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Enantioselective addition of organolithium reagents to 3,4-dihydroisoquinoline in the presence of (−)-sparteine as an external ligand. Application for the synthesis of isoquinoline alkaloids

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Abstract—Three isoquinoline alkaloids, (−)-salsolidine **2**, (+)-carnegine **6** and (−)-1-phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **7**, were obtained in high yield and with 17–46% e.e. by the enantioselective additions of organolithium reagents to dihydroisoquinolines **1** and **5**, in the presence of (−)-sparteine as a chiral ligand.

1. Introduction

The nucleophilic 1,2-addition of organometallic reagents to imine C=N double bonds is a valuable method for the synthesis of secondary amines. In the last decade enantioselective additions to prochiral imines in the presence of chiral catalysts/ligands have been developed as a new strategy for the synthesis of optically active amines, including alkaloids. The stereoselective addition of *C*-nucleophiles to the C=N bond has also been the subject of review articles.[1–3] The addition, in comparision with that of a carbonyl group, has been limited by the poor electrophilicity of the azomethine carbon atom. However, the reaction can be considerably accelerated by the use of chiral ligands/catalysts. A variety of compounds have been tested[3] as external chiral controllers of the enantioselectivity. The influence of (−)-sparteine on the reactions of organolithium compounds (RLi; R = Me, *n*-Bu, Ph, vinyl) with various aldimines has been reported by Denmark,[4] Itsuno[5] and North.[6]

Denmark et al.[4] were the first to successfully use (−)-sparteine in such reactions (72–91% e.e.). High enantioselectivities were observed even when the chiral promoter was used in catalytic amounts. The use of (−)-sparteine was particularly beneficial in *n*-butyllithium and phenyllithium additions to *N*-arylaldimines. Itsuno et al.[5] described the enantioselective addition of organolithium compounds to *N*-silyl, *N*-alumino, and *N*-boryl imines. The best results were obtained with benzaldehyde *N*-di-*iso*-butylalumino imine (74% e.e.) when the (−)-sparteine–BuLi complex was formed before addition to the imine. North et al.[6] studied (−)-sparteine induced addition of organolithium reagents to α,β-unsaturated *N*-arylaldimines, achieving e.e.s of 70–88%.

The lupine alkaloid, (−)-sparteine, is an inexpensive and commercially available, enantiomerically pure diamine used as a chiral bidentate ligand in many types of synthetic reaction. It has been used for several aspects of asymmetric syntheses such as deprotonation,[7–9] the polymerization of methacrylate esters,[10] the intra-[11] and intermolecular[12] carbolithiation of alkenes and the enantioselective addition of organolithium and Grignard reagents to carbonyl compounds.[13]

(−)-Sparteine has been used as an external ligand in the addition reactions of different types of imine but has not been applied to addition reactions of cyclic imines. In connection with our study on the asymmetric synthesis of isoquinoline alkaloids,[14] we planned to investigate this approach for the enantioselective synthesis of salsolidine **2**, a simple isoquinoline alkaloid. In a similar reaction, reported previously,[15] the addition of methyl-

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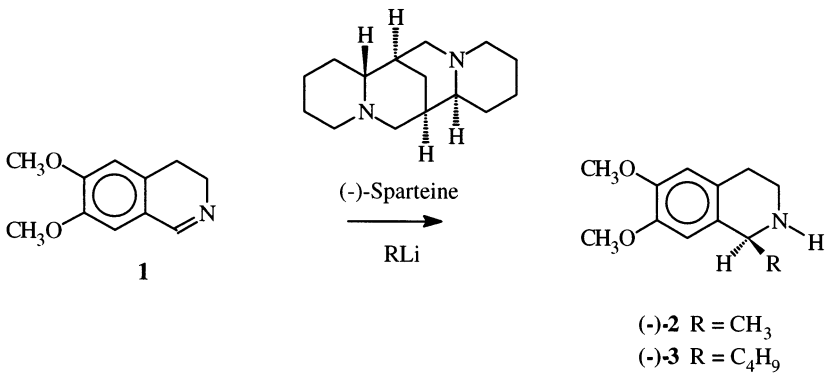
lithium to 3,4-dihydroisoquinoline **1** was carried out in the presence of (4*S*,5*S*)-5-(2-methoxyphenoxymethyl)-4-(4-methylthiophenyl)-2-phenyl-2-oxazoline to give (*R*)-(+)-salsolidine **2** in 41% e.e.

Herein, we describe the results of the addition of various organolithium reagents to 6,7-dimethoxy-3,4-dihydroisoquinoline **1** performed in the presence of (−)-sparteine applied as an external chiral ligand and/or catalyst (Scheme 1).

2. Results and discussion

We carried out the addition of methyl-, *n*-butyl- and phenyllithium to 6,7-dimethoxy-3,4-dihydroisoquinoline **1** in the presence of (−)-sparteine. In order to optimize the reaction conditions we investigated the influence of a number of factors, including the amount of chiral ligand/catalyst, the reaction temperature and the type of solvent, on the enantioselectivity. The results are shown in Tables 1–3. According to the previous results,[5] the (−)-sparteine–organolithium complex (1:1) was first generated at −76°C for 30 min before a solution of imine **1** was added, also at low temperature.

The enantiomeric excess (e.e.) was established by HPLC analysis using a Chiracel OD-H column (a comparison was made of the retention times of each enantiomer with that of a racemic sample and, in a few cases with the literature data[17]) and/or from the relative integration of ^{1}H NMR spectra of the product run in the presence of the chiral shift reagent, TADDOL.[18] The specific rotation measurements were used for determination of the sign of the optical rotation from which the absolute configuration of the product was deduced.



Scheme 1.

Table 1. Addition of methyllithium to imine **1**

Entry	(−)-Sparteine (mol equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)	Config.[a]	% e.e. HPLC	% e.e. NMR
1	1	Toluene	−76→−15	20	77	(*S*)-(−)	30.4	31.6
2	0.2	Toluene	−76→−15	20	50	(*S*)-(−)	4.0	2.9
3	1	Toluene	−20	2	75	(*S*)-(−)	15.0	14.0
4	0.2	Toluene	−20	2	85	(*S*)-(−)	14.0[b]	14.0
5	0.2	Et_2O	−20	2	86	(*S*)-(−)	12.0	13.6
6	0.2	THF	−20	2	90		0	2.0[c]
7	0.2	THF	−76	2	63		2.2[c]	3.1[c]
8	0.2	$(i\text{-Pr})_2O$	−20	2	81	(*S*)-(−)	12.9	15.1

[a] Confirmed by comparing the specific rotation with a literature value.[16]
[b] $[\alpha]_D$ −7.8 (0.51, EtOH).
[c] Racemic within error of the method.

Table 2. Addition of *n*-butyllithium to imine **1**

Entry	(−)-Sparteine (mol equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)	$[\alpha]_D$ ($CHCl_3$)	% e.e. HPLC
1	1	Toluene	−76	2	77	−20.3	46.5
2	0.2	Toluene	−76	3	90	−12.3	28.0
3	1	Et_2O	−76→−15	20	49	−4.6	9.6
4	1	THF	−76	2	63	0	0

Table 3. Addition of phenyllithium to imine **1**

Entry	(−)-Sparteine (mol equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)	Config.[a]	% e.e. HPLC	% e.e. NMR
1	1.0	Toluene	−76	2.5	34	(*R*)-(+)	17.0	–
2	1.4	THF	−76	1	64		2.1[c]	–
3	1.0	THF	−76	1.5	79		5.0	3.0
4	1.4	Et_2O	−76→−15	20	31		2.2[c]	–
5	1.0	Et_2O	−76	2	37	(*R*)-(+)	17.0[b]	17.0

[a] Confirmed by comparing the specific rotation with a literature value.[17,22]
[b] $[\alpha]_D$ +3.1 (0.96, $CHCl_3$).
[c] Racemic within error of the method.

As evidenced in Table 1, in additions of methyllithium to imine **1**, the best enantioselectivity was obtained for the reaction run in toluene in the presence of one molar equivalent of (−)-sparteine, at −76°C for the first 2 h and at −15°C for the next 18 h (entry 1). Salsolidine **2** in levorotatory (*S*)-form[16] (31.6% e.e. by HPLC) was isolated after column chromatography purification followed by (−)-sparteine. Results obtained for reactions run in THF (Table 1, entries 6, 7) suggested the formation of (±)-**2**.

Table 2 shows the results of the addition reactions of *n*-butyllithium to imine **1**. The addition of the preformed (−)-sparteine–*n*-butyllithium complex to imine **1** proceeded faster than in the reaction with methyllithium. The best result was achieved when the reaction was completed in toluene at −76°C for 2 h with equimolar (−)-sparteine (Table 2, entry 1). Pure, isolated 1-butyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **3** was shown to be levorotatory: $[\alpha]_D$ −20.3 (0.73, $CHCl_3$), obtained in 46.5% e.e. (by HPLC). To the best of our knowledge this compound has been reported in the literature only as the racemate.[19]

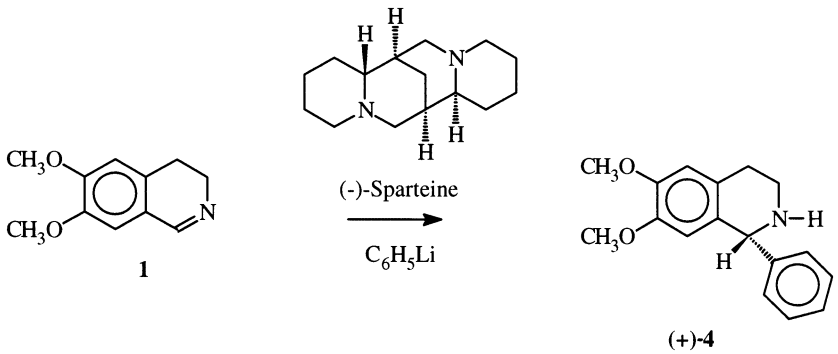
On the basis of a similarity of the CD spectra[20] of amines **2** and **3** and those reported for simple 1-alkyl- and 1-benzyltetrahydroisoquinoline alkaloids,[21] as well as analysis of the retention times for the (*S*)-enantiomers in HPLC analysis, we assigned (*S*)-configuration at the C(1) stereogenic center to compound **3**.

The results for the addition of phenyllithium to the 3,4-dihydroisoquinoline **1** leading to 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **4** are summarized in Table 3 (Scheme 2). The same e.e. of 17% was obtained regardless of the solvent used, toluene or diethyl ether (Table 3, entries 1, 5). The levorotatory enantiomer of compound **4**, $[\alpha]_D$ −20.0 (0.50, $CHCl_3$), was obtained for the first time in 1991 by Wiegrebe[22] from (±)-**4** by resolution of diastereomeric salts with (−)-diacetone-2-ketogulonic acid hydrate. The (*R*)-absolute configuration of the dextrorotatory enantiomer **4** (prepared from 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline using the asymmetric transfer hydrogenation procedure of Noyori et al.[17]) was established in 1996. Thus, the (*R*)-configuration of (+)-**4** could be assigned on the basis of the sign of the specific rotation and the retention time of the predominant enantiomer in HPLC analysis.[17]

To improve the enantioselectivity of the additions, a series of experiments were completed using 6,7-dimethoxy-3,4-dihydroisoquinolinium methiodide **5** as a substrate. It was hoped that the iminium salt **5** would be more reactive toward nucleophilic addition than imine **1**. The results are shown in Tables 4 and 5 and Scheme 3.

In the addition of methyllithium to methiodide **5** (*R*)-(+)-carnegine **6**,[23] another simple isoquinoline alkaloid, was formed. The enantioselectivity of these reactions was estimated by comparing the specific rotation with a literature value for the natural (*S*)-enantiomer ($[\alpha]_D$ −24.9 (4.45, EtOH))[16] and was disappointingly low (Table 4, entry 1, $[\alpha]_D$ +1.7 (1.0, EtOH), 7% e.e.).

The enantioselectivity of the phenyllithium addition reactions to the iminium salt **5** (Table 5) were even



Scheme 2.

Table 4. Addition of methyllithium to iminium salt **5**

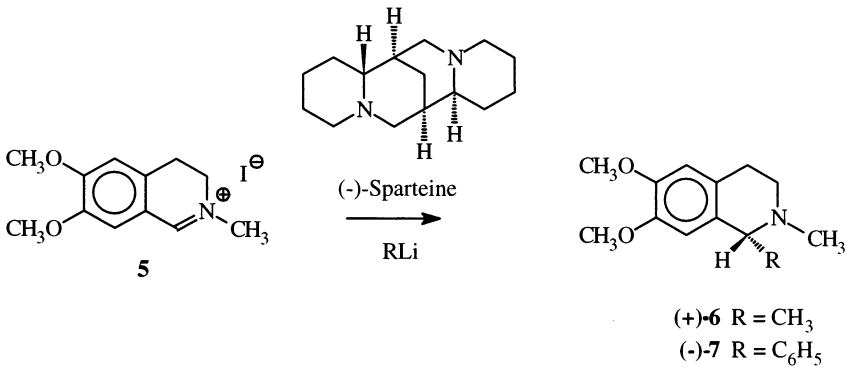
Entry	(−)-Sparteine (mol equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)	Config.[a]
1	1	Et_2O	−76→−10	24	67[b]	(*R*)-(+)
2	1	Et_2O	−76	2.5	59	(*R*)-(+)
3	1	Toluene	−76→−10	24	76	(*R*)-(+)
4	1	Toluene	−76	24	76	(*R*)-(+)

[a] Confirmed by comparing the specific rotation with a literature value.[23]
[b] $[\alpha]_D$ +1.7 (1.0, EtOH).

Table 5. Addition of phenyllithium to iminium salt **5**

Entry	(−)-Sparteine (mol equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)	Config.[a]
1	1	Et_2O	−76→−10	24	90	(*R*)-(−)
2	0.2	Et_2O	−76	24	52	(*R*)-(−)
3	0.2	Toluene	−76	24	52	(*R*)-(−)

[a] Confirmed by comparing the specific rotation with a literature value.[22]



Scheme 3.

lower than those obtained with methyllithium. The absolute configuration of the product, 1-phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **7**, can be suggested to be (*R*), knowing that the *N*-methylation of 1-phenylisoquinoline derivatives is accompanied by a reversal in the sign of the specific rotation.[24] Compound **7** has been reported so far as a synthetic product in enantiopure[22] and racemic form[25] and has also recently been isolated as a racemate from the leaves of *Adhatoda vasica* Nees.[26]

3. Conclusion

The enantioselective additions of organolithium compounds to the dihydroisoquinoline derivatives **1** and **5**, performed in the presence of (−)-sparteine as an external chiral ligand, resulted in the formation of several optically active 1-substituted 1,2,3,4-tetrahydroisoquinoline derivatives. The enantioselectivity of the addition reaction of the preformed (−)-sparteine–*n*-buthyllithium complex to dihydroisoquinoline **1** proved higher than that obtained when methyl- or phenyllithium was used. In the additions of methyl- and butyllithium to imine **1**, the (*S*)-enantiomer was formed, while phenyllithium addition resulted in formation of the (*R*)-enantiomer. Addition reactions to iminium salt **5** led in all cases to the formation of (*R*)-enantiomers. The lower enantioselectivity of reactions with isoquinolinium salt **5** relative to that of imine **1** could be a consequence of steric hindrance at the prochiral carbon atom caused by the *N*-methyl substituent.

Although the enantioselectivity of the above reported reactions is moderate, the additions of organolithium reagents to dihydroisoquinoline derivatives **1** and **5** is a convenient method for the synthesis of optically active isoquinoline alkaloids: (−)-salsolidine **2**, (+)-carnegine **6** and (−)-1-phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **7**, as well as optically active isoquinoline derivatives **3** and **4**. The method presented can afford a variety of isoquinoline derivatives in one-step and although in the work presented here (−)-sparteine was not as effective as in the case of acyclic imines, the search for a ligand of choice is still highly desirable.

4. Experimental

4.1. General

Melting points: determined on a Koffler block and are not corrected. IR spectra: Perkin Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, in $CDCl_3$, with TMS as internal standard. Mass spectra (EI): instrument AM D402. Specific rotation: Perkin Elmer polarimeter 242B at 20°C. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel 60_{254} for TLC. Analytical HPLC: Waters HPLC system with Mallinkrodt-Baker Chiracel OD-H column. (−)-Sparteine was purchased from the Aldrich Chemical Co., dried over KOH and distilled under reduced pressure. MeLi, *n*-BuLi and PhLi were purchased from the Aldrich Chemical Co.

4.1.1. Addition of methyllithium to 6,7-dimethoxy-3,4-dihydroisoquinoline 1. Synthesis of (−)-salsolidine 2. (−)-Sparteine (234 mg, 1 mmol) was dissolved in dry toluene (10 mL) under an argon atmosphere and the mixture cooled to −76°C. MeLi (1.6 M solution in Et_2O, 2 mL) was added and the solution was stirred for 30 min at the same temperature. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **1**[27] (191 mg, 1 mmol) in toluene (10 mL) was introduced dropwise. Stirring was continued for 2 h at −76°C and the reaction mixture was allowed to warm to −15°C and stirred at this temperature for a further 18 h. The reaction was quenched with 20% aqueous NH_4Cl at low temperature. When the mixture reached room temperature, the phases were separated and the aqueous was extracted with diethyl ether until the Dragendorff test was negative. The combined organic extracts were dried and the solvents removed under reduced pressure yielding an oil (268 mg). The crude amine **2** was purified by column chromatography (dichloromethane/methanol, 50:1). Pure salsolidine **2** (77%) obtained was identical to (±)-**2** in terms of spectral data[28] as well as TLC comparison. 30.4% e.e. by HPLC [hexane/propan-2-ol = 4:1; 0.5 mL/min; (*S*) isomer (major) 22.4 min, (*R*) isomer 29.1 min].

When the aqueous solution remaining from extraction of salsolidine **2** was rendered strongly alkaline (p$H = \sim$ 13) with 25% aqueous KOH and extracted with diethyl ether, dried and evaporated, an additional amount of amines (98 mg) was obtained which consisted mainly of (−)-sparteine. Some (−)-sparteine was also recovered from column chromatography purification (dichloromethane/methanol, 20:1→10:1).

4.1.2. Addition of *n*-butyllithium to 6,7-dimethoxy-3,4-dihydroisoquinoline 1. Synthesis of (−)-1-*n*-butyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 3. The reaction was carried out in the same way as in the case of methyllithium addition, on 1 mmol scale. *n*-Butyllithium (1.6 M solution in hexane, 1.4 mL) was used.

Pure amine **3** after column chromatography (dichloromethane/methanol, 100:1→50:1) was obtained as an oil. $[\alpha]_D$ −20.3 (0.73, $CHCl_3$); 46.5% e.e. by HPLC [hexane/propan-2-ol = 9:1; 0.5 mL/min; (*S*)-isomer (major) 24.2 min, (*R*)-isomer 31.9 min].

(−)-**3**·HCl mp 198–200°C, (±)**3**·HCl mp 199–202°C (MeOH–HCl) [lit.[19] (±)-**3**·HCl mp 206–207°C]; ^{1}H NMR δ ($CDCl_3$): 0.94 (t, $J = 6.8$ Hz, 3H, CH_3), 1.25–1.50 (m, 4H, $CH_2C\mathbf{H}_2C\mathbf{H}_2CH_3$), 1.64–1.86 (m, 2H, $C\mathbf{H}_2CH_2CH_2CH_3$), 1.72 (broad s, 1H, NH, disappeared with D_2O), 2.63–2.80 (m, 2H, $ArC\mathbf{H}_2CH_2N$), 2.90–3.00 (m, 1H, $ArCH_2C\mathbf{H}_2N$), 3.18–3.27 (m, 1H, $ArCH_2C\mathbf{H}_2N$), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87–3.92 (m, 1H, C(1)-H), 6.57 (s, 1H, ArH), 6.62 (s, 1H, ArH); MS *m*/*z* (%): 249 (M^+, 5.6), 248 (6.3), 192 (100), 176 (23.3), 148 (7.2), 131 (4.3).

4.1.3. Addition of phenyllithium to 6,7-dimethoxy-3,4-dihydroisoquinoline 1. Synthesis of (+)-1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 4. The reaction was carried out in the same way as for MeLi and *n*-BuLi addition on 1 mmol scale. PhLi [1.8 M solution in cyclohexane/ether (7:3) 1.3 mL] was used.

Pure amine **4** after column chromatography (dichloromethane/methanol, 200:1→100:1) was obtained as a solid; mp 131–133°C (methanol–propan-2-ol) [lit.[22] mp 132°C], $[\alpha]_D$ +3.1 (0.96, $CHCl_3$) {lit.[22] $[\alpha]_D$ −20.0 (0.50, $CHCl_3$)}; 17% e.e. by HPLC [hexane/propan-2-ol = 85:15; 0.5 mL/min; (*S*)-isomer 26.7 min, (*R*)-isomer (major) 37.6 min]. Spectral data were identical to those reported for the racemic compound.[22,25]

4.1.4. Addition of methyllithium to 6,7-dimethoxy-3,4-dihydroisoquinolinium methiodide 5. Synthesis of (+)-carnegine 6. The reaction was carried out similarly to the above on 1 mmol sale. To the preformed (−)-sparteine–methyllithium complex, a suspension of iminium salt **5**[27] in the solvent (see Table 4) was added. Work-up was the same as for amine **2**. Pure (+)-carnegine **6** was obtained after column chromatography (dichloromethane; dichloromethane/methanol, 100:1→50:1) as an oil. **6**·HCl mp 214–218°C (MeOH–HCl) [lit.[29] mp 209–211°C (EtOH)].

Spectral data of (+)-carnegine **6** obtained were identical to those reported in the literature.[28,29]

4.1.5. Addition of phenyllithium to 6,7-dimethoxy-3,4-dihydroisoquinolinium methiodide 5. Synthesis of (−)-1-phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 7. The reaction was carried out as in the case of carnegine **6**. PhLi [1.8 M solution in cyclohexane/ether (7:3), 1.2 mL] was used for formation of the complex with (−)-sparteine. Pure amine **7** was eluted from a chromatographic column with dichloromethane. Mp 90–92°C (ether–hexane); lit. mp 85–86°C,[22] 74–76°C (hexane).[25] The product had identical spectral data to those reported in the literature.[22,26]

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