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Enantioselective addition of organometallic compounds to 3,4-dihydroisoquinoline in the presence of oxazoline derivatives: synthesis of (*R*)-(+)- and (*S*)-(−)-salsolidine

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Abstract—The (*R*)- and (*S*)-enantiomers of salsolidine, **2**, were prepared in good yield and moderate enantioselectivity (33 and 27% e.e., respectively) by the addition of methyllithium to 6,7-dimethoxy-3,4-dihydroisoqiunoline **1** in the presence of the chiral oxazoline ligands **4** and **10**. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The enantioselective addition of organometallic reagents to prochiral imines in the presence of a chiral ligand/catalyst has been the subject of considerable interest[1–4] since it provides a synthetically useful methodology for preparing enantiopure amines, including alkaloids, e.g. isoquinoline alkaloids.

In the course of our studies on stereoselective syntheses of isoquinoline alkaloids based on enantioselective additions of organometallic reagents to imines,[5–7] we were interested in finding effective and readily available chiral ligands/catalysts suitable for such reactions. As a result of the (−)-sparteine-mediated additions of organolithium reagents to 3,4-dihydroisoquinoline derivatives, we have obtained simple isoquinoline alkaloids with modest e.e.s.[7] Similar results for the addition of organolithium compounds to acyclic imines, also performed in the presence of (−)-sparteine, were published recently by Lete et al.[8] We have chosen oxazoline derivatives as external inductors of asymmetry in this type of addition reaction[5,6] not only because of their well known efficiency in stereoselective transformations, both as chiral auxiliaries and catalytic ligands,[9–12] but also because some of these compounds can be readily obtained from (1*S*,2*S*)-2-amino-1-aryl-1,3-propanediols, for example (1*S*,2*S*)-(+)-thiomicamine, the industrial waste product.[13,14]

2. Results and discussion

Herein we report the results of our study on the effectiveness of oxazoline derivatives as chiral ligands in enantioselective additions of organometallic reagents to 6,7-dimethoxy-3,4-dihydroisoquinoline **1** in the presence of compounds **4**–**10**. Two of the ligands, **5**[13] and **8**,[5] were prepared earlier from (+)-thiomicamine and used as intermediates in the synthesis of oxazoline **3**.[5] Oxazoline **6** was obtained from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol and benzonitrile according to a literature procedure.[13] Oxazolines **9** and **10**[15] are commercially available, while compounds **4**[13] and **7**[16] were prepared by *O*-methylation of the precursors (**5** and **6**, respectively) with methyl iodide/NaH in DMF.[6] The starting imine **1** was obtained from 3,4-dimethoxyphenethylamine by the well-known Bischler–Napieralski cyclization.[17] In our experiments the addition of methyl nucleophiles to 6,7-dimethoxy-3,4-dihydroisoquinoline **1**, in the presence of the chiral oxazolines **4**–**10**, led to enantiomerically enriched (*R*)- or (*S*)-**2**,[18] depending on the structure of the oxazoline used and the type of organometallic reagent (Scheme 1). The previously reported addition of methyllithium to imine **1** performed in the presence of oxazoline **3** resulted in the formation of the *R* enantiomer of salsolidine, (*R*)-**2** with 41% e.e.[5]

In our preliminary studies, aimed at optimizing the reaction conditions, oxazoline **4** was used as the chiral ligand and methyllithium was the organometallic

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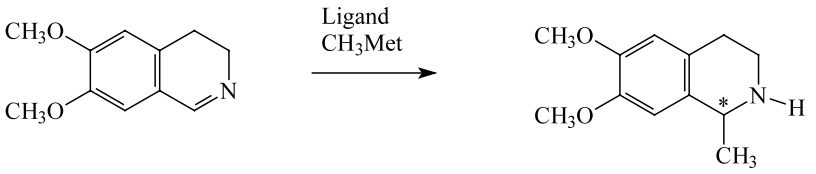

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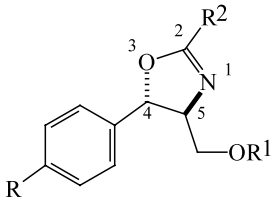

No	R	R^1	R^2
3	SCH_3	*o*-$CH_3OC_6H_4$	C_6H_5
4	SCH_3	CH_3	C_6H_5
5	SCH_3	H	C_6H_5
6	H	H	C_6H_5
7	H	CH_3	C_6H_5
8	SCH_3	*p*-$CH_3C_6H_4SO_2$	C_6H_5
9	H	H	CH_3
10	H	CH_3	CH_3

Scheme 1.

reagent. The influence of many factors on the enantioselectivity of the reaction, such as the type of solvent, the reaction temperature, the type of metal in the organometallic compound and the amount of chiral ligand/catalyst, were examined. On the basis of the results presented in Tables 1 and 2 (entries 1–4), the

Table 1. Addition of methyllithium to imine **1** in the presence of ligand **4**

Entry	Ligand **4** (mol. equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)	% e.e. NMR	Config.[a]
1	0.5	PhMe	−70→−40	48	25	5	(*R*)-(+)
2	0.5	PhMe	−20	2	66	32	(*R*)-(+)
3	1.0	PhMe	−20	2	45	20	(*R*)-(+)
4	2.6	PhMe	−20	1.5	56	33	(*R*)-(+)
5	0.1	PhMe	−20	3.5	47	5	(*R*)-(+)
6	0.5	THF	−20	2	50	0	
7	0.5	Et_2O	−20	2	42	12	(*R*)-(+)

[a] Confirmed by the sign of the specific rotation.[18]

Table 2. Addition of RMet to imine **1** in the presence of ligands **4**–**10**

Entry	Ligand (mol. equiv.)	RMet (mol equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)	% e.e. NMR	Config.[a]
1	**4** (0.5)	CH_3MgI (10)/ $BF_3{\cdot}Et_2O$ (1)[b]	THF/Et_2O	−70→−20	18	28	0	
2	**4** (0.5)	CH_3MgI (10)/ $BF_3{\cdot}Et_2O$ (10)	PhMe/Et_2O	−20→50	72	15	12	(*S*)-(−)
3	**4** (0.5)	$(CH_3)_2Zn$ (4)	PhMe	−20→reflux	72	Trace		
4	**4** (0.5)	$CH_3Ti(OiPr)_3$ (3)	PhMe	−20→50	72	Trace		
5	**5** (0.5)	CH_3Li (6)	PhMe	−20	2	72	11[c]	(*S*)-(−)
6	**6** (0.5)	CH_3Li (6)	PhMe	−20	22	47	0	
7	**7** (0.5)	CH_3Li (3)	PhMe	−20	3	50	5	(*R*)-(+)
8	**7** (0.5)	CH_3Li (3)	PhMe	−40	2	53	12	(*R*)-(+)
9	**8** (0.5)	CH_3Li (3)	PhMe	−20	1.5	41	0	
10	**8** (2 mol%)	$(CH_3)_2Zn/Ti(OiPr)_4$ (1.2)	PhMe	−30	22	Trace		
11	**9** (0.5)	CH_3Li (6)	PhMe	−20	1.5	50	0	
12	**10** (0.5)	CH_3Li (3)	PhMe	−20	1.5	77	27[c]	(*S*)-(−)

[a] Confirmed by the sign of the specific rotation.[18]
[b] Imine **1** was activated with $BF_3{\cdot}Et_2O$ prior to addition of ligand **4**.
[c] Additionally confirmed by HPLC.

optimal reaction conditions were determined. Thus, toluene, a solvent with low coordinating ability for organolithium reagents, was found to be superior to diethyl ether and THF (Table 1, entries 2, 6, and 7). The optimum temperature for the addition reaction was found to be −20°C and methyllithium was found to be a more effective nucleophile than methylmagnesium iodide, dimethylzinc and methyltriisopropoxytitanium in this reaction (Table 2, entries 1–4).

The best enantioselectivity was achieved when a substoichiometric quantity of ligand **4** (0.5 equiv.) was employed. When 2.6 equiv. of the ligand was used, the quantity applied by Tomioka et al.,[19] the enantioselectivity of this addition was comparable to those obtained with substoichiometric amounts of **4** (Table 1, entries 2 and 4). For this reason, and due to the poor solubility of most of the ligands **4**–**10** in toluene, we decided to run other experiments applying 0.5 equiv. of the oxazolines. In a typical run, imine **1** and the ligand were stirred in an appropriate solvent (toluene, Et_2O or THF) for 30 min at −20°C, then the organometallic reagent was added. The reaction mixture was then stirred for the time indicated in Tables 1 and 2, followed by quenching with 20% aqueous NH_4Cl and further work-up procedure.

The enantiomeric excess and the configuration of the salsolidine obtained from each reaction was established by peak integration of ^1H NMR spectra run in the presence of the chiral shift reagent, TADDOL[20] and/or by HPLC analysis using a Chiracel OD-H column. A comparison of the retention time of each enantiomer was made with that of the racemic sample and literature data.[7,21] The absolute configuration of the product was additionally confirmed by the sign of the specific rotation.

In the addition reactions mediated by ligands **4** and **7**, the dextrorotatory (*R*)-**2** was formed in yields of 53–66% with e.e.s of 12–33% (Tables 1 and 2, entries 7 and 8). The best enantioselectivity (33%) was obtained when oxazoline **4** was used as a ligand and methyllithium as the source of the nucleophilic. Addition of methylmagnesium iodide required Lewis acid-activation of imine **1** (1 equiv. of $BF_3{\cdot}Et_2O$). No enantioselectivity was observed (Table 2, entry 1), while completing the reaction with 10 equiv. of $BF_3{\cdot}Et_2O$ resulted in the formation of levorotatory (*S*)-**2** with 12% e.e. in low yield (Table 2, entry 2). (*S*)-Salsolidine **2** was also obtained in yields of 72–77% and 11–27% e.e. from the reactions using ligands **5** and **10** (Table 2, entries 5 and 12). When ligands **6**, **8** and **9** were used, no enantioselectivity was observed (Table 2, entries 6, 9–11). The additions of dimethylzinc and methyltriisopropoxytitanium to dihydroisoquinoline **1** in the presence of ligand **4** were not successful (Table 2, entries 3 and 4).

3. Conclusions

The best results obtained in the course of this study from the addition reactions of methyl organometallic reagents to 3,4-dihydroisoquinoline **1** in the presence of chiral ligands **4**–**10** are comparable to those reported for the reaction performed in the presence of oxazoline **3**[5] (33% versus 41% e.e.). The differences in the structure of the ligands have been shown to significantly influence the enantioselectivity of this process as well as the configuration of **2** produced in the reaction. Substituents at C-2 and the methylene group at C-5 seem to be responsible for the absolute configuration of **2** produced. The *R* isomer was formed when ligands **4** and **7**, with a methoxymethyl group at C-5 and a phenyl group at C-2 were used, while the (*S*)-**2** resulted from the reactions with ligand **5**, with a hydroxymethyl group at C-5 and a phenyl group at C-2. Ligand **10**, with a methoxymethyl group at C-5, and a methyl group at C-2, also led to the *S* enantiomer.

4. Experimental

4.1. General

^1H NMR spectra: Varian Gemini 300, in $CDCl_3$, with TMS as internal standard. Mass spectra (EI): instrument AM D402. IR spectra: Perkin Elmer 180 in KBr pellets. 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. MeLi was purchased from the Aldrich Chemical Co., Me_2Zn—from Fluka. $MeTi(OiPr)_3$ was prepared according to a literature procedure.[22]

4.2. Typical procedure for addition of methyllithium to 6,7-dimethoxy-3,4-dihydroisoquinoline, 1

4.2.1. Synthesis of (*R*)-(+)-salsolidine, 2. Oxazoline **4** (157 mg, 0.5 mmol) was dissolved in dry toluene (20 ml) under an argon atmosphere and the mixture cooled to −20°C. A solution of 3,4-dihydroisoquinoline **1** (191 mg, 1 mmol) in dry toluene (10 ml) was then introduced dropwise. This solution was stirred for 30 min at −20°C and then MeLi (1.6 M solution in Et_2O, 2 ml) was added. Stirring was continued for 2 h at −20°C. The reaction mixture was quenched with 20% aqueous NH_4Cl at the same temperature. When the reaction mixture reached room temperature, the phases were separated and the aqueous was extracted with Et_2O until the Dragendorff test was negative. The combined organic extracts were dried and solvents were removed under reduced pressure yielding an oil (257 mg), which was purified by column chromatography (dichloromethane–methanol; 100:1→10:1) to afford pure salsolidine **2** (103 mg, 50%), which was identical to (±)-**2** in terms of spectroscopic data[23] as well as TLC comparison; $[\alpha]_D$ +17.7 (*c* 1.30, EtOH) {lit.[18] $[\alpha]_D$ +59.9 (*c* 25.00, EtOH)}; 29% e.e. by ^1H NMR (spectra run with 2 equiv. of TADDOL).

When the aqueous solution (remaining after extraction) was rendered strongly alkaline (pH 13) with 20% aqueous NaOH and extracted with diethyl ether, dried

and evaporated, an additional amount of **2** (33 mg) was obtained. This was pure enough to obtain the ^{1}H NMR spectra and for accurate $[\alpha]_D$ measurement: $[\alpha]_D$ +19.7 (*c* 1.50, EtOH), 32% e.e. by ^{1}H NMR (spectra run with 2 equiv. of TADDOL). Total yield: 66%.

4.2.2. Synthesis of (*S*)-(−)-salsolidine, 2. The reaction was run in the same way as described in Section 4.2.1 using oxazoline **10** (103 mg, 0.5 mmol) in dry toluene (10 ml), imine **1** and MeLi. The oil obtained after work-up was purified by column chromatography yielding (*S*)-**2** (100 mg, 48% yield), $[\alpha]_D$ −16.1 (*c* 0.54, EtOH), 25% e.e. by HPLC [hexane/propan-2-ol = 4:1; 0.5 ml/min; *S* isomer (major) 20.4 min, *R* isomer 26.1 min].

Additional extraction of the aqueous liquors at pH 13 gave pure product **2** (60 mg), $[\alpha]_D$ −16.1 (*c* 1.45, EtOH), 27% e.e by ^{1}H NMR (spectra run with 2 equiv. of TADDOL). Total yield: 77%.

For the reaction completed with ligand **5**, toluene (100 ml) was used to dissolve it because of its very poor solubility.

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