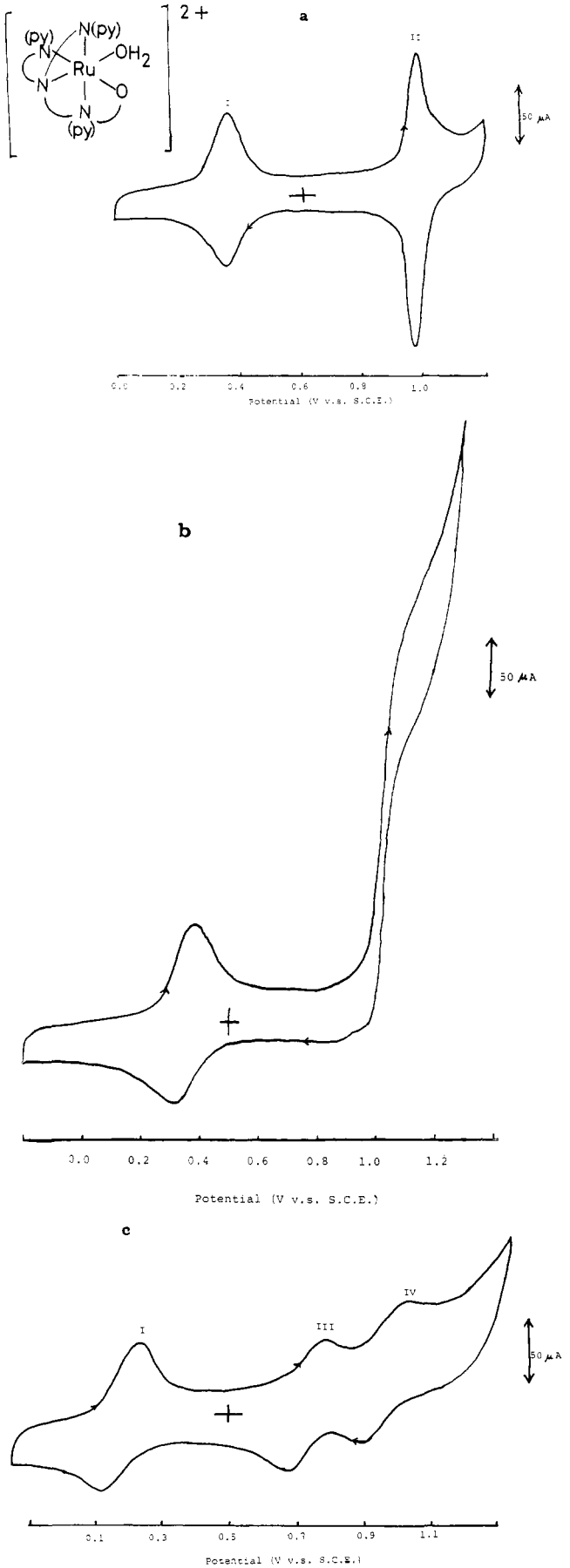

Figure 2. Cyclic voltammograms of $[Ru^{III}(N_4O)(OH_2)][ClO_4]_2$ (1 mM) in (a) 0.1 M $HClO_4$ (pH 1.1), (b) 0.1 M $HClO_4$ + isopropyl alcohol (1 M), and (c) acetate buffer (pH 4.2). Working electrode, edge-plane pyrolytic graphite; scan rate, 100 mV s^{-1}.

Table I. PhIO (150 mg) Oxidation of Organic Substrates Catalyzed by $[Ru^{III}(N_4O)(OH_2)][ClO_4]_2$ (2 mg) in Acetone (2 mL) at 25 °C

substrate	product[a]	turn-over[b]	yield, %[c]	reacn time, h
norbornene (150 mg)	*exo*-2,3-epoxynorbornane	14.0	7.3	2
styrene (1 mL)	styrene oxide	9.7	4.4	5
cyclohexene (1 mL)	cyclohexene oxide	58.0	43.2	3.5
	cyclohexenone	7.5	5.6	3.5
	cyclohexen-2-ol	1.7	1.3	3.5

[a] Organic products were identified by GC-MS; trace amounts of the products were found in the absence of the Ru catalysts. [b] Based on metal complex used. [c] Based on PhI formed.

oxidation of isopropyl alcohol to acetone when the $[Ru^{III}(N_4O)(OH_2)]^{2+}$ complex is oxidized at a glassy carbon electrode. Controlled-potential electrolysis in 0.1 M $HClO_4$ + 0.1 M $NaClO_4$ at 1.2 V vs. SCE in the presence of isopropyl alcohol (1 M) yielded acetone with a turnover number of 12 over a period of $4^1/_2$ h. More importantly, this Ru(III) complex provided a catalytic oxidation current that showed no signs of diminishing after several hours of continuous electrolysis. Preliminary rotating-disc experiments showed that the electrogenerated $[Ru^{V}(N_4O)(O)]^{2+}$ species is responsible for the oxidative reaction. Besides its capability to electrocatalytically oxidize organic substrates, $[Ru^{III}(N_4O)(OH_2)]^{2+}$ is also able to induce the transfer of an oxygen atom from PhIO to organic substrates such as norbornene, styrene, and cyclohexene. The results are tabulated in Table I. Selectivity has been clearly demonstrated in the case of cyclohexene, giving predominately cyclohexene oxide as the product.

Acknowledgment. We acknowledge support from the Committee of Research and Conference Grants from the University of Hong Kong. Vivian Wing-Wah Yam is a Croucher Studentship holder (1985-1987).

Absence of an Isotope Effect on the Metalation of Chiral Formamidines. The Mechanism of Asymmetric Alkylations Leading to Chiral Amines

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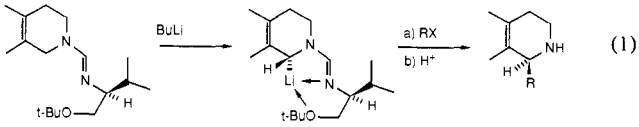
We have recently described the efficient asymmetric alkylation of various secondary amines containing the chiral formamidine moiety and their utility in the synthesis of various alkaloids in 90-98% ee (eq 1).[1] This unprecedented process[2] has drawn our



(1)

attention toward its mechanistic aspects and led us to propose[3] a preliminary "working hypothesis" which may account for the observed high stereoselectivity. We can now report, on the basis of additional evidence, that this process can be described with considerable certainty and conclude that the deprotonation step is *not* rate determining and the alkylation step proceeds with inversion of the C-Li bond. Our conclusions are based on the

(1) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108 and earlier work cited.
(2) For a recent modification using chiral oxazolines as the auxiliary, see: Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076.
(3) Loewe, M. F.; Boes, M.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *28*, 3295. For a review of earlier work, see: Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59.

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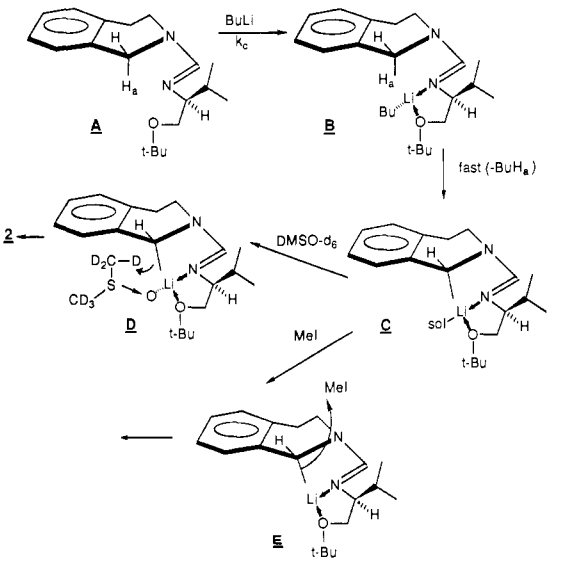
experimental results which follow.

We have prepared the 1-deuteriotetrahydroisoquinoline [(*R*)-**1**], with known absolute configuration, by cyclizing the known (*R*)-(−)-1-deuteriobenzylamine[4-8] with 2-bromoethanol according to Topson.[9] Heating **1** with the (*S*)-(−)-dimethylformamidine of valinol *tert*-butyl ether[1] gave the deuterated isoquinoline formamidine (*S*,*R*)-**2** (60%) with the diastereomeric ratios *SR*/*SS* of 95:5 ± 2.[9] The ratio of diastereomers in **2** was consistent with the 95:5 enantiomeric ratio of benzylamine.[4] When the protioisoquinoline **3** was metalated with BuLi (−78 °C, THF) and quenched with Me_2SO-d_6, the identical deuterated product **2** was formed in the same 95:5 ratio,[9] indicating the deuterium entered the lithiated species from the α-face. However, when methyl iodide was employed to quench lithiated **3**, methylation occurred (>98%) from the β-face, furnishing **4** and, after formamidine removal (N_2H_4, HOAc, EtOH, 50 °C), gave (*S*)-1-methylisoquinoline (**5**).[10] Thus, the deuteration proceeds in the opposite stereochemical sense to the alkylation. Furthermore, when **2** is metalated with BuLi, and alkylated with methyl iodide, the product observed is the monomethyl derivative **4**, devoid (<5%) of deuterium. After removal of the formamidine from **4**, only (*S*)-1-methylisoquinoline (**5**) was obtained (<5% D). It is therefore confirmed that only the *pro-R* proton in **3** (or the D in **2**) is removed by the butyllithium as previously suggested.[3] The stereoselective deuterium removal in **2** was rather surprising in view of the expected isotope effect which should be present. An experiment was performed to directly assess the extent of an isotope effect on the proton removal. An equimolar mixture of **3** (H, H) and **2** (H, D) was treated with 0.5 equiv of *n*-BuLi (THF, −78 °C) in an effort to determine the competitiveness of the deprotonation. After 15 min, methyl iodide was added and, upon workup, approximately ~50% of (*S*,*S*)-**4** was obtained (<3% D), but more importantly, the recovered starting materials **2** and **3** were analyzed for deuterium and proton content. To our surprise, the ratio of recovered **2** (H, D) and **3** (H, H) was 50.5 ± 1% and 49.5 ± 1%, respectively, indicating that *no isotope effect was present in the deprotonation step*. We are therefore forced to the conclusion that the proton or deuteron removal is not rate determining and that a complex formation prior to this event is the slow step in the process.[11] Additional information regarding the deprotonation step was gathered when the (*S*,*S*)-1-methylisoquinoline **4** was again metalated (*t*-BuLi, −78 °C, THF) and quenched with Me_2SO-d_6. The deuterated product **4** (D in place of H) contained >75% D due to incomplete metalation, yet **5** (D in place of H) possessed the same unaltered configuration, indicating once again that deuterium enters only from the α-face.[12]

Given this information, along with the known absolute stereochemistry of the alkylated chiral isoquinolines, the following mechanism becomes consistent with all the facts. Addition of butyllithium to A approaches from the side of the molecule farthest from the isopropyl group of the valinol ether and must arrange itself so that the bidentate chelate B assumes an orientation close to the proton on the α-face (H_a). This is most probably the rate-determining step (k_c). Once in position, the H_a proton (or deuteron in **2**) is rapidly removed, based on the observed insensitivity to the isotopic nature of the hydrogen as stated above. A similar lack of isotope effect has been noted by Saunders[13] in the enolization of isopropyl ethyl ketone, where it was suggested that a complex prior to proton removal may be responsible. Also, a recent discussion[14] on complex-induced proximity effects emphasizes the role of kinetically formed complexes prior to bond breaking. The resulting lithiated species C, depicted with an sp^3-hybridized C to Li may in fact have some sp^2 character along with ionic lithium. Deuteriation with the Me_2SO-d_6, via a chelated intermediate D, delivers the deuterium in an intramolecular six-membered transition state to the α-face, giving **2**. On the other hand, methyl iodide (or other alkyl halides) enters from the more accessible face and alkylates with inversion, furnishing the *S*-methylisoquinoline **4** (and **5**). Opposite modes of entry by deuteriation and alkylation have previously been observed[15] in chiral lithio sulfoxides.



In summary, this asymmetric alkylation of secondary amine carbanions proceeds through three distinct steps: (a) rate-con-

(4) (*R*)-α-D-benzylamine ($[\alpha]^{25}_D$ −1.39°, neat) was prepared according to Streitweiser[5] and Battersby[6] starting from (*S*)-α-D-benzyl alcohol (90% ee) described by Midland.[7] Benzaldehyde-d_1 was prepared according to Burgstahler.[8]

(5) Streitweiser, A.; Wolfe, J. R.; Schaeffer, W. D. *Tetrahedron* **1959**, *6*, 338.

(6) Battersby, A. R.; Staunton, J.; Summers, M. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1052.

(7) Midland, M. M.; Greer, S.; Tramantano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

(8) Burgstahler, A. W.; Walker, D. E.; Kuebrich, J. P.; Schowen, R. L. *J. Org. Chem.* **1972**, *37*, 1272.

(9) Deady, L. W.; Pirzada, N.; Topson, R. D. *J. Chem. Soc. D* **1971**, 799. (R)-**1** [$[\alpha]^{25}_D$ +0.116° (*c* 3.2, THF); $[\alpha]^{23}_{365}$ −2.32° (*c* 0.19, THF)] was shown to be >95% D via NMR and the enantiomeric excess (90 ± 2%) was determined by 270-MHz ($CDCl_3$) NMR on the formamidine (*SR*)-**2** which exhibited β/α-H ratios at 4.49 and 4.44 ppm, respectively.

(10) Absolute configuration of the methylisoquinoline **5** has been determined: Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504.

(11) Complexes of organolithium with *tert*-butylformamidines or hindered amides have been directly observed: Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2081. Meyers, A. I.; Reiker, W. F.; Fuentes, L. M. *Ibid.* **1983**, *105*, 2083. For a correction on these studies using dimethoxyethane as solvent for the complexation, see: Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1984**, *49*, 209.

(12) Quenching lithiated **3** or **4** with MeOD or D_2O gave poor stereoselectivity of **2** or **4** as epimers (~7:3). This may be due to the destruction of the intermediate chelate C prior to deuteration.

(13) Miller, D. J.; Saunders, W. H., Jr. *J. Org. Chem.* **1982**, *47*, 5041.

(14) Beak, P.; Meyers, A. I. *Acc. Chem. Res.*, in press.

(15) Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1978**, 467. Chassaing, G.; Lett, R.; Marquet, A. *Ibid.* **1978**, 471. A recent report challenges the stereochemistry of deuteriation in chiral sulfoxide anions: Iitaka, Y.; et al. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2801.

trolling complex formation; (b) rapid, proton removal from the α-face; and (c) alkylation with inversion of the C-Li bond.

It is noteworthy that a related system, described by Gawley in the accompanying report,[16] does not show stereospecific proton removal but proceeds to a thermodynamic lithiated species which alkylates in a similar fashion. The bidentate C described herein, as opposed to a monodentate species in Gawley's system, is probably responsible for the difference in deprotonation behavior, since strong chelation of organolithiums with chiral formamidines inhibits metalation of piperidines and pyrrolidine derivatives,[17] an event not observed with the oxazoline chiral auxiliary.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this program.

(16) Gawley, R. E. *J. Am. Chem. Soc.*, following paper in this issue.
(17) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.

Thermodynamic Control in the Asymmetric Alkylation of the Dipole-Stabilized Anions of Chiral Aminooxazolines†

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The alkylation of dipole-stabilized anions has become an increasingly important methodology for carbon-carbon bond formation adjacent to heteroatoms, especially nitrogen.[1] In recent years, *asymmetric* alkylation of nitrogen heterocycles using formamidines as chiral auxiliaries has shown tremendous potential.[2] Generally, dipole-stabilized anions are believed to exist in a conformation in which the carbanion lone pair (or the carbon-lithium bond) is orthogonal to the π-system, with a calculated 22.3 kcal/mol preference.[3] Moreover, dipole-stabilized anions are thought to be configurationally stable.[3a] Relatively little is known about the processes governing the asymmetric alkylation of chiral dipole-stabilized anions, although chiral tetrahydroisoquinoline and β-carboline formamidines undergo highly stereoselective deprotonations as the first step of an efficient asymmetric alkylation sequence.[4]

In our initial study of the asymmetric alkylation of (tetrahydroisoquinolyl)oxazolines, the diastereomer ratio (**2**/**3**, Scheme I) was not significantly affected by either the structure of the base (*n*-BuLi, *sec*-BuLi, or *t*-BuLi) or the deprotonation temperature, whereas the temperature of the alkyl halide quench did exert an effect.[5] These results are inconsistent with a seteroselective deprotonation as the source of the asymmetric induction. Evidence is now provided that *the β-proton at C_1 is indeed removed stereoselectively but that the resulting anion is equilibrated to a thermodynamic mixture of diastereomeric lithiated species and that the latter process accounts for the stereoselectivity observed in the overall process.*

Quenching of lithiated formamidines with CH_3OD has been shown to produce a mixture of deuteriated diastereomers, whereas

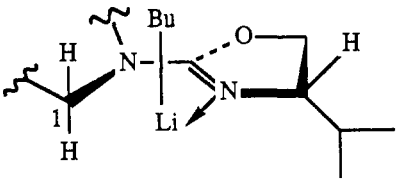
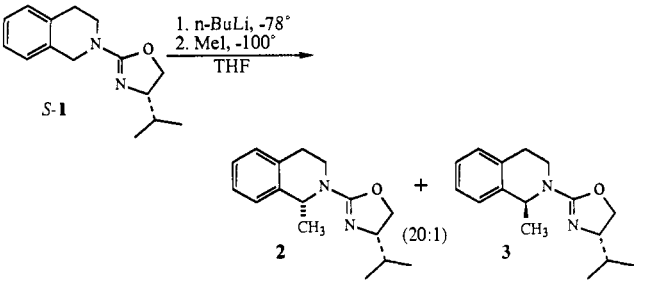
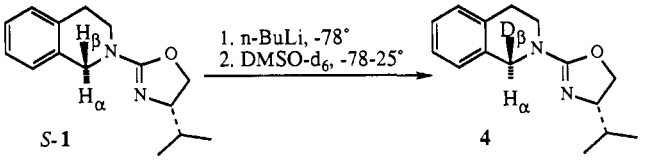


Figure 1. Coordination complex of (*S*)-**1** and butyllithium.

Scheme I



Scheme II



quenching with Me_2SO-d_6 is highly stereoselective.[4] The same behavior is exhibited by (tetrahydroisoquinolyl)oxazolines. Thus, when isoquinoline (*S*)-**1** is lithiated and quenched with CH_3OD, workup affords a 1:1 mixture of deuteriated epimers.[6] Quenching lithiated (*S*)-**1** with Me_2SO-d_6 at −78 °C and warming to room temperature afford a 96:4 mixture of the two 100% deuteriated[7] epimers, **4** (Scheme II). The absolute configuration of the major epimer at C_1 is *S*, as determined by comparison with an authentic sample.[8] It is noteworthy that the absolute configuration of the major deuteriated isomer at C_1 in **4** is opposite that in **2**. Furthermore, the stereoselective deuteriation does not occur until the reaction mixture is warmed up, conditions which afford poor asymmetric induction with methyl iodide.

When (β-deuterioisoquinolyl)oxazoline **4** was deprotonated at −78 °C and quenched with methyl iodide at the same temperature, the methylated product, **6**, was obtained in 84% de but contained 50% deuterium (Scheme III). Since the D/H ratio (1/1) is not the same as the diastereomer ratio (12/1), *the stereoselectivity observed in the overall alkylation cannot be due to stereoselectivity in the deprotonation.* In contrast, deprotonation and methylation of (α-deuterioisoquinolyl)oxazoline **5**[9] at −78 °C afforded about the same degree of asymmetric induction (82% de), but the products contained 97% deuterium.

Thus, *the deprotonation is stereoselective, but the selectivity of the deprotonation cannot account for the stereoselectivity observed in the overall process.* The selectivity of the deprotonation can be explained by a conformational preference of the

† Dedicated to Professor Ernest Eliel on the occasion of his 65th birthday.
(1) (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275-316. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Ibid.* **1984**, *84*, 471-523.
(2) For reviews, see: Meyers, A. I. *Lect. Heterocycl. Chem.* **1984**, *7*, 75-81. Meyers, A. I. *Aldricimica Acta* **1985**, *18*, 59-68. Meyers, A. I.; Fuentes, L. M.; Boes, M.; Dickman, D. A. *Chem. Scr.* **1985**, *25*, 25-31.
(3) (a) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4108-4110. (b) Bach, R. D.; Braden, M. L.; Wolber, G. J. *Ibid.* **1983**, *48*, 1509-1514.
(4) (a) Loewe, M. F.; Boes, M.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3295-3298. (b) For a more recent study, see: Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.*, preceding paper in this issue.
(5) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076-3078.
(6) The ratio of deuteriated epimers was determined by 360-MHz NMR. The C_1 proton of **4** (Scheme II) resonates at δ 4.575, whereas the C_1 proton of **5** (Scheme III) resonates at δ 4.535. Accurate integration was accomplished by simultaneous gated decoupling of the deuterium resonance.
(7) Deuterium incorporation was determined from mass spectroscopic data. At 40 eV, the molecular ions of compounds **1**-**3** are <5% abundant. The base peak for all three components is at M − 43, arising from loss of isopropyl, and the deuterium content is readily available by analysis of the M − 43 fragment ions of **4**-**6**.
(8) (*R*)-1-Deuteriotetrahydroisoquinoline has been synthesized independently from (*R*)-1-deuteriobenzylamine by D. A. Dickman and A. I. Meyers, see the preceding paper in this issue. A comparison has revealed that the 1-deuteriotetrahydroisoquinoline obtained by hydazinolysis of the mirror image of **4** also has the *R* configuration.
(9) Compound **5** was synthesized from (*R*)-**1**, by exchange of chiral auxiliaries from the enantiomer of **4** (Scheme II).

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