Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4791–4796

TETRAHEDRON:
ASYMMETRY

Transformation of (+)-thiomicamine into a new ligand for the enantioselective addition of methyllithium to prochiral imines

Danuta Brózda, Maria Chrzanowska, Agata Głuszyńska and Maria D. Rozwadowska *

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

Received 9 November 1999; accepted 9 December 1999

Abstract

A new ligand **2** was prepared from (+)-thiomicamine **1** and *o*-methoxyphenol, and its activity as an external controller of stereochemistry in enantioselective additions of methyllithium to prochiral imines **8**–**10** tested. The non-racemic secondary amines **11**–**13** were prepared in 60–90% chemical yield with the enantioselectivity ranging from 2 to 41%. 6,7-Dimethoxy-3,4-dihydroisoquinoline **8** was transformed into (+)-salsolidine **11** with an *e.e*. of 41%.

1. Introduction

Racemic 2-amino-1-aryl-1,3-propanediols are intermediates in the industrial synthesis of amphenicol-type antibiotics. After resolution only the (*R,R*)-enantiomers are further transformed into the therapeutic drugs while the (*S,S*)-isomers are available for organic synthesis. They have found wide application as enantiopure reagents and building blocks as well as chiral auxiliaries and ligands for stereoselective transformations.

In an attempt to make use of the synthetic potential of the aminodiols we have undertaken experiments aimed at transforming one of them, (+)-thiomicamine **1**,[1] into derivative **2**, and testing its effectiveness in the addition of organometallic reagents to prochiral imines. The structure of compound **2** bears a pattern of complexing sites similar to those which may be found in the catalysts represented by structures **3**–**7** — having been proven to be effective asymmetry inductors in additions to imines.

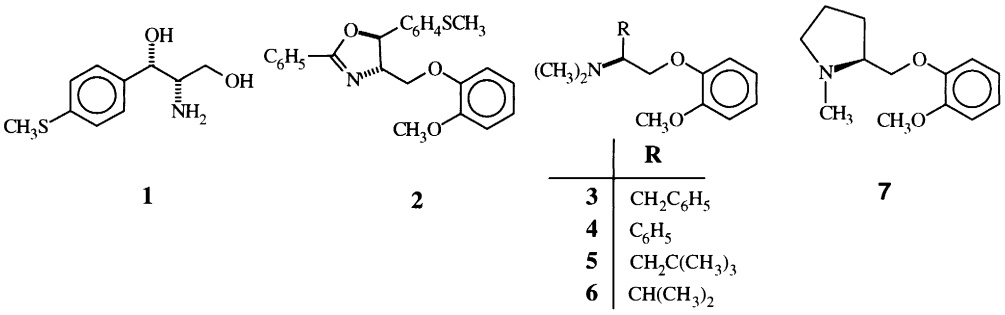
Chiral ligand-mediated enantioselective additions of organometallic compounds to prochiral imines as a method of synthesis of enantiomerically enriched amines has recently been studied extensively and described in several review articles.[2–5]

The first report on the addition of organolithium reagents to *N*-methoxyphenyl imines performed in the presence of an external chiral controller of stereochemistry was published by Tomioka and co-workers

* Corresponding author. E-mail: wzantk@main.amu.edu.pl

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00573-X

in 1990.[6] Among the various chiral ligands they applied, the tridentate amino ethers **3**–**5**, prepared from *o*-methoxyphenol and aminoalcohols derived from natural amino acids,[6–14] provided high levels of enantioselectivity with *e.e.* values up to 90% (Scheme 1).



1 **2**

	R
3	$CH_2C_6H_5$
4	C_6H_5
5	$CH_2C(CH_3)_3$
6	$CH(CH_3)_2$

7

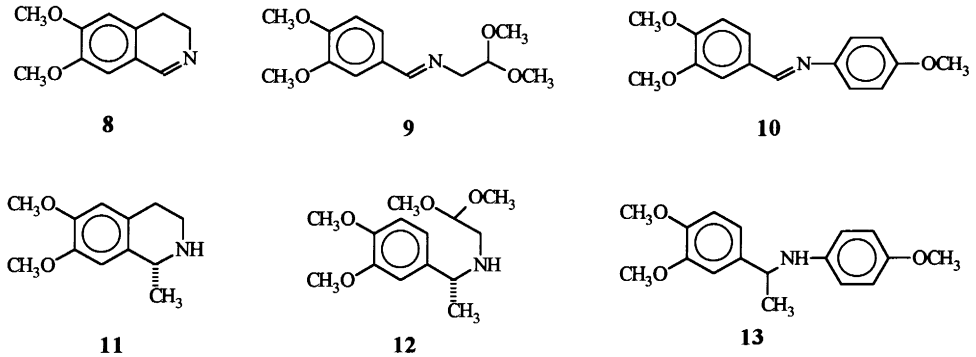
Scheme 1.

Recently, North and co-workers[15,16] have synthesized two other ligands of the same type, **6** and **7**, by coupling guaiacol with *S*-valine and *S*-proline derivatives, and used them in similar additions of organolithiums to imines, however with less satisfactory results.

2. Results and discussion

As one of the approaches to the stereoselective synthesis of isoquinoline alkaloids we have considered the enantioselective addition of organometallic reagents to imines **8**–**10** as the key step. In such a strategy the C-1 stereogenic center could be created at an early stage of the synthesis. For example, optically active salsolidine **11** could be prepared either directly from 3,4-dihydroisoquinoline by addition of methyllithium or from acyclic imines **9** and **10** by further transformations of the addition products **12**, **13**.

In this paper we describe the synthesis of compound **2** and results of reactions between methyllithium and imines **8**–**10** performed in the presence of **2**. The prepared secondary amines **11**–**13** were obtained in 60–90% chemical yield with the enantiomeric excess ranging from 2 to 41% (Scheme 2 and Table 1).



8 **9** **10**

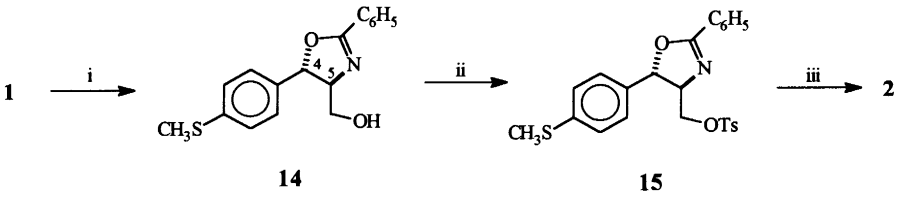
11 **12** **13**

Scheme 2.

Ligand **2** was prepared from guaiacol and (+)-thiomicamine **1**. Thus, (+)-thiomicamine **1** was converted into oxazoline **14**[17] which was *O*-tosylated with tosyl chloride in pyridine to give tosylate **15**. Treatment of **15** with guaiacol sodium salt in DMF then gave compound **2** in 71% overall yield from **1**. (Scheme 3).

Table 1
Addition of methyllithium to imines **8**–**10** in the presence of compound **2**

Reaction conditions				Products		
Imine	Solvent	CH_3Li (equiv.)	Temp.(°C)	Amine	Y (%)	*e.e.* (%)
8	Toluene	3.0	-20	**11**	80	41
8	THF	3.0	-72	**11**	78	0
9	Toluene	2.5	-42	**12**	60	5.6
9	THF	2.5	-42	**12**	60	2.0
10	Toluene	3.0	-20	**13**	88	3.2
10	THF	3.0	-76	**13**	90	5.4



Scheme 3. Reagents and conditions: (i) lit.;[17] (ii) TsCl/PyH, 0°C, 48 h; (iii) *o*-$CH_3OC_6H_4O^-Na^+$, DMF, 60°C

The starting imines were prepared according to the standard procedures: 6,7-dimethoxy-3,4-dihydroisoquinoline **8** by the Bischler–Napieralski cyclization,[18] imines **9** and **10** by condensation of veratraldehyde with α-aminoacetaldehyde dimethylacetal[19] and *o*-methoxybenzylamine,[20] respectively.

Addition of methyllithium to imines **8**–**10** in the presence of ligand **2** was carried out following the general reaction conditions described by Tomioka et al.:[6–14] toluene (50 ml per mmol of imine) or THF (40 ml per mmol of imine) were used as solvent and 2.5–3.0 equiv. of the organometallic reagent was applied. The amount of catalyst **2** could not reach the optimum 2.6 equiv. because of solubility problems. The best results in terms of the chemical yield and *e.e.* were achieved using 0.5 equiv. Due to its poor solubility, **2** could be recovered from the reaction mixture simply by dissolving the crude products in methanol from which it crystallized easily. The results of the experiments performed are shown in Table 1.

It is evident that the best enantioselectivity was achieved with imine **8**. The enantiomeric excess and (*R*)-configuration of the synthesized (+)-salsolidine were determined by comparison of the value of specific rotation with that of the known (*R*)-enantiomer[21] (41% *e.e.*) as well as by integration of the ^1H NMR spectrum run in the presence of 2 equiv. of TADDOL[22] (40% *e.e.*). The same solvating agent (3 equiv.) was used to determine the *e.e.* of amine **12**, whose structure was also verified by converting it into the known *N*-tosylate.[23] The *e.e.* of amine **13** was established by HPLC with Chiracel OD-H column.

3. Conclusion

The stereochemical result of the addition of methyllithium to imines carried out in the presence of compound **2** was not as satisfactory as might be expected with a ligand incorporating two structural fragments, oxazoline[24] and amino ethers **3**–**7**, both capable of high degree of asymmetric induction.

The usefulness of the above presented strategy for the synthesis of isoquinoline alkaloids seems to be promising particularly in the case of additions to 3,4-dihydroisoquinoline. The stereogenic C-1 center could be created at an earlier stage of the synthesis with no covalently bound chiral auxiliary being involved. Another example of utility of the enantiomerically pure and cheap 2-amino-1-aryl-1,3-propanediol **1** in asymmetric synthesis has been demonstrated.

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): Joel D-100, 75 eV. Specific rotation: Perkin–Elmer polarimeter 243B 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. (+)-Thiomicamine was purchased from the Aldrich Chemical Co. and used as received.

*4.2. Synthesis of ligand **2***

*4.2.1. (4S,5S)-5-Tosyloxymethyl-4-(4-methylthiophenyl)-2-phenyl-2-oxazoline **15***

To a solution of oxazoline **14**[17] (2.99 g, 10 mmol) in pyridine (30 ml) *p*-toluenesulfonyl chloride (2.86 g, 15 mmol) was added portionwise at 0°C during 1.5 h with stirring. The mixture was kept at 0°C for 48 h, then poured onto ice (210 g) and after rt was reached the solid was removed by filtration, washed with cold water (3×300 ml) and air-dried to give crude **15**. It was then dissolved in CH_2Cl_2 and washed with 1% NaOH followed by 20% NH_4Cl and dried; the solid precipitating during evaporation of solvent was filtered off to give 4.2 g (92.6%) of TLC-pure **15**, which was used in the next step of the synthesis without further purification. For characterization, a sample was crystallized from methanol, m.p. 59–61°C; $[\alpha]_D$ +11.7 (c=0.98, ethanol). IR cm^{-1}: 1647; ^1H NMR δ: 2.43 (s, 3H, Ar-CH_3), 2.48 (s, 3H, SCH_3), 4.16–4.21 (m, 1H, H-5), 4.28–4.38 (m, 2H, CH_2O), 5.45 (d, J=6.1 Hz, 1H, H-4), 7.19–7.95 (m, 13H, Ar-H); MS *m/z* (%): 453 (25), 281 (70), 268 (50), 130 (85), 105 (100). Found: C, 63.60; H, 5.06; N, 3.10. $C_{24}H_{23}NO_4S_2$ (453.55) requires: C, 63.55; H, 5.11; N, 3.10.

*4.2.2. (4S,5S)-5-(2-Methoxyphenoxymethyl)-4-(4-methylthiophenyl)-2-phenyl-2-oxazoline **2***

A solution of tosylate **15** (4.53 g, 10 mmol) and sodium 2-methoxyphenolate (1.61 g, 11 mmol) in DMF (40 ml) was kept at 60°C for 3 h under argon atmosphere, then left for 18 h at rt. The crystalline solid was filtered off and washed with excess of methanol to deposit 3.35 g (82.7%) of pure **2.** After crystallization from CH_2Cl_2/methanol, m.p. 168–169°C, $[\alpha]_D$ +17.3 (c=1, $CHCl_3$). IR cm^{-1}: 1648; ^1H NMR δ: 2.48 (s, 3H, SCH_3), 3.85 (s, 3H, OCH_3), 4.06 (t, J=8.7 Hz, 1H, CH_2O), 4.47–4.60 (m, 2H, H-5, CH_2O), 5.70 (d, J=6.5 Hz, 1H, H-4), 6.88–8.06 (4m, 13 H, Ar-H). MS *m/z* (%): 405 (M^+, 10), 375 (60),

268 (10), 210 (20), 165 (30), 151 (13), 137 (18), 130 (80), 105 (100). Found: C, 71.01; H, 5.52; N, 3.17. $C_{24}H_{23}NO_3S$ (405.49) requires: C, 71.08; H, 5.72; N, 3.45.

4.3. Synthesis of imines **9** and **10**

Veratraldehyde (1.66 g, 10 mmol) was added to a solution of amine (1.1 ml, 10 mmol aminoacetaldehyde dimethyl acetal or 1.23 g, 10 mmol *p*-anisidine) in toluene (40 ml), and the reaction mixture was refluxed for 3 h using a Dean–Stark trap. It was then concentrated under reduced pressure to give crude product which was purified by recrystallization.

4.3.1. (3,4-Dimethoxybenzylidene)-(2,2-dimethoxyethyl)-amine **9**

Colorless crystals (yield: 85%), m.p. 49–50°C (hexane–ether) (lit.[19] m.p. 49°C). IR cm^{-1}: 1642; ^1H NMR δ: 3.43 (s, 6H, OCH_3), 3.76 (d, J=5.2 Hz, 2H, CH_2), 3.92, 3.95 (2s, 3H each, OCH_3), 4.68 (t, J=5.2 Hz, 1H, CH), 6.88 (d, J=8.2 Hz, 1H, Ar-H), 7.17 (dd, J=1.9, 8.2 Hz, 1H, Ar-H), 7.43 (s br., 1H, Ar-H), 8.20 (s, 1H, CH=N); MS *m/z* (%): 253 (M^+,12), 178 (5), 151 (10), 92 (3), 75 (100). Found: C, 61.59; H, 7.89; N, 5.55. $C_{13}H_{19}NO_4$ (253.13) requires: C, 61.68; H, 7.56; N, 5.53.

4.3.2. (3.4-Dimethoxybenzylidene)-(4-methoxyphenyl)-amine **10**

Colorless crystals (yield: 88%), m.p. 131–132°C (hexane–ether) (lit.[20] m.p. 126°C). IR cm^{-1}: 1620; ^1H NMR δ: 3.83, 3.95, 3.99 (3s, 3H each, OCH_3), 6.93 (d, J=8,9 Hz, 2H, Ar-H), 7.21 (d, J=8.9 Hz, 2H, Ar-H), 7.30–7.61 (m, 3H, Ar-H), 8.39 (s, 1H, CH=N); MS *m/z* (%): 271 (M^+,100), 256 (64), 240 (12). Found: C, 70.59; H, 6.26; N, 5.12. $C_{16}H_{17}NO_3$ (271.32) requires: C, 70.83; H, 6.32; N, 5.16.

4.4. Addition of methyllithium to imines. General procedure

Ligand **2** (203 mg, 0.5 mmol) was dissolved in dry toluene (40 ml) or THF (30 ml) under an argon atmosphere and cooled to the temperature indicated in Table 1. The imine (1 mmol) in dry toluene (10 ml) or THF (10 ml) was added and the reaction mixture was stirred vigorously for 30 min at the same temperature, before MeLi (1.6 M solution in Et_2O; 2.5 mmol or 3.0 mmol) was introduced. Stirring was continued for 2 h, then quenched with 20% NH_4Cl at the low temperature. Phases were separated at rt and the aqueous one was extracted twice with ethyl ether (2× ca 50 ml). Combined organic extracts were dried and the solvents were removed under reduced pressure. In the case of amines **12** and **13** the residue was dissolved in methanol (ca. 20 ml) from which crystalline **2** was removed by filtration and the filtrate was concentrated in vacuo. Amines **11** and **12** were purified by column chromatography (silica gel, dichloromethane:methanol 50:1 for compound **11**; toluene:ethyl ether 99:1 for compound **12**) while **13** by crystallization.

4.4.1. (+)-Salsolidine **11**

Oil, $[\alpha]_D$ +24.0 (c=1.2, EtOH), 41% *e.e.* [lit.[25] $[\alpha]_D$+59.9 (c=25, EtOH)], was identical with racemic alkaloid in terms of spectral data[26] as well as chromatographic (TLC) comparison.

4.4.2. (2,2-Dimethoxyethyl)-[1-(3,4-dimethoxyphenyl)ethyl]-amine **12**

Oil,[19] IR cm^{-1}: 3430; ^1H NMR δ: 1.35 (d, J=6.6 Hz, 3H, CH_3), 1.57 (s, broad, N-H), 2.55 (dd, J=5.2, 12.1 Hz, 1H, CH), 2.63 (dd, J=5.5, 12.1 Hz, 1H, CH_2), 3.31, 3.36 (2s, 3H each, OCH_3), 3.71 (q, J=6.6 Hz, 1H, CH), 3.87, 3.89 (2s, 3H each, OCH_3), 4.43 (t, J=5.2, 5.5 Hz, 1H, CH_2), 6.82, 6.8, 6.89 (3s, Ar-H); MS *m/z* (%): 269 (M^+, 4), 254 (13), 206 (6), 165 (100), 121 (3), 75 (15).

N-Tosylate: crystals, m.p. 95–96.5°C (methanol); IR cm^{-1}: 1342, 1163; ^1H NMR δ: 1.5 (d, J=7.14 Hz, 3H, CH_3), 2.43 (s, 3H, Ar-CH_3), 3.03 (dd, J=6.3, 15.4 Hz, 1H, CH_2), 3.13 (dd, J=3.8, 15.4 Hz, 1H, CH_2), 3.2, 3.33, 3.62, 3.84 (4s, 3H each, OCH_3), 4.27 (dd, J=3.8, 6.3, 1H, CH), 5.03 (q, J=7 Hz, 1H, CH), 6.43, 6.73, 6.74 (3s, 3H, Ar-H), 7.32 (d, J=8.5 Hz, 2H, Ar-H), 7.80 (d, J=8.2 Hz, 2H, Ar-H); MS *m/z* (%): 423 (M^+, 4), 360 (4), 268 (16), 165 (72), 75 (100). Found: C, 59.28; H, 7.17; N, 3.38. $C_{21}H_{29}NO_6S$ (423.17) requires: C, 59.60; H, 6.91; N, 3.31.

*4.4.3. (4-Methoxyphenyl)-[1-(3,4-dimethoxyphenyl)ethyl]-amine **13***

Crystals, m.p. 81–82°C (ether). IR cm^{-1}: 3400, 1520; ^1H NMR δ: 1.49 (d, J=6.7 Hz, 3H, CH_3), 1.57 (s, 1H, NH), 3.70, 3.87, 3.89 (3s, 3H each, OCH_3), 4.35 (q, J=6.7 Hz, 1H, CH), 6.49 (d, J=8.9 Hz, 2H, Ar-H), 6.70 (d, J=8.9 Hz, 2H, Ar-H), 6.82–6.92 (m, 3H, Ar-H); MS *m/z* (%): 287 (M^+, 77), 165 (100), 150 (11), 123 (20). Found: C, 70.87; H, 7.37; N, 4.82. $C_{17}H_{21}NO_3$ (287.28) requires: C, 71.06; H, 7.37; N, 4.87.

Acknowledgements

This work was financially supported by KBN grant no. 3 T09A 027 17.

References

1. Coppi, L.; Giordano, C.; Longoni, A.; Panossian, S. *Chirality in Industry II*; John Wiley & Sons: Chichester, New York, 1997; pp. 353–362.
2. Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun*. **1996**, 999–1004.
3. Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946.
4. North, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2959–2971.
5. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.
6. Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681–6684.
7. Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095–3098.
8. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603–1606.
9. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429–4438.
10. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527–2533.
11. Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Chem. Pharm. Bull.* **1997**, *45*, 1705–1707.
12. Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Heterocycles* **1997**, *46*, 165–168.
13. Tomioka, K.; Satoh, M.; Taniyama, D.; Kanai, M.; Iida, A. *Heterocycles* **1998**, *47*, 77–80.
14. Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1999**, *10*, 221–223.
15. Jones, C. A.; Jones, I. G.; North, M.; Pool, C. R. *Tetrahedron Lett.* **1995**, *36*, 7885–7888.
16. Jones, C. A.; Jones, I. G.; Mulla, M.; North, M.; Sartori, L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2891–2896.
17. Rozwadowska, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 1615–1618.
18. Whaley, W. M.; Meadow, M. *J. Chem. Soc.* **1953**, 1067–1070.
19. Lejay, P; Viel, C. *Ann. Chim. (Paris)* **1977**, *2*, 87–96; [C. A. **1977**, *87*, 117645b].
20. Rai, M.; Kaur, B.; Dhir, B. S. *J. Indian Chem. Soc.* **1982**, *59*, 416–417.
21. Battersby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214–1221.
22. Bussche-Hunnefeld, C.; Beck, A. K.; Seebach, D. *Helvetica Chim. Acta* **1992**, *75*, 438–441.
23. Ponzo, V. L.; Kaufman T. S. *Tetrahedron Lett.* **1995**, *36*, 9105–9108.
24. Gant, T. G.; Meyers, A. I. *Tetrahedron* **1997**, *50*, 2297–2360.
25. Spath, E.; Dengen F. *Ber.* **1938**, *71*, 113–119.
26. Menachery, M. D.; Lavanier G. L.; Wetherly, M. L.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1986**, *49*, 745–778.