Asymmetric Tandem Additions to Chiral Naphthyloxazolines. A New and Potent Chiral Auxiliary Resulting in a Major Improvement in Convenience and Efficiency

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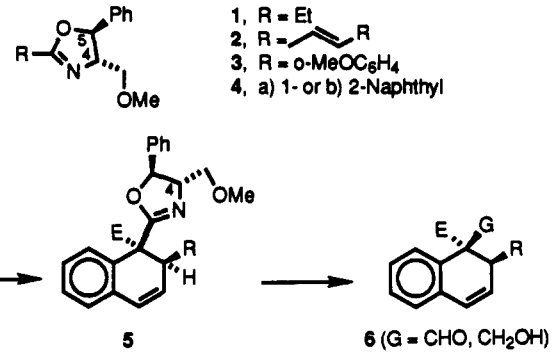
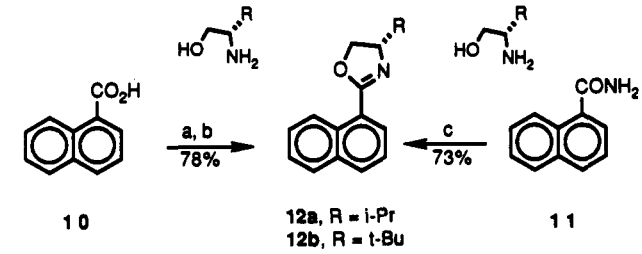
Summary: Excellent diastereofacial selectivities over a wide range of temperatures (−78 to 25 °C) were obtained with the title compounds with use of chiral oxazolines derived from (*S*)-valinol or (*S*)-*tert*-leucinol. These are the first useful levels of asymmetric induction observed without the presence of the chelating methoxyl groups. The dihydronaphthylcarbinols and aldehydes resulting from these additions were obtained in >98% ee.

Ever since the chiral oxazolines **1** were first introduced in 1974[1] as aza enolates in asymmetric carbon–carbon bond forming reactions, the field of asymmetric alkylations has exploded into what is today almost routine synthetic procedure.[2]

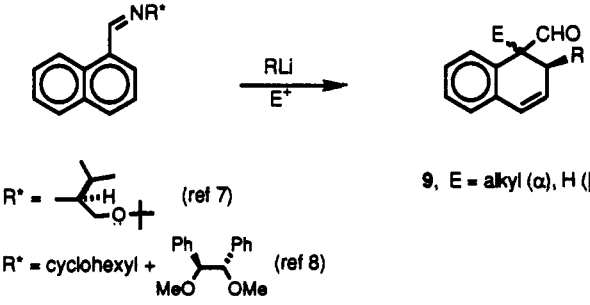


Subsequent to our first report using **1**, we were also successful in effecting asymmetric nucleophilic additions to α,β-unsaturated oxazolines[3] **2** and Grignard-mediated asymmetric biaryl syntheses[4] to **3**. In 1984, we described the nucleophilic tandem addition[5] to naphthyloxazolines **4**, giving rise to adducts **5** that, after hydrolysis and/or reduction, furnished the aldehydes or carbinols **6** in >95% ee.[6] The stereochemistry of the addition product was confirmed by X-ray studies, and the absolute configurations of the products were determined to be a function of the absolute stereochemistry of the pendant methoxymethyl group at C-4 in the oxazoline.[5] More recently, we and others have shown that chiral auxiliaries such as **7**[7] and the external chiral diether **8**[8] can also be used to direct diastereofacial addition to naphthalenes and provide the aldehydes **9** in high enantiomeric purity. However, the range of nucleophiles that were useful in the chiral imine procedure was rather limited, detracting from this potentially very important method.

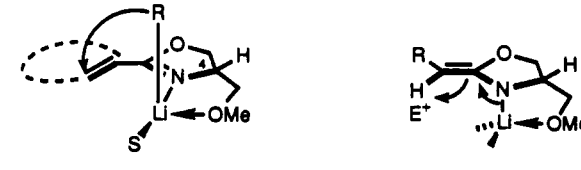
Scheme I[a]



[a] Key: a, oxalyl chloride, amino alcohol; b, $SOCl_2$; c, Et_3OBF_4, 1,2-dichloromethane amino alcohol.



The common thread that pervades all the chiral oxazoline and related systems studied to date is the critical need for a pendant alkoxy or equivalent ligand (as in **1**–**4** or **7**). In a large number of asymmetric C–C bond forming reactions[2] reported since 1974, the validity of the "chelated model" (A, B) for rigid topographical properties necessary for useful levels of diastereoselection has been repeatedly emphasized. Recently, Arnett[9] has presented strong structural and energetic evidence for lithium chelation in aminoalkoxides that supports all the notions mentioned previously.



A (Nucleophilic Addition) B (Electrophilic Addition)

(1) Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *96*, 268. A full account has appeared: Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567. For further discussion on the chelate models, c.f. Meyers, A. I. *Acct. Chem. Res.* **1978**, *11*, 375.

(2) For discussions on this subject of C–C bond forming reactions see: *Asymmetric Synthesis*; Academic Press: New York, 1982–1984; Vols. 2–4. *Stereoselective Synthesis*; Nogradi, M., Ed.; VCH: New York, 1987. *Asymmetric Synthesis-Construction of Chiral Molecules Using Amino Acids*; Coppola, G. M., Schuster, H. F., Eds.; J. Wiley–Interscience: New York, 1987. Seebach, D. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle-Sauerlander Verlag: Deerfield Beach, 1980. *Asymmetric Synthesis of Amino Acids*; Williams, R. M., Ed.; Pergamon: New York, 1989. For recent reviews, see: Tomioka, K. *Synthesis* **1990**, 541. Ward, R. S. *Tetrahedron* **1990**, *46*, 5029. Ojima, I. *Tetrahedron* **1989**, *45*, 6901. Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. Apsimon, J. *Tetrahedron* **1986**, *42*, 5157. Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. Posner, G. *Acc. Chem. Res.* **1987**, *20*, 72.

(3) Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266. A full account has appeared: Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250.

(4) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446 and earlier references cited.

(5) Meyers, A. I.; Barner, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 1865. A full account has appeared: Meyers, A. I., Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611 and earlier references cited.

(6) For a review on aromatic substitution using oxazolines, see: Meyers, A. I.; Reuman, M. *Tetrahedron* **1985**, *41*, 837.

(7) Meyers, A. I.; Brown, J. D.; Laucher, D. *Tetrahedron Lett.* **1987**, *28*, 5283.

(8) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266.

(9) Arnett, E. M.; Nichols, M. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 7059. For additional discussion on the importance of complexation and chelates in stereo- and regiochemistry, see: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

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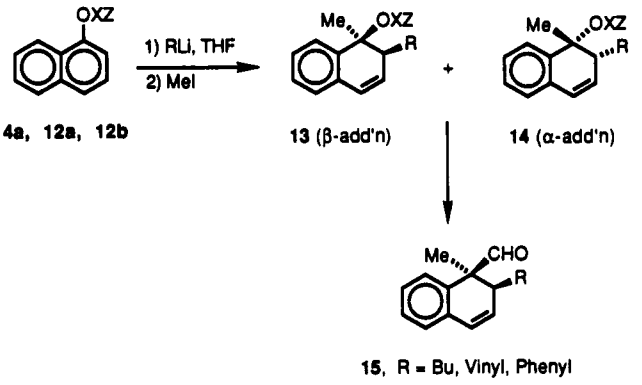
Table I. Addition of Organolithium–MeI to Naphthyloxazolines

naphthalene	R	addn T (°C)	reactn time (h)	% yield (total)	diastereomers[a] 13:14	% ee 15
R = CH_2OMe						
4a[b]	butyl	−78	2	97	96:4	90[d]
4a	vinyl[c]	−40	24	76	95:5	>98[e]
4a	phenyl	−40	3	86	83:17	78
R = *i*-Pr						
12a	butyl	−78	2	97	97:3	90
12a	vinyl[c]	−10	36	89	94:6	86[e]
12a	phenyl	−40	6	87	87:13	74
R = *t*-Bu						
12b	butyl	−78	2	99+	>99:1	>98
12b	vinyl[c]	0	36	94	>99:1	>98[e]
12b	phenyl	−40	6	81	95:5	90

[a] Determined by 300-MHz NMR and GLC. [b] Data taken from ref 5. [c] Generated in situ from vinyltributylstannane and MeLi. [d] The enantiomeric excess of all products in this column were determined by HPLC with use of Chiralcel OJ column and eluting with 3% EtOH–hexane. In each case, racemic 15 was prepared and separations were base line. [e] The vinyl aldehydes 15 (R = $CH{=}CH_2$) could not be separated (HPLC) into enantiomers, but the corresponding reduced vinylcarbinols were readily separated by HPLC and evaluated for ee.

Scheme II



We now describe a new, easily prepared chiral auxiliary that does not possess the pendant C-4 methoxymethyl group and gives even higher levels of diastereofacial additions. The chelation model still, in our opinion, exists, but takes on a different role (vide infra) not previously seen in these systems. Furthermore, the convenience in using this new auxiliary is only superseded by the truly unexpected stereochemical efficiency observed (Table I).

The starting naphthyloxazolines **12a** and **12b** were prepared conveniently from (*S*)-valinol[10] and (*S*)-*tert*-leucinol,[11,12] respectively, from naphthoic acid **10** or naphthamide **11** as shown in Scheme I. It was advantageous to study the efficiency of the tandem addition by comparing the diastereofacial selectivities resulting from alkyllithium addition to **12a**, **12b**, and the earlier utilized oxazoline **4**, which contains the ligand in the form of the methoxymethyl group (Scheme II). In each case, we compared the efficiencies of butyl-, vinyl-, and phenyllithium additions followed by trapping the aza enolate with methyl iodide to give **13** and **14**. The surprising results of this comparative study are given in Table I. The stereochemical outcomes of the two oxazolines without the chelating ligand (**12a** and **12b**) are equal or superior to the original oxazoline used, **4a**. In fact, the *tert*-butyloxazoline **12b** is somewhat more efficient than the isopropyl derivative **12a** wherein we were unable to detect any α-face addition by butyl- or vinyllithium to give **14**.

Table II. Effect of Temperature on Addition to 12b (MeI Trap)

RLi	reactn time (h)	reactn T (°C)	yield (%)	% ee, 15
vinyl	24	−40	0	
vinyl	36	0	94	>98[a]
vinyl	1	25	78	>98[a]
n-butyl	2	−78	99	>98
n-butyl	0.25	25	99	>98

[a] Since the aldehyde would not separate on chiral HPLC (see Table I), these are the corresponding carbinols, after $NaBH_4$ reduction.

Hydrolysis of **13** and **14** was accomplished by procedures described earlier[5] (MeOTf, 25 °C, 4 h; $NaBH_4$, 0 °C, 24 h; oxalic acid, 25 °C, 12 h) to give the aldehydes **15** that were assessed for enantiomeric excess using chiral stationary-phase HPLC (footnote, Table I). The yields for the hydrolysis ranged from 70–85%, and the enantiomeric purity, as seen in Table I, was excellent, particularly when the *tert*-butyloxazoline **12b** was employed. Of immediate interest was the absolute configuration of the products **15**. In this regard, the HPLC was very helpful (via elution order) since it showed that the major enantiomer was **15**, which was formed from all three chiral oxazolines **12a**, **12b**, and **4a**. Since the absolute configuration of **15** derived from **4a** was previously determined by X-ray crystal structure,[5] we can safely assume that the organolithium reagent is adding to the β-face of **12**. We also examined the effect of reaction temperature on the degree of stereoselection, and the interesting results are tabulated in Table II. Using vinyllithium (generated from vinyltributylstannane) and butyllithium as exemplary nucleophiles, we performed the additions to **12b** followed by trapping with methyl iodide to furnish **13** and **14**. As can be seen, reaction at −40 °C completely retards vinyl addition to the naphthalene **12b**. However, at 0 °C and room temperature reaction proceeds well and is almost complete after 1 h with virtually no loss in enantioselectivity in the product. Similar results are seen for *n*-butyllithium addition followed by methyl iodide trap. The reaction is over in 15 min at room temperature and with hydrolytic removal of the chiral auxiliary gave the aldehyde **15** (R = *n*-Bu) in essentially complete enantiomeric purity.

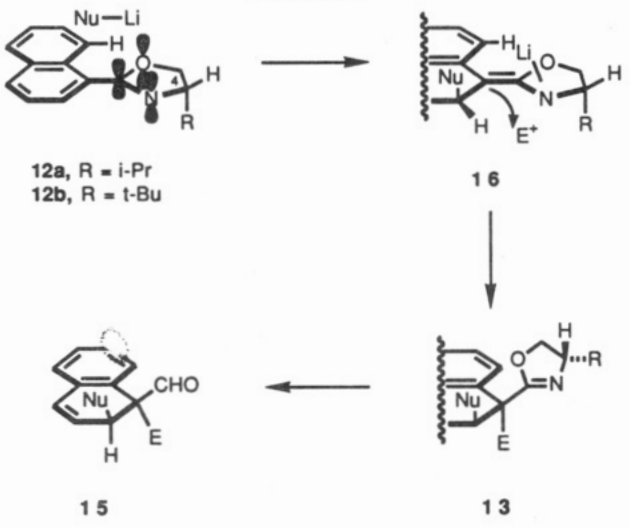
We currently are proposing that this extraordinary stereoselectivity occurs by the organolithium complexing to the β-face, opposite to the side carrying the large *tert*-butyl (or isopropyl) group (Scheme III). The π-system of the OC=N moiety in the oxazoline should function as a π-base, and this would allow complexation

(10) Aldrich Chemical Co., Milwaukee, Wisconsin. This may also be prepared by reduction ($LiAlH_4$ or $BH_3{\cdot}Me_2S$) of (*S*)-valine: *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 530.

(11) Kindly supplied by Degussa, Hanau, Germany. Commercial availability is still quite expensive from retail suppliers.

(12) Oxazolines derived from valinol, *tert*-leucinol, and phenylglycinol have recently been reported as chiral catalysts: (a) Lowenthal, R. E.; Abiko, A.; Masamune, M. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (c) Corey, E. J.; Imai, N.; Zhang, H.-Y. *Ibid.* **1991**, *113*, 728.

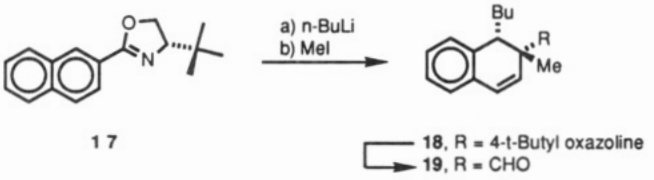
Scheme III



to the organolithium and delivery of the organo portion to the β-face of the naphthalene ring (**16**). The electrophile (i.e., MeI) is then added and enters from the more accessible α-face generating **13**, which is then observed as the overwhelmingly major product. Hydrolysis, after reduction of the C=N, gives the observed dihydronaphthalenes **15**. The steric effect in going from **12** to **16** must be very specific since the range of temperatures explored (−78 to 25 °C) has little effect on the outcome.[13]

(13) We have prepared and examined the alanine- and phenylalanine-derived oxazolines **12** (R = Me, Ph) to assess the sensitivity of the reaction to smaller steric influences. The de's (at −78 °C) for **12a** (R = Me) and **12b** (R = Ph) were 75:25 and 86:14 respectively.

Finally, we briefly examined the 2-naphthyl system[5] **17** that, upon addition of *n*-butyllithium at −78 or 25 °C gave, after methyl iodide addition, 94–98% yields of **18** and >99 and 97% diastereoselection, respectively. Here again, we observed a relatively small temperature effect. The reaction was complete in 2 h at −78 °C or 15 min at 25 °C. Removal of the oxazoline, in the manner stated earlier, gave the chiral aldehyde **19** in >98% ee from −78 °C reaction and >90% ee from the 25 °C reaction.



These impressive enantioselective results using a simple, easily prepared chiral oxazoline will now make these systems more convenient to utilize. Although the yields of product are comparable with all three oxazolines studied (**4**, **12a**, and **12b**), the stereochemical results using *tert*-butyl derivative appears to be overall superior and will ultimately be the system of choice. We are also examining these chiral oxazolines (**12b**) in other reactions (alkylations, aryl couplings, etc.).

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this work and to Merck, Sharpe & Dohme for a postdoctoral fellowship (D.J.R.).

Supplementary Material Available: Experimental details, spectral data, and HPLC data for enantiomeric determination (13 pages). Ordering information is given on any current masthead page.

A Simple Asymmetric Synthesis of 2-Substituted Pyrrolidines from 3-Acylpropionic Acids

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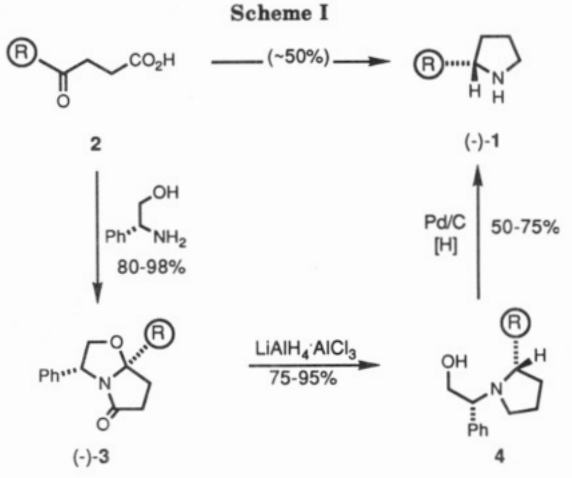
Summary: The title compounds have been prepared from 3-acylpropionic acids **2** and (−)-R-phenylglycinol in a three-step sequence in >98% enantiomeric excess. The R group in **2** ultimately becomes the 2-substituent in the chiral pyrrolidine.

In recent years, a number of laboratories have reported asymmetric and enantioselective routes to 2-substituted pyrrolidines.[1] In all these studies, either the enantiomeric purity of the final product or the inconvenience of a large number of synthetic steps, or both, detracted from the overall utility of the process. We wish to describe our preliminary results on a route to 2-substituted pyrrolidines

(1) (a) Tseng, C. C.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 29. (b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (c) Shiosaki, K.; Rapaport, H. *J. Org. Chem.* **1985**, *50*, 1229. (d) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. (e) Arseniyadis, S.; Huang, P. Q.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 631. (f) Skrinjar, M.; Wistrand, L.-G. *Tetrahedron Lett.* **1990**, *31*, 1775. (g) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (h) Ganem, B.; Liotta, L. J. *Synlett* **1990**, 503. (i) Maryanoff, B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911. (j) Morlacchi, F.; Losacco, V. *J. Heterocycl. Chem.* **1976**, *13*, 165. (k) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250. (l) Nordlander, J. E.; Njoroge, F. G.; Payne, M. S.; Warman, D. *J. Org. Chem.* **1985**, *50*, 3481.

Scheme I



which is both convenient to utilize and provides the final products in >98% enantiomeric excess. Scheme I portrays the overall three-step sequence which provides the nonracemic 2-substituted pyrrolidines in ~50% overall yield.

The starting keto acid **2**, if not commercially available, is readily prepared by using the elegant procedure of

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