = 2977, 2953, 2923, 2869, 1180, 1114, 1087, 1048, 970, 905, 881 cm<sup>-1</sup>; HRMS (EI):  $m/z$  calcd. for C<sub>13</sub>H<sub>19</sub>NO<sub>2</sub> (M<sup>+</sup>) 221.1416, found 221.1418;  $R_f$  = 0.20 (3/1 hexanes/EtOAc).

**(S)-3-(1-Methoxy-2,2-dimethylpropyl)-6,7-dihydro-5H-cyclopenta[c]pyridine 2-oxide (17a, C<sub>14</sub>H<sub>21</sub>NO<sub>2</sub>)** To a solution of 262 mg of **16a** (1.2 mmol) in 15 cm<sup>3</sup> of DCM under Ar atmosphere cooled down to 0 °C (ice water) was added 408 mg of MCPBA (1.8 mmol). After stirring at 20 °C for 1 h, the reaction mixture was quenched by addition of 10 cm<sup>3</sup> of K<sub>2</sub>CO<sub>3</sub> (sat. aq. solution) and stirred for 10 min. The phases were separated and the aqueous phase was washed with 3 × 30 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1 → 1/1 CHCl<sub>3</sub>/acetone) furnished 278 mg (99%) of title compound as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.11 (s, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 4.98 (s, 1H, CH), 3.17 (s, 3H, CH<sub>3</sub>), 2.90 (t,  $J$  = 7.5 Hz, 4H, 2 × CH<sub>2</sub>), 2.16 (p,  $J$  = 2H, CH<sub>2</sub>), 0.97 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 148.93, 143.70, 141.47, 135.14, 120.59, 82.69, 58.11, 37.23, 32.29, 30.61, 25.78, 25.55 ppm; IR (drift KBr):  $\bar{\nu}$  = 2968, 2953, 1305, 1263,

1248, 1219, 1189, 1147, 1096, 1066, 967 cm<sup>-1</sup>; HRMS (ESI):  $m/z$  calcd. for C<sub>14</sub>H<sub>21</sub>NO<sub>2</sub> (M<sup>+</sup>) 235.1572, found 235.1570;  $R_f$  = 0.35 (50/1 DCM/MeOH).

**(S)-6-(1-Methoxy-2,2-dimethylpropyl)-1,3-dihydrofuro[3,4-c]pyridine 5-oxide (17b, C<sub>13</sub>H<sub>19</sub>NO<sub>3</sub>)** To a solution of 147 mg of **16b** (0.66 mmol) in 9 cm<sup>3</sup> of DCM under Ar atmosphere cooled down to 0 °C (ice water) was added 225 mg of MCPBA (1.0 mmol). After stirring at 20 °C for 1 h, the reaction mixture was quenched by addition of 6 cm<sup>3</sup> of K<sub>2</sub>CO<sub>3</sub> (sat. aq. solution) and stirred for 10 min. The phases were separated and the aqueous phase was washed with 3 × 20 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1 → 3/2 CHCl<sub>3</sub>/acetone) furnished 156 mg (99%) of title compound as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.17 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 5.07 (s, 4H, 2 × CH<sub>2</sub>), 4.97 (s, 1H, CH), 3.18 (s, 3H, CH<sub>3</sub>), 0.96 (s, 9H, 3 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.61, 137.95, 137.07, 133.45, 117.77, 82.72, 72.86, 71.29, 58.25, 37.37, 25.70 ppm; IR (drift KBr):  $\bar{\nu}$  = 2968, 2956, 1272, 1245, 1195, 1180, 1153, 1096, 1051, 1033, 902 cm<sup>-1</sup>; HRMS (ESI):  $m/z$  calcd. for C<sub>13</sub>H<sub>19</sub>NO<sub>3</sub> (M<sup>+</sup>) 237.1365, found 237.1366;  $R_f$  = 0.33 (50/1 DCM/MeOH).

**6,6'-Bis((S)-1-methoxy-2,2-dimethylpropyl)-[2,2'-bipyridine] 1,1'-dioxide (20)** To a solution of 384 mg of **28** (1.1 mmol) in 20 cm<sup>3</sup> of DCM cooled down to 0 °C (ice water) was added 724 mg of MCPBA (3.2 mmol) and after stirring for 2 h at 20 °C, the second portion of 727 mg of MCPBA (3.2 mmol) was added to the cooled reaction mixture. After stirring at 20 °C for 19 h, the reaction mixture was quenched by addition of 5 cm<sup>3</sup> of NaOH (40% aq. solution) and stirred for 1 h. The phases were separated and the aqueous phase was washed with 3 × 20 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 40/1 → 10/1 CHCl<sub>3</sub>/acetone) and recrystallization from hexanes furnished 294 mg (70%) of title compound as a colorless solid. The recorded spectral data (SI) were in agreement with the published data [19].

**(S)-1-Phenylbut-3-en-1-ol (21)** To a solution of 50 mm<sup>3</sup> of benzaldehyde (**18**, 0.50 mmol), *N,N'*-dioxide (0.0025 mmol), and 130 mm<sup>3</sup> of DIPEA (0.75 mmol) in 2 cm<sup>3</sup> of DCM cooled to -78 °C, 115 mm<sup>3</sup> of allyl-trichlorosilane (0.75 mmol) was added. The mixture was stirred at -78 °C for 16 h, then the reaction mixture was quenched with 1 cm<sup>3</sup> of NaHCO<sub>3</sub> (sat. aq. solution) and extracted with 3 × 5 cm<sup>3</sup> of DCM. The combined organic fractions were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and

concentrated under reduced pressure. The yield was determined by  $^1\text{H}$  NMR analysis with 1,2,4,5-tetramethylbenzene as an internal standard. Analytically pure product **21** was obtained by column chromatography on silica gel (gradient 30/1  $\rightarrow$  20/1 hexanes/EtOAc). (*S*)-Configuration was determined by comparison of data with the literature [20]. The recorded analytical data (SI) were in agreement with the published data [18].

**(rac)-1-Phenylbut-3-en-1-ol ((rac)-21)** To a solution of 13 mg of  $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.035 mmol) in 10  $\text{cm}^3$  of ACN were added 100  $\text{mm}^3$  of allylboronic acid pinacol ester (0.52 mmol) and 35  $\text{mm}^3$  of benzaldehyde (**18**, 0.35 mmol). The reaction mixture was stirred at 20  $^\circ\text{C}$  for 5 h, then quenched with 3  $\text{cm}^3$  of water, and extracted with  $3 \times 10 \text{ cm}^3$  of DCM. The combined organic fractions were dried over  $\text{MgSO}_4$ , filtered, and concentrated under the reduced pressure. Column chromatography of the residue on silica gel (gradient 30/1  $\rightarrow$  20/1 hexanes/EtOAc) furnished 50 mg (97%) of the title compound as a colorless oil. All spectral data were in agreement with the chiral product **21**.

**Trichloro[(1-methoxyvinyl)oxy]silane (23)** To the vigorously stirred 10.0  $\text{cm}^3$  of  $\text{SiCl}_4$  (85 mmol) in two-neck 100- $\text{cm}^3$  flask was slowly added 4.1 g of **29** (11.3 mmol) followed by 0.6  $\text{cm}^3$  of  $(\text{Bu}_3\text{Sn})\text{O}$  (1.1 mmol). Mixture was stirred until the starting **29** was fully consumed (12 h, determined by  $^1\text{H}$  NMR), then mixture of  $\text{SiCl}_4$  and product **23** was distilled to 50- $\text{cm}^3$  three-neck flask connected with dry-ice condenser (50  $^\circ\text{C}$ , 2–5 mbar). Then  $\text{SiCl}_4$  was slowly distilled off (20  $^\circ\text{C}$ , 80 mbar) using the vacuum regulator to another flask. The purity (48%) of the title compound was determined by the amount of created aldol product in the reaction of a small sample of the oily residue with the excess of benzaldehyde in  $\text{DCM}-d_2$  and with 1,2,4,5-tetramethylbenzene as an internal standard. Because of its instability, the product **23** was able to be characterized only by  $^1\text{H}$  NMR. The recorded analytical data (SI) were in agreement with published data [17].

**(R)-Methyl 3-hydroxy-3-phenylbutanoate (24)** A solution of 23  $\text{mm}^3$  of acetophenone (**22**, 0.20 mmol) and *N,N'*-dioxide (0.02 mmol) in 1  $\text{cm}^3$  of DCM was cooled to  $-20 \text{ }^\circ\text{C}$ , then 100  $\text{mm}^3$  of **23** (48% purity, 0.3 mmol) was added. The reaction mixture was stirred at  $-20 \text{ }^\circ\text{C}$  for 18 h, then quenched with 1  $\text{cm}^3$  of  $\text{NaHCO}_3$  (sat. aq. solution), filtered through Celite<sup>®</sup>, and extracted with  $3 \times 5 \text{ cm}^3$  of DCM. The combined organic fractions were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The yield was determined by  $^1\text{H}$  NMR analysis with 1,2,4,5-tetramethylbenzene as internal standard. Analytically pure product **24** was obtained by column chromatography on silica gel (gradient 20/1  $\rightarrow$  7/1

cyclohexane/EtOAc). (*R*)-configuration was determined by comparison of data with the literature [17]. It should be also noted that because of the difficulty in the preparation and handling of the starting silyl ketene acetal **23**, the yields of **24** (namely in Table 4, entries 5, 6, and 11) could be influenced by changing the batch of this compound. But we truly believe that the purity of **23** is not influencing the enantioselectivity of the reaction. The recorded analytical data (SI) were in agreement with published data [17].

**(rac)-Methyl 3-hydroxy-3-phenylbutanoate ((rac)-24)** The racemic product was prepared by the same procedure as chiral product **24** using trimethylamine *N*-oxide as catalyst. All spectral data were in agreement with the chiral product **24**.

**(*S,S,aS*)-6,6'-Bis[(*S*)-2,2-dimethyl-1-[(2,4,6-trimethylbenzyl)oxy]propyl]-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S,S,aS*)-25b,  $\text{C}_{44}\text{H}_{56}\text{N}_2\text{O}_6$ ) and (*S,S,aR*)-6,6'-bis[(*S*)-2,2-dimethyl-1-[(2,4,6-trimethylbenzyl)oxy]propyl]-1,1',3,3'-tetrahydro[4,4'-bifuro[3,4-*c*]pyridine] 5,5'-dioxide ((*S,S,aR*)-25b,  $\text{C}_{44}\text{H}_{56}\text{N}_2\text{O}_6$ )** To a solution of 150 mg of **32b** (0.42 mmol) in 1.7  $\text{cm}^3$  of  $\text{Et}_2\text{O}$  cooled to  $-73 \text{ }^\circ\text{C}$  in 25- $\text{cm}^3$  Ar-flushed flask was dropwise added freshly prepared solution of LiTMP (0.46 mmol) in 0.9  $\text{cm}^3$  of THF. Mixture was stirred at  $-73 \text{ }^\circ\text{C}$  for 16 h, then a solution of 119 mg of  $\text{I}_2$  (0.46 mmol) in 1  $\text{cm}^3$  of dry THF was added in two portions in 2 h. The reaction mixture was let to warm up to 20  $^\circ\text{C}$  during the period of 3 h, then it was quenched by addition of 5  $\text{cm}^3$  of  $\text{Na}_2\text{S}_2\text{O}_3$  (sat. aq. solution), and extracted with  $5 \times 15 \text{ cm}^3$  of DCM. Combined organic phases were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1  $\rightarrow$  3/1 hexanes/EtOAc) furnished 19 mg (13%) of (*S,S,aS*)-25b as an amorphous solid and 63 mg (42%) of (*S,S,aR*)-25b as yellowish crystals. (*S,S,aS*)-25b:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.46$  (s, 2H, 2  $\times$  Ar-H), 6.86 (s, 4H, 4  $\times$  Ar-H), 5.32–5.25 (m, 2H,  $\text{CH}_2$ ), 5.21 (s, 2H, 2  $\times$  CH), 5.18–5.04 (m, 4H, 2  $\times$   $\text{CH}_2$ ), 4.80–4.70 (m, 2H,  $\text{CH}_2$ ), 4.44 (d,  $J = 10.8$  Hz, 2H, 2  $\times$  CH), 4.33 (d,  $J = 10.8$  Hz, 2H, 2  $\times$  CH), 2.31 (s, 12H, 6  $\times$   $\text{CH}_3$ ), 2.28 (s, 6H, 2  $\times$   $\text{CH}_3$ ), 0.97 (s, 9H, 3  $\times$   $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 151.41, 138.99, 137.94, 137.88, 136.02, 135.76, 131.20, 139.07, 118.58, 81.13, 73.14, 72.22, 66.64, 37.58, 25.88, 21.13, 19.73$  ppm; IR (drift KBr):  $\bar{\nu} = 2953, 2920, 2872, 2860, 1613, 1395, 359, 1263, 1219, 1192, 1087, 1042, 908, 854, 785 \text{ cm}^{-1}$ ; HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{44}\text{H}_{57}\text{N}_2\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 709.42111, found 709.42122;  $R_f = 0.33$  (3/1 hexanes/EtOAc);  $[\alpha]_D^{20} = -35.0^\circ$  ( $c = 0.34$ ,  $\text{CHCl}_3$ ). (*S,S,aR*)-25b: M.p.: 143.7  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.48$  (s, 2H, 2  $\times$  Ar-H), 6.85 (s, 4H, 4  $\times$  Ar-H), 5.38–5.31 (m, 2H,  $\text{CH}_2$ ), 5.25 (s, 2H, 2  $\times$  CH), 5.18–5.07 (m, 4H, 2  $\times$   $\text{CH}_2$ ), 4.67–4.61 (m, 2H,



CH<sub>2</sub>), 4.35 (s, 4H, 2 × CH<sub>2</sub>), 2.29 (s, 12H, 4 × CH<sub>3</sub>), 2.27 (s, 6H, 2 × CH<sub>3</sub>), 1.01 (s, 18H, 6 × CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 151.30, 139.97, 138.07, 137.87, 136.25, 136.10, 131.27, 129.02, 118.32, 81.00, 73.10, 72.49, 66.76, 37.51, 25.96, 21.13, 19.73 ppm; IR (drift KBr):  $\bar{\nu}$  = 2953, 2917, 2869, 1616, 1392, 1356, 1263, 1219, 1189, 1090, 1045, 908, 857, 785 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>44</sub>H<sub>56</sub>N<sub>2</sub>NaO<sub>6</sub> ([M + Na]<sup>+</sup>) 731.40306, found 731.40311; *R<sub>f</sub>* = 0.53 (3/1 hexanes/EtOAc); [α]<sub>D</sub><sup>20</sup> = + 301.6° (*c* = 0.32, CHCl<sub>3</sub>).

**6,6'-Bis((S)-1-Methoxy-2,2-dimethylpropyl)-2,2'-bipyridine (28)** To a suspension of 146 mg of NaH (60% w/w suspension in mineral oil, 3.7 mmol) in 5 cm<sup>3</sup> of dry THF in 100-cm<sup>3</sup> argon-flushed flask a solution of 399 mg of **27** (1.2 mmol) in 10 cm<sup>3</sup> of dry THF was added slowly. The reaction mixture was stirred at 20 °C for 1 h, then 0.30 cm<sup>3</sup> of MeI (4.9 mmol) was added slowly. After stirring at 20 °C for 16 h, the reaction mixture was quenched by addition of 10 cm<sup>3</sup> of water and extracted with 3 × 30 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 25/1 → 20/1) yielded 384 mg (88%) of the title compound as a colorless solid. The recorded analytical data (SI) were in agreement with the published data [21].

**Methyl 2-(tributylstannyl)acetate (29)** 27 cm<sup>3</sup> of *n*-BuLi (1.6 M in hexane, 42.8 mmol) was slowly added to a solution of 6 cm<sup>3</sup> of DIPA (42.4 mmol) in 150 cm<sup>3</sup> of dry THF cooled to 0 °C. Mixture was stirred for 20 min at 0 °C and then cooled down to -78 °C. Then 3.4 cm<sup>3</sup> of MeOAc (42.9 mmol) was added slowly and the mixture was stirred for 1 h at -78 °C. The solution was then added via a cannula to a solution of 10 cm<sup>3</sup> of Bu<sub>3</sub>SnCl (35.4 mmol) in 50 cm<sup>3</sup> of dry THF cooled to -78 °C during the course of 30 min. The reaction mixture was stirred at -78 °C for 10 min, then it was let to warm up to 20 °C during the course of 3 h, and then stirred at 20 °C for 30 min. Volatiles were evaporated under reduced pressure and then 150 cm<sup>3</sup> of hexane was added. White precipitate was removed by filtration through Celite® and the filtrate was concentrated under reduced pressure. Filtration through the short silica gel column (90/10/1 hexanes/EtOAc/Et<sub>3</sub>N) and Kugelrohr distillation (175 °C, 2 mbar) provided 11.9 g (93%) of the title compound as a colorless oil. The recorded analytical data (SI) were in agreement with the published data [17].

**2-(Bromomethyl)-1,3,5-trimethylbenzene (30) [22]** To a cooled (ice water) solution of 998 mg of 2,4,6-trimethylbenzyl alcohol (6.6 mmol) in 45 cm<sup>3</sup> of THF in dry-argon-flushed 100-cm<sup>3</sup> flask, 0.25 cm<sup>3</sup> of PBr<sub>3</sub> (2.6 mmol) was

added slowly. The reaction mixture was stirred at 20 °C for 2 h, quenched by addition of 20 cm<sup>3</sup> of water, extracted with 3 × 60 cm<sup>3</sup> of DCM, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient hexanes → 20/1 hexanes/EtOAc) provided 1103 mg (78%) of the title compound as a colorless solid. The recorded analytical data (SI) were in agreement with the published data [23].

**(S)-6-[2,2-Dimethyl-1-[(2,4,6-trimethylbenzyl)oxy]propyl]-1,3-dihydrofuro[3,4-c]pyridine (31b, C<sub>22</sub>H<sub>29</sub>NO<sub>2</sub>)** To a suspension of 15 mg of NaH (60% w/w suspension in mineral oil, 0.36 mmol) and 37 mg of NaI (0.25 mmol) in 1.5 cm<sup>3</sup> of THF in 25-cm<sup>3</sup> argon-flushed flask, a solution of 50 mg of **15b** (0.24 mmol) in 1.5 cm<sup>3</sup> of THF was added slowly. Mixture was stirred at 20 °C for 30 min, then 107 mg of **30** (0.50 mmol) was added slowly. After stirring at 20 °C for 20 h, the reaction mixture was quenched by addition of 3 cm<sup>3</sup> of water and extracted with 3 × 10 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 10/1 → 5/1 hexanes/EtOAc) yielded 39 mg (48%) of the title compound as colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.49 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 6.84 (s, 2H, 2 × Ar-H), 5.20–5.16 (m, 2H, CH<sub>2</sub>), 5.16–5.04 (m, 2H, CH<sub>2</sub>), 4.33 (d, *J* = 10.5 Hz, 1H, CH), 4.29 (d, *J* = 10.5 Hz, 1H, CH), 4.24 (s, 1H, CH), 2.28–2.24 (m, 9H, 3 × CH<sub>3</sub>), 0.91 (s, 9H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 160.32, 148.33, 141.19, 138.06, 137.66, 134.09, 131.74, 128.96, 114.89, 90.78, 73.09, 71.76, 66.27, 35.79, 36.48, 21.12, 19.70 ppm; IR (drift KBr):  $\bar{\nu}$  = 2950, 2917, 2860, 1610, 1574, 1395, 1362, 1335, 1078, 1048, 902, 881, 851 cm<sup>-1</sup>; HRMS (ESI): *m/z* calcd. for C<sub>22</sub>H<sub>30</sub>NO<sub>2</sub> ([M+H]<sup>+</sup>) 340.2277, found 340.2274; *R<sub>f</sub>* = 0.29 (5/1 hexanes/EtOAc).

**(S)-6-[2,2-Dimethyl-1-[(2,4,6-trimethylbenzyl)oxy]propyl]-1,3-dihydrofuro[3,4-c]pyridine 5-oxide (32b, C<sub>22</sub>H<sub>32</sub>NO<sub>3</sub>)** To a solution of 141 mg of **31b** (0.42 mmol) in 7 cm<sup>3</sup> of DCM under Ar atmosphere cooled down to 0 °C (ice water) was added 140 mg of MCPBA (0.63 mmol). After stirring at 20 °C for 2 h, the reaction mixture was quenched by addition of 5 cm<sup>3</sup> of K<sub>2</sub>CO<sub>3</sub> (sat. aq. solution) and stirred for 10 min. The phases were separated and the aqueous phase was washed with 3 × 15 cm<sup>3</sup> of DCM. Combined organic fractions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient 2/1 → 3/2 CHCl<sub>3</sub>/acetone) furnished 146 mg (99%) of title compound as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.20 (s, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 6.83 (s, 2H, 2 × Ar-H), 5.24 (s, 1H, CH), 5.16–4.97 (m, 4H, 2 × CH<sub>2</sub>), 4.38 (d, *J* = 10.4 Hz, 1H, CH), 4.25 (d,

$J = 10.4$  Hz, 1H, CH), 2.25 (s, 9H, 3  $\times$  CH<sub>3</sub>), 0.99 (s, 9H, 3  $\times$  CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 151.18, 137.97, 137.92, 137.38, 137.09, 133.45, 131.34, 129.02, 118.11, 81.00, 72.86, 71.37, 66.85, 37.50, 25.89, 21.12, 19.68$  ppm; IR (drift KBr):  $\bar{\nu} = 2950, 2920, 2869, 1416, 1272, 1153, 1081, 1045, 899, 581, 770$  cm<sup>-1</sup>; HRMS (CI):  $m/z$  calcd. for C<sub>22</sub>H<sub>33</sub>NO<sub>3</sub> ([M+H]<sup>+</sup>) 356.2226, found 356.2228;  $R_f = 0.29$  (30/1 DCM/MeOH).

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