Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2509–2516

TETRAHEDRON: *ASYMMETRY*

Deracemization of diarylmethanes via lateral lithiation–protonation sequences by means of sparteine

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Received 26 May 1998; accepted 9 June 1998

Abstract

Deracemization of diarylmethane derivatives was investigated by lateral lithiation–protonation mediated by (−)-sparteine. Treatment of racemic 4-phenyltetrahydroisoquinoline **1** with *s*-butyllithium–(−)-sparteine followed by protonation of the resulting anion afforded (*R*)-phenyltetrahydroisoquinoline **1** in up to 88% e.e. Following the same procedure, racemic 2-(1-phenylethyl)pyridine **2** was subjected to the lithiation–protonation sequence. The stereochemical outcome of the sequence proved to be highly dependent on the proton sources giving either (*S*)- or (*R*)-2-(1-phenylethyl)pyridine **2** with EtOH or *t*-BuOH respectively in up to 50% e.e.

1. Introduction

A large number of bioactive molecules possessing a chiral diarylmethane unit are reported in the literature. For instance, 4-aryltetrahydroisoquinolines,[1a–i] hexahydropyrrolo[2,1-a]isoquinolines[2] and sertraline[3] are of considerable interest due to their ability to inhibit uptake of the important central neurotransmitters such as serotonine, norepinephrine or dopamine at postsynaptic receptors. Another example is illustrated by pheniramines,[4] one of the most important classes of antihistaminic agents. Although most of these compounds demonstrated pharmocological enantioselectivity of action they are usually synthesized in their racemic form, requiring a supplementary step of resolution, generally expensive, time-consuming and inefficient.

To fill in this gap and as part of a research program on the development of asymmetric syntheses of diarylmethane derivatives, we intended to explore deracemization of racemic diarylmethane derivatives via the lateral lithiation–protonation sequence in the presence of an enantiodiscriminating ligand.

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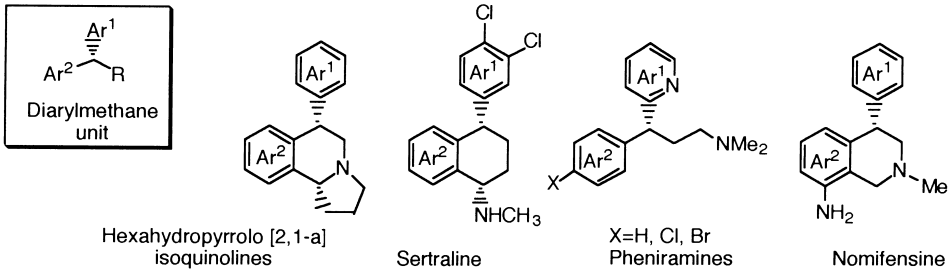
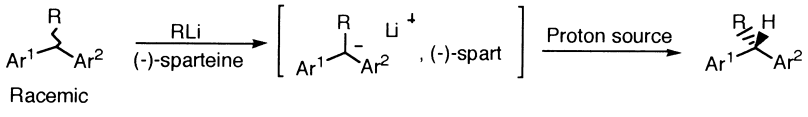
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00228-6

The readily available, naturally occurring alkaloid (−)-sparteine has been reported extensively as an effective chiral ligand in the deprotonation of prochiral benzyl compounds followed by an electrophilic substitution with various electrophiles. In numerous cases this methodology provided a high level of asymmetric induction and found practical development in asymmetric synthesis.[5]



Although this sequence has been abundantly studied during the asymmetric functionalization of a prochiral benzylic substrate, no synthetic application using this approach in the deracemization of a chiral racemic diarylmethane derivative via a lithiation–protonation sequence mediated by (−)-sparteine has been reported. As a result of these observations, we speculated that it might be of interest to evaluate the potential of a lateral lithiation–protonation sequence in the presence of RLi/(−)-sparteine to achieve the deracemization of diarylmethane derivatives (Scheme 1).



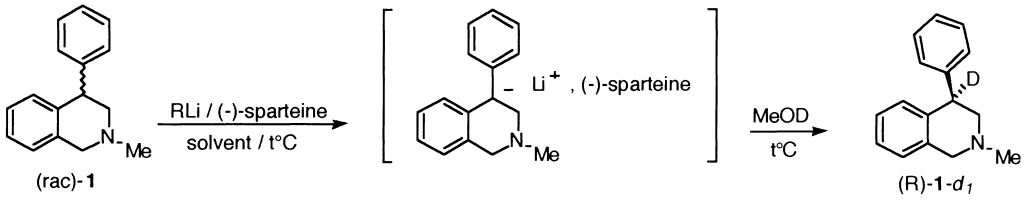
Scheme 1.

2. Results and discussion

We first focused on the deracemization of N-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **1**, an analog of nomifensine.[1a,e,f] A summary of the most significant results is listed in Table 2. Lateral lithiation of N-methyl-1,2,3,4-tetrahydroisoquinoline at C-4 has been reported with good yields in THF.[6] In initial experiments, deprotonation of **1** in THF at −78°C with *s*-BuLi or *t*-BuLi in the presence of (−)-sparteine and quenching with MeOD afforded a high deuterium incorporation of 90% at C-4, nevertheless with a poor enantioenrichment of 4% (entries 1 and 2). The **1**-d_1/**1** ratio was readily assessed by integration of the ^{1}H NMR spectra (Table 1) and enantiomeric excesses were measured by chiral HPLC analysis after flash chromatography. The rather disappointing results observed in THF may be a result of its strong coordinating properties which displaces sparteine from Li^+.[7]

We next surveyed a variety of solvents to optimise conditions to achieve good yields of lithiation and to promote strong associations between the benzylic carbanion and (−)-sparteine; both of these conditions being necessary to open up opportunities to attain high degrees of enantiomeric enrichments. The use of non-coordinating solvents such as toluene or hexane proved to be ineffective in terms of reactivity, yielding between 10% and 17% of the deuterium incorporation respectively when *s*-BuLi was employed at −78°C for 2 hours. Taking into account of the low deuterium incorporation, enantiomeric excesses were not measured in these experiments. However, changing the solvent from THF to Et_2O resulted in a high level of enantioselectivity (e.e.=65%) with respect to the percentage of deuterium incorporation (**1**-d_1/**1**=65/35) (entry 3). Finally, deprotonation proceeded to completion (**1**-d_1/**1**>95/5) within 24 h at −45°C affording **1**-d_1 in up to 88% e.e. in 60% isolated yield (entry

Table 1
Deracemization of N-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **1**



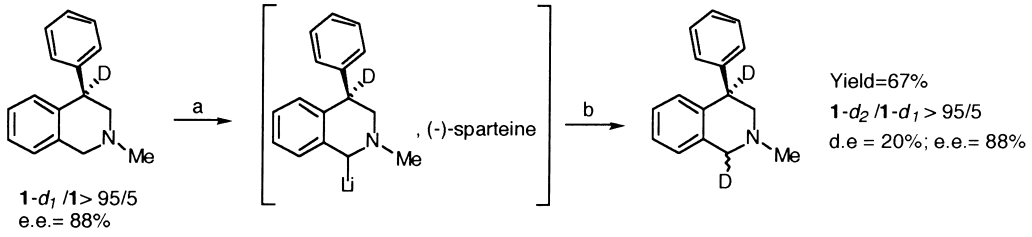
Entry	Solvent	Base (eq)	(-)-Spart eq	Lithiation t°C	Hours	Deuterolysis t°C	Ratio **1**-d_1/**1**[a]	E.e. (%)
1	THF	*s*-BuLi (4)	4	-78	2	-78	90/10	4
2	THF	*t*-BuLi (4)	4	-78	2	-78	90/10	4
3	Et_2O	*s*-BuLi (4)	4	-78	2	-78	65/35	65
4	Et_2O	*s*-BuLi (2)	2	-78	2	-78	62/38	60
5	Et_2O	*s*-BuLi (4)	4	-45	12	-45	90/10	83
6	Et_2O	*s*-BuLi (2)	2	-45	12	-45	90/10	82
7	Et_2O	*s*-BuLi (4)	4	-45	24	-45	>95/5	88
8	Et_20	*s*-BuLi (4)	4	-45	24	-78	>95/5	88

[a] 60% isolated yield

7). As can be seen, the main drawback of this deracemization procedure is the long lithiation time required to ensure complete deuterium incorporation. Our attempts to circumscribe this problem by conducting the deprotonation at a higher temperature (−45°C), led to complications arisen from the formation of by-products resulting from Emde-type 1,2-elimination.[6] The use of 2 equiv. of *s*-BuLi–(−)-sparteine complex did not affect significantly the asymmetric induction (entries 4 and 6). Upon decreasing the amount of *s*-BuLi–(−)-sparteine under 2 equiv., the percentage of deuterium incorporation was substantially diminished resulting in a drop in the enantiomeric excess. Lastly, under the best conditions selected [−45°C/24 h/Et_2O/*s*-BuLi–(−)-sparteine, 4 equiv.], the resultant carbanion was trapped with a variety of proton sources (EtOH, *t*-BuOH, AcOH, H_2O, DMSO) at −45°C leading in each case to no discernible change in enantioselectivity. Performing the protonation step at a lower temperature (−78°C) did not improve the enantiomeric excess (entry 8). Comparison of the optical rotation of **1** with literature values[1b,d] revealed that the major enantiomer obtained possesses in all experiments the (*R*) configuration at C-4.

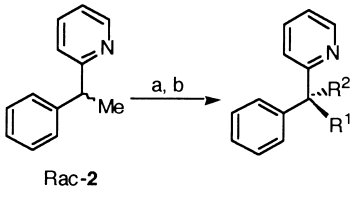
In the course of this study, a particularly unexpected result was observed when **1**-d_1 (e.e.=88%) was treated with 4 equiv. of *s*-BuLi–(−)-sparteine complex (2 h/−78°C). In contrast to **1**, deprotonation of **1**-d_1 took place exclusively at C-1 affording the dideuterated compound **1**-d_2 (**1**-d_2/**1**-d_1>95/5) in 67% yield after deuterolysis of the organolithium intermediate with MeOD (Scheme 2). It is noteworthy that deprotonation of 1,2,3,4-tetrahydroisoquinoline at C-1 is usually accomplished in the presence of a protecting group on the nitrogen which activates through chelate and dipole stabilization.[8]

Chiral HPLC of **1**-d_2 indicates that no racemization occurred at C-4. According to the ^{1}H NMR spectrum, **1**-d_2 was obtained as a 6:4 diastereoisomeric mixture. Thus, this deuterium isotope effect inverts the lithiation site from C-4 to C-1 when **1**-d_1 is subjected to deprotonation. This finding could open up the opportunities to provide a straightforward way to functionalized **1**-d_1 at C-1 without preliminary activation of this position.



Scheme 2. (a) *s*-BuLi–(−)-sparteine/Et_2O, 4 equiv./−78°C; (b) MeOD/−78°C

Table 2
Deracemization of 2-(1-phenylethyl)pyridine **2**. (a) *s*-BuLi–(−)-sparteine, 2 equiv./Et_2O/−78°C/2 h; (b) proton source/−78°C/15 min



Entry	R^1	R^2	Proton source	Yield	Ratio **2**-d_1 / **2**	E.e. (%)
1	Me	D	EtOD	85%	80/20	50 (S)
2	Me	H	EtOH	85%	/	50 (S)
3	H	Me	t-BuOH	85%	/	50 (R)

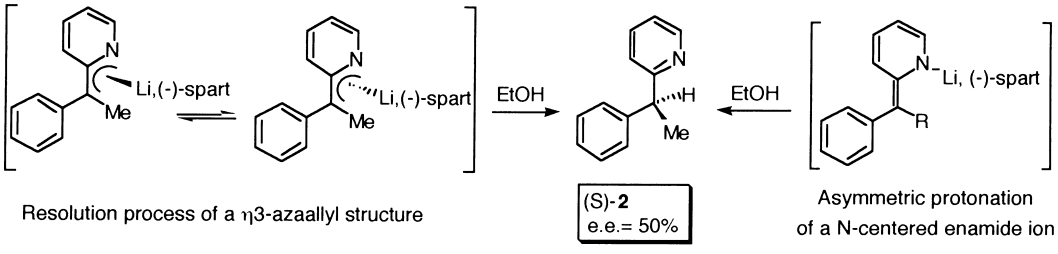
Then we turned our attention to the deracemization of 2-(1-phenylethyl)pyridine **2**, an analogue of pheniramines. The asymmetric synthesis of **2** has been previously reported in the literature either by a coupling reaction of optically pure 1-phenylethyl-2-sulfoxide with methylmagnesium bromide[9] or by a co-cyclotrimerization reaction of (*S*)-2-phenylpropanenitrile with acetylene.[10] A number of deprotonation/MeOD quench experiments were examined in order to attain optimum deuterium incorporation. Initial attempts to lithiate **2** in toluene or hexane in the presence of 2 equiv. of *s*-BuLi at −78°C for 2 hours led to the recovery of the starting material along with a low amount of **2**-d_1 (5–10%) after treatment with MeOD. The use of the former protocol in Et_2O gave the best result affording 80% of deuterium incorporation. In a last attempt, when the lithiation was conducted in Et_2O at 0°C for 2 hours, the percentage of the deuterium incorporation was not improved.

In spite of incomplete lithiation, **2** was subjected to deracemization in the presence of 2 equiv. of *s*-BuLi–(−)-sparteine for 2 hours at −78°C in Et_2O. Treating the organolithium intermediate with EtOD at −78°C afforded **2**-d_1 (**2**-d_1/**2**=80/20) in 50% e.e and in 85% yield (Table 2, entry 1). The absolute configuration of the so-obtained major enantiomer was assigned as (*S*) by comparison of the sign of the optical rotation with the literature data.[9] In contrast to **1**, the stereochemical outcome of the lithiation–protonation sequence is highly influenced by the nature of the achiral proton source. While EtOH led to (*S*)-**2**, *t*-BuOH preferentially afforded the opposite enantiomer (*R*)-**2** with the same magnitude of stereoselection (entry 3).

This result is of particular interest since the alkaloid sparteine is only available in one enantiomeric form. Independent to this practical consideration, it is noteworthy that only a few reports mentioned such inversion of stereoselectivity in stereoselective protonation processes simply on changing the achiral proton source. These include the stereoselective protonation of non-racemic chiral alkyllithium species[11] and the diastereoselective protonation of boron enolates.[12]

Hoppe and Beak carried out extensive work to elucidate the mechanism of asymmetric induction during deprotonation–substitution sequences of a prochiral benzylic substrate in the presence of (−)-sparteine.[5] Depending on the configurational stability of the benzylic carbanion, the enantioselectivity originates either from the lithiation step via an asymmetric deprotonation or from a post-lithiation step via a dynamic resolution. In the present deracemization process, the enantiodetermining step occurs

after the lithiation step to form either a configurationally unstable α-lithiated species which could undergo a dynamic resolution or a planar delocalized structure followed by an asymmetric protonation. In contrast to **1** affording most likely a pyramidal carbonion,[13] previous X-ray structural studies and NMR spectroscopic studies of 2-picolyllithium derivatives, closely related to **2**-Li species, revealed a strong tendency of these organolithiums to adopt either an 'enamido' or 'η^3-azaallyl' type of lithium complex.[14] Consequently, as the case may be, deracemization of **2** may be regarded either as a dynamic resolution process or an asymmetric protonation (Scheme 3).



Scheme 3. Possible pathways of asymmetric induction during the deracemization of **2**

As can be noted, if one wants to gain insight into the stereochemical course of this deracemization process, structural studies of organolithium intermediates should be addressed. NMR spectroscopic studies are in progress to decide between these different pathways of asymmetric induction and to be in a position to propose an explanation regarding the unusual inversion of stereoselection observed in the course of the deracemization of **2**. In summary, the asymmetric deprotonation–protonation sequence which has been widely used with success in the field of enolate chemistry[13] has been applied herein to the deracemization of diarylmethanes providing modest to good enantioselectivities. Lastly, in view of the lack of general methods for asymmetric electrophilic arylation of benzyl derivatives, this methodology should find synthetic applications for the preparation of further enantioenriched diarylmethanes, precursors of biological active compounds.

3. Experimental section

4-Phenyl-1,2,3,4-tetrahydroisoquinoline was prepared following the literature procedure by reductive amination of 1-phenyl-2-aminoethanol with benzaldehyde followed by cyclization under acidic conditions.[1a,f,i] Commercially available reagents were used unless otherwise stated. (−)-Sparteine was distilled under vacuum before use. ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz Bruker apparatus. Elemental analyses were performed on a Carlo–Erba 1106 analyser. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled on benzophenone/Na. *tert*-Butyllithium, *sec*-butyllithium and *n*-butyllithium were purchased from Fluka and their concentration was determined by titration of diphenylacetic acid[15] prior to use. Optical rotations were determined with a Perkin–Elmer 341 polarimeter using 10 cm cells.

3.1. rac-*N-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline* ***1***

To a stirred solution of 4-phenyl-1,2,3,4-tetrahydroisoquinoline (4.66 g, 22.27 mmol) in methanol (150 ml) was added paraformaldehyde (800 mg, 26.7 mmol). The mixture was stirred at reflux for 45 min and then allowed to reach room temperature. After addition of 20% $Pd(OH)_2$ (1 g), the solution was stirred under a hydrogen atmosphere for 12 h. After removal of the catalyst by filtration through Celite and

washing with methanol (2×30 ml), the filtrate was evaporated under reduced pressure to give 3.88 g (78%) of **1** as an oil. ^{1}H NMR ($CDCl_3$) δ 7.35–7.05 (m, 8H); 6.90 (d, 1H, *J*=7.5 Hz); 4.31 (t, 1H, *J*=7 Hz); 3.80 (d, 1H, *J*=15 Hz); 3.64 (d, 1H, *J*=15 Hz); 3.08 (dd, 1H, *J*= 11.5 and 5 Hz); 2.61 (dd, 1H, *J*= 11.5 and 8.5 Hz); 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 144.85, 137.04, 135.12, 129.29, 129.02, 128.28, 126.39, 126.23, 126.11, 125.90, 61.79, 58.45, 45.96, 45.89.

3.2. *Deracemization of N-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **1***

To a solution of (−)-sparteine (1.76 g, 7.52 mmol) in Et_2O (5 ml) was added a solution of *s*-BuLi in cyclohexane (5.8 ml, 1.3 M, 7.52 mmol). The resulting solution was stirred under Ar at −45°C for 1 h and then added dropwise to a precooled solution of *rac*-N-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **1** (420 mg, 1.88 mmol) in Et_2O (5 ml). The resultant purple solution was stirred for 24 h at −45°C under Ar. Addition of MeOD (760 μl, 18.81 mmol) at −45°C over a period of 5 min afforded a colourless solution which was kept at this temperature for a further 20 min. Saturated aqueous NH_4Cl (30 ml) was added and the solution was allowed to reach room temperature. Layers were separated and the aqueous phase was extracted with Et_2O (2×60 ml). The combined ether phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: toluene/EtOH/NH_4OH=9/0.9/0.1) to yield 250 mg (60%) of N-methyl-4-(phenyl-deuterio)-1,2,3,4-tetrahydroisoquinoline **1**-d_1 as a colourless oil. According to the ^{1}H NMR spectrum, the nondeuterated starting material **1** could not be detected (**1**-d_1/**1**>95/5). ^{1}H NMR ($CDCl_3$) δ 7.35–7.05 (m, 8H); 6.90 (d, 1H, *J*=7.5 Hz); 3.80 (d, 1H, *J*=14.85 Hz); 3.64 (d, 1H, *J*=14.85 Hz); 3.08 (d, 1H, *J*=11.5 Hz); 2.61 (d, 1H, *J*=11.5 Hz); 2.46 (s, 3H). The enantiomeric purity was determined to be 88%. Chromatographic conditions: Chiralcel OD (250×4.6 mm; 10 μm); UV detection (λ=230 nm); eluent: hexane/2-propanol (90/10); flow rate: 1 ml/min; temperature: 22°C; injection: 20 μl (0.5 mg of sample in 10 ml of hexane); R_f of minor peak: 4.3 min, R_f of major peak: 5.5 min. The absolute configuration of **1**-d_1 was assigned as *R* by comparison of the optical rotation of **1**-d_1, $[[\alpha]^{27}_D$=−11.0 (c=1.03 in methanol)] to the known rotation for *R*-**1** $[[\alpha]^{24}_D$=−16.7 (c=0.72 in methanol)].[1b,d]

3.3. *N-Methyl-1,4-dideuterio-4-phenyl-1,2,3,4-tetrahydroisoquinoline **1**-*d$_2$

Compound **1**-d_2 was obtained using a similar procedure to that described for the preparation of (*R*)-**1**-d_1 from a solution of (−)-sparteine (0.38 g, 1.61 mmol) in Et_2O (1.5 ml) and a solution of *s*-BuLi in cyclohexane (1.24 ml, 1.3 M, 1.61 mmol). The resulting solution was stirred under Ar at −78°C for 1 h and then added dropwise to a precooled solution of (*R*)-**1**-d_1 (e.e.=88%; **1**-d_1/**1**>95/5) (90 mg, 0.4 mmol) in Et_2O (1 ml). After stirring for 2 h at −78°C under Ar, the solution was treated with MeOD (160 μl). Work-up and purification were carried out as described above affording 67 mg of **1**-d_2 (67%). ^{1}H NMR ($CDCl_3$) δ 7.35–7.05 (m, 8H); 6.90 (d, 1H, *J*=7.5 Hz); 3.76 (s, 0.6H); 3.62 (s, 0.4H); 3.08 (d, 1H, *J*=11.5 Hz); 2.61 (d, 1H, *J*=11.5 Hz); 2.46 (s, 3H). MS 226 (MH^+).

3.4. rac-*2-(1-Phenylethyl)pyridine **2***

To a stirred solution of 2-benzylpyridine (3.92 g, 23.16 mmol) in dry Et_2O (100 ml) cooled to −78°C was added under Ar a solution of butyllithium in hexane (13.90 ml, 2.5 M, 34.75 mmol). After the solution was stirred at this temperature for 45 min, methyl iodide (9.86 g, 69.49 mmol) was added and the solution stirred at −78°C for a further 4 hours. After treatment with saturated aqueous NH_4Cl (50 ml), and extraction with Et_2O (2×50 ml), the organic layer was dried over $MgSO_4$ and evaporated under vacuum

affording a crude product which after chromatography on silica gel (eluent: cyclohexane/Et_2O=7/3) yielded 3.90 g (92%) of 2-(1-phenylethyl)pyridine **2** as a slightly yellow oil. ^1H NMR ($CDCl_3$) δ 8.58 (ddd, 1H, *J*=4.9, 1.8 and 1 Hz); 7.56 (td, 1H, *J*=7.6 and 1.8 Hz); 7.34–7.06 (m, 7H); 4.33 (q, 1H, *J*=7.0 Hz); 1.73 (d, 3H, *J*=7.2 Hz). Anal. calcd for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found: C, 85.05; H, 7.23; N, 7.77.

*3.5. Deracemization of 2-(1-phenylethyl)pyridine **2***

To a solution of (−)-sparteine (0.38 g, 1.64 mmol) in Et_2O (3.5 ml) was added a solution of *s*-BuLi in cyclohexane (1.26 ml, 1.3 M, 1.64 mmol). The resulting solution was stirred under Ar at −78°C for 1 h and then cannulated dropwise to a solution of *rac*-2-(1-phenylethyl)pyridine **2** (0.2 g, 1.09 mmol) in Et_2O (2 ml) cooled to −78°C. After 2 hours stirring at this temperature under Ar, the solution was treated with EtOD (0.2 g, 4.37 mmol) and kept at −78°C for a further 15 min. After treatment with saturated aqueous NH_4Cl (10 ml) and phase separation, the aqueous phase was extracted with Et_2O (2×15 ml). The combined organic phases were washed with 10% aqueous acetic acid (10 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded 260 mg of crude product as a yellow oil. Purification by flash chromatography on silica gel with cyclohexane/Et_2O (7/3) as eluent yielded 170 mg (85%) of enantiomerically enriched 2-(1-phenylethyl)pyridine **2**-d_1. The deuterium content was determined to be 80% by comparison with the ^1H NMR spectrum of 2-(1-phenylethyl)pyridine **2**. The enantiomeric purity was measured as 50% by chiral stationary phase HPLC. Chromatographic conditions: Chiralcel OD (250×4.6 mm; 10 μm). UV detection (λ=230 nm); eluent: hexane/2-propanol=99.5/0.5; flow rate: 1 ml/min; temperature: 22°C; injection: 20 μl (0.5 mg of sample in 10 ml of hexane); R_f of minor peak: 7.4 min, R_f of major peak: 8.0 min. The absolute configuration was assigned as *S* by comparison of the optical rotation with literature values. $[\alpha]^{23}_D$=+32 (c=1.18 in benzene). Literature value of (+)-(*S*)-2-(1-phenylethyl)pyridine **2**: e.e.=100%, $[\alpha]^{25}_D$=+63 (c=1.00 in benzene).[9]

Acknowledgements

We thank les Régions de Haute et Basse Normandie for financial support of this work (Réseau Interrégional Normand de Chimie Organique Fine).

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